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KIDNEY WEEK EDITION

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Abstract Supplement

KIDNEY WEEK 2023

Abstract Supplement

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- Translational Sessions
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TH-OR01

Heart-Specific LIM Protein (CSRP3) as a Novel Cardiorenal Connector in Acute Cardiorenal Syndrome-Related CKD Progression

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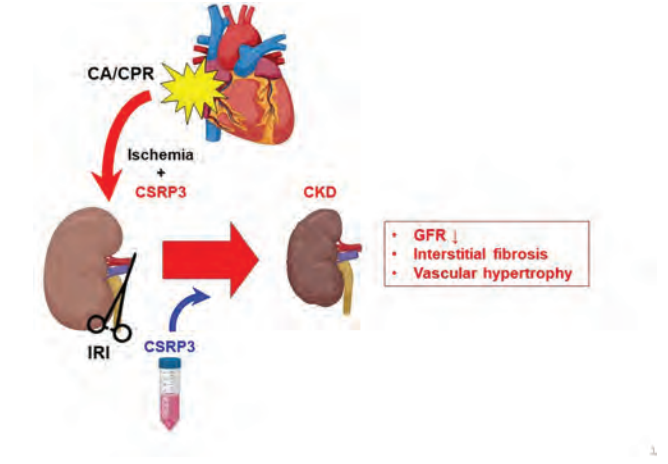
Background: Cardiorenal syndrome type 1 (CRS1) is acute kidney injury (AKI) caused by acute cardiovascular disease. Our translational CRS1 model, cardiac arrest and cardiopulmonary resuscitation (CA/CPR) causes AKI-CKD transition characterized by reduced GFR, increased fibrosis, renovascular hypertrophy, and elevated blood pressure--CRS1-induced AKI-CKD (CRACKD). Heart specific LIM protein (CSRP3) is secreted into blood stream by acute cardiac injury, and taken up by renal proximal tubular cells via megalin mediated endocytosis. We hypothesized that cardiac CSRP3 mediates CRACKD.

Methods: We generated inducible cardiac CSRP3 KO mice (iCSRP3KO, csrp3 flfl/myh6 cre-esr1). CA/CPR (8min cardiac arrest) or 8min ischemia reperfusion injury (IRI) was performed to C57BL6 mice, inducible proximal tubules megalin KO mice (iMegKO), or iCSRP3KO mice. IRI mice were injected 5ug CSRP3 or PBS. GFR, αSMA expression, and renovascular wall thickness were analyzed at 49 days. Research-designated human kidney proximal tubular epithelial cell (PTEC) was used in vitro.

Results: iCSRP3KO mice did not express CSRP3 in myocardium. SnRNA sequencing of CA/CPR kidney and bulk RNA sequencing of CSRP3 treated PTEC demonstrated similar alteration of fibrosis and myogenesis related genes. CSRP3-treated IRI mice (CSRP3-IRI) demonstrated reduced GFR (785.0±96.6 vs 933.3±148.6 (μg/min/100g), $p<0.05$), increased fibrosis ($V_{\alpha SMA}/V_{kidney}$: 2.37±0.99 vs 1.43±0.40, $p<0.05$) and renovascular hypertrophy (thickness index: 0.61±0.03 vs 0.50±0.03, $p<0.01$) compared with PBS-treated IRI mice. These CSRP3 induced phenotypic changes were attenuated by pharmacological megalin inhibition in CSRP3-IRI mice or iMegKO-CA/CPR mice. Compared with littermate control, deletion of cardiac CSRP3 ameliorated CA/CPR induced GFR loss (845.4±75.6 vs 723.3±75.5, $p<0.05$) and BP elevation (122.8±13.3 vs 145.1±15.7 (mmHg), $p<0.05$). (Mean+/-SD, Student's t-test)

Conclusions: Cardiac CSRP3 mediates renal fibrosis and myogenesis leading to CRACKD. We report a novel mechanism of CRS1 induced AKI-CKD transition.

Funding: Veterans Affairs Support



TH-OR02

The Epidermal Growth Factor Receptor Is an Essential Mediator of Interstitial Fibrosis Development Following AKI

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Background: In the kidney, tubulointerstitial fibrosis can result from incomplete recovery from acute kidney injury (AKI), toxic injury or other inflammatory insults. Activation of the Epidermal Growth Factor Receptor (EGFR) has been implicated as a potential mediator of interstitial fibrosis but underlying mechanisms of EGFR's actions have not been previously addressed.

Methods: To delete EGFR selectively in the fibroblast/pericyte population, we generated PDGFRβ-Cre/ERT2; mCherry (WT) and PDGFRβ-Cre/ERT2; mCherry; $EGFR^{f/f}$ (FibEGFR-/-) mice. Models of acute kidney injury included ischemia/reperfusion, UUO and folate and adenine nephropathy. In vitro studies utilized immortalized mouse fibroblasts.

Results: In all models of acute injury, FibEGFR-/- mice developed less tubulointerstitial fibrosis and isolated fibroblasts had decreased collagen mRNA expression. Fibroblast EGFR expression played an essential role in fibroblast migration and proliferation after injury. In cultured mouse fibroblast cells, EGFR activation induced proliferation but decreased expression of SMAD3 and myofibroblast markers. TGF-ß did not induce proliferation but reversed EGFR's inhibition and stimulated myofibroblast differentiation. SnRNAseq confirmed decreased markers of fibroblast proliferation and cell motility and numbers of myofibroblasts in FibEGFR-/- mice.

Conclusions: These studies provided evidence for a heretofore undescribed and important role for EGFR in kidney fibroblasts and pericytes as a specific initiator of interstitial fibrosis in response to kidney injury by stimulating pericyte/fibroblast migration and proliferation.

Funding: NIDDK Support, Veterans Affairs Support

TH-OR03

Prevention of Ischemia-Reperfusion Injury (IRI)-Induced AKI by Maintaining Na+/K+ ATPase Activity

Nadezhda N. Zheleznova,[1] Tamara A. Wahbeh,[1] Lei Wang,[1] Jie Zhang,[2] Jin Wei,[2] Nathan Hall,[1] Nohely Hernandez Soto,[1] Bo Chen,[1] Wei Chen,[1] Ruisheng Liu.[1] *[1]University of South Florida, Tampa, FL; [2]Boston University, Boston, MA.*

Background: IRI impairs Na/K ATPase pump function leading to cellular death. We developed a method using a 3rd Generation Synchronization Modulation Electric field (SMEF) to optimize Na/K ATPase activity during ischemia (Sci Trans Med. 2022). Now, advanced to a 4th Generation SMEF, we have incorporated dual-energy transformation functions and power injections for ATP generation, hypothesizing that it will more efficiently combat ischemia-reperfusion-induced acute kidney injury (AKI).

Methods: Male and female C57BL/6J mice were divided into 3 groups: sham control, AKI without 4th-SMEF, and AKI with 4th-SMEF. A right nephrectomy was performed, followed by warm ischemia induction by clamping of the left renal pedicle (20 min in males vs. 25 min in females). In the 4th-SMEF group, an electric field was applied to the left kidney pre-clamping. Plasma creatinine (Day 1,3,7), Glomerular Filtration Rate (day 7), KIM-1, and Na/K pump activity and expression were evaluated. A histological kidney tissue examination was conducted.

Results: The 4th-SMEF reduced plasma creatinine by 92% in males (4th-SMEF:0.21±0.10 mg/dL, untreated AKI:2.56±0.9 mg/dL) and 82% in females (4th-SMEF:0.34±0.3 mg/dL, untreated AKI 1.84±0.4 mg/dL), displaying similitude to sham groups. This outperforms the previous 3rd-SMEF approach, decreasing plasma creatinine by only 40% (Chen, 2022). GFR showed 60% improvement in males (4th-SMEF:255 μl/min, untreated AKI:110 μl/min) and 55% improvement in females (4th-SMEF: 220μl/min, untreated AKI:98μl/min). KIM-1 marker in the AKI-treated group, the sham, and 4th-SMEF-treated groups showed: (271±30 pg/ml, 60±9 pg/ml, and 66±21 pg/ml) respectively. Baseline Na/K expression is higher in females. AKI groups of both genders exhibited reduced activity, and expression, alongside cellular relocation. With 4th-SMEF, both genders reached equalized Na/K pump activity and degradation reduction. Histology conveyed diffuse renal tubular necrosis and casts comprising necrotic cells and debris in AKI groups. In contrast, the 4th-SMEF treatment essentially normalized the histopathologic changes aiding strong similarity to the sham group.

Conclusions: 4th-SMEF prevented AKI by equally normalizing Na/K pump activity in both genders of mice, leading to similar prevention of IRI-induced AKI.

Funding: NIDDK Support

TH-OR04

Analysis of the Immune Cell Landscape Identifies Immunosenescence as a Therapeutic Target in Rhabdomyolysis-Induced AKI

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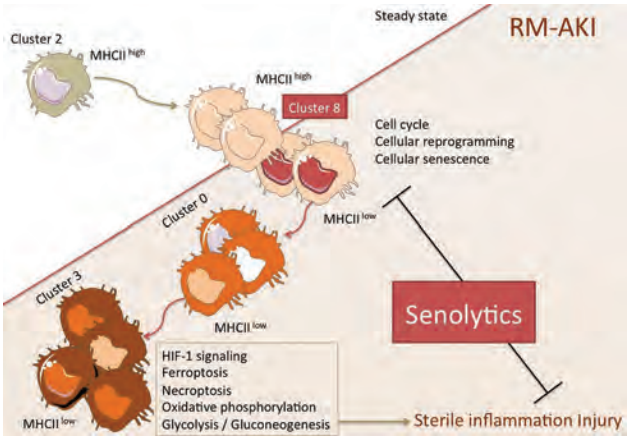
Background: Rhabdomyolysis (RM) accounts for 10% of the acute kidney injury (AKI) cases. The role of macrophages in the development of RM-AKI lesions has been clearly established, but a high resolution understanding of the changes in the immune landscape could help to improve targeted strategies.

Methods: Single-cell RNA sequencing was used in the murine glycerol-induced RM-AKI model to dissect the transcriptomic characteristics of CD45+ live cells sorted from kidneys 2 days after injury. A combination of senolytics (dasatinib and quercetin) was administered to mice exposed or not to RM-AKI.

Results: Unsupervised clustering of nearly 17,000 single-cell transcriptomes identified 7 known immune cell clusters. Sub-clustering of the mononuclear phagocyte cells (MPC), including monocytes, macrophages and dendritic cells, revealed 9 distinct cell sub-populations differently modified with RM. One macrophage cluster was particularly interesting since it behaved as a critical node in a trajectory connecting one MCHIIhigh cluster only present in control to 2 MCHIIlow clusters only present RM-AKI. Because this crucial cluster expressed senescence hallmark genes, the effect of combined dasatinib and quercetin (DQ) senolytics treatment was evaluated. DQ treatment in RM-AKI improved kidney function and blocked the known phenotypic switch from F4/80highCD11blow to F4/80lowCD11bhigh MPC.

Conclusions: scRNASeq identified novel renal myeloid subtypes after RM-AKI and unmasked a transition macrophage population affected by cellular senescence processes. This work provides a proof-of-concept that immunosenescence occurs during AKI and that senolytics deserve attention as potential nephroprotective drugs.



TH-OR05

Novel Anti-Inflammatory Effects of IL-1 Receptor in Kidney Myeloid Cells Following AKI

Yanting Chen,[1] Xiaohan Lu,[2] Jiahui Su,[2] Steven D. Crowley,[2] Jamie Privratsky.[1,3] *[1]Center for Perioperative Organ Protection, Department of Anesthesiology, Duke University Medical Center, Durham, NC; [2]Division of Nephrology, Department of Medicine, Duke University Medical Center, Durham, NC; [3]Division of Critical Care Medicine, Department of Anesthesiology, Duke University Medical Center, Durham, NC.*

Background: Acute kidney injury (AKI) is a leading cause of organ failure in hospitalized and critically ill patients. Following AKI, the canonical pro-inflammatory cytokine interleukin-1β (IL1β) is released predominantly from activated myeloid cells and binds to the interleukin-1 receptor R1 (IL1R1). IL1R1 activation is known to amplify the immune response and exacerbate AKI. However, the specific role of IL-1R1 on myeloid cells during AKI is poorly understood. Our objective was to study the function of myeloid cell IL-1R1 during AKI. As IL1R1 is known to signal through the pro-inflammatory Toll-like receptor (TLR)/MyD88 pathway, we initially hypothesized that myeloid cell IL1R1 activation would exacerbate AKI.

Methods: IL1R1 was selectively depleted in CD11c+ myeloid cells with *CD11cCre(+) / Il1r1$^{fl/fl}$* ($IL1R1^{CD11cKO}$) mice. $IL1R1^{CD11cKO}$ and littermate controls (*CD11cCre(-) / Il1r1$^{fl/fl}$* - $IL1R1^{CD11cWT}$) were subjected to kidney ischemia/reperfusion (I/R) injury. Kidney injury was assessed by serum creatinine and histologic injury scoring. Renal tubular cells (RTC) were co-cultured with CD11c+ bone-marrow derived dendritic cells (BMDC) from $IL1R1^{CD11cKO}$ and $IL1R1^{CD11cWT}$ mice.

Results: Surprisingly, compared to $IL1R1^{CD11cWT}$ mice, $IL1R1^{CD11cKO}$ mice displayed exaggerated I/R-induced kidney injury, as indicated by elevated levels of serum creatinine (mean ± SD: 1.24 ±0.85 vs 2.06 ± 1.17 mg/dl, $p<0.05$), BUN (mean ± SD: 90.91 ± 35.68 vs 134.87 ± 37.92 mg/dl, $p<0.01$), and histologic injury scoring. In support of these findings, *in vitro* co-culture studies showed that RTC co-cultured with $IL1R1^{CD11cKO}$ BMDC (in the presence of IL1β or LPS) exhibited higher mRNA levels of the kidney injury marker neutrophil gelatinase-associated lipocalin (NGAL) than those co-cultured with $IL1R1^{CD11cWT}$ BMDC. Furthermore, we observed that IL1R1 activation on $IL1R1^{CD11cWT}$ BMDC preferentially augmented expression of anti-inflammatory mediators tumor necrosis factor alpha induced protein 3 (A20) and interleukin-1 receptor antagonist (IL1Ra/Il1rn), effects that were abrogated by $IL1R1^{CD11cKO}$ BMDC.

Conclusions: Our findings suggest a novel function of IL1R1 is to serve as a critical negative feedback regulator of IL1 signaling in CD11c+ cells to dampen inflammation and limit AKI. Our results lend further support for cell-specific, as opposed to global, targeting of immunomodulatory agents.

Funding: NIDDK Support, Other NIH Support - NIGMS, Veterans Affairs Support

TH-OR06

The Kidney-Gut-Brain Axis in AKI

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Background: Although epidemiological studies suggest that long-term survivors of dialysis requiring AKI had increased risk of dementia, its underlying mechanisms remain uncertain. Based on recent data showing kidney-gut crosstalk mediated by immune modulation in AKI, we hypothesized that gut dysbiosis and aberrant gut immune response might contribute to the cognitive dysfunction following AKI.

Methods: In mouse long-term AKI survival model (1yr after kidney ischemia/reperfusion injury (IRI)), we determined functional and structural alterations of brain, changes in gut microenvironment including dysbiosis and immune cell phenotypes. For better insight about the causal relationship in kidney-gut-brain axis, we also tested the effect of fecal microbiota transfer (FMT) and cohousing (transfer microbiota by coprophage) on kidney and brain in long-term AKI mouse model.

Results: One year after kidney IRI, mice showed abnormal behaviors in open field test compared to age matched sham control. Transcriptosome of hippocampus demonstrated more than 120 differentially regulated genes including those involved in angiogenesis/immune and inflammatory response. We also found structural brain injury including disruption of BBB, neuroinflammation, oxidative stress as well as accumulation of amyloid-b fibrils and hyperphosphorylated tau proteins, suggesting the development of Alzheimer like dementia long after AKI. Gut microbiota structure 1yr after kidney IRI was also clearly distinguished from that of sham control and was associated with increased ratio of Th17/Tregs balance, showing the persistence of gut dysbiosis and aberrant gut mucosal immune response long after AKI. Both cohousing and FMT partially restored the gut mucosal inflammation and this also led to not only decreased kidney fibrosis but also improved cognitive function as well as neuroinflammation and tauopathy.

Conclusions: This is the first animal study that showed that AKI can lead to Alzheimer like neurodegeneration. Gut dysbiosis and aberrant mucosal immune response is thought to contribute to the development of tauopathy/neuroinflammation and congtivie dysfunction long after AKI. Our data provide new insights into "kidney-gut-brain" axis in the field of AKI and suggest that gut might be a new therapeutic target for the prevention of long-term adverse outcomes in AKI patients.

TH-OR07

Spatial Multi-Omic Atlas of Pyelonephritis

Xin Wang, Israel Cotzomi Ortega, Yuriko I. Sanchez-Zamora, Rishil H. Patel, Macie M. Kercsmar, Ashley R. Jackson, John D. Spencer, Brian Becknell, Juan de Dios Ruiz-Rosado. *Nationwide Children's Hospital, Columbus, OH.*

Background: Pyelonephritis (PN) causes renal injury, inflammation, and scarring. Over 80% of PN episodes are due to uropathogenic *Escherichia coli* (UPEC). The molecular mechanisms of acute kidney injury and renal fibrosis in PN patients are poorly understood, hindering the development of effective therapies.

Methods: We infected female C3H/HeOuJ mice via transurethral inoculation with UPEC. Spatial transcriptomics (ST, Visium 10x genomics) and PIPseq™ single-cell RNA-seq were performed on kidney samples at multiple time points (0, 1, 3, 5, 7, and 28 days post infection). The integrative analysis encompassed pathological evaluation, cell type annotation, spatial deconvolution, differential gene expression, cell-cell communication, pseudotime inference, and signaling pathway exploration, aiming to unravel the dynamic structural and molecular changes during PN.

Results: We characterized 20,831 spatial spots with deconvoluted cell-type compositions at six timepoints. We profiled 40,224 single cells representing 18 major cell types and identified infected proximal tubule cells with distinct cell-cycle and key signaling states. Integration of these multi-modal datasets revealed two distinct clustering structures of tissue abscesses that were specific to the infection and associated with fibrotic injury, repair, and remodeling. These abscess structures exhibited increased levels of colocalization between leukocytes, fibroblasts, and endothelial cells after infection, along with activations in leukocyte migration and proliferation, T cell activation, TNF-α signaling, and cell-cell adhesion. Signaling analyses unveiled unique spatial dependencies in hypoxia, apoptosis, proinflammatory responses, profibrotic and proliferative processes. The marginal regions of the renal abscess displayed dramatically increased activation in NF-κB, TNF-α, EGFR, and P53 signaling pathways, but decreased Stat1 and Wnt pathway activity.

Conclusions: Our study provides an integrative map of the spatial gene expression and gene-regulation networks involved in maintaining kidney homeostasis and immune responses during PN. We believe our findings will contribute to the advancement of mechanistic insights and potential therapeutic strategies to treat PN.

Funding: NIDDK Support

TH-OR08

Differential Roles of Regnase3 in Resident Macrophages vs. Renal Tubular Epithelial Cells in Kidney Injury

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Background: RNA-binding proteins are a class of proteins that regulate RNA and have been implicated in a wide range of diseases. Regnase3 as one of those proteins has been shown to promote inflammation by increasing TNF in macrophages (Mφ). However, the full extent of its functions in kidney disease remains unknown. We hypothesized that Regnase3 plays a role in both kidney resident Mφ and renal tubular epithelial cells (RTEC), influencing inflammation and kidney repair after injury.

Methods: A series of genetically-modified mice were developed, including the Pax8rTtA, TetOCre, receptor activator of nuclear factor kappa-B (Rank, a lineage tracer for kidney resident Mφ)-Cre (RankCre), and Regnase3 floxed (Regnase3fl/fl) mice. Upon these mice, we applied a range of kidney injury models involving unilateral ischemia-reperfusion and nephrocalcinosis. Furthermore, scRNA-seq and RNA-seq were utilized to investigate the underlying mechanisms.

Results: The scRNA-seq showed both Regnase3 is highly expressed in the kidney Mφ and positively correlated with the chemokines, Mφ phagocytosis, and Mφ maturation after kidney injury. In vivo, after the kidney injury, the RankCre-Regnase3fl/fl (Regnase3 conditional KO in kidney resident Mφ) mice suffered from more inflammation, characterized by CCR2 positive pro-inflammatory Mφ accumulation. In vitro, Regnase3 is involved in modulating resident Mφ polarization towards the pro-inflammatory and migration, indicating that it contributes to Mφ-related inflammation. Next, we aimed to examine the role of Regnase3 in RTEC. Through in silico, we found that Regnase3 is highly expressed in healthy RTEC but reduced following injury, and it controls early apoptosis. In vivo and in vitro experiments suggested that the Regnase3 deletion in RTEC (Pax8rTtA-TetOCre-Regnase3fl/fl) against kidney injury and promote the repair

of RTEC. Regnase3 targets pre-RNA and modulates alternative splicing by increasing skipped exon events and decreasing the probability of retained intron events.

Conclusions: Regnase3 contributes to kidney injury but the impact of it is contingent upon the specific cell lineage in question. The RankCre-Regnase3fl/fl leads to an exacerbation of kidney injury by increasing pro-inflammatory Mφ recruitment, whereas the Pax8rTtA-TetOCre-Regnase3fl/fl leads to an improvement after injury through its effects on cell death and RTEC repair.

TH-OR09

Role of YB-1 in the Early Pathogenesis of Acute Respiratory Distress Syndrome (ARDS) and Associated Renal Damage

Anna Leitz,[1] Daniela Hermert,[1] Vera Jankowski,[3] Yingying Gao,[1] Xiyang Liu,[1] Marcus Schultz,[2] Jürgen Floege,[1] Stefan Uhlig,[4] Tammo Ostendorf,[1] Lucy K. Reiss,[4] Ute Raffetseder.[1] *[1]Universitatsklinikum Aachen Klinik fur Nieren- und Hochdruckkrankheiten rheumatologische und immunologische Erkrankungen, Aachen, Germany; [2]Department of Intensive Care, Amsterdam University Medical Centres, Amsterdam, Netherlands; [3]Universitatsklinikum Aachen Institut fur Molekulare Herz Kreislauf Forschung, Aachen, Germany; [4]Institute of Pharmacology and Toxicology, Medical Faculty, RWTH Aachen, Aachen, Germany*.

Background: Acute respiratory distress syndrome (ARDS) is a life-threatening lung impairment that is associated with a mortality of 25% up to 45%. It is caused by acute inflammation and currently patients with ARDS can only be stabilized by mechanical ventilation and intensive care. Acute kidney injury (AKI) is the most common extrapulmonary organ dysfunction associated with ARDS, affecting more than 35% of the patients. Proteins with alarmin function, such as the highly conserved Y-box binding protein (YB-1), are good candidates for early progression of ARDS and the crosstalk between lung and kidney. YB-1 functions as a translation or transcription factor and is also secreted during inflammation.

Methods: Mice were mechanically ventilated in a mouse intensive care unit (MICU). The role of YB-1 in murine ARDS and its effect on the kidneys was evaluated in a two-hit- (intratracheal (i.t.) application of hydrochloric acid & ventilation) and a triple-hit- (hydrochloric acid i.t., lipopolysaccharide (LPS))- i.t. & ventilation) model in heterozygous *Yb1*-deficient (*Yb1*$^{+/-}$)-mice and after i.t.-application of recombinant YB-1 protein. In addition, tracheal secretion, urine and serum from ARDS patients were analyzed for (post-translationally modified) extracellular YB-1 by mass spectrometry.

Results: In both models, *Yb1*$^{+/-}$ mice were protected in terms of pulmonary inflammatory parameters. In the two-hit model, the improved lung function in the *Yb1*$^{+/-}$ mice deteriorated to wild-type (WT) level by additional i.t. application of recombinant YB-1. Interestingly, however, heterozygous YB-1 deficiency in the kidneys led to more intense inflammatory reactions. YB-1 i.t. (instillation in the absence of lung injury) already triggered nephritis. Extracellular YB-1 in murine and human ARDS was post-translational modified, and mass spectrometric analysis of ARDS patient samples showed a correlation of guanidinylated YB-1 levels in tracheal secretion/serum and disease severity.

Conclusions: Taken together, YB-1 expression in ARDS mouse models has opposite effects on the inflammatory process in the primarily damaged lung and the secondarily affected kidney. In addition, the intracellular or extracellular localization of YB-1 also determines its protective or destructive character.

Funding: Government Support - Non-U.S.

TH-OR10

Injured Tubular Epithelia-Derived CCN1 Promotes the Mobilization of Fibroblasts Toward the Injury Sites at the Acute Phase After Kidney Injury

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Background: Renal fibrosis is associated with the progression of renal injury. Conversely, the function of fibroblasts is indispensable for the reconstruction of normal tissue structure following injury in various organs. Consequently, the humoral factors that prompt fibroblasts to migrate to the injury site at an appropriate time point are deemed indispensable. However, the precise mechanisms through which these factors influence fibroblasts and promote migration to the tissue-injured site remain unclear.

Methods: To expound on the paracrine effects on fibroblasts (NRK49F), we subjected them to treatment with conditioned medium (CM) derived from either normal or injured tubular epithelial cells (NRK52E). Based on the transcriptomics data, we identified Cellular Communication Network Factor 1 (CCN1) signaling as a candidate and analyzed its impact on kidney injury.

Results: The CM from injured NRK52E expedited NRK49F chemotaxis and proliferation. Based on ligand-receptor analysis of RNA-seq between NRK49F and NRK52E in vitro, as well as proximal tubular-specific transcriptomics utilizing proximal tubular-specific tdTomato-reporter mice, we identified the upregulation of CCN1 signaling during the early phases of various kidney injury models. The enhanced fibroblast chemotaxis induced by CM from injured NRK52E was nullified by CM from injured NRK52E with CRISPR-mediated CCN1 knockout. CCN1 activated FAK-ERK signaling, thereby expediting the migration and proliferation of fibroblasts, which were attenuated by ERK and FAK inhibitors. Lastly, in vivo analyses utilizing proximal tubular-specific CCN1 knockout (SLC34a1GCE/CCN1-floxed) mice demonstrated the accumulation of fibroblasts surrounding injured tubular epithelial cells was scarcely observed during the acute phase following cisplatin-induced kidney injury in tubular CCN1 knockout mice. Furthermore, tubular injury was exacerbated in CCN1 knockout mice, suggesting that mobilized fibroblasts by tubule-derived CCN1 may impede the expansion of tubular injury.

Conclusions: During the acute phase after injury, the interaction between tubular epithelia and fibroblasts hinges upon the pivotal role played by damaged tubule-derived CCN1 in mobilizing fibroblasts toward the injury sites, thereby potentially inhibiting the progression of tubular injury expansion.

TH-OR11

Unified Cross-Species Kidney Single-Cell Atlas: Unraveling Conserved Cellular Features and Species-Specific Adaptations

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Background: The kidney plays a critical role in maintaining systemic homeostasis, yet our current understanding of species differences, health states, and changes in disease states remains limited. Owing to the kidney's complex cellular architecture, single-cell tools can provide pivotal insight into these processes.

Methods: We processed seven large renal single-nucleus RNA sequencing (snRNA-seq) and spatial transcriptomics datasets derived from healthy and disease-affected mouse, rat, and human samples. Following meticulous quality controls, we harmonized gene symbols and integrated data using deep generative modeling (scVI). A variety of computational tools were utilized to comprehend cell type conservations as well as species and disease state-specific changes.

Results: We present the first comprehensive, fully integrated interspecies renal snRNA-seq atlas, comprising more than 140 samples and over 1 million cells - the largest kidney cell atlas to date. Our atlas uncovers over 100 distinct cell states, providing a detailed understanding of conserved biological functions, marker genes, species-specific differences, and cellular adaptations in response to disease. Conserved cell types were anatomically positioned using spatial transcriptomics data. By employing the concept of Differentially Expressed Gene Ontology terms (DEGOs) – which focus on mean expression values for functional gene sets rather than individual genes – we highlighted the conserved renal physiology at the single-cell and spatial level. We observed notably fewer proximal tubule S3 segment cells in the human kidney compared to rodents. We identified a conserved injured proximal tubule subset with its unique markers. Additionally, we discovered novel cell types in the loop of Henle cluster expressing developmental process-related gene signatures.

Conclusions: This comprehensive kidney single-cell atlas serves as a valuable resource, offering a consistent reference across species with standardized cell terminology. It enables a deeper understanding of kidney biology and paves the way for developing novel therapeutic strategies.

Funding: NIDDK Support

TH-OR12

Extracellular miRNAs as Predictors of CKD Progression

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Background: Kidney fibrosis is final common pathway downstream of most renal injuries that contributes to progressive chronic kidney disease (CKD). Noncoding RNAs regulate kidney fibrosis through direct repression and/or expression of matrix genes and TGF-β signaling. We hypothesized that specific circulating microRNAs (miRNAs) are indicators of underlying kidney fibrosis and can serve as early biomarkers for CKD progression.

Methods: The study was performed using patient samples/clinical data from the Chronic Renal Insufficiency Cohort (CRIC) cohort (n= 3,471). The slowest and fastest progressors of CKD were defined based on the largest and smallest negative slope of eGFR change over time, using within-subject ordinary least-squares regression of follow-up eGFR readings. Next Generation Sequencing (NGS) was performed to identify miRNAs associated with CKD progression. Circulating RNAs from plasma samples were isolated and sequencing was performed on NovaSeq platform (Illumina, Inc). The raw counts, mapping, and differential expression analysis was done using R Bioconductor packages. Total of 500 genes with highest variance were used for principal component analysis and 35 genes with highest variance across samples were selected for hierarchical clustering. The biological effects, mechanisms and functions of identified miRNAs were analyzed using Ingenuity Pathway analysis.

Results: Global extracellular miRNA expression analysis showed presence of 1,888 miRNAs in plasma. Differential analysis using generalized linear models (GLMs) in edgeR was performed to identify the miRNA associated with rapid progression adjusting for sex, ethnicity, diabetes status, UAC Ratio and EGFR levels. Expression of 8 miRNAs (miR-887-5p, miR-1197, miR-6729-3p, miR-6774-3p, miR-6795-5p, miR-548f-3p, miR-3135a, miR-1469) varied significantly between fast and slow progressor groups. This differential expression of miRNAs between the two groups was significantly modulated by ethnicity and diabetic status of patient. Bioinformatic analysis showed pivotal role of these miRNAs in variety of important cell activities such as apoptosis, organ fibrosis, autophagy, metastasis etc.

Conclusions: This study identifies extracellular miRNAs that can serve as indicator of CKD progression. Identification of specific miRNA pathways for CKD progression will enhance diagnosis, enable risk stratification and lead to targeted interventions.

Funding: NIDDK Support

TH-OR13

Alternative Splicing in CKD

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Background: Alternative splicing (AS) is a process that can lead to variable genotype expression. The primary forms are exon skipping, intron inclusion, alternative 5′ and 3′ splice sites. The role of alternative splicing of VEGF has been shown to play an important role in chronic kidney disease (CKD) development, however a comprehensive assessment of AS events in CKD has not been undertaken yet.

Methods: Human kidney tissue (n=410) was collected from nephrectomies of healthy subjects and patients with diabetic or hypertensive CKD. Clinical demographics information was collected via honest broker and histopathology was analyzed in an unbiased manner. RNA was extracted from the tubular compartment and sequenced. RNA-seq reads were aligned to the human genome using STAR v 2.7.3. Outliers identified by Mahalanobis distance. Aligned BAM files were sorted and indexed using Samtools v1.17 and junctions were extracted using Regtools v 1.0. Differential splicing for was analyzed separately using leafcutter v 0.2.7 and adjusted for age, sex, race and RNA quality indices (RNA integrity number, 5'-3'bias, %ribosomal genes, total reads).

Results: When comparing healthy samples to those with eGFR of less than 60 cc/min/1.73m2 (CKD stage 3-5), we identified 31 intron cluster alternative splicing events at an adjusted p-value of 0.05. 26 of these were previously annotated. Pathway analysis using gene ontology (GO) terms showed enrichment for cell death and metabolic pathway. When comparing samples with less than 10% fibrosis to those with greater than 10% fibrosis, we identified 239 alternative differential splicing clusters. 233 of these were previously annotated. Pathway analysis using GO terms demonstrated these genes were enriched in the metabolic and immune pathways.

Conclusions: Large number of differential splicing events were observed in CKD compared to controls with enrichment in the metabolic and immune pathway genes.

Comparison	Samples (CKD vs control)	No. of Significant Differentially Spliced Genes	Top Genes	Top pathway enrichment by GO terms
GFR <60 ml/min/1.73m2	146 vs 264	31	RAB11FIP3 RPS24 AP2S1 FIS1 RPS3A	Regulation of cell death Negative regulation of cell death Generation of precursor metabolites and energy Cell death Homeostatic process
Interstitial Fibrosis >10%	170 vs 240	239	RPS24 RAB11FIP3 RACK1 TPM1 GLS	Small molecule metabolic process Organic acid metabolic process Positive regulation of immune system Positive regulation of leukocyte migration Organonitrogen compound

TH-OR14

Adenine Accumulation Induced by Hypoxia in Kidney Organoids

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Background: Kidney disease progression is thought to result from a multitude of metabolic and genetic changes, including hypoxia and adenine. Adenine-rich diet has previously shown to be nephrotoxic in rodent models. Recently, a pathway contributing to endogenous adenine production was identified (manuscript in revision). We explored the association between adenine, kidney hypoxia and kidney injury using a human kidney organoid system with multi-omic analysis.

Methods: Kidney organoids generated from human pluripotent stem cells and exposed to 1% O_2 for 24 h were split into 2 treatment groups: group 1 organoids were treated with C13-glucose for the last 3 hours of hypoxic treatment underwent targeted metabolomic analysis (C13 flux study) by LC-MS; group 2 untreated organoids were harvested for IF, qRT-PCR and sc RNA-seq. Organoids of both groups were embedded, sectioned and evaluated by MALDI-mass spectrometry imaging (MSI) using DAN matrix and the METASPACE platform.

Results: IF imaging of hypoxic kidney organoids revealed nuclear accumulation of HIF1α; targeted transcriptional analysis showed that HIF1's target gene expression, including glycolytic pathway genes, was increased. Single cell transcriptional profiling revealed increased expression of MTAP (methylthioadenosine phosphorylase) and reduced expression of APRT (adenine phosphoribosyltransferase) in proximal tubular cells and podocytes; mitochondrial gene expression was increased in kidney cell types of especially podocytes. Metabolomic analysis showed that the percentage of C13-labeled metabolites was increased in late glycolysis but decreased in TCA cycle. MALDI-MSI of hypoxic kidney organoids revealed an increased intensity of adenine metabolite and decreased intensity of TCA metabolites such as malic acid.

Conclusions: Our hypoxic kidney organoid model successfully recapitulates key transcriptional, protein and functional alterations associated with hypoxic conditions. Under these hypoxic conditions, MTAP pathway was perturbed leading to adenine accumulation in kidney organoid cells, suggesting a potential mechanism of endogenous adenine generation contributing to kidney disease.

Funding: NIDDK Support, Other NIH Support - NCATS, Commercial Support - Eli Lilly, Private Foundation Support

TH-OR15

Induced Senescent Cells Recruit Leukocytes and Permit Their Own Clearance from Healthy Young Kidneys

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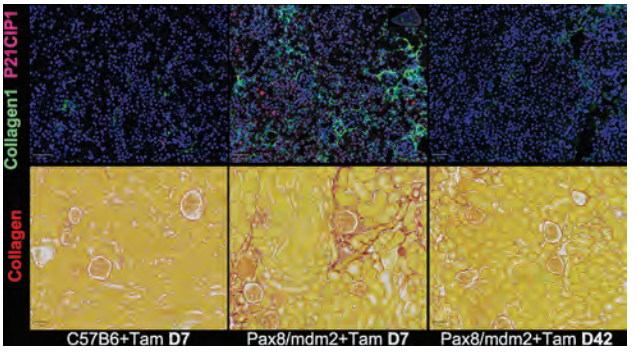
Background: Increasing evidence links senescent epithelia to fibrosis and functional loss in experimental and human kidney disease. Whether senescent cells themselves are sufficient to initiate and sustain kidney fibrosis is unknown. We hypothesised that induction of epithelial senescence alone, in absence of other renal injuries, is sufficient to initiate and sustain fibrosis.

Methods: We generated a Pax8creERT2;mdm2 fl/fl mouse ('TG') via a cross of two established stains and treated these and wild type (WT) mice with tamoxifen by oral gavage to induce epithelial restricted senescence via mdm2 deletion. Markers of fibrosis (Collagen I) and growth arrest (p21cip1) were quantified by immunofluorescence (IF), and total collagen by picrosirius red. Full transcriptomic analysis was undertaken using scRNA-seq (10X).

Results: Tamoxifen resulted in p21cip1 induction in renal epithelia in TG but not in wild WT mice by IF (10.45 ± 2.9 *vs* 3.15 ± 0.7, $p<0.05$). On scRNA-seq, TG (but not WT) kidneys contained transcriptionally distinct, cdkn1a+ epithelia, recruited leukocytes and increased activated myofibroblasts. IF confirmed increased renal fibrosis at D7 in TG *vs* WT (Collagen1 1.1 ± 0.3 *vs* 3.1 ± 0.5, $p<0.005$). By D42, scRNAseq analysis demonstrated clearance of cdkn1a+ senescent epithelia, normalisation of leukocyte counts and resolution of myofibroblast activation in TG kidneys, with confirmation by IF; showing no difference in p21cip1 levels between WT and TG mice (2.4 ± 1.4 *vs* 4.1 ± 1.1, $p=0.7$) and no progressive fibrosis.

Conclusions: Our results demonstrate that epithelial senescence is profibrotic in absence of injury to other cell lineages. Of importance, mechanisms in the healthy adult kidney allow detection and physiologic clearance of senescence and prevent ongoing fibrosis. Understanding how these pathways are lost with age and chronic injury may lead to new routes to promote clearance of profibrotic senescent epithelia.



TH-OR16

Identification of Noninvasive Biomarkers Reflecting Cellular Mechanisms of Endothelin A (ETA) Receptor Activity and Atrasentan Response in CKD

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Background: Endothelin pathway activation contributes to disease progression across multiple CKD etiologies. Atrasentan is a potent and selective endothelin A receptor (ET_A) antagonist that has demonstrated rapid and sustained reductions in proteinuria, preservation of kidney function and improved kidney outcomes in diabetic kidney disease patients. Single cell transcriptomic characterization of a preclinical mouse model of IgA nephropathy revealed specific ET_A activity and atrasentan responses associated with proximal tubular failed repair (FR-PTs). We conducted an analysis of patient-matched kidney biopsies and biofluids from the NURTuRE cohort with the aim to identify non-invasive biomarkers associated with specific cellular responses that will enable precision treatment in CKD.

Methods: Serum (n= 99) and urine samples (n= 22) from the NURTuRE biobank were assayed using Olink and SomaScan proteomics platforms, respectively. Patient-matched kidney biopsies for each sample were analyzed by RNA-Seq and scored for a gene signature reflecting atrasentan responses in the gddY mouse model. Correlation analysis of biofluid protein abundance with kidney mRNA expression and atrasentan response scores suggested candidate non-invasive biomarkers for further validation ($r \geq 0.4$ and $p \leq 0.05$).

Results: Proteomic analysis identified 173 serum and 174 urine proteins significantly correlated with atrasentan response score in CKD patients. Strong positive correlation of 16/173 serum and 12/174 urine proteins with kidney mRNA expression suggests these proteins could originate from the kidney. Importantly, the majority of the respective genes were expressed by FR-PTs or immune cells, likely reflecting

mechanisms of ET_A activation and atrasentan response in the kidney inflammatory and fibrotic microenvironment.

Conclusions: This study identified potential biomarkers reflecting cellular mechanisms of ET_A activation and atrasentan response in the NURTuRE CKD cohort. These biomarkers may be useful in assessing and differentiating cellular responses in atrasentan-treated CKD patients. To validate these initial findings, serum and urine collected at baseline and following treatment in the AFFINITY IgAN cohort are currently being analyzed.

Funding: Commercial Support - Chinook Therapeutics, Evotec SE

TH-OR17

LACTB Is a Kidney C Mitochondrial Metabolism

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Background: Genome-wide association studies (GWAS) have identified hundreds of loci where genetic variants are associated with kidney function. However, the causal variants, genes, cell types, and disease mechanisms remain mostly unknown.

Methods: We integrated GWAS, human kidney expression of quantitative trait analysis using Bayesian colocations, transcriptome-wide association studies, and summary-based Mendelian randomization studies to identify likely causal genes for kidney function. We used single-cell RNA and ATACseq data to identify causal cell types. Finally, we generated mice with genetic deletion to study kidney disease mechanisms.

Results: We identified serine beta lactamase-like protein (LACTB) as a kidney disease risk gene. LACTB is expressed in kidney tubule cells. LACTB knockout mice were more susceptible to acute and chronic kidney injury induced by cisplatin and folic acid. LACTB knockout mice had lower cardiolipin levels and abnormal mitochondria morphology, causing elevated mitochondrial injury and activation of the cytosolic nucleotide sensing pathways (cGAS-STING) with an increment of inflammation. Cardiolipin is a crucial lipid for maintaining mitochondrial morphology and function. Additionally, we discovered that as a protease, LACTB cleaves PLA2G6, an enzyme involved in cardiolipin biosynthesis, generating a more active fragment that promotes cardiolipin production.

Conclusions: In summary, the integration of GWAS, epigenome analysis, mouse models, and cultured cell systems has identified LACTB as a causal gene for kidney disease. LACTB plays a crucial role in regulating cardiolipin metabolism, mitochondrial function, and inflammation.

Funding: NIDDK Support

TH-OR18

Glutathione-Specific γ-Glutamylcyclotransferase 1 (CHAC1) Is a Kidney Disease Risk Gene by Controlling Ferroptosis

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Background: Despite GWAS identified over 800 loci associated with kidney function, the specific genes, cell types, and mechanisms influenced by these genetic variants largely remain unexplored. In our research, we leveraged human kidney gene expression and methylation quantitative trait data, as well as human kidney single nuclear gene expression and open chromatin analysis, to prioritize CHAC1 on chromosome 15 as a likely causal gene. CHAC1 is essential for maintaining cellular glutathione levels but the role of CHAC1 remains unknown in kidney disease development.

Methods: Using CRISPR technology, we generated CHAC1 heterozygous mice (CHAC1+/-). To study the role of CHAC1 in kidney disease, we induce kidney disease by streptozotocin or folic acid injections or by feeding adenine diet. To uncover the mechanistic role of CHAC1, we used cultured tubule cells and performed biochemical assays.

Results: CHAC1 heterozygous mice (CHAC1+/-) showed no basal differences in kidney function, birth, and growth defects. On induction of kidney disease using streptozotocin or folic acid injection, the CHAC1+/- mice demonstrated improved kidney function (measured by BUN, creatinine, and cystatin C), diabetic kidney injury, and less fibrosis compared to WT counterparts. On chronic adenine feeding by *ad libitum* chow, the CHAC1+/- mice showed lower chronic kidney disease. The single nuclear ATAC-seq, RNA in situ hybridization, and immunostaining analyses indicated CHAC1 expression in the Loop of Henle (LOH). Cultured primary tubule cells from CHAC1+/- mice showed lower ferroptosis (an iron-dependent form of cell death), preserved cell viability, reduced lipid peroxidation and reactive oxygen species. Derepressed levels of ferroptosis inhibitor, Glutathione peroxidase 4 (GPX4) and the system xCT, and available glutathione levels in CHAC1+/- primary tubule cells likely mediating the resistance to ferroptosis in the conditions of cysteine methionine deprivation or transforming growth factor beta. The lower ferroptosis in CHAC1+/- mice is likely the mechanism for lower fibrosis and better kidney function in disease states (as CHAC1 degrades glutathione).

Conclusions: Our research identified CHAC1 as a novel kidney disease risk gene with a significant role in modulating ferroptosis and cellular glutathione levels in kidney tubule cells.

Funding: NIDDK Support

TH-OR19

Calprotectin Is Associated with Vascular Calcification and Cardiovascular Complications During CKD

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Background: In patients with chronic kidney disease (CKD), vascular calcification is considered a major risk factor of cardiovascular (CV) mortality. The mechanisms of vascular calcification are complex and treatment options remain limited. Serum proteome analysis could help identify novel actors and potential therapeutic targets.

Methods: In this observational, European, multicenter study, we included 112 CKD3-4 patients from Spain, 171 dialysis patients from Toulouse and La Reunion (France), and 170 CKD5 patients from Sweden. Serum proteome analysis was performed using LC-MS/MS on a subset of 66 CKD3-4 patients. Circulating calprotectin concentration was validated in the serum or plasma from the full cohorts by ELISA. Calprotectin was associated with CV outcome (2-4 years of follow-up) or with vascular calcification score assessed by Von Kossa staining on a piece of epigastric artery collected during renal transplantation surgery. The effect of calprotectin on calcification was measured in primary human vascular smooth muscle cells (VSMCs) and mouse aortic rings. The anticalcific potential of calprotectin inhibitor paquinimod was studied in a 5/6 subtotal nephrectomy mouse model.

Results: We identified using serum proteome analysis and further validation by ELISA that calprotectin, a circulating damage-associated molecular pattern protein, was associated with vascular calcification, CV outcome and mortality in CKD and dialysis patients. In primary human VSMCs and mouse aortic rings, calprotectin exacerbated calcification. Treatment with paquinimod inhibited the pro-calcifying effect of calprotectin. Paquinimod also ameliorated calcification induced by serum of uremic patients in primary human VSMCs. Finally, treatment with paquinimod blocked vascular calcification in mice with chronic renal failure induced by 5/6 subtotal nephrectomy.

Conclusions: We identified calprotectin as a key factor associated with vascular calcification, CV outcome and mortality in CKD patients. Blockade of calprotectin by paquinimod might be a promising strategy to reduce the burden of vascular calcification in CKD.

TH-OR20

PCSK9 Targets Megalin in the Kidney Proximal Tubule and Aggravates Proteinuria in Nephrotic Syndrome

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Background: Proteinuria is a prominent feature of chronic kidney disease (CKD). Interventions that reduce proteinuria slow CKD progression and the associated risk of cardiovascular disease (CVD). We here propose a mechanistic coupling between proteinuria and the CVD-risk protein PCSK9 involving the receptor megalin.

Methods: Urinary PCSK9 excretion was determined in megalin knockout (KO) mice and patients carrying megalin pathogenic variants as well as minimal change disease patients at baseline and remission after standard prednisolone treatment (1 mg/kg/day). Mechanistical studies were performed in proximal tubular cell cultures (LLC-PK1 cells). PCSK9-mediated megalin regulation and proteinuria were investigated in PCSK9 KO mice, PCSK9 overexpressing mice as well as wildtype and nephrotic podocin KO mice treated with the PCSK9 inhibitor alirocumab (30 mg/kg/day and 50 mg/kg/day, respectively). Kidney injury was evaluated in podocin KO mice treated with alirocumab for 14 days.

Results: We find that PCSK9 undergoes glomerular filtration and is captured by megalin, the receptor responsible for driving protein reabsorption in the proximal tubule. Accordingly, megalin-deficient mice and patients carrying megalin pathogenic variants are characterized by elevated urinary PCSK9 excretion. Interestingly, PCSK9 knockout mice displayed increased renal megalin while PCSK9 overexpression resulted in its reduction. Furthermore, PCSK9 promoted trafficking of megalin to lysosomes in cultured proximal tubule cells, suggesting that PCSK9 is a negative regulator of megalin. This effect is potentially accelerated under disease conditions as genetic destruction of the glomerular filtration barrier in mice, and minimal change nephropathy in humans, resulted in markedly increased tubular PCSK9 uptake and urinary PCSK9 excretion. Pharmacological PCSK9 inhibition increased renal megalin, while reducing urinary albumin excretion and kidney injury markers in nephrotic mice.

Conclusions: In conclusion, glomerular damage increases filtration of PCSK9 and concomitantly megalin degradation, resulting in escalated proteinuria. Targeting PCSK9 may be beneficial to attenuate proteinuria-induced kidney injury in CKD.

Funding: Private Foundation Support

TH-OR21

Prediction of Kidney Failure Using Multiple Data Domains in Glomerulonephropathy: A CureGN Study

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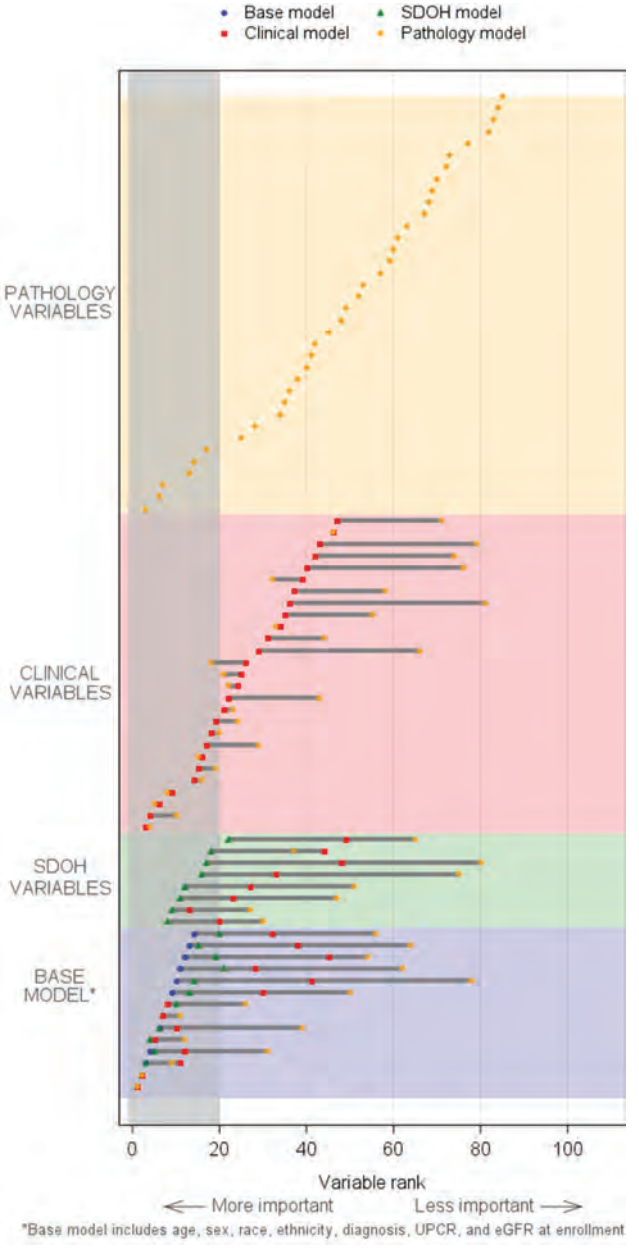
Background: Clinical risk factors do not fully predict kidney failure in patients with glomerular diseases. Using data from multiple domains in CureGN we applied machine learning to improve risk prediction and identify novel predictors of kidney failure.

Methods: Sequential ridge regression models using demographics (I), social determinants of health (SDOH; II), clinical (III), and pathology features (IV) were fitted to predict time to kidney failure (estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m^2 or treatment by dialysis or transplant). Discrimination was assessed by integrated area under the curve (iAUC); variables were ranked by absolute value of standardized coefficients.

Results: The kidney failure rate was 2.9 per 100 person years in 2,544 CureGN participants. 36 predictors were included (7 base, 2 socioeconomic, 27 clinical). Discrimination was similar between models I and II (iAUC=0.89) and higher for model III (iAUC=0.91). eGFR, urine protein to creatinine ratio, age, Black race, and FSGS were highly ranked across models I-III; the ranking of Black race was lower in model III (Figure). Medicaid as primary insurance, hypertension, renin angiotensin system inhibitor use, and serum albumin and urea nitrogen levels were highly ranked in model III. In model IV (n=670), interstitial fibrosis/tubular atrophy (IFTA), presence of tubular microcysts, and sclerotic glomeruli ranked as top predictors, displacing Black race, and reducing ranking of age and FSGS.

Conclusions: Machine learning improves prediction of kidney failure through incorporation of novel data domains. In CureGN, addition of these data improved prediction for kidney failure across conventional diagnostic categories and detected novel predictors that displaced traditional risk factors.

Funding: NIDDK Support



Varible rankings from models I-IV.

TH-OR22

Plasma Metabolic Profiles and Clinical Outcomes in Focal Segmental Sclerosis (FSGS) and Minimal Change Disease (MCD)

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Background: Metabolomics is a powerful approach to investigate the relationship between disease mechanisms and patients' phenotype. However, the association between plasma metabolic profiles and clinical outcomes of focal segmental glomerulosclerosis (FSGS) and minimal change disease (MCD) has not been studied well.

Methods: Plasma samples from 135 FSGS/MCD participants in the Nephrotic Syndrome Study Network (NEPTUNE) were studied. Samples were collected within 45 days from kidney biopsy. Untargeted metabolomics data were obtained using liquid chromatography mass spectrometry (LC-MS). We performed rigorous preprocessing to identify metabolites, remove outliers, and impute missing values. Outcomes with our interest were time to complete remission of proteinuria (UPCR<0.3) and, time to composite renal outcome (40% decline of eGFR or ESKD). Metabolites associated with clinical outcomes were selected by Cox-Elastic Net algorithm. Among the selected metabolites, a hypergeometric test was performed to identify the enriched metabolite categories.

Results: Among the 135 participants, 85 (63.0%) were male, 49 (36.3%) were pediatrics and 81 (60.0%) were FSGS. Median UPCR level was 1.65, and 42 (31.1%) demonstrated nephrotic range proteinuria (UPCR>3.5). Median eGFR levels was 84.2

at the time of sample collection. During the follow-up period (median: 51 months), 47 attained complete remission and 33 reached to composite renal outcome. From the metabolomics data, 371 high-quality named metabolites were analyzed. Cox-Elastic Net models selected 21 and 47 endogenous metabolites that associated with time to complete remission and eGFR decline or ESKD, respectively. Among 87 metabolite categories, hypergeometric tests revealed that Fatty esters and were associated with complete remission while Bile acids were associated with eGFR decline or ESKD.

Conclusions: Specific combinations of plasma metabolites, particularly included as lipids and lipid derivatives, were associated with clinical outcomes in FSGS/MCD, which could help to understand disease mechanisms and can be potential biomarkers to improve treatment strategies.

Funding: NIDDK Support, Other NIH Support - NCATS

TH-OR23

Idiopathic Collapsing Glomerulopathy Is Associated with APOL1 High-Risk Genotypes or Mendelian Variants in Most Affected Individuals in a Highly Admixed Population

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Background: Collapsing glomerulopathy (CG) is most often associated with fast progression to chronic kidney disease requiring renal replacement therapy (CKD-RRT). Its incidence is apparently higher in Brazil than in other countries, however the reason for this occurrence is unknown.

Methods: We performed an integrated analysis of clinical, histological, therapeutic, causative genetic and genetic ancestry data in a highly genetically-admixed cohort with 70 idiopathic CG (ICG) patients, including children and adults. Genetic analyses included targeted-gene panel or whole exome sequencing and a high-density SNP array for ancestry assessment.

Results: The disease onset occurred at 23 (17-31) years and 51.4% of patients progressed to CKD-RRT 36 months after diagnosis. Causative genetic bases were identified in 58.6% of patients. Among these cases, 80.5% harbored *APOL1* high-risk genotypes (HRG) and 19.5% causative Mendelian variants (MV). Self-reported non-White patients presented more frequently HRG. MV was an independent risk factor for progression to CKD-RRT at 36 months (HR: 2.583, 95%CI 1.151-7.076, p=0.024) and the end of follow-up (HR: 2.355, 95%CI 1.018-5.447, p=0.045). Older age at kidney biopsy and remission were independent protective factors against progression to CKD-RRT at 36 months (HR: 0.961, 95%CI 0.927-0.996, p=0.029; and HR: 0.230, 95%CI 0.085-0.623, p=0.004, respectively), and remission also at the end of follow-up (HR: 0.155, 95%CI 0.069-0.351, p<0.001). All HRG patients manifested CG at 9-44 years of age whereas in those with *APOL1* low-risk genotype the disease arose throughout life. HRG associated with higher proportion of African genetic ancestry. Novel causative MVs were identified in *COL4A5, COQ2,* and *PLCE1* and previously described causative MVs in *MYH9, TRPC6, COQ2, COL4A3,* and *TTC21B.* Three patients displayed HRG combined with a VUS (*ITGB4, LAMA5* or *PTPRO*). MVs was associated with worse kidney prognosis.

Conclusions: Our data revealed that the genetic status plays a major role in ICG pathogenesis, accounting for more than half of cases in a highly-admixed Brazilian population.

TH-OR24

Anti-Nephrin Antibody as a Potential Etiology in Primary Focal Segmental Sclerosis (FSGS)

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Background: Minimal change disease (MCD) and primary FSGS have long been pondered to have shared pathogenesis representing a spectrum of different stages of podocyte injury and repair. Recent discovery of anti-nephrin antibodies (Ab) in MCD led us to hypothesize that anti-nephrin Ab may also be present in primary FSGS.

Methods: We retrospectively reviewed all native kidney biopsies performed at BWH from 1/2018-4/2022. We identified 52 cases of primary FSGS (diffuse podocytopathy+segmental sclerosis). We compared the pathological and clinical features between patients (pts) who have punctate IgG deposition on biopsies (+IgG) and those without (-IgG). Anti-nephrin Ab was tested in select pts with +IgG.

Results: Among the 52 cases, 14 had +IgG on IF (27%). There was no difference in the presence of collapsing lesion (36% vs. 45%, P=0.6), percentage of segmental sclerosis (7% vs. 8%, P=0.6) and IFTA (18% vs. 20%, P=0.7) between +IgG and -IgG groups. There was a trend towards enrichment of tip lesions in the +IgG group (21% vs. 11%, P=0.3). Among the 40 pts with available clinical data at biopsy, median proteinuria was significantly higher in the +IgG compared to -IgG group (13 vs 8 g/g, P=0.01). Five pts with +IgG had anti-nephrin Ab tested during active disease and all were positive (Table 1); all 5 biopsies showed colocalization of the punctate IgG with nephrin (Figure 1).

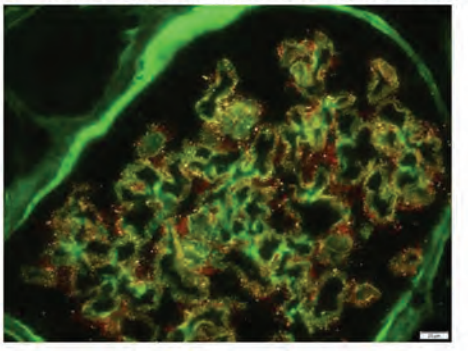
Conclusions: Punctate IgG deposition that colocalizes with nephrin is also observed in patients with primary FSGS and correlates with circulating anti-nephrin Ab. This suggests that anti-nephrin Ab-mediated podocyte dysfunction may be a shared disease mechanism between MCD and primary FSGS.

Table 1

Pt ID	Age/Race /Sex	FSGS subclass	IgG dusting	Serum anti-nephrin antibody	Disease activity when antibody tested	Time between biopsy and antibody testing (months)	Treatment after biopsy	Last known disease status (months from biopsy)
1	64 WM	tip	+	+	Active, initial presentation	0	steroid, rituximab	CR (3)
2	26 HM	perihilar	+	+	Active, relapse	0	steroid, cyclophosphamide, tacrolimus	None (9)
3	48 HF	tip	+	+	Active, initial presentation	0	steroid, rituximab	CR (11)
4	41 WM	NOS	+	+	Active, relapse	14	steroid, rituximab, tacrolimus	None (17)
5	69 WM	NOS	+	+	Active, initial	0	steroid	CR (21)

*WM=White male, HM=Hispanic male, HF=Hispanic female

Figure 1. Punctate IgG deposition with nephrin colocalization



TH-OR25

Exploring Epitope Spreading of PLA2R and Its Clinical Relevance in Idiopathic Membranous Nephropathy (IMN) Based on Yeast Surface Display System

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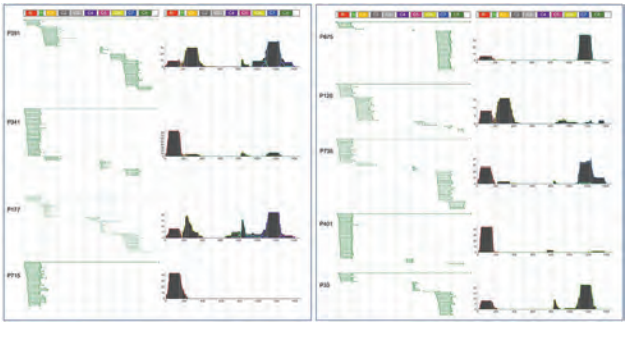
Background: PLA2R is the main target antigen of idiopathic membranous nephropathy (IMN). The PLA2R extracellular segment consists of Ricin, FNII and 8 CTLDs. The major epitope is located in Ricin, and CTLD1, CTLD7 and CTLD8 have also been found as epitopes. The presence of epitope spreading and its clinical significance are controversial.

Methods: A random library of PLA2R was constructed by yeast surface display technique and screened by serum from 18 patients with PLA2R-associated IMN. Serum was prospectively collected from 389 patients. A batch flow analysis was carried out with the monoclonal yeast of each epitope. The clinical value of epitope was explored. The dynamic changes of epitope profiles during follow-up were observed.

Results: 1. The first PLA2R yeast surface display system was constructed. 2. In addition to Ricin, CTLD1, CTLD7, and CTLD8, 3 new epitopes (CTLD4, CTLD5, and CTLD6) were found (Figure 1). 3. The positive rates of CTLD1 and CTLD7 were about 50%. CTLD6, CTLD8 and CTLD4 were weak epitopes with a positive rate of less than 10%. 69 (17.7%) patients had epitope limited to Ricin. 4. 24hUP increased with the number of epitopes. The relationship between epitope spreading and 24hUP in subgroup divided by anti-PLA2R titer was consistent with the whole cohort. 5. By multivariate COX regression, gender, age, baseline 24hUP, anti-PLA2R titer were adjusted. Patients with epitope number ≥4 had lower response rates than patients with only 1 epitope (HR 0.571, 95%CI 0.363-0.899, p=0.015). 6. Reversal of epitope spreading was observed in responders. Further epitope spreading was observed in non-responders.

Conclusions: We identified 3 new epitopes through PLA2R yeast surface display system. Epitope spreading in PLA2R was confirmed. The epitope number was correlated with 24hUP. Baseline epitope spreading had a prognostic value for remission independent of anti-PLA2R Ab titer and 24hUP. Clinical remission was accompanied with epitope reversal.

Funding: Clinical Revenue Support, Government Support - Non-U.S.



TH-OR26

eGFR Decline in Patients with IgA Nephropathy Treated with Nefecon or Placebo: Results from the 2-Year NefIgArd Phase 3 Trial

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Background: The novel targeted-release budesonide formulation Nefecon is designed to treat immunoglobulin A (IgA) nephropathy (IgAN) by downregulating IgA1 antibody production in the distal ileum. 9-month data from the first 199 patients (pts) in the Phase 3 NefIgArd trial demonstrated significant urine protein–creatinine ratio (UPCR) reduction and estimated glomerular filtration rate (eGFR) preservation with Nefecon vs placebo in pts with IgAN, as reported previously (Barratt J et al. Kidney Int 2023;103:391–402). Here, we present data for the complete study population from the full 2-year trial (9 months of treatment and 15 months of follow-up) comparing eGFR decline (measured as a confirmed 30% reduction in eGFR from baseline) in pts treated with Nefecon 16 mg/day vs placebo.

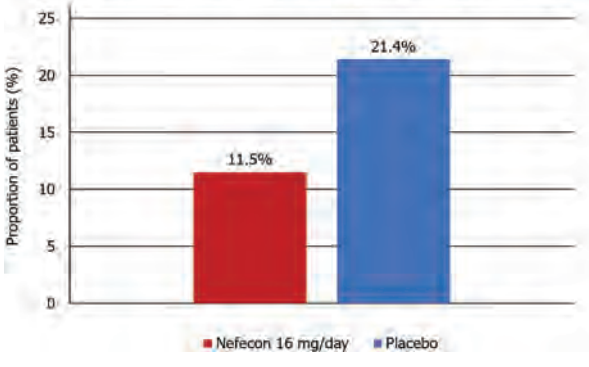
Methods: Pts (≥18 years) with primary IgAN, eGFR 35–90 mL/min/1.73 m^2, proteinuria ≥1 g/24 h despite renin–angiotensin system blockade, and blood pressure <140/90 mmHg, were eligible. A 30% reduction from baseline in eGFR (Chronic Kidney Disease Epidemiology Collaboration formula) was confirmed by 2 values.

Results: 364 pts were included in the full analysis set. The proportion of pts with a confirmed 30% eGFR reduction was lower in the Nefecon vs placebo arm (Figure). The time to a confirmed 30% reduction was significantly delayed with Nefecon vs placebo (hazard ratio [HR] 0.45 [95% confidence interval 0.26–0.75]; p=0.0014 [1-sided]). A pre-defined supplementary analysis with rescue medication use included as an event yielded a similar result (HR 0.51). Baseline UPCR (<1.5 and ≥1.5 g/g) did not affect outcome (HR 0.51 and 0.42, respectively).

Conclusions: The significantly longer time to a confirmed 30% reduction in eGFR with Nefecon vs placebo strongly indicates preserved kidney function and supports the role of Nefecon as a disease-modifying therapy.

Funding: Commercial Support - Calliditas Therapeutics

Figure. Proportion of patients with a confirmed 30% reduction in eGFR (in the absence of rescue medication) over the 2-year trial period



TH-OR27

Safety and Efficacy of Felzartamab in Primary Membranous Nephropathy (PMN): Final Analysis of the M-PLACE Study

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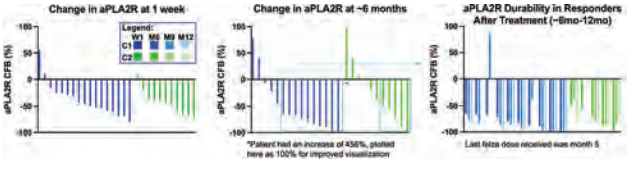
Background: PMN, a common cause of nephrotic syndrome with serious sequelae, is characterized by deposition of pathogenic autoantibodies forming immune complexes between podocytes and the basement membrane. Felzartamab (Felza), a fully human IgG1 anti-CD38 mAb, binds to CD38 antigen and depletes plasmablasts and plasma cells, the source of pathogenic aPLA2Rab.

Methods: M-PLACE (NCT04145440), a P1b/2a multi-national study, assessed safety and efficacy of felza in 2 adult cohorts with aPLA2R+ PMN requiring immunosuppressive therapy (IST). Cohort 1 (C1) enrolled newly diagnosed or relapsed patients and Cohort 2 (C2) enrolled IST-refractory patients. Nine infusions (16 mg/kg) were given over 5 months with a total observation period of 12 months.

Results: Among 31 patients (C1, n=18; C2, n=13) baseline characteristics include (Mean (SD)): Age 57.5 (11.8) yrs, serum aPLA2R titer 247.1 (259.3) U/mL, UPCR 6.4 (2.2) g/g, and serum albumin 26.8 (4.96) g/L. Most frequently reported TEAEs were infusion reactions in 9 patients (29.0%); 5 patients (16.1%) had serious TEAEs. Twenty-three patients (74%) achieved immunological response of > 50% aPLA2R reduction, with 8 (26%) achieving complete immunological response (aPLA2R changes shown in Fig. 1). Of the patients who received >5 Felza doses and no other IST, 7/15 (47%) patients in C1 and 2/11 (18%) patients in C2 achieved partial remission (UPCR reduction > 50%, UPCR < 3.0 g/g, and stable GFR) within the 12 month period. Consistent with the short period of follow-up, no patients achieved CR. Serum albumin increased in 11/15 (73%) patients in C1 and 7/10 (70%) patients in C2.

Conclusions: In high-risk patients with high unmet need (previously relapsing or refractory to IST, among the highest aPLA2R titer in a therapeutic clinical study to date), felza resulted in rapid, deep, and durable aPLA2R responses with associated improvements in proteinuria and serum albumin. Depleting CD20–/CD38+ plasma cells is a promising therapeutic strategy for treatment of PMN, including patients with high aPLA2R titers.

Funding: Commercial Support - Human Immunology Biosciences Inc, MorphoSys AG



TH-OR28

Remission, Glucocorticoid Toxicity, Health-Related Quality of Life, and Safety Outcomes in Patients with Renal Involvement in the ADVOCATE Trial

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Background: In the Phase 3 ADVOCATE trial comparing avacopan to a prednisone taper, 81% of patients with ANCA-associated vasculitis (AAV) had renal involvement based on the Birmingham Vasculitis Activity Score. This renal subgroup had a baseline mean estimated glomerular filtration rate of 45.1 mL/min/1.73 m^2.

Methods: This post hoc analysis evaluated remission, glucocorticoid (GC) use, GC toxicity index (GTI), health-related quality of life (HRQoL by SF-36), and safety in patients with baseline renal involvement for those treated with avacopan (N=134) versus a prednisone taper (N=134).

Results: Compared to the overall study population, for this subgroup the mean age was similar (62 vs 61 years), but there was a slightly higher proportion of patients with newly diagnosed AAV (74% vs 69%), myeloperoxidase+ ANCA (63% vs 57%), microscopic polyangiitis (52% vs 45%), and use of cyclophosphamide (39% vs 35%). The avacopan group achieved a higher sustained remission rate at week 52 (67.9% vs 56.7%) while receiving a (mean/median) 2.4-/5.3-fold less total GC dose than the prednisone taper group (**Table 1**). The GTI cumulative worsening and aggregate improvement scores were lower at weeks 13 and 26 in the avacopan group compared to the prednisone group. At weeks 26 and 52 the avacopan group reported a greater improvement in SF-36 physical and mental component summary scores. Serious adverse events occurred in 46% (2 deaths) and 49% (3 deaths) of patients in the avacopan and prednisone groups, respectively.

Conclusions: In the ADVOCATE trial, patients with AAV with baseline renal involvement treated with avacopan achieved higher sustained remission rates while receiving less GCs, experiencing less GC-related toxicity, and reporting greater improvements in HRQoL versus those treated with a prednisone taper.

Funding: Commercial Support - Amgen

Table 1: Baseline Characteristics, Remission Rates, Glucocorticoid Toxicity, Health-Related Quality of Life, and Safety for Patients with ANCA-Associated Vasculitis with Renal Involvement in the ADVOCATE Trial

	Avacopan (N=134)	Prednisone taper (N=134)
Baseline characteristics		
Age (years), mean ± SD	60.9 ± 14.6	62.2 ± 13.9
Male / Female	84 (63%) / 50 (37%)	76 (57%) / 58 (43%)
Newly diagnosed / Relapsed, n (%)	98 (73%) / 36 (27%)	100 (75%) / 34 (25%)
Proteinase 3+ / Myeloperoxidase+, n (%)	53 (40%) / 81 (60%)	47 (35%) / 87 (65%)
GPA / MPA, n (%)	65 (49%) / 69 (51%)	63 (47%) / 71 (53%)
Rituximab / Cyclophosphamide, n (%)	81 (60%) / 53 (40%)	82 (61%) / 52 (39%)
eGFR (mL/min/1.73 m²), mean ± SD	44.6 ± 27.7	45.6 ± 27.3
Key Results		
Disease remission week 26, n (%)	99 (73.9%)	95 (70.9%)
Sustained disease remission week 52, n (%)	91 (67.9%)	76 (56.7%)
Total all-source glucocorticoid dose during 52-week period, mg (mean / median)	1589 / 575	3801 / 3028
GTI-CWS at weeks 13 / 26, LSM ± SEM	24.1 ± 3.9 / 38.9 ± 3.9	37.7 ± 4.0 / 58.5 ± 4.0
GTI-AIS at weeks 13 / 26, LSM ± SEM	8.5 ± 3.9 / 11.2 ± 4.0	24.3 ± 4.0 / 24.3 ± 4.0
SF-36 PCS Score, Change from baseline at weeks 26 / 52, LSM ± SEM	4.8 ± 0.8 / 4.9 ± 0.8	1.9 ± 0.8 / 3.1 ± 0.8
SF-36 MCS Score, Change from baseline at weeks 26 / 52, LSM ± SEM	5.2 ± 0.9 / 6.6 ± 1.0	3.5 ± 1.0 / 5.1 ± 1.0
Serious Adverse Events, n patients (%), n events	61 (45.5%) 104 events	65 (48.5%) 148 events
Deaths, n (%)	2 (1.5%)	3 (2.2%)

AIS, aggregate improvement score; CWS, cumulative worsening score; eGFR, estimated glomerular filtration rate; GTI, glucocorticoid toxicity index; GPA, granulomatosis with polyangiitis; LSM, least squares mean; MCS, mental component summary; MPA, microscopic polyangiitis; PCS, physical component summary, SEM, standard error of the mean; SF-36, Short Form-36.

TH-OR29

Repeat Kidney Biopsies from the AURORA 2 Study of Voclosporin in Active Lupus Nephritis

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Background: Voclosporin is approved for the treatment of adults with active lupus nephritis (LN). Addition of voclosporin to MMF and low-dose glucocorticoids in the Phase 3 global AURORA studies led to significantly earlier and greater reductions in proteinuria while maintaining stable renal function. To characterize the long-term renal impact of voclosporin at the histologic level, we analyzed repeat kidney biopsies from a subset of patients in these studies.

Methods: Patients in AURORA 1 had biopsy-proven LN, UPCR ≥1.5 g/g (≥2 g/g for Class V), and eGFR >45 mL/min/m². Patients were randomized to voclosporin or control for 1 year in AURORA 1 and continued the same blinded therapy for 2 additional years in AURORA 2; all patients received MMF and low-dose glucocorticoids. A subset of patients had a kidney biopsy prior to screening and a repeat biopsy after approximately 18 months of therapy. Histopathologic grading according to NIH indices for LN activity and chronicity was conducted by Arkana Laboratories. Efficacy outcomes and mean eGFR over time were assessed.

Results: Repeat biopsy samples were collected from 16 patients in the voclosporin arm and 10 patients in the control arm. Baseline mean activity scores were similar between arms, with scores improving with treatment in both arms. Mean chronicity scores were also similar between arms at baseline and remained stable over time in most patients. Measures of renal function remained stable in both arms over the 3-year follow-up. Voclosporin-treated patients had numerically greater mean reductions from baseline in UPCR year-on-year compared to patients in the control arm.

Conclusions: As expected, mean activity scores improved in both treatment arms. Importantly, exposure to voclosporin was not associated with chronic injury, with the mean index remaining stable at follow-up. Similar to the overall population, patients treated with voclosporin saw greater reductions in UPCR over 3 years of treatment; safety outcomes from this small subgroup were also consistent with outcomes in AURORA 1.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

Table 1. Clinical outcomes, laboratory parameters, and activity and chronicity index scores over time

	Voclosporin n=16		Control n=10	
	Baseline	Month 36	Baseline	Month 36
CRR, % (n/n)	–	62.5% (10/16)	–	40.0% (4/10)
PRR, % (n/n)	–	81.3% (13/16)	–	70.0% (7/10)
UPCR, mean (SD) mg/mg	4.59 (2.5)	0.95 (1.4)	4.71 (2.6)	2.1 (4.6)
eGFR, mean (SD)	80.3 (16.4)	82.7 (15.4)	82.6 (12.3)	85.8 (13.3)
Urine protein, mean (SD) mg/dL	413.7 (277.2)	135.7 (264.0)	350.2 (234.1)	128.0 (284.7)
Magnesium, mean (SD) mg/dL	2.0 (0.1)	2.0 (0.2)	2.1 (0.1)	2.1 (0.2)
Potassium, mean (SD) mmol/L	4.0 (0.3)	4.3 (0.2)	3.9 (0.4)	4.1 (0.5)
Glucose, mean (SD) mg/dL	84.4 (9.0)	93.5 (7.9)	93.5 (38.5)	88.1 (15.3)
Creatinine, mean (SD) mg/dL	0.8 (0.3)	0.8 (0.4)	0.8 (0.2)	0.8 (0.3)
Systolic BP, mean (SD) mmHg	121.7 (9.05)	118.3 (10.4)	121.1 (14.9)	110.8 (4.8)
Diastolic BP, mean (SD) mmHg	79.6 (8.7)	74.7 (7.7)	80.4	76.9 (4.5)
Histology	**Baseline**	**Follow-up**	**Baseline**	**Follow-up**
Activity Index, mean (SD)	1.8 (3.0)	0.4 (1.0)	2.8 (3.2)	0.4 (1.0)
Chronicity Index, mean (SD)	3.8 (3.5)	4.1 (3.3)	2.9 (2.3)	2.8 (2.7)

Renal function assessed with corrected eGFR (Chronic Kidney Disease Epidemiology Collaboration equation) using a prespecified ceiling of 90 mL/min/1.73 m². Histopathologic grading based on the National Institutes of Health indices for lupus nephritis activity (scale 0-24) and chronicity (scale 0-12).[1] BP, blood pressure; CRR, complete renal response (UPCR ≤0.5 mg/mg, stable eGFR > 60 mL/min/1.73 m2, low-dose steroids, and no rescue medication) ; eGFR, estimated glomerular filtration rate; PRR, partial renal response (≥50% reduction from baseline in UPCR); SD, standard deviation; UPCR.

TH-OR30

Kidney-Related Outcomes in Patients with Active Lupus Nephritis Treated with Obinutuzumab: A Post Hoc Analysis of the Phase 2 NOBILITY Trial

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Background: Preservation of long-term kidney function is a major therapeutic goal in lupus nephritis (LN). In the randomized, double-blind, placebo-controlled, Phase 2 NOBILITY trial (NCT02550652; PMID: 34615636), patients with proliferative LN receiving obinutuzumab with standard-of-care therapy showed clinically meaningful improvement in complete and overall renal responses at Weeks 52, 76 and 104 compared with those receiving placebo and standard-of-care therapy. We conducted a post hoc analysis of NOBILITY to assess kidney-related outcomes.

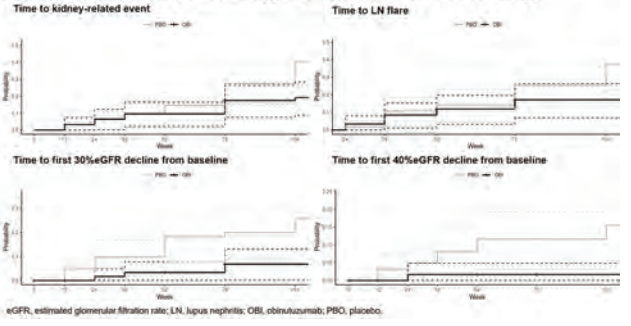
Methods: Cox regression analysis was conducted for the time to first kidney-related event (death, doubling of serum creatinine or treatment failure), LN flare and first 30% and 40% eGFR decline from baseline. The eGFR slope was assessed in a linear mixed-effects model.

Results: Obinutuzumab significantly reduced the risk of kidney-related events or death (HR, 0.40; 95% CI, 0.20 to 0.80), LN flare (HR, 0.43; 95% CI, 0.20 to 0.95) and first eGFR decline of 30% (HR, 0.20; 95% CI, 0.06 to 0.61) and 40% (HR, 0.09; 95% CI, 0.01 to 0.73) (**Figure**). Risk of sustained eGFR decline of 30% and 40% was numerically lower, and a significant difference in attenuation of eGFR slope decline was observed between patients receiving obinutuzumab and standard-of-care therapy and those receiving placebo and standard-of-care therapy (annual slope difference, 4.10 mL/min/year; 95% CI, 0.14 to 8.08).

Conclusions: Obinutuzumab, in addition to increasing the possibility of achieving a complete renal response, significantly reduced the risk of kidney-related events, eGFR decline, time to LN flare and eGFR slope decline in a post hoc analysis, suggesting that obinutuzumab in combination with standard-of-care therapy may positively impact kidney-related outcomes. Obinutuzumab is being evaluated in patients with active proliferative LN in the global registrational Phase 3 REGENCY trial (NCT04221477).

Funding: Commercial Support - This study was funded by Genentech, Inc., a member of the Roche Group. Editorial assistance was provided by Health Interactions, Inc., and funded by F. Hoffmann-La Roche Ltd.

Figure. Kidney-related outcomes over 104 weeks in patients with proliferative LN treated with obinutuzumab and standard-of-care therapy vs placebo and standard-of-care therapy



eGFR, estimated glomerular filtration rate; LN, lupus nephritis; OBI, obinutuzumab; PBO, placebo.

TH-OR31

PI3K/AKT/mTOR Pathway Regulates Renal Expression of Klotho

Aurora Perez-Gomez, Juan M. Diaz Tocados, Juan Diego Domínguez Coral, Alicia G. Carrasco, Jose M. Valdivielso. *Institut de Recerca Biomedica de Lleida Fundacio Dr Pifarre, Lleida, Spain.*

Background: Renal Klotho expression decreases early in chronic kidney disease (CKD), increasing circulating FGF23 and phosphate levels. This negatively affects renal disease progression and cardiovascular complications. Preserving renal Klotho expression is of interest, but the underlying mechanisms are unclear. During early stages of CKD, kidneys activate mechanisms of hypertrophy, in which the PI3K/Akt/mTOR pathway plays a role. This pathway is activated by growth factors such as insulin-like growth factor-1 (IGF-1). The main negative regulator of this pathway is PTEN, which reduces the activation of canonical insulin signaling. We aimed to investigate the role of PTEN and the PI3K/AKT/mTOR pathway in kidney Klotho levels and their possible implication in CKD.

Methods: We measured renal Klotho levels, circulating FGF23, and phosphate in mice lacking PTEN in renal proximal tubular cells (PTEC) and in HK2 cells in vitro. We also examined normal mice with models of decreased renal mass caused by uninephrectomy (UNX) and 5/6 nephrectomy (SNX). Additionally, we tested the effect of mTOR inhibition. Furthermore, we analyzed PTEN and Klotho expression in kidney samples from CKD patients.

Results: We found that PTEC with downregulated PTEN exhibited decreased Klotho expression both in vitro and in vivo, accompanied by increased mTOR activity. Animals with PTEN elimination in PTEC also showed increased circulating phosphate and FGF23

levels, as well as a decrease in the fractional excretion of phosphate. These alterations were normalized by treatment with rapamycin. Normal mice with UNX or SNX exhibited increased renal IGF-1 expression and activation of the PI3K/AKT/mTOR pathway. Furthermore, these mice showed a reduction in renal Klotho expression and an increase in circulating FGF23 and phosphate. Both of these alterations were restored with rapamycin administration. In renal samples from CKD patients, we observed a positive correlation between the expression of PTEN, KLOTHO, and glomerular filtration rate (GFR).

Conclusions: The overactivation of the PI3K/AKT/mTOR pathway in PTEC modulates Klotho levels in the kidney. Our findings represent a significant advancement in the search for new therapeutic targets to maintain and prevent reductions in renal Klotho levels, potentially benefiting kidney disease patients.

Funding: Government Support - Non-U.S.

TH-OR32

Spatial Genomics Localized Nephron Segment-Specific FGF23 and CKD Klotho-Dependent and -Independent Transcriptional Reprogramming

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Background: FGF23 acts in the kidney via Klotho (KL) to control phosphate metabolism. However, in CKD, KL is lost and FGF23 is pathologically increased, disrupting mineral homeostasis. KL is expressed in multiple nephron segments, thus localization of FGF23 actions in the nephron remain unclear. Herein, we tested for novel FGF23 bioactivity localized with KL, as well as hypothesized that CKD alters FGF23/KL signaling and causes spatially unique transcriptional reprogramming.

Methods: Visium spatial transcriptomics (ST) was performed on kidney sections from normal mice injected with FGF23 (250 ng/kg) for 1 or 4 h, and male mice with adenine diet induced CKD (0.2% for 4 weeks).

Results: The FGF23-injected and CKD kidney sections had >6900 genes/sequencing spot and formed 12 and 10 UMAP cell clusters, respectively. Mapping nephron segment markers showed clear demarcation of cortical and medullary gene expression. PT S1/S2 marker Slc5a2 was highly expressed in the cortex and S3 marker Eci3 localized to the outer stripe of the medulla (OSOM). FGF23 increased MAPK-dependent transcription factor Egr1 more at 1 h than 4 h. The vitamin D metabolic enzymes Cyp24a1 and Cyp27b1 mRNAs were increased or decreased, respectively, at 4 h and overlapped with KL. ST data was validated by qPCR and independent scRNAseq data from FGF23-injected mice. We also identified novel changes in response to FGF23, including increased cortical Cyp4b1 at 4 h, which CKD decreased. Mice with CKD had reduced KL mRNA and increased Cyp27b1. Consistent with CKD fibrosis, Col1a1, -1a2, -3a1, and -4a1 were ubiquitously increased, although Col3a1 was more focused to the inner stripe of the medulla (ISOM). Further, pro-fibrotic Tgfb1 broadly increased, whereas its target Mmp7 increased in the ISOM. In contrast, damage and injury markers C3 and Havcr1 were restricted to the cortex and OSOM, respectively. Finally, evidence of wider immune infiltration was present in CKD with elevated neutrophil marker Lcn2, and macrophage markers Cd68 and Ptprc.

Conclusions: Using ST, we identified unbiased, spatially identifiable effects of FGF23 bioactivity in kidney, including new potential FGF23 targets. We also localized pathologic KL-dependent and -independent CKD gene alterations that differentially occur in distinct cell populations.

Funding: NIDDK Support, Other NIH Support - R01-HL145528

TH-OR33

Role of miR-122 on FGF23 Cleavage

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Background: In chronic kidney disease (CKD), iron deficiency and inflammation contribute to elevated levels of intact fibroblast growth factor 23 (iFGF23) by increasing FGF23 production. Proteolytic cleavage of intact fibroblast growth factor 23 (iFGF23) yields C-terminal FGF23 peptides (Cter-FGF23) that play a protective role in iron deficiency anemia (IDA) and inflammation. O-glycosylation of iFGF23 cleavage site by GALNT3 protects iFGF23 from cleavage, but the regulation of GALNT3 is unknown. We found that IDA increases the expression of miR-122-5p (miR122), which is a predicted inhibitor of *Galnt3* expression. We hypothesized that inhibition of GALNT3 by miR122 results in increased iFGF23 cleavage in IDA.

Methods: Since miR122 is mainly produced by the liver, we generated mice harboring a conditional deletion of miR122 in hepatocytes (miR122cKO) by crossing miR122 floxed mice with mice expressing a Cre recombinase driven by the Albumin promoter. We induced IDA by feeding 3-week-old wild-type (WT) and miR122cKO mice either a control diet (Ctr) or a low iron diet (IDA) for 3 weeks. At 6 weeks of age, we analyzed serum biochemical and hematological parameters as well as bone Galnt3 expression in all mice.

Results: Compared to WT-Ctr, miR122cKO-Ctr mice exhibited reduced miR-122 levels, increased bone Galnt3 expression and iFGF23 levels, despite normal total cFGF23. These mice also showed reduced iron levels and transferrin saturation, but normal hemoglobin levels and red blood cells counts. As expected, WT-IDA mice were anemic and showed higher levels of miR122, reduced Galnt3 expression along with a 3.6-fold increase in total cFGF23 compared to WT-Ctr, and a slight but significant increase in iFGF23. Compared to WT-IDA, miR122cKO-IDA mice showed increased Galnt3 expression, total cFGF23 and iFGF23 levels, resulting in an increased i/cFGF23 ratio, a surrogate marker of FGF23 cleavage. miR122cKO-IDA mice also exhibited further reduced levels of iron and transferrin saturation, but this did not aggravate the severity of anemia in these mice.

Conclusions: Our results demonstrate that iron deficiency increases miR122, which inhibits osseous Galnt3 expression and results in increased FGF23 cleavage, elevated Cter-FGF23 but reduced iFGF23. miR122 could be a potential therapeutic target to reduce iFGF23 and thus improve adverse outcomes in early stages of CKD.

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TH-OR34

Direct Effects of FGF23 on Osteoblasts Contribute to Bone Defects in Dmp1KO Mice Independently of Phosphate

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Background: Fibroblast growth factor 23 (FGF23) is a phosphate (Pi)-regulating hormone produced in bone. Hereditary hypophosphatemic disorders are associated with FGF23 excess that leads to hypophosphatemia, impaired skeletal growth, rickets and osteomalacia. The blockade of FGF23 signaling to correct serum Pi levels has become a superior therapeutic strategy to Pi supplementation in X-linked hypophosphatemia, but remains untested in autosomal recessive hypophosphatemic rickets (ARHR). In this study, we compared the effects of reducing circulating FGF23 levels using osteocyte-specific deletion of *Fgf23* ($Fgf23^{cKO}$) to the effects of dietary Pi supplementation in the *Dmp1* knockout ($Dmp1^{KO}$) mouse model of ARHR.

Methods: We deleted *Fgf23* specifically in osteocytes ($Fgf23^{cKO}$) using a Dmp1-cre recombinase, in wild-type (WT) and $Dmp1^{KO}$ mice. In addition, we fed WT and $Dmp1^{KO}$ mice a diet containing either 0.5% (NP) or 2% Pi (HP). In parallel, we cultured primary osteoblasts isolated from WT, $Fgf23^{cKO}$, $Dmp1^{KO}$ and $Dmp1^{KO}$/$Fgf23^{cKO}$ mice to understand the direct impact of FGF23 and DMP1 on osteoblast differentiation and activity.

Results: Compared with WT mice and concurrent with successful *Fgf23* deletion, $Fgf23^{cKO}$ mice showed reduced serum FGF23 levels and increased serum Pi levels, whereas $Dmp1^{KO}$ mice displayed highly increased serum FGF23 levels, hypophosphatemia, impaired growth, rickets and osteomalacia. In contrast, $Dmp1^{KO}$/$Fgf23^{cKO}$ mice showed a near complete correction of FGF23 excess, which fully restored serum Pi levels, but only partially corrected the bone phenotype. Compared to NP diet, HP diet increased circulating FGF23 levels, PTH levels, and phosphaturia in WT mice. HP-$Dmp1^{KO}$ mice remained hypophosphatemic and showed exacerbated FGF23 production, hyperparathyroidism, and phosphaturia, resulting in a worsened bone phenotype. In vitro, we found that FGF23 directly impairs osteoblast differentiation and that DMP1 deficiency contributes to impaired mineralization independently of FGF23 or Pi levels.

Conclusions: To conclude, our data suggest that the direct effects of FGF23 and DMP1 on osteoblasts need to be considered to effectively correct ARHR-associated mineral and bone disorders, independently of hypophosphatemia.

Funding: NIDDK Support

TH-OR35

The Essential Roles of miRNA and mTORC1 in Parathyroid Function and in Maintaining Parathyroid Glands in the Adult

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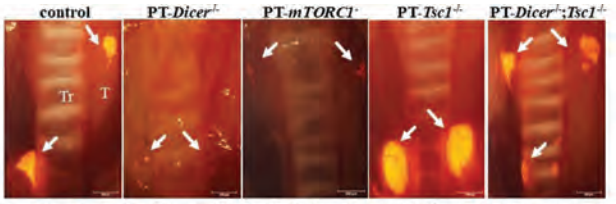
Background: Secondary hyperparathyroidism (SHP) of CKD is a leading cause of morbidity and mortality. The molecular mechanisms governing basal PTH levels and SHP are undefined. We have shown that the parathyroid mTORC1 pathway is activated in CKD-SHP and that ablation of the miRNA processing enzyme *Dicer* and hence miRNA prevents CKD-SHP with no effect on basal serum PTH.

Methods: We generated mice with parathyroid (PT) specific KO of *Dicer*, *mtorc1*, tuberous sclerosis complex 1 (*Tsc1*) or double $Dicer^{-/-}$;$Tsc1^{-/-}$ KO and tdTomato expression to identify the glands by fluorescent microscopy. Parathyroid sections were IF stained.

Results: Despite normal serum PTH, adult PT-$Dicer^{-/-}$ mice had no intact parathyroid glands, unlike controls. The glands were present at birth but soon after only clumps of parathyroid cells remained, indicating that Dicer and miRNA are not essential for parathyroid embryogenesis but rather for maintaining intact glands later in life. To characterize a miRNA-mTORC1 link in the parathyroid, we generated PT-$mTORC1^{-/-}$ mice that had parathyroid cell clumps from early after birth but normal serum PTH, resembling PT-$Dicer^{-/-}$ mice. In contrast, PT-$Tsc1^{-/-}$ mice with mTORC1 hyper-activation due to deletion of its inhibitor, had vastly larger (x10) glands and increased serum PTH and calcium levels. IF staining for parathyroid specific and proliferation markers supported the KO phenotypes. Importantly, a double PT-$Dicer^{-/-}$;$Tsc1^{-/-}$ mouse had intact parathyroid glands similar to controls, indicating that *Tsc1* ablation over-rides the aparathyoridism of *Dicer* KO.

Conclusions: miRNAs are essential for PTH stimulation in CKD induced SHP. Both miRNA and mTORC1 maintain intact glands in the adult.



Parathyroid specific *Dicer* and *Tsc1* double knock-out (PT-*Dicer*$^{-/-}$; *Tsc1*$^{-/-}$) reverses the aparathyroidism of PT-*Dicer*$^{-/-}$ mice. tdTomato parathyroid glands visualized by fluorescent microscopy in control (PT-*Dicer*$^{+/+}$;*Tsc1*$^{+/+}$) and parathyroid specific *Dicer*; *mTORC1*, *Tsc1*, or double *Tsc1* and *Dicer* ablation. Representative fluorescent microscope images overlaid over visible light images of the exposed neck area of 2 month old mice are shown. The arrows point to the parathyroid glands or cell clumps, T, thyroid, Tr, trachea.

TH-OR36

The Role of Osteopontin and Osteocyte-Derived Factors in Secondary Hyperparathyroidism-Induced Muscle Dystrophy

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Background: Secondary hyperparathyroidism (SHPT) leads to harmful effects, including muscle dystrophy. We have previously shown that parathyroidectomy (PTX) improves muscle function, but not muscle mass. We hypothesized that this improvement is related to muscle inflammatory modulation. Osteopontin (OPN), a bone matrix protein, is stimulated by PTH and phosphate, and regulates the immune system at different levels. In this study, we sought to investigate the relationship between changes in mineral and bone metabolism (MBD) in patients with SHPT pre- and post-PTX, muscle expression of osteocyte-derived factors and inflammatory markers.

Methods: We prospectively enrolled 30 patients on dialysis (39 ys, 62% female) referred for PTX. Muscle phenotyping involved tissue analysis by immunohistochemistry, multiplex protein quantification, and gene expression; DXA for body composition; physical evaluation by accelerometer. Muscle biopsies were obtained from the vastus lateralis at baseline and 6 months after PTX, and from healthy controls. Biochemical parameters were also collected.

Results: MBD, DXA, physical evaluation, and tissue analysis are shown in Table1. We found a significant decrease in systemic and muscle OPN concentrations. Higher muscle OPN expression was noted at baseline compared to controls (11vs 2.9%*) and PTX led to a marked reduction (11vs 3%*). Systemic and muscle cytokines concentrations also decreased. Muscle, but not systemic, RANKL and sclerostin concentrations decreased after PTX. *p<0.01.

Conclusions: Our findings suggest that muscle OPN and osteocyte-derived factors might play a role in CKD-associated sarcopenia. In addition to its role in mineralization, OPN may foster muscle tissue inflammation, which is blunted after PTX. Based on these results, new pathways are revealed as therapeutic targets for uremic sarcopenia.

Funding: Government Support - Non-U.S.

	Before PTX	After PTX
MBD parameters and cytokines levels		
PTH, pg/mL	1,526 (1,380 – 1,959)	119 (36 – 297)*
Phosphate, mg/dL	6 ± 1.6	4.8 ± 1.1*
Osteopontin, ng/mL	37.8 (17 – 68)	12.5 (3.7 – 21)*
TGFβ, pg/mL	21.8 ± 12	13 ± 9*
RANKL, pg/mL	14.8 (6.1 – 35)	18.3 (6.7 – 32)
Sclerostin, ng/mL	2.16 (1.18 – 2.64)	4.15 (2.25 – 5.58)*
Physical evaluation		
Steps/day	5,221 ± 3,578	7,245 ± 3,370 *
DXA parameters		
Bone mineral content, kg	1.9 (1.6 – 2.3)	2.2 (2 – 2.6)*
Appendicular mass, kg	17.3 (15.8 – 22.1)	18.3 (16.3 – 21.6)
Muscle protein concentration (pg/mg)		
Osteopontin	179 (103 – 505)**	54 (37 – 142)*
TGFβ	2.8 (1.9 – 5.6)	2.7 (2.1 – 3)*
RANKL	52 ±36	30 ± 13*
Sclerostin	2.01 (1.58 – 5.28)	1.82 (1.21 – 2.26)*
IL 1β	0.2 (0.15 – 1.2)	0.18 (0.13 – 0.24)*
IL 17	0.27 (0.16 – 1.66)	0.2 (0.11 – 0.52)*
TNF α	0.04 (0.03 – 0.06)	0.03 (0.02 – 0.05)*

*p < 0.05 vs. pre-PTX ** vs. controls

TH-OR37

Bone Quality in Uremic Patients: Interactions Between Parathyroid Hormone (PTH) and Propionic Acid

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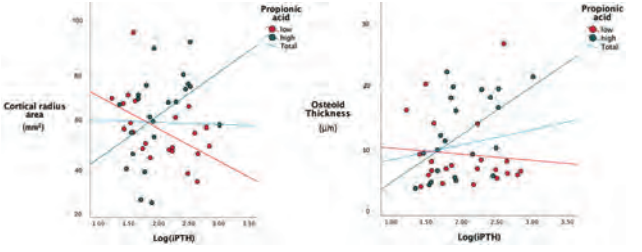
Background: Chronic kidney disease (CKD) associated hyperparathyroidism (HPT) results in impaired bone quality and strength. While calcitriol deficiency partially drives elevations in parathyroid hormone (PTH), skeletal resistance to PTH also contributes to progressive HPT. In mice with normal kidney function, short-chain fatty acids (SCFAs) produced by the gut microbiome, were shown to moderate PTH effects on bone. Interactions between SCFAs and PTH on bone quality in humans with CKD are unknown. We hypothesized that SCFAs moderate the skeletal effects of PTH in CKD.

Methods: In a cross-sectional study of 60 CKD patients with double label transiliac crest bone biopsies, we measured parameters of dynamic histomorphometry, PTH and 24 SCFA metabolites (Metabolon, Inc). Ages were 29-88 yrs, 13% were on dialysis and 40% were male. High resolution peripheral quantitative computed tomography (HRpQCT; resolution 60 μm3) imaging of the radius and tibia for cortical (Ct) and trabecular (Tb) geometry, density and microarchitecture was performed in a subset of 45 patients. SCFAs were dichotomized at the median. Generalized linear regression models were used to evaluate relationships between bone outcomes, PTH, SCFA, SCFA-PTH and SCFA-sex interactions.

Results: We found that the SCFA, propionic acid (PA), modified relationships between PTH and bone outcomes. In contrast to low levels of PA, high levels of PA and PTH were associated with thicker osteoid (β=3.32, SE 1.58, p=0.041) on histomorphometry, thicker cortices at the radius (β=12.50, SE 3.43, p=0.001) and tibia (β=24.46, SE 8.34, p=0.006) and greater Tb volumetric density (β=26.59, SE 11.28, p=0.024) at the radius by HRpQCT.

Conclusions: In conclusion, in a cohort of CKD patients with bone biopsy and HRpQCT imaging, we observed that PA modified the skeletal response to PTH. When PA levels were elevated, higher PTH was associated with better bone quality. In contrast, when PA levels were low, higher PTH levels were associated with catabolic effects on bone quality. Prospective studies are needed to investigate whether PA has a therapeutic role in the management of renal osteodystrophy.

Funding: NIDDK Support, Private Foundation Support, Clinical Revenue Support



TH-OR38

Calcium Isotope Ratios in Serum: A Novel Biomarker of Bone and Vessel Calcium Balance in Patients on Dialysis

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Background: Dysregulated mineral homeostasis in CKD can cause bone demineralization and vascular calcification. We have shown that non-radioactive calcium (Ca) isotopes, ^{42}Ca and ^{44}Ca, that are naturally present in our diet can be measured in serum, and their ratio ($\delta^{44/42}Ca_{serum}$) quantitatively determines changes in bone Ca balance (BCaB). Isotopically light ^{42}Ca is preferentially incorporated into bone, so $\delta^{44/42}Ca_{serum}$ increases when bone formation exceeds resorption and vice versa. We studied bone and arterial biopsies to determine the sensitivity of $\delta^{44/42}Ca_{serum}$ in estimating BCaB and vascular calcification.

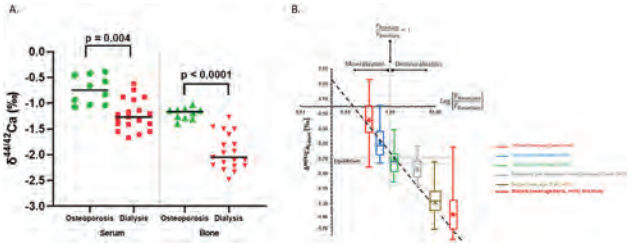
Methods: ^{44}Ca and ^{42}Ca were measured by inductively coupled plasma mass-spectrometry in the serum, bone and arterial biopsies of 19 chronic dialysis patients. Data were compared with adults with osteoporosis.

Results: $\delta^{44/42}Ca_{serum}$ and $\delta^{44/42}Ca_{bone}$ were significantly lower in dialysis patients (median age 59.8 years, time on dialysis 3.3 years) compared to adults with osteoporosis, implying lower BCaB in dialysis patients.(Fig 1). $\delta^{44/42}Ca_{serum}$ showed a strong positive correlation with $\delta^{44/42}Ca_{bone}$ and $\delta^{44/42}Ca_{vessel}$. $\delta^{44/42}$Ca serum and bone correlated positively with the BAP/TRAP5-b ratio and osteoblastic markers P1NP and inversely with osteoclastic markers PTH and RANKL. Although $\delta^{44/42}Ca_{serum}$ indicated low BCaB in 89%, only 31% manifested DXA confirmed osteoporosis (T-scores <-2.5). On histology $\delta^{44/42}Ca_{bone}$ inversely correlated with osteoid area and positively with absolute mineralized area and trabecular thickness. Significant and independent predictors of $\delta^{44/42}Ca_{serum}$ were

$\delta^{44/42}Ca_{bone}$ (p=0.01, 95%CI -1.35 to -0.26), BAP/TRAP5-b ratio (p=0.04, 95%CI 0.04 to 0.26) and osteoid area (p=0.03, 95%CI -1.11 to – 0.09), together predicting 79% of the variability in $\delta^{44/42}Ca_{serum}$.

Conclusions: $\delta^{44/42}Ca_{serum}$ is a significant and independent maker of BCaB, correlating with bone histology, and may provide a more sensitive and non-invasive measure of BCaB than bone biomarkers or DXA.

Funding: Government Support - Non-U.S.



TH-OR39

Role of Plasma Inorganic Pyrophosphate in Calciphylaxis: A Prospective Study

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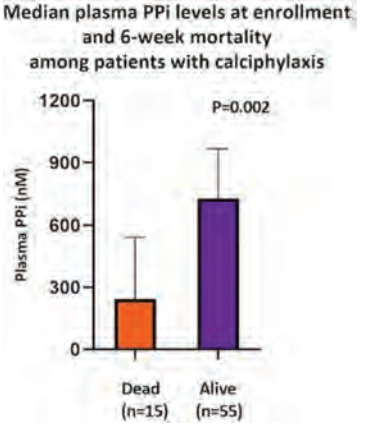
Background: Calciphylaxis is a devastating disorder characterized by painful skin lesions caused by calcific microvascular occlusion and no approved treatment. In experimental models and genetic disorders, deficiency of pyrophosphate (PPi) is linked with vascular calcification and neointimal proliferation. This study was conducted to investigate the influence of plasma PPi on severity and outcomes in calciphylaxis.

Methods: In this prospective study, we enrolled 70 patients with calciphylaxis. Plasma PPi levels were measured using an ATP Sulfurylase/Luminescence-based method at enrollment (n=70) and at 6-week follow up (n=30). We examined the associations of 1) PPi levels at enrollment with skin lesion count, pain severity (assessed by Brief Pain Inventory), and 6-week mortality, and 2) change in PPi levels over 6-week period after enrollment with 12-week mortality.

Results: Median age of our cohort was 60 years and 67% of patients had end-stage kidney disease. Median skin lesion count was 3 [IQR: 2-4] and median pain severity score was 5 [IQR: 4-7]. Median PPi levels were 568 nM [IQR: 253-1205] at enrollment and 1155 nM [IQR: 835-1456] at 6-week follow up. At enrollment, there were modest negative associations of PPi with skin lesion count (r=-0.26) and pain severity (r=-0.28). Mortality at 6 weeks was 21%. Among patients who died by 6-week follow up, PPi levels at enrollment were 66% lower compared to patients who were alive (p=0.002) **(Fig)**. In adjusted models, for every 100 nM decrease in PPi at enrollment, there was 25% increased risk of 6-week mortality. Decrease in PPi levels over 6-week period since enrollment was associated with increased 12-week mortality (p=0.04).

Conclusions: Our novel findings demonstrate the potential of PPi as a target for therapies aimed at improving patient-oriented and clinical outcomes in calciphylaxis.

Funding: Commercial Support - Inozyme Pharma



Plasma PPi and mortality in Calciphylaxis

TH-OR40

Loss of Renal Tubular Claudin-2 Increases Renal Calcification and Urinary Stone Disease

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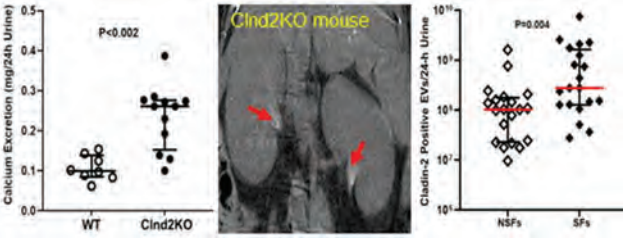
Background: Mechanisms of hypercalciuria-associated renal calcification and urinary stone disease (USD) are not completely understood. Global *Claudin-2* knockout (Cldn2KO) male mice share many key features of human hypercalciuric idiopathic calcium stone formers (ICSFs). Here we characterized urine biochemistry, urinary extracellular vesicles (uEVs), and renal pathophysiology to determine if uEVs could serve as a biomarker for human idiopathic, hypercalciuric, first time stone formers (SFs) with potential pathologic changes in renal claudin-2 (Clnd2) expression.

Methods: Twenty-hour (24-h) urine samples were collected from male mice (Cldn2KO (n=12) and age-matched wild type (WT; n=8)) and human SFs (n=20; hypercalciuric SFs and age-/sex-matched non-SFs (NSFs). *In vivo* renal calcification in mice were measured by Bruker high-resolution *in vivo* 3D X-ray microtomography. Data are presented as median (25^{th}, 75^{th} percentile) and analyzed by Wilcoxon rank-sum test to identify statistically significant (P<0.05) differences between groups.

Results: Age, body weight, total 24-h urine volume, milliosmole, excretion of 24-h urine albumin, Cl^-, phosphorous, K^+, protein, and Na^+ were not different between Cldn2KO and WT mice. However, 24-h excretion of urinary Ca^{2+} was greater (P<0.002; Fig.) in Cldn2KO compared to WT mice. Spontaneous renal papillary calcifications were identified in Cldn2KO (Fig.) but not WT mice. Cldn2 protein expression on uEVs was increased in SFs compared NSFs (P=0.004; Fig.).

Conclusions: Loss of renal tubular Clnd2 protein increased urinary Ca^{2+} excretion and papillary calcification in mice. Our nephrectomy patients study showed a significant decrease in Clnd2 expression in SFs compared NSFs. Thus, increased excretion of Cldn2 protein carrying uEVs in hypercalciuric SFs may reflect decreased tubular Cldn2 protein expression that results in reduced renal Ca^{2+} reabsorption and increased USD, and quantification of Clnd2 content of uEVs could serve as a useful biomarker for further studies.

Funding: NIDDK Support, Private Foundation Support



TH-OR41

The Relationship Between Patient Activation and Clinical Outcomes: A Longitudinal, Retrospective, Observational Study

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Background: Patient activation, defined as an individual's readiness, willingness, and ability to manage their own health and health care, is associated with healthy behaviors and improved outcomes. Patients undergoing in-center hemodialysis (HD) have low activation, but the association of patient activation with clinical outcomes among dialysis patients is unclear. We investigated the association between patient activation and outcomes in HD patients.

Methods: This cohort included 925 prevalent, in-center HD patients among 10 facilities in a mid-sized dialysis provider. Patients had completed a PAM-13 survey—a measure of patient activation—during a previous study. Patients were followed for 180 days after completion of the survey for the co-primary outcomes of (1) death and (2) the composite of death or hospitalization. Markers of non-adherence were examined as secondary outcomes, including (1) serum potassium >5.0 mEq/L; (2) serum phosphorus >5.5 mg/dL; (3) missed dialysis treatment due to absence (not hospitalization); and (4) interdialytic weight gain >4.0%. Univariate and adjusted regression models were fit to estimate associations of a 3-point increment in PAM-13 score with the outcomes of interest; adjustment factors comprised age, sex, dialysis vintage, serum albumin, and hospitalization history.

Results: A 3-point increment in PAM score was associated with lower hazard of death (univariate HR=0.89, 95% CI: 0.84 – 0.94; adjusted HR=0.91, 95% CI: 0.86-0.96), but not with the composite outcome of death or hospitalization (univariate HR=0.98, 95% CI: 0.96 – 1.00; adjusted HR=0.99, 95% CI: 0.96–1.00). There were no significant relationships between a 3-point increment in PAM score and any of the secondary outcomes in univariate and adjusted analyses.

Conclusions: In a cohort of prevalent, in-center HD patients, low activation was associated with mortality but not with hospitalization or measures of non-adherence.

Funding: Private Foundation Support

TH-OR42

Self-Efficacy and Social Support Determine Self-Reported Health in Hemodialysis Patients

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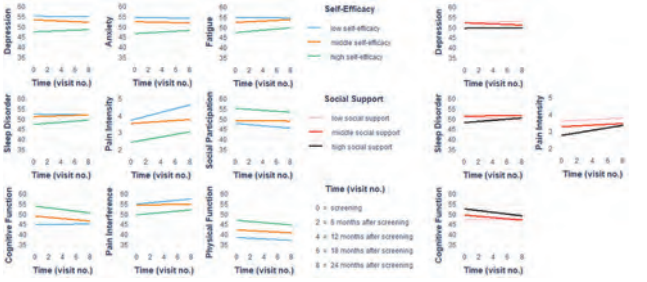
Background: Patients with kidney disease receiving dialysis are a highly vulnerable population. There is some evidence from small studies that Health-Related Quality of Life (HRQL) in these patients is influenced by psychosocial determinants, but their relevance for clinical outcomes is debated. We investigated whether Self-Efficacy (SE) and Social Support (SS) can explain differences in HRQL outcome domains over time in hemodialysis patients.

Methods: HRQL in 1264 participants from the CONVINCE randomized, controlled trial investigating hemodiafiltration versus hemodialysis were assessed, using screening and quarterly follow-up data up to 24 months. Measures included the MOS Social Support Scale, General Self-Efficacy Scale, Perceived Stress Questionnaire and PROMIS short forms for fatigue, physical function, pain interference and intensity, sleep disturbance, anxiety, cognitive function, depression, and ability to participate in social roles. SE and SS were included as independent variables and HRQL domains as dependent variables in a linear mixed effects model with random intercept and slope for SE and SS.

Results: Participants were 20-92 (M=62.33, SD=13.50) years old, 62.9% were male. Linear mixed effect regression models showed significant main effects for self-efficacy (β=.85-4.84, p<.001) on all HRQL domains. Main effects for social support were found for Cognition, Depression, Pain Intensity and Sleep (β=.27-2.17, p<.01). For time, significant main effects were found for Anxiety and Sleep (β=.56 & .50, p<.01). Significant SE x Time interactions were found for Anxiety, Depression and Sleep (β=.11-.19, p<.05). Significant SS x Time interactions were found for Cognition and Sleep (β=.17 & .18, p<.01).

Conclusions: Our results indicate that higher SE is associated with higher HRQL of dialysis patients over time. Effects of SE are larger than those of SS and larger than previously reported. This bears the chance to develop targeted psychosocial interventions to improve health outcomes when undergoing dialysis.

Funding: Government Support - Non-U.S.



TH-OR43

Impact of Conservative Management vs. Dialysis on the Survival of US Veterans with Advanced CKD

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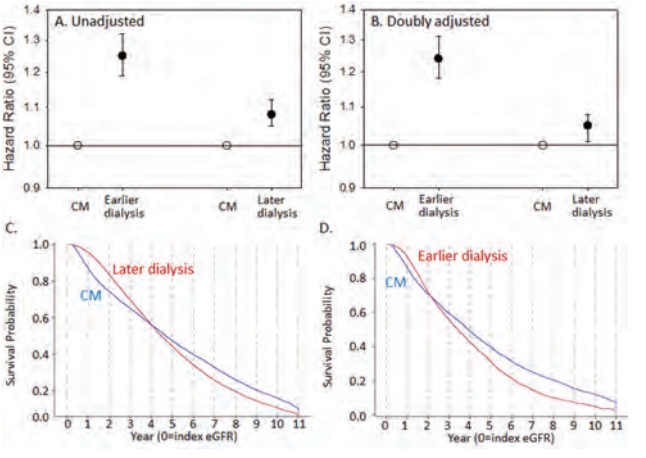
Background: Given that dialysis patients may experience high early mortality rates, healthcare utilization, and withdrawal, particularly in those of older age and multimorbidity, there has been interest in conservative management (CM) as an alternative treatment strategy for advanced CKD patients. Among a national cohort of US Veterans, we compared the impact of CM vs. dialysis on survival.

Methods: Using linked national VA, USRDS, and Medicare data, we examined Veterans with advanced CKD (≥2 eGFRs <25 separated by ≥90 days) categorized according to receipt of CM vs. dialysis (non-receipt vs. receipt of dialysis within 2-yrs of the 1st eGFR <25), with the latter group parsed into later dialysis (LD) vs. earlier dialysis (ED) (eGFRs <15 vs. ≥15 at dialysis transition, respectively). We compared survival in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio to address confounding by indication using Cox models.

Results: Among 91,598 patients who met eligibility criteria, 3628 CM patients were PS-matched to 3628 ED patients, while 9833 CM patients were PS-matched to 9833 LD patients. In PS-matched models, both ED and LD were each associated with higher mortality vs. CM: HRs (95%CIs) 1.25 (1.19-1.32) and 1.08 (1.05-1.12), respectively. Similar findings were observed in sensitivity analyses doubly-adjusted for PS covariates. When examining survival trajectories after the index eGFR date, ED and LD demonstrated worse survival vs. CM after 2-years and 4-years, respectively.

Conclusions: In a national cohort of US Veterans, earlier transition to dialysis was associated with worse survival compared to CM. Later transition to dialysis was also associated with worse survival vs. CM, albeit to a lesser degree. Further studies are needed to examine the impact of CM vs. dialysis transition on other hard endpoints and patient-centered outcomes.

Funding: NIDDK Support



TH-OR44

Encouraging a Standardized ESKD Transition Approach in a Comprehensive Kidney Care Contracting (CKCC) Program Is Associated with Increased Optimal Dialysis Starts

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Background: The standard care for chronic kidney disease (CKD) is shifting from a "fee-for-service" model that focuses on volume of care and profitability of services to a Value Based Care (VBC) model that rewards better outcomes. It is well-established that starting ESKD care with peritoneal dialysis (PD) or hemodialysis (HD) with either an arteriovenous (AV) fistula or AV graft, instead of HD with a central venous catheter (CVC), produces better mortality, morbidity, and cost outcomes. The purpose of this study was to determine if a standardized ESKD transition pathway could improve the number of optimal starts within Kidney Care Entities (KCEs).

Methods: All patients were in the Comprehensive Kidney Care Contracting (CKCC) program. The CKCC program defines an optimal start to be the initiation of dialysis without a CVC. We recorded the proportion of optimal starts and the initial modality type (HD vs PD) in adult Medicare patients at 4 geographically diverse KCEs within a single physician-led nephrology organization. Data were recorded quarterly (Q) during 2022. During Q1-Q2, patients and clinicians were formally instructed on the benefits of optimal starts only. Starting in Q3, a standardized care pathway was deployed for patients at high risk for transition to ESKD across all 4 KCEs, inclusive of electronic health record and analytics tools, and treatment teams were provided lists of patients who met the high risk criteria. The proportion of optimal starts and the proportional of initial PD from Q1-Q2 versus Q3-Q4 were compared with Student's t-test for proportions.

Results: In 2022, the 4 KCEs treated 9,099 patients with 5,457 (60.0%) having CKD. 371 patients initiated dialysis during the study period with 164 (44.2%) in Q1-Q2. The proportion of optimal starts increased from 37.2% (61/164) in Q1-Q2 to 53.1% (110/207) in Q3-Q4, p = 0.002. The proportion of PD starts increased from 11.0% (18/164) in Q1-Q2 to 26.1% (54/207) in Q3-Q4, p <0.001.

Conclusions: The deployment of a standardized ESKD transition pathway as part of an intensive VBC educational program is associated with a significant increase in both optimal starts and the number of patients starting on PD.

TH-OR45

Higher Patient-to-Patient Care Technician Ratios Associated with Worse Outcomes Among US In-Center Hemodialysis Patients

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Background: It is increasingly difficult to maintain adequate dialysis patient care technician (PCT) staffing at U.S. in-center hemodialysis (ICHD) facilities. We aimed to explore the associations of ICHD patient outcomes with facility-level PCT staffing.

Methods: U.S. patients (ages 18-100) initiating ICHD between 1/1/16 and 12/31/18 were included if they remained on ICHD for ≥90 days and had data on PCT staffing at their ICHD facility (*N*=236,126; mean age, 63.1; 57.6% male; 27.9% Black; 61.8% with diabetes; 60.2% starting ICHD with a catheter only). We estimated the association of time to 1-year patient outcomes with facility-level PCT staffing (=quartiles of patient:PCT ratios) using mixed-effects Poisson regression, with censoring as appropriate and adjustment for age, sex, race, pre-end-stage kidney disease nephrology care, diabetes, and first vascular access type.

Results: After adjustment, highest vs. lowest quartile of facility-level patient:PCT ratio was associated with 11%, 10%, and 10% higher rates of patient mortality, hospitalization, and readmission, respectively; associations with rates of waitlisting and transplant were not significant (**Figure 1**). Highest vs. lowest quartile of patient:PCT ratio was associated with 10%, 13%, and 22% higher rates of fluid overload-, sepsis-, and vascular access-related hospitalizations, respectively (**Figure 2**).

Conclusions: Patients initiating treatment in facilities with the least adequate PCT staffing may have worse early outcomes. While effects are modest and causal inference is limited, our results support further investigation of the effects of U.S. PCT staffing on patient safety and quality of U.S. ICHD care.

Funding: Other U.S. Government Support

Figure 1. Incidence rate ratios (IRRs) by quartile of patient:PCT ratio (Q2, Q3, Q4) vs. lowest quartile (Q1).

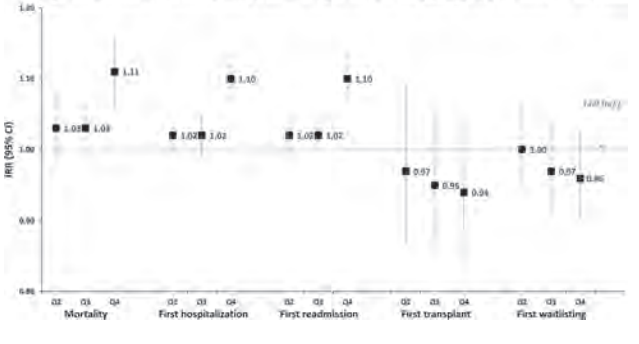
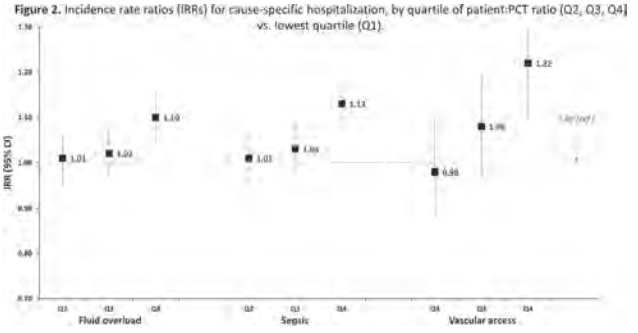


Figure 2. Incidence rate ratios (IRRs) for cause-specific hospitalization, by quartile of patient:PCT ratio (Q2, Q3, Q4) vs. lowest quartile (Q1).



TH-OR46

The Impact of Affordable Care Act Medicaid Expansions on Dialysis Facility Medicaid Enrollment and Quality Measures

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Background: The Centers for Medicaid and Medicare Services proposed using Medicare Medicaid dual eligible enrollment (DEE) to adjust for social risk in dialysis facility quality scores. Because Medicaid eligibility varies by state, in part due to variable uptake of Affordable Care Act (ACA) Medicaid expansions, we examined the extent to which dialysis facility location in an expansion state was associated with increased DEE and improved dialysis facility quality scores.

Methods: Using data from the ESRD Quality Improvement Program (QIP) and US Renal Data System, we identified a longitudinal cohort of US hemodialysis dialysis facilities with ESRD QIP data from 2012-2018. We tested whether location in an expansion state was associated with increases in the proportion of Medicaid-enrolled incident and dual-eligible enrolled prevalent dialysis patients as well as improved ESRD QIP total performance scores (TPS) and vascular access scores (VAS). We compared pre-expansion data (2012-2013) with early and late post-expansion times points (2015 and 2018, respectively). We used a difference-in-differences approach and adjusted for facility patient characteristics and area-level social vulnerabilities.

Results: Expansions were associated with increases in incident patient Medicaid enrollment in the early and late expansion periods (5.5 percentage points, 95% CI (4.6, 6.5) and 7.4 percentage points, 95% CI (6.4, 8.4), respectively) and increases in dialysis facility DEE in the late expansion period (1.3 percentage points, 95% CI (0.7, 1.9)). Facility location in an expansion state was also associated with an increase of 2.2 points (95% CI (1.3, 3.1)) in TPS in the late expansion period. Catheter measure scores were lower and fistula measure scores higher in facilities located in expansion states. There was not a clear pattern of improvement in VAS associated with expansions.

Conclusions: Dialysis facilities in states that have not implemented Medicaid expansions may experience lower growth of Medicaid enrollment due to limited Medicaid coverage available to their patients and may also have a greater decline in quality scores. Accordingly, adjustments to quality performance metrics based on DEE may favor facilities located in expansion states and further exacerbate health disparities among patients receiving dialysis.

Funding: Other NIH Support - NIH grant TL1TR002546, Private Foundation Support

TH-OR47

Roles of Matrix Metalloproteinase-2 and ETS Proto-Oncogene 1 in Rodent Arteriovenous Fistula Development

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Background: Arteriovenous fistulas (AVFs) have high rates of maturation failure with no proven effective treatments. A few clinical studies have reported that stenotic AVFs had increased expression of matrix metalloproteinases (MMPs) when compared to native veins, and post-surgery fibrosis in newly created AVFs was positively associated with maturation failure. This study therefore examined the roles of MMP-2, which is a critical MMP in vascular remodeling, and the transcription factor ETS proto-oncogene 1 (ETS-1), which is a potent pro-fibrotic factor, in AVF maturation development.

Methods: Carotid-jugular AVFs were created in global MMP-2 homozygous knockout (MMP-2 KO) mice on C57BL/6 background, with C57BL/6 mice serving as wild-type (WT) controls. Femoral AVFs were created in global ETS-1 heterozygous knockout (ETS-1 KO) rats on Sprague-Dawley (SD) background, with SD rats serving as WT controls. AVFs and contralateral non-surgical veins were harvested at 1 and 4 weeks after AVF creation for RNA sequencing (RNA-seq), histology, and morphometry.

Results: In our mouse studies, RNA-seq data indicated drastically different transcriptional profiles between non-surgical veins and AVFs at 1 week after AVF creation. Genes regulated by MMP-2 and ETS-1 were significantly enriched in AVFs. Both MMP-2 KO and ETS-1 KO had significantly increased open lumen area of the AVF veins when compapred to WT controls. In mouse studies, the percent open lumen area of

the AVF veins was significantly larger in MMP KO (39% ± 6%) vs. WT (11% ± 2%) at 1 week, as well as at 4 weeks (MMP-2 KO: 20% ± 4%, WT: 6% ± 3%) (p<0.05 for both time points). ETS-1 expression was decreased in MMP-2 KO when compapred to WT. In rat studies, the percent open lumen area of the AVF veins was significantly larger in ETS-1 KO (70% ± 9%) vs. WT (39% ± 15%) at 1 week (p=0.04) and trending larger in ETS-1 KO (52% ± 26%) vs. WT (22% ± 7%) at 4 weeks (p=0.13).

Conclusions: Our animal studies showed that inhibition of MMP-2 and ETS-1 by genetic knockout improved AVF development. Therapeutic approaches of inhibiting these molecules may enhance AVF maturation in hemodialysis patients.

Funding: NIDDK Support

TH-OR48

Long-Term Intervention Rate with Drug-Coated Balloons for Dysfunctional Arteriovenous (AV) Fistulas: Meeting KDOQI Targets in the IN.PACT AV Access Trial

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Background: A key KDOQI Guidelines target is to have ≤3 percutaneous or surgical interventions per year to maintain AV fistula (AVF) patency. We aimed to define the intervention and thrombosis rates per AVF-years through 36 months from the IN.PACT AV Access trial.

Methods: This global, 29-center, single-blinded pivotal study randomized participants with de novo or non-stented restenotic obstructive lesion(s) of upper extremity AVF 1:1 to treatment with an IN.PACT AV paclitaxel drug-coated balloon (DCB; n=170) or standard percutaneous transluminal angioplasty (PTA; n=160). Participants were followed for 36 months; intervention rates and fistula-years of use were captured and compared to KDOQI guidelines target. 36 month thrombosis rates were compared between DCB and PTA groups.

Results: Of the 330 participants randomized, 133 completed their 3-year visit. Including the index procedure, the rates of intervention ranged 1.24-2.55 per AVF-year for DCB group and 1.48-3.06 per AVF-year for PTA group (Table). The cumulative incidence rate of access circuit thrombosis at 36 months was 8.2% (10) in DCB group and 18.3% (19) in PTA group with a hazard ratio of 0.457 (95% confidence interval: 0.212- 0.983; P = 0.04).

Conclusions: The need for interventions to maintain patency and thrombosis rate was reduced with use of DCB compared with PTA at the 1-, 2-, and 3-year timepoints post index procedure for the treatment of dysfunctional AVF. At the 3-year timepoint, both DCB and PTA groups met the KDOQI targets for AVF interventions per year to maintain patency.

Number of target lesion interventions per fistula years

	IN. PACT AV DCB			Standard PTA					
Target lesion interventions	No. of events	No. of AVF years	Rate per AVF year	No. of events	No. of AVF years	Rate per AVF year	Rate ratio [95% CI]	Rate difference [95% CI]	P value
Through 180 days	202	79.1	2.55	230	75.3	3.06	0.84[0.69, 1.01]	-0.49[-1.02, 0.04]	0.069
Through 360 days	263	149.2	1.76	302	140.6	2.15	0.82[0.7, 0.97]	-0.38[-0.7, -0.06]	0.021
Through 720 days	363	266.8	1.36	395	245.4	1.61	0.85[0.73, 0.98]	-0.24[-0.46, -0.03]	0.023
Through 1080 days	424	343.0	1.24	449	303.7	1.48	0.84[0.73, 0.96]	-0.24[-0.42, -0.06]	0.009

AVF, arteriovenous fistula; DCB, drug-coated balloon; No, number; PTA, percutaneous transluminal angioplasty.

TH-OR49

Extreme Heat Exposure and Mortality Among Patients Receiving Dialysis

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Background: Patients receiving maintenance dialysis represent a population vulnerable to extreme weather events such as wildfires and hurricanes, but the dangers posed by extreme heat exposure remain to be determined.

Methods: In the United States Renal Data System, we identified adults living in US cities prone to extreme heat who initiated maintenance dialysis from 1997 to 2016. We defined an extreme heat event as a heat index of >40.6°C for ≥2 days or >46.1°C for ≥1 day. We estimated the risk of death during a heat event using adjusted Cox proportional hazards regression and tested for effect modification by age, sex, race and ethnicity, year of dialysis initiation, dialysis modality, poverty level, and climate region.

Results: Among 945,437 adults in 246 cities, the median age was 64 years and 44% were female. During a median follow-up of 3.7 years, 519,748 adults were exposed to at least one of 7,152 extreme heat events, and 530,616 deaths occurred. In adjusted models, there was an increased risk of death (HR, 1.18; 95% CI, 1.15 to 1.20) during exposure to extreme heat (Table). Relative mortality risk was higher among patients who were ≥65 years-old (P=0.003), male (P=0.04), and living in the Northern Rockies and Plains (P=0.03), Ohio Valley (P=0.02), Northeast (P=0.01), and Southeast (P<0.001). Relative mortality risk was lower among Hispanic patients (P=0.02) compared to non-Hispanic White patients (Figure).

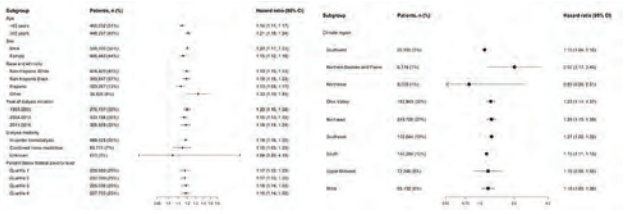
Conclusions: Patients receiving maintenance dialysis face an increased risk of death during extreme heat.

Funding: Other NIH Support - NHLBI

Risk of death with extreme heat exposure

Model	N	Deaths	Mortality HR (95% CI)	P
Unadjusted	945,437	530,616	1.16 (1.13-1.18)	<0.001
Demographics	915,268	512,445	1.18 (1.16-1.20)	<0.001
Demographics & Socioeconomic Status	915,149	512,203	1.18 (1.15-1.20)	<0.001

Demographics model adjusted for age, sex, race and ethnicity, body mass index, dialysis initiation year, dialysis modality, and climate region. Demographics and socioeconomic status model additionally adjusted for education level, poverty level, and housing cost.



Relative risk of death among subgroups accounting for multiplicative effect modification

TH-OR50

Exposure to Wildfire-Related Particulate Matter and Risk of Hospitalization and Mortality Among Hemodialysis Patients

Hyeonjin Song,[1] Nicole E. Sieck,[1] Jochen G. Raimann,[2] Peter Kotanko,[2,3] Franklin W. Maddux,[4] Evan A. Ellicott,[1] Amir Sapkota.[1] *[1]The University of Maryland, College Park, MD; [2]Renal Research Institute, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Fresenius Medical Care Holdings Inc, Waltham, MA.*

Background: Ongoing climate change is contributing to increases in frequency and severity of wildfires and the length of wildfire season. Wildfires are major sources of air pollution including fine particulate matter (aerodynamic diameter < 2.5 microns; $PM_{2.5}$) that may disproportionately impact vulnerable populations such as hemodialysis patients. We investigated the effect of wildfire-related $PM_{2.5}$ on hospitalization and mortality risk among hemodialysis patients.

Methods: We analyzed health records of 79,963 hemodialysis patients who received in-center hemodialysis treatment at 191 Fresenius Kidney Care clinics in Washington, Oregon, and California during 2005-2018. We estimated wildfire-related $PM_{2.5}$ for each of the clinics using satellite-derived smoke polygons (Hazard Mapping System) and ground-based $PM_{2.5}$ monitors (Air Quality System operated by Environmental Protection Agency). We conducted a time-stratified case-crossover analysis with a conditional Poisson model to investigate the association between exposure to wildfire-related $PM_{2.5}$ and risk of hospitalization and mortality among hemodialysis patients.

Results: The daily wildfire-related $PM_{2.5}$ concentration during the study period ranged from 0 to 551.3μg/m³ with the average of 0.7μg/m³ (SD=5.7μg/m³). A 10μg/m³ increase in wildfire-related $PM_{2.5}$ was associated with 1% higher risk of all-cause hospitalization (RR: 1.01, 95% CI: 0.99, 1.02), and 4% higher risk of all-cause mortality (RR: 1.04, 95% CI: 1.02, 1.06).

Conclusions: We observed positive associations between increases in wildfire-related $PM_{2.5}$ concentration and risk of all-cause hospitalization and mortality. Our findings highlight the need for targeted intervention, including early warnings, timely relocation of patients during wildfire events or improved air filtration systems to mitigate the adverse health effects of wildfire-related air pollution.

TH-OR51

Glycated Albumin and Adverse Clinical Outcomes in Patients with CKD

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Background: HbA_{1c} is widely used to estimate glycemia, yet it is less reliable in patients with CKD. There is growing interest in complementary use of glycated albumin (GA) to improve glycemic monitoring and risk stratification in this population. However, whether GA associates with long-term clinical outcomes in a non-dialysis dependent CKD population has not been investigated.

Methods: To determine the prognostic value of GA, we measured baseline serum GA levels in 3110 patients with CKD stages 2–4 enrolled in the prospective Chronic Renal Insufficiency Cohort study. Outcomes include 1) incident ESKD (requiring chronic dialysis or kidney transplant); 2) CVD events (a composite of myocardial infarction, congestive heart failure or stroke); and 3) all-cause mortality.

Results: Participant characteristics included mean age 59 (SD 10.8) years; 1357 (43.6%) female; 1550 (49.8%) with diabetes. The median GA was 18.7 (interquartile range, 15.8-23.3)%. During an average 7.9-year follow-up, there were 980 ESKD events, 968 CVD events, and 1084 deaths. In multivariable adjusted Cox models, higher GA levels were associated with greater risks of all outcomes in patients with CKD, regardless of diabetes status (Fig 1): hazard ratios for ESKD, CVD, and death among participants with the highest quartile compared with quartile 2 (reference) were 1.42 (95% CI, 1.19-1.69), 1.67 (CI, 1.39-2.01), and 1.63 (CI, 1.37-1.94), respectively. The associations with CVD and death appeared J-shaped, with increased risk also seen at the lowest GA levels (quartile 1 vs. reference). Among patients with coexisting CKD and diabetes, the associations of GA with outcomes remained statistically significant even after adjustment for HbA_{1c}. For each outcome, we observed a significant fraction of new prognostic information when both GA and HbA_{1c} were added to models.

Conclusions: Among patients with CKD, GA levels were independently associated with risks of ESKD, CVD, and mortality, regardless of diabetes status. GA added prognostic value to HbA_{1c} among patients with coexisting CKD and diabetes.

Funding: NIDDK Support, Private Foundation Support

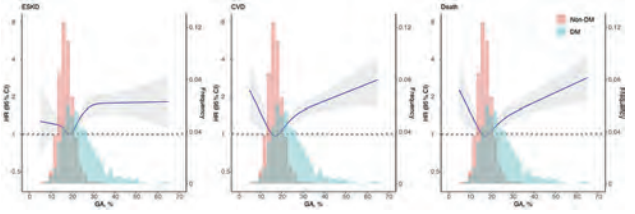

Fig 1. Adjusted HRs for GA Levels and Risks of ESKD, CVD and Death.

TH-OR52

Harnessing Kidney Transcriptome Profiles to Predict Rapid Progression of Diabetic Kidney Disease

Dianne Acoba,[1,2] Anna Levin,[3] Anna Witasp,[3] Johan C. Mölne,[4] Peter J. Greasley,[1] Jenny C. Nystrom,[5] Annika Wernerson,[3] Anna Reznichenko.[1] *[1]Research and Early Development, Cardiovascular, Renal and Metabolism, BioPharmaceuticals R&D, AstraZeneca, Gothenburg, Sweden; [2]Université Paris Cité, INSERM U1151, Institut Necker Enfants Malades (INEM), Paris, France; [3]Department of Clinical Science, Intervention and Technology, Division of Renal Medicine, Karolinska Institutet, Stockholm, Sweden; [4]Department of Laboratory Medicine, Institute of Biomedicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden; [5]Department of Physiology, Institute of Neuroscience and Physiology, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden.*

Background: Kidney gene expression has been shown to be associated with kidney function in diabetic kidney disease (DKD) patients by cross-sectional transcriptomics studies. However, how the renal transcriptome correlates to disease progression has not been established due to the paucity of longitudinal studies. We hypothesized that certain intra-kidney transcriptomic patterns associated with progressive DKD may elucidate disease drivers and predictive factors.

Methods: RNA-seq data from micro-dissected kidney biopsies and post-biopsy clinical data were available for 19 DKD patients. Patients were stratified into rapid and non-rapid progressors based on the following: eGFR decline more than ≤ -5 ml/min/year, CKD stage advancement, ≥30% UACR increase, nephrotic range albuminuria, and a composite outcome of kidney failure/≥40% eGFR loss. Gene signatures associated with rapid DKD progression were identified by differential expression (DEA), weighted gene co-expression network (WGCNA) and pathway enrichment analyses.

Results: We identified 265 statistically significant (*Padj* < 0.05) rapid progression-associated genes in the glomerular and tubulointerstitial compartments across all disease progression definitions through DEA. With WGCNA, 1 module in the glomeruli and 7 in the tubulointerstitium were found to be significantly correlated to eGFR slope ($P < 0.05$). The rapid progression-associated genes in the glomeruli were enriched for pathways linked to cell adhesion by integrins and syndecans, and signaling by NOTCH, MET and PTK2. Pathways involved in cellular response to starvation mediated by GCN2 and mTORC, SLIT signaling through ROBO receptors, and cytoskeletal reorganization were enriched in the tubulointerstitium. These pathways are less studied in the context of DKD progression and could elucidate novel disease understanding.

Conclusions: To the best of our knowledge, this study is the first to link baseline kidney compartment-specific gene expression to prospective DKD progression. We have identified transcriptomic profiles prognostic of rapid DKD progression that were distinct from those previously reported as associated with cross-sectional kidney function. Potentially, our findings can advance the understanding of DKD biology and steer towards discovery of prognostic biomarkers and therapeutic targets.

Funding: Government Support - Non-U.S.

TH-OR53

FIGARO-BM, a Biomarker Study of FIGARO-DKD, Reveals New Insights into the Mode of Action of Finerenone

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Background: Mineralocorticoid receptor (MR) overactivation contributes to tissue fibrosis and organ damage found in cardiorenal disease. FIGARO-BM is an exploratory biomarker study aimed at advancing the understanding of the longitudinal pharmacodynamic response to finerenone, a non-steroidal, selective MR antagonist.

Methods: Samples were derived from the phase III parent trial FIGARO-DKD, which investigated finerenone's efficacy on cardiorenal outcomes and safety in CKD patients with type 2 diabetes (T2D). This biomarker substudy included 945 subjects from 21 countries, overall comparable to the total population, and analyzed 2941 biomarkers in more than 4000 longitudinal post-randomization plasma samples using Olink EXPLORE proteomics. Subjects on treatment with either placebo or finerenone for at least 36 months, and alive to consent, were eligible to participate in FIGARO-BM. Biomarkers with a significant difference ($p \leq 0.05$) between treatment arms at more than one study visit (month 4, 12, 24, 36 and 48, based on a linear mixed model adjusted for gender) and with effect estimates above threshold were used for gene enrichment analysis using Metascape. Enriched terms were grouped into clusters based on membership similarities.

Results: 373 plasma protein biomarkers were modulated by finerenone treatment. Gene enrichment of the biomarker profile identified two clusters of extracellular matrix (ECM)-related pathways, involving several well-established markers of inflammation and fibrosis such as fibronectin, osteopontin, and members of the interleukin-17 family, along with novel markers of ECM remodeling. Other clusters linked directly to mineralocorticoid/aldosterone biology and diuresis reflecting target modulation.

Conclusions: For the first time, FIGARO-BM provides human biomarker evidence that finerenone acts on inflammation and fibrosis pathways, one key driver of cardiorenal disease progression in T2D. The study supports preclinical findings from animal models and provides insights to mechanisms leading to clinical benefits in a broad cardiorenal patient population. Future studies are needed to validate these findings.

Funding: Commercial Support - The study and this analysis were funded by Bayer AG, Wuppertal, Germany.

TH-OR54

Renal Effects of Empagliflozin Alone or in Combination with Semaglutide in Albuminuric Type 2 Diabetes: A Randomized, Placebo-Controlled Trial

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Background: Different mechanisms of sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 receptor (GLP-1) agonists indicate that combination therapy may have additive or synergistic effects. We investigated if combined treatment with empagliflozin (SGLT2) and semaglutide (GLP-1RA) can reduce urinary albumin creatinine ratio (UACR) compared to treatment with empagliflozin alone in individuals with type 2 diabetes and albuminuria.

Methods: Randomized, placebo-controlled, double-blind, parallel study including individuals with type 2 diabetes and albuminuria. All initiated open label empagliflozin in a run-in period of 26 weeks. Subsequently, they were randomized to subcutaneous injections of semaglutide or placebo for 26 weeks. Primary endpoint was change in UACR. Secondary endpoints were change in (1) HbA_{1c}; (2) body weight; (3) measured glomerular filtration rate (GFR); and (4) 24-hour systolic blood pressure.

Results: A total of 60 participants on empagliflozin were randomly assigned to additional semaglutide (n=30) or placebo (n=30). Mean age was 70.1 (SD 8.0) years, 22 % were female and median UACR was 128.2 [IQR 78.5-285.3] mg/g. Mean UACR change from randomization to week 52 was -15.5 ((95 % CI -34.0 to 8.0) %, p=0.17) in the semaglutide group and 14.8 ((-11.8 to 49.4) %, p=0.29) in the placebo group with a mean difference of -26.4 ((-48.2 to 4.6) %; p=0.086). The mean change in HbA_{1c} was -9.4 ((-13.5 to -5.2) mmol/mol, p<0.001) in the semaglutide group and -0.6 (-4.4 to 3.3) mmol/mol, p=0.77) in the placebo group with a significant difference between groups (mean difference: -8.8 (-14.3 to -3.3) mmol/mol, p=0.002). No difference between treatment groups in body weight (p=0.28), measured GFR (p=0.33) or 24-hour systolic blood pressure (p=0.26) was observed.

Conclusions: This randomized clinical trial could not demonstrate a significant effect of combined treatment with empagliflozin and semaglutide compared to empagliflozin alone on UACR, measured GFR, 24-hour systolic blood pressure or body weight in participants with type 2 diabetes and albuminuria. The combined treatment significantly improved glycemic control compared to treatment with empagliflozin alone.

Funding: Private Foundation Support

TH-OR55

Effects of Canagliflozin on Renal Oxygenation Evaluated Using Blood Oxygenation Level-Dependent MRI in Patients with Type 2 Diabetes

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Background: Results obtained in recent clinical trials suggest that SGLT2 inhibitors have protective effects against diabetic and chronic kidney disease, though the precise mechanisms remain largely unknown. Since the kidneys are susceptible to hypoxic damage, we hypothesized that use of an SGLT2 inhibitor improves renal oxygenation.

Methods: The effects of canagliflozin on renal oxygenation in patients with type 2 diabetes (T2D) were examined using blood oxygenation level-dependent (BOLD) MRI. Based on a method previously reported, T2* maps were generated, then primary analysis of cortical T2* values was performed using the 12-layer concentric objects (TLCO) method, while cortical oxygenation was also evaluated based on region of interest (ROI) method. The primary endpoints were change in T2* value from before (Day 0) to after the initial treatment (Day 1, about two hours after initial single dose) and also after five consecutive canagliflozin treatments (Day 5).

Results: Fourteen patients with T2D were enrolled, with median age 65.5 (interquartile range 59.0-72.0) years, body mass index 24.2 (22.3-26.7) kg/m^2, HbA1c 7.1% (6.9-7.7%), estimated glomerular filtration rate 59.2 (46.9-76.8) mL/min/1.73 m^2, and urinary albumin creatine ratio 20.5 (5.7-468.7) mg/gCr. Results with the TLCO method showed that canagliflozin treatment did not cause a significant change in T2* (mean and 95% confidential interval) from Day 0 [54.1 (51.4-56.9)] to Day 1 [55.2 (52.5-58.0)] (p=0.336) and also to Day 5 [53.4 (50.7-56.2)] (p=0.519). On the other hand, the T2* value was significantly increased from 52.8 (50.6-55.0) to 54.5 (52.3-56.9) (p=0.031) on Day 1, while no significant change from Day 0 to Day 5 [53.7 (51.5-56.0) (p=0.241)] was found with use of the ROI method.

Conclusions: The present findings indicate that canagliflozin administration may improve renal cortical oxygenation in patients with T2D.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation

TH-OR56

Insulin Resistance, Kidney Outcomes, and Effects of the Endothelin Receptor Antagonist Atrasentan in Patients with Type 2 Diabetes and CKD

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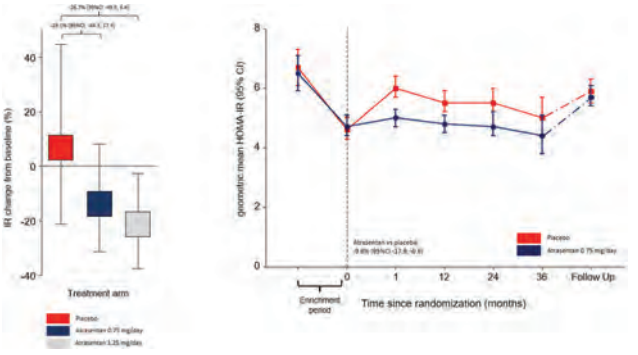
Background: Insulin resistance (IR) is a pathophysiologic hallmark of type 2 diabetes mellitus (T2DM) and associated with chronic kidney disease (CKD). Experimental studies suggest that endothelin-1 increases IR. We assessed the association between IR and cardio-renal outcomes and the effect of the selective endothelin receptor antagonist atrasentan on IR in patients with T2DM and CKD.

Methods: We used data from the RADAR and SONAR trials that recruited participants with T2DM and CKD [eGFR 25–75 mL/min/1.73 m2, urine albumin-to-creatinine ratio of 300–5000 mg/g]. IR was calculated using the homeostatic model assessment (HOMA-IR). The association between HOMA-IR and the pre-specified cardio-renal outcomes was assessed using multivariable Cox proportional hazards regression, and effects of atrasentan on HOMA-IR by a linear mixed effect model.

Results: In the SONAR trial, each log-unit increase in HOMA-IR was associated with an increased risk of the composite cardio-renal outcome [hazard ratio 1.32 (95%CI 1.09,1.60; p=0.004)], kidney outcome [hazard ratio 1.30 (95%CI 1.00,1.68; p-value = 0.048)], and the kidney or all-cause mortality outcome [hazard ratio 1.25 (95%CI 1.01,1.55; p-value = 0.037)]. After 12 weeks' treatment in the RADAR trial (N=123), atrasentan reduced HOMA-IR compared to placebo [0.75 mg/d 19.1% (95%CI -17.4, 44.3) and 1.25 mg/d 26.7% (95%CI -6.4, 49.5)]. In the SONAR trial (N=1914), long-term treatment with atrasentan 0.75 mg/day compared to placebo reduced HOMA-IR by 9.6% (95%CI 0.6, 17.9).

Conclusions: More severe IR is associated with increased risk of cardio-renal and mortality outcomes. The endothelin receptor antagonist atrasentan reduced IR, which may translate into clinical kidney benefits.



Atrasentan reduces insulin resistance. *Panel A*: Change from baseline in HOMA-IR in the RADAR trial. *Panel B*: Geometric mean HOMA-IR values per study visit in the SONAR trial.

TH-OR57

Single-Nephron Dynamics in Patients with Overt Diabetic Nephropathy

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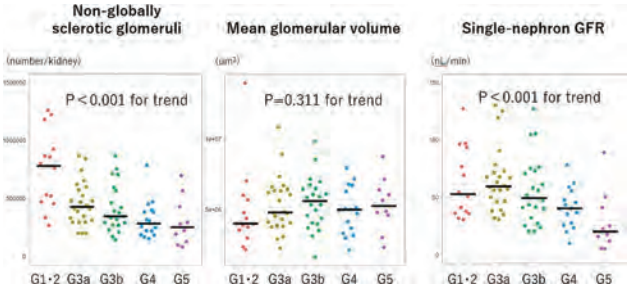
Background: In diabetic nephropathy (DN), total glomerular hyperfiltration is observed from early stage of the disease, and glomerular filtration rate (GFR) decreases with a marked increase in albuminuria, leading to renal failure. In the clinical course of such overt DN, the single-nephron GFR (SNGFR) is thought to be dysregulated with a decrease in the number of functioning nephrons. However, the single-nephron dynamics has not been studied in human DN due to technical difficulties. We applied novel methodology to explore single-nephron dynamics in DN.

Methods: The number of non-globally sclerotic glomeruli (N_{NSG}) per kidney was estimated using cortical volume assessment via unenhanced computed tomography and biopsy-based stereology. Mean glomerular volume (MGV) was calculated from the measured area of glomerular tufts. SNGFR and single-nephron urinary protein excretion (SNUPE) was calculated by dividing estimated GFR and UPE by the total number of N_{NSG} per body (per kidney x 2). Single-nephron parameters (MGV, SNGFR and SNUPE) were compared among CKD stages.

Results: This study included 86 patients with DN evaluated at kidney biopsy (median age 55 [quartile 46-67] years, 84% male, HbA1c 6.6 [5.9-7.3] %, 53% with nephrotic syndrome, and 64% on renin-angiotensin-system inhibitors prebiopsy). CKD stage were 16% CKD1+2, 28% CKD3a, 25% CKD3b, 19% CKD4, and 12% CKD5. With advancing CKD stage, sclerotic glomerular lesions increased, whereas N_{NSG} decreased from median 780,900 to 251,200 per kidney. In contrast to the higher MGV and elevated SNUPE, SNGFR was markedly decreased in patients with advanced CKD (**Figure 1**).

Conclusions: Despite residual glomerular hypertrophy, the progressive decrease in SNGFR with decreased number of functioning nephrons in advanced stage DN suggests glomerular filtration failure due to progressive glomerulosclerotic lesions and reduced filtration surface.



TH-OR58

Implementation of a Kidney Screening Intervention to Improve Early CKD Detection in Type 2 Diabetes (T2D)

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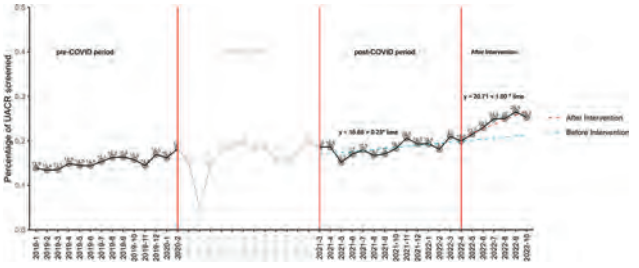
Background: American Diabetes Association and KDIGO guidelines recommend annual screening with UACR and eGFR in patients with T2D. To improve screening, we implemented clinical decision support (CDS) in April 2022 at University of Virginia Health System (UVA), including: (1) auto-enrollment of primary care patients with T2D in the EPIC health maintenance plan; and (2) prompting one-click ordering of the Kidney Profile (KP; panel including UACR and eGFR) or UACR alone, as needed, to satisfy screening.

Methods: We assessed effectiveness of the CDS by comparing screening across 3 periods (pre-COVID control: Jan 2019-Feb 2020; post-COVID control: Mar 2021- Apr 2022; post-CDS: May 2022 - Oct 2022) for all non-acute office, nursing and telehealth encounters in UVA primary care for T2D patients aged ≥22 years. Encounters with a coded diagnosis of CKD in the prior 4 yrs or fully screened for CKD in past 365 days were excluded. Orders for UACR testing within 30 days constituted screening. Rates were aggregated by calendar months and compared via interrupted time series. Sensitivity analyses included all primary care encounters during this period.

Results: There were 59,147 encounters (24,242 pre-COVID control; 23,413 post-COVID control; 11,492 post-CDS). The screening trend in both control periods was similar, therefore only the post-COVID control was considered further. Demographics, encounter types, and clinic distribution were similar in the control and post-CDS periods. There was no immediate impact on screening (p=0.4), but screening accelerated post-intervention (p=0.003, Figure). Results were similar if all primary care encounters were included (e.g., inclusive of acute visits).

Conclusions: Roll out of CDS coincided with acceleration of the screening rate for CKD among adult patients with T2D. These results suggest that simple CDS may be an effective intervention to promote annual CKD screening.

Funding: Other U.S. Government Support



Screening rates by month pre/post intervention. Blue line depicts the control rate of screening. Red line depicts observed screening after the intervention.

TH-OR59

Effects of GLP-1 Receptor Agonist Dulaglutide on Profile of Circulating miRNAs Associated with ESKD in Type 2 Diabetes

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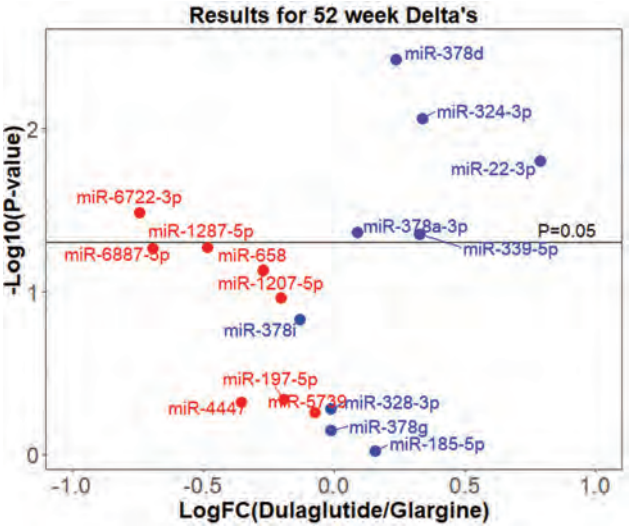
Background: Glucagon-like peptide-1 (GLP-1) receptor agonists have been shown to slow kidney function decline in patients with type 2 diabetes (T2D), but the underlying mechanism remains unclear. Circulating microRNAs (miRNAs) are short non-coding RNA molecules known to regulate proteins. Previously, we identified 17 plasma miRNAs (8 risk and 9 protective) that were predictive of end-stage kidney disease (ESKD) in T2D patients (Satake et al. JASN 2022). In this study, we investigated the treatment effect of the GLP-1 receptor agonist, Dulaglutide on longitudinal changes in plasma concentrations of these miRNAs in patients enrolled in the AWARD-7 trial.

Methods: Plasma samples were obtained from T2D patients with chronic kidney disease (CKD) stages 3-4 who received Dulaglutide 1.5 mg (n=29) or insulin Glargine (n=31) for 52 weeks. Using the HTG edgeSeq platform, we measured 17 ESKD-associated miRNAs at baseline and 52 weeks. Fold change (FC) values were calculated for each patient and each miRNA by dividing the concentration of miRNA at 52 weeks by its concentration at baseline.

Results: Comparing the FC values between Dulaglutide and Glargine groups, we observed that the plasma concentration of protective miRNAs (in blue) increased during Dulaglutide treatment, and 5 of them (miR-378d, -324-3p, -22-3p, -378a-3p and -339-5p) showed statistically significant increases (P<0.05). The plasma concentrations of all risk miRNAs (in red) were reduced with Dulaglutide treatment, but only the reduction of miR-6722-3p reached statistical significance (Figure).

Conclusions: Treatment of T2D patients with stage 3-4 CKD with Dulaglutide altered the profile of circulating miRNAs associated with ESKD, resulting in increased concentrations of protective miRNAs and decreased concentrations of risk miRNA in circulation.

Funding: NIDDK Support



TH-OR60

Earlier Intervention in Diabetic Kidney Disease Management Using the In Vitro Diagnostic Test PromarkerD Shows Economic Health Benefits over Current Standard of Care

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Background: Diabetic kidney disease (DKD) is present in 1 in 3 people with type 2 diabetes (T2D) and is the leading cause of end-stage renal disease (ESRD). PromarkerD is a newly developed biomarker-based blood test that predicts risk of DKD in people with T2D. Recent studies have shown the clinical benefit of early intervention with sodium glucose cotransporter-2 inhibitors (SGLT2s) in DKD management for patients with no or early-stage kidney disease. This study aimed to assess the consequent economic health benefit of earlier introduction of SGLT2s resulting from a proactive testing regime using the PromarkerD test versus current standard of care (SoC).

Methods: A ten-year model was developed according to the International Society of Pharmacoeconomics and Outcomes Research (ISPOR) guidelines to evaluate potential net savings from introducing PromarkerD testing versus SoC in a hypothetical cohort of 1 million people with T2D. Model inputs included costs and frequency of testing, costs associated with initiation of SGLT2s, and cost-savings from slowed DKD progression and averted renal replacement therapy for ESRD (dialysis and kidney transplants).

Results: PromarkerD testing could produce net savings for US payers exceeding $10 billion USD per one million people with T2D over the ten-year time horizon. In the baseline case, the total annual savings equal the costs after four years. Savings increase exponentially in subsequent years, significantly outweighing the associated costs compared to the current SoC without PromarkerD testing. The breakeven point occurs after six years, after which the total savings are greater than the total costs. Significant savings arise from slowing the progression of DKD, against costs from the use of SGLT2s and cost of PromarkerD testing over 10 years.

Conclusions: Earlier intervention with SGLT2s following implementation of the PromarkerD test could result in substantial savings to US payers in the management of DKD. PromarkerD testing would enable earlier intervention for those at high risk of DKD, before progression to more costly later stage disease requiring renal replacement therapy, as well as reduce unnecessary treatment in those at low risk.

Funding: Commercial Support - Proteomics International

TH-OR61

ApoA4 Mutations Cause Autosomal Dominant Tubulointerstitial Kidney Disease with Medullary Amyloidosis

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Background: We describe for the first time mutations in the *APOA4* gene as a cause of inherited kidney disease.

Methods: Whole genome sequencing was performed in 5 members of a large family with autosomal dominant tubulointerstitial kidney disease(ADTKD), and we then screened other ADTKD families in our registry for mutations in the identified gene.

Results: There was an ~15 megabase shared genomic region on chromosome 11 (chr11: 110012896- 124998347) with only one relevant candidate variant chr11:116692578 G>C (hg19) encoding for a missense mutation in *APOA4* (NM_000482.4): c.196C>G (p.L66V). Using Sanger sequencing and segregation analysis, we genotyped 19 individuals from the family. Of 12 genetically affected individuals (10 genotyped and two obligate heterozygotes), 10 had CKD, with two females being as yet clinically unaffected. Of nine genetically unaffected, the lowest eGFR was 59 ml/min/1.73m^2 at age 69. Screening families from our ADTKD registry, we identified two other distantly related families with the same variant and two distantly related families with a chr11:116693454 C>T (hg19) variant encoding the missense mutation p.D33N. All 31 clinically affected individuals suffered from CKD without proteinuria and a bland sediment and carried their familial pathogenic *APOA4* mutation. The mean age of end-stage kidney disease was 72.7±10.2 for the p.L66V mutation and 58.2±11.1 for the p.D33N mutation (p=0.009). In an individual with the p.L66V mutation, pathologic examination of a nephrectomy specimen revealed marked medullary amyloid deposition, with mass-spectrometric analysis revealing the p.L66V ApoA4 protein as the predominant constituent. Four kidney biopsies containing only cortical tissue revealed no cortical amyloid deposition, while another biopsy containing cortex and medulla showed medullary amyloid deposits but no cortical amyloid deposits. In summary, ApoA4 mutations may lead to marked medullary amyloid deposition and ADTKD.

Conclusions: For the first time, we identified mutations in the *APOA4* gene as a cause of ADTKD. *APOA4* mutations result in medullary ApoA4 deposition, which can be missed on routine kidney biopsies that only sample the renal cortex.

Funding: Private Foundation Support

TH-OR62

Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Stimulates Autophagy and Restores Mitochondrial Homeostasis to Treat Uromodulin-Associated Nephropathy

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Background: Autosomal dominant tubulointerstitial kidney disease due to uromodulin mutations (ADTKD-*UMOD*), a leading hereditary kidney disease, has no targeted therapies. UMOD is expressed in the thick ascending limb (TAL) tubules, and p.H177_R185del in-frame deletion is the most prevalent human mutation.

Methods: CRISPR/Cas9 was utilized to generate an ADTKD-*UMOD* mouse model carrying *Umod* p.Y178_R186del, analogous to human H177_R185del. To assess the functional role of mesencephalic astrocyte-derived neurotrophic factor (MANF) in ADTKD, inducible tubular cell-specific MANF transgenic and TAL-specific MANF knockout mice were generated. Meanwhile, stable HEK cell line harboring WT or H177_R185del was established. RNA sequencing was performed on isolated TAL cells. Immunoblot, q-PCR, immunofluorescence staining and electron microscopy were employed. Mitochondria function was assessed by Oroboros high resolution respirometry and mitochondrial ROS was monitored by ^{68}Ga-Galuminox PET/CT in live animals for the first time.

Results: Mutant TALs exhibit impaired autophagy/mitophagy and mitochondrial dysfunction. Subsequently, mitochondrial DNA leaking to cytosol leads to activation of stimulator of interferon genes (STING) signaling, inflammation and renal fibrosis in *Umod* Y178-R186del mice. MANF, a novel endoplasmic reticulum stress-regulated secreted protein, is induced in the mutant TALs. Genetic ablation of MANF in the mutant TALs worsens autophagy and mitochondrial failure and exacerbates kidney fibrosis. Most importantly, inducible tubular overexpression of MANF after the onset of disease stimulates autophagy/mitophagy and kidney clearance of mutant UMOD, as well as promotes mitochondrial biogenesis and oxidative phosphorylation through p-AMPK and downstream FOXO3 and PGC1a enhancement. Consequently, tubular MANF overexpression suppresses STING-mediated inflammation and fibrosis, thereby improving kidney function.

Conclusions: For the first time, we discover that MANF, as a novel biotherapeutic protein, can regulate organelle homeostasis and treat ADTKD, which may have broad therapeutic applications to treat various protein misfolding diseases.

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

TH-OR63

Inactivation of Ire1alpha Endoribonuclease Domain Slows Down ADPKD in Orthologous Mouse Models

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Background: The Ire1alpha-XBP1 pathway is the most conserved UPR branch from yeast to mammals. Our previous studies (abstract WCN23-2042) showed that genetic inactivation of XBP1 leads to significant improvement in disease severity in neonatal and adult Pkd1-dependent ADPKD mouse models through specific apoptosis of cystic cells. The endoribonuclease domain of Ire1α splices an intron from the XBP1 mRNA leading to the formation of active XBP1 which acts as a transcription factor to mitigate ER stress. Here we investigated whether a point mutation in the endoribonuclease domain of Ire1alpha can recapitulate the genetic XBP1 inactivation rescue in the context of orthologous ADPKD mouse models.

Methods: We generated an in vivo Ire1alpha endoribonuclease dead point mutation (K907A) via CRISPR/Cas9. We crossed the Ire1alpha mutant with Pkd1 deficient early and adult models and assessed the impact on disease severity via morphological and functional parameters. Finally, we examined the effect of XBP1 inactivation in bile ducts in polycystic liver disease models due to polycystin-1 deletion.

Results: We confirmed that the K907A mutation in the endoribonuclease domain of Ire1alpha leads to impaired XBP1 splicing activity as seen via western blotting. We generated Ire1alpha ^{K907A} animals and confirmed homozygous embryonic lethality. We then used Ire1alpha $^{K907A/flox}$ animals and crossed them with either Pkd1$^{flox/flox}$;Pkhd1-Cre (early model) or Pkd1$^{flox/flox}$;Pax8^{rtTA};Tet-OCre (adult model) mice to generate experimental Ire1alpha$^{K907A/flox}$;Pkd1$^{flox/flox}$;Pkhd1-Cre or Ire1$^{K907A/flox}$;Pkd1$^{flox/flox}$;Pax8^{rtTA};Tet-OCre mice. The mice showed significantly improved kidney to body weight ratio (KW/BW) compared with the Pkd1-SKO mice (0.095±0.011 vs 0.136±0.022, **p=0.008, early model; 0.088±0.031 vs 0.149±0.043, *p=0.027, adult model). Finally, when XBP1 was inactivated concomitantly with Pkd1 in bile ducts using Ubc-Cre, a dramatic impact on cystic disease severity was observed compared with the single Pkd1 KO animals.

Conclusions: Our results demonstrate that specific inactivation of the Ire1alpha endoribonuclease domain upstream of XBP1 is beneficial in slowing down ADPKD progression. Ire1alpha endoribonuclease inhibitors may serve as potential starting points for development of ADPKD therapeutics.

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

TH-OR64

Role of ER-Mitochondria Connection in the Pathogenesis of ADPKD

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Background: Mutations in PKD1 and PKD2 gene cause ADPKD. One hypothesis states that ADPKD is a ciliopathy. We have recently demonstrated that ER-localized PC2 is also important in anti-cystogenesis via K^+-Ca^{2+} exchange for ER Ca^{2+} release. Metabolic reprogramming and mitochondrial dysfunction are important in pathogenesis of ADPKD. Mitochondrial (Mito) translocation of the C-terminal tail of PC1 (CTT) is believed important. How PC2 regulates Mito function is unknown. 3 potential mechanisms underlie regulation of Mito by PC2-mediated ER Ca^{2+} release: direct ER-Mito Ca^{2+} transfer at mitochondria-associated ER membranes (MAMs) to regulate TCA enzyme, and cytosolic Ca^{2+} regulation of PGC1α (via CaMKII) and PPARα (via myc and miR17), two master regulators of Mito biogenesis.

Methods: TricB, an ER-restricted K^+ channel mediates K^+-Ca^{2+} exchange for Ca^{2+} release as an experimental tool for role of ER-localized PC2. Oxygen consumption rate (OCR) for Mito function and transmission EM (TEM) for Mito morphology.

Results: Mito DNA mass, PPARα, PGC1α, mitofusin-2 were downregulated while myc and miR-17 were upregulated in both Pkd1- and Pkd2-cKO kidneys. OCR decreased in proximal tubules isolated from both Pkd1- and Pkd2-cKO kidneys. TEM revealed ER in close contact with Mito forming MAMs. About 25% ER membrane and 60% Mito membrane form MAMs. Mito morphology (area, cristae density, roundness, etc) were altered in Pkd2-cKO kidneys. MAM distance was increased in Pkd2-cKO, indicating reduced ER-Mito contact. In many parameters measured, changes occurred in pre-cystic as well cystic stage. In all above, the changes by cKO were reversed at least partially by transgenic expression of TricB, indicating PC2-dependent ER Ca^{2+} release is important. To further demonstrate convergence of PC1 and PC2 function in ER, transgenic TricB expression reversed cystogenesis in Pkd1-cKO mice. Interestingly, PC1-CTT translocation to Mito decreased in Pkd2-cKO, which was reversed by TricB expression.

Conclusions: Both PC1 and PC2 deficiency result in mitochondrial dysfunction. TricB is not in cilia nor Mito; complementation of the deficiency by TricB supports an important role for ER Ca^{2+} homeostasis. ER-mitochondria connection is a downstream effector for PC1 and PC2 convergence and plays an important role in anti-cystogenesis of PCs.

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TH-OR65

Organoid Xenograft Model of Polycystic Kidney Disease Reveals Context-Dependent Cross-Talk Between Primary Cilium and Autophagy in Cystogenesis

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Background: In the past few years, organoid models have been developed to study polycystic kidney disease (PKD), including those derived from human pluripotent stem cells (PSC) and adult kidney tissue. Despite successful recapitulation of tubular cyst formation *in vitro*, most organoid models of PKD rely on stress stimulation to demonstrate disease phenotypes, possibly due to the lack of native tissue microenvironment. Novel organoid models of PKD need to be developed to reveal the pathogenetic underpinnings for human PKD.

Methods: We generated kidney organoids from PKD patient induced PSCs (iPSC) and gene-corrected iPSCs, followed by engrafting these kidney organoids into the sub-renal capsule space of immunocompromised mice. Genetic editing was performed in

PKD patient iPSCs to modulate primary cilium-autophagy signaling axis, followed by organoid generation and xenotransplantation. The organoid xenografts were recovered four weeks post engraftment for phenotypic assessment and single cell transcriptomic analysis.

Results: PKD patient iPSCs-derived kidney organoids spontaneously developed tubular cysts *in vivo*, whereas gene-corrected organoid xenografts showed an absence of cystogenesis. PKD organoid xenografts showed a myriad of structural and functional abnormalities reminiscent of human PKD. In particular, cellular autophagy was significantly compromised in PKD organoid xenografts. Primary cilium ablation in PKD organoid xenografts inhibited cystogenesis, alongside an upregulation of autophagy. On the contrary, primary cilium ablation in the gene-corrected organoid xenografts induced cystogenesis, in parallel with a significant downregulation of autophagy. Employing the organoid xenograft model of PKD, we evaluated the effect of an FDA-approved drug on cystogenesis *in vivo*.

Conclusions: The organoid xenograft model of PKD recapitulates spontaneous cyst formation *in vivo*, representing a more sophisticated system for revealing novel therapeutic targets and for evaluating the clinical potential of candidate drugs.

Funding: Government Support - Non-U.S.

TH-OR66

Downregulation of O-GlcNAcylation, a Metabolic Regulator, Attenuates PKD Progression

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Background: Altered cell metabolism is an important component of autosomal dominant polycystic kidney disease (ADPKD) pathogenesis, but drivers of these alterations are not understood. The addition of O-linked b-N-acetylglucosamine (O-GlcNAc) onto protein substrates by O-GlcNAc transferase (OGT) is a nutrient-sensitive post-translational modification that integrates multiple metabolic signals. We have reported that protein O-GlcNAcylation is increased in kidneys of ADPKD patients and PKD mouse models. Thus, we hypothesize that increased O-GlcNAcylation is pathogenic in ADPKD.

Methods: We generated juvenile and adult *Pkd1* conditional knockout (cko) and *Pkd1;Ogt* double knockout (dko) mice using the HoxB7-Cre and the doxycycline-inducible Pax8rtTA;LC1-Cre recombinases (induced from 4-6 weeks of age). Juvenile and adult mouse kidneys were analyzed on postnatal day (P)14 and at 4 months of age, respectively. To identify hyper-O-GlcNAcylated proteins in PKD, immunoprecipitation and Western blot were performed on mouse renal tissue extracts. Mass spectrometry is underway to map O-GlcNAcylation sites on identified proteins. To examine mechanisms in human ADPKD, cyst-lining epithelial cells were cultured in a 3D collagen matrix and an OGT inhibitor was tested on *in vitro* cyst formation.

Results: In juvenile mice, *Ogt* deletion in *Pkd1* cko mice reduced renal cystogenesis and kidney weight:body weight ratios (KW/BW); restrained renal cilia lengths; reduced inflammation and fibrosis; increased activation of the energy sensor AMPK; and improved kidney function. Further, while *Pkd1* cko mice die between P14-P20, *Pkd1;Ogt* dko mice continue to thrive beyond 14 weeks of age. Additionally, AMPK was found to be hyper-O-GlcNAcylated at P14 in *Pkd1* cko kidneys. Similarly, in adult mice, deletion of *Ogt* in *Pkd1* cko mice reduced renal cystogenesis and KW/BW. Finally, OGT inhibition reduced *in vitro* cyst formation by cultured human ADPKD cells.

Conclusions: In PKD, protein O-GlcNAcylation, including of AMPK, is increased, and deletion or inhibition of OGT reduces cyst growth and disease severity, demonstrating that O-GlcNAcylation is an important driver of PKD progression. We propose that targeting O-GlcNAcylation may have therapeutic potential in ADPKD.

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TH-OR67

Ciliary Exclusion of ARL13B or Loss of Its GEF Activity for ARL3 Suppresses Polycystic Kidney Disease in Mice

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Background: Polycystic kidney disease (PKD) and primary cilia are intricately linked. Mutations in *PKD1* and *PKD2*, which encode for ciliary polycystin proteins, are the most common genetic causes of PKD. Mouse models predict the presence of a cilia-dependent cyst activating (CDCA) pathway that functions in cilia to drive cystogenesis in mouse models of PKD. This CDCA pathway is normally inhibited by the polycystin proteins, yet the ciliary driver(s) of cyst pathogenesis remain unknown. ARL13B is an atypical ciliary GTPase which also possesses guanine nucleotide exchange factor (GEF) activity for another ARL family GTPase, ARL3. Recent work revealed a central role of ARL13B's cilia localization in cystogenesis, yet its role in the CDCA pathway is unknown.

Methods: To directly test ARL13B's role in the CDCA pathway, we engineered two distinct *Arl13b* mutant alleles at the endogenous locus in mice: (1) *Arl13b*^{V358A}, which mutates a single amino acid in ARL13B's cilia-localization motif; and (2) *Arl13b*^{R79Q}, which prevents ARL13B's GEF activity for ARL3. ARL13B^{V358A} retains all known ARL13B biochemical functions, is stably expressed, yet is undetectable in cilia. ARL13B^{R79Q} localizes to cilia, retains its GTPase activity, yet cannot activate ARL3. Using the *Pax8*^{rtTA}*; TetO-Cre* system, we induced kidney-specific loss of *Pkd1* alone (*Pkd1*$^{fl/fl}$) or in combination with either of these alleles (*Pkd1*$^{fl/fl}$; *Arl13b*$^{V358A/fl}$ or *Pkd1*$^{fl/fl}$; *Arl13b*$^{R79Q/fl}$) in adult mice. This adult induction model allowed us to directly test ARL13B's ciliary and enzymatic roles in kidney cystogenesis *in vivo*.

Results: At 18-weeks, control mouse kidneys had a kidney weight to body weight ratio (KW:BW) of 1.39±0.04. In adult induction models, loss of *Pkd1* alone led to severe cystic kidneys with KW:BW of 9.71±1.21, while concomitant loss of *Pkd1* and ciliary exclusion of ARL13B (V358A) or loss of GEF activity for ARL3 (R79Q) suppressed the cystic phenotype caused by loss of *Pkd1* alone with KW:BW of 2.69±0.47 and 2.44±0.43, respectively.

Conclusions: In mouse models, loss of ciliary ARL13B or loss of GEF activity for ARL3 suppressed the severe cystic kidney phenotype caused by loss of *Pkd1* alone. These results reveal that ARL13B regulates the CDCA through its GEF activity. Our findings indicate that ARL13B activates a pro-cystogenic pathway, providing a mechanism that could be targeted therapeutically.

Funding: NIDDK Support, Other NIH Support - NIGMS

TH-OR68

Deletion of the Circadian Clock Gene Bmal1 in Renal Collecting Ducts Leads to Rapid Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is an inherited kidney disease characterized by progressive cyst growth from the nephrons that can lead to loss of renal function and end stage renal disease. Here we examined if disruption of the circadian clock can alter ADPKD progression. Circadian rhythms are intrinsic, cyclical ~24-hour oscillations in behavior and physiology that coordinate biological processes with the time of day. In mammals, circadian rhythms are regulated by cell-autonomous circadian clocks. BMAL1 is a transcription activator, and a core component of the circadian clock, which plays an important role in physiological rhythms including the cell cycle, metabolism, and inflammation.

Methods: To determine the effect of Bmal1 gene deletion in ADPKD kidneys, we used the Pkd1$^{RC/RC}$ mouse, a Pkd1 gene hypomorph mouse model of ADPKD. Pkd1$^{RC/RC}$;Bmal1$^{f/f}$;Pkhd1^{cre} mice (RC/RC-Bmal1KO) in which Bmal1 (*Arntl1* gene) was specifically deleted in the renal collecting ducts and connecting tubules was generated on pure C57BL6/J background and compared with wild type (WT) and Bmal1$^{f/f}$;Pkhd1^{cre} mice (RC/RC-Bmal1KO). All the mice were sacrificed at 8 months of age at noon time and kidneys were analyzed

Results: We found that the disease progressed rapidly in RC/RC-Bmal1KO mouse kidneys. At 8 months, RC/RC-Bmal1KO littermates showed significantly larger kidneys with significantly higher kidney/body weight ratio and cyst area as compared to RC/RC kidneys. In addition, we found that RC/RC-Bmal1KO kidneys had increased cell proliferation and apoptosis as indicated by higher KI-67 and TUNEL staining, respectively. Immunoblot analysis showed significantly increased expression of pro-proliferative factors in RC/RC-Bmal1KO kidneys compared to RC/RC kidneys. Bulk RNA seq analysis indicated significantly reduced fatty acid metabolism in RC/RC mice as compared to WT mice, which was further reduced in RC/RC-Bmal1KO mice.

Conclusions: These results show for the first time that disruption of the renal circadian clock is a trigger for early and accelerated disease progression in ADPKD.

Funding: NIDDK Support

TH-OR69

Ablation of Long Noncoding RNA Hoxb3os Exacerbates Cystogenesis in Mouse Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a monogenic disorder characterized by the formation of cysts in the kidney, and is primarily caused by mutations in two genes, *PKD1* and *PKD2*. Long non-coding RNA (lncRNA) are >200 bp in length, lack an open reading frame, and have recently emerged as epigenetic regulators of development and disease. The involvement of lncRNAs in ADPKD is not known.

Methods: In this study, we investigated the role of lncRNA *Hoxb3os* in ADPKD by ablating its expression in the mouse.

Results: Phenotypic analysis revealed that *Hoxb3os*-null mice were viable and had grossly normal kidney morphology. At the molecular level, *Hoxb3os*-null kidneys showed activation of mTOR/AKT signaling and subsequent increase in cell proliferation. To determine whether downregulation of *Hoxb3os* affects cystogenesis, we crossed the *Hoxb3os*-null mouse to two orthologues Pkd1 mouse models: *Pkhd1*/Cre;*Pkd1*$^{F/F}$ (rapid cyst progression) and *Pkd1*$^{RC/RC}$ (slow cyst progression). Ablation of *Hoxb3os* exacerbated cyst growth in both mouse models. To gain insight into the mechanism(s) whereby *Hoxb3os* inhibition promotes cystogenesis, we performed proteomic analysis of mTOR/AKT pathway between single knockout (*Pkd1*$^{-/-}$, SKO) and double knockout (*Pkd1*$^{-/-}$ and *Hoxb3os*$^{-/-}$, DKO) mice. Compared to SKO, DKO mice displayed increased levels of total and phosphorylated RICTOR, a protein component specific to mTORC2. This was accompanied by enhanced phosphorylation of AKT at Ser473, a known mTORC2 phosphorylation site. Physiologically, kidneys from DKO mice displayed between 40-50% increase in cell proliferation.

Conclusions: Results from this study indicate that ablation of *Hoxb3os* in mouse ADPKD dysregulated mTORC2 and exacerbated cystogenesis.

Funding: NIDDK Support

TH-OR70

Aberrant Renal Microvascular Remodelling and Impaired Blood Perfusion Occur in the Early Stages of Autosomal Dominant Polycystic Kidney Disease

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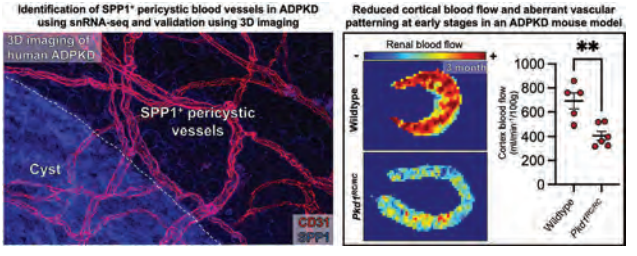
Background: The renal microvasculature is altered in autosomal dominant polycystic kidney disease (ADPKD); assumed to be a secondary consequence of expanding fluid-filled cysts. However, the vascular phenotype may be an important contributor from the initiation of PKD. Therefore, we assessed the molecular profile, structure, and function of the renal microvasculature in the early stages of ADPKD.

Methods: We amassed single nucleus RNA-seq (snRNA-seq) data of microvasculature from human ADPKD explants, validating findings using 3D confocal microscopy. A time-course of murine PKD carrying an orthologous mutation (p.R3269C) in *Pkd1* (*Pkd1*$^{RC/RC}$) was generated by assessing kidney:body weight ratio and blood urea nitrogen. Arterial spin labelling (ASL) and 3D confocal microscopy were leveraged to examine renal blood flow and microvascular structure at early (3 months) and late (9 months) timepoints in the *Pkd1*$^{RC/RC}$ murine model.

Results: A population of osteopontin (SPP1)$^{+}$ vessels was identified in pericystic regions of human ADPKD, but not in human kidney disease of other etiologies. Endothelial SPP1 was upregulated in mice at 3 months of age; long before kidney function declined in the mouse model. This was associated with reduction in renal blood flow in non-cystic regions of cortex of *Pkd1*$^{RC/RC}$ mice compared to controls at both 3 months (p = 0.005) and 9 months (p = 0.004) of age. In 3-month-old *Pkd1*$^{RC/RC}$ mice, abnormal microvascular patterning was found, including decrease in mean vessel length (p = 0.04) and increased vascular density (p = 0.01).

Conclusions: Multiple modalities applied to mouse and human tissues suggest that microvascular molecular profile, structure and function are altered in ADPKD prior to irreversible loss of renal function. Our findings advocate the renal microvasculature in ADPKD as a therapeutic target, with the potential to modulate or preserve organ function from early stages of the disease.

Funding: Government Support - Non-U.S.



TH-OR71

Live Imaging Coupled with Image-Based Machine Learning Uncovers Potential Drivers and Therapeutic Targets in a Human Model of Ischaemic Reperfusion Injury

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Background: During renal transplantation, kidneys are subjected to periods of hypoxia accompanied with nutrient deprivation, followed by reperfusion, stimulating the infiltration of immune cells into the kidney. There is growing interest in novel preservation methods to improve graft outcomes.

Methods: Primary proximal tubular epithelial cells (PTCs) were exposed to hypoxia (1% O_2) for 72 hours in Hanks Balanced Salt Solution (HBSS) to mimic nutrient deprivation, with or without foetal bovine serum (FBS). PTCs were re-oxygenated (21% O_2) in complete Dulbecco's Modified Eagle Medium (DMEM). PTCs were imaged live using deconvolution laser-scanning confocal microscopy. A supervised machine learning (ML) random forest pixel classifier was trained to extract cellular morphometrics and injury data.

Results: Nutrient deprivation was associated with greater cell death and injury independent of hypoxia and is partially ameliorated by FBS supplementation (P≤.001). Furthermore, distinct cellular morphological differences were observed between conditions, indicating specific patterns of cellular injury and death.

Conclusions: Nutrient Deprivation is associated with the greatest degree of renal tubular injury, regardless of oxygen concentration. FBS may help to reduce tubular injury in transplanted organs. Further work is required to define the protective properties exhibited by FBS. Live imaging and ML are promising modalities for exploring cell death and potential therapeutics in ischemic reperfusion injury.

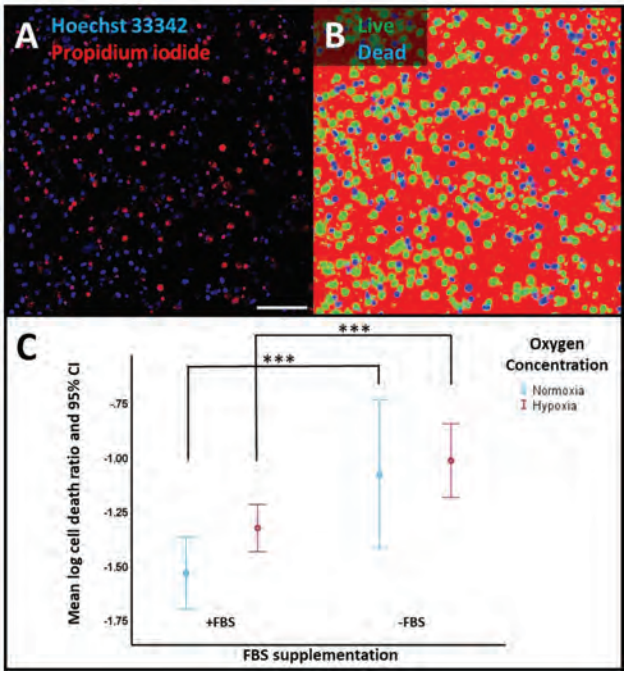

Figure 1: A) Nutrient deprived PTCs exposed to normoxia with no FBS (72h) and reoxygenated with complete DMEM (24h) B) ML mask generated from (A), C) Cell death ratios of PTCs +/- FBS generated from ML pipeline.

TH-OR72

PPARα, as a Key Determinant of Kidney Size, Revealed by Multi-Omics

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Background: Mechanisms involved in compensatory hypertrophy of the kidney remain incompletely understood. New '-omic' methodologies have been recently introduced that have the potential of identifying complex mechanisms. Here we seek to identify the earliest signaling changes in the contralateral kidney after unilateral nephrectomy (UNx) in mice using next-generation sequencing and proteomics techniques combined with lipid analysis.

Methods: Experiments were done in mice undergoing UNx and sham nephrectomy. At specific time points (24 hours and 72 hours) after surgery, the earliest portion of the kidney proximal tubule (PT-S1) was manually micro-dissected and utilized for transcriptomic analysis by single-tubule small sample RNA-Seq and single-tubule ATAC seq. Furthermore, quantitative proteomic analysis and lipid anlaysis were carried out using whole kidney.

Results: Kidney volume was already increased 24 hours after UNx, reaching a plateau at 72 hours. Quantitative morphometry in microdissected proximal tubules showed significant increases in outer diameter and mean cell volume, but no clear increase in the cell count per unit length. Measurements of DNA accessibility (ATAC-seq), transcriptome (RNA-seq) and proteome (quantitative protein mass spectrometry) independently identify patterns of change that are indicative of activation of the lipid-regulated transcription factor, PPARα. Among genes/proteins included as "Lipid Transport", Cd36, Fabp5, Atp8a1, Atp11c, Gm2a, Gramd1b, Npc2, Apoa2, Apoa4, Atg9a, Cert1, Osbpl9, Slc10a2 and Tex2 were identified as changed in our data integration analysis. Lipid analysis using gas chromatography shows an increased abundance of PPARα ligands in the hypertrophied kidney. Activation of PPARα by fenofibrate administration increases proximal tubule cell size, while genetic deletion of PPARα decreases it.

Conclusions: Compensatory growth of the kidney is associated with increased proximal tubule cell size, but not cell number. PPARα is an important determinant of proximal tubule cell size and is a likely mediator of compensatory proximal tubule hypertrophy. Early stages of compensatory hypertrophy are associated with altered fatty acid and cholesterol metabolism including anabolic pathways required for synthesis of new membranes needed for cell growth.

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TH-OR73

Spatiotemporal Immune Atlases of Two Gene-Edited, Pig-to-Human Kidney Xenotransplants

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Background: Xenotransplantation is a promising solution for the organ shortage, but enthusiasm to proceed to clinical trials is tempered by persistent knowledge gaps about the human immune response to porcine kidney xenografts and how best to control it. Preliminary data from our group and others have suggested a role for complement immune-mediated injury of the xenograft. We used state-of-the-art single-cell technologies to characterize the human immune response to porcine kidney xenografts in two brain-dead human recipients, one of whom received the C5a inhibitor eculizumab.

Methods: Kidneys from 10-gene modified pigs were transplanted into two nephrectomized brain-dead human recipients in the setting of standard immunosuppression (induction: anti-thymocyte globulin and rituximab; maintenance: tacrolimus, mycophenolate mofetil, prednisone). Decedent 2 also received eculizumab. Xenograft core biopsies were taken pre- and post-transplant (days 1, 2, and at termination on day 3) and assessed by spatial transcriptomics. Porcine and human CD45+ cells were sorted from the explanted xenograft and analyzed using single-cell RNA seq. Data were aligned to a custom porcine-human reference genome to distinguish porcine and human transcripts and analyzed using Seurat and cell2location.

Results: Human immune cells were uncommon in the xenograft biopsies; few human neutrophils and macrophages were detected 3 days after transplant. Human neutrophils were reduced by 7-fold in decedent 2. Myeloid cells were the predominant lineage in the porcine and human compartments, and both human and porcine macrophages expressed an anti-inflammatory gene signature. Notably, human B and T cells were absent in the xenograft cortex at all time points assessed in both decedents.

Conclusions: Limited human immune cells infiltrate the porcine kidney early after xenotransplantation. Eculizumab administration was associated with a decrease in neutrophils in the xenograft. These data suggest that the addition of a complement inhibitor to conventional immunosuppression may limit further innate immune cell graft infiltration in a preclinical human model of xenotransplantation. These data may help inform the immunosuppression design for upcoming clinical trials.

Funding: Commercial Support - United Therapeutics Corporation

TH-OR74

Subpopulations of Injured Proximal Tubular Cells in Allograft Kidneys: Computational Analysis of Available scRNAseq Datasets

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Background: Single-cell RNAseq has been used to investigate the cellular phenotypical landscape of allograft kidneys undergoing ischemia/reperfusion injury. Rather less attention has been paid to the proximal tubular cell (PTC) population. Here, we re-analyzed human single-cell (sc)RNAseq datasets of histologically normal and injured allograft kidneys to characterize PTC phenotypes.

Methods: We analyzed five publicly available human scRNAseq datasets, including data on histologically normal appearing kidney allografts (two datasets) and allografts with acute tubular injury (three datasets). Using R software (Seurat, DESeq2, clusterProfiler), we identified "injured" and "healthy" PTC populations, and determined their differentially expressed genes (DEGs) and enriched pathways. We compared the DEGs and pathways of "injured PTC populations" from histologically normal allografts with those of adverse allografts.

Results: In all datasets, we identified at least one healthy and one injured PTC population. The injured PTCs were characterized by the expression of established PTC injury markers (CDH6, SPP1, IL32). Most of the commonly dysregulated pathways in the injured PTCs were related to energy metabolism: fatty acid/amino acid metabolism, oxidative phosphorylation, glycolysis/gluconeogenesis. The injured PTCs in one of the two histologically normal allograft datasets presented markers of failed repair (upregulated DCDC, downregulated SLC5A12/SLC7A13). These PTCs also showed enrichment of Wnt- and Hippo-signaling pathways, previously identified in a mouse model of AKI-to-CKD progression. Although the average relative proportion of injured PTCs was lower in the histologically normal allografts (4,6% +/- 4,6%) compared to the injured allografts (15,1% +/- 9,9%), inherent inter-dataset heterogeneity did not reveal statistical significance.

Conclusions: We identified and characterized common PTC subpopulations across five allograft scRNAseq datasets. We found that histologically normal appearing allograft kidneys contain an injured PTC population, which is shared with allografts with acute tubular injury.

TH-OR75

Cold Storage-Mediated p38MAPK Activation: A Potential Contributor of Proteasome Dysfunction and Kidney Damage After Transplantation

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Background: The majority of donor kidneys require cold storage (CS) prior to transplantation, but this process usually leads to suboptimal outcomes, due to CS activating cellular pathways that damage kidney tissue. Previously, we demonstrated that the CS followed by transplantation decreases proteasome function in rat renal grafts; however, the mechanism of this dysfunction is not known.

Methods: Established in vivo (CS+Tx) and in vitro (CS+RW) models of rat kidney cold storage followed by transplantation. The proteasome function was performed using rat kidney homogenates and fluorescent-based peptide substrates. The subunit level of the proteasome subunit was characterized using renal extracts and western blotting.

Results: Western blots showed an unprecedented higher-molecular-weight band of Rpt6 subunit of the proteasome after CS+Tx, suggesting a post-translational modification (PTM) of the Rpt6 subunit. Non-denatured western blots for Rpt6 revealed aggregated proteasome levels after CS+Tx. Phosphatase treatment of renal extracts depleted the higher-molecular-weight band of the Rpt6 subunit in the CS+Tx, suggesting that the aggregation of Rpt6 was associated with phosphorylation. Renal (NRK) cells exposed to CS+RW showed a time-dependent increase p38MAPK activation. Treatment of NRK cells with p38MAPK inhibitor (SB202190 or VX-745) during CS followed by rewarming increased the cell viability and proteasome activity when compared to the CS+RW condition, suggesting p38 MAPK negatively regulates tubular cell viability during CS+Tx/RW. Finally, ex vivo treatment of the donor kidney with Bortezomib prior to transplantation (no CS) increased renal dysfunction after transplantation, suggesting normal proteasome function is needed to prevent renal injury in the transplants.

Conclusions: Together, our results suggest that CS-mediated activation of the p38MAPK may contribute to Rpt6 phosphorylation/aggregation, which then leads to decreased proteasome function and renal injury following CS+Tx. Therefore, p38MAPK could be a novel therapeutic target during CS to reduce CS+Tx-mediated graft failure.

Funding: NIDDK Support

TH-OR76

Mechanism of Cold Storage-Mediated Regulation of Heat Shock Proteins in Renal Grafts After Transplantation

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Background: Ischemia-reperfusion injury associated with cold storage (CS) followed by transplantation contributes to impaired protein homeostasis leading to kidney graft injury. However, the mechanisms of impaired protein homeostasis remain elusive.

Methods: Isolated donor rat kidneys were stored in University of Wisconsin (UW) solution at 4°C for 0- or 18-hr followed by transplantation to recipient rats (CS+Tx). To simulate in vitro model of CS+Tx, rat or human proximal tubular cells (PTCs) were exposed to UW solution at 4°C followed by rewarming (RW) at 37°C (CS+RW). RNA interference, overexpression studies, and western blotting were the key assays.

Results: Using *in vivo* and *in vitro* models of transplantation, we found that the two members of 70-KDa heat shock proteins (HSPs) were dysregulated—a robust increase of Hsp72 and a decrease of Hsc70—in kidney grafts after CS+Tx. HSF1 is a stress-activated transcription factor that induces HSPs during stress. Our data show that the HSF1 was significantly increased and modified during CS in both *in vitro* and *in vivo* transplant models, but decreases after reperfusion/rewarming episodes in kidney/renal cells. To investigate the mechanisms of excessive induction of Hsp72 after CS+Tx, the protein level of Hsc70 and/or HSF1 was modulated in PTCs, followed by CS+RW. Interestingly, Hsc70 knockdown in PTCs increased Hsp72 protein but decreased HSF1 protein. Whereas HSF1 depletion increased Hsc70 protein and did not change the Hsp72 protein level in PTCs, the double knockdown of HSF1 and Hsc70 significantly increased the Hsp72 protein levels. Finally, the HSF1 knockdown in PTCs followed by CS+RW decreased Hsc70 levels but increased the Hsp72 protein.

Conclusions: These data show a reciprocal relationship between Hsc70 and Hsp72 in PTCs and that the Hsc70 negatively regulates Hsp72 protein levels. Our data also indicated that the excessive increase of Hsp72 is not regulated by the classical HSF1 pathway, and the elevated Hsp72 protein negatively regulates kidney function after CS+Tx. Together, the results suggest Hsp72 as a potential therapeutic target during CS to improve outcomes after kidney transplantation.

Funding: NIDDK Support

TH-OR77

Evaluation of Porcine Cell Chimerism and Viral Transmission Using a Preclinical Human Brain-Dead Decedent Model

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Background: Xenotransplantation is a potential solution to the organ shortage crisis, but questions around the potential for zoonotic disease transmission need to be addressed before clinical trials can be safely undertaken. Because zoonotic transmission cannot be assessed in vitro or in preclinical animal models, we used a preclinical brain-dead

human decedent model to evaluate porcine cell chimerism in human tissues as well as the transmission of porcine endogenous retroviruses (PERVs) and porcine cytomegalovirus (PCMV) after porcine kidney xenotransplantation.

Methods: Kidneys were procured from a 10-gene modified pig, transplanted into two nephrectomized brain-dead human decedents, and followed for 3 days. Single-cell RNA seq (scRNAseq) was performed on peripheral blood mononuclear cells (PBMCs) sorted from the xenograft recipients before and after transplantation on post-operative (POD) days 1, 2, and 3. Single-nucleus RNA seq (snRNAseq) was performed on kidney biopsies collected pre-transplant and on POD 1 and 3, as well as distant tissues such as heart, lung, liver, spleen, lymph node, small bowel, and omentum upon termination of the experiment. Sequencing data were aligned to a novel PERV-PCMV-porcine-human merged reference genome to differentiate porcine and human cell types and assess for viral transcript expression. Data were analyzed using the package Seurat 4.0.

Results: ScRNAseq analysis of over 500,000 PBMCs revealed a small number of porcine cells (0.04% and 0.008%) in decedent 1 and 2, respectively, while there was no detection of porcine cells in any of the 150,000 sequenced cells from human organs. PERV-A and PERV-B (expression level range: 0.5-4) transcripts were detected in a small number of porcine kidney cells (0.79%) and within the porcine cells detectable in the human PBMCs; however, there was no detection of PERV-C. There was no detection of PERV in any of the human organs. No PCMV was detectable in any porcine or human compartment.

Conclusions: Sc- and snRNAseq can detect viral transcript expression and cell chimerism from mixed porcine-human samples. There was no detectable PERV or PCMV transmission early after xenotransplantation, but limited by the short duration of the study. Additional studies will be needed to address long-term safety profiles after xenotransplantation.

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TH-OR78

The Alteration of Monocyte Subsets and the Early Acute Rejection After Kidney Transplantation

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Background: Despite the use of recent immunosuppressive agents that mainly modulate adaptive immunity, early acute rejection (EAR) remains an unresolved problem in kidney transplantation (KT). Innate immune cells including monocyte/macrophage-lineage cells may contribute to the EAR occurrence, so we explored the population and phenotypic changes of circulating monocytes in KT recipients.

Methods: Pre- and post-KT peripheral blood mononuclear cells (PBMCs) from 60 KT recipients and 20 live donor samples were collected and analyzed by flow cytometry. Monocytes were classified into three types: classical ($CD14^{++}CD16^{-}$), intermediate ($CD14^{++}CD16^{+}$), and non-classical ($CD14^{+}CD16^{++}$) monocytes. Post-KT samples were collected at the same time as the protocol biopsy within post-operative days 14. The outcome was biopsy-proven acute rejection (BPAR) events excluding borderline T-cell mediated rejection.

Results: A total of 60 study population, BPAR was diagnosed in 10 of the KT recipients, and 7 of them received living donor KT. In recipients without EAR, the proportions of classical monocytes among $CD45^{+}$ cells were significantly increased (Fig. 1A, 8.90±5.40% vs 14.60±7.97%, p<0.001) after KT, and the proportions of non-classical monocytes were distinctly decreased(Fig. 1C, 1.45±1.70% vs 0.40±0.47%, p<0.001) after KT. In contrast, in BPAR patients, there were no significant differences in the proportions of all monocyte subsets after KT. Interestingly, the proportion of non-classical monocytes was the lowest in BPAR patients than KT recipients without rejection or kidney donors in both the pre-and post-KT periods(Fig. 1F. 0.72±0.42% vs 1.45±1.67% and 1.09±0.56% at pre-KT (p=0.150 and 0.652), 0.72±0.42% vs 0.37±0.37% and 1.09±0.56% at post-KT (p=0.035 and 0.204)).

Conclusions: Our findings suggest that changes in monocyte subsets before and after KT are associated with EAR occurrence in KT recipients. Non-classical monocytes, in particular, may play an important role in the development of EAR.

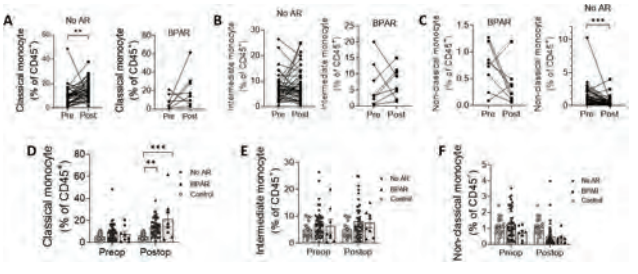

Figure 1. Changes in each monocyte subset before and after KT. (No AR; No acute rejection, BPAR; biopsy-proven acute rejection)

TH-OR79

MIF-CD74: A Novel Inflammatory Pathway that Suppresses Allograft-Infiltrating Tregs During Rejection

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Background: We previously showed that CD74, a key receptor of MIF, a pro-inflammatory cytokine, is upregulated in the urinary exosomal mRNAs of kidney transplant recipients during rejection. We investigated this pathway in allo-immunity and discovered a previously unknown critical role in suppressing immune regulation.

Methods: CD74KO (KO), and CD74fl/fl-Foxp3-GFP-Cre C57BL/6J mice were generated using CRISPR-Cas9 technology and used as recipients for fully mismatched BALB/c heart transplants. We performed single-cell and bulk RNA sequencing, CHIP-seq, immunophenotyping using flow cytometry, and various ex-vivo studies to assess the impact of the MIF-CD74 pathway on Tregs Homeostasis.

Results: CD74KO recipients of fully mismatched heart allograft displayed indefinite allograft survival with a 3-fold increase in allograft-infiltrating Tregs, compared to WT. While naïve Tregs and Tregs in the spleen of WT recipients did not express CD74, Tregs infiltrating the heart allograft and dLN and Tregs stimulated in vitro upregulated CD74 up to 5-fold. Furthermore, conditional deletion of CD74 in Tregs doubled allograft survival while resulting in a 2-fold increase in allograft-infiltrating Tregs. Moreover, compared to WT, KO Tregs displayed enhanced proliferative capacity, increased FoxP3 stability, and improved suppressive function in vitro and in vivo. Furthermore, MIF was predominantly produced by CD4 and CD8 effector cells upon antigen stimulation in vitro and in vivo. Congruently, our single-cell genomic analysis performed on allograft-infiltrating T cells endorsed the superior suppressive phenotype of CD74 deficient Tregs. While allograft-infiltrating WT Tregs had an interferon-responsive phenotype, KO Tregs had a KLRG1+Areg+ phenotype with higher Helios and PD1 expression. Our TCR clonal analysis also suggested that allograft-infiltrating KO Tregs are more antigen-specific. Furthermore, our genomic analysis revealed that Interferon Regulatory Factor 1 (IRF1), a transcriptional repressor of FoxP3, is downregulated in allograft-infiltrating KO Tregs. In vitro, MIF activates IRF1 in WT but not KO Tregs.

Conclusions: MIF produced by effector T cells in response to alloantigens negatively affects Tregs function and homeostasis via CD74 signaling. The MIF-CD74 pathway exerts this effect through IRF1.

TH-OR80

CER-001, a Recombinant HDL, Modulates Ischemia/Reperfusion Injury (IRI) in Hypothermic (HMP) and Normothermic Perfusion (NMP) Solutions Through pAKT/eNOS Activation

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Background: The growing use of expanded criteria donor leads to urgent need for efficient organ reconditioning strategies. CER-001 (Abionyx), a HDL lipoprotein particle, has shown clinical anti-inflammatory and protective vascular efficacy. This study aims to evaluate to role of CER-001 supplementation in perfusion solution to modulate IRI.

Methods: In an experimental model of donation in cardiac death (DCD), after 60 minutes of warm ischemia, pig kidneys were subjected to standard cold storage(12h). Oxygenated hypothermic and normothermic renal perfusion were carried out by PerKidney system(Aferetica) for 4h. Perfused organs were divided into the CTRL and CER-001 groups (CER-001 0.4 mg/ml) and compared to organs stored on ice (SCS). Endothelial cells exposed to H_2O_2, C5a and CER-001 (50-100 ug/ml) were analyzed by cell proliferation assay, qPCR, Western blot and FACS.

Results: During HMP and NMP treatments, resistances (mmHg/ml/min TEND CER-001 0.404 vs CTRL 0.766, change from T0, p=0.24) and flows significantly improved in CER-001 perfused group. ELISA data on perfusates showed a reduction in MCP-1, TNFα (CER-001 vs CTRL, p<0.05). In the SCS group, the tubules appeared dilated, interstitium with infiltrate, the floccule detached from the Bowman capsule. The use of CER-001 induced a reduction in the gene expression of *IL-6* and *Endothelin-1* in the CER-001 vs CTRL group. Urinary proteinuria measured during NMP was significantly decreased in CER-001 group. WB analysis revealed that CER-001 promoted the SR-BI-pAkt-eNOS pathway, the signaling pathway that through the phosphorylation of eNOS Serine 1177 lead to release of protective nitric oxide (NO). In vitro, CER-001 prevents apoptosis, endothelial dysfunction as observed by MTT and CD31/eNOS expression and reduced the levels of marker of endothelial activation (ICAM and VCAM).

Conclusions: The use of CER-001 in the perfusion liquid counteracted vasocostriction and inflammation and improved renal resistance during kidney perfusion, thereby increasing pool of organ for transplant.

TH-OR81

Chemogenetic Activation of Pericytes Alters Systemic and Renal Hemodynamics

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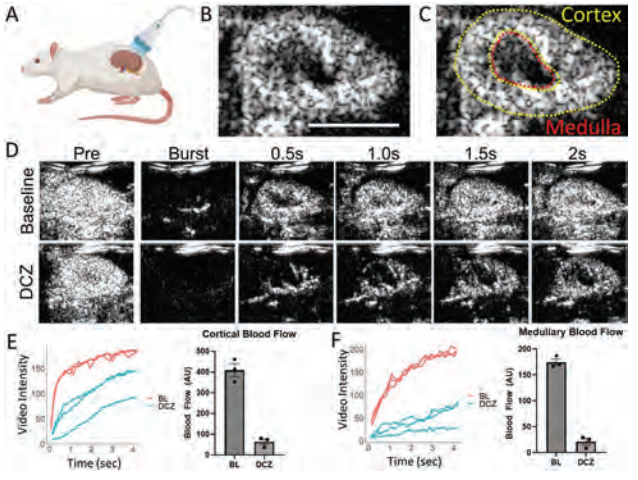
Background: Pericytes are specialized cells that wrap around capillaries to provide structural and metabolic support. Pericytes have also been shown to respond to vasoactive compounds, such as angiotensin II, to constrict capillaries. However, the full functional consequence of pericyte activation on systemic and renal hemodynamics are poorly understood. To determine whether pericytes regulate systemic or renal hemodynamics we coupled a pericyte expressing cre line (Pdgfrb-creERT2) with the Gq-DREADD (Designer Receptor Exclusively Activated by Designer Drug) mouse to create Peri-DREADD mice which have pericyte-specific activation in the presence of a DREADD agonist.

Methods: Chemogenetic activation of pericytes was induced with intraperitoneal injection of the DREADD-specific agonist deschloroclozapine (DCZ) in Peri-DREADD mice and control littermates. Activation of pericytes was determined by measurement of cFos accumulation in pericyte nuclei by immunohistochemistry. Acute blood pressures were measured with a Millar catheter. Cortical and medullary perfusion was measured by contrast enhanced ultrasound. Sodium excretion was measured from urine collected in metabolic cages followed by electrolyte quantification with flame photometry.

Results: We find that Peri-DREADD mice express DREADD protein within pericytes which accumulate nuclear cFos after activation with DCZ. DCZ treatment of peri-DREADD mice acutely increases arterial pressure and decreases medullary and cortical perfusion. Sodium excretion increases following pericyte activation by DCZ.

Conclusions: Pericytes are capable of altering hemodynamics, particularly within the kidney where we observed decreases in cortical and medullary perfusion after chemogenetic activation concurrent with an increased natriuresis that correlates with an increase in systemic blood pressure.

Funding: NIDDK Support, Private Foundation Support



Chemogenetic Activation of Peri-DREADD Mice Decreases Renal Perfusion.

TH-OR82

Piezo1 Participates the Mechanosensation of Juxtaglomerular Cells and Regulates Renin Production In Vitro and In Vivo

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Background: Renin is a key rate-limiting enzyme in RAS system, which is closely related to water and salt metabolism and the development of cardiovascular diseases such as hypertension. The synthesis and secretion of renin in juxtaglomerular (JG) cells are closely regulated by the blood pressure. To date, however, the molecular identity through which JG cells respond to the blood pressure remains unclear. Recent studies identified the nonselective cation channels Piezo1 as a novel mechanosensitive ion channel which plays an important role in various physiological functions. However, whether Piezo1 channels regulates renin expression remains undetermined.

Methods: In this study, we determined the expression and subcellular localization of Piezo1 in JG cells by qPCR, Western blot, Immunohistochemistry. Then, a Fluo-4 AM-based calcium-imaging system was used to detect the dynamic changes of intracellular calcium in response to Piezo1 specific agonist Yoda1 and mechanical stress (MS)-induced by perfusion. Piezo1 knockout JG cells abolished Yoda1-induced effect. Then, we used RNA-seq experiment to investigate the downstream signaling of Piezo1 in JG cells. Finally, we generated adeno-associated virus (AAV)-mediated kidney-specific Piezo1 knockdown mice to investigate the in vivo effect of Piezo1.

Results: We found that the calcium permeable ion channel Piezo1 was expressed in JG cells in mouse kidney slides as well as mouse JG cells. Activation of Piezo1 by its agonist Yoda1 and MS induced an intracellular calcium increase and reduced the expression of renin in these cells, while knockout of Piezo1 in JG cells abolished the effect of Yoda1. Mechanistically, RNAseq assay demonstrated that activation of Piezo1 upregulated the PTGS2 expression via the calcineurin-NFAT pathway and increased the production of PTGS2 (COX-2) and PGE2 in JG cells, which inhibited cAMP production and reduced renin expression in JG cells. In animal models, we demonstrated that activation of Piezo1 significantly downregulated the blood pressure in wildtype but not kidney-specific Piezo1 knockdown mice.

Conclusions: In summary, these results revealed that activation of Piezo1 could regulate the renin expression *in vitro* and *in vivo*, subsequently reduction of blood pressure, highlighting its therapeutic potential as a drug target of the renin-angiotensin system.

TH-OR83

Cellular-Level Transcriptomics and Three-Dimensional Imaging for Recruited Renin Cells

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Background: Renin synthesis is tightly regulated by the ability of juxtaglomerular cells (JG) to sense arterial pressure signals. Once severe hypotension occurs in adult animals, JGs promote renin synthesis first. Subsequently, a subset of vascular smooth muscle cells (VSMC) derived from renin progenitors turn on renin expression to restore homeostasis: this phenomenon is termed recruitment. However, identifying the mechanisms of the recruitment of renin lineage cells has been challenging due to their rarity and structural complexity. In this study, we investigated the transcriptome profiles and expression patterns of individual recruited renin cells by single-cell RNA-seq and three-dimensional (3D) imaging.

Methods: Since forkhead box protein D1 (FoxD1) expressing stromal cells are the progenitors for JGs and VSMCs of the renal arteriole, we generated *FoxD1-GC; R26R*^{TdTomato} mice, where all *FoxD1*$^{+}$ descendants express tdTomato reporter. We applied a surgical model of aortic coarctation (AoCo) between the base at the renal arteries of the left kidney (LK) and right kidneys (RK) that received low and high perfusion pressure, respectively. We FACS sorted tdTomato^{+} cells from the LK and RK cortices and performed single-cell RNA-seq to analyze the differentially expressed genes (DEG) and the gene ontologies between LK and RK. To visualize renin-expressing cells in 3D, we applied the clear, unobstructed brain/body imaging cocktails (CUBIC) protocol for clearing kidneys of the *Ren1*^{c}*-tdTomato* mice that underwent AoCo surgery. We used Zeiss Lightsheet7 for 3D imaging.

Results: By single-cell RNA-seq, FoxD1^{+} cells were clustered into JG, VSMC, and other cell types. DEG analysis in LK compared to RK showed that *Ren1* was the upregulated DEG in JG and VSMC. In VSMC, gene ontology analysis showed the upregulation of the cellular response to laminar fluid shear stress pathway in LK, suggesting that extracellular force changes affect the gene expression. By CUBIC protocol, renin-expressing cells in the *Ren1*^{c}*-tdTomato* mouse kidneys could be visualized in 3D. In LK, we could identify recruited VSMCs forming a stripped and ring pattern along with afferent arterioles, some extending close to or beyond the bifurcation point.

Conclusions: Severe hypotension causes the widespread recruitment of renin lineage VSMCs in the renal arteriole.

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TH-OR84

Identification and Characterization of a Vascular Calcification Mediator Originating in the Adrenal Glands

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Background: Patients undergoing dialysis for chronic kidney disease (CKD) often suffer from vascular calcification, leading to diverse cardiovascular complications. In this study, we conducted a comprehensive investigation to identify and characterize a newly discovered endogenous peptide that plays a regulatory role in vascular calcification processes. Our findings shed light on an unexplored cardioprotective function of the adrenal glands in the context of CKD-associated vascular calcification.

Methods: Chromatographic fractions derived from bovine adrenal glands were tested for their effect on vascular calcification processes using in vitro, ex vivo, and in vivo rat model of elastocalcinosis. To identify potential mediators, mass spectrometric analysis was conducted, and the results were compared with relevant databases.

Results: A 19-aa peptide was discovered and its levels were quantified in the serum of end-stage renal disease patients undergoing dialysis, as well as in matched controls. This newly identified peptide, named Calcification Blocking Factor(CBF), demonstrated significant protective effects against vascular calcification. Treatment with CBF effectively reduced the calcium content in cells, thoracic aortic rings cultured under calcifying conditions, and aortas from elastocalcinosis animal models. CBF exerts its protective effects by inhibiting the transdifferentiation of aortic smooth muscle cells into osteoblast-like cells, which are responsible for driving the progression of vascular calcification. CBF interacts with the sodium-dependent phosphate transporter PIT-1, and hinders NF-κB activation and the BMP2/p-SMAD pathway, all implicated in vascular calcification. CBF treatment reduced arterial stiffness in elastocalcinosis animals. CKD patients, susceptible to vascular calcification, showed decreased CBF concentration in serum. The 19-amino acid peptide is derived from the enzymatic cleavage of the adrenal protein chromograninA by calpain1 and kallikrein. Further analysis revealed that a specific 6-8 amino acid sequence within the 19-amino acid peptide serves as the active site responsible for the calcification-blocking properties of CBF.

Conclusions: Our findings suggest that CBF, a novel inhibitor of vascular calcification derived from the adrenal glands, plays a crucial role in reducing the risk of vascular calcification.

Funding: Government Support - Non-U.S.

TH-OR85

Mechanisms of Vascular Pathology Following Peritonitis in Peritoneal Dialysis Patients and Therapeutic Intervention

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Background: In PD patients, CV death is 10 times more likely than in the general population and this risk further increases following each peritonitis episode. Damage-Associated Molecular Patterns (DAMPs) play a critical role in inflammatory pathologies, notably via their activation of Toll-like receptors (TLRs), but their specific role in mediating long-term vascular pathology following an infection remains undescribed.

Methods: We investigated a potential role for DAMPs in mediating long-term CV risk following peritonitis by i) characterising the long-term vascular inflammatory changes induced by peritonitis in mice, ii) identifying potential target DAMPs following peritonitis by analysis of *in vivo* and PD patients' plasma samples, iii) mechanistically characterising the potential of our selected DAMP to promote key vascular inflammatory responses by critical cell types *in vitro*, iv) demonstrating, by pharmacologic inhibition, the critical contribution of a DAMP candidate to the maintenance of vascular pro-atherogenic responses following peritonitis in mice.

Results: Bacterial peritonitis in mice was resolved in 24h but led to vascular inflammatory responses, expected to promote CVD, that were maintained up to 28 days. These included higher proportions of inflammatory leukocytes, increased cytokine levels, higher adhesion molecules, and increased blood and aortic inflammatory and atherosclerosis-associated gene expression. These findings were maintained in nephropathic animals and exacerbated in animals routinely exposed to PD fluids. In parallel to these changes, a peritonitis episode led to elevated plasma levels of a specific TLR DAMP, Calprotectin, both in animals and PD patients. *In vitro*, Calprotectin could promote typical vascular inflammatory and pro-atherosclerotic responses: monocyte chemotaxis, foam cell formation, via a reduction of cholesterol efflux by macrophages and loss of endothelial resistance. *In vivo,* Calprotectin blockade robustly inhibited the short and long-term vascular inflammatory consequences of peritonitis.

Conclusions: This study demonstrates the major role that the Calprotectin-TLR pathway plays in driving long-term vascular pathology following a peritonitis episode.

TH-OR86

Single-Cell Pathological Landscape Analysis of Vascular Calcification in CKD by Imaging Mass Cytometry

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Background: Vascular calcification (VC) is regarded as an important pathological change which associated with high mortality in patient with chronic kidney disease (CKD). It is necessary to study changes of cell communication and their PTMs in situ.

Methods: A highly multiplexed imaging mass cytometry (IMC) panel was designed to simultaneously quantify 34 biomarkers of tissues from 38 patients with CKD and 2 donors to generate 64 highly multiplexed images at single-cell resolution. All cells were divided into different cell types according to the expression of markers. Neighboring cells were defined as the top 15th nearest cells to a cell. K-means clustering algorithm was then applied to cluster cell neighborhoods into numerous community clusters (CCs). Relevant to the stage of vascular calcification by Von Kossa staining was identified as a specific target for preventing vascular calcification.

Results: 8 cell types and 16 community clusters were defined. We found that contractile VSMCs and progenitor cells decrease with progression of vascular calcification. The osteochondrogenic VSMCs showed a trend of decreasing first and then increasing, which may be caused by the proliferation of synthetic VSMCs in the early stage of calcification. At the same time, community clusters changed with progression of vascular calcification. Contractile VSMCs and osteochondrogenic VSMCs mixed community clusters decreased with the progression of vascular calcification. On the contrary, osteochondrogenic VSMCs dominant community clusters osteochondrogenic VSMCs elevated in severely calcified vessels. In addition, expression of H3K27me3 of community cluster 10 that mainly composed of osteochondrogenic VSMCs and fibroblasts decreased with the progression of vascular calcification.

Conclusions: Our findings reveal for the first time the various topological function units of VC in CKD, which also presents the single-cell pathological landscape for VC in CKD. This work highlights the potential of a community cluster with a mixture of osteogenic VSMC and fibroblasts in driving vascular calcification, which may cause by the decreasing of H3K27me3.

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TH-OR87

CKD Causes Cardiac Metabolic Remodeling via FGF23 and FGFR4

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Background: In chronic kidney disease (CKD), serum levels of fibroblast growth factor (FGF) 23 are associated with increased risks of left ventricular hypertrophy (LVH), heart failure and death. We reported that FGF23 directly induces hypertrophic growth of cultured cardiomyocytes and structural cardiac remodeling in rodents via cardiac FGF receptor (FGFR) 4. Mitochondrial dysfunction and cardiac metabolic remodeling contribute to the development and progression of LVH and heart failure. We tested the hypothesis that FGF23-FGFR4 promote cardiac metabolic remodeling in CKD.

Methods: We induced CKD in FGFR4 global knock out mice, mice with inducible cardiomyocyte-specific deletion of FGFR4 and wildtype littermates using a 0.2% adenine diet for 16 weeks. At study end, cardiac structure, function, metabolism and mitochondrial composition and function was analyzed. In neonatal rat ventricular myocytes and bioengineered cardio-bundles we studied mitochondrial respiration, substrate utilization and cellular hypertrophy in response to FGF23 and inhibition of FGFR4.

Results: CKD induced robust changes to the cardiac mitoproteome (118 of 781 proteins significantly regulated) and impairs cardiac metabolism with significant alterations in cardiac organic acids, amino acids and acylcarnitines as well as mitochondrial respiration through complex I and II. Alterations in the cardiac metabolome preceded overt signs of structural cardiac remodeling and heart failure. In mice, deletion of FGFR4 prevented cardiac metabolic remodeling, mitochondrial dysfunction and heart failure in CKD. In cardio-bundles, FGF23 transcriptionally regulated metabolism. In cultured cardiomyocytes, FGF23 impaired mitochondrial respiration and substrate utilization via FGFR4, characterized by increased proton leak (fold change ctrl vs. FGF23: 1 ± 0.48 vs 1.43 ± 0.56*) and elevated glycolysis (fold change ctrl vs. FGF23: 1 ± 0.46 vs. 1.52 ± 0.66*; *=$p<0.05$).

Conclusions: Cardiac metabolic remodeling is an early complication of CKD that contributes to LVH. Mechanistically, FGF23-mediated activation of FGFR4 causes mitochondrial dysfunction including impaired respiration and increased glycolysis. We postulate that early pharmacologic inhibition of FGFR4 might serve as novel therapeutic intervention to attenuate heart failure in patients with CKD.

TH-OR88

Left Ventricular Systolic Dysfunction in the NBCe1-B/C Knockout Mouse: A Possible Unappreciated Phenotype of Congenital Proximal Renal Tubular Acidosis (pRTA)

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Background: Congenital proximal renal tubular acidosis (pRTA) is caused by autosomal recessive mutations in the *SLC4A4* gene that encodes the electrogenic $Na^+/2HCO_3^-$ cotransporter NBCe1. Congenital pRTA is characterized by severe acidemia due to the loss of the kidney-specific NBCe1-A variant, which consequently impairs proximal tubule HCO_3^- transport. However, congenital pRTA also presents with growth retardation, intellectual disability, and ocular and dental abnormalities. Intriguingly, a mouse model lacking NBCe1-B and NBCe1-C (variants which have predominantly extra-renal expression) but with intact NBCe1-A, recapitulates the spectrum of ailments of congenital pRTA without the acidemia. No cardiac phenotype has been reported in congenital pRTA patients, however recent evidence from a virally-induced partial knockdown of cardiac NBCe1 in rats suggests that NBCe1-B is cardioprotective. Therefore, we assessed NBCe1-B/C knockout mice ($KO_{b/c}$) for signs of cardiac impairment.

Methods: Echocardiography, intraventricular pressure-volume (PV), and electrocardiogram measurements were used to assess cardiac function in vivo. Heart-weight to body-weight ratio and cardiomyocyte area were used to assess for signs of cardiac hypertrophy. The Ca^{2+}-sensitive dye Fura-2 AM and an IonOptix imaging system was used to assess Ca^{2+}-transients in isolated cardiomyocytes. Lastly, RNA-seq was used to investigate transcriptional changes in $KO_{b/c}$ hearts.

Results: We observed elevated end-diastolic and end-systolic volumes as well as a reduced left ventricular ejection fraction in $KO_{b/c}$ mice. PV loop analysis revealed reductions in load-independent contractility but not relaxation. Cardiac hypertrophy was not present in $KO_{b/c}$ mice. The QT interval was not different between genotypes, however we observed increased QT variability in $KO_{b/c}$ mice. We further found a reduction in the amplitude of Ca^{2+}-transients in cardiomyocytes isolated from $KO_{b/c}$ mice, providing an explanation for the reduction in contractility. Lastly, RNA-seq analysis revealed upregulation of gene-sets associated with membrane excitability and calcium handling.

Conclusions: We conclude that congenital absence of cardiac NBCe1-B leads to mechanical and electrical cardiac dysfunction in $KO_{b/c}$ mice that is likely driven by dysregulated cardiomyocyte Ca^{2+}-handling.

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TH-OR89

Dopamine D4 Receptor Regulates Sodium Chloride Cotransporter in Renal Distal Convoluted Tubules

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Background: Dopamine D4 receptor (D4R) is expressed in the distal convoluted tubule (DCT) and the mice lacking D4R have kidney-related hypertension.

Methods: The regulation and mechanisms of D4R on NCC were determined in D4R null mice (20 weeks-old, mixed sex) and cultured mouse distal convoluted tubule (mDCT) cells.

Results: NCC activities, measured by response to NCC inhibitor hydrothiazide (30mg/kg/day, IP, 7d), were greater in *Drd4*$^{-/-}$ mice than *Drd4*$^{+/+}$ littermates in initial 6-hrs (UNa: 513±121 vs 635±87μmol/mg of Cr, n=8) with SBP (118±5 vs 104±6 mmHg, n=8, tail-cuff) normalized on days 4-7. The renal NCC protein abundance by immunoblotting (230±51, % of control, n=4-5, same as below) and immunofluorescence was greater but ubiquitinated-NCC levels (66±13) were lower in KO than in WT mice. mRNA levels of NCC by Q-PCR and phosphorylation-NCC were not altered. NCC abundance (121±9) in KO mice remained higher than WT under the infusion of dopamine via osmotic mini-pump (1μg/kg/min, 1wk). In the mDCT cells, the immunoprecipitation of D4R with NCC was increased by PD168077. Colocalization and interaction of them was seen with confocal microscopy and confirmed by Fret.D4R-siRNA (1.5nM, 48 hrs) increased the protein expression of NCC (152±34, n=4); D4R agonist PD168077 (0-10μM, 24 hrs) decreased NCC protein abundance concentration-dependently; D4R antagonist L-745,870 (10μM, 24 hrs) had no effect but blocked the D4R agonist-mediated inhibition of NCC abundance. Total NCC (72±18) was decreased but ubiquitinated-NCC was increased remarkably (266±114) by PD168077 (10μM). PD168077 internalized NCC by membrane-biotinlaytion-method and increased the NCC colocalization with lysosomal-associated membrane protein 1. The PD168077-induced NCC decrease was reversed by lysosomal inhibitor chloroquine (20μM). 1 hr PD168077 also decreased NCC-dependent-intracellular sodium transport (74±1, n=7), which was blocked by D4R antagonist L-745,870. AT1R protein abundances (96±8, n=4), *Ncc* mRNA levels (116±13, n=9) of were not altered in D4 agonist treated cells at 24 hrs.

Conclusions: D4R inhibits NaCl transport in renal DCT by reducing NCC activity and protein abundance with promoting its internalization, ubiquitination and consequent lysosomal degradation.

TH-OR90

Targeted Antibiotic Modulation of the Gut Microbiome Ameliorates Hypertensive Organ Damage

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Background: Gut microbiota play an important role in the development of hypertension. To better understand the role of the gut microbiota in modulating hypertensive organ damage, we used narrow-spectrum antibiotics without enteral absorption to specifically deplete gram-negative or -positive bacteria in double transgenic rats (dTGR).

Methods: Four-week-old dTGR (transgenic for human renin and angiotensinogen) were treated with oral Vancomycin (Vanco), Polymyxin B (Poly) or Vehicle (Veh) for 3 weeks. Seven-week-old SD rats were included as healthy controls. Flow cytometry, echocardiography, telemetric blood pressure (BP) measurement, shotgun metagenomic sequencing, clinical chemistry, and gene expression analyses (qPCR & bulk RNAseq) were employed to analyze the microbiome, clinical and immune phenotype.

Results: Hypertensive kidney damage was ameliorated in Vanco treated dTGR, as assessed by renal *Lcn2* expression, blood urea nitrogen and albuminuria. Vanco treated dTGR had significantly decreased cardiac hypertrophy. Poly treatment showed no effect. BP levels for both antibiotic treatments were not significantly different from Veh, despite a significantly improved endothelium-dependent and –independent vasorelaxation in isolated mesenteric arteries in both treated groups. Surprisingly, Vanco treatment led to a massive increase of gram-positive *Lactobacilli*. As the microbiome and immune system are closely connected, we performed in-depth flow cytometry of immune cells isolated from the heart, kidney, blood, spleen, and intestine. We observed a broad shift to pro-inflammatory immune cell subsets in dTGR. Vanco treatment could partially rescue the kidney inflammation as observed by a reduction in Th17 cells, classical dendritic cells and tissue infiltrating monocytes. Poly treatment did not alter the inflammatory signature.

Conclusions: Modulation of the intestinal microbiome by narrow-spectrum antibiotics affects hypertensive organ damage. Depletion of gram-positive intestinal bacteria by oral Vanco ameliorates organ damage independent of BP. Our data underscores the importance of the gut microbiome in modulating hypertensive organ damage and helps to identify potential therapeutic strategies in the microbiome (e.g. *Lactobacilli*).

Funding: Government Support - Non-U.S.

TH-OR91

Performance of eGFR Equations for Drug Dosing in Kidney Transplant Recipients

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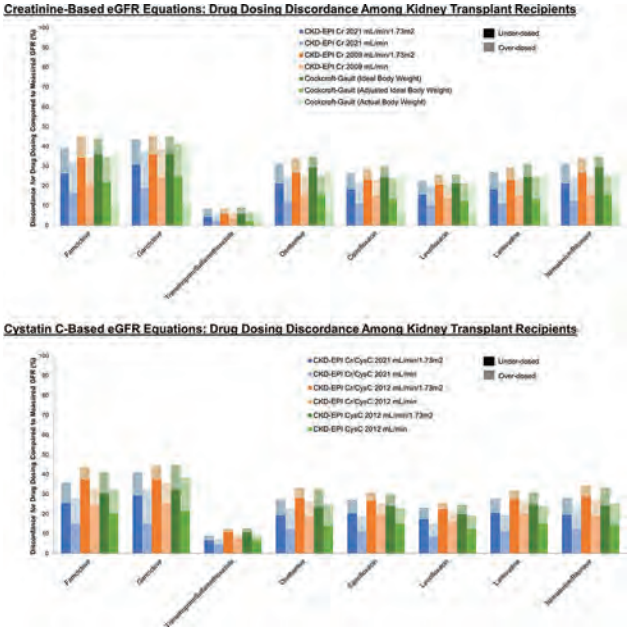
Background: For kidney transplant recipients (KTRs), drug dosing is most commonly determined by using eGFR as a surrogate for graft function. Which eGFR equation performs best for drug dosing in KTRs remains unknown.

Methods: Cross-sectional study of 415 stable KTRs from Canada and New Zealand with same-day values of serum creatinine and cystatin C along with measured GFR (^{99m}Tc-DTPA). We assessed the performance for drug dosing of CKD-EPI (both indexed to a standardized body surface area [BSA] of 1.73m^2 [mL/min/1.73m^2] and non-indexed to account for actual BSA [mL/min]) and Cockcroft-Gault (via 3 different weights: ideal, adjusted ideal, and actual body weight) eGFR equations relative to measured GFR based upon recommended renal dosing of 8 medications commonly prescribed to KTRs: famciclovir, ganciclovir, trimethoprim/sulfamethoxazole, oseltamivir, ciprofloxacin, levofloxacin, lamivudine, and nimatrelvir/ritonavir. The primary outcome was proportion of drug dosing discordance (under- or over-dosing) overall and stratified by obesity status (BMI < or ≥30kg/m^2).

Results: The non-indexed CKD-EPI equations led to a lower proportion of drug dosing discordance compared to the indexed CKD-EPI equations across all study drugs (**Figure**). The Cockcroft-Gault equations based upon adjusted ideal and actual body weight led to a lower proportion of drug dosing discordance compared to ideal body weight. These findings were most pronounced among obese KTRs. Overall, the non-indexed 2021 CKD-EPI eGFR equations showed the lowest proportion of drug dosing discordance across all study drugs.

Conclusions: When employing eGFR-based drug dosing for KTRs, actual BSA should be accounted for to mitigate the risks of under- or over-dosing. The non-indexed 2021 CKD-EPI equations provide the most accurate eGFR-based guidance for appropriate drug dosing among KTRs.



TH-OR92

Performance of Creatinine and Cystatin C-Based Equations Among Patients with Hematological or Solid Cancers: Real-World Data from a Clinical Cohort

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Background: Performance of creatinine-based eGFR equations in patients with malignancy may be worse than in the general population with implications for management including drug dosing.

Methods: We retrospectively studied all cases who had mGFR (urinary iothalamate clearance) performed at Mayo Clinic 2017-2023 and ICD codes for neoplasia (excluding in situ and benign lesions) up to one year prior to the mGFR date. Serum creatinine and cystatin C within 2 days of the mGFR were used to compute CKD-EPI 2021 eGFRcr and eGFRcrcys, and 2012 eGFRCys. Bias (absolute and % mGFR - eGFR) and P30 (% with eGFR >=30% different from mGFR) and confidence intervals (bootstrap) were computed. Analyses were stratified for cancer type.

Results: Results by cancer type are in the Table. Among 3719 patients with eGFRcr, the median bias was similar to that in the literature. Among the 522 patients with available creatinine plus cystatin C, eGFRcr had less bias but eGFRcrcys (15.5% [12.6 – 18.9]) was more accurate compared to eGFRcr (26.7% [23.1 – 30.8]) or eGFRcys (25.5% [12.6 – 18.9]). Results were similar by cancer type.

Conclusions: Our study suggests that among patients with either solid or hematological malignancies, the CKDEPI eGFRcrcys better reflects mGFR than either eGFRcr or eGFRcys. When possible, mGFR may be optimal for clinical decision making in these populations.

Table 1.

	Median Bias / CI (mL/min/1.73m2	P30 / CI (%)
Creatinine and Cystatin C available		
All patients (n=522)		
eGFRcr	-0.81 (-1.57, 0.44)	26.7 (23.08, 30.77)
eGFRcys	6.29 (4.65, 7.88)	25.5 (22.07, 29.07)
eGFRcrcys	3.06 (2.00, 4.27)	15.5 (12.60, 18.85)
Solid tumors (n=337)		
eGFRcr	-0.64 (-2.10, 0.60)	24.6 (20.24, 29.46)
eGFRcys	6.29 (4.48, 8.03)	24.3 (20.17, 29.06)
eGFRcrcys	3.16 (1.90 - 4.83)	15.7 (11.77, 19.05)
Hematological (n=185)		
eGFRcr	-1.85 (-4.24, 1.25)	31.0 (23.91, 37.21)
eGFRcys	6.18 (2.90, 9.18)	27.7 (21.2, 33.70)
eGFRcrcys	3.02 (0.95 - 5.77)	15.2 (10.07, 20.11)
Creatinine only available		
All patients (n=3719)		
eGFRcr	1.42 (0.79, 1.92)	18.0 (16.66 - 19.08)
Solid tumors (n=2039)		
eGFRcr	1.51 (0.91, 2.08)	18.4 (16.52, 20.16)
Hematological (n=1680)		
eGFRcr	1.23 (0.13, 1.92)	17.5 (15.6, 19.25)

TH-OR93

MTX652, a Novel Selective USP30 Inhibitor for the Treatment of AKI: Phase 1 Results in Healthy Subjects and Model-Driven Human Efficacious Dose Projections

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Background: New treatments are needed for AKI. Dysfunctional mitochondria in kidney tubule epithelia are key drivers of kidney injury, therefore approaches to improving mitochondrial quality may be beneficial in kidney disease. Here we describe the clinical stage molecule MTX652 (also known as MTX115652), a novel, potent and specific inhibitor of USP30, a mitochondrial deubiquitylating enzyme which naturally antagonizes ubiquitin-dependent mitochondrial quality control mechanisms. In preclinical studies MTX652 protected against tubular atrophy and fibrosis in models of ischemia-reperfusion injury and unilateral ureter obstruction at doses from 0.5 to 5 mg/kg.

Methods: We report data from a randomized, double-blind, placebo-controlled first-in human study of MTX652 with cohorts evaluating SAD/MAD, elderly subjects, relative bioavailability (capsule vs. suspension), food effect and the DDI potential with a CYP3A4 inhibitor. MTX652 was administered as a solution/suspension in seven single dose cohorts between 0.25 to 200mg and four multiple dose cohorts between 3.5 to 100mg QD for 14 days. Safety was evaluated through the review of adverse events, physical examinations, clinical laboratory tests, vital signs and electrocardiograms. A PK/PD model was constructed to predict human target engagement (TE) at exposures which were effective in preclinical models.

Results: There were no Serious Adverse Events or safety or tolerability concerns in healthy subjects. MTX652 was rapidly absorbed with a plasma half-life of 8 hours. C_{max} and AUC were dose proportional and there were no meaningful time-dependent effects on PK. Formulation (capsule) or food had no clinically relevant impact. Plasma exposures in elderly and younger adults were comparable. Simulations identified a once daily dosing regimen within the range tested in the clinic able to attain TE levels similar to those associated with maximal renal protective effects in preclinical models.

Conclusions: This is the first report of clinical data with a USP30 inhibitor. MTX652 presented an acceptable safety/PK profile in healthy subjects. PK/PD modelling enabled the selection of a safe and well tolerated dose predicted to have renal protective effects in humans. These results support further development of MTX652 as a potential therapy for AKI.

Funding: Commercial Support - Mission Therapeutics Ltd

TH-OR94

Treatment of Diuretic Resistance with a Kappa Opioid Agonist, an Inhibitor of Central Vasopressin Secretion

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Background: Prolonged use of furosemide for treatment of congestive heart failure can produce adverse effects including hypokalemia, hyponatremia, and diuretic resistance. We hypothesized that due to diuretic-induced excretion of water, increased vasopressin (AVP) secretion may be a key compensatory mechanism contributing to diuretic resistance. Since kappa opioid receptor (KOR) agonists act centrally to inhibit AVP secretion and produce water diuresis, we predicted that administration of difelikefalin, a KOR agonist, will reverse diuretic resistance to furosemide without enhancing urinary sodium/potassium excretion.

Methods: To test this, changes in 5-hr urine output (metabolic cages; no water) were measured daily in Sprague-Dawley rats following injection (9:00am) of saline (day 0) and furosemide (10 mg/kg, i.p.; days 1-5). Over days 6-10 rats were administered either, furosemide, furosemide + difelikefalin (F+D, 20 μg/kg, i.p.; days 6-10), or furosemide + tolvaptan (F+T, 1 mg/kg, i.p.) an AVP V2 receptor antagonist. After urine collection, rats received a 2nd drug treatment (2:00 pm) and were placed in home cages.

Results: Initial treatment (day 1) of rats with furosemide evoked a marked increase in urine output (V), urinary sodium excretion (UNaV), and urinary potassium excretion (UKV), with the magnitude of each greatly reduced by day 5 (day1:day5; V, 10.5±0.6 vs 5.6±0.4 ml/5hrs; UNaV, 971±55 vs 396±23 μEq/5hrs; UKV, 250±14 vs 193±20 μEq/5hrs). Over days 6-10, 5-hr urine output remained reduced throughout furosemide treatment (diuretic resistance). Combination treatment with either difelikefalin or tolvaptan over days 6-10 reversed diuretic resistance as noted by a sustained increase in V without increasing UNaV compared to furosemide alone (day 10, V; F, 5.6±0.2 ml/5hrs; F+D, 10.1±0.77 ml/5hrs; F+T, 11.1±0.9 ml/5hrs). Further, tolvaptan but not difelikefalin increased UKV over days 6-10.

Conclusions: These findings demonstrate that AVP plays a major role in mediating diuretic resistance to furosemide. Further, we show that combination therapy with a KOR agonist (difelikefalin) can reverse and potentially prevent diuretic resistance while improving loop diuretic induced hypokalemia and hyponatremia. (LSUHSC Research Enhancement Program)

TH-OR95

Cystatin C-Defined AKI in Children Treated with Cisplatin

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Background: Cisplatin chemotherapy causes acute kidney injury (AKI). Early AKI detection and mitigation may prevent long-term sequelae. Serum Cystatin C (CysC) may be an early AKI biomarker compared to SCr and is not impacted by muscle mass. We: 1) compared AKI defined by acute CysC change (CysC-AKI) to SCr-defined AKI (SCr-AKI) in children treated with cisplatin; 2) evaluated the relation of a) urine neutrophil gelatinase-associated lipocalin [NGAL] and kidney injury molecule-1 [KIM-1] with CysC-AKI and SCr-AKI and b) of CysC with SCr-AKI.

Methods: 12-centre prospective study of 159 children receiving cisplatin. Exclusions: CKD, missing CysC or baseline SCr. At early cisplatin infusions (1st or 2nd cisplatin cycle), SCr, CysC, urine NGAL and KIM-1 were measured pre-/post-infusion and at discharge. Outcomes: KDIGO SCr-AKI (yes/no). CysC-AKI was ≥1.5x rise from baseline or CysC-GFR<35ml/min/1.73m^2. We calculated kappa statistic for agreement of AKI definitions, Mann-Whitney U test to compare biomarker levels by AKI, and area under the curve (AUC) for a) NGAL/KIM-1 to predict CysC-AKI and SCr-AKI and b) for CysC to predict SCr-AKI.

Results: 154 children included (51% male, median age [IQR] 5.6 [2.4-11.7] years). SCr-AKI 7/154 (5%), CysC-AKI 25/154 (16%), 83% agreement (kappa=0.13, p=0.025). There was no significant difference in NGAL or KIM-1 concentrations by SCr-AKI or CysC-AKI at all time points (Figure1). Pre- and post-infusion NGAL performed similarly to predict SCr-AKI and CysC-AKI (Figure1). KIM-1 poorly predicted SCr-AKI and CysC-AKI (Figure1). Pre-infusion CysC had the highest AUC for predicting SCr-AKI (AUC 0.56).

Conclusions: CysC-AKI had a low level of agreement with SCr-AKI in children treated with cisplatin. CysC was not a strong predictor of SCr-AKI in this population. Future studies with more measurement time points are needed to determine if this is possibly due to earlier rise of CysC compared to SCr. NGAL and KIM-1 did not strongly predict AKI by either definition.

Figure1: Comparison of urinary biomarkers (NGAL/KIM-1) by SCr-AKI and CysC-AKI in children treated with cisplatin.

	SCr-AKI		CysC-AKI	
	No AKI	AKI	No AKI	AKI
NGAL				
Pre-Infusion	N=140	N=7	N=122	N=25
Concentration, pg/mg (median [IQR])	14.4 (30.1)	15.1 (49.8)	13.1 (35.4)	20.0 (23.3)
AUC (95% CI)	-	0.59 (0.40-0.79)	-	0.59 (0.48-0.71)
Post-Infusions	N=138	N=7	N=122	N=25
Concentration, pg/mg (median [IQR])	11.3 (23.5)	21.9 (16.2)	10.7 (27.7)	17.2 (20.8)
AUC (95% CI)	-	0.64 (0.50-0.77)	-	0.57 (0.46-0.69)
Discharge	N=136	N=7	N=118	N=25
Concentration, pg/mg (median [IQR])	15.2 (47.2)	29.8 (39.0)	15.9 (42.7)	15.8 (61.0)
AUC (95% CI)	-	0.61 (0.40-0.82)	-	0.54 (0.40-0.67)
KIM-1				
Pre-Infusion	N=140	N=7	N=122	N=25
Concentration, pg/mg (median [IQR])	397.9 (715.5)	454.4 (449.9)	434.6 (777.8)	310.7 (386.5)
AUC (95% CI)	-	0.50 (0.29-0.71)	-	0.44 (0.32-0.56)
Post-Infusions	N=138	N=7	N=122	N=25
Concentration, pg/mg (median [IQR])	230.6 (462.0)	321.1 (487.6)	246.6 (452.6)	190.9 (742.5)
AUC (95% CI)	-	0.57 (0.35-0.79)	-	0.46 (0.31-0.60)
Discharge	N=136	N=7	N=118	N=25
Concentration, pg/mg (median [IQR])	1588.6 (3579.8)	2227.1 (4858.3)	1739.3 (3790.4)	1316.7 (2396.8)
AUC (95% CI)	-	0.53 (0.29-0.77)	-	0.46 (0.33-0.59)

Abbreviations: NGAL = neutrophil gelatinase-associated lipocalin; KIM-1: kidney injury molecule-1; SCr-AKI: serum creatinine defined acute kidney injury; CysC-AKI: cysteine C defined acute kidney injury; AUC = area under the curve; CI= confidence interval; IQR = interquartile range.

TH-OR96

SGLT2 Inhibitor Protects from Repeated Low-Dose Cisplatin-Induced Chronic Kidney Damage

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Background: Cisplatin is Cognitive dysfunction is a well-known complication agent that causes a dose dependent acute kidney injury (AKI) in nearly a third of treated patients, which subsequently leads to chronic kidney disease (CKD). There are no current FDA approved medications to prevent cisplatin induced kidney damage. Sodium-glucose cotransporter 2 inhibitors (SGLT2i) reduce risk of AKI and CKD in humans, and have shown renoprotection in a single high dose experimental model of cisplatin-induced AKI. We hypothesized that SGLT2i could protect the kidney in a mouse model of repeated low dose cisplatin and cancer to better mimic the clinical scenario.

Methods: B6:129 mice with and without lung adenocarcinoma were treated with daily SGLT2i (empagliflozin or dapagliflozin) or vehicle control for 28 days beginning 1 week prior to the first dose of weekly cisplatin (7mg/kg) or vehicle control. Following the third cisplatin injection, biomarkers for kidney function, injury, fibrosis, inflammation, kidney histology and tumor growth were assessed and compared between SGLT2i and vehicle control.

Results: SGLT2i treatment attenuated cisplatin-induced alterations in kidney function and injury. Markers of kidney fibrosis including TGF-b, a-SMA, fibronectin and collagen were lower in mice co-administered SGLT2i and cisplatin as compared to mice given vehicle control and cisplatin. SGLTi did not alter tumor growth or response to cisplatin.

Conclusions: SGLTi demonstrate a beneficial effect against kidney damage in a model of repeated low dose cisplatin and lung cancer. Future studies are needed to determine if they can be used post cisplatin treatment to improve and/or prevent progression of kidney injury to fibrosis and CKD.

Funding: NIDDK Support

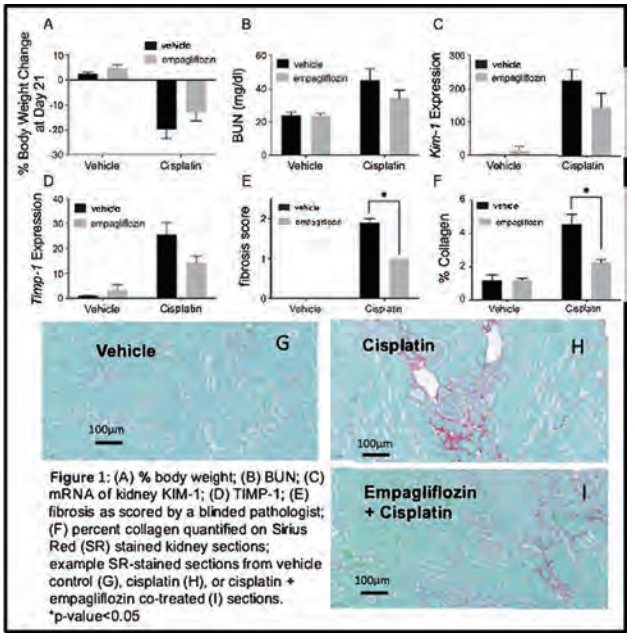

Figure 1: (A) % body weight; (B) BUN; (C) mRNA of kidney KIM-1; (D) TIMP-1; (E) fibrosis as scored by a blinded pathologist; (F) percent collagen quantified on Sirius Red (SR) stained kidney sections; example SR-stained sections from vehicle control (G), cisplatin (H), or cisplatin + empagliflozin co-treated (I) sections. *p-value<0.05

TH-OR97

Pharmacokinetics of Henagliflozin in Dialysis Patients with Diabetes

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) are recommended to treat heart failure, irrespective of the presence of type 2 diabetes. Heart failure is one of the most common complications in dialysis patients. Not all SGLT2i are recommended for use in dialysis patients because less glucose enters the proximal tubule and the effects of inhibiting glucose and sodium reabsorption are reduced, as well as due to a lack of efficacy and safety data. However, emerging evidence has suggested that SGLT2i improve heart failure outcome through the off-target effect. Therefore, patients on dialysis with heart failure may benefit from SGLT2i. We conducted this study to evaluate the pharmacokinetics and safety of Henagliflozin doses of 5 mg and 10 mg in dialysis patients with diabetes.

Methods: In this prospective, randomized, open-label study, 10 hemodialysis and 10 peritoneal dialysis patients with diabetes were randomized in a 1:1:1:1 ratio to oral administration of Henagliflozin in doses of 5 and 10 mg/day. The pharmacokinetics of a single dose of Henagliflozin on days 1 and 2, the minimum plasma concentration (*C*min) of the steady state on day 10, and single hemodialysis clearance of Henagliflozin were measured. Plasma concentrations of Henagliflozin were analyzed by using validated liquid chromatography-tandem mass spectrometry method.

Results: The mean values of *C*max were 70.2–77.0 ng/mL and 105–143 ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively; the mean values of AUCinf were 777–811 h*ng/mL and 1290–1730 h*ng/mL in the 5 mg and 10 mg Henagliflozin groups, respectively. The median *T*max values ranged from 1 to 3 h across the dose range. The mean values of *T*1/2 of Henagliflozin were 14.1–14.5 and 16.2–21.0 h in the 5 mg and 10 mg groups, respectively. The *C*min values of the steady state in dialysis patients taking 5 mg and 10 mg of Henagliflozin were 15.0 ± 4.4 ng/ml and 26.8 ± 16.3 ng/ml, respectively, which were 123.8% and 131.0% higher than those in diabetic patients with normal renal function, respectively. Henagliflozin concentration was decreased by 1.1% after hemodialysis treatment. No treatment-related serious adverse events or discontinuations occurred.

Conclusions: Henagliflozin at the current recommended dosage may be safe although it accumulates in patients on dialysis. Clinical trials should be conducted to examine the cardioprotective effects of Henagliflozin in dialysis patients.

Funding: Government Support - Non-U.S.

TH-OR98

Canagliflozin Pharmacokinetics at Steady State in Patients on Maintenance Hemodialysis

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Background: Sodium glucose co-transporter 2 (SGLT-2) inhibitors improve cardiovascular and kidney outcomes in patients with preserved renal function or with mild and moderate chronic kidney disease. However, they have not been studied in patients on maintenance hemodialysis (HD). Detailed study of SGLT-2 inhibitor pharmacokinetics in patients receiving HD is the first step to establishing their safety in this population.

Methods: Patients with kidney failure on maintenance HD for at least 3 months were invited to participate. Those with type 1 diabetes mellitus, euglycemic ketoacidosis, or liver disease were excluded. All participants received 100 mg of canagliflozin once daily for nine days. Venous blood samples were collected immediately before (0) and 1, 1.5, 2, 3, 4, 6, 9, 12, and 24 hours after canagliflozin administration for pharmacokinetic analyses on day 8 (a mid-week non-dialysis day) and hourly during hemodialysis on day 9. Canagliflozin plasma levels were measured with liquid chromatography- mass spectrometry and compared to published estimates in healthy controls.

Results: We enrolled 10 patients (59 ± 14 years old, 30% female, median dialysis duration 26 months). Canagliflozin levels reached steady state on day 4, based on a calculated half-life of 7.3 hours. Pharmacokinetic results on day 8 are shown in the **Table**. There were no significant differences in drug exposure, peak plasma levels, nor time to peak plasma levels between our patients and patients with preserved renal function. Canagliflozin levels were not modified by hemodialysis (p=0.39).

Conclusions: Drug exposure with canagliflozin 100 mg daily is similar between patients receiving HD and individuals with preserved kidney function, and levels were not affected by HD. These results suggest canagliflozin does not accumulate in HD patients and trials of canagliflozin may be safely conducted in patients on HD to test its efficacy.

Funding: Private Foundation Support

Canagliflozin pharmacokinetics in hemodialysis

Parameter	Hemodialysis	Preserved renal function	p-value
AUC0-24 (ng.h/ml)	8267 ± 4265	6377 ± 1285	0.19
Cmin (ng/ml)	87 (57-201)	-	-
tmax (hours)	2.1 (1.9-3.2)	2.0 (1.0-4.0)	0.18
Cmax (ng/ml)	1122 ± 537	943 ± 239	0.32

AUC0-24, drug exposure (area under the curve between 0 and 24h); Cmin, trough level; tmax, time to peak plasma concentration; Cmax, peak plasma concentration.

TH-OR99

Ondansetron and the Risk of Sudden Cardiac Death Among Patients Receiving Hemodialysis

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Background: Sudden cardiac death (SCD) is common among hemodialysis (HD) patients. Ondansetron, an antiemetic with known QT prolonging potential, has a Food and Drug Administration warning about its association with fatal arrythmias in the general population. The cardiac safety of ondansetron in the HD population is unknown.

Methods: We conducted a new-user, active-comparator, cohort study using US Renal Data System data (2012-2019) to assess the comparative 10-day risk of SCD between HD patients initiating ondansetron vs. non-QT-prolonging antiemetics (metoclopramide/ prochlorperazine/ promethazine). We used inverse probability of treatment weighting and Fine and Gray proportional subdistribution hazard models to estimate adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). We used an intention-to-treat approach and treated non-SCD as a competing event. In secondary analyses, we considered broader cardiac outcomes.

Results: Of 119,254 study patients, 64,978 (54.5%) initiated ondansetron and 54,276 (45.5%) initiated a comparator antiemetic. The mean age ± SD was 60 ±15 years, median (IQR) years on HD was 2.2 (0.9, 4.6), and 55% were female. Ondansetron vs. comparator antiemetic initiation was associated with higher relative and absolute 10-day risks of SCD, aHR (95% CI) = 1.45 (1.08, 1.93); weighted risk difference (95% CI) = 0.06% (0.01,0.11). The number needed to harm was 1,672 ondansetron initiations. Analyses of other cardiac outcomes yielded similar findings.

Conclusions: Ondansetron (vs. comparator antiemetic) treatment was associated with higher absolute and relative 10-day risks of SCD among HD patients. Our findings may inform prescriber decisions about antiemetic selection in the HD population.

Funding: Other NIH Support - NIH/NHLBI

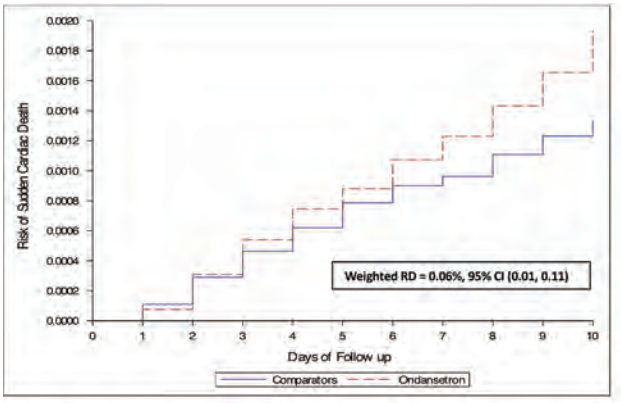

Figure 1. The 10-day SCD risk among hemodialysis patients initiating ondansetron vs. a non-QT-prolonging antiemetic.

TH-OR100

Safety Outcomes of Sodium-Glucose Cotransporter-2 Inhibitors in Patients with Diabetes Mellitus and Cancer

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Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors are glucose-lowering agents that reduce the risk of hospitalization for heart failure and chronic kidney disease progression. The risk of serious adverse events with SGLT2i use was low in large clinical trials, but patients with cancer were excluded from these trials. Therefore, the safety of SGLT2 inhibitors in patients with cancer is unknown.

Methods: Using our institute's electronic medical record system, we identified 5,478 patients with a history of diabetes mellitus and cancer who were prescribed an SGLT2 inhibitor, i.e., empagliflozin, dapagliflozin, canagliflozin or ertugliflozin, between 2013 and 2022. Data on adverse events, including urinary tract infections (UTIs), diabetic ketoacidosis (DKA), genital infections, and non-vertebral fractures, were collected using the ICD-9/10 diagnostic codes.

Results: The medical record query identified 5,478 patients who were prescribed an SGLT2 inhibitor. Each patient had a start and an end date for the SGLT2 inhibitor prescription, which added up to a total of 11,175 patient-years on SGLT2 inhibitors. The ICD diagnosis query revealed 424 instances of adverse events coinciding with the SGLT2 inhibitor prescription. The incidence rate of adverse events is shown in Table 1.

Conclusions: In this cohort of diabetic patients with cancer, the incidence rate of DKA in patients taking an SGLT2 inhibitor was higher (5.1 per 1000 patient-years) as compared to the incidence rate of DKA reported in a recent meta-analysis[1] of SGLT2 inhibitor trials (0.0-2.2 per 1000 patient-years) and a large observational study[2] (2.37 per 1000 patient-years). We also observed a high incidence rate of UTIs, genital mycotic infections, and non-vertebral fractures. To our knowledge, this is the first study to report the safety outcomes of SGLT2 inhibitors in diabetic patients with cancer. *[1]Impact of diabetes on the effects of SGLT2 inhibitors on kidney outcomes. Lancet. 2022 [2]Comparative Effectiveness and Safety of SGLT2 Inhibitors Versus GLP1-RA in Older Adults. Diabetes Care. 2021*

Incidence of adverse events of interest

	Diabetic patients (5478 patients, 11,175 patient-years)		
Diagnosis	Incidence	Per 1000 patient-years	No. of patients (%)
UTI	265	23.7	187 (3.4%)
DKA	57	5.1	49 (0.9%)
GENITAL INFECTIONS	54	4.8	43 (0.8%)
NON-VERTEBRAL FRACTURES	48	4.3	30 (0.5%)

FR-OR01

AKI Is Associated with Long-Term Decline in Cognitive Function at 3 Years: ASSESS-AKI Study

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Background: Cognitive dysfunction is a well-known complication of chronic kidney disease but it is less known whether these long-term adverse events are present in survivors of AKI. We hypothesized that an episode of AKI is associated with poorer cognitive function, mediated, at least in part, by persistent systemic inflammation.

Methods: ASSESS-AKI was a multicenter prospective cohort study that enrolled patients surviving three months after hospitalization with and without AKI who were matched based on demographics, comorbidities and baseline kidney function. A subset of patients underwent cognitive testing using the modified mini-mental test (3MS) at 3, 12 and 36 months. The 3MS is scored on a scale of 0-100. We examined the association of AKI with long-term cognitive testing using mixed linear models accounting for matching and loss to follow-up and assessed the proportion in risk mediated by 3-month systemic inflammatory biomarkers (sTNFR-1, IL-6 and IL-8).

Results: Among 1538 patients enrolled in the parent study (769 with AKI and 769 without), 1465 (95%) completed the 3MS at 3 months. Patients with AKI had lower 3MS scores at 3 months (difference -1.1 (95% CI: -2.0, -0.3) $p=0.01$) and at 3 years (-1.5 (95% CI: -2.4, -0.7) $p<0.01$) compared to matched patients without AKI. We also found that a higher proportion of patients with AKI had a clinically meaningful (>5 point) reduction in 3MS scores at 3 years compared to patients without AKI (10% and 5%, $p<0.01$). In mediation analyses, serum sTNFR-1 mediated 34% ($p=0.01$) of the AKI related risk for 3MS scores at 3 years, while IL-6 and IL-8 had non-significant proportion mediated.

Conclusions: We found that patients with AKI had significantly worse cognitive function at 3 years after hospitalization. We also found that sTNFR-1 levels appear to mediate a significant proportion of the risk of long-term cognitive impairment.

Funding: NIDDK Support

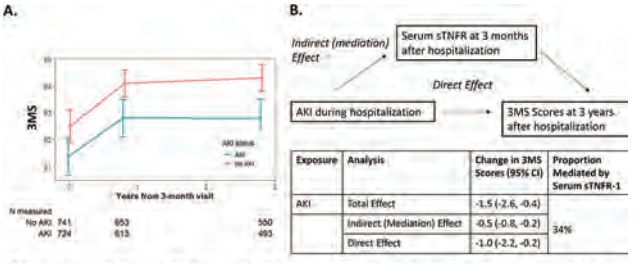

Figure Legend: (A) Displays the trajectory of 3MS scores in patients with AKI (blue line) and patients without AKI (red line) over 3 years of follow-up after hospitalization. Patients with AKI have significantly lower 3MS scores at 3 months and 3 years after hospitalization. (B) Mediation analysis testing the direct and indirect (mediation) effect of AKI on 3MS scores at 3 years. sTNFR-1 levels mediate 35% of the decreased 3MS scores in patients with AKI compared to no AKI.

FR-OR02

AKI, Glomerulonephritis, and Tubulointerstitial Nephritis Following Vaccination: VigiBase Analysis

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Background: Vaccination is the long-term established measure for disease prevention and worldwide outbreak of COVID-19 necessitates mass scale vaccination. However, there is a public concern on the risk of renal adverse reactions from several types of vaccination.

Methods: We analyzed VigiBase (n = 120,715,116 reports), the World Health Organization pharmacovigilance database from Dec 1967 to Jul 2022 using disproportionate Bayesian reporting. Information component (IC) compares observed and expected values to find the associations of vaccines with acute kidney injury (AKI), glomerulonephritis (GN) and tubulointerstitial nephritis (TIN).

Results: We found 5,484 AKI (13.8% fatal), 2,846 GN (29.4% fatal) and 289 TIN reports (23.2% fatal) as vaccine-associated adverse reactions. Almost reports indicated single drug suspected cases. Cumulative number of reports on AKI, GN and TIN gradually increased and Americas was most prevalent regions of reporting. Examining the different vaccines separately, reporting count of COVID-19 mRNA vaccines sharply increased and it solely was associated with significantly higher reporting of AKI (IC_{025} 1.09) and TIN (IC_{025} 0.48). Patients aged 12-17 years had the highest IC values for COVID-19 mRNA vaccine-associated AKI and TIN. Hepatitis B, encephalitis and COVID-19 mRNA vaccine were prominently over-reported among ten types of vaccines with significant signals of GN.

Conclusions: AKI, GN and TIN substantially occurred following vaccination and it was most noticeable in patients exposed to COVID-19 mRNA vaccines. Clinicians should consider the increased risk of renal adverse reactions after vaccination.

FR-OR03

Use of a Recurrent Neural Network to Predict Development of Nephrotoxic AKI in Adults

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Background: The Nephrotoxic Injury Negated by Just-in Time Action (NINJA) program identifies children with high exposure to nephrotoxic medications and has been shown to reduce rates of acute kidney injury (AKI) by 25% through preemptive medication adjustments. However, attempts to translate NINJA to the adult population have been hampered by the much larger patient volume at adult hospitals combined with NINJA's relatively low positive predictive value (PPV), which generates a high number of false alerts. We used a recurrent neural network (RNN) machine learning algorithm to improve nephrotoxic AKI prediction in patients with high nephrotoxin exposure.

Methods: We collected over 100 variables including demographics, laboratory data, vital signs, and medication usage on adult patients admitted to the University of Iowa Hospital from 2017-2022. Patients admitted for >48 hours who met the NINJA definition for high nephrotoxin exposure (≥ 3 nephrotoxins on 1 day or intravenous aminoglycoside or vancomycin for ≥ 3 days) were included in the final dataset. A gated recurrent unit (GRU)-based RNN was trained on 85% of the data, and then tested on the remaining 15%, with the goal of predicting AKI development (defined as a creatinine increase of ≥0.3 mg/dL or ≥1.5x baseline) within 48 hours. We then used an artificial neural network (ANN) to determine feature importance.

Results: There were 37,300 patient-days meeting criteria for NINJA high nephrotoxin exposure. In the testing cohort, 29% of exposures developed AKI within 48 hours (2.4 false alerts per true AKI). The RNN model predicted 48-hour AKI with a PPV of 0.58 (0.7 false alerts per true AKI) and a NPV of 0.87. Hospital day, lowest hemoglobin, lowest platelet count, lowest blood pressure, and highest white blood cell count were the 5 most important variables in the ANN model. Vancomycin, piperacillin-tazobactam, iopamidol, and lisinopril were the most important medication variables.

Conclusions: Our RNN machine learning model was able to dramatically reduce the number of false alerts for nephrotoxic AKI in adults, which may facilitate NINJA translation to adult hospitals by providing more targeted intervention with less resource utilization.

FR-OR04

Genome-Wide Association Study of Hospitalized AKI

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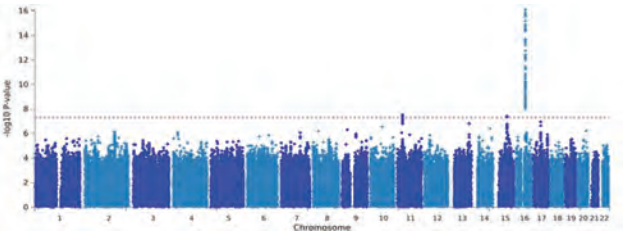
Background: AKI commonly complicates hospitalization and has a potential genetic basis for susceptibility.

Methods: We conducted a genome-wide association study of AKI in the Million Veteran Program(MVP) and Vanderbilt University's DNA biobank(BioVU). Among patients hospitalized during 2002-2019, AKI cases were defined as KDIGO Stage ≥2, or Stage 1 AKI for ≥2 days. Non-AKI controls were identified among hospitalized patients without historical evidence of AKI. Single variant logistic regression analyses were performed on imputed genetic variants, adjusting for sex, age, and the top 10 principal components of ancestry. Results were meta-analyzed using fixed effects analyses. A second meta-analysis was performed with summary statistics from UK Biobank, FinnGen, and BioBank Japan. Bioinformatic analyses were performed to provide functional information for significant variants.

Results: There were 58,891 patients with AKI(53,079 MVP,5,812 BioVU) and 139,098 non-AKI controls(127,627 in MVP, 11,471 BioVU). Three novel loci reached genome-wide significance (Fig): rs11642015 near *FTO*(odds ratio[OR] 1.07(95% confidence interval [CI], 1.05-1.09), p=8.2x10-17, EAF[effect allele frequency]=0.36); rs20654180 near *MPPED2*(OR 1.05(95% CI 1.03-1.06), p=2.9x10-8, EAF=0.68]); and rs8042910 near *INTS14*(OR 1.06(95%CI:1.04-1.08), p=3.9x10-8, EAF=0.20). Effects were consistent across groups and replicated in diagnosis code-based datasets. Within MVP, FTO remained significant after adjusting for BMI. Genome-wide meta-analysis of Biobank Japan, FinnGen, and UK Biobank (N=67,051 cases, 788,014 controls) identified one additional significant locus: rs76704066 in *NALCN* [EAF = 1.9%; OR 0.82 (95%CI:0.77-0.88)]. *FTO* and *MPPED2* remained significant (p= 1.0x10-17 and 9.6x10-9, respectively), while *INTS14* did not (p= 8.1x10-8).

Conclusions: Three loci were associated with AKI including one (*MPPED2*) previously associated with CKD. *FTO* may contribute to the risk of AKI independently of BMI. Further work to determine how these genes may contribute to AKI is ongoing.

Funding: Veterans Affairs Support



FR-OR05

Machine Learning-Guided Novel Subphenotypes of Sepsis-Associated Persistent AKI

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Background: Sepsis associated acute kidney injury (SA-AKI) is common and is associated with high mortality. AKI lasting 48 hours or longer, known as persistent AKI (pAKI), has much worse outcomes. SA-AKI is a heterogenous disease, however, it is unknown whether such heterogeneity exists in SA-pAKI. We aimed to identify subphenotypes (SP) of SA-pAKI using routinely collected data in electronic medical records.

Methods: We conducted a retrospective study using MIMIC IV database. We defined AKI and pAKI using both creatinine and urine output based KDIGO criteria. We identified adult patients (≥18y) with sepsis who developed SA-AKI within 48h and SA-pAKI within 96h of ICU admission. We used available features for demographics, comorbidities, SOFA score, vital signs, labs, fluid balance & vasopressors to identify SPs. We used factor analysis of mixed data for dimensionality reduction followed by k-means clustering to identify SPs. Outcomes were 30-day in-hospital mortality and 30-day AKI recovery while adjusting for competing risk of mortality.

Results: Among 6,681 patients with SA-pAKI, we identified 4 distinct SPs. Each SP demonstrated distinct characteristics and outcomes (Fig 1a & b). SP1 (n=1,137) included patients with severe AKI, low systolic BP, high INR, and WBC counts. It had highest mortality(47%) and low AKI recovery(37%). SP 2 (n=1,231) had moderate to severe AKI but low vasopressor requirements. It had low mortality (19%) but also low rates of AKI recovery (32%). SP3 (n=1315) included patients with high comorbidity burden but low disease acuity. Their mortality was between that of first two SPs and had high rates of AKI recovery (54%). SP4 (n=1,678) included patients with mild to moderate AKI and low disease acuity. They had highest rates of AKI recovery (56%) and lowest mortality (13%).

Conclusions: We identified 4 distinct SPs of SA-pAKI with differing patient characteristics and outcomes. Early recognition of these SPs will allow for personalized management strategies.

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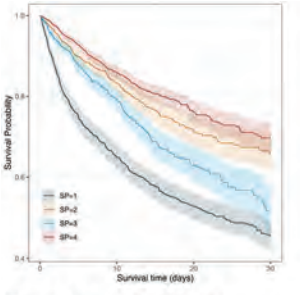


Figure 1a. 30-day survival probability for each subphenotype

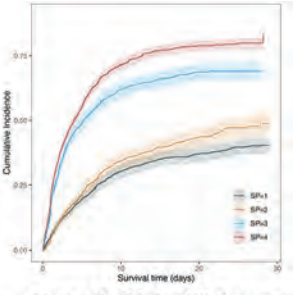


Figure 1b. 30-day AKI Recovery cumulative incidence for each subphenotype

FR-OR06

Arterial Stiffness and AKI in the Atherosclerosis Risk in Communities (ARIC) Study

Ester Oh,[1] Aditya L. Surapaneni,[2] Jessica B. Kendrick,[1] Josef Coresh,[4] Kunihiro Matsushita,[4] Morgan Grams,[2] Kristen L. Nowak,[1] Anna Jovanovich.[1,3] *[1]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO; [2]New York University Grossman School of Medicine, New York, NY; [3]VA Eastern Colorado Health Care System, Aurora, CO; [4]Johns Hopkins University, Baltimore, MD.*

Background: Acute kidney injury (AKI) is associated with prolonged hospitalization and increased in-hospital mortality risk. However, the prediction of incident AKI is inaccurate and additional predictors of AKI are strongly needed. Arterial stiffness, as measured by carotid-femoral pulse wave velocity (cfPWV), is associated with kidney

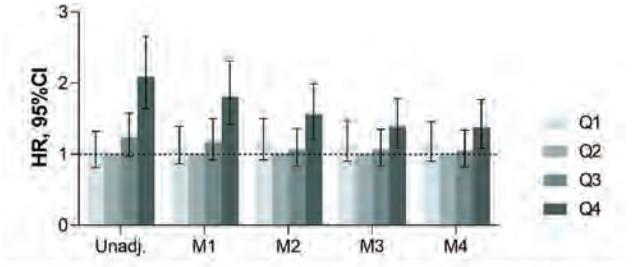
function decline and may serve as a plausible predictor of AKI. We hypothesized a higher cfPWV at baseline would be independently associated with AKI risk in community-dwelling older adults who participated in the Atherosclerosis Risk in Communities (ARIC) study.

Methods: We included adults with available PWV measures (i.e., cfPWV [primary predictor], heart-femoral PWV [hfPWV], heart-carotid PWV [hcPWV], heart-ankle PWV [haPWV], and brachial-ankle PWV [baPWV], femoral-ankle PWV [faPWV]). Cox proportional hazard models were used to examine the association between PWV measures and time to AKI. Given its J-shaped relation with AKI, PWV was modeled as a categorical variable in quartiles (Q), with Q2 serving as the reference category.

Results: A total of 4,245 participants (44% male; 77% white; mean±SD age 75±5 years; cfPWV 11.9±3.9 m/s) were included. There appeared to be a J-shaped association between cfPWV and AKI risk (Q1, hazard ratio 1.15 [95% confidence interval 0.90-1.46]; Q4, 1.38 [1.08-1.77] vs. Q2) after fully adjusting for demographics, CVD risk factors, and markers for kidney function and peripheral artery disease (Figure).

Conclusions: A higher arterial stiffness, measured by cfPWV, is an independent predictor of AKI in community-dwelling older adults.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support



	Q1	Q2	Q3	Q4
Events/Total	128/1062	133/1062	151/1061	227/1060
Unadj.	1.04 (0.81,1.32)	Ref.	1.24 (0.97,1.58)	2.09 (1.64,2.66)
M1	1.09 (0.86,1.39)	Ref.	1.17 (0.92,1.50)	1.81 (1.42,2.31)
M2	1.17 (0.92,1.50)	Ref.	1.06 (0.83,1.36)	1.56 (1.22,1.99)
M3	1.15 (0.90,1.47)	Ref.	1.06 (0.83,1.35)	1.39 (1.09,1.78)
M4	1.15 (0.90,1.46)	Ref.	1.05 (0.82,1.34)	1.38 (1.08,1.77)

Association between cfPWV and AKI risk. *M1:* age, sex, race; *M2:* M1 + cardiovascular risk factors (smoking, diabetes, CVD, hypertension, SBP, DBP, BMI, total and HDL cholesterol); *M3:* M2 + kidney function markers (eGFR, urinary ACR); *M4:* M3 + peripheral artery disease marker (ankle-brachial index).

FR-OR07

Noninvasive Identification of Acute Tubular Injury Using Plasma Proteomics

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Background: Biomarkers for the non-invasive assessment of acute tubular injury (ATI) are needed in patients with kidney disease.

Methods: Using the SomaScan proteomics platform, we measured 6592 circulating plasma proteins in 434 individuals with biopsy-confirmed kidney diseases and pathologist-adjudicated semi-quantitative assessments of histopathologic ATI. We identified proteomic correlates of ATI severity. For the proteins with the strongest associations with ATI, we evaluated cell-specific gene expression in patients with AKI in the Kidney Precision Medicine Project (KPMP).

Results: Fifty-three % of individuals had no ATI, 30% had mild ATI, 13% had moderate, and 3% had severe ATI. After multivariable adjustment and correction for multiple testing, 170 proteins were associated with ATI. The proteins with the strongest associations with greater ATI severity were osteopontin (p=9.8E-18), macrophage mannose receptor 1 (p=2.2E-16), and tenascin (p=1.4E-14) (Figure 1). Previously identified proteins such as kidney-injury molecule-1 and tumor necrosis factor receptor superfamily member 1 were also associated with ATI (p=9.9E-10 and 5.7E-06, respectively). The top proteins with inverse associations with ATI were plasma serine protease inhibitor (p= 6.1E-11), cholinesterase (p= 1.3E-10), and neuropeptide S (p=1.4E-10). In KPMP snRNA sequencing data, *SPP1* (the gene encoding osteopontin) was primarily expressed in thick ascending limb (TAL) and proximal tubular (PT) cell clusters (p=4.2E-141 and 5.2E-108, comparing the expression in TAL and PT with all other cell clusters, respectively).

Conclusions: Plasma proteomic approaches may identify novel biomarkers to non-invasively identify biopsy-proven ATI.

Funding: NIDDK Support

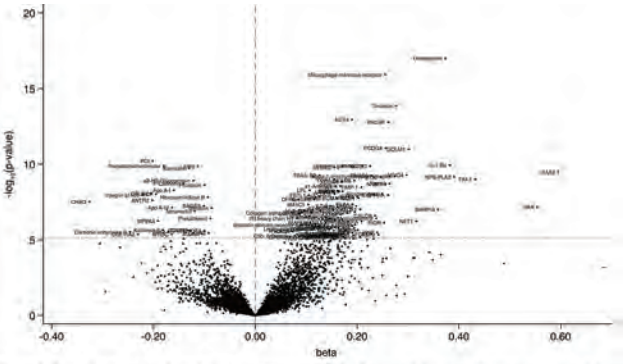

Figure 1. Proteomic discovery of circulating biomarkers associated with acute tubular injury. Linear regression models are adjusted for age, sex, race, and eGFR. The horizontal dotted line shows the Bonferroni-corrected significance threshold.

FR-OR08

AKI Diagnostic Accuracy and Implications of AKI Baseline Creatinine (ABC) vs. Other Baseline Creatinine Estimating Equations

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Background: Acute kidney injury (AKI) definitions rely on a known baseline creatinine (Cr_b), which is missing in up to 75% of hospitalized children. A new method (ABC equation) for estimating Cr_b was derived from children without kidney disease. We aim to externally validate the ABC method in an international cohort and assess how different Cr_b estimating equations alter AKI epidemiology.

Methods: AWARE is a prospective international study of 4984 critically ill children (age 0-25 years) from 32 PICUs. The validation of the ABC equations uses a subset of this cohort (n=2451) with a known Cr_b which serves as the gold standard, using statistical measures of accuracy and precision. The entire cohort is used for assessing changes in AKI epidemiology for different Cr_b estimating equations (3 ABC equations and 4 common eGFR equations). Univariate statistics determine how different Cr_b equations impact the incidence of AKI and its association with key clinical outcomes including 28-day mortality.

Results: The simplified ABC equation (requiring only age) performed similarly to existing Cr_b equations (e.g., new Schwartz). When an admission hospital creatinine value was available, the ABC equations outperformed all existing equations up to 19% in accuracy and 32% in precision. AKI incidence varied from 2-10% depending on Cr_b definition. Adverse clinical outcomes were rare: 28-day mortality (n=169) was 3.4% and ICU length of stay>=14 days (n=147) was 2.9%. Compared to previous Cr_b equations, ABC equations consistently perform better (or similar) to predict poor clinical outcomes. For example, relative risk (RR) of AKI using the ABC equation for 28-day mortality was 4.5 (95% CI 2.8-7.2); this was 5-29% higher RR than AKI defined by other Cr_b equations.

Conclusions: ABC equations outperform existing Cr_b estimating equations. This international cohort confirms earlier findings that ABC equations are improved methods for estimating Cr_b values. The data suggest ABC equations performed similarly, or perhaps better, in predicting select poor clinical outcomes.

FR-OR09

Vancomycin-Tacrolimus Combination Increases AKI Risk in Post-Hematopoietic Stem Cell Transplantation (HSCT) Patients

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Background: Acute kidney injury (AKI) is a common complication in hematopoietic stem cell transplant (HSCT) recipients, leading to prolonged hospital stays, increased healthcare costs and mortality rates. Drug-related effects are major contributors of AKI in this patient population. Immunosuppressive and antibacterial drugs, such as vancomycin and tacrolimus, have well-documented nephrotoxic effects. Combinations of tacrolimus and vancomycin with other drugs are known to induce AKI. However, the combined nephrotoxic effect of vancomycin and tacrolimus warrants further investigation. This study aims to evaluate their simultaneous nephrotoxic effects in HSCT patients.

Methods: Institutional Review Board approval was obtained for retrospective analysis of transplant outcomes. This retrospective cohort study includes 1444 HSCT patients (age>18) from 2018-2021 at Emory University Hospital. Patients with end-stage renal disease were excluded from the study. The KDIGO guidelines: increase in serum creatinine levels ≥0.3 mg/dL within 48 hours or ≥50% within 7 days, were used

to define AKI in the study population. Data was collected from day 0 to day +30 post-HSCT by reviewing in and out-patient medical records. Univariate and multivariable logistic regression was used to estimate the interaction effect between vancomycin and tacrolimus.

Results: The median patient age was 61, with 55% males, 58% white/35% black. Of the total patients, 51% had hypertension, 14% diabetes mellitus, 15% CKD, 8% congestive heart failure (CHF). The overall AKI incidence was 9.94%, with 19.81% among allogeneic transplant recipients and 7.24% among autologous transplant recipients (OR 3.28 p<0.001). Other AKI associated covariates were male gender (OR 1.59 p 0.022), CHF history (OR 2.26, p 0.006), high BMI (OR 1.06, p<0.001) and low creatinine clearance (OR 0.96 p<0.001). Using multivariate logistic regression, the primary outcome measure, the incidence of AKI was significantly higher in patients receiving a combination of vancomycin and tacrolimus (OR 5.50 p<0.001) than patients receiving tacrolimus alone without vancomycin (OR 4.04 p<0.001).

Conclusions: Concurrent administration of vancomycin and tacrolimus greatly increases the risk of AKI compared to the individual drugs alone. Thus, the simultaneous use of these medications should be avoided or minimized with close monitoring in allo-HSCT recipients.

FR-OR10

Heart Failure with Preserved Ejection Fraction (HFpEF) vs. Heart Failure with Reduced Ejection Fraction (HFrEF) After AKI

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Background: There is an increased risk of incident heart failure (HF) after acute kidney injury (AKI). Preclinical studies have shown AKI causes structural changes and diastolic dysfunction. The nature and phenotype of HF experienced by AKI survivors is unknown.

Methods: We conducted a case control study of adults at Vanderbilt University Medical Center. To ensure patients had established care at VUMC, we required at least one outpatient serum creatinine at least two years prior to the code for HF. Eligible patients were also required to have an echocardiogram within 30 days before or 1 year after HF diagnosis to determine HF subtype. Patients with a history of ESRD were excluded. The primary exposure was hospitalized AKI defined using creatinine-based KDIGO definitions during the exposure ascertainment period. The primary outcome was determined as HF, defined by either 1 inpatient or 2 outpatient diagnosis codes and classified using the echocardiogram closest to the HF diagnosis date (HFpEF if EF ≥45%, HFrEF if EF <45%). Baseline vitals, conditions, and medications were ascertained prior to AKI. Multivariable logistic regression was used to estimate the odds of AKI prior to HFpEF versus HFrEF.

Results: We identified 7,509 adults with incident HF (5,544 HFpEF, 1,965 HFrEF). AKI (stages 1-3) was associated with a 20% higher odds of HFpEF which was not statistically significant (OR 0.80, 95% CI 0.62 – 1.03). Stage 1 AKI was associated with a 40% higher odds of HFpEF (OR for HFrEF 0.60, 95% CI 0.42 – 0.85) whereas Stage 2-3 AKI was associated with a 17% higher odds of HFrEF, though this finding was not statistically significant (OR 1.17, 95% CI 0.81 – 1.68).

Conclusions: Stage 1 AKI was preferential towards incident HFpEF compared to HFrEF, with an association on par with other HFpEF risk factors such as female sex, obesity, atrial fibrillation, and hypertension. More severe AKI trended towards favoring HFrEF. Multimorbidity increases risk of HFpEF and may render patients susceptible to small fluctuations in serum creatinine when hospitalized. Further work is needed to elucidate mechanisms of this relationship.

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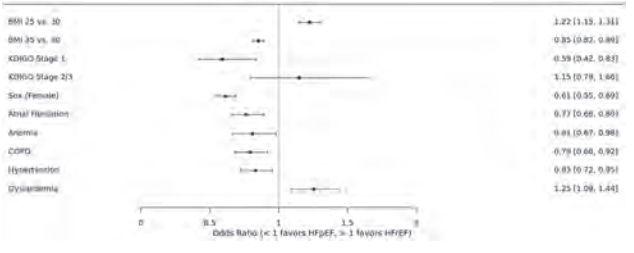

FR-OR11

Role of Biomechanics in the Regulation of Ureteric Bud Branching Morphogenesis

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Background: Branching morphogenesis is a fundamental developmental process driving the formation of several organs. Branching pattern in the developing kidney is stereotyped and involves geometrically distinct modes: tip bifurcation and trifurcation, and only very rarely lateral branching. The branching epithelium, known as ureteric bud (UB), undergoes a series of complex changes which first transform a single layered epithelial bud to an ampulla where then the terminal bifurcations take place. While the molecular mediators of tissue crosstalk during renal branching are rather well characterized, the mechanisms controlling exact branch-initiating cell identity in UB tips remain unknown. Moreover, the roles of cellular niche, extracellular matrix and biomechanics in branch point determination are poorly understood.

Methods: We utilize a combination of mouse genetics and a custom machine-learning based segmentation pipeline in MATLAB to quantify 3D UB epithelial cell shapes and sizes in wholemount kidneys to determine how cell shapes change and drive complex branching patterns. Live imaging of fluorescently labelled UB cells, traction force microscopy and primary UB cell cultures on matrices with varying stiffness are utilized to study how basic cellular features drive arborization of ureteric bud epithelium in normal and growth factor deficient kidneys.

Results: Cell shape characterization of 3D epithelium shows that individual cells in the bud stage are mostly elliptical but become significantly rounder as ureteric branching proceeds to the ampulla stage. In the next branch phase, the cells convert into elongated shape suggesting that the ampulla remodeling to bifurcated tips involves spatial constraints squeezing bud epithelial cells into tube-like organization. Accordingly, our results demonstrate not only remarkable differences in cell shapes in the MAPK/ERK-deficient UB epithelium incapable of complex branch formation but also clear fluctuations in adhesive forces exerted between epithelial cells themselves and towards their niche composed of nephron progenitors.

Conclusions: Our work describes the basic characteristics of ureteric bud epithelial cells during different branch formation phases. Together with our biomechanical studies, this provides a new cellular mechanism through which novel branch points are determined and how growth is regulated in developing kidney.

Funding: Government Support - Non-U.S.

FR-OR12

Multi-Omic Profiling of Human Renal Organoids Reveals PAX8 as a Critical Regulator of Human Renal Mesenchymal-to-Epithelial Transition

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Background: The nephron, the functional unit of the kidney that filters blood, is a tubular epithelial structure that arises from metanephric mesenchyme through a mesenchymal-to-epithelial transition (MET) during kidney development. Wnt signalling specifies nephron fate, however, the relationship between Wnt signalling and establishment of epithelial junctions and apical-basal polarity during renal MET is unclear, and in general, developmental MET processes *in vivo* are poorly understood.

Methods: To investigate transcriptional control of MET, we used human induced pluripotent stem cell-derived renal organoids, which recapitulate nephrogenesis and generate epithelial tubes that express molecular markers of nephron cell types. Organoids were harvested for single nucleus multi-omic (paired RNA-seq and ATAC-seq) profiling to investigate transcription factors driving MET. CRISPR-interference was used to perturb candidate transcription factors.

Results: Human renal organoids recapitulate MET with upregulation of epithelial genes including CDH1 (E-cadherin), establishment of apical-basal polarity and epithelial junctions. Organoids exhibit dynamic gene expression and chromatin accessibility signatures throughout MET driven by transcriptional activators and repressors. PAX8 is a critical upstream regulator of human renal MET. Previous studies found PAX8 was dispensable for mouse renal MET. We show using CRISPR-interference that PAX8 is essential for initiation of MET in human kidney organoids. Moreover, Wnt signalling must be deactivated for completion of MET; persistent Wnt activation prevented completion of epithelial polarisation.

Conclusions: These results reveal how the developing kidney balances fate-commitment and morphogenesis with implications for understanding both developmental kidney diseases and aberrant epithelial plasticity following adult renal tubular injury.

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FR-OR13

Interpreting Geometric Rules of Early Kidney Formation for Synthetic Morphogenesis

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Background: The kidney develops through coordinated growth of ureteric epithelial tubules (the future urinary collecting ducts), stroma, and nephron progenitors in the cap mesenchyme that surrounds each ureteric tip as they branch. Dynamic interactions between these tissues set nephron numbers for life, impacting the probability of adult disease. How then are the rates of nephron formation and ureteric tubule duplication balanced?

Methods: Here we study the geometric and mechanical consequences of tubule tip packing at the embryonic kidney surface for tip organization and nephron formation. We study whole-mount mouse embryonic kidneys and human iPSC-derived nephron progenitor organoids using confocal immunofluorescence, mechanical microindentation, Brillouin microscopy, laser microdissection, and spatial RNA sequencing.

Results: We find that over developmental time, kidney curvature reduces and 'tip domains' pack more closely, which together create a semi-crystalline tip geometry at the kidney surface. We apply a geometric parameter of tip domains called the shape index to predict a rigidity transition to more solid-like tissue properties at later developmental stages and confirm by micromechanical measurements. At the level of individual tips we use the shape index to define a tip 'life-cycle' between branching events, and find that nephrogenesis rate varies over this life-cycle. Applying force inference techniques

adapted from a cell vertex model and validating with laser ablation shows that tip domains experience a cyclical mechanical transient over each life-cycle. We then hypothesized that tip duplication periodically creates a mechanical microenvironment permissive to nephrogenesis. Indeed, mimicking a mechanical transient in human iPSC-derived nephron progenitor organoids increased Wnt-driven commitment to early nephron cell aggregates.

Conclusions: The data suggest that temporal waves of mechanical stress within nephron progenitor populations could constitute a clock that synchronizes nephron formation and ureteric tubule duplication. Ongoing work to understand the spatial and temporal regulation of nephron induction will clarify variation in nephron endowment between kidneys and advance engineered replacement kidney tissues for regenerative medicine.

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FR-OR14

ZEB2 Signaling Is Essential for Ureteral Smooth Muscle Cell Differentiation and Maintenance

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Background: Mowat-Wilson Syndrome (MWS) is an autosomal dominant complex disorder caused by mutations in the *ZEB2 that* plays a critical role in cell fate determination and differentiation during development. Congenital anomalies of the kidney and urinary tract (CAKUT), such as hydroureter and hydronephrosis, have been reported in MWS patients. However, the role of ZEB2 in urinary tract development and the cellular and molecular mechanism underlining the CAKUT phenotype in MWS remains unknown.

Methods: We performed ZEB2 protein expression analysis in the developing mouse ureter. We generated *Zeb2* ureteral mesenchyme-specific conditional knockout mice by crossing *Zeb2* floxed mice with Tbx18Cre mice (*Zeb2* cKO) and analyzed the urinary tract phenotypes in *Zeb2* cKO mice and their wild-type littermate controls by gross and histological examination. Ureteral cellular and molecular phenotypes were studied using cell-specific markers such as TAGLN, ACTA2, FOXD1, POSTN, CDH1, TBX18, and SOX9.

Results: We found that ZEB2 is expressed in TBX18$^+$ ureteral mesenchymal cells at E14.5 and E15.5 during mouse fetal development. Deletion of *Zeb2* in developing ureteral mesenchymal cells causes hydroureter and hydronephrosis phenotypes, leading to obstructive uropathy, kidney failure, and early mortality. Cellular and molecular marker analyses showed that the TAGLN$^+$ and ACTA2$^+$ ureteral smooth muscle cells (SMCs) layer is not formed in *Zeb2* cKO mice at E15.5, but the FOXD1$^+$ and POSTN$^+$ tunica adventitia cells layer is significantly expanded compared to wild-type littermate controls. CDH1$^+$ urothelium cells are reduced considerably in the *Zeb2* cKO ureters at E15.5. Mechanistically, we found that *Zeb2* cKO mice have significantly decreased TBX18 expression but an increased SOX9 expression in the developing ureter at E14.5 and E15.5 compared to wild-type littermate controls.

Conclusions: Our results show that ZEB2 is essential for mouse ureter development by maintaining ureteral mesenchymal cell differentiation into normal ureteral SMCs. Our study also shed new light on the pathological mechanism underlying the developmental abnormalities of the urinary tract and CAKUT phenotype in MWS patients.

Funding: NIDDK Support

FR-OR15

The Multimodal Role of TBX6 in Kidney and Urinary Tract Development and Disease

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Background: TBX6 is a transcription factor involved in fate-determination of neuromesoderm precursors (NMP). We recently implicated haploinsufficiency of TBX6 as a driver of the congenital anomalies of the kidney and urinary tract (CAKUT) observed in the chromosome 16p11.2 microdeletion syndrome. Although deletion in mice results in loss of posterior somites and formation of ectopic neural tubes (eNTBs), Tbx6-dependent mechanisms of genitourinary development remain elusive.

Methods: We generated an allelic series from independent null and hypomorphic *Tbx6* alleles. We then integrated bulk and single-cell transcriptomics, epigenetics, and transcription factor binding site analysis at E9.5 to identify target tissues and genes. Selected targets were validated by electrophoretic mobility shift assay and *in situ* hybridization.

Results: We found that severe inactivation of *Tbx6* at E9.5 results in a loss of inhibitory control of the *Kdm7a* promotor, leading to overexpression, driving NMPs to preferentially differentiate into posterior NTB cells and form eNTBs at the expense of intermediate mesoderm (IM). Furthermore, eNTBs likely secrete trophic factors that induce mal-patterning and ectopic positioning of the metanephric mesenchyme (MM). This therefore disrupts the normal interaction of the MM and ureteric bud (UB) required for kidney development resulting in renal agenesis and duplications of the collecting system. Interestingly, less severe Tbx6 inactivation does not yield eNTBs, but still causes renal hypodysplasia and ureteric obstruction. We found this to be due to a loss of Tbx6-dependent activation of the *Fgf9* promoter in the IM, leading to a mild depletion of this population.

Conclusions: Here we show spatially and temporally distinct mechanisms whereby Tbx6 influences urinary tract development. Severe inactivation exerts its effect through a *Kdm7a*-dependent pathway in NMPs, while less severe defects unmask a *Kdm7a*-independent, *Fgf9*-dependent effect on the IM. These findings illustrate the importance of spatially and temporally linked gene-dosage on multiorgan development and may also contribute to our understanding of regenerative medicine.

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FR-OR16

TGFβ Signaling Regulates Renal Patterning via Cadm1 During Nephrogenesis

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Background: Impaired nephrogenesis affects kidney health, causing childhood CKD and increasing CKD risk in adults. *Foxd1$^+$ kidney* stromal cells regulate nephron development by interacting with *Six2$^+$* nephrogenic precursors. Previously, we (Rowan CJ et al, *Development*, 2018) demonstrated that Hedgehog-GLI signaling in *Foxd1$^+$* stromal cells is required to promote murine nephrogenesis through TGFβ signaling, specifically via promoting the transformation of mesenchymal cells into epithelial cells (MET) in the *Six2$^+$* nephrogenic zone. However, the underlying molecular mechanisms that guide MET are incompletely defined. Here we aim to define molecular mechanisms by which TGFβ signaling regulates nephrogenesis.

Methods: Whole-kidney RNA seq and single-cell RNA seq to examine *Tgfβr2* deficiency in *Foxd1$^+$* stromal and *Six2$^+$* nephrogenic kidneys. We validated the bioinfrmatics data through immuno-staining and Western blot. Compound mutant mice were generated to investigate the deficiency of Cadm1 alone or both Tgfβr2 and Cadm1, followed by histological analysis, immunostaining, and nephron quantitation.

Results: Whole-kidney RNA seq (n=4) and scRNA seq (n=169 cell, P<0.001) in *Foxd1$^+$* stromal and *Six2$^+$* nephrogenic Tgfβr2-deficient kidneys identified Cadm1 (P<0.00003,P<0.0013) in *Foxd1$^+$*stromal cells as a TGFβ signaling downstream target. Western blot analysis in HEK-T293 cells (n=2) demonstrated that treatment with TGFβ1 induced CADM1 expression in a dose-dependent manner. Kidney tissue with Stromal and/or nephrogenic cell deficiency of Cadm1 exhibited normal nephrogenesis (n=2-3,P<0.01). Kidney tissue with deficiency of both *Tgfβr2* and *Cadm1* in *Foxd1$^+$* stroma exhibited renal hypodysplasia characterized by 32% reduction in kidney:body weight (n=6,P<0.0001), a 35% reduction in nephron number (n=3,P<0.05), expansion of *Six2$^+$* cells/UB tip (n=2,P<0.05), and loosely packed cortex and irregular stromal pattern (n=3). Similarly, kidney tissue with deficiency of both *Tgfβr2* and *Cadm1* in *Six2$^+$* nephrogenic cells exhibited renal hypodysplasia characterized by a 27% reduction in kidney:body weight (n=3,P<0.01), a 48% reduction in nephron number (n=2,P<0.05) and expansion of *Six2$^+$* cells/UB tip (n=3, P<0.01).

Conclusions: We conclude that Cadm1 is required for normal nephrogenesis in mice. Further, our data suggest that CADM1 may play a role in regulating the epithelialization of nephrogenic precursors under the influence of TGFβ signaling

Funding: Government Support - Non-U.S.

FR-OR17

ATP-Citrate Lyase (ACLY) Is a Key Modulator of Nephron Progenitor Cell Fate Decisions In Vivo

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Background: Nephron endowment at birth impacts long-term renal and cardiovascular health and is contingent on the nephron progenitor cells (NPC) pool. NPC fate decisions are influenced by the cell's metabolome. Acetyl-CoA is a key molecule involved in cellular metabolism. Acetyl-CoA provides energy and serves as a metabolic intermediate necessary for cellular growth and differentiation. However, the *in vivo* requirement of Acetyl-CoA for kidney development is still unknown.

Methods: Six2^{GFPCRE};Acly$^{f/+}$ males were bred to floxed Acly homozygous female mice to generate embryos lacking Acly expression in the NPC and nephrogenic lineage. Immunofluorescence (E14.5, E16.5, and P0) and organ culture (E12.5+24h) were used to characterize the mutant phenotype. NPC and fluorescence intensity quantifications were performed with ImageJ. H&E staining was used for morphological analysis and glomeruli counts.

Results: Removal of *Acly* (a gene that regulates cytosolic availability of acetyl-CoA) from the NPC pool during embryonic development led to a reduction in glomeruli counts (≈ 30%), depletion of cap-mesenchyme (WT = 44 vs MUT = 32 NPC/niche), and increased *Wnt4* expression at birth. Cap depletion and UB abnormalities were evident at E14.5 and E16.5. Sodium-acetate supplementation to cultured E13.5 mutant kidneys rescued cap mesenchyme depletion without hindering differentiation. Furthermore, *Six2Cre*-mediated removal of *Acly* led to the upregulation of Acyl-CoA Synthetase Short Chain Family Member 2 (Acss2) in nascent proximal tubules (PT) exclusively. Upregulation of *Acss2* suggested a compensatory route for acetyl-CoA production during PT nephrogenesis. The upregulation of *Acss2* was accompanied by an increased abundance of *Hnf4a*, a key regulator of proximal tubule maturation.

Conclusions: In conclusion, our findings revealed a crucial role of acetyl-CoA metabolism during kidney development and provided insights into the molecular mechanisms underlying early nephrogenesis. In addition, we identified a new molecular target with therapeutic potential to offset the programming process during early life to prevent the development of adult kidney disease.

Funding: NIDDK Support

FR-OR18

A Single-Cell Atlas of Human Fetal Kidneys Identifies Cell States Associated with Rare and Common Human Disease

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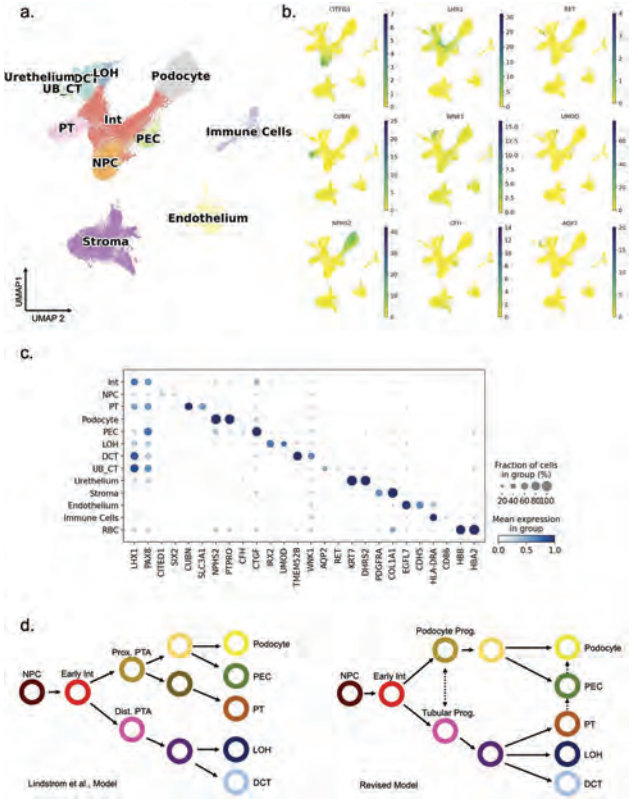
Background: Abnormal kidney development can present as congenital anomalies which can severely impact renal function. It is further thought that development may also influence more subtle phenotypes that can present later in life. Low birth weight is a risk factor for hypertension and prematurity is a risk factor for CKD.

Methods: We performed single cell RNA sequencing of 5 human fetal kidneys. We mapped developmental trajectories using RNA velocity and CellRank, creating a probabilistic model for cell differentiation in nephron development.

Results: We created an atlas of cells of human fetal kidney with a total of 65,348 cells, the largest, most comprehensive atlas of this tissue to date. This atlas demonstrates contiguous trajectories of cell states starting from a putative progenitor population to mature cell types. By examining diffusive properties within this map, we were able to identify and map previously hypothesized transitions between PTs, PECs and podocytes. We also applied this model to identify the cell states and transitions during fetal development to both common and rare human genetic disease, finding cell states that appear to be important in CAKUT, as well as cell states that influence adult eGFR.

Conclusions: We present the most complete atlas of the human fetal kidney to date. Using this atlas, we identify cell states are associated with human genetic disease and that these states are correlated by phenotype, leading to novel insights into developmental mechanisms of human disease.

Funding: NIDDK Support



FR-OR19

Identification of Genes and Regulatory Elements Affecting Human Kidney Function

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Background: The molecular mechanisms underlying human kidney disease remain largely unknown. Genome-wide association studies (GWAS) have identified hundreds of genomic loci associated with kidney function and disease. However, the genetic variants and genes mediating the effect of most of these loci remain unclear.

Methods: We performed a genome-wide association study (GWAS) of kidney function estimated using both creatinine and cystatin C in the UK Biobank and used functionally informed fine-mapping to identify putative causal kidney function variants. To determine the effect of genetic variants implicated in kidney function, we used scATAC-seq in human kidneys, genome-wide measurements of H3K27 acetylation (CUT&RUN), and measured the effect of CRISPR-mediated perturbation of regulatory elements on gene expression.

Results: We found that 58% of kidney function SNP-heritability localized to candidate regulatory elements of kidney tubule epithelial cells, an additional 6.5% localized to podocyte candidate regulatory elements, and <1% localized within endothelial, stromal, or immune cell-specific regulatory elements. We identified putative causal kidney function variants using functionally-informed fine-mapping and used these variants to identify regulatory elements and genes involved in kidney function. In human kidneys and primary tubule epithelial cells, we assessed how kidney function variants affect chromatin accessibility and enhancer function. We found that kidney function variants alter chromatin accessibility and enhancer function within tubule epithelial regulatory elements. A pooled screen targeting kidney function noncoding regulatory elements with CRISPR interference (CRISPRi) identified novel genes involved in human kidney function.

Conclusions: By integrating human genetics and studies of enhancer function, this work provides a framework for identifying variants, regulatory elements, and genes involved in human kidney disease. The combination of fine-mapping of GWAS-nominated variants, regulatory element identification, and mapping enhancers to regulated genes provides a framework for moving from GWAS to molecular mechanisms of disease.

Funding: NIDDK Support, Other NIH Support - NIAMS

FR-OR20

Genome-Wide Association Study Across Biobanks Identifies New Susceptibility Loci for Urinary Tract Infections

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Background: Urinary tract infections (UTIs) represent the most common bacterial infections worldwide and if untreated, can lead to pyelonephritis, urosepsis, and severe complications. Urologic abnormalities, immunosuppression, sexual activity, and other known risk factors do not completely explain why some individuals are more susceptible to severe or recurrent UTIs. Genetic predisposition to UTIs has not been well studied.

Methods: We designed an electronic phenotype for UTIs and defined 75,485 cases and 634,538 controls across several biobanks, including eMERGE, UKBB, BioVU, and All of Us. Cases were defined by ICD9/10 codes by ≥2 events ±1 week apart in the absence of known clinical risk factors. We performed a GWAS for UTI across diverse ancestries using REGENIE, controlling for age, sex, and genetic ancestry, followed by a fixed effects meta-analysis across individual biobanks. We also performed single cell RNA-seq (scRNAseq, 10x Genomics) of kidneys from mice ±UTI (n=10). We used UPEC isolate UTI89 in bacterial growth rate and recombinant protein binding assays.

Results: Our UTI GWAS meta-analysis defined several genome-wide significant loci, including the *PSCA* locus (P=2.9E-11). This gene is specifically expressed in urothelium and kidney papilla. Based on the latest kidney eQTL datasets, the risk allele at this locus was associated with lower *PSCA* expression in the tubulointerstitial compartment (P=8.8E-39). Our scRNAseq data demonstrated its expression in the kidney pelvic epithelial cells in both infected and noninfected mice, and RNA in situ localized kidney *PSCA* exclusively to the ascending thin limbs. In binding assays, we found *E. coli* bound to human PSCA, a heavily N-glycosylated protein (initial calculations show >1000 PSCA molecules/bacterium). Co-incubation with PSCA in vitro limited bacterial growth in a dose-dependent manner (0.35μM PSCA + 1E7 CFUs: 21% reduction at 8 hours (OD600 0.71±0.01 vs 0.56±0.02, p=0.004)).

Conclusions: Our large-scale multi-biobank-based GWAS combined with kidney scRNAseq data and bacteria binding assays identified *PSCA* as a candidate causal gene in human UTIs. *PSCA* is expressed in various urinary tract epithelia and inhibits bacterial growth in vitro. Our findings suggest that PSCA plays an important role in human innate immunity against bacterial UTIs.

Funding: NIDDK Support

FR-OR21

Empagliflozin Blunts Renal Mg2+ Wasting and Restores Distal Tubule Sodium Chloride Cotransporter (NCC) and TRPM6 Expression in Rats with Cisplatin-Induced Hypomagnesemia

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Background: The chemotherapeutic agent cisplatin is known to cause hypomagnesemia and renal Mg^{2+} wasting. Damage to the distal convoluted tubule (DCT), a key site of regulated Mg^{2+} reabsorption, may contribute. Recent clinical studies suggest that SGLT2 inhibitors increase serum Mg^{2+} concentration in patients with diabetes. However, the potential therapeutic use of SGLT2 inhibitors in a scenario of cisplatin-induced hypomagnesemia has not been investigated. This study tested the hypothesis that the SGLT2 inhibitor empagliflozin (EMPA) attenuates cisplatin-induced hypomagnesemia in rats through effects on the DCT.

Methods: Male Wistar rats (10 weeks of age) were treated weekly with cisplatin (2.5 mg/kg/or vehicle, i.p.) for five weeks. After three weeks of treatment, cisplatin (Cis) and vehicle-treated (Ctrl) rats were randomized and orally treated or not with EMPA (10 mg/kg/day) for two weeks.

Results: Cis-treated rats developed significant hypomagnesemia (1.42 ± 0.05 vs. 2.19 ± 0.03 mg/dl in Ctrl and 2.23 ± 0.03 mg/dl in Ctrl + EMPA, $P < 0.0001$) and increased fractional excretion (FE) of Mg^{2+} compared to control groups (14.3 ± 1.3 vs. 0.48 ± 0.10% in Ctrl and 0.65 ± 0.10% in Ctrl + EMPA, $P < 0.0001$). EMPA reduced FE Mg (2.2 ± 0.2 vs. 14.3 ± 1.3% vs. $P < 0.0001$) and restored Mg^{2+} serum levels in Cis-treated rats (2.21 ± 0.05 mg/dl). The mRNA and protein abundance of NCC and TRPM6 and NCC phosphorylation were reduced in Cis-treated rats and rescued by EMPA. EMPA-treated Ctrl rats displayed higher NCC and TRPM6 mRNA and protein expression and NCC phosphorylation levels than untreated Ctrl. The effects of cisplatin and EMPA on NCC were confirmed using a hydrochlorothiazide (HCTZ) challenge. The natriuretic response to HCTZ in Cis-treated rats was lower and in Ctrl + EMPA higher than the other groups of rats. No difference was found in the natriuretic response to HCTZ between controls and EMPA-treated Cis-rats. Remarkably, immunohistochemistry suggested that EMPA reversed Cis-induced DCT injury.

Conclusions: Empagliflozin blunts renal Mg^{2+} wasting and restores serum Mg^{2+} concentration in cisplatin-treated rats. The effects of the SGLT2 inhibitor were associated with reversal of DCT injury, rescue of expression of TRPM6, NCC, and phosphorylated NCC, and normalization of NCC activity.

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FR-OR22

Critical Role of mTORC2 in Maintaining Sodium and Potassium Balance: Implications for Aldosterone-Independent Regulation of Epithelial Sodium Channel (ENaC) in the Distal Nephron

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Background: mTOR complex-2 (mTORC2) is crucial for maintaining sodium and potassium balance in the kidneys and responding to high K^+ ingestion. Recent evidence supports the idea that, in contrast to the late connecting tubule (CNT) and cortical collecting duct (CCD), ENaC activity in the late distal convoluted tubule (DCT2) and early CNT is not aldosterone-dependent. Here, we examined the role of mTORC2 in distal nephron K^+ secretion by disrupting mTORC2 expression in various distal segments and examining its effects on potassium secretion during high dietary potassium conditions.

Methods: Rictor, a core component of mTORC2, was selectively knocked out (KO'd) in specific segments of the distal nephron or throughout the entire nephron using segment-specific Cre-Lox- KO techniques. Both WT and KO mice were fed a high K^+ diet for short-term (4 h) or medium-term (48 h). Various parameters, including urinary and blood electrolytes, renal transporter expression and activity, and phosphorylation status of mTORC2 targets were assessed.

Results: Mice lacking mTORC2 in the DCT2 and CNT (using Calbindin as Cre-driver) responded to high K^+ intake in a manner resembling mice in which Rictor was KO'd throughout the nephron (using Pax8/LC1): they developed hyperkalemia, increased urine output, elevated BUN levels, lower serum sodium, and elevated plasma aldosterone levels under both short (4 h) and medium (48 h)-term high K^+ diet conditions. After 48 h under HK diet, these mice showed severe pathophysiological changes including weight loss, reduced food intake, markedly reduced GFR and listlessness. Phosphorylation of mTORC2 targets, involved in ENaC regulation (SGK1 and Nedd4-2) was also reduced in KO mice. Mice lacking mTORC2 specifically in the AQP2-expressing distal part of the CNT and CCD displayed a milder phenotype with elevated aldosterone but normal plasma [K^+].

Conclusions: The data suggest that mTORC2 activity is crucial for maintaining aldosterone-independent ENaC activity in the late DCT and preserving potassium balance during high dietary potassium intake.

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FR-OR23

Role of KLHL3-S433 Phosphorylation in Potassium Homeostasis in Mice

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Background: Kelch-like 3 (KLHL3) is a component of an E3 ubiquitin ligase complex that binds and degrades with-no-lysine kinases (WNKs) in the kidney. Previously, we reported that volume depletion and potassium(K) changes regulate KLHL3 function by altering phosphorylation at S433, thereby regulating fluid homeostasis. The current study was designed to demonstrate the physiological importance of S433 in KLHL3 function in vivo in mice.

Methods: S433 of KLHL3 was substituted to non-phosphorylatable Ala by CRISPR/Cas9 (KLHL3-S433A knock-in mice: KI). Baseline characteristics, as well as the response to K loading and to salt restriction, were compared between wild-type (WT) and KI. Efects of intestinal K binding by sodium zirconium cyclosilicate (SZC) was also tested.

Results: KI showed a significant increase in plasma K levels that were attributable to the decreased renal excretion. KI also showed a decrease in plasma bicarbonate and an increase in blood pressure compared with WT. In KI, KLHL3 protein abundance (but not mRNA levels) was significantly reduced, which was accompanied by the increase in KS-WNK1, WNK4, and NCC, suggesting that S433 is important for the protein stability of KLHL3. In immunofluorescence, WNK1 puncta was observed not only in distal convoluted tubule but also in AQP2-positive collecting duct. In the renal cortex, K channel ROMK was decreased, not increased, in KI compared with WT. Given that $KLHL3^{S433A}$ can target WNK4 for degradation in vitro, we evaluated the response to K loading and to salt restriction. K challenge via 1% KCl did not alter plasma K in WT, while KI Plasma K increased to 1.7 mmol/L. In the kidney, NCC was significantly decreased by K in WT, whereas it remained unchanged in KI. Furthermore, although plasma K levels were significantly reduced by SZC in KI, NCC remained unaltered. Finally, increased aldosterone by a low-salt diet not alter plasma K in WT, whereas KI showed a significant reduction in plasma K in response to the same diet.

Conclusions: KLHL3-S433 regulates K homeostasis by controlling NCC and likely ROMK. The significant changes in plasma K levels in response to K loading and to volume depletion in KI indicate that the context-dependent regulation of renal K handling in high aldosterone states is compromised in this model, demonstrating the critical role of $KLHL3^{S433}$ phosphorylation in the molecular basis of aldosterone paradox.

FR-OR24

PIEZO1 Channels Are Necessary for BK Channel-Mediated Flow-Induced K+ Secretion (FIKS) in the Cortical Collecting Duct (CCD)

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Background: BK channel-mediated FIKS in intercalated cells (IC) of the CCD requires an elevation in intracellular calcium concentration $[Ca^{2+}]_i$ triggered by hydrodynamic forces associated with an increase in tubular fluid flow rate (TFFR). This increase in $[Ca^{2+}]_i$ is proposed to be due to influx of extracellular Ca^{2+} through apical and basolateral mechanosensitive Ca^{2+} channels and release of Ca^{2+} from internal stores. We previously identified functional expression of the mechanosensitive Ca^{2+} channel PIEZO1 at the basolateral membranes of CCD principal (PC) and ICs (ASN Kidney Week, 2021). We hypothesize that PIEZO1 contributes to the flow-induced increase in $[Ca^{2+}]_i$ necessary for BK channel-mediated FIKS.

Methods: To test this hypothesis, control and conditional IC-cell *Piezo1* KO mice were fed a high K^+ diet (HK, 5% K^+) for 10 d. Isolated CCDs were microperfused *in vitro* to measure flow-induced increases in $[Ca^{2+}]_i$ and net transepithelial transport (J_X) of Na^+ and K^+ at slow and fast tubular fluid flow rates (0.9 and 5.5 nl/min·mm).

Results: Both PCs and ICs from control mice exhibited typical biphasic increases in $[Ca^{2+}]_i$ in response to an acute increase in TFFR. However, flow-induced $[Ca^{2+}]_i$ transients were significantly dampened in ICs from conditional IC-cell *Piezo1* KO mice ($p \leq 0.001$, n=4/group). Similar rates (in pmol/min.mm) of flow-stimulated J_{Na} were observed in CCDs from control (49.9±5.5) and KO (51.2±5.2, p=0.7; n=6, including 3 male and 3 female/group) mice with no significant differences between sex. FIKS, present in control CCDs (5.3±1.2), was absent in tubules from conditional KO mice (1.0±1.2; $p<0.005$). IC-cell *Piezo1* KO male mice exhibited higher blood [K^+] vs controls, 30 and 60 mins after gavage administration of 5% KCl solution (7.8±0.91 and 6.4±0.89 vs 6.5±0.35 and 5.1±0.17 mmol/L, n=6/group; p=0.01 and 0.02 respectively).

Conclusions: We conclude that mechanoactivated PIEZO1 channels mediate basolateral influx of Ca^{2+} in CCD ICs, and are indispensable for BK channel-mediated FIKS. We further speculate that basolateral PIEZO1 channels are activated by increases in membrane tension associated with an increase in TFFR.

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FR-OR25

The Role of Renal Mechanotransduction in Blood Volume Sensing

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Background: The kidneys tightly control the composition of our internal environment to maintain homeostasis in the face of external variability. For example, the regulation of blood volume begins in the kidneys and is essential for vertebrate life in terrestrial environments where salt and water availability are unpredictable. Renin release by specialized juxtaglomerular cells of the kidney is the rate-limiting step in an essential hormonal cascade that modulates blood volume, filtration, and salt balance. For several decades, it was known that renin is released in response to a loss of mechanical cues triggered by relaxation of the afferent arteriole. However, the identity and physiological significance of the mechanosensor in these cells was unknown. Here we examine the expression, function, and requirement of force-gated ion channels in renal juxtaglomerular cells.

Methods: We use in situ hybridization and immunohistochemistry to characterize the localization of force-gated ion channels in the juxtaglomerular apparatus (JGA). We generated conditional knockout mouse lines targeting stromal progenitors, cells of renin lineage, and adult-inducible pericyte-like cells, encompassing both the mesangium and the renin-expressing JG cells. We then subjected male and female mice to measurements of RAAS pathways hormones, glomerular filtration rate, and systemic blood pressure. Additionally, we isolated glomeruli from the kidneys of transgenic mice and cultured primary renin-expressing and mesangial cells for whole cell voltage clamp electrophysiology in order to measure mechanically activated currents due to force-gated ion channels.

Results: We find that loss of mechanotransduction in renin-expressing JG cells perturbs renal function and RAAS under normal conditions and subcutaneous polyethylene glycol-evoked hypovolemia. Specifically, we observe that genetic loss of mechanotransduction

enhances renin release and RAAS function and promotes glomerular hyperfiltration. Furthermore, we find that primary cultured renin-expressing and mesangial cells are mechanosensitive and express functional force-gated ion channels.

Conclusions: Our findings highlight the importance of mechanotransduction within the JGA to renal blood volume sensing and represent the first molecular and cellular characterization of JGA mechanosensitivity and the consequences of its loss *in vivo*.

Funding: Private Foundation Support

FR-OR26

Kidney Tubular YAP Controls the Expression of Collecting Duct Aquaporins and Water Homeostasis

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Background: Final urine volume and concentration are defined by water reabsorption through the water channel proteins aquaporin (AQP)-2, -3 and -4 in the collecting duct. However, the transcriptional regulation of these AQPs is not well understood. The Hippo/YAP pathway plays an important role in organ size control and tissue homeostasis. When the Hippo pathway including the Mst1/Mst2 kinases is inhibited, YAP is activated and functions as a transcription co-activator. Our previous work revealed a pathological role of tubular YAP activation in chronic kidney disease, but the physiological role of YAP in the kidney remains to be established.

Methods: Tubule-specific Yap knockout (Yap cKO) mice were generated by crossing *Yap$^{f/f}$* mice with *Ksp-Cre* mice. Tubule-specific Mst1/Mst2 double (dKO) and Mst1/Mst2/Yap triple (tKO) mice were generated by crossing *Mst1$^{f/f}$;Mst2$^{f/f}$* or *Mst1$^{f/f}$;Mst2$^{f/f}$;Yap$^{f/f}$* mice with *Ksp-Cre* mice respectively. Primary mouse medullary collecting duct cells were isolated from control and Yap cKO mice. RNA sequencing was performed on the medullae of control and Yap cKO mice at 6 weeks of age. ChIP-qPCR was performed using an YAP antiboty to determine whether YAP binds to the promotors of the Aqp2 and Aqp4 genes. Immunoprecipitation experiments were carried out to examine the interactions of YAP and GATA2, GATA3 or NFATc1.

Results: Tubule-specific Yap knockout mice showed increased urine output and decreased urinary osmolality. Decreases in Aqp2, -3 and -4 mRNA and protein abundance in the kidney were evident in Yap knockout mice. Analysis of Mst1/Mst2 double knockout and Mst1/Mst2/Yap triple knockout mice showed that expression of Aqp2 and Aqp4 but not Aqp3 was dependent on YAP. Furthermore, YAP was recruited to the promoters of the Aqp2 and Aqp4 genes and stimulated their transcription. Interestingly, YAP was found to interact with transcription factors GATA2, GATA3 and NFATc1. These three factors promoted Aqp2 transcription in a YAP dependent manner in collecting duct cells. These three factors also promoted Aqp4 transcription whereas only GATA2 and GATA3 enhanced Aqp3 transcription.

Conclusions: Our results suggest that YAP promotes Aqp2 and Aqp4 transcription, interacts with GATA2, GATA3 and NFATc1 to control Aqp2 expression, while Aqp-2, -3 and -4 exploit overlapping mechanisms for their baseline transcriptional regulation.

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FR-OR27

Calcium-Binding Protein 39 (Cab39) Is Required for Na+-Cl- Cotransporter (NCC) Phosphorylation in Mice

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Background: The Na^+-Cl^- cotransporter (NCC), expressed along the distal convoluted tubule (DCT) in the kidney, is essential for sodium and potassium homeostasis and blood pressure (BP) regulation. We showed previously that WNK4 (with-no-lysine kinase 4) phosphorylates and activates SPAK (STE20/SPS1-related proline/alanine-rich kinase), which in turn phosphorylates and activates NCC. According to *in vitro* studies, calcium-binding protein 39 (Cab39) is a scaffold that facilitates SPAK activation by stabilizing a fully active kinase conformation. Cab39 and its homolog, Cab39-like (Cab39l), are both are expressed in the DCT. A previous study published in abstract form showed that Cab39l-knockout (Cab39l-KO) mice did not exhibit differences in electrolyte homeostasis or BP compared with wild-type mice. Here we created a Cab39/Cab39l double knockout mouse to test if the adaptor proteins are necessary for WNK-SPAK-NCC signaling *in vivo*.

Methods: Inducible NCC-Cre was used to remove Cab39 along the DCT, creating DCT-specific double knockout (DKO) mice against a background of global Cab39l-KO mice. With blood electrolyte analysis, protein quantification and localization analyses were carried out using Western blotting and immunofluorescence, respectively in wild-type or single Cab39l-KO and Cab39/Cab39l double knockout (DKO) mice.

Results: We showed that phosphorylated NCC abundance, a proxy for NCC function, and total NCC abundance were significantly lower in DKO mice. Despite having higher levels of WNK4 and equal levels of total and phosphorylated (active) SPAK, DKO mice on a low K^+ diet, a known activator of NCC function, had lower blood [K^+] and significantly less phosphorylated and total NCC abundance. Importantly, SPAK was distributed in puncta in the DKO mice, compared to the apical membrane of wild-type mice.

Conclusions: Our study demonstrates that Cab39 is critical for SPAK phosphorylation and localization and NCC function. Deletion of Cab39/Cab39l along the DCT prevents SPAK activation and causes SPAK to be confined to cytosolic puncta. Mice lacking Cab39 have compromised NCC function, reminiscent of Gitelman syndrome.

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FR-OR28

Extracellular Calcium-Sensing Receptor (CaSR) and Vasopressin Type 2 Receptor (V2R) Interaction: An Emerging Mechanism to Fine-Tune Water Permeability in Renal Cells

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Background: We have previously shown that Extracellular Calcium-Sensing Receptor (CaSR) signaling counteracts Vasopressin type 2 Receptor (V2R) signaling in renal collecting duct cells. In collecting duct principal cells, the V2R is expressed in both the basolateral and apical membranes.

Methods: Biochemical, computational, and functional methods were used to provide evidence that CaSR and V2R interact as multimeric complex. AQP2-mediated osmotic water permeability measurements were performed to evaluate the functional CaSR/V2R interaction.

Results: In collecting duct MDC4 cells and mouse kidney, immunolocalization and confocal xz reconstruction confirmed that both the CaSR and V2R are co-expressed in the apical membrane with a significant degree of co-localization. Moreover, the CaSR co-immunoprecipitated with the V2R, and stimulation with vasopressin increased the amount of immunoprecipitated CaSR. Proximity ligation experiments confirmed CaSR/V2R interaction and their sensitivity to vasopressin stimulation. In silico comparative modeling analysis allowed us to predict a possible structure of the CaSR/V2R protein complex. Functional data obtained in isolated perfused rat inner medullary collecting duct indicated that luminal vasopressin acts as a negative feedback system to the basolateral action of vasopressin on osmotic water permeability (Pf), and luminal CaSR activation further inhibited the Pf providing a functional significance to the described receptor-receptor interaction.

Conclusions: This study opens new perspectives on the regulation of AQP2 trafficking and function not considered when the two GPCRs are viewed individually.

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FR-OR29

Inhibition of Urate Transporters and Insulin-Activated Urate Transport by SGLT2 Inhibitors

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have well-established uricosuric and urate-lowering effects, with protective effects on gout. The mechanisms of these uricosuric effects are not clear, however, and direct effects on urate transporters have not been fully investigated. We report the effects of empagliflozin, canagliflozin, and dapagliflozin on urate transport in a human proximal tubular cell line and in *Xenopus* oocytes expressing individual urate transporters.

Methods: Western blotting, *in vitro* transcription of cRNA from cloned cDNA and urate transport assays in human renal proximal tubule epithelial cells (PTC-05) and *Xenopus laevis* oocytes expressing individual human urate transporters.

Results: SGLT2 inhibitors significantly inhibited net urate uptake in a dose-dependent manner in human PTC-05 cells, which express endogenous SGLT2 and the urate transporters GLUT9a, GLUT9b, OAT10, OAT1, NPT1, ABCG2 and ABCC4. In the *Xenopus laevis* oocyte expression system, these inhibitors inhibited the basal urate transport activities of URAT1, OAT10, OAT3 and ABCC4 but not GLUT9, OAT1, and ABCG2. OAT10 was only modestly sensitive to empagliflozin and canagliflozin (~38% and 28% inhibition with 500 μM empagliflozin and canagliflozin respectively). For URAT1, the IC50s for empagliflozin, canagliflozin, and dapagliflozin were 460, 230, and 487 μM, respectively; for OAT3 the IC50s were 42, 29, and 21 μM, respectively. In addition, SGLT2i inhibited insulin-induced stimulation of urate transport in PTC-05 cells, with dose-dependent inhibitory effects on insulin-induced phosphorylation of the downstream Akt and ERK kinases.

Conclusions: These results indicate that the uricosuric action of SGLT2 inhibitors is at least partially due to direct inhibition of the apical urate reabsorptive transporters URAT1 and OAT10. Additionally, SGLT2 inhibitors inhibited insulin-activated transport in a human proximal tubular cell line, with attenuated phosphorylation of Akt and ERK; given the key role for insulin-activated urate transport in the genesis of hyperuricemia this indicates another potential mechanism for SGLT2i-associated uricosuria.

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FR-OR30

ENaC Inhibition with Trimethoprim Occurs Without Changing Urinary H+ Excretion

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Background: There is growing consensus that collecting duct H^+ secretion occurs independent of changes in the transepithelial voltage (V_{te}). We recently identified a new mechanism how benzamil stimulates acute urinary alkalization. In addition to its

direct inhibition of the epithelial sodium channel (ENaC), benzamil acutely impairs H^+ excretion by blocking the H^+/K^+ ATPase. The latter effect explains benzamil's acute and marked effect on urine alkalization. However, the question remained whether inhibition of ENaC activity causes alterations in renal H^+ excretion. To revisit this question, we studied the effect of a direct ENaC inhibitor which is structurally different from benzamil. Here, we chose the antibiotic molecule trimethoprim, well-known to cause K^+ retention by direct ENaC inhibition.

Methods: *In vivo* experiments were performed in bladder-catheterized C57BL/6J mice, allowing real-time measurement of urinary pH, electrolyte, and acid excretion. Trimethoprim was administered as an intraperitoneal bolus injection (5 µg/g bw). Additionally, the effect of trimethoprim on H^+/K^+-ATPase activity was assessed *in vitro* in pig gastric H^+/K^+ ATPase enriched membrane vesicles under different pH and extracellular K^+ concentrations.

Results: We find that trimethoprim inhibits ENaC, acutely increasing natriuresis and decreasing kaliuresis, thus confirming earlier studies. However, trimethoprim had no effect on urinary pH or net acid excretion, contrasting the effects of benzamil that acutely alkalizes the urine and reduces net acid excretion. Moreover, *in vitro* experiments on isolated pig gastric H^+/K^+-ATPase proteins showed near to no effect of trimethoprim on the pump's activity, again contrasting the action of benzamil.

Conclusions: In comparison to benzamil, that inhibits both ENaC and the H^+/K^+-ATPase proteins, the renal action of trimethoprim appears to be confined to ENaC inhibition. These findings further support the hypothesis that inhibition of ENaC does not cause inhibition of H^+ secretion in the collecting duct. Thus, these results add an additional argument refuting the hypothesis of voltage-dependent H^+ secretion in collecting duct.

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FR-OR31

Decoding the Spatial Transcriptomic Landscape of Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is a major cause of chronic kidney disease globally. However, the lack of targeted treatments for renal fibrosis in DN is due to an incomplete understanding of disease progression. We generated a detailed map of human diabetic nephropathy by employing single-cell gene expression and spatial transcriptomic profiling of DN patients and controls.

Methods: We characterized the signature of diabetic nephropathy through spatial transcriptomics, analyzing eight patient biopsies using the 10x VISIUM-FFPE platform. Integrating spatially resolved transcriptomics with single-cell gene expression, we mapped cell types in space, revealing the spatial organization and structure of DN tissue. Our analysis included trajectory analysis for cell transition directions, spatial dependencies between signaling pathways and cell types, and gene-regulatory networks distinguishing DN from normal kidney tissue. Furthermore, subcellular characterization of 100 genes of interest was performed using Molecular Cartography on frozen tissues from the same patients.

Results: Deconvoluting spatial transcriptomic spots into cell-type abundances unveiled the spatial organization of kidney tissue, identifying major cell-type niches as structural building blocks. Within the glomerulus niche, we inferred a pseudotime trajectory from endothelial cells to pathogenic fibroblasts (*IGKC*+), supported by significant upregulation of *POSTN* in DN endothelial cells. We linked spatial cell composition information to cellular functions, detecting increased TGFß signaling activity in areas abundant in mesangial cells and fibroblasts. In the fibrotic niche, we observed strong dependencies between mesenchymal cells and leukocytes, highlighting the key role of macrophages in fibroblast activation. Subclustering fibroblasts and mesangial cells identified pathogenic fibroblasts (Fib 6) marked by *IGKC* and pathogenic mesangial cells (MES 2 & 3) marked by *TMSB4X*, *MYL9*, and *ACTA2*. Additionally, we discovered a novel innate immune checkpoint, *CD63*, highly expressed in DN samples and specifically overexpressed in Fib 6 and MES 2 & 3, supporting its crucial role in DN fibrogenesis.

Conclusions: Our study provides an integrative molecular map of diabetic nephropathy, serving as a vital reference for the field and facilitating advanced mechanistic and therapeutic investigations of diabetic kidney disease.

FR-OR32

Spatially Localized Mesangial Cell Communication in Diabetic Kidney Disease

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Background: Substantial knowledge has been gained regarding podocyte injury in diabetic kidney disease (DKD) but less is known about the mechanisms of mesangial expansion, nodule formation, and its relationship with neovascularization. Changes in communication between injured cells serve as both a marker of disease progression and a mediator, promoting injury responses through positive feedback in surrounding cells. In this study, we aim to spatially localize changes in intra-glomerular communication between mesangial, endothelial, and epithelial cells.

Methods: We subsetted the KPMP / HuBMAP snRNAseq atlas into reference (N=11) and diabetic (N=7) samples. Using the CellChat database, we modelled cell-cell communication in glomerular cell types. The snRNAseq atlas was used as reference to deconvolute 23 kidney spatial transcriptomics samples, including reference (N=6) and diabetic (N=10). The modelled cell-cell communication and associated pathway vectors were then localized onto glomeruli with COMMOT.

Results: The cellular communication decreases in diabetic glomeruli (442) when compared to reference (1092). The overall loss of receptor-ligand interaction is more pronounced in diabetic mesangial cells, from 309 to 55 (p value < 10^{-9}, Fisher's Exact). Some of the communication absent in diabetic mesangial cells include the JAG1 - NOTCH interaction with glomerular capillaries and podocytes and the Gas6 – TAM, cell proliferation, angiogenesis and immune activation. Associated pathways were differentially represented in healthy control and DKD spatial transcriptomic samples.

Conclusions: These studies indicate a change in the intercellular communication in diabetic glomeruli. Identified pathways are potentially implicated in the process of neovascularization, mesangial expansion and glomerulosclerosis.

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FR-OR33

Interferon-γ (IFN-g) Signaling in Diabetic Kidney Disease (DKD) Associated with ESKD

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Background: The mechanisms by which circulating pro-inflammatory factors modulate kidney signaling and disease progression in DKD remain poorly defined.

Methods: SOMASCAN plasma proteomics (n=162) and RNA profiles (n=74) from kidney biopsies of Southwest Native Americans with type 2 diabetes were used to identify differentially expressed genes (DEGs) and proteins and upstream regulators (URs) associated with progression to ESKD. Based on quantitative transcriptomic analysis, activation scores for IFN-g signaling were computed and associated with structural lesions and outcomes in DKD patients. These findings were validated in cultured human kidney cell lines, kidney tissue from 2 DKD mouse models (DBA/2 podocyte-JAK2 transgenic and uninephrectomized BKS ReninAAV db/db mice) and human kidney organoid cultures.

Results: Plasma IFN-g was upregulated in ESKD patients and identified as the top predicted UR for ESKD-associated kidney DEGs. Higher IFN-g activation scores, in both glomeruli and tubulo-interstitium correlated (r=0.40 and 0.35, respectively, p<0.05) with faster GFR decline. Participants with higher scores were more likely to reach ESKD (p<0.05). IFN-g significantly increased activation scores in cultured human kidney podocytes and proximal tubular cells (p<0.0001). Inhibition of the IFN-g pathway by a JAK1/2 inhibitor baricitinib reduced the activation scores and ameliorated albuminuria and mesangial expansion in podocyte JAK2 transgenic DBA/2 mice. Similar phenotypic improvements were observed in ReninAAV db/db uNx mice after treatment with the JAK1/2 inhibitor, ruxolitinib. Single cell profiling of IFN-g-treated organoids demonstrated the presence of IFN-g receptors and downstream target gene *CXCL10* in kidney cell types. Higher kidney organoid IFN-g scores following stimulation with IFNG were suppressed with baricitinib. Secreted CXCL10 protein strongly associated with the IFN-g activation score in organoids.

Conclusions: Circulating IFN-g levels were directly associated with alterations in kidney transcriptomic programs and the progression to ESKD in human DKD and multiple models. A clinically available drug (baricitinib) reversed IFN-g activation and albuminuria in murine models identifying IFN-g as a target for treatment in DKD.

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FR-OR34

Metabolomic and Transcriptomic Reveal Signature of Citrate Homeostasis in Diabetic Kidney Disease

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Background: Kidneys are highly metabolic organs, and the TCA cycle primarily fulfills the enormous energy required to maintain their normal function. In our previous cross-sectional study, low urinary citrate was associated with chronic kidney disease progression in Type 2 Diabetic patients. In this study, we performed a longitudinal targeted urinary metabolomic screening in 4 cohorts of Type 1 Diabetic (T1D) patients and single-cell RNAseq analysis of separate kidney biopsies to explore potential metabolic reprogramming in diabetic kidney disease (DKD).

Methods: Metabolomic markers for DKD progression were investigated in a case-control study of four geographically and ethnically distinct cohorts (EDC, CACTI, STENO, and FinDiane) of type 1 diabetic patients. Cases were identified among patients with yearly eGFR decline ≥3 ml/min/1.73m2, while controls had yearly eGFR decline <1 ml/min/1.73m2. 42 urinary metabolites were measured using ZipChip mass spectrometry over 1750 participants. Comparative transcriptomics analysis was conducted in 11 kidney resident cells using Kidney Precision Medicine Project (KPMP) single-cell RNAseq data sets. Spatial metabolomic analysis in kidney biopsies was performed using MALDI-MSI.

Results: Glycolic acid and three TCA cycle metabolites, citrate, succinate, and fumarate, were significantly decreased in the cases compared to the control. Among them, citrate and glycolic acid were significantly associated with rapid eGFR decline and albuminuria. Single-cell RNAseq analysis demonstrates increased fatty acid uptake, impaired β-oxidation, improved glycolysis, partially maintained TCA cycle, and mitochondrial citrate accumulation in proximal tubules of DKD patients. Spatial metabolomic analysis reveals citrate accumulation in kidney biopsies of T1D patients compared to healthy control. Proximal tubule-specific upregulation of ACLY indicates the entry of accumulated citrate in *de novo* lipogenesis. The downregulation of both apical and basolateral membrane citrate transporters SLC13A2 and SLC13A3 implies dysregulation of tubular citrate flux in DKD.

Conclusions: Low urinary citrate could be a potential marker for CKD progression in T1D patients, and intracellular citrate homeostasis could be associated with DKD progression.

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FR-OR35

Whole Blood DNA Methylation Signature, Circulating Proteins, and Risk of Progression to ESKD in Type 1 Diabetes (T1D)

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Background: Diabetic Kidney Disease (DKD) can progress to end stage kidney disease (ESKD) which increases morbidity and mortality. Since commonly utilized clinical variables do not adequately predict ESKD onset, there is an unmet need to update the current ESKD risk prediction model with more sensitive biomarkers. We examined whether DNA methylation (DNAme) can fulfil this need.

Methods: Using human EPIC DNAme arrays, we profiled DNAme in whole blood DNAs of 277 well characterized T1D participants with DKD (median eGFR 52.2mL/min/1.73m^2 and ACR 728.9mg/g) from the Joslin Kidney Study; 51% of our cohort developed ESKD during follow-up (7-20 years). We then performed epigenome-wide analysis followed by integration with genetics and circulating proteins data (Olink) from the same cohort, and developed statistical models including DNAme for ESKD-risk prediction.

Results: We identified DNAme at 17 CpGs associated with ESKD risk (ESKD-associated CpGs) independent of major demographic/clinical risk factors. These CpGs were located in/near genes related to pathogenesis of DKD and/or ESKD, including inflammation. Notably, 7 of these ESKD-associated CpGs had methylation quantitative trait loci SNPs. Some of these SNPs could affect binding sites for key transcription factors with functions related to DKD, suggesting novel links between genetic variants and ESKD via DNAme. Moreover, the impact of 5 of these CpGs on ESKD-risk were partially mediated by several circulating proteins previously reported to be associated with ESKD e.g. TNF-R27 and KIM1, suggesting downstream functions of these CpGs on target cells/tissues related to inflammation and renal injury. Notably, using our ESKD-associated CpGs, we developed two updated ESKD prediction models by adding DNAme at selected CpGs, or a DNAme score (imputed using selected CpGs) to the Clinical Model (using only clinical predictors). Both updated models markedly improved ESKD prediction (by 20%) compared to the Clinical Model alone.

Conclusions: Our results identified novel putative epigenetic DNAme prognostic biomarkers to significantly improve ESKD risk prediction in T1D, and uncovered molecular mechanisms of DNAme involvement in ESKD, both important for early detection and prevention.

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FR-OR36

Single-Cell Resolution Drug Effects on RAAS Blockade in ZSF1 Rat Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of renal failure worldwide. Overactivation of the renin-angiotensin-aldosterone system (RAAS) is associated with detrimental outcomes in DKD patients. RAAS inhibitors such as enalapril have been used for decades as antiproteinuric, antihypertensive, and kidney protective agents. Still, the exact cell type of action and the main drivers of drug action remain elusive.

Methods: To this end, in addition to detailed biochemical, histological, and tissue proteomics analysis of the ZSF1 obese rat with or without enalapril treatment, we leveraged single-cell transcriptomics (scRNA-seq). We exploited state-of-the-art analyses of unbiased tensor decomposition, differential gene expression, pathway enrichment, cell trajectories, RNA velocity, weighted gene correlation networks, integration with CITE-seq imputed antibody-derived tags, and cell-cell communication. Results from the ZSF1 model were validated in human kidney samples and datasets.

Results: RAAS inhibition via enalapril ameliorated hypertension, proteinuria, kidney tissue levels of progression markers, and fibrosis in the ZSF1 rat model of DKD. ScRNA-seq highlighted immune cell enrichment, endothelial and tubular cell depletion. Unbiased tensor decomposition analysis showed distal nephron tubule cells were associated with treatment status. Enalapril downregulated cathepsin D (*Ctsd*) in diabetic distal nephron and myeloid cells. *Ctsd*+ injured tubule cells of the distal nephron were enriched in DKD and depleted upon enalapril treatment. *Ctsd* was also a marker for *Trem2*+ residential macrophages, which demonstrated an inflammatory phenotype and interacted strongly with distal nephron tubule cells. *CTSD* was particularly enriched in kidneys from DKD patients and correlated with outcome-relevant parameters such as fibrosis and glomerular filtration rate.

Conclusions: We report previously unknown injury cell states of the distal nephron, describe CTSD as an important regulator of enalapril effects, and reveal *Trem2*+ residential macrophages as top receivers of distal nephron cell-cell communication. Finally, we show that our findings translate to humans and demonstrate that enalapril-associated gene signatures allow stratification of human kidney samples by disease-relevant outcome measures such as kidney function and fibrosis.

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FR-OR37

Long Noncoding RNA (lncRNA) PVT1 Induces Mitochondrial Damage and Inflammation via TRIM56 in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD), one of the chronic microvascular complications of diabetes mellitus (DM), is the leading inducement of end stage renal disease (ESRD) globally, and increasing number of studies have demonstrated that immunity and inflammation are key pathogenic mechanisms in DKD. Notably, hyperglycemia-induced mitochondrial dysfunction played a pivotal role in activating innate immunity. However, the concrete mechanisms responsible for mitochondrial damage and inflammation of podocytes during DKD remain poorly understood.

Methods: The role of *PVT1* was investigated by resorting to cultured podocytes, podocyte-specific deletion of *Pvt1* (*Nphs2-Cre/Pvt1$^{flox/flox}$*) mice and human samples. RT-qPCR, western blotting, RNA-FISH, TEM, histology staining, immunofluorescence, RIP, MeRIP, RNA pull-down, luciferase reporter assays, and Seahorse XF Cell Mito Stress Test were utilized for mechanistic study of the interaction between *PVT1*, TRIM56 and AMPKα further.

Results: We observed a significant upregulation of long non-coding RNA (lncRNA) *PVT1* in plasma of patients with DKD. And we generated mice with podocyte-specific deletion of *Pvt1* (*Nphs2-Cre/Pvt1$^{flox/flox}$*) and confirmed that *PVT1* deletion ameliorated diabetes-induced podocyte injury, glomerular pathology and proteinuria. We further demonstrated a novel role of *PVT1* in regulating podocyte mitochondrial dysfunction and inflammation through TRIM56-mediated cGAS-STING signaling pathway. Similar results were validated in podocyte-specific deletion of *Trim56* (*Nphs2-Cre/Trim56$^{flox/flox}$*) in DKD mice models. Mechanistically, *PVT1* was upregulated due to m6A demethylation under hyperglycemia conditions, and the stabilized *PVT1* involved in mitochondrial dysfunction by interacting with TRIM56 post-transcriptionally to manipulate the ubiquitination of AMPKα, which subsequently induced mitochondrial injury. Meanwhile, the cytosolic mtDNA, released from damaged mitochondria, was recognized by the cGAS-STING pathway, linking mitochondrial homeostasis disruption to inflammatory responses in podocytes. Moreover, TRIM56 could catalyze STING in a ubiquitous manner to mediate inflammation directly in podocytes under high glucose environment.

Conclusions: Our study proposes the important role of *PVT1* and TRIM56 in mitochondrial damage and inflammation, providing a potential therapeutic target against DKD.

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FR-OR38

NDUFS4 Regulates Cristae Remodeling in Diabetic Kidney Disease

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Background: Despite considerable progress in understanding the role of mitochondrial remodeling in kidney cells, the exact role and nature of mitochondrial electron transport chain (ETC) in the diabetic environment remains elusive.

Methods: We examined ETC remodeling in podocytes of established mouse models of diabetic kidney disease (DKD), and generated diabetic mice with podocyte-specific overexpression of Ndufs4 (NADH: ubiquinone oxidoreductase iron-sulfur protein 4, $Ins2^{Akita/+}$;$Ndufs4^{podTg}$), an accessory subunit of mitochondrial complex I, as a model to investigate the role of ETC integrity in DKD. APEX2 proximity labeling and complexsome profiling were performed to seek the Ndufs4 interactome in the context of mitochondrial respiratory supercomplexes (RSCs).

Results: We found that diabetic mice with conditional overexpression of Ndufs4 in podocytes ($Ins2^{Akita/+}$;$Ndufs4^{podTg}$) showed reduced albuminuria coupled with marked improvement in cristae morphology and mitochondrial dynamics. Importantly, primary podocytes from these mice exhibited increased ATP production, oxygen consumption rates, and complex I activity along with significantly reduced mitochondrial ROS and mitochondrial fission as compared to diabetic $Ins2^{Akita/+}$ mice. Using cryo-electron tomography, we found that diabetes-induced cristae remodeling was significantly improved with the forced expression of NDUFS4. By coupling proximity labeling, streptavidin pulldown assays, complexsome profiling and super-resolution imaging approaches, we identified a possible interaction between STOML2, a 39 kDa cristae shaping protein, and NDUFS4 in the context of improved supercomplexes assembly as the main explanation for the NDUFS4-mediated improvement in the cristae morphology. We further validated this interaction and found that two regions of the β-pleated sheet structures in STOM domain of STOML2 were crucial for its binding to NDUFS4.

Conclusions: Our findings uncover an unexpected role of Ndufs4 as a powerful regulator of cristae remodeling and mitochondrial dynamics. We propose that impaired mitochondrial respiration is a key defining feature of mitochondrial dysfunction in the diabetic environment, and targeting Ndufs4 could be a promising approach for developing therapies to slow the progression of DKD.

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FR-OR39

The Transcription Factor ChREBP Links Mitochondrial Lipidomes to Mitochondrial Morphology and Progression of Diabetic Kidney Disease

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Background: Recent studies have suggested that both mitochondrial dynamics and lipid metabolism contribute to the pathogenesis of diabetic kidney disease (DKD). However, the precise interplay between these two key metabolic regulators is not fully understood. We recently showed that the expression of carbohydrate-response element-binding protein (ChREBP), a glucose-responsive transcription factor and a master regulator of lipogenesis, is induced by high glucose in podocytes (*J Long, et al, JBC 2020*). Here we examine the role of ChREBP on progression of DKD *in vivo* and its role as a link between mitochondrial dynamics and lipid metabolism

Methods: An inducible podocyte-specific ChREBP knockout mouse model was generated by crossing floxed ChREBP mice with tamoxifen-inducible Cre transgenic mice controlled by human podocin promoter. These mice subsequently rendered diabetic by crossing with *db/db* mice. The triple transgenic mice were assessed for kidney function, morphometric analyses and mitochondrial morphology. To explore whether ChREBP-mediated lipidomes plays a role in mitochondrial remodeling, we generated a stable ChREBP-knockdown cell line in podocytes and carried out an untargeted mitochondrial lipidomic profiling. ChIP-qPCR, site-directed mutagenesis and luciferase assay were used to validate whether glyceronephosphate O-acyltransferase (GNPAT), an enzyme involved in the *de novo* biosynthesis of plasmalogens phospholipids, serve as a direct transcriptional target of ChREBP.

Results: We find that ChREBP deficiency in podocytes of diabetic mice improves key biochemical and histological features of DKD in addition to significantly reducing mitochondrial fission. Using mitochondrial lipidomic analysis, we find that the abundance of plasmalogen, but not that of diacyl or alkyl subclasses of PC or PE, is increased by high glucose and reversed with ChREBP knockdown, suggesting a modulatory role of ChREBP on plasmalogen phospholipids biosynthesis. Importantly, overexpression of GNPAT reverses the protective phenotype of ChREBP deficiency on mitochondrial fragmentation. Finally, our findings suggest that ChREBP bind to *Gnpat* promoter to activates its transcription.

Conclusions: Our results uncover a distinct plasmalogen phospholipids as the mechanistic link between ChREBP-mediated lipid metabolism and mitochondrial remodeling.

Funding: NIDDK Support

FR-OR40

Transcriptomics of SGLT2-Positive Proximal Tubule S1 Segments in Mice: Response to Diabetes, SGLT1/2 Inhibition, or GLP1 Receptor Agonist

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Background: SGLT2 inhibitors (SGLT2i) and GLP1 receptor (GLP1R) agonists have kidney protective effects. However, their molecular effects on SGLT2-expressing early proximal tubule S1 segments, which have negligible SGLT1 expression, have not been fully understood.

Methods: Fourteen week-old male wildtype (DBA) and diabetic (DBA-Akita) mice ± systemic Sglt1 knockout (ko) were given vehicle or SGLT2i dapagliflozin (Dapa; 10mg/kg diet) for 2 weeks, while other DBA-Akita received GLP1R agonist semaglutide (Sema; 3nmol/[kg body weight*day], s.c.). RNA sequencing was performed in SGLT2-positive proximal tubule segments isolated by immunostaining-guided laser capture microdissection (IS-LCM) using a Sglt2 ko-validated antibody (n=6 mice/group).

Results: Blood glucose in DBA-Akita was significantly reduced by Dapa (254±11mg/dL) and Sglt1 ko (367±11mg/dL) but not by Sema (407±44mg/dL) vs. vehicle (480±33mg/dL). A total of 20,748 annotated protein-coding genes was detected by RNA sequencing, and robust enrichment of S1 segment genes was confirmed by ranking marker genes based on the number of transcripts. DBA-Akita showed 116 differentially expressed genes vs. DBA (DEGs; adjusted $p<0.1$, log2FC +/-0.6) suggesting downregulation of metabolic pathways like unsaturated fatty acid and carboxylic acid metabolism. Dapa restored 40/116 genes and increased genes in lipid metabolic pathway, carboxylic acid metabolism and organic anion transport. Meanwhile, Dapa changed only 2 genes in DBA. Moreover, Sema and Sglt1 ko restored only 11 and 0 of the DEGs in DBA-Akita. Sglt1 ko enhanced the Dapa effect in DBA-Akita (207 DEGs and 64 restored genes) possibly due to additive effects on blood glucose (193±15mg/dl).

Conclusions: Transcriptomic profiling of SGLT2-positive S1 segments was established by IS-LCM. Despite SGLT2 expression in these segments, SGLT2i had little effect on transcriptomics in non-diabetic conditions. In diabetic mice, however, it restored transcription for multiple metabolic pathways, while targeting GLP1R or SGLT1 showed little effect. The approach warrants further studies in SGLT1-expressing S3 segments, which compensate during SGLT2i, and in glomeruli.

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FR-OR41

Effect of Dietary Acid Reduction on Acid-Base Status of Patients with CKD but with Normal eGFR: A 5-Year Randomized Trial

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Background: Previous studies show that high acid-producing diets contribute to metabolic acidosis in subjects with chronic kidney disease (CKD) stage G3 and to eubicarbonatemic acidosis in those with stage G2, conditions of acid accumulation that have been associated with adverse outcomes. We tested the hypothesis that high acid-producing diets have discernible effects on acid-base status of those with CKD but with normal baseline eGFR.

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants with eGFR (>90 ml/min/1.73 m2) and baseline high acid-producing diets (potential renal acid load [PRAL, mean (SE)] = 61.7 (0.83) mmol/day) were randomized to Usual Care (UC, n=51) or to base-producing fruits and vegetables (F+V, n=51) in amounts to reduce dietary PRAL by half, or oral NaHCO3 (HCO3, n=51) 0.4 mmol/kg bw/day. They were followed for 5 years, measuring eGFR (CKD-EPI equation) and plasma total CO2 (PTCO2) annually and the following at baseline and 5 years: plasma citrate (Pcit), 8-hour urine citrate excretion (UcitV), and acid retention by comparing observed to expected increase in PTCO2 in response to retained HCO3 (dose minus UHCO3V) 2 hours after oral NaHCO3 bolus (0.5 mmol/kg bw), assuming 50% body weight HCO3 apparent space of distribution.

Results: Baseline values were similar among groups. For both F+V and HCO3 relative to UC, 5-year eGFR was higher ([mean (SE)], F+V [96.5(0.79)], HCO3 [95.9 (0.96)] vs. UC [92.1 (1.23), ml/min/1.73 m2, ps<0.001]). For both F+V and HCO3 relative to UC, 5-year PTCO2 was higher (PTCO2, F+V [26.7(0.08)], HCO3 [26.7 (0.08)] vs. UC [26.2 (0.09), mM, p<0.001]). For both F+V and HCO3 relative to UC, 5-year Pcit and UcitV, were higher (Pcit, F+V [0.159 (0.001)], HCO3 [0.158 (0.002)] vs. UC [0.157 (0.001), mmol/ml, p<0.02]; UcitV, F+V [1.163 (0.011)], HCO3 [1.141 (0.002)] vs. UC [1.124 (0.006), mmoles/8 hours, ps<0.05]). For both F+V and HCO3 relative to UC, 5-year acid retention was lower (acid retention, F+V [-1.19(1.61)], HCO3 [-1.72 (1.58)] vs. UC [5.23 (1.55), mmol, ps<0.003]).

Conclusions: In participants with CKD and normal eGFR eating high acid-producing diets at baseline, dietary acid reduction over 5 years with either F+V or NaHCO3 yielded small but discernible improvements in acid-base status that might mediate slower CKD progression.

FR-OR42

Supporting Self-Management of Healthy Behaviors (SMART-HABITS) in CKD and Hypertension: A Pilot Trial

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Background: Home blood pressure monitoring (HBPM) and physical activity monitoring may have health benefits, but the feasibility and acceptability among individuals with chronic kidney disease (CKD) and hypertension (HTN) are not known.

Methods: In a 12-week study among individuals with stage 3-4 CKD and HTN, we evaluated the acceptance and feasibility of SMART-HABITS, a smartphone-based intervention to support physical activity and HBPM. Participants were asked to perform HBPM and share results at least 3x/wk and share step counts daily. For 6 weeks, two approaches to communicate HBPM were: 1) text message and 2) a smartphone application (app) connected to a Bluetooth-enabled BP machine, with the sequence determined via randomization. Step counts were monitored with a wearable device (Fitbit) and communicated via the Fitbit app for 12 weeks. Primary outcomes were 1) acceptance- assessed through surveys and interviews, and 2) feasibility- assessed with measures of adoption, adherence, and usability with the System Usability Survey (SUS). Secondary outcomes were maintenance (a HBPM or step count transmission ≥1x/wk), change in survey scores related to CKD knowledge, electronic health (eHealth) literacy, self-efficacy, self-management, QOL, BP, and daily step counts.

Results: Forty-seven participants were randomized. Mean age was 63 years, 49% women, and 48% were Black. For HBPM, 44 participants (94%) completed the text phase and 43 (92%) completed the Bluetooth phase. Adoption was reflected in a 92% retention rate, HBPM adherence was 81% in the text phase and 69% in the Bluetooth phase, and step count adherence was >83% over 12 weeks. Usability was adequate (SUS score ≥68), and participants rated SMART-HABITS as acceptable. CKD knowledge scores significantly increased (63 vs 66.7), but scores of self-management, self-efficacy, and QOL did not increase. eHealth literacy scores were inadequate at baseline (adequate score <32) and did not change. Forty-three (91.5%) participants communicated HBPM and/or step count data ≥1x/wk. Mean daily step counts significantly increased by 3414 steps, but BP did not change.

Conclusions: In this study of individuals with CKD and HTN, implementing a smartphone-based tool to support physical activity and HBPM is feasible and acceptable despite low eHealth literacy levels.

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FR-OR43

Association of Leukotriene Antagonist Use with the Incidence of ESKD

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Background: Pro-inflammatory lipid mediators known as leukotrienes (LTR) have been implicated in the etiology of chronic kidney disease (CKD). We have found that short-term inhibition of cysteinyl LTRs in mice with montelukast inhibits CKD progression after acute kidney injury. Whether LTR inhibitor use is associated with a reduction in kidney disease in humans is not known. We examined the association of LTR inhibitor (LTRi) therapies with the risk of developing end stage kidney disease (ESKD).

Methods: In a national cohort of 651,509 US Veterans with a diagnosis of asthma or allergic rhinitis, we identified 50,895 incident users of LTRi (montelukast or zafirlukast) and 600,614 patients who did not receive LTRi. We examined the association of LTRi with ESKD in competing risk regressions and cause-specific Cox models. We used propensity score (PS) weighing to account for differences in demographics, comorbidities, relevant medication use and laboratory values between the two groups. ESKD was determined using USRDS data.

Results: The overall mean (SD) age was 61±13 years, 91% were male and 79% were white. The mean (SD) baseline eGFR and BMI were 73±21 ml/min/1.73m^2 and 29±6.4 kg/m^2, respectively. UACR of 30-300 and >300 mg/gm was present in 10% and 3.6% of patients at baseline, respectively. There were 4,055 cases of incident ESKD over a median follow-up of 9.8 years, with 160 events in LTRi treated patients (event rate and 95%CI: 5.0/1000PY, 4.2-5.7) and 3,895 events in untreated patients (7.1/1000PY, 6.9-7.4). LTRi use was associated with a significantly lower risk of incident ESKD in both PS-weighed competing risk regression and in a PS-weighed cause-specific Cox model (Table).

Conclusions: In this large cohort of patients with a diagnosis of asthma and allergic rhinitis, use of LTRi was associated with a lower risk of incident ESKD.

Funding: Veterans Affairs Support

		ESKD Competing Risk	P-value	ESKD Cox Model	P-value
	Event Rate per 1000PY (95% CI)	Subhazard Ratio (95% CI)		Hazard Ratio (95% CI)	
No LTRi Treatment (N=600,614)	0.71 (0.69, 0.74)	Referent	0.008	Referent	0.047
LTRi Treatment (N=50,895)	0.49 (0.42, 0.57)	0.76 (0.62, 0.93)		0.81 (0.66, 1.0)	

FR-OR44

Initiation of ACE Inhibitor and ARBs in Patients with Advanced CKD

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Background: The treatment benefit of ACEi/ARB initiation on the risk of kidney failure with replacement therapy (KFRT) and mortality remains unclear in patients with CKD stage 4-5 who were not well-represented in individual trials evaluating the use of these agents.

Methods: We pooled individual-level data from 15 trials that included patients with eGFR<30 mL/min/1.73 m^2 to examine the effect of ACEi/ARB use on the risk of the onset of KFRT, or secondarily, death using Cox models. We performed pre-specified subgroup analyses and tested for interaction to evaluate the effect of ACEi/ARB inhibitor use by baseline albuminuria (<300 mg/g versus ≥300 mg/g), eGFR (≤20 versus >20 mL/min/1.73 m^2), age (<65 versus ≥65 years), race, and history of diabetes. All analyses were conducted in an intention-to-treat approach.

Results: We included 1752 participants from 15 trials, of whom 611 (35%) required KFRT and 215 (12%) died. Overall, ACEi/ARB use was associated with lower risk of KFRT (HR 0.71 [95% CI 0.60-0.83]) but not death (HR 0.95 [95% CI 0.72-1.24]). However, there was heterogeneity in the effect of the intervention on KFRT by baseline severity of albuminuria ($p_{interaction}$=0.08). ACEi/ARB initiation was associated with lower risk of KFRT in those with severe albuminuria (HR 0.68 [95% CI 0.57-0.80]), but not in those without severe albuminuria (HR 1.05; 95% CI 0.60-1.86). There was no interaction between ACEi/ARB use and baseline eGFR, diabetes, race, or age for KFRT (all $p_{interaction}$>0.10). For example, the risk of KFRT in those who started ACEi/ARBs was 0.73 (95% CI 0.57-0.94) in those with baseline eGFR ≤20 mL/min/1.73 m^2 and 0.69 (95% CI 0.56-0.85) in those with eGFR >20 mL/min/1.73 m^2.

Conclusions: Data from this pooled individual-level analysis demonstrated a benefit of ACEi/ARB use in delaying onset of KFRT, but not death in patients with stages 4-5, regardless of the baseline eGFR.

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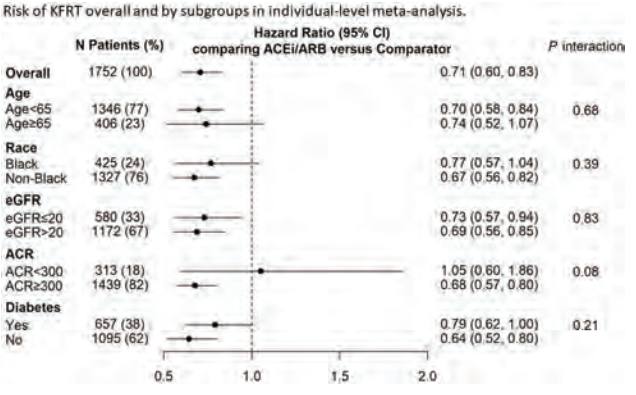

FR-OR45

Sotagliflozin and Kidney and Cardiorenal Outcomes in SCORED

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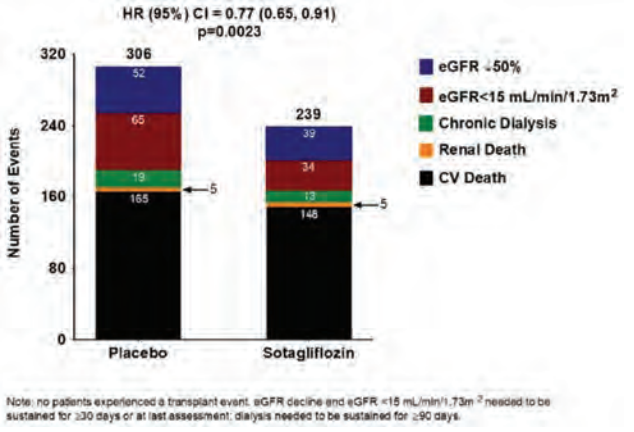
Background: SGLT2 inhibitors reduce kidney and cardiovascular (CV) outcomes in patients with and without type 2 diabetes (T2D). The aim of this exploratory analysis was to evaluate the effect of sotagliflozin (SOTA), a dual SGLT1 and 2 inhibitor, on kidney and cardiorenal outcomes in patients with T2D and chronic kidney disease (CKD).

Methods: SCORED, a Phase 3, double-blind, placebo-controlled study, randomized 10,584 patients with T2D, CKD, and CV risk factors to SOTA or placebo (1:1). Kidney criteria for inclusion were an eGFR 25 to 60 mL/min/1.73m^2 regardless of UACR. The outcomes in this analysis included kidney and cardiorenal composites derived using laboratory values, with treatment comparisons by proportional hazards models.

Results: At baseline, median eGFR was 45 mL/min/1.73m^2 and 35, 34, and 31% of patients were categorized as having normo-, micro-, and macroalbuminuria, respectively. Over a median follow up of 16 months, SOTA reduced the primary CV endpoint by 26% (p<0.001). SOTA reduced the risk of the composite of first event of 50% decline in eGFR, eGFR<15 mL/min/1.73m^2, chronic dialysis, renal transplant, or renal or CV death (p=0.0023, Figure 1). Results were generally consistent when using different eGFR decline thresholds and/or only renal death (all p<0.01, Figure 2).

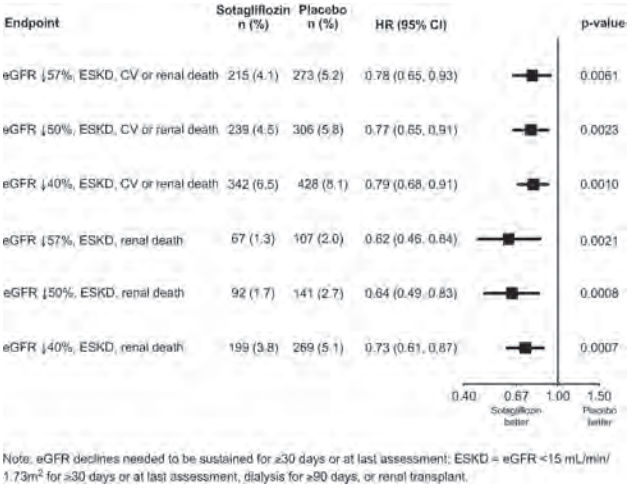
Conclusions: SOTA reduced the risk of kidney and cardiorenal endpoints in patients with T2D and CKD.

Funding: Commercial Support - Lexicon Pharmaceuticals, Inc.



Note: no patients experienced a transplant event. eGFR decline and eGFR <15 mL/min/1.73m $^{-2}$ needed to be sustained for ≥30 days or at last assessment; dialysis needed to be sustained for ≥90 days.

Figure 1. First event within cardiorenal composite



Note: eGFR declines needed to be sustained for ≥30 days or at last assessment; ESKD = eGFR <15 mL/min/1.73m² for ≥30 days or at last assessment, dialysis for ≥90 days, or renal transplant.

Figure 2. Forest plot of various cardiorenal composites

FR-OR46

Impact of Primary Kidney Disease on the Effects of Empagliflozin in Patients with CKD

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Background: The EMPA-KIDNEY trial reported that empagliflozin reduced the risk of its primary composite outcome of kidney disease progression or cardiovascular death in a broad range of patients with CKD at risk of progression. We now compare effects on kidney outcomes among the different types of kidney diseases studied.

Methods: Eligible patients with eGFRs ≥20-45, or ≥45-90 ml/min/1.73m² with a urinary albumin-to-creatinine ratio of ≥200 mg/g, and receiving renin angiotensin system inhibitor, where indicated and tolerated were randomised to empagliflozin 10mg once daily vs matching placebo. Kidney disease progression was defined as a sustained ≥40% eGFR decline from randomisation or to <10 mL/min/1.73m², start of maintenance dialysis or receipt of a kidney transplant, or renal death, and the effects of empagliflozin were analysed using a pre-specified Cox model. Testing for heterogeneity of effect between pre-specified kidney disease subgroups was performed, including exploratory analyses by specific glomerular disease aetiologies.

Results: 6609 participants were followed for a median of 2.0 years. 2057 (31%) had diabetic kidney disease, 1669 (25%) had glomerular disease, 1442 (22%) had hypertensive or renovascular disease, and 1441 (22%) had other or unknown causes. Overall, empagliflozin reduced the risk of kidney disease progression by 29% (empagliflozin 384/3304 *vs* placebo 504/3305; hazard ratio 0.71, 95%CI 0.62-0.81). This relative risk reduction appeared broadly similar in subgroup analyses by primary cause of kidney disease and by different types of glomerular disease, with limited data in participants with focal segmental glomerulosclerosis (Fig. 1).

Conclusions: EMPA-KIDNEY studied a large number of patients with diabetic and non-diabetic causes of CKD and showed that empagliflozin reduced risk of kidney disease progression with relative risk reductions that were broadly similar across the different CKD aetiologies.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly (Clinicaltrials.gov: NCT03594110).

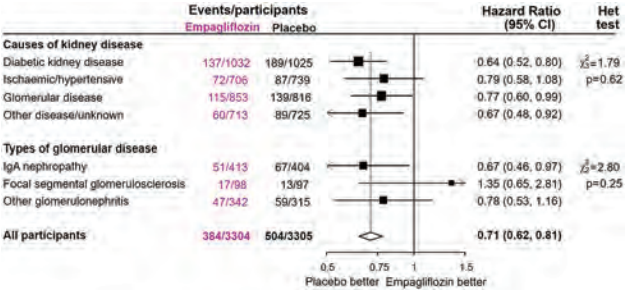

Fig. 1: Effect of empagliflozin on kidney disease progression by cause of kidney disease

FR-OR47

Effect of Tirzepatide on Kidney Function in People with Excess Body Weight: A Post Hoc Analysis of the SURMOUNT-1 Trial

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Background: The prevalence of chronic kidney disease due to obesity is rapidly increasing, but few proven effective therapies are available. Tirzepatide, a glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist, has shown potential in attenuating the decline in estimated glomerular filtration rate (eGFR) in people with type 2 diabetes (T2D) at high risk for cardiovascular disease. In the SURMOUNT-1 trial in people with obesity or overweight without T2D, tirzepatide significantly reduced body weight and blood pressure by week 72 (the primary endpoint) compared with placebo. This post-hoc analysis assessed the potential impact of tirzepatide compared with placebo on kidney function in SURMOUNT-1 trial participants.

Methods: Data from all participants randomly assigned to treatment were included (pooled tirzepatide [5, 10, and 15 mg], N = 1896; placebo, N = 643). Assessments included CKD-EPI creatinine- and cystatin-C-based eGFR (Cr-eGFR and CysC-eGFR, respectively), and urine albumin-to-creatinine ratio (UACR). The change from baseline to week 72 was analyzed using a mixed model for repeated measures with on-treatment data.

Results: Baseline mean Cr-eGFR was 98.1±18.0 mL/min/1.73m² and CysC-eGFR was 95.5±19.1 mL/min/1.73m²; 27%-36% of participants had mean eGFR <90 mL/min/1.73m². Baseline median UACR was 6.0 mg/g (interquartile range 4.0-11.0 mg/g); 8.6% of participants had UACR ≥30 mg/g. The estimated treatment difference (ETD) between pooled tirzepatide groups and placebo on the change from baseline Cr-eGFR was -0.2 mL/min/1.73m² (95% confidence interval [CI] -1.2, 0.9; p=0.780). For CysC-eGFR the ETD was 3.2 mL/min/1.73m² (95% CI 2.1, 4.3; p<0.001). The ETD on the percent change in UACR was -8.4% (95% CI -14.7, -1.6; p=0.017). In participants with baseline UACR ≥30 mg/g, the ETD was -42.3% (95% CI -60.8, -15.0; p=0.006).

Conclusions: Tirzepatide demonstrated an increase in CysC-eGFR and reductions in UACR compared with placebo, suggesting renoprotective effects. These results warrant a long-term, prospective kidney outcome trial for people with obesity or overweight.

Funding: Commercial Support - Eli Lilly and Company

FR-OR48

Practice Patterns for Patient Pain Control and Outcomes Among CKD Patients: A CKDopps Analysis

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Background: Chronic kidney disease (CKD) patients often suffer from poorly managed pain. Opioid and analgesic abuse is of concern. This study examines international pain management practices for non-dialysis-dependent CKD patients and the association between pain and patient-reported outcomes.

Methods: Data from the CKD Outcomes and Practice Patterns Study, a cohort of Stage 3-5 CKD patients from Brazil, France, Germany, and the US, were analyzed. Self-reported pain was assessed using the Kidney Disease Quality of Life Short Form, and analgesic prescriptions were categorized. Outcomes included depression, functional status, health-related quality of life and prescription practices.

Results: The study included 4,160 patients. A majority reported some degree of pain interference, with levels varying with CKD stage and country. Extreme pain was associated with eGFR and higher BMI. Analgesic prescriptions, notably NSAIDs and

opioids, were most frequent in the US followed by Germany, Brazil and France. Pain levels were directly associated with poorer health-related quality of life, with patients reporting lower general health, physical function, and emotional well-being. Patients who were prescribed analgesics reported similar levels of health-related quality of life to those not prescribed. Patients prescribed analgesics were more often females, had lower eGFR, slightly higher BMI, and were more commonly diagnosed with cardiovascular and psychiatric disorders.

Conclusions: The results highlight a significant pain burden in CKD patients and variations in international pain management practices. The findings emphasize the importance of improved pain management strategies in CKD care, necessitating comprehensive pain assessment, patient education, and consideration of pharmacokinetic alterations due to CKD. Consensous pain management guidlines and discussions are imperative.

Table 1. Prevalence of analgesics prescription by country and CKD stage

	Brazil			France			Germany			US		
	Stage 3	Stage 4	Stage 5	Stage 3	Stage 4	Stage 5	Stage 3	Stage 4	Stage 5	Stage 3	Stage 4	Stage 5
N	192	326	114	1594	1247	118	584	1807	17	640	1081	272
Any Analgesic	40%	48%	40%	24%	24%	21%	11%	13%	6%	17%	18%	24%
Opioid	0.6%	0.3%	0%	7%	6%	6%	11%	13%	6%	17%	18%	24%
NSAID	39%	47%	40%	2%	1%	1%	13%	12%	0%	54%	52%	44%
Other	1%	1%	3%	19%	20%	17%	17%	21%	24%	8%	11%	8%

FR-OR49

Implications of Follow-Up Time on the Optimal Weighting of the Acute and Chronic Slopes to Predict Treatment Effects on Clinical End Points

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Background: We have shown in a meta-analysis of 66 randomized treatment comparisons (RTCs) that treatment effects on the established clinical endpoint (CE) based on doubling of serum creatinine (SCR), GFR ≤ 15 ml/min/1.73m^2 or kidney failure are in aggregate predicted accurately by the mean GFR slope over 3 years. We evaluate implications of follow-up time for the optimal weighting of the acute and chronic GFR slopes to predict treatment effects on the CE.

Methods: For each RTC, we used a mixed effects model to estimate treatment effects on the acute (evaluated from baseline to 3 months) and chronic (evaluated after 3 months) GFR slopes, and Cox regression to estimate treatment effects on the CE. We used an extended multivariable Bayesian meta-regression model to relate the treatment effects on the CE jointly to those on the acute and chronic slopes. The extended model expresses the optimal weighted average of the acute and chronic slopes as $\alpha\times$[*Acute Slope*]+(1-α)$\times$[*Chronic Slope*], and allows α to depend on the median follow-up time of each RTC.

Results: The multivariable model accurately predicted the treatment effect on the CE (median R^2 = 0.97 for a RTC with 3 years follow-up). The optimal weight α for the acute slope relative to the chronic slope had a strong inverse relationship with the median follow-up time, decreasing from a median (95% Bayesian credible interval) of 0.105 (0.065, 0.154) at 2 years by 34% to 0.069 (0.049,0.091) at 3 years and by 65% to 0.037 (0.013,0.075) at 4.5 years.

Conclusions: The optimal weighting of the acute and chronic slopes for predicting the treatment effect on the CE assigns a major role to the acute effect when the CE is evaluated over a relatively short follow-up time typical of some CKD trials, but deemphasizes the acute effect and more closely approximates the chronic slope when the CE is evaluated over longer follow-up times which are relevant to patients.

Funding: Private Foundation Support

Effect of Follow-up Time on Optimal Weighted Average of Acute and Chronic Slopes

Term	Median	95% Bayesian CI
Intercept	-0.02	(-0.08, 0.04)
% hazard reduction in the CE per 0.75 ml/min/1.73m2/year greater effect on optimal weighted average of the acute and chronic GFR slopes	33%	(27%,38%)
Optimal α when evaluating CE over 2 years	0.105	(0.065,0.154)
Optimal α when evaluating CE over 3 years	0.069	(0.049, 0.091)
Optimal α when evaluating CE over 4.5 years	0.037	(0.013,0.075)
Trial level R2 with follow-up standardized to 3 years	0.97	(0.82, 1.00)

FR-OR50

Improvement in Anemia by SGLT2 Inhibitors Were More Prominent Among Those with Inflammation

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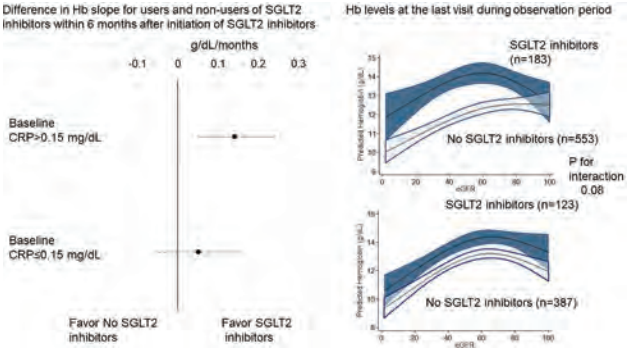
Background: SGLT2 inhibitors (SGLT2i) were reported to increase hemoglobin (Hb) by suppressing hepcidin and increasing erythropoietin, similar to hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors. We hypothesized that an increase in Hb by SGLT2i might be more prominent among patients with inflammation similar to HIF-PH inhibitors.

Methods: In this retrospective cohort study, diabetic outpatients from 2019 to 2020 at our hospital were enrolled. Exposure was the use of SGLT2i. The Hb slope within 6 months after initiation of SGLT2i (the first 6 months of the observation period for non-users) was analyzed using a mixed-effects model. Non-linear regression models were fitted with restricted cubic splines to investigate Hb levels at the last visit across different eGFR levels. Analyses were performed separately for those with higher and lower than the median baseline C-reactive protein (CRP) levels. The data were adjusted for potential confounders.

Results: Among 1,246 patients, 306 were on SGLT2i. During the first 6 months, CRP and eGFR trajectories were not significantly different between users and non-users of SGLT2i. Differences in Hb slope between users and non-users of SGLT2i were 0.14 (0.05–0.24) and 0.05 (-0.05–0.15) g/dL/month for those with higher and lower baseline CRP, respectively, after adjustment for confounders including time-dependent eGFR. Hb levels at the last visit were significantly higher among SGLT2i users across the range of eGFR levels, and it was more prominent among those with higher CRP (p for interaction<0.1).

Conclusions: SGLT2i use was associated with higher Hb levels, especially among those with inflammation across the range of eGFR levels. The results suggest that SGLT2i could improve anemia among patients with anemia of chronic kidney disease and inflammation which are refractory to treatment with erythropoiesis-stimulating agents.



FR-OR51

Membranous-Like Glomerulopathy with Masked Immunoglobulin G (IgG) Kappa Deposits: A Clinicopathologic Analysis of 247 Patients

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Background: Membranous-like glomerulopathy with masked IgG kappa deposits (MGMID) is a rare autoimmune kidney disease that disproportionately affects young women and causes proteinuria and progressive chronic kidney disease. Since discovery of serum amyloid P (SAP) as a specific biomarker, there is increased recognition and the pathologic spectrum has broadened. Here, we examine 247 patients with MGMID to characterize histopathology and outcomes.

Methods: Patients with a diagnosis of MGMID were identified from 3 institutions. Clinical and laboratory data at the time of biopsy and at follow-up were obtained. Histopathology was reviewed, including light microscopy (LM), routine and paraffin immunofluorescence (IF), electron microscopy (EM), and immunostaining for SAP.

Results: 286 kidney biopsies corresponding to 247 patients with MGMID were identified, including 278 native and 8 allografts. LM demonstrated mesangial hypercellularity in 42%, segmental sclerosis in 68%, endocapillary hypercellularity in 8%, and fibrinoid necrosis and/or crescents in 9%. Over one-third had significant tubulointerstitial fibrosis. On IF, the majority of cases had 'masked' immune deposits without IgG staining on frozen sections (76%). SAP immunostaining was positive in all cases tested. EM showed subepithelial deposits and mesangial deposits in 86%. Of patients with follow-up (n=166), 58% achieved complete or partial remission, 42% had no remission or disease progression of which 9% developed ESKD. Disease flares occurred in 16%. The majority of patients received RAAS blockade and immunosuppression varied (see table).

Conclusions: MGMID has multiple histopathologic patterns and variable outcomes. Further follow-up is ongoing to identify the clinical impact of different treatments on disease progression.

Clinical data		Histopathology	
Demographics		Light microscopy	
Total patients (n)	247	Total biopsies (n)	286
Age	31.0 ± 16.7 yrs	Global glomerulosclerosis	25.7 ± 25.7%
Sex	62 M, 175 F	Segmental sclerosis	67.5%
		IF/TA - none	103 (36.3%)
Follow-up		IF/TA - mild	75 (19.4%)
Follow-up (n)	166	IF/TA - moderate	60 (21.5%)
Complete remission	36 (21.7%)	IF/TA - severe	46 (16.1%)
Partial remission	61 (36.7%)	Arteriosclerosis	54 (19.2%)
No remission	69 (41.6%)	Arteriolar hyalinosis	29 (10.3%)
End-stage disease	15 (9.0%)	Mesangial hypercellularity	120 (42.0%)
Transplant	4	Endocapillary hypercellularity	23 (8.0%)
Transplant recurrence	2	Crescents ± necrosis	25 (8.7%)
Treatments		Immunofluorescence + Electron microscopy	
ACE/ARB therapy	99 (59.6%)	IgA	20 (7.6%)
Immunosuppression	80 (48.2%)	IgM	57 (20.5%)
Corticosteroids	49 (29.5%)	C3	180 (64.8%)
Calcineurin inhibitors	23 (13.9%)	C1q	12 (4.3%)
Mycophenolate	33 (19.9%)	IgG (routine, not masked)	66 (23.7%)
Rituximab	12 (7.2%)	Subepithelial deposits	255 (86.7%)
Hydroxychloroquine	12 (7.2%)	Subendothelial deposits	29 (10.7%)
SGLT2i and other	12 (7.2%)	Mesangial deposits	233 (86.0%)
Combination therapy	71 (42.8%)		
None	17 (10.2%)	Secondary diagnosis	
Dialysis	15 (9.0%)	Glomerular	15
		Tubulointerstitial	19

Clinicopathologic features of MGMID

FR-OR52

The Characteristics of Concurrent Anti-Glomerular Basement Membrane Nephritis and Membranous Nephropathy

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Background: Concurrent anti-glomerular basement membrane (GBM) nephritis and membranous nephropathy (MN) is rare and has been previously addressed only in case reports and small series (≤12 patients). Its target antigen is unknown.

Methods: We studied the clinicopathologic characteristics and outcome of 28 patients with anti-GBM nephritis and MN diagnosed at a large nephropathology laboratory over a 23-year period. A pathologic diagnosis of anti-GBM nephritis was defined by the immunofluorescence finding of intense linear GBM staining for IgG, in the absence of (or much weaker) staining for albumin, and concurrent MN was defined by the presence of segmental or global subepithelial deposits by electron microscopy.

Results: These cases are among 449 (6.2%) anti-GBM nephritis and 5183 (0.5%) non-lupus MN. The patients were 57% male and a median age of 54 years (range 15-82) at diagnosis. Most (96%) patients presented with acute kidney injury with a median serum creatinine at biopsy of 7.8 mg/dL (range 1.2-24.0), proteinuria (median 3.5 g/day, range 0.4-11) and hematuria. Kidney biopsy showed classic (n=26) or atypical (n=2) anti-GBM nephritis. Most patients received immunosuppressive therapy. After a median follow up of 17 months, 11% had complete remission (including the 2 with atypical anti-GBM nephritis), 27% had persistent kidney dysfunction, 62% progressed to ESKD. The rate of progression to ESKD was 93% in those on dialysis at presentation. The dominant IgG subclass of granular staining was different from that of linear staining, a feature facilitating the recognition of granular staining and thus the diagnosis of concurrent MN, particularly when EM unavailable. Immunostains for PLA2R, THSD7A, NELL-1 and EXT2 was negative in all cases tested. Proteomic analysis (n=8) of glomeruli did not detect any of the known or novel target antigens.

Conclusions: Concurrent classic anti-GBM nephritis and MN has poor prognosis, particularly in patients requiring dialysis at presentation, while atypical anti-GBM nephritis and MN has a favorable outcome. It is not associated with any of the known MN antigens and no novel target antigen(s) detected by mass spectrometry, favoring that the MN target antigen is likely an exposed structural GBM antigen.

FR-OR53

Clinicopathologic Features of Anti-Brush Border Antibody Disease: A Series of 66 Patients

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Background: Anti-brush border antibody disease (ABBA) is an autoimmune tubulointerstitial kidney disease that primarily affects older individuals and results in progressive kidney failure. It is a rare entity with only 20 cases reported to state. Therefore, the histopathologic spectrum, clinical associations, prognosis, and response to therapy are poorly understood.

Methods: We performed a retrospective clinicopathologic analysis of kidney biopsies and identified 66 cases with ABBA including 63 native and 3 recurrence in an allograft identified from 4 institutions. Demographics, clinical findings, and laboratory data were obtained. Histopathologic data included light, immunofluorescence, electron microscopy, and immunostaining for LRP2, CUBN, and AMN. Follow-up data was available from 49 patients, examining treatment(s), laboratory values, and outcome measures.

Results: Patients with ABBA were predominantly male (74%) with a mean age of 70.0 ± 12.3 years. Progressive chronic kidney disease was the most common biopsy indication. The mean serum creatinine was 3.5 ± 2.6 mg/dL, proteinuria 2.7 ± 2.9 g/day, and 66% had hematuria. Acute tubular injury with LRP2-positive tubular basement membrane deposits were seen in 94% patients, with one case demonstrating CUBN and AMN positivity in addition to LRP2. Thirty-eight patients (57.6%) had secondary diagnoses, most commonly glomerular diseases with high proteinuric states. These included podocytopathies, membranous nephropathy, IgA nephropathy, lupus nephritis, crescentic glomerulonephritis, acute or chronic tubulointerstitial nephritis, and renal involvement by B-cell lymphoma. The majority of patients with available follow-up data were treated with immunosuppression (73.5%). Complete or partial remission was achieved for 32.7%, 67.3% had no remission, and 22.5% required dialysis or were deceased at follow-up. Patients not treated with immunosuppression were at the highest risk of kidney failure.

Conclusions: ABBA is frequently concurrent with other kidney diseases, which may lead to under-diagnosis of this important cause of kidney failure.

FR-OR54

Clinicopathologic Characteristics, Etiologies, and Outcomes of Secondary Oxalate Nephropathy

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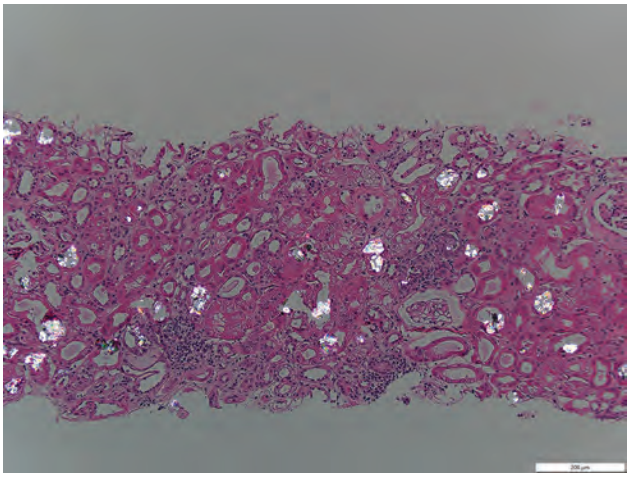
Background: The characteristics of secondary oxalate nephropathy (ON) are not well define, and the rate of recurrence after kidney transplant (Tx) and Tx outcome are unknown. We report the largest series on secondary ON to date

Methods: Retrospective analysis of clinicopathologic and outcome characteristics of 113 patients with secondary ON in the native kidney diagnosed at a large tertiary care academic center.

Results: Biopsy incidence was 0.97%. ON was attributed to enteric hyperoxaluria in 60% (most commonly RYGB), excessive ingestion of foods high in oxalate or oxalate precursors in 23% (most commonly vitamin C), and was idiopathic in 17%. Most patients presented with AKI (particularly in the ingestion group) or AKI on CKD, and 63% were diabetic. Calcium oxalate (CaOx) crystals were more abundant in the ingestion than enteric group, and were accompanied by acute tubular injury, inflammation, and interstitial fibrosis and tubular atrophy (IFTA). Concurrent pathologic conditions were present in 53%, most commonly diabetic nephropathy. After a median follow up of 36 months, 27% had kidney recovery, 19% had persistent kidney dysfunction, 54% developed kidney failure, and 29% died. The mean kidney survival was worse for patients with a concurrent pathologic lesion (30 vs. 96 months for those without, $p<0.001$). Independent predictors of kidney failure were degree of IFTA and nadir eGFR but not degree of crystal deposition. After a median follow up of 58 months in 23 patients who received kidney TX, 4 had graft loss (due to ON in 3). The 2-, 5-, and 10-year graft survivals were 90%, 79%, and 50%.

Conclusions: ON is a rare cause of AKI or AKI on CKD. Most patients have co-morbid pathologic conditions, particularly diabetic nephropathy, which worsen the prognosis. Recurrence in the renal allograft and graft loss may occur if hyperoxaluria is not controlled.



Abundant calcium oxalate crystals are seen under polarized light

FR-OR55

Computationally Derived Tubular Features Are Prognostic of Clinical Outcomes in Glomerular Kidney Diseases

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Background: The visual semiquantitative assessment of chronic and acute tubular damage has limited reproducibility and prognosticating/predictive power. We hypothesize that sophisticated, computationally assessed, domain-inspired tubular pathomic features can enhance prognostication of proteinuria diseases.

Methods: We developed and applied tubular segmentation algorithms for tubular lumen (TL), epithelium (TE), nuclei, and basement membranes (TBM), to 235 PAS NEPTUNE/CureGN PAS-stained whole slide images (124 FSGS,111 MCD/MCD-like). From these segmentations, 56 features were extracted and summarized at the patient level. We used MRMR to select 10 features most prognostic for time from biopsy to 40% eGFR decline/kidney failure, and proteinuria remission, and Ridge regression models to estimate prognostic accuracy.

Results: Features (Fig.2-A), reflecting TE simplification and TBM thickening/smoothing, were most prognostic of disease progression; when added to other parameters, they increased prognostic accuracy for both outcomes (Fig.2-B).

Conclusions: Computational quantification of tubular pathomic features provides prognostic information above routine measures in glomerular diseases.

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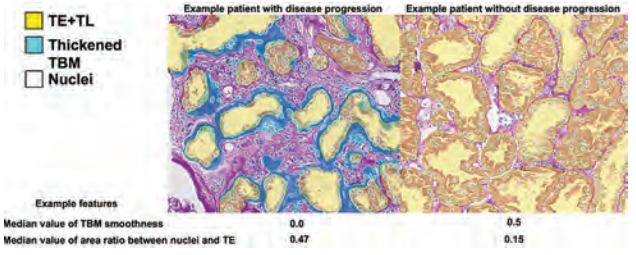

2 selected features contrasting patients with worse/better outcome

A. Top 10 features for both outcomes

Feature name	Feature description (at patient level)	Association with proteinuria remission (Ridge coefficient)	Association with disease progression (Ridge coefficient)
TBM_SMOOTH_Median	The median value of smoothness of the outer boundary of TBM	0.0802	-0.172
TBM_SMOOTH_Min	The minimal value of the smoothness of the outer boundary of TBM (i.e. maximum jaggedness)		-0.100
TBM_SMOOTH_StdDev	The variability of smoothness of the outer boundary of TBM in a single biopsy		0.1707
TBM_SMOOTH_Kurt	A measure of the outliers in TBM thickness	-0.1345	
TE_SMOOTH_Median	A median value of smoothness of the outer boundary of TE	0.0321	0.011
TE_SMOOTH_Min	The minimal value of the smoothness of the outer boundary of TE (i.e. maximum jaggedness)	0.0801	
LMEN_THICK_MAX_StdDev	A measure of the variability of TL diameter		0.1441
TBM_THICK_MIN_StdDev	A measure of the variability of the minimum TBM thickness	-0.0785	0.0537
TE_LMEN_THICK_MIN_Kurt	A measure of outliers in minimal TE+TL thickness	-0.1114	0.0722
TBM_THICK_STD_Kurt	A measure of outliers in variability of TBM thickness	0.0569	
NCLEI_TE_AREA_RTIO_Median	A measure of the median of the ratio of nuclear area to TE area		0.1059
TE_TBM_AREA_RTIO_Min	A measure of the minimal area ratio of TE to TBM		-0.0469
LMEN_TBM_AREA_RTIO_Min	A measure of the minimal area ratio of TL to TBM (e.g., atrophic tubules)	0.0707	
TE_LMEN_TBM_THICK_RTIO_Max	A measure of the maximum ratio of TE+TL diameter to TBM thickness (e.g., tubular hypertrophy)	-0.1077	
TUBULE_TBM_THICK_RTIO_Min	A measure of the minimum ration of tubular diameter (TE+TL+TBM) to TBM thickness (e.g., atrophic tubules)	0.0951	
NCLEI_TBM_BORDER_DIS_STD_Min	A measure of the minimum value of the variability of the distance between the nuclear membrane and TBM outer boundary		0.1707

B. IAUC results for different models

Models	Proteinuria remission (n=176)	Disease Progression (n=202)
Demographics (Demo) and clinical (Clin) characteristics	0.689	0.627
Demo+Clin+%Tubular Atrophy (TA)+%Acute Tubular Injury (ATI)	0.695	0.718
Demo+Clin+%TA+ATI+%Interstitial Fibrosis (IF)+%Inflammation	0.712	0.713
Maximum Relevance Minimum Redundancy (MRMR) top 10 tubular features	0.741	0.781
Demo+Clin+MRMR top 10 tubular features	0.750	0.776
Demo+Clin+%TA+ATI+MRMR top 10 tubular features	0.743	0.777
Demo+Clin+%TA+ATI+%IF+%Inflammation+MRMR top 10 tubular features	0.744	0.769

FR-OR56

Quantitative Characterization of Nonsclerotic Glomeruli Is Prognostic of Clinical Outcomes in Proteinuric Diseases

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Background: Visual assessment of segmentally (SS), globally (GS) and non-GS/SS glomeruli is used clinically for the diagnosis and prognostication of glomerular diseases. We hypothesized that encoded in non-GS/SS glomeruli are computationally derivable subvisual features prognostic of outcome.

Methods: N=186 (99 MCD/MCD-like, 87 FSGS) patients from the NEPTUNE/CureGN cohorts with at least one PAS whole slide image (WSI) containing ≥4 non-GS/SS glomeruli were included. A previously validated pipeline for glomerular segmentation and classification was applied to WSIs, yielding 272 GS, 113 SS, and 2661 non-GS/SS glomeruli. Percent of SS and GS was calculated. From non-GS/SS glomeruli, 108 intensity, shape, and texture features were computed. Patient-level summary statistics were produced using mean, standard deviation, kurtosis, minimum, maximum, and median. Maximum Relevance Minimum Redundancy (MRMR) selected the 10 most prognostic features for time from biopsy to disease progression (≥40% eGFR decline with last eGFR<90 or kidney failure), and to first complete proteinuria remission (UPCR<0.3). Ridge regression models estimated prognostic accuracy of non-GS/SS glomerular features.

Results: Prognostic features (Table 1) reflect the heterogeneity of intra-glomerular organization. These features were the most prognostic of disease progression compared to other models and increased the prognostic accuracy of both clinical outcomes when added to conventional parameters (Table 2).

Conclusions: Computational methods allow for extraction from non-GS/SS glomeruli of information prognostic of clinical outcomes above and beyond conventional

methods. This novel approach may enable early diagnosis and facilitate risk-stratification independently from the presence of conventional diagnostic lesions of sclerosis.

Funding: NIDDK Support, Private Foundation Support

Disease Progression (n=182)				Proteinuria Remission (n=152)			
Top 10 MRMR Features	Patient Summary Statistic	Ridge Coefficient	Feature Type	Top 10 MRMR Features	Patient Summary Statistic	Ridge Coefficient	Feature Type
Glcm Difference Variance	Standard Deviation	0.605	Texture	Glcm Run Percentage	Maximum	0.021376	Texture
Extent	Mean	0.771	Shape	First-order Root Mean Squared	Kurtosis	-0.01639	Intensity
Glcm Small Dependance Low Gray Level Emphasis	Standard Deviation	0.315	Texture	Elongation	Kurtosis	-0.00824	Shape
Minor Axis Length	Standard Deviation	-0.509	Shape	Euler Number	Minimum	0.00910	Shape
Glcm MCC	Standard Deviation	-0.191	Texture	Glszm Small Area High Gray Level Emphasis	Kurtosis	-0.01265	Texture
Glszm Size Zone Non-Uniformity	Kurtosis	0.526	Texture	Extent	Kurtosis	0.020566	Shape
First-order Root Mean Squared	Kurtosis	0.314	Intensity	Glcm Contrast	Kurtosis	0.016828	Texture
Euler Number	Standard Deviation	-0.598	Shape	Gldm Run Length Non-Uniformity	Mean	-0.01479	Texture
Elongation	Standard Deviation	0.444	Shape	Glszm Large Area Low Gray Level Emphasis	Minimum	0.000352	Texture
Minor Axis Length	Kurtosis	-0.388	Shape	Ngtdm Strength	Kurtosis	0.000968	Texture

Table 1: Top 10 MRMR features and their patient summary statistic, ridge coefficient, and feature type for each outcome

Models	Disease Progression (n=172)	Proteinuria Remission (n=146)
Demographic + Clinical	0.560	0.696
Demographic + Clinical + % GS & % SS glomeruli	0.691	0.711
MRMR top 10 glomerular features	0.835	0.701
Demographic + Clinical + MRMR top 10 glomerular features	0.781	0.753
Demographic + Clinical + % GS & %SS glomeruli + MRMR top 10 glomerular features	0.832	0.761

Table 2: AUC results for different models

FR-OR57

A Spatial Atlas of the Human Kidneys of Cell Types and Functional Tissue Units Identified in Highly Multiplexed Immunofluorescence Images

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Background: Kidney tissue can be defined at the cell level and at the level of unique functional tissue units (FTUs, e.g. glomeruli and tubules). FTUs are tightly linked to the spatial organization of the kidney. Several single cell transcriptomic atlases have been developed for the kidney, but a spatially anchored comprehensive atlas for cell types and FTUs based on protein expression has yet to be described.

Methods: Mesoscale sequential sections from reference kidney tissue spanning from cortex to papilla were imaged using Fusion-Phenocycler, a mesoscale highly multiplexed fluorescence imaging platform. 40 markers were used to identify major cell types (epithelial, immune, endothelial), states (stress, repair, cycling) and FTUs. An analytical pipeline was developed to perform image registration, followed by cell and FTU segmentation, labeling, mapping, and neighborhood definition.

Results: Over 4 million cells from 5 donors and 18 tissue sections were incorporated in the analytical pipeline, which resulted in the identification of over 30 cell types distributed across the kidney and localized in structures that align with FTU ontologies. A cell-based neighborhood analysis captured tubular niches unique to the renal cortex and outer or inner stripe of the medulla. This spatial segregation was complemented with interstitial niches unique to the cortex or medulla. FTU segmentations mapped the major FTUs of the kidney, including vasculature, glomeruli, several tubules and interstitium. Using sequential sections interrogated with Fusion-Phenocycler, FTU segmentation were used to generate 3D models of renal FTUs highlighting the 3D arrangement of kidney FTUs.

Conclusions: We establish a reference mesoscale spatial atlas to define anatomically and functionally distinct compartments of the kidney with single cells and FTUs. This work begins to define: 1) the 3D relationship of FTUs, including the relationship between vasculature and tubules, 2) a comprehensive map of cell-types in the human kidney and their organization into FTUs and the how cellular niches vary across the kidney. This atlas provides a cellularly resolved and spatially anchored reference to understand kidney function in health and disease.

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FR-OR58

Multiplexed Single-Nucleus RNA and ATAC Sequencing in the Renal Biopsy Specimen

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Background: Multi-omic technology allows simultaneous transcriptomic and epigenomic profiling in various kidney cell types, bringing about opportunities to identify crucial pathways, novel biomarkers, and physiology-relevant disease subtypes, while limited by cost and the amount of tissue required.

Methods: We developed a novel multiplexed droplet-based single-cell/nucleus sequencing technique to achieve higher throughput and lower cost with less tissue. We applied this method to simultaneously profile transcriptomic (RNAseq) and chromosomic access (ATACseq) data in 27 patients who underwent renal biopsy due to various kidney diseases, ten time-zero transplant biopsy samples, and seven paracancerous kidney samples.

Results: After quality control, we yielded about 120,000 nuclei (mean nuclei number 2727 per sample) with both transcriptomic and epigenomic profiling data. For snRNAseq, the median gene number per cell is more than 1100. For snATAC-seq, the median fragments number per cell is about 6000, and the TSS enrichment score is 8.83. Major renal cells types including proximal tubule cells, descending thin limb cells, thick ascending limb cells, distal convoluted tubule cells, connecting tubule cells, principal cells, intercalated cells, podocytes, endothelial cells, vascular smooth muscle cells, as well as infiltrating B cells, T cells, and fibroblasts can be robustly identified from the snRNAseq dataset.

Conclusions: We developed a novel single-nucleus multi-omic approach that offers rich transcriptomic and epigenomic data, showing promise as a molecular renal pathology technique.

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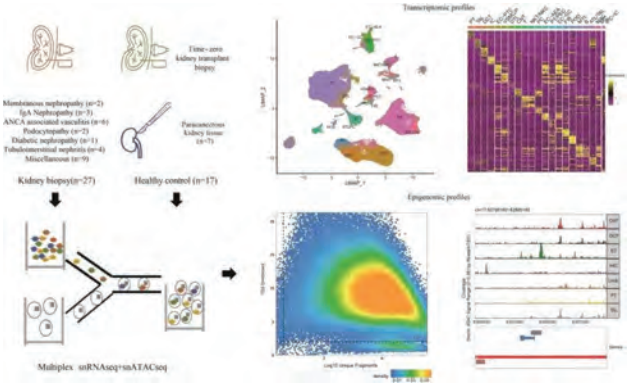

FR-OR59

T Cell-Receptor (TCR)-Independent Activation of CD8 Effector T Cells by IL-15 and IFNβ Drives Kidney Damage in Lupus Nephritis

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Background: Lupus nephritis (LN) implies morbidity in Systemic Lupus Erythematosus (SLE). A T cell-rich infiltrate parallels deposition of antibodies. How infiltrating T cells contribute to kidney damage is unclear. They can also be observed in urine, which thus can be used as a "window into the kidney" to investigate the cellular pathogenesis of LN. We report analysis of kidney infiltrating T cells found in urine to test if a renal autoimmune reaction contributes to tubulointerstitial inflammation (TII).

Methods: Urinary T and tubular epithelial cells (TEC) were quantified by flow cytometry (FC) in LN patients. T cells were subjected to single cell RNA sequencing after FC sort from urine and blood of five LN patients at flare. Comparison of gene transcription revealed putatively pathogenic cells. 67 T cell receptors (TCR) from expanded clonotypes were cloned to test specificity; T cell subsets from blood were subjected to in-vitro experiments. T cell stimulating cytokines were determined in urine from LN and healthy donors, reflecting the renal milieu.

Results: Majority of urinary T cells in LN are of CD8 lineage, the amount of which correlates with urinary TEC, a proxy for kidney damage. Mainly being of effector memory phenotype they are recruited partially from a CX3CR1 positive subset in blood which has a of type I interferon (IFN) signature. TCR analysis revealed expanded CD8 clones, none of which reacted with autologous TEC (0/18). Reactivity to viral CMV and EBV epitopes was shown for 15/67 clones. CMV or EBV was not detectable in respective kidney biopsies. In kidney tissue and/or urine we detected elevated levels of T cell stimulating cytokines, like IL-15. In-vitro, stimulation of CD8 T cells with IL-15 and IFNβ caused TCR-independent activation, degranulation and secretion cytokines TNF and IFNγ, almost exclusively by CX3CR1 positive CD8 effector T cells.

Conclusions: Contribution of CD8 T cells to TII and TEC damage in LN is antigen and TCR independent. In-vivo stimulation with IL-15 and type I IFN may be sufficient to trigger effector functions of a CX3CR1 positive subset. Targeting these cells in the blood, their migration, their response to cytokines or reducing renal cytokine levels may prevent LN flares and represent a tailored treatment.

FR-OR60

Adoptive Cellular Immunotherapy for the Control of Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (PMN) is an autoimmune podocytopathy caused by subepithelial immune deposits that thicken the glomerular basal membrane and fusion of podocyte processes, causing proteinuria. It is the most common cause of non-diabetic nephrotic syndrome in adults. It is caused in 80% of cases

by antibodies targeting podocytes' M-type receptor of phospholipase A2 (PLA2R), in 5% against thrombospondin 7A type-1 (THSD7A), or other recently described antigens. A third of affected patients evolve into terminal kidney disease. Immunotherapy based on chimeric antigen receptors (CAR)-T cells has been an extraordinary advance in the fight against cancer. The current proposal aims to generate a chimeric anti-PLA2R autoantibody receptor (PLA2R-CAAR) and anti-THSD7A autoantibody receptor (THSD7A-CAAR) to target antibody-producing B cells.

Methods: In this pre-clinical study, human T lymphocytes were obtained from healthy volunteers. The design, generation, and production of PLA2R-CAAR and THSD7A-CAAR will be carried out, with subsequent evaluation of their cytotoxic properties and cytokine production, through an *in vitro* model.

Results: We have identified and cloned the genetic sequence corresponding to PLA2R and THSD7A. The PLA2R-CAAR construct has been generated from domain binding, leader peptide, extracellular domain (either PLA2R or THSD7A), and intracellular domains from A2-CHAR (developed in our laboratory). We produced lentiviral particles with the construct in HEK-293T cells. After the isolation of CD3+ cells from healthy volunteers, transduction and production of PLA2R-CAAR and THSD7A-CAARs is performed. CAAR-T cell's cytotoxic properties were assessed using serum samples containing anti-PLA2R or anti-THSD7A antibodies from patients with membranous nephropathy.

Conclusions: This strategy may be the prelude to a new immunotherapy for patients with membranous nephropathy who have anti-PLA2R or anti-THSD7A antibodies in circulation.

Funding: Private Foundation Support

FR-OR61

Correlation of HLA Matchmaker and PIRCHE Reveals T Cell Epitope Mismatches High Risk for Donor Specific Antibodies (DSA) and Antibody-Mediated Rejection (AMR)

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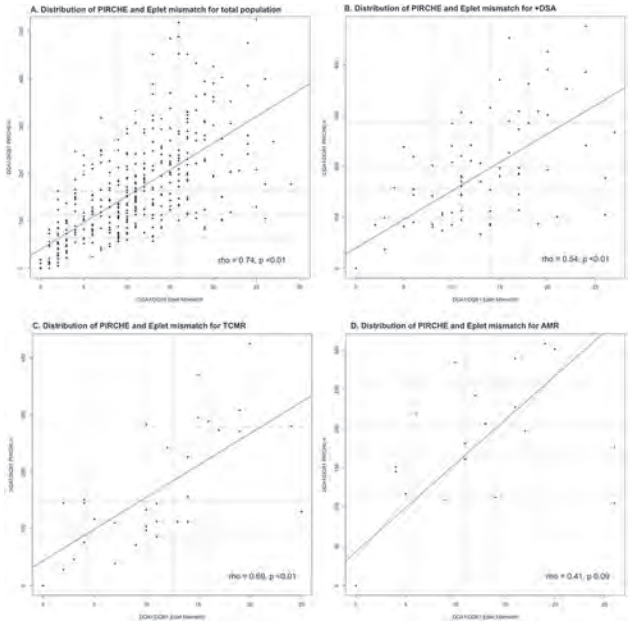
Background: Both HLA Matchmaker and PIRCHE algorithms associate with de novo donor specific antibody (DSA) in kidney transplant recipients (KTR), but each predicts a different mechanism of the alloimmune response. Activation of CD4 T helper cells via indirect allorecognition (PIRCHE) occurs upstream of T-B cooperation resulting in antibody production (HLA Matchmaker). Given this, we aim to describe their correlation and hypothesize PIRCHE can provide insight as to the molecular mismatches highest risk for DSA and subsequent rejection.

Methods: KTR between 2017 to 2022 with high-resolution HLA typing were identified. Eplet mismatches were calculated with HLA Matchmaker and PIRCHE score determined. Spearman correlation was preformed and results plotted with quintile cutoffs.

Results: We identified 420 adult (n= 377) and pediatric (n= 43) KTR. Median age 52 years old, 68% male, 68% deceased donor and median time 20 months from transplant. DQA1/DQB1 had the strongest association with DSA when assessed with each algorithm. Distribution and correlation of PIRCHE and eplet mismatches for the entire cohort, +DSA, TCMR and AMR are shown in Figure 1, panels A-D. There was moderate correlation between the algorithms but more discordance of high PIRCHE/low eplet mismatch in DSA and AMR.

Conclusions: Our results demonstrate moderate strength correlation of PIRCHE and HLA matchmaker with transplant outcomes. High PIRCHE in setting of lower eplet mismatch in those with DSA and AMR suggests PIRCHE is predicting mismatched T cell epitopes that may be relevant for antibody formation and rejection. This cohort is limited by its retrospective nature and small sample size, but our next phase aims to test this hypothesis by quantifying *ex vivo* alloreactivity in donor/recipient pairs with high predicted T-cell epitope mismatches.



FR-OR62

Validation of Diagnostic, Prognostic, and Predictive Performances of a Novel Urinary Exosomal mRNA Clinical Test

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Background: Urinary Exosomes contain a biological payload of proteins and nucleic acids that reflect the physiology of the parent cells (kidney cells and immune infiltrates). Here we further characterize diagnostic performances of a novel urinary exosomal mRNA multigene signature for the diagnosis of any-cause rejection in kidney transplant, and describe its prognostic and predictive performances.

Methods: A total of 411 urine samples -from 366 patients- were collected at time of clinically indicated or protocol kidney biopsy. The transcript of 17 gene targets were pre-amplified and evaluated by RT-qPCR. Cross validation was applied to estimate the performance of the gene signatures. A composite endpoint of subsequent events were determined using the electronic medical records, and outcomes in subjects with positive and negative exosome signature were compared.

Results: The multi-gene classifier accurately distinguished any-cause rejection from no rejection, in the for-cause cohort (AUC 0.731) and the protocol biopsies cohort (AUC 0.781). We further identified a 5-gene signature (*IL18BP, CXCL11, CD74, CD44, C3*) that accurately distinguishes TCMR from ABMR with an AUC of 0.756. Majority of rejection negative by biopsy classified as positive by our model (false positive) showed significant underlying inflammation on biopsy such as lymphoproliferative infiltrate, moderate to significant lymphocytic infiltration, interstitial nephritis (BKV nephritis or acute interstitial nephritis), glomerulopathy or immune complex deposition. Furthermore, the remaining inflammation negative but positive urinary exosome scores were associated with three-fold increase in risk development of composite outcomes of subsequent rejection, decrease eGFR and loss of allograft at 3 years. The exosomal score showed a mean decrease of -0.05666 (p 0.0431) in responders to rejection treatment.

Conclusions: Urinary exosomal mRNA is a non-invasive clinical test that offers an insight into the status of the immune activation in the kidney allograft, and complement other laboratory surveillance strategies as a diagnostic, prognostic and predictive marker and risk-stratification tool in kidney transplant recipients. This assay is now ready for clinical use.

Funding: Other NIH Support - T32 Ruth L. Kirschstein Institutional National Research Service Award, Commercial Support - ExosomeDx, a Biotechne brand

FR-OR63

Differential cfDNA Methylation in Kidney Allograft Rejection

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Background: Acute allograft rejection (AAR) is a risk for kidney allograft failure, however, knowledge of the molecular pathophysiology of rejection is lacking. Allograft life is limited and organ availability is scarce, emphasizing the need to understand rejection pathophysiology to preserve the primary allograft. Cell-free DNA (cfDNA) serves as a real-time marker of organ injury and immune response. DNA methylation patterns dictate gene expression. Generally, hypermethylation silences gene expression and hypomethylation indicates active transcription. We propose methylation changes in cfDNA during AAR inform the biologic pathways involved in its development and sequelae.

Methods: Methylation status of total plasma cfDNA samples from 20 pediatric kidney transplant recipients at the time of allograft biopsy was assessed using whole genome bisulfite sequencing. 7,789 differentially methylated CpG sites (DMCs) between individuals with *vs* without AAR were determined through logistic regression analysis (≥20% difference in methylation rate, q-value <0.05) and were assessed for gene associations and pathway/functional enrichments.

Results: AAR was present in 7 patients. 3,390 DMCs were relatively hypermethylated in the setting of AAR and 4,399 were relatively hypomethylated; these DMCs were associated with 114 and 138 genes, respectively. On enrichment analysis, "Relationship between inflammation, COX-2 and EGFR", "Negative regulation of mononuclear cell proliferation", "Regulation of cysteine-type endopeptidase activity in apoptotic process", "Regulation of interleukin-8 production", and "PID CD8 TCR Pathway" were among the most significant WikiPathways, canonical pathways, and Gene Ontology (GO) Terms in hypermethylated genes ($P < 0.005$). "Response to oxidative stress" and "Regulation of leukocyte mediated cytotoxicity" were among top GO Terms in hypomethylated genes ($P \leq 0.01$).

Conclusions: Our data implicate differential immune responses in acute rejection compared to non-rejection in kidney transplant recipients. These differences include the innate and adaptive immune responses and involve the differential regulation of leukocytes and mediation of cytokines. These results provide evidence that methylation differences of cfDNA inform the mechanisms of AAR.

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FR-OR64

Urinary Endotrophin Excretion Is Associated with Graft Failure and Mortality in Kidney Transplant Recipients

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Background: Kidney fibrosis is a suggested cause of kidney failure and premature mortality, regardless of the underlying cause. Since collagen type VI is closely linked to kidney fibrosis, we aimed to evaluate whether endotrophin, a profibrotic signaling molecule that reflects collagen type VI formation, in the urine was independently associated with graft failure and mortality among kidney transplant recipients (KTR).

Methods: We used data of KTR with a functioning graft ≥ one year that were enrolled in the TransplantLines Biobank and Cohort Study. Endotrophin was measured by the PRO-C6 enzyme-linked immunosorbent assay in the 24h urine.

Results: There were 621 KTR (age 53 ± 13 years old, 43% female, 5.2 [2.0-12.0] years after transplantation, eGFR 45 ± 19 mL/min/1.73 m²) included in the analyses. The 24h urinary endotrophin excretion at baseline was 5.6 [3.1-13.5] µg/24h. During median follow-up of 5.3 years, 70 KTR (11.3%) developed graft failure and 134 KTR (21.6%) died. 24h urinary endotrophin excretion was prospectively associated with both increased risk of graft failure and mortality, independent of potential confounders **(Table)**.

Conclusions: Urinary endotrophin excretion is independently associated with an increased risk of graft failure and mortality in KTR. Further studies with different KTR populations are needed to confirm these findings.

Funding: Commercial Support - Astellas BV and Chiesi Pharmaceuticals BV, Government Support - Non-U.S.

Cox proportional-hazards analyses for the association of 24h urinary endotrophin excretion with graft failure and mortality.

	Graft Failure		Mortality	
Model	HR per doubling (95% CI)	p-value	HR per doubling (95% CI)	p-value
Crude	1.59 (1.44-1.75)	<0.001	1.26 (1.15-1.37)	<0.001
Model 1	1.63 (1.47-1.80)	<0.001	1.31 (1.20-1.42)	<0.001
Model 2	1.16 (1.02-1.33)	0.027	1.19 (1.07-1.33)	0.001
Model 3	1.19 (1.03-1.38)	0.018	1.17 (1.05-1.30)	0.005
Model 4	1.22 (1.05-1.42)	0.009	1.16 (1.04-1.29)	0.009

Model 1 was adjusted for age, sex, and time after transplantation at inclusion. Model 2 was further adjusted for estimated glomerular filtration rate and log2 24h urinary protein excretion. Model 3 was further adjusted for body mass index and diabetic nephropathy as primary kidney disease. Model 4 was further adjusted for donor age and history of delayed graft function.

FR-OR65

Elevated Glycolytic Markers in Urinary Extracellular Vesicles in Kidney Transplant T Cell-Mediated Rejection

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Background: Urinary extracellular vesicles (UEV), containing components of their parent cells, are released from cells lining the kidney and urinary tract. Changes in kidney protein expression are reflected in the proteome of UEV and its use as a non-invasive marker of allograft function is of particular interest in kidney transplantation. Under stress, renal energy metabolism switches from fatty acid oxidation to glycolysis. We evaluated changes in glycolytic control proteins in UEV at the time of clinically-indicated kidney transplant biopsies and correlated this with histological lesions described in the Banff classification.

Methods: This prospective observational study involved collection of pre-biopsy urine samples from kidney transplant recipients at the time of indication biopsy. UEV were isolated by differential ultracentrifugation. Western blots were performed to confirm vesicle markers (CD9, TSG101 and Tamm-Horsfall protein) and then probed for glycolytic markers.

Results: The cohort of 25 subjects (mean age 50.6 years, 60% male) included 5 cases of T-cell mediated rejection (TCMR), 4 cases of borderline TCMR and 16 normal biopsies. TCMR and borderline TCMR were analysed as one group (n = 9) and the following glycolytic markers were detected in this group: phosphofructokinase-liver, isoenzymes of 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase (PFKFB2, phosphorylated ser461 PFKFB2, phosphorylated ser483 PFKFB2, PFKFB3, PFKFB4) and pyruvate kinase (PK-M2, PK-LR). There was significantly increased expression of PFKFB3+ UEV in 3/9 (33%) of TCMR samples compared to 0/16 of normal biopsy samples (p=0.04). PFKFB4+ UEV was expressed in 6/9 (66%) of TCMR samples compared to 1/16 of normal biopsy samples (p=0.003).

Conclusions: This study demonstrates elevated expression of PFKFB3 and PFKFB4 in UEV in kidney transplant recipients with biopsy-proven TCMR. This may represent altered energy metabolism in the form of increased renal glycolysis in association with cell mediated rejection.

FR-OR66

Proenkephalin A 119-159 as a Novel Biomarker for Early Detection of Delayed Graft Function After Kidney Transplantation

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Background: Delayed graft function (DGF) frequently occurs following kidney transplantation and adversely affects patient outcomes such as length of hospital stay, impaired long-term graft function and ultimately quality of life. Though a universal definition of DGF is lacking, a common classification is the need for dialysis in the first postoperative week excluding the first 24 hours. The aim of this study was to evaluate the capabilities of the novel kidney function biomarker proenkephalin A 119-159 (penKid) to predict DGF compared to serum creatinine (SCr).

Methods: In the currently ongoing study, penKid has been quantified from plasma using a chemiluminescence immunoassay in our daily routine in all freshly transplanted patients since November 2022. PenKid is quantified the day of transplantation and every weekday following transplantation. For this preliminary analysis, penKid levels were compared to SCr. The end of data collection is June 30, 2023.

Results: In a preliminary analysis including 70 kidney transplant recipients (70% cadavric transplants), results suggest, that penKid may discriminate patients with delayed graft function from patients with primary graft uptake earlier than SCr. In contrast to SCr, penKid was able to distinguish between DGF and no DGF as early as 24 hours after transplantation (Figure 1). In addition, other than SCr, penKid levels do not seem to be affected by dialysis.

Conclusions: PenKid is a promising new biomarker for the early prediction of DGF after kidney transplantation and may enable clinicians to adjust their treatment in high-risk patients accordingly. However, more clinical data is needed to validate our findings and to establish the clinical utility of penKid in the management of kidney transplant patients.

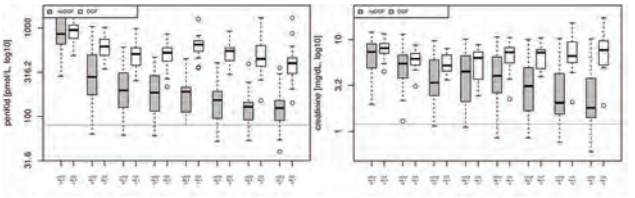

Figure 1: Proenkephalin A 119-159 (penKid) is an early indicator for predicting delayed graft function, (penKid DGF vs. no DGF: day 0: p>0.05; day 1-7: p<0.001), whereas serum creatinine levels provide a much later signal for distinguishing DGF from no DGF (SCr DGF vs. no DGF: day 0-3: p>0.05; day 4: p=0.02; day5-7 p<0.001). DGF: delayed graft function, defined as need for dialysis within 7 days after transplant, excluding the first 24h. Biomarker measurement at day 0 was performed before transplantation.

FR-OR67

Uncontrolled Hypertension Is Associated with Increased Risk of Graft Failure in Kidney Transplant Recipients: A Nationwide Population-Based Study

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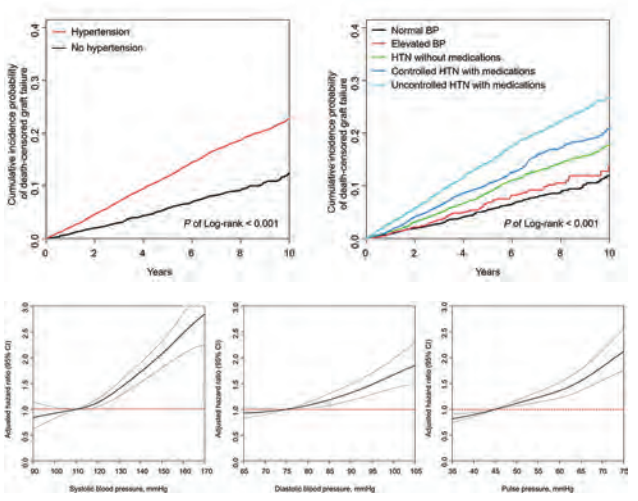
Background: Hypertension is highly prevalent in patients with kidney transplantation caused by transplantation-related immunologic or non-immunologic risk factors. However, whether a strict definition of hypertension (≥130/80 mmHg) and subdivided blood pressure (BP) groups are associated with an increased risk of graft failure after kidney transplantation using a nationwide large cohort study are still unknown.

Methods: Using Korena National Health Insurance Service data, we included 14,249 patients who underwent kidney transplantation from 2002 to 2016. Patients were categorized into five BP groups according to the 2021 Kidney Disease: Improving Global Outcomes practice guidelines for BP management: normal BP (<120/80 mmHg), elevated BP (120–129/<80 mmHg), incident hypertension (≥130/80 mmHg), and controlled or uncontrolled hypertension with anti-hypertensive medications.

Results: The primary outcome was graft failure, which occurred in 1,934 (13.6%) participants during the 6-year follow-up. After adjusting for covariates, hypertension was associated with a higher risk of graft failure [Adjusted hazard ratio (AHR), 1.70; 95%

confidence interval (CI), 1.48–1.96)] than no-hypertension. The AHR for graft failure was the highest in patients with uncontrolled hypertension (AHR, 2.13; 95% CI, 1.80–2.52). The risk of graft failure had a linear relationship with systolic and diastolic BP, and pulse pressure.

Conclusions: In this nationwide population-based study, hypertension ≥ 130/80 mmHg based on the 2021 KDIGO BP guidelines in kidney transplantion recipients, and elevated systolic and diastolic BP, and pulse pressure were associated with the risk of developing graft failure in kidney transplant recipients.



FR-OR68

The Molecular Microscope Diagnostics System (MMDx) Does Not Identify Molecular T Cell-Mediated Rejection (TCMR) in Cases with Borderline Changes or Isolated Intimal Arteritis in the Absence of Microvascular Inflammation

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Background: Borderline changes suspicious for T-cell mediated rejection (TCMR) and isolated intimal arteritis (v-lesion) represent a particular challenge. Even though the Molecular Microscope Diagnostics System (MMDx) has not been trained on borderline changes and v-lesions, it has been suggested that MMDx may reclassify a subgroup of cases to molecular TCMR.

Methods: In this single-center cohort of 326 kidney allograft biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 153 cases with isolated tubulitis (i0, t1-3; n=114), borderline changes (n=10), and isolated intimal arteritis (i0, t0-2, v1; n=39) in the presence (n=81) and absence (n=72) of microvascular inflammation (MVI). 83 cases without histologic lesions suspicious for TCMR (i0, t0, v0) were used for comparison of rejection phenotype scores. Any cases with overlapping pathologies were excluded from the analysis.

Results: 41 of 81 cases (51%) with suspicion for TCMR and MVI showed molecular rejection (30 cases with molecular ABMR, 4 cases with molecular ABMR/TCMR (2 cases with isolated tubulitis, 1 case with borderline changes, 1 case with isolated intimal arteritis), and 7 cases with minor ABMR) compared to 6 of 32 cases (19%) without suspicion for TCMR but MVI (5 cases with molecular ABMR, 1 case with molecular ABMR/TCMR; p=0.003). However, 1 of 72 cases (1%) only with suspicion for TCMR, but no MVI showed molecular rejection (1 case with minor ABMR). No pure molecular TCMR was identified in any group. 11 of 153 cases (7%) with suspicion for TCMR showed a TCMR phenotype score (R2) ≥0.10 (7 cases with isolated tubulitis and 4 cases with isolated intimal arteritis) compared to 5 of 83 cases (6%) without suspicion for TCMR (p=1).

Conclusions: MMDx may identify molecular TCMR among cases with MVI irrespective of histologic suspicion for TCMR. MMDx does not identify molecular TCMR in cases with isolated tubulitis, borderline changes, or intimal arteritis without MVI. TCMR phenotype scores do not differentiate between isolated tubulitis, borderline changes, isolated intimal arteritis, or no histologic lesions suspicious for TCMR.

Funding: Private Foundation Support

FR-OR69

Donor-Derived Cell-Free DNA (dd-cfDNA) in Kidney Transplant Recipients with Indication Biopsy: Results of a Prospective German Single-Center Trial

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Background: Donor-derived cell-free DNA (dd-cfDNA) identifies allograft injury and discriminates active rejection from no rejection. With a number of studies investigating the benefit of dd-cfDNA in US American transplant cohorts, we aimed at evaluating the performance of dd-cfDNA in a cohort of German kidney transplant recipients.

Methods: We enrolled 106 kidney transplant recipients with clinically indicated biopsy between November 2020 and March 2023 at the Department of Nephrology at Heidelberg University Hospital. dd-cfDNA was quantified using the AlloSeq cfDNA assay (CareDx) at time of biopsy to correlate dd-cfDNA levels with histopathological reporting and on days 7, 30 and 90 following biopsy to assess the utility of dd-cfDNA in monitoring treatment response.

Results: Of the 108 allograft biopsies, 36 (33%) were classified as different types of rejection. Patients with ABMR or TCMR (N=13) showed significantly higher dd-cfDNA levels with a median (IQR) of 1.60% (0.38–3.35) compared to the 0.44% (0.20–1.10) in patients with borderline changes (N=23) and the 0.2% (0.11–0.53) in patients with no signs of rejection (N=72) (P<0.05 and P<0.001, respectively). The AUC for dd-cfDNA to differentiate any type of rejection including Borderline changes from no rejection was at 0.72 (95% CI 0.62–0.83). The optimal cut point for dd-cfDNA to discriminate active rejection was at a threshold of 0.57%, yielding a sensitivity of 53% (95% CI 37–68%), a specificity of 81% (95% CI 70–88%), a PPV of 58% (95% CI 41–73%), and a NPV of 77% (95% CI 67–85%). In patients receiving anti-rejection treatment, dd-cfDNA levels decreased significantly during the 7-, 30-, and 90-day follow-up compared to levels at the time of biopsy (P=0.006, P=0.002, and P<0.001, respectively).

Conclusions: Our data verify the good performance of dd-cfDNA to correctly identify kidney transplant recipients with active rejection at a German transplant center. We show that dd-cfDNA may aid the clinician in recognizing patients at risk and in decision-making regarding the need for a graft biopsy. The potential benefit of dd-cfDNA to assess response to therapy needs further validation.

Funding: Commercial Support - CareDX

FR-OR70

Pretransplant HbA1C as a Predictor of Kidney and Pancreas Allograft Survival in Simultaneous Pancreas-Kidney Transplantation: A Retrospective Nationwide Study

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Background: Simultaneous pancreas-kidney transplant (SPKT) is a therapeutic option for patients with end-stage kidney disease (ESKD) and diabetes mellitus (DM). Hemoglobin A1C (HbA1C) is a widely used biomarker for glycemic control in DM patients. However, its role in predicting SPKT outcomes remains unclear. This study aimed to investigate the association of pre-transplant HbA1C levels with kidney and pancreas allograft survival in patients with SPKT.

Methods: Using data from the United Network for Organ Sharing (UNOS) database, a total of 3,351 SPKT recipients were included in the analysis. Cox proportional hazards regression models with time varying covariates were used to evaluate the association between HbA1C and allograft survival.

Results: Our results showed that higher pre-transplant HbA1C levels were significantly associated with lower kidney and pancreas allograft survival rates. Compared to patients with HbA1C levels ≤7%, patients with HbA1C levels >7% had a hazard ratio of 3.38 (95%CI: 2.40-4.75, P< 0.01) and 7.99 (95%CI: 6.02-10.60, P< 0.01) for kidney and pancreas allograft failure, respectively (Figure 1A and 1B). Moreover, this association remained significant after adjusting for relevant potential confounders, including age, gender, body mass index, and donor types.

Conclusions: Pre-transplant HbA1C is a strong predictor of both kidney and pancreas allograft outcomes in SPKT recipients. Our findings highlight the importance of glycemic control in uremic diabetic patients as one of the pre-transplant preparation strategies to improve allograft survival after successful SPKT.

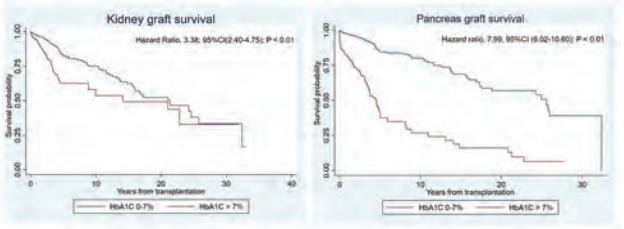

Figure 1A : Kidney graft survival **Figure 1B : Pancreas graft survival**

Figure 1 : Graft Survival

FR-OR71

The Standardized Discontinuation Ratio: A Novel Measure for Real-Time Monitoring of Home Dialysis Discontinuation

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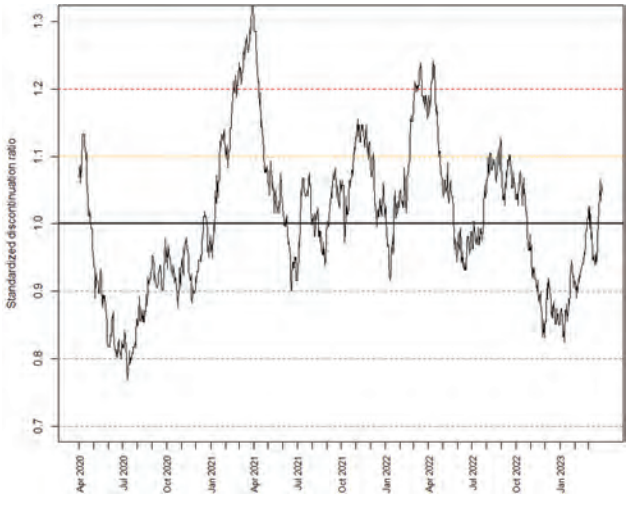
Background: Home dialysis attrition is a significant challenge. Attrition slows growth, and discourages both nurses and patients who devote great effort to training. Many measures, including the "churn rate" and the cumulative incidence of all-cause attrition, are not ideal for real-time quality monitoring, due to slow evolution and the inclusion of kidney transplantation, a positive outcome. We developed a novel measure, the standardized discontinuation ratio (SDR), that facilitates ongoing assessment of whether the composite event of conversion to in-center hemodialysis or death is occurring more or less frequently than is expected.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. On any given day, we defined the SDR as the ratio of actual versus expected discontinuations from home dialysis during the past 13 weeks. Discontinuation was defined by either conversion from home dialysis to in-center hemodialysis or death. The expected number of discontinuations was summed from patient-day probabilities of discontinuation, estimated as a function of age, modality, and time since home dialysis initiation.

Results: During the 4-year period ending on May 15, 2023, there were 288 discontinuations among 1011 home hemodialysis (HHD) patient-years and 1557 discontinuations among 5430 peritoneal dialysis (PD) patient-years. C-statistics for modality-specific models of discontinuation were 0.61 for HHD and 0.58 for PD. As displayed, the organization-wide SDR from April 2020 to March 2023 varied widely, ranging from 0.77 on July 11, 2020, to 1.34 on March 30, 2021. The SDR was between 1.1 and 1.2 on 12.2% of days during the 3-year period ending in March 2023, and greater than 1.2 on 6.5% of days.

Conclusions: The SDR can be used in real-time to monitor trends in home dialysis discontinuation for the purpose of organizational quality improvement.



FR-OR72

Breaking Through Barriers with Home Hemodialysis (HHD) Group Training, Enhancing Access and Improving Patient Experience: A Single-Center Experience

Maria Bermudez, Waleed Zafar. *Geisinger Medical Center, Danville, PA.*

Background: Despite emerging evidence supporting greater quality of life (1) and improved cardiovascular outcomes (2, 3), HHD remains underutilized in the U.S. (4) Two barriers to widespread adoption are delayed access to HHD due to a shortage of HHD units and staff; and patient apprehension about taking dialysis in their own hands. Group training for HHD remains underutilized in the US with less than 5% of units implementing this training strategy. Given lack of experience, little is known about group training in HHD. We describe a single center experience of instituting group training for HHD.

Methods: All patients and their care-partners currently enrolled in HHD program who underwent group training were surveyed. We evaluated the impact of group training on duration of training, unit census growth, need for retraining, incidence of complications and patient experience.

Results: A total 6 consecutive groups of 2 and 3 patients at a time for a total of 16 patients were trained in HHD over a period of 7 months. Training time averaged 30-40 days and was similar for all groups and comparable to solo training. Unit census tripled during this period going from 7 patients to 23. Demographic characteristics are described in table 1. 14 (87.5%) patients had no missed treatments over a 3 month period and no patient needed retraining over the follow up period. 1 patient transitioned to in-center dialysis and 1 died. All patients who were surveryed agreed that group training was an enjoyable experience and strongly recommended to others.

Conclusions: In our experience, group training has proven to be an effective strategy for scaling HHD training. It has helped overcome two major barriers to HHD: prompt access to training and patients' need for strong support in the early training phase. Ongoing longitudinal data collection will help us evaluate association of group HHD training with outcomes including missed treatments, need for retraining and respite care, and patient quality of life scores. Group training has the potential to be an empowering tool for our patients and to enhance our ability to cross train nurses in HHD thus potentially helping with nursing attrition.

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FR-OR73

Hospitalisation Risk in the Integrated Home Dialysis Model: Analysis of the Canadian Organ Replacement Register

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Background: The integrated home dialysis model proposes the initiation of dialysis with peritoneal dialysis (PD) followed by transition to home hemodialysis (HHD) after PD ends. Outcomes of integrated home dialysis versus a "direct to HHD approach" are poorly known. We aimed to compare the hospitalization risk of patients in integrated home dialysis (before, during and after transfer to HHD) with patients directly initiating HHD.

Methods: We studied patients in the Canadian Organ Replacement Register who initiated PD or HHD between 2005 and 2018. A 1:1 propensity score was used to match patients transitioning from PD to HHD in less than 90 days after PD ("PD+HHD" group) to patients with HHD as the first home-dialysis modality ("HHD" group). Our outcome was all-cause hospitalization, assessed from the beginning of home dialysis (PD or HHD) until transfer to facility HD, death, end of follow-up (December 31st 2019) or kidney transplant. Hospitalizations were compared between groups with shared frailty models in three periods: before PD-HHD transition, during transition, and after transition (Fig 1).

Results: From 63,327 patients, 13,726 initiated PD and 745 initiated HHD. 4,420 patients transferred from PD to facility HD and 163 transferred to HHD (3.6% of transfers; median time on PD 1.9 years). Hospitalization risk was similar between groups in the period before and after the PD-HHD transition but was significantly increased during the transition period (Table). Similar trends were observed when these periods were sub-divided by year (Fig 2).

Conclusions: Patients transitioning from PD to HHD do not have an increased hospitalization risk outside their transfer period when compared with patients who start dialysis directly in HHD.

Funding: Government Support - Non-U.S.

Figure 1:

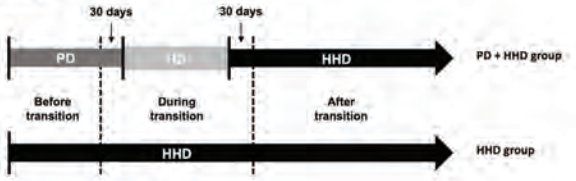
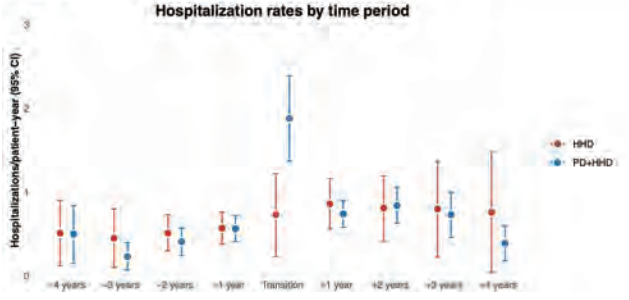


Table:

Time period	Hospitalization rate (PD-HHD; events/pt-year)	Hospitalization rate (HHD; events/pt-year)	Hazard ratio (95% CI)
Before transition	0.44	0.52	0.91 (0.61-1.37)
During transition	1.88	0.73	2.69 (1.25-5.82)
After transition	0.73	0.79	0.83 (0.56-1.24)

Figure 2:



FR-OR74

Physical Activity Perceptions and Practices of People Receiving Peritoneal Dialysis: An International Cross-Sectional Survey

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Background: Life participation is a core patient-reported outcome for people receiving peritoneal dialysis (PD) that is dependent on physical activity engagement and adequate physical function. Little is known about exercise practice patterns or perceptions of people receiving PD. The aim was to describe the physical activity and exercise practices and perceptions of people receiving PD to inform patient education, future areas of research, and clinical recommendations.

Methods: A cross-sectional, descriptive, web-based 25 item survey (16 perception and practice questions, 9 demographic questions) was co-developed and pilot tested by persons living with kidney disease, PD clinicians and exercise specialists. Adults who currently or previously received PD were invited to participate in the survey. Recruitment was completed through national and international kidney organization websites and social media platforms. All variables were reported descriptively, and free text responses were collated and summarized.

Results: There were 114 respondents, 6 excluded due to duplication or incompletion, the majority were from Canada (68%), United Kingdom (25%) and 7% other. Women represented 55% of respondents, with most 50-64 years old (43.5%). Forty-one percent received PD for 1-3 years and 72.9% had post secondary education. Physical activity was felt to be beneficial by 91.8% of respondents and 40% reported they had good physical function (could walk an unlimited distance without stopping). Variable medical advice regarding swimming and weightlifting emerged: 44% were told they could or could not swim, and respondents were told to limit weight lifting from 2 to 45 kg. A minority of respondents reported receiving instructions on draining PD fluid prior to physical activity (28% yes, 53% no, 19% unsure).

Conclusions: Survey respondents were knowledgeable regarding benefits of exercise and physical activity on physical and mental health for people receiving PD. Knowledge gaps emerged including maximum weightlifting, whether exercise was safe with or without intrabdominal PD fluid in situ, and whether swimming is allowed. Education for both health care providers and patients is needed regarding the practice of exercise for people receiving PD.

FR-OR75

Decreasing the Burden: A Single-Centre Experience of Decremental Peritoneal Dialysis (PD) in Toronto, Canada

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Background: The 2020 International Society of Peritoneal Dialysis (ISPD) recommendations on providing high-quality peritoneal dialysis (PD) prescriptions highlight shared-decision making principles that deemphasize the focus on Kt/V clearance targets. As a result, incremental PD has gained popularity amongst care providers in recent history. However, "decremental PD", a practice in which PD dose is reduced after patients are started on high dose PD (>10L/day), has not been well described in the literature. Decremental PD utilizes the principles of goal-directed therapy as outlined by the ISPD to reduce prescriptions where possible; particularly when treatment is burdensome for patients. We describe our experience with this approach and potential benefits to both patients and the healthcare system.

Methods: Nine prevalent patients on high-dose automated PD prescriptions seen between August 1-December 31, 2019, were included in this analysis. All patients reported prescriptions were burdensome. Patients were offered a reduced dose in their prescription after clinical assessment and laboratory investigations were reviewed. Patients were compared 6 months before and after the change in prescription for any significant differences in hospitalization, peritonitis rates and technique failure. Small solute clearance using Kt/V and creatinine clearance along with residual urine output were also compared.

Results: Total dialysis volume and time on cycler were significantly reduced from a mean of 12.6 L to 9.2L ($p < 0.001$) and from 8.7 to 8.2 hours ($p < 0.035$). No statistically significant differences in Kt/V and CrCl values 6 months after the change in prescription were observed. There were no observed peritonitis episodes or hospitalizations six months after prescription change. All patients remained on PD 12 months after the intervention with no further prescription changes. The reduced prescription resulted in a 19.2% cost reduction per patient at six months compared to high-dose prescription.

Conclusions: We demonstrate that decremental PD prescriptions align with ISPD recommendations in maintaining patient-centered care while reducing cost.

	Mean prior to prescription change	Mean after prescription change	P value (95%)
PD Volume (mL)	12688.89 ± 3835.18	9244.44 ± 3280.67	*P <0.001*
Time on cycler	8.67 ± 0.71	8.22 ± 0.67	*P = 0.035*
Total Kt/V_{urea}	2.79 ± 0.87	2.51 ± 0.51	P = 0.48
Total CrCl (L/week)	83.33 ± 29.28	77.50 ± 18.67	P = 0.50
Residual urine output (mL/day)	946.13 ± 786.19	1071.33 ± 801.14	*P = 0.035*

CrCl – Creatinine clearance

	Prior to change	After change	Cost Difference	% Change
Cost of solutions for 6 months*	$49,883.40	$40,312.80	$9,570.60	⇓19.2%

**Total cost of solutions for all patients 6 months before and 6 months after prescription change.*
These costs reflect solutions only and not supplies nor other materials related to routine daily care.
All prices are in Canadian dollars

FR-OR76

CKD-Associated Pruritus: Prevalence and Association with Quality of Life for Peritoneal Dialysis Patients, International Results from PDOPPS

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Background: Chronic kidney disease associated pruritus (CKD-aP) is associated with morbidity. The prevalence and burden of CKD-aP in peritoneal dialysis (PD) is not well-known. We sought to determine the CKD-aP prevalence, identify factors associated with a high severity of CKD-aP and the impact of CKD-aP on quality of life (QOL) among patients in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS).

Methods: We analyzed cross-sectional data on QOL and CKD-aP from PDOPPS patients from Australia, Canada, Japan, New Zealand, Republic of South Korea, Thailand, the UK, and US between 2014-22. CKD-aP severity in the preceding 4 weeks was self-rated by patients using a 5-point Likert scale from 1: "Not at all bothered by itch" to 5: "Extremely bothered by itch". Factors associated with CKD-aP 3-5 (moderate to extreme) v. 1-2 were analyzed using logistic regression. Adjusted linear regressions were used to compare CKD-aP and QOL, assessed using the physical and mental component summary scores (PCS and MCS) of the 12-item Short-Form (SF-12) on the same questionnaire.

Results: 43% of the 5534 patients reported moderate to extreme itch; ranging from 50% and 49% (Thailand and the UK, respectively), to 32% (the US). Adjusted logistic regression revealed several parameters associated with CKD-aP (Figure 1). MCS and PCS were negatively associated with increasing CKD-aP severity ($p < 0.0001$).

Conclusions: Worldwide, CKD-aP is highly prevalent among PD patients and associated with poor quality of life. Efforts to better identify and manage CKD-aP for PD patients are urgently needed.

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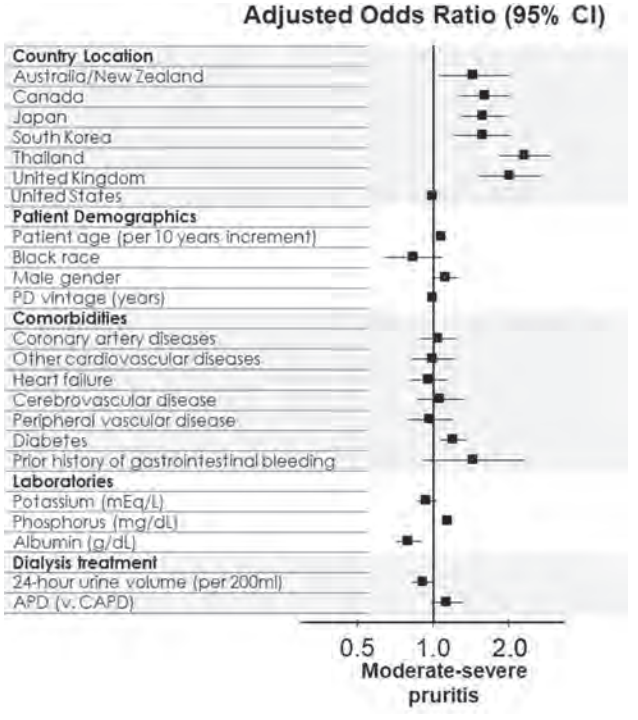

FR-OR77

Outcomes of an Assisted Peritoneal Dialysis Program in the United States

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Background: Staff-assisted peritoneal dialysis (PD) can support patients to initiate or remain on PD following challenges to self-care. These programs are not currently supported by Medicare in the Unites States (US) despite the intentions put forward in the Advancing American Kidney Health initiative to increase home dialysis utilization.

Methods: Assistance was provided by trained non-nurse healthcare personnel to patients with short-term limitations to self-care who lacked adequate support by family or friends. Descriptive statistics are provided on indications, services, and outcomes.

Results: A total of 121 referrals were received. Mean patient age was 71 (SD 14) years, and 45% were female. Forty five percent of the referrals were before completion of PD training, while the remaining 55% were for prevalent patients. The main indications for referral were physical function limitations (57%), cognition (47%), and psychosocial reasons such as anxiety (46%). A total of 48 referrals were cancelled due to resolved needs or inability to continue PD. A total of 604 visits (12% virtual) were provided for 73 patients, with a median of 5 (interquartile range [IQR]: 3 to 10) visits per patient over a median of 8 (IQR 2 to 21) days. Services provided included setting up and observing PD treatments (81%), exit site care (36%), checking the blood pressure (36%), and checking the weight of the patient (28%). A total of 68 (93%) patients were discharged on PD, with no further need for staff assistance. Three patients died during the course of the program and two transferred to in-center hemodialysis. No peritonitis or exit site infections were reported. During post-discharge follow up, 74% and 62% of patients continued on PD at six and 12 months.

Conclusions: Staff-assisted PD programs in the US delivered by non-nursing staff are feasible and effective. With a brief period of assistance, patients were able to successfully initiate or continue PD, leading to positive outcomes.

FR-OR78

QuickCheck: A Point-of-Care Method for Rapid Cell Counting in Peritoneal Dialysis-Associated Peritonitis

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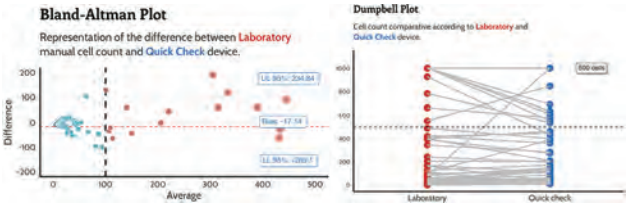
Background: Peritoneal dialysis (PD) associated peritonitis is a severe complication, often requiring hospitalization and transfer to hemodialysis. Diagnostic criteria include clinical features, effluent white cell count, and culture. The standard method of cell counting is manual microscopy, which is expensive and time-consuming. QuickCheck is CE marked, point-of-care device that utilizes laser light to instantly determine the cell count. We assess the comparability in detecting the number of cells in PD effluent samples and evaluate accuracy and precision in diagnosis of peritonitis.

Methods: A non-interventional study for method comparison was conducted in PD unit of Tallaght University Hospital, Manchester Royal Infirmary, and Birmingham Heartlands Hospital. From June 2022 to April 2023, effluent samples from patients with suspected peritonitis were analyzed with QuickCheck and manual microscopy. We included patients >18 y old, on PD, suspected peritonitis, and PD effluent culture. Reproducibility was assessed using intra-class correlation coefficients (ICC), validity by sensitivity, specificity, predictive values, and likelihood ratios. Bland-Altman graphs estimate bias and limits of agreement.

Results: 89 patients were included. The median cell count was 48 (IQR 18-662) for manual microscopy and 86 (IQR 18.5-595) for QuickCheck. The ICC agreement was 0.93 (95%CI 0.89-0.95), and consistency 0.93 (CI95% 0.89-0.95). Blant-Altman graphic is detailed. Sensitivity was 71% and 75%, specificity 78% and 69%, PPV 83% and 78%, NPV 65% and 66%, LR+ 3.2 and 2.47, LR- 0.36 and 0.35, accuracy 74% (CI95% 64-83) and 73% (CI95% 63-82) for QuickCheck and manual microscopy, respectively.

Conclusions: QuickCheck is comparable to manual microscopy in accuracy and reproducibility in cell counting. The high specificity with a cell count >100 cells suggests that QuickCheck is a reliable point-of-care method for rapid diagnosis and treatment of PD-associated peritonitis. Its speed, simplicity, and portability make it an attractive option for use at the point-of-care.



FR-OR79

A Cutting-Edge Multiphoton Microscopy-Based Approach to Test the Structure of the Peritoneal Membrane Reveals the Protective Effects of Glucose-Sparing Solution

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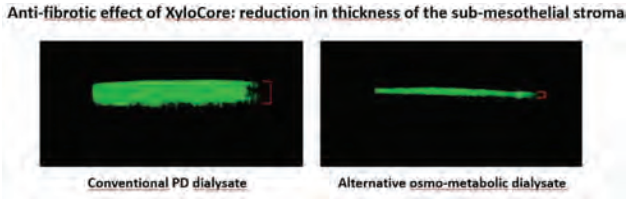
Background: Peritoneal dialysis (PD) is a renal replacement therapy that enables metabolic waste products and excess fluids to be eliminated through the peritoneal membrane. Exposure to conventional dialysates at high glucose content is considered critical for the pathogenesis of peritoneal fibrosis, angiogenesis, and epithelial-mesenchymal transition and leads to technique failure. Pre-clinical research in this field suffers from limited *in vivo* models. Here, we propose a method, based on multi-photon microscopy (MPM), that aims to study the physiology of the peritoneal membrane during dialysis exchange and to validate the effects of biocompatible dialysates in animal models.

Methods: By imaging the parietal peritoneum by MPM we are able to quantify blood flow, degree of fibrosis and vessels distribution. *In vivo* microscopy evaluation of peritoneal membrane was conducted in rats receiving for 15 days a daily i.p. injection of conventional glucose containing dialysate or a new glucose-sparing dialysate that keep iso-osmolality by substituting glucose with carnitine and xylitol (XyloCore).

Results: Treatment with XyloCore was associated with a lower thickness of the sub-mesothelial collagen deposition compared to glucose containing solution (p=0.013). In addition, the density of collagen fibers (p=0.012) and the vascular composition (p=0.006), as well as the number of branch points (p=0.0335), when compared to rats treated with a conventional PD solution was significantly lower. All these parameters were associated with a better functional performance at the PET test in the glucose-sparing group. Finally, metabolomic analysis of membrane extract and dialysate showed a marked difference in metabolic pathways.

Conclusions: Previous *in vitro* studies have shown that XyloCore is able to counteract the glucotoxic effects on the peritoneal membrane induced by conventional dialysates. Our *in vivo* approach confirms these findings and suggests that long-term protective effects may be achieved with XyloCore.



FR-OR80

Pregnancies in Women with Kidney Failure on Home Dialysis

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Background: Women with kidney failure have impaired fertility and are at a higher risk of maternal and fetal morbidity and mortality. Little is known about pregnancies in women receiving maintenance home dialysis in the United States.

Methods: Using data from the United States Renal Data System, a cohort of 26,387 women aged 15-49 years with kidney failure receiving maintenance home dialysis in 2005-2018 was examined. We calculated pregnancy rates and identified factors including the modality associated with pregnancy on home dialysis.

Results: Overall, 437 pregnancies were identified in 26,837 women on home dialysis. Unadjusted pregnancy rate was 8.6 per 1000 person-years (PTPY). The unadjusted pregnancy rate was higher on home hemodialysis (16.0 vs. 7.5 PTPY) than on peritoneal dialysis. Women on home hemodialysis had a higher adjusted likelihood of pregnancy than women on peritoneal dialysis (HR, 2.34; 95% CI, 1.79-3.05). Compared with women aged 20–24 years, the likelihood of pregnancy was lower in women 30-34 years (HR, 0.64; 95% CI, 0.43-0.96), 35–39 years (HR, 0.53; 95% CI, 0.35-0.79), 40–44 years (HR, 0.32; 95% CI, 0.21-0.49), and 45-49 years (HR, 0.21; 95% CI, 0.13-0.33). While Black women had a higher likelihood of pregnancy (HR, 1.40; 95% CI, 1.07-1.83), there was no difference in likelihood of pregnancy in Asian, Hispanic, and Native Americans as compared to Whites. Body mass index, cause of kidney failure, socioeconomic status, rurality, pre-dialysis nephrology care, or dialysis vintage were not significantly associated with pregnancy on home dialysis.

Conclusions: The pregnancy rate in women with kidney failure undergoing home dialysis is higher with home hemodialysis than with peritoneal dialysis. Younger age and Black race/ethnicity are associated with a higher likelihood of pregnancy among women on home dialysis. This information can guide clinicians in preconception counseling and making informed treatment decisions for pregnant women on home dialysis.

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FR-OR81

Representativeness of Randomized Control Trials in Kidney Transplantation

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Background: Differences between participants in randomized controlled trials (RCTs) and the target patient population may impact the intervention effect of trial findings in clinical practice. The purpose of this study was to determine the extent to which participants in clinical trials were similar to transplant recipients who underwent transplantation in the U.S. at the time of clinical trial enrolment.

Methods: We undertook a systematic search of PubMed, Embase and ClinicalTrials.gov for RCTs completed between 1990 to 2020 that included adults ≥ 18 years of age in kidney transplant recipients. Trials were included if at least one U.S. center participated and ≥ 100 participants were randomized. For each trial, the inclusion and exclusion criteria were extracted and applied to the scientific registry of transplant recipients (SRTR) to identify patients undergoing transplantation during the trial enrollment period. Demographics of interest included participant age, the proportion of women, and the proportion of patients from race and ethnic minority groups.

Results: Our search identified 5206 records, 43 trials met the study inclusion criteria. Participants characteristics included age, sex, race/ethnicity, cause of kidney failure, donor source, and comorbid conditions. From the trials, a total of 13591 participants enrolled. 74% enrolled patients only in the U.S., and 52% were multicenter studies. After searching each trial's inclusion and exclusion criteria during the trial enrollment period, 1,011,861 transplant recipients were identified in the SRTR who were potentially eligible for trial participation. Trial participants were younger, more likely to be White, and less likely to be Black or Asian (table 1). Demographic differences between trial participants and transplant eligible transplant recipients in the U.S. persisted in more recent trials.

Conclusions: We conclude that women and non-White patients are under-represented in kidney transplant trials. These differences may limit the applicability of trial findings to the real-world setting. Efforts to improve the representativeness of transplant trials are needed.

	Trial participants Mean (SD)	Contemporary trial Mean (SD)	P value
Age (years)	47.7 (± 3.0)	49.1 (±1.8)	0.02
Women (%)	35.7 (± 6.3)	39.0 (± 1.8)	<0.01
Race (%)			
White	66.7 (± 18.5)	53.6 (± 3.4)	<0.01
Black	20.7 (± 12.9)	26.0 (± 1.0)	<0.01
Asian	5.0 (± 4.2)	5.1 (± 1.1)	0.06
Hispanic ethnicity (%)	15.0 (± 11.9)	13.6 (± 2.0)	0.6

FR-OR82

Primary Care Clinician Perspectives on APOL1 Testing for Kidney Diseases

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Background: Black and Hispanic individuals experience a disproportionate burden of ESKD and CKD progression compared to White counterparts. These disparities are multifactorial and related to health-harming socio-contextual factors and partly explained by high-risk genetic alleles including APOL1, and gene-environment interactions. Despite the growing importance of high-quality patient-centered communication around genetic risk, little is known about the perspectives of front-line primary care physicians regarding APOL1 testing for kidney disease risk.

Methods: We conducted, recorded, and transcribed 15 semi-structured interviews in 2014-2016 with general internists and family physicians in New York, NY. Two independent trained researchers coded transcripts, modified discrepancies through consensus, and used modified grounded theory to identify themes.

Results: Interviewed clinicians had a mean age of 38 years, 10 (67%) were female, 8 (52%) self-identified their race as White, 3 (20%) as Asian, 2 (13%) as Black, and 1 (7%) self-identified as Hispanic. Participants mentioned environmental and behavioral factors as contributors to kidney risk and patients' fear of dialysis as a primary driver of HTN-related behavioral change. Additional emergent themes included 1) desires for additional training opportunities to effectively communicate testing considerations and implications of genetic testing, including potential stigma, 2) challenges identifying individuals appropriate for testing based on race/ethnicity and other sociodemographic characteristics 3) the need for low literacy, culturally-tailored, action-oriented post-testing instructions and guidance for patients, 4) fears that *APOL1* disclosure would result in fatalism and decreased engagement in health promoting behaviors, and 5) the importance of ensuring *APOL1* testing discussions are attentive to patient-level barriers including racial discrimination and medical mistrust.

Conclusions: Primary care physicians describe a broad interest in clinical decision-support for *APOL1* genetic testing and return of results, as well as clear guidance regarding effective communication about risk and modifiable actions to reduce risk.

Funding: Other NIH Support - National Human Genome Research Institute (NHGRI) (Grant Nos. 5U01HG007278 and U01HG006380) and the National Center for Advancing Translational Sciences (NCATS) (Grant No. UL1TR000067). Neither the NHGRI nor the NCATS was involved in the study design, collection, analysis or interpretation of data, writing of this article, or decision to submit it for publication. The authors thank the genomics board; the Genetic Testing to Understand Renal Disease Disparities team of academic, community, and clinical partners as well as the study coordinators and staff members at the study sites; and their partners in the Implementing Genomics in Practice (IGNITE) Network for their valuable contributions to this project.

FR-OR83

Association of Unmet Social Needs with Blood Pressure Severity and Target Organ Injury: Interim Analysis of the SUPERHERO Study

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Background: Hypertension (HTN) is a leading cause of cardiovascular disease and when uncontrolled is associated with increased risk for target organ injury (TOI). The burden of HTN disproportionately falls on individuals of low socioeconomic status (SES) and racial and ethnic minorities. Studies in adults have shown that low, including education, income, and neighborhood characteristics are linked to poor blood pressure (BP) control. Data in youth relating to the influence of SES factors on HTN epidemiology are sparse.

Methods: Cross-sectional analysis of baseline electronic health record data from the SUPERHERO Registry in youth referred to subspecialists for ICD-10 code-defined HTN disorders from 1/1/2015 – 12/31/2022. We excluded those with pregnancy, kidney transplantation, or dialysis. We examined the association of individual-level social drivers (transportation, financial, food access, housing, education, employment, occupational exposures, physical environment, social environment, family, and crime) by ICD-10 codes with BP severity and risk of TOI in youth using unadjusted generalized linear models.

Results: Of our cohort of 11,580 participants, 56% (6,508 of 11,580) were Caucasian and 27% (3,114 of 11,580) African American. Of the 47 with documented unmet social needs, 57% (n = 27) were African American vs 26% (n = 12) were Caucasian. Stage 2

HTN was noted in 23% (2,663 of 8,859), 35% (4,092 of 8,859) had stage 1 HTN and 18% (2,104 of (8,859) had BP. TOI was present in 8% (n = 903) of those with no unmet social needs and 6% (n = 3) of those with unmet needs.

Conclusions: In our large cohort of youth referred for HTN disorders, we found that unmet social needs were not associated with worse BP severity and greater risk of TOI at baseline. These findings are likely due to lack of inquiry into social needs by providers.

FR-OR84

Association of Unmet Social Determinants of Health (SDOH) with Quality of Life (QoL) in Patients on Hemodialysis (HD)

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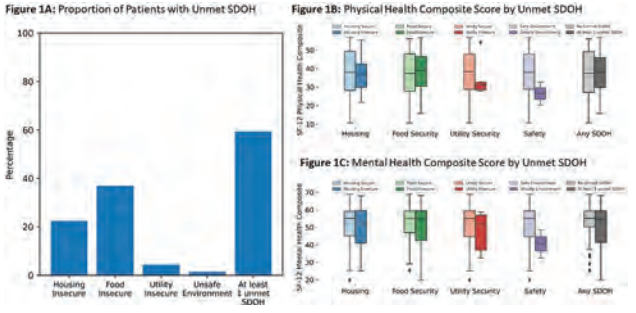
Background: Patients on hemodialysis (HD) have low quality of life (QoL). Social determinants of health (SDOH) are the non-medical aspects of a patient's life that affect their health. Whether unmet SDOH are associated with QoL in patients on HD has not previously been studied.

Methods: We prospectively surveyed patients on their living situation, food security, transportation, utilities, and safety using the AHC-HRSN and their QoL using the KDQOL-36. From the KDQOL-36, we calculated the physical component score (PCS), mental component score (MCS), and scores for effect, burden, and symptoms of kidney disease. Patients were included if they were over the age of 18, had been on HD for more than 30 days, and was able to complete the surveys with minimal assistance. Patients completed the surveys during their HD treatments. Laboratory values of hemoglobin, albumin, calcium, phosphorus, intact parathyroid hormone, and Kt/V were obtained from the monthly blood work closest to the survey administration. QoL scores were compared using Student's T-test. We used linear regression to evaluate the association between SDOH and QoL while adjusting for age and gender.

Results: A total of 138 patients participated in the study, 53% were female, 50% were Black, and 43% were Hispanic. Unmet SDOH were common in our patients, with 40% of patients reporting food insecurity and 23% of patients reporting housing insecurity (Figure 1A). Patients with unmet SDOH had lower scores for PCS and MCS, and higher scores for effect, burden, and symptoms of kidney disease, although these were not statistically significant (Figure 1B&C). There was no clinically or statistically significant difference in laboratory values between patients with and without unmet SDOH. There was no significant association between SDOH measures and the PCS or MCS of the KDQOL-36.

Conclusions: Unmet SDOH are common in patients on HD, particularly food and housing insecurity. Patients with unmet SDOH report lower QoL and higher effect, burden, and symptoms of kidney disease. While not statistically significant, this may be related to a small sample size.

Funding: NIDDK Support



FR-OR85

Exploring Unconscious Bias in Peer-to-Peer Interactions in Medical Conferences: A Retrospective Analysis

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Background: Unconscious bias in academic interactions has garnered increasing attention across several disciplines, including the field of medicine. We explored the presence of these biases using speakers' introductions at ASN (American Society of Nephrology) Kidney Week.

Methods: We screened 535 archived sessions from ASN Kidney Week 2019 and 2021 to conduct this study. The moderators' gender and academic title were documented, along with the presence of the speaker's academic title, first name, and last name in each announcement. R.4.2.2 was used for inferential and descriptive statistics.

Results: The professional title announcement frequency from highest to lowest were female moderators introducing female speakers (85%), female moderators introducing male speakers (77%), and male moderators introducing male (73%) or female speakers (72%). A multivariate logistic regression using variables "speaker rank," "moderator rank," "speaker gender," "moderator gender," "first name announcement," and "last name announcement" found female moderators had the highest odds ratio of title announcement (OR = 1.76 (Female vs Male), p = 0.01) and high academic rank had the lowest odds ratio of title announcement (OR = 0.66 (higher rank), p = 0.01). Another multivariate analysis combining variables of "moderator gender" with "speaker gender" and "moderator rank" with "speaker rank" found that males (moderators) introducing females (speakers) had the lowest (OR = 0.48, p = 0.05), whereas associate professors introducing professors had the highest title announcement odds (OR = 4, p = 0.001).

Conclusions: Our findings suggest the possibility that unconscious bias exists in peer to peer interactions in renal academic circles, though larger studies are necessary to understand the extent of this issue and the interplay of additional variables.

Title Announcement Odds Predictors (Only Statistically Significant Results Included)

Predictor Variable	OR (Odds Ratio)	Standard Error	p-value
Moderator Gender	1.762	.2482	.01
Moderator Rank	.6594	.1909	.01
Male Moderator/Female Speaker Introductions	.4885	.4271	.05
Associate Professor Moderator/Professor Speaker Introductions	4.141	.4617	.001

FR-OR86

County-Level Structural Racism Predicts Black-White ESKD Patient Mortality Disparities

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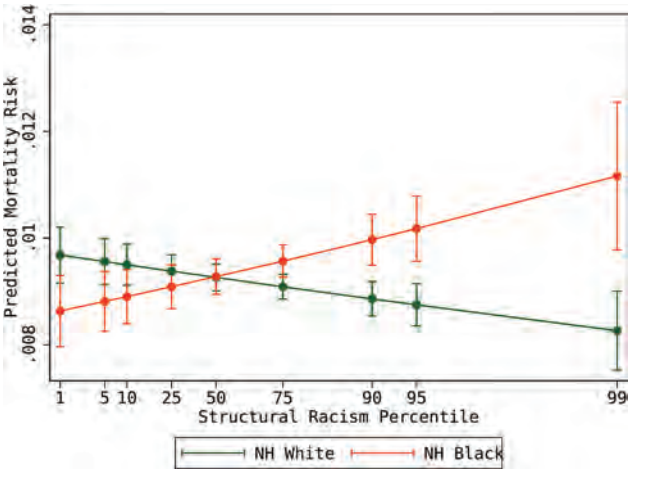
Background: Despite numerous call for structural racism (SR) research in nephrology, no prior research has employed multidimensional, empirical measures of SR to racial disparities in ESKD mortality. We estimate the first-ever analysis of the role of SR in racial disparities in ESKD patient mortality.

Methods: We analyze data from United States Renal Data System (USRDS), American Community Survey 2006-10 (ACS), and Vera Institute (VI), linked by county. USRDS ESKD who were alive on Jan. 1, 2011 and lived in a county with ≥1,000 White and Black residents were included. SR was constructed from ACS and VI county Black-White disparities in imprisonment, homeownership, college graduation, median income, unemployment, poverty, and segregation. Black-White disparities in each measure were converted to county z-scores and summed. Patient person-months through Dec. 2019 were analyzed using complementary log-log discrete time survival models. Monthly ESKD treatment was assigned based on treatment received on 1st day of each month (hemodialysis, peritoneal dialysis, deceased donor kidney transplant, living donor kidney transplant). Models controlled for region, county racial composition, and patient gender and birth cohort.

Results: Black race statistically significantly interacted with SR to predict monthly mortality risk among ESKD patients. Black patients experienced survival advantages compared to Whites at lower levels of SR, but experienced survival disadvantages compared to Whites at higher levels of SR. When stratified by monthly treatment, the core finding that Black survival advantages are eroded or erased at higher SR levels was replicated within each treatment group.

Conclusions: County-level SR is a significant determinant of ESKD patient mortality. Future research should prioritize including area-level measures of SR in ESKD disparities research.

Funding: NIDDK Support



FR-OR87

Significant Variation in Kidney Disease Indicators Within Cook County, IL: Findings from Geospatial Analysis of 2022 National Laboratory Data

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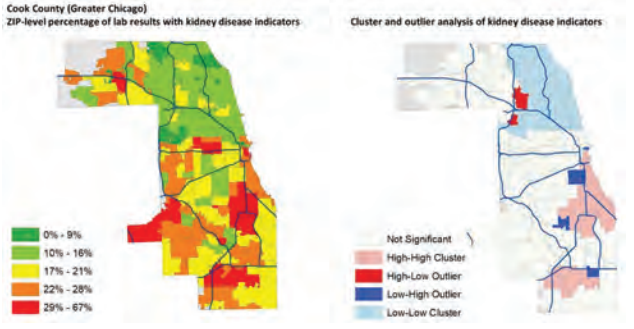
Background: Chronic Kidney Disease (CKD) is frequently diagnosed through routine laboratory tests. There is not currently a source for population-level data on kidney disease and it is therefore difficult to assess prevalence at the local level. We sought to assess the feasibility of analyzing data from one of the largest clinical laboratory networks in the US to measure the extent of variation in kidney disease indicators found within a single county by ZIP code.

Methods: Data from approximately 600,000 Labcorp tests, resulted in 2022, for estimated glomerular filtration rate (eGFR) and urine albumin:creatinine ratio (UACR) in the greater-Chicago area of Cook County, IL were utilized. The presence of a kidney disease indicator was defined as an eGFR < 60 ml/min/1.73m^2 or a UACR > 30 mg/g. The overall ZIP code percentage of lab results with kidney disease indicators were visualized with ArcGIS, stratified by Jenks Natural Breaks (5 classes). ZIP codes with less than 10 results were suppressed. Optimized hotspot analyses were conducted with the Getis-Ord Gi* statistic and Moran's I statistic was applied for the outlier analysis. The interstate system was included to aid visualization.

Results: Kidney disease indicators varied markedly at the ZIP code level across Cook County, IL. The ZIP code percentage of lab results with kidney disease indicators ranged from a low of 0% to a high of 67%. Hotspot analysis indicated a clear high-high cluster in south and southeastern sections of the county. The northeastern section of the county appeared to be a low-low cluster, or cold spot. Both high-low and low-high outliers were found.

Conclusions: We demonstrate the feasibility of utilizing a large national laboratory database for mapping kidney disease indicators and identification of hotspots of kidney disease within a county. This work has the potential to support CKD surveillance systems to guide area-level CKD prevention and population health improvement initiatives.

Funding: Other U.S. Government Support



FR-OR88

Barriers and Opportunities to Increase Home Dialysis Among African American Patients

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Background: Home dialysis offers patients another treatment option for kidney failure. Home dialysis use is lower in African American patients. In this study we sought to understand the experiences that patients and care partners face and uncover influencing factors and barriers to home dialysis use.

Methods: A total of 29 participants (African American patients at a dialysis provider, both in-center and home, and their care partners) were recruited to join in-person focus groups held in December 2022 and February 2023. Focus groups were audio and video recorded and transcribed verbatim. Responses were analyzed using inductive thematic analysis.

Results: Patients reported that physicians did not make a clear connection between poor management of underlying health conditions and kidney failure; irrespective of a patient's access to primary care. Patients and care partners want improved/additional education, especially regarding modality selection as some information was lost or forgotten. African American patients and care partners primarily rely on healthcare professionals (HCP) for information. However, if the patient or care partner feels the HCP is less than forthcoming or insensitive when providing information, their trust is quickly eroded. Unsurprisingly, care partners are a critical part of the decision to choose and remain on home dialysis. Faith plays a significant role for many respondents in terms of disease experience (i.e., "God is in control") and emotional support. Physician guidance was cited as the most important factor in the initial modality decision for African American patients and care partners. While most patients and care partners acknowledge the benefits of home dialysis, significant barriers included the fear of being solely responsible for a complex procedure, risk of infection, and loss of social interaction and/or support from other dialysis patients and center staff.

Conclusions: Opportunities exist for early and direct linkage of co-morbidities with kidney disease and consideration of patient concerns in home dialysis modality education.

FR-OR89

Experiencing Discrimination Reduced the Effectiveness of the TALK Intervention on Kidney Failure Patients

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Background: Although kidney transplantation (KT) is the optimal treatment for patients with kidney failure, few patients receive it. Our study tested the effect of an empirically-developed culturally-concordant education intervention on increasing KT evaluation completion rates for patients starting the evaluation process. We also examined the impact of novel social determinants of health (e.g., experience of discrimination) on outcomes.

Methods: We recruited patients for a baseline interview before their first KT evaluation appointment. We randomly assigned patients to receive the Talking About Live Kidney Donation (TALK) intervention or no intervention at their evaluation appointment. The TALK group received an educational booklet and video encouraging shared decision making and informed consideration of kidney failure treatment options. We called patients after two weeks to address questions and encourage review of materials. We conducted a second interview to assess intervention engagement and other outcomes after patients completed or discontinued evaluation.

Results: Our study sample included 1028 participants (63% male; mean age=56.7 yrs; 45% ≤ high school graduates; 71% non-Hispanic White; 21% Black). Using a Fine-Gray proportional subdistribution hazards model for time to evaluation completion, and controlling for demographic, medical, cultural, psychosocial, and transplant knowledge covariates, we found no significant difference in the likelihood of evaluation completion between TALK and no-TALK (SHR = 1.13, 95% CI = 0.96-1.34, p=0.153). Interaction analyses showed that the TALK intervention increased the rate of evaluation completion among people who reported *never* experiencing discrimination in healthcare (SHR=1.26, 95%CI=1.04-1.52, p=0.019), but not among those who reported *ever* experiencing discrimination.

Conclusions: Our findings suggest that TALK education materials alone did not promote higher KT evaluation completion rates and that the impact of experiencing discrimination in healthcare may be particularly relevant. Patients, especially those who have experienced discrimination, may need additional or different support to encourage their completion of KT evaluation, such as a social worker, peer mentor, or community health worker.

Funding: NIDDK Support, Private Foundation Support

FR-OR90

Regional Variation in the Use of Percutaneous Kidney Biopsy in Japan

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Background: Several studies have conducted questionnaires on kidney biopsies performed in Japan, but there is no exhaustive survey of all kidney biopsies in Japan. Moreover, it is unknown whether there is a regional variation in the use of percutaneous kidney biopsies in Japan.

Methods: The number of percutaneous kidney biopsies stratified by the demographic data of the patients was obtained from the National Database of Health Insurance Claims and Specific Health Checkups of Japan. Data from other nationwide surveys, including the population census, kidney transplant registry, dialysis registry and statistics of physicians, were also used. Pearson's product-moment correlation coefficient was calculated using the R system for statistical computing.

Results: A total of 22,419 health insurance claims for percutaneous kidney biopsy in the fiscal year 2020 was registered in the database. The majority (99.9%) was inpatient percutaneous kidney biopsy. There was a large difference in the number of inpatient percutaneous kidney biopsies per population among prefectures, which could be up to 4.8 times as large in one prefecture than in another, even after adjusting for age. The number of inpatient percutaneous kidney biopsies per population positively correlated with the number of annual kidney transplants per population ($R = 0.39$, $p = 0.006$) and the number of patients on peritoneal dialysis per population ($R = 0.47$, $p < 0.001$). There was a weak negative correlation between the number of inpatient percutaneous kidney biopsies per population and the prevalence of reduced kidney function in the population aged 40–74 years ($R = -0.36$, $p = 0.013$). The frequency of kidney biopsy had no correlation with the number of patients on hemodialysis or the number of nephrologists or urologists per population.

Conclusions: The National Database of Health Insurance Claims and Specific Health Checkups of Japan revealed for the first time that more than 20,000 kidney biopsies were performed per year in Japan, as of 2020. Peritoneal dialysis and kidney transplant are offered more frequently in prefectures with a higher frequency of kidney biopsy. Further research is warranted to understand the reason for the wide regional variation in the frequency of kidney biopsy.

FR-OR91

One-Month Treatment with Dapagliflozin Triggers Renal Water Conservation and Thus Prevents Osmotic Diuresis in Patients with Chronic Heart Failure

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Background: It is unclear whether SGLT2 inhibitors improve cardiac outcomes due to their osmotic-diuretic potential. We tested the hypothesis that SGLT2 inhibition with dapagliflozin does not promote renal water excretion in patients with chronic heart failure.

Methods: DAPA-Shuttle1 was a mechanistic, double-blind, randomized trial which investigated the early (48h) and late (4 weeks) effects of dapagliflozin on urine volume generation and body solute handling. Participants with chronic heart failure NYHA classes I/II were randomly assigned to receive dapagliflozin 10mg daily or placebo for 4 weeks. The primary endpoint was change from baseline in urine osmolyte concentration. ClinicalTrials.gov registration NCT04080518.

Results: 29 participants (placebo n=14; dapagliflozin n=15) completed the study (age 59±14 years). Dapagliflozin increased glucosuria by 3.3±0.4 mmol/kg/d ($p<0.0001$) within 48h; this effect persisted after 4 weeks (2.7±0.4 mmol/kg/d, $p<0.0001$). Dapagliflozin did not increase natriuresis (early: p=0.68; late: p=0.64), and did not change MRI-determined tissue Na^+ content (early: p=0.62; late: p=0.90). Despite sustained glucosuria, urine volume remained stable in the dapagliflozin group after one month (+0.9±2.4 ml/kg/d, p=0.70). Dapagliflozin increased plasma copeptin (early: +5.5±2.5 pmol/L, $p<0.05$; late: +7.8±2.5 pmol/L, $p<0.01$), leading to proportional reductions in free water clearance (early: -9.1±2.5 ml/kg/d, $p<0.001$; late: -11.0±2.5 ml/kg/d, $p<0.0001$) and increases in urine concentration (late: +134±47 mmol/L; $p<0.01$).

Conclusions: SGLT2 inhibition with dapagliflozin triggered a vasopressin-driven water conservation response in patients with chronic heart failure, and thereby prevented a 800-1000 ml/d glucose-driven increase in urine volume. In contrast to saluretic diuretics, which promote solute excretion to increase free water excretion in the urine, SGLT2 inhibitors reduce solute-free water excretion, abolishing the osmotic-diuretic effect of glucosuria.

Funding: Commercial Support - AstraZeneca

FR-OR92

Association of Polygenic Risk Scores for Blood Pressure with Incidence of Hypertension and CKD

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Background: Genetic risk for elevated blood pressure (BP) has been associated with a higher risk of hypertension and cardiovascular disease. However, the generalizability of previous findings has been limited due to a lack of studies among Asian populations. This study aimed to investigate whether genetic risk for BP predicts the incidence of hypertension and chronic kidney disease (CKD).

Methods: We constructed polygenic risk scores (PRSs) for systolic and diastolic BP (SBP and DBP, respectively) using genome-wide association data from the Biobank Japan. We then examined the association between BP PRSs and incident hypertension or CKD in the Korean Genome and Epidemiology Stduy. The study included participants without hypertension, cardiovascular disease, or CKD at baseline (n = 4351, median age 48 years, 48.8% men). Participants were categorized into four groups based on their PRS percentile (<5%, 5-50%, 50-95%, >95%).

Results: The PRS for SBP and DBP showed independent associations with SBP and DBP, respectively (both P <0.001). Compared to individuals with the lowest 5% SBP PRS, those with SBP PRS in the 50 to 95 percentile range and the highest 5% had a 1.62-fold (95% confidence interval [CI], 1.24–2.11; P <0.001) and 1.75-fold (95% CI, 1.23–2.49, P = 0.002) higher risk of hypertension, respectively. Elevated DBP PRS was associated with 1.47-fold (95% CI, 1.11–1.94, P = 0.006), 1.79-fold (95% CI, 1.35–2.35, P <0.001), and 2.03-fold (95% CI, 1.41–2.91, P <0.001) higher risk of hypertension in the 5 to 50 percentile, 50 to 95 percentile, and the highest 5%, respectively. The highest PRS percentile for SBP and DBP was associated with earlier onsets of hypertension by 5.9 years (95% CI, 2.9–8.9) and 6.7 years (95% CI, 3.9–9.4), respectively, compared to the lowest PRS percentile for SBP and DBP. However, both SBP and DBP RPSs were not associated with incident CKD.

Conclusions: Genetic risk for elevated BP was associated with a higher risk of incident hypertension and earlier onset of hypertension in the general population. However, there was no association between PRS for elevated BP and the incidence of CKD.

FR-OR93

Polygenic Scores for Incident Myocardial Infarction in CKD

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Background: Improving prediction of cardiovascular events in CKD has focussed on integrating kidney biomarkers to existing models. In the general population, genetic data may provide orthogonal information to clinical variables, identifying individuals at high risk of coronary artery disease (CAD) even in the absence of classical risk factors. In CKD, where cardiovascular risk is elevated and underlying aetiology may differ, the utility of CAD polygenic scores (PGS) has not been assessed.

Methods: Individuals with genetic data at risk of incident myocardial infarction (MI) in the Chronic Renal Insufficiency Cohort (CRIC) were included. Following relevant quality control and imputation of array-derived genotypes, variants with an imputation quality RSQ ≥ 0.3 or RSQ ≥ 0.8 with minor allele frequency <0.01 were retained. Individuals were stratified as European [EUR] or African [AFR] ancestry (based on self-report and genotype). We applied PGS derived in European and multi-ancestry populations (pgscatalog.org), for CAD and for estimated glomerular filtration rate (eGFR), to Cox-proportional hazard models sequentially adjusted for: first 10 PCs, age, sex, baseline eGFR and statin use. The primary outcome was incident MI; over the follow-up period and after censoring at dialysis initiation.

Results: 1175 AFR and 1607 EUR individuals in CRIC included, had 142 (12.1%) and 156 (9.7%) MI events, respectively, including 79 (6.7%) and 113 (7.0%) events occurring before dialysis initiation. Variant availability limited application of some PGS (Tcheandjieu 2022). Among EUR individuals, one standard deviation increase in European-derived CAD PGS was associated with 31% increased hazard of MI (95% confidence interval [CI] 1.1 – 1.56). This result was similar when events were censored at dialysis (1.35, 95% CI 1.1 – 1.66). However, the CAD-PGS association was not significant in CRIC AFR individuals or when using PGS for eGFR in both AFR or EUR individuals.

Conclusions: Current PGS for CAD predicts incident MI in European ancestry individuals with CKD but no significant effect was revealed in African ancestry individuals. As PGS is being considered as a potential tool for prediction in clinical practice, there is a pressing need to understand the genetic architecture of CAD in the milieu of CKD and how PGS perform in the context of diverse ancestry.

Funding: Other NIH Support - National Heart, Lung, and Blood Institute

FR-OR94

Kidney Function Trajectories, Risk Factors, and Outcomes in Left Ventricular Assist Device (LVAD) Recipients

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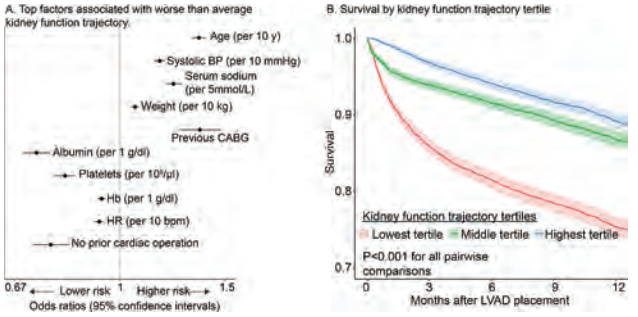
Background: LVAD (Left ventricular assist device) implantation can improve or worsen kidney function due to several known and hypothesized causes. However, competing risks of death and transplantation, patterns of missing data, and inaccuracy of estimating equations complicate kidney outcome assessment. To enable additional insight into the effects of LVAD implantation on kidney health, we investigate use of a continuous metric (trajectory of log eGFR) to summarize long-term post-LVAD kidney health.

Methods: We identified adults who received isolated primary continuous-flow LVADs from 2012 to 2017 in a US national database of LVAD recipients (INTERMACS). We assessed eGFR-Cr (CKD-EPI 2021) from pre-LVAD implantation to 12 months, fitting linear mixed models with random slopes and intercepts to natural log-transformed eGFR values (so that slopes would approximate proportional changes), adjusted for baseline eGFR. We then investigated how baseline factors related to worse than average kidney function trajectory and how kidney function trajectory related to mortality risk.

Results: We identified 15,052 LVAD recipients (median age 59 years, 21.2% female, median pre-LVAD eGFR 62 ml/min/1.73m^2). The median eGFR trajectory slope was approximately -5.6% over one year; only 23.3% had a positive trajectory slope. The ten baseline factors most associated with worse than average kidney function trajectory are shown in Figure 1A: ‘older age’ was the most significant risk factor; ‘no prior cardiac operation’ was the most significant protective factor. In addition, mortality was progressively higher with worse kidney function trajectory (Figure 1B).

Conclusions: A log eGFR trajectory measure over one year may be a useful summary outcome metric in investigating the effects of LVADs on kidney health/function. As a continuous summary metric, this may provide improved power to study determinants of kidney outcomes in LVAD recipients. In addition, as a log trajectory measure, it may be less susceptible to the imprecision and non-kidney-related confounding inherent in estimating GFR.

Funding: NIDDK Support



FR-OR95

Associations Between Clonal Hematopoiesis of Indeterminate Potential and Cardiovascular Disease in Three Prospective CKD Patient Cohorts

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is an age-related condition characterized by the clonal expansion of blood cells carrying somatic mutations to specific driver genes. Although CHIP has been established as an important contributor to cardiovascular diseases (CVD) in the general population, its association with CVD in a pro-inflammatory chronic kidney disease (CKD) setting has not been examined.

Methods: We examined prospective associations between CHIP status and CVD events in three cohorts that included a total of 3,414 CKD patients: the Chronic Renal Insufficiency Cohort (CRIC), the African American Study of Kidney Disease (AASK), and the Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT). Primary analyses tested associations between CHIP status and a composite CVD endpoint of myocardial infarction (MI), stroke, congestive heart failure (CHF), or peripheral artery disease (PAD). Cox proportional hazards regression models were used, adjusting for demographic, lifestyle, and clinical covariables, including cardiovascular risk factors. Secondary analyses investigated individual CVD endpoints. Random-effect meta-analyses were employed to combine effects across studies.

Results: Study participants had an average age of 68.8 years and a mean eGFR of 40.2 ml/min/1.73m^2. As expected, participants had a high frequency of hypertension (95%) and diabetes (49%), with CHIP identified in 25% of participants. Those with large CHIP clone size (VAF≥10%) and a non-*DNMT3A* CHIP gene mutation exhibited 38% (95% CI:2%-85%) and 42% (95% CI: 6%-90%) higher risks of the composite CVD endpoint, respectively, compared to noncarriers. Compared to non-CHIP status, large clone size was further associated with incident CHF (HR: 1.53, 95% CI: 1.13-2.00).

Conclusions: CHIP carrier status may be an important risk factor for CVD among CKD patients, with associations mirroring those observed in the general population.

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

FR-OR96

Effects of Aprocitentan for Blood Pressure Lowering and Proteinuria in Patients with CKD and Resistant Hypertension

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Background: Hypertension is often difficult to control in patients with CKD. In the phase 3 PRECISION trial, the dual endothelin receptor antagonist aprocitentan (APRO) at 12.5 and 25mg once-daily demonstrated significant BP reductions vs placebo (PBO) in patients with resistant hypertension. We evaluated APRO in patients with CKD enrolled in PRECISION.

Methods: Participants had unattended automated office systolic BP (SBP) ≥140mmHg despite use of ≥3 antihypertensive drugs. This subgroup analysis included patients with an eGFR of 15 to <60mL/min/1.73m^2. Reductions in office SBP, ambulatory BP monitoring (ABPM), and urinary albumin-to-creatinine ratio (UACR) were assessed following the double-blind treatment phase (Week 4), after 32-week single-blind APRO 25mg treatment (Week 36), and after 4 weeks of randomized withdrawal (Week 40).

Results: Changes in office BP and UACR in 162 CKD patients included in this analysis are summarized in the table below. Both doses of APRO resulted in a more pronounced BP reduction from baseline to week 4 compared to PBO. This was confirmed by ABPM. At Week 4, edema or fluid retention occurred in 18% and 24% of patients receiving APRO 12.5mg and 25mg, respectively, vs 2% with PBO; this rate was 34% in subjects exposed to APRO 25 mg during the trial. 55% of them were treated with diuretics (90% loop); 2 discontinued treatment due to this event. Five patients receiving APRO 25mg and 1 receiving placebo had heart failure leading to hospitalization; all but one had a history of heart disease.

Conclusions: In patients with CKD stage 3 or 4 and resistant hypertension, APRO 12.5 and 25mg added to ≥3 antihypertensive drugs resulted in a substantial reduction of both office and ambulatory BP and UACR. Edema and fluid retention were manageable with additional diuretics.

Funding: Commercial Support - Janssen Pharmaceuticals and Idorsia Pharmaceuticals, Ltd

(mean values)	APRO 12.5mg	APRO 25mg	PBO
Baseline Office SBP (mmHg)	154.1	153.5	154.7
Week 4 Office SBP (mmHg)	140.6	134.6	148.0
Week 36 Office SBP (mmHg)	Not applicable	134.8	Not applicable
Week 40 Office SBP (mmHg)	Not applicable	136.1	143.5
Baseline UACR (mg/g)	109.2	63.4	114.9
Week 4 UACR (ratio from baseline)	0.72	0.56	0.96
Week 36 UACR (ratio from baseline)	Not applicable	0.50	Not applicable

FR-OR97

Increased Coronary Artery Pathology in Type 2 Diabetes Without Cardiovascular Disease but with Albuminuria

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Background: Advances in non-invasive imaging enables combined structural and functional assessment of coronary artery pathophysiology. We evaluated sub-clinical coronary artery pathology using multimodal imaging in persons with type 2 diabetes.

Methods: Cross-sectional study including persons with type 2 diabetes, without known cardiovascular disease or symptoms. Coronary microcalcification activity was measured using ^{18}F-sodium fluoride positron emission tomography/computed tomography (PET/CT). Plaque inflammation was measured using ^{64}Cu-DOTATATE PET/CT and estimated as coronary inflammation activity. Myocardial flow reserve was calculated using ^{82}Rubidium PET/CT, and the coronary artery calcium score was quantified using CT.

Results: We included 90 participants, 30 had normoalbuminuria (urine albumin creatinine ratio (UACR) <30 mg/g) and 60 had current albuminuria or a history of albuminuria (UACR ≥ 30 mg/g). Mean age was 65 (SD 7.5) years, 19 % were females. Participants with albuminuria had increased microcalcification activity (median 0.75 [IQR: 0.30 -1.85]) compared to normoalbuminuria (0.43 [0.24 - 0.87]; p=0.04), but not after adjustment for clinical risk factors for cardiovascular disease (p=0.09). Microcalcification activity was positively associated with the current level of UACR (standardized β=0.53, p=0.008), and a trend remained after adjustment (β=0.44, p=0.05). Mean myocardial flow reserve was lower in participants with albuminuria (2.5 (SD 0.7)) compared to normoalbuminuria (2.9 (0.7); p=0.02), but not after adjustment (p=0.07). Coronary inflammation activity and coronary artery calcium score were similar between albuminuria groups (p≥0.40). Higher current level of UACR was associated with lower myocardial flow reserve (β=-0.42, p=0.03) and higher coronary artery calcium score (β=0.40, p=0.03) in unadjusted analysis. Current level of UACR was not associated with coronary inflammation activity (p=0.74).

Conclusions: In persons with type 2 diabetes, without cardiovascular disease, the presence of albuminuria was associated with sub-clinical coronary artery pathology and microcalcifications when compared to normoalbuminuria.

Funding: Private Foundation Support

FR-OR98

Podocyte-Specific Knockout (KO) of the Natriuretic Peptide Clearance Receptor (NPRC) Ameliorates Glomerular Injury in a Mouse Model of Focal Segmental Glomerulosclerosis (FSGS)

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Background: Natriuretic peptides (NPs) have podocyte protective effects by stimulating cGMP generation (J Am Soc Nephrol 28: 260, 2017). NPs stimulate cGMP production by binding to NP receptors (NPRs). Atrial NP (ANP) and the C-type NP (CNP) stimulate cGMP generation by binding to NPRA and NPRB, respectively.

In contrast, the NP clearance receptor (NPRC) binds and degrades NPs and, in turn, negatively regulates the beneficial effects of NPs. Podocytes express all three NPRs (NPRA, NPRB, and NPRC). We previously found that pharmacologic blockade of NPRC reduced proteinuria in a mouse model of FSGS (Physiological Reports. 2021;9:e15095). In this study, we investigated the effects of podocyte specific KO of NPRC in FSGS using the same mouse model.

Methods: NPRC was deleted specifically in podocytes in a transgenic (TG) mouse model of FSGS created in our laboratory (J Clin Invest 125:1913, 2015). These TG mice express a constitutively active Gq α-subunit specifically in podocytes (Gq mice). In these animals (Gq mice), treatment with a single dose of the podocyte toxin puromycin aminonucleoside (PAN) causes robust albuminuria, but only mild disease in wild type (WT) mice.

Results: Podocyte specific KO of NPRC significantly reduced albuminuria in Gq mice 10 days after PAN injection (6094 ± 1130 [NPRC+/+] vs. 2740 ± 627 [NPRC-/-] ug/mg creatinine; P = 0.007). KO of NPRC also significantly reduced the number of Gq mice with glomerular sclerosis (GS) (85% [NPRC+/+; N = 20] vs 46% [NPRC-/-; N = 13]; P = 0.026). Consistent with the GS results, there was a significant increase in mRNA and protein levels of the myofibroblast marker alpha-smooth muscle actin (alpha-SMA) in NPRC+/+ Gq mice, and this increase in alpha-SMA expression was significantly reduced in NPRC-/- Gq mice. Treatment with PAN also decreased expression of both nephrin and podocin in NPRC+/+ Gq mice, which was prevented by podocyte specific KO of NPRC.

Conclusions: Podocyte specific KO of NPRC significantly decreased albuminuria, reduced GS, decreased myofibroblast activation and preserved expression of the podocyte proteins nephrin and podocin in a mouse model of FSGS. These data suggest that strategies to augment the effects of NPs might be a useful therapeutic approach for treating FSGS.

Funding: Other NIH Support - NCATS, Veterans Affairs Support

FR-OR99

Hemizygous Loss of Vegfa in Cap Mesenchyme Is Associated with Thrombotic Microangiopathy and Metabolic Reprogramming of the Thick Ascending Limb (TAL) Epithelium

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Background: Tonic secretion of VEGFA from nephron progenitors and their epithelial derivatives plays a key role in both development and homeostatic maintenance of kidney microvascular beds. Reduction of Vegfa production by podocytes or tubular epithelial cells results in glomerular endotheliosis and loss of peritubular capillaries, respectively. Here, we report a kidney epithelial-specific, hemizygous *Vegfa* knockout mouse model. Fifty per cent reduction of Vegfa in Six2-progenitor cells results in a thrombotic microangiopathy phenotype, with progressive loss of glomerular function after 4 weeks of age.

Methods: *Vegfa* floxed mice were generated using the CRISPR-Cas9 system and were crossed with transgenic *Six2-eGFPCre* mice to generate *VegfA*$^{\Delta/+}$*;Six2-Cre* mice, leading to excision of *Vegfa* from nephron progenitor cells of cap mesenchyme. Kidneys from 1, 2, and 4 week old mice were examined histologically using light and electron microscopy and single-cell RNAseq libraries were generated from knockout and control kidneys at 2 and 4 weeks which were analyzed in R using Seurat.

Results: *VegfA*$^{\Delta/+}$*;Six2-Cre* mice began to develop albuminuria at 2 weeks. On light microscopy, kidneys from *VegfA*$^{\Delta/+}$*;Six2-Cre* mice were indistinguishable from those of their control littermates at 1 week. Electron microscopy at 2 weeks showed evidence of glomerular injury, with subendothelial expansion and podocyte foot process effacement. At 4 weeks, *VegfA*$^{\Delta/+}$*;Six2-Cre* glomeruli exhibited florid thrombotic microangiopathy. In scRNAseq data, glomerular endothelial cell clusters from *VegfA*$^{\Delta/+}$*;Six2-Cre* mice exhibited decreased expression of transcripts encoding markers of glomerular identity. Analysis also identified a new population of thick ascending limb (newTAL) cells that were found only in knockout kidneys at both time points. Compared to other TAL clusters, newTAL cells expressed cytokeratin 19 as well as classic genes such as *UMOD*. Pathway analysis of differentially expressed genes in the newTAL showed downregulation several metabolic pathways with enrichment of growth factor signaling.

Conclusions: *Vegfa* gene dosage in renal epithelium is important for the maintenance of the glomerular endothelium and plays a role in the metabolic programming of the TAL.

FR-OR100

SMPDL3b Modulates Podocyte Innate Immunity via Stimulator of Interferon Genes (STING) Activation in CKD

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Background: Chronic kidney disease (CKD) is a global problem with rising incidence, prevalence and poor understood pathogenesis. Our prior studies support the hypothesis that sphingolipids are major determinants of podocyte function and survival, where sphingomyelin phosphodiesterase acid like 3b (SMPDL3b) plays an important role. Sphingolipids are known regulators of inflammation, also a major contributor to CKD progression. We reported that activation of the stimulator of interferon genes (STING), an important innate immune signaling protein, contributes to alterations in podocyte foot processes, proteinuria, and CKD progression. Here we test the hypothesis that increased SMPDL3b expression leads to podocyte injury through activation of STING.

Methods: Immortalized control or overexpression (SMP OE) human podocytes were used. Illumina sequencing RNA data analysis, qRT-PCR and Western blot analysis were used to characterize the cells. c-diAMP, a STING specific agonist, treatment (10μM) was performed for 24h. Glomeruli isolated from 8-week-old mice with podocyte specific Smpdl3b deficiency (pSMP$^{fl/fl}$) or overexpression (pSMP^{Tg}) were used to evaluate STING activation. pSMP$^{fl/fl}$ and pSMP^{Tg} mice were intraperitoneally injected with a single dose of c-diAMP, 50mg/kg or 5% DMSO and sacrificed 72h after, followed by urinary albumin-to-creatinine ratio (ACR), histological and serum analyses. Two-tailed t-test or One-Way ANOVA followed by Tukey's post-test were used to detect statistical changes.

Results: Genes involved in the cytosolic DNA sensing pathways in SMP OE podocytes are significantly regulated. *In vitro* and *in vivo* studies demonstrated that SMP OE podocytes and glomeruli isolated from pSMP^{Tg} mice have increased levels of STING phosphorylation (pSTING). Treatment with c-diAMP resulted in increased pSTING in control, but not in SMP OE podocytes. While both pSMP$^{fl/fl}$ and pSMP^{Tg} mice did not develop proteinuria at the baseline, treatment with c-diAMP resulted in significantly increased ACR in pSMP^{Tg}, but not in pSMP$^{fl/fl}$ mice. No changes in serum BUN and creatinine levels were observed in pSMP$^{fl/fl}$ and pSMP^{Tg} mice treated with c-diAMP.

Conclusions: Our data indicate that SMPDL3b overexpression is associated with STING activation in podocytes *in vitro* and STING-dependent proteinuria *in vivo*.

Funding: NIDDK Support, Private Foundation Support

FR-OR101

Podocyte-Derived Endothelin-1 and Cross-Talk with Endothelial Cells Through EdnrA Is Essential for Glomerular Injury

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Background: Crosstalk between activated podocytes and glomerular endothelial cells (GECs) has been demonstrated in mouse models of focal segmental glomerulosclerosis (FSGS). We have previously demonstrated that podocytes activation can result in GEC stress and dysfunction and concomitant albuminuria via increased endothelin-1 and endothelin receptor A (Edn1/Ednra) signaling. However, the mechanistic link between podocyte activation and Edn1 production, GEC injury, and reciprocal crosstalk that results in podocyte loss and albuminuria remains unclear.

Methods: Transforming growth factor-β (TGFβ) is a cytokine that is implicated in glomerular diseases and podocyte depletion. We examined the effects of TGFβ on podocyte activation in culture on *Edn1* expression on podocytes in culture, as well as in podocytes with inducible TGFβR1 expression; PodTgfbR1, treated with doxycycline (Dox). We performed RNAseq analysis on GECs treated with Edn1 and isolated from Dox treated PodTgfbR1 mice. We generated a mouse model through targeted gene deletion of *Edn1* in podocytes using the Cre-loxP system (*Npsh2:Cre-ET1*$^{fl/fl}$) and a quadruple transgenic mice line with podocyte specific Edn1 knockout, and inducible, podocytes specific TGFβR1 signaling (*Nphs2:Cre-ET1-Nephs1TgfbrI*). Mice were treated with adriamycin (i.p.) or with Dox (food) to induce nephropathy.

Results: TGFβ signaling resulted in a significant increase in *Edn1* expression and Edn1 release by podocytes in culture, which was prevented by a TGFβR1/Smad inhibitor or by knockout (ko) Smad2 or double ko Smad2/3, suggesting canonical TGFβ signaling dependent pathway is required for Edn1 production. RNAseq from Edn1 treated GECs showed upregulation of cellular responses to stress and endothelial dysfunction. Compared to adriamycin treated control *Npsh2:Cre-ET1*$^{+/+}$, adriamycin treated *Npsh2:Cre-ET1*$^{fl/fl}$ mice had reduced glomerular injury, albuminuria and podocyte depletion. Compared to *Nephs1TgfbrI*, *Nphs2:Cre-ET1-Nephs1TgfbrI* mice treated with Dox had no glomerular injury, albuminuria and podocyte depletion was completely prevented, and there was no increase in GEC associated Ednra expression.

Conclusions: Our studies provide evidence for the essential role of podocyte derived Edn1 upon activation and crosstalk with GECs via Ednra that results in GEC injury, podocyte depletion and albuminuria in experimental FSGS.

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

FR-OR102

Conditional Knockout of YAP Decreases Podocyte Adhesion and Exacerbates FSGS Progression Through α3β1 Integrin

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Background: The occurrence of proteinuria in FSGS patients is closely related to the decreased adhesion and further loss of podocytes. Previous studies showed YAP nuclear exclusion contributes to podocyte apoptosis and FSGS progression, but its role in the podocyte adhesion remains unclear.

Methods: We generated podocyte-specific *Yap* gene knockout mice (*Yap*^{podoKO}) by crossing *Yap*$^{flox/flox}$ mice with NPHS2-Cre mice. We then constructed Adriamycin induced FSGS model by using *Yap*^{podoKO} mice and control mice. Furthermore, we treated the above mice with pyrintegrin, an agonist of α3β1 integrin.

Results: By 16 weeks of age, compared to *Yap*$^{flox/flox}$ mice, *Yap*^{podoKO} mice developed decreased podocyte adhesion including reduced α3β1 integrin and focal adhesion (examined by double immunofluorescence staining of vinculin and F-actin), with effacement of a few of foot process under the electron microscopy, although showed no significant difference in morphology by light microscopy, proteinuria, serum creatinine and BUN. Compared to Adriamycin treated *Yap*$^{flox/flox}$ mice, *Yap*^{podoKO} mice aberrantly aggravated decrease in α3β1 integrin, focal adhesion and podocyte number induced

by Adriamycin, with markedly increased segmental or global glomerulosclerosis, foot process effacement and proteinuria. Of note, pyrintegrin treatment largely improved the podocyte adhesion and ameliorated the disease progression of FSGS caused by Adriamycin treatment with or without podocyte-specific *Yap* knockout.

Conclusions: This study, for the first time, demonstrated that podocyte-specific *Yap* gene knockout can reduce podocyte adhesion thus aggravating the process of FSGS via α3β1 integrin. This is important to report because, so far, there is no clinical strategy to treat FSGS by targeting α3β1 integrin and its regulatory factors.

FR-OR103

Paracrine Effects of Injured Podocytes on the Transcriptome of Neighboring Cells

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Background: Knowledge gaps in glomerular diseases include how podocytes respond to different forms of injury and the crosstalk between injured podocytes and neighboring cells (healthy podocytes or parietal epithelial cells (PECs)). The goal of this study was to establish an *in vitro* microfluidic coculture model to distinguish podocyte's responses to different injuries, and to determine what mediators from injured podocytes cause paracrine damage to neighboring cells in the glomeruli.

Methods: We engineered an open microfluidic coculture device consisting of two separate but interconnectible chambers. The outer chamber was seeded with primary human podocytes and the inner chamber was seeded with human podocytes or PECs in different series of experiments. Following the induction of podocyte injury in the outer chamber by cytotoxic sheep anti-podocyte IgG (IgG), puromycin (PAN), Adriamycin (ADR), chambers were connected to study the paracrine effects between injured podocytes and naïve podocytes or PECs. Imaging, cell viability and RNA-sequencing were temporally measured in cells of both chambers.

Results: Injured human podocytes displayed foot process effacement, cell body shrinkage, and decreased cell viability. In the podocyte-podocyte coculture, gene set enrichment analysis showed several common pathways for injury by IgG, PAN, and ADR, including apoptosis, complement, p53, TNFα, IFN, Wnt/β-catenin, and reactive oxygen species (ROS). IgG and ADR but not PAN increased TGFβ or inflammatory response (IL2, IL6, KRAS). ADR and PAN but not IgG increased DNA repair. The naïve podocytes cocultured with injured ones showed similar enrichments. Among the 65 ligand-receptor pairs shared by all three injuries were CSF1 & CSF1 receptor, BMP2 & BMP type I receptors, IL1A & IL1 receptor, and GDNF & RET receptor. The transcriptomic results from podocyte-PEC experiments are pending.

Conclusions: The *in vitro* open microfluidic coculture device represents a new model for studying autocrine and paracrine signaling between injured podocytes and healthy neighboring cells. The paracrine injury response of podocytes is similar to the direct injury response. Mechanistic studies are currently ongoing to identify which ligands from the injured podocytes and which receptors on naïve podocytes mediate these paracrine effects.

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FR-OR104

A Novel Small Therapeutic Peptide with Potential for Treating αvβ3-Mediated Glomerular Damage

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Background: αvβ3-mediated podocyte injury represents an initial pathological event observed in several glomerular diseases. However, effective clinical strategies targeting αvβ3 integrin remains elusive. Our recent research has unveiled a new function of inducible costimulatory ligand (ICOSL), which acts as an endogenous antagonist of αvβ3 integrin through its RGD motif. In this study, we identified a novel 19-mer peptide derived from ICOSL and evaluated its therapeutic potential for mitigating αvβ3-mediated podocyte injury.

Methods: The binding affinity of human ICOSL and its small linear peptide (hICOSL-peptide) to αvβ3 Integrin was assessed using surface plasmon resonance (SPR) at the molecular level, along with podocyte adhesion assays at the cellular level. Subsequently, we evaluated the therapeutic potential of hICOSL-peptide in proteinuric mice challenged with LPS by measuring ACR and BUN. To improve the pharmacokinetics (PK), a PEG12 molecule was introduced to the N terminal of hICOSL-peptide and the resulting PEG12-hICOSL-peptide was analyzed for its PK profile using ELISA.

Results: Our study showed that ICOSL binding favored the active αvβ3 integrin rather than the inactive form and showed no or weak affinity for other integrins. Through the analysis of ICOSL's crystal structure, we have successfully identified a 19-mer peptide possessing an RGD sequence. This peptide exhibited robust binding to the active form of αvβ3 integrin and exerted a strong influence on integrin-dependent podocyte adhesion. Moreover, administration of hICOSL-peptide effectively mitigated albuminuria in LPS-challenged ICOSL knockout (KO) mice, highlighting the therapeutic potential of hICOSL-peptide. Importantly, PEGylation process did not compromise the functional interaction of these peptides with αvβ3 integrin, but significantly enhanced the pharmacokinetic profile of hICOSL-peptide by a five-fold increment, further emphasizing its augmented therapeutic promise.

Conclusions: We identified a novel 19-mer linear peptide derived from ICOSL. This peptide exhibited the ability to specifically target αvβ3 integrin in podocytes and effectively reverse proteinuria in mice. These finding suggests that ICOSL and ICOSL-based small peptides hold significant promise as novel and safe therapeutic options for treating αvβ3-mediated glomerular diseases.

Funding: NIDDK Support

FR-OR105

Prevention of Proteinuria by a Novel, Subnanomolar ApoL1 Inhibitor

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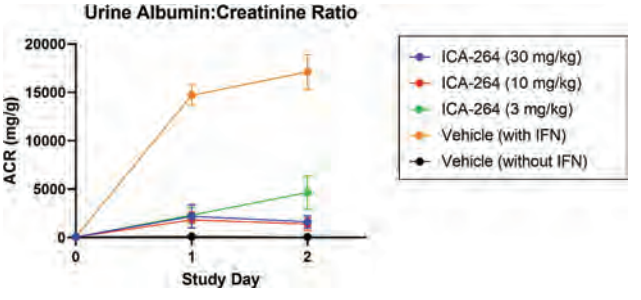
Background: Genetic variants of human ApoL1, which have arisen under evolutionary pressure to target mutant trypanosomes, have also been associated with an increased risk of developing chronic kidney diseases (CKD) in people of African ancestry[1]. Recently reported clinical results suggest inhibition of ApoL1 ion channel function may produce clinical benefit in patients with ApoL1-induced nephropathies[2]. 1. doi: 10.2215/CJN.15161219 2. doi: 10.1056/NEJMoa2202396

Methods: We established stable HEK-TREx cell lines in the EIK haplotype expressing human G1 and G2 variants under control of an inducible promoter and identified compounds for evaluation via high throughput screening, in silico profiling and medicinal chemistry design. Tl^+ flux and electrophysiology assays were used to assess *in vitro* efficacy of compounds against ApoL1 function. A human transgenic mouse model expressing ApoL1-G1 EIK and exhibiting a significantly elevated urinary albumin/creatine ratio (uACR) following IFNγ challenge was used to assess *in vivo* efficacy. Compound efficacy was determined by assessing inhibition of proteinuria.

Results: Our lead compound, ICA-264 demonstrated concentration-dependent inhibition of ApoL1-G1 mediated Tl^+ flux with an IC_{50} value of 4 nM (95% CI 3.5-4.4 nM, n=196). The potency was similar against ApoL1-G2 (IC_{50} = 5 nM, 95% CI 4.4-6.0 nM, n=77). Directly measuring ApoL1 current in electrophysiological experiments demonstrated potent inhibition with IC_{50} values at -80 mV and +60 mV of 0.6 nM and 0.4 nM (95% CI 0.35-0.47 and 0.49-0.65, respectively). Analogs of ICA-264 were identified with IC_{50} values as low as 0.26 nM in electrophysiological assays. In our *in vivo* model oral dosing of ICA-264 (BID) at 3, 10, and 30 mg/kg decreased the IFNγ-induced rise in uACR by 73%, 92%, and 91%, respectively (n=6) on day 2.

Conclusions: ICA-264 is a novel ApoL1 inhibitor with excellent drug-like properties and *in vivo* efficacy. This merits further consideration as a potential novel therapeutic for the treatment of ApoL1-induced nephropathies.

Funding: Commercial Support - OmniAb, Inc.



FR-OR106

Dynll1-PI31 Facilitated Proteasome-Mediated Degradation as a New Therapeutic Target for Interferon 2 (INF2)-Related FSGS

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Background: Mutations in Inverted formin 2 (INF2) gene leads to treatment lacking, autosomal dominant Focal Segmental Glomerulosclerosis (FSGS). We found the R218Q mutation in INF2 disrupts the INF2-Dynll1 interaction, leading to dysregulation of dynein-mediated trafficking and degradation of nephrin in *in vitro* and *in vivo* models of INF2-mediated podocytopathy. Our previous study found Dynll1 facilitates lysosomal degradation of nephrin via adaptor Histone deacetylase 6 (HDAC6). Here, we identified Proteasomal Inhibitor of 31kD (PI31) as a new adaptor protein which mediates dynein-driven proteosome-mediated degradation. We hypothesized that the INF2-R218Q disinhibits dynein-mediated trafficking of nephrin to the proteasome for degradation via enhanced Dynll1-Pi31 interaction and treatment with Bortezomib (a proteasome protease inhibitor), could become a therapeutic target for INF2-related FSGS.

Methods: Proteasome-mediated degradation of nephrin was studied in immortalized podocytes harboring INF2 R218Q mutation, with or without siRNA silencing of *Dynll1* or *PI31*. Puromycin aminonucleoside nephropathy (PAN) was established in *INF2 R218Q* knockin (KI) mice and effects of Bortezomib versus normal saline control among the different genotypes were evaluated by quantifying severity of proteinuria and podocytopathy.

Results: Increased Dynll1-PI31 interaction was shown in R218Q KI podocytes, correlated with the R218Q disrupted Dynll1-INF2 interaction. The nephrin protein in R218Q KI cells could be stabilized by 1) dynein inhibitor Ciliobrevin D and by

Bortezomib, suggesting an enhanced dynein-mediated degradation of nephrin via proteasome; or by 2) siRNA mediated knockdown of either Dynll1 or PI31, suggesting a critical role for Dynll1-PI31 interaction in nephrin depletion caused by INF2-R218Q. The Bortezomib treatment rescued the PAN of the INF2-R218Q KI mice by attenuating the dynein-facilitated degradation of nephrin via proteasome and preserving the surface trafficking of nephrin that is needed to maintain the slit diaphragm.

Conclusions: The R218Q mutation disrupts the Dynll1-INF2 interaction and facilitates dynein-mediated trafficking of nephrin to the proteasome via an increased Dynll1-PI31 interaction. Enhanced dynein facilitated proteasome-mediated degradation of nephrin represents new therapeutic target for INF2-related FSGS.

Funding: Other NIH Support - NIH K12HD027748, Private Foundation Support

FR-OR107

Fasting-Mimicking Diet and Podocyte Protection

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Background: Dietary management is of particular importance in the context of kidney disease. Our data indicate that periodic cycles of a fasting-mimicking diet (FDM) can ameliorate kidney damage by preventing podocyte loss. Using different tools and animal models, we showed the renoprotection of the FDM in the contest of glomerulopathies. We also showed, in a small pilot clinical trial that FMD is safe, feasible, and potentially beneficial to patients with CKD.

Methods: Damage in rats was established by puromycin (PAN). Rats were fed with six cycles of FMD or ad-lib. Morphological, physiological, and spatial transcriptomics (ST) data were collected at long term. Early molecular changes induced by the FMD were studied by snRNA-seq after one cycle. We used our Alport-podocyte-FUCCI (Fluorescence Ubiquitin Cell Cycle Indicator) mice to study the podocyte cell cycle. We administered 3 cycles of FMD to a small cohort of 13 patients (9 men and 5 women, 38-63 years) with stage III CKD.

Results: FMD downregulated proteinuria, ameliorated glomerular sclerosis, and protected podocyte number. ST showed that ctrl and FMD-rats present very similar spatial gene maps vs the PAN-rats. snRNA-seq showed that in PAN-rat, the FMD activated podocyte-specification genes, revealing the important role of fasting followed by refeeding in inducing transcriptional changes in podocytes after damage. In the Alport-podocyte-FUCCI mice, FMD lowered the podocyte number in G1 and increased the podocyte number in G0. In CKD patients, FMD downregulated IGF1, protein C, proteinuria, epicardial fat, and upregulated flow-mediated dilation value (indicating amelioration of endothelial function).

Conclusions: These results indicate that FMD promotes the maintenance of glomerular structure and function by inducing podocyte repair and by preserving the G0 state in these cells. FMD cycles could represent a potential treatment for patients affected by progressive kidney disease.

SA-OR01

IMPROVE AKI: Sustainability of Team-Based Coaching Interventions to Improve AKI in a Cluster-Randomized Trial

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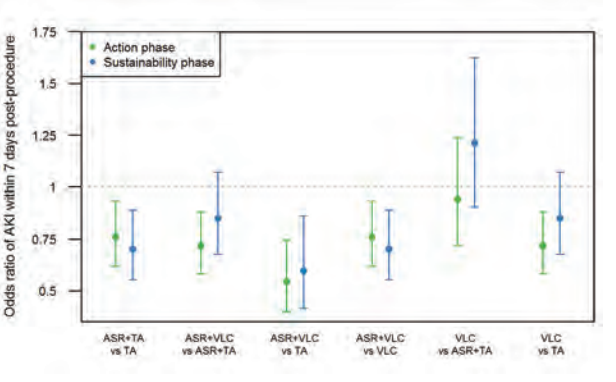
Background: Up to 14% who undergo cardiac catheterization procedures in the U.S. each year may experience acute kidney injury (AKI). An absence of standards for implementing known interventions hinders efforts to prevent AKI. In a 2x2 factorial cluster-randomized trial, we found the combination of team-based coaching and a data-driven surveillance dashboard reduced the odds of AKI by 46%. We hypothesized these improvements would persist in the period following the active intervention phase of the trial.

Methods: A 2x2 factorial cluster-randomized trial was conducted that randomized 20 Veteran Affairs hospitals to receive team-based coaching in a Virtual Learning Collaborative (VLC) compared to Technical Assistance with an AKI Prevention Toolkit (TA), both with and without Automated Surveillance Reporting (VLC+ASR and TA+ASR). Patient outcomes were collected over 18 months following the active intervention phase. Multilevel logistic models for AKI were fit with site-level random effects to account for the clustered design.

Results: Across 20 randomized sites, 440 of 4,160 patients experienced AKI during 18-months following the active intervention phase, including 216 of 1,260 patients with pre-existing chronic kidney disease (CKD). We observed a substantial reduction in AKI within the VLC+ASR cluster compared to the TA cluster (aOR=0.60; 0.42-0.86) consistent with the effect previously reported for the active intervention phase (aOR=0.54; 0.40-0.74).

Conclusions: Team-based coaching along with a data-driven surveillance dashboard can sustainably reduce AKI by 40%, even after active participation in the trial is complete. These combined interventions are an effective, scalable framework to establish aggressive AKI prevention protocols.

Funding: NIDDK Support



The following patient features were included for adjustment: age, race, tobacco use, anemia, heart failure, CKD, diabetes, hypertension, and prior percutaneous coronary intervention.

SA-OR02

Effects of Avasopasem Manganese on Cisplatin-Induced AKI and CKD

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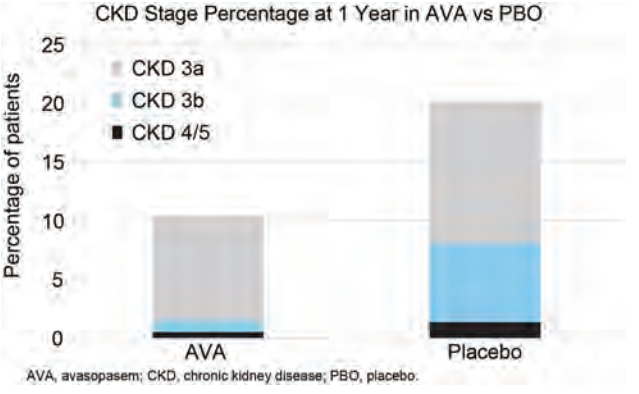
Background: Nephrotoxicity is a major complication of cisplatin treatment in cancer patients. Rates of acute kidney injury (AKI) range from 31-68%, and about 30% of cancer survivors receiving cisplatin develop chronic kidney disease (CKD) within 1 year. Superoxide production plays a crucial role in cisplatin-induced AKI and CKD. Avasopasem (AVA) is a selective superoxide dismutase mimetic shown in phase 3 to reduce severe oral mucositis in head and neck cancer (HNC) patients receiving radiation plus high-dose cisplatin.

Methods: We analyzed renal function data from a phase 3, double-blinded, randomized trial that compared 90 mg AVA vs placebo (PBO) during cisplatin (weekly or every 3 weeks) and radiation therapy (CRT). Renal adverse events (AEs) were AKI, creatinine increase, or hypomagnesemia meeting grade 3+ criteria of the Common Terminology Criteria for Adverse Events for patients receiving cancer therapy. Creatinine was measured pretreatment, weekly during CRT, and then every 3 months for 1 year. CKD was staged at 1 year based on eGFR calculated using the CKD-EPI formula.

Results: 241 patients were randomized to AVA and 166 to PBO. Grade 3+ AKI was reported in 0.8% of AVA group vs 3.8% of PBO, grade 3+ creatinine increase in 1.2% vs 2.4%, and grade 3+ hypomagnesemia in 3.3% vs 5.4%. 202 AVA and 149 PBO patients were available to assess at 1 year with 10.4% CKD incidence in AVA group compared to 20.1% in PBO (p=0.004), primarily due to a reduction in stage 3b or greater disease (Figure).

Conclusions: In patients with HNC receiving radiation plus high-dose cisplatin, AVA, a superoxide dismutase mimetic, was significantly associated with decreased incidence and severity of CKD, with a trend towards decreased incidence of grade 3+ acute renal AEs. AE profile was otherwise consistent with expectations for CRT.

Funding: Commercial Support - Galera Therapeutics, Inc.



AVA, avasopasem; CKD, chronic kidney disease; PBO, placebo.

SA-OR03

Effect of Terlipressin Treatment on the Incidence of Renal Replacement Therapy in Patients with Hepatorenal Syndrome and Fluid Overload: A Post Hoc Analysis of the Phase 3 CONFIRM Study

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Background: Terlipressin (terli) is an FDA-approved vasopressin analogue for the treatment of patients with hepatorenal syndrome (HRS). However, in the Phase III CONFIRM study, terli use was associated with respiratory failure in 10% of terli-treated patients; this could have been due to increased intravascular volume, which is often managed with renal replacement therapy (RRT). In this analysis, we retrospectively examined the subgroup of patients in CONFIRM with fluid overload to determine the incidence, indications, and modality of RRT.

Methods: This post hoc analysis of the Phase III, randomized, placebo (pbo)-controlled CONFIRM study (NCT02770716) evaluated the incidence of RRT, indications, and modes of RRT used, in the subgroup of patients with fluid overload (pooled term for: hemodynamic edema, effusions, and fluid overload), as determined by investigator assessment. Incidence of RRT was determined on Days 14, 30, 60, and 90 in patients treated with terli or pbo; RRT was initiated after treatment discontinuation. Indications and mode of RRT were determined up to Day 14. Statistical analysis was determined using a Chi-square or Fisher Exact test.

Results: The CONFIRM study enrolled 300 patients (terli, n=199; pbo, n=101), of which 88 patients had fluid overload (terli: n=69; pbo, n=19). RRT incidence was significantly lower in the terli versus pbo group by Day 14 (23.2% [16/69] vs 47.4% [9/19], *P*=.039), and similar results were observed by Days 30, 60, and 90 (*P*≤.05). The indications for RRT up to Day 14 did not differ significantly between treatment groups, and the most common indications for both terli and pbo were fluid overload (14.5% [10/69] vs 15.8% [3/19]; *P*=1.000) and pulmonary edema (5.8% [4/69] vs 10.5% [2/19]; *P*=.606). Hemodialysis (terli vs pbo: 10.1% [7/69] vs 36.8% [7/19], *P*=.005) was the only mode of RRT with a significant difference between treatment groups.

Conclusions: This analysis from the CONFIRM study demonstrated that the incidence of RRT in patients with HRS and fluid overload was lower in terli-treated patients compared with pbo-treated patients. Improved renal function with terli may lead to reduced RRT requirements in patients with HRS and fluid overload.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals

SA-OR04

Niacinamide and Renal Recovery After AKI: A Randomized, Controlled Trial

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Background: Incomplete recovery following community acquired acute kidney injury CA-AKI may be seen in 15-20% of patients. Strategies to improve recovery rates and follow-up of such patients are required. The impaired NAD+ biosynthesis pathway has been recently implicated in AKI. Niacinamide, which bypasses the salvage denovo pathway and produces NAD, could be protective. Its role in recovery following AKI has been postulated. In this pilot phase of clinical trial, role of niacinamide supplementation in recovery after CA-AK was investigated.

Methods: The study was an open label, randomized, controlled trial. Patients of CA-AK aged 18-70 years were enrolled. Underlying CKD, urinary tract obstruction, malignancy, heart failure, pregnancy, lactating women or poor performance status were excluded. Participants were randomized to receive either niacinamide (500 mg BD for 14 days) or no intervention. Follow-up visits were at 1and 4 months after hospital discharge. The primary outcome was difference in renal recovery at 4 months after discharge. Renal recovery was defined as eGFR ≥60 ml/min/1.73m^2 at 4 months after hospital discharge. Secondary outcome measures were differences in eGFR between groups at 1 and 4 months after hospital discharge. Trial was prospectively registered (CTRI/2022/03/040892).

Results: Over a period of 6 months starting June 2022, 89 patients were screened. 50 patients were enrolled and randomized. Infections (70%), toxic envenomations (8%), rhabdomyolysis (8%) and drug induced AKI (6%) were leading causes. Majority (49 of 50) had stage 3 AKI with 32 (64%) requiring kidney replacement therapy. 6 patients expired and one patient did not report for follow up. Finally 43 patients were analyzed for outcome measures. The clinical characteristics: age, sex, DM, HT, AKI stage, were similar between groups at baseline. Renal recovery at 4 months was significantly higher in the niacinamide group (20/21, **95.2%)** as compared to the controls (15/22, **68.18%** p0.023). eGFR (ml/my/1.73m^2) at 1 month (99.9±27.9 *vs* 71.9±33.3 p0.040) and 4 months (108.2±26.2 vs 77.7±31.3 p0.001) after hospital discharge were also significantly higher in the intervention group as compared to control group. No major drug-related adverse events were recorded.

Conclusions: Niacinamide supplementation improved renal recovery at 4 months after hospital discharge in patients with severe AKI.

Funding: Government Support - Non-U.S.

SA-OR05

Impact of Using Blood Warmer During Continuous Kidney Replacement Therapy on Adverse Kidney Events and Mortality

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Background: Hypothermia is a complication of continuous kidney replacement therapy (CKRT). Blood rewarming is often used to prevent hypothermia; however, its impact on adverse kidney outcomes is unknown.

Methods: Patients with acute kidney injury (AKI) who required CKRT between 1/1/2012 and 1/1/2021 and admitted at a tertiary academic hospital were included. Major adverse kidney events (MAKE) is a composite outcome of need of kidney replacement therapy, doubling of the serum creatinine from baseline or death. We assessed MAKE at 30 and 90 days after CKRT initiation.

Results: There were 669 patients with AKI that required CKRT during the study period. There were 324 (48%) patients in whom a blood warmer was used on first day of CKRT. Patients where a blood warmer was used were more likely to be diagnosed with sepsis/septic shock (81% vs 74%, p=0.04), and were in a less positive fluid balance at the time of CKRT initiation (1.0 vs 1.3 L, p=0.03) compared to patients where a blood warmer was not used. There was no difference in hypotensive episodes during first day of CKRT between the two groups. MAKE-30 and MAKE-90 occurred in 376 (56%) and 422 (63%) of the patients, respectively. Patients who developed MAKE-30 were older (62 vs 56) and had higher SOFA score (10.5 vs 9), higher norepinephrine equivalent (NEE) requirement (0.15 vs 0.07 mcg/kg/min), higher lactate (5.5 vs 3.3 mmol/L), higher Charlson comorbidity index (CCI) (8 vs 7), lower mean arterial pressure (MAP) (74 vs 80 mmHg) and were more likely to be requiring mechanical ventilation (75% vs 63%) at CKRT initiation compared to patients who did not develop MAKE-30, p<0.001. Baseline creatinine was not different between the two groups (1.2 mg/dl). After adjusting for age, CCI, baseline serum creatinine and SOFA score, lactate, MAP, mechanical ventilation and NEE at CKRT initiation, the use of a blood warmer was independently associated with MAKE-30 (OR: 1.6, 95% C): 1.1-2.2, p=0.009) but not MAKE-90 (OR: 1.3, 95% CI 0.9-1.98, p-value=0.1). In adjusted Cox proportional hazard model, use of blood warmer was independently associated with mortality: hazard ratio 1.33 (95% CI: 1.1-1.6, p=0.002).

Conclusions: Blood warming techniques were associated with worse outcomes in patients with AKI on CKRT. More studies are required to explain this relationship.

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SA-OR06

Machine Learning-Guided Personalized Diuretic Strategy in Patients with Sepsis-Associated AKI

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Background: Fluid overload is common in patients with sepsis associated acute kidney injury (SA-AKI) and is associated with worse outcomes. Loop diuretics are commonly used to manage fluid overload, but their role in patients with SA-AKI is unclear. In this study we aimed to develop a personalized strategy for use of loop diuretics in patients with SA-AKI using machine learning.

Methods: This was a retrospective study using MIMIC IV database. We defined AKI using both creatinine and urine output based KDIGO criteria. We identified patients with sepsis who developed AKI within 48 hours of ICU admission. The primary outcome was AKI recovery within 48 hours of AKI onset. We used available features for demographics, comorbidities, SOFA score, vital signs, laboratory measurements, fluid balance, vasopressors and mechanical ventilation to estimate time varying individual treatment effects (ITE) using a two-model approach employing gradient boosting. The policy tree algorithm with pruning was then employed to identify subpopulations with the highest average treatment effects (ATE) for loop diuretic therapy, enabling a personalized diuresis strategy.

Results: Of 10,739 patients with SA-AKI, 37.8% had AKI recovery within 48 hours. Loop diuretics were used in 3,661 patients within 48 hours after onset of SA-AKI. ATE of loop diuretics was HR 0.935 (95% CI: 0.934, 0.937). Further policy tree analysis identified a personalized strategy for use of loop diuretics with goal to increase AKI recovery within 48 hours (Fig 1a). Specifically, patients with SA-AKI with Blood Urea Nitrogen (BUN)<=18 and red cell distribution width (RDW)<=14.2 benefited from loop diuretic therapy with an ATE of HR 1.086 (CI: 1.080, 1.091) (Fig 1b).

Conclusions: In this study we identified subgroups of patients with SA- AKI who may benefit from loop diuretic therapy to improve the likelihood of recovery of AKI within next 48 hours. This study shows the potential of machine learning to help personalize therapies for patients with AKI.

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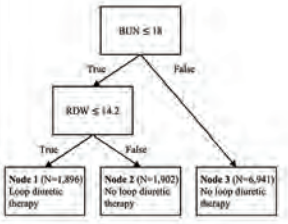

Figure 1a. Policy tree for personalized loop diuretic therapy to improve AKI recovery within 48 hours.

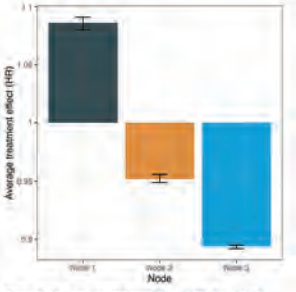

Figure 1b. Average treatment effects per each node from the personalized loop diuretic therapy

SA-OR07

Association of Post-Hospitalization Vascular Biomarker Clusters with Future Heart Failure

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Background: Individual vascular biomarkers helped elucidate the connections between acute kidney injury (AKI) and future heart failure (HF). The role of combined vascular biomarkers in recently discharged patients with risk of future hospitalizations with HF is unknown.

Methods: Using the ASSESS-AKI cohort, we performed an unsupervised spectral cluster analysis with 9 plasma biomarkers measured at 3 months post-hospitalization *[Angiopoietin (angpt)-1, angpt-2, vascular endothelial growth factor (VEGF)-A, VEGF-C, VEGF-d, VEGF receptor 1 (R1), solubleTie-2 (sTie-2), placental growth factor (PlGF), and basic fibroblast growth factor (bFGF)]* in 1,497 patients, half of whom had AKI. We used a Cox regression analysis to evaluate the associations between clusters and future hospitalizations with HF. Models were adjusted for demographics, cardiovascular disease risk factors, medications, ICU status, lung disease, sepsis, serum creatinine, proteinuria, and admission center.

Results: 3 biomarker-derived clusters were identified: Cluster 1 [n=302, Vascular Injury (VI) phenotype] had higher levels of vessel injury markers, whereas Cluster 2 [n=728, Vascular Repair (VR) phenotype] had higher levels of vessel repair markers. Cluster 3 (n=467) had lower levels of both repair and injury markers (dormant phenotype). The median time to HF was 4.7 years (IQR: 2.93-5.93). Participants with the VI phenotype were twice as likely to have a HF event [aHR 2.23 (1.56, 3.18)] compared to the VR phenotype. The dormant phenotype was also significantly associated with HF [1.98 (1.22, 3.21)] compared to the VR phenotype. AKI was a significant effect modifier for the relationship between clusters and HF with an interaction *P*-value of <0.01. Among those with AKI, the relationship between the VI phenotype and HF was significant [aHR 2.13 (95%CI: 1.36-3.36)].

Conclusions: Vascular biomarkers can be used to derive clusters to risk-stratify patients for future HF events. Vascular panels may be used to tailor post-AKI follow-up to minimize risk of future HF.

Funding: NIDDK Support

SA-OR08

The Association of Female Sex Hormones and AKI

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Background: Women have a lower risk of chronic kidney disease progression; however, controversy exists as to the relative roles of comorbid, biological, and socioeconomic factors. Whether the reno-protective effects of female gender extend to AKI remains to be established.

Methods: Our cohort consisted of hospitalized patients without kidney failure in the Montefiore Health System, Bronx, NY, from October 1, 2015, to December 31, 2018. We defined community-acquired AKI(CAAKI) as meeting criteria defined by KDIGO within the first 48 hours of admission and hospital-acquired AKI(HAAKI) as to a within 48-hour window rise in creatinine occurring after 48 hours of admission and before discharge. We categorized age into prepubertal (<16 years), adult (16-55years), and post-menopausal (>55 years). We used logistic regression and stratified models by age category to examine the association of sex with AKI in progressive models adjusting for:1-age and race/ethnicity only, 2-addition of previous comorbidity, 3-addition of census tract level socioeconomic status (SES) normalized to the NY state mean SES.

Results: Of the 286,383 hospitalizations, 120,711(42.1%) were men, 30,576 (10.7%) were White, and 82,505(28.8%) were Black, 44,172 (15.4%) were prepubertal, 100,115(35.0%) were adult and 142,101(49.6%) were older than 55 years. Of the 56,731 (19.8%) who developed AKI, 33,207(58.5%) had HAAKI and 23, 524(41.5%) had CAAKI. Males had a higher odds of developing both types of AKI (1.46 (1.43-1.49) in HAAKI and 1.31(1.27-1.34) in CAAKI). The odds of AKI were higher in males in all 3 age categories but was strongest in adults (Table 1). Adjustment for comorbidity attenuated the male risk in adults only, adjustment for socio-economic status did not change the strength of the association meaningfully.

Conclusions: Men are more likely than women to develop AKI. The attenuation of sexual dimorphism in AKI incidence before puberty and after menopause suggests that female sex hormones are protective in AKI.

Table 1: Logistic regression models stratified by age categories, of the association between sex and AKI incidence in progressively adjusted models.

	Model 1: adjusting for age and race	Model 2=Model 1+adjustment for comorbidity*	Model 3=Model 2 +adjustment for SES
Odds of AKI in age<16; n=44,170 Female Male	1 1.12(1.03-1.22)	1 1.14(1.03-1.25)	1 1.15(1.04-1.26)
Odds of AKI in those aged 16-55; n=100,114 Female Male	1 2.04(1.96-2.11)	1 1.71(1.65-1.79)	1 1.73(1.66-1.81)
Odds of AKI in those aged >55 years; n=142,099 Female Male	1 1.28(1.24-1.31)	1 1.21(1.18-1.24)	1 1.22(1.19-1.25)

** adjustment for BMI, history of smoking, rheumatologic, peripheral vascular disease, liver disease, illicit drug use, diabetes, chronic obstructive pulmonary disease, cancer, HIV disease, heart failure, alcohol, cerebrovascular disease, preterm birth, congenital heart or neuromuscular disease, congenital kidney disease, inborn error of metabolism, low birth weight, asthma, hypertension and CKD stage 5 and All Patient Risk (APR) score*

SA-OR09

Dialysis Weaning Is Uncommon in the Treatment of Outpatient AKI Requiring Dialysis (AKI-D)

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Background: Recovery from dialysis-requiring acute kidney injury (AKI-D) often occurs after discharge from the hospital, following treatment in outpatient hemodialysis units. The dialysis weaning strategies employed during outpatient recovery (weaning dialysis frequency, weaning dialysis session duration, or proceeding directly to a trial of complete dialysis cessation) have not been described.

Methods: We examined outpatient dialysis orders for a cohort of 1,754 AKI-D patients initiating in-center hemodialysis between 7/1/2017 and 6/30/2022 across 67 different dialysis units operated by a medium-sized, not-for-profit dialysis provider. We followed patients for 3 months after first outpatient hemodialysis treatment (or until recovery defined as discharge from dialysis with no readmission or death within the next two weeks). During follow-up, we assessed changes in prescribed hemodialysis frequency and session duration.

Results: 95% of AKI-D patients were initially ordered for ≥3x/week dialysis frequency. At 3 months after first outpatient hemodialysis treatment, 41% had recovered, 49% continued to receive dialysis, and 10% had died. During follow-up, 70% had no changes to either prescribed dialysis frequency or session duration. Among those who recovered, dialysis frequency was weaned in 18% and dialysis session duration was weaned in 9%; all others discontinued dialysis without a change from their initial prescription. Among those who remained on dialysis or died, frequency was weaned in 11%.

Conclusions: In this contemporary cohort of patients with AKI-D in outpatient hemodialysis centers, dialysis weaning was uncommon. That many patients were able to transition directly from thrice-weekly treatment to no hemodialysis suggests there may be substantial opportunity to wean dialysis more often (e.g., to twice weekly treatment), likely resulting in cost savings and quality of life improvement.

Funding: NIDDK Support, Commercial Support - Satellite Healthcare Inc., not-for-profit dialysis provider

Outpatient dialysis prescriptions for AKI-D patients, stratified by outcomes 3 months after first outpatient dialysis

	Recovered	Continued receiving dialysis	Died without recovery
Sample size (N)	725	862	167
No prescription change during follow-up	522 (72%)	569 (66%)	133 (80%)
Decrease in dialysis frequency (sessions/week) during follow-up	132 (18%)	95 (11%)	14 (8%)
Decrease in dialysis session duration (minutes/session) during follow-up	62 (9%)	77 (9%)	8 (5%)

SA-OR10

Prediction of Postdischarge Kidney Disease Progression Among Patients with Hospitalized AKI: The ASSESS-AKI Study

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Background: Acute kidney injury (AKI) occurs frequently during hospitalization, but only a fraction of patients progress to chronic kidney disease (CKD) after discharge. Biomarkers of kidney injury, inflammation, and repair have been shown to be informative of long-term kidney disease risk.

Methods: We evaluated data from 723 hospitalized patients with AKI and post-discharge follow-up in the prospective Assessment, Serial Evaluation, and Subsequent Sequelae of AKI (ASSESS-AKI) Study. We investigated 75 candidate predictors, including 11 urinary and 28 plasma biomarkers measured at 3-month post-discharge follow-up. We employed both random forests and least absolute shrinkage and selection operator (LASSO) regression to predict major adverse kidney events (MAKE): CKD incidence, CKD progression, or development of end-stage kidney disease. The data was split into training (80%) and test (20%) datasets. We used multiple imputation to handle missing data and independent test data for unbiased estimates of model performance.

Results: A total of 235 patients developed MAKE over 3 years of follow-up. While a prediction model containing 9 key clinical variables yielded an area under the receiver-operating characteristic curve (AUC) of 0.75 (0.63-0.87), random forest and LASSO models using all 75 variables yielded AUC values of 0.81 (0.71-0.92) and 0.80 (0.70-0.91), respectively (**Table 1**). The top 5 predictive biomarkers based on random forest modeling were sTNFR1, sTNFR2, NT-proBNP, FGF-23, and Ang2, all measured in the plasma and yielded an AUC of 0.75 (0.63-0.88). A combination model leveraging both clinical variables and the top 5 biomarkers demonstrated an AUC of 0.77 (0.65-0.89).

Conclusions: A parsimonious prediction model using a combination of key clinical variables and top biomarkers offers moderately strong discrimination in identifying patients with hospitalized AKI at highest risk of progression of kidney disease long-term.

Funding: NIDDK Support

Table 1. Model discrimination

Model	Variables	Number of predictors	AUC [95% CI]
Random forest	9 key clinical variables + 28 plasma biomarkers + 11 urine biomarkers + 10 drug classes + 17 other patient and hospitalization-related variables	75	0.81 (0.71-0.92)
LASSO	9 key clinical variables + 28 plasma biomarkers + 11 urine biomarkers + 10 drug classes + 17 other patient and hospitalization-related variables	75	0.80 (0.70-0.91)
Key clinical variables	Age, sex, race, BMI, diabetes mellitus, systolic blood pressure, AKI stage, Urine Alb/Cr, and 3-month eGFR	9	0.75 (0.63-0.87)
Top 5 biomarkers	plasma sTNFR1, NT-proBNP, sTNFR2, FGF-23, Ang2	5	0.75 (0.63-0.88)
Clinical variables + top 5 biomarkers	Age, sex, race, BMI, diabetes mellitus, systolic blood pressure, AKI stage, Urine Alb/Cr, and 3-month eGFR + plasma sTNFR1, NT-proBNP, sTNFR2, FGF-23, Ang2	14	0.77 (0.65-0.89)

Confidence intervals calculated with Rubin's rules for multiple imputation models
Ang2 = angiopoietin-2, FGF-23 = fibroblast growth factor-23, NT-proBNP = N-terminal pro-brain natriuretic peptide, sTNFR1 = soluble tumor necrosis factor receptor-1, sTNFR2 = soluble tumor necrosis factor receptor-2

SA-OR11

Development of Physiologically Relevant In Vitro Model of Human Kidney Collecting Duct System Toward a Functional Kidney Replacement

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Background: A significant number of patients with end-stage kidney disease face a restricted supply of kidney donors. Urgently needed alternatives are necessary due to the shortcomings of dialysis. Engineered kidney models have mainly focused on the proximal nephron, with little attention given to recapitulating the kidney collecting duct (CD) system. The collecting system refines formative urine and is vital for regulating acid-base balance, Na+ and K+ handling, and body water homeostasis. Applying microfluidic and 3D bioprinting methods to the development of kidney CD systems can potentially lead to a mature understanding of CD function in health and disease, as well as serve as an important component of functional kidney replacement.

Methods: PDMS soft lithography was employed to create a three-compartment cell culture device in which channels are separated by phase guides. These phase guides allow for in situ hydrogel formation while enabling subsequent fluidic exchange. These devices were designed to support both 2D cell culture for preliminary tests and as an enclosed system for fitting 3D-bioprinted tubes. Each channel is connected to a peristaltic pump channel, enabling shear stress in 2D or 3D culture. Ureteric bud-derived CD cells were seeded in the central channel, while the surrounding channels can be potentially used to culture stromal cells and endothelial cells to resemble the in vivo setting.

Results: Preliminary testing of the fabricated devices exhibited high cytocompatibility and the ability to withstand shear stress values up to 10 dynes/cm^2 in the channels without mechanical failure or cell detachment. In situ hydrogel formation demonstrated the effectiveness of the phase guides in preventing mixture before crosslinking, while allowing fluidic transfer between the channels. The hydrogel structures within the devices showed sustained resistance to flow flows with no structural defects.

Conclusions: Our human kidney CD system can be used to model the CD in health and disease, as well as serve as a potential component for kidney functional replacement. Our initial studies involve demonstrating the functionality of this system to study human CD system physiological function in health and in models of genetic disease.

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SA-OR12

Induced Pluripotent Stem Cell (iPSc)-Derived and Primary Podocyte-Like Cells Are Capable of Macromolecular Sieving After Culture in Scalable Scaffolds

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Background: With the growing demand for donor kidneys and insufficient donor organs, there is an urgent need for alternatives to dialysis and kidney transplantation. Our team has developed a biocompatible engineered glomerular tissue construct comprising hollow vascular and epithelial networks separated by a porous biomimetic membrane. The scaffolds are seeded with endothelial cells and podocytes that when perfused under vascular pressure, recapitulate glomerular function to produce a primary filtrate. The glomerular units are seeded with primary cells isolated from non-transplantable human donor kidneys of by isolation of cells from human induced pluripotent stem cells (iPSCs), that have been differentiated into endothelial cells and podocyte-like cells. We evaluated filtration dynamics and cell characteristics.

Methods: Human primary podocytes and endothelial cells are isolated by enzymatic digestion and glomerular isolation by sieving. Podocytes and endothelial cells were isolated by subsequent glomerular digestion and FACS sorting. Isolates were perfusion seeded. Human iPSCs were differentiated into endothelium using an established protocol. Human kidney organoids were generated using published methods with modifications. MAFB positive podocyte clusters were isolated using enzyme digestion and size filtration and expanded to form a monolayer. Cell seeded scaffolds were cultured using custom bioreactors and perfusion control units. Physiology was assayed by vascular perfusion under defined backpressure to generate primary filtrate through the epithelial channel.

Results: Acellular control scaffolds are highly permissive to transmembrane fluid flux and produce filtrates which contain micro- and macromolecules. Histological analysis of fixed primary and iPSC scaffolds shows cellular coverage within the endothelial and podocyte channels, indicating good cellular attachment and survival under perfusion for a minimum of 7 days. Pressurized perfusion of cellularized scaffolds with a blood-like buffer containing physiologic albumin and hematocrit through the vascular channel, produced RBC-free filtrate which resists macromolecule loss from the vasculature.

Conclusions: Our results demonstrate that both primary and iPSc derived endothelial and podocyte-like cells are a viable option for physiologically relevant engineered renal tissues.

Funding: Commercial Support - Iviva Medical

SA-OR13

A Novel Vascularized Human Kidney Organoid to Study Podocyte and Endothelial Health and Disease

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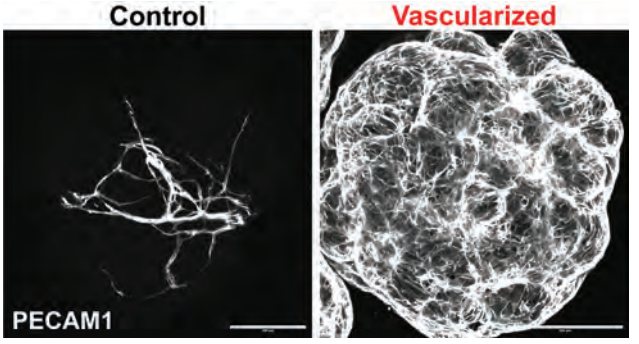
Background: Recapitulating vasculature in *in vitro* kidney systems is critical for mechanistic studies due to its important role in health and disease. Many methods for vascularizing have been taken, however, few have been robust, reliable, high-throughput, and can be used to study podocyte/endothelial morphology and morphological changes in injury settings.

Methods: Here, we generate vascularized human kidney organoids by mixing an inducible *ETS translocation variant 2* (*ETV2*) human induced pluripotent stem cell line (iETV2-hiPSC), which directs endothelial fate, with a non-transgenic iPSC line in suspension organoid culture.

Results: We demonstrate that the addition of iETV2-hiPSCs to an established kidney organoid protocol generates a vascularized human kidney organoid with a ~10-fold increase in endothelial cells and a 60% increase in organoid diameter. Podocyte clusters were consistently encased in a network of endothelial cells with invagination. On snRNAseq we found vascularized podocytes exhibit enhanced VEGF signaling, basement membrane maturation, and endothelial differentiation markers. Additionally, we demonstrate that vascularization of human kidney organoids enables the formation of a functional interstitium with drug responsive renin+ cells. These renin cells existed within podocyte clusters of vascularized organoids only. Finally, we show that iETV2-hiPSCs undergo co-development with kidney organoid parenchymal tissue, thus generating mature fenestrated kidney-specific endothelial networks.

Conclusions: We generated a vascularized human kidney organoid with increased maturation of nephron structures including more mature podocytes with improved foot process interdigitation, a fenestrated endothelium, and the presence of renin+ cells. This represents the first demonstration of renin+ cells in a kidney organoid without the use of exogenous stimulation. The creation of an engineered vascular niche capable of improving kidney organoid maturation and cell type complexity is a significant step forward in the path to clinical translation.

Funding: NIDDK Support, Other NIH Support - T32EB001026, R01 EB028532



SA-OR14

A Mouse Glomerular Nanoscale Spatial Atlas

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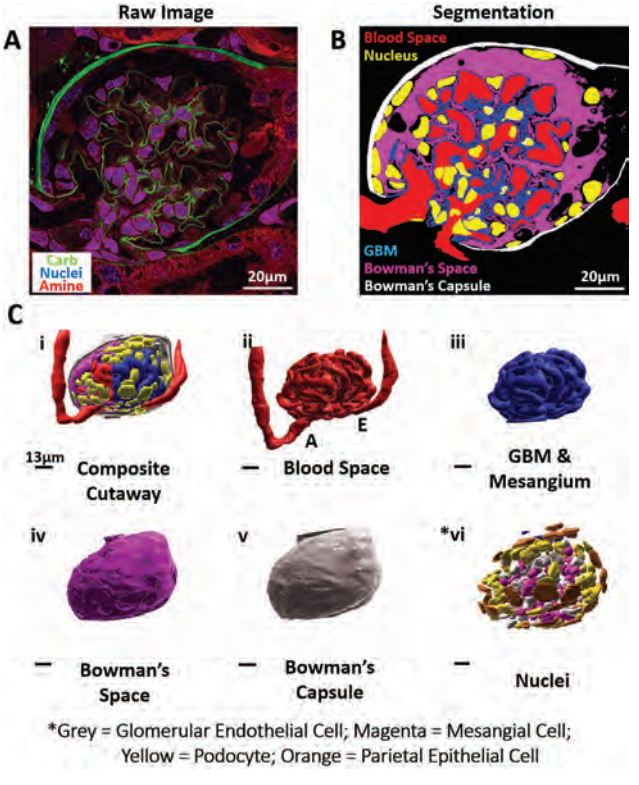
Background: Glomeruli are anatomically complex structures essential to kidney function. Much of our current understanding of glomeruli comes from optical microscopy, for general physiology and molecular distributions, and electron microscopy, for ultrastructure. While powerful, these methods yield uncorrelated results obtained on different pieces of tissue and typically for thin sections at random angles. Researchers therefore generally study small regions of glomeruli, rather than viewing them as distinct, functioning units. We are creating a Glomerular Nanoscale Spatial Atlas (GNSA) that will provide a detailed, annotated collection of high-resolution 3D reconstructions of whole mouse glomeruli. Our goals are to identify previously unknown glomerular phenotypes and to create a rich, downloadable resource.

Methods: We used optical super-resolution microscopy methods at 50-100nm resolution together with advanced tissue labeling techniques and a mix of manual and deep-learning-based data analysis techniques to image and segment major structures in whole mouse glomeruli.

Results: We have reconstructed and analyzed 7 glomeruli (3F, 4M) from healthy adult mice (3-6mo), whose models reveal Bowman's capsule, Bowman's space, blood space, all cell types and locations, glomerular basement membrane and mesangial matrix.

Conclusions: We have established a pipeline for creating detailed 3D models of whole renal glomeruli. We are performing a detailed spatial analysis of the models and acquiring new results for aged and model diseased mice with a focus on identifying spatial correlations between components of glomeruli. Once published, the unique data sets of the GNSA may be mined for diverse purposes by the nephrology community.

Funding: NIDDK Support



SA-OR15

A Novel Glomerular Endothelium-Targeting Adeno-Associated Virus (AAV) Delivers Bacterial Proteinase to Treat Glomerulonephritis

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Background: The breakdown of glomerular filtration barrier (GFB) is relevant to the pathogenesis of most kidney diseases. Targeting the GFB by conventional drugs is challenging due to the lack of cell-targeting specificity, which consequently compromises the therapy efficacy. Adeno-associated virus (AAV) as a promising *in vivo* gene delivery platform shows the advantage in delivering therapeutic molecules to those difficult or non-druggable cells. However, natural AAV serotypes have insufficient targeting specificity and transduction efficiency in kidney cells, thus approaches to broaden the tropism of AAV and screenings for kidney-specific AAV vectors are particularly needed. In this study, we aimed to discover new AAV vectors targeting the renal glomerulus.

Methods: We developed a selection protocol specifically for kidneys and screened a random AAV2 display peptide library *in vivo*. Integrative experimental and bioinformatics workflows were conducted to identify the most promising AAV vectors enriched in renal glomeruli. The targeting specificity and transduction efficiency of the selected AAV were evaluated *in vivo* under both physiological and pathological conditions.

Results: We identified a new AAV vector termed AAV2-GEC, which specifically and efficiently targeted the glomerular endothelial cells (GEC) after systemic administration. AAV2-GEC exhibited robust GEC tropism in C57BL/6J, Balb/c mice and Sprague Dawley rats, as well as in disease models causing GEC damage. The potential of AAV2-GEC for kidney-targeting therapy was evaluated by delivering a bacterial cysteine proteinase originally purified from Streptococcus pyogenes (IdeS) to the GEC. IdeS, also known as imlifidase, is an antibody-cleaving enzyme used in the clinic to eliminate pathogenic IgG. We showed that AAV2-GEC-IdeS transduction efficiently produced IdeS in GEC, which provided sustained clearance of kidney-bound IgG and successfully prevented the progression of anti-glomerular basement membrane glomerulonephritis.

Conclusions: This study establishes an AAV *in vivo* screening approach for renal glomeruli. It identifies a novel GEC-targeting AAV vector with robust tropism maintained cross species in both physiological and pathological settings. The identification of AAV-GEC demonstrates the feasibility of future GFB-targeting strategies for novel kidney therapies.

Funding: Government Support - Non-U.S.

SA-OR16

Comprehensive Single-Cell Transcriptomic, Epigenomic, and Metabolomic Profiling Reveals Anatomical and Metabolic Heterogeneity in Human Kidneys

Haikuo Li, Dian Li, Qiao Xuanyuan, Nicolas Ledru, Haojia Wu, Benjamin D. Humphreys. *Washington University in St Louis, St Louis, MO.*

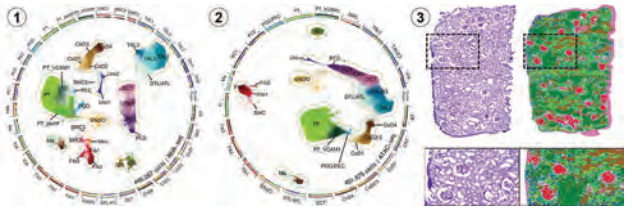
Background: The human kidney has a distinct spatial organization, with multiple anatomic structures constituted by diverse cell types and performing unique metabolic functions. We lack a large-scale spatially-resolved multimodal (transcriptome, epigenome, metabolome) single-cell atlas for the human kidney.

Methods: We developed an optimized, split-pool barcoding-based multimodal profiling method based upon SHARE-seq (concurrent scATAC/RNA-seq). We profiled 50 human kidney samples from cortex, medulla, papilla, ureter and renal artery. Computational analysis (e.g. gene regulatory network, module enrichment analysis) identified molecular signature of different anatomic regions. Mass spectrometry spatial metabolomics was used to identify region-specific metabolites at single-cell resolution. Clinical data were used to identify novel genes in kidney disease progression.

Results: We generated transcriptomes of 446,000 cells, chromatin accessibility profiles of 401,000 cells & spatially resolved metabolomes of 408,000 cells. Multiomic analysis revealed cell types in different anatomic regions are characterized by markedly different transcriptome & chromatin accessibility profiles depending on the region (e.g. cortical vs. medullary vs. papillary TAL cells). Healthy PT (proximal tubule)-to-maladaptive PT transition is accompanied by acquisition of a distinct metabolic signature (e.g. reduced fatty acid oxidation, elevated lipid accumulation). Tubular cell types had non-overlapping metabolomic profiles. We developed MALDIpy, a package for single-cell analysis of imaging mass spectrometry data.

Conclusions: Our optimized SHARE-seq achieved single-cell multiome profiling at 20-fold lower cost compared to 10X Genomics. We developed a comprehensive single-cell multiomics atlas of human kidneys covering diverse anatomic structures. Distinct signatures of cells in different regions suggest cellular plasticity and metabolic heterogeneity. Genes (e.g. PPFIBP1) correlated with disease severity were identified as potential therapeutic targets.

Funding: NIDDK Support



1/2) UMAPs for scRNA/ATAC-seq. 3) Metabolomics clustering of kidney cortex.

SA-OR17

Improving Patient Activation via a Novel Digital Health Intervention: My Kidneys and Me, a Multicenter Randomized Controlled Trial

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Background: Self-management is an important component of chronic kidney disease (CKD) healthcare which requires knowledge, skills and confidence (patient activation). Evidence-based and theory-driven resources to support self-management are lacking but digital health interventions (DHIs) may offer cost-effective and equitable education delivery. We co-produced My Kidneys & Me (MK&M), an educational DHI, and tested its effect on patient activation in a multicenter randomized control trial.

Methods: Patients from 26 sites in England were randomized 2:1 to intervention (MK&M) or control groups. MK&M provided theory-based education sessions and trackers for goals, symptoms, physical activity and clinical measures. The Patient Activation Measure (PAM-13) was collected at baseline, 10 and 20 weeks. A 4-point increase in PAM-13 was deemed a meaningful important difference. Intention-to-treat (ITT) and per-protocol (PP) analyses (including patients who used MK&M at least once) were conducted.

Results: 421 patients (mean age 59.9±13.4 years, 60% males, eGFR 39.5±24.6 ml/min/1.73m^2) were recruited: 281 randomized to receive MK&M, 140 to control. 205 (73%) participants used MK&M at least once. Changes in PAM-13 are shown in Figure 1. Significant between group differences in PAM-13 were observed at 20 weeks in PP analysis. In those with low PAM-13 at baseline, MK&M significantly improved PAM-13 by 9.3-11.4 points. No changes were seen in those with high baseline PAM-13 scores.

Conclusions: Use of the MK&M DHI increased patient activation (measure of self-management). Greater benefit was seen with frequent and sustained usage, and in those with low PAM-13. As higher patient activation is associated with better outcomes, MK&M may improve CKD healthcare management.

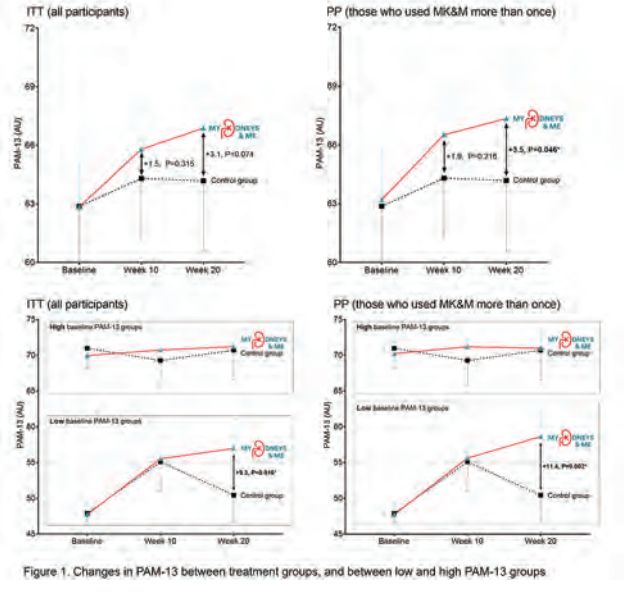

Figure 1. Changes in PAM-13 between treatment groups, and between low and high PAM-13 groups

Figure 1

SA-OR18

The Effect of a Novel Digital Physical Activity Intervention on Health-Related Quality of Life in People with CKD: A Multicenter Randomized Controlled Trial (Kidney BEAM)

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Background: Remote digital health interventions (DHI) to enhance PA (PA) provide a potential solution to improve health related quality of life (HRQoL) for people with chronic kidney disease (CKD). The Kidney BEAM trial evaluated the effect of a 12-week PA DHI on HRQoL.

Methods: 340 participants with CKD from 11 UK Kidney units were recruited and randomized (1:1) to Kidney BEAM PA DHI (www.beamfeelgood.com) or a waitlist control. The primary outcome was a powered 3-point difference in the Kidney Disease Quality of Life SF 1.3 Mental Component Summary (KDQoL-SF1.3 MCS) between baseline and 12-weeks. Secondary outcomes included KDQoL-SF1.3 Physical Component Summary and sub-scales; physical function (sit-to-stand 60, STS60); patient activation (Patient Activation Measure 13, PAM13); anxiety/depression (Patient Health Questionnaire, PHQ4); and fatigue (Chalder Fatigue Scale, CFS). Outcomes were analysed by intention-to-treat approach utilising an analysis of covariance model.

Results: 340 participants were included in the intention-to treat analyses. At 12-weeks there was a significant mean difference between Kidney BEAM and waitlist control in KDQoL MCS score of 3.1 {95% confidence interval (CI): 1.8 to 4.4} arbitrary units ($p<0.001$). KDQoL burden of kidney disease, energy/fatigue, and social function sub-scales ($p=0.049$, $p=<0.001$, and $p=0.013$, respectively) all improved in favour of the intervention. Physical function also improved (STS60 mean between-group difference: 4 {95% CI: 3 to 5} repetitions ($p<0.001$) and patient activation was enhanced (PAM13 mean between-group difference: 6.9 {95% CI: 4.9 to 8.8} points ($p<0.001$)). Fatigue and anxiety/depression were unchanged ($p=0.33$ and $p=0.08$, respectively).

Conclusions: These results demonstrate that the Kidney BEAM DHI is an effective innovation to improve mental HRQoL in people with CKD. This is the first large randomised controlled trial of an effective, and deliverable, PA DHI for people with CKD.

SA-OR19

Hemodialysis Patient App Promotes Patient Engagement and May Improve Patient Outcomes Such as Hospitalisation and Phosphate Control

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Background: Mobile applications (apps) have been shown to improve engagement in patients with chronic diseases. The aim of this study was to investigate patient engagement with our patient app (MyCompanion) and assess the impact of app usage on the outcomes of our hemodialysis (HD) patients.

Methods: We conducted a retrospective review of 2,970 chronic HD patients from 33 dialysis clinics in Singapore over a 2-year period (July 2020 - June 2022). An online survey was disseminated to gather user feedback. We compared the demographics, clinical, laboratory and outcome variables between app users and non-users using linear regression, and changes to the variables before and after app usage (1-year period) using paired t-test.

Results: As of June 2022, 13.5% (194 out of 1594 total active in-centre HD patients) of the patients logged in to the app at least once monthly. From the online survey with 64 respondents, a vast majority (87.5%) reported that the app empowered them for self-care. Out of the 5 core features within the app, patients ranked treatment data (39.1%) followed by laboratory results (32.8%) as the most favoured. For the analysis of outcome variables, 822 app users and 2,148 non-users were identified. App users were statistically significantly younger (60.1 vs 66.0 years), had longer dialysis vintage (3.9 vs 2.0 years), higher dry body weight (70.7 kg vs 65.6 kg in males and 59.3 kg vs 56.7 kg in females)

and lower adjusted Charlson Comorbidity Index (5.0 vs 5.5) (p<0.001). The percentage of patients achieving the phosphate target (≥2.5 and <5.5 mg/dL) was higher in app users (68.9%) compared to non-users (66.4%) (p<0.001). Phosphate control improved after 1 year of app usage from 62.2% to 69.4% (p=0.001). Hospitalisation rate (events per patient year) was 1.55 for app users and 1.97 for non-users (p<0.001). The number of hospitalization days per patient year for users and non-users were 10.2 and 10.9 days, respectively (p<0.001). The impact of app usage on patients' interdialytic weight gain was not statistically significant.

Conclusions: HD patient app promotes patient empowerment and self-care. Additionally, app usage may improve medical outcomes such as phosphate and hospitalisation.

Funding: Commercial Support - Fresenius Medical Care

SA-OR20

Integrated Proteomic and Metabolomic Modules Associated with Risk of Kidney Function Decline

Pascal Schlosser,[1] Aditya L. Surapaneni,[2] Eugene P. Rhee,[3] Josef Coresh,[1] Morgan Grams.[2] On Behalf of the CRIC and CKD BioCOn Writing Group. *[1]Johns Hopkins University Department of Epidemiology, Baltimore, MD; [2]Division of Precision Medicine, New York University School of Medicine, New York, NY; [3]Massachusetts General Hospital, Boston, MA.*

Background: Proteins and metabolites play crucial roles in various biological functions and are frequently interconnected through enzymatic or transport processes. Many molecules have been linked to kidney disease, and several of them are potentially representing pathways or endophenotypes.

Methods: We present an integrated analysis of proteomics (4,091 proteins) and metabolomics (634 metabolites) via a dimensionality reduction clustering method in the Chronic Renal Insufficiency Cohort (CRIC) Study. We split the 1,708 participants (mean age 59; mean eGFR=42.8 mL/min/1.73m^2) with a random split in discovery (2/3) and replication (1/3). Linear regressions (eGFR decline) and Cox proportional hazards models (CKD progression, ESKD) were comprehensively adjusted for demographics and risk factors including eGFR and PCR. Multiple testing in discovery and replication was accounted for by Bonferroni adjustment. Identified modules were characterized through pathway enrichment analyses.

Results: We identified 139 modules of correlated proteins and metabolites in the discovery data. The mean module size was 34 proteins / metabolites. There were 286 principal components (PCs) used to represent the 139 modules. Module membership and PC directions were projected onto the replication dataset. The average follow-up period was 9.5 and 7.4 years for ESKD and CKD progression respectively (537 and 685 events). Eight module PC to endpoint associations originating from four different modules were identified and replicated (1 eGFR decline; 3 CKD progression; 4 ESKD). One module showed associations with all three traits and ESKD concordance in the replication dataset was improved (87% to 88%, p=0.03) by the addition of this module to the full model of ten covariables. All five protective protein components of this module (ATF6, CLSTN1, EGFR, GHR, C1GALT1C1) were transmembrane proteins and several transmembrane related terms were significantly enriched among the 298 module components. Transmembrane-ephrin receptor activity displayed the largest odds ratio among these (OR = 13.2, P-value = 5.5e-5).

Conclusions: In summary, this study demonstrates that the integration of the proteome and metabolome can identify functions of (patho-) physiologic importance in human health and disease. Specifically, the ephrin receptor activity pathway might play a role on a systemic level.

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

SA-OR21

A Soluble ACE2 Protein Improves Survival and Lowers Viral Titers in a Lethal Mouse Model of SARS-CoV-2 Infection with the Delta Variant

Cosimo L. Cianfarini, Jan Wysocki, Ahmed K. Ismail, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

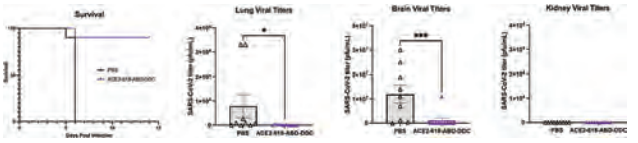
Background: Severe Acute Respiratory Syndrome Coronavirus Type 2 (SARS-CoV-2) utilizes Angiotensin Converting Enzyme 2 (ACE2) as its main receptor for cell entry. We have previously shown that a bioengineered soluble ACE2 protein designed to have increased binding to the SARS-CoV-2 spike protein and with extended duration of action can neutralize SARS-CoV-2 in the k18hACE2 mouse model infected with the ancestral SARS-CoV-2 strain (Washington isolate). Here we investigated the preventative/therapeutic potential of intranasally administering this soluble ACE2 protein in the same lethal mouse model infected with the SARS-CoV-2 delta variant which causes severe disease in humans.

Methods: k18hACE2 mice were inoculated with SARS-CoV-2 delta variant (2x10^4 PFU) and followed for up to 14 days in a BSL-3 facility. ACE2-618-ABD-DDC or PBS as vehicle control (n=10 per group) were administered intranasally 6h prior as well as 24 and 48hrs after viral inoculation. Infected animals were observed for weight loss, a clinical score, and mortality. Viral load was assessed by plaque assay in brain, lung, and kidney tissue.

Results: All untreated animals had succumbed to the disease at day 6, whereas survival at day 14 was 90% in mice receiving ACE2-618-ABD-DDC (Fig, left panel). Brain and lung viral titers were markedly reduced in mice receiving ACE2-618-ABD-DDC (Fig, middle panels). Despite uniform lethality of the disease in untreated animals, infected mice showed absence of kidney viral titers in all groups (Fig, right panel).

Conclusions: This study demonstrates the protective effect of ACE2-618-ABD-DDC in a lethal mouse model of SARS-CoV-2 infection with the delta variant. This soluble ACE2 protein markedly improved survival in the otherwise lethal model and reduced viral titers in lungs and brains to almost undetectable levels. It also shows a consistent lack of replicating virus in the kidney of animals infected with the delta variant. Taken together with our previously published experiments, the data supports a universal protective effect of our soluble ACE2 protein against infections with different SARS-CoV-2 variants.

Funding: Private Foundation Support



SA-OR22

University of California Health Systems Kidney COVID Study Inpatient Cohort

Hiba Hamdan, Brian M. Paciotti, Blythe Durbin-Johnson, Brian Y. Young, Juan P. Moreno-Ortiz, Baback Roshanravan. *UC Davis Health, Sacramento, CA.*

Background: Understanding long term changes in kidney function following moderate to severe COVID-19 is important. The aim of our study was to compare changes in eGFR between people hospitalized with and without COVID-19 to better understand its longer-term kidney sequelae.

Methods: We conducted a retrospective cohort study of adults receiving care within the five major University of California (UC) Health Systems, who underwent PCR testing for SARS-CoV-2 between March 1, 2020, and December 31, 2021, and were hospitalized within 10 days of testing. The cohort was restricted to those without ESKD, with a serum creatinine (sCr) within 12 months prior to SARS-CoV-2 testing or normal kidney function on admission, length of stay ≥1 day, no pregnancy throughout the study period, and at least one outpatient sCr 30 days after initial PCR test. Individuals were classified as COVID/non-COVID based on the index SARS-CoV-2 PCR result and those classified as non- COVID were required to remain negative. The outcome was the difference in the rate of eGFR change among those who survived hospitalization. The cohort was followed until December 31, 2022. Descriptive statistics were used to compare patient characteristics. Trajectories of eGFR were compared between those with and without COVID using linear mixed models with inverse probability weighting to account for missingness of baseline and follow-up eGFR measurements. Three linear mixed models were fitted as detailed in attached figure.

Results: The cohort included 2,356 and 26894 patients hospitalized with and without COVID, respectively. Patients hospitalized with COVID-19 were more likely to be male, Hispanic, reside in areas with higher Area deprivation index (ADI), and have pre-existing chronic diseases, including DM, HTN and CKD. The results of the three fitted models are shown in attached figure.

Conclusions: In a large cohort from one of the largest health care systems in California, we did not observe a significant difference in eGFR decline over almost 2 years of follow up. This study has the longest reported follow up of kidney function post SARS COV 2 infection.

Funding: Other NIH Support - UC Davis School of Medicine

Estimates of Annual eGFR Change in Inpatients from Linear Mixed Effects Models

Variable	Estimate	95% CI Lower Bound	95% CI Upper Bound	P-Value
Model 1				
Annual eGFR Change in Non-COVID	-1.739	-1.936	-1.541	< 1e-05
Annual eGFR Change in COVID	-2.270	-2.933	-1.608	< 1e-05
Difference	-0.532	-1.223	0.160	0.16523
Model 2				
Annual eGFR Change in Non-COVID	-1.761	-1.956	-1.566	< 1e-05
Annual eGFR Change in COVID	-2.307	-2.954	-1.659	< 1e-05
Difference	-0.546	-1.222	0.131	0.13039
Model 3				
Annual eGFR Change in Non-COVID	-1.717	-1.954	-1.479	< 1e-05
Annual eGFR Change in COVID	-2.301	-2.954	-1.648	< 1e-05
Difference	-0.584	-1.264	0.096	0.10851

Model 1-unadjusted. Model-2 adjusted for age, race, gender, ADI, UC site of care and BMI. Model-3 adjusted for all variables in Model 2 and Baseline eGFR, Diabetes, hypertension, CHF, smoking status, and COVID month of testing

LME Models

SA-OR23

Machine Learning-Based Multi-Omics Analyses Predict Disease Severity and Identify Molecular Mechanisms of COVID-Associated Kidney Injury

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Background: Studies show a higher prevalence of acute kidney injury (AKI) in COVID-19 patients, however mechanisms leading to severe kidney outcomes are unclear. Identifying these mechanisms may help develop therapies for the management of COVID-associated nephropathy (COVAN). In this multicenter study, we combine urinary proteomics and machine learning (ML) to predict severe kidney outcomes in COVID-19 patients and further combine multiomic datasets to identify gene networks driving disease (Fig 1A).

Methods: Quantitative LC-MS/MS analysis of urine samples from hospitalized participants was performed. For ML algorithm construction, samples were stratified into

severe and mild outcomes and randomized into discovery and validation set at a 2:1 ratio. Limma test was used to identify differentially abundant proteins (DAPs) and the Boruta feature selection method was used to select features to construct the ML algorithm.

Results: Limma test on the discovery set identified DAPs in severe vs mild outcome cohort (Fig 1B). The top features identified using Boruta feature selection method used for random forest model construction demonstrated good predictive power of greater than 76% accuracy for both discovery and validation set (Fig 1C, D). Enrichment analysis showed significant upregulation of exocytosis and immune related processes and downregulation of cell adhesion and extracellular matrix organization related processes in severe COVID-19 (Fig 1E, F). The top features showed expression in multiple nephron segments based on the public KPMP data (Fig 1G).

Conclusions: The novel biomarkers identified here can be used for assessment of kidney function in patients with COVAN.

Funding: NIDDK Support

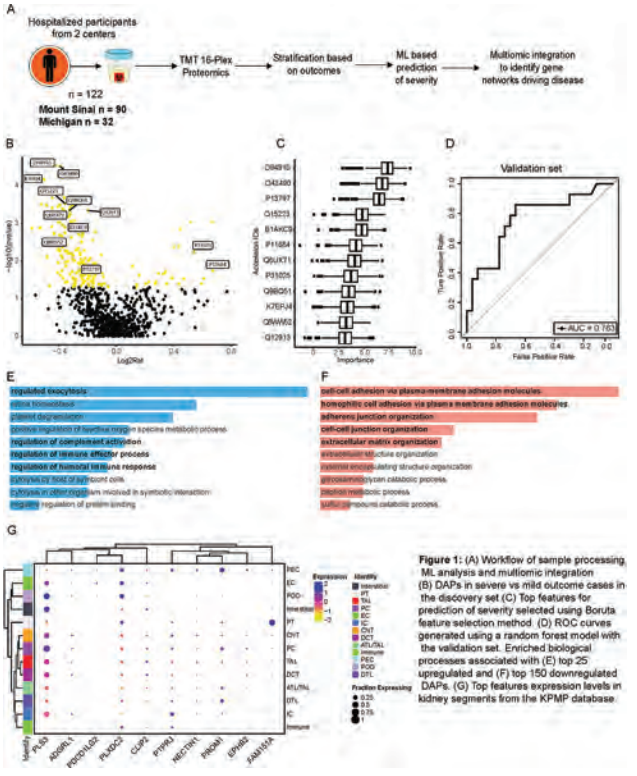

Figure 1: (A) Workflow of sample processing, ML analysis and multiomic integration (B) DAPs in severe vs mild outcome cases in the discovery set (C) Top features for prediction of severity selected using Boruta feature selection method (D) ROC curves generated using a random forest model with the validation set. Enriched biological processes associated with (E) top 25 upregulated and (F) top 150 downregulated DAPs. (G) Top features expression levels in kidney segments from the KPMP database.

SA-OR24

Longitudinal Kidney Outcomes of COVID-19-Associated AKI

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Background: COVID-19 infection is associated with a high incidence of acute kidney injury(AKI). The long-term impact of COVID-associated AKI on kidney function trajectory remains unknown.

Methods: This was a longitudinal health record cohort study that included 9624 adults hospitalized with AKI within a large New England health system assessing the association of COVID-19-associated AKI with the slope of estimated glomerular function rate (eGFR) for up to 2-yrs after discharge using multivariable linear mixed effects models. Three groups were compared: 1) patients hospitalized with COVID-19-associated AKI; 2) patients hospitalized during the COVID pandemic who tested negative for SARS CoV-2 and had AKI due to other causes (Other-AKI); and 3) patients hospitalized with influenza-associated AKI in the 5yrs before the COVID pandemic (Flu-AKI). A key secondary outcome included 2-yr major adverse kidney events (MAKE-a composite of mortality, ≥25% eGFR decline from discharge or end-stage kidney disease diagnosis) assessed using multivariable time-to-event analyses.

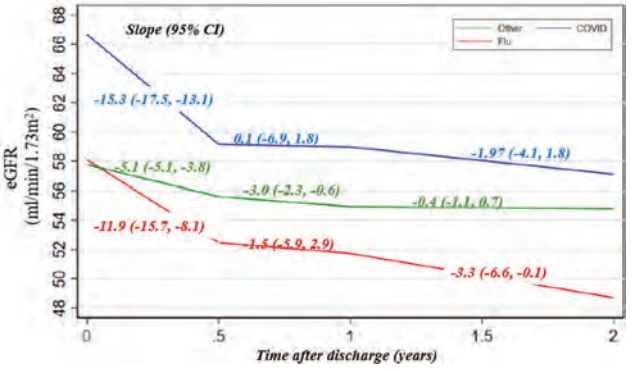
Results: The adjusted eGFR slope was -6.79ml/min/1.73m^2 per year (95%CI -7.93,-5.64) following COVID-AKI, -5.55 (95%CI -7.45,-3.65) following Flu-AKI, and -2.60 (95%CI -3.01,-2.20) following Other-AKI. COVID-AKI was associated with lower 2-yr MAKE (adjHR: 0.67, 95%CI: 0.59-0.75), with lower 2-yr mortality (adjHR: 0.31, 95%CI: 0.24–0.39, p<0.001) and lower 2-yr renal progression (adjHR 0.78, 95%CI: 0.69–0.88, p<0.001) compared to Other-AKI.

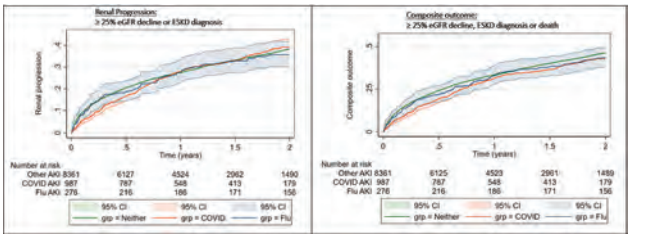
Conclusions: While survivors of COVID-AKI experience an initial faster eGFR decline compared to AKI due to other causes, they have higher eGFR on discharge and exhibit lower rates of longitudinal renal progression and mortality.

Funding: Other U.S. Government Support

Annualized rate of eGFR decline over 2yrs of follow up

Group Name	Unadjusted eGFR Slope (ml/min/1.73m^2 per year)	p-interaction	Adjusted eGFR Slope (ml/min/1.73m^2 per year)	p-interaction
COVID-AKI	-6.86 (-8.00, -5.73)	<0.001	-6.79 (-7.93, -5.64)	<0.001
Flu-AKI	-5.24 (-7.10, -3.37)	0.005	-5.55 (-7.45, -3.65)	0.003
Other-AKI	-2.50 (-2.90, -2.10)	.	-2.60 (-3.01, -2.20)	.





SA-OR25

Monovalent and Bivalent mRNA Vaccine Effectiveness Against Severe COVID-19 Associated with Omicron Variant in Maintenance Dialysis Patients

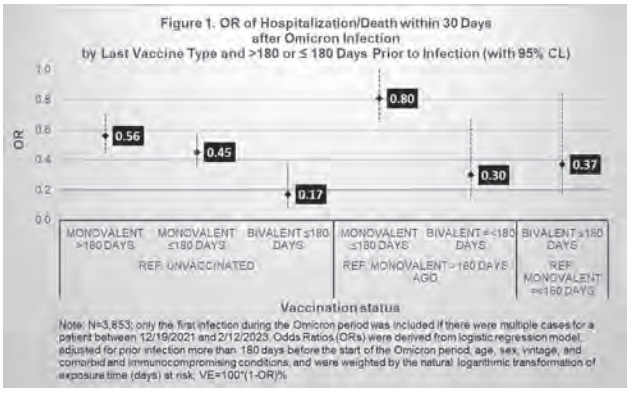
Nien Chen Li,[1] Harold Manley,[1] Antonia Harford,[1] Monica Shieu,[1] Caroline M. Hsu,[2] Dana Miskulin,[2] Daniel E. Weiner,[2] Doug Johnson,[1] Eduardo K. Lacson.[1] *[1]Dialysis Clinic Inc, Nashville, TN; [2]Tufts Medical Center, Boston, MA.*

Background: Recent data suggest that SARS-CoV-2 bivalent (BV) booster is more effective than monovalent (MV) booster against severe Omicron infection. We compared the effectiveness (VE) of BV and MV booster regimens in a national population of maintenance dialysis patients.

Methods: All adult patients receiving maintenance dialysis during the Omicron era (12/19/21-2/12/23) at Dialysis Clinic, Inc. (DCI) facilities who had COVID-19 during this time were included. Vaccination status was categorized as unvaccinated or received MV or BV booster <180 or ≥180 days prior to COVID. A logistic model was used to determine odds ratio (OR) of hospitalization/death within 30 days of infection by vaccination status. The model was adjusted for COVID prior to the Omicron period, age, sex, dialysis vintage, COPD, thyroid disease, PVD, diabetes, and immunocompromising conditions, and weighted by the natural log transformation of exposure time at risk.

Results: Among 3,853 eligible patients, mean age was 63 (±15) years; 55% were male and 31% Black. Figure 1 shows ORs of hospitalization or death within 30 days of infection by vaccination status. Relative to unvaccinated, the VE, defined as 100*(1-OR)%, was 44% (95% CI 30-56%) for MV booster doses received more than 180 days before Omicron infection; was 55% (42-65%) for MV received within 180 days; and was 83% (62-93%) for BV received within 180 days of infection. Relative to MV received more than 180 days before infection, the VE for MV and BV received within 180 days of infection were 20% (0.2-35%) and 70% (33-87%), respectively. The VE was 63% (16-84%) for BV relative to MV when both were received within 180 days of infection.

Conclusions: Bivalent SARS-CoV-2 vaccine is more effective than monovalent vaccine against severe Omicron infection in maintenance dialysis patients. Vaccine effectiveness declines after 180 days in this population suggesting a need for revaccination.



SA-OR26

Excess Mortality During the COVID-19 Pandemic in a Mid-Sized Dialysis Provider

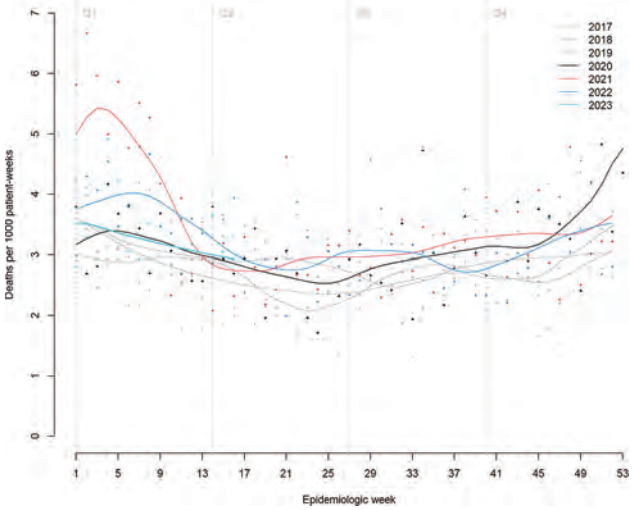
Eric D. Weinhandl,[1,2] Wael F. Hussein,[1,3] Gopa B. Green,[1] Graham E. Abra.[1,3]
[1]Satellite Healthcare, San Jose, CA; [2]University of Minnesota Twin Cities College of Pharmacy, Minneapolis, MN; [3]Stanford University School of Medicine, Stanford, CA.

Background: Before widespread availability of vaccination, the coronavirus disease 2019 (COVID-19) pandemic incited a sharp increase in the all-cause death rate among chronic dialysis patients. Whether excess mortality has persisted during 2022 and early 2023 remains uncertain.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. During each epidemiologic week from week 1 of 2017 to week 16 of 2023, we identified all chronic dialysis patients in centers in California, Hawaii, Tennessee, and Texas. For each patient-day, we collected age, sex, and duration of end stage kidney disease (ESKD). We fit a logistic regression of death with generalized estimation equations, adjusted for age, sex, duration of ESKD, state, and seasonality; and estimated excess mortality in 9 pandemic intervals, relative to the interval from week 1 of 2017 to week 11 of 2020, overall and by setting (in-center, home).

Results: During the pandemic era, there were 4175 deaths, or 16.5 deaths per 100 patient-years; in contrast, there were 14.5 deaths per 100 patient-years during the pre-pandemic era. As displayed, the rate of death was initially elevated between September 2020 and March 2021 (excess mortality factor, 1.34; 95% CI, 1.24-1.45), and remained elevated from July 2021 to October 2022, with excess mortality factors ranging from 1.11 to 1.18. From November 2021 to February 2023, excess mortality was more pronounced among home dialysis patients (range of excess mortality factors, 1.20-1.35 among home patients versus 1.07-1.14 among in-center patients). Since March 2023, the rate of death has been in line with the pre-pandemic norm (excess mortality factor, 0.96; 95% CI, 0.81-1.14).

Conclusions: Excess mortality during the pandemic has gradually decreased since Winter 2020-2021, although it dissipated more slowly among home dialysis patients. In Spring 2023, excess mortality is absent.



SA-OR27

Kidney Transplant Graft Loss During 2020

Kirsten L. Johansen,[1] David T. Gilbertson,[1] Jiannong Liu,[1] Kayla L. Horak,[1] Elaine Ku.[2] *[1]Hennepin Healthcare Research Institute Chronic Disease Research Group, Minneapolis, MN; [2]University of California San Francisco, San Francisco, CA.*

Background: We hypothesized that disruption of clinical care during the COVID-19 pandemic in 2020 led to an increase in kidney transplant graft loss compared with rates in 2018 and 2019.

Methods: We examined point prevalent cohorts of adult kidney transplant (KT) recipients with functioning allografts on January 1 of 2018, 2019, and 2020. We calculated rates of all-cause graft loss and death-censored graft loss during each quarter. We used Poisson regression to estimate incidence rate ratios (IRR) for each quarter, comparing rates in 2020 to those in 2018-2019, adjusting for age, sex, race/ethnicity, type of donor, and duration of transplant (<1 year, ≥1 year).

Results: There were 220,079, 228,549, and 238,578 individuals in the 2018, 2019, and 2020 cohorts. In 2020, mean age was 55.3 years, 62.4% were deceased donor KT recipients, and 9.8% were within one year of KT. 51.9% were White, 20.5% Black, 16.1% Hispanic, and 11.4% other. All-cause graft failure rates ranged from 5.6 to 6.8 per 100 person years and death-censored rates from 2.6 to 3.2 per 100 person years. Compared with earlier years, rates of all-cause graft loss were higher in quarters 2-4 of 2020 (**Table**). There was a statistically significant interaction between race/ethnicity and year (2018-2019 vs 2020) across quarters; during 2020, there was a greater increase in all-cause graft loss among Black and Hispanic than among White individuals. Contrary to our hypothesis, there was no statistically significant increase in death-censored graft loss in 2020 compared with 2018-2019 overall or for any race/ethnicity group. The increase in overall graft loss in 2020 and the stable or lower rates of death-censored graft loss were consistent among recipients with shorter (<1 year) versus longer graft vintage (p-values for interaction >0.3).

Conclusions: All-cause graft loss increased in 2020 compared with 2018-2019, but death-censored graft loss did not. COVID-19 related mortality likely dominated all-cause graft loss, but surviving patients did not experience higher rates of graft loss.

Funding: NIDDK Support

IRR for all-cause and death-censored graft loss in 2020 compared with 2018-2019

Quarter	All-cause graft failure, IRR (95% CI)	Death-censored graft failure, IRR (95% CI)
Quarter 1 (Jan-Mar)	0.94 (0.90, 0.98)	0.93 (0.88, 0.98)
Quarter 2 (Apr-Jun)	1.10 (1.05, 1.14)	0.87 (0.82, 0.93)
Quarter 3 (Jul-Sept)	1.14 (1.10, 1.19)	0.97 (0.92, 1.04)
Quarter 4 (Oct-Dec)	1.24 (1.19, 1.29)	0.90 (0.85, 0.96)

SA-OR28

Abrupt Estimated Glomerular Filtration Rate Decline After Initiating Sodium-Glucose Cotransporter-2 Inhibitors Predicts Clinical Outcomes: A Systematic Review

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Background: The initiation of sodium-glucose cotransporter-2 inhibitors (SGLT2i) typically leads to a reversible initial decline or "dip" in estimated glomerular filtration rate (eGFR). However, the implications of this phenomenon on clinical outcomes are not well-defined.

Methods: We searched MEDLINE, Embase, and Cochrane Library from inception to March 23, 2023 to identify randomized controlled trials and cohort studies comparing kidney and cardiovascular outcomes in patients with and without initial eGFR dip after initiating SGLT2i. Pooled estimates were calculated using random-effect meta-analysis.

Results: We included seven studies in our analysis, which revealed that an initial dip in eGFR following the initiation of SGLT2i was associated with less annual eGFR decline (mean difference: 0.64, 95% confidence interval [CI]: 0.437-0.843 mL/min/1.73m^2). The risk of major adverse kidney events was similar between non-dipping and dipping groups but reduced in patients with a 0-10% eGFR dip (hazard ratio [HR]: 0.915, 95% CI: 0.865-0.967). No significant differences were observed in the composite of hospitalized heart failure and cardiovascular death (HR: 0.824, 95% CI: 0.633-1.074), hospitalized heart failure (HR: 1.059, 95% CI: 0.574-1.952), or all-cause mortality (HR: 0.83, 95% CI: 0.589-1.170). However, trial sequential analysis indicated that the required sample size had not been reached to make conclusive claims about cardiovascular and mortality outcomes. The risk of serious adverse events (AEs), discontinuation of SGLT2i due to AEs, kidney-related AEs, acute kidney injury, and volume depletion were similar between the two groups. However, patients with >10% eGFR dip had a higher risk of hyperkalemia compared to the non-dipping group.

Conclusions: The findings of this study suggested that the initial dip in eGFR following the initiation of SGLT2i might be associated with less annual eGFR decline. Additionally, there were no significant differences in the risks of adverse kidney and cardiovascular outcomes between the dipping and non-dipping groups.

SA-OR29

Global Burden of CKD and Attributable Risk Factors in 38 Organization for Economic Cooperation and Development (OECD) Countries: Results from GBD 2019

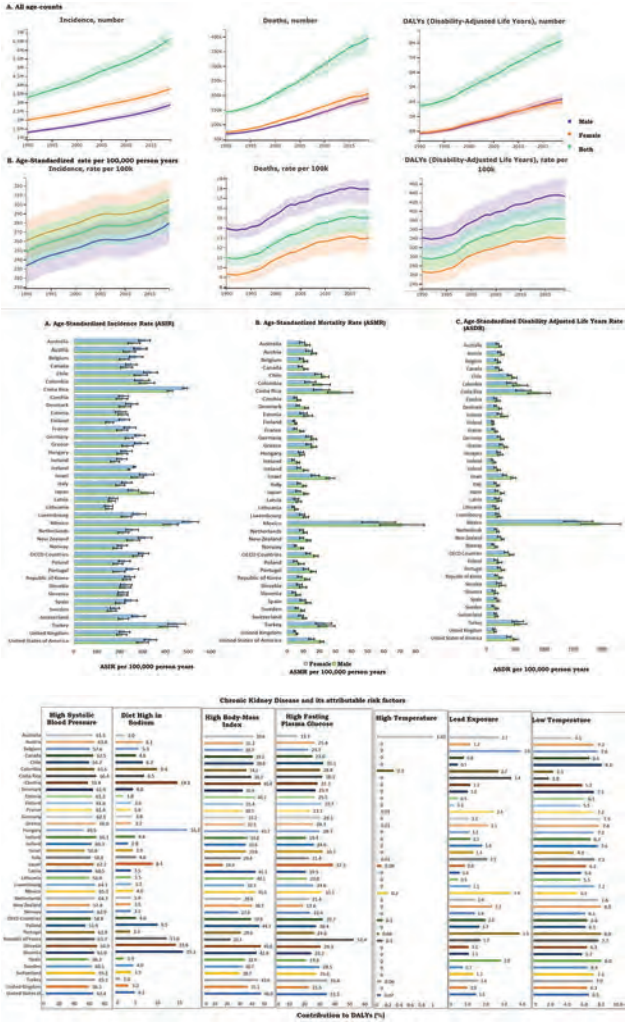
Hardik Desai,[1] Joseph Lieber,[2] Bijin Thajudeen,[3] Vishrant Amin,[4] Mohammed Dheyaa Marsool Marsool,[5] Juhi Patel,[4] Sumit Kyada,[4] Mohit Lakkimsetti,[6] Arushi Dhawan.[7] *[1]Gujarat Adani Institute of Medical Science, Bhuj, India; [2]Mount Sinai Health System, New York, NY; [3]Banner University Medical Center South, Tucson, AZ; [4]Gujarat Medical Education and Research Society Medical College & Hospital Valsad, Valsad, India; [5]University of Baghdad, Baghdad, Iraq; [6]Mamata Medical College, Khammam, India; [7]Punjab Institute of Medical Sciences, Jalandhar, India.*

Background: CKD was the 8th leading cause of death in Organization for Economic Cooperation and Development(OECD) nations in 2019, accounting for 3.5% of all fatalities.

Methods: This study utilized the Global Burden of Disease methodology to analyze CKD incidence, mortality, disability-adjusted life years(DALYs), and associated risk factors in OECD countries.

Results: In 2019, OECD countries accounted for 35.06% of total global incident cases, 27.7% of deaths, and 19.6% of DALYs attributed to CKD. Within the combined OECD countries, CKD incident cases increased by 103%, deaths by 179%, and DALYs by 120% from 1990-2019. Age-standardized incidence rates(ASIR) increased by 18%, ASDR by 29%, and ASMR by 37% between 1990-2019. In absolute counts, the United States(US) had the highest numbers with 1.7million incident cases (95%UI:1.5-1.8million),106,954 deaths(95,861–114,383), and 2.2million DALYs(2.1-2.4million) in 2019. Japan, Mexico, Germany, and Turkey followed suit. When comparing ASR, the US had a relatively lower ASIR(318) compared to countries such as Mexico(469) and Turkey(432) in 2019, but higher than Chile(316), Israel(299), and Japan(292).

Conclusions: CKD represents a significant burden in the 38 OECD countries. The high prevalence rates, association with cardiovascular disease, economic costs, health disparities, and impact on quality of life emphasize the need for comprehensive strategies to address CKD.



SA-OR30

The Risk of CKD in Lithium-Treated Individuals

Gisli Gislason,[1,2] Olafur S. Indridason,[2] Engilbert Sigurdsson,[1,2] Runolfur Palsson.[1,2] *[1]Heilbrigdisvisindasvid - Haskoli Island, Reykjavik, Iceland; [2]Landspitali, Reykjavik, Iceland.*

Background: The use of lithium may contribute to chronic kidney disease (CKD) but studies have yielded conflicting results. The aim of this study was to examine the risk of developing CKD stage 3 and above among persons treated with lithium.

Methods: This was a retrospective cohort study of all persons in Iceland using lithium in the years 2008-2018. Patients with affective disorders (ICD-10 codes F30-F39) attending the outpatient clinics of the Landspitali–The National University Hospital Mental Health Services in 2014-2016 who had not been prescribed lithium served as controls. CKD stages 3-5 was defined as eGFR <60 ml/min/1.73 m^2, eGFR was calculated using the serum creatinine (SCr) based CKD-EPI equation. Individuals with fewer than 2 SCr measurements during the study period and those with CKD stages 3-5 prior to 2008 were excluded. Cox regression was performed to assess the risk of CKD associated with lithium treatment in a time dependent manner, adjusting for important confounding factors where acute kidney injury (AKI), hypertension, diabetes mellitus (DM) and cardiovascular diseases were treated as time-dependent covariates.

Results: A total of 2760 persons received lithium treatment during the study period, of whom 2046 (74.1%) were included in the study. Of those, 221 (10.9%) developed CKD stages 3-5. Of the 1615 persons in the control group, 1220 (75.6%) were included, of whom 39 (3.2%) developed CKD 3-5. Lithium use was associated with incident CKD (hazard ratio [HR] 1.93, 95% confidence interval [CI] 1.37–2.74) in the adjusted model. Age per year (HR 1.03, 95% CI 1.02–1.04), initial eGFR per mL/min/1.73 m^2 (HR 0.92-0.96, 95% CI 0.92–0.99), DM (HR 1.73, 95% CI 1.15–2.48) and AKI (HR 1.89, 95% CI 1.32–2.74) were other significant CKD risk factors. When compared to individuals not exposed to lithium the HR for CKD in adjusted analysis was 1.24 (95% CI 0.81–1.89) for those with mean lithium concentration of 0.3-0.59 mmol/L, 2.88 (95% CI 1.97–4.20) for those with mean lithium concentration of 0.6-0.79 mmol/L, and 5.23 (95% CI 3.31-8.26) for those with mean lithium concentration of 0.8-0.99 mmol/L.

Conclusions: Long-term lithium use is associated with risk of CKD in a concentration-dependent manner among patients with bipolar and unipolar mood disorders. Therefore, the mean blood concentration of lithium should be kept as low as possible for adequate mood stabilization and treatment.

Funding: Government Support - Non-U.S.

SA-OR31

CKD Among Childbearing Age Women in the United States: NHANES 1999-2018

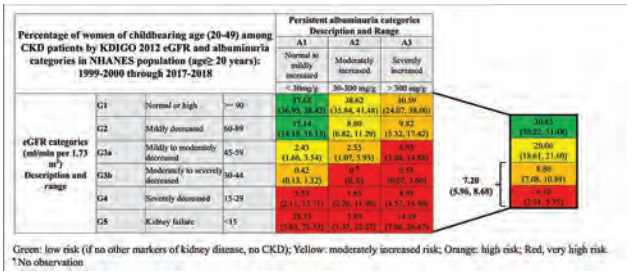
Zihe Zheng,[1] Ajay K. Singh,[1,2] Youssef M. Farag.[3,2] *[1]Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: Previous studies reported 3% and up to 6% prevalence of CKD among pregnant women and women of childbearing age in high income countries, respectively. However, the prevalence and severity of CKD among women of childbearing age (20-49) in the US has not been well characterized. We aimed to examine this epidemiology evidence gap in a representative sample of the US adult population.

Methods: We analyzed data from the National Health and Nutrition Examination Survey (NHANES), 1999-2018. The definition of childbearing age for women was derived from the CDC vital and health statistics report. We used KDIGO guidelines to define CKD and the prognosis risk categories. We examined common kidney risk factors in the age group between 20 to 49, including eGFR, albuminuria, blood pressure, HbA1c, glucose, hemoglobin, BMI, and lipids. We used Poisson regression to estimate the CKD prevalence ratio comparing women to men in this age group.

Results: The weighted period prevalence of CKD among childbearing age women in the US was 7.51%, while the prevalence of CKD among men in the same age group was 5.08%. Non-Hispanic black and Hispanic women of childbearing age had higher prevalence of CKD (9-10%). Fig 1 shows that more than 1 in 5 CKD patients with moderately increased KDIGO risk and more than 1 in 14 CKD patients with high/very high KDIGO risk were women of childbearing age. The percentage of Hispanics was higher among childbearing age females (20.2%) compared to females≥ age 50 (8.4%) in CKD patients. After adjusting for race/ethnicity and age, female gender was independently associated with 47% increased prevalence for CKD in the childbearing age group (PR=1.47, 95% CI 1.32, 1.63), yet female CKD patients showed largely more favorable profiles of common kidney risk factors compared to their male counterparts.

Conclusions: Our study highlighted that women of childbearing age had disproportionally higher prevalence of CKD in the US, especially among Hispanic women, than previously reported. Our findings quantify disparities and highlight the need and gaps in kidney/reproductive health among one of the most vulnerable populations in CKD patients.



Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk.
*No observation

SA-OR32

Mortality and Transplant After Delivering on Hemodialysis: A Matched Cohort Study

Andrea L. Oliverio, Mia Wang, Jennifer L. Bragg-Gresham, Rajiv Saran, Michael Heung. *University of Michigan Medical School, Ann Arbor, MI.*

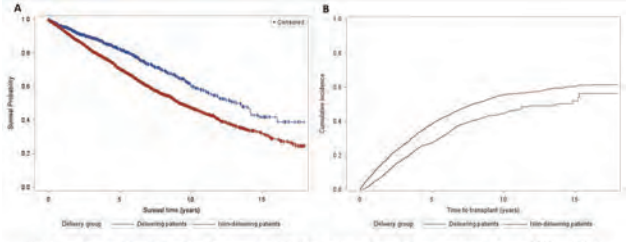
Background: Rates of successful pregnancies among women with ESKD on hemodialysis (HD) are increasing, however risk of preeclampsia and cesarean delivery remain high. Subsequent mortality and transplantation after delivery on HD are unknown.

Methods: Using USRDS data, women treated with HD who delivered an infant between 2002 and 2019 were identified from ICD-9/10-CM codes and matched up to 1:4 by age, vintage, race and ethnicity, and diabetes as primary cause of ESKD to contemporary women on HD who did not deliver. We assessed mortality and transplantation rates over time. A Cox proportional hazards model was fit to compare mortality and transplantation rates between delivering and non-delivering women. Logistic regression was used to evaluate 1 and 5 year transplant rates for delivering vs. non-delivering female patients. All models were adjusted for age, vintage, BMI, race, Hispanic ethnicity, incident comorbidities, area deprivation index, rural-urbanicity, nephrology care pre-ESKD, Medicare insurance, and prior transplant history; patient waitlist status and PRA values were also adjusted in the transplant models.

Results: 1,109 delivering women were matched to 4,404 non-delivering women. Unadjusted mortality and transplantation rates for delivering vs non-delivering women were 4.5 vs 7.2 and 6.0 vs. 8.6 per 100 patient-years, respectively (**Figure**). In adjusted models, the HR (95% CI) for mortality and transplant are 0.69 (0.64, 0.74; p<.0001) and 0.76 (0.71, 0.81; p<0.0001), respectively, in delivering compared to non-delivering women. 1 and 5 year transplantation rates were lower in delivering women compared to non-delivering women.

Conclusions: While pregnancy on hemodialysis is associated with significant risk of preeclampsia and preterm delivery, delivery on hemodialysis was associated with a lower risk of subsequent mortality. Residual confounding may explain superior survival of delivering women vs. non-delivering women, however persistently lower transplant rates in delivering women warrant further research.

Funding: NIDDK Support



Unadjusted survival time (A) and time to transplant (B) of delivering and non-delivering women between 2002 and 2019.

SA-OR33

Performance of Creatinine-Based GFR Estimating Equations in Young Adults

Lesley A. Inker. CKD-EPI and CKiD. *Tufts Medical Center, Boston, MA.*

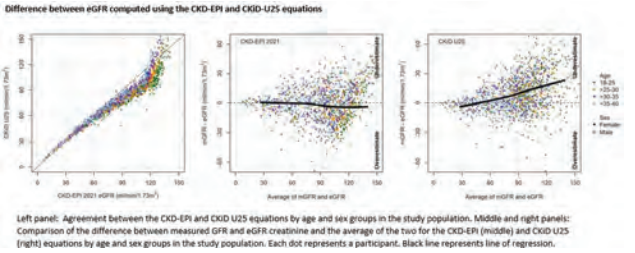
Background: In the United States, GFR is estimated using serum creatinine and the 2021 CKD-EPI equation for individuals ≥ 18 years or the 2021 CKiD-U25 equation for those 1-25 years with CKD. These equations may result in different eGFR values at 18 years and older, leading to uncertainty in level of GFR.

Methods: We compared the CKD-EPI, CKiD-U25, and European Kidney Function Consortium (EKFC) equations in young adults (aged 18 to 40 years) in an independent dataset from which all three equations were developed (1491 participants from 21 studies). Performance compared to measured GFR was assessed as bias (median difference between mGFR and eGFR) and percentage of eGFR within 30% of mGFR (P_{30}).

Results: Mean (SD) age was 31.7 (6.0) years and mGFR was 92.7 (32.7) mL/min/1.73m². The equations provided similar estimates for participants with eGFR less than 60 mL/min/1.73 m². At eGFR ≥ 60, CKD-EPI yielded higher eGFR (Figure). For the CKD-EPI equation, there was minimal bias between mGFR and eGFR overall ([-0.5 (95%CI -1.5 to 0.7) mL/min/1.73m²], with small variation by GFR. In contrast, the CKiD-U25 equation moderately underestimated mGFR overall [7.2 (6.1, 8.3) mL/min/1.73m²], with larger bias at higher levels of eGFR. There was greater variation by age groups with CKiD-U25 than CKD-EPI, with larger bias at younger adult ages for CKiD (e.g. age 18-25 year, 12.0 (7.7, 15.5) for CKiD vs -3.3 (-5.0, 0.0) for CKD-EPI) vs older age (e.g. age 35-40, 4.8 (2.8, 6.7) for CKiD vs 1.0 (-0.3, 2.2) for CKD-EPI. Results for EKFC were similar to that of CKiD, with underestimation at higher levels of GFR and in the younger age group.

Conclusions: The results support use of the 2021 CKD-EPI equation for reporting of eGFR by clinical laboratories in individuals older than 18 years of age. For young adults with childhood CKD, our results support continuing use of the CKiD-U25 equation, during the transition to adult services, to maintain consistency of eGFR. Additional research in young adults to resolve differences observed at high levels of GFR and refine recommendations for use of eGFR equations is needed.

Funding: NIDDK Support



Left panel: Agreement between the CKD-EPI and CKiD U25 equations by age and sex groups in the study population. Middle and right panels: Comparison of the difference between measured GFR and eGFR creatinine and the average of the two for the CKD-EPI (middle) and CKiD U25 (right) equations by age and sex groups in the study population. Each dot represents a participant. Black line represents line of regression.

SA-OR34

Discrepancy Between eGFR Cystatin C and eGFR Creatinine in Recently Hospitalized Adults

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Background: Having a lower estimated glomerular filtration rate using cystatin C (eGFRcys) than creatinine (eGFRcr) is associated with a higher risk of cardiac disease and death in the outpatient setting. However, the distribution of this discrepancy and its prognostic values in recently hospitalized adults are not well described.

Methods: In 1534 hospitalized adults enrolled in the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) cohort, we characterized the difference between eGFRcys and eGFRcr at 3 months after discharge. We used survival analysis to determine the associations between differences in eGFRcys and eGFRcr and risk of end-stage kidney disease (ESKD), major adverse cardiac events (MACE), first heart failure hospitalization, and death after a median follow up of 4.7 years.

Results: The mean age of study participants was 64.5 years, 37.3% are female, and 50% had AKI during hospitalization. At 3 months after hospitalization, eGFRcys was lower than eGFRcr by a large margin (Table). The difference between eGFRcys and eGFRcr at 3 months was 4.4% (2.4%- 6.5%) and 7.1% (3.8%- 10.5%) larger in those with AKI and sepsis during hospitalization, respectively. Having a lower in eGFRcys than eGFRcr was further associated with a higher risk of MACE, heart failure, ESKD, and death (Table), and these associations are consistent in participants with and without AKI (p for interaction with AKI all > 0.1).

Conclusions: By systematically measuring eGFRcys and eGFRcr in a cohort of recently hospitalized adults, we found that having lower eGFRcys than eGFRcr is commonly observed and provides additional prognostication for adverse clinical events.

Funding: NIDDK Support

eGFR estimates and their differences at 3 months after hospitalization#		Overall cohort (N= 1534)			
eGFRcr		71.5 (51.9, 92.6)			
eGFRcys		50.5 (34.1, 71.9)			
eGFRcys-eGFRcr absolute difference		-16.3 (-26.1, -6.3)			
eGFRcys-eGFRcr percentage difference, %		-29% (-44%, -15%)			
eGFRcys-eGFRcr ratio ≤0.7 (i.e. eGFRcys at least 30% lower than eGFRcr), N(%)		639 (41.7%)			
Adjusted Hazard Ratio (95% CI)*		Adverse Clinical Outcomes			
		Death (320/1534)	MACE (154/1534)	Heart Failure (216/1534)	ESKD (58/1534)
Per 10% lower in eGFRcys relative to eGFRcr		1.3 (1.22, 1.4)	1.11 (1.01, 1.21)	1.12 (1.03, 1.21)	1.18 (0.99, 1.41)
eGFRcys-eGFRcr ratio	≤0.7 (n=639)	2.05 (1.61, 2.62)	1.29 (0.92, 1.81)	1.41 (1.05, 1.89)	1.92 (1, 3.69)
	>0.7 (n=895)	Reference	Reference	Reference	Reference

#Descriptive data are presented as median (IQR), eGFR estimates and absolute difference are presented in ml/min/1.73m².

*Models are adjusted for age, sex, Black race, heart failure, atherosclerotic cardiovascular disease, hypertension, and diabetes at baseline (prehospitalization), sepsis, intensive care unit status, and AKI severity during hospitalization, eGFRcr, body mass index, and smoking status at 3 months after hospitalization.

SA-OR35

Comprehensive Evaluation of CKD Heat Map

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Background: The 2012 KDIGO heat map framework for CKD analyzed five outcomes in 1.2 million participants. We comprehensively evaluated this framework using new equations for eGFR using creatinine alone and in combination with cystatin C (eGFRcr and eGFRcr-cys; CKD-EPI 2021 and EKFC) and more categories of albuminuria, assessing their individual and combined associations with ten adverse outcomes, overall and by age, sex, diabetes, and cardiovascular disease.

Methods: Individual-level data analysis: 27,503,140 participants from 114 global cohorts (eGFRcr); 720,736 participants from 20 cohorts (eGFRcr-cys). Outcomes: kidney failure with replacement therapy, all-cause mortality, cardiovascular mortality, acute kidney injury, hospitalization, coronary heart disease, stroke, heart failure, atrial fibrillation, and peripheral artery disease.

Results: Mean participant eGFRcr was 90 ml/min/1.73 m² (SD, 22) and median ACR was 11 mg/g (interquartile range 8-16 mg/g). Lower eGFRcr and higher ACR were associated with higher risk of all ten adverse outcomes, including in the mildest categories of CKD (eGFR 45-59 ml/min/1.73 m² and ACR <30 mg/g, or ACR 30-299 mg/g) and within subgroups. Associations were generally stronger and with less U-shape in the higher range of eGFR for eGFRcr-cys compared with eGFRcr.

Conclusions: This comprehensive evaluation of the heatmap framework in >27 million people demonstrated that the framework holds for associations with previous endpoints as well as novel kidney and cardiovascular endpoints; across subgroups of age, sex, diabetes, and cardiovascular disease; and for different GFR equations, including those incorporating cystatin C.

Funding: NIDDK Support, Private Foundation Support

Hazard ratios of eGFRcr and albuminuria categories with adverse outcomes

Overall	ACR, mg/g					ACR, mg/g				
eGFRcr	<10	10-29	30-299	300-999	1000+	<10	10-29	30-299	300-999	1000+
	All-cause Mortality: 82 cohorts Study size=26,444,384; events=2,604,028					Myocardial Infarction: 64 cohorts Study size=22,838,356; events=451,063				
105+	1.6	2.2	2.9	4.3	5.8	1.1	1.4	2.0	2.7	3.8
90-104	ref	1.3	1.8	2.6	3.1	ref	1.3	1.6	2.2	3.2
60-89	1.0	1.3	1.7	2.2	2.8	1.1	1.3	1.6	2.2	3.1
45-59	1.3	1.6	2.0	2.4	3.1	1.4	1.7	2.0	2.8	3.7
30-44	1.8	2.0	2.5	3.2	3.9	1.9	2.0	2.4	3.2	4.3
15-29	2.8	2.8	3.3	4.1	5.6	2.7	3.1	3.1	4.2	5.1
<15	4.6	5.0	5.3	6.0	7.0	4.6	5.6	4.8	6.0	6.0
	Cardiovascular Mortality: 76 cohorts Study size=26,022,346; events=776,441					Stroke: 68 cohorts Study size=24,746,436; events=461,785				
105+	1.4	2.0	3.0	4.1	5.4	1.2	1.6	2.2	3.1	4.3
90-104	ref	1.3	1.9	2.7	3.6	ref	1.3	1.6	2.4	3.1
60-89	1.0	1.4	1.7	2.4	3.2	1.1	1.3	1.7	2.2	3.0
45-59	1.4	1.7	2.2	2.8	3.8	1.4	1.6	1.9	2.3	2.9
30-44	2.0	2.3	2.8	3.7	4.6	1.6	1.7	2.0	2.4	3.0
15-29	3.2	3.1	3.5	5.0	6.5	1.8	2.1	2.1	2.7	3.0
<15	6.1	6.4	6.4	7.3	8.2	3.2	2.8	2.9	3.2	3.8
	Kidney Failure with Replacement Therapy: 57 cohorts; Study size=25,466,956; events=158,846					Heart Failure: 61 cohorts Study size=24,603,016; events=1,132,443				
105+	0.54	1.2	2.9	7.7	25	1.2	1.7	2.7	4.2	6.9
90-104	ref	1.8	4.3	12	43	ref	1.3	2.0	2.8	4.2
60-89	2.3	4.9	10	27	85	1.1	1.4	1.9	2.7	4.2
45-59	13	19	37	89	236	1.6	1.8	2.4	3.4	5.0
30-44	50	58	115	240	463	2.2	2.5	3.1	4.2	6.5
15-29	283	301	443	796	1253	3.6	3.5	4.1	5.8	8.1
<15	770	1040	1618	2297	2547	5.1	5.7	5.8	7.9	9.9
	Acute Kidney Injury: 49 cohorts Study size=23,914,614; events=1,408,929					Atrial Fibrillation: 50 cohorts Study size=22,886,642; events=1,068,701				
105+	1.0	1.6	2.4	3.7	5.5	1.1	1.3	1.7	2.4	3.5
90-104	ref	1.4	2.1	3.2	5.0	ref	1.2	1.5	1.9	2.3
60-89	1.6	2.2	3.1	4.3	6.7	0.99	1.2	1.4	1.7	2.2
45-59	3.5	4.0	5.1	6.9	9.0	1.2	1.3	1.5	1.8	2.4
30-44	5.6	5.9	6.8	8.6	11	1.4	1.5	1.7	2.0	2.4
15-29	8.3	8.0	8.5	9.9	10	1.9	1.8	2.0	2.6	3.0
<15	8.5	11	7.9	5.5	5.7	2.6	2.5	3.1	3.6	4.2
	Hospitalization: 49 cohorts Study size=25,426,722; events=8,398,637					Peripheral Artery Disease: 54 cohorts Study size=24,830,794; events=378,924				
105+	1.4	1.7	2.1	2.1	2.3	0.89	1.4	1.9	2.8	5.0
90-104	ref	1.1	1.3	1.5	1.7	ref	1.3	1.9	2.8	4.3
60-89	1.0	1.1	1.3	1.5	1.8	0.99	1.3	1.8	2.5	3.8
45-59	1.3	1.3	1.5	1.7	2.1	1.5	1.7	2.1	2.9	4.2
30-44	1.5	1.5	1.6	1.9	2.3	2.0	1.9	2.5	3.6	5.0
15-29	1.8	1.8	1.9	2.4	2.8	3.3	3.3	3.8	5.7	8.1
<15	2.7	2.8	3.0	3.2	3.6	9.1	9.0	9.6	13	14

SA-OR36

Hospital Health Care Costs Following Incident CKD in Japan, Sweden, and the United States

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Background: Chronic kidney disease (CKD) affects an estimated 10% of the global population. It is associated with cardiorenal complications (e.g. end stage kidney disease and heart failure [HF]), premature mortality, and high healthcare burden and costs. Here we assess hospital healthcare costs following incident CKD.

Methods: This study uses secondary data from electronic health records or claims data sources from Japan, Sweden and the US. Adult patients with incident CKD (defined as having either: two estimated glomerular filtration rate [eGFR] measurements ≥ 90 days apart of ≤ 60 mL/min/1.73 m² or an eGFR measurement ≤ 60 mL/min/1.73 m² followed by a CKD diagnosis) were identified during 2016–2023. Cumulative costs per patient for hospitalizations associated with a main diagnosis of HF, CKD, myocardial infarction (MI), stroke or peripheral artery disease (PAD) were summarized for up to 5 years after index (date of second eGFR measurement or CKD diagnosis).

Results: Overall, 549 884 patients were included (Japan, 74 285; Sweden, 76 133; US, 399 466). In Japan, Sweden and the US, respectively: median ages were 81, 78 and 74 years; 54%, 48% and 37% were males; and across countries the majority (68%) of patients did not have type 2 diabetes. Median eGFR measurements were similar across countries. Hospital healthcare costs associated with cardiorenal events (CKD and HF) were high (Figure). Atherosclerotic cardiovascular disease (MI, stroke and PAD) contributed less to hospital healthcare costs.

Conclusions: Hospital healthcare costs were high and largely driven by cardiorenal events (CKD and HF) among patients with incident CKD. This was consistent across all three countries, despite differences in healthcare systems.

Funding: Commercial Support - AstraZeneca

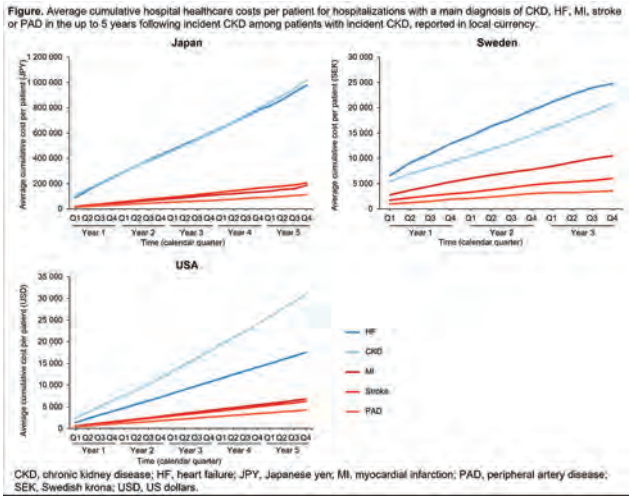

Figure. Average cumulative hospital healthcare costs per patient for hospitalizations with a main diagnosis of CKD, HF, MI, stroke or PAD in the up to 5 years following incident CKD among patients with incident CKD, reported in local currency.

CKD, chronic kidney disease; HF, heart failure; JPY, Japanese yen; MI, myocardial infarction; PAD, peripheral artery disease; SEK, Swedish krona; USD, US dollars.

SA-OR37

External Validation of the Klinrisk Model in US Commercial, Medicare Advantage, and Medicaid Populations

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Background: Chronic kidney disease (CKD) is typically undiagnosed till the majority of kidney function (eGFR) is lost. Accurate risk prediction tools for progressive CKD can enable early intervention for high risk individuals. The Klinrisk machine learning model accurately predicts progressive CKD using routinely collected laboratory data. We aimed to validate this model in US commercial, Medicare Advantage, and Medicaid populations.

Methods: The Klinrisk random survival forest model predicts progressive CKD (40% decline in eGFR or kidney failure) using the values of age, sex, and 20 laboratory variables, including results from complete blood cell counts, chemistry panels, comprehensive metabolic panels, and urinalysis. We assessed model performance at 2- and 5- years post-index (first available serum creatinine result) in patients with/without urinalysis results (albumin-to-creatinine ratio, protein-to-creatinine-ratio, and semi-quantitative dipstick) in a large representative US population. Performance was assessed with discrimination (area under the receiver operating characteristic curve), Brier scores, and calibration plots.

Results: A total of 4,410,131 patients were evaluated with commercial insurance, 341,666 with Medicare Advantage, and 93,056 patients with Medicaid coverage. Discrimination was excellent across all forms of payor and with or without the results of urinalysis. In all cohorts, for prediction of the progression, AUCs ranged between 0.80 to 0.83 at 2 years, and 0.78-0.83 at 5 years. When urinalysis data were available, AUCs ranged between 0.81 to 0.87 at 2 years, and 0.80 to 0.87 at 5 years (Table). Brier scores were below 0.071 (0.068 to 0.075) for each combination of urinalysis availability and insurer type.

Conclusions: A machine model trained on routine laboratory data can predict progression of CKD in a large representative US population of adults with or at risk for kidney disease. Implementation of the Klinrisk model can help identify patients who benefit from early intervention to delay CKD progression and reduce health care costs.

Funding: Commercial Support - Boehringer Ingelheim

AUC at 2- and 5- years (95% confidence interval)

Insurer	All patients Commercial, n = 4,410,131 Medicare, n = 341,666 Medicaid, n = 93,056	UACR directly measured Commercial, n = 178,266 Medicare, n = 25,954 Medicaid, n= 9,353	Urine ACR or urine PCR Commercial, n = 193,992 Medicare, n = 28,120 Medicaid, n = 10,108	Urine ACR, urine PCR, or semi-quantitative dipstick result Commercial, n = 1,061,762 Medicare, n = 92,410 Medicaid, n = 38,867
Commercial (2 years) Commercial (5 years)	0.83 (0.82 - 0.83) 0.81 (0.81 - 0.81)	0.86 (0.85 - 0.87) 0.84 (0.83 - 0.85)	0.86 (0.85 - 0.87) 0.85 (0.84 - 0.85)	0.87 (0.86 - 0.97) 0.85 (0.84 - 0.85)
Medicare (2 years) Medicare (5 years)	0.80 (0.79 - 0.80) 0.78 (0.78 - 0.79)	0.79 (0.77 - 0.80) 0.78 (0.77 - 0.79)	0.79 (0.78 - 0.81) 0.78 (0.77 - 0.80)	0.81 (0.80 - 0.82) 0.80 (0.79 - 0.80)
Medicaid (2 years) Medicaid (5 years)	0.83 (0.83 - 0.83) 0.83 (0.83 - 0.83)	0.84 (0.81 - 0.87) 0.87 (0.84 - 0.90)	0.84 (0.81 - 0.87) 0.86 (0.83 - 0.90)	0.84 (0.83 - 0.86) 0.87 (0.85 - 0.89)

SA-OR38

The Effect of Thiazide Diuretics on Urinary Prostaglandin E2 Excretion and Serum Sodium in the General Population

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Background: Recent data suggest that thiazide-induced hyponatremia (TIH) is induced by prostaglandin E2 (PGE2)-mediated water reabsorption and that people with a single nucleotide polymorphism (SNP) in SLCO2A1 are more susceptible for TIH. Here, we hypothesize that higher urinary PGE2 excretion is also associated with lower serum sodium in the general population and that this association is stronger in thiazide users.

Methods: PGE2 and its metabolite PGEM were measured in spot urines from the population-based Rotterdam Study cohort and expressed as ratio with creatinine. The association between PGE2 and serum sodium and its interaction with thiazide use was analyzed using regression analysis with adjustments for potential confounders (sex, age, BMI, baseline eGFR, smoking status, systolic blood pressure, ACE-inhibitor use). A propensity score-matched cohort was generated by matching on the same confounders in addition to serum potassium and diabetes status. The contribution of SNPs was analyzed using genome wide association studies (GWAS).

Results: 2178 patients were included in the analysis (65% female, age 64 ± 8 years). Thiazide users (n=190) had a significantly lower serum sodium compared to non-thiazide users (140.9 vs. 141.3 mmol/l, p=0.007) but had similar urinary PGE2 (101.7 vs. 101.5 pg/mmol, p=0.7) and PGEM (55.6 vs. 56.3 pg/mmol, p=0.6) excretions. Urinary PGE2 and PGEM excretions were negatively associated with serum sodium in the multivariable analysis (PGE2: p=0.002, PGEM: p<0.001) and this association was stronger in thiazide users (Figure 1). Similar findings were observed in the propensity score matched cohort. The GWAS data is currently being analyzed.

Conclusions: Urinary PGE2 and PGEM excretions are higher in people with lower serum sodium, and this association is stronger in thiazide users. Our findings provide further evidence for the role of PGE2 in renal water handling, even within the normal range of serum sodium, and its potential contribution to hyponatremia and TIH.

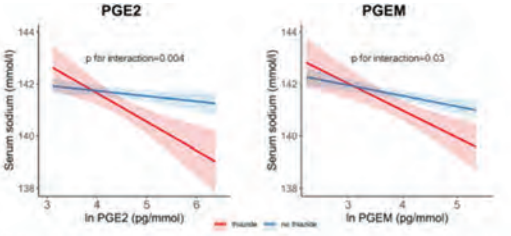

Figure 1. Multivariable analyses for the associations between urinary PGE2 / PGEM excretion and serum sodium. The association is stronger in thiazide users.

SA-OR39

The Plasma Metabolome and Risk of Incident Kidney Stones

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Background: The pathogenesis of kidney stone disease is not completely understood. Information on metabolomic profiles in kidney stone formers is limited, with most studies focusing on urine metabolomics or on pediatric populations using cross-sectional designs. To examine independent associations between plasma metabolomic profiles and the risk of incident, symptomatic kidney stones in adults, we conducted prospective nested case-control studies in two large cohorts.

Methods: We performed plasma metabolomics on 1,758 participants, including 879 stone formers (346 from the Health Professionals Follow-up [HPFS] cohort, 533 from the Nurses' Health Study [NHS] II cohort) and 879 non-stone formers (346 from HPFS, 533 from NHS II) matched for age, race, time of blood collection, fasting status and (for NHS II) menopausal status and luteal day of menstrual cycle for premenopausal participants. Conditional logistic regression models were used to estimate the odds ratio of kidney stones corresponding to a one standard deviation increase in metabolite levels, adjusted for confounders. A plasma metabolite based score reflecting risk of incident kidney stones was developed in each cohort in a conditional logistic regression model with a lasso penalty. The scores derived in the HPFS ('KMS_HPFS') and the NHS II ('KMS_NHS') were each tested for its association with kidney stone risk in the other cohort.

Results: In each cohort, a variety of individual metabolites were associated with incident kidney stone formation at prespecified levels of metabolome-wide statistical significance. We identified three novel metabolites associated with kidney stones in both HPFS and NHS II, all with inverse associations with kidney stones risk: beta-cryptoxanthin, sphingomyelin (d18:2/24:1, d18:1/24:2), and sphingomyelin (d18:2/24:2). The standardized KMS_HPFS yielded an OR for stones in the NHS II cohort of 1.23 (95% CI 1.05, 1.44; p-value = 0.008). The standardized KMS_NHS was in the expected direction but did not reach statistical significance in HPFS (OR 1.16, 95% CI 0.97, 1.39; p-value = 0.10).

Conclusions: The findings of specific metabolites associated with kidney stone status in two cohorts as well as a plasma metabolomic signature in stone formers offers a novel approach to characterize stone formers and to elucidate the pathogenesis of stone formation with the future potential to personalize therapeutic approaches.

Funding: NIDDK Support

SA-OR40

Dietary Potassium and Potassium Supplementation Differentially Affect Plasma Potassium in Patients with CKD

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Background: Guidelines advise increased potassium (K^+) intake to prevent hypertension and cardiovascular disease, but whether patients with chronic kidney disease (CKD) can safely increase K^+ intake is unknown.

Methods: We performed a systematic review and meta-analyses of intervention studies that assessed the acute or short- to long-term effects of increased K^+ intake on plasma K^+ in patients with CKD. Studies were eligible if they studied the effects of specified amounts of dietary K^+, K^+ supplementation, or K^+-enriched salt substitution in patients with CKD and provided plasma K^+ at baseline and end of study (for pre-post intervention studies) or at end of study in control and intervention groups (for randomized trials).

Results: Fourteen eligible studies were identified (2 randomized, 12 pre-post intervention studies). K^+ supplementation for five days to two years increased plasma K^+ by on average 0.7 (95% confidence interval, 0.2-1.1) mmol/L and caused hyperkalemia in 4-33% (3 studies, 370 participants). In contrast, increased dietary K^+ intake for two weeks to three years did not significantly increase plasma K^+ (7 studies, 275 participants). One study reported two hyperkalemia occurrences on the high K^+ diet, another study reported lower hyperkalemia incidence on the high K^+ than on the low K^+ diet, and five studies reported that no hyperkalemia occurred. These results suggest that increased dietary K^+ intake may be safer than K^+ supplementation (**Table**). However, they do not rule-out the risk of postprandial hyperkalemia, i.e. hyperkalemia occurring after a K^+-rich meal. Unfortunately, no studies assessed the acute effects of a K^+-rich meal on plasma K^+ in CKD. Acute K^+ supplementation increased plasma K^+ by 1.2 (95% confidence interval, 0.9-1.6) mmol/L (4 studies, 35 participants). We found no studies that assessed the safety of K^+-enriched salt substitution in CKD.

Conclusions: In the short- to long-term, K^+ supplementation increases plasma K^+ and the risk of hyperkalemia, although the majority maintains normokalemia. Conversely, increased dietary K^+ intake does not increase plasma K^+ in the short- to long-term. Whether a K^+-rich meal causes postprandial hyperkalemia is unknown.

	K^+ supplementation	Dietary K^+	K^+-enriched salt
Short- to long-term effects on plasma K^+	+ 0.7 mmol/L	No change	?
Acute effects on plasma K^+	+ 1.2 mmol/L	?	?

SA-OR41

HARMONIZE ASIA: A Phase 3 Study to Investigate the Safety and Efficacy of Sodium Zirconium Cyclosilicate in Patients with Hyperkalemia in China

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Background: Sodium zirconium cyclosilicate (SZC) is an oral potassium (K^+)-lowering therapy for adults with hyperkalemia (HK). HARMONIZE Asia (NCT03528681) evaluated SZC safety and efficacy in patients (pts) with HK in China.

Methods: This Phase 3, randomized, double-blind, placebo (PBO)-controlled study recruited pts with serum K^+ (sK^+) ≥5.1 mmol/L at 35 sites in China. Pts received SZC 10 g three times daily for 24 or 48 hours in an open-label phase (OLP). Those achieving normokalemia (sK^+ 3.5–5.0 mmol/L) entered a 28-day randomized treatment phase (RTP), randomized 2:2:1 to receive SZC 5 g, SZC 10 g, or PBO once daily. The primary endpoint measured mean sK^+ level during RTP days 8–29. Secondary endpoints included mean change in sK^+ level during the OLP, proportion of pts achieving/maintaining normokalemia during the RTP, and time to recurrence of HK.

Results: In total, 270 pts received SZC during the OLP and 256 (94.8%) completed the OLP. The mean eGFR was 17.9 mL/min/1.73m^2. During the OLP, mean sK^+ decreased by 1.11 mmol/L from baseline (5.85 mmol/L; P<0.001) and 87.4% of pts achieved normokalemia. During the RTP, SZC 5 g and 10 g (both P<0.001) reduced mean sK^+ vs. PBO in a dose-dependent manner; least-squares means (95% confidence interval [CI]) sK^+ were 4.86 mmol/L (4.71, 5.01), 4.44 mmol/L (4.30, 4.58), and 5.23 mmol/L (5.06, 5.40), for SZC 5 g, 10 g, and PBO, respectively. At RTP end, 58.8%, 76.5%, and 36.8% of pts maintained normokalemia with SZC 5 g, 10 g, and PBO, respectively. Pts were more likely to maintain normokalemia with SZC 5 g and 10 g vs. PBO (odds ratios: 2.54, 95% CI 1.07, 6.05; P=0.035 and 6.25, 95% CI 2.56, 15.27; P<0.001). Risk of recurrent HK was reduced by 61.0% and 84.0% with SZC 5 g and 10 g (both P<0.001), vs. PBO, respectively. AE incidence during the RTP was higher with SZC 5 g (50.0% of pts) and 10 g (44.0%) vs. PBO (36.0%). The incidence of constipation was higher in the SZC 5 g (7.0%) and 10 g (5.0%) groups compared to the placebo group (0).

Conclusions: Both SZC doses were statistically significant to PBO for all confirmatory sK^+ analyses, with dose-dependency observed during the RTP. The safety profile of SZC was generally consistent with previous studies.

Funding: Commercial Support - AstraZeneca

SA-OR42

Effect of Protein Supplementation on Plasma Sodium Levels and Urinary Urea Excretion in Patients with Chronic Syndrome of Inappropriate Antidiuresis (SIAD): A Monocentric Open-Label Proof-of-Concept Study

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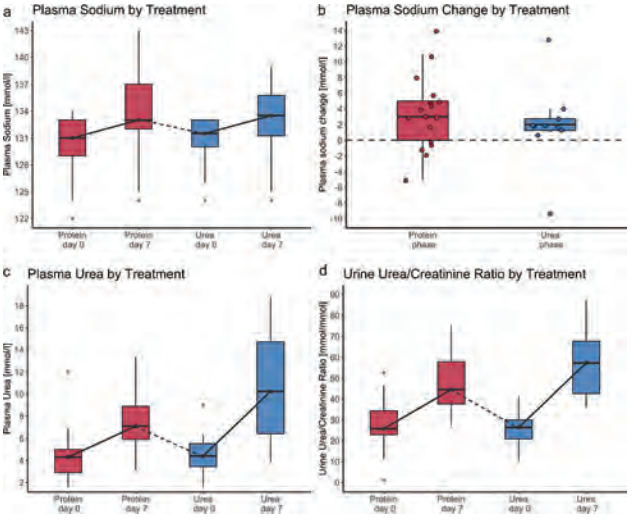
Background: The syndrome of inappropriate antidiuresis (SIAD) can be treated with oral urea. We hypothesized that dietary proteins could increase free-water clearance through urea-induced osmotic diuresis and aimed to investigate the effect of a high-protein supplementation on plasma sodium levels in chronic SIAD.

Methods: This is a monocentric open-label proof-of-concept trial conducted at the University Hospital of Basel, Switzerland, between 10/2021 and 02/2023. Adult outpatients with chronic SIAD received 90 g protein daily for 7 days in the form of protein powder. After a wash-out period of at least a week, patients received 30 g of oral urea daily for 7 days. The primary endpoint was the increase in sodium levels from baseline to the end of the 7-day protein supplementation.

Results: Seventeen patients were included (14 females, median age 68 [61, 79]). After 7 days of 90 g daily protein supplementation (n = 17), plasma sodium levels increased by a median of 3 mmol/l [0, 5], plasma urea by 3 mmol/l [1.7, 4.9] and urinary urea corrected for urine creatinine by 21.2 mmol/mmol [6.2, 29.1]. After 7 days of oral urea (n = 10), sodium levels increased by a median of 2 mmol/l [1, 3], plasma urea by 5.8 mmol/l [2.7, 9.2] and urinary urea corrected for urine creatinine by 31.0 mmol/mmol [18.7, 45.1].

Conclusions: Our findings suggest that a high-protein supplementation with protein powder increases plasma sodium levels in patients with chronic SIAD through protein-induced ureagenesis and osmotic diuresis. The effects are comparable to oral urea intake.

Funding: Commercial Support - OMANDA AG (provided study material, i.e., protein powder, but not any financial support), Private Foundation Support, Government Support - Non-U.S.



(A) Course and (B) change in plasma sodium levels, (C) plasma urea, and (D) urine urea/creatinine ratio visualized by treatment phase (protein phase in red; urea phase in blue).

SA-OR43

Safety and Efficacy of Proactive vs. Reactive Administration of DDAVP in Severe Symptomatic Hyponatremia: A Randomized Controlled Trial

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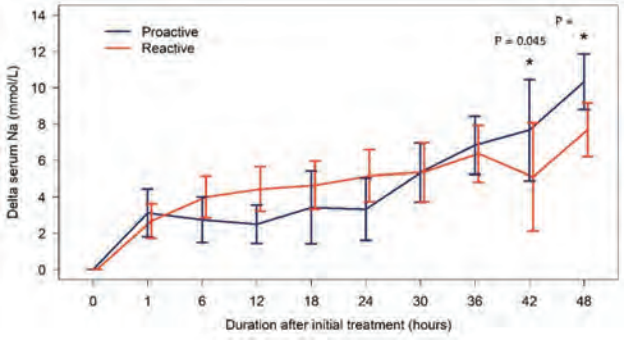
Background: DDAVP is effective in preventing and reversing overcorrection of hyponatremia. However, the recommended strategy for its use remains unclear and is based on retrospective data. This study aims to compare the safety and efficacy of proactive and reactive DDAVP strategies in severe symptomatic hyponatremia.

Methods: This randomized controlled trial included patients with severe symptomatic hyponatremia (serum sodium < 125 mmol/L) from June 20, 2022, to February 20, 2023. Patients were assigned to either the proactive group, which received DDAVP immediately after diagnosis, or the reactive group, which received DDAVP only if the serum sodium level tended to overcorrect. The primary outcome was the incidence of overcorrection between the two groups.

Results: The study enrolled 49 patients, with 24 in the proactive group and 25 in the reactive group. There was no significant difference in the incidence of overcorrection between the two groups (16.7% vs. 28%, P = 0.54), nor in the change of serum sodium levels at 1, 6, 12, and 24 hours. However, at 48 hours, the proactive group had a higher change in serum sodium levels than the reactive group (10.3 ± 3.6 vs. 7.7 ± 3.6, P = 0.013), but it remained within the safety range. The time to symptom improvement, total amount of intravenous fluid administered, dose of DDAVP, urine volume, length of hospital stay, incidence of ODS, and 28-day mortality did not differ significantly between the two groups.

Conclusions: This study found no significant difference in the incidence of overcorrection between the proactive and reactive strategies for treating severe symptomatic hyponatremia. However, future large studies are needed.



Primary outcome.

Variables	Proactive strategy (n=24)	Reactive strategy (n=25)	P – value
Overcorrection	4 (16.7)	7 (28)	0.543

SA-OR44

Monitoring Serum Potassium Concentration in Patients with Severe Hyperkalemia: The Role of Bloodless Artificial Intelligence (AI)-Assisted Electrocardiography

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Background: Severe hyperkalemia is a potentially life-threatening emergency requiring prompt recognition with rapid management and surveillance. Although bloodless artificial intelligence (AI)-enabled electrocardiography (ECG) provides real-time detection of severe hyperkalemia, its application to monitor blood potassium (K^+) levels during management has not been evaluated. This study aimed to determine the value of AI-enabled ECG (AI-ECG) for blood K^+ monitoring in patients with severe hyperkalemia.

Methods: This retrospective cohort study was performed at an emergency department (ED) of a single academic medical center over 2.5 years. Patients with true severe hyperkalemia defined as Lab-K^+ ≥ 6.5 mmol/L with matched AI-ECG K^+ ≥ 5.1 mmol/L were included. AI-ECG K^+ was quantified by ECG12Net as developed previously. The following ECG K^+ and Lab-K^+ were measured almost simultaneously during or after K^+-lowering therapy at least 2 times. Clinical characteristics, therapeutic intervention, and pertinent laboratory data were analyzed.

Results: Seventy-eight patients fulfilled the enrolled criteria. Most of them had acute on chronic kidney injury, advanced CKD not yet on dialysis, and dialysis-dependent renal failure. Their initial Lab-K^+ and AI-ECG K^+ were 7.2 ± 0.7 and 6.6 ± 0.5 mmol/L, respectively. During and after K^+-lowering therapy, both Lab-K^+ and ECG-K^+ were significantly declined in parallel in the patients both treated medically (n=37) and with hemodialysis group (n=41). Of note, six patients showing persistent ECG-K^+ hyperkalemia despite the normalized Lab-K^+ levels.

Conclusions: Point-of-care AI-ECG K^+ may provide an effective monitoring of blood K^+ changes for severe hyperkalemia and also reveal the pseudo-positive patients with the underlying cardiac structure changes or disorders.

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SA-OR45

The ΔAG/ΔHCO3 Ratio in Lactic Acidosis: Time for a New Baseline?

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Background: The ratio of Δanion gap and Δbicarbonate ($\Delta AG/\Delta HCO_3$) is used to detect co-existing acid-base disorders in patients with high anion gap (AG) metabolic acidosis. Prior studies demonstrating that in lactic acidosis (LA) the $\Delta AG/\Delta HCO_3$ is approximately 1.6-1.8:1 used mean normal values for anion gap and serum HCO_3. This study is the first to examine the $\Delta AG/\Delta HCO_3$ using each patient's individual baseline AG and serum HCO_3.

Methods: This was a retrospective cohort study of adult Kaiser Permanente Southern California (KPSC) health system members admitted to the ICU with sepsis. Baseline AG and albumin measurements were obtained 1-24 months prior to ICU admission. An albumin-corrected $\Delta AG/\Delta HCO_3$ ratio was calculated using each patient's individual baseline AG and serum HCO_3. The association between ΔHCO3 and ΔAG was examined using Pearson correlation, a linear regression model was constructed, and 95% prediction limits were computed.

Results: 293 patients were included. $\Delta AG/\Delta HCO_3$ was calculated for 177 patients who had elevated serum lactate levels (≥1.9 mM). The mean $\Delta AG/\Delta HCO_3$ for all patients with elevated serum lactate levels was 1.44 (SD 1.89). The correlation between ΔHCO_3 and ΔAG with 95% prediction limits is shown in Figure 1.

Conclusions: The mean $\Delta AG/\Delta HCO_3$ was 1.44. To our knowledge, this is the first study to determine the $\Delta AG/\Delta HCO_3$ using each patient's individual baseline AG and serum HCO_3. This has important clinical implications given the wide interindividual variability in AG and HCO_3. Regardless, even using the baseline AG and serum HCO_3 to calculate the $\Delta AG/\Delta HCO_3$, the wide 95% prediction limits (Figure 1) suggest that $\Delta AG/\Delta HCO_3$ should be used cautiously in the diagnosis of mixed acid-base disorders.

Funding: Commercial Support - The research is supported by a grant from the Regional Research Committee of Kaiser Permanente. Grant No. KP-RRC-20210504.

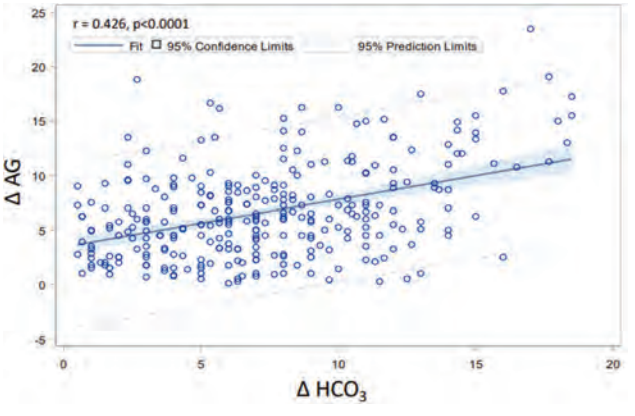

Figure 1: Correlation between ΔHCO_3 and ΔAG

SA-OR46

Arterial pCO2 and Arterial pH from Venous Blood Gas Concurrent Measurements from 7470 Samples: An Easy Conversion of Venous to Arterial Blood by Formula

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Background: Venous blood gas sampling to estimate blood pH and pCO2 has become standard medical practice with limited scientific data to avoid the cumbersome performance of arterial sampling. Efforts to estimate arterial pCO2 from venous blood and, in particular, blood pH from venous pH suffer from the limitation of observations made in relatively small databases (at the most hundreds of patients) and it is not always clear that the measurements were done simultaneously. We reasoned that existing estimations of arterial pH and pCO2 from venous blood could be improved using contemporary data extracted from a large database available from the electronic medical record.

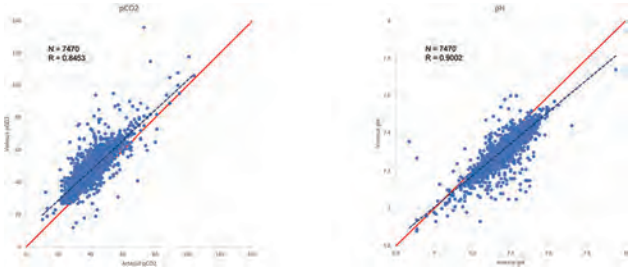
Methods: We used de-identified data on venous and arterial blood gas measurements from Northwestern Medicine over 7 years (2016-2023). We extracted data from de-identified subjects with a total of 7470 samples where it was verified that the sampling for venous and arterial blood gas performed at the same time and by the same blood gas

laboratory. The data was provided by an independent observer and verified that the times of sampling coincided with each other.

Results: From the 7470 samples, the relationship between arterial and venous pCO2 was strong (r= 0.845) and as expected, the venous pCO2 was higher than arterial pCO2 (see dotted line vs. line of identity in red, Fig. left panel). The correlation between the venous pH and arterial pH in the same 7470 samples was also very strong (r = 0.9) and as anticipated the venous pH was lower than the corresponding arterial pH and therefore most of the pH points are below the line of identity (Fig. right panel).

Conclusions: The correlations between venous and arterial pH and pCO2 in a database unique because of the large sample size and concurrent measurements in venous and arterial blood show that estimations of each one of the two acid-base parameters can be reasonably made with formulas derived from the correlations here reported that will be incorporated in an App that should be available at the time of the ASN 2023 meeting.

Funding: Private Foundation Support



SA-OR47

Minimizing Hypoglycemia After Intravenous Insulin Regular Therapy for Hyperkalemia

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Background: Intravenous (IV) insulin regular is utilized for the management of hyperkalemia. There is data demonstrating that weight-based (0.1 unit/kg) insulin results in less hypoglycemia while maintaining equivalent efficacy. The objective of this project was to evaluate if weight-based IV insulin regular dosing would minimize rates of hypoglycemia at our institution.

Methods: This single-center, pre-post design project included adult patients with hyperkalemia (potassium > 5 mEq/L) treated with IV insulin regular in the emergency department at a large tertiary care medical center. Historical management utilized fixed-dose 10 units of insulin regular (pre-intervention group). Exclusion criteria were patients who received insulin products for indications other than hyperkalemia, treated with hemodialysis, or received continuous dextrose fluids. The hyperkalemia order set was updated to 0.1 unit/kg IV insulin regular (maximum 10 units) and expanded point-of-care (POC) glucose monitoring from one hour to a total of four hours (post-intervention group). The primary outcomes were rates of hypoglycemia (blood glucose < 70 mg/dL) and severe hypoglycemia (blood glucose < 50 mg/dL). Secondary outcomes were reduction in potassium levels, administration of additional potassium lowering agents, and compliance to weight-based dosing and expanded POC monitoring.

Results: A total of 68 patients were included in the pre-intervention group and 58 patients in the post-intervention group. Hypoglycemia was more frequent in the pre-intervention group compared to the post-intervention group (26.5% versus 17.2%). Similar results were seen with severe hypoglycemia (7.3% versus 1.7%). The median reduction in potassium levels in the pre-intervention group was 0.95 mEq/L and 0.85 mEq/L in the post-intervention group. For patients who received insulin regular only and with no concomitant potassium lowering agent, the median reduction in potassium in the pre-intervention group was 0.7 mEq/L (IQR 0.5-1.55) compared to 0.85 mEq/L (0.35-1.33). There was 36.2% compliance with weight-based insulin regular dosing and 0% compliance with the extended POC monitoring schedule in the post-intervention group.

Conclusions: This project found that using weight-based insulin regular dosing may lead to a reduction in hypoglycemia, especially severe hypoglycemia, without needing additional potassium lowering agents.

SA-OR48

Role of Midodrine in Prevention of Intradialytic Hypotension: A Randomized Cross-Over Controlled Trial

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Background: Intradialytic hypotension (IDH) is one of the most common complications in hemodialysis (HD) patients. It is associated with reduced quality of life as well as an increased risk of myocardial infarction and mortality. Although midodrine, an α-1 adrenergic receptor agonist, has been proposed as a potential benefit in the prevention of IDH and has demonstrated efficacy in some studies, its long-term use with normal dialysate calcium has not yet been established.

Methods: This cross-over, placebo-controlled trial recruited adult patients who received thrice-weekly HD and had frequent IDH during the past 3 months. Participants were randomized to receive either oral 10-mg midodrine or placebo pills. The administration of the drugs took place 30 minutes prior to each dialysis session over a duration of 2 months (24 sessions) in each phase, with a one-week washout period between phases. All patients were prescribed a dialysate calcium concentration of 2.5 mEq/L. The trial protocol for this study was registered at thaiclinicaltrials.org (TCTR20211007003).

Results: In the midodrine treatment group, the incidence rate of IDH was significantly lower compared to the placebo group (8.5 vs. 16.0 events per 100 HD sessions, p = 0.004). Furthermore, the midodrine group demonstrated significantly reduced incidence rates of dizziness (7.7 vs 16.2 events per 100 HD sessions, p < 0.001) and headache (0 vs 1.3 events per 100 HD sessions, p = 0.04). However, there were no significant differences observed between the midodrine and placebo groups in terms of nadir systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and heart rate (HR). Regarding safety, there were no significant differences in the incidence of adverse events between the two treatment groups.

Conclusions: Midodrine demonstrates safety and efficacy as a prophylactic intervention for IDH while also effectively mitigating symptoms of dizziness and headache in patients undergoing hemodialysis with a normal dialysate calcium concentration.

Funding: Commercial Support - Cosma trading Ltd., Government Support - Non-U.S.

SA-OR49

Association of Calcium Channel Blocker Use with Intradialytic Hypotension

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Background: Calcium channel blockers (CCBs) are commonly used as anti-hypertensive agents among patients receiving maintenance hemodialysis (HD). Despite this, little is known regarding the association of CCBs with intra-dialytic hypotension (IDH), an important adverse outcome that is associated with cardiovascular morbidity and mortality.

Methods: Using detailed data from kinetic modeling sessions of the Hemodialysis Study, random-effects regression models were fit to assess the association of CCB use versus not with IDH (defined as systolic blood pressure (SBP) <90 mm Hg if pre-HD SBP <160 mm Hg or <100 mm Hg if pre-HD SBP ≥160mm Hg. Models were adjusted for age, sex, race, Kt/V assignment, flux assignment, heart failure, ischemic heart disease, peripheral vascular disease, diabetes mellitus, BUN, ultrafiltration rate, access type (catheter, fistula, graft), pre-HD SBP, and other anti-hypertensive use.

Results: Data was available for 1,838 patients and 64,538 sessions; at baseline 49% of patients were prescribed CCBs. The overall frequency of IDH was 14% with a mean decline from pre- to nadir-SBP of 33 ±15 mmHg. CCB use was associated with a lower adjusted odds of IDH, compared with no use (OR 0.81; 95%CI 0.75, 0.87). The association was most pronounced for those with (OR 0.77; 95%CI 0.69, 0.86) versus without (OR 0.87; 95%CI 0.78, 0.98) a history of HF at baseline (P-interaction=0.05).

Conclusions: Among patients receiving thrice-weekly HD in the Hemodialysis study, CCB use was associated with a lower risk of developing IDH, independent of pre-HD SBP and other anti-hypertensive use. Mechanistic studies are needed to better understand the effects of CCB and other anti-hypertensives on peri-dialytic blood pressure parameters among patients receiving maintenance HD.

Table 1. Baseline characteristics of participants according to CCB use

	Not taking CCB (n=930)	Taking CCB (n=908)
Age (years), mean ± SD	58.4 ± 13.6	57.1 ± 14.5
Female, n (%)	518 (56%)	514 (57%)
Black, n (%)	552 (59%)	598 (66%)
Diabetes Mellitus, n (%)	400 (43%)	420 (46%)
Ischemic heart disease, n (%)	384 (41%)	338 (37%)
Heart failure, n (%)	371 (40%)	358 (39%)
Peripheral vascular disease, n (%)	242 (26%)	228 (25%)
Pre-HD SBP, mean ± SD	146.7 ± 25.6	156.7 ± 24.7
Ultrafiltration rate, mean ± SD	11.8 ± 5.5	12.7 ± 5.9
Access		
Graft	548 (58%)	544 (59%)
Fistula	317 (34%)	308 (34%)
Catheter	65 (7%)	56 (6%)
Pre-HD BUN, mean ± SD	57.1 ± 17.3	57.1 ± 17.3
Angiotensin Converting Enzyme, n (%)	203 (22%)	257 (28%)
Beta Blockers, n (%)	257 (28%)	296 (33%)
Alpha-1 Blockers, n (%)	42 (4.5%)	83 (9%)
Other hypertensives, n (%)	145 (16%)	194 (21%)
Nitrates, n (%)	152 (16%)	163 (18%)
Angiotensin II Receptor Blockers, n (%)	8 (0.9 %)	17 (2%)
Minoxidil, n (%)	15 (2%)	17 (2%)
Adrenergic blockers, n (%)	29 (3%)	32 (3%)
Kt/V assignment, n (%)	464 (50%)	451 (50%)
Flux assignment, n (%)	454 (49%)	463 (51%)

Pre-HD: pre-hemodialysis; SBP: Systolic blood pressure; BUN: Blood urea nitrogen

SA-OR50

Association Between Ultrafiltration Rates and All-Cause Death in Patients Undergoing Extended-Hours Hemodialysis Using Time-Fixed and Time-Dependent Models: The LIBERTY Cohort

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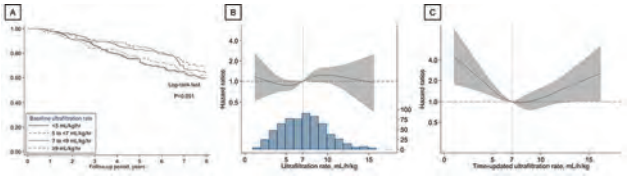
Background: Overhydration or excessive fluid removal during dialysis sessions is a risk for congestive heart failure (CHF) and death for dialysis patients, as evidence shows that the ultrafiltration rate (UFR) was associated with CHF and all-cause death. Studies have shown that extended-hours hemodialysis (EHD, >18 hr/w) improves various dialysis-related parameters such as hemoglobin, phosphate, and left ventricular hypertrophy, as well as survival. Although EHD may prevent congestion, the appropriate range of UFR in patients undergoing EHD is unknown.

Methods: Using data from 636 patients undergoing EHD in the LIBeralized diet Extende-houRs hemodialysis TherapY (LIBERTY) cohort, we examined the association between UFR and all-cause death in time-fixed or time-dependent multivariable Cox models adjusted for dialysis conditions and laboratory data. UFR was calculated by fluid removal (mL) per hour divided by dry weight (kg) and averaged in a week (mL/h/kg). UFR and covariates at baseline (within 6 months from EHD initiation) were used in the time-fixed model, while, the mean values of UFR and covariates every 3 months in a time-updated manner were used in the time-dependent model.

Results: The mean age was 62 years and male participants comprised 65%. Median UFR was 7.0 mL/kg/h. The median time since starting dialysis was 1.8 [IQR, 0.1–5.6] years. During a median of 6.4 [IQR, 3.4–10.3] years, 230 patients died. Overall survival at 5 years from the baseline was 79% (95% CI, 76–83%). Baseline UFR was not associated with all-cause death (Log-rank test P=0.091, Figure A). In the multivariable-adjusted models, baseline UFR was not associated with the outcome, while low or high time-updated UFR was associated with the outcome (Figures B and C).

Conclusions: UFR at the start of EHD was not associated with all-cause mortality, while time-updated UFR <7 mL/kg/h, which may represent reduced dietary intake, was associated with short-term prognosis.

Funding: Government Support - Non-U.S.



SA-OR51

Impact of ESRD on Stroke Risk in Atrial Fibrillation Patients

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Background: Patients with end-stage renal disease (ESRD) are at higher risk of atrial fibrillation (Afib) due to multiple underlying factors. However, the impact of concomitant Afib and ESRD on stroke risk is now well established. The purpose of this study is to evaluate the impact of concomitant Afib and ESRD on stroke risk compared to individuals with Afib alone.

Methods: The national inpatient sample (NIS) database 2016-2018 was used to identify individuals with Afib uaing ICD-10 codes. Patients with age less than 18 or those with history of stroke were excluded. 1:1 propensity matching was used to match patients with ESRD to those without ESRD on different comorbidities. Univariate analysis pre- and post-match were performed. Binary logistic regression was performed after matching to assess whether ESRD was independently associated with stroke risk. A p-value of <0.05 was considered statistically significant.

Results: A total of 1,749,172 patients were included in the study with 89,741 being ESRD. ESRD patients were younger and had higher prevalence of baseline comorbidities except for COPD, CAD, and smoking. Oral anticoagulation use and aspirin use was less in ESRD patients. On univariate analysis, ESRD patients had significantly lower ischemic stroke (1.8% vs 2.9%), hemorrhagic stroke (0.3% vs 0.6%), transient ischemic attack (TIA) (0.4% vs 0.7%). However, mortality was higher in ESRD group (8.1% vs 4.8%). Post-match analysis showed that ESRD patients had significantly lower ischemic stroke [OR: 0.59], hemorrhagic stroke [OR: 0.37] and TIA [OR: 0.76] along with higher mortality [OR: 1.95].

Conclusions: Concomitant presence of Afib and ESRD was associated with a lower stoke rates compared to Afib alone. The platelet dysfunction associated with ESRD along with exposure to heparin during dialysis sessions might explain this decrease in stroke risk. Additional large-scale studies are necessary to validate our findings.

Post-match regression analysis of stroke, hemorrhagic stroke, TIA, and Mortality in ESRD vs No-ESRD patients

	OR	CI	P-value
Stroke	0.59	0.55-0.63	<0.001
Hemorrhagic Stroke	0.37	0.31-0.43	<0.001
TIA	0.76	0.65-0.88	<0.001
Mortality	1.95	1.87-2.04	<0.001

SA-OR52

Use and Association of Rate Control and Anti-Arrhythmic Medications with Risk of Subsequent Stroke and Mortality Among Hemodialysis Patients with Atrial Fibrillation

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Background: Atrial fibrillation (AF) is highly prevalent amongst patients with kidney failure on maintenance dialysis and is associated with poor clinical outcomes. Treatment of AF in this population is particularly challenging, as associations of the core AF management strategies of antiarrhythmic and rate-control medications with clinical outcomes in dialysis patients are unknown.

Methods: We evaluated patients with kidney failure on maintenance dialysis and incident AF from Kaiser Permanente Northern and Southern California. We evaluated associations between time-updated use of rate-control medications alone, antiarrhythmic medications alone, use of both medications, and use of neither medication (referent group) with the composite outcome of ischemic stroke and all-cause mortality using Cox regression models, with adjustment for multiple covariates.

Results: Among a total of 2,100 patients, 44.0% were newly initiated on rate-control medications alone, 4.6% were on antiarrhythmic medications alone, 8.5% were on both, and 42.9% were on neither medication within 12 months of incident AF diagnosis. Over a median (IQR) follow-up of 1.66 (0.45, 3.39) years, we observed 1,406 composite events. Use of antiarrhythmic medications alone (adjusted HR 0.73, 95% CI 0.57-0.95), or both medications (adjusted HR 0.70, 95% CI 0.56-0.88) was associated with lower risk of ischemic stroke or death compared to neither medication use (**Table**). Use of rate-control medications alone was not associated with decreased risk for the composite outcome.

Conclusions: While the use of antiarrhythmic medications was low in AF patients on maintenance dialysis, antiarrhythmic medication use alone or with rate-control medications was associated with decreased risk of ischemic stroke or all-cause mortality. Future trials are needed to confirm the efficacy and safety of antiarrhythmic medications in dialysis patients.

Funding: NIDDK Support, Other NIH Support - NHLBI: R01 HL142834, Private Foundation Support

Table: Associations of time-updated rate and antiarrhythmic medication use with the composite of stroke and all-cause mortality by Cox regression

Ischemic stroke or all-cause mortality	N of events	Rate per 100 person-years	Unadjusted HR (95% CI)	Adjusted HR 1 (95% CI)	Adjusted HR 2 (95% CI)
Medication use status	1406	13.5 (12.8-14.2)			
Rate control only	621	15.0 (13.9-16.2)	0.93 (0.85-1.01)	0.93 (0.84-1.03)	0.94 (0.85-1.04)
Anti-arrhythmic only	58	6.7 (5.2-8.7)	0.71 (0.57-0.90)	0.70 (0.54-0.91)	0.73 (0.57-0.95)
Both	77	7.0 (5.6-8.7)	0.67 (0.54-0.83)	0.68 (0.54-0.85)	0.70 (0.56-0.88)
Neither	650	15.0 (13.9-16.2)	1.0 (Referent)	1.0 (Referent)	1.0 (Referent)

Model 1: Adjusted for age, gender, race and ethnicity, education, and income
Model 2: Adjusted for the components of Model 1 plus dialysis vintage, chronic liver disease, prior stroke, transient ischemic attack, peripheral vascular disease, heart failure, myocardial infarction, coronary artery bypass graft, percutaneous coronary intervention, valvular disease, hypertension, diabetes, systolic blood pressure, body mass index, and use of warfarin

SA-OR53

Hemoglobin Stability in the ASCEND-TD Trial

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Background: Daprodustat (Dapro), a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI), has been investigated as a treatment for anemia of chronic kidney disease (CKD) in the ASCEND program. Maintaining hemoglobin (Hb) levels in the target range per clinical guidelines for patients (pts) with CKD is complex. Primary efficacy results for dapro administered three times weekly (TIW) are reported (Coyne DW. *CJASN* 2022). Here we examine additional Hb stability data of Dapro dosed TIW.

Methods: ASCEND-TD (NCT03400033) was a randomized, double-blind, double-dummy, active comparator study evaluating the efficacy and safety of Dapro dosed over 52 weeks compared with epoetin alfa (EPO) in pts receiving hemodialysis. Various Hb stability measures were assessed in a pre-specified manner. Responders were defined as pts with mean Hb within the Hb analysis range (10–11.5 g/dL) during the evaluation period (EP, Weeks 28–52).

Results: 322/407 (79%) pts had evaluable Hb during the EP. The difference in response rate (dapro-EPO) was 0.1645 (95% CI [0.06, 0.27]) and demonstrated nominal superiority. Median time Hb was in the analysis range (% [interquartile range]) was higher in pts administered Dapro compared with pts administered EPO (70.83 [50.98; 91.07] and 61.76 [29.69; 85.19], respectively). The Hodges-Lehmann estimate of the median treatment difference (dapro-EPO) of 11.18% met non-inferiority. Dapro TIW was also nominally superior to EPO for percentage of time Hb was within the analysis range according to the van Elteren's test stratified by region (one-sided P=0.0034; **Table**). The proportion of pts with evaluable Hb <7.5 g/dL and ≥12 g/dL during the EP and the proportion of time Hb ≥12 g/dL during the EP was lower in pts administered Dapro compared with pts administered EPO.

Conclusions: In ASCEND-TD, Dapro TIW demonstrated a potential benefit in maintaining stable Hb compared with EPO. Further analysis is required to understand this effect and to provide conclusive evidence of better Hb stability for Dapro compared with EPO.

Funding: Commercial Support - The study and this analysis were funded by GSK.

Table. Analysis of % time Hb within the analysis range during the EP using evaluable Hb values

	Daprodustat (N=270)	EPO (N=137)
n † (%)	215 (80)	107 (78)
Median (%) time in range (10–11.5 g/dL)	70.83	61.76
Hodges–Lehmann estimate of treatment difference (daprodustat–EPO) (%)	11.18	
Hodges–Lehmann two-sided asymptotic 95% CI (%)	(2.83, 19.56)	
One-sided P-value ‡	0.0034	

† Participants who have at least two post-randomization evaluable Hb values on different days, where at least one evaluable Hb value is contained within the EP and another evaluable Hb value occurs within the range of the Week 16 visit through to the Week 52 visit, inclusive. ‡ Treatment group comparisons are based on van Elteren's test stratified by region. CI, confidence interval; EP, evaluation period; EPO, epoetin alfa; Hb, hemoglobin.

SA-OR54

Depletion of Plasma Aromatic Amino Acids During Hemodialysis Is Associated with Fatigue

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Background: The etiology of fatigue in hemodialysis (HD) patients remains elusive. Aromatic amino acids (AAA – tryptophan, phenylalanine, and tyrosine), the precursors of neurotransmitters serotonin, dopamine, and norepinephrine, are implicated in the pathogenesis of fatigue. A significant amount of AAA is lost during a dialysis. We examined the association of changes in AAA during a dialysis session with fatigue.

Methods: 114 adult HD patients self-reported fatigue on a dialysis day using validated Brief Fatigue Inventory. Pre- and post-dialysis plasma AAA levels were measured by HPLC-mass spectrometry. Spearman correlation was used to assess the relationship between AAA levels and fatigue.

Results: Post-dialysis plasma levels of phenylalanine and tyrosine decreased significantly compared to the baseline pre-dialysis levels except for tryptophan ($p < 0.0001$, 0.04, and 0.62, respectively). None of the pre-dialysis plasma levels of amino acids were associated with fatigue ($p > 0.05$ for all correlations). Post-dialysis plasma levels of phenylalanine, tryptophan, and AAA correlated inversely with fatigue score ($p < 0.05$ for all correlations). The relative decline (post – pre/pre values) in phenylalanine, tyrosine, and AAA levels during dialysis was positively correlated with fatigue score ($p < 0.05$ for all correlations). Compared to the HD patients in the lowest tertile of fatigue score, those in the highest tertile had greater relative decline in plasma AAA levels between pre- and post-dialysis, p=0.045 (Figure).

Conclusions: Plasma AAA depletion during a dialysis session is associated with fatigue, suggesting possible neurotransmitters imbalance as a contributory factor. Future studies are warranted to explore the role of neurotransmitters to the pathogenesis of HD fatigue using functional MRI.

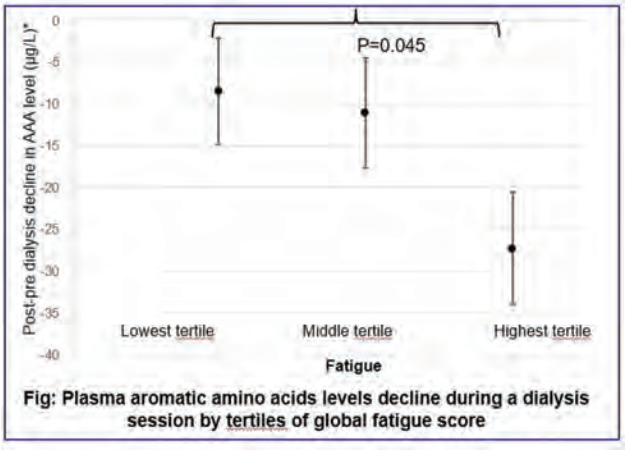

Fig: Plasma aromatic amino acids levels decline during a dialysis session by tertiles of global fatigue score

SA-OR55

Association Between Circulating Extracellular Matrix (ECM)-Associated Molecules and Cardiovascular Outcomes in Hemodialysis Patients

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Background: The extracellular matrix (ECM) is a complex network of non-cellular components that provide structural support for the tissues. Circulating ECM-associated molecules are increased during cardiovascular (CV) remodeling process and can be potential biomarkers of adverse CV outcomes. However, their clinical significance in hemodialysis patients is unclear.

Methods: A total of 372 hemodialysis patients were enrolled from a prospective multicenter cohort study. We measured four plasma ECM-associated proteins: matrix metalloproteinase (MMP)-2, MMP-9, tenascin-C, and thrombospondin-2. The primary outcome was set as a composite of cardiac and noncardiac vascular events.

Results: Plasma MMP-2 levels were significantly higher in patients with future CV events than in those without ($p = 0.004$), while the others were not. All the measured molecules had significant correlations with NT-proBNP levels, but the correlation coefficient was most strong with plasma MMP-2 (Rho = 0.317, $p < 0.001$). In logistic regression analysis, elevated plasma MMP-2 levels were independently associated with LV diastolic dysfunction (adjusted odds ratio [OR] per standard deviation, 1.48; 95% confidence interval [CI], 1.05 – 2.08; $p = 0.024$). Cox regression analysis showed that plasma MMP-2 levels were associated with a 1.30-fold risk for the composite of CV events (per a standard deviation increase; 95% CI, 1.04 – 1.63; $p = 0.022$) after multivariable adjustments

Conclusions: Plasma MMP-2 levels were independently associated with an increased risk of LV diastolic dysfunction and adverse CV outcomes in hemodialysis patients. Our results suggest that MMP-2 levels can be a useful biomarker in identifying hemodialysis patients at high risk of future CV events.

SA-OR56

Plasma Aβ42/Aβ40 Ratio as a Biomarker for Cognitive Impairment in Patients Undergoing Hemodialysis: A Multicenter Study

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Background: Mild cognitive impairment (MCI) and dementia, are more prevalent in patients undergoing hemodialysis. Although the cerebrospinal fluid amyloid beta (Aβ) and tau have proven to be valid biomarkers for the diagnosis of Alzheimer's disease in the general population, the roles of plasma Aβ and tau for the diagnosis of cognitive impairment in patients undergoing hemodialysis remain unknown.

Methods: We conducted a cross-sectional study including patients receiving hemodialysis in three hospitals in Shanghai. All patients completed the Montreal Cognitive Assessment Basic (MoCA-B). To validate the effectiveness of MoCA-B score for screening MCI, a subset group underwent neuropsychological batteries. Serum proteomes were compared in patients with normal cognitive function and dementia undergoing HD. Plasma $A\beta_{42}$, $A\beta_{40}$, and total tau were measured using a single molecule array.

Results: A total of 311 patients undergoing hemodialysis were enrolled (mean age, 63 years; 55% male). The best cut-off score of MoCA-B for differentiating MCI and normal cognition was 24 with an area under the curve of 0.94. Serum proteomics revealed that neurodegenerative pathways related to Alzheimer's disease were enriched in patients with dementia undergoing hemodialysis. The plasma $A\beta_{42}/A\beta_{40}$ ratio was significantly reduced in patients with MCI and dementia. The plasma $A\beta_{42}/A\beta_{40}$ ratio was independently associated with cognitive function after adjusting for age, sex, and educational levels.

Conclusions: We validated the MoCA-B as an optimal cognitive function screening instrument for MCI in patients undergoing hemodialysis. The plasma $A\beta_{42}/A\beta_{40}$ ratio was a potential biomarker in distinguishing normal cognition, MCI, and dementia in populations undergoing hemodialysis.

Funding: Government Support - Non-U.S.

SA-OR57

Using Internal Pilot Data to Create a Dynamic Recruitment Strategy: Experience from the NightLife Trial

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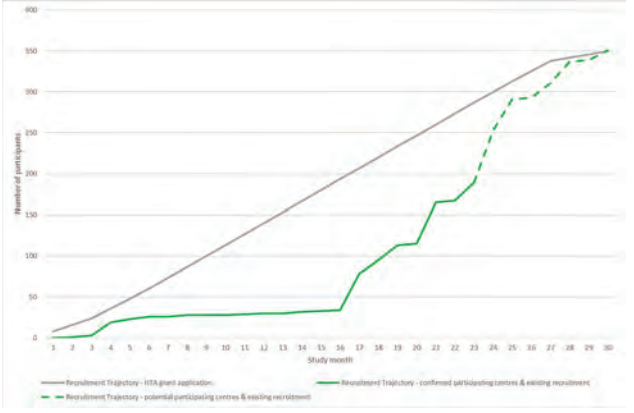
Background: The NightLife study is a randomised controlled trial to evaluate the impact of in-centre nocturnal haemodialysis (INHD) compared to conventional haemodialysis on quality of life. At 12-months, an internal pilot review was completed to evaluate trial feasibility.

Methods: Recruitment and retention rates across sites were reviewed. The site set-up processes and associated timelines were mapped out. Findings were utilised to model the recruitment trajectory for the remaining 18-month study period.

Results: Eight dialysis units contributed to the internal pilot, achieving the 12-month site set-up target. Site set-up was completed in ≈14 months. Recruitment was below the 12-month target (30 participants randomised, 12-month target was 96). Participant retention was higher than expected; the crossover rate from intervention to control 3%, much below the anticipated 25%. Participating sites were categorised as *naïve* (require INHD service set-up) or *established* (existing INHD service). 63% of the recruited participants were obtained from a *naïve* site; recruitment occurred rapidly until INHD bed capacity was saturated. Recruitment from the *established* sites relied on natural flow of patients through the service (e.g. change in dialysis modality, transplantation), with a rate of ≈1 participant per month. Fifteen sites had expressed an interest to join the NightLife study; 14 were *naïve*. The recruitment trajectory was remodelled, demonstrating study feasibility (Figure 1).

Conclusions: Remodelling of NightLife study recruitment demonstrated it is non-linear with participants joining in a stepwise manner. This resulted in a shift in focus to assisting *naïve* sites in INHD service development. Understanding and modelling of bed capacity aids service design, alteration to dialysis regimens and research delivery.

Funding: Other NIH Support - National Institute for Health and Care Research



NightLife study metrics: actual recruitment from Year 1 and projected recruitment for Year 2 and 3

SA-OR58

Posoleucel Associated with Reduction of BK Viremia and Persistence of BK-Reactive T Cells in a Phase 2 Trial

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Background: Kidney transplant recipients (KTRs) with BK virus infection are at risk of nephropathy & graft loss. Posoleucel (PSL) is an off-the-shelf allogeneic multivirus-specific T cell therapy targeting BKV.

Methods: In this phase 2 double-blind study (NCT04605484), KTRs with BK viremia were randomized 1:1:1 to receive PSL cells wkly for 3 wks then q14 (PSL1) or q28 d (PSL2), or placebo (PBO) for 12 wks. Patients (pts) were followed for 12 wks after treatment. Primary objective was safety; secondary was plasma BK viral load (VL) reduction.

Results: Baseline (BL) characteristics of 61 dosed pts were similar across groups. No deaths, GVHD, or cytokine release syndrome were seen. 3 pts in PSL groups had graft rejection but none deemed treatment-related: 1 pt had history of rejection, 1 had renal TB, and 1 had rejection 68 d after last PSL dose. eGFR was stable in all groups. Table shows VL changes in 52 pts with stable immunosuppression (IS) in the 30 d before randomization who completed study. Superior antiviral effects were seen in both PSL groups vs PBO. Greatest effect on BK VL was at wk 24 in PSL1 pts with BK VL ≥10,000 cp/mL at screening: 75% (6/8) had a ≥1 $\log_{10}$ cp/mL decrease from BL (median -1.4 log) vs 25% (1/4) of PBO (-0.4 log). At BL most pts with high BK VL had no BK-specific T cell immunity. Over the 6 months after PSL infusion, circulating frequency of BK-reactive T cells increased vs PBO, more so in PSL1 group, coincident with VL reduction. PSL presence & persistence were confirmed by TCRvβ deep sequencing, with higher levels in pts with high VL.

Conclusions: PSL was generally safe & well tolerated. Clinically meaningful BK VL reductions & increases in BK-reactive T cells were seen in PSL pts, particularly those with high VL who are at highest risk for renal impairment.

Results at Wk 24 in Patients with Stable IS* before Randomization

Endpoint	PSL1 N=20	PSL2 N=18†	PBO N=14‡
Pts w/ BK VL decreased by ≥1 log10 BKV DNA cp/mL vs BL, n (%)	10 (50)	5 (28)	2 (14)
BK VL reduction from BL, median log10 BKV DNA cp/mL (min, max)	-0.9 (-2.1, 0.1)	-0.45 (-1.8, 0.5)	-0.15 (-2.1, 0.3)
BK VL ≥50% reduction, n (%)	17 (85)	10 (56)	6 (43)

*<50% IS reduction within 30 (+/-2) d of randomization.

†2 pts lost to follow-up (LTFU) & 2 had IS reduction.

‡1 pt LTFU & 4 had IS reduction.

SA-OR59

A Phase 1/2a Trial of Autologous Regulatory T Cell Therapy Together with Donor Bone Marrow Infusion in Kidney Transplantation

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Background: In preclinical models combining Treg therapy with donor bone marrow transplantation leads to mixed hematopoietic chimerism and tolerance without myelosuppressive recipient conditioning, avoiding the adverse effects of irradiation or cytotoxic drugs.

Methods: A single center, controlled, first-in-human phase I/IIa trial is conducted in HLA-mismatched living donor kidney transplant recipients. In vitro expanded polyclonal recipient Tregs and MNC-separated donor bone marrow cells are administered within 3 days after transplant, tocilizumab is injected s.c. for the first 3 weeks. No irradiation or cytotoxic drugs are given. Immunosuppression (IS) consists of thymoglobulin, belatacept, sirolimus and steroids. Starting at 6 months, sirolimus and steroids are gradually withdrawn in stable study group patients. A parallel control group receives the same IS, but no Tregs, bone marrow or tocilizumab. Total leukocyte donor chimerism and safety are co-primary endpoints. Immune monitoring accompanying the trial includes NGS of the TCR repertoire (of the recipient and Treg cell product), flow cytometric leukocyte subset analysis, scRNAseq and protocol biopsies (at 6, 12, 24, 36 and 60 months) including transcriptomic analysis.

Results: Ten patients have been enrolled and treated so far. One additional patient was enrolled but not treated as Treg manufacturing failed. Treg (1.1-1.5x10^7 cells/kg) and bone marrow cell (0.7-1.9x10^8 nucleated cells/kg) infusions were well tolerated. The study group developed low levels of total leukocyte donor chimerism (<1%) in the first weeks post-transplant, whereas no chimerism was detectable in the control group. The study group shows a favorable clinical course, with GFRs of 50-82 ml/min/1.72m2 at latest follow-up (median follow-up 23 months) and no safety signals were observed. IS reduction has been completed in three patients currently maintained on belatacept monotherapy q8 weeks and is in progress in all other patients. Protocol biopsies at 12 months were clear.

Conclusions: Combined Treg therapy and bone marrow transplantation is safe and feasible in living donor kidney transplantation and induces low-level chimerism.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

SA-OR60

Reduction of Renal Graft Fibrosis with Valganciclovir Prophylaxis for Cytomegalovirus Prevention Compared to Preemptive Therapy: Long-Term Outcomes of Randomized Controlled Trial (OVERT Study)

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Background: Prevention of cytomegalovirus (CMV) infection including CMV indirect effects is essential in kidney transplantation. The 12-month results of OVERT Study showed less subclinical rejection and a trend toward lower incidence of acute rejection in recipients receiving valganciclovir prophylaxis compared to preemptive therapy. Here we report long-term results of OVERT Study.

Methods: This was an open-label, single-center, randomized clinical trial of valganciclovir prophylaxis vs preemptive therapy in 140 kidney transplant recipients recruited between June 2013 and May 2018. CMV-seronegative recipients with negative donors (D-R-) were excluded. Patients were randomized 1:1 to receive either valganciclovir prophylaxis for 3 months (or 6 months in D+R-) (n=70) or preemptive valganciclovir for significant CMV DNAemia detected in predefined assessments through month 24 (n=70). The primary outcome was the incidence of moderate to severe interstitial fibrosis and tubular atrophy (IFTA) in protocol biopsy at 3 years. Key secondary outcomes included acute rejection, CMV disease and DNAemia, patient and graft survival.

Results: Among the 127 patients who had a protocol biopsy specimen available at 3 years, 5 (8%) of 66 patients in the prophylaxis group and 14 (23%) of 61 patients in the preemptive group had moderate to severe IFTA (P=0.015). At 3 years the incidence of acute rejection was lower with valganciclovir prophylaxis (13% vs 36%, P=0.052). In spite of 5 (7%) additional patients with CMV DNAemia after month 12 in the prophylaxis group in contrast to none in the preemptive group (P=0.025) the cumulative incidence at 2 years remained lower with prophylaxis (51% vs 75%, P<0.001). Both regimens prevented CMV disease (6% vs 4%, P=0.733). While the 4-year graft survival was comparable (96% vs 93%, P=0.460) patient survival was improved in the prophylaxis group (100% vs 94%, P=0.042).

Conclusions: Among kidney transplant recipients, the use of valganciclovir prophylaxis, compared with preemptive therapy, led to less severe IFTA at 3 years after transplantation.

SA-OR61

Outcomes Associated with Sodium-Glucose Cotransporter-2 Inhibitors in Kidney Transplant Recipients: A Real-World Analysis Using a Global Federated Database

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Background: Several trials have shown the effectiveness of sodium-glucose cotransporter-2 inhibitors (SGLT2i) in cardiovascular events and its nephroprotective effects among patients with native kidney disease, but little is known about the safety and efficacy of SGLT2i in the kidney transplant setting. The study aimed to investigate the benefits of SGLT2i in kidney transplant recipients.

Methods: A retrospective cohort study was performed of adult renal transplant patients (≥ 18 years) using electronic medical records from a TriNetX database searched on 19th May 2023. Cohorts were grouped by receipt of SGLT2i and 1:1 propensity-score matched for demography (age, gender, & ethnicity), baseline co-morbidities (cardiovascular disease, diabetes mellitus & smoking status), laboratory data (estimated glomerular filtration rate & proteinuria) and immunosuppression. Logistical regression produced odds ratios with 95%CI for incident 3-year graft failure, rejection, major adverse cardiac events (MACE), all-cause mortality, and genitourinary infections. All statistical analyses were performed on the TriNetX online platform.

Results: The propensity score matching identified 3,450 patients (Mean age 59.4 SD± 11.9, 65% Male), each in the SGLT2i and non-SGLT2i treated renal transplant cohorts. The table shows the outcomes, odds ratio (OR), and 95% confidence interval (CI) for the SGLT2i and non-SGLT2i treated renal transplant patients 3 years post-index event.

Conclusions: Kidney transplant patients treated with SGLT2i demonstrated a significant reduction in graft failure, rejection, MACE, all-cause mortality, and genitourinary infections. These data call for a Randomized Control Trial to evaluate the long-term kidney and cardiovascular outcomes of SGLT2i therapy in the renal transplant setting.

Outcome	Cohorts	Number with outcome	Odds Ratio (OR)	95% CI	P-value
Kidney Transplant Failure	non- SGLT2i	346	-	-	-
	SGLT2i	82	0.25	0.20-0.32	< 0.0001
Kidney Transplant Rejection	non- SGLT2i	695	-	-	-
	SGLT2i	186	0.28	0.23-0.33	< 0.0001
Major Adverse Cardiac Events	non- SGLT2i	503	-	-	-
	SGLT2i	173	0.39	0.31-0.47	< 0.0001
All-Cause Mortality	non- SGLT2i	577	-	-	-
	SGLT2i	181	0.36	0.30-0.43	< 0.0001
Genitourinary Infections	non- SGLT2i	472	-	-	-
	SGLT2i	166	0.37	0.31-0.45	< 0.0001

SA-OR62

Deceased Donor Kidney Function Is Determined by Branch Chained Amino Acid Metabolism During Ex Vivo Normothermic Perfusion

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Background: Current kidney perfusion protocols are not optimized for addressing ex vivo physiological and metabolic needs of the kidney. We studied kidney function parameters and their link with metabolic competence during a 12-hour ex vivo normothermic perfusion (EVNP).

Methods: Eight human kidneys from deceased donors deemed unsuitable for transplantation were preserved using 12 hours of EVNP during which markers of function and injury were monitored. Kidneys were grouped into good and poor performers based on their functional parameters. Metabolic profile from kidney cortex samples were obtained throughout the perfusion.

Results: The mean age of the deceased kidney donors was 43 ± 16 yrs with a mean cold ischemia time of 37 ± 12 hrs. Hemodynamics parameters such as urine output (mean=99.5 ml/hr) and creatinine clearance (mean=32.6 ml/min) progressively increased and peaked at 6 hours post perfusion among good performers (**Figure 1**). Urinary neutrophil gelatinase-associated lipocalin was also significantly different at 6 hours between the two groups (mean difference=85.8 ng/ml, *P*=0.02) (**Figure 1B**). Peak functional differences at 6 hours coincided with tissue accumulation of branch chain amino acids (BCAA) among poor performers compared to good performers (**Figure 2**).

Conclusions: We identified impaired BCAA metabolism at 6 hours of EVNP as the metabolic phenotype distinguishing poor and good performing kidneys. Future studies with larger sample sizes are needed to validate the association of impaired BCAA metabolism with kidney functional decline.

Funding: NIDDK Support

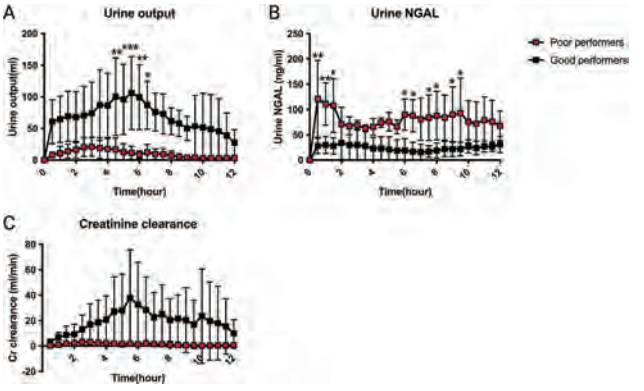

Figure 1. Functional parameters comparing poor and good performers.

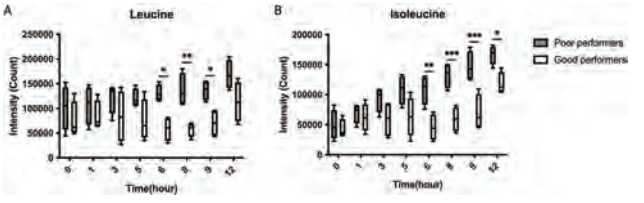

Figure 2. Tissue BCAA levels among poor and good performers.

SA-OR63

The Association Between V-Set Ig Domain-Containing 4 (VSIG4) Expression and Chronicity in Transplant Kidneys

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Background: A Banff-based chronicity index is asociated with graft outcomes in patients with a kidney transplant. Recent studies have highlighted the association of V-set Ig domain-containing 4 (VSIG4) with epithelial-mesenchymal transition in various diseases, including chronic kidney diseases. However, its role in kidney transplantation remains unclear. This study aimed to assess the significance of serum and urinary VSIG4 levels in kidney transplant patients who underwent biopsy.

Methods: A total of 44 patients (24 males, 20 females, average age 50.9 ± 12.8 years) were categorized into three groups based on their chronicity index (1-4, 5-8, and >9) as per the 2019 Banff classification. The chronicity index, with a maximum score of 15, represents the sum of scores for interstitial fibrosis, tubular atrophy, chronic vasculopathy, and chronic glomerulopathy. Serum and urinary VSIG4 levels were measured using ELISA, with urinary levels adjusted for urine creatinine levels.

Results: The mean serum creatinine was 1.92 ± 0.88 mg/dL, and eGFR was 41.2 ± 16.1 ml/min/1.73m^2. The mean number of HLA mismatches was 3.44 ± 1.40. The mean activity index and chronicity index were 2.07 ± 0.87 and 6.27 ± 2.34, respectively. Significant differences in both serum and urinary VSIG4 levels were observed among the three groups using the Kruskal-Wallis test: serum VSIG4 (ng/mL) - lower group median (IQR): 66.5 (59.1, 73.4); middle group: 69.6 (49.9, 133.1); higher group: 125.1 (116.8, 351.6), p = 0.019; urinary VSIG4 (ng/mgCr) - lower group : 3.66 (2.67, 4.29); middle group: 9.46 (4.99, 23.8); higher group: 17.8 (14.3, 26.9), p = 0.039. Spearman's rank test revealed positive correlations between serum VSIG4 levels and the total chronicity index (r = 0.391, p = 0.009), age (r = 0.377, p = 0.013), and BUN (r = 0.439, p = 0.003). Negative correlations were found with eGFR (-0.554, p < 0.001) and albumin (r = -0.469, p = 0.003). Urinary VSIG4 levels showed a negative correlation with eGFR (r = -0.367, p = 0.009). However, both serum and urinary VSIG4 levels did not differ significantly based on the total activity score.

Conclusions: This study concludes that serum and urinary VSIG4 levels are associated with chronic changes in patients with kidney transplantation. Given the relationship between the chronicity index and allograft loss, these levels may serve as markers for graft outcomes.

Funding: Government Support - Non-U.S.

SA-OR64

Overlapping Pathologic Findings in the Kidney Allograft Biopsy: Pitfalls for the Molecular Microscope Diagnostics System (MMDx)

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Background: The Molecular Microscope Diagnostic System (MMDx) has been suggested to add diagnostic value in cases suspicious of antibody-mediated (ABMR) and T cell-mediated rejection (TCMR). Other overlapping pathologies, however, have the potential to mimic molecular rejection.

Methods: In this single-center cohort of 326 indication kidney transplant biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 66 cases with overlapping pathologic findings by histology: 15 cases with pyelonephritis, 21 cases with BK nephropathy (BKVN), 5 cases with acute interstitial nephritis (AIN), and 28 cases with recurrent/de novo glomerulonephritis (GN).

Results: Pyelonephritis: 5 of 15 cases (33%) with pyelonephritis showed minor molecular findings (normal rejection score but abnormal ABMR and/or TCMR score or vice versa), which were diagnosed in only 18 of 260 (7%) cases without overlapping pathologies (p=0.004). 8 of 15 cases (53%) with pyelonephritis showed a TCMR phenotype score (R2) ≥0.10. BKVN: 4 of 21 cases (19%) with BKVN showed minor molecular findings, whereas 3 (14%), 3 (14%), and 6 (29%) of 21 cases showed ABMR, TCMR, and ABMR/TCMR, respectively. 11/21 cases (52%) with BKVN showed an all ABMR rejection phenotype score (sum of R4, R5, and R6) ≥0.20, none of which had proven ABMR by histology. AIN: 3 of 5 cases (60%) with AIN showed molecular TCMR, of which 2 cases showed mixed ABMR/TCMR in the absence of any antibody-mediated changes by histology. GN: 21 of 28 cases (75%) with GN showed no molecular ABMR/TCMR, whereas 2 of 28 cases (7%) showed minor molecular findings, and 5 of 28 cases (18%) showed ABMR. Surprisingly, 16 of 28 cases (57%) showed an all ABMR rejection phenotype score ≥0.20, and 8 of 28 cases (29%) showed a late-stage ABMR score ≥0.20.

Conclusions: Minor molecular findings should always suggest the presence of any overlapping pathology. Cases of pyelonephritis, BKVN, and AIN mostly mimic molecular rejection and might be misleading in their interpretation. Although GN does not show molecular rejection in most cases, the elevated ABMR scores suggest a GN-associated phenomenon.

Funding: Private Foundation Support

SA-OR65

The Impact of Subclinical T Cell-Mediated Rejection on Subsequent Rejections and Allograft Survival in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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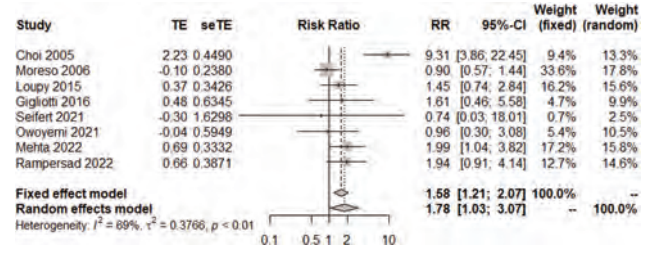
Background: Subclinical T cell mediated rejection (SC-TCMR) refers to the presence of histological features of acute rejection on renal biopsy without a decline in renal function. Although single centers have reported an adverse impact of SC-TCMR on allograft outcomes, there is a dearth of data on this subject.

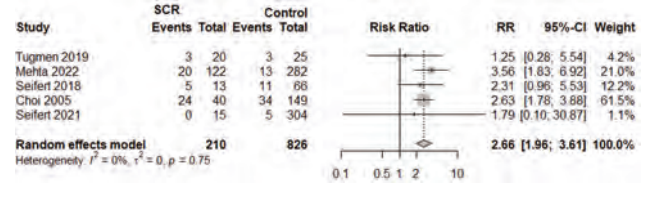
Methods: We conducted a comprehensive systematic search on PubMed, EMBASE, and the Cochrane Library from inception to May 16th, 2023. We included studies involving adult patients (>18 years old) who underwent kidney transplants and exhibited SC-TCMR detected through surveillance biopsy. Studies involving non-human subjects or lacking available data were excluded. The primary outcome measure was death-censored allograft loss, while the secondary outcome was subsequent rejection. A random-effects model was used to determine the risk.

Results: A total of nine studies were selected, encompassing a pooled population of 2,423 patients. SC-TCMR was found to be associated with an increased risk of death-censored graft loss (Risk ratio (RR) 1.78, 95% confidence interval (CI) 1.03 to 3.07), although heterogeneity was high (I2 69%). Furthermore, SC-TCMR was also associated with a higher risk of subsequent rejection (RR 2.66, 95% CI 1.96 to 3.61, I2 0%).

Conclusions: SC-TCMR diagnosed through surveillance biopsy was found to be linked with an elevated risk of subsequent rejection and death-censored graft loss.



Forest plot of the association between Subclinical T cell mediated rejection (SC-TCMR) and death-censored graft loss



Forest plot of the association between Subclinical T cell mediated rejection (SC-TCMR) and subsequent rejection

SA-OR66

Cell Subtypes and Cell-Specific Pathways Associated with Acute-to-Chronic Injury Transition in Posttransplant AKI

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Background: Kidney transplants (KT) offer a unique opportunity to evaluate molecular pathways involved in development and response to acute kidney injury (AKI). This study of transplanted kidneys with AKI aims to identify cells involved in injury or impaired reparation.

Methods: A total of 14 kidney samples (normal donor kidneys, n=5, normal allografts, n=4, and samples from patients with post-KT AKI, n=4 (<6weeks post-KT)) were evaluated using single nuclei (sn) RNA-seq.

Results: The analyses of 49,787 combined nuclei showed increased fibroblasts in post-KT AKI samples. Fibroblasts in post-KT AKI compared to normal allografts showed increased expression of genes enriched in extracellular matrix (ECM) organization, proteoglycans, ecollagen formation, and response to wounding. The analyses of these fibroblasts in 3 sex-mismatched cases using an XY-gene expression signature showed both donor- and recipient-derived fibroblasts (**Fig 1A**) not observed in normal allografts. Up-regulated genes in recipient fibroblasts were enriched in laminin interactions, ECM organization, and cellular response to TGF-β stimulus. Increased macrophages (MΦ) proportions in AKI samples, and 3 MΦ subsets were identified, including: MΦ1 (*MRC1, LGMN, STAB1*) and MΦ3 (*FCN1, LYN1, KYNU1, RTN11*), and the MΦ2 (*CSF3R, LUCAT1, NCF1, LIMK2*) (**Fig 1B-C**) characterized by markers of myofibroblasts/fibroblast-like (*COL18A1, COL4A3, COL4A4, VCAN, AB3BP, FGL2, GAS6, THSD4*). Resident and infiltrating MΦ present a pro-inflammatory profile and enriched in immunoregulatory response signaling pathways.

Conclusions: These novel data emphasize the critical role of resident MΦ in responding to injury transform into MΦ with fibroblast-like markers and a transcriptomic phenotype leading to impaired repair.

Funding: Other NIH Support - R01DK109581-01 and R01DK122682-01

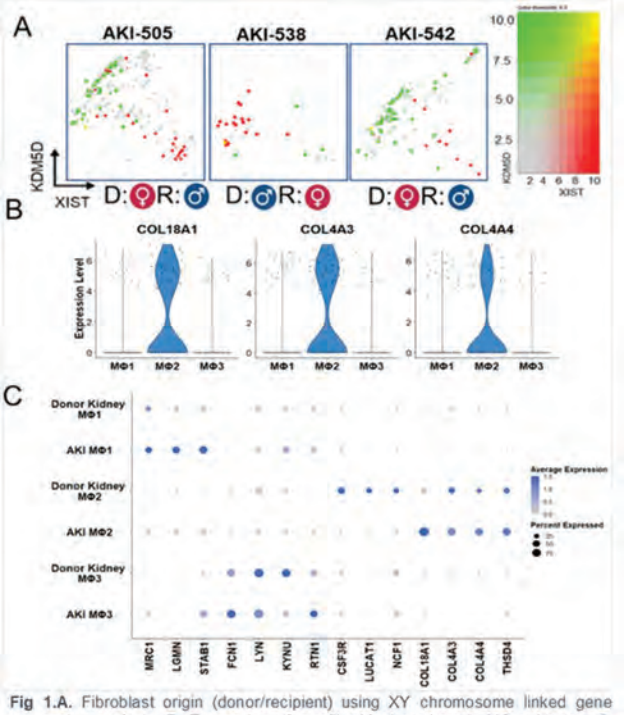

Fig 1.A. Fibroblast origin (donor/recipient) using XY chromosome linked gene expression analysis. **B.** Expression of myofibroblast markers in MΦ subtypes. **C.** MΦ subcluster DEGs represented by dot plot analysis.

SA-OR67

Suitability to Donate and Attitude Toward Living Kidney Donation in Older Adults: Results from the BIS Study

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Background: Guidelines differ regarding thresholds of glomerular filtration rate (GFR) and albuminuria (ACR) to accept living kidney donation (LKD). We aimed to assess the proportion of community-dwelling older adults suitable to LKD according to different GFR and ACR thresholds, and their attitude towards LKD.

Methods: We used data from the BIS-study, a cohort of adults aged ≥70 years. Kidney-related contraindications to LKD were defined using KDIGO (high and low GFR thresholds of 90 and 60ml/min/1.73m2 using the EKFC equation based on creatinine and cystatin C, respectively; LKD can be discussed between these thresholds) and British Transplantation Society (BTS; age- and sex-specific GFR thresholds) guidelines. The ACR thresholds were 30mg/g (low threshold for both guidelines), 100mg/g (high KDIGO threshold), and 300mg/g (high BTS threshold). Participants' attitude towards LKD was asked at the first follow-up visit.

Results: Among the 2069 participants (median age 80 years, 53% women, median estimated GFR 63ml/min/1.73m2), none had an estimated GFR above the high KDIGO GFR threshold at baseline. Considering the combination of other GFR and ACR thresholds, prevalence of renal contraindication to LKD ranged from 38 to 54%. Ninety-three percent of participants presented ≥1 non-kidney-related contraindication to LKD, among which heart failure, coronary artery disease, and cancer were the most frequent. Prevalence of suitability to LKD ranged from 0 to 6%, depending on combinations of thresholds of GFR and ACR. After an 8-year follow-up period, 11 to 16% of participants suitable to LKD at baseline maintained their suitability criteria, 6 to 11% had died, and none of them developed CKD stage 4-5. Overall, 73% of all participants agreed to donate a kidney to a relative, but this percentage rose to 85 to 87% in participants suitable to LKD.

Conclusions: Most older adults were theoretically willing to donate a kidney to a relative. Regardless of the low percentage of participants without any contraindication to LKD, their absolute sample size could be an opportunity to increase the number of kidney donors at the population level. To this purpose, the choice of GFR and ACR thresholds may be crucial.

Funding: Government Support - Non-U.S.

SA-OR68

The Association Between Potassium Intake and Risk of CKD

Hyo Jeong Kim,[1,2] Hee Byung Koh,[3] Tae ik Chang,[4] Connie Rhee,[5] Diana S. Kalantar,[5] Kamyar Kalantar-Zadeh,[5] Seung Hyeok Han.[2] *[1]Gangnam Severance Hospital, Seoul, Republic of Korea; [2]Yonsei University Institute of Kidney Disease, Seodaemun-gu, Seoul, Republic of Korea; [3]Catholic Kwandong University International Saint Mary's Hospital, Incheon, Republic of Korea; [4]National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [5]University of California Irvine School of Medicine, Irvine, CA.*

Background: High dietary potassium intake is associated with lower risk of cardiovascular disease. However, the association between potassium intake and chronic kidney disease (CKD) development in the general population is uncertain.

Methods: From UK biobank cohort, we included 317,162 participants without CKD between 2006-2010. The main predictor was spot urine potassium-to-creatinine ratio (KCR) as a surrogate of potassium intake. The primary outcome was incident CKD, defined by ICD-10 and OPCS-4 codes. In secondary analyses, we examined dietary potassium intake as an additional predictor in 141,180 participants who completed 24-h dietary recall questionnaires.

Results: At baseline, individuals with higher KCR had lower levels of blood pressure, BMI, and inflammation were less likely to have diabetes and hypertension vs. those with lower KCR. During a median follow-up of 11.9 years, the primary outcome occurred in 15,255 (4.8%) participants. In cause-specific models, the adjusted hazard ratio (aHR) per 1-SD increase in KCR for incident CKD was 0.90 (95% confidence interval [CI], 0.89-0.92). In addition, compared with quartile (Q)1 of KCR, the aHRs (95% CIs) for Q2, Q3, and Q4 were 0.98 (0.94–1.02), 0.90 (0.86–0.95), and 0.80 (0.76–0.84), respectively. In secondary analyses, higher potassium consumption was also inversely associated with risk of CKD. Compared with Q1 of dietary potassium intake, the corresponding aHRs (95% CIs) for each Q were 0.85 (0.78–0.92), 0.73 (0.67–0.81), and 0.67 (0.60–0.75), respectively.

Conclusions: In this large-scale population-based cohort study, higher urinary potassium excretion and dietary potassium intake were significantly associated with a lower risk of incident CKD development. Our findings provide new insight into dietary interventions among healthy adults to prevent CKD development.

Table 1. HRs for the incident CKD outcomes according to spot urinary KCR and dietary potassium intake

Main cohort	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Continuous						
per SD increase	0.86 (0.85 - 0.84)	<0.001	0.86 (0.84 - 0.88)	<0.001	0.90 (0.88 - 0.92)	<0.001
Quartile						
Q1	reference		reference		reference	
Q2	0.99 (0.94 - 1.03)	0.509	0.92 (0.89 - 0.97)	<0.001	0.98 (0.94 - 1.02)	0.308
Q3	0.88 (0.85 - 0.92)	<0.001	0.83 (0.79 - 0.86)	<0.001	0.90 (0.86 - 0.94)	<0.001
Q4	0.72 (0.68 - 0.75)	<0.001	0.70 (0.67 - 0.74)	<0.001	0.80 (0.76 - 0.84)	<0.001
Secondary cohort	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Continuous						
per SD increase	0.84 (0.81 - 0.87)	<0.001	0.84 (0.82 - 0.87)	<0.001	0.93 (0.79 - 0.87)	<0.001
Quartile						
Q1	reference		reference		reference	
Q2	0.85 (0.78 - 0.92)	<0.001	0.84 (0.78 - 0.91)	<0.001	0.85 (0.78 - 0.92)	<0.001
Q3	0.72 (0.66 - 0.78)	<0.001	0.72 (0.66 - 0.78)	<0.001	0.73 (0.67 - 0.81)	<0.001
Q4	0.65 (0.60 - 0.70)	<0.001	0.66 (0.60 - 0.71)	<0.001	0.67 (0.60 - 0.75)	<0.001

Model 1: unadjusted

Model 2: age, sex, BMI, Townsend deprivation index, handgrip strength, alcohol history, smoking history, SBP, medication history including statin, RAAS blocker, diuretics, past medical history including diabetes, cardiovascular disease

Model 3: Model 2+ laboratory parameters including hemoglobin, albumin, log-transformed hs-CRP, total cholesterol, log-transformed urinary NaCr. In secondary analysis dietary energy, dietary protein, and dietary fiber intake were further adjusted.

Note: Primary outcome was incident CKD, defined based on ICD-10 and OPCS-4 codes. Secondary cohort includes participants who completed 24-hour dietary recall questionnaire and dietary potassium intake was used as a predictor.

Abbreviations: CKD, chronic kidney disease; KCR, potassium-to-creatinine ratio; HR, hazard ratio; CI, confidence intervals; SD, standard deviation; BMI, body mass index; SBP, systolic blood pressure; RAAS, renin-angiotensin-aldosterone system; hs-CRP, high sensitivity C reactive protein; NaCr, sodium-to-creatinine ratio; ICD, international classification of diseases; OPCS, operating procedure codes; supplement.

SA-OR69

Estimated Potassium Intake in Patients with CKD Is Associated with CKD Progression: The Fukuoka Kidney Disease Registry (FKR) Study

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Background: Higher potassium intake is associated with a lower odds ratio of chronic kidney disease (CKD) prevalence among the general population. On the other hand, because of the limited evidence examining the benefits and risks of encouraging potassium intake or restricting potassium in patients with CKD, the Kidney Disease Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative guidelines only recommend potassium restriction in hyperkalemic patients with CKD, without making any recommendations regarding potassium intake.

Methods: A total of 4,092 patients aged 18 years or older in Japan were prospectively followed for 5 years using data from the Fukuoka Kidney Disease Registry (FKR) Study. Patients were divided into quartiles according to estimated potassium intake (EPI) levels assessed by the Tanaka formula from spot urine samples (Q1: <1609.5, Q2: 1609.5–1887.2, Q3: 1887.2–2184.4, Q4: >=2184.4 mg/day). The primary outcome was a progression of CKD defined as a composite of a 1.5-fold increase in creatinine from baseline and/or development of end-stage kidney disease. We estimated the relationship between EPI levels and outcomes using Cox proportional hazards models and Fine–Gray models.

Results: A total of 1,407 patients developed primary outcome during follow-up periods with an incidence rate of 89.0 per 1,000 person-years. Patients in Q1 had a significantly higher hazard ratio (HR) for the progression of CKD than those in Q4 in the multivariable-adjusted Cox proportional hazards models (multivariable-adjusted HR [95% confidence interval {CI}], 1.33 [1.10–1.59]). The HR (95% CI) for each 1-SD decrease in EPI levels was 1.13 (1.06–1.22, p <0.05). Similarly, patients in Q1 had a significantly higher subdistribution HR for the progression of CKD than those in Q4 in the multivariable-adjusted Fine–Gray model with all-cause death as a competing risk (subdistribution HR [95% CI], 1.29 [1.08–1.55], p <0.05).

Conclusions: Lower estimated potassium intake is associated with the progression of CKD among patients with CKD. Future studies are needed to determine whether increasing potassium intake has an impact on preserving kidney function.

SA-OR70

Association of Dietary Potassium and Fiber Intake with Death Risk in a Prospective Hemodialysis Cohort

Yoko Narasaki,[1] Kamyar Kalantar-Zadeh,[2] Seung Hyeok Han,[3] Tae ik Chang,[4] Diana S. Kalantar,[1] Tracy Nakata,[1] Danh V. Nguyen,[1] Connie Rhee.[1] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [4]National Health Insurance Service, Wonju, Gangwon-do, Republic of Korea.*

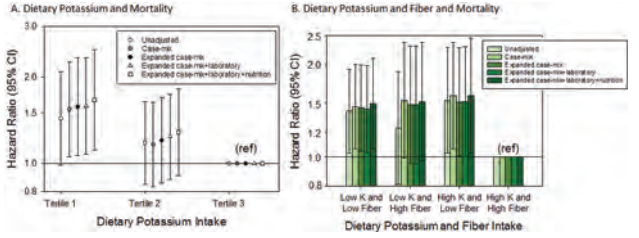
Background: In ESKD patients, guidelines recommend dietary potassium (K) restriction given concerns about potential hyperkalemia leading to malignant arrhythmias and mortality. Yet there are sparse data informing recommendations for dietary K intake in this population. We examined the relationship between dietary K intake and death risk in a prospective HD cohort.

Methods: In 687 hemodialysis patients from the multi-center NIH MADRAD cohort recruited from 16 outpatient dialysis clinics, dietary K intake data were obtained using protocolized Food Frequency Questionnaires (FFQs) administered over 10/2011-9/2022. We examined associations of dietary K intake categorized as tertiles with mortality using multivariable Cox regression. Given the high fiber content of plant-based K-rich foods, we also examined different pairings of dietary K and fiber intake across four exposure groups (low K/low fiber, low K/high fiber, high K/low fiber, high K/high fiber) with survival.

Results: In expanded case-mix analyses, the lowest dietary K intake tertile was associated with higher mortality (ref: highest tertile): HR (95%CI) 1.58 (1.07, 2.33) (Fig A). After further adjustment for laboratory+nutritional covariates, associations showed greater magnitude of risk: HR (95%CI) 1.66 (1.11, 2.49). In adjusted analyses of dietary K/fiber pairings, patients with low K/low fiber intake and those with high K/low fiber intake had worse survival vs. those with high K/high fiber intake: HRs (95%CIs) 1.45 (1.04, 2.00) and 1.51 (1.03, 2.28), respectively (Fig B).

Conclusions: In a prospective HD cohort, lower dietary K intake was associated with higher mortality. When examined in combination with fiber intake, both low K/low fiber and high K/low fiber intake were associated with worse survival. These findings suggest excessive dietary K restriction as well as high K intake from foods with lower fiber content (animal-based sources) may be deleterious in HD patients. Further studies are needed to determine the optimal amount and sources of dietary K intake in ESKD.

Funding: NIDDK Support



SA-OR71

Effects of a Whole-Food, Plant-Based Nutrition Education Program on Blood Pressure and Potassium Levels in CKD

Scott E. Liebman,[1] Ted D. Barnett,[2] Thomas M. Campbell,[1] Luojing Chen,[1] Susan Friedman,[1] Shamsul Hasan,[1] Thu H. Le,[1] Rebeca D. Monk,[1] Nellie Wixom,[1] Anne Zhang,[1] Erin K. Campbell.[1] *[1]University of Rochester Medical Center, Rochester, NY; [2]Rochester Lifestyle Medicine Institute, Rochester, NY.*

Background: Evidence suggests adoption of a predominately whole food plant based diet (WFPBD) may be beneficial in management of CKD. Concerns over adherence and the potential for hyperkalemia may limit enthusiasm for this approach. This pilot trial tested the hypothesis that individuals with CKD 3 or 4 who attend an education program (known as Jumpstart [JS])- designed to foster lifestyle changes including adoption of a WFPBD via a combination of lectures, support systems and food demonstrations - would achieve lower blood pressure (BP) without an increased risk of hyperkalemia.

Methods: 40 subjects with CKD 3 or 4, with HTN but without proteinuria or hyperkalemia, were randomized to attend the JS education program or not (controls). Participants had vital signs, laboratory studies, and food diaries done before and at the completion of the 15 day JS program (or equivalent times for the controls). At the end of the trial, t-tests were use to compare values between the intervention and control groups.

Results: JS participants (n = 20) saw a greater decrease in systolic BP from baseline to day 15 compared with controls (n = 20) but this did not reach statistical significance (-8 vs 2.8 mm Hg, p=0.12). Potassium changed by -0.01 mEq/L in the JS group and -0.08 mEq/L in the control group (p=0.62). JS subjects had a statistically significant decrease in body mass (3.0 vs. 0.12 kg, p< 0.0001) BMI (1.08 vs. 0.18, p= 0.0002), total cholesterol (39.35 vs. 4.95 mg/dl, p< 0.0001), LDL (28.35 vs. 0.6 mg/dl), HDL (8.15 vs. 0.4 mg/dl, p=0.008) and BUN (7.35 vs. 0.75 mg/dl, p=0.0001) compared with controls. Changes in albumin, phosphorus, PTH, other chemistry values, and measures of urinary 8-isoprostane, a marker of oxidative stress, were not different between the groups.

Conclusions: Subjects with CKD 3 or 4 attending the 15-day JS program emphasizing a WFPBD had non-significant reductions in systolic BP without increased risk of hyperkalemia. JS attendees achieved greater reduction in weight, BMI and most cholesterol values, without adverse effects on albumin and phosphorus. Larger trials are warranted to investigate potential long-term benefits of this approach.

Funding: Clinical Revenue Support

SA-OR72

Effect of Dietary Acid Reduction with Fruits and Vegetables vs. Oral NaHCO3 on Parameters of Cardiovascular Health in Stage 1 CKD: A 5-Year Randomized Trial

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Background: Patients with macroalbuminuric (urine albumin-to-creatinine ratio [ACR] > 200 mg/g cr) chronic kidney disease (CKD) have increased cardiovascular disease (CVD) risk. As high acid-producing diets are associated with increased CVD risk, we compared effects of base-producing fruits and vegetables (F+V) vs. oral NaHCO3 on contributors to cardiovascular health and on indices of CVD risk in participants with normal eGFR (> 90 ml/min/1.73 m2 or stage G1).

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants on ACE inhibitors were randomized to receive F+V (n=51) in amounts to reduce dietary potential renal acid load 50%, oral NaHCO3 (HCO3, n=51) 0.4 meq/kg bw/day, or no additional intervention (Usual Care, n=51). They were followed annually for 5 years, measuring systolic blood pressure (SBP), eGFR, isoprostane 8-isoprostaglandin F2α (8-iso), BMI, ACR, and Lp(a). Mixed linear regressions with random person intercepts tested differential group trajectories, p-values from the relevant interaction terms are included below.

Results: We highlight group differences at year-5 for brevity and provide p-values from the full model. At 5 years, SBP and BMI were lower in F+V than HCO3 and UC (SBP [mean (SE)], F+V[128.9 (0.70)], HCO3 [135.0 (0.73)], UC [134.6 (0.62)], mm Hg, ps<0.001); BMI, F+V [27.0 (0.25)], HCO3 [28.4 (0.26)], UC [28.0 (0.30)], ps<0.001). For both F+V & HCO3 relative to UC, 5-year eGFR was higher (eGFR, F+V [96.5(0.79)], HCO3 [95.9 (0.96)] vs. UC [92.1 (1.23), ml/min/1.73 m2, ps<0.001]) and 8-iso was lower (8-iso, F+V [1.08 (0.02)], HCO3 [1.06 (0.02)] vs. UC [1.27 (0.03)], μg/g cr, ps<0.001]). Five-year Lp(a) was lower in F+V than HCO3 and UC (Lp(a), F+V [53.3 (1.2)], HCO3 [62.2 (1.4)], UC, [60.8 (1.5), mg/dl, ps<0.001]). Furthermore, 5-year ACR was lower for F+V and HCO3 than UC (F+V [306 (8.5)], HCO3 [308 (8.4)] vs. UC [416 (15), mg/g cr, ps<0.001]).

Conclusions: Dietary acid reduction with either F+V or NaHCO3 over 5 years yielded similar eGFR preservation, systemic oxidative stress reduction, and lower ACR benefits. Dietary acid reduction with F+V compared to NaHCO3 and UC yielded better SBP control, lower BMI and lower Lp(a) and yielded better overall CVD protection in macroalbuminuric patients with initially normal eGFR.

SA-OR73

Food Insecurity, Dietary Intake, and Mortality Among Adults with CKD

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Background: Food insecurity in adults has been associated with a higher risk of diabetes, hypertension, chronic kidney disease (CKD), and mortality. We sought to examine the role of dietary intake in mortality risk due to food insecurity in adults with CKD.

Methods: We used data from the National Health and Nutrition Examination Survey (1999–2018) to assess differences in demographics, comorbidities, socioeconomic status (SES), and dietary intake in food secure versus food insecure adults with CKD (*N*=8935). Marginal, low, or very low household food security defined food insecure. Using publicly available mortality-linked data, we explored mortality related to food insecurity, food intake, and other risk factors using Cox regression.

Results: Approximately 22% of adults with CKD reported food insecurity. These adults were younger, had lower SES and rates of health insurance, were more likely to be from a racial minority group, and had higher prevalence of obesity and diabetes. Food insecure adults had overall higher calorie intake, but fiber and potassium intake were lower, while carbohydrate and sodium intake were higher. Adjusting for demographics only, food insecure adults had a higher mortality rate (HR=1.46, *P*<0.0001). Risk decreased when comorbidities, income, and education were considered (HR=1.22, *P*=0.006). Dietary intake did not further reduce this association.

Conclusions: Differing nutrient intake was seen in adults with CKD and food insecurity, yet these differences did not attenuate food insecure-related mortality risk; however, the potential role of diet in inducing comorbidities overtime is not excluded. Future work may consider the higher risk of comorbidities in food insecure adults with CKD to improve health outcomes.

Funding: Other U.S. Government Support

Measure	% or Mean			Measure	% or Mean		
	Food Secure	Food Insecure	p-value		Food Secure	Food Insecure	p-value
Demographics:				*SES: (%)*			
Age (years)	61.5	52.5	***<.0001***	Income < $45k/year	48.9	77.2	***<.0001***
Male (%)	43.0	40.6	0.10	Health insurance	91.7	75.4	***<.0001***
Race/Ethnicity: (%)				No HS diploma	20.9	36.3	***<.0001***
Non-Hispanic White	75.9	46.4	***<.0001***	*Daily Dietary Intake:*			
Non-Hispanic Black	9.9	19.5	***<.0001***	Total Calories (kcal)	1,897	1,988	***0.0039***
Other Non-Hispanic	9.1	19.4	***<.0001***	Protein (g)	73	75	0.1708
Mexican	3.5	10.1	***<.0001***	Carbohydrates (g)	228	241	***0.0012***
Other Hispanic	5.0	14.7	***<.0001***	Total Fat (g)	73	75	0.1579
Comorbidities: (%)				Fiber (g)	15.5	14.5	***0.0023***
Obesity	39.7	49.6	***<.0001***	Sodium (mg)	3,126.3	3,246.8	***0.0384***
Diabetes	26.5	36.7	***<.0001***	Potassium (mg)	2,540.4	2,369.8	***<.0001***
Hypertension	65.6	61.4	***<.0001***				

SA-OR74

Dietary Inflammatory Potential and Kidney Function in the Hispanic Community Health Study/Study of Latinos

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Background: Inflammation is implicated in the pathogenesis and progression of CKD. Diet modulates chronic inflammation and possibly kidney health. We evaluated the association of diet-related inflammation and kidney function among US Hispanic/ Latino adults.

Methods: Data were from participants in the Hispanic Community Health Study/ Study of Latinos (HCHS/SOL), a population-based study of Hispanic/Latino adults 18-74 years old from 4 US communities, who were examined at visit 1 (V1) (2008-2011) and visit 2 (V2) (2014-2017) and had data on dietary intake and serum creatinine. Dietary inflammatory potential was assessed using the dietary inflammatory index (DII®). Scores were adjusted for total energy intake (E-DII®) and categorized into tertiles: T1 having the lowest dietary inflammatory potential, and T3 having the highest (most pro-inflammatory). Creatinine-based eGFR was calculated using the 2021 CKD-Epi equation. Primary outcomes were incident CKD (eGFR <60 ml/min/1.73m² at V2 and ≥25% eGFR decline from V1 to V2) and rapid kidney function decline (RKFD) (≥30% decline in eGFR from V1 to V2). We excluded participants with eGFR <15 ml/min/1.73m², and for incident CKD, those with eGFR <60 ml/min/1.73m² at V1. Logistic regression models adjusting for study center and baseline socio-demographics, comorbidities, behavioral factors, medications, anthropometric measures, eGFR and albuminuria were used to compare E-DII® tertiles and determine odds ratio for incident CKD and RKFD.

Results: Of 10,574 participants, median age was 49 years, 22% had diabetes, 46% had hypertension. Median eGFR was 101.7 ml/min/1.73m². Median E-DII® was 0.18 (IQR -1.06 to 1.30). Over a mean follow-up of 6 years, 122 incident CKD and 196 RKFD events occurred. Participants with the most pro-inflammatory dietary patterns compared to the lowest had 2.2-fold higher odds of incident CKD (95% CI: 1.14 – 4.31) after adjusting for covariates. The E-DII® was not significantly associated with RKFD.

Conclusions: A pro-inflammatory dietary pattern is associated with a higher likelihood of incident CKD among US Hispanic/ Latino adults. To prevent kidney disease, US Hispanic/ Latino adults may opt to reduce intake of foods with higher pro-inflammatory potential (e.g., processed or fried foods, red meat, sweetened beverages).

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SA-OR75

Personalized Patient Education on Lifestyle Modification and Nutrition Management in CKD Using ChatGPT

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Background: Lifestyle modifications are critical for managing CKD. Patients struggle to access reliable information on modifying lifestyle. AI-based natural language processing technology, like ChatGPT, has the potential to provide information on lifestyle modification and nutrition. This study aimed to evaluate the effectiveness of ChatGPT in providing education by addressing questions related to lifestyle modification and nutrition in CKD.

Methods: 15 frequently asked questions were generated using the Kidney Disease Improving Global Outcomes (KDIGO) guidelines "CKD evaluation and management 2012", "Diabetes in CKD 2022", and "Lipids in CKD 2013". The questions were categorized into 4 steps to evaluate the versatility of ChatGPT in generating responses. ChatGPT (March 23 Version) provided responses were evaluated by nephrologists and compared to KDIGO guidelines.

Results: Overall the response to addressing patient queries for original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with incomplete sentences, and paraphrased questions with misspelled words were similar. ChatGPT provided accurate responses to 13 out of 15 FAQs across various complexity levels and paraphrasing variations. In 2 questions some statements made by ChatGPT could have been misleading to patients, such as "medications like erythropoietin stimulating agents and phosphate binders may affect the patient's ability to engage in physical activity." Statements such as "high protein intake can result in accumulation of metabolites like ammonia in tubular cells" and "excessive protein intake can activate renin angiotensin aldosterone system" could be confusing to providers when these statements are not proven in human studies. Consultation with nephrologist was encouraged by ChatGPT in all the questions.

Conclusions: This research highlights the potential of ChatGPT as an effective tool for providing patient education. ChatGPT's response in addressing patient queries was comparable to the assessments provided by the KDIGO guidelines. Rare statements though made by ChatGPT could be misleading. Further advancements are necessary to enhance ChatGPT's performance in addressing more intricate aspects of lifestyle modification and nutrition management.

SA-OR76

Intradialytic Cycling Exercise Improves Arterial Stiffness in Hemodialysis Patients

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Background: Cardiovascular diseases are the main causes of death and morbidity in hemodialysis patients. Arterial stiffness is an essential predictor of cardiovascular mortality. Exercise has been shown to contribute vascular and physical benefits in healthy populations. Physical function would affect the quality of life in hemodialysis patients. Intradialytic cycling exercises provide regular exercise with good supervision. We conducted this randomized controlled project to examine the vascular and physical effects of intradialytic exercise in hemodialysis patients.

Methods: One hundred and fourteen hemodialysis patients were randomly assigned to either intradialytic cycling exercise group (EX) or to a regular care group (RC) for 12 months. We compared the effect of intradialytic cycling on arterial function (carotid-femoral pulse wave velocity, cfPWV) as primary endpoint and physical performance (gait speed and 5 times sit to stand) as secondary evaluations in these participants.

Results: Among 114 participants, 89 and 82 patients completed the tests at 6 and 12 months, respectively. We observed a significantly decrease in cfPWV in the EX group compared to the RC group (95% confidence interval (CI): (-5.71, -2.90), p <0.001). With further evaluation with GEE analysis, there was a significant difference on group-by-time interaction of cfPWV (p <0.001 both after 6 and 12 months). In the secondary outcomes, we observed a significantly faster gait speed in the EX group compared with RC group (95% confidence interval (CI): (0.03, 0.30), p =0.019). However, the difference in group-by-time interaction of gait speed between the two groups was not observed during further evaluation with GEE analysis (p =0.134 and 0.435, after 6 and 12 months, respectively). There were no significant differences in blood pressure, pulse rate, 5 times sit-to-stand test and body compositions between the two groups throughout the trial.

Conclusions: Our investigation demonstrated that cfPWV improved after intradialytic cycling exercise with significant benefit. In addition, profound benefit was revealed with a longer duration of exercise. Physical performance as gait speed also showed improvement in the exercise group. Therefore, intradialytic cycling is an effective exercise to achieve arterial health and physical performance in the hemodialysis population.

SA-OR77

Oxygen Consumption Recovery Is Delayed After the Long Interdialytic Period

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Background: Prolonged interdialytic periods leading to accumulation of uremic toxins and volume changes may be associated with alterations in ventilatory response to exercise. O_2 uptake (VO_2) kinetics during the early recovery period on cardiopulmonary exercise testing (CPET) have strong prognostic value in patients with heart failure and have the advantage of being independent of achieving maximal volitional effort. In this study, we sought to examine the effects of the long interdialytic interval on VO_2 kinetics.

Methods: We analyzed data from the ongoing, "Effects of long interdialytic intervals on Cardiovascular Functional Capacity (ECON)" study, a randomized crossover trial of patients on conventional HD. CPET was performed on three study visits: post-HD (baseline; BL), and at the end of a 2-day and the 3-day interdialytic intervals. VO_2 recovery (%) was calculated using the following formula: (VO_2 peak–VO_2 at minute 1 of recovery)/VO_2 peak.

Results: A total of 30 patients (n=19 men, mean [SD] age=54 [11] years, dialysis vintage=71.1 [63] months) were included in this analysis. No differences between visits were observed in VO_2Peak (BL=1.00 [IQR: 0.84-1.14] L/min; 2-day=0.96 [0.83-1.22] L/min; 3-day=0.99 [0.87-1.20] L/min; p=0.71) nor in VO_2 at ventilatory threshold (BL=0.67 [0.15] L/min; 2-day=0.67 [0.15] L/min; 3-day=0.68 [0.14] L/min; p>0.9). However, post-HD fatigue limited the patients' effort during the BL CPET, as reflected by a lower peak respiratory exchange ratio compared to non dialysis day visits (p=0.014). VO_2Recovery was lower during the 3-day interval (20 [9] %) compared to BL (25 [8] %; p=0.013), while no differences were observed between the 2-day interval (22 [11] %) and BL (p=0.11). Additionally, heart rate (p=0.044) and minute ventilation (p=0.025) after 1 minute of recovery were higher during the 3-day interval compared to BL.

Conclusions: The long interdialytic period may be associated with slowed replenishment of energy stores in peripheral muscles as reflected by the delay in VO_2 and ventilation recovery following maximal exercise. VO_2Peak assessment the same day following HD may be confounded by post-HD fatigue, therefore exercise recovery kinetics may provide incremental prognostic data and unveil subclincial pathophysiological alterations occurring during interdialytic intervals.

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SA-OR78

Liddle Syndrome Caused by Loss-of-Function Mutations in the Ubiquitin Ligase NEDD4L

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Background: Liddle Syndrome (Pseudohyperaldosteronism) is an autosomal dominant form of hereditary hypertension characterized by early-onset hypertension, hypokalemia, low blood aldosterone and renin levels, and metabolic alkalosis. In most patients it is caused by a pathogenic variant in the PY motifs (PPxY) of the b (*SCNN1B*) or g (*SCNN1G*) subunits of the amiloride-sensitive Epithelial Na^+ Channel, ENaC. Mutant ENaC exhibits increased retention and function at the plasma membrane in the distal nephron, increased reabsorption of luminal Na^+, increased circulatory blood volume and hypertension. These ENaC variants impair its binding to NEDD4L, an E3 ubiquitin ligase comprised of C2-WW(4)-HECT domain architecture. Impaired NEDD4L binding to ENaC leads to reduced cell surface ENaC ubiquitination, impaired channel endocytosis and degradation, thus explaining the increased retention of ENaC at the plasma membrane.

Methods: Targeted exome sequencing was used, which included *SCNN1A, SCNN1B, SCNN1G* and *NEDD4L*. The patient's variants on either allele of NEDD4L were generated by site-directed mutagenesis and tested for self-ubiquitination *in vitro*, substrate ubiquitination against a model substrate and against cell-surface αβγENaC in kidney Hek293T cells. Cell surface ENaC stability was analyzed in parallel.

Results: Unlike most Liddle syndrome patients with pathogenic *ENaC* variants, a subset of patients have normal ENaC. Here we describe the discovery of novel compound heterozygous pathogenic variants in the *NEDD4L* gene in a patient with Liddle syndrome and normal ENaC genes. Both parents are unaffected carriers. The maternal allele is a frameshift variant that yields a truncated NEDD4L protein devoid of the entire catalytic HECT domain. The paternal allele is a missense variant in the HECT domain that exhibits a severe loss of its enzymatic activity. This results in a dramatic reduction in ENaC ubiquitination, thereby increasing the stability of this channel at the plasma membrane.

Conclusions: This is the first demonstration of a novel recessive form of Liddle syndrome caused by loss of function of the ENaC suppressor NEDD4L. On this basis, it will be important to include *NEDD4L* in commercial hypertension gene panels to facilitate the diagnosis of other Liddle syndrome patients with normal *SCNN1* (ENaC) genes.

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SA-OR79

Recessive Variants in MYO1C as a Potential Novel Cause of Nephrotic Syndrome

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second leading cause of chronic kidney disease in the first three decades of life. The identification of monogenic causes of SRNS has revealed ~60 single-gene etiologies. While in 12-30% of patients with SRNS a causative variant may be detected, many remain without a molecular diagnosis (Sadowski *JASN* 26:1279, 2015).

Methods: To elucidate novel monogenic causes of NS, we performed whole exome sequencing (WES) in an international cohort of 1,382 NS patients.

Results: We identified homozygous missense variants in *MYO1C* in 2 unrelated children with nephrotic syndrome (c.2273 A>T, p.Lys758Met; c.292C>T, p.Arg98Trp). Myosins including MYO1C are actin-based molecular motors that actively participate in various cellular functions including intracellular trafficking, cell adhesion, motility and maintenance of membrane tension. Podocyte-specific MYO1C knockout shows MYO1C is critical for TGF-β-signaling in podocyte disease pathogenesis (Ehtesham *KI* 96:139, 2019). We evaluated publicly available kidney single-cell RNA sequencing datasets and found *MYO1C* to be predominantly expressed in podocytes (Cebrian *Development* 145:16, 2018). We then performed structural modeling in molecular viewer PyMol using the *super* function aligning shared regions within both partial structures (*4byf* and *4r8g)*. In both structures, calmodulin, a common regulator of myosin activity, is shown to bind to the IQ motif. At both residue sites (K758, R98W), there are ion-ion interactions stabilizing intradomain and ligand interactions: R98W binds to nearby D220 within the Myosin Motor Domain and K758 binds to E14 on a calmodulin molecule. Variants of these charged residues to non-charged amino acids could ablate these ionic interactions, weakening protein structure and function establishing the importance of these variants. Future *in vivo* knockout and mutagenesis models are required to confirm mutation pathogenicity.

Conclusions: We, here, identified recessive mutations in *MYO1C* as a potential novel cause of nephrotic syndrome in children.

SA-OR80

Circulating Nephrin Autoantibodies Are Present in Almost 2/3 of Steroid-Naïve Pediatric Idiopathic Nephrotic Syndrome

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Background: Children who present with idiopathic nephrotic syndrome (INS) are initially treated with corticosteroids (CS) and do not routinely require a renal biopsy unless they have atypical features or subsequent resistance to CS. We recently identified circulating nephrin autoantibodies in approximately 30% of children and adults with biopsy proven MCD. As the majority of these patients had already received CS prior to serum sampling we hypothesized that this likely underestimated the true prevalence of pediatric nephrin autoantibody positive INS.

Methods: In this North American, multicenter, prospective study (via the Pediatric Nephrology Research consortium (PNRC)) we evaluated serum samples obtained from children at presentation and following GC monotherapy for nephrin autoantibodies by indirect ELISA. A threshold for positivity was determined from a healthy control cohort without renal disease. Patients received either no GC therapy (steroid naïve) or up to 2 days of GC therapy (minimal steroids) prior to the initial presentation sample. Patients were categorized into steroid sensitive (SSNS) and steroid resistant (SRNS) dependent on whether they achieved complete remission within 7 weeks of GC monotherapy.

Results: The median age was 4 years (IQR 3-11years) and 45% male. Almost two thirds, 63% (n=12/19) of steroid naïve INS patients were positive for nephrin autoantibodies at initial presentation and of those 75% (n=9/12) became negative following CS therapy. Including patients with minimal steroids prior to initial presentation revealed that 59% (n=17/29) were nephrin autoantibody positive. In those children who were steroid naïve at initial presentation, 69% (n=9/13) with SSNS were nephrin autoantibody positive compared with 50% (n=3/6) with SRNS.

Conclusions: We found that just under 2/3 of children with INS who were steroid naïve at initial presentation were serologically positive for nephrin autoantibodies. Furthermore, we identified nephrin autoantibodies in both SSNS and SRNS, and although the mechanism of GC in INS remains to be determined, B-cell targeted therapies are effective in treating some patients with SSNS and SRNS. This raises the possibility that nephrin autoantibodies may serve as an important biomarker to guide B cell targeted therapies in both SSNS and SRNS.

Funding: Private Foundation Support

SA-OR81

Unveiling the Disproportionate Impact of Rare Kidney Diseases on Kidney Failure: A Longitudinal Analysis Using the UK National Registry of Rare Kidney Diseases (RaDaR)

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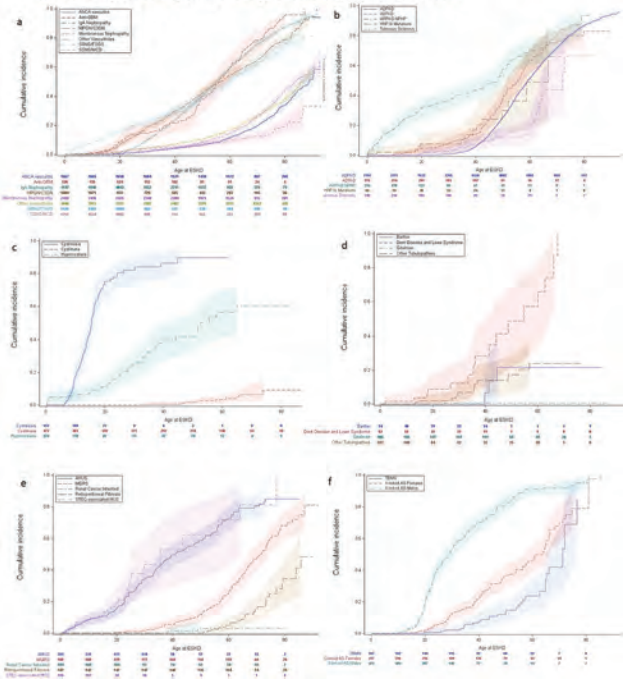
Background: Patients with rare kidney diseases account for <10% of people living with CKD, but make up 25% of prevalent patients on Renal Replacement Therapy (RRT). The natural history of rare kidney diseases are poorly described. Formed in 2010, RaDaR gathers longitudinal data from UK rare kidney disease patients. We used these data to study outcomes of death and RRT initiation for these conditions.

Methods: RaDaR recruited patients from 108 UK renal units. Incidence rates for mortality and ESKD were calculated and compared to those from unselected UK patients using population estimates of CKD and UK Renal Registry RRT incidence data. Cumulative incidence and Kaplan Meier survival estimates were calculated for a)Age at RRT start b) age at death c) time from RRT start to death d) time from diagnosis to eGFR thresholds allowing calculation of time from last eGFR ≥75 to first <30mls/min/1.73m^2 (therapeutic window).

Results: 27,293 patients in 20 Rare Disease Groups (RDGs) were included. RaDaR patients had higher 5 year incidence rates of ESKD compared to 2.81 million patients with all cause CKD (28% vs 1%) and better survival rates (Standardised Mortality Ratio 0.45, 95% CI 0.37-0.54). There was heterogeneity in median age at RRT start between RDGs (Fig 1). Time in therapeutic window varied between 20 years in Retroperitoneal Fibrosis to 1.3 years in Monoclonal Gammopathy of Renal Significance.

Conclusions: Patients with rare kidney diseases differ from the general CKD population: they are more likely to reach ESKD and half as likely to die with CKD stages 3-5, so are disproportionately represented in the RRT population. Successfully addressing unmet need in rare diseases may therefore have a disproportionate effect on RRT demand long term.

Figure 1: Cumulative incidence of End Stage Kidney Disease for a) Glomerular b) Cystic c) Metabolic d) Tubular e) Other kidney conditions f) Alport Syndrome



Characteristics and Outcomes for Neonates Receiving Dialysis

Characteristics	Total n=183	AKI n=105	ESKD n=55	Hyperammonemia n=15	Other/Unknown n=8
Gestational Age (wks)*	37 (36,39)	38 (37,39)	36 (34,37)	39 (38,40)	36 (36, 38)
Sex (male), n (%)	107 (58)	57 (54)	34 (62)	10 (67)	6 (75)
Race n (%)					
White	110 (6)	65 (62)	35(56)	7(47)	7(88)
Black	29 (16)	14 (13)	13(20)	3(20)	1(12)
Other	44 (24)	26 (25)	13(24)	5(33)	0
Birth Weight (g)*	2995 (2380,3290)	3137 (2686,3375)	2450 (2094, 3020)	3200 (2990-3610)	3175 (2646-3388)
CAKUT, n (%)*	68 (38)	11 (10.5)	52(95)	0	0
Baseline eGFR*	28.5 (16,40)	27.9 (15,40)	5.8 (4.2,7.7)	56.5 (27.2,71.9)	32.6 (12.4,44.9)
eGFR at dialysis initiation*	34.5 (9,16)	18.2 (10.9,29.3)	4.5 (3.2,8.5)	26.2 (10.2,35.4)	14.9 (8.2,25.5)
% above dry weight at dialysis initiation*^	13 (1,34)	23 (7,47)	50(12)	0 (0,2)	—
Age at dialysis initiation (days)*	8 (1,43)	9 (5,34)	7 (3,13)	4 (1,10)	10 (2.5,11.5)
Dialysis Indication, n (%)					
Fluid Overload	122 (67)	57 (53)	36 (47)	2 (13)	7 (88)
Anuria/Oliguria	96 (52)	62 (59)	31 (56)	0	3 (38)
Hyperkalemia	27 (15)	15 (14)	11 (20)	1 (7)	0
Uremia	51 (28)	25 (24)	24 (43)	0	2 (25)
Acidosis	21 (11)	15 (14)	6 (10)	0	0
IEM**	10 (5)	1 (1)	1 (2)	8 (53)	0
Hyperammonemia	17 (9)	2 (1)	0	15 (100)	0
Other	10 (5)	1 (1)	9 (16)	0	0
Initial dialysis modality, n (%)					
PD**	48 (26)	22 (21)	15 (46)	0	1 (13)
HD^^^	4 (2)	2 (2)	1 (2)	1 (7)	0
CAVH^^^	47 (26)	15 (14)	22 (40)	4 (27)	6 (75)
CRRT with ECMO	83 (45)	66 (63)	6 (11)	10 (67)	1 (13)
Unknown	1 (1)	0	1 (2)	0	0
Changed dialysis modality, n (%)	45 (25)	27 (26)	14 (25)	0	1 (12)
Death during initial dialysis admission, n(%)	96 (52)	62 (59)	26 (47)	5 (33)	3 (38)
Discharged/transferred on dialysis, n(%)	35 (19)	9 (9)	25 (45)	0	1 (13)
Dialysis modality at discharge, n(%)					
PD**	30 (16)	8 (8)	21 (38)	0	1 (13)
HD^^^	4 (2)	1 (1)	3 (5)	0	0
Other/Unknown	1 (1)	0	1 (2)	0	0

*Denotes median(IQR), ^CAKUT, **IEM= inborn error of metabolism, ^Formula for % above dry weight at initiation= [Weight (g) at initiation – estimated dry weight]/estimated dry weight, **PD= peritoneal dialysis, ^^^HD= hemodialysis, ^^^CRRT= continuous renal replacement therapy

SA-OR82

Contemporary Infant and Neonatal Dialysis (COINED) Study: Practice Patterns and Outcomes

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Background: Neonatal dialysis is technically challenging and rare. Prior neonatal dialysis research is primarily limited to medical claims/coding data. There are critical knowledge gaps specific to neonatal dialysis. Our objective was to describe contemporary neonatal dialysis demographics, access, modalities, complications, and outcomes.

Methods: This is a preliminary report from a multicenter retrospective cohort study of 14 centers in the Pediatric Nephrology Research Consortium. Neonates initiated on dialysis within the first 30 post-natal days between June 2017-May 2022 were enrolled. Neonates with a dialysis catheter placed post-cardiac surgery for fluid management without kidney dysfunction were excluded. Data were collected until initial hospital transfer/discharge.

Results: 183 neonates on dialysis were enrolled. 58% were diagnosed with acute kidney injury (AKI) and 30% with end-stage kidney disease (ESKD). The majority received some form of continuous kidney replacement therapy (CKRT) (71%). 25% experienced a change in dialysis modality, 52% died before hospital discharge, and 19% remained on dialysis at discharge/transfer on dialysis.

Conclusions: In this multicenter, cohort, a larger number of neonates received CKRT, many neonates changed dialysis modalities prior to discharge/transfer, and mortality rates are far greater than previously reported. Future research to inform development of evidence-based guidelines is needed to improve neonatal dialysis management and outcomes.

Funding: Private Foundation Support, Clinical Revenue Support

SA-OR83

Risk Factors and Impact of Peritoneal Podoplanin in Children on Chronic Peritoneal Dialysis

Maria Bartosova,[1] Conghui Zhang,[1] Fabian Eibensteiner,[2,5] Rebecca Herzog,[2,5] Iva Marinovic,[1] Betti Schaefer,[1] Karel Vondrak,[3] Bradley A. Warady,[4] Klaus Kratochwill,[2,5] Claus Peter Schmitt.[1] Int. Pediatric PD Biopsy Study Group. *[1]UniversitatsKlinikum Heidelberg, Heidelberg, Germany; [2]Medizinische Universitat Wien, Wien, Austria; [3]University Hospital Motol Prague, Prague, Czechia; [4]Children's Mercy Kansas City, Kansas City, MO; [5]Christian Doppler Laboratory for Molecular Stress Research in Peritoneal Dialysis, Medical University of Vienna, Vienna, Austria.*

Background: Diffuse, peritoneal podoplanin staining (DPS) positivity has been described with encapsulating peritoneal sclerosis (EPS) in patients on peritoneal dialysis (PD). The pathophysiological role in PD is uncertain.

Methods: Peritoneal tissues from 250 children (8.5, IQR 2.5, 13.2 years), with normal renal function (NRF), CKD5, and on chronic PD with fluids that contain low and high glucose degradation product (GDP) concentrations underwent digital histomorphometry and high-dimensional multiplexed imaging mass cytometry followed by deep learning-based segmentation and spatial single-cell and cellular neighbourhood interaction analysis.

Results: Children with NRF and CKD5 exhibited no DPS. 21% of children on low-GDP PD and 46% on high-GDP PD were DPS positive, but without clinical, radiological or histological features of EPS. PD duration and peritonitis incidence were similar in DPS positive and as in non-DPS PD patients. DPS positive patients were younger, had higher dialytic glucose exposure and more arteriolar lumen narrowing. Dialytic glucose exposure, PD duration, lower body surface area (BSA) and epithelial-to-mesenchymal (EMT) transformed cell counts were independently associated with DPS. DPS and lower mesothelial surface coverage independently associated with arteriolopathy. In subgroups matched for age, PD duration and dialytic glucose exposure, DPS positive children had higher submesothelial leucocyte (CD45+) and macrophage (CD68+) counts, and higher lipopolysaccharide and hyaluronan receptor CD44 abundance. DPS intensity was higher with history of peritonitis. Hierarchical clustering demonstrated highest similarity of DPS positive areas with CD68 positive areas, classified as M2 macrophages (CD68+CD163+), followed by fibroblastic cells (αSMA+PROX1-CD31-CD68-CD163-); DPS signals from M1 macrophages (CD68+CD163-) were low.

Conclusions: DPS is prevalent in children on PD devoid of EPS, and is independently associated with peritoneal arteriolopathy. Independent DPS risk factors are high dialytic glucose and GDP exposure, history of peritonitis, BSA, peritoneal inflammatory and EMT cell invasion; M2 macrophages presumably play a key role.

Funding: Government Support - Non-U.S.

SA-OR84

Preliminary Findings from the Phase 2 EPPIK Study of Sparsentan in Pediatric Patients with Selected Proteinuric Glomerular Diseases

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Background: Sparsentan (SPAR) is a novel, non-immunosuppressive, single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) approved by the US FDA for the treatment of adults with IgA nephropathy (IgAN) at risk of rapid disease progression and is being investigated for focal segmental glomerulosclerosis (FSGS).

The ongoing Phase 2 EPPIK study is examining the safety and long-term antiproteinuric and nephroprotective potential of SPAR in pediatric patients with FSGS, minimal change disease (MCD), IgAN, IgA vasculitis (IgAV), and Alport syndrome (AS). Here we report preliminary findings.

Methods: This open-label, single-arm, multicenter trial is evaluating the safety, efficacy, and pharmacokinetics of SPAR in ~30 patients aged 1-<18 years with FSGS and/or MCD (Population 1) and ~27 aged 2-<18 years with IgAN, IgAV, or AS (Population 2) over 108 weeks with a 4-week safety follow-up. SPAR is administered once daily in a liquid formulation with dose adjusted to body weight. Patients receiving RAASi undergo a 2-week washout prior to study medication start (baseline). Primary endpoints include safety and efficacy (change in urine protein/creatinine ratio [UP/C] from baseline over 108 weeks).

Results: At data cutoff (4/5/23) 23 participants had received ≥1 dose of SPAR. Baseline characteristics are shown in **Table**. UP/C decreased over 12 weeks by 26% and 52% in Populations 1 and 2 and 35% overall (**Figure**). SPAR has been safe and generally well-tolerated.

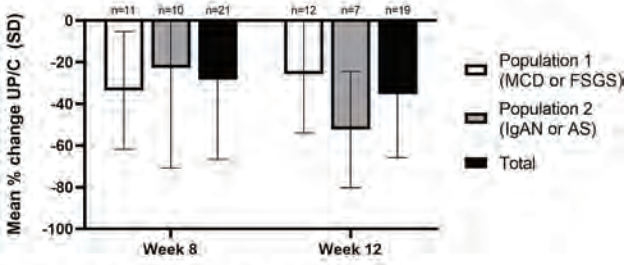
Conclusions: SPAR treatment reduced proteinuria over the initial 12 weeks in pediatric patients with a range of proteinuric glomerular diseases. SPAR was safe and generally well-tolerated, consistent with findings from ongoing FSGS and adult IgAN trials.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table: Baseline characteristics

	Population 1 (n=13)	Population 2 (n=10)	Total (N=23)
MCD/FSGS, n (%)	8 (61.5) / 5 (38.5)	–	8 (34.8) / 5 (21.7)
IgAN/AS, n (%)	–	3 (30.0) / 7 (70.0)	3 (13.0) / 7 (30.4)
Age at screening, years, median (IQR)	8 (6, 13)	13 (12, 14)	12 (7, 14)
UP/CR, g/g, median (IQR)	3.0 (2.5, 5.7)	2.5 (2.1, 3.2)	2.8 (2.3, 5.0)
Nephrotic range proteinuria, UP/C ≥2 g/g, n (%)	12 (92.3)	8 (80.0)	20 (87.0)
eGFR, mL/min/1.73m², mean (SD)	106 (50)	87 (27)	98 (42)
Immunosuppression at baseline, n (%)	8 (61.5)	1 (10.0)	9 (39.1)

Figure: Mean percent change from baseline in UP/C with 12 weeks SPAR treatment



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SA-OR85

Assessing Baseline Cardiovascular Disease for Kids Initiating Kidney Replacement Therapy: ABCD4Kids Study

Priyanka Khandelwal,[1] Jonas Hofstetter,[2] Claus Peter Schmitt,[2] Anette Melk,[3] Uwe Querfeld,[4] Franz S. Schaefer,[2] Rukshana Shroff.[1] 4C Study Consortium. *[1]Great Ormond Street Hospital for Children NHS Foundation Trust, London, United Kingdom; [2]Center for Pediatrics and Adolescent Medicine, University of Heidelberg, Heidelberg, Germany; [3]Department of Pediatric Kidney, Liver and Metabolic Diseases, Hannover Medical School, Hannover, Germany; [4]Charité Children's Hospital, Berlin, Germany.*

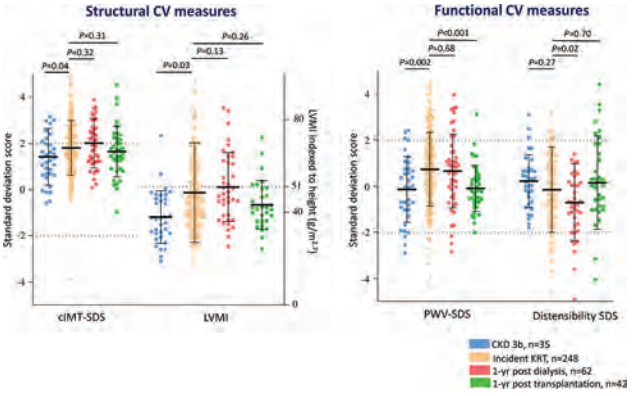
Background: Information on cardiovascular (CV) damage in children initiating kidney replacement therapy (KRT) is limited. We evaluated the CVD burden in incident dialysis and preemptive transplant recipients from two multicenter cohorts: Cardiovascular Comorbidity in Childhood CKD (4C) and Haemodiafiltration, Heart and Height (3H) studies.

Methods: The incident KRT cohort was compared with independent cross-sectional cohorts: CKD stage 3b (median eGFR 34 ml/min/1.73m²), 1-year on dialysis, and 1-year after transplantation. Structural (carotid intima-media thickness, cIMT-SDS, left ventricular mass index, LVMI) and functional (pulse wave velocity, PWV-SDS; and distensibility SDS) CVD indices were measured in all.

Results: 248 incident KRT patients, median age 14 yr, eGFR 12.2 ml/min/1.73m², 63% boys were studied. 82 (33%) were pre-emptively transplanted. At KRT initiation, pre-emptively transplanted patients had higher eGFR and lower 24-hr mean arterial BP, PWV-SDS and PTH compared to patients starting dialysis (P<0.01 for all). Incident KRT patients had significantly higher CV burden than the CKD3b cohort: elevated cIMT-SDS and PWV-SDS in 40% and 21% respectively and LV hypertrophy in 41% (**Fig**). Incident KRT patients had uncontrolled ambulatory (23%) and masked (21%) hypertension; whereas systolic BP and 24-hr mean arterial BP were lower following KRT initiation. While PWV-SDS was lower in transplanted patients, there was no difference in cIMT-SDS or LVMI (**Fig**). In incident KRT patients the independent predictors of PWV-SDS were systolic BP SDS (ß=0.36, P<0.001) and higher PTH (ß=0.27; P=<0.001). LVMI independently associated with systolic BP SDS (ß=0.30, P<0.001), higher BMI SDS (ß=0.20; P=0.001), lower hemoglobin (ß=0.17; P=0.008) and lower calcium (ß=0.15; P=0.01).

Conclusions: Incident KRT patients have a high burden of sub-clinical CVD comparable to that seen in chronic dialysis patients. Early intervention to manage modifiable risk factors is essential.

Funding: Government Support - Non-U.S.



SA-OR86

Molecular Pathways Associated with Early Vascular Calcification in Pediatric CKD

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Background: Children with advanced stages of chronic kidney disease (CKD) are at high risk of cardiovascular disease (CVD) and vascular calcification (VC) may already occur during childhood. This study comprehensively investigated the molecular pathways underlying early VC in children with CKD stage 5.

Methods: Arterioles from children with normal renal function and CKD5, (median age 8.9 and 8.8 years) were analyzed using digital quantitative histomorphometry, von Kossa staining and ^{18}F-sodium autoradiography (^{18}F-NaF) for calcium deposit quantification. Arteriolar transcriptome and proteome analyses were followed by gene set enrichment (GSEA) and Ingenuity pathway analysis. Based on literature mining, a VC pathway library was established consisting of 442 biological processes and molecular functions and associated genes were extracted from Gene Ontology database. The identified key molecular mechanisms were validated in independent pediatric CKD5 cohorts (n=32) and healthy controls (n=20) using quantitative immunostaining.

Results: Von Kossa staining did not reveal calcium deposits, but ^{18}F-NaF autoradiography demonstrated arteriolar microcalcifications in children with CKD5. Compared to children with normal renal function, the arteriolar lumen/vessel ratio was reduced (p=0.001), due to intima and media thickening (p<0.0001/0.02), together with CD68+ macrophage infiltration in the subendothelial space (p=0.001/0.02). Multi-omics VC pathway analysis identified 30 pathways primarily associated with actin cytoskeleton, Wnt signaling, extracellular matrix (ECM) organization, complement activation, apoptosis, and ossification regulation. In independent age-matched cohorts, two components of the Wnt pathway, DKK3 and Wnt2b, were decreased (p=0.0004/0.009). Fibronectin-1, a major regulator of ECM, was identified as a hub gene in VC and showed reduced abundance in children with CKD5 (p=0.001). Arteriolar osteoglycin, involved in ectopic bone formation, was increased in CKD5 (p<0.001).

Conclusions: Arteriolar microcalcifications are already present in young children with CKD5. We provide a comprehensive analysis of underlying molecular pathways and identified processes involved in vascular remodeling which open new avenues for potential therapeutic targets.

SA-OR87

Prospective Validation of the PERSEVERE-II AKI Prediction Model in Pediatric Septic Shock

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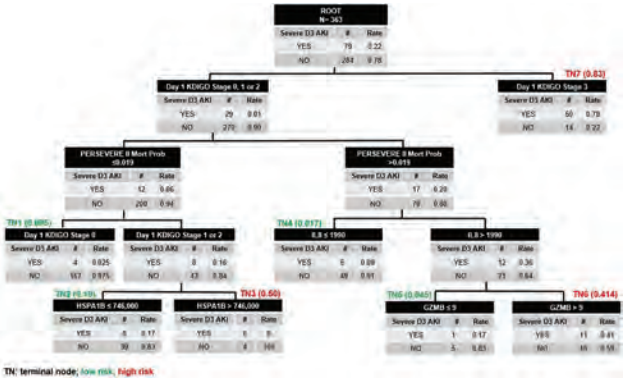
Background: Treatment of sepsis-associated AKI (SA-AKI) is supportive, without effective therapies. Identification of patients at risk for severe SA-AKI could facilitate targeted kidney protection and enrich future trials. We derived the multi-biomarker PERSEVERE-II AKI Model that predicts Day (D) 3 severe SA-AKI with strong test characteristics (AUC 0.95, 95%CI 0.92-0.98, sensitivity 92%, specificity 89%). We aimed to prospectively validate this tool.

Methods: Secondary analysis of a prospective study of patients aged 0-25 admitted to 11 PICUs with septic shock from 3/19 to 12/22. D1 PERSEVERE biomarker values (C-C chemokine ligand 3, granzyme B [GZMB], heat shock protein 70 kD 1B [HSPA1B], IL-8 and MMP8) were combined with platelet count to assign a PERSEVERE-II mortality probability (PII MP). D1 KDIGO Stage, PII MP, GZMB, HSPA1B and IL-8 levels were used to assign a D3 severe AKI probability (**Figure 1**). Model performance was assessed and compared to D1 serum creatinine (SCr) elevation.

Results: Seventy-nine of 363 subjects (22%) had D3 severe AKI. The model predicted D3 severe AKI with an AUC 0.89 (95%CI 0.85-0.93), sensitivity 77% (95%CI 66-86) and specificity 88% (95%CI 84-92). Compared to subjects with D1 SCr-based AKI, those predicted to have severe AKI by the model (n=94) had more D3 severe SA-AKI (65% *vs* 45, p=0.003) and kidney replacement therapy use (40% *vs* 26%, p=0.021), and lower rates of renal recovery from early AKI (37% *vs* 53%, p=0.019) (**Figure 2**). Model performance was superior to D1 SCr elevation above baseline (p=0.004).

Conclusions: We have prospectively validated the PERSEVERE-II AKI Model for prediction of D3 severe AKI in pediatric septic shock. The next step to translating this tool to the bedside is timely biomarker availability.

Funding: Other NIH Support - National Center for Advancing Translational Sciences of the National Institutes of Health (KL2TR001426, PI: Natalja L. Stanski). The original study was funded by National Institute of General Medical Sciences (R35GM126943, PI: Hector R. Wong).



	PERSEVERE-II AKI Model Predicted	Day 1 SCr AKI	p
N (%)	94 (26)	152 (42)	–
Age, yrs	10.7 (2.9-17.2)	11.6 (4.0-17.5)	0.24
Sex, n (% M)	50 (53)	84 (55)	0.75
PRISM III	13 (9-17)	11 (7-16.8)	0.06
PII MP	0.189 (0.019-0.33)	0.093 (0.007-0.30)	0.003
D3 Severe AKI, n (%)	61 (65)	69 (45)	0.003
AUC	0.89 (0.85-0.93)	0.82 (0.76-0.88)*	0.004
Sensitivity, %	77 (66-86)	87 (78-93)	
Specificity,%	88 (84-92)	71 (65-76)	
PPV, %	65 (54-74)	45 (37-54)	
NPV, %	93 (89-96)	95 (91-98)	
D1-7 KRT, n (%)	38 (40)	40 (26)	0.021
D1-2 AKI, n (%)	82 (87)	152 (100)	–
D3 Renal Recovery, n (%)	30 (37)	80 (53)	0.019
PICU-free days	13.5 (0-23)	20.5 (0-25)	0.012
Mortality, n (%)	13 (14)	13 (8.6)	0.19

*AUC for degree of SCr above Baseline

SA-OR88

IFNγ-Induced APOL1 Expression and Pyroptotic Angiopathy in Human Kidney Organoids Mirrors a Nephrotic Gene Signature in Patient Biopsies

Benjamin A. Juliar,[1] Ian B. Stanaway,[1] Kelly D. Smith,[1] Jennifer L. Harder,[2] Sean Eddy,[2] Matthias Kretzler,[2] Jonathan Himmelfarb,[1] Benjamin S. Freedman.[1] *[1]University of Washington School of Medicine, Seattle, WA; [2]University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: The cytokine interferon-γ (IFNγ) is an essential mediator of the innate immune response, including induction of apolipoprotein L1 (APOL1). Risk variants of APOL1 can cause glomerular nephropathy in coordination with inflammatory stimuli, but how distinct nephron segments are affected by IFNγ itself during glomerular disease progression remains poorly characterized.

Methods: Cell-type dependent changes in organoid gene expression and morphometrics were quantified with single-cell RNA sequencing and quantitative fluorescence-based assays. RNA-sequencing of kidney biopsies quantified relative differences in gene expression between patient cohorts depending on disease severity.

Results: IFNγ-mediated expression of APOL1 in wild-type kidney organoids was accompanied by endothelial network degradation (**Fig1A**) and upregulation of pyroptosis-associated genes across organoid cell types, especially endothelial cells (ECs) (**Fig1B**). Transcriptional profiling identified a similar pyroptotic gene signature in biopsies from patients with poor clinical outcomes. Pharmacological blockade of IFNγ signaling inhibited APOL1 expression, prevented upregulation of pyroptosis-associated genes, and rescued the endothelial network in organoids.

Conclusions: Our results suggest that simultaneous triggering of endothelial insult and epithelial priming towards pyroptosis by IFNγ may synergistically contribute to APOL1-mediated disease progression (**Fig2**), which can be targeted therapeutically.

Funding: Other NIH Support - NIH Awards: U01DK127553, UG3TR003288, UC2DK126006. Department of Defense Award: W81XWH2110007, Other U.S. Government Support

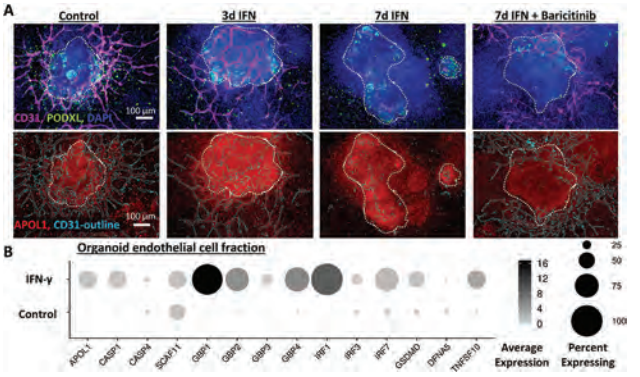


Fig1. (A) JAK½ inhibition prevents IFN-γ-induced APOL1 upregulation and degradation of endothelial networks. (B) scRNA-seq reveals a pronounced pyroptotic gene signature in organoid ECs.Edit

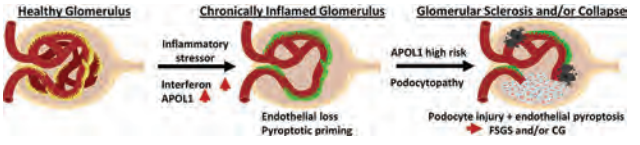


Fig2. Hypothetical model of IFNγ-mediated endothelial insult as a "second-hit" in APOL1-mediated nephropathy.

SA-OR89

Plasma Proteome Profiling for Remission Diagnosis in ANCA Vasculitis

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Background: Systemic anti-neutrophil cytoplasmic autoantibody (ANCA)-associated vasculitis (AAV) requires intensive immunosuppressive treatment that is deescalated once patients achieved remission. Thus, reliably diagnosing remission has therapeutic implications but remains challenging. We hypothesized that the plasma proteome harbors objective information that may assist clinicians in diagnosing AAV remission.

Methods: Plasma proteomes from 50 healthy controls (HC), 59 active, and 55 remission AAV patients were analyzed with LC-MS/MS based proteomics. For data analysis, a machine learning pipeline was established, containing confounder analysis, LASSO regression and Likelihood ratio test. After "leave-one-out" validation the final biomarker combination for ANCA disease status assignment was tested on the 20/80 data split.

Results: From 970 identified proteins, 605 passed the quality check for quantification and 325 were differently expressed. The principal component analysis showed excellent separation of active and remission AAV patients. Using machine learning, we identified a 5-protein biomarker combination with the potential to separate active AAV from remission patients, namely leucine-rich alpha-2-glycoprotein 1, beta-2-microglobolin, insulin-like growth factor-binding protein 3, tenascin X, and alpha-2-HS-glycoprotein. Assessing all AAV patients, the 5-protein panel showed an AUC of 0.94 with a negative predictive value (NPV) of 87.5% and performed better than ANCA titer (AUC 0.75, NPV 63.6%) or c-reactive protein (CRP) (AUC 0.91, NPV 73.3%) using a binary logistic regression model of remission diagnosis. In challenging remission patients with positive ANCA, the panel was the better classifier compared to CRP (AUC 0.96, NPV 85.7% versus AUC 0.92, NPV 75.0%), and better than ANCA in challenging remission patients with increased CRP (AUC 0.82, NPV 83.3% versus AUC 0.68 without any value in diagnosing remission).

Conclusions: Using proteomics combined with machine learning, we identified a protein signature that may assist clinicians in diagnosing AAV remission and guiding immunosuppressive treatment.

SA-OR90

Development of Novel Selective DDR1 Inhibitors with the Potential to Treat CKD

Nicolas E. Guisot, Daniel J. Wilcock, Inder Bhamra, Kay Eckersley, Gayle E. Douglas, Kelvin Ho, Cliff Jones, Daniel J. Leng, Jack W. Lloyd-Weston, Amy B. Marshall, Helen Mckeever, Caroline Phillips, Shân Preece, James Ryan, Robert J. Street, Richard Armer. *Redx Pharma plc, Macclesfield, United Kingdom.*

Background: Discoidin domain receptors (DDRs) are collagen-activated receptor tyrosine kinases which have been shown to have increased expression in many fibrotic diseases. Inhibition or knockout of DDR1 has previously been shown to decrease fibrosis and protect kidney function in multiple preclinical mouse models of kidney fibrosis. However, to date there are no approved selective inhibitors of DDR1 in the clinic. In this study, the protective role of REDX-DDR1, a novel and selective orally bioavailable small molecule inhibitor of DDR1 was investigated in a mouse unilateral ureteral obstruction (UUO) model.

Methods: For therapeutic intervention, mice were subjected to UUO and subsequently from day 5 to treatment with vehicle, REDX-DDR1 *via* oral gavage. Animals were sacrificed at day 10 and kidneys were collected and processed for histological analysis of collagen deposition and myofibroblast transformation in stained tissue sections.

Results: REDX-DDR1 exhibits nanomolar potency in cells and target engagement in the kidney as measured by suppression of phospho-DDR1. REDX-DDR1 is highly selective when tested against a panel of 468 kinases. REDX-DDR1 has a favourable *in vitro* and *in vivo* ADME profile including good *in vivo* exposure across species and low potential for drug-drug interactions. Early safety pharmacology assessment showed no findings in standard ion channel panels. *In vitro* genetic toxicology showed no genotoxic findings in 5-strain Ames test. The favourable selectivity and pharmacokinetic profiles of REDX-DDR1 allow for selective inhibition of DDR1 in mouse models of chronic kidney disease. Animals treated with REDX-DDR1 had a significant reduction in histological markers of inflammation and fibrosis in the therapeutic mouse UUO model. REDX-DDR1 suppressed inflammation and fibrosis as measured by F4/80, α-SMA and PSR respectively. In addition REDX-DDR1 suppressed a number of pro-fibrotic genes.

Conclusions: These data show that selective inhibition of the DDR1 receptor via REDX-DDR1 results in anti-fibrotic efficacy in the UUO model. Selective inhibition of DDR1 represents an attractive approach for further investigation towards the development of new treatments for CKD.

Funding: Commercial Support - Redx Pharma Plc

SA-OR91

Spatial Metabolomics Identifies Novel Glomerular Metabolite Signatures of Normal and Diabetic Kidneys

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Background: The Zucker Diabetic Fatty (ZDF) rat is a model of type 2 diabetes as it develops pathologic changes in the glomerulus similar to human disease. Untargeted matrix-assisted laser desorption/ionization (MALDI) - mass spectrometry imaging (MSI) can be a powerful platform to identify metabolic pathways linked to pathologic features. However, quantification of metabolites from specific regions of interest in an unbiased manner via MALDI-MSI is challenging. MSI-DeepPath is a new computational platform that enables spatial quantitation of metabolites.

Methods: Control and ZDF male rats (age 6 mo, n=3/group) were used for the current study. Spatial metabolomic analysis of glomeruli in Control and ZDF rat kidneys was performed using MALDI-MSI at 20 µm spatial resolution from replicate samples per animal. Metabolites were detected at mass accuracy <2 ppm using Q-Exactive orbitrap MS followed by annotations using METASPACE. SygnaMap's MSI-DeepPath computational platform was used to register each glomerulus in a section to the corresponding MSI pixels and then quantify the annotated metabolites per glomerular pixel.

Results: Of 1600 metabolites annotated at m/z range 70-500 Da the top features were selected by ranking individual metabolite intensity per pixel in the normal and the diabetic groups. The top metabolite in normal glomeruli was L-glutamic acid and in diabetic glomeruli was D-glucose. Based on the top 20 enriched metabolites, the most prominent pathway in the normal glomeruli was Arginine biosynthesis whereas the most prominent pathway in the diabetic glomeruli was Glyoxylate and dicarboxylate metabolism.

Conclusions: For the first time, MSI-DeepPath enables quantification of spatial metabolomics of glomeruli using untargeted MALDI-MSI data. With MSI-DeepPath-based analysis of kidney sections from the ZDF rat, we identified that Glyoxylate-dicarboxylate metabolism was the most prominent pathway in the diabetic glomeruli. As glyoxylate is a highly reactive aldehyde and can be nephrotoxic via conversion to oxalate, further studies on glomerular glyoxylate-dicarboxylate metabolism will shed new light on its potential role in diabetic glomerular disease.

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

SA-OR92

Single-Nucleus Transcriptome Profiling of the Kidney Glomerulus Identifies Cell-Specific Responses in an Autoimmune Mouse Model of Membranous Nephropathy

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Background: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in adults. However, the pathogenic mechanisms remain poorly understood due to a missing comprehensive characterization of cell-specific changes during disease progression.

Methods: We developed a novel pipeline involving the gentle enrichment of glomeruli followed by single-nucleus RNA-sequencing (snRNA-seq). We applied this technique to mice with experimental autoimmune THSD7A-associated MN at different time points.

Results: We generated a transcriptomic landscape involving 91,114 single-nuclei, with >95% deriving from glomerular cells, i.e. podocytes, mesangial cells and endothelial cells (ECs). This procedure provided a high-quality dataset with only minimal technical perturbations such as stress gene activation during the single cell dissociation process. Distinct changes in gene expression specific to podocytes were identified in MN model mice. A side-by-side comparison with other snRNA-seq datasets revealed both an MN-specific gene expression profile as well as transcriptomic alterations observed also in other glomerular nephropathies. Pathways enriched in MN model mice included regulation of focal adhesion, actin cytoskeleton, cell migration, and changes in kinase activities in podocytes. We further found increased infiltration of immune cells with disease progression and a cluster of proliferating/ repairing cells mainly consisting of mesangial cells and ECs in MN model mice. Interestingly, mesangial cells and ECs were identified to participate in modulation of leukocyte transendothelial migration, cytokine signaling, and cell-cell/cell-matrix interactions, indicating the involvement of various glomerular cell types in the pathogenesis of MN.

Conclusions: Our study identifies cellular pathways underlying podocyte injury in experimental MN and provides important novel molecular insights into the pathogenesis of MN.

SA-OR93

Lymphangiogenesis Regulates the Differentiation and Function of Th1 Cells in Experimental Anti-Glomerular Basement Membrane (GBM) Crescentic Glomerulonephritis (cGN)

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Background: Increasing evidence has shown the critical role of Th1 cells in the pathogenesis of anti-GBM cGN, however, the underlying mechanism is unclear. Our previous study has reported lymphangiogenesis regulate the activation and polarization of T cells in chronic kidney diseases. However, whether lymphatic vessel endothelial cells (LECs) controls the differentiation of Th1 cells in anti-GBM cGN remains unknown.

Methods: To address this question, we established the selective proliferating lymphatic vessel knockout mice for experimental anti-GBM cGN. Single-cell RNA sequencing, Bulk RNA sequencing and histological methods were used to investigate the immunopathological features of various renal T cells in anti-GBM cGN. Intra-renal LECs were obtained through multicolor flow cytometry and smart sequencing technology was applied to analyze the transcriptional signature of LECs.

Results: We found lymphangiogenesis is actively involved in anti-GBM cGN. Deletion of proliferated LECs protects against anti-GBM cGN. Most significantly, the proportion of Th1 cells in the LECs knockout mice decreased with a significantly down-regulated interferon response. Smart sequencing analysis on LECs revealed that the expression of IFN-γ which promotes Th1 differentiation increased significantly in anti-GBM cGN group, but decreased in LECs knockout group. At the same time, the function of cDC1, the main effector cell to induce Th1 differentiation, changes from pro-inflammatory activation to regulation of tolerance. In addition, the transcriptional expression profiles of T cells enriching the signal pathways related to Th1, Th2 and Th17 cell differentiation were inhibited after LECs knockout. It is further demonstrated that LECs also produce chemokines CCL5 and XCL1 to recruit cDC1, which was reversed by LECs knockout in anti-GBM cGN.

Conclusions: Our studies reveal functionally crosstalk between LECs and T cells in anti-GBM cGN. LECs directly or indirectly involved in the chemotaxis, differentiation and activation of Th1 cells. In conclusion, the findings uncover a previously unidentified role for lymphangiogenesis in progressive immune-mediated kidney disease, implying that LECs-Th1 cell axis can be a novel and effective immunotherapy target for anti-GBM cGN.

SA-OR94

Bub1 Is a Potential Mediator of TGFβ-Induced Renal Fibrosis

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Background: Budding Uninhibited by Benzimidazole 1 (Bub1) is a widely conserved eukaryotic kinase and Bub1 gene-deficient mice are embryonic lethal. Bub1 has long been recognized to localise to the centromere in mitosis as a component of the spindle checkpoint complex and to regulate chromosome segregation. Meanwhile, on siRNA screening targeting human kinases against cancer cell lines, it has been suggested that Bub1 may co-activate with TGFβ receptors to regulate SMAD2/3 phosphorylation. Since TGF-β/SMAD pathway is a major pathway in fibrosis, it is assumed that Bub1 may be involved in development of fibrosis as a novel mediator of the TGF-β/SMAD pathway. These findings are limited to cancer cell lines, therefore, it remais unknown whether similar events will be identified in the kidney.

Methods: The expression and localization of Bub1 was confirmed in the kidney of wild type (BL6) mice. To generate conditional Bub1 knockout mice, the $Bub1^{fl/fl}$ mice were crossed with gGT-Cre mice or FSP1-Cre mice. Renal fibrosis was induced in 8-10 week old male conditional Bub1 knockout mice by unilateral ureteral obstruction (UUO) model. In vitro, human renal proximal tubular epithelial cells (HK-2) were cultured, then Bub1 knockdown was performed by siRNA transfection.

Results: In wild-type mice, Bub1 was expressed in renal tubular epithelial cells by immunofluorescence staining with LTA. The Bub1 staining was diminished in conditional Bub1 renal knockout mice. Renal fibrosis and the expression of aSMA induced by UUO were attenuated in the mice with Bub1 proximal tubular cells (PTCs) knockout compared to wild type mice. On the other hand, the renal fibrosis induced by UUO in the mice with Bub1 fibroblasts knockout was not changed compared to wild type mice. Furthermore, knockdown of Bub1 in HK-2 cells attenuated the phosphorylation of SMAD3 by TGF-β stimulation.

Conclusions: These results uncovered that Bub1 deficiency of renal proximal tubular cells plays a protective role in renal fibrosis triggered by UUO via TGF-β/SMAD pathway.

Funding: Government Support - Non-U.S.

SA-OR95

Protective Role of RBPjk in HIV-Related CKD

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Background: The Notch signaling is activated in HIV-associated Nephropathy. The Notch signaling is initiated when a ligand binds to a Notch receptor and leads to cleavage and translocation of the Notch intracellular domain (NICD) into the nucleus. NICD binds to RBPjk and converts it into a transcriptional activator from a repressor and leads to activation of Notch downstream targets. The HIV-LTR promoter contains two RBPjk binding sites. It is thought that RBPjk is a repressor of HIV-LTR. This would imply counterintuitive roles of Notch and RBPjk in HIV-related diseases. Here we investigate for the first time the *in vivo* roles of RBPjk in regulating the podocyte and myeloid-specific HIV gene expression.

Methods: The Tg26 mice harbor the active HIV-LTR promoter in many cells/tissues. Tg26 mice were bred with floxed RBPjk mice. The resulting mice were further bred with mice harboring *podocin-cre* or *lysM-cre* promoters to drive the RBPjk deletion in podocytes or myeloid precursors, respectively. The resulting mice, Tg26: RBPjkKO-Pod or Tg26:RBPjkKO-LysM were compared with normal or Tg26 mice. Renal disease severity was assessed by histology, renal function and inflammation assessment. *Nef* gene expression served as a measure of HIV-LTR activity.

Results: Deletion of RBPjk alone in podocytes led to disease aggravation and early lethality in Tg26 mice. Compared to Tg26 mice, Tg26:RBPjkKO-Pod mice exhibited increased collapsing glomerular phenotype, focal segmental glomerulosclerosis, blood urea nitrogen, tubular dilations and fibrosis. There was an increase in inflammatory markers IL6 and MMP10. NFkB (p65) was drastically elevated in the glomerular and tubular compartments. RBPjk deletion in podocytes of Tg26 mice did not affect N3ICD expression. Moreover, a significant increase in the *nef* expression was observed. Similarly Tg26:RBPjkKO-LysM mice had increased disease severity compared to Tg26 mice but less than Tg26:RBPjkKO-Pod mice.

Conclusions: RBPjk deletion in podocytes may be sufficient to activate the HIV-LTR promoter which increases expression of HIV genes leading to inflammation and disease aggravation. This indicates a non-canonical Notch signaling activation and Notch-independent roles of RBPjk in HIV-related diseases. Elucidating these mechanisms are important for treatment strategies and add to our understanding of the latency caused by HIV in people treated with antiretroviral therapy.

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SA-OR96

Changes in Gene Expression in Fatty Acid Metabolism and De Novo Lipogenesis Are Conserved in Human CKD and Animal Models

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Background: Lipid accumulation has been consistently observed in kidneys of patients and animal models of kidney disease. Altered fatty acid oxidation (FAO) and de novo lipogenesis (DNL) signaling are proposed to drive the fatty kidney's transition to kidney disease. However, changes in lipid composition and mechanisms of lipid accumulation that specifically drive alterations in FAO, DNL, and lipid uptake have not yet been characterized in unbiased manner.

Methods: We collected control (healthy) and diseased (diabetic and hypertensive kidney disease) human kidney samples from surgical nephrectomies. Demographics, clinical information, and estimated Glomerular Filtration Rate (eGFR) were collected, and histological analysis was performed by our renal pathologist. We analyzed gene expression changes in 405 microdissected human kidney tubule samples by RNA sequencing (RNA-seq). Bulk RNA-seq data from 3 mouse induced CKD models–unilateral ureteral obstruction (UUO, n=3), folic-acid induced nephropathy (FAN, n=3), and tubule-specific deletion of mitochondrial transcription factor A (TFAM, Ksp-Cre/$Tfam^{flox/flox}$, n=3)–was generated. Furthermore, an unbiased metabolomics analysis was performed on both human and mouse kidney samples using the Metabolon platform.

Results: Kidney metabolomics data indicated complex changes in lipid levels. We observed accumulation of glycerophospholipids in diseased kidney samples. Transcripts related to FAO (ACOX1, ACOX2, CPT1, CPT2, ESRRA, FABP, HADHA, HADHB, PGC1a, PPARa, SLC25A20) were lower in kidneys of mouse CKD models. Their expression levels positively correlated with kidney fibrosis and negatively correlated with eGFR. Genes associated with DNL genes (ACSS2, ChREBP, SCAP) showed higher expression in mouse kidney disease models; their expression levels negatively correlated with fibrosis and slightly positively correlated with eGFR.

Conclusions: Unbiased metabolomics and gene expression analysis of human and mouse kidneys indicated increased lipid accumulation in diseased kidneys. Decrease in FAO and to some degree an increase in DNL likely contribute to lipid accumulation.

Funding: NIDDK Support, Commercial Support - Regeneron, Gilead, Novo Nordisk, Genentech, Novartis Boehringer Ingelheim, Bayer, Ventus, Variant Bio, Maze

SA-OR97

Humanized IGHA1 Mouse Induced by Lactobacillus casei Cell Wall Extract: A Novel Galactose-Deficient Immunoglobulin A1 (IgA1) Elevated Mouse Model of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis in the world. A 'multi-hit' hypothesis has been proposed to explain the pathogenesis of IgAN and galactose-deficient IgA1 (Gd-IgA1) was defined as the first hit. In this study, we constructed a novel Gd-IgA1 elevated mouse model with typical histopathology features of IgAN, by immunizing the immunoglobulin heavy constant alpha 1 knock-in ($IGHA1^{+/+}$) mice with *Lactobacillus casei* Cell Wall Extract (LCWE).

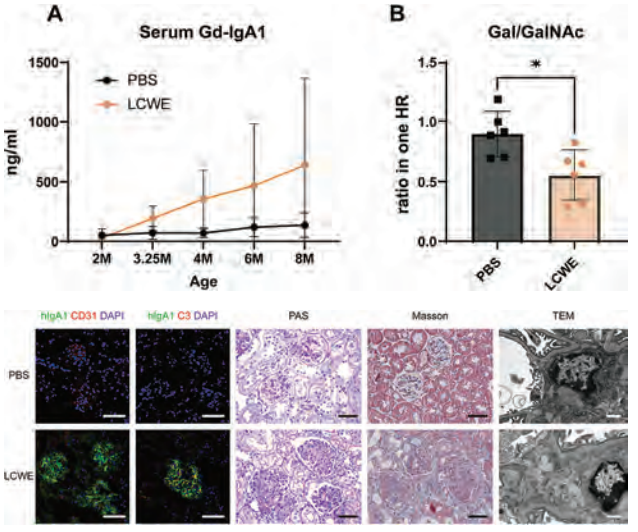
Methods: $IGHA1^{+/+}$ mice were generated by replacing the endogenous mouse *Igha* gene with the human *IGHA1* gene via a CRISPR/Cas9 system. 2-month-old male $IGHA1^{+/+}$ mice were injected i.p. with either 0.5mg/g LCWE plus complete Freund's adjuvant (CFA) or PBS eight times. 8-month-old mice were euthanized for further examination.

Results: $IGHA1^{+/+}$ mice expressed human IgA1 heavy chain instead of mouse IgA. Human IgA, human IgA-mouse IgG complex, and CD89-binding pIgA1 complex levels were significantly increased from 4 months old in the serum of $IGHA1^{+/+}$ mice induced by LCWE plus CFA compared with PBS. Meanwhile, as observations continued, the

serum Gd-IgA1 absolute value and relative proportion to hIgA1 increased 4 times in IGHA1$^{+/+}$-LCWE mice. We quantitatively analyzed the *O*-glycopeptides of human IgA1 hinge region (HR) using LC-MS analysis and found HR from IGHA1$^{+/+}$-LCWE mice showed hypo-galactosylation than IGHA1$^{+/+}$-PBS mice. IGHA1$^{+/+}$-LCWE mice showed a continuous and stable human IgA1 (positive rate: 100%) kidney mesangial deposition with C3 co-deposits (positive rate: 81.25%) until 8 months old. Histology demonstrated a significant rise in mesangial expansion and hypercellularity. Electron microscopy showed typical mesangial electron-dense deposits in IGHA1$^{+/+}$-LCWE mice.

Conclusions: We established a novel serum Gd-IgA1 elevated mouse model presenting typical pathological characteristics of IgAN, which will be used to further explore the mechanisms and new therapeutic strategies.

Funding: Government Support - Non-U.S.



TH-PO001

Revolutionizing Kidney Transplantation Education: Evaluating ChatGPT's Accuracy on Core Questions

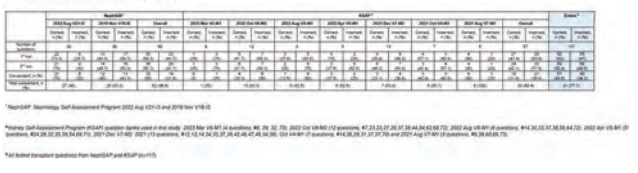
Oscar A. Garcia Valencia, Andrew J. Bentall, Naim S. Issa, Mireille El Ters, Iasmina Craici, Charat Thongprayoon, Paul W. Davis, Wisit Cheungpasitporn. *Mayo Clinic Division of Nephrology and Hypertension, Rochester, MN.*

Background: ChatGPT is a state-of-the-art, high-capacity language model that has shown proficiency in various processing tasks, such as generating responses resembling those of human beings. While there is growing speculation about ChatGPT serving as a potential substitute for physicians in a clinical environment, its proficiency in clinical subspecialties remains unclear. The aim of this study is to evaluate the performance of ChatGPT in answering questions related to kidney transplantation.

Methods: We conducted an evaluation of ChatGPT's accuracy in answering questions related to kidney transplantation using the Nephrology Self-Assessment Program and Kidney Self-Assessment Program of the American Society of Nephrology (ASN). Questions containing images were excluded due to current limitations in ChatGPT's image processing capabilities. A total of 117 questions were included in the evaluation, 60 from NephSAP and 57 from KSAP. Each question bank was executed twice using ChatGPT (Mar 14 version, OpenAI), and the level of concordance between the runs, conducted 2 weeks apart, was determined.

Results: On the 60 NephSAP questions, ChatGPT achieved accuracies of 58.3% and 58.3% on the 1st and 2nd runs, respectively, with an overall concordance of 86.7%. Similarly, on the KSAP question banks (57 questions), the accuracy of ChatGPT was 47.4% and 42.1% on the 1st and 2nd runs, respectively, with a concordance of 68.4%. The overall concordance between the two runs was 77.8%. The concordance in correct answers was found to be higher than that of incorrect answers (43.6 vs 34.2%).

Conclusions: Upon evaluating ChatGPT's performance in answering questions related to kidney transplantation, we found that its accuracy was below the passing threshold set by the ASN for both Nephsap and KSAP. Excluding questions with clinical images, the overall accuracy of ChatGPT (Nephsap + KSAP) was found to be 53% on the 1st try and 50.4% on the 2nd one. From this we conlclude that the current version of ChatGPT is not yet a reliable medical education tool for training nephrologists, and requires further development.



TH-PO002

Assessing Drug Interactions with Tacrolimus: Evaluating ChatGPT as a Promising Resource for Drug Interactions with Tacrolimus

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Background: Tacrolimus is the most common immunosuppressant in kidney transplant recipients. However, its blood concentration can be affected by other medications and thus, assessing drug interactions is essential to optimize its efficacy and minimize toxicity. ChatGPT is a high-capacity language model proficient in natural language processing tasks. This study aims to evaluate the accuracy of ChatGPT in assessing drug interactions involving tacrolimus.

Methods: We used the Micromedex Drug Interactions and Lexicomp databases to evaluate ChatGPT's ability to correctly assess if a drug interaction with Tacrolimus was present and in what direction should the tacrolimus dose be adjusted. A total of 79 drugs were chosen based on the risk rating of D (consider therapy modification) or X (avoid combination). Each question was executed twice using ChatGPT (03/2023, OpenAI), and we determined the concordance between the 2 runs, conducted 2 weeks apart. An additional assessment was conducted using ChatGPT to draw a conclusion from our study.

Results: The overall accuracy of ChatGPT in assessing the presence of drug interactions with tacrolimus was found to be 96% on the 1st run and 98% on the 2nd run. The direction of adjustment was correct in 87% on both runs. The concordance in correct answers was 96% for the need of adjustment and 86% on the direction. ChatGPT itself acknowledged these results, emphasizing that while it exhibits promising accuracy, it should not be the sole source of information for clinical decision-making. Comprehensive and reliable assessment of drug interactions and dosing adjustments should involve consultation with additional resources and healthcare professionals.

Conclusions: ChatGPT demonstrated an accuracy exceeding 96% regarding the presence of drug interactions involving tacrolimus. However, when asked about the adjustment direction, the accuracy dropped to 87%. The integration of ChatGPT in clinical practice should be accompanied by caution and should not replace consultation with healthcare professionals or the utilization of comprehensive resources. Future steps should focus on refining ChatGPT's capabilities to ensure its safe and effective use in assessing drug interactions involving tacrolimus.

TH-PO003

The Performance of ChatGPT in CKD: An Assessment Using NephSAP and KSAP

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Background: ChatGPT is an AI-powered cutting-edge language model that has demonstrated outstanding capabilities in numerous natural language processing tasks, such as producing responses that closely resemble those generated by humans. While there has been growing discussion about ChatGPT's potential to serve as a replacement for physicians in clinical contexts, its proficiency in nephrology, specifically chronic kidney disease, remains unclear. The objective of this study is to evaluate ChatGPT's accuracy in answering essential questions related to chronic kidney disease, such as diagnosis, treatment, and management.

Methods: We evaluated ChatGPT's performance using the Nephrology Self-Assessment Program (NephSAP from 2011-2019) and Kidney Self-Assessment Program (KSAP from 2020-2023) of the ASN. Questions containing images were excluded. A total of 308 questions were included, with 205 from NephSAP and 103 from KSAP. Each question bank was executed twice using ChatGPT, and agreement between the initial and subsequent runs was determined.

Results: ChatGPT's performance in chronic kidney disease fell below the minimum passing threshold of 75% set by the ASN for nephrologists. On the NephSAP question banks, ChatGPT achieved accuracies of 53.2% and 55.6% on the first and second runs, respectively, with an overall agreement of 78.1%. On the KSAP question banks, ChatGPT's accuracy was 48.5% and 44.7% on the first and second runs, respectively, with an agreement of 66.0%. The overall agreement between the two runs was 74.0%. ChatGPT's level of agreement between initial and subsequent runs was higher for correct answers compared to incorrect ones.

Conclusions: Based on these results, it can be concluded that the current version of ChatGPT is not yet a fully reliable and useful medical education tool for clinical physicians, medical students, and nephrologists, and requires further development.

TH-PO004

Unraveling ChatGPT's Performance in Addressing ESKD: Implications for Artificial Intelligence (AI)-Assisted Healthcare

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Background: ChatGPT, an artificial intelligence language model, is at the forefront of cutting-edge technology. It has shown abilities in natural language processing tasks, producing responses resembling those crafted by human beings. While there is discourse

about the potential of ChatGPT as a substitute for physicians, its abilities in the field of nephrology, particularly in ESKD including dialysis, remains uncertain. The objective of this study is to assess the performance of ChatGPT in addressing fundamental inquiries pertaining to ESKD.

Methods: We conducted an evaluation of ChatGPT's accuracy in answering questions related to CKD, ESKD, including hemodialysis, and peritoneal dialysis, using the ASN eLEARNING CENTER (nephSAP vol1-No2 and Dialysis Core Curriculum 2021). There were 95 questions included. Each question set was executed twice using ChatGPT (Mar 14 version, OpenAI), and the level of agreement between the initial and subsequent run, conducted two weeks apart, was determined. Also, an assessment was performed using ChatGPT using the query, "Based on these findings, what is ChatGPT's performance, and is ChatGPT ready to provide answers pertaining to ESKD?"

Results: In our study evaluating ChatGPT's performance in answering questions related to CKD and ESKD, we found that on the two different question banks combined, ChatGPT achieved accuracies of 54% and 57% on the first and second runs, respectively. The overall agreement between the two runs was 71%. The study revealed that the level of agreement between the initial and subsequent runs of ChatGPT was higher for correct answers compared to incorrect ones, concordance of 46% vs 24%, respectively. Among the 28 instances where ChatGPT provided different responses, it changed from incorrect to correct in 10 questions (36%), from correct to incorrect 7 times (25%). ChatGPT acknowledged these results, further highlighting its limitations in accurately addressing questions related to ESKD.

Conclusions: The current study demonstrates that ChatGPT's accuracy in answering questions related to ESKD is below the minimum passing threshold of 75% set by the ASN for nephrologists, with an accuracy of 55% (average of the two runs), indicating the need for further development and training to improve its accuracy and consistency.

TH-PO005

ChatGPT vs. a First-Year Nephrology Fellow in Electrolyte and Acid-Base Disorders

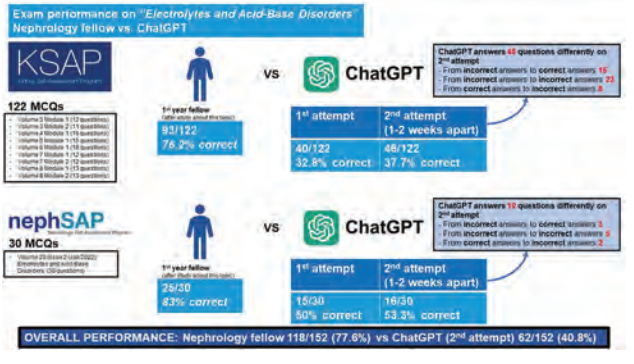
Poemlarp Mekraksakit, Pajaree Krisanapan, Iasmina Craici, Kambiz Kalantari, Charat Thongprayoon, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ChatGPT is a leading natural language processing model known for its impressive ability to generate human-like responses in various tasks. This study aims to assess ChatGPT's proficiency in addressing electrolyte and acid-base disorders in Nephrology.

Methods: In our study, we used nephSAP and KSAP, provided by the American Society of Nephrology (ASN), to assess ChatGPT's accuracy in answering basic questions about electrolyte and acid-base disorders. Questions with images were excluded as ChatGPT cannot process images. We evaluated a total of 152 questions, with 122 from KSAP and 30 from nephSAP. ChatGPT was tested twice, with the initial and subsequent runs conducted 1 to 2 weeks apart. To compare scores, we considered the performance of a first-year Nephrology fellow who extensively studied this topic. The complete set of questions can be found at https://education.asn-online.org/.

Results: In the 122 KSAP question banks, ChatGPT achieved accuracies of 32.8% and 37.7% on the first and second runs, respectively. In comparison, a first-year Nephrology fellow achieved an accuracy of 76.2%. On the nephSAP question banks, consisting of 30 questions, ChatGPT demonstrated an accuracy of 50% on the initial run and 53.3% on subsequent runs. The first-year Nephrology fellow correctly answered 83% of the questions. Notably, ChatGPT changed its answers on the second run for 56 out of 152 questions (36.8%). Out of these 56 questions, ChatGPT corrected its answers from incorrect to correct in 18 cases, but also changed its answers from correct to incorrect in 10 instances.

Conclusions: ChatGPT's proficiency in addressing electrolyte and acid-base disorders in nephrology is limited. It did not achieve the minimum passing threshold of 75% set by the ASN for nephrologists. Its accuracies were lower compared to a dedicated first-year Nephrology fellow. ChatGPT's responses were inconsistent across different runs. Therefore, ChatGPT is not a suitable replacement for human clinicians in this clinical setting.



TH-PO006

Exploring ChatGPT's Aptitude in Essential Concepts of Hypertension

Maria Lourdes Gonzalez Suarez, Gary L. Schwartz, James R. Gregoire, Stephen B. Erickson, Charat Thongprayoon, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ChatGPT is a state-of-the-art language model with human-like response generation capacity for various tasks. While there are debates about the possibility of ChatGPT replacing clinicians in clinical settings, its competence in nephrology, specifically in hypertension, remains uncertain. This study aims to assess ChatGPT's proficiency in addressing fundamental queries related to the diagnosis, treatment, and management of hypertension.

Methods: Using the Nephrology Self-Assessment Program (NephSAP) issues 2016-2022: V15N1, V17N1, V19N1, V21N4 from the American Society of Nephrology, we conducted a rigorous evaluation of ChatGPT's accuracy in answering questions related to hypertension. We excluded questions containing images due to ChatGPT's current limitations in image processing. The analysis included 95 questions from NephSAP. Each question set was executed 3 times using ChatGPT (version Mar 14, OpenAI), and we determined the level of agreement between the initial and subsequent attempts, conducted 2 weeks apart.

Results: Our analysis revealed that ChatGPT achieved accuracies of 65.5% on first attempt, and 76.4 and 78.1 % on second and on third attempts, respectively, for the NephSAP questions. We noted that ChatGPT had a higher level of correct answers compared to incorrect ones, and it improved its knowledge after every attempt (table 1).

Conclusions: Our findings indicate that ChatGPT's accuracy in addressing core concepts related to hypertension management falls below the minimum passing threshold of 75% established by the ASN for nephrologists, with an initial accuracy rate of 65.5%. This emphasizes the need for further development and training to improve ChatGPT's accuracy and consistency in the area of hypertension. Our study's outcomes have significant implications for ChatGPT's potential use as an educational tool for clinicians, highlighting the importance of ongoing research and development to broaden its proficiency in clinical subspecialties.

Accuracy of ChapGPT on Hypertension Questions

KSAP Issue	First Attempt, (%)	Second Attempt, (%)	Third Attempt, (%)
V15N1	62	75.9	79.3
V17N1	83.3	93.3	93.3
V19N1	53.3	63.3	66.6
V21N4*	63.3	73.3	73.3
Total accuracy	65.48	76.45	78.12

* Questions 1-25

TH-PO007

The Accuracy of Artificial Intelligence in Identifying Potentially Harmful Non-Prescription Medications and Dietary Supplements in Patients with Kidney Diseases

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Background: Search engines are commonly used to obtain health-related information, including information about drug safety. Non-prescription medications and supplements are generally perceived as safe, however, may be harmful to patients with kidney diseases. ChatGPT is a cutting-edge language model that has gained attention for its potential to improve clinical decision making. Its ability to serve as a drug information resource for patients with kidney disease has not been determined. This study aimed to evaluate ChatGPT's accuracy in discerning the safety of medications in patients with kidney diseases when compared to Micromedex, a widely used tertiary drug information reference.

Methods: One hundred twenty-four commonly used non-prescription medications and supplements were evaluated in ChatGPT using the query "Is X potentially harmful in people with kidney disease?" The resultant output was evaluated and categorized into one of three categories: "generally safe", "potentially harmful", or of "unknown" level of harm. Safety of the non-prescription medications and supplements was also evaluated in Micromedex and categorized similarly. Concordance between the two resources was summarized.

Results: Micromedex identified 68(55%) medications as safe, 52(42%) as potentially harmful, and 4(3%) as unknown. ChatGPT identified 74(60%) medications as safe, 26(21%) as potentially harmful, and 24(19%) as unknown. The overall agreement between Micromedex and ChatGPT was 65% with ChatGPT identifying only 46% of potentially harmful medications. Supplements as a subclass had the lowest concordance between ChatGPT and Micromedex, with a rate of 56%. Among the 24 medications identified as unknown by ChatGPT, 21(87%) were supplements.

Conclusions: ChatGPT's ability to accurately assess the safety of non-prescription medications, particularly supplements, was modest in patients with kidney disease when compared to a contemporary drug information resource. The findings suggest that ChatGPT neither be considered nor recommended as a drug information resource for patients with kidney disease or their healthcare professionals. Further development would be necessary to improve its accuracy and reliability in this domain.

TH-PO008

Application of Large Language Models such as ChatGPT to Support Nutritional Recommendations for Dialysis Patients

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Background: The diversity of food preferences has increased over the past years and provides challenges to dietitians working in dialysis clinics. We explored the use of Large Language Models (LLM), such as ChatGPT, to support nutritional advice given to patients.

Methods: We applied a simple LLM syntax that allows us to consider a variety of factors that determine personalized dietary recommendations/menu options. The syntax integrates several domains, such as patient demographics (e.g., age, sex, dialysis vintage) and food preferences (e.g., vegetarian, Indian, Mediterranean, etc.), laboratory data (e.g., levels of phosphate, potassium), and clinical characteristics (e.g., weight, BMI, blood pressure). We deployed these characteristics as queries to ChatGPT (ChatGPT (openai.com)). The resulting dietary recommendations were reviewed by an experienced renal dietitian.

Results: The ChatGPT command line allowed simple input of inquiries. We were able to narrow down and personalize requests in a short dialogue with the bot, for example: "*John is a hemodialysis patient aged 65, with diabetes, CHF and fluid overload, his weight is 95 Kg, BMI is 32, his albumin is 3.5 g/dl, potassium is 4.8 mmol/L, phosphorous is 5.3 mg/dl. John likes Mediterranean food. Could you develop a few recipes for him?*" We created multiple requests for several imagined patients. The review of the bot's dietary recommendations by a renal dietitian was in general satisfactory. However, while the amount of phosphate was in target, phosphate additives were not considered by the LMM. We also explored the use of ChatGPT to create personalized dietary recommendations/menu options in different languages, such as Mandarin. The translations, as judged by native speakers, were reliable.

Conclusions: While we identified some gaps, LLMs such as ChatGPT hold promise to provide personalized nutritional guidance to diverse populations of hemodialysis patients. As a next step, exploring their application in clinical practice will be important.

Funding: Commercial Support - Renal Research Institute

TH-PO009

Artificial Intelligence Language Processing Models in Literature Reviews for Nephrology

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Background: Literature reviews are a valuable tool for summarizing and evaluating the available evidence in various medical fields, including Nephrology. However, identifying and selecting relevant literature can be time-consuming for clinicians and researchers. ChatGPT is a novel artificial intelligence (AI) language model renowned for its exceptional ability to generate human-like responses across various tasks. However, whether ChatGPT can effectively assist medical professionals in identifying relevant literature is unclear. Therefore, this study aimed to assess the effectiveness of ChatGPT in identifying references to literature reviews in Nephrology.

Methods: We keyed the prompt "What are the references to literature reviews in Nephrology, with subgroup analysis in specific areas?" into ChatGPT (03/23 Version). We selected all provided results by ChatGPT and assessed them for existence, relevance, and author/link correctness. We recorded each resource's citations, references, authors' names, and links. The relevance of each resource was assessed by its citation index on Google Scholar.

Results: Of the total 511 references in Nephrology literature, only 319 (62.43%) of the references provided by ChatGPT existed, while 30.3% did not exist, and in 7.3% of recommendations, they were incomplete. Additionally, 208 (40.7%) of the listed authors were found to be incorrect, and the digital object identifier (DOI) was inaccurate in 357 (69.86%) of the references. Moreover, among those with a link provided, the link was correct in only 108 (21.14%) cases, and 7.4% of the references were irrelevant. Notably, analysis of specific topics in electrolyte, hemodialysis, and kidney stones found that >60% of the references were inaccurate or misleading, with less reliable authors and links provided by ChatGPT.

Conclusions: Based on our findings, the use of ChatGPT as a sole resource for identifying references to literature reviews in Nephrology is not recommended. Future studies could explore ways to improve AI language models' performance in identifying relevant Nephrology literature.

TH-PO010

Identification of Topics from Trainee Posts on Nephrology from Public Forums

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Background: Interest in a career in nephrology has waned. Career perceptions that are freely shared on social media sites may influence a trainee's decision when choosing a subspecialty. Examining topics of discussion on public forums have not previously been done.

Methods: We extracted threads from a popular online forum, the student doctor network (SDN), with titles that contained the keywords Nephrology, Nephrologist, Nephro, Dialysis, Kidney, and Renal. We removed posts with <20 words. We performed topic modeling using BERTopic. BERTopic is a topic modeling technique in the Python library that combines transformer embeddings and clustering model algorithms to identify topics using natural language process. We then manually reviewed three posts per topic to better characterize the topics. Additionally, two authors conducted a manual review of 1000 posts to gauge the underlying sentiments expressed. When disagreement occurred, a third reviewer was asked to rate the post and the most frequent category was used.

Results: We included a total of 1725 posts in our final analysis. BERTopic identified 23 topics (Figure 1A). The topics with the largest number of posts were "Nephrology responsibilities and reimbursements", "Fellowship programs mislead", and "Academic vs private practice nephrology". The top 10 topics are visualized in 2D space in figure 2B, where each point represents a post, and topics are separated by color. With manual review, 46% were classified as negative while only 6% were classified as positive. The remaining posts were unclear or irrelevant.

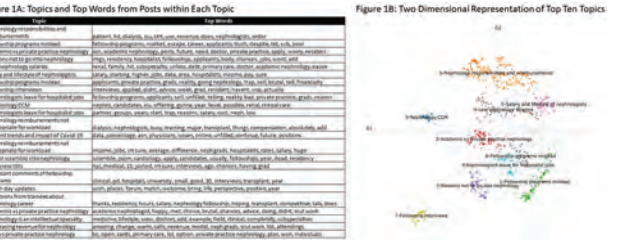
Conclusions: Discussions regarding nephrology careers are present on social media. Topics vary from workload to financial compensation. Unfortunately, a large proportion of posts are negative. To improve the nephrology workforce, we must address the concerns of trainees identified here.

Funding: NIDDK Support

Figure 1A: Topics and Top Words from Posts within Each Topic

Topic	Top Words
Nephrology responsibilities and reimbursements	patient, hd, dialysis, icu, kfr, use, revenue, does, nephrologists, order
Fellowship programs mislead	fellowship programs, crushed, escape, career, applicants, fourth, despite, hd, rule, post
Academic vs private practice nephrology	am, academic nephrology, penis, future, need, doctor, private practice, apply, overly, resident
Reasons not to go into nephrology	drugs, residency, hospitalist, fellowships, opportunity, body, chances, jobs, want, add
Low nephrology salaries	renal, family, hd, subspecialty, unless, dark, primary care, doctor, academic nephrology, easier
Salary and lifestyle of nephrologists	salary, starting, lighter, jobs, data, area, hospitalists, income, data, sure
Fellowship programs mislead	applicants, private practice, grads, reality, going nephrology, trap, sad, brutal, tad, financially
Fellowship interviews	interviews, applied, didn't, advice, week, grad, resident, haven't, visa, actually
Nephrologists need for household jobs	fellowship programs, applicants, sad, unfilled, telling, reality, bad, private practice, grads, reasons
Nephrology CCM	nephro, candidates, icu, offering, gonna, year, faced, possible, renal, clinical care
Nephrologists leave for household jobs	partner, groups, years, start, trap, reasons, salary, exit, reign, loss
Nephrology reimbursements not appropriate for workload	dialysis, nephrologists, busy, training, major, transplant, things, compensation, absolutely, add
Current trends and impact of Covid-19	data, percentage, am, physicians, issues, online, unfilled, continue, future, positions
Nephrology reimbursements not appropriate for workload	income, jobs, im sure, average, difference, nephrologists, hospitalists, rates, salary, huge
Do not override clinic nephrology	scientific, zoom, cardiology, apply, consultants, visuals, fellowships, year, fraud, residency
Interview tips	fun, medical, 15, joined, im sure, interviews, ago, chances, having, glad
Applicant comments of Fellowship programs	clinical, get, hospitals, university, small, good, 30, interviews, transplant, year
Match day updates	wish, places, fun im, match, outcome, bring, life, perspective, positive, year
Questions from trainees about nephrology career	thanks, residency, hours, salary, nephrology fellowship, hoping, transplant, clomiphene, talk, times
Academics vs private practice nephrology	academics nephrologist, happy, met, choice, brutal, chances, advice, doing, didn't, real world
Nephrology is an intellectual specialty	medicine, lifestyle, view, disliked, add, example, field, clinical, completely, subspecialties
Declaring heart of nephrology	growing, things, starts, calls, revenue, mental, negligent, kind wants, hd, attendings
Grief vs private practice nephrology	hd, open, cards, primary care, bit, option, private practice nephrology, plan, work, individuals

Figure 1B: Two Dimensional Representation of Top Ten Topics



TH-PO011

Kidney Outcome Comparisons of Clinician Evaluated Electronic AKI Alerts

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Background: The personalized recommendations for hospitalized patients with Acute Kidney Injury (AKI) using a Kidney Action Team (KAT-AKI) trial is an ongoing multicenter randomized clinical trial evaluating early recommendations for AKI. It is unknown whether clinician adjudication of an electronic alert for AKI can improve AKI diagnosis.

Methods: We used data from KAT-AKI trial that utilizes an EHR alert for real-time diagnosis of AKI in hospitalized patients. The alert implements the KDIGO serum creatinine(sCr) based AKI criteria (≥50% ↑ or 0.3mg/dL ↑) in 7day and 48hour windows. A trained team of a physician and pharmacist receives an InBasket EHR alert. The team independently reviews sCr trend to adjudicate the AKI diagnosis then select agree or disagree. Patients with eGFR ≤15ml/min/1.73m^2, end-stage kidney disease or admission sCr ≥4mg/dL were excluded. We compared the distribution of ΔsCr_{72} (a difference between sCr at AKI and the maximum sCr in the subsequent 72hrs), ΔsCr_{any} (difference between AKI sCr and max sCr in the next hospital days), 14-day progression to a higher AKI stage, length of stay(LOS) between alerts flagged as AKI_{yes} and AKI_{no}. We used Wilcoxon-Rank Sum test to compare continuous variables and χ^2 test for categorical variables.

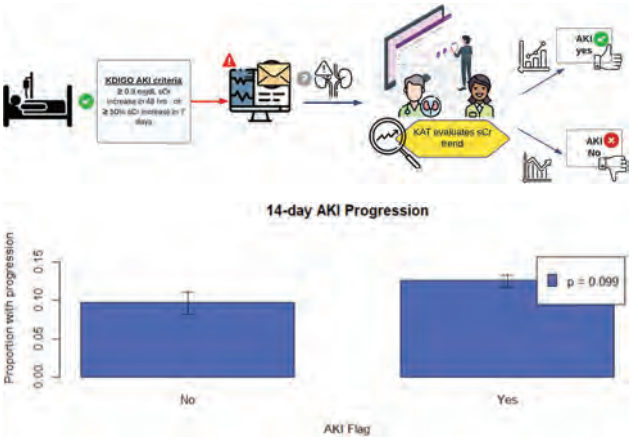
Results: Between November 2021 and April 2023, 2414 alerts were screened. The team disagreed with 431(17.9%) of EHR alerts. Baseline sCr and AKI sCr were lower in the AKI_{no} group(Table1). Median(IQR) ΔsCr_{72} was -0.02[-0.20, 0.21]mg/dL (AKI_{yes}) vs 0.00 [-0.10, 0.12]mg/dL (AKI_{no}), while ΔsCr_{any} was 0.02[0.00,0.35]mg/dL vs 0.10[0.00, 0.34]mg/dL, respectively. 14-day AKI progression was 12.6%(AKI_{yes}) vs 9.7%(AKI_{no}), p~0.099. There was no difference in LOS.

Conclusions: Real-time clinician adjudication of an AKI alert did not improve AKI diagnosis as measured by prediction of AKI persistence or progression.

Funding: Other U.S. Government Support

Table1

Baseline Characteristics	AKI_{No} n = 413	AKI_{Yes} n = 1983	p-value
Age, median (IQR)	68.48 [56.85, 79.66]	73.21 [61.93, 82.75]	< 0.001
Female sex, n (%)	244 (56.6)	493 (47.6)	0.001
Race/Ethnicity, n (%)	7 (1.6)	26 (1.3)	0.473
Asian	77 (17.9)	393 (19.8)	.
Black	297 (68.9)	1388 (70.0)	.
White	59 (13.7)	198 (10.0)	.
Hispanic	0.70 (0.40, 1.30)	1.09 (0.80, 1.51)	< 0.001
Baseline sCr, median (IQR), mg/dL	1.03 (0.60, 1.64)	1.58 (1.28, 2.07)	< 0.001
sCr at AKI, median (IQR), mg/dL	415 (96.3)	1847 (93.1)	0.051
KDIGO AKI stage, n (%)	13 (3.0)	112 (5.6)	
1	3 (0.7)	24 (1.2)	
2			
3			



TH-PO012

Noninvasive Artificial Intelligence (AI)-Enhanced Electrocardiographic Detection of Hyperkalemia in the Emergency Department (ED) and ICU

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Background: We have previously trained a convolutional neural network using an all-patient cohort to produce an AI algorithm that can detect hyperkalemia from the surface ECG. In this validation study, we assessed the network's performance among ED and ICU patients.

Methods: We included adult patients presenting to the ED at all Mayo Clinic sites between February and August 2021 (ED cohort) and patients admitted to the ICU at Mayo Clinic St. Mary's Hospital, Rochester, MN between August 2017 and February 2018 (ICU cohort) if they provided research authorization, had a standard 12-lead supine ECG and had a blood K value within 4 hours of the ECG. The network analyzed leads I and II of the 12-lead ECG to calculate the probability of hyperkalemia, defined as K>6 mEq/L. The ED and ICU cohorts were analyzed separately. Exploratory subgroup analyses were performed for patients with eGFR<45 ml/min and eGFR<30 ml/min.

Results: 40,128 ED patients and 2636 ICU patients were included. The prevalence of hyperkalemia was 0.9% in the ED cohort and 3.3% in the ICU cohort. The AI-ECG had AUCs of 0.88 in both cohorts with sensitivities and specificities ≥ 80%. Negative predictive values (NPVs) were >99% in both cohorts. Although positive AI-ECGs quadrupled the probability of hyperkalemia, positive predictive values (PPVs) were relatively low: 3.5% in the ED and 14% in the ICU in part due to low hyperkalemia prevalences. Low eGFR subgroups had higher hyperkalemia prevalences and higher PPVs as shown in the Table.

Conclusions: The AI-ECG demonstrated excellent discrimination with AUCs of 0.88 in both cohorts. It was highly effective at ruling out hyperkalemia with NPVs>99% in both cohorts, but with much lower PPVs, suggesting that it is most useful as a screening test to exclude hyperkalemia. One method by which PPVs can be increased is by limiting testing to high-risk populations, such as those with reduced eGFR.

Funding: Clinical Revenue Support

		ED			ICU	
	All	eGFR<45	eGFR<30	All	eGFR<45	eGFR<30
N	40128	5298	2298	2636	745	429
AUC	0.88	0.85	0.83	0.88	0.85	0.85
Sensitivity	80%	86%	86%	82%	84%	88%
Specificity	80%	65%	60%	82%	72%	67%
PPV	3.5%	10%	15%	14%	23%	29%
NPV	99.8%	99.0%	98.2%	99.2%	97.9%	97.4%
K>6 Prevalence	0.87%	4.6%	7.7%	3.3%	9.3%	13.3%

TH-PO013

Machine Learning Algorithm in Predicting Non-Diabetic Kidney Disease in Type 2 Diabetes Mellitus: Development and Validation of a Noninvasive Predictor Scoring Model

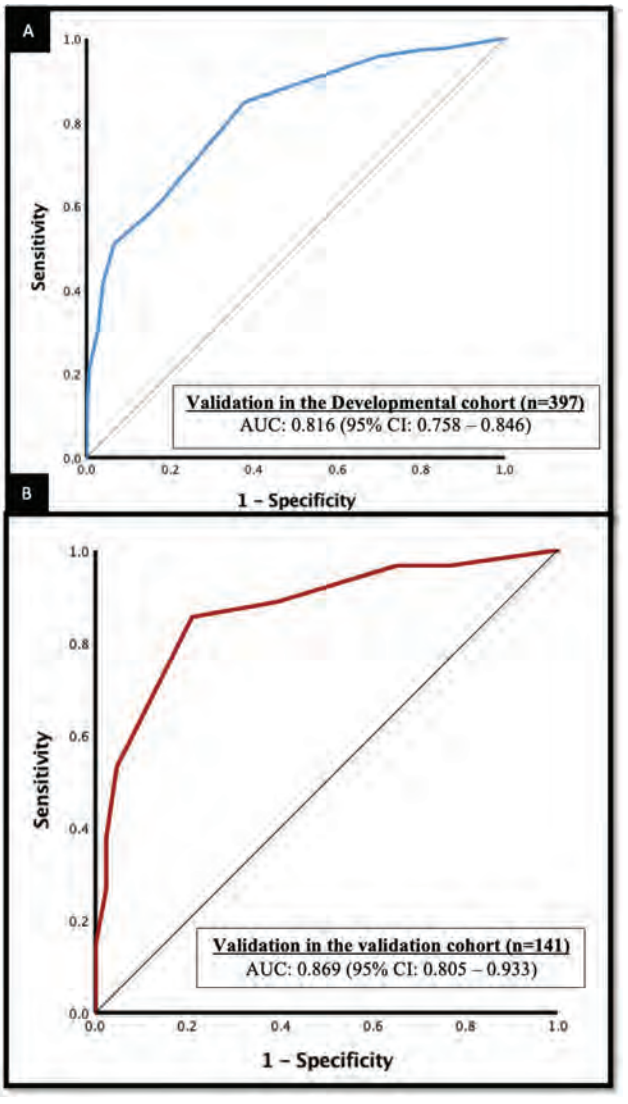
Vamsidhar Veeranki, Narayan Prasad, Jeyakumar Meyyappan. Nephro-SGPGI. *Sanjay Gandhi Post Graduate Institute of Medical Sciences, Lucknow, India*.

Background: Identifying non-diabetic kidney disease (NDKD) is essential in retarding the progression of chronic kidney disease among patients with type-2 diabetes mellitus(T2DM). Renal biopsy, despite being the gold standard in detecting the presence of NDKD, has an inherent risk of life-threatening complications. The current study aims to develop a non-invasive scoring model to predict the presence of NDKD using clinical and laboratory parameters.

Methods: Patients with T2DM who underwent biopsy for various indications were included and were divided into derivational and validation cohorts. Using the variables significantly associated with presence of NDKD on biopsy on univariate analysis, a model was developed using multivariate logistic-regression based machine learning algorithm. The model was then run on the derivational(internal validation) and validation cohort(temporal-validation) and the performance was assessed by receiver operating characteristic(ROC) curve.

Results: A total of 538 patients with T2DM were included in the study analysis; 376 in derivational cohort and 162 in validation cohort. The final model consists- diabetes mellitus duration< 5 years, absence of coronary artery disease, absence of diabetic retinopathy, presence of oliguria, acute rise in creatinine, & low serum complement-C3 level significantly predicted presence of NDKD on renal-biopsy. The model performed robustly with AUC-ROC of 0.869(95%CI:0.805-0.933) in validation cohort.

Conclusions: The clinical and laboratory parameter-based prediction model robustly predicted the NDKD among T2DM patients, and a cut-off total score of ≥ 6 has a high sensitivity & specificity of 86% & 80% in predicting NDKD.



Derivation and validation of the prediction model

TH-PO014

The Renal Prognosis Prediction Model of Diabetes Nephropathy Based on Machine Learning

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[2]*Institute of Computing Technology, Chinese Academy of Sciences, Beijing, China*.

Background: Diabetes nephropathy (DN) has become one of the most common causes of chronic kidney disease (CKD). This study is to establish a prognosis prediction model of DN using machine learning methods.

Methods: This retrospective cohort study enrolled 247 DN patients diagnosed by renal biopsy at Peking Union Medical College Hospital from December 2012 to September 2021 and collected clinical data from the EMR system. The primary endpoint

was all-cause mortality, end-stage renal diseases (ESRD) requiring dialysis and kidney transplantation. We used maximum likelihood estimation to complete the missing data and principal component analysis to standardize the data. K-means, hierarchical, and SOM clustering were compiled in Python to classify the data set. The weight of each variable in the clustering model was measured by several model misjudgments after removing the variable. The weight Analysis was to find the potential risk factors for poor prognosis.

Results: 1. About 57.5% of patients had renal insufficiency, and 62% with massive proteinuria. A total of 100 of them reached the primary endpoint with a median renal survival time of 2 years. Multivariate Cox regression showed that the independent risk factors for renal survival included proteinuria (OR = 1.13, 95%CI (1.07, 1.20), P<0.001), grade 3 hypertension (OR = 2.55,95%CI (1.09, 5.99), P<0.031) and low eGFR (OR = 1.02, 95%CI (1.00, 1.03), P=0.043). 2. By cluster analysis, two groups of patients had significant differences in renal survival at six months (OR=3.06, 95%CI (1.05, 8.92)), 12 months (OR=4.00, 95%CI (1.65, 9.70)), and 24 months (OR=2.46, 95%CI (1.78, 3.40)), as well as 24hUP (p<0.001), urinary red blood cells (p<0.001), hemoglobin (p=0.003), and albumin (p<0.001). 3. The machine learning models using LR, xgboost, and AdaBoost have the highest accuracy of prediction results in the test set, with an accuracy of up to 87.8% and auc = 0.87; The ten characteristics with the highest weight in this model were blood chlorine, hypertension grade, creatinine, EGFR, gender, diabetes retinopathy, age since the onset of diabetes, free triiodothyronine, urinary red cells, and platelet count.

Conclusions: Machine learning models combined with patient history and laboratory examination are a potentially powerful method for predicting the DN prognosis.

Funding: Government Support - Non-U.S.

TH-PO015

Impact of Retinal Photography-Based Deep Learning System on Risk Stratification for CKD Progression

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Background: We had previously developed a deep-learning-based risk evaluation system from retinal photographs, Reti-CKD, for stratifying chronic kidney development risk in kidney function preserved people. This study aims to evaluate whether Reti-CKD can improve risk assessment of kidney disease progression in diabetic patients with prevalent CKD.

Methods: Total of 5348 diabetic patients from two tertiary hospitals in Korea were evaluated. Patients with estimated glomerular filtration rate (eGFR) <90 ml/min/1.73m^2 or albuminuria were included. Those with missing data for retinal photograph, serum creatinine, or albuminuria were excluded. Patients were categorized into low-risk, moderate-risk, and high-risk groups according to the KDIGO criteria for prognosis of CKD. The KDIGO groups were additionally dichotomized based on Reti-CKD score (Reti-CKD <20 and ≥20). CKD progression was compared between the categories using Cox regression models. Primary outcome was CKD progression, defined as incremental progression to a higher NKF-KDOQI CKD stage.

Results: The mean age of the patients was 62.4 ± 11.4 years and 60.6% were male. Mean eGFR was 86.6 ± 15.3 mL/min per 1.73 m^2 and albuminuria was present in 46.9%. During a median follow-up of 5.0 (interquartile range, 2.5-7.8) years, primary outcome developed in 1379 (25.8%) patients. The primary outcome incidence rate gradually increased with higher KDIGO and Reti-CKD combined risk categories. The risk for CKD progression progressively increased in KDIG moderate-risk and high-risk groups compared to low-risk. When Reti-CKD was incorporated to the KDIGO category, significant stratification of CKD progression risk was noted in the KDIGO low-risk and moderate-risk groups. Additionally, the combination of KDIGO and Reti-CKD classification showed better discrimination power compared to the KDIGO only classification (delta c-statistics, 0.03; 95% CI 0.02 to 0.040).

Conclusions: Retinal photography-based deep learning system (Reti-CKD) further stratifies the risk of CKD progression and improves predictability in diabetic patients with reduced renal function.

TH-PO016

Computed Tomography Radiomics Analysis for Discrimination and Severity Assessment of Diabetic Kidney: A Retrospective Machine Learning Study

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Background: Kidney radiomics has been evaluated for the development of accurate diagnostics tools for renal tumors. However, there is a scarcity of radiomics studies focused on diabetic kidney disease (DKD). In this study, we aimed to investigate whether computed tomography (CT) radiomics features can differentiate DKD from normal kidneys and assess the severity of DKD.

Methods: We analyzed type 2 diabetes mellitus (T2DM) patients and healthy controls (HCs) who underwent abdominal CT scans between November 2014 and November 2022. CT volumetric data of both kidneys were extracted using a deep-learning model, enabling radiomics feature extraction. T2DM patients were categorized into risk groups based on estimated glomerular filtration rate (eGFR) and degree of albuminuria. Machine learning (ML) models were used to differentiate DKD patients from HCs and classify DKD risk groups. The models were trained and evaluated on separate patient data sets, with performance metrics such as sensitivity, specificity, accuracy, and area under the curve (AUC).

Results: The study included 462 T2DM patients and 90 HCs, who were randomly assigned to a training set (n=386; mean age ± standard deviation, 60.9 years ± 16.2; 239 men) or a test set (n=166; mean age, 60.7 years ± 15.7; 91 men). A total of 1,219 radiomics features were extracted. The random forest model showed excellent performance in differentiating between HCs and patients with low-risk DKD, with an AUC of 1.00 and an accuracy of 100% in the training set and an AUC of 0.84 and an accuracy of 80.6% in the test set. It also showed a good performance in discriminating between DKD groups based on eGFR (AUCs, 0.99-1.00, in the training set; AUCs, 0.70-0.94, in the test set) (Table1).

Conclusions: CT-derived radiomics analysis of the kidneys can effectively differentiate diabetic kidneys from normal kidneys and assess the severity of DKD. These findings suggest that radiomics data capture pathological changes in the kidneys associated with diabetes.

Funding: Government Support - Non-U.S.

Table. Diagnostic performance of the radiomics models in the training and the test set

		AUC	Accuracy (%)	Sensitivity (%)	Specificity (%)
Differentiation of HC and DKD					
Training set		0.99	99.7	99.4	100
Test set		0.85	80.3	94.2	66.5
Differentiation of HC and low-risk DKD (eGFR)					
Training set		1.00	100	100	100
Test set		0.84	80.7	90.1	71.2
Differentiation of HC and low-risk DKD (KDIGO)*					
Training set		1.00	100	100	100
Test set		0.84	75.9	75.9	75.9
Differentiation of DKD grade based on eGFR*					
Training set	Grade I vs II	0.99	95.4	93.1	97.7
	Grade II vs III	0.99	99.4	99.2	99.5
	Grade I vs III	1.00	99.5	99.0	100
Test set	Grade I vs II	0.70	64.8	60.7	74.1
	Grade II vs III	0.83	64.2	38.2	90.1
	Grade I vs III	0.94	90.2	100	80.3

*KDIGO risk group : low (eGFR≥60, albuminuria <30mg/g), moderate (eGFR≥60, albuminuria 30-300mg/g; eGFR 45-59, albuminuria <30mg/g), high (eGFR<30, any albuminuria; eGFR 45-59, albuminuria 30-300mg/g; eGFR ≥60, albuminuria>300mg/g)

**DKD grade based on eGFR : grade I, eGFR ≥60; grade II, eGFR 15-59; grade III, eGFR<15)

TH-PO017

Machine Learning Classification of Kidney Biopsy Smartphone Images for Adequacy Assessment

Odianosen J. Eigbire-Molen, Clarissa A. Cassol, Shana M. Coley, Daniel J. Kenan, Johnathan O. Napier, Shree G. Sharma. *Arkana Laboratories, Little Rock, AR.*

Background: Kidney biopsy is the gold standard for diagnosis of medical renal diseases. A biopsy that yields predominantly medulla or not enough renal cortex is an unsatisfactory result. There has been a significant increase in the rate of inadequate kidney biopsies. Unfortunately, not all centers have access to trained professionals who can assess biopsy adequacy in real time. Therefore, we aim to create a machine-learning model capable of classifying smartphone images of kidney biopsy tissue as adequate or inadequate.

Methods: 747 kidney biopsy cores and corresponding smartphone macro images were obtained from unused deceased donor kidneys. Each core was imaged, formalin fixed, sectioned and stained with Periodic acid–Schiff (PAS). A photo of the fresh unfixed core was taken using the macro camera on an iPhone 13 Pro. The amount of cortex in each core (percent cortex), was determined by two renal pathologists review of the PAS sections. Biopsies with less than 30% cortex were labelled as inadequate. Biopsies with 30% or more cortex were labeled as adequate. The images were split into a training (n=643), validation (n=30), and test (n=74) sets. The preprocessing steps were converting from HEIC iPhone format to JPEG, normalizing, and detecting the renal tissue; a U-Net deep learning model was trained to segment renal tissue from the background. After preprocessing, a deep learning model was trained on the renal tissue region of interest and corresponding class label. See Figure 1.

Results: The deep learning model had an accuracy of 87% on the training data. On the test dataset, the model had an accuracy of 82%. For inadequate samples in the test dataset, the model had a sensitivity of 71%. The area under the receiver operating curve was 0.79.

Conclusions: We developed and tested a machine learning model to classify smartphone images of kidney biopsy as adequate or inadequate, based on the amount of cortex determined by a renal pathologist. With further work, such models can be deployed as a smartphone application to aid in real time assessment of renal biopsy adequacy.

Funding: Other NIH Support - SBIR Grant Number: 1R43DK134273-01

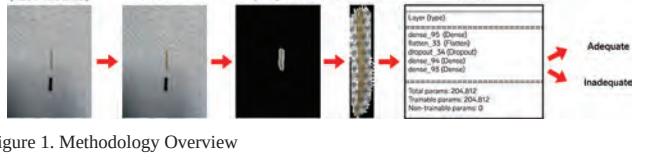


Figure 1. Methodology Overview

TH-PO018

Machine Learning to Predict Unplanned Dialysis in Advanced CKD

Leslie P. Wong,[1] Chenlee Condie,[1] Mark J. Durst,[1] Kristin F. Mote,[1] Jonathan Sanchez,[2] Michelle Schneider,[2] Peter Calderone.[2] Intermountain Kidney Services. *[1]Intermountain Healthcare, Salt Lake City, UT; [2]MDClone, Beer-Sheva, Israel.*

Background: Unplanned dialysis occurs when dialysis is initiated in the hospital setting and results in increased morbidity, mortality, and healthcare costs. Patients with advanced chronic kidney disease (CKD) are at higher risk for unplanned dialysis, but it is difficult to identify those who might benefit from targeted interventions. Machine learning was used to attempt to predict unplanned dialysis in a large CKD cohort.

Methods: A retrospective analysis of 15,424 patients in a large U.S. health system with stage 4 and 5 CKD between January 2018 to March 2023 was performed using the MDClone ADAMS Platform and a proprietary CKD temporal staging algorithm. Variables included age (71.4 ± 14.9 years), gender (Female, 55%), most recent eGFR (32.4 ± 16.7 ml/min/1.73m^2), count of emergency department visits in two years prior (2.2 ± 3.3), count of all clinical encounters in two years prior (33.3 ± 35), BMI (30.2 ± 9.8), hypertension (77.3%), diabetes (58.6%), obstructive sleep apnea (34.1%), peripheral arterial disease (32.7%), and systolic blood pressure (134.4 ± 24.4 mmHg). XGBoost, a gradient boosting algorithm, was employed to predict unplanned dialysis events.

Results: The model's performance predicting unplanned dialysis was evaluated using accuracy, precision, recall, and F1 score metrics. The model achieved accuracy of 90.5%, precision of 55.2%, and recall of 54.7%, resulting in a F1 score of 0.55. Discrimination was high with an AUC 0.89 (Figure 1).

Conclusions: The model developed using a XGBoost machine learning algorithm demonstrated high accuracy and discriminatory power to identify stage 4 and 5 CKD patients at risk for unplanned dialysis. This predictive model has potential to help guide targeted interventions to prevent these events in the advanced CKD population.

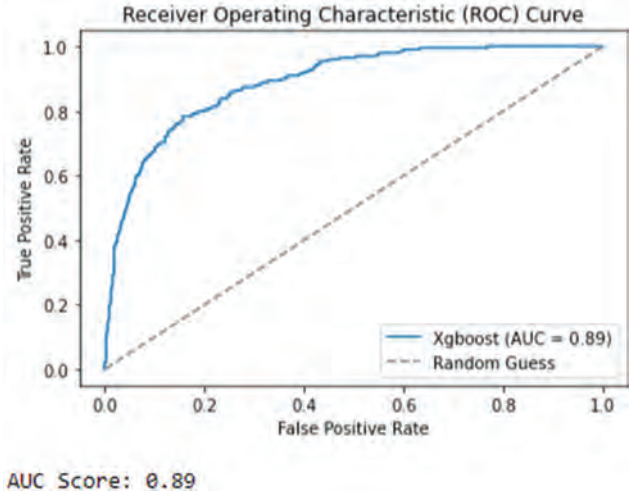


Figure 1. Model Reciever Operating Characteristic Curve

TH-PO019

Machine Learning-Based Risk Prediction Model for ICU Survival After Continuous Renal Replacement Therapy Initiation: A WEROCK Study

Shina Menon,[1,2] Sameer Thadani,[5] Katja M. Gist,[3] Danielle E. Soranno,[4] Danny T. Wu.[3] WE-ROCK. *[1]University of Washington, Seattle, WA; [2]Seattle Children's Hospital, Seattle, WA; [3]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [4]Indiana University School of Medicine, Indianapolis, IN; [5]Baylor College of Medicine, Houston, TX.*

Background: Continuous renal replacement therapy (CRRT) is preferred in critically ill pediatric patients with acute kidney injury (AKI) and/or fluid overload (FO). Prediction of clinical outcomes in patients on CRRT is challenging given heterogeneous clinical practices and study population. Our aim was to predict survival to intensive care unit (ICU) and hospital (HOSP) discharge using machine learning (ML) techniques.

Methods: The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) study is a retrospective international multicenter study (32 centers, 7 nations). Our methods have been published previously. We included 991 patients aged 0-25 years treated with CRRT for AKI and/or FO from 2018-2021. Primary outcomes were survival to ICU and HOSP discharge. Feature selection was done manually through team discussions, resulting in 61 out of 119 demographics variables. The data were split into training(80%) and testing(20%) subsets. The ML process included 5 algorithms (Logistic Regression with L2 regularization, Decision Tree, Random Forest, Gradient Boosting Machine, and Support Vector Machine with linear kernel) and used 5-fold cross validation to train the models. The model performance was determined by the Area Under the Curve of the Receiver Operating Characteristic (AUCROC). The performance of the best trained model on the testing dataset was reported using standard metrics (Table 1).

Results: Random Forest was our highest performing algorithm. Table 1 shows that our models (WE-ROCK) achieved comparable or slightly higher AUROC compared to previous studies in adults.

Conclusions: This is the first ML model to predict survival to ICU and hospital discharge in pediatric patients requiring CRRT. The performance was similar to previously published models in critically ill adults. We will continue refining our models by expanding the input variables, conducting a more sophisticated feature selection, experimenting advanced ML and deep learning algorithms.

Source	Best Model	AUC	Sensitivity	Specificity	Precision	Accuracy	F1-score
Survival to ICU discharge							
Kang et al.	Random Forest	0.784	NR	NR	NR	0.690	0.762
WE-ROCK	Random Forest	0.799	0.922	0.648	0.720	0.719	0.808
Survival to Hospital discharge							
Kang et al.	Random Forest	0.768	NR	NR	NR	0.711	0.790
WE-ROCK	Random Forest	0.788	0.887	0.573	0.719	0.714	0.794
Hung et al.	Gradient Boost Models	0.823	0.742	0.787	0.881	0.756	0.801

Table 1. ML model performance for ICU & Hospital mortality
Kang et al. is published in 2020 and available at https://doi.org/10.1186/s13054-020-2752-7
Huang et al. is published in 2022 and available at https://doi.org/10.3390/diagnostics12061496
NR: Not reported in the paper
ICU-D: Survival to ICU discharge
HOSP-D: Survival to ICU discharge

Table 1

TH-PO020

Early Identification of the Need for CRRT in Children: A Machine Learning Approach

Shina Menon, Qingyang Li, David R. Van De Sompele, Alexander J. Doud, Kin L. Vong, Hillary Bourdrez, Mark W. Wainwright. *Seattle Children's Hospital, Seattle, WA.*

Background: Continuous Renal Replacement Therapy (CRRT) is the preferred modality of renal replacement in critically ill children with acute kidney injury. We sought to develop a machine learning (ML) model to identify patients at least one day before the CRRT initiation.

Methods: We used data from patients admitted to the pediatric ICU with a length of stay >24 hours from 2008-2021. Candidate data elements were selected based on clinical expertise and anticipated United States Core Data for Interoperability requirements. To address the class imbalance problem, we oversampled data from the CRRT patient group and then selected using a random 24-hour window preceding the outcome of interest for each new sample. By including test cases with data collected 1 day before the CRRT decision, this process ensures earlier identification of the need for CRRT. We engineered features by vectorizing the patient state and then selected features using correlation-based feature selection (CFS) and information gain (IG) feature selection in combination with 5 methods of classification: random forest, logistic regression, Naïve Bayes (NB), support vector machine, and extreme gradient boosting. Data curation, analyses and development were conducted using Python (version 3.9).

Results: 19457 PICU encounters (159 received CRRT) were identified and stratified into training(85%) and test(15%) sets after data augmentation. Models constructed using IG contained 436 features versus 42 features using CFS. The top features included blood urea nitrogen, creatinine, platelets, Glasgow coma score, and fluid balance. NB model outperformed the other approaches. NB with IG feature selection achieved area under the ROC curve (AUROC) 0.925, area under the precision-recall curve (AUPRC) 0.813, accuracy 0.88, F1 score 0.88, whereas the NB model with CFS achieved comparable accuracy and F1-score but the performance was slightly better with 0.945 AUROC, 0.890 AUPRC.

Conclusions: We present a model that uses ML and leverages structured, time-series data to identify patients likely to need CRRT in the ICU. The study's limitations include being conducted in a single institution and not considering unstructured data, which may improve the model's performance.

TH-PO021

Machine Learning Models for IgA Nephropathy Diagnosis: A Retrospective Study on Predictive Performance and Influential Variables

Ryunosuke Noda, Daisuke Ichikawa, Yugo Shibagaki. *St. Marianna University School of Medicine, Kawasaki, Japan.*

Background: IgA nephropathy often requires therapeutic modalities associated with potential complications, such as steroids, and so requires definitive diagnosis by invasive renal biopsy rather than non-invasive clinical diagnostic measures. Although the efficacy of machine learning (ML) for diagnostic purposes has been underscored in recent years, its application in the context of nephrology remains unclear. In this study, we investigated the diagnostic performance of ML algorithms for IgA nephropathy.

Methods: We conducted a retrospective cohort study on 1,419 cases that underwent renal biopsy in our hospital from January 2006 to September 2022. Cases with indeterminate diagnoses and overlapping pathologies were excluded. The remaining cases were randomly divided into train and test datasets at an 8:2 ratio. We utilized a total of 44 variables, which included age at the time of renal biopsy, gender, blood tests, and urinalysis, as explanatory variables. Subsequently, multiple machine learning algorithms were evaluated, including K-nearest neighbor, support vector machines, random forest, extreme gradient boosting, and LightGBM, using Python. The model with the highest average Area Under the Curve (AUC) was identified through stratified 5-fold cross-validation in the train set. Thereafter, we compared the AUC of this model in the test

set to that of the logistic regression (LR) model in the test set. To interpret the predictive outcomes, we deployed the SHapley Additive exPlanations (SHAP) methodology.

Results: In the train set, LightGBM outperformed the other ML models, exhibiting the highest AUC of 0.92, which also mirrored its performance in the test set (LightGBM 0.92, LR 0.88). SHAP analysis unveiled that the variables contributing to prediction were, in descending order, urinary red blood cell count, serum albumin, IgA/C3 ratio, urinary protein/creatinine ratio, and age.

Conclusions: Our study indicated that ML, particularly the LightGBM model, could improve IgA nephropathy diagnostic performance beyond conventional logistic regression. The influential variables identified were consistent with those reported in the existing literature. This highlights the potential utility of ML in IgA nephropathy diagnosis, necessitating further validation for clinical use.

Funding: Private Foundation Support

TH-PO022

Machine Learning Models for the Prediction of Kidney Stone Composition and Recurrence

Matteo Bargagli, Daniel G. Fuster. *Department of Nephrology and Hypertension, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland.*

Background: Kidney stones are prevalent and cause high patient morbidity and healthcare cost. Kidney stone treatment depends on stone type and recurrence risk. We hypothesized that machine learning (ML) methods provide higher accuracy compared to current approaches for stone type and recurrence risk prediction.

Methods: Data from three comprehensively phenotyped Swiss cohorts comprising 1505 kidney stone formers with demographic, anthropometric and clinical information, stone composition analysis, and 24-h urine measurements were included. Several supervised ML models, including logistic regression, parallel-tree boosting (XGBoost), random forests, and neural networks, were trained independently to predict the stone type and the 5-year recurrence risk.

Results: XGBoost performed with generally high specificity (>90%), except for calcium oxalate stones which demonstrated lower sensitivity. The algorithm achieved an accuracy of 85% when distinguishing between uric acid-containing and calcium phosphate-containing stones. Key features informing the model included age at first stone event, body mass index, 24h urine calcium and pH. The 5-year recurrence risk predicted by the neural network ranged between 48% and 83%, closely aligning with observed recurrence risk ($R^2 = 0.913$).

Conclusions: The developed ML models demonstrated remarkable accuracy in predicting the risk of stone recurrence. These findings have the potential to address an unmet clinical need by assisting healthcare specialists in clinical decision-making, and ultimately enhancing patient outcomes and quality of life for those affected by recurrent kidney stone disease.

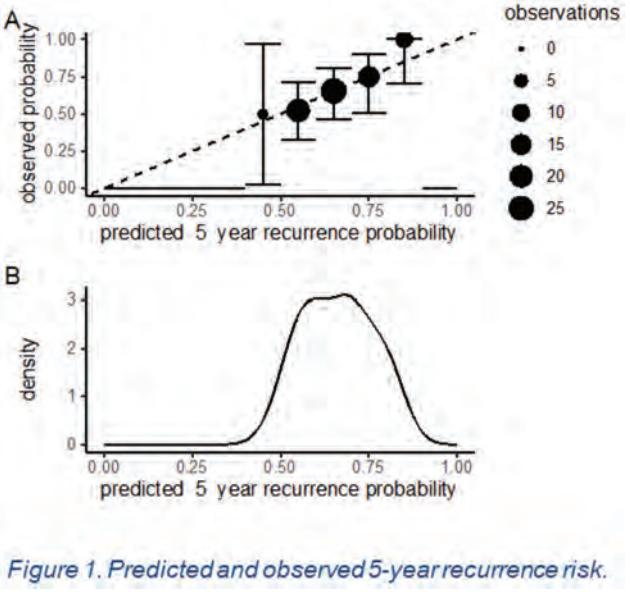


Figure 1. Predicted and observed 5-year recurrence risk.

TH-PO023

Integrating Electronic Health Data Records to Develop and Validate a Predictive Model of Hospital-Acquired AKI in Non-Critically Ill Patients

Alfonso Segarra,[1,2] Jacqueline Del Carpio Salas,[3,1] Natalia Ramos,[4] Jorge González,[1] Jose Bruno Montoro Ronsano,[4] Silvia Pico Fornies,[1] Marina Canales Navarro,[2] María P. Marco,[1] Elias A. Jatem,[1] Pamela J. Chang.[1] *[1]Hospital Universitari Arnau de Vilanova, Lleida, Spain; [2]Institut Catala de la Salut, Lleida, Spain; [3]Universitat Autonoma de Barcelona, Barcelona, Spain; [4]Hospital Universitari Vall d'Hebron, Barcelona, Spain.*

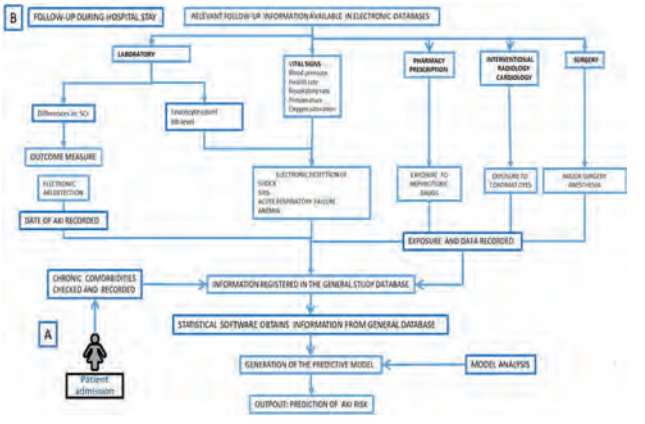
Background: Models developed to predict hospital-acquired acute kidney injury(HA-AKI) in non-critically ill patients have low sensitivity, do not include dynamic changes of risk factors and do not allow the establishment of a time relationship between exposure to risk factors and AKI. We developed and externally validated a predictive model of HA-AKI integrating electronic health databases and recording the exposure to risk factors prior to the detection of AKI.

Methods: The study set 36852 non-critically ill hospitalized patients admitted from January-December 2017. Using stepwise logistic analyses, including demography, chronic comorbidities and exposure to risk factors prior to AKI detection, we developed a multivariate model to predict HA-AKI. Externally validated in 21545 non-critical patients admitted to the validation centre from June 2017-December-2018.

Results: Incidence of AKI in study set was 3.9%. Among chronic comorbidities, the highest ORs chronic kidney disease, urologic disease and liver disease. Among acute complications, the highest ORs acute respiratory failure, anaemia, systemic inflammatory response syndrome, circulatory shock and major surgery. Model showed AUC 0.907, sensitivity 82.7 and specificity 84.2 to predict HA-AKI. In validation set, incidence of AKI 3.2%. Model showed AUC 0.905, sensitivity 81.2 and specificity 82.5 to predict HA-AKI and had an adequate goodness-of-fit.

Conclusions: By using electronic health data records, our study provides a model that can be used in clinical practice to obtain an accurate dynamic and updated assessment of the individual risk of HA-AKI during the hospital admission period in non-critically ill patients.

Funding: Commercial Support - Amgen S.A and Menarini S.A



Schematic representation of the interrelation between electronic databases performed to obtain updated clinical information during hospital stay.

TH-PO024

Classification of Arteriovenous Access Aneurysm in Hemodialysis Patients Using Artificial Intelligence Application

Zijun Dong,[1] Hanjie Zhang,[1] Lin-Chun Wang,[1] Sarah Ren,[1] Lela Tisdale,[1] Maggie Han,[1] Shahzre Mohib,[1] Laura Rosales M.,[1] Sindhuri Prakash-Polet,[2] Denzil Douglas,[2] Piotr Starakiewicz,[2] Dean C. Preddie,[2] Stephan Thijssen,[1] Peter Kotanko.[1,3] *[1]Renal Research Institute, New York, NY; [2]Azura Vascular Care, New York, NY; [3]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Arteriovenous (AV) access aneurysms in hemodialysis (HD) patients may lead to severe and potentially life-threatening consequences, such as rupture. To address this issue, we developed an artificial intelligence-based app that utilizes images of the AV access to classify AV aneurysms (Zhang, Clin Kidney J, 2022). Our objective

was to assess the correlation between the classification results generated by our aneurysm classification app and the independent clinical examination performed by physicians specializing in access care.

Methods: As described recently (Zhang, Clin Kidney J, 2022), AV accesses were photographed, and the images were transferred to the cloud, where they were classified as "Advanced" or "Not Advanced" by a convolutional neural network algorithm (Fig. 1A). We compared classifications made by physicians who were blinded to the app results (i.e., the ground truth) and those generated by our app.

Results: We studied 28 subjects (Fig. 1B). Twenty out of 22 aneurysms were accurately classified as "Not Advanced" and 5 out of 6 as "Advanced" (Fig. 1C), resulting in an accuracy of 89%, sensitivity of 83%, specificity of 91%.

Conclusions: Our preliminary results show that an AI-powered app can classify AV aneurysms with actionable accuracy in a demographically diverse HD population. If these results are corroborated in a larger patient population, our tool has the potential to support the development of a robust aneurysm monitoring system, enabling timely detection, facilitating referrals, and avoiding emergency interventions associated with aneurysms.

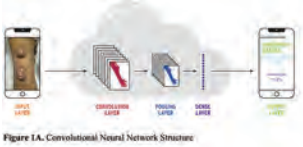


Figure 1A. Convolutional Neural Network Structure

		Physician Assessment	
		Advanced	Not Advanced
Model Assessment	Advanced	5	2
	Not Advanced	1	20

Figure 1C. Model versus Physician Assessment of AV Aneurysm

		Physician Assessment		
		Total	Advanced	Not Advanced
	Patient	28 (100%)	6 (21%)	22 (79%)
	Age [years]	67.0 ± 17.3	68.3 ± 12.0	66.5 ± 18.7
Sex	Male	18 (64%)	3 (50%)	15 (68%)
	Female	10 (36%)	3 (50%)	7 (32%)
Race	Asian	1 (3%)	0 (0%)	1 (5%)
	Black	16 (57%)	4 (67%)	12 (54%)
	Other	1 (3%)	0 (0%)	1 (5%)
	White	10 (37%)	2 (33%)	8 (36%)
Ethnicity	Hispanic	6 (21%)	1 (17%)	5 (23%)
	Non-Hispanic	22 (79%)	5 (83%)	17 (77%)
Access	AV Fistula	23 (82%)	6 (100%)	17 (77%)
	AV Graft	5 (18%)	0 (0%)	5 (23%)
Access Type	Radiocephalic	11 (39%)	1 (17%)	10 (45%)
	Brachiocephalic	16 (57%)	5 (83%)	11 (50%)
	Transposed Brachiobasilic	1 (4%)	0 (0%)	1 (5%)

Figure 1B. Baseline Characteristics. Values are in mean ± standard deviation or count (%). Classifications of "Advanced" and "Not Advanced" are based on physicians' assessments.

TH-PO025

Derivation and Validation of Machine Learning Models for the Prevention of Unplanned Dialysis in Advanced CKD Patients

Martin M. Klamrowski,[1] Ran Klein,[2] James Green,[1] Chris Mccudden,[2] Cedric A. Edwards,[2] Babak Rashidi,[2] Ayub Akbari,[2] Gregory L. Hundemer.[2] *[1]Carleton University, Ottawa, ON, Canada; [2]University of Ottawa, Ottawa, ON, Canada.*

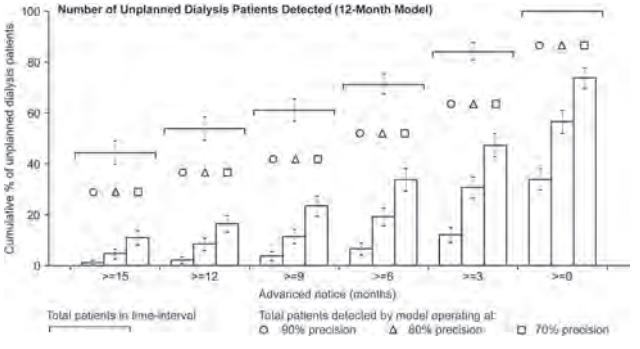
Background: A short timeframe kidney failure risk prediction model may serve to prevent unplanned dialysis starts, a detrimental outcome associated with increased morbidity, mortality, and healthcare costs. To date, no such clinical tool exists.

Methods: We developed and externally validated models for prediction of kidney failure over short timeframes of 6 and 12 months. The models were fit in 2,432 consecutive advanced CKD patients from The Ottawa Hospital. Models were externally validated in two independent advanced CKD cohorts from the Kingston General Hospital (N=724), and the Sunnybrook Health Sciences Center (N=323). All hospitals are in Ontario, Canada. Patients lost to follow-up, under conservative care management, or with <12 months of follow-up were excluded. Random forest classifiers were used to predict the 6- and 12-month probability of kidney failure for each patient at each follow-up visit. Input features included age, sex, and commonly available laboratory measurements and features characterizing their trajectory. The percentage of patients detected within clinically actionable timeframes of 3-15 months were computed for both models.

Results: Internally, upon presentation, patients had a mean±SD age 66±15 years, and eGFR 18±7 mL/min/1.73m^2, and median (IQR) ACR 164 (49, 333). Internal ROC-AUCs (95% CI) of 0.88 (0.87-0.88) and 0.86 (0.86-0.87) were achieved by the 6- and 12-month models, respectively. Models were well-calibrated. Internally, at 70% precision, patients requiring dialysis were correctly identified with at least 6 months advanced notice in 20% and 34% of cases using the 6- and 12-month models. Performance did not significantly differ at either external site.

Conclusions: Machine learning-based short timeframe kidney failure risk prediction models accurately identify advanced CKD patients at high risk for imminent dialysis, including a substantial proportion destined for unplanned (or "crash") dialysis initiation.

Funding: Government Support - Non-U.S.



TH-PO026

Predictive Model of the Time to Renal Replacement Therapy Using Machine Learning

Jun Okita, Takeshi Nakata, Hiroki Uchida, Akiko Kudo, Akihiro Fukuda, Hirotaka Shibata. *Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan.*

Background: In the treatment of chronic kidney disease, nephrologists are expected to prolong the renal prognosis for those at high risk for end-stage renal disease (ESRD). It is also important to estimate the time to renal replacement therapy (RRT) in patients at high risk of ESRD. In Japan, the "time-series data of estimated glomerular filtration rate (eGFR)" is used to estimate the time to RRT based on the annual decline rate. In this study, we used machine learning to predict the time to RRT from the "data obtained at a single time point."

Methods: Patients who underwent hemodialysis at our hospital from April 2016 to March 2021 were included, and a data set, including 30 laboratory data items (BUN, creatinine [Cr], etc.), six patients' background demographic background, and medications were extracted retrospectively from the electronic medical records. 75% of the data were randomly split for training and 25% for testing, and the predictive models were created with several algorithms: linear regression, ridge regression, least absolute shrinkage selection operator (LASSO) regression, elastic nets, random forests, and gradient boosting decision trees. We also predicted the time to RRT using "time-series data of eGFR" and compared the accuracy by the coefficient of determination (R^2) and mean absolute error (MAE).

Results: A total of 13,323 data were extracted from 147 patients of which 99 were males, resulting in a final total of 1,801 data groups with no missing data. The mean age at dialysis induction was 60.8 years, the most common etiology for ESRD was diabetic nephropathy (44 %), the mean Cr was 7.6 ± 2.0 mg/dL, and the mean eGFR was 6.1 ± 1.7 ml/min/1.73 m^2. The prediction model based on LASSO was moderately accurate with R^2 0.62 and MAE 416, while the prediction based on the "time-series data of eGFR" was highly inaccurate with R^2 of -17.1 and of MAE 2466, indicating that the machine learning is superior in predicting the onset of dialysis.

Conclusions: The machine learning method was used to predict the time to RRT using "data obtained at a single time point," and a moderately accurate prediction model was obtained. The ability to specify the time to RRT, even approximately, is useful not only for medical staff to make treatment decisions, but also for patients to motivate themselves to receive treatment and making long-term plans.

TH-PO027

Prediction of the Presence of Vesicoureteral Reflux Using Kidney Ultrasound Images with Deep Learning

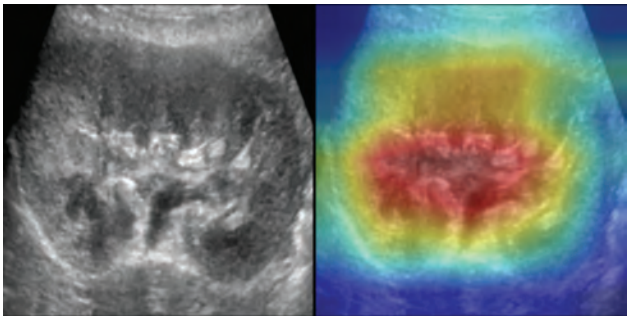
Yuichi Morimoto, Keisuke Sugimoto, Kohei Miyazaki. *Kinki Daigaku, Higashiosaka, Japan.*

Background: In previous studies, detection of vesicoureteral reflux (VUR) and renal scarring by ultrasonography has been attempted, but the results have not yet been satisfactory.

Methods: Patients who underwent ultrasonography and VCUG examinations in the course of a thorough examination for congenital renal urinary tract abnormalities at our hospital from January 1, 2010 to January 1, 2021 were included in the study. We used a deep learning image classification method to create a discriminant model of VUR using kidney echo images as training data and VCUG examination results as teacher data. After creating the model using the training and validation data, the sensitivity and specificity were evaluated using the test data. The model was then evaluated for sensitivity and specificity using the test data. The model was visualized using the Grad-cam to determine the explanatory power of the model.

Results: In this study, 46 VCUG cases (male cases [57%], median age 4.5 years [0 months to 10 years]) were included. 23 of the 46 cases had VUR, 12 were Grade I-III and 11 were Grade IV-V. 230 echo images (115 each) from the groups with and without VUR were used for transition learning For VUR detection, the deep learning model had a sensitivity of 58%, specificity of 87.5%, positive predictive value of 82.4%, negative predictive value of 67.7%, and accuracy of 71.7% (Figure 1).

Conclusions: It was suggested that the presence of VUR could be predicted from renal echographic images and may contribute to the decision of VCUG indication. In addition, it has been reported that thickening of the renal pelvis wall due to reflux has been observed, and in the visualization of features performed with the model created in this study (Figure 1), similar areas may have contributed to the AI's judgment. If the presence and severity of VUR can be determined with a certain degree of accuracy from renal echo images, the pain and radiation exposure caused by VCUG may be avoided.



Features visualized by Gradcam

TH-PO028

Bloodless Artificial Intelligence Electrocardiography Detecting Thyrotoxic Periodic Paralysis Following SARS-CoV-2 Infection

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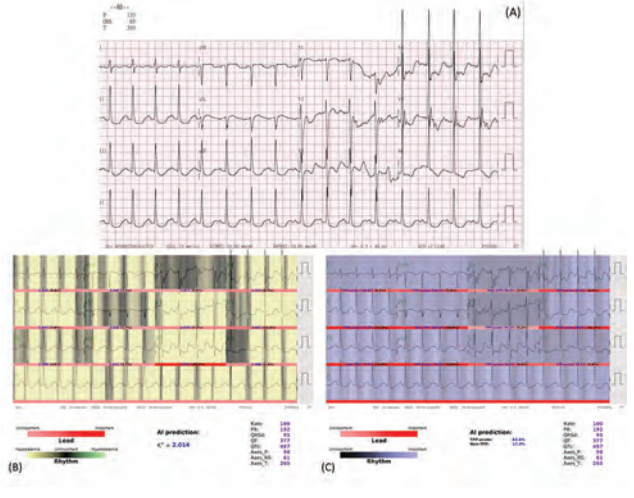
Introduction: Hypokalemic paralysis, a metabolic muscle paralysis emergency, is divided into hypokalemic periodic paralysis (HypoPP) due to acute intracellular K^+ shift, and non-HypoPP due to profound K^+ deficiency. Thyrotoxic periodic paralysis (TPP), a form of HypoPP, is characterized by acute muscle paralysis, hypokalemia, and hyperthyroidism and can be triggered by any kind of thyrotoxicosis and occasionally by viral infection. This case highlights a young Chinese male with TPP following SARS-CoV-2 infection, rapidly identified via artificial intelligence electrocardiography (AI-ECG).

Case Description: A 22-year-old man recently infected with SARS-CoV-2 presented with acute paralysis in his lower limbs and palpitations post-exercise. Examination showed symmetrical areflexia and an enlarged thyroid. AI-ECG detected hypokalemia and high TPP likelihood (Figure 1). Intravenous K^+ supplementation began and subsequent test showed hypokalemia (1.6 mmol/L). Treatment with intravenous K^+ normalized muscle strength and serum K^+ while hormone studies confirmed Graves' disease. Hyperthyroidism was managed with antithyroid drug and β-blocker. He had subclinical hyperthyroidism without relapse 3 months later.

Discussion: Despite the incidence of COVID-19-related thyrotoxicosis, TPP following SARS-CoV-2 infection are rare. Rapid diagnosis and appropriate TPP management are vital. The implementation of AI-ECG system, featuring hypokalemia and TPP detection models, allows for rapid identification and treatment initiation. Given the high incidence and swift emergence of COVID-19-related hyperthyroidism, evaluations of thyroid function, electrolytes, and use of AI-ECG are warranted in patient with neuromuscular symptom to ensure early TPP detection and reduces serious complications.



(A) Prolonged QT interval and prominent U wave; (B, C) AI-ECG analysis indicates hypokalemia and high likelihood of TPP

TH-PO029

Artificial Intelligence Prediction of Dialysis Access Complications

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Background: The single most important factor determining quality of dialysis is adequate access. This begins with the placement of an access that is optimized for the individual patient and may include a fistula, graft, or in some cases a catheter. Constant monitoring of the fistula or graft is needed to avoid future complications and with the EMR we can provide this in real time using the dialysis machine / EMR interface. We evaluated an AI approach to prediction venous stenosis at different locations with sufficient warning that an intervention can be performed prior to interruption of dialysis.

Methods: Data were obtained from the University of Louisville dialysis electronic medical record system and the Interventional Nephrology program for the years 2018 to 2020. Routinely collected information at the time of initiation as well as intradialytic data were obtained. Events were determined by direct examination within the interventional facility and segregated into inflow, outflow, central, and other stenosis. Event classification was performed using sequential vector of predictors consisting of target and achieved blood flow rate, arterial pressure, arterial resistance, venous pressure, venous resistance, and mean arterial pressure. Resistance was defined as the ratio of pressure to blood flow rate. Events were predicted 1 week in advance. Classification was performed using tree ensembles (AdaBoost) and Artificial Neural Network.

Results: Data set contained 2369 samples with 27 inflow, 133 outflow, 54 central, and 59 other stenosis events. Classifiers were trained using 10-fold cross-validation. Additionally, 10% of the data were held out for testing. Table 1 shows comparison of the classifier performance on the test data between the two methods.

Conclusions: Sufficient information exists during the dialysis procedure that can be leveraged using advanced mathematical techniques to adequately predict dialysis access complications. The methodology applied also allows for the explanation of the observations seen and can provide predictions through a mathematical model or an expert system in the form of a decision tree.

	Inflow		Outflow		Central		Other	
Method	Tree	NN	Tree	NN	Tree	NN	Tree	NN
True Positive Rate	100	100	66.4	98.7	100	100	78.7	100
True Negative Rate	73.6	97.4	77.1	89.2	42.9	97.4	85.3	92.2
False Positive Rate	26.4	2.6	22.9	10.8	57.1	2.6	14.7	7.8
False Negative Rate	0	0	33.6	1.3	0	0	21.3	0

TH-PO030

Deep Learning-Based Prediction of Postoperative AKI After Noncardiac Surgery Using Intraoperative Vital Sign Parameters in a Minute Scale

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Background: Certain models were used to predict the risk of PO-AKI mainly with preoperative characteristics; however, complex intraoperative vital sign information was difficult to be combined to such strategy although intraoperative hemodynamic alteration is one of the major factor affecting PO-AKI risks. We aimed to construct an externally validated deep learning-based prediction model for PO-AKI, including complex, real-time collected hemodynamic information.

Methods: We collected systolic and diastolic pressure values and heart rate information collected from the real-time intraoperative monitoring in a tertiary university hospital (N = 51,345). The test and the internal validation set was split as 8:2 manner, and additional external validation was performed in two additional tertiary university hospitals (N = 47,093 and 12,259). Total collected measured points of blood pressure values were 17,816,251 (systolic) and 17,793,025 (diastolic) and of heart rate was 17,505,759. Deep-learning model was constructed using the EfficientNet based CNN model. The outcome was PO-AKI and critical AKI events, and the critical AKI was defined as high stage AKI or AKI associated with death or dialysis. We compared the model performances with AUC-ROC values, and the conventional SPARK classification was used as the reference model.

Results: The deep-learning model only including intraoperative variables showed moderate but tolerable discrimination power against PO-AKI [AUC-ROC 0.707 (development), 0.637 and 0.729 (validation)] or critical AKI [AUC-ROC 0.724 (development), 0.729 and 0.716 (validation)] events. When major PO-AKI risk factors were incorporated to the models, the powers outperformed the conventional SPARK model; for PO-AKI [0.765 (development), 0.716 and 0.761 (validation)] and for critical AKI [0.816 (development), 0.741 and 0.794 (validation)]. The model performances even improved in the ensemble model learning both preoperative tabular data and the intraoperative prediction models.

Conclusions: Complex intraoperative vital sign information, including blood pressure and heart rate, can be used to develop tolerable deep-learning based PO-AKI risk stratification model that can be used after non-cardiac surgeries.

TH-PO031

Ultrasound-Based Imaging Methods for the Assessment of Kidney Fibrosis on Artificial Intelligence

Dan Zhao. *Shanghai Tongji Hospital, Shanghai, China.*

Background: Renal fibrosis is the common pathway leading to end stage kidney disease, but the assessment of renal fibrosis remains limitations. Artificial intelligence (AI)-based ultrasound imaging has showed high specificity and sensibility in disease diagnosis via image recognition. Hereby, we intend to use artificial intelligence technology to explore a new method for early non-invasive assessment of renal fibrosis through ultrasound images.

Methods: A retrospective cohort of patients receiving kidney biopsy was developped from our hospital between January 2018 and July 2022. All participant underwent kidney ultrasound within one week. The magnitude of renal intersitial fibrosis (RIF) was evaluated by two experienced pathologists according to Banff criteria. All ultrasound images were preprocessed, then randomly divided into training and test sets in a 7 to 3 ratio. Radiomic features extracted from selected regions of interest (ROI), including firstorder, texture, and wavelet-transformed features. Two-sample t-test, LASSO, and Spearman correlation analysis were used to reduce feature dimension. Three machine learning models and one deep learning model were established to distinguish mild and moderate-severe fibrosis. The area under the curve (AUC) of the receiver operating characteristic curve was employed to assess the models' performance.

Results: A total of 193 paients were enrolled in this study, including 100 with mild fibrosis and 93 with moderate-severe fibrosis. 837 radiomic features were extracted from gray scale ultrasound images. After feature dimension reduction, 10 features were retained, of which 9 were wavelet-transformed features. Based on 10 selected radiomic features, three machine learning models were established: LR, SVM and RF. In test sets, the AUCs were 0.75, 0.80, and 0.89, respectively. The accuracy were 60%, 63.7%, and 65% respectively. RF model achieved the best classification performance. For further visualization, LR prediction model were visualized as nomogram. In addition, based on full kidney ultrasound images, VGG16 network model were also establisehed, with AUC of 0.76 (95% CI, 0.63-0.90) and the accuracy of 77%.

Conclusions: AI-assisted imaging analysis endows traditional ultrasound techniques with the promising potential for early diagnosis of renal fibrosis. Our study would provide new insights for the future exploration of noninvasive assessment methods.

TH-PO032

Development of Artificial Intelligence Model for the Prediction of AKI, Acute Kidney Disease, and CKD After General Anesthesia Surgery

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Background: After the occurrence of AKI, ongoing renal pathophysiologic process leads to acute kidney disease (AKD) or chronic kidney disease (CKD). Postoperative AKI is associated with increased mortality and morbidity in patients undergoing surgeries performed under general anesthesia. A machine learning-based prediction model for postoperative AKI, AKD, and CKD is needed.

Methods: In this retrospective cohort analysis, noncardiac surgeries performed between 2009 and 2019 at 7 university hospitals in South Korea were included. According to the creatinine-criteria of KDIGO, postoperative AKI was defined as an increase of serum creatinine at least 1.5 times the baseline value or initiation of renal replacement therapy occurring over 7 days or less after surgery; AKD was defined as persistent AKI over 7 and 90 days; CKD was defined as persistent AKD beyond 90 days. Data imbalance was adjusted using the SMOTE algorithm, and four machine learning prediction models were tested: deep neural networks, decision tree, random forest, and light gradient boosting machine (GBM). Model performance was compared using the area under the curve (AUC) of the receiver-operating characteristic, accuracy, and F1 score.

Results: Among 239,267 surgeries, 2,716 postoperative AKI (1.14%), 97 AKD (0.04%), and 1,203 CKD (0.5%) events occurred. Four machine learning methods were run on 32 independent preoperative predictors. While the model run on random forest exhibited a higher AUC (0.80) than light GBM (0.77), accuracy (0.95), weighted F1 score (0.94), micro-average F1 score (0.95), and macro-average F1 score (0.31) were highest in the model run on light GBM.

Conclusions: In our comprehensive comparison of machine learning approaches, light GBM demonstrated the best performance to predict postoperative AKI, AKD and CKD. The current model may be implemented in clinical practice to predict short- and long-term kidney outcomes after surgery.

TH-PO033

Deep Learning-Based Quantitative Assessment of Renal Chronicity Indices in Lupus Nephritis

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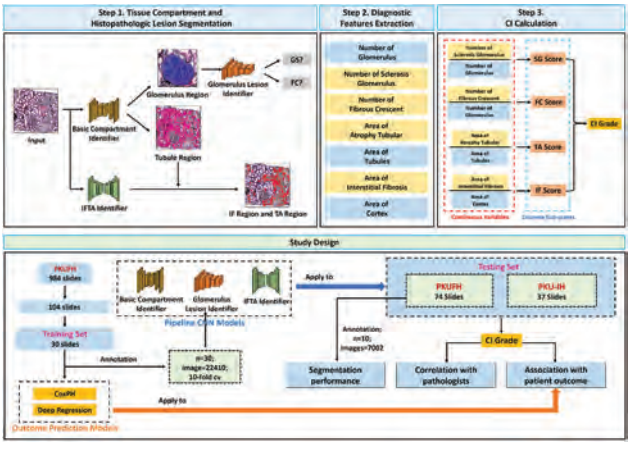
Background: Lupus nephritis (LN) is a common condition in patients with SLE. Evaluating kidney chronicity indices (CI) is crucial for diagnosing LN and predicting outcomes. Deep learning (DL) has shown promise in improving the workflow of pathologists. In renal pathology, DL has demonstrated high accuracy in identifying various histopathologic lesions. However, existing studies have not adequately addressed the challenges of assessing CI in LN, such as integrating features at different levels and dealing with class imbalances among tissue compartments.

Methods: This study enrolled 141 patients from two distinct cohorts. Training of the CNN model involved annotating 22,410 images from 30 biopsy slides, which were subsequently tested on 111 slides. The evaluation process encompassed the segmentation of tissue compartments, correlation analysis with pathologists' assessments, and investigating associations with patient outcomes utilizing CoxPH models.

Results: 1) The developed pipeline exhibited an accuracy of over 0.91 in identifying six tissue compartments and histopathologic lesions, surpassing previous segmentation performance benchmarks. 2) Consistent with the evaluations by expert pathologists, our pipeline exhibited an agreement of over 0.85 in assessing CI in both cohorts, highlighting its reliability and consistency. 3) The application of the CoxPH model to predict patients' outcomes achieved a score of 0.82 and 0.78 in the two cohorts.

Conclusions: Our study showcases the state-of-the-art performance of our deep learning pipeline in identifying tissue compartments and histopathologic lesions in lupus nephritis. The pipeline demonstrates strong agreement with pathologists' CI assessments and maintains the correlation between CI and patient outcomes. This automated approach has the potential to enhance pathological assessment and disease stratification in lupus nephritis.

Funding: Government Support - Non-U.S.



TH-PO034

Using Artificial Intelligence (AI) to Predict Mortality in AKI Patients: A Systematic Review and Meta-Analysis

Rupesh Raina,[1,2] Raghav Shah,[3] Sidharth K. Sethi,[4] Jay L. Koyner,[5] Javier A. Neyra.[6] *[1]Cleveland Clinic Akron General, Akron, OH; [2]Akron Children's Hospital, Akron, OH; [3]Northeast Ohio Medical University, Rootstown, OH; [4]Medanta The Medicity Medanta Institute of Kidney and Urology, Gurugram, India; [5]The University of Chicago Medicine, Chicago, IL; [6]Division of Nephrology, University of Alabama at Birmingham, Birmingham, AL.*

Background: Acute kidney injury (AKI) is associated with increased morbidity and mortality. With the recent advent of artificial intelligence (AI), novel models for mortality prediction in AKI patients have been developed using machine learning (ML). We reviewed the performance of different ML models for evidence generation to support their applicability and implementation in the clinical setting.

Methods: A literature search was conducted through Pubmed, Embase, and Web of Science Databases. Performance metrics of the ML models to predict hospital mortality in adult AKI patients were extracted. The between-study heterogeneity was assessed using the I^2 test and random [for $I^2 \geq 50\%$] and fixed effects model were used. The AUROC of two models were compared using DeLong's test (p-value ≤ 0.05 considered significant). R software version 3.1.0 was used in the analysis.

Results: A total of 8 studies [8 derivation and 6 validation cohorts] with 37,032 adult AKI patients were included. The hospital mortality was 18% in the derivation and 15.8% in the validation cohorts. The pooled AUC (95% CI) was observed to be highest for logistic regression [0.86 (0.80 - 0.93)] and lowest for proposed clinical [0.77 (0.72 - 0.81)] models used as reference. Despite substantial variability, the pooled AUC (95% CI) of logistic regression did not differ significantly from other models except proposed clinical model [Delong's test p=0.022].

Conclusions: Our results show that logistic regression is equally effective as other ML models in predicting in-hospital mortality among AKI patients, with substantial variability across models. Studies evaluating the features influencing mortality and their impact on different models are needed.

Meta-analysis of AUC in assessing in-hospital mortality among AKI patients

AI/ML Model	No. of Mortality / Sample size	No of cohorts; no of studies	Pooled AUC (95% CI)	I2 (95% CI); p values
Logistic regression	1,225/5,690	3 D and 3 V cohort; 3 studies	0.862 (0.795 - 0.928)	96.17% (93.77% - 97.64%); p<0.0001
Broad learning system models*	278/540	2 D and 2 V cohort; 1 study	0.852 (0.820 - 0.883)	44.88% (0.00% - 81.61%); p=0.1421
Elastic Net final model fitted*	544/870	1 D and 1 V cohort; 1 study	0.852 (0.813 - 0.891)	48.05% (8.04% - 75.25%); p=0.1653
Extreme gradient boost	2,525/5,642	3 D and 2 V cohort; 3 studies	0.816 (0.752 - 0.880)	95.09% (91.20% - 97.26%); p<0.0001
Random Forest	5,613/27,467	7 D and 5 V cohort; 6 studies	0.816 (0.782 - 0.851)	90.14% (84.72% - 93.64%); p<0.0001
Support vector machine	4,571/23,816	3 D and 1 V cohort; 3 studies	0.804 (0.760 - 0.849)	93.89% (87.53% - 97.01%); p<0.0001
ANN / MLP	4,571/23,816	3 D and 1 V cohort; 3 studies	0.793 (0.752 - 0.833)	87.22% (69.38% - 94.66%); p<0.0001
Proposed clinical model	1,831/9,587	1 D and 1 V cohort; 1 study	0.765 (0.716 - 0.814)	98.96% (97.92% - 99.48%); p<0.0001

*Fixed effect models, for other random effect models

D:Derivation, V:Validation, ANN:Artificial Neural Network, MLP:Multi-layer perceptron

TH-PO035

A Systematic Review of Artificial Intelligence Algorithms for Predicting AKI

Marcelo R. Bacci. *Faculdade de Medicina do ABC, Santo Andre, Brazil.*

Background: Acute kidney injury increases mortality and costs in hospitalized patients. New methods for early AKI identification have been developed with targeted biomarkers and electronic health records data analysis. Machine learning use in diagnostics and health data analysis has recently increased. We performed a systematic review to analyze the use of ML for AKI prediction in hospitalized adults.

Methods: Pubmed, EMBASE, Cochrane, and Web of Science databases were searched until 31st March of 2023. English-language studies using ML in adults for AKI prediction were included using predetermined eligibility search terms such as acute kidney injury, machine learning, and artificial intelligence. Two reviewers evaluated the publications' titles, abstracts, and full texts separately and obtained appropriate data. The main outcome was an area under the curve result of at least 0.70.

Results: Ten studies in 102 articles were included involving 242,251 patients. Deep learning (AUC 0.907 in critical care AKI; AUC 0.797 in hospitalized patients AKI was similar to Logistic regression (AUC 0.877 in critical care AKI; AUC 0.789 in hospitalized patients). Decision tree constructions had similar AUC.

Conclusions: AKI is multifactorial;however, ML performed well with different etiologies, such as cardiac-related AKI, drug-related AKI, and critical care patients. Overfitting data and constructing black box models are limitations that might jeopardize the generalization and comprehension of the results. Most studies were single-center, and three manuscripts used the same database with a predominantly Caucasian population resulting in a lack of diversity and reducing external generalization. In conclusion, ML could effectively predict AKI in hospitalized adults. Future directions rely on including a more diverse population and completing prospective and controlled trials.

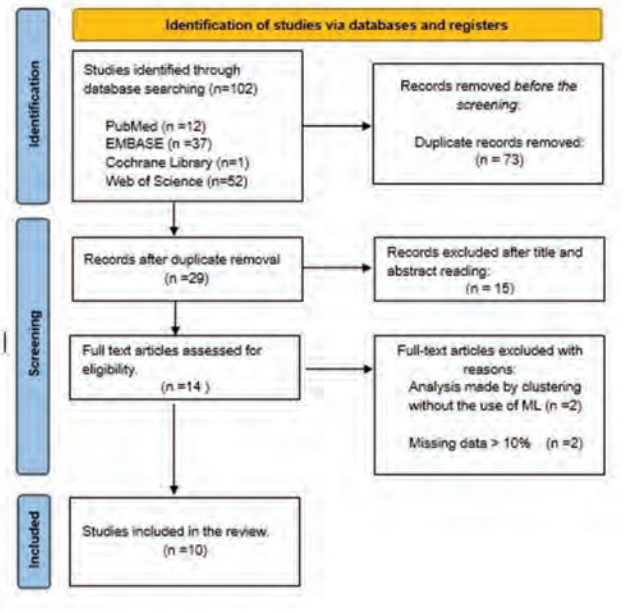


Figure 1. Flow diagram of the identification of relevant studies

TH-PO036

Predictive Modeling of Graft Failure Risk in Deceased Donor Kidney Transplants: Leveraging Machine Learning for Improved Outcomes and Data-Driven Insights

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Background: Machine learning (ML) has shown its potential to improve patient care over the last decade. The 1-year graft failure rate remains a major concern among ethnic disparities in the deceased donor kidney transplantation (KT). The aim of the study was to evaluate graft failure within a year and determine risk factors associated with these events in ethnic groups.

Methods: The KT data between 2000 to 2020 was obtained from Organ Procurement and Transplantation Network. After data preprocessing n=75000 White, n=35000 Black, and n= 5000 Asian KT were qualified for further data analysis. The random forest (RF) and light gradient-boosting machine (LGBM) models were used to classify the most important variables for further 1-year GF-associated risk factors.

Results: Thus, the number of initial variables was reduced from 490 to 40 in every three groups after significance-test validation. LGBM demonstrated better discrimination of GF-related risk factors among three groups ((AUC=0.78; White), (AUC=0.77; Black), and (AUC=0.73; Asian)) in fivefold cross-validation. Interestingly, the top features for prediction of graft failure were such as donor hepatitis C-virus (HCV) antibody, donor and recipient tattoo, type of perfusion solution, age, arterial blood gas PH level, diabetes, hypertension, etc. Then, LGBM predicted variables were further analyzed in Cox proportional hazard ratio (HR), and the leading risk factor for graft failure was donor HCV antibody level ((HR 1.9; White, HR 2.2; Black, and HR 1.75; Asian, all p values were 0.005). In contrast, donor and recipient tattoos were independent risk factors (HR 1.2; P <0.02) for Asian while arterial blood gas PH (HR 1.2; P <0.01), posttransplant malignancy (HR 1.25-2.2; P <0.005), and organ flushing solution (HR 1.2; P <0.005) associated with 1 -year graft failure for all three groups. Interestingly, Cox proportional HR analysis demonstrated that ML-predicted risk factors such as diabetes, age, BMI, and hypertension were not associated with 1-year graft failure in all three groups.

Conclusions: Taking together, ML algorithms predicted risk factors accuracy almost the same as traditional statistical methods on prediction of 1-year graft failure among ethnic disparities.

TH-PO037

Prospective Study of a Predictive Algorithm of Real-Time Fluid Status in Hemodialysis Patients

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Background: An accurate per-session determination of volume status in dialysis patients would have considerable clinical utility.

Methods: We prospectively assessed a predictive algorithm for fluid status in an observational study of hemodialysis (HD) patients. Algorithm performance was compared to clinical volume assessment. Individualised predictions were compared with bioimpedance (BCM) measures at 2-week intervals. Internal validation for linear regression algorithms predicting BCM-based normohydration weight and pre-HD overhydration (OH) has been described (SA-PO351 ASN 2022). MAE, RMSE and Bland-Altman plots were used for continuous outcomes. Precision, recall and F1 score were used for fluid categories: overhydration ≥1.1L, normohydration -1.1L to 1.1L, underhydration ≤-1.1L.

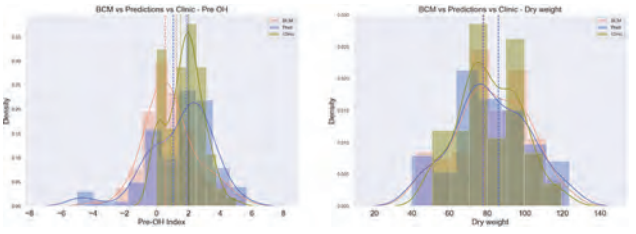
Results: 630 HD sessions were assessed. Root mean squared error (RMSE) for the pre-dialysis overhydration index=2.1kg compared to RMSE=1.6kg in the internal validation set. No significant difference was observed between the BCM normohydration weight versus the predicted value [mean difference 0.22 ± 2.25 kg, t (93) = 0.96, p=0.34]. A histogram showed a close alignment in distribution of predicted noromohydration weight and BCM values (Figure). Nursing staff overestimated fluid overload (Table).

Conclusions: The algorithm showed an ability to discriminate fluid categories compared to nursing staff, but overall accuracy was poor. Additional algorithm training in a larger, heterogeneous dataset would be expected to improve precision of fluid status predictions.

Funding: Commercial Support - Enteprise Ireland Disruptive Technologies Innovation Fund grant DTIF 2019_86, Government Support - Non-U.S.

Fluid categories

	Clinical	BCM	Predictions
	%	%	%
Pre-dialysis OH			
≥1.1L	70.8	36	65.96
-1.1L to 1.1L	29.2	57.5	25.53
≤-1.1L	0	6.4	8.52
Post-dialysis OH			
≥1.1L		8.5	16
-1.1L to 1.1L		25.5	37.2
≤-1.1L		65.9	46.7



Histograms of BCM, predicted and clinical pre-dialysis OH and dry weight

TH-PO038

The Prediction of In-Hospital Mortality in Elderly Patients with Sepsis-Associated AKI Utilizing Machine Learning Models

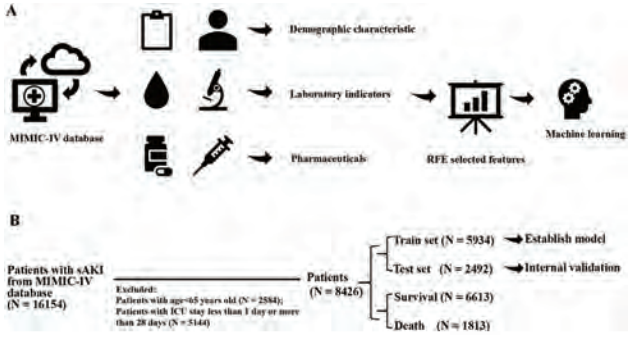
Xin He, Qiongjing Yuan, Zhangzhe Peng. *Xiangya Hospital Central South University, Changsha, China.*

Background: Sepsis-associated acute kidney injury (SA-AKI) is a severe complication associated with poorer prognosis and increased mortality, particularly in elderly patients with sepsis. Currently, there is a lack of accurate mortality risk prediction models for these patients in clinic. This study aimed to develop and validate machine learning models for predicting in-hospital mortality risk in elderly patients with SA-AKI.

Methods: Machine learning models were developed and validated using the public, high-quality Medical Information Mart for Intensive Care (MIMIC)-IV critically ill database. The recursive feature elimination (RFE) algorithm was employed for key feature selection. Eleven predictive models were compared, with the best one selected for further validation. Shapley Additive Explanations (SHAP) values were used for visualization and interpretation, making the machine learning models clinically interpretable.

Results: A total of 8,426 SA-AKI patients were included in this study (median age: 77.0 years; female: 45%). They were randomly divided into a training cohort (5,934, 70%) and a validation cohort (2,492, 30%). Nine key features were selected by the RFE algorithm. The CatBoost model achieved the best performance, with an AUC of 0.844 in the training cohort and 0.804 in the validation cohort. SHAP values revealed that AKI stage, PaO_2, and lactate were the top three most important features contributing to the CatBoost model.

Conclusions: We developed a model capable of predicting the risk of in-hospital mortality in elderly patients with SA-AKI.



Flowchart of this study

TH-PO039

Developing a Risk Index Predicting Kidney Transplant Dropout for African American and Hispanic Patients Using Artificial Intelligence/ Machine Learning

Amy D. Waterman,[1] Enshuo Hsu,[1] David Axelrod,[2] Stephen L. Jones,[1] Shefali A. Patel,[1] Solaf Al Awadhi,[1] Andrea M. Meinders,[1] Catherine Pulicken,[1] Faith Parsons,[1] Victoria Cassell,[1] Ioannis A. Kakadiaris.[3] *[1]Houston Methodist, Houston, TX; [2]University of Iowa Hospitals and Clinics, Iowa City, IA; [3]University of Houston, Houston, TX.*

Background: On average, kidney patients who receive a transplant live longer and have a better quality of life than those who remain on dialysis. Since African American (AA) and Hispanic patients are more likely to drop out before receiving a transplant than White patients, identifying patients at higher risk of dropout can improve care.

Methods: We created a dataset from Houston Methodist sources, including EPIC Clarity, Phoenix, and United Network for Organ Sharing (UNOS), and external databases including Health Resources Services Administration (HRSA), Centers for Disease Control and Prevention (CDC), and the US Census Bureau for community-level characteristics. The final transplant analytical registry included 4,245 kidney patients pursuing transplants from 6/2016 to 5/2022 and contained clinical, demographic, social, and transplant variables. The data was preprocessed to apply AI/ML methods to predict the risk index of patients who began transplant evaluation but were never listed for transplant within 12 months. F1 and AUROC were the evaluation metrics used.

Results: Of the 4,245 individuals who presented for transplant evaluation, 1,999 (47.1%) were waitlisted after 12 months, and 550 (13.0%) were transplanted. AA (7.23%) and Hispanic (12.20%) patients received fewer transplants compared to White patients (19.70%). Our AI/ML-based risk index predicted the probability of not being listed for transplant within 12 months (AUROC=0.732). Patients predicted to be low dropout risk (0-30%) had an 81.3% listing rate, middle risk (30-60%) had a 54.3% listing rate, and high risk (>60%) had a 27% listing rate within 12 months (Figure 1). Compared to low-risk patients, high-risk patients were more likely to be African American (44.2% vs. 19%), Hispanic (31.5% vs. 25.3%), unemployed (91.2% vs. 25%), spent more time on dialysis (488 vs. 131 days), without intended living donors (3% vs. 64.5%), and live in areas with more residents living below the poverty line (28% vs. 17%).

Conclusions: Applying the risk index, we will identify patients at higher risk of dropout and explore health delivery improvements within the transplant care process to slow or eliminate transplant dropout for underserved communities.

Funding: Other NIH Support - AIM AHEAD - Data Science at NIH

TH-PO040

Machine Learning-Based Approach to Classifying Risk of Progression of Membranous Nephropathy to ESKD Using Electron Microscopy

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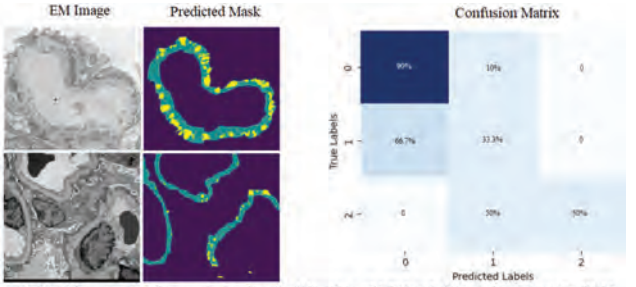
Background: Membranous nephropathy (MN) is an immune complex-mediated process that can result in nephrotic syndrome. Machine learning applications in medicine have emerged as powerful tools that can analyze large volumes of medical data (i.e., imaging, patient records) and extract patterns and relationships with diagnostic and prognostic insights. This work aims to use clinical and classical morphological image features to determine the risk of MN progression to end-stage kidney disease (ESKD).

Methods: Eighty MN cases from multiple institutions, each with available electron micrographs (EMs) of glomerular basement membrane (GBM) and corresponding baseline clinical metrics (albumin, eGFR, creatinine) were collated. An attention U-Net model was trained to perform multiclass segmentation of the GBM, electron-dense deposits, and background. Fifteen morphological features (i.e., total number of deposits, aspect ratio, circularity) were extracted from the predicted mask. Then, an artificial neural network (ANN) was trained to classify cases according to 3 risk tiers: low, intermediate, and high progression to ESKD. The same features were used to train an ANN to predict remission (no remission or complete remission).

Results: The segmentation model achieved a Dice score coefficient of 78%. Moreover, the ANN obtained classification accuracies of 73.3%, 67%, and 73.3% on the test set using clinical metrics alone, morphological features alone, and both clinical and morphological features, respectively. Another ANN trained to predict remission achieved 40% accuracy with both clinical and morphological features.

Conclusions: Clinical and morphological features can predict risk levels with reasonable accuracy. However, the same features are poor predictors of remission. Morphological features combined with clinical features do not improve risk classification accuracy. More meaningful and discriminative morphological features are needed to enhance predictive ability.

Funding: NIDDK Support



Left: Multiclass segmentation result showing the delineation of GBM and electron dense deposits. Right: Confusion matrix illustrating the classification performance of an ANN model for predicting the risk of progression of MN to ESKD (0: low, 1: intermediate, 2: high risk of progression to ESKD).

TH-PO041

A Novel Clinical Prioritization Tool Stratifies Nephrology Patients by Acuity and Change over Time

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Background: Finding information to prioritize patient care is a difficult task with the growing amount of data in the electronic health record (EHR). Systems that highlight clinically meaningful patterns in laboratory data can support decision making, particularly

for nephrology patients whose disease severity often correlates with abnormalities in metabolic balance. In this work, we present and evaluate a novel tool which captures a patient's acuity and degree of change based on laboratory data, then places patients in four clinically applicable categories to aid in prioritization.

Methods: An algorithm was developed to use laboratory data to calculate a unique score for patient (1) clinical acuity and (2) degree of change. Data was collected for diverse patient encounters from a tertiary care pediatric hospital. Scores were used to categorize patients as well, chronically sick, acutely sick or improving. To evaluate categorizations, results were compared to physician assessment of eight patient cases using C^2 goodness of fit.

Results: There was agreement in categorization between physicians and the tool ($p<0.001$). Patient categorization by the tool matched what was expected for their encounter and subspeciality type. Patients labeled as "acutely sick" were in the PICU (70% of acutely sick patients). Patients categorized as "chronically sick" were split between inpatient and outpatient encounters. Most chronically sick inpatients were outside of the PICU (89% of chronically sick inpatients) and most chronically sick outpatients were nephrology patients (70% of chronically sick outpatients).

Conclusions: This clinical priority scoring tool supports a physician's recognition of meaningful patterns in the EHR that matches their clinical assessment of patients. The tool also detected subtle trends in the trajectory of patients not otherwise captured by physicians on their first assessment. Specifically, the tool categorized nephrology patients as being chronically sick as compared to other patients which correlates with the electrolyte and acid/base imbalance, anemia and metabolic bone disease often seen in this population. Using the tool to categorize patients, physicians can rapidly identify which patients in the outpatient setting may need further evaluation for admission and which patients in the hospital may need intensive care.

Funding: NIDDK Support, Private Foundation Support

TH-PO042

Using an Ensemble Model to Improve ESA Prescription in Hemodialysis (HD)

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Background: How the ensemble model trained by new indexes can improve the ESA prescription is unclear.

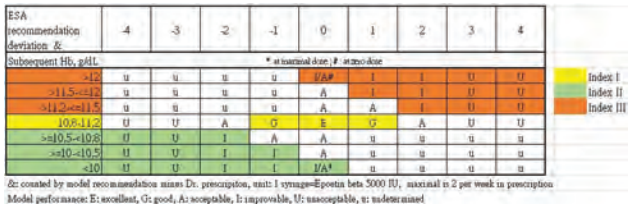
Methods: We have compiled a dataset from 2013-2020, including bi-monthly ESA prescriptions, Iron doses, Hb, and relevant data of HD patients in our hospital. We divided all records into six categories, status 1 to 6, based on subsequent hemoglobin(sHb), using cut-off values of 10.8 and 11.2 and direction of change (not decreasing: 1-3 vs. decreasing:4-6). Indexes I, II, and III were used to evaluate how the ESA dose deviations of model recommendations theoretically impacted sHb. Index I assesses how model deviations keep sHb near 11 g/dL (positive index), while II and III are away from 11 g/dL (negative index). (Figure 1) Besides the traditional ESA-prescription algorithm (TEA, Figure 2), we have trained various models, including a meta-learning model (MLM).

Results: 25,632 records of 315 ESKD patients were included, with 71.9% of the Hb levels between 10-12mg/dL. Besides TEA, we selected a generalized linear mixed-effect tree model (GLMM) and a weighted random forests model (WRF) for sHb and ESA dose prediction. The overall results are shown in Table 1. Our WRF and MLM can almost preserve the proper prescriptions (Index I), and avoid those improvable or unacceptable recommendations (Index II & III). The MLM can theoretically improve 65.4% and 43.8% of prescriptions with sHb >11.5 and <10.5, respectively. (undetermined)

Conclusions: The ensemble model trained by new indexes can theoretically recommend more proper ESA dosages.

Funding: Clinical Revenue Support

Total n=25,632	sHb between 10.8-11.2 Status 2, n=2,727; Status 5, n=2,550						sHb below 10.8 Status 1, n=3,859; Status 6, n=5,767						sHb above 11.2 Status 3, n=7,345; Status 4, n=3,384							
Index (Score assigned to record)	I (1)		Undetermined (0)		Unaccepted (-2)		II (-1)	II unaccepted (-2)		Undetermined (0)			III (-1)		III unaccepted (-2)		undetermined (0)		Total score	
Model/Status	2	5	2	5	2	5	1	6	1	6	1	6	3	4	3	4	3	4	Positive	Negative
TEA, %	91.4	74.5	6.2	21.8	2.4	3.7	2.2	25.5	0.3	1.7	97.5	72.8	2.4	0.2	0.3	0.03	97.6	99.8	1530	-434
GLMM, %	71.8	57.0	18.6	27.1	9.6	15.8	1.2	13.1	1.3	2.8	97.5	85.1	11.2	4.7	4.9	3.4	88.9	95.3	789	-581
WRF, %	95.3	97.5	3.6	2.3	0.9	0.2	4.2	9.4	0	0.03	95.8	90.6	3.7	1.9	0.2	0	96.1	98.1	2518	-312
MLM,%	95.5	97.7	3.2	2.2	1.3	0.2	3.3	7.6	0	0.03	96.7	92.4	3.2	1.6	0.3	0	96.5	98.4	2510	-244



&: counted by model recommendation minus Dr. prescripiton, unit: 1 syringe=Epoetin beta 5000 IU, maximal is 2 per week in prescription
Model performance: E: excellent, G: good, A: acceptable, I: improvable, U: unacceptable, u: undetermined

2-week prescripiton as example

Hb at presciption, g/dL	2-week presciopiton* ESA dose= prior dose + the following, syringe	Hb at presciption, g/dL	3-week prescropiton* ESA dose= prior dose + the following, syringe
<9.2	4	<9.2	6
9.2-<9.7	3	9.2-<9.5	5
		9.5-<9.7	4
9.7-<10.2	2	9.7-<10.2	3
10.2-10.7	1	10.2-<10.5	2
		10.5-10.7	1
>10.7-11.2	±0	>10.7-11.2	±0
>11.2-11.5	-1	>11.2-11.3	-1
		>11.3-11.5	-2
>11.5-11.8	-2	>11.5-11.7	-3
>11.8-12.1	-3	>11.7-11.9	-4
		>11.9-12.1	-5
>12.1	-4	>12.1	-6

*the maximal dosage is 2 syringes per week, equal to 10,000 IU epoetin beta

TH-PO043

Machine Learning Approach to Predict Hemoglobin Levels for Erythropoietin Dosing in Hemodialysis Patients

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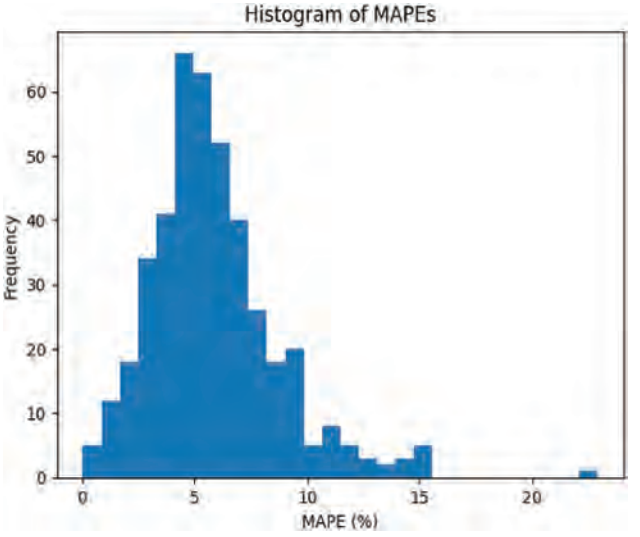
Background: Erythropoiesis-stimulating agents (ESA) are commonly used to treat anemia in HD patients. However, prediction of patient-specific hemoglobin (Hgb) response to ESA remains challenging. Here we used machine learning techniques to predict Hgb response to ESAs in HD.

Methods: We included patients undergoing HD in Sanderling clinics who were receiving intravenous (IV) ESA (Mircera ®) and IV iron and had ≥5 Hgb measurements. ESA dose, iron dose, demographics and clinical variables were collected. Data was preprocessed to create a patient-specific bi-weekly dataset. We used a range of machine learning models, including long short-term memory networks, random forest, XGBoost and support vector machine. Each model was implemented individually for each patient with K-fold cross-validation. Performance of models to predict future Hgb levels was defined using mean absolute percentage error (MAPE) (average absolute percentage error between the predicted future Hgb and the observed future Hgb).

Results: Among 427 HD patients, the mean age was 65 ± 14 yrs and 44% were female. Patients received, on average, 93 ± 77 mg per week IV iron, and mean Mircera dose of 103 ± 183 mcg per month. The mean Hgb was 10.1 ± 1.4 mg/dl, and transferrin saturation 32 ± 15 %. The average MAPE for the model over the study cohort was 5.9% vs. Hgb variation of 13.9%. Figure 1 provides distribution of the MAPE for patients included in the analysis.

Conclusions: Our results showed the promising performance of machine learning models in predicting future Hgb levels within 6% of observed levels in HD patients. Future studies should focus on refining these models with the goal of personalized ESA dosing to maximize on-target Hgb levels.



Histogram of MAPE for Hgb prediction.

TH-PO044

Machine Learning Approach for Hemodialysis Prescription: Model Development and Validation Study

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Background: The prediction model of hemodialysis prescription is established based on machine learning to achieve precise hemodialysis treatment.

Methods: We obtained 108,638 hemodialysis sessions in 965 independent maintenance hemodialysis(MHD)patients in our hospital from October 1, 2020 to June 31, 2021 using random sampling. The sessions were randomly divided into training (70%), calibration (10%), and testing (20%) sets. Apply XGBoost to analyze and extract effective feature data. XGBoost, RF, KNN, SVR, LR, MLP were used to develop the prescription model and model fusion. Training and update the model using reinforcement learning. The area under the receiver operating characteristic curves, the area under the precision-recall curves, F1 scores and MSE obtained to assess model stability and accuracy.

Results: There were 108,638 dialysis records in 965 patients, of whom 62.2 were male, the average age was 59.3±13.2 years, the median dialysis age was 102.3 months, BMI was 23.8±3.9, and the primary disease was diabetic nephropathy (38.6%). There are 13 labels in the hemodialysis program, of which 6 labels are continuous variables and the regression model is used, and 7 labels are discontinuous variables. The average accuracy is greater than 0.88, and the mean square error is less than 0.067.

Conclusions: The artificial intelligence dialysis prescription established based on machine learning has better stability and accuracy.

Funding: Government Support - Non-U.S.

TH-PO045

Using an Artificial Intelligence Tool Incorporating Natural Language Processing to Identify Low-Prevalence Cases of ANCA-Associated Vasculitis in Electronic Health Records

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Background: Anti-neutrophil cytoplasmatic antibody (ANCA)-associated vasculitis (AAV) is a rare, life-threatening, systemic auto-immune disease. Due to the low prevalence and heterogenous registration, there is an urgent need to improve identification of AAV patients within the electronic health record (EHR)-system of health organizations to facilitate clinical research.

Methods: Our aim was to identify, with a high sensitivity, low-prevalence AAV patients within large EHR-systems (>2.000.000 records) using an artificial intelligence (AI)-search tool. We combined a search on structured and unstructured data with natural language processing (NLP)-based exclusion. We developed the method in an academic center with an established AAV training set (n=203) and validated the method in a non-academic center with a validation set (n=84). We anonymously reviewed all identified patient records for AAV diagnosis.

Results: The final search strategy combined four queries on disease description, laboratory measurements, medication and specialisms. In the training center, this search identified 608 patients, of which 346 were AAV patients upon manual review. 197/203 patients of the training set were retrieved, indicating a sensitivity of 97%. Employing NLP-based exclusion resulted in 444 patients with 339 AAV patients, resulting in an increase of positive predictive value (PPV) from 57% to 78% and a sensitivity of 96%. In the validation center the search strategy identified 333 patients, of which 194 were AAV patients, including 82/84 (98%) patients of the validation set. After NLP-based exclusion 223 patients remained, including 196 AAV patients, improving PPV from 58 to 86% with a sensitivity of 98%. Our identification method outperformed ICD-10 coding predominantly in identifying myeloperoxidase (MPO)-positive AAV patients and patients with few specialisms involved.

Conclusions: We demonstrated excellent performance of an AI-based identification method, incorporating NLP, to identify AAV patients in EHRs and we validated the applicability and transportability. This method can accelerate research efforts, while avoiding the limitations of ICD-10-based registration.

Funding: Commercial Support - Vifor Pharma

TH-PO046

Impact of Nationwide Utilization of a Machine Learning Model to Identify Home Therapy Candidates

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Background: Home therapy (HT) modalities offer excellent treatment options for dialysis patients but are underutilized. As part of a larger effort to provide support to patients, there is a team of Kidney Care Advocates (KCAs) who provide education on treatment modality options with a goal of empowering patients to choose a home modality when appropriate. Towards this, a machine learning (ML) predictive model was built to identify which in center hemodialysis (ICHD) patients would be good candidates to target for HT.

Methods: Patient (n=298552) data collected from 2016-2019 were used to develop an XGBoost ML model to predict the likelihood of an ICHD patient switching to peritoneal dialysis or home hemodialysis in the next 90 days and staying on that HT for at least 90 days. The data were split into training (70%) and validation (30%) datasets, maintaining the 2.5% positive prevalence in both. Data sources included ICHD treatments, labs, hospitalizations, missed treatments, demographics (age, marital status, and vintage), comorbidities, clinical assessments, clinic home program information, and Zillow housing data based on zip code, resulting in 2475 variables. KCAs contacted ICHD patients identified by the model to offer education and services. From January-November 2020, KCAs completed an assessment when a patient was contacted (n=26055), which included questions on if the patient was interested in HT and how the patient was referred to the KCA.

Results: The model achieved good performance with an area under the curve of 0.87 for the validation dataset. Using a threshold set to the positive class prevalence (0.025), recall was 0.77 and precision was 0.09. The top predictors used by the model were dialysis vintage, previously expressing interest in or being referred to HT, age, and dining with one's spouse. During the time examined, KCAs reported contacting 20734 patients. Of those, the model was the sole referral source for 5382 patients and 1219 of them expressed interest in HT. In 2020-2021, 487 ICHD patients referred to KCAs by only the ML model switched to HT.

Conclusions: Through close collaboration with KCAs, an ML model was successfully used to identify ICHD patients who were good candidates for HT. Use of this model had measurable impact with hundreds of ICHD patients switching to HT who otherwise might not have been referred to a KCA.

Funding: Commercial Support - Fresenius Medical Care

TH-PO047

A Risk-Based Reinforcement Learning Algorithm to Predict Intradialytic Hypotension During Kidney Replacement Therapy

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Background: Kidney replacement therapy (KRT) after acute kidney injury is associated with intradialytic hypotension (IDH) in up to 30% of sessions. IDH is associated with premature termination of therapy and is an independent predictor of mortality. Thus, there is a critical need to develop a clinical decision support tool that predicts IDH and preemptively suggests optimal therapy.

Methods: We constructed a reinforcement learning (RL) algorithm that generates personalized, dynamic treatment plans for IDH during intermittent KRT. The RL model was trained and validated using clinical data from a cohort of 277 patients undergoing 1,595 hemodialysis treatments in a tertiary care center. A random forest classifier was used to generate individualized risk trajectories for IDH, which were incorporated with patients' physiological features to define a discrete state space. The RL was trained for an optimal action every 15 minutes. To ensure that selected actions aligned with clinical intuition, a bias term prevented the RL from over-recommending clinically rare actions. Finally, a Q-learning algorithm used risk rewards as intermittent feedback to learn a personalized sequence of optimal actions.

Results: The RL agent tended to recommend interventions more frequently than clinicians, with an RL intervention frequency of 41.7% compared to a clinician intervention frequency of 18.4%. The most frequently recommended clinical intervention by both clinicians and the RL agent was a change in ultrafiltration rate (clinician, 17.8%, RL, 40.8%), followed by administering mannitol or vasopressors (clinician, 0.6%, RL, 0.8%). Implementing the learned policy decreased the occurrence of IDH and increased fluid goal achievment *in silico*, as seen in Table 1 below.

Conclusions: Dynamic risk forecasting and RL generated risk prediction of IDH and personalized treatment plans for IDH during intermittent KRT. These dynamic policies recommend more than twice as many interventions as clinicians. We showed RL agents could decrease the frequency of IDH while meeting therapeutic goals and improving clinical outcomes.

Funding: NIDDK Support

Table 1.

	IDH [count (%)]	Fluid Goals Achieved [count (%)]
RL Treatment Policy	1817 (7.3)	23265 (93.1)
Clinician Treatment Policy	253 (15.0)	1082 (64.2)

TH-PO048

Polygenic Prediction of Estimated Glomerular Filtration Rate in Individuals of African Descent and from the Americas

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Background: Chronic kidney disease more often impacts individuals of African descent (AFR) or those from origin from the Americas (AMS), who are under-represented in genome-wide association studies (GWAS). Polygenic scores have been proposed for disease risk prediction. However, polygenic scores developed from GWAS of individuals of European ancestry have limited transferability into other populations, reflecting differences in allele frequencies and linkage disequilibrium across populations. Previous

studies have demonstrated their performance is poor for estimated glomerular filtration rate (eGFR) in AFR and AMS populations. Here, we investigate the predictive power of polygenic scores for eGFR developed in AFR and AMS for African American and Hispanic/Latino individuals.

Methods: We used summary data from eGFR GWAS meta-analyses and the Bayesian Regression and Continuous Shrinkage Priors (PRS-CS) approach to train polygenic scores in: (i) AFR + AMS (66,825 individuals); (ii) AFR-specific (40,001 individuals); and (iii) AMS-specific (26,824 individuals). We compared the performance of the AFR + AMS, and AFR- or AMS-specific polygenic scores in two additional test samples with GWAS data of 8,270 African Americans from the Women's Health Initiative (WHI-AA) and 8,291 Hispanics/Latinos from the BioMe Biobank (BIOME-HA). We assessed the strength of the association and the variance explained of the three polygenic scores in each validation studies.

Results: When applied to WHI-AA, the AFR polygenic score outperformed the AMS score and explained 12.5% of the eGFR variance, while the AFR + AMS polygenic score had the best performance, explaining 13.5% of the eGFR variance. For scores applied to BIOME-HA, the best performance was for the AFR + AMS score, which explained 5.2% of the eGFR variance, compared to the AMS score that explained 2.4%. All polygenic scores were significantly associated with eGFR in the validation datasets.

Conclusions: In this largest aggregated GWAS of AFR and AMS individuals, we showed increased predictive power offered by a multi-population polygenic score for eGFR in both African Americans and Hispanics/Latinos. This study has shown the largest variance explained by a polygenic score in AFR, enhancing resources for disease prediction in this population.

Funding: NIDDK Support

TH-PO049

Empowering Dialysis Patients to Self-Manage Hyperphosphatemia with Mobile Health Technology: Insights from the FOSFO-OK Study

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Background: mHealth apps are cost-effective technologies that can assist dialysis patients in achieving their therapeutic goals. Since many patients fail to control their phosphate levels, the main objective of this project is to develop a mHealth environment that empowers CKD patients to self-management their hyperphosphatemia under medical supervision. Such an environment will allow nephrologists to provide patients with information beyond their traditional point of care and enable patients to receive timely feedback on their condition.

Methods: We developed a web-based management system that delivers patient's phosphate levels results and medical recommendations through a cloud-based IT environment. Patients with phosphate levels > 6 mg/dL and PTH <88 pmoL/L were included in the study. Patients were randomly assigned to receive the app or continue with the usual educational program. Changes in phosphate binders or vitamin D were allowed and analytical results were collected monthly. The degree of satisfaction of patients and nephrologists was evaluated.

Results: The study included 42 patients (21 in each group). The baseline phosphate levels were 6.94±1.43 mg/dL in the group that received the app vs 6.61±0.99 in the control group (p=ns). At the 3-month follow-up, the group that use the app had a phosphate of 5.64±1.73 mg/dL (81% of the patients reduced phosphate levels), while only 57% of the patients in the control group managed to reduce their phosphate level, with mean levels of 6.06±1.44 mg/dL (p=0.018). These results were maintained at 6 months, and 82% of the patients with the app had improved their phosphate levels, compared to only 56% of the patients who did not use the app. Patients who used the app found it to be useful, and nephrologists were also satisfied with the app.

Conclusions: Patient benefits from a virtual assistant via their smartphone, through an integrated system of participatory, personalized, predictive, and preventive medicine. This study demonstrates that virtual tools through a participatory and personalized medicine system help CKD patients to control hyperphosphatemia.

Funding: Commercial Support - CSL Vifor

TH-PO050

Terlipressin Therapy in Patients with HRS and Comorbidities: The North American Experience

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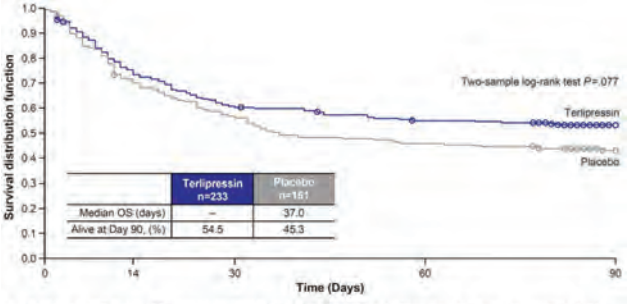
Background: Hepatorenal syndrome (HRS)—a rapid kidney failure—occurs in patients (pts) with decompensated cirrhosis and ascites. Terlipressin (Terli) is FDA-approved to treat pts with HRS. Certain pts with HRS and alcoholic hepatitis (AH), systemic inflammatory response syndrome (SIRS), or low mean arterial pressure (MAP) may suffer from a portal hypertension/splanchnic vasodilation-related inflammatory response, which may be attenuated by Terli.

Methods: Data from the 3 largest prospective, randomized, placebo (Pbo)-controlled, clinical studies in pts with HRS (OT-0401, REVERSE, and CONFIRM) were pooled to assess the role of Terli vs Pbo (both plus albumin) on HRS reversal in the subpopulation of pts with AH, MAP <70 mm Hg, or SIRS. HRS reversal was defined as at least 1 serum creatinine (SCr) value of ≤1.5 mg/dL while on treatment.

Results: In the pooled population, 394/608 pts had AH, SIRS, or low MAP, and 214/608 pts did not. At baseline, SCr and MELD score were comparable between treatment groups (gps). Among pts with AH, SIRS, or low MAP, HRS reversal was achieved by 81/233 (35%) pts in the Terli gp vs 21/161 (13%) pts in the Pbo gp (*P*<.001). Among pts with AH, SIRS, or low MAP, fewer pts in the Terli gp (vs Pbo gp) needed renal replacement therapy (RRT) by Day 30 (26% vs 35%, *P*=.049), Day 60 (28% vs 38%, *P*=.046), and Day 90 (30% vs 38%, *P*=.104). Overall survival (OS) up to 90 days demonstrated a positive trend in pts in the Terli gp vs the Pbo gp (*P*=.077; **Figure**).

Conclusions: Pts with HRS who had AH, SIRS, or low MAP had a significantly higher HRS reversal rate and lower RRT rate at Days 30 and 60, and a trend for better OS when randomized to Terli vs Pbo.

Funding: Commercial Support - Mallinckrodt Pharmaceuticals



AH, alcoholic hepatitis; ITT, intent-to-treat; MAP, mean arterial pressure; OS, overall survival; SIRS, systemic inflammatory response syndrome.

Figure. OS among patients with AH, SIRS, or MAP <70 mm Hg, pooled ITT population

TH-PO051

Association of AKI-Hepatorenal Syndrome (HRS) with Mortality in Hospitalized Cirrhotic Patients Requiring Renal Replacement Therapy: Results from the HRS-HARMONY Consortium

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Background: While AKI-RRT is associated with mortality in heterogeneous inpatient populations, the epidemiology of AKI-RRT in hospitalized cirrhotic patients is not fully known. Herein, we evaluated the association of etiology of AKI with mortality in hospitalized cirrhotic patients with AKI-RRT.

Methods: This is a multicenter retrospective cohort study using data from the HRS-HARMONY consortium which included 15 hospitals in the U.S. (01/2019-12/2019). Consecutive hospitalized adult (≥18 years) cirrhotic patients with AKI-RRT were included in this study. The primary outcome was 90-day mortality and the main independent variable was AKI etiology, classified as hepatorenal syndrome (HRS-AKI) vs. other. AKI etiology was adjudicated by at least 2 independent adjudicators. We performed multivariate Cox regression analysis adjusting for age, gender, race, transplant listing status, MELD-Na score, requirement of CRRT, pressor use, and study site.

Results: Of 2063 hospitalized cirrhotic patients with AKI, 374 (18.1%) had AKI-RRT. Among these, 65 (17.4%) had HRS-AKI and 309 (82.6%) had other etiologies of AKI which included ATN in the majority of cases (62.6%). The HRS-AKI (vs. other AKI etiology) group required less CRRT than hemodialysis as the initial RRT modality (56.9% vs. 73.9%, p=0.006), more HRS vasoconstrictor use (81.5% vs. 67.9%, p=0.03), and less mechanical ventilation use (50.8% vs. 64.3%, p=0.04). In a fully adjusted model, HRS-AKI (vs. other AKI etiology) was not associated with 90-day mortality (aHR=1.16, 95% CI: 0.75-1.79, p=0.51). Clinical parameters independently associated with 90-day

mortality included liver transplant listing (aHR=0.22, 95% CI: 0.14-0.35), MELD-Na score (aHR=1.04, 95% CI: 1.02-1.05), and the need of CRRT (aHR=2.64, 95% CI: 1.68-4.13).

Conclusions: Among hospitalized adult cirrhotic patients with AKI-RRT, HRS-AKI was diagnosed in about one-fifth of patients, but did not confer an independent increased risk of 90-day mortality when compared to other AKI etiologies. Higher MELD-Na score and the need of CRRT were independently associated with increased 90-day mortality in this susceptible population.

TH-PO052

Improvement in Serum Creatinine Was Associated with Favorable Clinical Outcomes in Patients with Hepatorenal Syndrome: A Post Hoc Analysis of the CONFIRM Study

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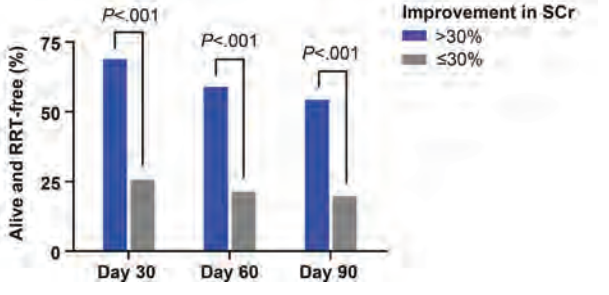
Background: Hepatorenal syndrome (HRS) is a life-threatening but potentially reversible form of acute kidney injury. More patients (pts) with HRS who were treated with terlipressin (terli), achieved verified HRS reversal than placebo (pbo) in the Phase III CONFIRM study (terli 29.1%; pbo 15.8%; *P*=.012). This post hoc analysis assessed pt data from CONFIRM to determine if an improvement in serum creatine (SCr) of >30% was associated with improved clinical outcomes.

Methods: CONFIRM enrolled adult pts with cirrhosis, ascites, HRS, and a SCr ≥2.25 mg/dL with a projected doubling in SCr within 2 weeks. Pts were treated intravenously with terli 1 mg every 6 hours or matched pbo; plus albumin, recommended. Pts from the CONFIRM intent-to-treat (ITT) population were analyzed by their improvement (>30% vs ≤30%) in SCr level from baseline (Day 0; or a prestudy value, if Day 0 value was missing) to the end of treatment (EOT) for the following: length of intensive care unit (ICU) stay; incidence of renal replacement therapy (RRT) and RRT-free survival at Days 30, 60 and 90; as well as survival at Day 90.

Results: More pts in the terli vs pbo group had a >30% improvement in SCr from baseline to EOT (43.7% vs 21.8%; *P*<.001). Among pts admitted to the ICU, the mean (SD) length of stay was numerically shorter (5.8d [3.25] vs 9.4d [11.62]; *P*=.673) among those who had a >30% vs ≤30% improvement in SCr. Fewer pts in the >30% (vs ≤30%) improvement in SCr subgroup required RRT (Day 90: 18.3% vs 40.3%; *P*<.001). Overall, a higher proportion of pts (N=300; terli + pbo combined) who achieved >30% improvement in SCr were alive (67.0% vs 42.9%, *P*<.0001); and alive and RRT-free by Day 90 (55.0% vs 20.4%, *P*<.001) (**Figure**).

Conclusions: Significantly more pts in the terli group achieved a >30% improvement in SCr versus pbo. Pts with a >30% improvement in SCr had significant improvements in clinical outcomes through Day 90.

Figure. Proportion of patients alive and renal replacement therapy (RRT)-free by improvement in serum creatinine (SCr) from baseline to end of treatment



TH-PO053

Outcomes of AKI on CKD in Hospitalized Cirrhotic Patients: Data from the HRS-HARMONY Consortium

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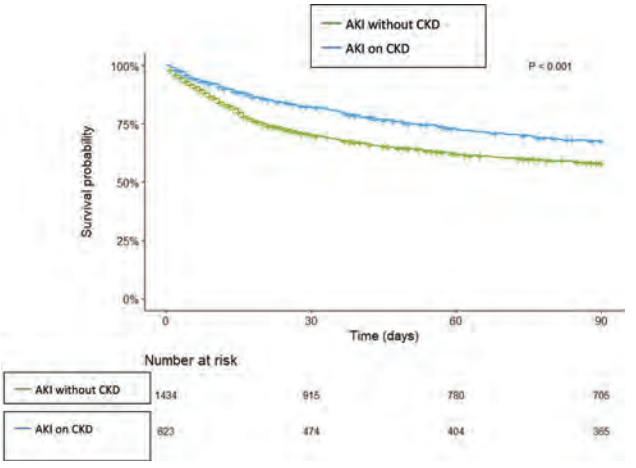
Background: The frequency of chronic kidney disease (CKD) is increasing in cirrhosis and these patients frequently suffer acute kidney injury (AKI). Direct comparisons of outcomes between AKI vs AKI on CKD are not well described in cirrhosis.

Methods: 2,057 cirrhotic patients with AKI across 11 hospital networks from the HRS-HARMONY consortium were analyzed (70% AKI without CKD and 30% AKI on CKD). Primary outcome was unadjusted and adjusted 90-day mortality, with transplant as a competing risk.

Results: Compared to patients without CKD, patients with AKI on CKD had higher admission creatinine (2.24 [IQR 1.7, 3.18] vs 1.83 [1.38, 2.58] mg/dL) and peak creatinine (2.79 [2.12, 4] vs 2.42 [1.85, 3.50] mg/dL) but better synthetic liver function (total bilirubin 1.5 [IQR 0.7, 3.1] vs 3.4 [1.5, 9.3] mg/dL; and INR 1.4 [IQR 1.2, 1.8] vs 1.7 [1.39, 2.2]; p<0.001 for all). Patients with AKI on CKD were more likely to have NASH cirrhosis (31% vs 17%) and less likely to have alcohol-associated liver disease (26% vs 45%; p<0.001 for all). Patients without CKD had higher unadjusted mortality (39% vs 30%), intensive care unit admission (52% vs 35%), and use of renal replacement therapy (29% vs 15%; p<0.001 for all). After adjusting for age, race, sex, transplant listing status and MELD-Na score; AKI on CKD was associated with a lower 90-day mortality compared to AKI without CKD (sub-HR 0.73 [95% CI 0.61, 0.88]).

Conclusions: In cirrhotic hospitalized patients, AKI on CKD is associated with lower 90-day mortality compared to AKI without CKD. This surprising finding may be due to worse synthetic liver function in the AKI without CKD group as underlying liver function is a strong driver of short-term outcomes in this population. Further study of the complicated interplay between acute and chronic kidney disease in cirrhosis is needed.



TH-PO054

Pre-Liver Transplant Acute Kidney Disease Highlights Impaired Renal Function Recovery Phase

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Background: Acute kidney disease (AKD), the phase between acute kidney injury (AKI) and chronic kidney disease (CKD), represents a crucial time window for initiation of therapies that may significantly augment renal function recovery. Herein, we aim to study the impact of duration of AKI in patients with decompensated cirrhosis on subsequent renal function recovery post-liver transplantation.

Methods: This is a single-center, retrospective study of adults who underwent single-organ, orthotopic liver transplant (OLT) from Jan 2015 to Dec 2021. AKD was defined as persistence of AKI for greater than a week but up to 90 days. The study cohort was classified by pre-transplant AKI duration and renal replacement therapy (RRT) status into four groups: normal kidney function, AKI requiring RRT within 7 days of onset (AKI_RRT), AKD without RRT (AKD_noRRT), and AKD with RRT (AKD_RRT). Renal function was compared with serial measurements of eGFR before and after OLT.

Results: Approximately half of the patients required RRT prior to OLT (81/170, 47.6%): 24% (41/170) required RRT within 7 days of AKI and other 23.7% (40/170) during the AKD phase. Only 6.5% (11/170) underwent OLT with AKD but without RRT. The remaining cohort had normal renal function (78/170, 45.8%). Patients who were commenced on RRT during the AKD phase had significantly lower eGFRs at 3 months and 1 year compared to AKI_RRT group [AKD_RRT vs. AKI_RRT; 41.6 ml/min vs. 56.6 ml/min, p < 0.05 (3 months); and 49.7 ml/min vs. 59.2 ml/min, p < 0.05 (1 year)]. No significant deterioration of eGFR was found in the normal function group.

Conclusions: Our study findings suggest AKD is associated with significantly reduced renal function recovery at 1-year post-liver transplantation. Our study demarcates the critical phase of AKI associated with maximal renal function recovery in cirrhotic patients for OLT and inform when best to initiate therapies that are linked with renal function recovery.

Post-liver transplant eGFR Trajectories

Variable	Normal Creatinine Function	AKI_RRT	AKD_noRRT	AKD_RRT	p-value
Participants - n	78	41	11	40	
eGFR at transplant	86.8 ± 46.9	15.7 ± 17.7	51.2 ± 27.8	15.6 ± 15.2	<0.05
At 3 months*	77.3 ± 42.7	56.6 ± 27.3	52.3 ± 15.7	41.6 ± 25.9	<0.05
At 1 year**	77.2 ± 41.5	59.2 ± 29.6	55.3 ± 22.6	49.7 ± 29.2	<0.05

*missing values - 3 for 3 months (defined as -2 weeks to +6 weeks of 3 months)

** missing values - 22 for 1 year (± 4 weeks from 1 year mark)

TH-PO055

Cholemic Tubulopathy as a Cause of AKI: A Cohort Study

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Background: Cholemic tubulopathy (i.e., bile cast nephropathy) is a type of acute kidney injury (AKI) described in individuals with acute cholestasis (obstructive, drug-induced, infectious, acute alcoholic). However, most of the available evidence comes from isolated case reports. We aimed to describe the clinical characteristics of patients diagnosed with cholemic tubulopathy within a single-center prospective AKI cohort.

Methods: We established prospective data collection in patients with AKI stage ≥ 2 (AKIN) over 5-years. Each patient completed microscopic examination of the urinary sediment (MicroExUrSed). The presence of hyaline casts (HC), waxy casts (WxC), renal tubular epithelial cell casts (RTECC), granular casts (GC), and muddy brown granular casts (MBGC) were recorded. We identified patients with documented cholestasis without cirrhosis. Demographic and clinical characteristics were extracted. Cases of shock liver were excluded.

Results: Among 483 patients with AKI without cirrhosis, 22 (4.6%) patients were found to have cholemic tubulopathy as the primary cause of AKI [32% women, 46% white, 27% black, median age 57 (20-84)]. Causes of cholestasis included biliary obstruction due to primary or metastatic cancer (5), biliary stricture (1), drug-induced cholestasis (1), cholelithiasis (6), acute viral hepatitis (3), alcoholic hepatitis (4), and acute liver failure of unknown etiology (2). One case was biopsy-proven bile cast associated acute tubular injury (acute hepatitis A). Median serum bilirubin was 22.8 (5.3-57.7) mg/dL and serum creatinine at presentation was 3.1 (1.4-8.6) mg/dL. By MicrExUrSed, HC, RTECC, GC, MBGC, and WxC were identified 13%, 41%, 64%, 55%, and 28% of patients, respectively. Among patients which had crystals reported, leucine crystals were seen in 5/17 (29%) and bilirubin crystals were seen in 4/17 (24%). Among patients with cholemic tubulopathy, 11 (50%) patients required dialysis, 6 (27%) died, and 6 (27%) recovered kidney function.

Conclusions: Cholemic tubulopathy should be suspected as a cause of AKI in patients with cholestasis with severe hyperbilirrubinemia without an alternative etiology of AKI. Overt evidence of tubular injury is often found by MicrExUrSed.

TH-PO056

A Case of Bile Cast Nephropathy Treated with Plasma Exchange Therapy for AKI Associated with Acute Hepatitis A

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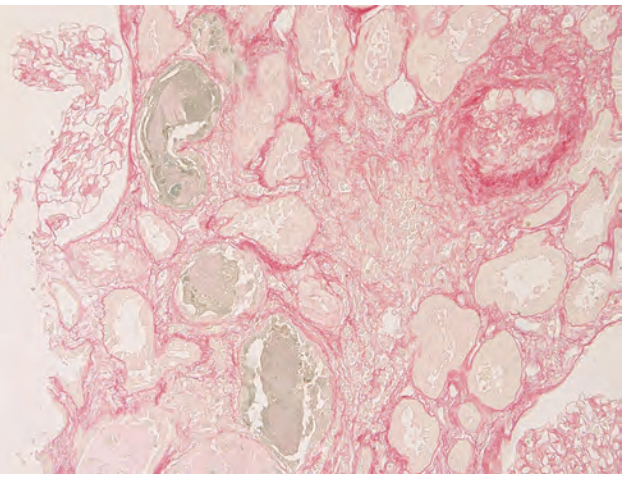
Introduction: Bilirubin-induced renal injury has been reported as bile cast nephropathy (BCN) or cholemic nephropathy (CN) which was a rare form of acute kidney injury (AKI) in Japanese. Although the improvement of hyperbilirubinemia is effective for renal dysfunction, the treatment strategies of blood purification therapy has not been established. Here, we report a case of bile cast nephropathy associated with acute hepatitis A in which hyperbilirubinemia was treated by plasma exchange therapy and AKI was improved.

Case Description: The patient, a 45-year-old man, was admitted to the hospital with acute hepatitis A. His transaminase and serum direct bilirubin (D-Bil) was severely increased (AST: 197 1U/L, AST: 2652 U/L, and D-BIl: 8.31 mg/dL), but serum creatinine (Cr) was normal (0.81 mg/dL). While his transaminase tended to improve with the best supportive care his D-Bil was elevated to 37.6 mg/dL, and Cr was also elevated to 4.5 mg/dL on day 30. Based on the course of the disease, the possibility of BCN was suspected, and plasma exchange therapy was administered 5 times on alternative days from day 30. On day 42, we performed a percutaneous renal biopsy, and we observed bilirubin columns in the renal tubules, and we made diagnosis as BCN. After plasma exchange therapy, his D-Bil was dramatically decreased and the renal dysfunction was recovered as serum Cr level of 1.2 mg/dL.

Discussion: Despite the improvement of transaminase, the elevated D-Bil induced the renal dysfunction, and we suspected BCN as the cause of AKI and successfully treated AKI due to BCN by plasma exchange therapy. BCN is rare in Japanese, and moreover, there have been few reports of renal biopsy in surviving patients. The treatment strategies of blood purification therapy to remove bilirubin have not been established, and further study is needed.



TH-PO057

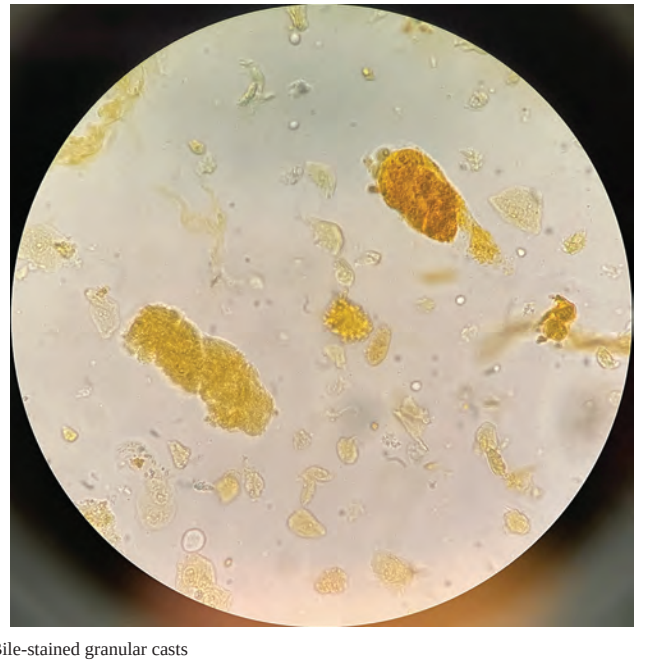
Bile Cast Nephropathy: A Diagnostic Odyssey Beyond Hepatorenal Syndrome

Samira M. Samant, Camilo Cortesi. *The Permanente Medical Group Inc, Santa Clara, CA.*

Introduction: Bile cast nephropathy (BCN) is a rarely recognized and often overlooked complication of hyperbilirubinemia leading to acute kidney injury (AKI). We present a case of BCN in a patient with alcohol hepatitis initially managed as hepatorenal syndrome (HRS).

Case Description: A 66-year-old male with severe alcohol abuse and baseline creatinine of 1.5 mg/dL presented with altered mental status and acute alcohol intoxication, requiring ICU admission. Laboratory tests showed AST 751 U/L, ALT 238 U/L, ALKP 768 U/L, total bilirubin 22.9 mg/dL, direct bilirubin 12.4 mg/dL, INR 2.4, ammonia 181 umol/L, and creatinine 2.6 mg/dL with FENa 0.1%. Ultrasound revealed diffusely hyperechoic liver, diagnosing alcoholic hepatitis with impending liver failure. Glucocorticoids were initiated, with octreotide, albumin, and midodrine for HRS. However, renal function worsened as total bilirubin peaked at 54 mg/dL. Urine microscopy identified bile-stained granular casts, prompting reassessment of the initial HRS diagnosis.

Discussion: HRS is often considered in AKI with liver dysfunction, but urine microscopy should not be overlooked. In AKI, urine microscopy to rule out BCN is crucial, especially when total bilirubin exceeds 20 mg/dL. Bilirubin's nephrotoxic effects involve oxidative damage to renal tubules, bile cast obstruction, and toxicity of sulfated bile salts. Renal biopsy for definitive diagnosis is unsafe in liver disease due to coagulopathy. Treatment focuses on improving hepatic function and relieving biliary obstruction if present. Timely diagnosis and intervention can reverse renal injury; refractory cases may require plasmapheresis or dialysis. Steroids, ursodeoxycholic acid, and lactulose provide minimal benefit. This case highlights the challenges of differentiating BCN from HRS, emphasizing the importance of urine microscopy.



Bile-stained granular casts

TH-PO058

Prevent Cardiac Surgery-Associated AKI by Perioperative Implementation of Care Bundles

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Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a serious complication after cardiac surgery. Perioperative implementation of care bundles was recommended for high-risk patients. The study evaluated the impact of care bundles on the incidence and severity of CSA-AKI.

Methods: Patients underwent cardiac surgery with cardiopulmonary bypass in Ningbo No.2 Hospital from 1st October 2020 to 30th September 2021 were retrospectively collected as the control group, and patients from 1st October 2021 to 30th September 2022 were prospectively collected as the intervention group. In the intervention group, patients were treated by care bundles from nephrologists in addition to the standard care perioperatively. The clinical data, the incidence and severity of CSA-AKI were compared between two groups.

Results: A total of 135 patients were included in this study, including 80 cases in the control group and 55 cases in the intervention group. There were 24 patients (43.6%) in the intervention group developed CSA-AKI versus 41 patients (51.2%) in the control group. In the intervention group 7 patients (12.7%) had stage 2-3 AKI, and in the control group 15 patients (18.8%). Both the incidence and severity of AKI showed a decreasing trend in the intervention group. Patients who used febuxostat and statins in the intervention group were significantly higher than the control group (20.0% vs. 1.3%, P=0.001; 40.0% vs. 21.3%, P=0.018). The intervention group had a higher proportion of completing urine examination and urinary albumin-to-creatinine ratio test than the control group (100.0% vs. 58.8%, P<0.001; 100.0% vs. 1.3%, P<0.001). Patients who used contrast agents within 48 hours prior to surgery was significantly less in the intervention group (3.6% vs. 15.0%, P=0.033). Compared with the control group, the intervention group had a higher proportion of use of albumin (83.6% vs. 53.8%, P<0.001), epinephrine (70.9% vs. 50.0%, P=0.015), norepinephrine (60.0% vs. 41.3%, P=0.032), and insulin (45.5% vs. 21.3%, P=0.003). Patients in the intervention group also had a higher mean arterial pressure than the control group (63.4±12.6mmHg vs. 40.5±16.6mmHg, P<0.001).

Conclusions: Perioperative implementation of care bundles may reduce the occurrence of CSA-AKI and prevent progression of CSA-AKI, larger sample size is needed for further verification.

TH-PO059

SGLT2 Inhibitor Dapagliflozin Reduces Biomarkers of Tubular Injury in Patients with Acute Heart Failure

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Background: Sodium-glucose co-transporter 2 (SGLT2) inhibitors improve renal and cardiovascular outcomes in heart failure patients, and there is growing evidence that it would decrease the risk of acute kidney injury (AKI). The aim of this study was to assess the effect of SGLT2 inhibitor on biomarkers of tubular injury in patients with acute heart failure (AHF).

Methods: Patients who hospitalized for AHF were randomized to dapagliflozin added to standard therapy or control group for 28 days. The primary outcome was the change of urinary [TIMP-2] x [IGFBP7] by NephroCheck® from baseline. The secondary outcome was incidence of AKI, the change of serum creatinine from baseline, adverse events and 28-day mortality.

Results: A total of 32 patients underwent randomization. Compared with control group, dapagliflozin group significantly reduced urinary [TIMP-2] x [IGFBP7] after 7 days [dapagliflozin: -0.03 ± 0.37 $(ng/mL)^2/1000$; control: +0.4 ± 0.50 $(ng/mL)^2/1000$; P = 0.022] and continue this trend until the end of the study [dapagliflozin: -0.09 ± 0.79 $(ng/mL)^2/1000$; control: +0.67 ± 0.91 $(ng/mL)^2/1000$; P = 0.096] (Figure 1). In terms of clinical outcomes, dapagliflozin has demonstrated a trend towards decrease in AKI events compared with control (33.3% vs 46.2%; P = 0.513). The change of serum creatinine, adverse events and 28-day mortality showed no differences in both groups.

Conclusions: Initiation of SGLT2 inhibitors in patients with AHF significantly decrease the urinary AKI risk markers TIMP-2 and IGFBP7, that supported protective effect of SGLT2 inhibitor on renal tubular injury.

Funding: Government Support - Non-U.S.

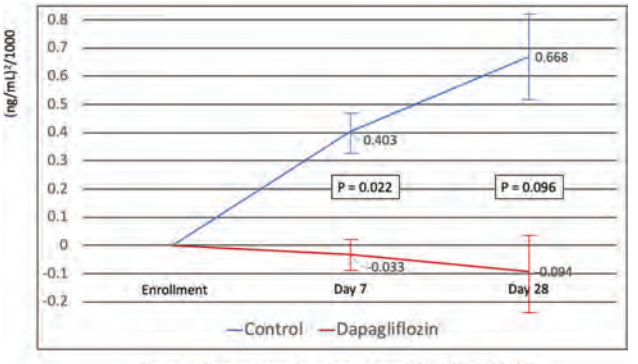

Figure 1: Changes from baseline Urinary [TIMP-2] x [IGFBP7]
Notes: p-value compared changes from baseline between both groups

TH-PO060

Probiotics in Septic AKI: A Double-Blind, Randomized Control Trial

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Background: During sepsis-induced acute kidney injury (AKI), the intestinal microbiota has profound negative changes, this dysbiosis could aggravates AKI. It is possible that modulating the intestinal dysbiosis with probiotics will favor kidney function recovery (KFR) and clinical outcomes.

Methods: In this double-blind clinical trial, patients with sepsis-induced AKI were randomized to receive probiotics or placebo for 7 days. The primary outcome was the rate of KFR by day 7. Secondary outcomes were mortality, kidney replacement therapy (KRT) requirements, urea reduction, modifications in urine volume, electrolyte abnormalities and treatment related adverse events.

Results: A total of 92 patients from February 2019 to March 2022 were randomized, 48 to probiotics and 44 to placebo. Compared to placebo, probiotics did not improve KFR by day 7(HR 0.93, 0.52-1.68, p = 0.81), mortality hazard ratio at 6 months was 0.57 (95%CI 0.32-1.04, p = 0.06). Urea (mg/dL) decreased significantly in the probiotic group from 154 to 80 mg/dl (p = 0.04) as compared to the placebo group (130 to 109 mg/dl (p=0.09). No significant differences were observed with respect to urinary volume, KRT requirement and electrolytes abnormalities. Adverse events were frequent and similar in both groups. (ClinicalTrial.gov NCT03877081) (registered 03/15/2019)

Conclusions: In septic-induced AKI, administration of probiotics for 7 days was safe; however, they did not improve KFR or reduce mortality.

TH-PO061

The Impact of Statin Use Before Intensive Care Unit Admission on Patients with AKI After Cardiac Surgery

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Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a common and serious complication after cardiac surgery. The influence of statin use before surgery on the renal outcome of patients undergoing cardiac surgery is controversial. The purpose of this study was to evaluate the effect of statins on postoperative renal outcomes in patients undergoing cardiac surgery.

Methods: This is a retrospective observational study. We included CSA-AKI patients in the Medical Information Mart for Intensive Care- IV database, and were divided into statin group and non-statin group according to whether they used statins before entering ICU. The main outcome was inpatient mortality and 30-day mortality, and the secondary outcomes were 60-day mortality and 90-day mortality. We used PSM to adjust for confounding factors. The 95% CI and risk ratio were calculated by COX proportional regression model, and the two groups of ICU LOS were compared by multiple linear regression. At the same time, stratified analysis was used to explore whether the relationship between the statins use before ICU and mortality was different in each subgroup, and whether the relationship between different doses of statins and mortality was different. Finally, CSA-AKI patients in the ICU of the First Affiliated Hospital of Jinan University were used as external validation data.

Results: 675 pre-ICU statin and 2095 non-statin user were identified. In the COX proportional regression model, pre-ICU statin use was associated with the decreased in-hospital mortality (HR=0.407, 95%CI 0.278-0.595, P<0.001) and 30-day mortality (HR=0.407, 95%CI 0.279-0.595, P<0.001). The survival rate of patients who took statins before entering ICU was significantly higher than that of those who did not use statins at 30 days, 60 days and 90 days. In subgroups of patients with age>65 years (HR=0.373, 95%CI 0.240-0.581, P<0.001), AKI grade I (HR=0.244, 95%CI 0.118-0.428, P<0.001), and without post-myocardial infarction syndrome (HR=0.344, 95%CI 0.218-0.542, P<0.001), statin use can reduce the risk of 30-day mortality in CSA-AKI patients. The in-hospital mortality of CSA-AKI patients treated with atorvastatin≥80mg was significantly reduced (P=0.030).

Conclusions: The pre-ICU statin use was significantly associated with decreased risk in-hospital and 30-day mortality, especially the loading dose of atorvastatin (≥80mg).

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TH-PO062

Association of Inpatient Metformin Use After Recovery from AKI with Lactic Acidosis and Mortality in Type 2 Diabetes Mellitus (DM)

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Background: Acute kidney injury (AKI) in the hospitalized setting is an independent risk factor for mortality. The higher the degree of AKI, the higher the rate of mortality. Metformin is a baseline antiglycemic therapy for patients with type

2 diabetes melitus (T2DM) without other comorbidy. Recent studies have shown that metfomin has pleiotropic effect and has been linked with lower cardiovascular mortality. The use of metfomin in the inpatient setting is controversial. We are exploring if metformin use after AKI recovery is associated lower mortality and higher degree of lactic acidosis.

Methods: This is a retroscpective cohort study employed the Medical Information MART for Intensive Care IV (MIMIC-IV) databse, which was released by the Massachusetts Institute of Technology Laboratory for Computational Physiology The database contained intensive care unit data from a single teriary care hospital from 2008-2019. The propensity-score matching study was conducted to analyze the outcomes for the sensivity analyses.

Results: Only 37 of 922 metformin users and 3747 of 5175 metformin nonusers had lactate level evaluated. The median level (IQR) WAS 1.4 (1.0-1.7) in the metformin user versus 1.4 (1.1-1.8) in non-users with P 0.902. There was no statistical difference in the degree of lactic acidossi s developed between two groups.

Conclusions: Metformin therapy during hospitalization after AKI recovery in patients with T2DM is not associated with increased risk of lactic acidosis. In addition, metformin user after recovery from AKI stage 2 and stage 3 is associated with lower 1- year mortality than the metfomin non-users.

TH-PO063

Associations of RAASi Discontinuation with Mortality Among Hospitalized Patients with Cardiovascular Disease in Brazil

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Background: It is consensus that renin-angiotensin-aldosterone system inhibitors (RAASi) are a pillar of drugs used for cardiovascular and renal protection, however their effects during an AKI episode are still controversial and most guidelines suggest their discontinuation. The aim of the study is to compare the mortality of hospitalized patients with cardiovascular diseases who developed AKI and discontinued the inhibitors with those who maintained their use.

Methods: We analyzed data from a cohort of hospitalized patients in Hospital de Base - São José do Rio Preto with cardiovascular disease (coronary artery disease and heart failure) identified by an AKI alert, in 2018 and 2020, based on the KDIGO creatinine criteria, who were using RAASi. Discontinuation of RAASi was defined as the suspension of their prescription for up to 3 days after the AKI alert. We used a Poisson model to estimate the adjusted risk of death predicted by the RAASi discontinuation. Race, sex and age were used as possible confounders.

Results: Our cohort consisted of 1683 patients, with a mean age of 63 years of age with 56% male. Of the patients there were using RAASi within 24 hours of the AKI alert, 729 remained off the medications 72 hours later. The patients that discontinued RAASi had a greater risk of death (31% vs 19%) when compared to the patients who remained using them. When accounting for possible confounders, the risk of death for the RAASi discontinuation group was 54% higher (RR=1.54 (1.30, 1.83)) than for those that remained using the drugs.

Conclusions: In patients with cardiovascular disease, that developed AKI during the hospital stay, the strategy of RAASi discontinuation may be associated with higher mortality. Although there are limitations, due to the observational nature of this analysis, this data supports that this class of drugs should not be withdrawn routinely in the inpatient setting.

TH-PO064

Using Kinetic eGFR for Vancomycin Dosing When Renal Clearance Is Acutely Changing: A Simulation Study

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Background: Achieving target vancomycin trough (VT) levels in acutely ill patients is a challenge. Using Cockcroft Gault estimated creatinine clearance (CGeCrCl) for drug dosing lacks validation when the creatinine level is unsteady. In this cohort of hospitalised patients treated with CGeCrCl based vancomycin dosing, we used Kinetic estimated GFR (KeGFR) and MDRD eGFR to predict VT levels and to simulate vancomycin dosing frequencies and explored the likelihood of achieving target VT levels.

Methods: Among 111 methicillin-resistant *Staphylococcus aureus* bacteremic patients treated with intravenous vancomycin who had creatinine levels varying by > 5% during treatment, a study subgroup (SSG) consisted of 38 patients who had VT levels checked after the first (loading) dose and before the second dose. Predicted VT using CGeCrCl, KeGFR and MDRD eGFR calculated using population pharmacokinetic equations and compared to the true (observed) VT using Bland Altman (BA) plots for agreement in the SSG. The dosing frequency was simulated using KeGFR and MDRD eGFRs based on the hospital vancomycin dosing protocol and the likelihood of achieving the target VT (10-20mg/L) was estimated for each method.

Results: VT levels of 41 patients (37%) were <10mg/L. In the SSG, CGeCrCl was 23.3ml/min (IQR 14.3,30.3), 34% had acute kidney injury (AKI) or were recovering from AKI and 79% had at least 5% variation in 2 consecutive creatinine levels including the level used to determine the vancomycin dosing frequency. 17 (45%) patients had subtherapeutic VT levels in the SSG. KeGFR-predicted VT showed the best agreement with true VT with a mean difference of -0.128 using the BA method. The mean difference was +3.81 for CGeCrCl predicted VT and +0.78 for MDRD predicted VT. In the dose frequency simulation model, 11 of the 17 patients with VT <10mg/L were likely to achieve the target VT when KeGFR is used, compared to 10 patients when MDRD eGFR is used and 2 patients with target VT levels were likely to attain subtherapeutic levels when MDRDeGFR is used.

Conclusions: KeGFR based vancomycin dosing is more likely to achieve target VT levels in comparison to CGeCrCl and MDRD eGFR based dosing in patients with fluctuating creatinine levels. KeGFR based vancomycin dosing will need to be further validated prospectively in a randomised clinical trial.

TH-PO065

Ciprofloxacin Crystal-Induced Acute Tubular Injury: A Case Series

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Background: Ciprofloxacin crystal-induced acute tubular injury (ATI) is a rare etiology of acute kidney injury (AKI) characterized by precipitation of ciprofloxacin crystals in the kidney tubules causing obstruction and tubular damage. Ciprofloxacin crystalluria is often seen in these cases. However, most of the available evidence comes from isolated case reports. We aimed to compile a series of cases in which ciprofloxacin crystal-induced ATI was the presumed cause of ATI.

Methods: We prospectively collected demographic and clinical data of patients seen in inpatient nephrology consultation who had a urine specimen subjected to microscopic examination of the urinary sediment (MicrExUrSed) as part of the clinical evaluation over 5 years. We identified cases in which ciprofloxacin crystalluria was identified by MicrExUrSed, recent exposure to ciprofloxacin was confirmed, and ciprofloxacin crystal-induced ATI was considered the likely cause of AKI without a possible alternative diagnosis. Urinary ciprofloxacin crystals were identified based on morphology under direct bright field light microscopy and polarized light.

Results: Of 747 AKI cases who underwent MicrExUrSed, we identified 6 cases in which ciprofloxacin crystal-induced ATI was the most likely cause of AKI. The morphology of the identified crystals was consistent across all cases. Median age was 63 (41-79), 4 were women, all 6 were white. None had preexisting CKD, 2 had cirrhosis. Mean number of days from initiation of ciprofloxacin to onset of AKI was 4 (1-12). The route of ciprofloxacin was 3 oral, and 3 IV. Urinary pH averaged 5.3. Mean serum creatinine at presentation was 2.6 (1.2-4.7) mg/dL. One patient developed concomitant shock which could have contributed to the AKI. Four patients needed dialysis. One patient returned to baseline renal function upon discharge and 3 patients died or were discharged to hospice.

Conclusions: Ciprofloxacin crystal-induced ATI should be suspected in individuals who present with AKI shortly after initiation of ciprofloxacin. This case series demonstrates the utility of MicrExUrSed under direct bright field light microscopy and polarized light as a diagnostic tool to aid in the diagnosis of AKI. Further studies are needed to correlate ciprofloxacin crystalluria with pathological evidence of crystal-induced ATI.

Funding: Other U.S. Government Support

TH-PO066

AKI in a Kidney Transplant Patient Started on Ranolazine

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Introduction: Ranolazine is an antianginal agent only rarely associated with kidney failure (< 1%). We present a case of a kidney transplant recipient who experienced acute kidney injury (AKI) and hyperkalemia after starting ranolazine, and subsequently improved after it was stopped.

Case Description: A 74-year-old man with end-stage kidney disease (ESKD), presumed secondary to diabetic nephropathy, received a deceased-donor kidney transplant in 2014. Post-transplant course was complicated by BK nephropathy with persistent low-grade viremia and atypical hemolytic uremic syndrome treated with ravulizumab. He presented to the Emergency Department at the request of his hematologist for hyperkalemia and acute kidney injury discovered on routine labs. Baseline serum creatinine was 1.3-1.6 mg/dL. At presentation, serum creatinine was 3.23 mg/dL and potassium 7.3 meq/L. After a standard evaluation, there was no obvious etiology for AKI, and an urgent transplant kidney biopsy was performed. Biopsy showed severe tubular injury with interstitial inflammation and focal tubulitis, mild interstitial fibrosis and tubular atrophy (30%). There was no evidence of T-cell or antibody mediated rejection, transplant glomerulopathy, de-novo glomerulonephritis, or recurrent atypical hemolytic uremic syndrome. On review, the only new medication prescribed was ranolazine. This was held and he was treated medically for his hyperkalemia. Renal function subsequently improved, with a new baseline creatinine of 1.8-2.3 mg/dL. Hyperkalemia resolved. He is asymptomatic off ranolazine.

Discussion: This patient developed AKI and hyperkalemia approximately 6 months after starting ranolazine. This is a rare adverse effect with only a few reported cases in the literature. A previous report implicated ranolazine as a cause of AKI due to drug-induced phospholipidosis, with the finding of zebra bodies on electron microscopy. Our patient's biopsy did not have zebra bodies present, making drug-induced phospholipidosis less likely. The mechanism is unclear. This case demonstrates that a thorough medication review and cessation of any possibly offending agents is vital in assessing AKI of unclear etiology. *Disclaimer: The views expressed in this Abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the United States Government.*

TH-PO067

A Case of Rhabdomyolysis and Acute Tubular Necrosis with Lower than Expected Creatinine Kinase Level in a Patient with Cocaine Abuse

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Introduction: Clinicians rely on serum creatinine kinase (CK) levels to assess the severity of rhabdomyolysis (RM) and predict the development of acute kidney injury (AKI). It is widely accepted that rhabdomyolysis with CK levels less than 5000 U/L is unlikely to cause AKI. We report a case of cocaine induced rhabdomyolysis and subsequent development of myoglobinuric acute tubular necrosis (ATN) in a young healthy male with CK levels of 928 U/L at presentation.

Case Description: A 33-year-old male with a past medical history of poly-substance abuse presented with headache following intake of crack cocaine three days prior to the presentation. Examination were remarkable for blood pressure of 171/108 mmHg and dry mucous membranes. Laboratory studies were significant for serum creatinine (Cr) of 21 mg/dl, Blood Urea Nitrogen (BUN) of 113 mg/dl and CK of 928 U/L. Urine sample obtained after bladder catheterization revealed gross blood with 3-5 red blood cells (RBCs)/hpf, proteinuria of 100 mg/dl and the urine toxicology was positive for cocaine. Renal ultrasound was non-contributory. Patient did not meet the criteria for urgent dialysis and the patient was started on intravenous (IV) fluids. The patient remained anuric. All the work ups done for etiologies of AKI were negative. Renal biopsy was consistent with diffuse ATN with myoglobin casts. Outpatient follow-up and continued supportive treatment resulted in resolution of ATN and normal kidney function.

Discussion: Cocaine induced RM can be traumatic due to seizure and/or hyperpyrexia and non-traumatic due to direct toxic effects of cocaine on skeletal muscle. CK and myoglobin levels change in parallel and CK levels correlate well with the severity of RM but its correlation and property to predict development of AKI is less reliable compared to serum myoglobin levels.

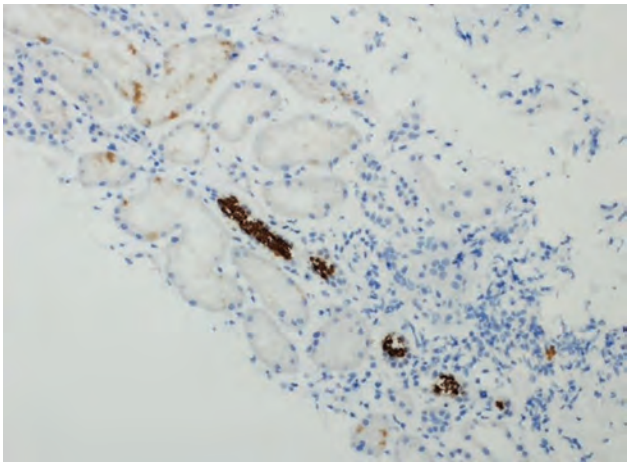


Figure showing Myoglobin Casts

TH-PO068

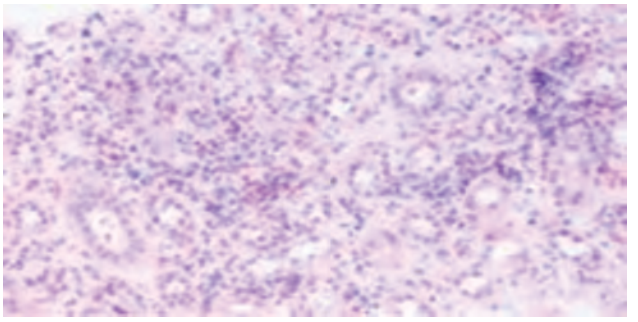
Cocaine-Associated Acute Tubular Injury and Acute Interstitial Nephritis

Akhila Arya P V, Jia Wei Tan. *Bridgeport Hospital Internal Medicine, Bridgeport, CT.*

Introduction: Cocaine can affect various compartments of the nephron, leading to conditions such as rhabdomyolysis-induced acute kidney injury (AKI) and rarely, cocaine-associated acute interstitial nephritis (AIN). In our case, the patient presented with AIN and acute tubular injury (ATI) without rhabdomyolysis.

Case Description: A previously healthy 37-year-old male presented with left flank and epigastric pain for three days. He denied taking any medication or recreational drugs. On admission, his blood pressure was 147/84 mmHg. He appeared euvolemic and had no rashes, purpuras, or arthralgias. Labs showed serum creatinine of 10.7 mg/dL without a prior baseline, blood urea nitrogen of 58 mg/dL, bicarbonate of 19 mmol/L, anion gap of 23, phosphorous of 9.6 mg/dL and creatinine kinase of 66 international units. Urinalysis showed 1+ proteinuria, 1 RBC/hpf, and 1 WBC/hpf. His protein/creatinine ratio was 0.57 mg/mg Cr. C3 and C4 were normal. Hepatitis B, C, and HIV were negative. ANA was negative, and the ANA was 1:40 in a perinuclear pattern. Renal ultrasound showed normal-sized kidneys and CT abdomen did not reveal any pathological findings. A renal biopsy confirmed the presence of diffuse AIN and ATI (Image 1, H & E, 40x). The patient's kidney function gradually improved without steroid treatment and a follow-up outpatient visit showed serum creatinine of 1.67 mg/dL.

Discussion: We highlight the importance of considering cocaine-associated renal complications, even in the absence of rhabdomyolysis, and highlight the rare presentation of concomitant ATI and AIN. The clinical, biochemical and urinalysis of AIN can be subtle and non-specific, making it challenging to diagnose. However, if there is a strong clinical suspicion of AIN, renal biopsy should be pursued to allow early recognition and potential treatment. Our patient's renal function recovered with supportive management alone, but further data are needed to fully understand the clinical course and treatment strategies for cocaine-associated AIN and ATI.



Light microscopy showing patchy diffuse acute interstitial nephritis and focal acute tubular injury

TH-PO069

Mimicking Ulcerative Colitis Flare-Ups Induced by Azathioprine Causes AKI

Mitsuru Yanai, Makoto Araki. *Sapporo Tokushukai Hospital, Sapporo, Japan.*

Introduction: Inflammatory bowel disease (IBD) is correlated with various renal ailments, including renal lithiasis, glomerulonephritis, renal amyloidosis, and drug-induced nephropathy. But no prior reports have documented drug-induced renal dysfunction with azathioprine (AZA) in IBD.

Case Description: A 61-year-old male was referred to our facility for ulcerative colitis flare-up. He had previously tried various medications, including 5-aminosalicylic acid (5ASA), AZA, and anti-TNFα antibody. Achieving remission with 30 mg prednisolone (PSL), he began novel anti-IL12/23 antibody treatment. Over 8 weeks, the PSL dose was gradually reduced without relapse. During the second dose of the anti-IL12/23 antibody, AZA at 25 mg/day replaced PSL. The next morning, the patient experienced chills, fatigue, and worsening diarrhea (over 10 times per day) shortly after the morning dose. Diarrhea persisted, the patient lost appetite, and became anuric. Subsequently, on the fourth day after anti-IL12/23 antibody administration, the patient was ambulance-transported to our hospital. Compared to values from four days prior, white blood cell count increased from 7500 to 9130/μL, C-reactive protein level rose from 0.32 to 41.37 mg/dL, and creatinine level escalated from 1.01 to 8.29 mg/dL. Considering possible infectious enteritis or worsening ulcerative colitis, the patient promptly received intravenous fluids, antibiotics, and 30 mg PSL. Hemodialysis was initiated. On the fourth day of hospitalization, a renal biopsy revealed massive cellular infiltration of the interstitium, leading to the diagnosis of acute interstitial nephritis due to azathioprine hypersensitivity syndrome. The PSL dose was quickly increased to 60 mg. Renal function gradually improved, and dialysis was completed in three sessions. After one month, creatinine levels returned to baseline, and steroid treatment ceased. Subsequently, the patient received a third dose of the anti-IL12/23 antibody without any adverse events.

Discussion: Azathioprine hypersensitivity syndrome is a systemic allergic reaction to immunosuppressive drugs, resulting in acute interstitial nephritis in the kidneys. Severe inflammatory reactions of heightened intensity mimic an exacerbation of the underlying disease or sepsis, frequently leading to delayed treatment. Timely diagnosis and prompt administration of steroids can influence the renal prognosis.

TH-PO070

Ashwagandha Overdose-Induced AKI: A Novel Case Report

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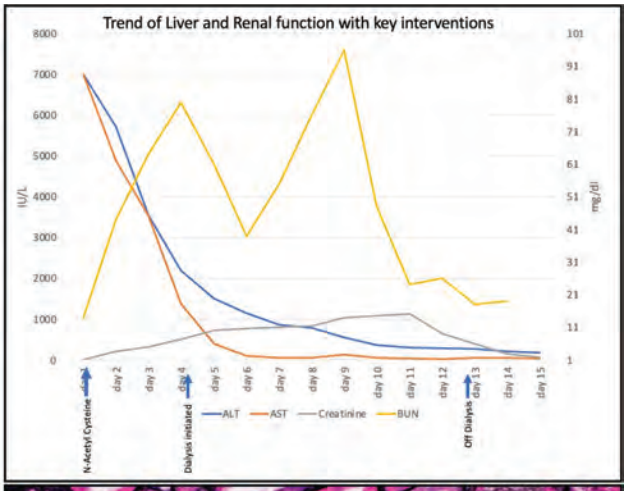
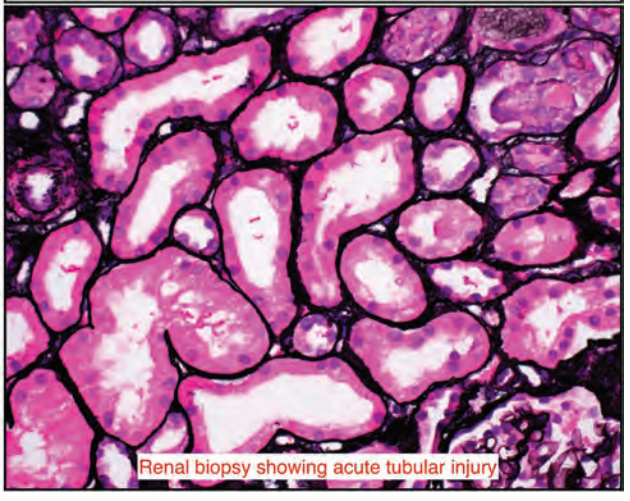
Introduction: Ashwagandha (Withania somnifera) is an Ayurvedic herb with various therapeutic properties, such as anti-inflammatory, antitumor, immunomodulatory, and adaptogenic effects. However, its safety profile is not well established. This abstract highlights the first case of kidney toxicity associated with ashwagandha overdose.

Case Description: A 26-year-old female presented with a 2-day history of progressive abdominal pain, nausea, and vomiting after taking high doses of ashwagandha (6000mg per meal) for a week to treat anxiety. Vital signs were normal, and the physical exam revealed right upper quadrant tenderness. Blood tests showed severe drug-induced liver injury with elevated ALT/AST (>7000 U/L), total bilirubin 2.1 mg/dl, and alkaline phosphatase 82 U/L. Treatment with N-acetyl cysteine improved liver function, but renal function rapidly declined on the second day. Urinalysis showed no hematuria but identified 2+ proteinuria, and a subsequent renal biopsy revealed acute tubular injury. Temporary hemodialysis was required, and the patient eventually recovered with normal kidney function in 2 weeks.

Discussion: Ashwagandha is known for its potential therapeutic benefits in stress, anxiety, and inflammation. However, the optimal daily dosage remains to be determined. Clinical trials used 300-1000mg/day, while commercial preparations may have higher amounts. A recent in-vitro study suggested that an overdose of the herb's primary metabolite, Withanone, may overwhelm the glutathione detoxifying system and cause DNA damage. Acute tubular injury observed may result from impaired renal tubule protection against oxidative stress. Kidney function returned to normal after discontinuing

the medication. Healthcare providers should be vigilant for ashwagandha-related renal toxicities and manage them promptly.





TH-PO071

An Unusual Cause of Cloudy Urine in a Patient with Sepsis

Michael Chang, Martin Sedlacek. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Cloudy urine is usually caused by pyuria. Here, we present the case of a patient whose viscous, cloudy urine was caused not by pyuria but by acyclovir crystalluria.

Case Description: A 71-year-old woman with HFpEF and history of diverticulitis was admitted for colostomy trauma. Her hospital stay was complicated by rapid atrial fibrillation, fluid overload and enterococcal urinary tract infection. In her sixth week of hospitalization she developed sepsis secondary to a hepatic abscess, requiring intensive care and treatment with Meropenem and Vancomycin. She also was treated empirically with Acyclovir 600mg IV q 8hrs for suspected HSV encephalitis. Nephrology was consulted for oliguric AKI with a creatinine increase from 0.8mg/dl to 1.57mg/dl and elevated vancomycin trough level. The urine was viscous and cloudy. On microscopy the urine was loaded with needle shaped birefringent crystals, typical of acyclovir crystalopathy. With medication dose adjustments the oliguria resolved and the urine showed no more crystals and rare granular casts. Four days later the patients serum creatinine had decreased to 0.84mg/dl. The patient completed two weeks of acyclovir treatment, eventually recovered and was discharged to rehablitation 6 weeks later.

Discussion: Intravenous Acyclovir can cause transient oliguric AKI with crystalluria so heavy that it resembles pyuria. Despite the dramatic presentation, renal recovery can occurr swiftly wth dose adjustment. There may be additional causes of AKI precipitating the event.

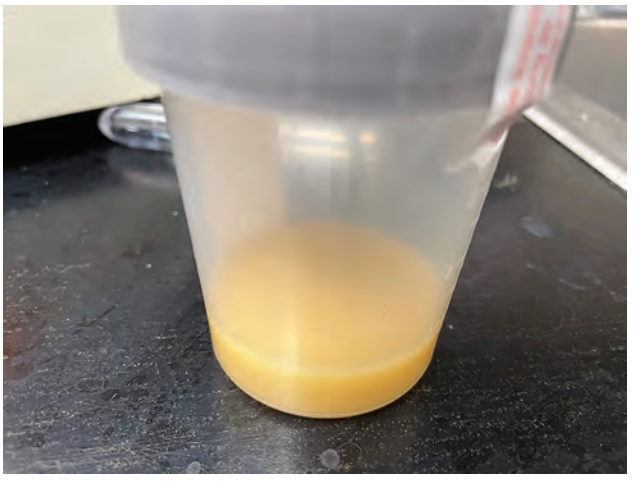


Figure1: cloudy urine

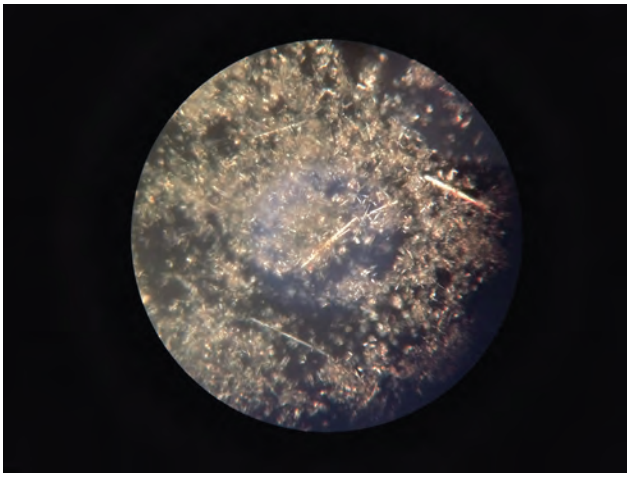


Figure 2: birefringent needle shaped acyclovir crystals

TH-PO072

Anticoagulant-Related Nephropathy in Patients with Mechanical Valves: A Challenging Case and a Possible Solution

Rui Song, Hussam Al Hennawi, Muhammad Shan Ul Abedin, Majid A. Khan. *Abington Memorial Hospital, Abington, PA.*

Introduction: Anticoagulant-related nephropathy (ARN) is a novel form of acute kidney injury (AKI) associated with anticoagulant (AC) use. Management is challenging for patients on long-term AC who develop ARN.

Case Description: A 62-year-old Male with a history of chronic kidney disease [CKD, baseline serum creatinine (sCr) of 1.7 mg/dL], atrial fibrillation (Afib), mechanical aortic valve replacement on warfarin, and non-ischemic cardiomyopathy status post ICD insertion who presented with epistaxis. His medications include aspirin, carvedilol, furosemide, pantoprazole, simvastatin, and warfarin. He had a recent admission for AKI with microscopic hematuria needing workup for glomerulonephritis. The complements, ANA, ANCA, anti-GBM antibody, serum protein electrophoresis, and serum light chains were within normal range. Ultrasonography showed no evidence of kidney stones or hydronephrosis. The cause of AKI was unclear but his sCr improved to 1.96mg/dL from 2.5mg/dL after briefly holding warfarin for an INR of 3.9. Warfarin was continued on discharge. During this admission, labs showed a sCr level of 4.3 mg/dL and an INR of 5.8 on day 0. Warfarin was held and intravenous heparin drip was started. Patient had hematuria with a urine protein/creatinine ratio of 0.92 mg/g and a kidney biopsy was obtained for AKI on CKD. Pathology showed RBC casts and tubular injury consistent with ARN and underlying IgA nephropathy. His sCr improved to 1.7mg/dL and warfarin was restarted

again on discharge. Five months later, he developed AKI on CKD requiring intermittent hemodialysis (HD). AC was held per the patient's request. After holding warfarin, renal function recovered with no further HD needs. His sCr ranged between 1.7 to 2 mg/dL for the next six months. Due to the high risk of stroke given mechanical valve and Afib without AC, Cardiology, Hematology and Nephrology coordinated the care and a trial of apixaban 2.5 mg twice daily was started. His sCr has been followed closely and is stable to date.

Discussion: ARN is often caused by high intensity warfarin usage but has been reported in patients on direct-acting oral AC. For patients with ARN needing lifelong AC, risks and benefits discussion is warranted. Multidisciplinary team effort is required. Trial of alternative low dose AC with close monitoring of sCr could be a possible solution.

TH-PO073

Karyomegalic Interstitial Nephritis in a Patient Treated with Ifosfamide

Sirisha Gudlawar. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Ifosfamide is an alkylating used in treating wide variety of cancers including germ line tumors of testes, soft tissue sarcomas, bladder cancer and cervical cancer. It can lead to reversible Fanconi syndrome, acute kidney injury (AKI). Here in, we present a case of karyomegalic interstitial nephritis (KIN) in a patient treated with ifosfamide.

Case Description: 47-year-old female with history significant for high grade extra skeletal osteosarcoma underwent tumor resection with flap reconstruction. She was started on chemotherapy with Adriamycin, Ifosfamide, Mesna and received a total of three cycles of chemotherapy. She developed AKI with creatinine of 1.5 mg/dl (baseline creatinine of 0.8 mg/dl) along with hypokalemia, hypophosphatemia and metabolic acidosis, due to which Nephrology consultation was sought. Her blood pressure was 143/78 mmHg, Heart rate of 79 beats per minute. Urine analysis was performed which showed glucosuria and microscopy was bland. Initial sodium was 141 mmol/L, potassium 2.8 mmol/L, chloride of 116 mmol/L, bicarbonate 16 mmol/L, blood urea nitrogen 12 mg/dL, Serum creatinine (SCr) of 1.59 mg/dL, phosphorus 1.5 mg/dL. She was treated conservatively with electrolyte supplementation and intravenous fluids, discharged home with outpatient follow up. Due to progressive decline in renal function (SCr 2.2 mg/dL) she underwent biopsy which showed chronic interstitial nephritis with karyomegalic features, and severe interstitial fibrosis and tubular atrophy (IFTA 70%). She was started on steroids and creatinine improved to 1.7 mg/dL. Thereafter, her creatinine remained steady at 2 mg/dL. There was no recurrence of cancer and is currently in remission.

Discussion: KIN is a rare form of familial interstitial nephritis, As per previous case reports, AKI occurs between 12 months to 5 years after exposure to the drug. In our case, it was 3 months after the initiation of chemotherapy. About 40% of these patients respond favorably to corticosteroids where as those with chronic tubulointerstitial nephritis responded poorly. This case report illustrates the importance of performing early kidney biopsy with persistent renal dysfunction following chemotherapy. Early diagnosis and initiation of steroids could potentially recover kidney function or prevent the progression of the disease.

TH-PO074

A Rare and Serious Reaction to Frequently Used Rituximab

Gabriel J. Torres-Rivera, Carlos Cortes, Carlos S. Rosado-Rodriguez, Nicole Rivera-Bobe. *VA Caribbean Healthcare System, San Juan, Puerto Rico.*

Introduction: Rituximab is an anti-CD20 monoclonal antibody used in malignancies, and rheumatologic and kidney diseases. Rituximab is seldom associated with life threatening complications. Cytokine Release Syndrome (CRS) is a systemic response following an extensive release of inflammatory cytokines due to activation of myeloid cells and lymphocytes. Depending on its severity, it can present with rash, fever, abdominal pain, mental status changes, and respiratory failure. Few cases are reported in the literature, most leading to a catastrophic cascade of events. We herein present a man with B-Cell lymphoma who became critically ill with severe lactic acidosis, altered mental status, and renal failure within minutes of receiving his first rituximab dose.

Case Description: A 68 y/o man with hypertension went to the ER complaining of chills at night and weight loss. Normal vital signs but found with bilateral cervical and axillary lymphadenopathy. Labs with increased creatinine: 0.9>1.31mg/dL and Ca+: 11mg/dL. He was admitted to Oncology due to symptomatic hypercalcemia, AKI, and lymphadenopathy with suspected malignancy. Lymph node biopsy yielded B-cell lymphoma diagnosis and he was started on rituximab. Minutes after starting the infusion, he presented with chills, tachypnea, tachycardia, hypertension, and altered mental status. No edema or skin rash but presented abdominal discomfort. Infusion was stopped and he was given IV diphenhydramine and solumedrol. Lactic acid: 21.2mmol/L, blood pH: 7.2, Anion Gap: 34, K+: 5.0mEq/L, and PO4-: 5.9mg/dL, LDH 2212 U/L, CPK 55 U/L. Elevated lactic acid without evidence of hypoperfusion and his electrolytic disturbances suggest rapid destruction of tumor cells by rituximab leading to CRS. Initially provided with supportive therapy, but became anuric 2 days later for which a trial of hemodialysis was started. There was no improvement with worsening pancytopenia, the family opted for comfort measures and the patient was discharged home under hospice care.

Discussion: Because of its efficacy, Rituximab is widely and frequently used. Rituximab-associated CRS is very rare but carries a high morbidity and mortality risk. This case is important for the community since it highlights a very rare and overlooked reaction of rituximab which is being used more frequently.

TH-PO075

Plasmapheresis as Adjunctive Treatment for Life-Threatening Rituximab-Induced Acute Respiratory Distress Syndrome

Christopher Yang, Anip Bansal. *University of Colorado Anschutz Medical Campus, Aurora, CO.*

Introduction: Rituximab is a monoclonal antibody targeted against the B-cell surface antigen CD20. It is used as therapy for a variety of conditions including hematologic malignancies and autoimmune diseases. Use of rituximab has been associated with hypersensitivity reactions (HSR) which can be classified as infusion-related, cytokine-release, type I (IgE/non-IgE), mixed, type III, and type IV reactions. While rituximab is typically associated with largely benign infusion reactions, it occasionally leads to serious type I reactions, which can cause life-threatening anaphylaxis. Rituximab can cause lung toxicity due to immediate hypersensitivity, via cytokine release and by a delayed HSR. We report the management of a patient with severe shock and ARDS attributed to a mixed HSR to rituximab infusion, which improved with plasmapheresis.

Case Description: A thirty-year old woman with myasthenia gravis (MG) was admitted with an acute exacerbation of MG after missing her maintenance dose of rituximab. She was initially treated with five sessions of plasmapheresis without any complications. Subsequently, she was treated with rituximab, per the standard protocol. Several hours after her rituximab infusion, she developed refractory shock, hypoxia, and hemoconcentration (Hgb 12 to 17 g/dl). Despite treatment with high dose steroids and broad-spectrum antibiotics, she rapidly developed ARDS requiring mechanical ventilation, oliguric acute kidney injury, and severe lactic acidosis. Her echocardiogram showed normal cardiac function and infectious work-up was ultimately negative. She was treated with one additional session of plasmapheresis to facilitate elimination of rituximab based on prior case reports. She subsequently had rapid improvement in clinical parameters with resolution of shock in three days, resolution of AKI soon after and extubation after six days.

Discussion: Severe HSR, while rare, can be a potentially fatal adverse effect of rituximab. There is no well-described treatment of this reaction. We describe a case with rapid improvement after one treatment of adjunctive plasmapheresis. With the widespread use of rituximab for a variety of conditions, clinicians need to be aware regarding the diagnosis and management of the spectrum of HSRs associated with this drug.

TH-PO076

Oxalate Nephropathy in a Diabetic with Intentional Weight Loss

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Introduction: Oxalate induced nephropathy is a rare cause of acute kidney injury and has the potential to progress to end stage kidney disease.

Case Description: We saw a 60 years old diabetic female with an acute increase in serum creatinine and was admitted for acute renal failure, unspecified renal failure type. She has a history of hypertension, CKD 3b, reported retinopathy and a 50lbs intentional weight loss during the summer. She particularly resorted to foods like nuts and spinach with the avoidance of dairy. Routine evaluation revealed mild hyponatremia (which was attributed to the use of HCTZ). There was also microscopic hematuria. FeNa was 53% which was consistent with intrinsic renal pathology and Renal USG was ordered which revealed a slightly elevated bladder with non- obstructive nephrolithiasis. Testing for antibodies revealed negative ANCA, Anti GBM and ANA. HCTZ and metformin were held as part of initial management with regular monitoriing. Her clinical presentation pointed towards a list of suspected differentials like Acute tubular necrosis secondary to hypotension, RPGN or a possible CKD secondary to T2DM. A lack of improvement in the creatinine levels despite the initial management prompted towards the need of a kidney biopsy. The biopsy revealed mild to moderate tubular injury with frequent oxalate crystals along-with features suggestive of diabetic nephropathy (renal pathology class 2b) Her acute rise in creatinine was attributed to the oxalate deposition (and not diabetes) and she was advised to avoid vitamin C and oxalate containing foods. A regular out patient follow-up had been scheduled and a discussion regarding genetic predisposition to oxalate deposition was initiated.

Discussion: There were a few challenges to the diagnosis. Retinopathy is a predictor of nephropathy in diabetic patients which posed the first obstacle towards diagnosis. The absence of proteinuria is another interesting finding, although it is now commonly accepted that a proportion of patients either with type 1 diabetes or type 2 diabetes have renal function loss without proteinuria, referred to as nonproteinuric diabetic kidney disease. The biopsy finding of oxalate crystals was in line with her history of rapid intentional weight loss where she resorted to foods like nuts and green leafy vegetables.

TH-PO077

Interesting Biopsy of a Patient with AKI on a Background of Systemic Mastocytosis

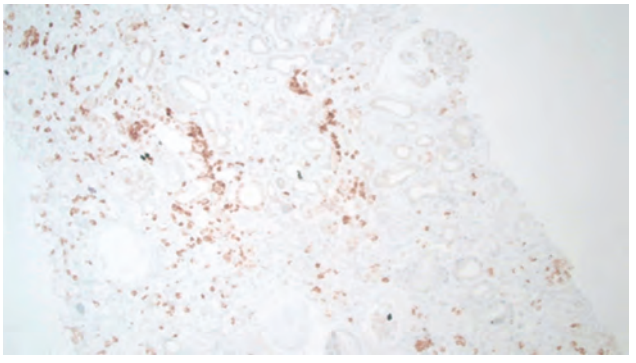
Sorcha O'Brien,[1] Brenda Griffin,[1] Anthony M. Dorman.[2] *[1]St James's Hospital, Dublin, Ireland; [2]Beaumont Hospital, Dublin, Ireland.*

Introduction: Systemic mastocytosis (SM) is a rare disorder characterised by infiltration of clonally derived mast cells in bone marrow and other extracutaneous organs. The most common genetic mutation in SM is *KIT* D816 V and is resistant to

Imatinib, other *KIT* mutations have been identified. F522C accounts for 1% of all SM-associated *KIT* mutations and has been reported to be sensitive to Imatinib.

Case Description: A 72-year-old woman was diagnosed with systemic mastocytosis (*KIT* F522C mutation) following bone marrow biopsy showing mast cell infiltrate and stained positive for CD117. She was commenced on antihistamines and Montelukast. Following the results of the bone marrow sample showing F522C mutation, she was commenced on Imatinib. She initially had a good response to treatment, however she subsequently lost response to Imatinib and required frequent courses of tapering steroids. Two years after diagnosis, she presented to emergency department (ED) with an acute history of facial flushing and oliguria. Her bloods on presentation to ED showed elevated creatinine and tryptase levels. She initially required renal replacement therapy for several days, renal function then recovered. A renal biopsy was arranged. The biopsy showed acute tubular necrosis (ATN) and inflammatory cell infiltration of the interstitium. Immunohistochemical staining showed focal aggregates of CD117 positive cells indicating an infiltrate of mast cells (~10%). Following discussion with the patient, she opted not for further management. She became oliguric and developed disseminated intervascular coagulation without evidence of bleeding. She was transferred to a hospice for where she passed away.

Discussion: Renal involvement in SM is rare and has not been described much in the literature. Consideration needs to be given to other causes of AKI in SM, eg. ATN or acute interstitial nephritis secondary to Imatinib. Renal mastocytosis is typically progressive and leads to chronic kidney disease/end stage kidney disease despite treatment.



Renal cortex with CD117 positive mast cells

TH-PO078

A Case of IgG4-Related Kidney Disease with a Rare Renal Cyst

Hiroki Uchida,[1] Jun Okita,[1] Akiko Kudo,[1] Takeshi Nakata,[1] Akihiro Fukuda,[1] Noriko Uesugi,[2] Hirotaka Shibata.[1] *[1]Department of Endocrinology, Metabolism, Rheumatology and Nephrology, Faculty of Medicine, Oita University, Yufu, Japan; [2]Department of Pathology, Fukuoka University School of Medicine, Fukuoka, Japan.*

Introduction: IgG4-related kidney disease (IgG4-RKD) is characterized by tubulointerstitial nephritis with elevated IgG4-positive plasma cells. Characteristic imaging findings of IgG4-RKD include diffuse kidney enlargement, multiple low-density lesions, solitary masses, and diffuse thickening of the renal pelvis wall. Here, we report a case of IgG4-RKD with a rare renal cystic formation that shrank after steroid treatment.

Case Description: A 73-year-old man was admitted to our hospital with acute kidney injury and tubulointerstitial disorder. Blood tests showed elevated IgG and IgG4 (IgG 3941 mg/dL,IgG4 425 mg/dL). CT imaging showed enlargement of both kidneys, and a solitary mass in the left kidney. Renal biopsy of the right kidney showed tubulointerstitial nephritis with storiform fibrosis and increased IgG4-positive plasma cells, which led to a diagnosis of IgG4-RKD. Ultrasonography showed no substantial component or blood flow within the kidney mass, and MRI showed diffusion-weighted images with heterogeneous diffusion restriction inside the kidney mass, and no clinical findings to suggest infection, suggesting a simple cystic lesion. Steroid treatment for IgG4-RKD improved kidney function and IgG4 levels, in addition, CT imaging showed a markedly reduction of cystic renal mass (Fig 1).

Discussion: In one case, a benign renal lesion due to IgG4-RKD was found after nephrectomy, while in another case, a renal mass thought to be a benign renal lesion was found to be renal cancer after steroid treatment. In this case, the mass lesion shrank following steroid treatment, and CT and MRI imaging findings suggested a cystic renal mass caused by IgG4-RKD. Careful judgment is required when deciding if renal masses may be benign or malignant in patients with IgG4-RKD. Here, we report a rare case of a solitary renal cystic mass associated with IgG4-RKD.

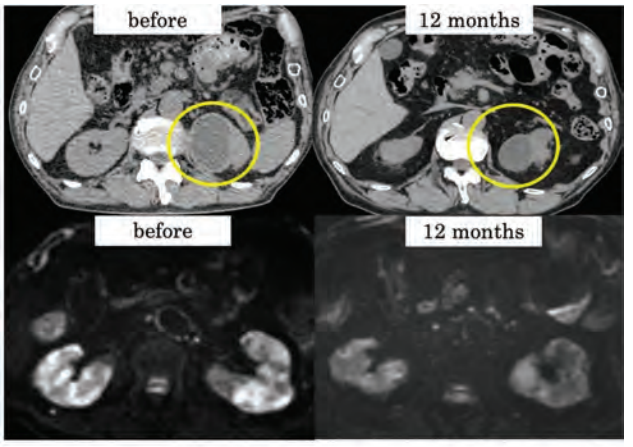


Fig 1. Changes in the solitary mass in the kidney as revealed by CT and MRI findings; before and 12 months after steroid therapy.

TH-PO079

Single-Cell Dissection of Cellular and Molecular Features Underlying Mesenchymal Stem Cell Therapy in Ischemic AKI

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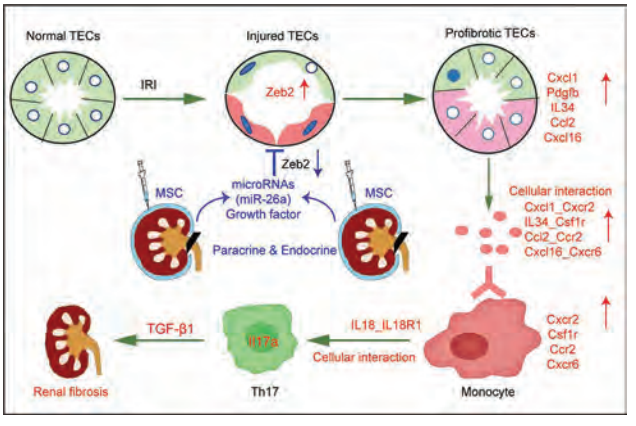
Background: Mesenchymal stem cells (MSCs) exert beneficial therapeutic effects in acute kidney injury (AKI), while the detailed repair mechanism remains unclear.

Methods: Single cell sequencing was used for the first time to delineate the mechanism of MSC treatment for AKI induced by bilateral ischemia reperfusion injury in C57 mice. Receptor-ligand interaction analysis focused on the elucidation of intercellular communication. Extracellular vesicles (EVs) derived from MSCs were extracted by ultracentrifugation combined with size exclusion chromatography. Transmission electron microscopy, nanoparticle tracking analysis, cell transfection, flow cytometry, RT-qPCR, Western blot, and immunohistochemistry were used to evaluate cellular function.

Results: Our analyses uncovered renal tubular epithelial cells (TECs) and immune cells transcriptomic diversity and highlighted a repair trajectory involving renal stem/progenitor cell differentiation. Our findings also suggested pro-fibrotic factors such as ZEB2 and PDGFβ expressed by TECs promoted the recruitment of inflammatory monocytes and Th17 cells to injured kidney tissue, inducing TGF-β1 secretion and renal fibrosis. Finally, in addition to activating the repair properties of renal progenitor/stem cells, we uncovered a role for MSC-derived miR-26a in mediating the therapeutic effects of MSCs by inhibiting Zeb2 expression and suppressing pro-fibrotic TECs and its subsequent recruitment of immune cell subpopulations.

Conclusions: Exogenous MSCs promote the potential repair trajectories involving renal stem/progenitor epithelial differentiation and the inhibition of the miR-26a/Zeb2 pathway on immune cells infiltration and fibrosis in response to MSC therapy during AKI-CKD progression, which helps to optimize future AKI treatment.

Funding: Government Support - Non-U.S.



Summary of the role of MSCs in the regulation of kidney repair and fibrosis during AKI-CKD progression.

TH-PO080

Cannabigerolic Acid (CBGA) Ameliorates Renal Inflammation and Fibrosis in Mouse Nephropathic Models

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Background: Cannabinoids are a major class of compounds in cannabis, comprising some ~100 structurally related but diverse molecules, where cannabidiolic acid (CBDA) and tetrahydrocannabinolic acid (THCA) being the major components in most plant varieties. In some plant varieties, cannabigerolic acid (CBGA) has been reported the dominant molecular species. CBD, the decarboxylated version of CBDA, is thought have multiple biological effects, including the ability to attenuate inflammatory processes. Cannabigerols (CBGA and its decarboxylated CBG molecule) have pharmacological profiles similar to CBD. The endocannabinoid system has recently emerged to contribute to kidney disease, however, the therapeutic property of cannabinoids in kidney disease remains largely unknown. In this study, we determined whether CBD and CBGA can attenuate kidney damage in cisplatin-induced acute kidney injury model. In addition, we evaluated the anti-fibrosis effect of these cannabinoids in Unilateral Ureteral Obstruction (UUO) mice as a chronic kidney disease model.

Methods: CBD or CBGA (10 mg/kg) were injected daily in cisplatin administered mice and UUO mice. Kidneys were collected at day 3 from cisplatin administered mice and used for qRT-PCR, western blotting and TUNEL assay. UUO Kidneys were collected at day 7 and used for immunostaining of Ki-67 and extracellular matrix. We also assessed the effect of CBGA and CBD to ion channel by patch-clamp technique.

Results: We find that CBGA protects the kidney from cisplatin-induced nephrotoxicity. CBGA also strongly suppressed mRNA of inflammatory cytokines and apoptosis through inhibition of caspase-3 activity in cisplatin-induced acute kidney injury, whereas CBD treatment was only partially effective. In UUO kidneys, both CBGA and CBD prevented kidney atrophy, tubule loss, proliferation and maintained overall morphology. Both cannabinoids also strongly reduced renal fibrosis in UUO kidneys. Finally, we find that in contrast to CBD, CBGA has a potent inhibitory effect on the channel-kinase TRPM7 and the TRPM7 protein expression was significantly suppressed in cisplatin-induced acute kidney injury.

Conclusions: We conclude that CBGA and CBD have a reno-protective efficacy in kidney damage, with CBGA especially having a stronger inhibitory effect to prevent inflammation in acute kidney injury by TRPM7 blockage.

Funding: Other NIH Support - National Center for Complementary and Integrative Health: R01AT011162

TH-PO081

AKI-Induced Circulating TNFR1/2 Elevations Correlate with Persistent Kidney Injury and Progression to Fibrosis

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Background: Elevated levels of circulating Tumor-Necrosis-Factor-Receptors 1 and 2 (cTNFR1/2) predict CKD progression. Whether acute kidney injury drives cTNFR1/2 elevations and whether they predict disease outcomes after AKI remains unknown.

Methods: We used AKI patient serum and urine samples, mouse models of kidney injury (ischemic, obstructive, toxic) and progression to fibrosis, nephrectomy, and related single cell RNA-sequencing datasets.

Results: We show that TNFR1/2 serum and urine levels are highly elevated in all mouse models of kidney injury tested, beginning within one-hour post-injury, and correlate with its severity. Consistent with this, serum and urine TNFR1/2 levels are increased in AKI patients and correlate with severity of kidney failure. Interestingly, the extracellular particle (EP)-bound forms of cTNFR1/2 correlate with renal function better than their soluble forms. TNF neutralization does not affect early cTNFR1/2 elevations, suggesting that cTNFR1/2 levels do not reflect injury-induced TNF activity. Kidney tissue expression of TNFR1/2 after AKI is only mildly increased and bilateral nephrectomies lead to strong cTNFR1/2 elevations, suggesting release of these receptors by extrarenal sources. cTNFR1/2 remain elevated for weeks after severe kidney injury and at these later timepoints cTNFR1/2 correlate to remaining kidney injury. During AKI-to-CKD transition, kidney expression of TNFR1/2 and cTNFR2 levels, correlate with development of fibrosis.

Conclusions: Our data demonstrate that AKI drives acute increases in cTNFR1/2 serum levels which negatively correlate with kidney function, in particular their EP-bound forms. Sustained TNFR1/2 elevations after kidney injury during AKI-to-CKD transition correlate with persistent tissue injury and progression to kidney fibrosis.

Funding: Private Foundation Support

TH-PO082

COPT Nanoparticles Ameliorate the AKI-to-CKD Transition via Inducing BNIP3-Mediated Mitophagy

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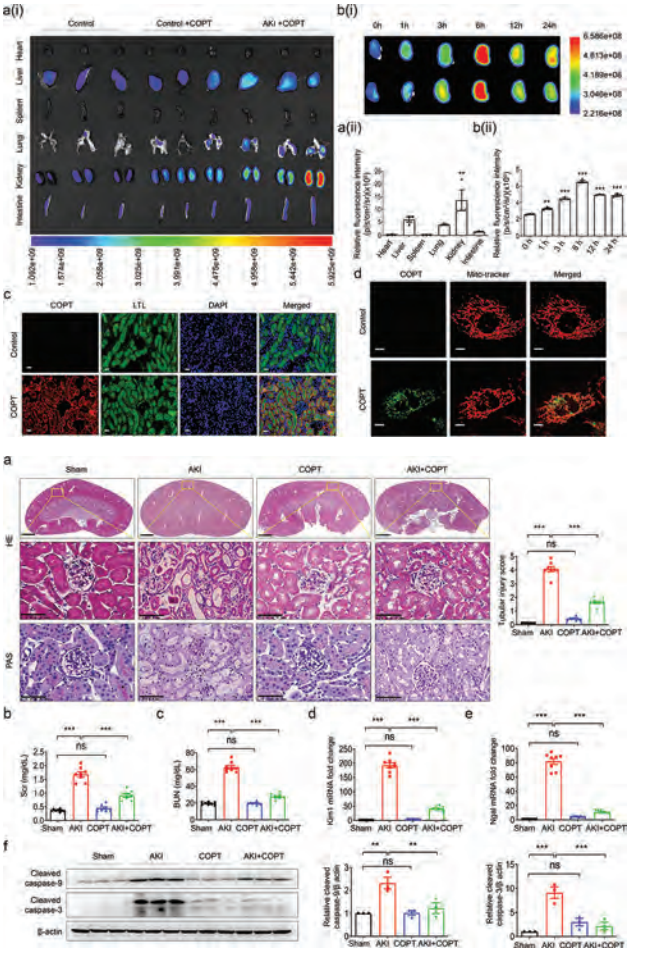
Background: Accumulating evidence highlights mitochondrial dysfunction as a crucial factor in the pathogenesis of acute kidney injury (AKI), thus novel therapeutic strategies maintaining mitochondrial homeostasis are highly anticipated. Recent studies have shown that cobaltosic oxide has peroxidase-like catalytic activities, although its role and mechanism remain elusive in AKI.

Methods: Cobaltosic oxide-polyethylene glycol-triphenylphosphine (COPT) nanoparticles were synthesized by conjugating cobaltosic oxide with polyethylene glycol and triphenylphosphine. Its theranostic effect was evaluated by using AKI mice, zebrafishes and cells.

Results: COPT preferentially accumulated in the renal proximal tubule cells, and significantly alleviated ischemic AKI in mouse and zebrafish models. COPT also inhibited the transition from AKI to chronic kidney disease (CKD), with few side effects. Further, COPT localized in the mitochondria, and ameliorated hypoxia-reoxygenation (HR)-mediated mitochondrial damage through enhancing mitophagy. Mechanistically, COPT dose-dependently induced the expression of Bcl-2/adenovirus E1B 19-kDa interacting protein (BNIP3), while knockdown of BNIP3 attenuated COPT-induced mitophagic flux and mitochondrial protection.

Conclusions: COPT nanoparticles ameliorate AKI and its progression to CKD through inducing BNIP3-mediated mitophagy, indicating that COPT may serve as a promising mitochondria-targeting therapeutic agent against AKI.



TH-PO083

The Role of C5aR vs. C3 in Thrombotic Microangiopathy, Ischemic Kidney Necrosis, and AKI Induced by Cholesterol Crystal Embolism

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Background: Certain thrombotic microangiopathies (TMA) respond to inhibition of complement factor C5, which abrogates formation of the membrane attack complex and hence impairs host defense. Inhibition of C5a receptor (C5aR) avoids this safety problem and still controls autoimmune systemic vasculitis. We speculated that targeting C5aR could be sufficient also in TMA, e.g., related to cholesterol crystal embolism (CCE).

Methods: We induced experimental TMA in C3-/-, C5aR-/- or wildtype mice by injecting CC into the left kidney artery of mice and analyzed thrombotic angiopathy, drop in measured glomerular filtration rate (GFR), and ischemic necrosis 24 hours after CCE.

Results: In wildtype mice, CC injection caused diffuse TMA followed by a consistent drop of GFR compared to baseline and ischemic kidney necrosis. Genetic deficiency in C3 convertase profoundly attenuated TMA and hence GFR drop and ischemic kidney necrosis indicating a key role of the complement system in CCE-related TMA. Genetic deficiency of C5aR attenuated TMA, GFR drop and ischemic necrosis to the same extent indicating that C5aR provides the main contribution of the complement system to the pathogenesis of TMA.

Conclusions: We conclude that targeting the C5a/C5aR axis could be sufficient to attenuate also TMA for which a better safety profile would be expected as compared to C5 inhibition.

Funding: Clinical Revenue Support

TH-PO084

Induction of Cell Cycle Inhibitor p16Ink4a and Cellular Senescence in Heme Protein-Mediated AKI

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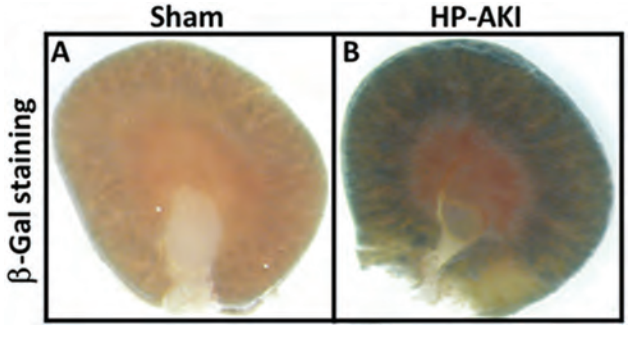
Background: Senescent cells (SCs) exhibit cellular arrest due to upregulation of cell cycle inhibitors such as $p16^{Ink4a}$. In this study, we demonstrate senescence in heme protein-mediated acute kidney injury (HP-AKI) with the upregulation of $p16^{Ink4a}$ gene along with a senescent phenotype exhibited by murine kidneys.

Methods: $p16^{Ink4a}$ mRNA expression was assessed by RT-PCR and RNAish in the murine glycerol model of HP-AKI, and in murine kidneys after administration of hemoglobin, myoglobin, and hemin. A senescent phenotype was assessed by β-galactosidase staining and lamin B1 protein expression using immunofluorescence and western blotting.

Results: Renal $p16^{Ink4a}$ mRNA was significantly increased at 8, 24, and 48 hours in the glycerol model of HP-AKI. Localization of mRNA using RNAish revealed significantly increased $p16^{Ink4a}$ mRNA expression in the proximal tubules. Similarly, administration of hemoglobin, myoglobin, or hemin to mice with intact kidneys significantly increased $p16^{Ink4a}$ mRNA expression in the kidney. RNAseq analysis of the HP-AKI model showed telomere erosion as reflected by reduced expression of genes in the 1MB telomeric region in HP-AKI model. A senescent phenotype within HP-AKI kidneys was additionally demonstrated by increased β-galactosidase activity and decreased lamin B1 protein expression.

Conclusions: Glycerol-induced HP-AKI resulted in upregulation of the cell cycle inhibitor, $p16^{Ink4A}$, the latter mainly induced in proximal tubules. HP-AKI also resulted in telomere erosion as revealed by reduced expression of genes in the 1MB telomeric region. Confirmation of a senescent phenotype in HP-AKI was provided by increased β-galactosidase activity and decreased lamin B1 protein expression. The kidney subjected to HP-AKI thus exhibits a senescent phenotype which we suggest is driven by upregulation of $p16^{Ink4a}$ mRNA expression within the injured kidney.

Funding: NIDDK Support



β-Galactosidase staining at 24 hours after HP-AKI in the kidney of **A)** sham and **B)** HP-AKI mice

TH-PO085

The Class B Scavenger Receptors BI and BII Exacerbate Acute Kidney and Liver Injury in Murine Abdominal Sepsis Model

Naoki Hayase,[1] Irina Baranova,[2] Tatyana Vishnyakova,[2] Alexander V. Bocharov,[2] Rohit R. Chari,[1] Alef Aragao Carneiro dos Santos,[1] Xuzhen Hu,[1] Peter S. Yuen,[1] Robert A. Star.[1] *[1]National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD; [2]National Institutes of Health, Bethesda, MD.*

Background: The class B scavenger receptors BI (SR-BI) and BII (SR-BII) are expressed in multiple tissues and known to recognize various pathogen-associated molecular patterns. Recently, we found that both receptors bind and internalize bacteria and boost proinflammatory cytokine production in HeLa cells transfected with SR-Bs. Moreover, we developed human SR-BI and BII transgenic mice (driven by pLiv-11) that overexpress hSR-BI and BII transgenes in the liver (to a lesser extent in the kidney). LPS I.P. injection markedly increases expression of proinflammatory cytokines in the liver and kidney of both transgenic mice. However, their roles in a clinically relevant sepsis model are unknown.

Methods: We performed cecum ligation and puncture (CLP) surgery in hSR-BI and BII transgenic and wild-type (WT) mice and treated them with antibiotics and fluids. A seven-day survival study was conducted. In a separate experiment at 24 h after CLP surgery, we collected blood, peritoneal lavage fluid, kidney, liver, and lungs for bacterial count, histological and biochemical examination.

Results: First, hSR-BI and BII transgenic mice had significantly worsened survival compared to WT mice (SR-BI vs. WT, 0.0% vs. 28.6% on Day 7, n = 5-7 per group, p = 0.002; SR-BII vs. WT, 0.0% vs. 28.6% on Day 7, n = 5-7 per group, p = 0.003). Second, the blood bacterial count was lower in both hSR-B transgenic mice than WT, while there was the similar trend in the number of bacteria in the peritoneal fluid. Alanine aminotransferase levels of hSR-BI and BII transgenic mice were significantly higher than WT. The kidneys of hSR-BI transgenic mice had abundant vacuole degeneration and the highest tubular injury score among the experimental groups.

Conclusions: In summary, our findings suggest that hSR-BI and BII overexpression contributes to higher mortality in the CLP sepsis by exacerbating liver and/or kidney injury. Future studies are planned (especially endocytosis of bacteria via the receptors, and production of proinflammatory cytokines) to further elucidate the pathogenetic roles of SR-BI/BII in a clinically translatable abdominal sepsis model.

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

TH-PO086

Aging and Immune Response to the Late Recovery Phase of Ischemic AKI

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Background: Kidney immune cells play important roles in acute kidney injury (AKI) and the repair process. Considering that aging affects immune cell compositions and their function in multiple organs, the effect of aging on kidney and extrarenal immune responses in the recovery phase after ischemic AKI was evaluated.

Methods: C57Bl/6 mice with three different age groups, including 7-week, 6- and 12-month-old, underwent unilateral ischemia-reperfusion injury (UIRI) for 45 min. Mice were followed up until 4 weeks, and kidneys and spleens were collected. Serum creatinine and cystatin-C levels were measured. Kidney and splenic lymphocytes were analyzed by flow cytometry.

Results: Serum creatinine (7-week-old, 0.25±0.05; 6-month-old, 0.41±0.04, P=0.01; 12-month-old, 0.39±0.02mg/dL, P<0.01) and cystatin-C (548.67±30.35; 545.00±30.25, P=0.99; 914.60±96.40ng/ml, P=0.01) levels were higher in older mice at 4 weeks after UIRI, although both were comparable between groups at baseline. NK T cells (6.27±0.47 vs 2.51±0.30%, P<0.01) and Tregs (13.42±1.11 vs 7.87±0.53%, P<0.01) were lower in post-ischemic kidneys of 12-month-old mice than 7-week-old mice, whereas they were comparable in contralateral kidneys (NK T cells, 10.83±1.10 vs 9.56±0.65%, P=0.82; Tregs, 2.13±0.15 vs 2.13± 0.62%, P=0.99). There were no differences in the proportion of CD4 T cells and CD8 T cells among total T cells in both post-ischemic and contralateral kidneys. Activated B cells from older mice were higher in post-ischemic kidneys (10.00±1.06; 16.37±2.01, P=0.04; 19.77±1.74%, P<0.01) as well as in contralateral kidneys (2.78±0.19; 6.52±1.07, P<0.01; 7.81±0.42%, P<0.01). Splenic CD4 T cells (60.13±1.68 vs 91.32±2.35% of total T cells, P<0.01) were higher, and splenic Tregs (8.30±0.33 vs 5.34±1.22% of CD4 T cells, P=0.03) were lower in 12-month-old mice compared to 6-month-old mice. Splenic T cells from older mice had higher expression of CD69 (7.83±0.30; 15.95±2.05, P=0.097; 19.62±3.93% of total T cells, P=0.01).

Conclusions: Aging affects long-term intrarenal and systemic immune responses to ischemic AKI during the recovery phase. Older hosts showed an accelerated proinflammatory and diminished anti-inflammatory responses. Future studies are needed to evaluate senescent immune reaction in ischemic AKI.

TH-PO087

Kidney Injury Released HMGB1 Is a Pathogenic Agent to the Development of Acute Lung Injury

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Background: Acute kidney injury (AKI) could induce respiratory complications, resulting in a high mortality rate, but molecular mechanisms and mediators of AKI to acute lung injury (ALI) are not yet well understood.

Methods: Male C57BL/6 mice were used to establish bilateral renal ischemia-reperfusion injury (I/R) model. Single-cell RNA sequencing analysis was used to explore which molecule play a crucial role in AKI-ALI. The role of high mobility group box 1 (HMGB1) was verified by constructing renal tubular epithelial cell-specific HMGB1 knockout mice and injecting HMGB1 neutralizing antibodies. The post-translational modification of HMGB1 and its influence on other proteins in injured kidney was detected by the proteomic analysis. Immunoprecipitation, and immunofluorescence co-staining were used to identify the HMGB1 receptor in ALI.

Results: We found renal I/R induced ALI, especially at day one after surgery. The expression of HMGB1 in renal tubular cells increased rapidly after I/R, with the cytoplasmic migration of HMGB1. Specific knockout of HMGB1 in renal tubular cells or injection of HMGB1 neutralizing antibody alleviated AKI-induced ALI. The acetylation of HMGB1 in the kidney increased after I/R, which accelerates the release of HMGB1 into the peripheral circulation. In addition, we found 2469 sites of 1050 proteins were increased in acetylation compared to that in sham mice. Knockout of HMGB1 in renal tubular epithelial cells decreased acetylation of 1093 sites of 698 proteins, which are key proteins involved in several energy metabolism pathways. We further found that the binding receptor for HMGB1 on the membrane of lung tissue cells is depend on the advanced glycation end products (RAGE). After antagonizing RAGE, kidney I/R-induced ALI was alleviated, but kidney damage was not affected. It was further found that the HMGB1-RAGE axis participated in the progression of ALI via impairment of oxidative phosphorylation and the subsequent mitochondrial dysfunction.

Conclusions: Our work identifies HMGB1 released by the injured kidney as a causal key mediator of ALI, which provides a potential therapeutic target for this specific interorgan crosstalk of AKI to ALI.

Funding: Government Support - Non-U.S.

TH-PO088

IL-22 Secreted from Proximal Tubule Cells Regulates Cell Fate During AKI

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Background: Acute kidney injury (AKI) occurs in ~13% of hospitalized patients and is associated with a fourfold increase in mortality. Proximal tubule cells (PTCs) are key to the outcome of AKI as they are the most sensitive cells to AKI and respond by secreting a number of inflammatory and/or pro-reparative cytokines. Interleukin-22 (IL-22) is an IL-10 family cytokine produced after tissue injury. IL-22 is secreted exclusively by immune cells subsets, mainly T cells, while its receptor is expressed on epithelial cells, such as PTCs. Functionally, IL-22 acts as a double-edged sword, with both protective and pathological functions in kidney injury. Here we elucidated the source of IL-22 in the kidney and its physiological function in nephrotoxic injury.

Methods: Patient biopsies were obtained as part of standard clinical practice. IL-22 RNA was detected by RNAScope in situ hybridization staining. IL-22 protein was detected by injecting mice with the secretion inhibitor brefeldin A and immunofluorescence staining. Nephrotoxic AKI was induced by administration of aristolochic acid (AA) or cisplatin in 8 to 12-week-old male wild-type (WT); IL-22 globally knockout mice (IL-22KO), and kidney specific IL-22 receptor knockout (Six2:IL-22RA1fl/fl, IL-22DPT). Rag1 knockout mice were used as an immune deficient model.

Results: RNAScope staining revealed that injured PTCs were a source of IL-22 in both human and mouse AKI. Under basal conditions, no RNA or protein expression of IL-22 was observed in the kidneys. In patient biopsies and all kidney injury models, PTCs stained positive for IL-22 RNA and protein. Urinary IL-22 was 10x higher than serum levels following AKI. Immune deficient Rag1KO mice, lacking mature T and B cells, produced similar urinary IL-22 concentration compared to WT mice. Next, we analyzed the role of IL-22 in nephrotoxic kidney injury by injuring IL-22KO and IL-22DPT mice with cisplatin or AA. Both IL-22KO and IL-22DPT mice had reduced markers of DNA damage and cell death following injury, as well as increased survival and improved kidney function compared to WT.

Conclusions: PTCs represent the first epithelial cells found to express IL-22 and are the main contributors to urinary IL-22. Blocking IL-22 or deletion of the IL-22 receptor prevents PTC cell death and restores kidney function.

TH-PO089

Shiga Toxin Downregulates ERG Protein in Endothelial Cells and Impairs Angiogenesis

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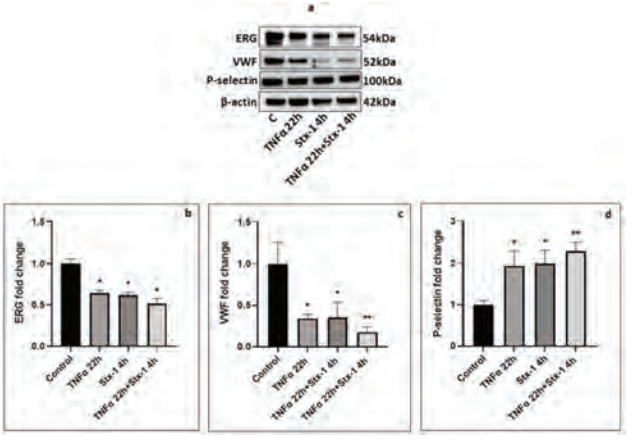
Background: Shiga toxin (Stx) activates inflammatory signaling, leading to vascular dysfunction and pro-thrombotic tissue microenvironment. Stx can trigger enterohemorrhagic hemolytic uremic syndrome (HUS)--thrombocytopenia, hemolytic anemia, and AKI, most often in children, and may require dialysis. Damage may occur in GI tract, pancreas, brain and cardiovascular system, with death in 2-5%. Typical HUS is a thrombotic microangiopathy with endothelial cell (EC) injury and platelet fibrin thrombus formation in glomerular arterioles and arterioles of other affected organs. To elucidate microangiopathy mechanisms, we examined in human ECs the regulation of the platelet adhesion proteins P-selectin and von Willebrand factor, along with the downregulation of erythroblast transformation-specific transcription factor (ERG), a key regulator of angiogenesis and megakaryocyte development.

Methods: von Willebrand Factor (VWF), P-selectin, and ERG levels were determined using immunofluorescence and western blot (WB) in human umbilical endothelial cells (HUVECs). HUVECs treated with tumor necrosis factor-alpha (TNF), Stx-1 or both, compared to normal controls. Capillary morphogenesis on Matrigel was performed in HUVECs treated, for 22 hours with TNF, Stx-1, or both, or treated 4 hours with Stx-1 alone or in combination with TNF for 22 hours.

Results: Stx-1 significantly reduced ETS transcription factor (ERG) and VWF expression on HUVECs, but upregulated P-selectin expression. ERG level decreased with Stx-1 alone or in combination with TNF, in the nuclear, perinuclear and cytoplasmatic regions. Stx-1 reduced capillary morphogenesis, while Stx-1-TNF combined treatment reduced capillary morphogenesis still further.

Conclusions: In the presence of Stx-1 or TNF or both treatments, ECs were activated, expressing higher levels of P-selectin and lower levels of VWF. Our findings, further, provide evidence that Stx-1 downregulates ERG, repressing angiogenesis *in vitro*.

Funding: NIDDK Support



WB of ERG, VWF and P-selectin with TNF-α or Stx-1 or both, cf. normal confirmed findings by immunofluorescence.

TH-PO090

Altered Signaling Pathways in ZSF1 Rats with AKI and Metabolic Disease

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Background: Acute kidney injury (AKI) is a common cause of kidney failure and mortality. No treatments are approved for AKI. We reported at ASN in 2022 (TH-PO088) that obese and diabetic ZSF1 rats subjected to ischemia-reperfusion injury (IRI) exhibit more severe renal function decline and slower renal function recovery relative to lean non-diabetic rats. To further understand the molecular mechanisms underlying the observed phenotypes, RNA-Seq and pathway analysis were performed.

Methods: RNA-Seq was conducted in obese and lean rat kidneys (n=4-6 each) collected at 24 hours (acute phase of AKI) or 7 days post IRI (repairing phase of AKI). Control group included rats without surgery and sham surgery. Pathway enrichment analysis for the differentially regulated genes was carried out using KEGG and Ingenuity Pathway Analysis (IPA). Enrichment *p*-values were adjusted for multiple hypothesis testing using the Benjamini-Hochberg method (p values < 0.05). Further, the correlation analysis was performed to study the potential association between the plasma creatine levels and the expression level of differentially expressed genes.

Results: Principal component analysis showed that the transcriptomic profiling data from RNA-seq was clustered into three distinct groupings: (1) Obese/IRI 24 h, (2) Lean/IRI 24 h and (3) rest of the groups (Lean/IRI/7d, or Obese IRI/7d or control groups). We observed that 509 and 180 genes were significantly dysregulated in obese vs lean rats at 24 hours and 7 days post IRI, respectively. Pathway analysis revealed profound downregulation of the *de novo* NAD synthesis related tryptophan metabolism pathway and activation of proinflammatory interleukin-17 (IL-17) signaling pathway at 24 hours post IRI. Interestingly, IL-17 signaling pathway remained significantly activated even at 7 days post IRI. The expression of genes in the IL-17 pathway correlated with plasma creatinine levels.

Conclusions: Our study suggests *de novo* NAD synthesis and IL-17 as potential pathways involved in AKI progression and highlights novel therapeutic approaches for AKI.

Funding: Commercial Support - Johnson & Johnson

TH-PO091

Renoprotective Effect of Tamm-Horsfall Protein in Crystalline Nephropathy

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Background: Tamm-Horsfall protein (THP) has an immunomodulatory role in the kidney. Our hypothesis is that the immunomodulatory function of THP is impaired in acute kidney injury (AKI) induced by crystalline nephropathy, and the exogenous administration of THP can play a renoprotective role in the disease.

Methods: Eight weeks old C57BL/6J mice were randomly allocated into four groups: 1. Control (saline 0.9%,i.p); 2. THP (exogenous THP–5µg/animal, single injection i.p); 3. NaOx (sodium oxalate–9mg/100g of body weight, single injection i.p); 4. NaOx administration and THP treatment. The animals were placed in metabolic cages for 24 hours before euthanasia and organ harvest. The results presented as mean ± S.D. were analyzed by two-way ANOVA and a Bonferroni post hoc test using GraphPad Prism software. $p<0.05$ was considered statistically significant.

Results: Treatment with exogenous THP alone did not change any parameter analyzed. Urinary THP excretion was decreased in the NaOx group [(arbitrary units) NaOx:100.1±20.2 vs. Control:195.2±7.9, p=<0.0001] and the co-treatment with exogenous THP prevented that change [(arbitrary units) NaOx+THP:169.3±31.8 vs. NaOx:100.1±20.2, p=0.0002. Interaction: p=0.0012]. Using immunofluorescence imaging, we observed that the treatment with NaOx induced THP clusters formation in the tubular lumen, which was prevented by concomitant with exogenous THP. Treatment with NaOx significantly increased mRNA expression for KIM-1, Ki67, MCP-1, TNFα, IL-1β, and IL-6, consistent with kidney injury. Co-treatment with exogenous THP prevented these changes (Fold change from control for NaOx+THP vs. NaOX, respectively): KIM-1 [95.2±121.7 vs. 730.0±182.5, p=<0.0001. Interaction p=0.0001], Ki67 [2.0±1.0 vs. 5.7±1.7, p=0.0001. Interaction p=0.0006], MCP-1 [1.9±1.8 vs. 8.2±3.8, p=0.0008. Interaction p=0.0030], TNFα [1.3±0.7 vs. 4.0±2.2, p=0.0087. Interaction p=0.0216], and IL-6 [5.4±7.5 vs. 84.4±46.2, p=0.0002. Interaction p=0.0010].

Conclusions: Our results indicate that exogenous THP may have a renoprotective effect on nephropathy crystalline-induced AKI.

Funding: Government Support - Non-U.S.

TH-PO092

Ischemia-Reperfusion-Mediated Kidney Injury Is Attenuated in a New Complement 5 Knockout Model

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Background: Acute kidney injury (AKI) affects over 13 million people each year around the world due to renal injury caused by ischemia. Additionally, 70% of transplanted kidneys are sourced from deceased donors, and organs are transported in static cold storage (CS) to maintain tissue viability, with the consequence of subjecting the kidney to ischemic conditions. Renal ischemia has been previously attributed to the aberrant activation of the complement system during AKI and transplant. The terminal cascade begins with the cleavage of complement 5 (C5) and drives downstream membrane attack complex (C5b-9) formation, but the role of this terminal pathway during renal ischemia is not fully understood.

Methods: In this preliminary study, we developed a novel C5 knockout (C5KO) rat model via CRISPR/Cas9 deletion of C5 exon 3. Furthermore, C5KO Lewis rats were introduced in a model of renal ischemia-reperfusion (I/R) via 40-minute bilateral clamping of the renal vessels and right nephrectomy. Animals were sacrificed day 1 post-procedure and characterized in terms of arterial blood gases/chemistry, mitochondrial respiration, and fluorescence activated cell sorting (FACS).

Results: We have observed a fertile animal with normal mitochondrial function and no health concerns. I/R resulted in significant elevation of serum creatinine (SCr) and blood urea nitrogen (BUN) in C5+/+ rats compared to sham (n=4 per group; p=0.0004 and 0.0019, respectively). This effect was attenuated by C5-/- for SCr (n=4; p=0.005) and BUN (n=4; p=0.0223). C5+/- also significantly decreased SCr (n=4; p=0.0165) after I/R when compared to C5+/+, but not BUN.

Conclusions: Knockout (or partial knockout) of complement component C5 results in a reduction in SCr and BUN during I/R compared to wild-type, suggesting that targeting C5 during kidney injury may confer a protective effect. This model may be useful in future studies focused on the role of C5 during AKI or CS+Tx.

Funding: NIDDK Support

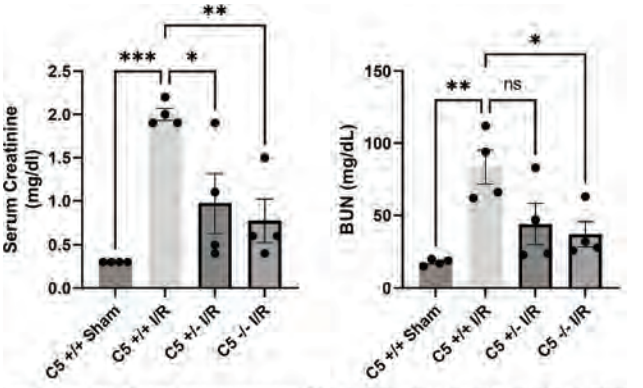

Fig. 1. Knockout of complement component C5 attenuates renal ischemia-reperfusion injury in Lewis rats. Data are shown as the mean +/- SEM. *p<0.05; **p<0.005; ***p<0.0005.

TH-PO093

Caveolin-1 Protects Against AKI via Regulating Endoplasmic Reticulum Stress

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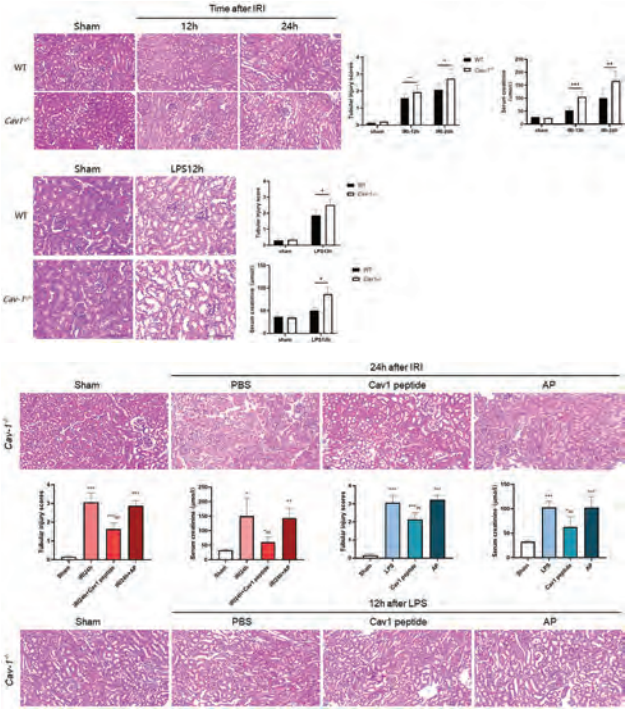
Background: Acute renal injury (AKI) is a serious medical condition characterized by a rapid loss of renal function. Recent evidence has suggested that endoplasmic reticulum (ER) function is important for protein homeostasis (‘proteostasis’) in the kidney, and that ER stress is a component of acute kidney injury. Caveolin-1 (Cav1), a multifunctional membrane protein, is the main component of caveolae on the plasma membrane. Caveolae serve as a platform to regulate stress responses, cellular endocytosis, and signal transduction. Previous studies have shown that the expression of Cav1 was increased in AKI models induced by ischemia-reperfusion and gentamicin. However, the crucial role of Prdx1 in AKI remains unclear.

Methods: Cav1-deficient mice were used to determine its function and potential mechanisms in AKI.

Results: In ischemic-reperfusion-induced AKI mice, a significant increase in the expression of Cav1 in kidney tissue was observed. Similar observations were also obtained in the lipopolysaccharide (LPS)-induced AKI mouse model. Likely, the expression of Cav-1 was increased in patients with AKI. Cav1 deficiency worsened renal function and caused more tubular injury in AKI induced by ischemia-reperfusion and LPS. Furthermore, i.p. injection of Cav1 peptide in *Cav1*$^{-/-}$ mice improves kidney function and attenuates kidney tubular injury in ischemic-reperfusion and LPS-induced AKI mice. Additionally, knockout of Cav1 aggravated endoplasmic reticulum stress and apoptosis in primary renal tubular epithelial cells.

Conclusions: Our results revealed that Cav1 may play a protective role in AKI by regulating ER stress, thereby identifying a novel and important therapeutic target for AKI.



TH-PO094

Clathrin-Mediated HMGB1 Endocytosis Promotes Acute Kidney Ischemia-Reperfusion-Induced Lung Injury

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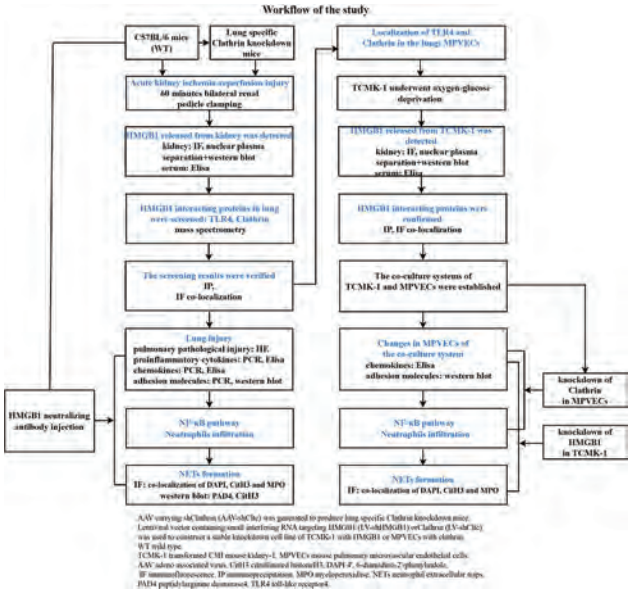
Background: Acute kidney injury (AKI) further increases mortality when combined with acute lung injury (ALI). Blockade of high mobility group box1 (HMGB1) may reduce AKI induced ALI. However, the potential molecular mechanisms in kidney-lung crosstalk after AKI remain elusive. We hypothesized that circulating HMGB1, released form ischemia-reperfusion (I/R) injured kidney, enters the lung cells and promotes AKI induced ALI by modulating neutrophil extracellular traps (NETs) formation.

Methods: Workflow of the study is shown in Fig.

Results: Analysis of cytokines and chemokines and lung histology revealed increased lung inflammation and injury following kidney I/R. Serum HMGB1 level increased gradually with the continued extracellular release of HMGB1 from kidney cells following the extension of I/R time. The interaction of clathrin, screened by mass spectrometry, with HMGB1 and its receptor TLR4 in lung endothelial cells was confirmed by co-IP and IF co-localization, and the lung specific knockdown of clathrin decreased lung inflammation and injury induced by kidney I/R in mice. Increased expression of PAD4 and CitH3 and the co-localization of CitH3 and MPO suggested that kidney I/R induced NETs formation in lung. Blockade of HMGB1 by neutralizing antibody in vivo and knockdown of HMGB1 in vitro inhibited NETs formation and ameliorated AKI induced ALI.

Conclusions: HMGB1 released from I/R kidney promotes AKI-induced ALI in mice by modulating NETs, and clathrin-mediated endocytosis is required for HMGB1-TLR4 to enter lung endothelial cells and regulate neutrophils infiltration. Induced NETs formation leads to lung injury that could be rescued by HMGB1 neutralizing antibody, suggesting that targeting NETs and the HMGB1 pathway might extend effective therapeutic strategies to minimize AKI-induced ALI.



AAV carrying shClathrin (AAV-shClic) was generated to produce lung specific Clathrin knockdown mice.
Lentiviral vector containing small interfering RNA targeting HMGB1 (LV-shHMGB1) or Clathrin (LV-shClic) was used to construct a stable knockdown cell line of TCMK-1 with HMGB1 or MPVECs with clathrin.
WT wild type.
TCMK-1 transformed CMI mouse kidney-1. MPVECs mouse pulmonary microvascular endothelial cells.
AAV adeno-associated virus. CitH3 citrullinated histone H3. DAPI 4', 6-diamidino-2'-phenylindole.
IP immunoprecipitation. MPO myeloperoxidase. NETs neutrophil extracellular traps.
PAD4 peptidylarginine deiminase4. TLR4 toll-like receptor4.

TH-PO095

Endothelial Cells Regulate Post-Ischemic Kidney Repair Through PHD/HIF-Dependent Hyperglycolysis

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Background: Recently, we showed that inhibiting the oxygen-sensing molecule prolyl hydroxylases (PHDs) controls human endothelial cell (EC) metabolism and angiogenic ability. However, in the context of acute kidney injury (AKI), little is known about the functions of endothelial PHDs. Here, we used a genetic approach in conjunction with scRNA-seq to investigate the roles of endothelial PHDs in post-ischemic kidney repair.

Methods: To delete PHD1, PHD2, and PHD3 in ECs, VECadherin (Cdh5)-CreER transgenic mice were crossed to mice carrying conditional PHD1, PHD2, and PHD3 alleles, generating *PHD* ^{TiEC} mice. For our loss of function studies, we generated mice that lack the constitutive HIF-1β (*ARNT*) in ECs (*ARNT* ^{iEC}). Ischemia-reperfusion injury (IRI) was induced by uni-/bilateral renal artery clamping, and tamoxifen treatment was started at day 1 post IRI, followed by analysis at day 14.

Results: Compared to *Cre*$^{-}$ controls, day 14 post IRI kidneys of *PHD* ^{TiEC} showed significant upregulation of profibrotic genes *Loxl2, Tgfβ1,* and *Acta2,* increased collagen deposition (n=6-8, p≤0.05), higher tubular injury, and reduced capillary density. Further, *PHD* ^{TiEC} showed a 26% reduction in glomerular filtration rate than *Cre*$^{-}$ controls (n=7, p≤0.01). Suppression of post-ischemic EC-HIF signaling in *ARNT* ^{iEC} mice ameliorated kidney injury and fibrosis assessed by similar analyses as indicated above (n=6-7, P≤0.5). scRNA-seq analysis of the day 14 post-IRI kidney revealed a hyperglycolysis signature in the medullary EC of *PHD* ^{TiEC} mice compared to *Cre*$^{-}$ mice. Among the significantly upregulated glycolytic genes was *Slc16a3,* a HIF target gene that encodes the lactate transporter MCT4, known to mediate lactate efflux. Notably, post-ischemic administration of the dual MCT4/MCT1 inhibitor Syrosingopine (Syro) attenuated kidney injury in *PHD* ^{TiEC} mice (n=4, P≤0.5). In vitro, Syro or MCT4 siRNA suppressed the hypoxia/reoxygenation+IL1-β (1ng/ml) induction of EC-adhesion molecules VCAM1 and ICAM1, leading to reduced monocyte adhesion to human EC (n=3, P≤0.5).

Conclusions: In summary, endothelial PHDs regulate post-ischemic kidney repair through HIF-dependent mechanisms. Furthermore, our studies identify the endothelial MCT4 as a potential target for renoprotective therapies.

Funding: NIDDK Support

TH-PO096

Hedgehog Interacting Protein (Hhip) Deficiency in Endothelial Cells Prevents Ischemia Reperfusion-Induced Renal Tubular Cell Injury Through Inhibition of NF-KB Signaling

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Background: Acute kidney injury (AKI) caused by renal ischemia reperfusion (R I/R) is a major clinical issue that is lacking viable therapies, and its underlying mechanisms are poorly understood. Given the important role of hedgehog interacting protein in chronic kidney disease-related renal fibrosis, we investigated whether Hhip knockout in endothelial cells (EC) (Hhip^{EC} KO) could prevent R I/R-induced kidney injury in vivo and in vitro.

Methods: Male Hhip^{EC} KO and control Hhip$^{fl/fl}$ mice at 10-weeks old were subjected to 45 minutes of the unilateral R I/R or sham surgery, both with contralateral nephrectomy. The AKI time-course was examined at Day1, Day 3, Day7 and Day 21. In vitro, naïve renal proximal tubular cells (IRPTCs) exposed to the conditioned media harvested from mouse endothelial cell (mECs) with or without Hhip (siRNA) ± gentamicin treatment, were studied.

Results: Compared to the respective controls, R I/R mice (Hhip$^{fl/fl}$ and Hhip^{EC} KO) body weight loss (BW, g) occurred from Day 1 until Day 21, regardless of Hhip deficiency. In line with the AKI time course, Hhip$^{fl/fl}$-R I/R mice displayed kidney dysfunction marked by increased urinary albumin-to-creatinine ratio; tubular/endothelial cell injury and fibrosis as assessed by kidney morphological staining (Periodic Acid-Schiff, Masson's trichrome and Sirius Red) with enhanced cystatin C-, kidney-induced molecular 1-and TGFβ1- immunoexpression in their kidneys. Maladaptive and inadequate renal tubular damage repair was observed by enhanced vascular cell adhesion protein 1 and NF/kB (p50/p65) expression. In contrast, these changes were significantly ameliorated in the kidneys of Hhip^{EC} KO -R I/R mice. In vitro, naïve IRPTCs exposed to the conditioned media harvested from mECs treated with gentamicin (2.5mg/ml) had lower wound healing ability/capacity, higher cellular senescent activity and increased NF/kB expression. Those changes were largely prevented in naïve IRPTCs exposed to conditioned media harvested from Hhip KO mECs treated with gentamicin.

Conclusions: Our data suggest that Hhip knockout in endothelial cells prevented AKI-induced renal tubular injury. This action might be mediated, at least, in part, by inhibition of NF-KB signaling.

Funding: Government Support - Non-U.S.

TH-PO097

VEGF-R2 Signaling in Renal Stroma Exacerbates Post-AKI CKD Progression

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Background: A dire consequence of AKI is progression to CKD. AKI patients are at more than twice the increased risk of progressive CKD that leads to excessive morbidity and mortality. Understanding the mechanisms by which AKI progresses to CKD is essential for establishing a new therapeutic target since no established therapy to date is available for. Renal microvasculature, including pericytes and endothelial cells, are damaged in AKI, leading to recruitment of inflammatory cells which contributes to progression to CKD. It was recently shown that Platelet-derived growth factors (PDGFs) are predicted to signal via VEGF-R2, particularly in disease conditions. However, the functional implications of VEGF-R2 in the renal stroma, which gives rise to renal pericytes, in CKD remain poorly understood. This informed us an overarching hypothesis that renal stroma specific VEGF-R2 signaling dysregulates microvascular recovery and exacerbates post-AKI progression to CKD.

Methods: We generated genetic mouse models for renal stromal cells (RSCs)-specific loss-of-function of *VegfR2* with constitutively expressed Foxd1-Cre (*VegfR2*$^{RSC-/-}$) as well as tamoxifen inducible Foxd1-Cre (*iVEGF-R2*$^{RSC-/-}$) to interrogate timing specific role of *VegfR2* in renal stroma in AKI-to-CKD. CKD models induced either by a renal ischemia/reperfusion injury (IRI) or by low/dose repeated treatment of cisplatin were performed. Mice were monitored for the development of AKI and post-AKI CKD using serum chemistries and tissue analysis.

Results: We found that *VegfR2*$^{RSC-/-}$ mice have reduced inflammation and vascular injury after renal IRI and have reduced renal intertitial fibrosis after renal IRI as well as reduced interstitial lipid deposition. Consistently, *VegfR2*$^{RSC-/-}$ are protected against progression to CKD in a cisplatin CKD model. Mechanistically, *VegfR2*$^{RSC-/-}$ kidneys

have reduced expression of a pro-inflammatory signaling axis of Thrombospondin-1 (TSP1)/ CD148 and have increased expression of fatty acid metabolism associated genes contributing to the enhanced protection. Furthermore, *iVegfR2*$^{RSC-/-}$ mice are significantly protected against renal IRI.

Conclusions: These data suggest that VEGF-R2 signaling in renal stroma exacerbates renal IRI and its CKD progression as well as cisplatin CKD.

Funding: NIDDK Support

TH-PO098

Protective Mechanisms of Lymphangiogenesis During Kidney Injury

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Background: Lymphangiogenesis is demonstrated to be a protective response in multiple etiologies of kidney injury. As injury-related lymphangiogenesis is driven by the release of the growth factor VEGF-C by tubular epithelial cells, this signaling pathway is a candidate for future kidney therapeutics. However, the mechanisms by which kidney lymphangiogenesis protects the kidney against injury remain uncertain. Recent investigations in other organ systems have revealed lymphatic endothelial cells (LECs) secrete factors termed "lymphoangiocrine" molecules which directly promote protection against injury in surrounding tissues. Our hypothesis is that lymphangiocrine factors are also released by kidney LECs and convey protection against kidney injury.

Methods: We generated a conditional mouse model to promote lymphangiogenesis (*VegfcGOF*) through overexpressing VEGF-C in the kidney tubules using the Pax8-rtTA-TetOcre driver strain. The ischemia-reperfusion mouse model of acute kidney injury (IR-AKI) was performed on *VegfcGOF* mice and littermate controls and kidneys were collected 7 days post-injury. Kidneys were processed for standard histology, tissue clearing with 3D light-sheet imaging of the vasculature, and single-cell RNA sequencing.

Results: *VegfcGOF* mice demonstrate an expansion of lymphatic capillaries throughout the kidney cortex, which is further potentiated by IR-AKI. There is no baseline difference in BUN, creatinine, or blood pressure between *VegfcGOF* mice and littermate controls. At 7 days post-injury, kidneys demonstrate a similar level of peritubular capillary rarefaction, and expression of the injury marker *Kim-1*, however, *Vegfc*GOF mice have a reduction in a distinct set of previously identified genes (*Dcd2a, Sema5a,* and *Vcam1)* that signify proximal tubule epithelial cells (PTECs) which have failed to repair after injury. Additionally, the known cardiac lymphangiocrine factor Reelin (RELN) is expressed by kidney LECs during injury with its receptor integrinß1 (ITGB1) expressed in tubule epithelial and stromal cells.

Conclusions: Kidney lymphangiogenesis is robustly induced in the *VegfcGOF* mice without overt consequence to kidney function at baseline. In the setting of kidney injury, kidney LECs may promote successful repair of PTECs with RELN-ITGB1 signaling being a potential mechanism of this protective effect.

Funding: NIDDK Support, Private Foundation Support

TH-PO099

Renalase Ameliorates AKI by Altering Mitochondrial Function to Induce Cellular Repair Mechanisms

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Background: Renalase (RNLS) is a protein that activates kinases linked to survival and attenuates acute ischemic and cisplatin (CP)-induced kidney injury. We now study RNLS role in inducing changes in mitochondrial function to assist in survival and repair of injured tissue.

Methods: RNLS knockout (KO) and wild type (WT) mice were given CP at 15 mg/kg or vehicle control. Kidney mitochondrial structure was analyzed by electron microscopy (EM), and mitochondrial proteins were analyzed by immunoblotting, co-immunoprecipitation and patch clamp recording. The activities of complex I and II were evaluated in mitochondria isolated from kidneys of WT and KO with and without CP.

Results: Both RNLS and its receptor PMCA4b were detected in WT mitochondria by immunofluorescence and RNLS was localized to the inner mitochondrial membrane or matrix by pan-Expansion Microscopy. CP induced severe renal damage in RNLS deficient animals as evidenced by a 7.8-fold increase in plasma creatinine (KO 1.18 ± 0.29 mg/dL, n=13 vs WT 0.15 ± 0.03 mg/dL, n=14, $p<0.005$). By EM, WT kidney demonstrated decreased mitochondrial area (suggesting fission) and osmotic changes; in contrast mitochondria in RNLS KO were deficient in these activities. Cisplatin induced increased markers of mitophagy and stress in KO vs. WT; Parkin, p-AMPKα and p-AMPKβ were increased, OPA-1 expression was decreased. RNLS KO mouse kidneys exhibited reduced mitochondrial complex I and II activities as compared to WT ($p<0.005$ and $p<0.05$, respectively, n=5); recombinant RNLS rescued these activities in RNLS KO kidneys (n=3, $p<0.001$). Physiological recording of mitochondrial inner membranes of KO and WT animals showed that RNLS addition increased the conductance of the mitochondrial inner membrane.

Conclusions: RNLS alters mitochondrial morphology and function in response to renal injury. The absence of RNLS increases mitophagy, possibly *in lieu* of metabolic repair mechanisms during CP-AKI. These data suggest that RNLS modifies renal injury by encouraging metabolic repair mechanisms as opposed to mitochondrial removal via mitophagy.

TH-PO100

MAVS Modulates Inflammation and Apoptosis in Renal Ischemia-Reperfusion Injury

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Background: Mitochondria have a central role not only in the initiation of ischemia-reperfusion injury (IRI) but also are involved in recovery processes. Mitochondrial antiviral-signaling protein (MAVS) is a component of innate immunity, leading to cytokines production upon activation. Here, we characterize the role of MAVS in tubular epithelial cells during the various phases of IRI-induced AKI, and their relative importance to renal fibrogenesis.

Methods: We performed unilateral renal artery clamping for 50 minutes in wild-type mice (C57BL/6) and MAVS knockout mice and assessed the pathology at the acute kidney injury phase (Day2, Day5) and chronic phase (Day20).

Results: Compared with their wild-type counterparts, MAVS knockout mice showed less urine protein and tubular injury scores, tubular epithelial cell apoptosis in the acute stage of AKI, and attenuated fibrosis in the late stage. Immunostaining revealed that MAVS is mainly expressed in the renal tubules in the physiological state, and strongly expressed in the injured proximal tubules after renal ischemia-reperfusion. Transient transfection of MAVS in HEK293T cells increased TRAF6 expression, nuclear translocation of NFκB, and phosphorylation of MAPK (p38, ERK, JNK), suggesting that it activates inflammation and apoptosis. Moreover, MAVS inhibition resulted in less mitochondrial reactive oxygen species and pro-inflammatory cytokines production after hypoxia.

Conclusions: Collectively, we identify MAVS as a pro-inflammatory contributor to renal tubules in the early phase of AKI and it might be a therapeutic target.

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TH-PO101

Inhibition of Retinoic Acid Signaling in Proximal Tubules Protects Against AKI by Enhancing Kim1-Dependent Efferocytosis

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Background: Retinoic acid receptor (RAR) signaling is activated in proximal tubules (PTs) and macrophages (Møs) after IRI-AKI, and systemic inhibition of RARs increases Mø-dependent injury after IRI-AKI. It is unknown whether RARs are activated in other forms of AKI, and the functional role of PT RAR signaling after AKI remains unknown.

Methods: GSEA for RAR targets enriched in a snRNA seq database from patients with sepsis-associated AKI (SA-AKI) (Hinze, 2022). RARE-LacZ (RAR reporter mice); PEPCK-CRE; R26R-dominant negative RAR (PT-DN RAR), bilateral IRI- or rhabdomyolysis-AKI (rhabdo-AKI). Injury and RARE-LacZ localization evaluated by BUN, QRT-PCR, LacZ staining, and IF. Renal Møs by RNA seq and FACS; PT proliferation, metabolic activity, and Kim-1 function in primary PTs. Efferocytosis by quantifying PT apoptosis +/- a lysosome inhibitor, Bafilomycin, after IRI-AKI.

Results: These is enrichment for RAR targets in PTs from patients with SA-AKI. The same gene set was upregulated in mouse kidneys after rhabdo-AKI. In contrast to IRI-AKI where reporter activation was transient, there was prolonged activation of RARE-LacZ in PTs throughout the kidney after rhabdo-AKI. Inhibition of PT RAR signaling in PT-DN RAR mice protected against acute tubular injury (ATI) in rhabdo-, and to a lesser extent, IRI-AKI. This was unexpectedly associated with increased Kim-1 expression; PT de-differentiation, proliferation, and metabolic reprogramming (increased glycolysis and ox phos), in PT-DN RAR kidneys and cultured PTs. Kim-1-dependent uptake of oxidized LDL was increased in PT-DN RAR PTs, and there was reduced PT apoptosis after IRI- and rhabdo-AKI. This was reversed by Bafilomycin treatment, indicating that decreased apoptosis is dependent on PT efferocytosis. Consistent with increased efferocytosis as a protective mechanism in AKI, there was also a reduction in pro-inflammatory renal Møs after IRI-AKI in PT DN RAR mice.

Conclusions: These findings indicate that there is extensive activation of PT RAR signaling in experimental and human AKI, and that inhibition of RAR signaling in PTs protects from AKI by promoting PT de-differentiation and enhancing Kim-1 dependent efferocytosis. This suggests that activation of RAR signaling in PTs after AKI is a compensatory response that reestablishes PT differentiation and function after ATI.

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TH-PO102

Indoxyl Sulfate Influences Susceptibility of Proximal Tubule Epithelial Cells to Gentamicin Cytotoxicity

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Background: Patients with chronic kidney disease (CKD) are at increased risk of acute kidney injury (AKI) following exposure to nephrotoxic medications, and there is a critical need to understand the molecular pathogenesis of acute-on-chronic kidney disease. CKD leads to systemic bioaccumulation of uremic solutes, such as the tryptophan metabolite indoxyl sulfate (IS), which have direct effects on the kidneys that promote CKD progression. The objective of this study was to the determine the effect of IS on proximal tubule epithelial cell (PTEC) and test the hypothesis that IS exposure increases susceptibility to gentamicin-induced cytotoxicity.

Methods: Cultured immortalized PTECs (HK-2 cells) were treated with IS and gentamicin at varying concentrations, and cell viability was assessed using the Trypan blue and MTT assays. TMT proteomic profiling with IBAQ quantitation and gene set enrichment analysis was used to identify differentially abundant proteins and pathways that are dysregulated by IS exposure and could mediate the cytotoxic effects of IS influence susceptibility to gentamicin cytotoxicity.

Results: Treatment with 100 μM IS had a modest cytotoxic effect (15-20% cell death after 24 hours). Proteomic profiling identified 10,030 proteins, and IS treatment induced changes in the abundance of 60 proteins, including increased expression of kidney injury molecule-1 and VCAM-1 and down regulated mitochondrial complex V ATPase subunits and mitochondrial ribosomal proteins. GSEA found that there was a decrease in mitochondrial translation following IS exposure. These results suggest that IS is directly cytotoxic to PTECs and negatively impacts mitochondrial dynamics and cellular respiration. Pretreatment with IS increased susceptibility of HK-2 cells to 10 mM gentamicin cytotoxicity as assessed by Trypan blue staining (30.1% +/- 6.4% cells stained positive without IS pretreatment vs 46.1 +/- 3.1% with IS pretreatment, $p < 0.001$), and this effect was confirmed using the MTT assay.

Conclusions: IS induces modest cytotoxicity to PTECs and increases their susceptibility to gentamicin cytotoxicity. These effects are associated with downregulation of mitochondrial gene translation that could reflect broad perturbations in mitochondrial dynamics and impaired cellular respiration.

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TH-PO103

Comparative Effects of Cyclosporine and Voclosporin on Primary Human Proximal Tubular Epithelial Cell (PTEC) Gene Expression

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Background: The development of calcineurin inhibitors (CNIs) dramatically changed the face of transplantation, with the majority of solid organ transplant patients prescribed CNI-based therapeutics. Cyclosporine, a CNI that complexes with cyclophilin to competitively inhibit calcineurin phosphatase activity, has significant side effects with chronic nephrotoxicity the primary clinical concern. Cyclosporine related toxic effects include glomerulosclerosis, thrombotic microangiopathy and tubular vacuolization. Voclosporin, a recently approved CNI for treating adults with active lupus nephritis on a background of immunosuppression, is structurally similar to cyclosporine, with improved binding to calcineurin, higher potency and better tolerability.

Methods: To compare the tubular effects of these two CNIs, we exposed cultures of primary human PTEC in either standard 2D tissue culture or when grown in a 3D kidney microphysiological system (MPS).

Results: Exposure to increasing concentrations (0-10 μM) of cyclosporine or voclosporin [HJ1] revealed only minimal toxicity after 48 hr. in 2D culture. Similarly, exposure of MPS to 10 μM voclosporin or cyclosporine for 48 hr. did not significantly increase KIM-1, a urinary biomarker of acute kidney injury, in MPS effluents. To further differentiate these two CNIs, we performed bulk RNAseq analysis from the MPS studies and observed 443 differentially-expressed genes in the cyclosporine-treated MPS versus 45 genes in the voclosporin cohort. Biological process gene ontology analysis revealed 26 significant pathways in the cyclosporine group and none in the voclosporin group with the majority related to cell cycle processes. PTEC were labeled with a GFP-cytochrome C biosensor to monitor mitochondrial responses. Treatment with either CNI at 1 μM for 48 hr. revealed no changes whereas treatment with 10 μM of either CNI resulted in modest changes in mitochondria as measured by signal intensity and complexity of the network.

Conclusions: Ongoing studies include longer term CNI exposures and effects of CYP3A5 genotype as this enzyme is polymorphic, expressed in the kidney and produces isozyme-specific metabolites of cyclosporine. Our results to date support differential effects of voclosporin versus cyclosporine on PTEC gene expression.

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TH-PO104

Role of KIM-1 and TBX1 in AKI to CKD Transition

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Background: Acute kidney injury (AKI) affects 20% of hospitalized patients. The most common cause is renal ischemia-reperfusion injury (IRI). Patients who survive mild-to-moderate AKI often have complete renal recovery, but severe AKI can progress to the development of chronic kidney disease (CKD). Kidney Injury Molecule-1 (KIM-1) is a transmembrane receptor expressed by proximal tubular epithelial cells (PTECs) during injury. Notwithstanding that, severe AKI leads to persistent KIM-1 expression and drives renal fibrosis. Using microarray analysis, we identified T Box-1/TBX1 as a potential KIM-1 regulated gene that may mediate its maladaptive effects during severe AKI.

Methods: KIM-$1^{+/+}$ and KIM-$1^{-/-}$ C57BL/6 mice were subjected to sevre unilateral ischemia reperfusion injury (UIRI) by clamping the renal artery for 55 minutes. Kidneys were isolated after 7 and 42 days of reperfusion to assess histology and, markers of injury and fibrosis. RNA sequencing of kidneys from the KIM-$1^{+/+}$ and KIM-$1^{-/-}$ mice after 55 min UIRI was performed. In order to assess the fibrogenic potential of TBX1 *in vivo*, Tamoxifen-inducible PTEC-specific TBX1 knockout ($TBX1^{pKO}$) mice were generated. *In vitro* model for gain of TBX1 function was created by using primary PTECs isolated from murine cortical kidney subjected to biochemical and functional assays.

Results: Compared to the ipsilateral kidneys from KIM-$1^{-/-}$ mice, the kidneys from KIM-$1^{+/+}$ mice were markedly shrunken and fibrotic at 42 days after UIRI. We also observed a significant upregulation of mRNA encoding a panel of pro-inflammatory cytokines and growth factors at both 7 and 42 days after UIRI in KIM-$1^{+/+}$ kidney compared to KIM-$1^{-/-}$ kidneys. Primary PTECs isolated only from KIM-$1^{+/+}$ kidneys significantly increased the chemotaxis of Raw macrophages whereas KIM-$1^{+/+}$ PTECs became arrested at the G2/M phase of the cell cycle, and adopted a senescent phenotype. Conditional silencing of KIM-1 was associated with a significant reduction in TBX1 expression at both mRNA and protein levels. TBX1 expression profile positively correlated with fibrosis in KIM-$1^{+/+}$ mice exposed to severe IRI. TBX1 enhanced PTEC migration, acquisition of a senescence phenotype, production of extracellular matrix and profibrotic factors.

Conclusions: Our results suggest that sustained KIM-1 expression following severe AKI may drive murine kidney fibrosis due to activation of TBX1.

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TH-PO105

Mass Spectrometry Imaging Reveals Metabolic Switch to Glycolysis in Proximal Tubules During AKI

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Background: Aberrant glucose metabolism has been reported in the pathogenesis of acute kidney injury (AKI). *In vitro* studies of proximal tubular cells showed damaged cells that were unable to fully recover underwent a metabolic switch to glycolysis during the AKI to CKD transition. Additionally, *In vivo* data of AKI murine models also demonstrated upregulated expression of rate-limiting enzymes of glycolysis in mice with AKI. However, changes in energy metabolism under AKI in human patients remain an enigma. We performed a comprehensive analysis of metabolites in proximal tubules of kidney biopsies from AKI patients vs healthy reference tissues (HRT).

Methods: A matrix-assisted laser desorption/ionization (MALDI)-mass spectrometry imaging (MSI) platform was employed to characterize the metabolic profile in kidney biopsies from AKI patients (n = 6) and HRT (n = 6) *in situ* (spatial resolution: 20 μm). SCiLS Lab was used for raw data processing. METASPACE was applied for metabolite annotations at 20% FDR. Univariate (*t*-test) and multivariate (e.g., PCA and PLS-DA) analyses were performed to compare metabolic profiles in kidney biopsies between AKI and HRT.

Results: In total, 1797 *m/z*'s were annotated as different metabolite species in human kidney biopsies. Specifically, seven metabolites from the tricarboxylic acid cycle and 10 intermediates from glycolysis were measured. Multivariate analyses showed clearly separated clusters between AKI and HRT biopsies, suggesting aberrant metabolic changes in AKI kidneys. Univariate analysis revealed that 361 metabolites were significantly different in proximal tubules of AKI compared to HRT. Particularly, several glycolytic intermediates including lactic acid ($P = 0.0251$), 2-phosphoglycerate ($P=0.0152$), and fructose-6-phosphate ($P=0.0013$) were found to accumulate in proximal tubules of AKI renal biopsies, suggesting the potential role of metabolic switch to glycolysis in the kidney with AKI.

Conclusions: These findings demonstrate an accumulation of glycolytic intermediates in proximal tubules of AKI kidney biopsies which may play an important role in the pathogenesis of AKI. Our human kidney biopsy data reveal a potential metabolic switch to glycolysis in damaged proximal tubular cells during the AKI to CKD transition.

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TH-PO106

Mouse Model of Local Iron Homeostasis Disruption in AKI

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Background: Iron plays an essential role in many critical biological processes including oxygen transport, cell proliferation, and regeneration. However, when iron is present in excess, it is toxic to the kidneys. Acute kidney injury (AKI) and iron-related disorders are associated with significant morbidity and mortality. Dysregulation of iron homeostasis plays an important pathogenic role in kidney disease, but limited data are available on successful iron targeting therapies in AKI. Ferroportin (FPN) is expressed in the kidney and is known as the iron exporter and central regulator of iron metabolism, but its function in the pathogenesis of AKI still unclear. Through this work, we will determine whether the disruption of local iron homeostasis by selective depletion of FPN in renal proximal tubules cells (PTCs) alters the response to AKI.

Methods: We are testing this hypothesis by generating conditional knockout mice to target iron trafficking proteins and determine their roles in AKI and the molecular and genetic mechanisms regenerating of PTCs. We selectively expressed Cre in PTCs with a Pepck promoter (PepcK-Cre) and confirmed deletion with a red-green reporter (mT/mG) to produce FPNf/f; Pepck-cre; mT/mG (FPN-KO) mice.

Results: FPN-KO mice were generated and deletion of FPN was confirmed. Mutant mice showed no gross morphology or renal phenotype. FPN-OK and controls mice were subjected to either folic acid or renal ischemia-reperfusion models. Blood and tissue

samples were collected at 0, 2, 7, and 28 days after injury. Kidney function and iron deposition were measured. Histology, immunohistochemistry, RNA isolation, and immunoblot analysis and qualification were performed. Data indicate that FPN-KO mice subjected to AKI models developed pronounced iron deposition in PTCs. Damaged tubules lead to worsening interstitial fibrosis, ferroptosis, and failure to recover and regenerate injured tubules compared to controls.

Conclusions: Despite the essential role in life, excessive iron is toxic due to its ability to generate reactive oxygen species. Disrupting iron trafficking in PTCs by manipulating the expression of FPN increases AKI severity and impairs recovery. Understanding the molecular mechanisms underlying the regulation of local iron homeostasis and ferroptosis may provide therapeutic strategies for progressive kidney disease and ferroptosis-associated disorders.

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TH-PO107

Proximal Tubular-Specific Cell Cycle Arrest Ameliorates AKI in Mice

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Background: Acute kidney injury (AKI) is a major medical and economic burden. Renal tubular epithelial cells are normally arrested in the G0 phase of the cell cycle (CC), but are rapidly entering the CC after AKI. Recent studies indicate that regulated CC is required for optimal regeneration following AKI. Cyclin D1 (Ccnd1) is essential for CC progression from G1- to S-phase. We characterized a proximal tubular (PT)-specific Ccnd1 knock-out (KO) and a siRNA-based Ccnd1 knock-down (KD) in a murine ischemia-reperfusion (IRI) model.

Methods: Tamoxifen (tam)-inducible proximal tubular Ccnd1 KO mice (Ccnd1flox/flox::Slc34a1CreERT2) underwent IRI surgery following vehicle (veh) or tam treatment. Serum creatinine/urea, histology, leukocyte infiltration, cell cycle phases, and fibrosis were assessed (2h, 1d, 3d, 7d, 14d, 28d after IRI; n=8 per group). A Ccnd1-siRNA KD was established in vitro (primary tubular epithelial cells) and in vivo (1nmol siRNA/g mouse; 24h before and at reperfusion) and evaluated by the abovementioned parameters on day 14 after IRI. To evaluate the underlying mechanism, RNAseq analysis of isolated PT (n=3) and MALDI-TOF-MSI of kidneys 1d after IRI (n=5) were performed.

Results: PT-specific Ccnd1 KO attenuated the functional decline of AKI (S-crea 312±74% vs. 142±11% (3d relative to 0d); p=0.036). KD mice showed a comparable outcome. At day 1 and 3 after IRI, KO kidneys had reduced histological damage (AKI score maximal 4; 1d: 2.26±0.13 vs. 1.84±0.11; p=0.028; 3d: 2.68±0.12 vs. 2.06±0.16; p=0.009). KO kidneys showed a 15-fold reduction in leukocyte infiltration (3d: 12.8±0.75% leukocytes/all cells vs. 0.81±0.14%; p<0.0001). At later time points after IRI (28d), KO mice showed no damage/regeneration benefit (histology and brush border staining). RNAseq analysis revealed a decreased expression of CC-associated genes in KO proximal tubules. Moreover, depletion of adenosine monophosphate was strongest in the cortex of WT kidneys.

Conclusions: Specific ablation of Ccnd1 in the proximal tubule or systemic antagonism of Ccnd1 reduced proliferation in the kidney after IRI. This was associated with reduced AKI injury at early time points after IRI in KO and KD models. Our data suggest a cell cycle-associated, energy-dependent mechanism of protection.

TH-PO108

Autophagy Inhibition Aggravates Renal Microvascular Injury Secondary to Ischemia-Reperfusion

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Background: Ischemia-reperfusion injury (IRI) is an integral component of kidney transplantation. Programmed cell death (PCD) of endothelial cells (EC) in peritubular capillaries (PTCs) post-IRI is a major predictor of long-term loss of renal function. We have shown that caspase-3-deficient mice show reduced PTC apoptosis post-IRI and preserved long-term renal function. Autophagy is a cellular stress response that protects against PCD. However, the precise role of PTC autophagy post-IRI remains unclear. Here, we characterize the dynamics of PCD activation and the effect of autophagy inhibition on the renal microvasculature post-IRI.

Methods: Transgenic GFP-LC3 mice were subjected to unilateral renal artery clamping for 30 minutes with contralateral nephrectomy. Mice were injected intraperitoneally with PBS or chloroquine (CHQ), an autophagy inhibitor, on the day of surgery and every day post-surgery until sacrifice. Mice were sacrificed 1, 2, 7, or 21 days post-IRI. Kidney function was assessed by measuring serum creatinine levels. Activation of Caspase-3-dependent apoptosis and necroptosis (pRIPK3) were measured by immunohistochemistry (IHC). Autophagy activation was evaluated by confocal immunofluorescence microscopy for GFP-LC3 puncta. PTC rarefaction, myofibroblast accumulation, and collagen deposition were assessed.

Results: IRI induced a specific pattern of apoptosis, necroptosis, and autophagy in PTCs. PTCs showed sustained apoptosis from day 1 to day 21 post-IRI, whereas necroptosis showed an early increase at days 1 and 2 with a rapid return to basal level at day 7. GFP-LC3+ autophagy puncta increased steadily until day 21 in PTCs. CHQ inhibited autophagic flux in PTC and worsened renal function with higher serum creatinine levels post-IRI 1 day. In the long term (21 days), microvascular rarefaction was significantly increased in the CHQ-injected group compared to the vehicle-treated group. This was associated with increased renal fibrosis, increased α-SMA, and collagen deposition within the PTC.

Conclusions: The results indicate that IRI induces progressive autophagy activation in PTC EC. Inhibition of autophagy aggravates renal dysfunction and increases microvascular injury, myofibroblast differentiation, and collagen deposition post-IRI.

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TH-PO109

Effect of Peroxidase Reductase 5 and Ferroptosis in Contrast-Induced AKI (CI-AKI)

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Background: Our previous study found the expression of urinary peroxidase reductase 5 (PRDX5) decreased significantly in CI-AKI patients by proteomics,and ferroptosis was involved in CI-AKI. The aim was to identify PRDX5 involved in the mechanism of ferroptosis in CI-AKI.

Methods: Human renal tubule epithelial cells (HK-2) were cultured and divided into control group, CI-AKI group (HK-2 cells were added 200 mg I/ml iodohexol for 12h), CI-AKI+ FeI group (HK-2 cells were added 200 mg I/ml iodohexol and ferroptosis inhibitor, 10μmol/L for 12h), PRDX5 overexpression group (PRDX5 overexpression plasmid was constructed), PRDX5 overexpression +CI-AKI group (PRDX5 overexpression HK-2 cells were added 200 mg I/ml iodohexol for 12h). The cell activity was determined by MTT assay. The expressions of ferroptosis related protein GPX4, SLC7A11 and ACSL4 were detected by western blot. Iron Assay Kit was used to measure intracellular iron. Mitochondrial ROS levels were detected by DCFDA/H2DCFDA fluorescent probe.

Results: Compared with control group, the cell proliferation rate of CI-AKI group slowed down significantly, while that of CI-AKI+ FeI group was increased, compared with CI-AKI group, (P<0.05). In terms of ferroptosis mechanism, compared with control group, the protein content of ACSL4, GPX4 and SLC7A11 in HK-2 cells in CI-AKI group was significantly increased (p<0.05), the protein contents of GPx4 and SLC7A11 were significantly decreased (p<0.05), the iron content was significantly increased (p<0.05), and the mitochondrial ROS level was significantly increased (p<0.05). After adding ferroptosis inhibitor, the above indexes were relieved (p<0.05). The expression of PRDX5 mRNA and protein in CI-AKI group was significantly decreased compared with control group (p<0.05), and that in PRDX5 overexpression group was significantly increased (p<0.05). Compared with CI-AKI group, PRDX5 overexpression+CI-AKI group increased cell proliferation rate (P<0.05). Compared with CI-AKI group, the expression of ferroptosis related protein ACSL4, GPX4 and SLC7A11 were significantly decreased (p<0.05), iron content was significantly decreased (p<0.05), and mitochondrial ROS level was significantly decreased (p<0.05) after overexpression of PRDX5.

Conclusions: Ferroptosis is involved in CI-AKI. PRDX5 has a protective effect on the mechanism of ferroptosis in CI-AKI.

TH-PO110

SIRT2 Regulates Cisplatin-Induced Endoplasmic Reticulum Stress Through Heat Shock Factor 1 Deacetylation

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Background: Nephrotoxicity is an important cisplatin-induced adverse reaction and restricts the use of cisplatin to treat malignant tumors. Endoplasmic reticulum (ER) stress is caused by the accumulation of misfolded proteins, and can be induced by cisplatin in the kidney. SIRT2, a nicotinamide adenine dinucleotide (NAD^+)-dependent deacetylase, is a member of the sirtuin family. In this study, we evaluated role of SIRT2 in cisplatin-induced ER stress.

Methods: To investigate the effect of SIRT2 on cisplatin-induced ER stress, we used SIRT2 knockout mice and human proximal tubular epithelial cells (HK-2 cells). We treated HK-2 cells with cisplatin (20 μg/mL) and administered cisplatin (20 mg/kg, i.p.) to mice to induce acute kidney injury. We evaluated the changes of ER stress and its signal mechanism.

Results: *In vivo* experiment, cisplatin administration was found to significantly increase the expressions of PRKR-like ER kinase (PERK), phosphorylation of eukaryotic translation initiation factor 2α (eIF2α), and the C/EBP homologous protein (CHOP) and caspase-12 in the kidneys of SIRT2-wild type mice. However, cisplatin-induced increases in the expressions of p-PERK, p-eIF2α, CHOP and, caspase-12 were diminished in kidneys of SIRT2 knockout mice. *In vitro*, cisplatin significantly increased the expressions of p-PERK, p-eIF2α, CHOP, and caspase-12 in HK-2 cells. When the effect of SIRT2 on cisplatin-induced ER stress was evaluated using SIRT2-siRNA (ON-TARGET plus human SIRT2 siRNA) or the SIRT2 inhibitors, AGK2 and AK1, knockdown or inhibition of SIRT2 significantly attenuated the cisplatin-induced protein expression of p-PERK, p-eIF2α, CHOP, and caspase-12. Immunoprecipitation studies showed SIRT2 bound physically to heat shock factor (HSF)1 and that HSF1 acetylation was significantly increased by cisplatin. In addition, knockdown of SIRT2 increased cisplatin-induced HSF1 acetylation and increased the expression of heat shock protein (HSP)70.

Conclusions: These observations suggest that suppression of SIRT2 ameliorates cisplatin-induced ER stress by increasing HSF1 acetylation and HSP expression.

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TH-PO111

Kinetics of the De Novo NAD/NADH Pathway from AKI to CKD

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Background: Energy metabolism deficiency is part of the acute kidney injury (AKI) pathophysiology. Recent studies highlighted the role of nicotinamide adenine dinucleotide (NAD) production in the pathogenesis of AKI. NAD is an electron carrier for mitochondria and a cofactor for cytoplasmic redox reactions. Its production is decreased during AKI following a decrease of the expression of PGC1α (Peroxisome proliferator activated receptor gamma co-activator-1-α) and an alteration of its *de novo* synthesis pathway: with a reduction in the expression of the Quinolinate PhosphoRibosylTransferase (QPRT). The modulation of this *de novo* pathway has been studied mainly in the acute phase immediately after AKI. However, its correlation with the severity of the ischemic insult and its evolution during the transition from AKI to CKD have not been described yet.

Methods: Renal ischemia-reperfusion was performed in C57Bl6/J male mice after nephrectomy of the contralateral kidney. For the 'severity' study, a 5-30 minutes ischemia was performed. Renal function was assessed 24h after ischemia. For the 'AKI to CKD' study, renal ischemia was performed during 10 minutes. Mice were sacrificed 1, 2, 3, 6 and 28 days after ischemia. PGC1α and QPRT mRNA expression was measured by RT-qPCR.

Results: We induced AKI in mice by unilateral ischemia reperfusion injury of increasing time to induce several degrees of AKI severity. PGC1α and QPRT mRNA expression decreased progressively with ischemia severity until reaching a plateau at 15 minutes of ischemia for PGC1α, like plasma creatinine and urea, whereas QPRT decrease is linear until 30 min of ischemia. PGC1α mRNA decrease is also inversely correlated to kidney dysfunction ($p<0.001$). A 10-minute ischemia led to the development of Chronic Kidney Disease (CKD), as evidenced by an incomplete recovery of the kidney function at 28 days. QPRT and PGC1α mRNA expression showed a progressive but incomplete recovery during the transition from AKI to CKD compared to sham mice.

Conclusions: In addition to confirming the decrease of PGCα and QPRT mRNA expression during AKI, we show that it is correlated to the severity of the ischemic AKI. Furthermore, we describe the recovery during renal repair and transition to CKD.

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TH-PO112

Targeting Oxidative Stress to Prevent Cardiorenal Syndrome in Right Ventricular Failure

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Background: Renal dysfunction remains an independent risk predictor of death and hospitalization in right ventricular failure (RVF) and RV function plays a pivotal role in preventing CRS. However, the pathophysiology of RV failure induced CRS remains poorly understood. The heart and the kidney have complex bidirectional interlinks and there is a growing body of evidence that oxidative stress is a major bidirecional crosstalk mediator of the Heart-kdiney in left ventricualr dusfunction. Clinically driven experimental modeling is crucial to investigate pathophysiology based therapy.

Methods: This study on RVF- Induced CRS investigated changes in antioxidants and oxidative stress in compensated CRS and if antioxidant prevents the pathophysiological heart-kidney cross talk. RVF-Induced CRS in rats was produced by alkaloid (ALK) injection. Rats were treated with antioxidant-LOS, 1 wk. pre & post-ALK injection. At 1 and 2 weeks post-ALK injection, echocardiography was performed to monitor cardiac function. RV systolic pressure (RVSP), RV hypertrophy (RVH), RV function, kidney and RV levels of superoxide dismutase (SOD), catalase, glutathione peroxidase (GSHPx) and lipid peroxidation (LPX). were measured. After sacrificing animals, hearts and kidneys were removed for histopathology and wet /dry weight ratios measurement.

Results: At 1 week, ALK-induced CRS resulted in RVSP, RV hypertrophy and LPX in RV myocardium as well as the kidney. There was a mild increase in antioxidant enzymes activities including SOD and GSHPx in RV and the kidney with no histopathological finding of kidney injury. At 2 weeks post-ALK injection there was RV failure and a significant increase in oxidative stress and antioxidant enzymes in RV and the kidney. Kidney histopathology with Periodic acid-Schiff (PAS) staining demonstrated ATN. Antioxidant-LOS treatment prevents ALK-induced CRS and decreased oxidative in the RV myocardium and the kidney. no change in RV and kidney wet/dry weight ratio between CRS and control animals were obsreved that suggest there was no renal or RV congestion at 2 weeks post ALK-indced CRS.

Conclusions: Since RVF-induced CRS was associated with oxidative stress and antioxidant was able to inhibit these pathophysiological heart-kindey cross talk it is proposed that antixodant modulates cardiac remodelling and ATN in CRS. Therefore, targetting of oxidative stress as an adjunt therapy is suggested.

TH-PO113

Renal Mitochondria Exhibit Cell Type-Specific Heterogeneity and Are Functionally Dynamic

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Background: Mitochondrial dysfunction is a key component of both acute and chronic kidney disease. Across tissues, mitochondria differ in composition and substrate utilization. As the kidney contains many different cell types, we hypothesize that there is intra-renal mitochondrial heterogeneity contributing to cell-specific mitochondrial function. To interrogate this, we utilized a novel mitochondrial tagging technique to isolate mitochondria in a cell-type specific manner. Here, we investigate the proteomes, metabolomes, and mitochondrial functional capacities of the early and late proximal tubule (PT) and distal convoluted tubule (DCT).

Methods: We generated three lines of mutant mice: early PT (*Slc34a1-CreERT2;MITO-Tag*); late PT (*Ggt1-Cre;MITO-Tag*); and DCT (*PvAlb-Cre;MITO-Tag*), capable of cell-specific isolation of hemagglutinin (HA)-tagged mitochondria. Mice were either fed ad libitum or fasted for 24 hours before kidneys were harvested. Cell-specific mitochondria were isolated using anti-HA magnetic beads and processed for proteomics, metabolomics, or functional analyses. Mitochondrial fatty acid oxidation (FAO) functional capacity was assessed using palmitoyl-CoA/carnitine (CPT1-dependent) or palmitoylcarnitine (CPT1-independent) as substrates and measured by Seahorse (Agilent).

Results: Using these MITO-Tag models, we demonstrated the ability to isolate renal mitochondria in a cell-specific manner. We observed differential mitochondrial protein and metabolite profiles of these cell types at both baseline and in fasting conditions. Pathway analysis revealed FAO as a key differentially regulated process, including CPT1A and CPT1B. CPT1A expression significantly increased with fasting in the late PT, and CPT1B expression was significantly higher in the DCT as compared to the PT cell types. Compared to the fed state, CPT1-dependent mitochondrial FAO capacity significantly increased in both the late PT and DCT in the fasted state. Surprisingly, when mitochondrial FAO capacity was assayed independent of CPT1, DCT mitochondria had significantly lower FAO capacity compared to late PT mitochondria in both baseline and fasting conditions.

Conclusions: We demonstrated the successful use of a system to study cell type-specific mitochondria in the mouse kidney. Our data suggest that FAO is differentially regulated in the renal PT and DCT.

Funding: Other NIH Support - NIGMS

TH-PO114

Renal Tubular CD24 Upregulation Aggravates Folic Acid-Induced AKI Through Inhibition of T-Regulatory Cells in Mice

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Background: Acute kidney injury (AKI) is characterized by cell death and inflammation. CD24 is a protein which is induced during tissue damage and is not expressed in matured renal tissue. We explored the role of CD24 in the pathogenesis of folic acid induced AKI (FA-AKI) in mice.

Methods: A single i.p. injection of folic acid induced AKI in WT and $CD24^{-/-}$ mice. Renal function tests, histological analysis, immunohistochemistry, Western blot analysis, and ELISA were performed to assess the severity of renal damage and the intensity of the inflammatory response.

Results: FA-AKI induced CD24 in the distal tubular epithelial cells. Compared to WT mice, FA-AKI $CD24^{-/-}$ mice exhibited an attenuated reduction in renal function and histological injury, lower serum IL-10 and interferon γ, and decreased expression of renal TNFα. In contrast, renal and systemic IL-33 upregulation were augmented. $CD24^{-/-}$ FA-AKI animals exhibited increased splenic margination and renal infiltration of regulatory T cells (Tregs). At day 7, FA-AKI $CD24^{-/-}$ mice exhibited increased expression of tubular pro-apoptotic and decreased anti-apoptotic proteins compared to WT animals. Anti CD24 antibody administration to FA-AKI mice attenuated the decrease in renal function and attenuated histological injury. Renal biopsies from patients with ATN stained strongly for CD24 in the distal tubules.

Conclusions: During AKI, upregulation of CD24 promotes renal inflammation through inhibition of Tregs infiltration and diversion of cell death towards necrosis rather than apoptosis. Neutralization of CD24 may prove as a target for future therapies in AKI.

TH-PO115

Stress-Inducible p53 Isoform in the Kidney

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Background: The need for understanding p53 biology and controlling p53 expression in the setting of AKI is compelling. Beyond its role as a tumor suppressor, p53 acts as a crucial stress-response gene involved in a variety of pathophysiological conditions. The basic functions of p53 include cell cycle arrest, apoptosis, and DNA repair. p53 has many other nuanced properties and the role of p53 under various circumstances remains elusive. Here, using a murine model of endotoxemia, we report a distinct p53 isoform that emerges during the recovery phase of AKI.

Methods: C57BL/6 male mice were injected with endotoxin 4 mg/kg and kidney tissues were harvested at various time points. Full-length cDNA sequencing was done

using the direct cDNA Nanopore protocol on MinION Flow Cells (total n = 40). DEXseq was used to identify differentially expressed isoforms across the time course. Based on the mouse data, we generated two p53 mutant human cell lines in which 1) cryptic exon splicing signals were abolished by sequentially applying the CRISPR knock-in strategy, or 2) the entire cryptic exon was excised by using the dual-sgRNA strategy.

Results: We found that RNA isoform switching is prevalent during the recovery phase of endotoxemia in the kidney. The isoform switching was observed in a distinct set of stress-responsive genes including p53. The alternative p53 isoform involves a cryptic exon that is repressed under basal condition and appears exclusively in the late phases of endotoxemia. To investigate the role of the alternative p53 isoform, we generated human cell lines that cannot express the alternative isoform. We found that these mutant cell lines (lacking the cryptic exon or its splicing signals) exhibit increased expression of the canonical p53 transcript as well as its downstream target genes such as p21. As a result, the proliferation rate decreased in these mutant cell lines.

Conclusions: The alternative p53 isoform encodes no protein and emerges during the recovery phase of endotoxemia at the expense of canonical p53 expression. Such reciprocal isoform switching could serve as an endogenous downregulation mechanism for canonical p53, enabling cells to exit cell cycle arrest and promote tissue recovery. We envision that controlling the balance between canonical p53 and its non-coding isoform could provide a route for rescuing cells from a maladaptive state or extending a beneficial adaptive state.

Funding: Other NIH Support - NIAID, Veterans Affairs Support

TH-PO116

Prioritizing Pathways Shared Between Humans and Mice in AKI-to-CKD Transition

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Background: Gaps in our understanding of the transition from acute kidney injury (AKI) to chronic kidney disease (CKD) remain a major unmet medical need due to lack of effective therapeutics for CKD in >850 million people worldwide. Pathways with important roles in AKI-to-CKD transition have not been prioritized on a cross-species level, potentially impairing the development of new target approaches and drugs for human kidney disease.

Methods: Here, we analyzed recent single-cell datasets from humans with AKI and CKD as well as several mouse models along the AKI-to-CKD spectrum. Using 3 human and 3 mouse datasets generated by different research groups, we performed differential gene expression analysis between disease and physiological conditions. Differentially expressed genes (DEGs) were mapped to orthologous human genes, if necessary, and fed into pathway enrichment analysis, allowing for a standardized, unified comparison of datasets and disease conditions on the pathway level. Finally, we validated our results on 2 separate human and mouse proximal tubule trajectory datasets.

Results: Despite an unexpectedly low overlap among top DEGs of clinically similar models/conditions along the AKI-to-CKD axis (suggesting high disease state specificity), biological processes and pathways along this continuum were well-conserved: processes already enriched during mild AKI, such as hypoxia, TNFα/NFκB signaling, immune processes, epithelial-to-mesenchymal transition, and IL18 signaling, were sustained and increasingly enriched as AKI severity increased and AKI transitioned to CKD. Conversely, cell matrix and adhesion pathways were enriched specifically in milder AKI, whereas solute carrier-mediated ion transport predominated in successfully repaired and healthy control states. Our studies inform on commonalities of human and murine renal pathophysiology after AKI. Nonetheless, our analysis called out inconsistencies and considerable inter-dataset variability, which is important when considering future research prioritizing potential drug targets for people with AKI.

Conclusions: Our studies inform on the consensus of human and murine renal pathophysiology after AKI, call out inconsistencies between single-cell datasets, and are meant to serve as a primer to prioritize efforts for future research in the AKI-to-CKD community.

Funding: Government Support - Non-U.S.

TH-PO117

Acrolein Promotes Tubular Cell Death in Ischemia Reperfusion-Induced AKI

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Background: We previously showed that ischemia–reperfusion injury in the kidney was attenuated in arginase 2 knockout (KO) mice or arginase inhibitor-treated mice. Arginase 2 is an enzyme involved in arginine metabolism and one of its metabolites is polyamine. Polyamines, essential for cell growth and proliferation, are known to inhibit cardiovascular disease. However, under conditions of cellular damage, toxic acrolein is produced from polyamines by the enzyme spermine oxidase (SMOX).

Methods: We used a mouse renal ischemia-reperfusion model to investigate changes in the amount and localization of acrolein due to injury. We also used human proximal tubule cells (HK-2) to study whether acrolein induces renal tubular cell death. To inhibit acrolein-induced cell death, an acrolein scavenger cysteamine, or spermine oxidase (SMOX) siRNA was added to HK-2 cells. Acrolein was detected with acrolein antibody in the kidney. In HK-2 cells, acrolein was visualized with acroleinRED. To expose cells to hypoxia-reoxygenation, HK-2 cells were cultured under 1% oxygen for 24 hours, then switched to 21% oxygen for 24 hours. Mitochondrial membrane potential was determined by MitoTrackerCMXRos. Cell viability was measured by WST-8.

Results: Acrolein was accumulated in ischemia-reperfusion kidneys, particularly in tubular cells. When HK-2 cells were hypoxia-reoxygenated, acrolein accumulated and SMOX mRNA and protein levels were increased. Acrolein induced cell death and fibrosis-related TGFβ1 mRNA in HK-2 cells. Administration of cysteamine suppressed the acrolein-induced upregulation of TGFβ1 mRNA. Cysteamine also inhibited a decrease in the mitochondrial membrane potential, and cell death induced by hypoxia-reoxygenation. The siRNA-mediated knockdown of SMOX also suppressed hypoxia reoxygenation-induced acrolein accumulation and cell death.

Conclusions: Acrolein promotes tubular cell death. Accumulated acrolein in the kidney during ischemia-reperfusion injury suggested that acrolein may be directly involved in tubular cell death. Treatment to control the accumulation of acrolein might be an effective therapeutic option for renal ischemia-reperfusion injury.

TH-PO118

Polyploid Tubular Cells Promote Tubulointerstitial Fibrosis After AKI via TGF-β1 Activation

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Background: We recently showed that tubular cell (TC) polyploidy is triggered by Acute Kidney Injury (AKI). Polyploid TC are required to promote survival in the early phase after AKI, but promote fibrosis and chronic kidney disease (CKD) progression in the long term. However, the molecular mechanism governing the link between polyploid TC and kidney fibrosis remains to be clarified.

Methods: We employed transgenic mouse models based on the FUCCI2aR reporter and *in vivo* single cell RNA-sequencing (scRNA-seq) to identify polyploid TC. *In vitro* scRNA-seq followed by sorting of polyploid TC was employed to characterize the expression profile of pro-fibrotic polyploid TC.

Results: Immediately after AKI, the expression of cell cycle markers identifies a population of DNA damaged polyploid TC. Polyploid TC accumulate DNA damage and survive, eventually resting in G1 phase of the cell cycle, while diploid TC die. *In vivo* and *in vitro* scRNA-seq along with sorting of polyploid TC show that these cells with DNA damage acquire a pro-fibrotic phenotype culminating in TGF-β1 expression. *In vitro* stimulation proved that TGF-β1 directly promotes TC polyploidization. *In vivo* interactome analysis revealed that TGF-β1 signaling fosters a reciprocal activation loop among polyploid TC, macrophages and fibroblasts to sustain kidney fibrosis and promote CKD progression.

Conclusions: Collectively, this study contributes to the ongoing revision of the paradigm of kidney tubule response to AKI, supporting the existence of a tubulointerstitial crosstalk mediated by TGF-β1 signaling produced by polyploid TC with DNA damage. Finally, these results further demonstrate that TC polyploidization is a self-sustained mechanism.

TH-PO119

PPP1R3G Promotes Necroptosis in Ischemia Reperfusion-Induced AKI by RIPK1 Dephosphorylation

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Background: Recent discoveries have revealed necroptosis as a major contributor to the pathogenesis of acute kidney injury (AKI). Protein phosphatase 1 regulatory subunit 3G (PPP1R3G) has been linked to the essentiality of RIPK1-dependent apoptosis and type I necroptosis. Nonetheless, the involvement of PPP1R3G in the regulation of necroptosis during ischemia reperfusion-induced acute kidney injury (IR-AKI) has yet to be elucidated.

Methods: Here, we investigated the role of PPP1R3G in the regulation of necroptosis in IR using an *in vitro* cellular I/R model and *in vivo* IRI-AKI mouse model. Primary proximal tubular cells (PTCs) from C57BL/6 and Ppp1r3g$^{-/-}$ mice were cultured and cell I/R was induced through hypoxia/reoxygenation. Cell viability and necroptosis were analyzed using a LUNA-II cell counter and flow cytometry, respectively. The expression levels of necroptosis, oxidative stress, and inflammation factors were determined by real-time PCR, western blotting, immunofluorescence staining, and ELISA. In the *in vivo* IRI-AKI model, the kidney injury and function were evaluated by plasma creatine, BUN, and KIM-1 levels and GFR values, respectively. Morphological evidence of kidney injury was assessed by PAS staining and cell death by immunofluorescent staining.

Results: We found that knockout of PPP1R3G significantly decreased (by 35-50%) hypoxia-inducible factor-1α (HIF-1α), as well as the levels of necroptosis factors (RIP1, RIP3, and Sirtuin-2), and inflammatory factors (IL-6, IL-10 and TNF-α) in I/R injury cells and IR-AKI mice. Deletion of PPP1R3G attenuated the I/R induced kidney injury indicated by 54% decrease in the plasma creatine (2.28±0.12mg/dL vs. 1.09±0.07mg/dL, $p<0.0001$) and 45% higher GFR values than WT mice at day 3 after reperfusion. Histology showed less diffuse renal tubular necrosis, casts, and debris in Ppp1r3g$^{-/-}$ mice, as well as 60% less cell death compared to WT mice. Moreover, the application of chemical compounds to prevent inhibitory phosphorylations of RIPK1 significantly reinstated cell death in Ppp1r3g$^{-/-}$ cells.

Conclusions: In conclusion, our findings demonstrate, for the first time, that Ppp1r3g-mediated necroptosis significantly promotes IRI-AKI. Therefore, targeting Ppp1r3g to reduce necroptosis in the kidney holds promising potential for significant clinical benefits.

Funding: NIDDK Support

TH-PO120

The AMPK Activator ATX-304 Reprograms Tubular Cell Metabolism to Protect Against Cisplatin-Induced AKI

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Background: Acute kidney injury (AKI) is characterized by widespread disruption of energy metabolism pathways. Targeting the metabolic regulator AMP-activated protein kinase (AMPK) is a potential strategy for addressing the problem of AKI. ATX-304 is a novel PAN-AMPK activator with reported benefits in models of diabetes, obesity and aging.

Methods: C57Bl/6 mice were fed chow containing ATX-304 (1mg/gm) versus control chow for 7-days prior to cisplatin-induced AKI (CI-AKI). Primary cultures of tubular epithelial cells (TECs) were pre-treated with ATX-304 (20 μM, 4-hrs), prior to exposure to cisplatin (20 μM, 23-hours).

Results: ATX-304 protected against CI-AKI as measured by serum creatinine at 48-hours (control 0.05±0.03 mM vs ATX-304 0.02+0.01 mM, P=0.004), western blot for neutrophil gelatinase-associated lipocalin (NGAL) (control 3.3±1.8-fold vs ATX-304 1.2±0.55-fold, P=0.002), RT-PCR for NGAL (control 99.6±22.8-fold vs ATX-304 35.2±5.9-fold, P=0.006), monocyte chemoattractant protein-1 (control 18.7±5.1-fold vs ATX-304 10.4±1.3-fold, P=0.048) and receptor-interating protein kinase 3 (CI-AKI control 6.9±2.4-fold vs CI-AKI ATX-304 4.9±1.3-fold, P=0.02), and histological injury score (control 3.5±0.59 vs ATX-304 2.7±0.74, P=0.03). In TECs, pre-treatment with ATX-304 protected from cisplatin mediated cell death, measured by lactate dehydrogenase release assay (control 27.1±4.2% lysis vs ATX304 -0.6±2.5% lysis, p<0.0001), and maintained cell viability in the presence of cisplatin, as measured by MTS assay. ATX-304 protection against cisplatin was lost in AMPK-null murine embryonic fibroblasts. In TECs metabolomic analysis revealed that ATX-304 (20 μM, 4-hrs) altered the level of 66/126 detected metabolites, including changes in fatty acids, tricarboxylic acid cycle metabolites, and amino acids. Energy metabolism studies of live TECs using the XFe96 Seahorse analyser found ATX-304 increased basal oxygen consumption rate by 38%, whereas maximal respiration was unchanged.

Conclusions: The mechanism of ATX-304 protection against cisplatin injury is AMPK- dependent and involves widespread metabolic reprogramming. AMPK activation by ATX-304 is a promising therapeutic strategy for AKI.

Funding: Commercial Support - Amplifier Therapeutics (Betagenon), Government Support - Non-U.S.

TH-PO121

Unveiling the Role of Lactate Dehydrogenase A (LDHA) in AKI: Insights from a Transgenic Mouse Model Study

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Background: Acute kidney injury (AKI) is a pressing global health concern, affecting millions of individuals worldwide. Despite its high prevalence, the prognosis of AKI remains poor, and effective biomarkers, prevention strategies, and treatment options are limited. Accumulating evidence from clinical, animal, and in vitro studies supports a close association between AKI, inflammation, and metabolic dysregulation. Notably, proximal tubule cells (PTCs) within the kidney play a vital role in AKI, as they possess numerous mitochondria with high metabolic activity, serving as both early sensors and major effectors in this condition. Additionally, under hypoxia and LPS-induced inflammation, lactate dehydrogenase A (LDHA), an enzyme involved in fermentative glycolysis, is upregulated in PTCs. However, the specific role of LDHA in AKI remains unexplored.

Methods: To generate kidney proximal tubule-specific LDHA knockout mice, we used PEPCK Cre crossbreeding with LDHA floxed mice. To confirmed the deletion of LDHA, we use western blot and immunostaining for characterization To induce AKI in both the LDHA knockout (KO) mice and wild-type (WT) mice, we administered a single dose of cisplatin (20mg/kg, IP) To assess the severity of AKI, we utilized various measurements, including serum creatinine levels, survival rates, and glomerular filtration rate (GFR). GFR was evaluated by employing transdermal measurement of excretion kinetics FITC.

Results: In our preliminary study, baseline observations did not reveal any phenotype changes in LDHA KO mice within the proximal tubules. However, when subjected to cisplatin-induced AKI through a single dose injection, LDHA KO mice exhibited more severe injury compared to wild-type (WT) mice. This phenotype was confirmed by increased serum creatinine levels at day 3 post-injection in KO mice (KO: 0.689 mg/dl vs WT: 0.338 mg/dl; p=0.0062), a lower 5-day survival rate in KO mice (KO: 70% vs WT: 90%), and reduced glomerular filtration rate (GFR) in KO mice (KO: 82.6 ml/min/100g b.w. vs WT: 256.6 ml/min/100g b.w. ; p= 0.022).

Conclusions: Overall, our findings suggest that LDHA may play a significant role in exacerbating AKI may through the facilitation of glycolytic switch within the proximal tubule.

Funding: NIDDK Support

TH-PO122

Lactate Dehydrogenase (LDH): Not Just a Marker of Kidney Injury

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Background: Lactate dehydrogenase (LDH) catalyzes the final step in glycolysis, the conversion of pyruvate to lactate. The release of LDH into extracellular fluids has been used for decades as a clinical and experimental marker of cell injury. However, the role of LDH as a mediator of cell injury has not been examined. Glycolysis is increased in AKI leading to the accumulation of lactate. Here we show that LDH and lactate are, in fact, not just markers but potent mediators of AKI.

Methods: C57BL6 male mice were subjected to bilateral ischemia reperfusion injury (IRI). Mice received LDH inhibitors (oxamate 300 mg/kg or NCATS SM1441 10 mg/kg), lactate (2g/kg), the Mrs2 inhibitor CPACC (10 mg/kg/d) or vehicle. Renal function and structure were assessed 24 hr after reperfusion.

Results: Oxamate-treated mice developed substantially less structural damage and kidney dysfunction (BUN 38±7 mg/dl, Cr 0.37±0.06 mg/dl) than vehicle-treated mice (BUN 148±25, Cr 0.93±0.12, P<0.0001). NCATS SM1441 also prevented ischemic AKI (NCATS BUN 31±6, Cr 0.23±0.06 vs saline BUN 111±10, Cr 1.59±0.3, P<0.0001). Administration of NCATS up to 6 hours after reperfusion also reduced IRI. LDH inhibitors also reduced hypoxic and cisplatin-induced cell death in renal epithelial cells *in vitro*. Moreover, the administration of L-lactate (but not D-Lactate) sensitized mice to a subsequent mild (22 min) ischemic insult (BUN L-lactate 95±8 vs D-lactate 22±6, P<0.0001) and also abrogated the protective effects of LDH inhibitors. In prior work, we showed that lactate stimulates mitochondrial Mg^{2+} uptake via Mrs2 and that Mrs2 mediates ischemic AKI. Here, we found that lactate did not exacerbate AKI in the absence of Mrs2. Finally, inhibition of LDH or Mrs2 starting 3 days after IRI, when injury is established, preserved kidney function and reduced fibrosis and atrophy measured at day 28.

Conclusions: These results indicate that the production of lactate via LDH is an important mediator of ischemic AKI and support the view that lactate-triggered mitochondrial Mg^{2+} uptake mediates AKI. These results also support the view that a sustained increase in glycolysis contributes mechanistically to the AKI-CKD transition. Finally, we provide preclinical evidence that LDH inhibitors may be highly effective in preventing ischemic AKI when administered before or shortly after injury and in preventing the development of CKD when administered after AKI.

TH-PO123

Proximal Tubule-Specific Transcriptomic Changes Mediate Sex Differences in Susceptibility to Aristolochic Acid I-Induced AKI in Mice

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Background: Previous studies have demonstrated the role of sex differences in susceptibility to human and murine models of AKI. However, proximal tubule (PT)-specific transcriptomic changes that mediate these differences have not been previously described. Here, we aim to investigate the sex-specific transcriptomic differences that mediate the susceptibility to AKI in Aristolochic Acid I (AAI)-induced injury model.

Methods: Age-matched male and female mice were administered DMSO (vehicle) or AAI (2mg/kg) every 72 hours for a total of 4 doses. FITC-sinistrin was used to measure GFR. Histological analysis and immunostaining were performed to determine extent of tubular injury and interstitial fibrosis. In addition, single nuclear multiome (RNA and ATAC) sequencing using 10X Genomics to assess changes to the transcriptome and chromatin accessibility.

Results: Immunostaining for AAI DNA adducts showed no significant differences between male and female mice. However, AAI-treated male mice demonstrated an increase in tubular injury and interstitial fibrosis based on H&E, PAS, and immunostaining (Cytokeratin 20) with a decrease in GFR. Single-nuclear multiome data showed all PT segments clustered distinctly between male and female mice (DMSO or AAI) with 2 unique PT clusters only present in the AAI-treated male as compared to all other groups. Key TF motifs were enriched in these 2 unique PT clusters were (cluster 1: *Elf4, Ets1, Irf1, Klf2, Stat2*) and (cluster 2: *Ebf1, Hivep2, Nfkb1, Pax8* and *Relb).* Pathway enrichment analysis showed enrichment in ribosome, ubiquitin mediated proteolysis and mitophagy-related pathways in these injured PT clusters. In comparison, key TF motifs were enriched in the female PT clusters such as *Atp5a1, Ndufa11, Ndufb10* (oxidative phosphorylation) and *Aldoa, Dld, Eno1, G6pc, Gapdh* (glycolysis and gluconeogenesis). Conversely, key TF motifs enriched in the male PT clusters were *Ank3, Atp2b1, Cadm, Cask, Cdh2, Agrn, Cask, Dab1, Epb41, Gphn (*splicing factor NOVA regulated synaptic proteins).

Conclusions: To date, this is the first study to demonstrate PT-specific changes to the transcriptome and chromatin accessibility that might mediate sex differences in susceptibility to AKI post-AAI treatment.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO124

Sexual Dimorphism and Epigenetic Control of the Kidney Disease Marker Klotho

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Background: Preclinical studies investigating physiological and pathophysiological processes in the kidney are mainly performed in males. This is due to a higher susceptibility to kidney injury and faster subsequent disease progression in male rodents. In consequence, sexual dimorphism of kidney injury markers like Klotho is often overlooked. *Klotho* is well-linked to renal health and its deletion in mice results in severe phenotype and premature death. Here, we identified putative *Klotho* enhancers and investigated their functions in males and females using mice with deletions in the *Klotho* associated enhancers.

Methods: We generated mutant mice carrying deletion of putative *Klotho* enhancers using CRISPR/Cas9 gene editing. Warm ischemia-reperfusion surgery was performed bilaterally to induce acute kidney injury and unilaterally in a fibrosis model. Using ChIP-seq and RNA-seq, we analyzed chromatin features and gene expression in mouse kidney. ELISA assay was utilized to measure serum FGF23 levels.

Results: We detected *Klotho* gene expression being twice as high in males compared to females at baseline. Enhancer deletion decreased *Klotho* mRNA levels more effectively in female than in male mice (90 vs. 50%). ChIP-seq data suggest additional regulatory elements present only in male mice, as promoter marks remain more pronounced in males even after deletion. Weight, lifespan and fertility of the knockout mice was not impacted. Baseline serum FGF23 level was significantly higher only in female enhancer knockouts (192.4 vs. 599.6pg/ml, p=0.0003). Severe bilateral ischemia resulted in similar creatinine increase in male and female WT and knockout mice, but only male knockout mice displayed higher *Havcr1* expression after injury than controls (1048 vs. 231.4, p=0.0016). 28 days after unilateral renal ischemia, fibrosis as measured by *Acta2* and *Tgfb* expression and Masson Trichrome staining was not significantly changed regardless of genotype.

Conclusions: Our results demonstrate sexual dimorphism of *Klotho* gene expression and its enhancer regulation. Despite having a larger effect in female mice, including changes in baseline FGF23 levels, only male knockout mice are more susceptible to acute injury and the deletion has no impact on the fibrosis model. Further dissection of the mechanisms of *Klotho* regulation is necessary to reexamine its efficacy as a kidney injury marker.

Funding: NIDDK Support

TH-PO125

Development of an Analytical Approach to Quantify Ammonium Flux in Tissue and Biofluids

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Background: Ammonia is a waste product of amino acids and other nitrogen-containing compounds, and its accumulation in the body can be toxic. The detection of abundance and flux is challenging because of its volatile nature, its conversion to ammonium and its fixation and excretion in other metabolic cycles such as the urea cycle. Here, we aimed to develop a method for quantifying changes in ammonia metabolism in multiple organs, urine, and plasma.

Methods: We modified the Berthelot method to derivatize ammonium into a measurable molecule called indophenol. Using ultra-high pressure liquid chromatography – triple quadrupole tandem mass spectrometry, this allows for quantifying both normal (^{14}N) and heavy (^{15}N) labeled ammonia through indophenol derivatization. The method was validated by measuring the pure indophenol and replicating the same peak when analyzing different dilutions of derivatized ammonium chloride standards.

Results: Standard curves correlated with initial concentrations of the standards. We then used a porcine kidney injury model with unilateral IRI and infused heavy labeled 15N-ammonium chloride to trace the handling of ammonia in different organs. The ^{15}N to ^{14}N ratio was used to observe changes in the handling of the infused heavy ammonia in different organs during kidney injury, revealing strong alterations in the inner medulla.

Conclusions: The data also allowed for calculation of fluxes, revealing altered detoxification into urea. This method will be used in future studies to determine changes in waste product metabolism during kidney injury.

TH-PO126

Mechanistic Representation of NAG Release in Renal Proximal Tubular Cellular Injury

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Background: N-acetyl-beta-D-glucosaminidase (NAG) is a novel biomarker for early detection of tubular injury in the event of acute kidney injury (AKI). While elevated levels of NAG in urine have been associated with renal tubular cell breakdown, the mechanistic underpinnings of NAG release remain poorly understood. In this study, we investigated the relationship between NAG release and potential mechanisms of proximal tubular injury.

Methods: We developed a mathematical model of NAG release from proximal tubule cells (PTCs) within the framework of RENAsym, a quantitative systems toxicology model of drug-induced AKI. The model was designed to represent urinary NAG increase as a result of cellular necrosis and brush border loss. In RENAsym, ATP decline results in various forms of cellular injury including microfilament disruption and cellular necrosis. NAG release was simulated using a driving signal from either necrosis or microfilament disruption and parameterized using observed urinary NAG in rats treated with cisplatin [1] and cyclosporine A (CsA) [2]. [1] Weichert-Jacobsen, K J et al. Cancer research vol. 59,14 (1999): 3451-3. [2] Nephrotoxicity biomarker evaluation after repeat dose oral administration of cyclosporine A in male rats. AstraZeneca, 2007.

Results: The results of our mathematical model of the NAG response indicate that the kinetics of urinary NAG in rats treated with cisplatin and CsA can be predicted using cellular necrosis. The model correctly predicted the peak time of urinary NAG in rats after single dose of 5 mg/kg cisplatin with time to resolution of ~48 hours. Furthermore, the model could recapitulate the dose-dependent response of NAG release in rats treated daily with CsA for two weeks. Specifically, NAG peak time occurred on day 5 or 6 and levels remained elevated until day 14. Simulated urinary NAG was shown to saturate at CsA doses of 30 mg/kg and higher, in line with observed data.

Conclusions: We developed a mechanistic model of NAG release in connection with cellular necrosis. The model predicts NAG kinetics for CsA- and cisplatin-mediated AKI as a useful biomarker for monitoring tubular injury in (pre)clinical settings.

Funding: Commercial Support - RENAsym development is funded by the RENAsym Consortium, which includes Janssen, AstraZeneca, AbbVie, Servier, Merck KGA, Gilead, and GSK as current members.

TH-PO127

Multi-Trait Genome-Wide Association Study (GWAS) and Functional Genomics Identifies Novel Genetic Traits and Dynamic Networks for FGF23

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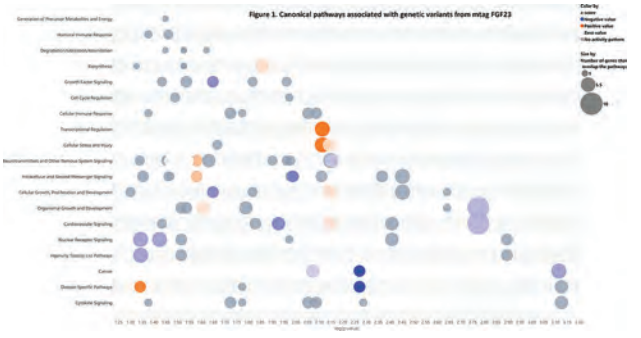
Background: Multi-trait analysis of Genome-wide association (MTAG) is a novel method to explore overlapping genetic architecture between traits. In this study, we investigated genetic traits common to mineral metabolism (MM) to identify novel genetic associations for fibroblast growth factor 23 (FGF23).

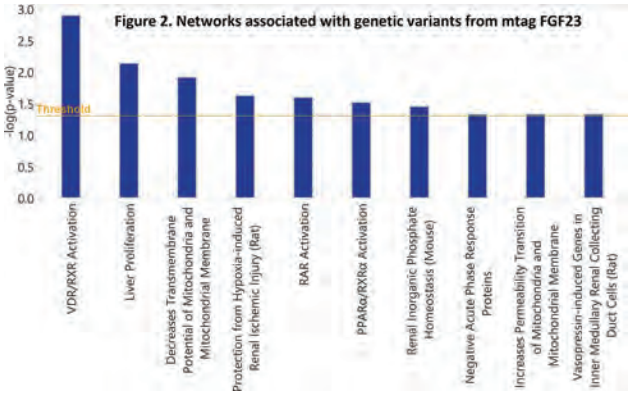
Methods: We applied MTAG to genetic variants common to 5 genetically correlated mineral metabolism markers (phosphorus, FGF23, calcium, 25(OH)D and PTH) in European-ancestry subjects from UKBioBank GWAS for phosphate and calcium (n=366,484), and two GWAS from the CHARGE consortium for PTH (n=29,155) and FGF23 (n=16,624). We used a functional genomics approach to model interactive and dynamic networks to identify novel associations between MM and FGF23.

Results: MTAG identified independent genome-wide significant SNPs for all traits, including 47 novel and known loci for FGF23. Using gene ontology and pathway analysis, we identified 9 overlapping networks including canonical pathways associated with cardiac hypertrophy and hematopoiesis. VDR and TGFβR2 signaling pathways were identified as the top regulator effect networks and MAPK signaling molecules were common to the top 5 causal networks (Figure 1 and 2). In addition, Coordinated Lysosomal Expression and Regulation (CLEAR) signaling pathway that regulates lysosomal function, autophagy and cellular response to nutrient sensing had the highest predicted activation z-score.

Conclusions: Novel genetic traits for FGF23 were identified with MTAG. Functional genomics revealed networks that inform unique biologic processes and cellular functions that could be targeted to develop therapeutics for mineral disorders.

Funding: NIDDK Support





TH-PO128

The Association Between Fibroblast Growth Factor 23 and Blood Pressure in a Hemodialysis Cohort

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Background: Mineral bone disease (MBD) is associated with mortality in hemodialysis (HD) patients, and we recently found associations between hyperphosphatemia and vasoconstriction/endothelial cell dysfunction in a small HD cohort. We hypothesized that fibroblast growth factor 23 (FGF23), the earliest MBD marker, would be independently associated with blood pressure in this cohort.

Methods: In a cohort of hypertensive HD patients, we measured plasma FGF23 from remaining frozen samples using ELISA. We conducted correlation and linear regression analysis to determine the association between FGF23 and peridialytic BP metrics and other lab parameters.

Results: There were 34 participants (53% women, 59% Black, 45% with diabetes) with a mean age of 46.8 years, mean pre-HD systolic BP of 160 (19) mmHg, mean serum phosphate of 6.5 (2.3) mg/dL and median FGF23 of 3264 (1042-6817) ng/mL. LogFGF23 did not differ based on diabetes status or sex, but it was higher in Black vs. White participants (p=.003). FGF23 correlated with phosphate (r=0.5, p=.001), but not PTH. Table 1 shows that logFGF23 was associated with almost all peridialytic BP metrics in univariate analysis that remained independent after controlling for phosphate, but were no longer significant after controlling for race.

Conclusions: FGF23 was associated with phosphate in hypertensive HD patients, and it was higher in Black vs. White participants. Associations between FGF23 and BP were independent of phosphate, but race was a confounding variable in this small cohort. Further larger studies are required better understand mechanisms by which FGF23 and MBD in general impact BP and CV health as well as to determine the generalizability of the race-based differences found in this study.

Funding: NIDDK Support, Veterans Affairs Support

Linear Regression Analysis Using LogFGF23 as the Outcome Variable

	Univariate Regression Coefficient (p-value)	Multivariate regression coefficient (p-value) controlling for phosphate	Multivariate regression coefficient (p-value) controlling for phosphate and race
Seated Pre-HD SBP	12.9 (0.01)	14 (0.02)	6 (0.3)
Seated Post-HD SBP	6.98 (0.2)	-	-
Seated Pre-HD MAP	11 (0.01)	10.7 (0.05)	4.98 (0.3)
Seated Post-HD MAP	10.3 (0.005)	9.6 (0.02)	9.1 (0.03)
Standing Pre-HD SBP	12.1 (0.03)	16.5 (0.01)	3.76 (0.6)
Standing Post-HD SBP	14.7 (0.3)	15.0 (0.04)	8.1 (0.3)
Standing Pre-HD MAP	11.7 (0.009)	11.8 (0.02)	4.2 (0.4)
Standing Post-HD MAP	12.1 (0.01)	11.2 (0.04)	8.1 (0.2)

HD=Hemodialysis, SBP=Systolic Blood Pressure, MAP=Mean Arterial Pressure

TH-PO129

Interactive Simulator for Model-Based Predictions of Parathyroid Hormone (PTH) Levels in Hemodialysis Patients

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Background: Secondary hyperparathyroidism is a prevalent condition among hemodialysis (HD) patients and a significant contributor to chronic kidney disease-mineral bone disorder (CKD-MBD). CKD-MBD poses a considerable risk of vascular calcification and cardiovascular events. The KDIGO guidelines strongly emphasize the importance of managing parathyroid hormone (PTH) levels in hemodialysis patients (Kidney Int Suppl 2017). Considering this, we have built an interactive simulator to predict PTH levels based on interventions targeting phosphate and calcitriol levels tailored to exemplary patients.

Methods: We utilized a comprehensive physiology-based mathematical model of parathyroid gland biology (Schappacher-Tilp, Physiol Rep, 2019) which has been employed successfully to predict individual PTH levels in HD patients (Pirklbauer, Front Med, 2021). The simulator follows a client-server architecture (**Fig 1A**) and features a user-friendly graphical user interface (GUI) allowing the user to select various parameters for the simulation (**Fig 1B**). Within the simulator, users can set treatment targets for serum phosphate and calcitriol levels, along with specifying the target time horizon.

Results: The interactive simulator provides users with the ability to select specific treatment targets and track the response of intact parathyroid hormone (iPTH) over time, as depicted in **Fig 1C.**

Conclusions: Our simulator predicts iPTH levels for various patient groups based on user-specified treatment targets for phosphate and calcitriol, serving as an effective educational tool to illustrate the effect of phosphate and calcitriol on iPTH levels.

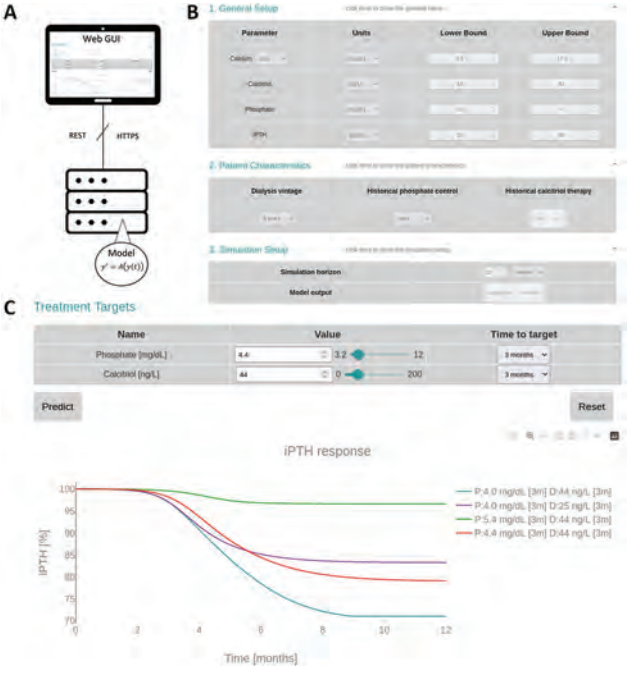

Fig 1: A The client-server architecture and **B** GUI. **C** iPTH level predictions for an exemplary patient (5 years HD, poor historic phosphate control, no calcitriol therapy history)

TH-PO130

Risk Factors Associated with Hip and Vertebral Fractures in CKD: The Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Fracture risk is substantially higher in patients with chronic kidney disease (CKD) than those without CKD and may have different pathophysiology, yet risk factors for fracture in CKD have largely been generalized from studies in non-CKD populations.

Methods: We used Cox regression to test associations of putative demographic and clinical risk factors with the composite hip and vertebral fracture assessed using hospital discharge diagnosis codes in 3,939 participants from the Chronic Renal Insufficiency Cohort (CRIC). Estimated glomerular filtration rate (eGFR) and proteinuria assessed by 24-hour urine collection were time-updated exposures. Serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D, and 24,25-dihydroxyvitamin D_3 were measured in a subset of 1,786 participants by liquid chromatography-tandem mass spectrometry.

Results: Mean cohort age was 58 years, 45% were female, 42% were Black, and 13% were Hispanic. Mean (standard deviation [SD]) eGFR was 44.4 (15.2). There were 82 hip and 24 vertebral fractures over a mean (SD) follow-up of 11.1 (4.8) years (incidence rate 2.4 events per 1000 person-years [95% CI: 2.0, 2.9]). Black race was associated with lower fracture risk after adjusting for demographics, comorbidity, medication use,

and eGFR and proteinuria. Older age, lower body mass index, and lower eGFR were associated with higher fracture risk after full covariate adjustment. Neither proteinuria, parathyroid hormone, nor other biomarkers of mineral metabolism were associated with fracture risk after full covariate adjustment.

Conclusions: Older age, non-Black race, and lower body mass index and eGFR were associated with fracture risk. None of the biomarkers of mineral metabolism tested in this study were associated with elevated risk of fracture experienced by patients with CKD.

Funding: NIDDK Support

Table 1. Associations of demographic and clinical risk factors with hip and vertebral fractures in the Chronic Renal Insufficiency Cohort (CRIC).

	N at risk (N events)	Incidence rate (events/1000 person-years)	Hazard Ratio (95% CI)	
			Model 1	Model 2
Age, per decade higher:			1.92 (1.51, 2.42)*	1.96 (1.51, 2.54)*
Sex				
Female	1778 (55)	2.7 (2.0, 3.4)	Reference	Reference
Male	2161 (151)	7.2 (6.1, 2.5)	0.78 (0.53, 1.14)	0.76 (0.48, 1.19)
Race and ethnicity				
Non-Hispanic White	1638 (60)	3.2 (2.4, 4.0)	Reference	Reference
Non-Hispanic Black	1650 (33)	1.9 (1.2, 2.5)	0.60 (0.39, 0.92)*	0.46 (0.28, 0.75)*
Hispanic	497 (9)	1.8 (0.6, 2.9)	0.64 (0.31, 1.28)	0.49 (0.23, 1.05)
Other	154 (4)	2.2 (0.0, 4.3)	0.77 (0.28, 2.11)	0.69 (0.21, 1.67)
Body Mass Index, per 5 kg/m^2 lower			1.26 (1.08, 1.47)*	1.30 (1.10, 1.52)*
eGFR, per 10 ml /min per 1.73 m^2 lower[1]			1.23 (1.10, 1.38)*	1.20 (1.06, 1.37)*
Proteinuria, per 1g gCr higher[2]			1.05 (0.96, 1.15)	0.98 (0.87, 1.10)
25(OH)D, per 1 SD lower[2]			1.44 (0.97, 2.13)	1.58 (0.99, 2.50)
1,25(OH)$_2$D, per 1 SD lower[2]			1.33 (0.99, 1.78)	1.06 (0.77, 1.44)
24,25(OH)$_2$D$_3$ to 25(OH)D$_3$ ratio, per 1 SD lower[2]			1.38 (1.07, 1.78)*	1.17 (0.87, 1.58)
PTH, per 1 SD higher log-transformed PTH			1.15 (0.93, 1.43)	1.12 (0.88, 1.43)
FGF-23, per 1 SD higher log-transformed FGF-23			1.35 (1.11, 1.65)*	1.23 (0.96, 1.52)
Serum calcium, per 1 mg/dL lower			0.96 (0.64, 1.44)	0.86 (0.57, 1.29)
Serum phosphate, per 1 mg/dL higher			1.59 (1.13, 2.00)*	1.34 (0.96, 1.84)
Urine calcium excretion, per 100mg/24 hours higher			0.80 (0.58, 1.12)	0.91 (0.63, 1.30)
Urine phosphate excretion, per 100mg/24 hours higher			0.97 (0.91, 1.04)	1.03 (0.94, 1.08)

Model 1: adjusted for age, sex, and race and ethnicity (excluding the variable when it was the exposure). Model 2: additionally adjusted for diabetes, smoking status, self-reported physical activity, systolic blood pressure, body mass index, dietary and supplemental calcium intake, dietary and supplemental vitamin D intake, anti-hypertensive use, statin use, bisphosphate use, estrogen-containing medications, steroid use, eGFR, and log-transformed proteinuria (excluding body mass index, eGFR, or proteinuria when it was the exposure).

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; 25(OH)D, 25-hydroxyvitamin D; SD, standard deviation; 1,25(OH)$_2$D, 1,25-dihydroxyvitamin D; 24,25(OH)$_2$D$_3$, 24,25-dihydroxyvitamin D$_3$; PTH, parathyroid hormone; FGF-23, fibroblast growth factor-23.

[1]These exposures were time-updated.
[2]These exposures were measured in a subset of 1,780 participants in CRIC.
*p<0.05

TH-PO131

Lower Parathyroid Hormone Levels Are Associated with Lower Risk of Fractures in Japanese Hemodialysis Patients: A Nationwide Cohort Study

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Background: Secondary hyperparathyroidism is associated with high-turnover bone disease in hemodialysis patients. However, conflicting evidence exists as to whether parathyroid hormone (PTH) levels are associated with fracture risk and whether the relationship is linear or U-shaped.

Methods: Using data from the Japanese Society for Dialysis Therapy Renal Data Registry, we analyzed 180,333 adult hemodialysis patients with data on serum albumin, calcium, phosphorus, and intact or whole PTH at the end of 2016 and data on hospitalization in 2017. The primary outcome was the composite of hospitalizations due to hip, vertebral, and other fractures. The secondary outcomes included hospitalization due to site-specific fracture. Fracture risk was assessed using Cox proportional hazards models, adjusted for potential confounders. We also examined the association between percent change in PTH levels during a 1-year baseline period and subsequent risk of fractures.

Results: At baseline, the median intact PTH level was 141 pg/mL (interquartile range, 78–226 pg/mL). During the 1-year follow-up, there were a total of 3,762 fractures requiring hospitalization (1,361 hip, 551 vertebral, and 1,850 others). In adjusted analyses, increasing PTH levels were associated with a monotonically increasing risk of fractures (odds ratio per doubling of intact PTH, 1.06; 95% CI, 1.03–1.09). When analyzed in deciles, the risk of fracture was lowest in the lowest decile of intact PTH levels (<39 pg/mL). The relationship between PTH levels and fracture risk was more pronounced for hip fractures, whereas there was no association between PTH levels and vertebral fractures. Changes in PTH levels were also associated with fracture risk: the adjusted odds ratio of fractures per 30% reduction in PTH during a 1-year baseline period was 0.97 (95% CI, 0.95–0.99).

Conclusions: Lower PTH levels are associated with a monotonically decreasing risk of fractures. Further studies are needed to determine whether intensive control of PTH decreases fracture risk.

TH-PO132

Improving Treatment of CKD-Mineral Bone Disorder (CKD-MBD) Through the Incorporation of Agatston Scores

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Background: KDIGO targets for CKD-MBD for Ca, P, and PTH are surrogates for the real damage that takes place in bone and the cardiovascular (CV) system. Vascular calcification (VC) correlates strongly with CV disease and death in individuals with CKD. We have modeled CKD-MBD through a series of mass balance equations describing movement of mineral between bone and soft tissue. We hypothesize that incorporation of measures and biomarkers of VC into a quantitative systems pharmacology model optimized using reinforcement learning will improve therapy by identifying alternative targets.

Methods: Data were abstracted from the Chronic Renal Insufficiency Cohort (CRIC) consisting of 5499 individual subjects with a mean CKD EPI eGFR of 47.7 ml/min/1.73m2 and a range between 3.0 and 126. Total and site specific Agatston scores were calculated and used for analysis. A total of 3230 Agatston scores were reported with a mean of 350 ± 767 and a range of 0 to 8247. A Cox Proportional hazard analysis was performed on CV death comparing Agatston score, site specific scores, and measured markers of inflammation (CaxP, Neutrophil/Lymphocyte Ratio (NLR), Fatty Acid Binding Protein (FABP), N-Acetyl-Beta-Glucosamide (NABG), Beta-2 Microglobulin (B2M), Beta-Trace Protein (BTP), Kidney Injury Molecule 1 (KIM1).

Results: The effects of inflammation markers on Total Agatston score and site-specific scores were not different, so only Total Agatston score will be reported. The results of the Cox model are shown in Table 1 following modeling with backwards elimination. All factors entered the model as an increased risk of CV death except for Beta-Trace Protein.

Conclusions: Substituting Agatston score for Ca net balance and modeling inflammatory intermediates NLR, B2M, BTP and FABP will optimize the CKD-MBD model. Leveraging artificial intelligence in the form of reinforcement learning will yield new pathways for treatment by targeting more proximal surrogates of disease.

Funding: Veterans Affairs Support

	B	Sig	Exp(B)
Agatston Score	0.000	<0.001	1.000
CaxP Product	0.023	<0.001	1.023
Neutrophil/Lymphocyte	0.095	<0.001	1.100
Urine N-Acetyl-Beta Glucosaminidase	0.052	<0.001	1.054
β-2 Microgloblin	0.183	<0.001	1.201
Beta Trace Protein	-0.164	<0.001	0.849
Liver Fatty Acid-Binding Protein	0.001	<0.001	1.001

TH-PO133

Association Among Bone Mass, Muscle Mass and Strength, Mortality, and CKD Progression in Older Adults

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Background: Chronic kidney disease (CKD) causes a progressive loss of muscle and bone mass. However, the impact of sarcopenia, low bone mineral density (BMD), and osteosarcopenia on CKD progression is yet to be determined.

Methods: This longitudinal prospective cohort study included 251 (median age 76 years; 35% women) outpatients aged ≥65 years with nondialysis-dependent CKD (NDD-CKD). Sarcopenia was defined according to the 2014 criteria of the Asian Working Group for Sarcopenia (AWGS), and low BMD was defined as a T-score of ≤−1.0. The patients were divided into four groups: normal (no sarcopenia/normal BMD), only low BMD (no sarcopenia/low BMD), only sarcopenia (sarcopenia/normal BMD), and osteosarcopenia (sarcopenia/low BMD). The primary outcome was a composite of all-cause deaths, end-stage kidney disease (ESKD), and admissions owing to major cardiovascular events (MACEs). The secondary outcome was a kidney composite outcome that included a 30% estimated glomerular filtration rate (eGFR) reduction and ESKD. The outcome risk was determined using stratified Cox models adjusted for potential confounders.

Results: During a median follow-up period of 5.2 years, there were 22 deaths, 117 30% eGFR reductions, 48 ESKDs, and 18 admissions owing to MACEs. The osteosarcopenia group rather than the only low BMD or only sarcopenia groups exhibited a higher risk of the primary (hazard ratio [HR]: 2.81, 95% confidence interval [CI]: 1.32–5.99) and kidney composite (HR: 1.90, 95% CI: 1.01–3.57) outcomes. Low handgrip strength (HGS) was associated with a high risk of primary and kidney composite outcomes (HR: 2.38, 95% CI: 1.40–4.05; HR: 1.55, 95% CI: 1.01–2.37, respectively). The increase in HGS but not the body mass index, skeletal muscle mass index, or BMD was associated with a lower risk of primary and kidney composite outcomes (HR: 0.67, 95% CI: 0.52–0.87; HR: 0.76, 95% CI: 0.63–0.93 per 5 kg, respectively).

Conclusions: Osteosarcopenia was associated with poor survival and kidney outcomes. Low HGS was associated with increased mortality risk and kidney function decline. These findings bring insights into the pathogenesis of the kidney–bone–muscle axis and improving muscle strength may mitigate CKD progression.

Funding: Government Support - Non-U.S.

TH-PO134

The Vitamin D Metabolite Ratio Is Associated with Volumetric Bone Density in Older Men

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Background: The ratio of the vitamin D catabolic product (24,25-dihydroxyvitamin D) to 25(OH)D (vitamin D metabolite ratio or VMR) has been suggested as a superior marker of vitamin D status than 25(OH)D. High-resolution peripheral quantitative computed tomography (HR-pQCT) provides information on bone health beyond bone mineral density (BMD), providing volumetric BMD (vBMD) and bone strength data. We evaluate the associations of the VMR and 25(OH)D_3 with vBMD and bone strength, in the distal radius and tibia in 545 participants in the Osteoporotic Fractures in Men (MrOS) Study.

Methods: We used multivariable linear regression in models adjusted for demographics, season, study site, physical activity, BMI, smoking status, diabetes, blood pressure and estimated glomerular filtration rate (eGFR) among 545 men aged ≥ 65 years who participated in MrOS and provided HR-pQCT data in visit 4 (Year 14 of the study). Our primary outcome was vBMD and secondary outcome was estimated failure load (EFL) at both the distal radius and tibia.

Results: Mean age was 84± 4 years, 88.3% were White, and 32% had an estimated glomerular filtration rate (eGFR) <60ml/min/1.73m^2. In fully adjusted models, each two-fold higher VMR was associated with 9% (3%, 16%) and 6% (0.4%, 11%) higher vBMD at the distal radius and tibia, respectively (**Table**). In contrast, we found no association of 25(OH)D_3, with vBMD at either anatomic site. Similarly, each two-fold higher VMR was associated with 13% (5%, 21%) and 10% (4%, 16%) EFL at the distal radius and tibia, respectively (**Table**). In contrast, we found no association of 25(OH)D_3, with EFL at either anatomic site.

Conclusions: Among community-living older men, a higher VMR is associated with higher vBMD and EFL while 25(OH)D_3 was not. The VMR may serve as a valuable predictor of skeletal health in older men at risk for osteoporosis and fractures.

Funding: NIDDK Support, Other NIH Support - NHLBI, NIA, NIAMS, NCATS, Private Foundation Support

Association of the VMR and 25(OH)D_3 with vBMD and Estimated Failure Load among 545 participants of the MrOS Study

	Total vBMD		Estimated Failure Load	
	Percent Higher vBMD Per 2-fold higher Vitamin D Biomarker (95%CI)	P	Percent Higher EFL Per 2-fold higher Vitamin D Biomarker (95%CI)	P
VMR				
Radius	9% (3%, 16%)	0.005	13% (5%, 21%)	0.001
Tibia	9% (3%, 15%)	0.002	10% (4%, 16%)	0.001
25(OH)D_3				
Radius	-2% (-7%, 4%)	0.578	-1% (-8%, 6%)	0.855
Tibia	-1% (-6%, 4%)	0.669	0.3% (-5%, 6%)	0.910

TH-PO135

Serum Bicarbonate Is Associated with Bone Density Among Adults with Type 2 Diabetes: Results from the African American Diabetes Heart Study

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Background: Osteoporosis is a significant cause of morbidity and mortality in the aging population. Individuals with type 2 diabetes (T2D) typically have higher bone density but also a higher rate of fractures. Serum bicarbonate may be a risk factor for bone loss, but studies are conflicting, and little is known about this relationship in T2D, especially in African Americans.

Methods: We examined the longitudinal relationship between serum bicarbonate and change in bone density in 300 participants with T2D in the African American - Diabetes Heart Study (AA-DHS). Serum bicarbonate was measured at baseline, and bone density was assessed using CT volumetric bone mineral density (vBMD) scans of the thoracic and lumbar spines at baseline and after an average of five years of follow up. Multivariate linear regression models assessed associations between baseline serum bicarbonate and longitudinal change in vBMD.

Results: At baseline, the cohort was 50% female, with a mean age of 55.1 years and a mean duration of diabetes of 10.2 years. The mean baseline serum bicarbonate was 26.6 (SD 3.3) mEq/L; the median baseline lumbar spine vBMD was 179.3 (IQR 148.2, 208.9) mg/cm3, and the median baseline thoracic spine vBMD was 204.9 (IQR 171.6, 231.9) mg/cm3. In adjusted analyses, every 1 mEq/L increase in baseline serum bicarbonate was significantly associated with a relative improvement in lumbar vBMD (1.04 (0.73, 1.36) mg/cm3, p < 0.01), as well as thoracic vBMD (1.36 (0.77, 1.94) mg/cm3, p < 0.01).

Conclusions: In this cohort of African-Americans with T2D, higher baseline serum bicarbonate levels associated with improved changes in bone density over time. Further studies are needed to determine if treatment of metabolic acidosis would lessen bone loss and fractures in this population.

Funding: Other NIH Support - Funding: 2R01DK071891

Figure 1: Serum Bicarbonate and Change in vBMD

Associations between Serum Bicarbonate and Change in Lumbar vBMD

	Parameter Estimate (per 1 mEq/L increase in serum bicarbonate)	95% Confidence Limits		P-value
Model 1 *	1.01	0.71	1.32	< 0.01
Model 2 #	1.03	0.73	1.33	< 0.01
Model 3 ^	1.04	0.73	1.36	< 0.01

Associations between Serum Bicarbonate and Change in Thoracic vBMD

	Parameter Estimate (per 1 mEq/L increase in serum bicarbonate)	95% Confidence Limits		P-value
Model 1 *	1.34	0.86	1.82	< 0.01
Model 2 #	1.32	0.82	1.81	< 0.01
Model 3 ^	1.36	0.77	1.94	< 0.01

* Model 1: Includes time between measurements and baseline vBMD
# Model 2: Model 1 + age, sex, body mass index, hemoglobin A1c, eGFR, and smoking status.
^ Model 3: Model 2 + use of inhaled corticosteroids, hormone replace therapy, and serum calcium and 25-hydroxyvitamin D levels

TH-PO136

Effect of Citrate-Buffered, Magnesium-Enriched Dialysate on Calcification Propensity in Hemodialysis Patients: Results of a Randomized Controlled Trial (CitMag Study)

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Background: Accelerated serum calcification propensity (lower T50 time) is directly associated with increased risk of cardiovascular events and mortality in dialysis patients. Several solitary interventions have been reported to improve T50 but whether a combination of these interventions yields further increases T50 is unknown. Therefore, the effect of substituting acetate for citrate buffer in combination with increases in magnesium concentration in dialysate on T50 was investigated.

Methods: In a randomized, controlled trial, 60 chronic hemodialysis patients were allocated to either continue on standard (S) dialysate (3 mmol/l acetate, 0.5 mmol/l magnesium) or a sequence of magnesium-enriched ($Mg_{0.75}$) dialysate (3 mmol/l acetate, 0.75 mmol/l magnesium) for 2 weeks followed by citrate-buffered, magnesium-enriched (Cit+$Mg_{0.75}$) dialysate (1 mmol/l citrate, 0.75 mmol/l magnesium) for 3 weeks. The primary endpoint was the difference in T50 times between the S group and the Cit+$Mg_{0.75}$ group at 5 weeks.

Results: There was no significant difference in T50 time between the S group compared to the Cit+$Mg_{0.75}$ group (236 ± 77 vs. 265 ± 97 minutes, p=0.23). The size of secondary calciprotein particles (CPP-2_{Rh}) did not differ between the S group and the Cit+$Mg_{0.75}$ group (294 ± 95 vs. 309 ± 91 nm, p=0.55). In longitudinal analyses, serum magnesium concentrations increased from 1.07 ± 0.17 to 1.24 ± 0.17 mmol/l with the $Mg_{0.75}$ dialysate (p<0.0001) but decreased again to 1.19 ± 0.16 mmol/l with the Cit+$Mg_{0.75}$ dialysate (p<0.0001). Serum bicarbonate levels did not change significantly throughout the study.

Conclusions: The combination of citrate-buffer with increased magnesium concentration in dialysate does not improve T50 and may even be antagonistic when administered concurrently.

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TH-PO137

Histologic Specificity in Calciphylaxis

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Background: Skin biopsy is often used to support the diagnosis of calciphylaxis, otherwise termed calcific uremic arteriolopathy (CUA), but the specificity is unknown. We previously showed that many of the findings ascribed to CUA were also present in amputation specimens of patients without CUA. To better understand the specificity of histology in CUA and thus the underlying pathophysiology, we prospectively compared involved and uninvolved tissue from 18 subjects with a clinical diagnosis of CUA.

Methods: 16 patients undergoing skin biopsies for CUA consented for a biopsy of uninvolved skin, usually on the contralateral extremity. In an additional 2 cases, skin samples were obtained at autopsy. Sections were stained with hematoxylin and

eosin and von Kossa calcium stain. The clinical diagnosis was made by the consulting dermatologist, who also performed the punch biopsies. The biopsies were reviewed by one of two pathologists and scored for the following: calcification, thrombosis, or intimal hyperplasia of small arteries or arterioles, and extravascular calcification.

Results: The characteristics of the subjects were as follow: age, 58 +/- 3 years; gender, 67% female; end-stage renal disease, 89%; warfarin use, 50%. Locations of the biopsies were thigh (11), lower leg (4), arm (1), abdominal wall (1), and mons pubis (1). Small vessel calcification was seen in half of the lesional samples and 44% of control samples. Extravascular calcification was seen in 44% of lesional samples and 22% of control samples. In contrast, thrombosis (50%) and intimal hyperplasia (33%) of small vessels were observed only in lesional samples. Of the lesional biopsies with thrombosis or intimal hyperplasia, small vessel calcification was present in 78% and 83% respectively. There were nondiagnostic histologic findings in 6 lesional biopsies and 7 control biopsies.

Conclusions: The similar proportions of small vessel calcification in lesional and control biopsies indicate a lack of any specificity and suggest that this is not sufficient to cause of CUA. Thrombosis or intimal hyperplasia were specific to lesional biopsies, suggesting a pathogenic role and consistent with the ischemic nature of the lesions. While not a specific finding, calcification was present in most of the lesional biopsies with thrombosis or intimal hyperplasia, suggesting a contributory role.

Funding: Clinical Revenue Support

TH-PO138

Patients' Experience of Calciphylaxis: Living with a Disease of Uncertain Etiology and Management

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Background: Calciphylaxis is a condition with sudden, unpredictable onset that predominantly affects people with end-stage renal disease (ESRD). Caused by the calcium-based occlusion of the microvasculature, calciphylaxis results in large, extremely painful non-healing skin ulcers. Calciphylaxis has no cure and a one-year mortality between 40 and 80% for patients who have ESRD. Prior research has focused on identifying the biological mechanisms of the disease with the goal of developing treatment. Little is known about how patients currently living with calciphylaxis manage their illness and care, especially regarding the treatment options and severe, often debilitating, symptoms.

Methods: Using purposive sampling, we recruited participants (n=15) who had contact with a calciphylaxis clinical practice in the Northeast United States. This qualitative study utilized semi-structured phenomenological interviews to investigate the lived experience of patients with calciphylaxis. These 1-hour interviews focused on specific domains of patients' experience: process to diagnosis, treatment process, and social and emotional support.

Results: There were 5 major findings of this study: 1) unpredictability resulting from acuity of disease and uncertain clinical diagnosis and treatment options; 2) severity of pain affecting basic functioning and access to clinical care; 3) central role of social support due to the debilitating nature of pain; 4) coping and challenges of the disease; 5) becoming a self-advocate in the clinical setting in order to navigate clinical care. Two issues tie these findings together. A lack of clinical attention to pain management affected both daily functioning and patients' ability to access other aspects of calciphylaxis care. Patients' experiences of uncertainty were exacerbated by limited communication and lack of coherent calciphylaxis clinical knowledge.

Conclusions: Our findings are the first to describe, in depth, patients' experiences with calciphylaxis. They inform various clinical recommendations, for both calciphylaxis and other conditions with acute, unpredictable onset and potentially debilitating symptoms. In particular, inclusion of pain management specialists as core members of a care team could improve the quality of life of calciphylaxis patients and help communicate the challenges patients face to other members of the care team.

TH-PO139

Decision Tree Model Simulating the Burden of Hyperphosphatemia in US Adult Patients with ESKD on Dialysis

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Background: Hyperphosphatemia is a common complication in patients with end-stage kidney disease (ESKD) on dialysis. It can lead to vascular calcification, secondary hyperparathyroidism, increased risk for fractures, and other poor health outcomes. It is important to understand the extent of serum phosphate control benefit in this population.

Methods: A decision tree model was built to simulate the population-level effect of reducing serum phosphate levels in US adult patients with ESKD on in-center hemodialysis (n=480,516) over a 5-year time horizon. Patients were assigned an initial serum phosphate level derived from the US Renal Data System's 2022 Annual Data Report, after which a reduction of 2.0 mg/dL was applied. Changes in hospitalization (all-cause, cardiovascular, and fracture), parathyroidectomies, mortality, and healthcare costs were calculated by the model based on published literature and Medicare cost data. The model does not specify how patients' serum phosphate levels are reduced; thus, direct drug costs are not assessed.

Results: The greatest benefit observed with modeled serum phosphate reduction is reduced mortality, with 16,565 fewer deaths occurring over the 5-year period in the simulated population compared with a population that maintained the initial serum phosphate level. There were 46,308 additional all-cause hospitalizations in the simulated population over the same time period, which comprised the majority of an additional $165.9M in Medicare costs. Key limitations of the model are that simulated serum phosphate levels did not fluctuate as they would in the real world, and that the data were derived from older retrospective studies that may not represent the present-day ESKD population.

Conclusions: Simulated reduction of serum phosphate levels in patients with ESKD on dialysis decreased mortality. This pronounced effect in mortality leads to an increase in all-cause hospitalization, resulting in additional Medicare costs. However, serum phosphate control is only one component of managing patients with ESKD on dialysis; there are numerous contending comorbidities and extenuating factors. These results highlight the need to continue exploring how management of patients with ESKD can provide the best patient outcomes.

Funding: Commercial Support - Akebia Therapeutics, Inc.

TH-PO140

Impact of Accessibility to Non-Calcium-Based Phosphate Binders and Calcimimetics on Mineral Outcomes in Maintenance Hemodialysis

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Background: Traditional management of CKD-MBD with calcium and active vitamin D results in hypercalcemia and calcification. Newer drugs including non-calcium-based phosphate binders (NCBPBs) and calcimimetics may help achieving the treatment targets with less hypercalcemia and calcification. In our country, NCBPBs and calcimimetics are not covered in social security and universal coverage reimbursement schemes (SS/UC), whereas they are covered in civil servant and state enterprise reimbursement schemes (CS/SE). Our institution serves both groups of patients providing a unique opportunity to study the differences in mineral outcomes.

Methods: This is a retrospective cohort study that included maintenance hemodialysis (MHD) patients between 2015–2022. Patients were categorized into two groups according to their reimbursement schemes (SS/UC or CS/SE). Differences in mineral parameters were compared using linear mixed models. The composite endpoint of parathyroidectomy and severe hyperparathyroidism (HPT) (PTH ≥1500 pg/mL) was analyzed by multivariate Cox-Proportional Hazard regression.

Results: A total of 714 patients were included. The average serum calcium and phosphate and proportions of patients with hypercalcemia and hyperphosphatemia were substantially higher in SS/UC group compared with CS/SE group. Parathyroid hormone levels were comparable but the proportion of patients with HPT was significantly higher in SS/UC group. The composite endpoint of parathyroidectomy and severe HPT was also significantly higher in SS/UC group. A sensitivity analysis in 563 patients who were prescribed at least 1 type of CKD-MBD medications yielded similar findings.

Conclusions: MHD patients who did not have access to NCBPBs and calcimimetics showed poorer mineral outcomes compared with those who had access to the drugs.

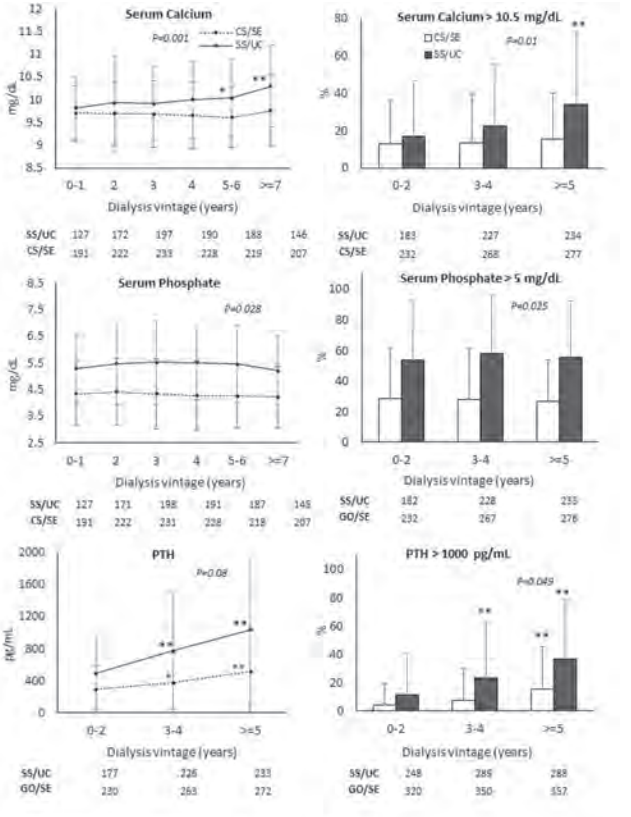

Figure 2 Mineral parameters according to dialysis vintage

Number of available laboratory data are shown below each graph. CS/SE, government/state enterprise; SS/UC, social security/universal coverage. P-values in the graphs represent between group differences over the study period. *P<0.05 and **P<0.001 vs. 0-1 years or 0-2 years of the same group

TH-PO141

Effects of a Low Phosphorus Diet on Phosphorus and Calcium Whole-Body Balance and Intestinal Absorption: Results of a Pilot Study in Adults with Moderate CKD

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Background: Dietary P restriction is often used as a management strategy to prevent and treat hyperphosphatemia and CKD-MBD progression. It is presumed that a low P diet results in lower P balance or retention, but this has not been determined, nor the effects on Ca absorption and balance.

Methods: This pilot two-phase crossover, controlled feeding, metabolic balance study investigated the effects of dietary P level (low P [LP], 800 mg/d; high P [HP], 1500 mg/d) on P and Ca balance and absorption in N=3 adults with moderate CKD. Nutrient content was similar, including low Ca (500 mg/d). Each phase consisted of 1wk run-in on the diet, 1wk inpatient metabolic balance, and 3wk washout between phases. Complete timed urine and feces were collected inpatient. Oral and IV Ca and P isotopes were administered and serial serum and urine samples analyzed for their concentrations to determine fractional intestinal absorption by kinetic modeling. Balance was calculated as intake minus urine and fecal excretion. Serum iPTH, iFGF, and 1,25D were measured at baseline and end of each phase.

Results: Intestinal fractional P absorption varied widely among participants (51-95%) but appeared unaffected by dietary P level in all participants. Thus, absolute intestinal P absorption (mg/d) was approximately doubled in the HP compared to the LP. 24h urine P was lower in all participants with the LP diet. The response in P balance to dietary P level varied among subjects. The response in fractional intestinal Ca absorption and Ca balance also varied. 24h urine Ca was very low in all subjects (6-20 mg/d) and did not change with the LP diet. Serum 1,25D was not associated with intestinal fractional P or Ca absorption nor in response to dietary P. iPTH and iFGF23 were lower with LP in two participants who had moderately elevated levels at baseline and with HP.

Conclusions: In adults with moderate CKD, Ca and P balance and intestinal absorption are variable in response to different controlled dietary P intakes. In this pilot study, fractional P absorption did not change with dietary P level and was not associated with 1,25D. Further studies are needed to identify explanatory factors for the observed variation in whole-body Ca and P physiology in adults with CKD.

Funding: NIDDK Support

TH-PO142

Management of Serum Phosphorus over a Six-Month Follow-Up in Home Hemodialysis Patients Prescribed Sucroferric Oxyhydroxide as Part of Routine Clinical Care

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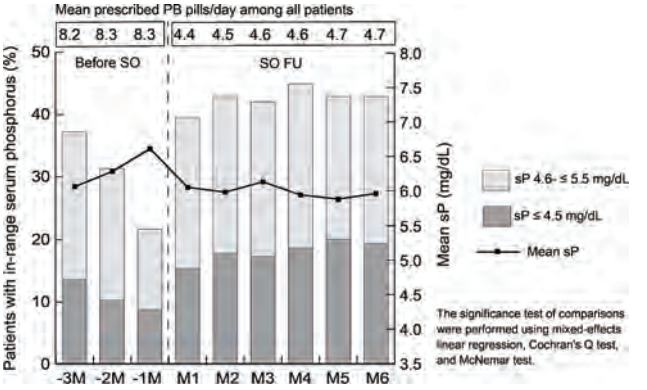
Background: With the growing use of home hemodialysis (HHD) and the increasing trend of physicians prescribing sucroferric oxyhydroxide (SO) in recent years, this real-world data analysis examines the serum phosphorus (sP) management with SO in HHD patients (pts) over 6 months.

Methods: Eligible HHD pts (n=713) were adults from Fresenius Kidney Care first prescribed SO monotherapy during 9/2016-12/2020 and had sP measured the month (mo) before SO start (-1M). sP was assessed up to 3 months (mos) before (baseline, BL; -3M to -1M) and 6 mos following SO initiation (follow up, FU; M1 to M6). Pts were censored from the analysis upon transplant (n=53), discharge (n=94), and discontinuation of SO (n=177 including n=80 prescribed another phosphate binder (PB) after SO stop). Comparisons of parameters were made between -1M and other mos.

Results: Pts (n=713) were on average 53 years, 42 mos vintage, and 34% female. The PB distribution in pts with PB recorded at BL (78%): sevelamer 51%, calcium acetate 21%, lanthanum carbonate 3%, ferric citrate 8% and >1 PB 16%. sP increased over the BL, from 6.1 mg/dL at -3M to 6.6 mg/dL at -1M but declined after SO start (5.9 to 6.1 mg/dL during FU; p<.0001). Accordingly, the % of pts with sP≤ 5.5 mg/dL increased from 22% at -1M to 43% at M6 (p<.0001), and the % with sP≤ 4.5 mg/dL increased from 9% at -1M to 19% at M6 (p<.0001), with pill burden decreasing from 8.3 to 4.7 pills/day (p<.0001). Serum calcium showed a significant decline from -1M to M6 (9.15 to 9.03 mg/dL, p<.001). No significant changes (p=0.3) were observed in iPTH following SO prescription (518 pg/mL at -1M and 525 to 553 pg/mL during FU).

Conclusions: HHD pts prescribed SO as part of routine clinical care experienced improvements in sP control and reductions in PB pill burden over a 6-month FU, compared to BL.

Funding: Commercial Support - Fresenius Medical Care



TH-PO143

Optimal Initiation of Tenapanor Treatment Analyzed by Baseline Phosphate Binder Dose: A Subanalysis of the OPTIMIZE Study

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Background: Tenapanor (TEN) is a novel phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). TEN is being evaluated for control of serum phosphate (sP) in adult patients (pts) with chronic kidney disease (CKD) on maintenance dialysis. Real world data shows that nearly 80% of pts are unable to consistently maintain adequate control of sP over a 6-month period with the use of phosphate binders (PBs) alone. OPTIMIZE (NCT04549597) was an open-label study of TEN initiation in pts on dialysis that evaluated sP control, pill burden, and quality of life (QOL).

Methods: OPTIMIZE study design was previously described. In Cohort 1 (C1; n=151) pts stopped PBs and initiated TEN 30 mg bid. In Cohort 2 (C2; n=152) pts reduced PB dose by ≥50% and added TEN 30 mg bid. The PB/TEN dose could be adjusted to achieve sP ≤5.5 mg/dL. Dose up-titration for PBs was not allowed until week (wk) 2. Pts in C1 and C2 were categorized into two groups: low PB (LPB) dose (≤6 pills/day at baseline) and high PB (HPB) dose (>6 pills/day at baseline). We evaluated sP response (sP reduction ≥1.2 mg/dL at ≥2 of 3 measurements) at wks 1–4 and wks 6–10 of treatment. A QOL survey was administered at the end of wk 10.

Results: Overall, 87 and 93 HPB pts and 60 and 55 LPB pts were randomized to C1 and C2, respectively. For HPB pts, sP response was achieved at wk 4 by 24.1% (C1) and 47.3% (C2) of pts. Median sP-lowering pill burden (including TEN) reduction at wk 4 was 7 (C1) and 4 (C2) pills/day. For LPB pts, sP response was achieved at wk 4 by 38.3% (C1) and 47.3% (C2) of pts. Median sP-lowering pill burden reduction was 2.5 (C1) and 1 (C2) pills/day. Overall, 60–80% of those who achieved a sP response at wk 4 continued to have a sP response later. Both cohorts achieved consistent sP control throughout the entire study by adding TEN, independent of how TEN was initiated.

Conclusions: Both cohorts experienced improved sP control, self-assessed QOL, and reduction in PB pill burden. HPB pts may have better early sP control by initiating TEN with a 50% reduction in PB dose, while LPB appeared to have a similar early response regardless of TEN initiation method.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO144

Tenapanor Effect on Decrease in Phosphate Binder Pill Burden for Hyperphosphatemia in Japanese Patients Undergoing Hemodialysis: A Phase 3 Long-Term Study

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Background: Phosphate binders (PBs) are commonly prescribed for treating hyperphosphatemia. However, management with PBs often requires a high pill burden which is a significant issue in hemodialysis (HD) patients. Tenapanor (TEN) is a novel drug that reduces paracellular phosphorus absorption via the selective inhibition of sodium/hydrogen exchanger isoform 3, and the dose consists of one small tablet taken twice daily. We aimed to evaluate the ability of TEN to decrease PB pill burden for hyperphosphatemia in Japanese HD patients in the long-term safety study.

Methods: This was a multicenter, open-label, single-arm, phase 3 study. HD patients whose serum phosphorus level was 3.5–7.0 mg/dL at baseline received TEN 5 mg BID added to their PB regimen. The TEN dose was titrated in a stepwise manner within the range of 5, 10, 20 and 30 mg BID. The dose of TEN and PBs was adjusted based on serum phosphorus levels from Week 2, while controlling serum phosphorus levels and switching

from PBs to TEN. While the primary endpoint was safety of the 52-week TEN treatment, the key secondary endpoint was a ≥30% reduction in the total pill number of daily PBs and TEN from baseline.

Results: Overall, 212 patients started treatment, and 154 patients completed the study. At Week 52 or the time of discontinuation, 158 patients (77.5%) achieved a ≥30% reduction in the total daily pill number of PBs and TEN. Complete switching from PBs to TEN was achieved in 93 patients (45.6%). From Week 0 to Week 52, the mean (SD) daily pill number of PBs decreased from 11.4 (7.62) to 3.1 (5.48). Mean (SD) serum phosphorus levels were well controlled, 5.24 (0.96), 4.01 (1.14), and 5.11 (1.17) mg/dL at baseline, Week 2, and Week 52, respectively. The major drug-related adverse event was diarrhea (56.6%), and most events were mild in severity. Nine patients (4.2%) discontinued because of diarrhea. There were no clinically relevant changes other than serum phosphorus level for study period.

Conclusions: TEN demonstrated its ability to significantly decrease the pill number of PBs and was well tolerated in the long-term administration. These results suggest that TEN could achieve the dual targets of decreasing PB pill burden and controlling serum phosphorus levels.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

TH-PO145

Efficacy and Safety of Tenapanor in Japanese Peritoneal Dialysis Patients with Hyperphosphatemia: Results of a Phase 3 Study

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Background: Hyperphosphatemia develops in most peritoneal dialysis (PD) patients and is treated with diet and phosphorus binders (PBs), however some patients do not respond adequately to these treatments. Tenapanor is a novel drug for hyperphosphatemia that blocks intercellular influx of phosphorus from intestinal tract by binding the sodium/hydrogen exchanger 3 transporter (NHE3) expressed on the apical membrane of intestinal epithelial cells. This is the first study to evaluate the efficacy and safety of tenapanor in Japanese PD patients with hyperphosphatemia.

Methods: This was a multicenter, open-label, single-arm, phase 3 study in Japanese PD patients with hyperphosphatemia. The study consisted of a screening period, PB-washout period, and treatment period. Patients were enrolled if serum phosphorus level was 3.5–7.0 mg/dL at screening and elevated to 6.1–9.9 mg/dL after PB-washout. Tenapanor dose was started at 5 mg and titrated to a maximum of 30 mg for 16 weeks to manage serum phosphorus levels within the target range of 3.5–6.0 mg/dL. After week 8, use of only one PB was allowed when serum phosphorus levels were not in the target range. The primary endpoint was the mean change in serum phosphorus at week 8 from baseline. The data for the change in serum phosphorus levels from baseline were carried forward for missing changes using the last observation carried forward method.

Results: A total of 54 subjects received tenapanor. Serum phosphorus levels decreased from a baseline of 7.65 mg/dL to 6.14 mg/dL in week 8 and 5.44 mg/dL in week 16. The change in serum phosphorus at week 8 (primary endpoint) and at week 16 from baseline was −1.18 mg/dL (95% confidence interval −1.54 mg/dL, −0.81 mg/dL) and −1.65 mg/dL, respectively. The proportion of patients who achieved the target levels at week 8 and at week 16 was 46.3% (19/41) and 76.5% (26/34), respectively. The most common adverse event was diarrhea (74.1%, 40/54). All were mild or moderate in severity and only three subjects (5.6%) discontinued due to diarrhea. These results were comparable to those of the phase 3 study in Japanese hemodialysis (HD) patients.

Conclusions: Tenapanor could be a new treatment option for PD patients with hyperphosphatemia as well as HD patients.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

TH-PO146

Safety Analysis of Tenapanor Monotherapy vs. Sevelamer Carbonate in Patients on Maintenance Dialysis with Hyperphosphatemia

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Background: Tenapanor (TEN) is a novel phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). TEN is being evaluated for the control of serum phosphate (sP) in adult patients (pts) with chronic kidney disease on maintenance dialysis. PHREEDOM (NCT03427125) was a phase 3 trial that evaluated TEN in pts on dialysis with HP. The phosphate binder (PB) sevelamer (SEV) was used as a safety control. Here we evaluate overall safety from PHREEDOM and present exposure-adjusted safety analyses.

Methods: The study design has been previously described. The trial enrolled pts on maintenance dialysis with sP ≤10.0 mg/dL and an sP increase ≥1.5 mg/dL after PB washout. The first 26 weeks was an open-label randomized treatment period (RTP) with pts randomized 3:1 to TEN 30 mg bid or SEV per package insert. Safety data collected during the RTP were from pts who received ≥1 dose of study drug. We calculated the exposure-adjusted incidence rates per 100 pt-years.

Results: Safety data is shown in the **Table**. 63.5% of pts randomized to the SEV arm (n=137) had received SEV prior to study entry. During the RTP, one death occurred in the TEN arm (n=419) due to a treatment-emergent adverse event (AE) unrelated to TEN. While the incidence of AEs leading to study drug discontinuation was higher in the TEN arm, the incidence of serious AEs (SAEs) and AEs leading to hospitalization was lower in the TEN arm than the SEV arm. The exposure-adjusted rates of SAEs were similar in both arms.

Conclusions: Incidence of AEs leading to hospitalization was lower in the TEN arm than the SEV arm. The analysis confirmed TEN has an acceptable safety profile.

Funding: Commercial Support - Ardelyx, Inc.

	TEN (n=419)	SEV (n=137)
Pt-years	157.4	64.3
Pts with any treatment-emergent AE (TEAE), n (%)*	337 (80.4%)	88 (64.2%)
Exposure-adjusted incidence rate of AEs per 100 pt-years	214.1	136.9
Pts with any serious TEAE, n (%)	73 (17.4%)	32 (23.4%)
Exposure-adjusted incidence rate of serious AEs per 100 pt-years	46.4	49.8
Pts with any TEAE leading to death, n (%)	1 (0.2%)	0
Pts with any TEAE leading to study drug discontinuation, n (%)	102 (24.3%)	2 (1.5%)
Pts with any TEAE leading to hospitalization, n (%)	73 (17.4%)	32 (23.4%)

*63.5% of pts in the SEV arm had received SEV prior to study entry, potentially confounding the interpretation of AEs in favor of SEV, as demonstrated by the lower AE incidence than reported in its label. Serious AEs should have been largely unaffected by prior exposure.

TH-PO147

Patient Education Improves Tenapanor Tolerability in OPTIMIZE Study

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Background: Tenapanor (TEN) is a novel phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). TEN is being evaluated for the control of serum phosphate (sP) in adult patients (pts) with chronic kidney disease (CKD) on maintenance dialysis. TEN has demonstrated efficacy and acceptable safety in two pivotal monotherapy hyperphosphatemia clinical studies, BLOCK (NCT02675998) and PHREEDOM (NCT03427125). Diarrhea was the most common adverse event, observed in >5% of pts. Here, we evaluate the benefit of pt education on gastrointestinal tolerability during the OPTIMIZE (NCT04549597) study.

Methods: Methods for the trials have been previously described. The majority of patients were started on TEN at 30 mg bid. We assessed data from the analysis period in BLOCK (8-week treatment period [TP]), PHREEDOM (first 8 weeks of TP), and OPTIMIZE (10-week TP). In OPTIMIZE, pts were educated at study start about TEN, how to take TEN, what they may experience on TEN, medications to be discontinued before starting TEN, and how best to mitigate the potential onset of loose stools or diarrhea.

Results: As expected, given the mechanism of action and data from past trials, most diarrhea events (75.7%–79.6%) occurred within the first 2 weeks of treatment in all three studies and the majority of cases were mild to moderate. Overall, the diarrhea incidence was lower during the analysis period in OPTIMIZE (39.3%) than in BLOCK and PHREEDOM (47.9% and 47.7%, respectively), and was also lower during the first two weeks of study treatment in OPTIMIZE (33.6%) vs BLOCK and PHREEDOM (38.0% and 39.4%). Discontinuation rates due to diarrhea were lower during the 10-week analysis period of OPTIMIZE (6.0%) than the 8-week analysis periods of BLOCK or PHREEDOM (7.0% and 13.4%).

Conclusions: Pt education may help ameliorate TEN-related diarrhea in dialysis pts. Specifically, since many pts on dialysis take medications to alleviate constipation, advising pts to discontinue these medications prior to starting TEN may also help reduce the occurrence of diarrhea.

Funding: Commercial Support - Ardelyx, Inc.

TH-PO148

Association Between Sevelamer Use and Risk of Gastrointestinal Bleeding in Patients with Kidney Failure

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Background: Phosphate binders are used to manage hyperphosphatemia in patients with kidney failure requiring replacement therapy. There have been multiple case reports postulating an association between sevelamer use and risk of gastrointestinal bleeding (GIB).

Methods: Using the US Renal Data System and Medicare Parts A, B, and D claims data from 2015 to 2019, we compared the risk of incident GIB hospitalization and death between sevelamer initiation and non-sevelamer phosphate binder initiation among patients on incident hemodialysis (new user, active comparator). We fit Cox regression models with inverse probability of treatment weights to estimate the adjusted hazard ratios (HR) and repeated across relevant subgroups.

Results: We identified 19,939 sevelamer and 19,166 non-sevelamer containing phosphate binder users (mean age 69 years, 52% females, 70% White, 24% Black, and mean dialysis vintage 8.2 months). There were 5,904 GIB hospitalizations and 12,591 deaths after an average of 1.8 years of follow-up. Compared with initiation of

non-sevelamer binders, sevelamer was not associated with an increased risk of GIB hospitalization (HR 1.02, 95% CI 0.97 – 1.07) or all-cause mortality (HR 1.01 95% CI 0.98 – 1.05). Findings were similar across key subgroups, including those defined by diabetes, smoking, anticoagulation, sodium polystyrene, and cholestyramine status.

Conclusions: The initiation of sevelamer versus non-sevelamer containing phosphate binders was not associated with an increased risk of GIB hospitalization in patients on hemodialysis.

Table. IPTW-HR of Incident Gastrointestinal Bleed (GIB) After Phosphate Binder Initiation in Patients on Hemodialysis using an Intention-To-Treat Analysis

	Unweighted No. of Events/N		IPTW-IR (95% CI), per 1000 PYs		
Intention to Treat	Sevelamer	Non-Sevelamer	Sevelamer	Non-Sevelamer	IPTW-HR
Total GIB[a]	3,021/19,939	2883/19,166	86 (81, 90)	84 (81, 87)	1.02 (0.97 - 1.07)
Upper	1,631 (54%)	1,511 (52%)	49 (46, 53)	46 (44, 49)	1.06 (0.99 - 1.13)
Lower	422 (14%)	412 (14%)	13 (11, 15)	13 (12, 15)	0.98 (0.85 - 1.12)
NOS	968 (32%)	960 (33%)	30 (27, 32)	30 (29, 32)	0.97 (0.89 - 1.07)
GIB with Procedure[b]	1,287/19,939	1239/19,166	39 (36, 42)	39 (37, 41)	1.01 (0.93 - 1.09)
Upper	824 (64%)	763 (62%)	26 (23, 28)	24 (23, 26)	1.05 (0.95 - 1.16)
Lower	182 (14%)	182 (15%)	6 (5, 7)	6 (5, 7)	0.97 (0.79 - 1.19)
NOS	281 (22%)	294 (24%)	9 (8, 10)	10 (9, 11)	0.93 (0.79 - 1.10)
All-Cause Mortality	8,201/19,939	7,808/19,166	214 (207, 220)	211 (206, 216)	1.01 (0.98 - 1.05)

Adjusted for 38 covariates across demographics, medical comorbidities, and medication dispense history.

[a] GIB and location (Upper, Lower, & NOS) was defined by ICD hospitalization codes in any billing position

[b] GIB with Procedure was defined by ICD/CPT code for endoscopy within 7 days of hospitalization

Abbreviations: IPTW, inverse probability of treatment-weighting; HR, hazard ratio; NOS, Not otherwise specified; ICD, International Classification of Disease; CPT, Current Procedural Terminology

TH-PO149

Calcimimetic Reimbursement Changes in 2021: Impact of Etelcalcetide Discontinuation on Parathyroid Hormone (PTH) Levels in US Hemodialysis Patients

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Background: Calcimimetics, including etelcalcetide and cinacalcet, are often prescribed to hemodialysis (HD) patients to prevent complications of elevated parathyroid hormone (PTH) levels. In January 2021, US reimbursement policy switched from the transitional drug add-on payment adjustment (TDAPA) to an increased bundled payment, with $10.09 per session added for all patients to cover the expense for calcimimetics, whether patients are taking etelcalcetide or not. The impact on calcimimetic prescription practices and mineral and bone disorder (MBD) markers is unknown.

Methods: Data from 23,359 US in-center HD patients were extracted from the prospective Dialysis Outcomes and Practice Patterns Study (DOPPS). Within-patient changes in PTH and other MBD markers in the 6 months before (pre) vs. 6 months after (post) etelcalcetide discontinuation were compared using linear regression among patients who discontinued etelcalcetide between December 2020 to April 2021 – when discontinuation was more likely driven by policy change than patient indication.

Results: From July 2020 to July 2021, etelcalcetide use decreased from 12% to 5%. Among 713 patients who discontinued etelcalcetide between December 2020 and April 2021, the prevalence of PTH >600 pg/mL increased from 28% to 43% overall and from 32% to 50% among Black patients. Mean serum calcium and phosphorus levels increased by 0.42 and 0.16 mg/dL, respectively. Adjusted model results were consistent (Figure).

Conclusions: In the US HD setting, etelcalcetide use decreased substantially following the end of TDAPA designation in January 2021 in spite of the increased bundle payment. We observed a swift and sustained impact on PTH levels, especially among Black patients, raising concerns about disparities and potential downstream impact on clinical outcomes.

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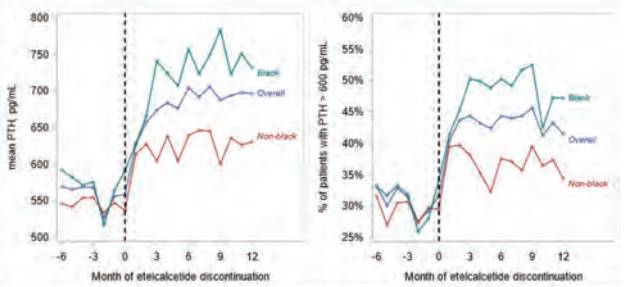

Outcome	N	Pre	Post	Adjusted difference
PTH, pg/mL	680	444[312,634]	556[379,802]	106.5(79.7,133.3)
Calcium, mg/dL	713	8.7±0.6	9.2±0.6	0.42(0.37,0.47)
Phosphorus, mg/dL	712	5.5±1.3	5.7±1.4	0.16(0.09,0.23)
PTH > 600 pg/mL	680	28%	43%	15%(11%,19%)
PTH > 1000 pg/mL	680	10%	14%	5%(2%,7%)
Calcium < 7.5 mg/dL	713	2%	1%	-1%(-2%,0%)
Calcium < 8.4 mg/dL	713	28%	12%	-17%(-20%,-13%)
Calcium > 10.2 mg/dL	713	1%	3%	3%(1%,4%)
Phosphorus > 5.5 mg/dL	712	46%	49%	4%(0%,7%)

'Pre' labs calculated as mean of values measured in the 6 months prior to etelcalcetide discontinuation
'Post' labs calculated as mean of values measured in the 6 months after etelcalcetide discontinuation
Model adjusted for age, sex, vintage, black race, comorbidities, and albumin.

TH-PO150

Etelcalcetide and Long-Term Control of Parathyroid Hormone Levels

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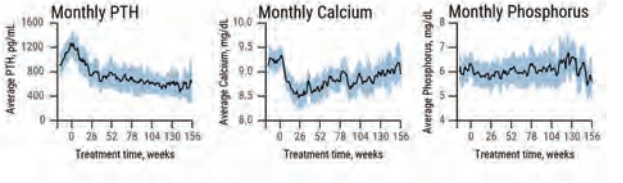
Background: Secondary hyperparathyroidism is a common situation in end stage kidney disease patients receiving hemodialysis. Elevated PTH levels have correlated with vascular complications, accelerated vascular calcification and abnormal bone metabolism, and in clinical practice is used as a surrogate of bone health. Etelcalcetide was approved by the FDA in 2017 for control of moderate to severe hyperparathyroidism in hemodialysis patients. Original studies evaluated the efficacy and safety for a period of up to 26 weeks. The long-term efficacy in controlling PTH levels as well as calcium and phosphorus has not been described.

Methods: All hemodialysis patients treated with Etelcalcetide at Emory hemodialysis centers for at least 3 months were identified and their medical records reviewed. Patients were followed while on treatment if Etelcaetide. Basic demographic information and laboratory data were extracted from the medical record. Median values with IQR are presented unless stated otherwise.

Results: Since 2018, 209 hemodialysis patients were treated with Etelcalcetide and 185 of them received the drug for at least 3 months and represent the study cohort described here. 50% were female. Age was 58 (48-68) years, predominantly Black (96%) and the time on renal replacement therapy before initiation of Etelcalcetide was 4.6 (2.5-7.9) years. Figure 1 shows average PTH, calcium and phosphorus levels during treatment with Etelcalcetide. Median (IQR) PTH levels decreased from 1050pg/mL (861-1396) at time zero to 550pg/mL (351-890) at 6 months and the proportion of patients with PTH below 600 pg/mL was 58.4% compared to 0% at the beginning of treatment. Use of Etelcalcetide was associated with significant reductions of serum calcium specially during the first 6 months of treatment. Phosphorus levels were not significantly affected by the use of Etelcalcetide.

Conclusions: Etelcalcetide was effective lowering serum PTH in a sample of predominantly black patients. The effects of the drug were sustained over a period of 3 years. Treatment with Etelcalcetide was associated with significant decrease in serum calcium during the first 6 months of treatment.



TH-PO151

Predictors of Post-Parathyroidectomy Hypocalcemia in ESRD Patients with Resistant Renal Hyperparathyroidism

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Background: Post-operative hypocalcemia following parathyroidectomy (PTX) for resistant renal hyperparathyroidism(rRHPT) is a major complication that is preventable yet highly prevalent despite protocolized perioperative management. We aimed to determine the predictors of post operative hypocalcemia in our centre from patient characteristics and routine biochemical parameters in order to aid our review of the current centre protocol.

Methods: 75 ESKD patients who underwent parathyroidectomy for rRHPT between May 2016 and October 2022 were enrolled in the study. We collected patients' demographic data, serum levels of albumin, calcium, phosphate, intact parathyroid hormone (iPTH), alkaline phosphatase (ALP), doses of phosphate binders (calcium based and non-calcium based), vitamin D and cinacalcet before and for up to seven days after parathyroidectomy.ROC curves with AUC for iPTH and ALP levels against hypocalcemia were used to determine cutoffs. Multivariable logistic regression model was used to determine the odds ratio and as the incidence rate of the outcome was high, generalized linear models using Poisson regression with robust error variance were used to estimate relative risk.

Results: 37 men and 38 women with mean age of 53.8 ± 11.4 years at the time of surgery were enrolled. The median serum iPTH and ALP levels were 169.8 pmol/L (IQR 113.7, 266.7) and 272U/L (IQR 169, 463) respectively. The mean dialysis vintage was 73.4 months. 43(57%) patients developed severe hypocalcaemia (< 2mmol/L). Patients with severe hypocalcaemia had higher median pre-operative serum iPTH and ALP levels (216pmol/L vs.129.75pmol/L, 380U/L vs. 220.5U/L respectively) and significantly longer mean post operative hospitalization (10.5 vs 4.3 days). Preoperative iPTH level was the only significant predictor of hypocalcemia. iPTH level of >166 pmol/L had 72% sensitivity and 73% specificity for predicting post-operative hypocalcaemia with a relative risk of 2.00 [95% CI 1.27-3.33], p=0.003.

Conclusions: Pre-operative iPTH levels >166 pmol/L can predict post PTX hypocalcemia in ESRD patients. A clinical protocol utilising this iPTH level for risk stratification to determine frequency of calcium level monitoring and calcium and vitamin D supplementation in the peri operative period may help reduce the risk of hypocalcemia.

TH-PO152

The Importance of Parathormone Control in Kidney Transplant Candidates to Avoid Persistent Hyperparathyroidism and Graft Dysfunction

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Background: Persistent hyperparathyroidism (PHPT) after kidney transplantation (KTX) has been associated with poor graft outcome, bone loss, increased risk of fracture, and cardiovascular morbidity. In Brazil, there is a high prevalence of secondary hyperparathyroidism (SHPT) among patients on hemodialysis. We hypothesized that SHPT would increase the incidence of PHPT, which, in turn, would be associated with graft dysfunction.

Methods: We analyzed data from a retrospective cohort of 3,492 patients enrolled in a kidney transplant waiting list at a tertiary Hospital from Jan/2011 to Dec/2020. Parathormone (PTH) was measured in 2,910 individuals, and 870 patients were submitted to KTX during the study. PHPT was defined as calcium > 10.2 mg/dl and/or PTH > 100 pg/ml. Poor graft function was defined as eGFR < 30 ml/min 1 year after KTX.

Results: In the entire cohort, median PTH was 287 (142-544) pg/ml; 1,396 (47.9%) had PTH > 300 pg/ml; 654 (22.4%) had PTH > 9 times the upper limit of the reference range and 399 (13.7%) had > 800 pg/ml, which should be indicative of parathyroidectomy (PTX). However, only 58 (1.9%) were previously submitted to PTX. In those who were submitted to KTX, 428 (49.1%) had PTH > 100 pg/ml, 133 (16.4%) had total calcium > 10.2 mg/dl, and 460 (52.8%) had PHPT after 12 months. PHPT was independently associated with pre-KTX calcium (each 1 mg/dl of Ca increased the risk by 51.6%), PTH (each 100 pg/ml increased the risk by 20%) and graft function (each 1 ml/min increase in eGFR was associated with a decrease in the risk of PHPT by 2.1%). PTX was performed only in 17 patients (2%) during the first year after KTX. PHPT increased the risk of poor graft function by 2.3 times (P<0.001), in a model adjusted for age, sex, race, and donor type.

Conclusions: The high prevalence of SHPT in patients waiting for a kidney transplant is associated with an increased proportion of KTX recipients with PHTP. The consequent impact of PHPT on graft function highlights that CKD-MBD management must be a priority for all CKD patients, even KTX candidates.

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TH-PO153

Long-Term Effects of Hypercalcemia in Kidney Transplant Recipients with Persistent Hyperparathyroidism

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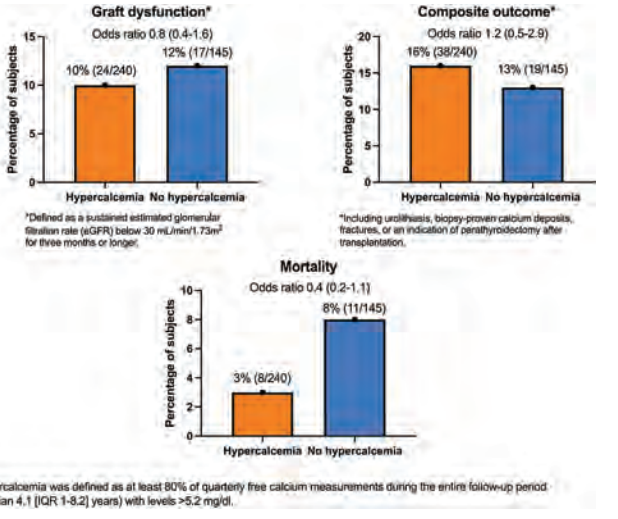
Background: Hypercalcemia is prevalent in kidney transplant recipients (KTRs) with hyperparathyroidism. However, its long-term impact on graft function is uncertain.

Methods: Prospective cohort study investigating adverse graft outcomes associated with persistent hypercalcemia (free calcium >5.2 mg/dL in ≥80% of measures) and inappropriately elevated PTH (>30 pg/mL) in KTRs. Asymptomatic mild hypercalcemia was observed unless complications developed.

Results: We included 385 KTRs. During a 4-year (IQR 1-8.2) median follow-up, 62% of KTRs presented persistent hypercalcemia. Compared to KTRs without hypercalcemia, there were no significant differences in graft dysfunction (10% Vs. 12%, p=0.61), symptomatic urolithiasis (5% Vs. 3%, p=0.43), biopsy-proven calcium deposits (6% Vs. 5%, p=1.0), fractures (6% Vs. 4%, p=0.64), and a composite outcome of urolithiasis, calcium deposits, fractures, and parathyroidectomy indication (10% Vs. 5%, p=0.55) in subjects with persistent hypercalcemia. In a subset of 76 KTRs, those with persistent hypercalcemia had higher urinary calcium (median 84 [43-170] Vs. 38 [24-64] mg/day, p=0.03) and iFGF23 (median 36 [24-54] Vs. 27 [19-40] pg/mL, p=0.04) levels, and lower 25D levels (11.3±1.2 Vs. 16.3±1.4 ng/mL, p<0.001). An iPTH level <300 pg/mL was associated with a reduced risk of post-transplant hypercalcemia in a multivariate analysis (OR 0.51, 95% CI 0.32-0.80).

Conclusions: Long-term persistent mild hypercalcemia, with inappropriately elevated iPTH, was frequent in KTRs after transplantation. This condition closely resembled a mild form of primary hyperparathyroidism, with hypophosphatemia and hypovitaminosis D as well as increased urinary calcium and iFGF23 levels. Despite these symptoms, the risk of adverse graft outcomes was low.



Outcomes associated with hypercalcemia

TH-PO154

How Do We Treat Mineral Bone Disease After Transplantation? A Single-Centre Experience

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Background: Mineral bone disease (MBD) causes increased morbidity and mortality. Previous studies report resolution of hyperparathyroidism in 30% of kidney transplant recipients (KTR) after 1 year and 57% 2 years post transplantation. Current guidelines recommend different strategies of treating hyperparathyroidism without guidance on de-escalation of therapy post transplant. Some centres stop all MBD treatment at the time of transplantation. We looked to determine what medical treatments our KTR were taking for management of MBD.

Methods: A cross-sectional retrospective observational study of all KTR at our centre between 2021-2022 were included. Clinical outcome data was collected from electronic patient records including medications were grouped into; Cinacalcet, Alfacalcidol, Vitamin D3(VitD3) and/or combinations of these for treatment of MBD. The length of time KTR were on these medications and biochemical data was collected. Paired t-tests and ANOVA were used to perform statistical analysis with a $p<0.05$ significant level.

Results: There were 509 KTR between 2021-2022. 9 were excluded due to missing data. 275 male, 225 female with a median age 56yrs (21-87yrs). 500 KTR; 2% were on Cinacalcet, 4% Cinacalcet+Alfacalcidol, 1% Cinacalcet+Alfacalcidol+VitD3, 30% Alfacalcidol, 15% Alfacalcidol+VitD3, 21% VitD3 and 27% on none. Mean time after transplantation was; 8.1yrs, 6.4yrs, 7.1yrs, 7.7yrs, 10.6yrs, 10.7yrs and 10.6yrs, respectively. Mean Creatinine was significantly different between the 2021 and 2022 in the different treatment groups ($p<0.04$) with no significant changes in mean GFR. Mean Creatinine in all the groups except the cinacalcet alone decreased. Those on Cinacalcet+Alfacalcidol or Cinacalcet+Alfacalcidol+VitD3 had the highest creatinine's that decreased from 2021 to 2022. Mean PTH (pmol/L) levels decreased from 2021-2022 in all of the groups (11.7-10.7, 36-14.2, 71.8-61.3, 16.2-13.1, 12-8, 10-9, 9.2-8.7, respectively, $p<0.05$). Calcium adjusted (CA) levels were lower in the Alfacalcidol+VitD3 and VitD3 groups alone (2.0mmol/L). Mean Phosphate levels remain unchanged. Phosphate binders were used in all groups except Cinacalcet and VitaminD3.

Conclusions: A range of combination therapies are used for MBD management. We propose a de-escalation of therapy post transplantation guidance will reduce polypharmacy. Limitation is a single centre experience.

TH-PO155

Bone Disease in Kidney Transplantation: How Are the Bones of Long-Term Kidney Transplant Recipients?

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Background: Kidney transplant (KT) recipients may present persistent chronic kidney disease mineral and bone metabolism disorder (CKD-MBD), changes in bone turnover secondary to immunosuppression, de-novo MBD, and age-related bone loss. The aim of this study was to assess the osteometabolic profile and factors associated with loss of bone mass in long-term transplant patients.

Methods: This was a cross-sectional, retrospective study. Clinical parameters assessed were: age, sex, CKD etiology, dialysis time, KT time, donor type, and immunosuppression. Laboratory tests: intact parathyroid hormone (iPTH pg/dL), calcium, phosphorus, total alkaline phosphatase, 25OH vit D, creatinine and glomerular filtration rate (GFR). Bone mineral density was assessed using densitometry. According to the T-score, patients were divided into two groups: osteoporosis (T-score ≤ -2.5) and non-osteoporosis (T-score > -2.5). A comparative analysis between groups was performed; univariate and multivariate analyzes were undertaken to determine the risk factors for osteoporosis.

Results: We studied 38 patients (60.5% female), with a median age of 57 years, 74% with CKD of undetermined etiology, the median time of dialysis 71 months. Seventy-one percent of KT were from deceased donors and the median time of KT was 181 months. The median GFR was 54 mL/min. The median T-score in the femoral neck and lumbar spine were -1.9 and -2.5, respectively. Twenty patients (52.6%) presented osteoporosis. Patients with and without osteoporosis were distinguished by: age (62 x 50; p=0.002), KT time (252 x 95; p=0.009), iPTH (131 x 234; p=0.034) and use of tacrolimus (35% x 72%; p=0.025). Univariate analysis revealed that age (OR: 1.13; p=0.004), KT time (OR: 1.01; p=0.01) and use of tacrolimus (OR: 0.21; p=0.025) were associated with osteoporosis. In the multivariate analysis, only age (OR: 1.12; p=0.025) was an independent risk for osteoporosis. We observed a positive correlation between iPTH and the T-score, in the lumbar spine (R 0.25; p=0.028) and in the femoral neck (R 0.35; p=0.003).

Conclusions: In long-term kidney transplant recipients, we observed a high prevalence of osteoporosis and confirmed that the loss of bone mass is determined by aging. In the late phase of KT, lower iPTH levels seem to be more associated with loss of bone mass.

TH-PO156

Efficacy of Cinacalcet in the Treatment of Persistent Hyperparathyroidism in Late Kidney Transplantation

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Background: Despite the recovery of renal function after a successful kidney transplant (KT), 20 to 50% of patients present with persistent hyperparathyroidism (PHPT) at the end of the first year, with a low chance of spontaneous remission over time. Permanently high levels of parathyroid hormone (PTH) causes hypercalcemia, hypophosphatemia and loss of bone mass. Most studies that assess the effectiveness of cinacalcet in PHPT have included patients with less than 5 years of KT. The aim of this study was to assess the response to cinacalcet in patients with PHPT with a long duration of KT.

Methods: This was a retrospective observational study. The definition of PHPT was: intact PTH (iPTH)>100 pg/dL and calcium (Ca)>10.5 mg/dL, in patients with glomerular filtration rate (GFR CKD-EPI)>30mL/min/1.73m^2. Ca control (Ca≤10.5) was considered as a response to cinacalcet. According to the response, patients were divided into two groups: responder (RG) and non-responder (NRG). The clinical parameters assessed were: age, sex, etiology of chronic kidney disease (CKD), time on dialysis, time on KT, type of donor and immunosuppression. The laboratory parameters were: iPTH, Ca, phosphorus (mg/dL), total alkaline phosphatase (U/L), creatinine (mg/dL) and GFR. The observation period was one year. A comparative analysis was performed between the groups, as well as an analysis of how the exam results evolved over time.

Results: Twenty patients were included in the study, with a median GFR of 63 mL/min/1.73m^2, (60% female), a median age of 57 years, most with CKD of undetermined etiology, a median time on dialysis of 59 months and a median time of KT of 108 months (70 % deceased donors). A response to cinacalcet was observed in 75% of patients. At baseline, there was no difference between the RG and NRG, except for the iPTH which tended to be lower in the RG (216 x 494; p=0.06). Over the course of a year, Ca in the RG decreased from 10.7 to 9.4 (p=0.003), the same occurred with iPTH, from 216 to 88 (p=0.02). No changes were observed in the Ca and iPTH of the NRG group. The GFR remained stable throughout the observation period in both groups.

Conclusions: Cinacalcet proved to be effective and safe in the treatment of PHPT, even after almost a decade of KT. Our results suggest that the initial iPTH levels seem to influence the response to cinacalcet.

TH-PO157

Dietary Vitamin K Is Inversely Associated with Parathyroid Hormone (PTH) in People with CKD: The PROGREDIR Cohort Study

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Background: Dietary intake has a relevant role in mineral and bone disorder in chronic kidney disease (CKD-MBD), being an important part of the treatment of this condition. However, most studies have focused on intake of phosphorus and calcium, and there is limited literature on possible nutritional determinants of parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). In this study, we evaluated the association of macro and micronutrients from dietary intake with intact PTH (iPTH), 1-84 PTH, and FGF23 in a cohort of people with CKD.

Methods: We included 441 participants from the Progredir Study, a cohort of people with CKD based in São Paulo, Brazil. Food and nutrient intakes were estimated by a food frequency questionnaire. We evaluated the association of these variables with iPTH, 1-84 PTH, and FGF23 by linear regression using SPSS software (version 21).

Results: The median age and 2021 CKD-EPI eGFR were 68 years old and 40 mL/min/1.73 m2, respectively. The median iPTH was 92 pg/mL (IQR 63, 140), 1-84 PTH was 36 pg/mL (IQR 28, 51), and FGF23 was 93 pg/mL (IQR 69, 128). In the univariate linear regression, vitamin K was associated with log iPTH and 1-84 PTH. No associations were observed for FGF-23 and macro or micronutrients. After adjusting for age, sex, eGFR, skin color, diabetes, nutritional status, energy intake, serum calcium, calcium carbonate use, and warfarin use, vitamin K intake remained associated with iPTH (β = -0.13, 95% CI -0.21, -0.04, p = 0.003). Similar result was seen for 1-84 PTH (β = -0.08, 95% CI -0.14, -0.02, p = 0.02).

Conclusions: In these analyses, dietary vitamin K intake was inversely associated with iPTH and 1-84 PTH, even after adjustments for possible confouding variables. To our best knowledge, this is the first study to show this association. Future studies are needed to replicate this finding, investigate mechanisms underlying this association, as well as determine whether interventions in vitamin K lead to changes in PTH levels.

Funding: Government Support - Non-U.S.

TH-PO158

Association of Parathyroid Hormone Concentration with Incident Atrial Fibrillation in Older Persons with Kidney Failure Initiating Dialysis

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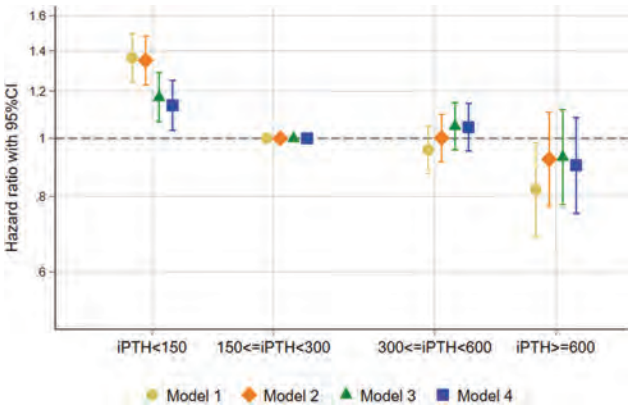
Background: Atrial fibrillaton (AF) is common in persons with kidney failure on hemodialysis (KF-HD). In the general population, higher intact parathyroid hormone (iPTH) levels were found to be associated with presence of AF. Whether iPTH associates with AF in patients with KF-HD is unknown.

Methods: Using merged USRDS-DaVita data (2006-2011) we selected persons aged 67+ years who initiated HD and survived 120 days. Eligible persons had continuous Medicare A+B coverage from 2 years prior to KF and no diagnosis of AF. Sociodemographic, comorbidity, and clinical information was abstracted from Medicare forms, billing claims, and electronic health records. iPTH was categorized consistent with work by Block et al (JASN 2004). Patients were followed for incident (ie, newly-diagnosed) AF as reflected in inpatient and outpatient claims. Unadjusted and multivariable Cox regression was used to estimate the associations of time-updated iPTH category (ref: 150-<300 pg/mL) with incident AF.

Results: Of 15,225 patients initiating HD, surviving 120 days, and without a prior diagnosis of AF, iPTH (in pg/mL) at baseline was <150 in 4479, 150-<300 in 5964, 300-<600 in 3479, and ≥600 in 1064 persons. During 21,845 patient-years 2857 patients had incident AF (rate, 13.1/100 person-years). Hazard ratios with increasing levels of adjustment are shown in the Figure. After multivariable adjustment, patients with iPTH<150 pg/mL had 13% (95% CI, 3-25%) higher AF incidence compared with the 150-<300 pg/mL group, but no association was found for those with iPTH 300-<600 or iPTH ≥600 pg/mL.

Conclusions: Among persons with incident KF-HD, compared with those whose iPTH was between 150 and <300 pg/mL, lower iPTH was independently associated with higher AF incidence; however, no association with AF was identified for higher iPTH levels.

Funding: NIDDK Support



Models: 1) unadjusted; 2) +socio-demographics; 3) +comorbidities & clinical variables; 4) +calcium & phosphorus.

TH-PO159

Is the Discordance Between Spine and Hip Bone Mineral Density in Patients on Dialysis by Vascular Calcification?

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Background: End-stage kidney disease (ESKD) patients with long-standing maintenance dialysis had at greater risk of developing vascular calcification, osteoporosis and cardiovascular disease. In general population, many studies had undergone to identify the association between vascular calcification and bone mineral density (BMD). However, the pathophysiology of vascular calcification in dialysis patients is different from general population, and the study evaluating relationship of vascular calcification with bone mineral density is scarce. In addition, it is not well-known that which bone is more affected to vascular calcification. Therefore, we aimed to evaluate the association between BMD and vascular calcification in patients with maintenance dialysis

Methods: In this multicenter, prospective, observational study of ESKD patient, 576 patients with older than 50 years old or menopausal state of women were analyzed. Vascular calcification was measured by Kaupplia score and BMD of lumbar spine and hip was measured by dual-energy X-ray absorptiometry. Using T-scores, association of vascular calcification with each site of BMD (femur, spine, and lowest score of either femur or spine) was evaluated. Additional analysis with discordance between hip and spine BMD was also performed.

Results: Among 268 (46.5%) women patients, 242 (90.3%) were menopausal state. Median age of study participants was 63.0 (57.0-70.0) years. Spine BMD showed negative correlation with vascular calcification (R=0.1, P=0.014), but hip and lowest score of both BMD were not significant (R=-0.051, P=0.02; R=-0.029, P=0.49, respectively). 282 (52%) patients were concordance between hip and spine BMD, and correlation was not significant in all the hip, spine, and lowest score of both BMD (R=0.0034, P=0.95; R=0.073, P=0.22; R=0.0037, P=0.95, respectively). In discordance group, spine BMD was also negatively correlated (R=0.19, P=0.0023) and hip BMD was positively correlated (R=-0.12, P=0.053), with more prominent in low BMD of less than -2.5 (R=-0.22, P=0.048).

Conclusions: In dialysis patients with discordance BMD, vascular calcification is positively associated with hip BMD (especially in low BMD of less than -2.5) and negatively associated with spine BMD.

TH-PO160

Efficacy and Side Effects of Denosumab for Stage 3b-4 CKD Patients with Osteoporosis: An Open-Label, Prospective Pilot Clinical Study

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Background: We sought to evaluate the efficacy and safety of denosumab, including denosumab-induced hypoglycemia, in patients with chronic kidney disease (CKD) stage 3b-4 and osteoporosis. We also aimed to evaluate whether denosumab affects coronary artery calcium score (CAC) in these patients.

Methods: A total of 27 female patients with CKD stage 3b-4 and osteoporosis were enrolled. Twenty patients received denosumab plus calcium carbonate and vitamin D, and 7 control patients received calcium carbonate and vitamin D for 1 year. Osteoporosis was confirmed by using dual-energy X-ray absorptiometry (DXA). Coronary multi-detector CT was performed to calculate the coronary calcium score.

Results: No significant differences were found in medication history, demographics, eGFR, BMI, lumbar and hip BMD, bone turnover markers, 25(OH)D, homocysteine, CAC between the two groups at baseline. There was significant improvement of BMD in the denosumab treatment group. Lumbar spine, femur neck, total hip T score increased by 5.6±5.9%, 3.6±3.2%, 3.4±3.8% respectively, from baseline in the denosumab-treated group, while, 2.7±3.9%, -0.7±4.4%, -1.9±2.1% changes were observed in the control group. (Lumbar; *P*=0.273, femur neck; *P*=0.033, total hip; *P*=0.001). Among bone turnover markers, the percent change in bone ALP and CTX was -31.1±30.0% and -49.2±29.9% in the denosumab treatment group and -4.5±32.0% and -17.7±28.0% in the control group (ALP; *P*=0.027 and CTX; *P*=0.025). PTH level change were not different between two groups (denosumab; 9.0±81.7% vs. control; -0.7±79.4%, p=0.580). There were no significant changes in calcium, ionized calcium, phosphorus, and PTH levels throughout the study. CAC, and homocysteine percent change did not differ between groups (CAC; *P*=0.563 and homocysteine; *P*=0.143)

Conclusions: Denosumab has provided significant benefits without hypocalcemia for 1 year in patients with stage 3b-4 CKD when used judiciously. However, denosumab treatment did not affect homocysteine and CAC in these patients.

Funding: Private Foundation Support

TH-PO161

International Variations in Serum PTH and Calcium Levels and Their Mortality Associations in Peritoneal Dialysis Patients: Results from PDOPPS

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Background: Mineral bone disorder (MBD) in chronic kidney disease (CKD) is associated with high symptom burden, fractures, vascular calcification, cardiovascular disease, and increased morbidity and mortality. CKD-MBD studies have been limited in peritoneal dialysis (PD) patients. Here, we describe calcium and parathyroid hormone (PTH) control, and mortality associations in PD patients.

Methods: We used data from 8 countries [Australia and New Zealand (A/NZ), Canada, Japan, Thailand, South Korea, United Kingdom, United States (US)] participating in the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS; 2014-2022) among patients receiving PD for >3 months. We analyzed the association of baseline PTH and albumin-adjusted calcium ($calcium^{Alb}$) with all-cause mortality using Cox regression, adjusted for potential confounders.

Results: Mean age ranged from 54.6 yrs in South Korea to 63.5 yrs in Japan. PTH and serum $calcium^{Alb}$ were measured at baseline in 12,642 and 14,244 patients, respectively. Median PTH ranged from 161 (Japan) to 363 pg/mL (US); mean $calcium^{Alb}$ ranged from 9.1 (South Korea, US) to 9.8 mg/dL (A/NZ). The PTH/mortality relationship was U-shaped with lowest risk at PTH 300-599 pg/mL. Mortality was nearly 20% higher at serum $calcium^{Alb}$ 9.6+ mg/dL vs 8.4-<9.6 mg/dL.

Conclusions: A large proportion of PD patients in this multi-national study have Ca and/or PTH levels in ranges associated with substantially higher mortality. These observations point to the need to substantially improve MBD management in PD to optimize patient outcomes.

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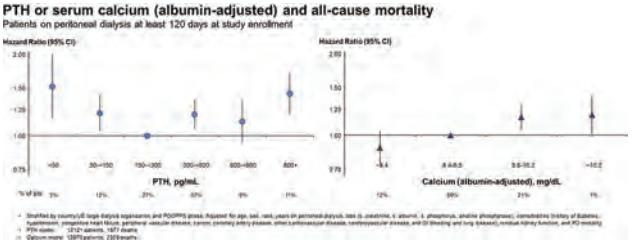

TH-PO162

Serum Parathormone Trajectory During the First Year of Hemodialysis: A Roadmap to Severe Hyperparathyroidism

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Background: Previous studies have shown that uncontrolled hyperparathyroidism is more common in patients that initiate dialysis therapy with high parathormone (PTH). In Brazil, optimal control of PTH is challenging and many patients are in waiting lists for parathyroidectomy (PTX). However, data on PTH levels during dialysis initiation and its behaviour during the first year of therapy is still scarce. We hypothesized that high PTH

levels at beginning of therapy, as well as poor control of CKD-MBD parameters would contribute to the high percentage of severe forms of hyperparathyroidism in prevalent patients on hemodialysis.

Methods: We included 1,973 individuals starting therapy between Feb 1, 2012, and Dec 31, 2016, who completed 1 year of dialysis. Data evaluated included age, sex, race, diabetes mellitus, body mass index (BMI), paying source (Public Health System or private), place of first dialysis (clinic or hospital), calcium, phosphorus, albumin, urea, alkaline phosphatase and PTH. Patients were divided into 3 groups according to baseline and 12-months PTH values (<150, 150-600 and >600 pg/mL).

Results: The percentage of patients with PTH <150, 150-600 and >600 pg/mL was 28.1%, 53.5% and 18.4%, respectively at the study entry and 30.7%, 52.5% and 16.8% after 1 year of follow-up. From patients with a baseline PTH >600 pg/mL, 44.9 % and 10.2% reached 150-600 and <150 pg/mL, respectively, but 44.9% remained with high serum PTH. Patients with PTH >600 pg/mL at 12 months were younger, mostly non-white and financed by Public Health System, less likely to have diabetes. In addition, they had higher PTH, phosphate, alkaline phosphatase, and albumin serum levels at baseline. Multivariate analysis confirmed that age [CI 0.981 (0.973-0.990)], diabetes [CI 0.595 (0.445-0.795)], baseline alkaline phosphatase [CI 1.003 (1.001-1.004)], and baseline PTH >600 [CI 4.003 (3.055-5.325)] were independently associated with uncontrolled PTH after 1 year of therapy.

Conclusions: A considerable proportion of dialysis patients in Brazil initiate therapy with high PTH levels, indicating a poor control during conservative management. Also, the inadequate management of medically therapy during the first year of dialysis might expose high number of individuals to a risk of future need of PTX.

Funding: Government Support - Non-U.S.

TH-PO163

Serum Magnesium Levels and Cognitive Function in Hemodialysis Patients: A Cross-Sectional Study

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Background: Dementia is a global challenge for geriatric care and social welfare, including for aging dialysis patients. Previous studies have suggested a potential association between cognitive function and chronic kidney disease-mineral and bone disorder (CKD-MBD). The present study aims to evaluate this association among patients with hemodialysis.

Methods: We conducted a cross-sectional study of patients with hemodialysis to examine the association between cognitive functions, as assessed by the Montreal Cognitive Assessment (MoCA) and the Mini-Mental State Examination (MMSE), and serum magnesium, intact parathyroid hormone (PTH), 25-hydroxyvitamin D(OHD), Fibroblast Growth Factor(FGF)-23, and soluble α-Klotho.

Results: This study involved 390 patients whose median age was 74 (70-80) years and who had been receiving hemodialysis for an average of 87 (36-168) months. The mean serum magnesium level was 2.4 ±0.3 mg/dL, and the median intact PTH and 25-OHD levels were 157 (94-238) pg/mL and 14.1 (10-19.6) ng/mL. The median intact FGF-23 and soluble α-Klotho levels were 1921 (602-4840) pg/mL and 381 (300-517) pg/mL. The median MoCA and MMSE scores were 25 (22-26) and 28 (26-29). The MoCA and MMSE score were significantly higher (cognitive function is preserved) in patients with higher magnesium levels than lower magnesium after adjusted multivariate analysis (β coefficient [95% confidence interval], 0.91 [0.03, 1.78]; P=0.043 for MoCA, and 0.82 [0.13, 1.5]; P=0.019 for MMSE). There were no significant associations between cognitive functions and serum intact PTH, 25OHD, FGF-23, and soluble α-Klotho levels.

Conclusions: Higher serum magnesium levels were associated with preserved cognitive function in hemodialysis patients, and avoiding hypomagnesemia may be recommended to protect cognitive function. On the other hand, no significant associations were observed between cognitive functions and serum intact PTH, 25OHD, FGF-23, and soluble α-Klotho levels.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO164

Marrow Adipocytes Do Not Suppress Mineralization by Osteocytes in Hemodialysis Patients

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Background: Increased marrow adipocytes induce low bone turnover in non-CKD and CKD subjects (Bone Rep. 21, Endocr Rev. 19). And bone marrow adiposity is increased in CKD subjects (Osteoporos Int. 15). It was revealed recently that the osteocyte plays the important roles which affect bone turnover and osteocytic perilacunar/canalicular turnover in dialysis patients (Bone. 18, Kidney Int. 18, JBMR Plus. 19). In this research, the relationship between marrow adiposity and mineralization by osteocytes after parathyroidectomy for secondary hyperparathyroidism (IIHPT) was investigated in hemodialysis (HD) patients.

Methods: Thirty one HD patients with IIHPT, including Group I (n = 15, Age; 56.1 ± 6.5 yr, duration of HD; 17.7 ± 5.9 yr, serum intact PTH (iPTH); 1482.5 ± 860.7 pg/mL) and Group II (n = 16, Age; 56.7 ± 9.1 yr, duration of HD; 13.4 ± 8.2 yr, serum iPTH; 1330.4 ± 659.2 pg/mL) were investigated. These patients were treated with total parathyroidectomy with immediate autotransplantation (PTX) and received 2.0μg/day of alfacalcidol for four weeks after PTX. The patients underwent transiliac bone biopsies before and 1 week (Group I) and 4 weeks (Group II) after PTX. Oc.S/BS (%), Ob.S/BS (%), BFR/BS ($mm^3/mm^2/yr$), hypomineralized bone area (HM.B.Ar/B.Ar; %) and marrow adipocyte area (Ad.Ar/Ma.Ar; %) were measured in cancellous bone.

Results: In Group I, serum iPTH decreased from 1482.5 ± 860.7 to 43.2 ± 81.6 pg/mL. Oc.S/BS significantly decreased and Ob.S/BS increased after PTX. And Ad.Ar/Ma. Ar increased from 13.6 ± 8.2 to 25.8 ± 12.4 % (p = 0.002) after PTX. In Group II, serum iPTH decreased from 1330.4 ± 659.2 to 20.6 ± 24.8 pg/mL. Oc.S/BS decreased from 4.4 ± 3.7 to 0.1 ± 0.5 % (p < 0.001) and Ob.S/BS also decreased from 22.3 ± 11.4 to 15.0 ± 17.2 % (p = 0.004) after PTX. BFR/BS was significantly lower than that of the other HD patients with IIHPT (n = 14, iPTH = 755.7 ± 341.5 pg/mL) (0.022 ± 0.014 vs. 0.051 ± 0.027 $mm^3/mm^2/yr$, p = 0.003). HM.B.Ar/B.Ar decreased from 17.0 ± 13.5 to 2.8 ± 3.4 % (p < 0.001) although Ad.Ar/Ma. Ar increased from 16.7 ± 11.2 to 26.6 ± 8.3 % (p = 0.030) after PTX in Group II.

Conclusions: Increased marrow adiposity was closely associated with low bone turnover, however, mineralization by osteocytes was not suppressed after PTX.

Funding: Private Foundation Support

TH-PO165

Effect of Gastrointestinal Factors on Bone Turnover Markers in ESRD

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Background: Chronic kidney disease - mineral and bone disorder (CKD-MBD) is a serious but not yet fully understood complication to CKD. Recent studies show that an oral glucose challenge affects bone resorption to a larger extent than intravenously administered glucose – the so-called gut-bone axis. Here, we investigated the effect of gastrointestinal factors on bone-turnover in end-stage renal disease.

Methods: Plasma samples from a previously published study involving 10 patients receiving chronic hemodialysis treatment (ESRD) and 11 healthy controls (CTRL) with normal glucose tolerance were analyzed post hoc. On two separate examination days, participants were studied in a fasted state with a 3h oral glucose tolerance test (OGTT) and an isoglycemic intravenous glucose infusion (IIGI) mimicking the plasma glucose excursions on the OGTT day. Carboxy-terminal collagen type 1 crosslinks (CTX), procollagen type I N-terminal propeptide (PINP), bone-specific alkaline phosphatase (BAP) and intact parathyroid hormone (PTH) were measured at baseline and every 30 minutes during OGTT and IIGI. All bone-turnover marker concentrations were evaluated relative to baseline levels and average excursions calculated using baseline-subtracted area under the curve (AUC). Values are expressed as median [IQR] or mean (95% CI).

Results: Median baseline concentrations of CTX (2.3 [1.9;4.9] (ESRD) vs. 0.4 [0.4;0.8] ng/ml (CTRL), P = 0.014) and PTH (292 [146;500] (ESRD) vs. 44 [32;73] pg/ml (CTRL), P = 0.003) were significantly elevated in patients compared to controls while PINP (142 [54;274] (ESRD) vs. 67 [60;78] ng/ml (CTRL)) and BAP (13.4 [10.8;20.5] (ESRD) vs. 15.3 [11.4;17.1] μg/l (CTRL)) were comparable. CTX was significantly suppressed during OGTT in both groups but to a significantly lesser extent in ESRD compared to CTRL (-15 (-20;-9)%) vs. (-43 (-50;-36)%; P < 0.001). During IIGI, CTX was significantly suppressed in CTRL (-15 (-21;-9)%) but not in ESRD (-1 (-6; 4)%). Neither P1NP nor BAP changed from baseline in response to OGTT or IIGI whereas PTH showed significant suppression in response to OGTT (but not to IIGI) in CTRL (-9 (-15;-4)%).

Conclusions: Suppression of the bone resorption marker CTX in response to OGTT is impaired in ESRD indicating that gastrointestinal factors may play a role in CKD-MBD.

Funding: Private Foundation Support

TH-PO166

Impact of an EHR Alert on SGLT2 Inhibitor Use in Patients with Type 2 Diabetes (DM2) and CKD

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Background: SGLT2-inhibitors have been shown to reduce the risk of progression to ESRD in patients with CKD. Both KDIGO and ADA strongly recommend that all patients with CKD and DM2 should be prescribed an SGLT2-inhibitor. However, SGLT2-inhibitors remain under prescribed, especailly amongst non-nephrologists. We implemented a quality improvement project to increase SGLT2-inhibitor prescribing and to narrow the gap between nephrologists and non-nephrologists by developing an EHR alert recommending SGLT2-inhibitors at time of patient visit.

Methods: This was a quality improvement project in which an EHR alert targeting patients with DM2 with last eGFR between 30 and 60 ml/min and last ACR > 300 was rolled out on 6/22/2022. Inclusion criteria for the EHR alert were age 18-85, CKD G3

with last eGFR between 30-59 ml/min, most recent ACR > 300 mg/gm or PCR > 0.5 within past 12 months, and on ACEi or ARB or intolerance. Data was deidentified and collected cross sectionally monthly from a diabetes registry and reviewed quarterly. We tracked SGLT2 inhibitor use within 1 year of index date. SGLT2-inhibitor use was compared to patients with eGFR > 60 ml/min with ACR > 300 mg/gm who were not included in the EHR alert.

Results: Prior to the EHR alert, SGLT2 inhibitor was prescribed at a higher rate in patients managed by nephrology vs. patient not managed by nephrology (28.5% vs. 10.7%). By 8 months after its rollout, this gap had increased further (44.5% vs. 16.3%). Prior to EHR alert, SGLT2 inhibitors were prescribed in 18.6% of patients with eGFR between 30 to 60 ml/min and ACR > 300 mg/gm vs. 10.2% in patients with eGFR ≥ 60 ml/min and ACR > 300 mg/gm. By 8 months afterwards, this had increased to 32% and 15.7% respectively. Amongst patients not followed by nephrology, SGLT2 inhibitor was prescribed in 13% of patients with eGFR between 30 to 60 ml/min and ACR > 300 mg/gm vs. 9.4% in patients with eGFR ≥ 60 ml/min and ACR > 300 mg/gm prior and 23.6% vs. 13.3% by 8 months after the EHR alert.

Conclusions: We saw a greater increase in SGLT2 inhibitor prescribing in patients with CKD targeted by an EHR alert compared to patients not targeted by an EHR alert. However, overall SGLT2 prescribing remained low and we were unable to close the gap between patients managed and not managed with nephrology.

TH-PO167

Trajectory of Glomerular Filtration Rate Decline and Fluctuation in Albuminuria Leading to ESKD: An Observational Cohort Study of Biopsy-Confirmed Diabetic Kidney Disease

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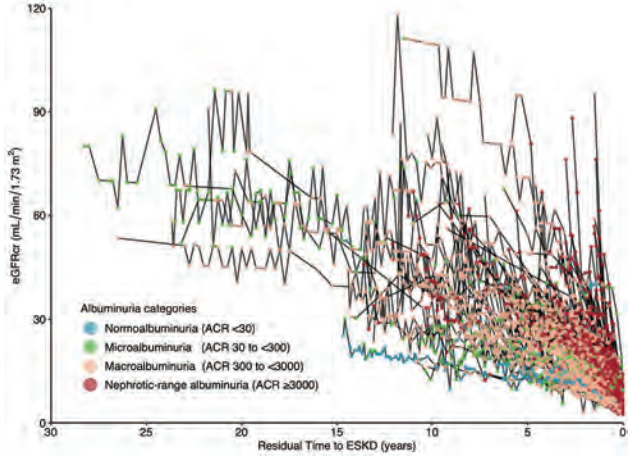
Background: Data on trajectory of kidney function decline and fluctuation in albuminuria leading to end-stage kidney disease (ESKD) is sparse in patients with type 2 diabetes.

Methods: Using data from an observational study of biopsy-confirmed diabetic kidney disease (DKD), panel data analyses were performed to quantify patterns of trajectory of estimated glomerular filtration rate (eGFR) decline to ESKD associated with repeated measures of urine albumin-to-creatinine ratio (ACR).

Results: During a median follow-up of 3.25 years, 156 out of 312 developed ESKD. Among them, 84.0% showed a curvilinear pattern of eGFR trajectory, 62.2% moved into a different albuminuria status from that at baseline, and 84.6% of patients developed nephrotic-range albuminuria, many of whom remained nephrotic. Mixed-effects models for repeated measures showed that speed of eGFR decline for normo- [ACR <30 mg/g], micro- [ACR 30 to <300 mg/g], macro- (non-nephrotic range albuminuria) [ACR 300 to <3000 mg/g] and nephrotic-range albuminuria [ACR ≥3000 mg/g] were -2.50 (95% CI, -8.62 to 3.62; P =0.423), -4.76 (95% CI, -8.94 to -0.57; P =0.026), -6.39 (95% CI, -8.31 to -4.48; P <0.001) and -9.51 (95% CI, -11.75 to -7.28; P <0.001) mL/min/1.73 m^2/year, respectively.

Conclusions: Majority of patients with biopsy-confirmed DKD who developed ESKD showed a curvilinear eGFR trajectory with fluctuation in ACR. Although there were high inter- and intra-individual variability in changes in eGFR and ACR, ACR were inversely associated with eGFR decline, which suggests that close monitoring of ACR fluctuation over time instead of a single assessment of ACR may be necessary to detect eGFR decline to ESKD.



TH-PO168

AWARD-7 Post Hoc Analysis: Circulating Proteins Measured by Joslin Kidney Panel Identify Dulaglutide Responders

Brandon E. McFarlin,[1] Sok Cin Tye,[2] Eiichiro Satake,[2] Zaipul Md Dom,[2] Joseph Ricca,[2] Afton V. Kechter,[1] Jonathan M. Wilson,[1] Kevin L. Duffin,[1] Andrzej S. Krolewski.[2] *[1]Eli Lilly and Company, Indianapolis, IN; [2]Joslin Diabetes Center, Boston, MA.*

Background: The AWARD-7 trial demonstrated that the glucagon-like peptide-1 receptor agonist (GLP1-RA) dulaglutide (DULA) can slow the decline in estimated glomerular filtration rate (eGFR) in diabetic patients with chronic kidney disease (CKD). Previously we've identified 21 circulating proteins (Joslin Kidney panel – JKP) that are associated with progression to end-stage kidney disease (Kobayashi et al. 2022). We aimed to investigate whether we could leverage the JKP to discern between patients for whom DULA is associated with reduced odds of rapid eGFR decline from those with no impact.

Methods: Plasma samples were obtained from AWARD-7 patients who received DULA 1.5 mg (n=124) or insulin glargine (n=125) for 52 weeks. The 21 JKP was measured using Olink custom-made platform. Proportion of fast decliners (eGFR loss >5.0 ml/min/yr) was evaluated according to plasma concentration of the 21 JKP proteins at baseline, 26- and 52- weeks of the trial.

Results: Concentration of 21 JKP proteins at baseline and 52 weeks did not provide information to predict effectiveness of DULA on reduction of fast decliners. Among patients with above median change in protein concentration from baseline to 26 weeks (26 DELTA), DULA was associated with lower odds of rapid eGFR decline compared with glargine. Specifically, 26 DELTA above median for EHNA4, SYND1, TNF-R1A, -R1B, GFRa1, or DLL1 was associated with significantly lower odds of fast eGFR decline in DULA arm. There was no difference between treatments in patients with below median change in protein concentration.

Conclusions: DULA arm was associated with lower odds of rapid eGFR decline in patients with the greatest change in 6 circulating risk proteins. Further studies are necessary to validate the use of these JKP proteins as effective biomarkers of treatment responders.

Funding: Commercial Support - Eli Lilly and Company

Associations of rapid eGFR decline with change in protein concentration from baseline to 26 weeks (26 DELTA)

Protein	Treatment	Below median		Above median		$P_{interaction}$
		Frequency [n,N (%)]	OR (CI)	Frequency [n,N (%)]	OR (CI)	
TNF Receptors						
TNF-R1A	Glargine	8, 62 (13)		19, 63 (30)		
	DULA	7, 62 (11)	0.86 (0.29, 2.53)	4, 62 (7)	0.16 (0.05, 0.50)	0.04
TNF-R1B	Glargine	6, 62 (10)		21, 63 (33)		
	DULA	6, 62 (10)	1.00 (0.30, 3.29)	5, 62 (8)	0.18 (0.06, 0.50)	0.03
Neuronal - axon guidance						
EFNA4	Glargine	7, 62 (11)		20, 63 (32)		
	DULA	8, 62 (13)	1.16 (0.39, 3.43)	3, 62 (5)	0.11 (0.03, 0.39)	0.01
GFRa1	Glargine	10, 62 (16)		17, 63 (27)		
	DULA	8, 62 (13)	0.77 (0.28, 2.10)	3, 62 (5)	0.14 (0.04, 0.50)	0.04
Pro-fibrotic						
DLL1	Glargine	10, 62 (16)		17, 63 (27)		
	DULA	8, 62 (13)	0.77 (0.28, 2.10)	3, 62 (5)	0.14 (0.04, 0.50)	0.04
SYND1	Glargine	10, 62 (16)		17, 63 (27)		
	DULA	9, 62 (15)	0.88 (0.33, 2.35)	2, 62 (3)	0.09 (0.02, 0.41)	0.01

Below median defines patients within quartile 1 and 2 or pateints with lowest change from baseline. Above median defines pateints within quartile 3 and 4 or patients with highest change from baseline. Rapid eGFR decline is defined as >5 ml/min/1.73m^2/year loss of eGFR. The number of rapid decline cases (n) per patient population (N) and frequency (%) are displayed. OR (CI) defines the risk of eGFR decline >5 ml/min/1.73m^2/year. P value for interaction represents the statistical comparisons between the two odds ratios. TNF-R3, -R4, -R6B, -R7, -R10A, R19L, R27, WFDC2, PI3, CD160, EPHA2, LAYN, KIM1, IL1RT1, and PVRL4 were also measured but did not reach statistical significance.

TH-PO169

Renal Autologous Cell Therapy (REACT) to Delay Dialysis in Advanced CKD

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Background: Few treatments delay CKD progression. Cell-based options may offer destination therapy to preserve kidney function and avoid/delay renal replacement therapy (RRT).

Methods: Adults with Type 2 diabetes (T2DKD) and eGFRs 14-20 ml/min/1.73m^2 participated in a multisite, FDA-approved phase 2 open label single arm trial (NCT03270956). After a kidney biopsy and *ex vivo* cell expansion, 2 percutaneous injections of REACT into the renal cortex were performed ~6 months apart. Patients were followed for up to 24 months to end of study (EOS) after the last injection. Outcomes

included estimated glomerular filtration rate (eGFR) slope change (mixed linear effects analysis), time to dialysis, and adverse events (AEs).

Results: Ten patients were enrolled: 8 White race, 3 Hispanics, 5 Women. The cohort's mean age was 58.3 ±5.0 years and BMI 35.20 ±8.4 kg/m^2. Nine patients had two injections and selected parameters are displayed in Table 1. Median time to dialysis was 19.4 months (IQR 13.3-27.9) and two patients were alive and dialysis free at EOS. Pre-injection eGFR slope improved 2.9 and 3.5 ml/min/1.73m^2/year post 1st and 2nd injections. AEs: Six patients progressed to sustained RRT, two deaths occurred without RRT due to COVID-19 pneumonia and diabetes complications with COVID-19. Biopsy-related AEs: 1 each hematoma (no transfusion) and AVF. Injection-related AEs: 6 small-moderate hematomas (no transfusions), 1 each: hematuria, perinephric fluid, anemia, fatigue, and pain. REACT-related AEs: none.

Conclusions: REACT was tolerated and preserved function to decelerate eGFR decline, suggesting a non-dialytic treatment option for T2DKD progressing to RRT. Phase 3 randomized controlled trials and safety monitoring are underway.

Funding: Commercial Support - ProKidney

Table 1. Trial parameters

Parameter	Baseline n=10	12 months n=5	EOS n=2
Serum Cr mg/dL	3.62±0.7	4.46±1.0	4.33±1.9
eGFR ml/min/1.73m^2	15.5±2.7	12.6±3.3	14.8±7.7
Phosphate mg/dL	4.75±0.9	4.18±0.6	5.3±2.0
Potassium mEq/L	5.19±0.5	4.65±0.3	4.7±0.7
Bicarbonate mEq/L	19.24±2.5	19.22±2.3	18.50±5.9
Calcium mg/dL	8.95±0.6	9.06±0.7	9.0±0.4
PTH ng/L	220.9±126.3	253.6±208.1	297.3±301.0
Hemoglobin	10.49±1.1	10.18±1.8	11.3±0.2
Kidney Function (eGFR slope change ml/min/1.73m^2/year)			
Timeframe		Patients (n)	eGFR slope (SE)
Pre-injection		10	-6.3 (1.29)
Post-1st injection		10	-3.4 (0.56)
Post-2nd injection		9	-2.8 (1.01)

TH-PO170

Canagliflozin Treatment Impact on Collagen Type III Turnover Is Associated with a Reduced Mortality Risk in CANVAS

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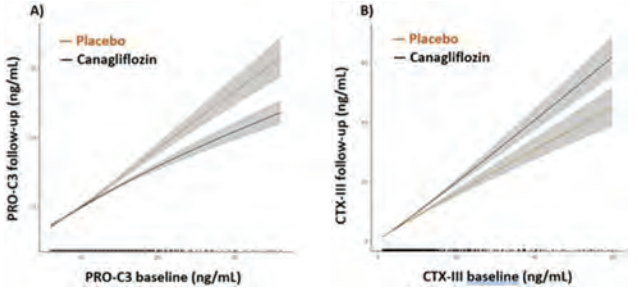
Background: The precise mechanism underlying the beneficial effects of SGLT2 inhibition remains uncertain; however, it has been suggested that it may be related to a decrease in inflammation and tissue fibrosis. Collagen type III (COL III) is one of the major constituents of the extracellular matrix in different organs and is markedly upregulated in fibrotic conditions. In this study, we examined the effect of canagliflozin treatment on biomarkers of COL III turnover in the CANVAS trial.

Methods: Fragments reflecting COL III formation (PRO-C3) and degradation fragments of both cross-linked (CTX-III) or non-cross-linked COL III (C3M) were assessed with ELISA in plasma (n=2141, 1549, 2155, respectively). The change in biomarker levels from baseline to year 3 were investigated in plasma samples from both placebo (PBO)- and canagliflozin (CANA)-treated patients using a linear model. Investigated outcomes included all-cause mortality (n=116). Hazard ratios (HR) with 95% CI represent a comparison of the 75th percentile versus 25th percentile. The p-values presented are derived from a Wald test.

Results: At follow-up,PRO-C3 was significantly lower (p<0.0001; **Figure 1A**) and CTX-III was significantly higher in CANA-treated patients compared to PBO-treated patients (p=0.0002; **Figure 1B**). There was no impact on C3M (p=0.06, not shown). In the entire cohort, an increase in PRO-C3 was significantly associated with all-cause mortality (HR [95% CI] = 1.07 [1.05-1.10], p<0.0001). The prognostic ability of an increase in PRO-C3 to predict all-cause mortalitywas significantly higher in the PBO-treated patients than in the CANA-treated patients (1.28 [1.11-1.47] vs 1.07 [1.04-1.10], p=0.04).

Conclusions: The observed decrease in fragments reflecting COL III formation, as well as the increase in cross-linked COL III degradation fragments following canagliflozin treatment may reflect the anticipated potential anti-fibrotic effect of the treatment. An increase in COL III formation was associated to an increase in the risk of all-cause mortality.

Funding: Commercial Support - Janssen and Nordic Bioscience



TH-PO171

Circulating Proteins Protect Against Fast Kidney Function Decline and ESKD in Early Diabetic Kidney Disease

Zaipul Md Dom,[1,2] Helen C. Looker,[3] Eiichiro Satake,[1,2] Robert G. Nelson,[3] Andrzej S. Krolewski.[1,2] *[1]Joslin Diabetes Center, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ.*

Background: We recently identified circulating protective proteins against ESKD and kidney function decline in advanced diabetic kidney disease (DKD) (Md Dom *et al.* Sci Transl Med 2021). Proteins that protect against kidney failure/decline in early stages of DKD will further complement and offer valuable insights into underlying mechanisms.

Methods: We followed 294 subjects (45% female) with T1D from Joslin Proteinuria Cohort (median uACR 491 mg/g) with normal baseline kidney function (median eGFR 100 ml/min). We conducted a replication study in an independent cohort of 162 Pima Indians with T2D and very early stage of DKD (median GFR 149 ml/min); 105 subjects had research kidney biopsies obtained in close proximity to baseline examination. We quantified 550 proteins in baseline plasma samples using the SOMAscan platform.

Results: In the Joslin cohort, 39% subjects reached the composite outcome of ESKD or 40% GFR loss within 10 years. Sixty-two (38%) of Pima subjects developed the composite outcome. In univariable logistic model, 54 proteins were significantly associated (Bonferroni-corrected) with protection against kidney failure/decline in the Joslin T1D cohort. Ten proteins were replicated in the Pima T2D cohort. Odds ratios remained significant after adjustment for key confounders. Proteins were clustered into 3 groups. A three-marker panel (FGF17, BMP10, PRLR) was derived and this panel, with added clinical parameters, significantly improved prediction of the composite outcome (c=0.852, p=0.026). BMP10 had significant positive correlations with podocyte density (r=0.30) and filtration slit frequency (r=0.21), and inverse correlations with global glomerular sclerosis (r=-0.28), mesangial fractional volume (r=-0.21) and podocyte foot process width (r=-0.20). Kidney transcriptomic profiles suggest a non-kidney source of circulating protective proteins.

Conclusions: In two independent cohorts with different types of diabetes and racial groups, we identified ten plasma proteins in early DKD associated with no/slow progression to ESKD, which may be therapeutic targets for delaying or preventing the onset of ESKD.

Funding: NIDDK Support

Cluster	Gene Name	Joslin T1D Cohort Odds Ratio	Pima T2D Cohort Odds Ratio	Combined Cohorts Adjusted Odds Ratio	Adjusted p
1	IgG	0.56	0.63	0.69	9.56E-04
	APOD	0.61	0.74	0.75	9.11E-03
	FGF8	0.60	0.66	0.71	2.33E-03
	FGF17	**0.64**	**0.69**	**0.73**	**5.58E-03**
	MMP16	0.57	0.60	0.73	5.10E-03
	IL13	0.61	0.71	0.70	1.36E-03
2	CD84	0.57	0.63	0.66	1.68E-04
	BMP10	**0.56**	**0.65**	**0.66**	**3.32E-04**
	KIT	0.59	0.68	0.67	8.47E-06
3	**PRLR**	**0.60**	**0.72**	**0.70**	**1.27E-03**

Three-marker panel is indicated in bold.

TH-PO172

Evaluation of Extracellular Matrix Turnover Proteins as Risk Markers in Persons with Type 2 Diabetes and Microalbuminuria

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Background: Increased turnover of extracellular matrix (ECM) proteins has been demonstrated in many diseases and is an underlying and driving feature of pathogenesis. We investigated whether biomarkers of ECM turnover were risk markers for occurrence of cardiovascular disease (CVD), mortality and progression of chronic kidney disease (CKD) in persons with type 2 diabetes (T2D) and microalbuminuria. Altered levels of the biomarkers were hypothesized to be detrimental.

Methods: Serum concentration of TUM (tumstatin, a matrikine of collagen type IV), TGF-β (a pro-fibrotic cytokine), C1M (a degradation product of collagen type I), CTX-III (a degradation product of cross-linked collagen type III), PRO-C7 (a pro-peptide of collagen type VII) and PRO-C28 (a C-terminal of collagen type XXVIII) was measured in 192 participants with T2D and microalbuminuria included in an observational, prospective study at Steno Diabetes Center Copenhagen in Denmark from 2007-2008. Endpoints were CVD, mortality and CKD progression (>30% decline in estimated glomerular filtration rate (eGFR)) with mortality as competing risk.

Results: Mean (SD) age was 59 (9) years, eGFR was 89 (17) ml/min/1.73m^2, median (IQR) urine albumin excretion rate (UAE) was 102 (39–229) mg/24-h and 75 % were males. Median follow-up ranged from 4.9 to 6.3 years, and 38 CVD events, 24 deaths and 40 CKD events were recorded. Higher C1M was associated with higher risk of CKD progression in the crude model (hazard ratio (per doubling): 1.62 (95% CI: 1.01-2.61), p=0.047), but not after adjustment for sex, age, body mass index, LDL cholesterol,

smoking, HbA1c, plasma creatinine, systolic blood pressure and UAE (p=0.15). None of the other markers were associated with CKD progression (p≥0.20), and none of the markers were associated with mortality (p≥0.11) or CVD (p≥0.19).

Conclusions: In this cohort of individuals with T2D and microalbuminuria, higher level of a degradation product of collagen type I (C1M) was associated with CKD progression, but not independent of other risk factors. None of the extracellular matrix turnover proteins were associated with risk of CVD or mortality.

Funding: Private Foundation Support

TH-PO173

Plasma Biomarkers and Mortality Among REGARDS Participants with Diabetes and CKD

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[1]University of California San Francisco, San Francisco, CA; [2]San Francisco VA Health Care System, San Francisco, CA; [3]University of Washington, Seattle, WA; [4]Tufts Medical Center, Boston, MA; [5]New York University, New York, NY; [6]Johns Hopkins University, Baltimore, MD; [7]The University of Alabama at Birmingham, Birmingham, AL; [8]University of California San Diego, La Jolla, CA; [9]University of Vermont, Burlington, VT.

Background: Individuals with diabetes and chronic kidney disease (CKD) are at increased risk of death but their clinical course varies. We aimed to determine whether six plasma biomarkers of kidney injury, inflammation, and repair further captured mortality risk.

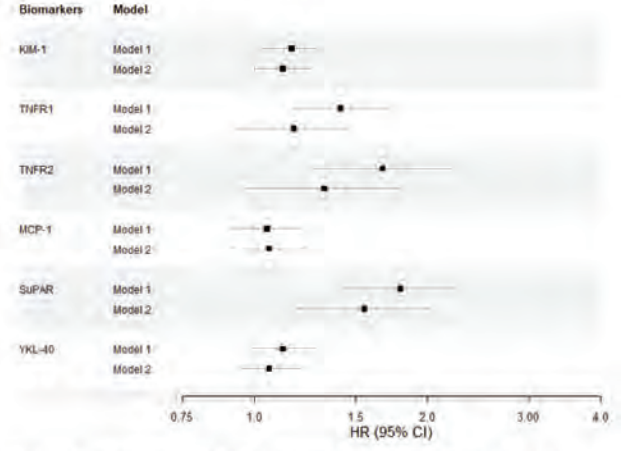
Methods: Among a cohort of REGARDS participants with diabetes and creatinine-based eGFR (eGFRcr) <60 ml/min/1.73 m^2 (n=594), we used Cox proportional hazards regression to evaluate associations of plasma KIM-1, TNFR1, TNFR2, MCP-1, suPAR, and YKL-40 concentrations with all-cause mortality. Covariates included sociodemographic and clinical factors, UACR, and eGFRcr or cystatin C-based eGFR (eGFRcys).

Results: At baseline, mean age was 70 years, 47% were men, 53% were Black, mean eGFRcr and eGFRcys were 44 and 38 ml/min/1.73 m^2, and median UACR was 32 mg/g. TNFR1, TNFR2, and suPAR strongly correlated with cystatin C (r=0.73-0.79). Over a mean follow-up of 6.2 years, 332 participants died. Higher baseline levels of KIM-1, TNFR1, TNFR2, and suPAR were associated with higher mortality risk in fully adjusted models that included eGFRcr (**Figure 1**). When accounting for eGFRcys rather than eGFRcr, however, only the association of suPAR with mortality persisted.

Conclusions: Among adults with diabetes and CKD, higher plasma KIM-1, TNFR1, TNFR2, and suPAR are associated with mortality, independent of baseline eGFRcr and albuminuria. However, the attenuation by eGFRcys suggests that the associations of KIM-1, TNFR1, and TNFR2 with mortality may, in part, reflect residual confounding by GFR.

Funding: NIDDK Support, Other NIH Support - NINDS and NIA, Other U.S. Government Support

Figure 1: Forest plot of plasma biomarker associations with all-cause mortality among REGARDS participants with diabetes and CKD



Hazard ratios are per two-fold higher baseline level. Model 1 adjusted for age, sex, race, education, systolic blood pressure, use of hypertension medications, body mass index, smoking, coronary heart disease, stroke, C-reactive protein, eGFRcr, and urine albumin-to-creatinine ratio. Model 2 replaces eGFRcr with eGFRcys.

TH-PO174

Identification of Circulating Metabolites to Predict Cardiorenal Outcomes in Patients with Type 2 Diabetes (T2D)

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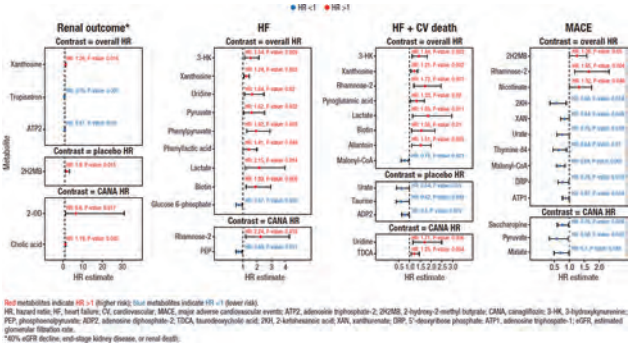
Background: Individuals with type 2 diabetes mellitus (T2D) are at elevated risk of adverse cardiorenal outcomes. Additional biomarkers are needed to better identify patients at highest risk of adverse outcomes and to better understand pathways associated with risk. We examined if baseline plasma metabolites predict renal and cardiovascular (CV) outcomes in the Canagliflozin Cardiovascular Assessment Study (CANVAS) participants with T2D at high cardiovascular risk.

Methods: Plasma metabolites were assayed from a subset of the CANVAS study participants by HPLC (HILIC & AMIDE)-mass spectrometry using targeted assays. Cox proportional hazard regression analysis was used to examine the association of 105 baseline metabolites with the renal outcome (40% eGFR decline, end-stage kidney disease, or renal death), and CV outcomes including heart failure, heart failure and CV death, and MACE. The predicted hazard ratio (HR) for a 1-unit increase in the log metabolite values, 95% confidence intervals, and p-values were calculated. Results were calculated overall and broken out by treatment when a significant treatment interaction was observed.

Results: We included 934 (22%) of the 4,330 CANVAS participants. The Figure below shows a summary of the metabolites across the renal and CV outcomes where a 1-unit increase in the log metabolite was associated with either increased or decreased risk in a fully adjusted model, (age, gender, race, BMI, HbA1C, cholesterol, blood pressure, history of heart failure, baseline ACR and eGFR).

Conclusions: A number of metabolites were identified and associated with higher or lower risk of cardiorenal outcomes. Further research is required to better understand and validate these findings.

Funding: Commercial Support - Janssen Research & Development, LLC.



TH-PO175

Global Proteomic Search for Circulating Proteins Associated with Albuminuria in Patients with Diabetic Kidney Disease

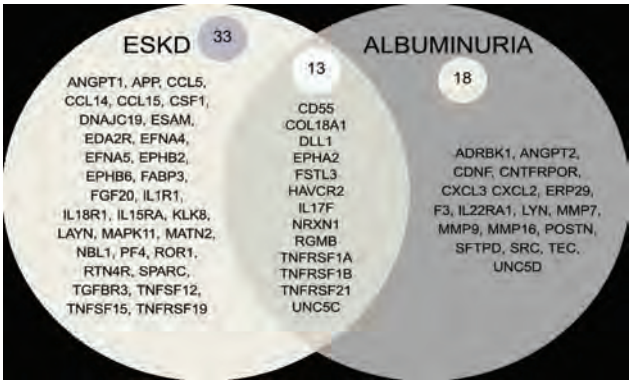
Sok Cin Tye,[1] Helen C. Looker,[2] Zaipul Md Dom,[1] Eiichiro Satake,[1] Joseph Ricca,[1] Robert G. Nelson,[2] Andrzej S. Krolewski.[1] Section of Genetics and Epidemiology, Joslin Diabetes Center. *[1]Joslin Diabetes Center, Boston, MA; [2]Chronic Kidney Disease Section, National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, AZ.*

Background: Fast kidney function decline and the presence of albuminuria are traditional predictors of progression to end-stage kidney disease (ESKD) in patients with diabetic kidney disease (DKD). In this study, we aim to identify circulating proteins associated with albuminuria in patients with DKD and to compare them with 46 novel proteins associated with fast kidney function decline previously reported by us [1].

Methods: Using the SOMAscan proteomics platform, we measured the baseline concentration of 550 circulating proteins in participants with type 1 diabetes from the Joslin Kidney Cohort (JKC, N=294), and with type 2 diabetes from the Pima Indian cohort (N=162). Spearman rank correlation was used in an untargeted analysis to assess the association between measured proteins and albuminuria in both cohorts. We used a Venn diagram to describe proteins contributing to the development of albuminuria and/or ESKD.

Results: In the JKC and Pima Indian cohorts, 196 proteins (P<0.00001) and 55 proteins (P<0.001), respectively, were associated with albuminuria; 31 of them were common to both cohorts. Comparing these 31 proteins to the 46 proteins associated with the risk of progression to ESKD, we identified 13 proteins associated with both outcomes (Figure 1).

Conclusions: Our findings indicate that the underlying disease processes for albuminuria and progressive kidney function decline are very different. Only a few circulating proteins are common indicators for both processes. **References:** 1. Kobayashi, H., et al., Results of untargeted analysis using the SOMAscan proteomics platform indicates novel associations of circulating proteins with risk of progression to kidney failure in diabetes. Kidney Int, 2022. 102(2): p. 370-381.



TH-PO176

Baseline and Short-Term Change of Concentration of Plasma Proteins Measured by Joslin Kidney Panel and Progression to ESKD in the Chronic Renal Insufficiency Cohort (CRIC)

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Background: The Joslin Kidney Panel (JKP) of 21 circulating proteins is associated with increased risk of ESKD in patients with diabetes (Kobayashi *et al.* KI 2022). We evaluated the JKP as a tool for assessing prognosis in Chronic Renal Insufficiency Cohort (CRIC).

Methods: We conducted a case-cohort study involving 218 participants with diabetes and impaired renal function at baseline. Using assays developed by OLINK inc. to measure JKP 21 proteins we quantified concentration of the proteins at Baseline and at follow-up (interval 2 years apart) in study groups; cases were those who progress to ESKD within 10-years (n=89), and controls were those who did not progress to ESKD within 10-years (n=129). We employed logistic regression models to determine the association of baseline concentration, longitudinal change (DELTA), and INDEX (Baseline and DELTA) for each biomarker with progression to ESKD.

Results: Higher levels of 19 of 21 proteins at baseline and 20 of 21 DELTAs and INDEXs were statistically and significantly associated with an increased risk of progression to ESKD within 10 years. Among the 20 INDEXs, 5 including TNF-R7, WFDC2, SYND1, KIM-1, and PVRL4 remained statistically significant after adjusting for GFR-INDEX and baseline 24-hour urinary protein (24h-UP).

Conclusions: Higher levels of most proteins at baseline, DELTAs, and INDEXs in JKP were significantly associated with increased ESKD risk within 10 years. INDEXs for the 5 proteins were better in prediction of risk of ESKD than GFR-INDEX. Further studies are needed to validate the utility of measuring INDEXs for prediction of ESKD and monitoring the effectiveness of reno-protective therapies. CRIC data was provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases, and this study was supported by a grant from Renalityx Inc.

Funding: NIDDK Support

TH-PO177

Serum Sphingolipids as Indicators of ESRD Risk in Diabetic Patients

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Background: Chronic kidney disease (CKD) is a complication of diabetes that affects one-third of diabetic patients; 15% of CKD patients with diabetes develop end-stage renal disease (ESRD). Underlying genetic, environmental, and biological factors contribute significantly to CKD risk. Sphingolipids are a class of lipids that have been associated with increased insulin resistance and hepatic steatosis. Through analysis of longitudinal data from participants in Chronic Renal Insufficiency Cohort (CRIC) study and newly generated lipidomic data, this project investigates the potential use of longitudinal serum sphingolipid measurements as an indicator for risk of progression to ESRD.

Methods: We analyzed ESRD outcomes in participants of CRIC with type II diabetes and CKD (n = 1054). We performed targeted lipidomics measuring 55 sphingolipids in patient serum samples from their fifth CRIC visit. Data from this visit served as the baseline for evaluating time to progression to ESRD and change in serum sphingolipids over time. Additionally, patients' health variables available through the CRIC dataset were investigated for correlation with all sphingolipids at baseline for a larger cohort of 1618 patients with diabetes and CKD. Each variable was analyzed for correlation with each sphingolipid using a standardized linear regression model; variables were then grouped using hierarchical clustering according to both p-value and adjusted R-squared value.

Results: At baseline, 506 patients had early stage CKD (CKD stages 1-3) and 546 patients had late stage CKD (CKD stages 4-5). 257 of 1054 patients developed ESRD in the range of 517 to 5048 days after the first CRIC visit, with a mean of 2619 days. Seven of 55 serum sphingolipids were significantly ($p < 0.05$) associated with time to ESRD; none explained greater than 0.01% of variability. Additionally, we identified 3 clusters of patient health variables that were significantly ($p < 0.05$) associated with the same sphingolipids and with each other. These clustered health variables included lipid measurements, indicators of kidney function, and quality of life evaluation.

Conclusions: Our analysis indicates that serum sphingolipids measured at baseline are correlated with progression to ESRD. As we continue our analysis, we further investigate the relationship between average sphingolipid measurements over time and rate of progression through CKD stages to ESRD.

Funding: NIDDK Support

TH-PO178

High High-Density Lipoprotein Cholesterol (HDL-C) Levels May Indicate a Higher Risk of ESRD and All-Cause Mortality in Patients with Type 2 Diabetes Mellitus (T2DM) and CKD

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Background: To investigate the relationship between high-density lipoprotein cholesterol (HDL-C) and end-stage renal disease (ESRD) and all-cause mortality in patients with both diabetes mellitus (DM) and chronic kidney disease (CKD).

Methods: We enrolled 375 participants with confirmed diabetic kidney disease (DKD) via renal biopsy between January 2008 and September 2020 in our longitudinal observational study. Additionally, a total of 3,267 participants with DM and CKD from the National Health and Nutrition Examination Survey (NHANES) spanning 1999-2018 were included to examine the association between HDL-C concentration and all-cause mortality.

Results: Patients were divided into Group 1 (HDL-C<1.03mmol/L), Group 2 (1.55mmol/L>HDL-C≥1.03mmol/L), and Group 3 (HDL-C≥1.55mmol/L). Overall, of the 375 patients, after a median follow-up of 36 months, 165 participants (44%) developed ESRD. The Kaplan-Meier curves revealed a higher risk for ESRD among patients in Group 3 (p<0.001). After adjusting for potential confounders, patients in Group 3 were still found to have a significantly higher risk of ESRD compared to patients in Group 1, with an adjusted HR (95%CI) of 1.68(1.03, 2.71) (p=0.036). Higher levels of HDL3 and lower levels of HDL2 were associated with a higher risk for ESRD. Moreover, a total of 3,262 individuals with both DM and CKD in NHANES 1999-2018 were analyzed. After a median follow-up of 75 months, 1,369 participants (42%) had died. The weighted Kaplan-Meier curves reveal that higher HDL-C levels are associated with a higher risk of all-cause mortality (p=0.02). Notably, in patients with CKD stage 1-2, multivariate Cox regression analysis suggests that patients in Group 3 had a significantly higher HR of 1.61 (95%CI: 1.19, 2.19) (p=0.002).

Conclusions: This study identified a significant positive association of high concentration of HDL-C with incident ESRD and all-cause mortality in DKD patients. These findings may be different from previous beliefs about the role of HDL-C as "good cholesterol".

TH-PO179

PRO-C3 as a Risk Marker for Kidney Disease Progression and Mortality in Type 1 Diabetes

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Background: Kidney fibrosis, a hallmark of diabetic kidney disease, is characterized by impaired extracellular matrix remodeling, causing excessive collagen deposition. We investigated if biomarkers of collagen type III (PRO-C3), VII (PRO-C7) and XXVIII (PRO-C28) formation, and a fragment of degraded crosslinked collagen type III (CTX-III), were related to kidney disease progression and mortality in people with type 1 diabetes (T1D).

Methods: The biomarkers were measured in serum by ELISA. Endpoints were 1) a composite kidney endpoint including ≥30% decline in estimated glomerular filtration rate (eGFR), onset of kidney failure (eGFR ≤15 ml/min/1.73m^2, dialysis, or transplantation) and all-cause mortality; and 2) all-cause mortality. Associations with baseline biomarker levels were tested using Cox proportional hazard models after log2 transformation. Hazard ratios (HRs) are reported per doubling and adjusted for age, sex, HbA_{1c}, eGFR, systolic blood pressure, body mass index, smoking, urinary albumin excretion rate, diabetes duration and treatment with a renin-angiotensin-aldosterone system inhibitor.

Results: We enrolled 667 individuals with T1D, 311 with normal (<30 mg/24h), 166 with moderately (30-299 mg/24h), and 190 with severely increased (≥300 mg/24h) urinary albumin excretion. Median follow-up was 5.2-6.2 years. Higher PRO-C3 was associated with development of the composite kidney endpoint (events: 125) and

all-cause mortality (events: 58); adjusted HR: 1.51 (95% CI: 1.08-2.11, p=0.017) and 1.65 (1.05-2.61, p=0.031), respectively. Higher PRO-C7 was associated with a higher risk of the composite kidney endpoint (1.56 (1.16-2.09), p=0.003), but not after adjustment (p=0.40), and not associated with mortality. PRO-C28 and CTX-III were not associated with the endpoints (p≥0.13).

Conclusions: PRO-C3, a marker of collagen type III formation, was associated with kidney disease progression and death, highlighting PRO-C3 as a potential risk marker of severe complications in T1D.

Funding: Private Foundation Support

TH-PO180

The Influence of Bone on Kidney Disease Progression in Persons with Type 1 Diabetes

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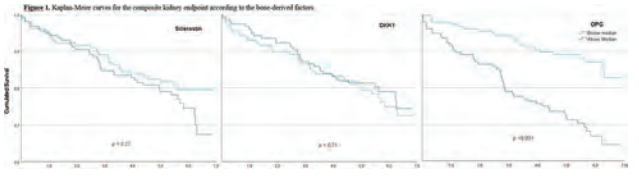
Background: The number of patients with chronic kidney disease (CKD) and diabetes is expected to increase. Identification of mechanisms influencing the progression of CKD is of great importance. In CKD, a bone-vascular cross-talk has been described, but if bone influences on kidney function has been sparsely investigated. The aim of this study was to explore the influence of bone-derived factors (sclerostin, Dickkopf-1 (DKK1), and osteoprotegerin (OPG)) on the progression of kidney disease in persons with type 1 diabetes (T1D).

Methods: This was a prospective cohort study. Blood samples from persons with T1D were collected between 2009-2011. Outcomes were: 1) End-stage kidney disease (ESKD) defined as estimated glomerular filtration rate (eGFR) <15 mL/min/1.73m^2, initiation of dialysis, or kidney transplantation; 2) Progression of albuminuria (from 0-30 mg/day to 30-300 mg/day or from 30-300 mg/day to >300 mg/day); 3) An eGFR decline ≥30%; 4) A composite kidney endpoint consisting of all three endpoints. Kaplan-Meier curves and Cox proportional hazard regression models were used.

Results: Among the 318 persons, the mean age was 56 years, 50% were men, and the median eGFR was 79 mL/min/1.73m^2. During a median follow-up of 5.5 years, 3.5% met the ESKD endpoint, 6.3% progressed in albuminuria, 14.2% had a decline in eGFR ≥30%, and 21.1% met the composite kidney endpoint. The Kaplan-Meier curves showed no association between sclerostin or DKK1 and kidney disease progression, whereas OPG above median had a lower survival for all endpoints except for albuminuria progression (Figure 1). In unadjusted Cox regression models, sclerostin and DKK1 were significantly associated with ESKD, while OPG was significantly associated with all kidney endpoints except for eGFR decline ≥30%. After adjustment for age, gender, systolic blood pressure, diabetes duration, eGFR, and UACR, only OPG was significantly associated with the composite kidney endpoint (p=0.047).

Conclusions: In this prospective cohort study, OPG, but not sclerostin or DKK1, was associated with progression of CKD, and could have prognostic importance in patients with T1D.

Funding: Private Foundation Support



TH-PO181

Utility of Serum β2-Microglobulin for Prediction of Kidney Outcome Among Patients with Biopsy-Proven Diabetic Nephropathy

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Background: Little is known regarding the importance of serum β2-microglobulin (β2-MG) on subsequent decline in kidney function among patients with diabetic nephropathy (DN). Here, we aimed to examine whether the addition of serum β2-MG to known predictors could improve the prediction performance for incident kidney failure with replacement therapy (KFRT) among patients with biopsy-proven DN.

Methods: A retrospective observational study consists of patients with biopsy-proven DN between June 1981 and December 2014. Patients complicated with other kidney diseases were excluded. Exposure of interest was log-transformed serum β2-MG levels measured at the time of kidney biopsy. The outcome variables were KFRT. Multivariable Cox regression models and competing-risk regression models, with all-cause mortality as a competing event, were performed with adjustments for previously known risk factors. Model fit by adding serum β2-MG levels was calculated using the Akaike information criterion (AIC). The net reclassification improvement (NRI) and integrated discrimination improvement (IDI) indexes were examined based on the 5-year cumulative incidence of KFRT, and the improvement of predictive performance for KFRT by serum β2-MG levels was evaluated.

Results: Among 408 patients, 99 developed KFRT during a median follow-up period of 6.7 years. A higher serum β2-MG level (1-unit increase in log-transformed serum β2-MG level) was associated with a higher incidence of KFRT, even after adjustments for previously known clinical and histological risk factors (hazard ratio [95% confidence interval (CI)]: 3.30 [1.57–6.94] and subdistribution hazard ratio [95% CI]: 3.07 [1.55–6.06]). Subgroup analyses revealed no effect modification by creatinine-based estimated glomerular filtration rate or kidney histological findings. The addition of log-transformed serum β2-MG level reduced AIC, and improved the prediction of KFRT (NRI and IDI: 0.32 [0.09–0.54] and 0.03 [0.01–0.56], respectively).

Conclusions: Among patients with biopsy-proven DN, serum β2-MG was an independent predictor of KFRT and improved prediction performance. In addition to serum creatinine, serum β2-MG could be also evaluated for DN.

TH-PO182

Levels of Oxidative Stress and Inflammation in Different Degrees of Diabetic Kidney Disease Caused by Diabetes Mellitus Type 2

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Background: Chronic inflammation is related to its progression and cardiovascular and infectious complications, alterations in the immune response, which translates into a greater risk of morbidity and mortality. Oxidative stress is considered a non-traditional risk factor for all causes of mortality, considering it a prognostic factor and a target for the prevention and treatment of CKD.

Methods: Retrospective observational descriptive study in adult patients >18 years of age, with type 2 Diabetes Mellitus (DM2) and CKD grades 1 5 according to the KDIGO, who attended the Nephrology clinic at the IMSS HGR46. We evaluate the levels of oxidative stress and inflammation in the different degrees of diabetic kidney disease in patients with DM2.

Results: We included 80 patients diagnosed with diabetic CKD were included and the serum levels of Superoxide dismutase SOD and Malondialdehyde MDA were determined. We classified according to the severity of the disease using KDIGO based on eGFR into three groups: patients with mild, moderate and severe. Plasma SOD levels were determined in patients with CKD; the average SOD was 2.07 ± 0.64. According to the severity of the CKD, no significant differences were identified p=0.46, although there were numerical differences with a tendency to lower levels in patients with severe CKD. Regarding MDA, a significant difference was observed in the levels according to the severity of the CKD. With higher levels in patients with mild CKD, and with lower levels according to the severity of the disease p=0.003.

Conclusions: Serum levels of SOD and MDA seem to reduce as eGFR decreases, being higher in the mild disease group, which may be related to greater inflammation at the onset of CKD.

Funding: Government Support - Non-U.S.

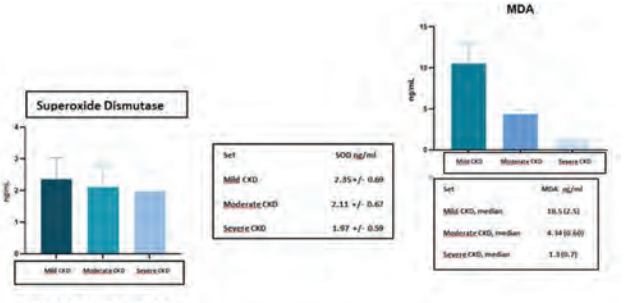

Table 3. Laboratory studys

	Total N=80	Mild CKD N=5	Moderate CKD N= 47	Severe CKD N= 28	p
Glucose mg/dL, median (IQR)	112 (100-152)	130 (107-152)	114 (101-175)	106 (81-123)	0.17
Creatinine mg/dL, median (IQR)	2.04 (1.46-2.73)	1.36 (1.24-1.37)	1.66 (1.38-2.66)	2.55 (1.95-2.82)	0.004
Albumin mg/g, median (IQR)	500 (52-1782)	33 (11-901)	272 (22-791)	1074 (500-3787)	0.002
Uric acid mg/dL, median (IQR)	6.4 (5.6-8.2)	6.3 (5.8-7.5)	6.4 (5.6-8.2)	6.5 (5.1-8.4)	0.97
Cholesterol ng/dL, median (IQR)	186 ± 51.9	173.1 ± 64	180 ± 49.3	198 ± 54.7	0.35
Triglycerides mg/dL, media (IQR)	184.9 ± 123.7	111.3 ± 61.6	190.7 ± 129.4	187.9 ± 120.5	0.47
HbA1c, %, median (IQR)	7.3 (6-9.54)	6.6 (6.5-6.9)	7.2 (6.0-9.54)	7.5 (6.7-9.7)	0.67

IQR, interquartile range

TH-PO183

Correlation Between Serum suPAR and Severity of Renal Injury and Renal Function Progression in Diabetic Kidney Disease

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Background: To analyze the correlation between serum soluble urokinase Plasminogen Activator Receptor (suPAR) and renal function in diabetic kidney disease(DKD).

Methods: 152 DKD patients and 105 T2DM patients were recruited. The patients with DKD were divided into microalbuminuria group (30mg/g≤UACR < 300mg/g), macroalbuminuria group (UACR≥300mg/g). Spearman correlation and partial correlation analysis were conducted to compare the correlation between suPAR and various clinical indicators. End events were defined as Estimated glomerular filtration rate (eGFR) decrease of ≥30%, urinary protein advancement, progress to end-stage renal disease (ESRD) or receive renal replacement therapy. According to the median serum suPAR level, all patients were divided into low-level suPAR group (suPAR < 5.76ng/ml) and high-level suPAR group (suPAR≥5.76ng/ml). Survival curves were plotted by Kaplan-Meier method, and differences in renal cumulative survival at different serum suPAR levels were measured by Log-rank test. Cox regression analysis was used to analyze the influence factors for renal progression in DKD. The predictive value of suPAR in renal function progression was evaluated by Receiver operating characteristic curve (ROC).

Results: The mean age was 60.30±11.89 years old. SuPAR level in T2DM group was significantly lower than that in microalbuminuria group and macroalbuminuria group ($P < 0.05$). Serum suPAR in DKD patients was positively correlated with UACR, BUN, Scr, SUA, RBP and CysC (all $P < 0.05$), and negatively correlated with Hb, ALB, TBIL and eGFR (all $P < 0.05$). Kaplan-Meier survival analysis showed that the cumulative survival rate of kidney in the high-level suPAR group was significantly lower than that in the low-level suPAR group (P =0.001). The results showed that higher levels of RBP and suPAR, lower levels of ALB were independent risk factors for renal function progression in DKD patients (P < 0.05). The area under ROC curve of suPAR level to predict renal function progression was 0.791, the critical value was 8.15ng/ml, the sensitivity was 66.7%, and the specificity was 84.9%.

Conclusions: Serum suPAR level increased in DKD patients, which was positively correlated with the severity of renal impairment. High level of suPAR is an independent risk factor for renal progression in patients with DKD.

Funding: Government Support - Non-U.S.

TH-PO184

Autoantibodies to Erythropoietin Receptor and Clinical Outcomes in Patients with Type 2 Diabetes and CKD: A Post Hoc Analysis of the CREDENCE Trial

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Background: Anti-erythropoietin receptor (EPOR) antibodies have been identified in patients with various kidney diseases. This study aimed to assess the association of anti-EPOR antibodies with kidney, cardiovascular and mortality outcomes in the CREDENCE trial, and to determine whether the effects of canagliflozin on hemoglobin and hematocrit were modified by anti-EPOR antibodies.

Methods: Patients with type 2 diabetes (T2D) and CKD were randomly assigned to receive canagliflozin 100mg daily or a matching placebo. Serum anti-EPOR antibodies at baseline were measured using an indirect enzyme-linked immunosorbent assay. The primary composite outcome consisted of a doubling of serum creatinine, end-stage kidney disease, or death from kidney or cardiovascular reasons. The secondary outcome was death from any cause. Multivariable adjusted Cox proportional hazard regression was used to estimate associations between anti-EPOR antibodies and outcomes. The effects of canagliflozin on hemoglobin and hematocrit over time were assessed with a repeated measures mixed effect model.

Results: Of 2600 (59.1%) CREDENCE participants with available samples, 191 (7.3%) were positive for anti-EPOR antibodies. During a median follow-up of 2.8 years, the primary composite outcome and all-cause death occurred in 348 (13.4%) and 227 (8.7%) individuals, respectively. Higher baseline levels of anti-EPOR antibodies were independently associated with increased risk of the primary outcome (HR per 1-SD increase 1.12 [95%CI 1.01, 1.24], p=0.04) and all-cause death (HR 1.27 [95%CI 1.08, 1.48], p<0.01). Canagliflozin, compared to placebo, increased hemoglobin and hematocrit by 7.0 g/L (95%CI 6.2, 7.9, p<0.01) and 2.4% (95%CI 2.2, 2.7, p<0.01), respectively. These effects were consistent in patients with and without anti-EPOR antibodies (p-interaction=0.39 and 0.70).

Conclusions: In patients with T2D and CKD, anti-EPOR antibodies were associated with the composite kidney and cardiovascular outcome and all-cause mortality. Canagliflozin increased hemoglobin and hematocrit regardless of the presence of anti-EPOR antibodies.

Funding: Commercial Support - Janssen Research and Development, Government Support - Non-U.S.

TH-PO185

Iron Biomarkers and Effects of Canagliflozin in Patients with Type 2 Diabetes and CKD: A Post Hoc Analysis of the CREDENCE Trial

Akihiko Koshino,[1,2] Brendon L. Neuen,[3] Clare G. Arnott,[3,4] Bruce Neal,[3] Meg Jardine,[3,5] Sunil Badve,[3,6] Kenneth W. Mahaffey,[7] Carol A. Pollock,[8,9] Michael K. Hansen,[10] Takashi Wada,[2] Hiddo J. Heerspink.[1,3] *[1]University Medical Center Groningen, Groningen, Netherlands; [2]Kanazawa University, Kanazawa, Japan; [3]The George Institute for Global Health, Newtown, NSW, Australia; [4]Royal Prince Alfred Hospital, Camperdown, NSW, Australia; [5]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [6]University of New South Wales, Sydney, NSW, Australia; [7]Stanford Center for Clinical Research, Stanford University School of Medicine, Stanford, CA; [8]Kolling Institute of Medical Research, St Leonards, NSW, Australia; [9]Royal North Shore Hospital, St Leonards, NSW, Australia; [10]Janssen Research and Development LLC, Spring House, PA.*

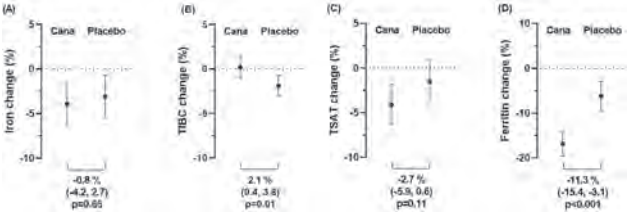
Background: Disturbed iron homeostasis occurs commonly in patients with chronic kidney disease (CKD) and is implicated in the development of anemia and adverse clinical events. This study aimed to determine the effects of canagliflozin on iron parameters in the CREDENCE trial and to assess whether the effects of canagliflozin on anemia and clinical outcomes were modified by iron deficiency (ID).

Methods: Patients with type 2 diabetes (T2D) and CKD were randomized to canagliflozin 100mg or placebo. We measured serum iron, total iron binding capacity (TIBC), transferrin saturation (TSAT) and ferritin at baseline and year 1. The effects of canagliflozin, relative to placebo, on iron markers were assessed with analysis of covariance. Interactions between baseline ID, defined as TSAT<20%, and the effects of canagliflozin on hemoglobin and clinical outcomes were evaluated with mixed effect models and Cox regression models, respectively.

Results: 2414/4401 (54.9%) participants had available serum samples. Canagliflozin, compared to placebo, increased TIBC by 2.1% (95% CI 0.4, 3.8; p=0.01) and decreased ferritin by 11.3% (95% CI 3.1, 15.4; p<0.001) with no clear effect on iron and TSAT (Figure). At baseline, 924 (38.3%) participants had ID. Canagliflozin increased hemoglobin over time by 7.3 g/L (95% CI 6.2, 8.5; p<0.001) and 6.7 g/L (95% CI 5.2, 8.2; p<0.001) in patients with and without ID, respectively (p-interaction=0.38). Canagliflozin reduced CKD progression (HR 0.70, 95% CI 0.56-0.87) regardless of ID (p-interaction=0.83).

Conclusions: One-year treatment with canagliflozin increased TIBC and decreased ferritin in patients with T2D and CKD, suggesting improvement in iron use.

Funding: Commercial Support - Janssen Research and Development



TH-PO186

Distal Tubule Urinary Biomarkers in Diabetic Kidney Disease: Results from the VA NEPHRON-D Trial

Christina L. Tamargo,[1] David Hu,[1] Heather Thiessen Philbrook,[1] Joseph V. Bonventre,[4] Linda F. Fried,[2] Steven G. Coca,[3] Chirag R. Parikh.[1] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]UPMC, Pittsburgh, PA; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Brigham and Women's Hospital, Boston, MA.*

Background: Urinary biomarkers of proximal renal tubule injury (KIM-1, NGAL, L-FABP) have demonstrated associations with DKD progression, but investigations of biomarkers of distal tubular health in DKD have been limited.

Methods: We evaluated associations between two distal tubular urinary biomarkers, epidermal growth factor (EGF) and uromodulin (UMOD), and DKD progression among 1135 participants in the Veterans Affairs Diabetes iN Nephropathy (VA NEPHRON-D) study. EGF and UMOD were measured by electrochemiluminescence assay in a single batch in urine samples collected at randomization.

Results: At baseline, the mean age was 64.9 years, the mean eGFR was 56.2 (18.9) ml/min/1.73 m^2, and the median urine albumin-to-creatinine ratio was 840 (IQR 423-1761) mg/g. One hundred forty-eight patients (13.0%) had DKD progression over a median of 2.2 years of follow-up. Higher levels of EGF and UMOD were both independently associated with a lower risk of DKD progression in continuous models after adjustment for several covariates (adjusted HR 0.58 (0.34, 0.98) and 0.80 (0.66, 0.97); Figure 1).

In categorical models, patients with the highest tertiles of both biomarkers had the lowest risk of DKD progression. However, associations were attenuated in models that adjusted for albuminuria, particularly for EGF (adjusted HR 0.70 (0.42, 1.15) and 0.55 (0.34, 0.89) for UMOD).

Conclusions: Among veterans with DKD, higher levels of distal tubular health markers were independently prognostic for a lower risk of DKD progression. Distal tubular health deserves further investigation in DKD cohorts and clinical trials.

Funding: NIDDK Support

Figure 1. Baseline Urinary EGF and UMOD associations with DKD progression

Urinary Biomarker		Event rate per 1000 person-years (95% CI)	Hazard ratio (95% CI) for DKD progression[a]	
			Model 1[b]	Model 2[c]
EGF (pg/mL)	Continuous	63 (53, 74)	**0.41 (0.27, 0.64)**	**0.58 (0.34, 0.98)**
	T1: <786	91 (71, 115)	1.0 (referent)	
	T2: 786-1061	54 (40, 73)	**0.56 (0.38, 0.83)**	0.68 (0.45, 1.04)
	T3: >1061	44 (32, 62)	**0.51 (0.33, 0.80)**	0.70 (0.42, 1.15)
UMOD (µg/mL)	Continuous	63 (53, 74)	**0.65 (0.55, 0.78)**	**0.80 (0.66, 0.97)**
	T1: <21.78	100 (79, 126)	1.0 (referent)	
	T2: 21.78-48.47	57 (43, 77)	**0.59 (0.40, 0.87)**	0.79 (0.53, 1.17)
	T3: >48.47	35 (24, 50)	**0.35 (0.23, 0.56)**	**0.55 (0.34, 0.89)**

[a]DKD progression was defined as eGFR decline (≥30 ml/min/1.73 m^2 if eGFR at randomization was ≥60 ml/min/1.73 m^2, or ≥50% if eGFR at randomization was <60 ml/min/1.73 m^2) or incident end-stage kidney disease. [b]Model 1: Adjusted for urine creatinine concentration, age, sex, race, ethnicity, BMI, systolic blood pressure, hemoglobin A1c, and treatment assignment at baseline. [c]Model 2: Model 1 + natural log-transformed UACR at 0 months + eGFR at 0 months.
Bolded values indicate statistical significance. T, tertile.

Figure 1. Baseline Urinary EGF and UMOD associations with DKD progression

TH-PO187

Tubular Biomarker Trajectories in Type 1 Diabetes

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Background: Evaluation of kidney tubular biomarker trajectories over the course of type 1 diabetes (T1D) may provide insight into how tubulointerstitial disease progresses over time.

Methods: We assessed biomarkers of tubular injury and function over time in two prospective T1D cohorts: the Renin Angiotensin System Study (RASS; n=283, 5 year follow-up) of adults with early T1D and no clinical evidence of kidney disease, and the Preventing Early Renal Loss in Diabetes Study (PERL; n=530, 3 year follow-up) of adults with longstanding T1D and CKD or risk for kidney disease progression. We measured the following at baseline, mid-study, and study end: KIM-1, sTNFR1, arginine-citrulline ratio in plasma; UMOD, EGF excretion in timed urine; urinary clearances of 8 secretory solutes summarized as a composite tubular secretion score.

Results: At baseline, RASS participants had mean age 30 years, diabetes duration 11 years, iohexol-GFR (iGFR) 129 ml/min/1.73m^2, AER 6 µg/min, and HbA1c 8.6%; PERL participants had mean age 51 years, diabetes duration 35 years, iGFR 68 ml/min/1.73m^2, AER 285 µg/min, and HbA1c 8.2%. Overall, KIM-1, sTNFR1, and UMOD were higher and arginine-citrulline ratio, EGF, and tubular secretion score were lower in PERL versus RASS (**Table**). Tubular biomarkers changed significantly over time at rates similar to and sometimes faster than iGFR and AER. Baseline HbA1c was associated with tubular marker changes in multivariate models (% change/year per 1% higher HbA1c [95% CI]): in RASS, KIM-1 0.8% (0,1.6), sTNFR1 0.4% (0.1,0.7), EGF -1.1% (-2.1,0), arginine-citrulline ratio 1.1% (0.4,1.7); in PERL, sTNFR1 1.0% (0.6,1.4), tubular secretion score 0.7% (0.2,1.2). Neither ACEi/ARB versus placebo in RASS nor allopurinol versus placebo in PERL affected tubular biomarker trajectories.

Conclusions: Plasma KIM-1 and sTNFR1 significantly increase over the course of T1D, suggesting early onset of tubulointerstitial pathology and progression over time. Higher HbA1c is associated with faster rise in sTNFR1.

Funding: NIDDK Support

Table. Tubular biomarker median values and changes over time

	Median (Q1 median, Q3 median)		Absolute change per year (95% CI)		Percent change per year (95% CI)	
	RASS	PERL	RASS	PERL	RASS	PERL
KIM-1, plasma (pg/mL)	38.0 (28.8, 56.0)	114.3 (69.8, 204.9)	5.7 (1.6, 9.8)	7.5 (3.3, 11.8)	5.4 (4.0, 6.7)	2.9 (1.6, 4.1)
sTNFR1, plasma (pg/mL)	894.5 (794.4, 1023.6)	1587.1 (1254.0, 2079.9)	14.2 (3.6, 24.8)	75.0 (64.6, 85.4)	1.3 (0.8, 1.8)	3.4 (2.9, 3.9)
Arginine-citrulline ratio, plasma	1.9 (1.6, 2.2)	1.5 (1.2, 1.9)	-0.03 (-0.05, -0.01)	0.01 (-0.02, 0.03)	-1.7 (-2.7, -0.8)	0.1 (-1.0, 1.3)
UMOD urinary excretion (mg/day)	52.9 (24.2, 108.4)	65.7 (34.6, 111.0)	0.6 (-1.6, 2.7)	-3.7 (-6.4, -1.0)	0.7 (-2.3, 3.8)	-5.8 (-9.3, -2.2)
EGF urinary excretion (µg/day)	25.7 (20.2, 33.7)	10.5 (6.7, 15.7)	-0.2 (-0.5, 0.1)	-0.3 (-0.7, -0.008)	-1.5 (-3.0, 0.1)	-4.6 (-6.3, -2.8)
Tubular secretion score	68.9 (66.1, 71.0)	64.9 (60.5, 68.6)	0.1 (-0.1, 0.3)	-0.6 (-0.8, -0.3)	0.1 (-0.4, 0.6)	-1.2 (-1.7, -0.6)
iGFR (ml/min/1.73m^2)	126.0 (113.0, 136.8)	65.0 (51.8, 77.5)	-1.4 (-1.7, -1.1)	-1.8 (-2.2, -1.5)	-1.2 (-1.6, -0.7)	-3.4 (-3.8, -2.9)
AER (µg/min)	4.7 (3.6, 6.2)	56.8 (10.5, 257.8)	0.6 (-17.0, 18.2)	52.6 (34.1, 71.1)	-2.7 (-5.5, 0.1)	7.3 (4.5, 10.3)

Biomarkers represent various aspects of tubular health: tubular injury (KIM-1), inflammation (sTNFR1), synthesis (arginine-citrulline ratio; UMOD), viability (EGF), and secretion (clearance of secretory solutes). Tubular secretion scores were calculated from the clearances of 8 secretory solutes (cinnamoylglycine, indoxyl sulfate, isovalerylglycine, kynurenic acid, p-cresol sulfate, pyridoxic acid, tiglylglycine, xanthosine). Clearances for each solute were log-transformed then min-max scaled. Afterwards, scaled values for all solutes were averaged to generate a summary tubular secretion score.

TH-PO188

Association of Urinary DNlite IVD-103 with CKD and Coronary Artery Disease in Diabetic Nephropathy

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Background: Fetuin-A is associated with inflammation and vascular complications in diabetes. We evaluated association of urinary post-translationally modified fetuin-A (DNlite IVD-103) in diabetics with chronic kidney disease (CKD) and coronary artery disease (CAD).

Methods: A cross-sectional study was conducted in patients with diabetic nephropathy. Patients and divided into those having only albuminuria, CKD or CAD. eGFR (Glomerular Filtration Rate) was calculated using CKD-EPI equation, and an eGFR <60ml/min/1.73m2 was considered CKD. Severity of CAD was assessed using SYNTAX score. Spot urine was tested for urine albumin to creatinine ratio (UACR), and DNlite-IVD103 (Fetuin) was measured using ELISA test kit. Urinary Fetuin:creatinine ratio (UFCR) was calculated. Statistical analysis was carried out using SPSS v23.0. A p value of <0.05 was considered significant.

Results: 137 patients were included, with 61% being men. The mean age, eGFR, UACR, and FCR were 56.4±11.8 years, 64.5±36.4 ml/min/1.73m^2, 1359±2030.6 mg/g, and 175±268.9 ng/g, respectively. Of these, 20.4% of patients had CAD, 39.4% had albuminuria, and 40.1% had CKD. There was a significant difference in UACR and UFCR between the groups. UACR had significant positive correlation with age and negative correlation with eGFR (p<0.05). UFCR had significant negative correlation with eGFR. UFCR was also significantly higher in patients with CKD compared to CAD (p<0.05). Compared to albuminuria patients, UACR, and UFCR were significantly increased in patients with CAD (p<0.05) and CKD (p<0.01). In patients with CAD, SYNTAX II score had significant negative correlation with UFCR (p<0.05) but not UACR (p=0.58)

Conclusions: DNlite IVD-103 is significantly associated with worsening renal function, and is not influenced by age. It was also significantly different between CAD & CKD, and also had significant correlation with severity of CAD. UFCR could be used to stratify patients with micro- or macrovascular disease (albuminuria, CAD, CKD).

Funding: Commercial Support - Bio Preventive Medicine Corp, Taiwan

	Albuminuria (n=54)	CAD (n=28)	CKD (n=55)	p value
Age (years)	52.3 ± 12.6	55.9 ± 9.03	59.8 ± 10.86	<0.01
Gender				0.224
Male	37 (68.5%)	18 (64.3%)	29 (52.7%)	
Female	17 (31.5%)	10 (35.7%)	26 (47.3%)	
Serum Creatinine (mg/dl)	0.8 ± 0.19	0.8 ± 0.17	3.2 ± 2.56	<0.001
eGFR (ml/min/1.73m2)	95.3 ± 20.08	93.7 ± 12.63	28.9 ± 15.38	<0.001
UACR	685.4 ± 796.7	1282.1 ± 1515.7	1921 ± 2756.3	<0.01
UFCR	80.4 ± 136.8	156.2 ± 134.2	275.4 ± 357.2	<0.001
SYNTAX II score		12.7 ± 7.36		

TH-PO189

Relationship Between Urinary DcR2/Cr Levels and Poor Prognosis of Diabetic Nephropathy

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Background: Urinary decoy receptor 2 is closely associated with interstitial injury in diabetic kidney disease, and the aim of this paper was to investigate whether urinary DcR2/Cr levels could be used as a biomarker to predict poor prognosis in diabetic kidney disease.

Methods: A total of 96 patients diagnosed with diabetic kidney disease by pathological biopsy and with urine specimens retained were included. Basic data, laboratory findings, and pathological information were collected for retrospective analysis, and patients were followed up, and the follow-up time and endpoint events were recorded. The follow-up (composite) endpoint was defined as a doubling of the patient's serum creatinine level or entry into ESRD. ESRD was defined as a patient's eGFR <15 ml/(min-1.73 m2) or initiation of renal replacement therapy. According to the urinary DcR2/Cr levels, they were divided into three groups, group 1: DcR2/Cr <287ng/mmol, group 2: 287≤DcR2/Cr≤544ng/mmol, group 3: DcR2/Cr>544ng/mmol. Analyzed using Kaplan–Meier and Cox regression analyses.

Results: With the increase of DcR2/Cr levels, urinary protein quantification, urinary albumin creatinine ratio (ACR), cystatin C (CYC), blood creatinine, total cholesterol, triglycerides, and LDL levels tended to increase, while the estimated glomerular filtration rate (eGFR), hemoglobin, and serum albumin levels gradually decreased (P<0.05). Correlation analysis revealed that DcR2/Cr levels were positively correlated with ACR (P<0.01), CYC (P<0.01), and blood creatinine (P<0.05) and negatively correlated with eGFR (P<0.05); DcR2/Cr levels were positively correlated with IFTA score (P<0.01) and renal atherosclerosis score (P<0.05). COX regression analysis revealed that The Kaplan-Meier survival curves showed that the risk of adverse prognosis was 5.213 times higher

in the DcR2/Cr3 group than in the DcR2/Cr1 group. The higher the DcR2/Cr level, the worse the prognosis of the patients.

Conclusions: Urinary DcR2/Cr is closely associated with DKD interstitial injury and is a valid biomarker for predicting poor prognosis in DKD.

Funding: Private Foundation Support

TH-PO190

Urinary Podocyte Stress Marker as a Prognostic Indicator for Diabetic Kidney Disease

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Background: Diabetic kidney diseases (DKD) is a the most common cause of end-stage kidney disease (ESKD) around the world. Previous studies suggest that urinary podocyte stress biomarker, e.g. podocin:nephrin mRNA ratio, is a surrogate marker of podocyte injury in non-diabetic kidney diseases.

Methods: We studied 118 patients with biopsy-proved DKD and 13 non-diabetic controls. Their urinary mRNA levels of nephrin, podocin, and aquaporin-2 (AQP2) were quantified. Renal events, defined as death, dialysis, or 40% reduction in glomerular filtration rate, were determined at 12 months.

Results: Urinary podocin:nephrin mRNA ratio of DKD was significantly higher than the control group (p=0.0019), while urinary nephrin:AQP2 or podocin:AQP2 ratios were not different between groups. In DKD, urinary podocin:nephrin mRNA ratio correlated with the severity of tubulointerstitial fibrosis (r = 0.254, p = 0.006). and was associated with the renal event-free survival in 12 months (unadjusted hazard ratio [HR], 1.523; 95% confidence interval [CI] 1.157-2.006; p = 0.003). After adjusting for clinical and pathological factors, urinary podocin:nephrin mRNA ratio have a trend to predict renal event-free survival (adjusted HR, 1.327; 95%CI 0.980-1.797; p = 0.067), but the result did not reach statistical significance.

Conclusions: Urinary podocin:nephrin mRNA ratio has a marginal prognostic value in biopsy-proven DKD. Further validation is required for DKD patients without kidney biopsy.

Funding: Government Support - Non-U.S.

TH-PO191

A Second Dose of Allogeneic Neo-Islets (NIs) Further Reduces Insulin Need and HbA1c and Preserves Renal Function Long Term in Autoimmune T1DM Pet Dogs (INAD 012-776)

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Background: Spontaneously T1D dogs, like T1D humans, never spontaneously revert to a non-diabetic state. Their insulin needs remain stable or increase. They experience progressive CKD, hyperlipidemia, hepatic steatosis, diabetic neuropathy and retinopathy, malignancies, hypoglycemic events, and other complications, making them an ideal translational model for T1DM. We reported (n=8 dogs) that one dose of Neo-Islets (NIs), organoids of Mesenchymal Stromal Cells (MSCs) and culture expanded Islet Cells, when administered i.p. engraft in the omentum where they physiologically secrete insulin and other islet hormones, thereby reducing the need for insulin in autoimmune, spontaneously T1DM pet dogs by up to 50% for up to 3 years. As the MSC component is immune-modulatory, NIs require no antirejection drugs. Here we demonstrate that NIs' beneficial effects are enhanced through administration of a 2nd dose.

Methods: 4 of the original 8 NI-treated, autoimmune diabetic dogs were administered a second dose of 2x10e5 NIs/kg bw i.p. at various times post the first dose. Dogs were assessed for antibodies to NIs, changes in serum glucose, HbA1c, insulin need, liver and renal function, blood counts, adverse and serious adverse events and their relation to administration of the study drug.

Results: A dog who had been unresponsive to the first dose of NIs received a 2nd dose 4 years post the 1st dose. 1 year later, she has a 25% reduced need for insulin, and a 17% reduction in serum glucose. Of the 3 dogs re-dosed within a year of the first administration, insulin need has decreased 25- 50%, and serum glucose levels decreased 40-59%. HbA1c levels are ~4 percentage points reduced, and within normal range. No significant changes in renal function, serum chemistries or blood counts have been observed in the 2-12 months since redose. No dog has developed antibodies to NIs subsequent to either dose. No AEs or SAEs have been attributed to NI therapy.

Conclusions: Allogeneic-NI therapy, which delivers insulin physiologically, is safe durably effective, requires no anti-rejection drugs, can be safely re-administered, and preserves renal function long term. As with human islet transplants, redosing potentiates therapeutic efficacy, and several doses may be required to achieve insulin independence.

Funding: Commercial Support - SymbioCellTech

TH-PO192

Identification and Validation of Neutrophil Extracellular Traps-Associated Genes in Diabetic Kidney Disease: Integration Data from Bulk RNA and Single-Nucleus RNA Sequencing Analyses

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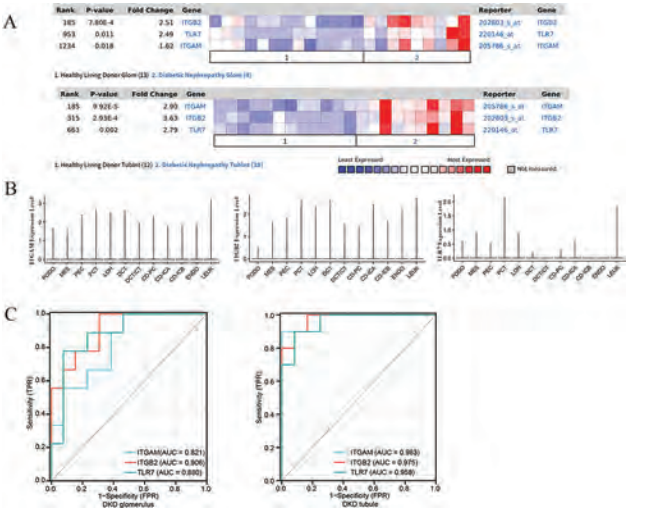
Background: Accumulating data shows that immune response has crucial pathogenic contributions in diabetic kidney disease (DKD), but the contribution of Neutrophil Extracellular Traps (NETs) is limited.

Methods: The differentially expressed genes of NETs in human DKD were selected using the bulk RNA-seq of kidney biopsy from DKD patients (GSE30528 and GSE30529). The characteristic NETs-associated genes were further identified by machine learning algorithms. The DKD bulk RNA sequencing (GSE30122) and single-nucleus RNA-seq (GSE195460) were used to validate the genes expression.

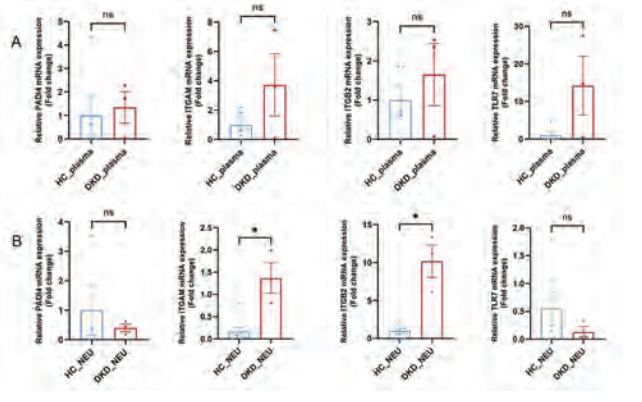
Results: Three candidate genes (ITGAM, ITGB2 and TLR7) were all significantly upregulated in human DKD using machine learning approach. Single-cell analysis indicated that the three transcriptional expressions were mostly increased in leucocytes. GSEA further suggested that hub genes play key roles in IL-2/STAT5 signaling pathway (p=0.029). Good diagnostic performance for DKD were also shown. Our polit data validated ITGAM and ITGB2 expressions in the peripheral active neutrophils isolated from DKD patients.

Conclusions: Dysregulation of ITGAM and ITGB2 may play pathogenic roles for DKD, and drugs that target these genes in neutrophil may have therapeutic potential for DKD.

Funding: Private Foundation Support



Three identified NETs related genes expression validated in human DKD datasets.



NETs related targets validation in human plasma and DKD neutrophils using RT-qPCR.

TH-PO193

The Search for Liquid Biopsies: Serum Biomarkers and Kidney Structure in Early Diabetic Kidney Disease

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Background: The Joslin Kidney Panel (JKP) of 21 circulating proteins biomarkers linked to inflammation, axon guidance, fibrosis, and tubular damage is associated with kidney failure in Caucasians with type 1 diabetes from the Joslin Kidney Study and in American Indians with type 2 diabetes. We examined the association of these proteins with early kidney structural lesions in a subset of the American Indians who also underwent a research kidney biopsy.

Methods: GFR was measured by the urinary clearance of iothalamate and serum samples collected at these visits were measured on an OLINK platform using a proximity extension assay. Research kidney biopsies were obtained a median of 1.3 years from the clearance study. Kidney structure was assessed using standard morphometric techniques. Regression models with Lasso selection and k-fold cross-validation were used to assess best biomarkers for each measure.

Results: Mean age of the 107 participants (78 women) was 45.5 (SD 9.6) years, blood pressure 123 (13) / 77 (9) mmHg, HbA1c 9.2 (2.3)%, GFR 150 (47) ml/min, and median diabetes duration was 12.8 (IQR 11.0-19.4) years. All participants had GFR >60 ml/min; 40 (37%) had moderate albuminuria and 21 (20%) had severe albuminuria. Biomarker concentrations correlated positively with global glomerular sclerosis, glomerular basement membrane width, mesangial fractional volume, cortical interstitial fractional volume, and podocyte foot process width and negatively with glomerular filtration surface density, total filtration surface density, podocyte density, and percentage of endothelial fenestrations (Figure). KIM1 was the leading biomarker for most morphometric parameters based on regression models (Figure).

Conclusions: The JKP of biomarkers that includes proteins linked to multiple diabetic kidney disease (DKD) pathways demonstrated associations with a broad range of early structural lesions associated with DKD progression.

Funding: NIDDK Support

	GBM width	Mesangial fractional volume	Surface density	Total filtration surface	Podocyte density	Foot process width	Endothelial fenestration	Cortical interstitial fractional volume	Glomerular sclerosis
CD27	0.27	0.46*	-0.35	-0.34	-0.27	0.17	-0.37	0.24	0.25
CD160	0.15	0.27	-0.23	-0.32	-0.11	-0.01	-0.31	0.15	0.19
Delta like Canonical Notch Ligand 1	0.34	0.43	-0.35	-0.35	-0.32	0.15	-0.42	0.22	0.21
Ectodysplasin A2 receptor	0.25	0.41	-0.36	-0.40	-0.24	0.20	-0.29	0.38	0.38*
Ephrin A4	0.24	0.30	-0.26	-0.33	-0.21	0.09	-0.23	0.23	0.25
Ephrin type A receptor 2	0.30	0.39	-0.42	-0.42	-0.29	0.25	-0.39	0.30	0.34
GDNF family receptor alpha-1	0.29	0.45	-0.41	-0.38	-0.36	0.21	-0.34	0.37	0.28
Interleukin 1 receptor type 1	0.20	0.15	-0.16	-0.15	-0.10	-0.01	-0.12	0.07	0.02
Kidney injury molecule 1 (KIM1)	0.50*	0.53*	-0.61*	-0.39	-0.49*	0.46*	-0.41	0.30	0.20
Layilin	0.28	0.47	-0.40	-0.41*	-0.29	0.19	-0.36	0.38*	0.27
Lymphotoxin beta receptor	0.28	0.35	-0.34	-0.34	-0.23	0.20	-0.44	0.25	0.28
Peptidase inhibitor 3	-0.06	0.13	-0.15	-0.22	-0.07	0.06	-0.14	0.15	0.14
Poliovirus receptor related protein 4	0.27	0.43	-0.40	-0.39	-0.20	0.24	-0.28	0.34	0.22
Syndecan 1	0.18	0.20	-0.23	-0.19	-0.22	0.15	-0.08	0.24	0.14
Tumor Necrosis Factor Receptor 1	0.26	0.39	-0.32	-0.32	-0.29	0.12	-0.49*	0.20	0.22
Tumor Necrosis Factor Receptor 2	0.27	0.36	-0.28	-0.30	-0.23	0.17	-0.43	0.14	0.22
Tumor necrosis Factor Receptor superfamily member 4	0.27	0.38	-0.34	-0.37	-0.24	0.20	-0.36	0.24	0.31
Tumor necrosis Factor Receptor superfamily member 6b	0.23	0.23	-0.21	-0.21	-0.23	0.16	-0.09	0.20	0.30
Tumor necrosis Factor Receptor superfamily member 10a	0.24	0.31	-0.24	-0.32	-0.17	0.12	-0.36	0.15	0.20
Tumor necrosis Factor Receptor superfamily member 19L	0.11	0.17	-0.13	-0.22	-0.17	0.06	-0.16	0.18	0.29
WAP four-disulfide core domain 2	0.23	0.41	-0.39	-0.36	-0.28	0.21	-0.18	0.38	0.26

p<0.01
p<0.05
Orange = positive correlation
Blue = negative correlation
* Selected in regression model

TH-PO194

Significance of Non-B Cell-Derived Immunoglobulin G in the Renal Tubulointerstitium of Chinese Patients with Type 2 Diabetic Kidney Disease

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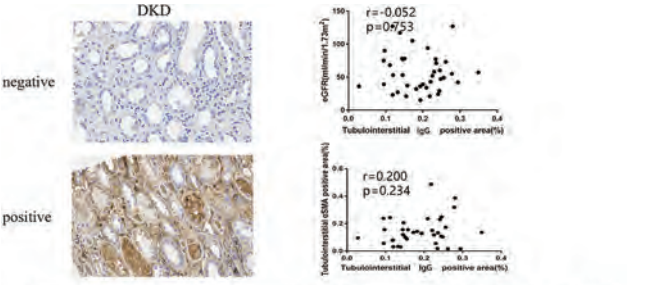
Background: Epithelial-mesenchymal transition (EMT) is critical in the progression of DKD. Studies have reported that positive IgG staining in renal tubules in patients with DKD, but the significance is unknown. Studies have demonstrated that renal intrinsic cells, including renal tubular epithelial cells, can produce IgG (non-B IgG). Therefore, we clarified the non-B IgG in the tubulointerstitium of patients with DKD and its clinicopathological features, and may contribute to renal tubule EMT.

Methods: A total of sixty patients with type 2 diabetes mellitus and biopsy-proven DKD was studied retrospectively. The monoclonal antibody RP215 can screen out human non-B IgG rather than B-IgG. The clinicopathological features of non-B IgG deposition in the renal tubulointerstitium were compared with and without. The risk factors for poor renal function and interstitial lesions were evaluated using logistic regression analysis. In addition, the relationship between tubulointerstitial non-B IgG deposition and EMT was assessed in 30 patients with DKD.

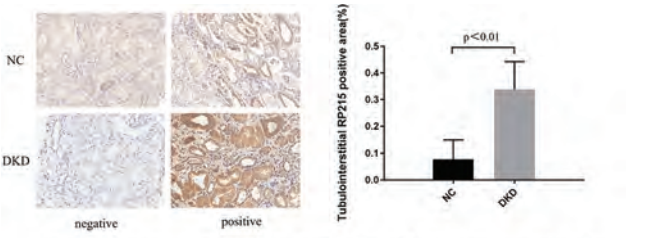
Results: The non-B IgG positive patients showed decreased eGFR (p=0.038) and more severe anemia(p=0.002). Multivariate logistic regression analysis showed that tubulointerstitial non-B IgG deposition was an independent risk factor for poor renal function(p=0.037) and interstitial lesions(p=0.030). The positive area of non-B IgG in DKD renal tubulointerstitium and α-SMA showed a positive correlation (p=0.034).

Conclusions: Renal tubulointerstitial non-B IgG deposition in patients with DKD showed poorer renal function and severe interstitial lesions. The renal tubule EMT was more sever in positive tubulointerstitial non-B IgG staining, suggesting that non-B IgG may be involved in DKD kidney injury by promoting EMT.

Funding: Government Support - Non-U.S.



Immunohistochemical results of commercialized IgG (non-specific IgG antibodies) in the renal tubulointerstitial of DKD (40×) And with eGFR α- Correlation Analysis of SMA Positive Area.



Immunohistochemical results of RP215 (non-B cell IgG specific antibody) of normal group near cancer (NC, n=6) and DKD group (DKD, n=60) (40 ×) in renal tubulointerstitium

TH-PO195

Cardiovascular Benefits and Safety of Sacubitril-Valsartan in ESKD: A Systematic Review and Meta-Analysis

Mariam Charkviani, Pajaree Krisanapan, Charat Thongprayoon, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: End-stage kidney disease (ESKD) patients often experience heart failure, which significantly contributes to their high mortality rates. Despite the crucial role of sacubitril-valsartan in heart failure management, limited data exists on its cardiovascular benefits and safety in ESKD patients. This systematic review aims to assess the efficacy and safety of sacubitril-valsartan compared to standard care in ESKD patients on dialysis, addressing this critical knowledge gap.

Methods: A comprehensive search of was conducted in Embase, MEDLINE, and Cochrane databases though February 2022 to identify studies assessing cardiovascular and/or safety outcomes of sacubitril-valsartan in ESKD patients on dialysis. Effect estimates were derived and consolidated using a random-effect model and the generic inverse variance approach.

Results: Analysis of 12 studies involving 799 eligible ESKD patients demonstrated notable improvements in left ventricular ejection fraction (LVEF) with sacubitril-valsartan compared to the control group, resulting in a pooled mean difference (MD) of 6.58 (95% CI 1.86, 11.29). Subgroup analysis revealed significant differences between heart failure patients with reduced ejection fraction (HFrEF) or moderately reduced ejection fraction (HFmrEF) versus preserved ejection fraction (HFpEF) (p<0.0001). LVEF significantly improved in patients with LVEF <50% (HFrEF and HFmrEF) with an MD of 12.42 (95% CI 9.39, 15.45). However, patients with LVEF >50% (HFpEF) did not show a statistically significant effect, reporting an MD of 2.6 (95% CI 1.15, 6.35). Notably, sacubitril-valsartan significantly enhanced LVEF in HFrEF patients, with a pooled MD of 13.8 (95% CI 12.04, 15.82). Safety analysis revealed no significant differences in the incidence of hyperkalemia (pooled odds ratio [OR] 0.72; 95% CI 0.38, 1.36) or hypertension (pooled risk ratio [RR] 1.03; 95% CI 0.36, 2.98) between sacubitril-valsartan and standard care groups. No cases of angioedema were reported.

Conclusions: Our systematic review suggests that sacubitril-valsartan, compared to standard care, provides benefits to ESKD patients with HFrEF and HFmrEF by improving LVEF, without increasing the risk of hyperkalemia, hypotension, or angioedema.

TH-PO196

Nocturnal Systolic Blood Pressure Dipping and Progression of CKD

Jun Hye Seo,[1] Hyojin Ahn,[1] Cheol Ho Park,[1] Boyoung Nam,[2,1] Jaejin Ryu,[2,1] Gyu R. Kim,[2,1] Tae-Hyun Yoo,[1] Hyung Woo Kim,[1] Seung Hyeok Han,[1] Shin-Wook Kang.[1] *[1]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [2]Yonsei University Institute of Kidney Disease, Seodaemun-gu, Seoul, Republic of Korea.*

Background: The relationship between declining nocturnal blood pressure (BP) and adverse cardiovascular outcomes is well-recognized. However, the relationship between diurnal BP profile and the risk of chronic kidney disease (CKD) progression is unclear.

Methods: We analyzed 1,061 participants from Cardiovascular and Metabolic Disease Etiology Research Center-High Risk (CMERC-HI). The main exposure was diurnal systolic BP (SBP) profile and diurnal SBP difference ([nighttime SBP-daytime SBP]×100/daytime SBP). The primary outcome was CKD progression, defined as a composite of ≥ a 50% decline in the estimated glomerular filtration rate from baseline or the initiation of kidney replacement therapy.

Results: During 4,749 person-years of follow-up (median, 4.8 years), the composite outcome occurred in 380 (35.8%) participants. Compared to dippers, the hazard ratios (HRs) for the risk of adverse kidney outcomes were 1.02 (95% confidence interval [CI], 0.64–1.62), 1.30 (95% CI, 1.02–1.66), and 1.40 (95% CI, 1.03–1.90) for extreme dipper, non-dipper, and reverse dipper, respectively. In a continuous modeling, a 10% increase in diurnal SBP difference was associated with a 1.21-fold (95% CI, 1.07–1.37) higher risk of CKD progression.

Conclusions: Decreased nocturnal SBP decline was associated with adverse kidney outcomes in patients with CKD. Particularly, patients with non-dipping and reverse dipping patterns were at higher risk for CKD progression than those with a dipping pattern.

TH-PO197

The 2021 KDIGO Blood Pressure Target and the Progression of CKD: Findings from KNOW-CKD

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Background: The 2021 KDIGO clinical practice guideline for management of blood pressure (BP) in chronic kidney disease (CKD) recommends a target systolic BP of remains unknown.

Methods: We examined the association of the 2021 KDIGO BP target with CKD progression compared with the 2012 KDIGO BP target among 1724 participants from the Korean Cohort Study for Outcomes in Patients With CKD. The main exposure was BP status categorized according to the 2012 or 2021 KDIGO guideline: 1) controlled within 2021 target; 2) controlled within 2012 target only; and 3) above both targets. The primary outcome was a composite kidney outcome of ≥50% decline in estimated glomerular filtration rate from baseline or the initiation of kidney replacement therapy during the follow-up.

Results: During 8,078 person-years of follow-up (median, 4.9 years), the composite kidney outcome occurred in 650 (37.7%) participants. The incidence rates of this outcome were 55, 66.5, and 116.4 per 1,000 person-years in BP controlled within the 2021 and 2012 KDIGO targets, and BP above both targets, respectively. In the multivariable cause-specific hazard model, hazard ratios for the composite outcome were 0.76 (95% confidence interval, 0.60-0.95) for BP controlled within the 2021 target and 1.36 (95% confidence interval, 1.13-1.64) for BP above both targets, compared with BP controlled within 2012 target only.

Conclusions: The newly lowered BP target by the 2021 KDIGO guideline was associated with improved kidney outcome compared with BP target by the 2012 KDIGO guideline.

TH-PO198

Early Decline in GFR Predicts Long-Term Renal Events in Hypertensive CKD Patients Using Renin-Angiotensin System (RAS) Blockers

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Background: Renin-angiotensin-aldosterone inhibitors (RASIs) are essential in treating chronic kidney disease (CKD), but their initiation can lead to a decline in glomerular filtration rate (GFR). Limited research exists on the impact of RASI-induced GFR changes on long-term GFR variations and albuminuria.

Methods: This observational cohort study extends an open-label, case-controlled randomized clinical trial (NCT01552954) with hypertensive CKD patients(estimated GFR (eGFR) ≥30ml/min/1.73m^2, random urine albumin-to-creatinine ratio (UACR) ≥30mg/g creatinine). After an 8-week screening phase (0-week) after discontinuing RASIs, participants were prescribed an angiotensin receptor blocker (ARB: Olmesartan 40mg/day) and underwent a second visit at 8 weeks with randomization into intensive or conventional low-salt diet education. Third visit was conducted at 16 weeks. We recruited participants for cohort observation and completed at 38 months(29-48) after a 0-week visit. Patients were grouped into tertiles based on percent change in initial GFR during the first 8 weeks (**pcGFRi**).

Results: We analyzed data from 174 people finished 38-month observation among 235 participants enrolled for the trial phase. Groups 1, 2, and 3 (first, second, and third tertiles) showed percent changes in GFR of -16.0(-41.5~-8.1), -2.8(-7.3~-1.6), and 8.3(1.8~28.4)%, respectively. At the 0-week visit, there were no differences in the tertile groups' age, gender, GFR, 24hr UACR, or 24hr sodium excretion. These factors positively correlated with the percent change in GFR during the study period (factor B=8.180, p<0.001 for the group; factor B=0.801, p<0.001 for pcGFRi). The GFR slopes during a study peroid were, in order, -2.9(-4.0~-1.8), -1.3(-2.4~-0.3), and 0.1 (-1.0~1.2)ml/min/1.73 m^2/year (p=0.001 by the ANCOVA test). The relative risks to eGFR decrease ≥30% in groups 2 and 3 compared to 1 were 0.237 (0.07~0.798, p=0.020) and 0.035 (0.004~0.302, p=0.035). The pcGFRi's AUC to eGFR decrease ≥30% was 0.787 (0.685–0.889, p0.001). The cut-off value for pcGFRi eGFR decline ≥30% is 7.25% (71.4 % sensitivity, 70.9% specificity).

Conclusions: The decline of GFR by initiation of RASI predicts long-term renal event of GFR decline ≥30% in users of RASI, strongly. Further research comparing renal outcomes between RASI users with initial decrease in GFR and non-users is needed to guide RASI usage based on initial change in GFR.

TH-PO199

Association of Tricuspid Regurgitant Jet Velocity with Kidney Function in Patients with Heart Failure with Preserved Ejection Fraction in TOPCAT

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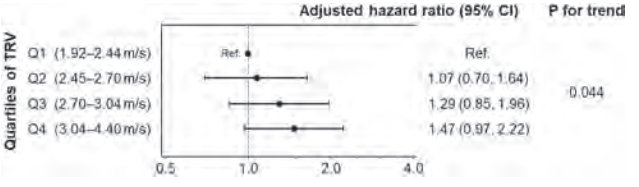
Background: Pulmonary hypertension is common and associated with higher mortality in heart failure with preserved ejection fraction (HFpEF). While increasing evidence suggests that venous congestion can cause worsening kidney function, the association of pulmonary artery systolic pressure (PASP) with kidney function remains uncertain in patients with HFpEF.

Methods: This post-hoc analysis of the Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) trial analyzed patients with HFpEF who had an echocardiogram at baseline. The exposure variable was tricuspid regurgitant jet velocity (TRV), a surrogate of PASP. In a cross-sectional analysis, the association of TRV with eGFR at baseline was assessed using linear regression. In a longitudinal analysis, the association of quartiles of TRV with time to eGFR decline of ≥30% was assessed using a Cox proportional hazards regression. Covariates, including patient demographics, comorbidities, laboratory data, medications, and randomized group, were adjusted in the multivariable models.

Results: Among 450 patients, median age, TRV, and eGFR at baseline were 73 years, 2.7 m/s, and 61 mL/min/1.73 m^2, respectively. In a multivariable analysis, each 1.0 m/s higher TRV was significantly associated with a 3.9 (95% confidence interval, 0.2–7.6) ml/min/1.73 m^2 lower eGFR at baseline. Over a median follow-up of 94 weeks, 52 patients died and 203 had an eGFR decline of ≥30%. Patients with a higher quartile of TRV had a higher risk of eGFR decline of ≥30% (Figure). There was no interaction by randomized group ($P_{interaction}$ =0.45). An analysis using all-cause death as a competing event did not substantially change the results.

Conclusions: A higher TRV was associated with a higher risk of kidney function decline among patients with HFpEF in TOPCAT.



TH-PO200

Association of Pulmonary Arterial Pulsatility Index (PAPi) with Kidney Outcomes Among Patients Admitted for Acute Decompensated Heart Failure

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Background: Pulmonary arterial pulsatility index (PAPi), defined as (pulmonary artery (PA) systolic pressure - PA diastolic pressure)/right atrial pressure, has emerged as a novel marker to capture right ventricular failure. Lower PAPi is associated with increased risk of death but has not been studied in association with renal outcomes.

Methods: Records for patients requiring a PA catheter for acute decompensated heart failure (ADHF) admissions to a single quaternary center between 2015-2021 were reviewed. PAPi was calculated based on the initial measurements; values were log-transformed given their skewed distribution. Linear regression models were used to examine the cross-sectional association of PAPi with baseline estimated glomerular filtration rate (eGFR) and in-hospital eGFR slope. Patient records were linked to the US Renal Data System to capture dialysis outcomes. We used multivariable Cox proportional hazards regression models to examine the association of PAPi with dialysis and the composite endpoint of death or heart transplant (HT). Covariates included demographics, measures of cardiac disease severity and medications.

Results: Among 753 patients with mean age 62 (SD 14) years, median PAPi was 2.0 (IQR 1.4, 3.2), mean eGFR of 58 (SD 27) ml/min/1.73m^2 and mean eGFR slope was 1.2 (SD 6.2) ml/min/1.73m^2/week. For every doubling of PAPi, there was a 3.3 ml/min/1.73m^2 (95% CI 1.5, 5.2) higher baseline eGFR, and 0.7 (95% CI 0.3, 1.2) ml/min/1.73m^2/week higher in-hospital eGFR slope. Over median follow-up of 23 (IQR 8, 47) months, 62 (8%) reached dialysis and 365 (48%) reached the composite endpoint. Higher PAPi was associated with significantly lower risk of requiring dialysis both in unadjusted and adjusted models (Table). Higher PAPi also trended toward decreased risk for the composite outcome (Table).

Conclusions: Higher PAPi is associated with higher baseline eGFR, higher in-hospital eGFR slope and lower risk of progression to dialysis in patients admitted for ADHF.

Funding: NIDDK Support

Table. Hazard ratios for risk of composite outcome of death or heart transplant and need for dialysis per doubling of PAPi.

Outcome	Need for Dialysis	Death/Heart Transplant
N	753	753
Number of Events	62	365
Unadjusted HR (95% CI)	0.64 (0.49, 0.83)	0.92 (0.83, 1.03)
Adjusted HR (95% CI) *	0.70 (0.51, 0.96)	0.92 (0.82, 1.04)

*Adjusted for age, sex, ejection fraction, diabetes, estimated glomerular filtration rate and use of renin angiotensin aldosterone system blockade, mineralocorticoid receptor antagonists, angiotensin receptor/neprilysin inhibitors, and inotropes.

TH-PO201

Is the Increased Risk of Heart Failure with Preserved Ejection Fraction (HFpEF) and Heart Failure with Reduced Ejection Fraction (HFrEF) in CKD in Type 2 Diabetes (T2D) explained by Hypertension (HTN)?

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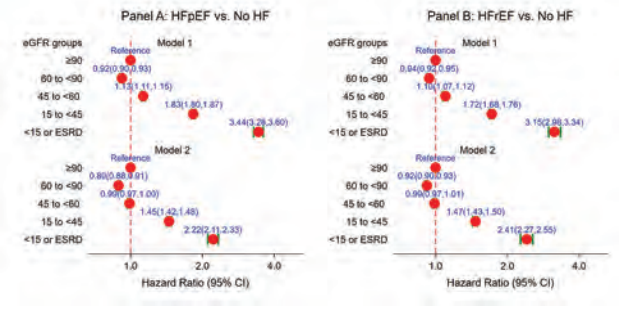
Background: CKD is a clear risk factor for HFpEF and HFrEF but the degree to which HTN it plays a role in the pathogenesis of these disorders in CKD is unknown.

Methods: We used the VA Informatics and Computing Infrastructure to create a national cohort of veterans with T2D but without HF (using ICD9/10 codes) who had at least 2 outpatient CKD-EPI eGFR measured from 1/1/2000 to 12/31/2021 (n=2,462,350). Incident HF through 12/31/2021 were identified using ICD 9/10 codes. Using ejection fraction (EF) data extracted with natural language processing from echocardiograms done within 180 days of HF diagnosis, HFpEF (EF ≥ 50%) and HFpEF (< 50%) were defined. We related CKD stages at baseline with time to HFpEF or HFrEF incidence while adjusting for demographics, baseline comorbidities, BMI, duration of T2D, diabetic retinopathy, T2D meds, statins and A1C in separate Cox regression models. We then adjusted for baseline hypertension, blood pressure (BP) and BP-modulating medications.

Results: Out of 410,783 (16.7%) patients who developed HF over 1.78 million patient-years of follow up, 289,508 (70.5%) had an echocardiogram within 180 days of diagnosis (median days for the closet echo with diagnosis 1 with IQR 0 to 13). Mean EF was 45±15%. Overall, 168,079 (6.8%) patients developed HFpEF and 121,421 (4.9%) HFrEF. As shown in the Figure, adjusted for demographics, comorbidity and other factors, more advanced CKD was associated with higher risk of HFpEF and HFrEF. Adjusting for baseline hypertension, SBP and DBP and BP meds resulted in modest to moderate attenuation of the associations of CKD stages with HFpEF or HFrEF.

Conclusions: HTN appears to play a role in both HFpEF and HFrEF, particularly in CKD stages 3a and 3b to 4. Intensive BP control might reduce the risk of HFpEF and HFrEF in these stages of CKD than in stage V/ ESRD.

Funding: Veterans Affairs Support



TH-PO202

Is Pulmonary Hypertension (PH) Associated with the Type of Hemodialysis Access and Is PH a Barrier to Kidney Transplant?

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Background: In hemodialysis (HD) patients, PH is multifactorial. Surgically created arterio-venous (AV) fistulas/grafts may contribute to PH by increasing right ventricular preload. We compared the prevalence of PH among patients with AV accesses to those with hemodialysis central venous catheters (CVC). We then examined whether PH was a contraindication to kidney transplantation.

Methods: A single-center 10-year retrospective cross-sectional study of right heart catheterizations (RHC) in randomly selected HD patients, were identified with the CPT codes: 93451 and ICD10 Z99.2. Patients with a previous solid organ transplantation or advanced heart failure requiring inotropic or mechanical support were excluded. Categorical variables were compared with Fisher's exact tests and continuous variables were compared with t-tests.

Results: 3834 charts were extracted, 257 were reviewed, and 107 were included. 65% were male and 63% had diabetic renal disease. The median dialysis vintage was 26 months (IQR:61.8months). 64.5% patients had mean pulmonary arterial pressure of >20mmHg, 43% had pulmonary capillary wedge pressure ≥15mmHg, and 22% had pulmonary vascular resistance of ≥3.00. The type of HD access was not associated with PH (47%CVC vs 41%AV, p=0.65). Among 26% patients with vascular duplex, there was no difference between AV access flow rates in those with and without PH (median(IQR):1483(2139) vs 1267(2092), p=0.29). 86% survived after 1-year of RH and mortality was not associated with prevalance of PH. There was no difference in transplant candidacy between those with and without PH (81% vs 75%, p=0.47).

Conclusions: PH was common in HD patients (42%), and the type of vascular access was not associated with PH between. Diagnosis of PH had no direct effect on transplant candidacy.

Table 1: Baseline characteristic

	Venous Catheter (17)	AV access (90)
Age, years, mean (SD)	59.1 (11.7)	65.1 (9.5)
Gender, male (%)	7 (41.2%)	63 (70%)
Race, n (%)		
• Caucasian	3 (17.6%)	10 (11.1%)
• African American	8 (47.1%)	60 (66.7%)
• Hispanic	4 (23.5%)	14 (15.6%)
• Asian	-	5 (5.6%)
• Others	2 (11.8%)	1 (1.1%)
Causes of ESRD, n (%)		
• Diabetes Mellitus	14 (82.4%)	54 (60%)
• Hypertension	-	17 (18.9%)
• Nephrotic syndrome	-	3 (3.3%)
• Nephritic syndrome	-	3 (3.3%)
• Others	1 (5.9%)*	10 (11.1%)*
• Not mentioned	2 (11.8%)	3 (3.3%)
Duration on dialysis, months, median (IQR)	6 (4 -11.5) (1 missing)	35 (13-82)
Location of access, n (%)		
• Internal jugular	17 (100%)	-
• Axillary	-	3 (3.3%)
• Brachial	-	72 (80%)
• Radial	-	14 (15.6%)
• Femoral	-	1 (1.1%)
Weight difference, kg, mean (SD)#	1.1 (5.2) (6 missing)	0.8 (3.3) (25 missing)

*2 with adult polycystic kidney disease, 2 had concern for IgA nephropathy vs other causes, 2 developed obstructive uropathy, 1 had idiopathic nodular glomerulosclerosis, 1 had solitary kidney and 2 had 'uncertain' cause of their ESRD, declared by nephrologist

Table 2: Comparison between patients with Pulmonary Hypertension

	Venous Catheter (17) (1 missing)	AV access (90) (3 missing)	p-value
Total, n, %	8 (47.1%)	37 (41.1%)	0.65
Dialysis vintage, months, median (IQR)	6 (5-9.5) (1 missing)	34 (13-82)	
Weight difference, kg, mean (SD)#	1.1 (6.1) (2 missing)	0.9 (3.4) (8 missing)	0.85
Symptomatic at time of RHC	7 (41.2%) 1 missing	22 (24.4%)	0.15
Transplant status, n (%)			
• Accepted/listed/ transplanted	2 (11.8%)	20 (22.2%)	0.33
• Declined	-	8 (8.9%)	
• Not available	6 (35.3%)	9 (10%)	
Died, n (%)	3 (17.6%) (3 missing)	8 (8.9%) (12 missing)	0.28

#Weight at time of RHC as compared to dry weight

TH-PO203

Assessing Heart Rate Variability in Patients with CKD: Association with Vascular Dysfunction

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Background: Autonomic dysfunction (AD) has been recognized as an important contributor to poor outcomes in patients with chronic kidney disease (CKD) characterized by adrenergic overdrive and/or loss of parasympathetic activity. Heart rate variability (HRV) is a measure of the exact changes between successive R-R intervals in a heartbeat and reflects the balance between sympathetic and parasympathetic tone. HRV has been associated with all-cause mortality and vascular dysfunction in patients with cardiovascular diseases, but very few studies have assessed its association with vascular disease and dysfunction in CKD. Thus, this study examined HRV in patients with CKD and how it associates with vascular dysfunction.

Methods: This study cross-sectionally pooled baseline data from three clinical studies conducted in patients with stage 3-4 CKD. Five-minute electrocardiogram readings at rest with paced breathing were analyzed using an automated HRV analysis tool in the LabChart software. HRV parameters were compared to age-matched healthy controls. Regression models were used to evaluate associations of low HRV with other vascular parameters: endothelial dysfunction (brachial artery flow-mediated dilation [FMD_B%]), central arterial stiffness (carotid-femoral pulse-wave velocity [CFPWV]), local arterial compliance (carotid artery compliance), cerebrovascular stiffness (resting middle cerebral artery pulsatility index), and cerebrovascular reactivity (middle cerebral artery blood flow-velocity response to hypercapnia) in the CKD group.

Results: Forty-four participants with CKD (33/11 M/F; mean age (years) ± s.d 68±7, eGFR 44±11 ml/min/1.73m^2) were compared to nine age-matched controls (4/5 M/F;

65±8 years, eGFR 97±18 ml/min/1.73m^2). Patients with CKD had lower HRV (pRR50; Percent of adjacent R-R intervals with a difference greater than 50 ms) compared to controls (CKD: 7.7±4.2; control: 25.0±16.5; P=0.0001). Low pRR50 was inversely associated with endothelial dysfunction (FMD_B%) (r = -0.4320, P<0.05), but not with other vascular parameters.

Conclusions: Patients with CKD had lower HRV (autonomic dysfunction) than age-matched healthy controls. Low HRV associates with endothelial dysfunction. This observation should be explored in a larger cohort with further covariate adjustment.

Funding: NIDDK Support

TH-PO204

Phenotyping of Heart Failure (HF) Risk in CKD Using 12-Lead ECG

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Background: H in CKD is associated with high rates of mortality and recurrent hospitalizations. Early identification of individuals at increased risk for HF in CKD would facilitate improved risk stratification and modification of treatment strategies. Current tools to predict de novo HF in CKD are lacking. We aimed to analyze associations of standard ECG features and the risk of incident HF in CKD.

Methods: We assembled a dataset of clinical and ECG data on individuals at NYU with at least two eGFR measurements <60 mL/min/1.73m^2 ≥90 days apart and an ECGs done at NYU between 2012-2021. The index ECG was the first ECG after an eGFR measurement. We excluded individuals with existing history of HF or HF admission within 30 days of index ECG. HF event was defined as primary inpatient discharge diagnosis identified using validated ICD codes. Univariate associations were analyzed using KM curves, multivariable associations of ECG features and incidence HF event were analyzed using Cox proportional hazards adjusting for relevant covariates.

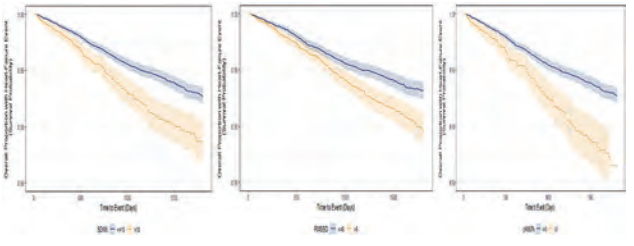
Results: Among 14,503 individuals included, HF event rate was 6.2% with median time to event of 672 days (340,1625). eGFR stages and sex were similar among those with and without HF. Standard ECG features such as PR, QRS, QT, QTc, P and T axis as well as HRV parameters derived from ECG such as SDNN, RMSSD, PRR50% differed significantly between the two groups on univariate analyses (Figure). The concentrations of potassium, albumin, and calcium were significantly different in those with and without HF. In the best fit model standard ECG but not HRV parameters were independent predictors of HF (Table).

Conclusions: Standard ECG features when combined with demographic and comorbidities data can predict incident HF in CKD.

Funding: Commercial Support - ASN Donal E. Wesson Fellowship grant

Variables	Hazard Ratio	Lower 95% CI for HR	Upper 95% CI for HR	P-Value
Payor Type				
Private				
Medicare	1.11	0.80	1.53	0.54
Medicaid	2.05	1.32	3.19	0.00
Other/Unknown	3.40	1.54	7.49	0.00
Age	1.02	1.01	1.03	0.01
PR Interval	1.01	1.00	1.01	<0.001
QT Interval	1.00	1.00	1.01	0.10
QT Corrected	1.01	1.01	1.01	<0.001
T-Axis	1.00	1.00	1.01	0.00
Albumin	0.59	0.47	0.74	<0.001
BUN	1.01	1.00	1.02	0.01
Carbon Dioxide	1.03	1.00	1.06	0.09
Hematocrit	0.98	0.96	1.00	0.13
Potassium	1.22	1.00	1.49	0.05
Cardiac Arrhythmias	1.91	1.52	2.39	<0.001
Valvular Disease	1.42	1.09	1.83	0.01
Pulmonary Circulation Disorders	2.02	1.35	3.04	0.00
Peripheral Vascular Disorders	1.29	1.02	1.64	0.04
Hypertension Uncomplicated	1.31	0.92	1.87	0.14
Diabetes Uncomplicated	1.29	1.03	1.63	0.03
Diabetes	1.23	0.95	1.58	0.12
Elixhauser Score	0.99	0.98	1.00	0.13

Cox PH model



HF survival probability in the CKD cohort with and without abnormal HRV

TH-PO205

Liver Elasticity in Heart Failure Patient: The Role of Kidney in Cardio-Hepatic Interaction

Hirohito Sugawara.[1,2] *[1]Showa Daigaku Yokohama-shi Hokubu Byoin, Yokohama, Japan; [2]Bokoi Tenshi Byoin, Sapporo, Japan.*

Background: Liver elastography is a novel ultrasound technique assessing elasticity of liver tissue. Previously, it had been reported that the more elevated liver stiffness, the poorer the prognosis in heart failure indicating cardio-hepatic interaction. However, clinical indication of liver elastography remains unrevealed. Moreover, reports about relationship between liver stiffness and heart failure subtypes haven't well been published. Therefore, we have investigated the cardio-hepatic interaction using liver elastography in heart failure subtypes.

Methods: We prospectively enrolled 58 consecutive patients with heart failure admission from April 2022 to March 2023. Liver elastography, transthoracic echocardiography and blood sampling were done at the time of discharge from heart failure treatment.

Results: Patients were divided into two groups according to the left ventricular ejection fraction (LVEF) of echocardiography: heart failure with reduced ejection fraction (HFrEF) group (EF ≦40%, n = 11) and non-HFrEF group (EF >40%, n = 31). The mean age of all patients was 83 ± 11 years. The mean age and the prevalence of hypertension and diabetes mellitus was higher in non-HFrEF group than in HFrEF group. The prevalence of taking SGLT2 inhibitors was lower in non-HFrEF group than in HFrEF group. LV end-diastolic diameter, LV end-systolic diameter was larger in HFrEF group than in non-HFrEF group. Tricuspid regurgitation pressure gradient (TRPG) was higher in non-HFrEF group than in HFrEF group. Inferior vena cava diameter was not different between two groups. The mean values of almost liver function tests of all patients were within the normal range. eGFR was lower in non-HFrEF group than in HFrEF group. Liver elasticity was higher in non-HFrEF group than in HFrEF group (7.1 ± 2.7 vs. 5.1 ± 1.5 hPa; P=0.008) indicating liver stiffness. Pearson's correlation coefficient showed that liver elasticity was positively correlated with the prevalence of diabetes mellitus, LVEF, TRPG, serum creatinine, AST, GGT and was negatively correlated with LV end-diastolic diameter, LV end-systolic diameter.

Conclusions: Liver stiffness was elevated and renal function was decreased in EF-preserved heart failure patients. Liver elasticity was correlated with the parameter of congestion (TRPG) and useful for the assessment of congestion. Renal function was also correlated with liver elasticity.

TH-PO206

Role of Dual-Energy Computed Tomography (DECT) in Detection of Carotid Artery Monosodium Urate Deposition (MSU) in Patients with CKD

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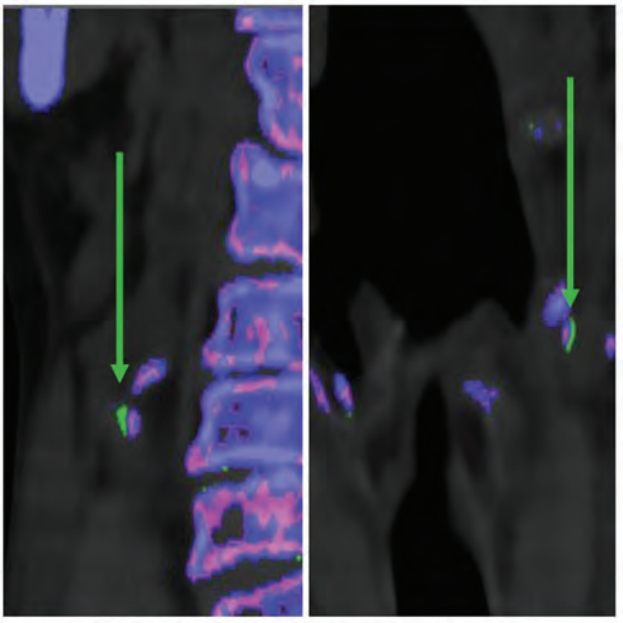
Background: To find out if a Dual energy CT can detect MSU deposition in carotid arteries in patients with CKD and whether the presence of monosodium urate crystals has any effect on atherosclerotic disease in terms of plaque volume.

Methods: This is a retrospective study. All patients with CKD who underwent Dual energy neck imaging (like carotid angiogram, neck soft tissues or cervical spine) from January 2015 to December 2022 were included. Charts were reviewed to find CKD patients and potential confounding variables like isolated gout or smoking which can add to atherosclerotic disease. Same number of healthy controls were included which were then age (within 5 years), sex and confounders-matched to CKD patients using MedCalc. DECT datasets were post-processed using Syngo.ViaVB30 with MSU application and Calcium scoring application for volumetric analysis of atherosclerotic plaque.

Results: Out of total 2157 patients who underwent dual energy neck imaging during study period, 85 were established CKD cases with confirmed clinical and laboratory evidence. Of 85 CKD cases, 2 were excluded due to presence of artefacts from dentures, n=83. Out of 83, MSU was detected in carotid arteries of 10 patients (12%). None of the matched control patient demonstrated MSU deposition. Volumetric analysis of atherosclerotic plaque demonstrated larger plaque volumes in CKD patients with MSU (n=10) than matched CKD patients without MSU (n=10) and matched control/non-CKD patients (n=10) (p value of 0.03).

Conclusions: 1. Dual energy CT is an effective tool to detect MSU deposition in carotid arteries of patients with CKD. 2. MSU deposition increases atherosclerosis which can lead to increased TIA/strokes and hence has significant role in patient's morbidity.



Positive MSU carotid plaque in patient with CKD

TH-PO207

Outcomes with Inpatient Use of Midodrine in Patients on Maintenance Hemodialysis with Heart Failure

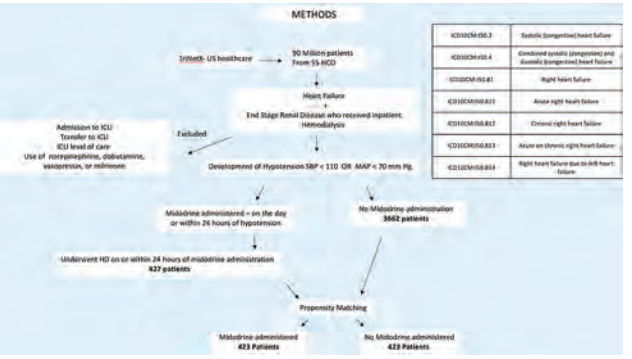
Neev Patel,[1] Bruno Alvarez Concejo,[1] Meenakshi Mishra,[4] Kevin Bryan Lo,[3] Adrian P. Sequeira,[1] Ayeesha Kattubadi,[1] Janani Rangaswami.[2] *[1]LSU Health Shreveport, Shreveport, LA; [2]The George Washington University School of Medicine and Health Sciences, Washington, DC; [3]Albert Einstein Medical Center, Philadelphia, PA; [4]Ochsner Center for Academic Excellence, New Orleans, LA.*

Background: Midodrine, a peripheral vasoconstrictor, is commonly used in kidney failure patients for predialytic and intradialytic hypotension. However, in patients with systolic and/or right heart failure (HF), midodrine is potentially harmful. No known studies examine the safety of midodrine in hospitalized patients with kidney failure and HF.

Methods: We queried TriNetX database for inpatients with kidney failure and systolic and/or right HF who had at least an event of hypotension (SBP < 110 mm Hg or MAP < 70 mm Hg). Patients requiring critical care, inotropes or vasopressors were excluded. Cohorts were separated based on midodrine use. Temporality was established between hypotension, midodrine use, and hemodialysis, as shown in figure. Cohorts were matched for relevant comorbidities.

Results: In patients receiving midodrine, 6-month mortality risk ratio (RR) was significantly higher than no midodrine use (RR 1.53, 95% CI 1.037 to 2.246). Kaplan Meier survival analysis log-rank test at 6 months revealed a Hazard Ratio of 1.54 (95% CI 1.022 to 2.317).

Conclusions: In patients with systolic and/or right HF and kidney failure, hypotension is a limiting factor for decongestion and guideline directed therapy implementation, making midodrine a tool used in real world practice for stabilization. Our exploratory results in noncritically ill inpatients show an association between use of midodrine and higher 6-month mortality. This may reflect deleterious effects from vasoconstriction and/or unmeasured confounders in sicker patients with HF and kidney failure that increase mortality risk. This study has multiple limitations. Given its observational nature, it cannot establish a cause-effect relationship. Other limitations include the lack of data regarding dosage and duration of midodrine, and severity and etiology of heart failure. Our study demonstrates increased mortality associated with midodrine use for hypotension, warranting further research and consideration of alternative strategies.



Methods

TH-PO208

The Characteristics of Myocardial Fibrosis and Analysis on Related Influencing Factors in Hemodialysis Patients

Bing Zhuang, Yuan Luo, Guiling Wei, Hong Ye, Junwei Yang. *The Second Affiliated Hospital of Nanjing Medical University, Nanjing, China.*

Background: This study aimed to analyze the characteristics of myocardial fibrosis and related influencing factors in hemodialysis patients, and to explore whether cardiovascular magnetic resonance (CMR) based on T1 mapping technique has prognostic value in predicting cardiovascular events.

Methods: This was a prospective observational study. The clinical data and dialysis parameters were collected, and laboratory tests were conducted. All patients underwent CMR, T1 mapping technique was used to identify myocardial interstitial fibrosis and LGE positive was used to identify alternative myocardial.

Results: A total of 42 hemodialysis patients were enrolled, the mean native T1 value of the entire heart was 1277.34±54.95ms. The native T1 value was positively correlated with heart rate and the ratio of transmitral Doppler early filling velocity to tissue Doppler early diastolic mitral annular velocity (E/e') (r=0.366, P=0.017; r=0.386, P=0.014), and negatively correlated with six-minute walk distance (r=-0.474, P=0.002). E/e' was found to be a risk factor for the mean native T1 value of the entire heart in hemodialysis patients (OR=1.508, 95% CI: 1.008-2.258, P=0.046). LGE scans were completed in 39 patients, of whom 12 (30.8%) were LGE positive and 27 (69.2%) were LGE negative. Compared with the LGE negative group, the LGE positive group had a shorter six-minute walk distance (P=0.029), larger left ventricular end-systolic volume (LVESV) and left ventricular mass (LVM) (P=0.023 and P=0.025, respectively). Left ventricular mass was found to be a factor influencing LGE positivity (OR=1.045, 95% CI: 1.003-1.088, P=0.035). Logistic regression analysis showed that the higher the native T1 value, the greater the probability of cardiovascular events occurring within six months (OR=1.1, 95% CI: 1.003-1.206, P=0.043).

Conclusions: E/e' is a factor influencing interstitial fibrosis in hemodialysis patients and the left ventricular mass is a factor influencing alternative fibrosis. The native T1 value has predictive value for cardiovascular events within six months.

Funding: Government Support - Non-U.S.

TH-PO209

Large Artery Stiffness and New-Onset Diabetes in the Chronic Renal Insufficiency Cohort

Harini Sarathy,[1] Raymond R. Townsend,[2] Mahboob Rahman,[3] Julio A. Chirinos,[2] Jordana B. Cohen.[2] *[1]University of California San Francisco School of Medicine, San Francisco, CA; [2]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [3]UH Cleveland Medical Center, Cleveland, OH.*

Background: Chronic kidney disease (CKD) accelerates large artery stiffness (LASt), which can cause damage to low-resistance high-flow microvascular beds in the liver, skeletal muscle, and pancreas, and which may affect insulin sensitivity. Our goal was to explore the relationship of LASt with new-onset diabetes in adults with CKD.

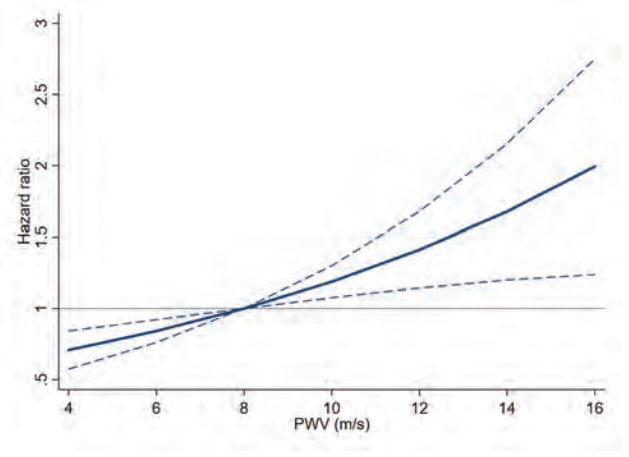
Methods: Carotid femoral pulse wave velocity (CFPWV) was performed in 1,512 participants of the Chronic Renal Insufficiency Cohort (CRIC) Study without diabetes. We used Cox regression and generalized estimating equations to evaluate baseline and time-updated CFPWV and incident diabetes, adjusting for age, sex, race, BMI, MAP, heart rate, eGFR, UPCR, smoking, total cholesterol, HDL, antihypertensives, and family history of diabetes. We assessed for effect modification by age, sex, prediabetes, and proteinuria.

Results: Participants in the highest tertile of CFPWV (median 10.8 m/s) were older (66 vs 53 years), had higher MAP (90 vs 84 mmHg) and lower eGFR (41 vs 50 mL/min/1.73m^2) compared to the lowest tertile (median 6.5 m/s). Over a median of 9 years, CFPWV was associated with new-onset diabetes (unadjusted HR 1.25, 95% CI 1.07-1.46 per standard deviation increase in CFPWV [sHR]; Figure), which dissipated after multivariable adjustment (sHR 1.15, 95% CI 0.95-1.38) but persisted in multivariable-adjusted models incorporating time-updated CFPWV (sOR 1.18, 95% CI 1.04-1.33).

There was significant effect modification by proteinuria. Higher CFPWV was associated with new-onset diabetes among participants with UPCR <1g/g (sHR 1.27, 95% CI 1.03-1.56) but not ≥1 g/g.

Conclusions: Among adults with CKD, LASt was associated with new-onset diabetes, particularly in those without significant proteinuria. LASt may have a key mechanistic role in abnormal glucose metabolism and could be a helpful marker of diabetes risk among patients with non-proteinuric CKD.

Funding: NIDDK Support



Association of CF-PWV and new-onset diabetes

TH-PO210

Relationship Between Pulse Wave Velocity and Nocturnal Blood Pressure in Hypertensive Subjects: A Retrospective Study

Marwa Abdalla,[1] Arvin Daneshmand,[2] Negiin Pourafshar.[1] *[1]MedStar Georgetown University Hospital, Washington, DC; [2]University of Florida, Gainesville, FL.*

Background: Tonometric pulse wave velocity (PWV) has been established as a non-invasive method for assessment of arterial stiffness[1]. Arterial stiffness as measured by PWV is an emerging tool for Cardiovascular risk evaluation and stratification[2]; as in hypertensive patients, elevated PWV could be associated with an increased risk of cardiovascular death[3]. The purpose of this study was to assess the relationship between nocturnal blood pressure (BP) decline and PWV in the hypertensive subjects.

Methods: This is a retrospective study of patients who underwent ambulatory blood pressure monitoring between April 2021 and June 2022 at Medstar Georgetown University Hospital. Fifty-two subjects with essential hypertension were included. BP was measured by ambulatory monitoring every 30 min between 06:00 am and 22:00 pm and every 30 min at night, throughout 48 hours with a Mobil-o-graph device. Carotid-femoral PWV was also measured as an index of aortic stiffness, by using the Mobil-o-graph which uses a validated transfer function.

Results: Among the 52 subjects, 42% were female, 58% were male, and the average age range was 64 years old. Forty-eight hour systolic/diastolic BP were 127.9 (± 13.1)/77.8 (± 10.7) mmHg, mean nocturnal BP was 119.1 (± 15.1)/ 70.3 (± 11.9) mmHg and nocturnal BP changes was -8.5 (± 10.2)/-12.2 (± 11.3) mmHg. Among subjects, 40.3% of were dipper, 9.6% were extreme dipper, and 50% were non-dipper. Mean PWV was 8.2 m/sec. Nocturnal systolic BP had a significant correlation with PWV (r=0.72; p=0.000). No significant correlation was observed between PWV and diurnal BP.

Conclusions: Nocturnal blood pressure may assist physicians in identifying hypertensive subjects with higher arterial stiffness, who are at higher cardiovascular risk. Further studies are needed to assess advantages of lowering nocturnal blood pressure. Ambulatory blood pressure monitoring could be useful to appropriately evaluate cardiovascular risk in hypertensive subjects.

TH-PO211

Associations Between Urine Sodium and Potassium Level, Elevated Arterial Stiffness, and Hypertension in a Population-Based Study: A Mediation Analysis

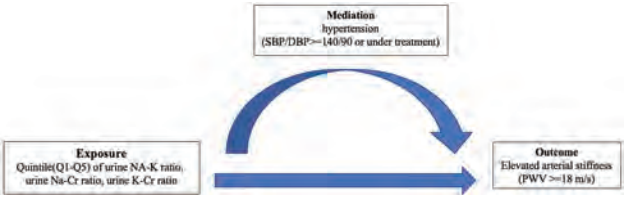
Xiaohong Fan, Jie Ma. *Peking Union Medical College Hospital, Dongcheng-qu, China.*

Background: The urinary sodium-potassium ratio (Na-K ratio) has recently been regarded as another hypertension indicator. The current study aims to assess the association of urine sodium and potassium level with elevated arterial stiffness and investigate how this association is mediated via blood pressure.

Methods: We performed a cross-sectional study of 10,281 participants in rural China. First void morning urine was collected to detect urine creatinine(Cr), sodium(Na), and potassium(K) levels. All subjects underwent brachial-ankle pulse wave velocity (baPWV) measurement to estimate arterial stiffness. *Hypertension* was defined as a systolic BP≥140mmHg or diastolic BP≥90mmHg, a self-reported history of hypertension, or the use of antihypertensive medications in the past three months. We analyzed the direct and indirect effects of urine Na-K ratio, Na-Cr ratio, and K-Cr ratio on elevated arterial stiffness (baPWV>=18 m/s) by hypertension in a mediation framework. Analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC) and R version 4.0.2.

Results: The mean age of the study population was 55.4±10.0 years; 47.1% were males. Study findings indicated a significant direct association between urine Na-K ratio and elevated baPWV(OR= 1.07; 95% CI, 1.02–1.11). A significant indirect association was also observed between urine Na-K ratio and elevated baPWV (OR= 1.04; 95% CI, 1.03–1.05), indicating that 59.2% of the association of urine Na-K ratio with elevated baPWV was mediated by hypertension. Hypertension accounted for 30.3% of the association between urine Na-Cr ratio and elevated baPWV(direct association: OR= 1.09; 95% CI, 1.05–1.14; indirect association: OR= 1.03; 95% CI, 1.02–1.04). Though, we found a significant direct association between urine K-Cr ratio and elevated baPWV(OR= 1.05; 95% CI, 1.00–1.09), which was not mediated by hypertension (indirect association: OR= 0.98; 95% CI, 0.97–0.99).

Conclusions: Three-fifth of the association of urine Na-K ratio with elevated arterial stiffness may be accounted for hypertension. The urine Na-K ratio is a valuable marker of hypertension and high arterial stiffness risk.



TH-PO212

Association Between Systolic Blood Pressure Time in Target Range and Progression of CKD: Findings from KNOW-CKD Study

Cheol Ho Park,[1] Hyung Woo Kim,[1] Jung Tak Park,[1] Tae ik Chang,[2] Tae-Hyun Yoo,[1] Shin-Wook Kang,[1] Seung Hyeok Han.[1] *[1]Yonsei University College of Medicine, Seodaemun-gu, Seoul, Republic of Korea; [2]National Health Insurance Service Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea.*

Background: Time-in-target range (TTR) is determined by the proportion of time during which the systolic blood pressure (SBP) remains within a defined range. It has emerged as a good metric for assessing SBP control over time. However, whether TTR of SBP can predict progression of chronic kidney disease (CKD) is uncertain.

Methods: We investigated the association between SBP-TTR during the first year of enrollment and CKD progression among 1,758 participants from KNOW-CKD (Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease). Participants were categorized into 4 groups according to SBP-TTR (0%, 1–50%, 51–99%, and 100%). The primary outcome was a composite kidney outcome of a ≥50% decline in eGFR from baseline measurement or the initiation of kidney replacement therapy.

Results: During a follow-up period of 9,212 person-years (median, 5.4 years), the composite outcome occurred 710 (40.4%) participants. In multivariable cause-specific hazard model, a 1-SD increase in SBP-TTR was associated with an 11% lower risk of the composite outcome (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.82–0.97). Additionally, compared to the patients with SBP-TTR 0%, the HRs (95% CIs) for the SBP-TTR 1–50%, 51–99%, and 100% were 0.86 (0.68–1.08), 0.77 (0.61–0.97), and 0.73 (0.56–0.95), respectively. Moreover, the corresponding slopes of eGFR decline were -2.71 (-3.13 to -2.30), -2.52 (-2.80 to -2.23), -2.25 (-2.50 to -2.01), and -2.06 (-2.34 to -1.78) ml/min/1.73m^2, respectively.

Conclusions: Higher SBP-TTR was associated with a decreased risk of CKD progression in patients with CKD.

Funding: Government Support - Non-U.S.

TH-PO213

Uncovering the Added Benefits of Lowering Resting Heart Rate by Physical Activity in Reducing the Incidence and Mortality Risks of CKD and Proteinuria

Chi Pang Wen, Min Kuang Tsai. *National Health Research Institutes, Zhunan, Taiwan.*

Background: Physical activity (PA) is known to be able to reduce Chronic Kidney Disease (CKD) mortality, but the effect was perceived as too little, too late to motivate exercisers. However, smart types of exercise could be employed to double the effect by simultaneously lowering resting heart rate (RHR). The added role of RHR in enlarging the benefits of physical activity to prevent or to reduce CKD has not been reported.

Methods: A medical screening cohort of 680,277 adults in Taiwan was successively recruited during 1996-2017, and 64,577 deaths were identified by National Death File and 5,671 cases of ESRD after a medium follow up of 18 years. CKD was analyzed by 5 component stages, eGFR values and proteinuria tested by dipstick. RHR came from electrocardiogram taken after rest in a supine position, with 80-99/min considered as elevated but within normal limits. Physical activity was expressed as MET-h/week, which was a product of exercise intensity and duration. Exercise status was classified as inactive, low, medium high or very high active. The association of RHR with CKD at entry points or with various CKD associated all-cause mortality risks during follow up was both calculated by Cox model.

Results: A triangular interactive relationship existed among PA, RHR and CKD, with PA able to reduce both RHR and CKD and with RHR associated with less CKD when slowed down by PA. Increasing RHR per 10 beats from 60/min up was associated with 30% increase in CKD, 39% increase in proteinuria and 30% increase in GFR<45. Physical activity, as officially recommended, was associated with 18% reduction of CKD, with the more vigorous intensity, the larger the reduction. It was also inversely associated with RHR, and vigorous intensity exercise for 3 months was associated with a lowering of RHR by 11 beats/min. Not all PA could slow RHR, mostly by those with vigorous intensity. Most CKD people were inactive (>80%) and could benefit from engaging in all types of PA recommended. When participants exercised, majority (60%) lowered RHR and small minority (9%) increased RHR, with remaining unchanged.

Conclusions: The incidence and mortality of CKD and proteinuria could be maximally reduced by vigorous physical activity when RHR was simultaneously lowered. Promoting the kind of exercise that reduced RHR may double the reduction of CKD or proteinuria.

TH-PO214

The Association Between Subclinical Reductions in Kidney Function and Major Adverse Cardiovascular Events in Young Adults: A Population-Based Retrospective Cohort Study

Manish M. Sood,[1] Junayd Hussain,[1] Mark Canney,[1] Meghan J. Elliott,[3] Gregory L. Hundemer,[1] Navdeep Tangri.[2] *[1]University of Ottawa School of Epidemiology and Public Health, Ottawa, ON, Canada; [2]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada; [3]University of Calgary Cumming School of Medicine, Calgary, AB, Canada.*

Background: Cardiovascular risk factors and disease in young adults (18-39 years) are on the rise. Whether early reductions in kidney function (i.e., estimated glomerular filtration rate [eGFR] above the current accepted threshold for chronic kidney disease [>60 mL/min/1.73m^2], but below age-expected values) are associated with elevated risk is unknown. We aim to examine age-specific associations of subclinical eGFR reductions in young adults with major adverse cardiovascular events (MACE).

Methods: We conducted a retrospective cohort study of 8.7 million individuals (3.6 million aged 18-39 years) using linked provincial healthcare datasets from Ontario, Canada from January 2008-March 2021. Cox models examined the association of categorized eGFR (50-120 mL/min/1.73m^2) with MACE (first of cardiovascular mortality, acute coronary syndrome, ischemic stroke) and MACE-plus-heart failure (MACE+), stratified by age (18-39, 40-49, 50-65 years).

Results: In our cohort (mean age 41.3, mean eGFR 104.2, median follow-up 9.2 years), a stepwise increase in the relative risk of MACE and MACE+ was observed as early as eGFR<90 in young adults (e.g., for MACE, at eGFR 70-80, ages 18-30: 2.37 events per 1000 person-years(p-y), HR 1.31(1.27-1.40); ages 40-49: 6.26/1000p-y, HR 1.09(1.06-1.12); ages 50-65: 14.9/1000p-y, HR 1.07(1.05-1.08)). Elevations in relative risk occurred for 18-39-year-olds at higher eGFR levels than ages 40-49 and 50-65. This persisted when examining each component individually and in additional analyses (stratified by past CV disease, accounting for index albuminuria, defining index eGFR from repeated measures).

Conclusions: In young adults, eGFR levels above the current threshold for chronic kidney disease associated with an elevated risk for MACE and MACE+, warranting age-appropriate risk stratification, proactive monitoring, and timely intervention.

TH-PO215

Seize the Night: A Retrospective Cohort Analysis on the Timing of Antihypertensive Agents on Nocturnal Blood Pressure

Sean Michael, Hammad I. Huda, Monicka Felix. *HCA Florida Oak Hill Hospital, Brooksville, FL.*

Background: Hypertension is a long standing modifiable risk factor in cardiovascular disease. Blood pressure follows a circadian rhythm in response to hormonal and environmental factors. However, when this balance is disrupted it may lead to an elevated nighttime blood pressure which is a more significant predictor of cardiovascular mortality than daytime hypertension. This study aims to see if the timing of antihypertensive agents among those with hypertension and chronic kidney disease may reduce night-time blood pressure.

Methods: In this retrospective cohort analysis, 8814 patients (3975 female/4839 male, 65+/-9 years of age) with hypertension or chronic kidney disease who were admitted to HCA healthcare in 2021 and 2022 were categorized based on receiving blood pressure medication in the morning (n=2142), evening (n=176), or morning and evening (n=6209). In response, patients blood pressure at night time were measured to see if there was a normal blood pressure lowering pattern of 10-20% at night-time.

Results: The results showed patients who had evening only blood pressure medicaiton were 1.842 times as a likely to have a night-time drop in blood pressure compared to patients whom had medication administered in the morning only(p=0.001, 95% CI [1.253-2.710] when all other variables were held constant.

Conclusions: Patients who administer an evening dose blood pressure medication are more likely to have an appropriate drop in night-time blood pressure. Clinicians can therefore consider switching antihypertensive agents to evening among patient with nocturnal hypertension. Furthermore, this study raises awareness regarding nocturnal hypertension, an often overlooked aspect in the treatment of hypertension.

Funding: Private Foundation Support

TH-PO216

A Systematic Review and Meta-Analysis of Myocardial Fibrosis in CKD and ESKD Assessed by Cardiac MRI T1 Mapping

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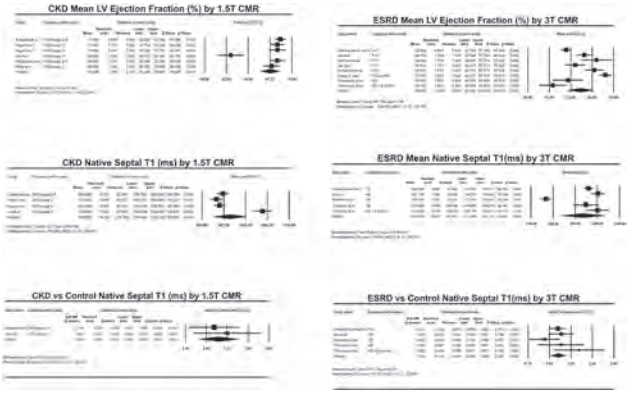
Background: Non-atherosclerotic fibrotic changes to the cardiac myocardium occur early in Chronic Kidney Disease (CKD) and End Stage Kidney Disease (ESKD) patients. Uremic myocardial fibrosis can lead to arrhythmias and heart failure. T1 mapping technique in Cardiac MRI (CMR) estimates myocardial fibrosis and offers a non-invasive way to characterize the severity of cardiac remodeling.

Methods: A systematic search was done in PubMed, Google Scholar, Embase, and Web of Science from inception to February 2023. Studies were divided according to scanner field strength (1.5 or 3 Tesla). The random effects model was used to calculate pooled mean, 95% confidence interval, standard error (SE), and standardized mean difference (SMD). The heterogeneity between study-specific estimates was assessed by the I^2 statistic.

Results: The initial search retrieved 765 studies. From these, 25 studies met the inclusion criteria that had 697 CKD (mean age of 55.5 years; 65.5% males; mean eGFR of 41 mL/min/1.73m2) and 658 ESKD patients on dialysis (mean age of 55.6 years; 63.3% males; mean dialysis duration of 5 years). The mean native septal T1 is 998.2ms (970-1026.3) for CKD and 1267.4ms (1217.8-1317.1) in ESKD patients. The SMD of native T1 measurements in CKD vs. controls is 1.09 (0.73-1.46), and SMD for ESKD vs. controls is 1.12 (0.85-1.38).

Conclusions: CKD and ESKD patients with preserved LVEF have increased T1 values indicating an increased fibrosis burden. T1 mapping can be used in the early detection of cardiomyopathy and as a risk-stratification tool. Large, randomized trials are needed to confirm these findings and find long-term effects of dialysis on cardiac fibrosis.



Forest plots of LVEF, Native T1 measurements in CKD and ESKD

CMR sequence	Method	Assessment
Cine Imaging	Usually done by a method called balanced steady-state free precession (SSFP) that produces bright signals from stationary tissues and suppresses signals from moving tissues and blood.	LV Volume and mass
T1 Mapping	When done without a contrast agent is called 'Native T1 mapping'. It measures the longitudinal magnetization recovery time after being disturbed by a magnetic field. Mapping is done by combining a series of T1 relaxation times.	Myocardial fibrosis, scar

TH-PO217

Health Care Resource Use and Costs in the Year Following a Major Bleeding Event in Patients with and Without ESKD

Alejandro Victores,[1] Lori D. Bash,[1] Nicholas S. Roetker,[2] Dena Rosen R. Ramey,[1] James B. Wetmore,[2] Marc P. Bonaca.[3] *[1]Merck & Co Inc, Rahway, NJ; [2]Hennepin Healthcare Research Institute Chronic Disease Research Group, Minneapolis, MN; [3]University of Colorado Anschutz Medical Campus School of Medicine, Aurora, CO.*

Background: Patients with end-stage kidney disease (ESKD) are at an elevated risk of major bleeding events which may result in substantial healthcare resource use(HCRU). There is limited information on HCRU following a major bleeding event in those with ESKD.

Methods: Retrospective cohorts of patients ≥66 years were created using the US Renal Data System (USRDS) for ESKD patients receiving in-center hemodialysis (HD) and 20% sample general Medicare database for non-ESKD patients. The index date was the date of hospital admission for an incident major bleeding event between 2015 and 2019. Only those enrolled in Medicare Part D were included in follow-up analysis. All-cause HCRU and costs were calculated (including the index event) for up to 1 year. HCRU is expressed as a percent or rate per 100 person-years. Per person per year adjusted costs are expressed in 2019 dollars.

Results: A total of 68,608 non-ESKD patients and 11,881 ESKD patients with incident major bleeding were included in the follow-up analysis. Patients with ESKD had significantly more admissions, inpatient days, and emergency visits than those without. Use of outpatient (OP) cardiac rehabilitation was significantly lower among ESKD patients. Post-index OP encounters had the largest magnitude difference, with 460.8 more OP encounters per 100 person-years among those with ESKD. Total costs for inpatient encounters, observation unit visits, ED visits, and OP encounters were statistically significantly higher for ESKD patients compared with non-ESKD patients.

Conclusions: In the year following an incident major bleed, Medicare beneficiaries with ESKD have significantly higher all-cause HCRU and total healthcare costs than patients without ESKD who experienced the same event; these differences persist after adjustment.

Funding: Commercial Support - Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Table 1. HCRU in the year following incident major bleeding event in patients with and without ESKD, adjusted for age, sex, and race*

	Non-ESKD	ESKD (In-center HD)	Difference (95% CI)
Number of patients in follow-up analysis	68,608	11,881	
30-day readmission (%)	18.2	29.6	11.4 (10.5, 12.2)
90-day readmission (%)	30.8	50.2	19.4 (18.4, 20.4)
Number of inpatient hospital admissions	125.9 (0.554)	289.3 (2.922)	163.5 (157.2, 169.3)
Number of inpatient hospital ICU admissions	44.4 (0.288)	113.2 (1.647)	68.8 (65.8, 71.9)
Number of days in inpatient hospital	9.3 (0.053)	22.2 (0.285)	12.9 (12.3, 13.5)
Number of observation unit encounters	18.0 (0.156)	38.1 (0.768)	20.1 (18.5, 21.7)
Number of emergency department encounters	76.6 (0.438)	147.1 (1.947)	70.5 (66.6, 74.5)
Number of outpatient encounters	1061.9 (3.600)	1522.7 (13.061)	460.8 (433.8, 486.9)
Number of other institutional care visits	305.0 (1.154)	402.7 (4.107)	97.8 (89.9, 106.2)
Number of outpatient cardiac rehabilitation encounters	35.5 (1.081)	12.5 (1.596)	-23.0 (-26.8, -19.1)
Number of physician encounters (all specialties)	3752.2 (7.937)	6417.3 (33.380)	2665.1 (2594.6, 2734.2)
Number of cardiology/vascular physician encounters	644.3 (2.434)	1137.1 (10.486)	492.8 (471.6, 513.1)
Number of neurology/neurosurgery physician encounters	156.0 (1.104)	143.5 (3.024)	-12.5 (-18.6, -6.1)
Number of physiatry physician encounters	122.3 (1.282)	133.3 (4.827)	11.0 (0.9, 20.1)
Number of hematology physician encounters	176.7 (1.929)	114.9 (3.852)	-61.8 (-70.0, -53.2)
Number of gastroenterology physician encounters	303.4 (1.119)	485.2 (4.991)	181.8 (171.4, 191.6)
Number of primary care physician encounters	1575.8 (4.517)	2491.5 (21.787)	915.6 (868.6, 959.8)
Number of blood transfusion events	154.7 (0.274)	202.1 (1.488)	47.4 (44.4, 50.5)

*Frequency of 30-day and 90-day readmission expressed as percentage. All other post-index encounter types expressed as rate (SE) per 100 person-years.

TH-PO218

Survival Benefit of Anticoagulation in Patients with ESKD and Atrial Fibrillation

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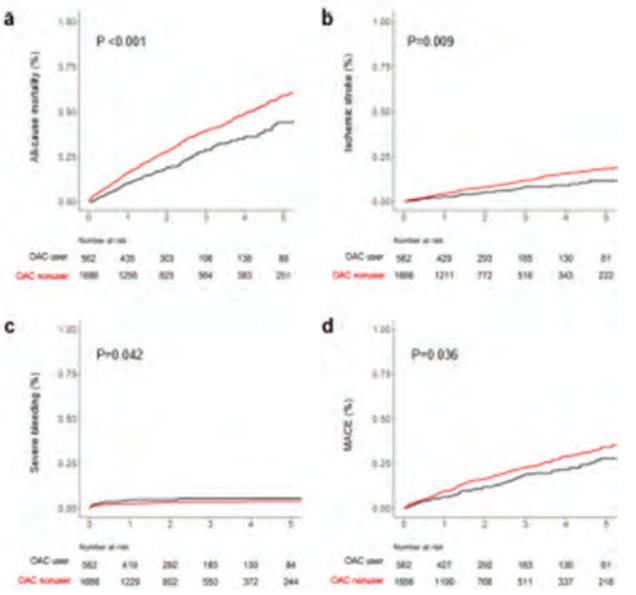
Background: Prevalence of atrial fibrillation (AF) in patients with end stage kidney disease (ESKD) is high and increasing, however, current evidence is insufficient and conflicting regarding oral anticoagulant (OAC) use in patients with ESKD and AF.

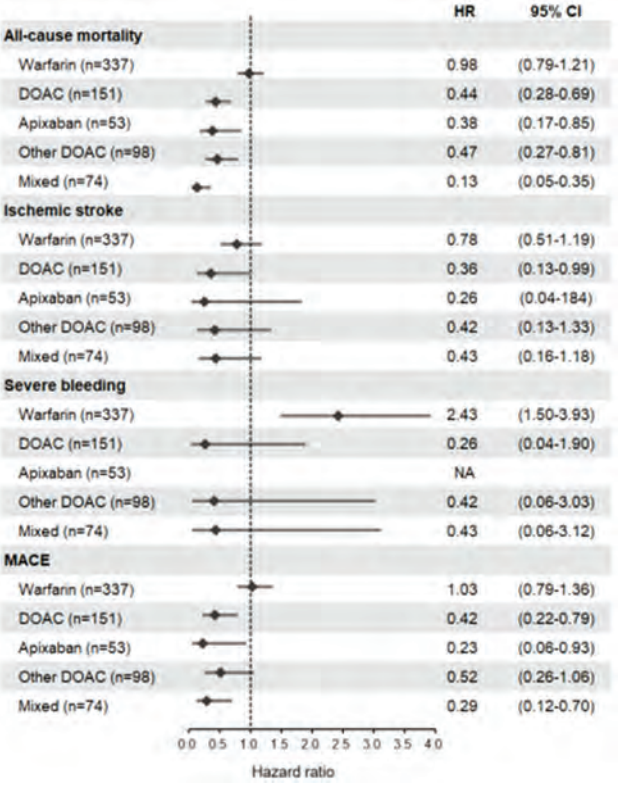
Methods: A retrospective cohort study of patients diagnosed with AF after ESKD was conducted using the Korea National Health Insurance System Database from January 2007 to December 2017.

Results: Compared with OAC nonuser OAC user were associated with lower risk of all-cause death (hazard ratios (HR) 0.71; 95% confidence interval (CI) 0.58-86), ischemic stroke (HR 0.63; 95% CI 0.43-92), and MACE (HR 0.76; 95% CI 0.59-0.98) without increased risk of severe bleeding (HR 1.58; 95% CI 0.99-2.52). Patients used direct OAC showed significantly lower risk of all-cause death (HR 0.44; 95% CI 0.28-0.69), ischemic stroke (HR 0.36; 95% CI 0.13-0.99), and MACE (HR 0.42; 95% CI 0.22-0.79) than those of OAC-nonuser, but no association with severe bleeding (HR 0.26; 95% CI 0.04-1.90).

Conclusions: In patients with ESKD and AF, OACs were associated with reduced all-cause death, ischemic stroke, and MACE risks.



Kaplan–Meier curve analyses for each outcome. a. All-cause mortality, b. ischemic stroke, c. severe bleeding, and d. MACE.



Subgroup analysis for all-cause mortality, ischemic stroke, severe bleeding, and MACE according to type of oral anticoagulant.

TH-PO219

National Rates of Primary Aldosteronism Screening in Patients with CKD

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Background: Primary aldosteronism (PA) is a common, treatable cause of resistant hypertension and kidney fibrosis but is vastly underdiagnosed. Limited evidence exists regarding screening rates and outcomes of screening for PA among patients with chronic kidney disease (CKD).

Methods: In a national cohort of US Veterans diagnosed with incident hypertension and followed from January 2000 to December 2021, we identified patients with new indications for PA screening (i.e., hypertension with hypokalemia or resistant hypertension). We evaluated rates of PA screening and results of screening among those with and without CKD (eGFR <60 vs. ≥60 mL/min/1.73m^2) using Cox regression, adjusted for age, sex, race, systolic blood pressure, heart rate, insurance status, smoking, substance abuse, homelessness, cardiovascular disease, obstructive sleep apnea, and diabetes.

Results: A total of 457,395 patients met inclusion criteria, among whom 73,747 (16%) had CKD at the time of developing a new indication for PA screening. Those with CKD were older (mean 72 vs. 61 years) and had higher serum potassium levels (4.2 vs. 4.0 mEq/L) and higher prevalence of diabetes (42% vs. 30%) and cardiovascular disease (25% vs. 18%) compared to those without CKD. In the overall cohort, 7,427 (1.5%) patients underwent PA screening, among whom 1,068 (14%) had biochemical evidence of PA. Patients with CKD were 55% more likely to undergo PA screening than those without CKD (adjusted HR 1.55, 95% CI 1.44-1.67), which was similar across all CKD stages. Among those who underwent PA screening, biochemical evidence of PA was similar in patients with and without CKD (adjusted HR 0.92, 95% CI 0.75-1.12). Patients with CKD had similar rates of adrenalectomy but were less likely than those without CKD to be appropriately treated with a mineralocorticoid receptor antagonist (adjusted HR 0.86, 95% CI 0.78-0.94), excluding patients with serum potassium >4.5 mEq/L.

Conclusions: In a national cohort of Veterans with indications to undergo PA screening, those with CKD were more likely to undergo PA screening and had similar rates of PA compared to those without CKD, but were less likely to receive appropriate treatment with a mineralocorticoid receptor antagonist. Overall, rates of PA screening among all groups were exceptionally low.

Funding: Other NIH Support - NHLBI

TH-PO220

Salt Sensitivity and Hypertensive Nephropathy: A Link to Be Discovered

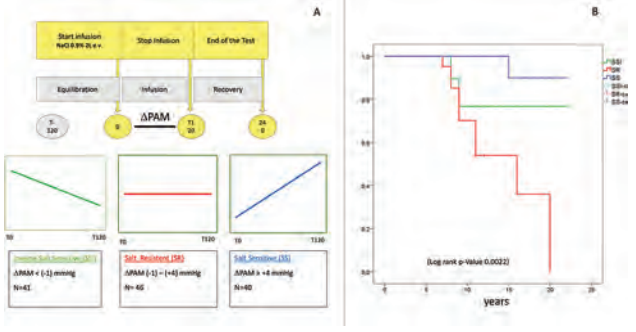
Francesca Tunesi, Luca D'Urbano, Marco Simonini, Lorena Citterio, Laura Zagato, Paolo Manunta, Chiara Lanzani. *IRCCS Ospedale San Raffaele, Milano, Italy.*

Background: Sodium sensitivity (SS) is a change in blood pressure (BP) depending on Na^+ intake, 30% of population has it. Either a salt load test or a sodium dietary protocol can be used to stratify the population into 3 groups based on BP variation: sodium sensitive (SS), sodium resistant (SR), inverse sodium sensitivity (ISS), based on an increase, a non-significant variation or a decrease in BP following the administration of Na^+. SNPs located in genes related with Na^+ metabolism, aldosterone synthesis and kidney tubular Na^+ reabsorption are related to this phenotype.

Methods: We analyzed data collected from the follow-up (FUP) of 127 subjects with a new diagnosis of hypertension, categorized by their profile through acute salt load test. We analyzed the kidney damage by annual decline of eGFR and development of microalbuminuria. Genetic polymorphism analysis has been executed.

Results: No differences in the decline of eGFR are observed among the groups (-1.3084 ml/min ± 0.16 p= 0.372). SR subjects seem to be more prone to develop earlier microalbuminuria (χ 2 10.682, p= 0.005) even with an adequate BP control (P-Anova SBP 0.766; P-Anova DBP 0.856). An inverse correlation exists between pressure-natriuresis ratio and decline in eGFR (R -0.194 p= 0.016). Polymorphism in CYP11B2 (0.72 OR p= 0.045) and NEDD4L (0.74 OR p=0.027) are protective against eGFR decline. ADD3 polymorphism (3.73 OR p= 0.049) is a risk factor for development of microalbuminuria. KL (0.15 OR p= 0.034), PKD and TRPC6 (p-Value 0.037, p-Value 0.009) polymorphism are protective factor against microalbuminuria.

Conclusions: SR patients are more at risk of developing hypertensive nephropathy earlier than other groups; steeper pressure natriuresis ratio is involved in quicker decline in renal function possibly accelerating development of hypertensive nephropathy. Further studies with larger sample and standardization in salt sensitivity test are needed to translate this knowledges into clinical setting.



A) salt load test; B) microalbuminuria

TH-PO221

Clinical Impact of Diastolic Dysfunction in ESKD

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Background: Diastolic dysfunction with left ventricular hypertrophy and myocardial fibrosis is an important characteristic of uremic cardiomyopathy (UCM) in end-stage kidney disease (ESKD). We investigated clinical courses and risk factors of mortality and major adverse cardiac event (MACE) in ESKD patients starting kidney replacement therapy (KRT) according to the grade of diastolic dysfunction.

Methods: A total of 1038 patients who underwent surgery for vascular or peritoneal access and started KRT between 2010 and 2020 were enrolled. We classified patients according to the diastolic dysfunction grade (DDG) evaluated by echocardiography. Patients with atrial fibrillation (AF) were classified separately. The primary outcome was a composite outcome of all-cause mortality and MACE.

Results: The median age was 62 years, and 662 patients (63.78%) were male. Patients were divided into six groups based on the pre-KRT echocardiography: normal (n=280), DDG 1 (n=149), DDG 2 (n=192), DDG 3 (n=23), DDG undetermined (n=338), and AF (n=56). All-cause mortality and the incidence of MACE were significantly higher in pre-KRT DDG 1 and AF groups (P<0.01). However, after adjusting for age and underlying ischemic heart disease (IHD) at the initiation of KRT, pre-KRT diastolic dysfunction or AF did not affect to mortality and MACE (P=0.75). Furthermore, post-KRT echocardiography was performed at least 6 months after starting KRT, and the patients were regrouped: post-KRT normal (n=132), DDG 1 (n=311), DDG 2 (n=168), DDG 3 (n=23), DDG undetermined (n=303), and AF (n=101). Patients with post-KRT normal diastolic function showed better survival compared to patients with diastolic dysfunction or AF (P<0.01). In a multivariable analysis including post-KRT echocardiographic parameters, post-KRT DDG 2 (HR 2.61, 95% CI 1.08 – 6.30, P=0.03) and post-KRT AF (HR 3.20, 95% CI 1.26 – 8.12, P=0.01) were identified as significant risk factors for all-cause mortality and MACE. Low left ventricle ejection fraction after KRT was associated with increased risk of mortality and MACE (HR 0.98, 95% CI 0.97 – 0.99, P<0.01).

Conclusions: Age and IHD were more important prognostic factors compared to pre-KRT diastolic dysfunction. However, post-KRT echocardiographic findings, including diastolic dysfunction, and AF could be considered as prognostic markers in ESKD patients.

TH-PO222

Nocturnal Hypertension in Patients with Controlled Daytime Blood Pressure

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Background: 24-hour ambulatory blood pressure monitoring (ABPM) is the modality of choice for the diagnosis of hypertension (HTN). Besides assessment of blood pressure (BP) and its variability while awake, it also provides BP readings during sleep. Sleep BP is the single most important factor for adverse HTN related cardiovascular outcomes. 24-hour ABPM is underutilized, misclassifying many patients as 'treated or controlled' based solely on awake BP while in fact they have persistent nocturnal hypertension.

Methods: The study was carried out at the Renal hypertension program of The Ottawa Hospital which is a tertiary care hospital based HTN program serving catchment area of approximately 1.2 million people. We extracted data from completed and technically satisfactory 24-hour ABPMs from incident patients treated in our clinic from January 01, 2019 to March 31, 2023. For each patient who underwent 24-hour ABPM, only the first report was considered for this study. We defined daytime HTN as mean systolic BP >=140 mmHg and/or mean diastolic BP>=90 mmHg and nocturnal HTN as mean nighttime systolic BP >= 125 mmHg and/or mean diastolic BP >=75 mmHg.

Results: Our cohort included 1024 patients. Mean (SD) age was 60.6 (16.3) years, females 486 (46.7%), mean BMI (SD) 30.0 (7.9) kg/m^2. 388 (37.2%) patients had uncontrolled HTN during daytime, and out of these, 272 (26.1%) also had nocturnal HTN. More importantly though, in patients with controlled day time HTN (n= 654, 62.8%), 21.5% (n=141) had nocturnal HTN with mean (SD) nocturnal BP of 132/75 (6.3/10.4).

Conclusions: Our data show that a significant segment of patients with controlled daytime HTN (documented by ABPM) still have nocturnal HTN. As nocturnal BP is an important factor for adverse HTN related cardiovascular outcomes, one could certainly consider low utilization of 24-hour ABPM among patients with HTN as a missed treatment opportunity contributing to unnecessary and potentially preventable adverse cardiovascular events. We advocate for a broader utilization of 24-hour ABPM in patients with HTN.

Funding: Commercial Support - Otsuka

TH-PO223

Statewide Burden of CKD due to Hypertension (HTN) from 1990 to 2019 in the United States: Analysis for the Global Burden of Disease Study

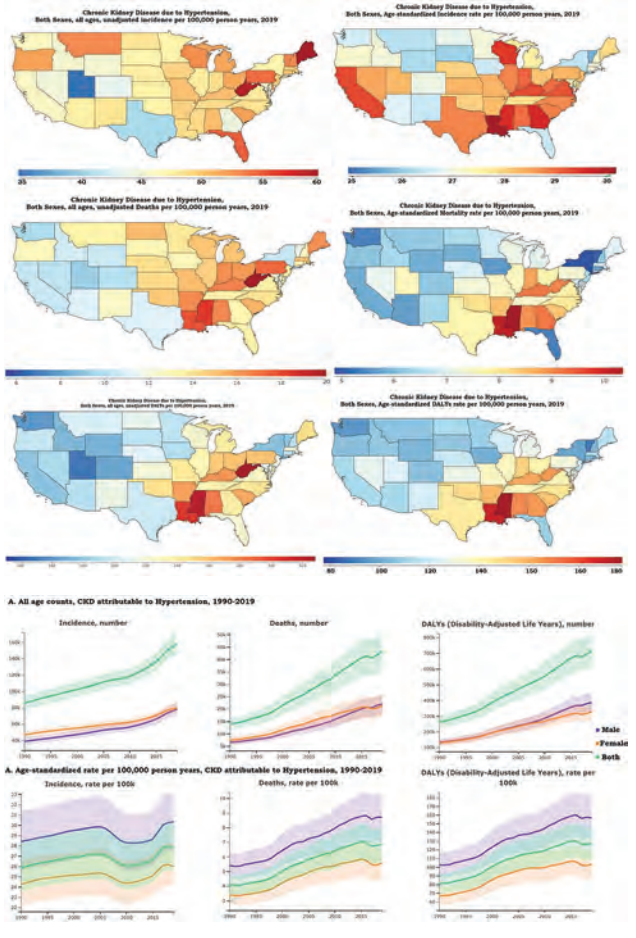
Rohan Gajjar,[1] Hardik Desai,[2] Bijin Thajudeen,[3] Sahas Reddy Jitta,[4] Shasank Rachapudi,[5] Jobby John,[6] Abhiraj Patel,[7] Viswaja Koppana.[8] *[1]John H Stroger Jr Hospital of Cook County, Chicago, IL; [2]Gujarat Adani Institute of Medical Science, Bhuj, India; [3]Banner University Medical Center Tucson, Tucson, AZ; [4]Mercy Hospital St Louis Area, Saint Louis, MO; [5]Kurnool Medical College, Kurnool, India; [6]Dr Somervell Memorial CSI Medical College and Hospital, Thiruvananthapuram, India; [7]Our Lady of Fatima University College of Medicine, Valenzuela City, Philippines; [8]Mayo Clinic Minnesota, Rochester, MN.*

Background: CKD due to HTN ranks as the 2nd leading cause of death among all causes of CKD in United States (US). We sought to assess the burden of CKD due to HTN within the US.

Methods: Using Global Burden of Disease methodology, prevalence, incidence, death, and disability-adjusted life year (DALYs) of CKD due to HTN assessed by age, sex, year from 1990-2019 for all resident in US.

Results: The prevalence has shown a steady increase over the years, with the total number of cases rising from 1.5 million (95% uncertainty interval [UI]:1.4-1.7million) in 1990 to 2.8 million (95%UI:2.6-3.1million) in 2019. Simultaneously, the number of deaths has tripled, from 13,960 in 1990 to 43,329 in 2019. The highest Annual Percentage of Change (APC) in the age-standardized mortality rate (ASMR) was found in West Virginia(101%), Iowa(95%) and Minnesota(93%). For the ASIR, the highest rates were observed in Utah and California, both at 11%, with Iowa at 10%. The ASDR revealed West Virginia(87%), Iowa(81%), and Kentucky(80%) as the areas with the highest burdens. These conditions are more prevalent in older populations, significantly impacting that group.

Conclusions: CKD attributed to HTN has shown a rapid increase across the US, given the substantial APC in prevalence rose by 86%. From 1990-2019, the DALY numbers and the age standardized DALYs per 100,000 population caused by CKD due to HTN increased by 171% and 57%, respectively.



TH-PO224

Representation of Real-World Adults with CKD in Clinical Trials Supporting Blood Pressure Treatment Targets

June Li,[1,2] Jaejin An,[3,4] Mengjiao Huang,[1] Matt M. Zhou,[3] Maria E. Montez-Rath,[2] Fang Niu,[5] John J. Sim,[4,6] Alan C. Pao,[2,7] Vivek Charu,[2,8] Michelle Odden,[1,2] Manjula Tamura.[1,2] *[1]VA Palo Alto Geriatric Research Education and Clinical Center, Palo Alto, CA; [2]Stanford University School of Medicine, Stanford, CA; [3]Kaiser Permanente Southern California Department of Research & Evaluation, Pasadena, CA; [4]Kaiser Permanente Bernard J Tyson School of Medicine, Pasadena, CA; [5]Kaiser Permanente Southern California, Pasadena, CA; [6]Kaiser Permanente Los Angeles Medical Center, Los Angeles, CA; [7]VA Palo Alto Health Care System, Palo Alto, CA; [8]Stanford University Department of Pathology, Stanford, CA.*

Background: Little is known about how well trial participants with CKD represent real-world adults with CKD. We assessed the population representativeness of clinical trials supporting the 2021 Kidney Disease: Improving Global Outcomes blood pressure (BP) guidelines in real-world adults with CKD.

Methods: We identified two real-world population of patients with CKD who met the guideline definition of hypertension based on use of antihypertensive medications or a sustained systolic BP ≥120 mm Hg in 2019 in the Veterans Health Administration (VA) and Kaiser Permanente of Southern California (KPSC). We applied the inclusion and exclusion criteria from three BP target trials, the Systolic Pressure Intervention Trial, the Action to Control Cardiovascular Risk in Diabetes trial, and the African American Study of Kidney disease, to estimate the proportion of adults with a systolic BP above the guideline recommended target of <120 mm Hg and the proportion who met eligibility criteria for ≥1 trial.

Results: We identified 503,480 adults in VA and 73,412 adults in KPSC with CKD and hypertension in 2019. We estimated 79.7% in the VA population and 87.3% in the KPSC population had a systolic BP ≥120 mm Hg; only 23.8% (95% CI: 23.7% - 24.0%) in the VA and 20.8% (95% CI: 20.5% - 21.1%) in KPSC were trial-eligible. BP trials were representative of <15% of adults with CKD and diabetes, age <50 years, or stage 4 CKD. More than 50% of trial-ineligible adults met ≥1exclusion criteria.

Conclusions: Fewer than one in four real-world adults with CKD and hypertension were represented in major BP target trials. A large proportion of adults who are at risk for cardiovascular morbidity from hypertension and susceptible to potential adverse treatment effects still lack relevant treatment information.

Funding: NIDDK Support

Table 2. Percentage of real-world adults with chronic kidney disease and hypertension in the VA and KPSC cohorts in 2019 with BP above the 2021 KDIGO guideline recommended target, and percentage who meet eligibility criteria of blood pressure trials.

Characteristic	All adults with CKD		CKD without Diabetes		CKD with Diabetes	
	Veterans Affairs	KPSC	Veterans Affairs	KPSC	Veterans Affairs	KPSC
Number with hypertension	503,480	73,412	217,427	33,205	286,053	40,207
BP above guideline recommended target, %	79.7	87.3	80.9	87.6	78.8	86.9
Meet SPRINT inclusion, %	46.2	50.0	48.7	50.8	-	-
SPRINT eligible, %	17.1 (17.0, 17.2)	19.0 (18.8, 19.3)	39.5 (39.3, 39.7)	42.3 (41.6, 42.6)	-	-
Meet ACCORD inclusion, %	14.5 (14.4, 14.6)	11.1 (10.9, 11.3)	-	-	25.9 (25.4, 25.7)	20.3 (19.9, 20.7)
ACCORD eligible, %	5.8 (5.7, 5.9)	1.4 (1.3, 1.5)	-	-	10.2 (10.1, 10.3)	2.6 (2.4, 2.7)
Meet AASK inclusion, %	4.4	1.8	8.5	2.9	-	-
AASK eligible, %	1.8 (1.7, 1.8)	0.8 (0.8, 0.9)	4.3 (4.2, 4.3)	1.7 (1.7, 17)	-	-
Eligible for at least one trial, %	23.8 (23.7, 24.0)	20.8 (20.5, 21.1)	41.8 (41.6, 42.0)	42.8 (42.5, 43.4)	10.2 (10.1, 10.3)	2.6 (2.4, 2.7)
Ineligible for all trials, %	76.2 (76.0, 76.3	79.2 (78.9, 79.5)	58.2 (58.0, 58.4)	57.2 (56.6, 57.7)	89.8 (89.7, 89.9)	97.4 (97.3, 97.6)

Footnote:
Eligibility is defined as patients who met inclusion and had no exclusion criteria.
95% CIs presented in the table are for percentages derived from multiple imputation estimates, percentages without 95% CIs are calculated.
Narrow CIs are a result of large sample sizes.

Percentage of real-world adults who meet eligibility criteria of blood pressure trials in the VA and KPSC.

TH-PO225

Blood Pressure Control Before and After the Updated 2017 Guidelines in Patients with Proteinuric Kidney Disease

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Background: We hypothesized that the stricter 2017 ACC/AHA Task Force hypertension (HTN) guidelines led to improved blood pressure control (BPC) in patients with proteinuric renal disease after 2017.

Methods: Data from existing electronic health record documentation for each patient up to May 1, 2022 was extracted on adult patients (≥18) from the Kidney Research Network multi-center electronic health record registry of patients with glomerular disease. Baseline diagnosis of HTN was defined using blood pressure measurements, ICD-9/10 codes, and medication records. BPC was defined as BP < 120/80 for ≥75% of follow-up recordings following hypertension diagnosis. Follow-up was split into two eras,

pre-2017 and post-2017. We used generalized linear models with a log odds outcome and an unstructured correlation matrix to evaluate the adjusted association between era and BPC.

Results: In this analysis, 725 patients were included of which 55% were male and median eGFR was 62. Only 6% had normal BP at diagnosis. In the pre-2017 era 10% of patients demonstrated BPC compared to 14% in the post-2017 era. In adjusted analysis, patients were more likely to achieve BPC after 2017, however not statistically significant (OR 1.7; CI 0.96-3.02) (Figure 1). More severe prior HTN and higher medication burden were associated with worse BPC.

Conclusions: In adjusted analyses, BPC improved modestly after 2017. However, BPC in patients with proteinuric CKD remains poor, especially when compared to more recent stricter recommendations. Future analysis with greater follow-up time, and using the most contemporary data possible, are needed to understand opportunities to do more to achieve greater BPC in this population.

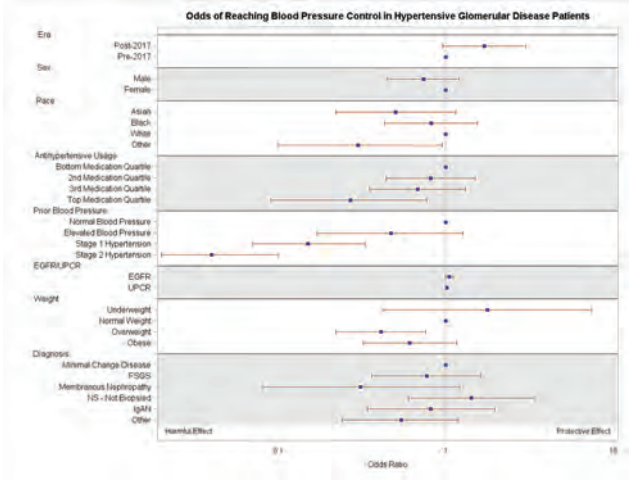

Figure 2. Odds of reaching blood pressure control in hypertensive glomerular disease patients

TH-PO226

A Multicentre Audit of Standardised Office Blood Pressure Measurement in Ireland

Eithne M. Nic an Riogh,[1,2] Anees Anees,[1] Lynn Redahan,[1] Yvonne M. O'Meara,[1] Frank Ward,[2] Denise M. Sadlier.[1] *[1]Mater Misericordiae University Hospital, Dublin, Ireland; [2]Tallaght University Hospital, Dublin, Ireland.*

Background: Hypertension is a common comorbidity of chronic kidney disease (CKD) and increases the risk of cardiovascular disease, end-stage kidney disease and death. The KDIGO 2021 Clinical Practice Guideline on the Management of Blood Pressure in CKD recommends a target systolic blood pressure (BP) target <120 mmHg in adults with CKD. Importantly, the guideline distinguishes between routine and standardised office BP measurement with the latter more likely to be an accurate measure of BP. In this study, adherence to standardised office BP measurement was assessed in busy nephrology outpatient clinics in two hospitals.

Methods: The KDIGO guidelines describe eighteen criteria to achieve standardised office BP measurement (e.g. patient sitting relaxed >5 mins, avoidance of caffeine/tobacco in 30 minutes prior to BP measurement, position of BP cuff). Adherence to these criteria was prospectively assessed by direct observation of BP measurements. Basic demographics and BP data from patients attending nephrology outpatient departments in two Dublin teaching hospitals were collected electronically. Adherence to 18 criteria was assessed using descriptive statistics. This audit is now expanding to include cardiology clinics as well as a questionnaire to assess patient awareness of hypertension.

Results: From January 2022–2023, 308 patients were recruited. Of the 18 criteria assessed, 6 had an adherence of > 90% and 5 criteria had an adherence of <10%. Areas with poorest compliance included supporting the arm during BP measurement 18.2% (n=56), averaging >/= 2 readings 0.3% (n=1) and noting the time antihypertensive medication was last taken 2.3 % (n=7). Measurement of BP in both arms at the initial visit was not carried out for any patients. The mean BP was 136/72 mmHg and Systolic BP <20 mmHg was achieved in 22% (n=33) patients. Clinical practice was similar across both sites other than a statistically significant difference in practice: informing patients of their BP verbally (99.3% vs 12%, P <0.001) and in writing (100% vs 1.9%, p <0.001).

Conclusions: Current clinic BP measurement does not meet the definition of standardised office BP measurement as outlined by KDIGO. However, simple changes to clinical practice could be implemented through education to significantly improve BP measurement as a more accurate measure of treatment response.

TH-PO227

Exploring the Spectrum of Blood Pressure Associations with CKD: The International 24-Hour Aortic Blood Pressure Consortium (i24ABC)

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Background: Chronic kidney disease (CKD) has emerged as a significant public health concern. The kidneys are primarily exposed to pulsatile rather than steady hemodynamics, which complicates the bidirectional relationship between CKD and hypertension. We aimed to explore relationships between blood pressure (BP) parameters and renal function in a pooled dataset from 21 centers worldwide.

Methods: The dataset included clinical and hemodynamic information. All participants underwent office BP measurements, in addition to 24-hour ambulatory BP monitoring (ABPM) with the same validated automated brachial oscillometric device (Mobil-O-Graph, I.E.M., Germany) using a transfer function for central pressure, and mean/diastolic pressure calibration. Renal function was estimated using the CKD-EPI equation and subjects classified into the 6 eGFR categories following the KDIGO 2021 guideline.

Results: We included 5204 subjects, 46.1% females, with a mean age of 60.8 ± 13.9 years. Diabetes was noted in 14.7% and hypertension in 70.3% of subjects, 76% of whom were on antihypertensive therapy. The mean eGFR was 88.5 ± 19.9 mL/min/1.73 m^2. More than half of the participants (56.5%) had a normal or high eGFR (G1) and only 1.9% had a severely decreased eGFR (G5). The prevalence of hypertension increased progressively across GFR categories with 95.7% of subjects in G5 vs. 67.7% in G1 (p<0.001) with hypertension. Diastolic BP tended to decrease (p<0.001) and SBP to increase (p<0.001) with decreasing eGFR. These associations were consistent for both brachial and central values, and for office and ABPM measurement techniques. Systolic reverse dipping status was independently associated with decreased eGFR after adjustment for gender and age, and irrespective of hypertension status (β=-1.74, p=0.004).

Conclusions: CKD is associated with adverse hemodynamic changes, both at the brachial and the aortic level, and in office and out-of-office measurements, indicative of arterial stiffening.

TH-PO228

Risk Factors for Progressive Cardiorenal Syndrome in CKD Patients

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Background: Cardiorenal syndrome (CRS) is linked with poor outcomes. We studied the incidence and risk factors for progressive CRS (pCRS) in CKD patients.

Methods: 3,557 CKD patients in the Chronic Renal Insufficiency Cohort (CRIC) Study were included in this analysis after excluding those with heart failure (HF) at baseline. The mean follow-up was 10.5 years. pCRS was defined as development of both HF and renal failure (RF) (ESKD) within 12 months of each other. Cox proportional hazards models were used to examine the association of risk factors and pCRS. Risk factors for CRS type 2 (HF preceded RF) and CRS type 4 (RF preceded HF) were also analyzed.

Results: The average age was 59 years for those with pCRS and 57 years for those without. Age-adjusted incidence was 4.5/1000 person years, and was 5.0 in Men and 5.9 in Black. Traditional risk factors [multivariable-adjusted hazard ratios (95% CI)] for

pCRS were less than high school education [1.82 (1.21, 2.73)], history of CVD [1.48 (1.03, 2.12)], lower eGFR [per 1SD,1.83 (1.40, 2.39)], and higher uACR [per 1SD, 2.26 (1.78, 2.86)]. The significant multivariable-adjusted HRs associated with novel risk factors are presented in **Table**. The risk factor associated with both CRS type 2 and 4 were kidney dysfunction, albuminuria, and mineral bone disorder (higher alkaline phosphatase and FGF23), inflammation (TNF-α), and fibrotic factor (GDF-15).

Conclusions: This study indicates that education level, history of CVD, kidney dysfunction, albuminuria, mineral bone disorder, diabetes control, anemia, volume overload, inflammation, and fibrotic factor are associated with pCRS. Further studies are warranted to assess the benefits of specific interventions to improve CRS outcomes.

Funding: NIDDK Support

Multivariable-Adjusted Hazard Ratios of Progressive Cardiorenal Syndrome Associated with Novel Risk Factors

Variables (per SD)	Multivariable-adjusted*		
	HR	(95% CI)	P-value
Hemoglobin (1.77 g/dL)	0.82	(0.68, 0.99)	0.049
Hemoglobin A1C (1.53 %)	1.31	(1.14, 1.52)	0.001
Log (alkaline phosphatase, 0.32 U/L)	1.18	(1.00, 1.38)	0.045
Log (brain natriuretic peptide, 1.25 pg/mL)	1.32	(1.10, 1.57)	0.002

*Adjusted for age, sex, race, clinic sites, and significant traditional risk factors

TH-PO229

The Association Between Food Insecurity and Hypertension in the Context of CKD: Reviewing the Literature

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Background: Hypertension (HTN) and dietary choices are closely related. HTN is a leading cause of CKD and a poor diet contributes to about 80% of HTN. Food insecurity (FI) is defined as the lack of secure access to sufficient amounts of safe and nutritious food for normal growth and development of an active and healthy life and is prevalent and determines dietary choices. The prevalence of FI for adults has increased by 84% in the last 20 years and the mortality rate from CKD has also increased by over 40% in the same time frame making this a relevant issue to address. We wanted to explore the relationship between the modifiable risk factors of FI and HTN in the context of CKD.

Methods: A narrative review was performed using a systematic search in PubMed. Search terms were food insecurity, chronic disease, hypertension, social determinants of health and for years 2004-2023. After manual appraisal of each study, findings were narrowed down to exclude other literature or systematic reviews. Data synthesis was conducted according to a thematic synthesis approach.

Results: Out of a total of 147 articles, 26 studies were included in the final review. The thematic synthesis enabled the construction of 4 themes: "Low income negatively affects diet and is associated with food insecurity and HTN"; "Education and health literacy affect diet and the correlation between food insecurity and HTN"; "Access to healthy food feeds into the association between food insecurity and HTN"; and "Poor diet aggravates other adverse health conditions and is correlated to food insecurity and HTN".

Conclusions: FI is correlated to poor nutrition and HTN. Both FI and HTN together are an increasing global public health concern. The literature indicated how diet and health behavior are modifiable by addressing low income, limited access to healthy food and poor education thereby making it relevant to mitigate the negative dietary consequences of food insecurity on HTN and cardiovascular disease at a local and global scale. This is a threat also for the development of CKD. Relevance Statement: Globally, HTN is a leading non-communicable risk factor for cardiovascular morbidity and mortality. Hypertension is one of the leading causes of CKD. FI is associated with HTN, and these global health threats beg for urgent attention to improve health outcomes on a worldwide scale.

TH-PO230

Cardiovascular Health and CKD Progression Among US Hispanic/Latino Adults of the Hispanic Community Health Study/Study of Latinos, 2008-2017

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Background: The primary cause of death in chronic kidney disease (CKD) is cardiovascular (CV) disease. "Life's Essential 8" (LE8) is an established measure of CV health. Our objective was to examine the relationship between CV health (LE8) and CKD progression among US Hispanic/Latino adults, an understudied but growing population.

Methods: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) is a longitudinal cohort of Hispanic/Latino adults 18-74 years old from four US cities, examined at visit 1 (V1) (2008-2011) and V2 (2014-2017). At V1, participants underwent a comprehensive assessment of health behaviors (diet, smoking status, physical activity, sleep duration) and clinical measurements (body mass index, blood pressure, cholesterol, fasting glucose, medication use) used to estimate a LE8 score (range: 0 to 100). Estimated glomerular filtration rate (eGFR) was calculated from serum creatinine and cystatin C using the 2021 CKD-Epi equation and albumin to creatinine ratio (ACR) was measured from urine. CKD was defined as eGFR < 60 ml/min/1.73m^2 or ACR ≥ 30mg/g. Change in eGFR and log ACR were defined as the difference in each measure between V1 and V2. To estimate the association between LE8 score with change in eGFR and log ACR, we used linear regression models adjusted for follow-up time, demographic, socio-economic, and clinical factors. All analyses accounted for HCHS/SOL complex survey design.

Results: Among 1,284 Hispanic/Latino participants with CKD at V1, mean age was 48.6, 57.2% were women, and mean LE8 was 61.1 (SE: 0.7). Over an average of six years of follow-up, eGFR declined by 5.8 ml/min/1.73m^2 and log ACR declined by 0.60. From multivariable adjusted models, for each 10-unit increment (improvement) in LE8 score, eGFR declined by 0.99 less (95% CI: -1.97, -.02) and log ACR declined an additional 0.15 (95% CI: 0.06, 0.28) between V1 and V2.

Conclusions: Among diverse US Hispanics/Latino adults with CKD, greater LE8 score (better CV health) was associated with modest but statistically significantly lower declines in eGFR and greater improvements in log ACR over six years.

Funding: NIDDK Support

TH-PO231

Ideal Cardiovascular Health and CKD Progression in Hispanic Adults

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Background: The American Heart Association developed the Life's Simple 7 metric to promote cardiovascular health. We evaluated the association of this metric with chronic kidney disease (CKD) progression among Hispanic individuals with CKD.

Methods: We conducted a prospective observational cohort study of 663 adults with CKD enrolled in the Mexico and Hispanic Chronic Renal Insufficiency Cohorts (HCRIC and MCRIC), with entry estimated glomerular filtration rate (eGFR) 20-70 ml/min/1.73 m^2. Ideal levels of Life's Simple 7 (score range 0-14) were the following: nonsmoker; body mass index <25 kg/m^2; ≥150 minutes/week of physical activity; healthy dietary pattern (high in fruits and vegetables, fish, and fiber-rich whole grains; low in sodium and sugar-sweetened beverages); total cholesterol <200 mg/dL; blood pressure <120/80 mm Hg; and fasting blood glucose <100 mg/dL). The primary outcome was CKD progression defined as 30% and 40% decline in eGFR from baseline. Cox proportional hazards regression analyses were used.

Results: At study entry, mean (SD) age was 56 (12) years, 238 (36%) were female, and 408 (62%) had diabetes. Mean (SD) baseline eGFR was 45 (17) ml/min/1.73m^2, and median (IQR) urine protein excretion was 0.6 (0.1-2.6) g/24 hours. The median (IQR) Life's Simple 7 score was 7 (6-9) points, and 47% of participants had ideal or intermediate cardiovascular health (score 8-14 points). During a median follow-up of 3.4 years, there were 415 (63%) and 341 (51%) CKD progression events for 30 and 40% eGFR decline, respectively. In analyses adjusted for age, sex, education, and baseline eGFR and proteinuria, each point higher Life's Simple 7 score was associated with 10-12% lower risk of 30% and 40% eGFR decline (HR, 95% CI, 0.90,0.85-0.94 and 0.88, 0.84-0.93), respectively.

Conclusions: In this cohort of Hispanic adults with CKD, the prevalence of ideal cardiovascular health was low. Higher Life simple 7 score was associated with reduced risk for CKD progression.

TH-PO232

Cardionephrology Clinic for Comprehensive Care of Patients with CKD and Cardiovascular Disease: A Promising Opportunity

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Background: The coexistence of CKD and CV disease poses significant challenges in patient management, CV disease is the leading cause of mortality among CKD patients. This study aims to describe the establishment of a specialized cardio-nephrology clinic and report the initial and follow up results.

Methods: Since 2022, the cardio-nephrology clinic has been established, involving the participation of a nephrologist, cardiologist, nephrology fellows, medical students, and a nutritionist. Together, we conduct simultaneous clinical evaluations of patients using ultrasound (VEXUs) and bioimpedance. The clinic aims to enhance care, optimize pharmacological and non-pharmacological management, reduce hospitalizations, slow disease progression, and ultimately improve patient outcomes.

Results: 50 patients completed one year follow-up, 30 (60%) being male, mean age of 43.8±13.5 yrs. The baseline and outcomes of the patients are presented in Table 1.

Conclusions: The establishment of a specialized cardio-nephrology clinic offers comprehensive management and care for pts. living with CKD and CVD. The clinic aims to reduce the risk of complications and improve long-term prognosis for these patients. In addition, nearly all of these patients have experienced successful outcomes, including effective management of their comorbidities and the utilization of appropriate medications and overall clinical improvement. As a result, patients experience an enhanced quality of life.

Baseline measurements and Outcomes n = 50 pts			
LVEF	**Baseline n(%)**	**Follow up n(%)**	
Reduced	11 (22)	7 (14)	Improved LVEF 10 pts (20%)
Borderline	7 (14)	6 (11)	
Preserved	32 (64)	37 (74)	
VEXUS	**Baseline n(%)**	**Follow up n(%)**	
0	33 (66)	39 (78)	Improved VEXUs 12 pts (24%)
1	13 (26)	9 (18)	
2	4 (8)	2 (4)	
BNP	**Baseline**	**Follow up**	
Mean/ED	1927 (3148)	832 (1817)	Improved 33 pts (64%) 1094 (2770)
NYHA	**Baseline n(%)**	**Follow up n(%)**	
1	39 (78)	45 (90)	Improved NYHA 12 pts (24%)
2	7 (14)	5 (10)	
3	4 (8)	0 (0)	
Elective for KT protocol	**Baseline**	**Follow up**	**KT** / **On protocol eligible pts**
n (%)	0	15 (30)	3 (6) / 12 (24)
	HF Drugs	**Frecuency use n(%)**	
	ACEi/ARA	5 (10)	
	sacub/valsar	26 (32)	
	BB	27 (54)	
	espironolactone	19 (38)	
	SGLT2i	20 (40)	

TH-PO233

Influence of Baseline Depressive Symptoms on the Effect of Blood Pressure (BP) Intervention on Cognitive Outcomes in the SPRINT Trial

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Background: We examined the hypothesis that baseline depressive symptoms might modify the effects of BP control on cognitive outcomes.

Methods: We used data from SPRINT, an RCT that tested the effects of SBP goal <120 vs <140 mmHg on cardiovascular and cognitive outcomes. Based on Patient Health Questionnaire (PHQ)-9, we defined 3 groups: no (score 0), minimal/mild (score 1-9), moderate/ severe (Scores 10-27) depressive symtpoms. We examined interactions of baseline PHQ9 groups and SBP intervention on adjuducated cognitive outcomes of mild cognitive impairment (MCI) or probable dementia (PD).

Results: Among 8487 SPRINT participants included in the analysis, the three baseline PHQ9 groups were 34.6, 57.9, 7.3 respectively. There were 1243 MCI events and 322 PD events. As shown in Table 1, BP intervention lowered the risk of MCI/PD composite whereas higher baseline PHQ 9 scores were assoicated with higher risk of MCI/PD. Interaction p-values for BP intervention X PHQ 9 groups for MCI/PD, MCI alone and PD alone were 0.94, 0.73 and 0.56, repsectively.

Conclusions: Intensive SBP control resulted in decreased hazard of develpoing MCI/PD and presence of baseline moderate/severe depression was assiocated with significant increase in hazard of developing PD and PD/MCI. Nonetheless, there was no evidence that the effects of BP intervention on cognitive outcomes were modified by baseline depressive symptoms.

Funding: NIDDK Support

Outcome	Hazard Ratios (95% Confidence Interval)			
	SBP Intervention	PHQ-0 = 0	PHQ-9 1-9	PHQ-9 10-27
MCI/PD	0.90 (0.81, 1.00)	Reference	1.08 (0.97, 1.22)	1.30(1.02,1.66)
MCI alone	0.88(0.78,0.98)	Reference	1.04(0.92,1.18)	1.10(0.84,1.43)
PD	0.91(0.72,1.14)	Reference	1.25(0.97,1.61)	1.84(1.07,3.16)

TH-PO234

Depressive Symptoms and Achieving Blood Pressure (BP) Goals in the Systolic Blood Pressure Intervention Trial (SPRINT)

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Background: We examined the hypothesis that depressive symptoms might result in lower adherence to systolic BP intervention (SBP goal < 120 vs. < 140 mmHg) in a post-hoc analysis of SPRINT data.

Methods: Based on baseline depressive symptoms assessed by the Patient Health Questionnaire (PHQ) - 9 scores, we defined depressive symptom groups as no (score = 0), minimal/mild (score =1-9), moderate/severe (score = 10-27) depressive symptoms. We used mixed effects models to relate baseline PHQ9 groups to post-randomization delta SBP (achieved standard arm SBP -achieved intensive arm SBP and delta number of antihypertensives).

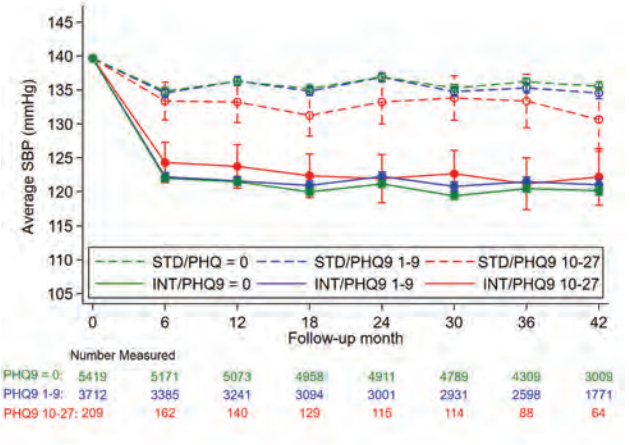
Results: In the 9340 included SPRINT participants, achieved SBP by baseline PHQ9 groups in standard and intensive arms are presented in Fig 1. Delta SBP and delta antihypertensives are presented in Table 1.

Conclusions: Moderate/severe depressive symptoms were associated with less separation of achieved SBP in SPRINT. Addressing depressive symptoms might be important to achieve adherence to interventions.

Funding: NIDDK Support

Table 1

Depressive symptoms	Delta SBP	Delta # antihypertensives
Absent	14.8 (14.4, 15.3)	-0.8 (-0.8,-0.7)
Mild	14.0(13.4,14.6)	-0.7 (-0.7,-0.6)
Moderate/Severe	9.0(5.6,12.4)	-0.8(-1.0,-0.5)



TH-PO235

Population Trends in the Incidence, Treatment, and Outcomes of Myocardial Infarction and Stroke in Patients with Kidney Failure: A National Data-Linkage Study

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Background: Temporal trends of myocardial infarction and stroke are declining in the general population, but have not been evaluated in patients with kidney failure (ie. on dialysis/with a kidney transplant). We describe national trends in the incidence, treatment and outcomes of myocardial infarction and stroke in patients with kidney failure over a 20-year period, stratified by age and sex.

Methods: In this retrospective national data-linkage study, all patients with kidney failure in Scotland (UK) experiencing an incident myocardial infarction or stroke between 01/01/1996 and 12/31/2016 were linked to national hospitalization, prescribing and death records. The primary outcome was 1-year cardiovascular death. Generalized additive models were constructed to estimate age-standardized, sex-stratified incidence rates and trends in mortality.

Results: Amongst 16,050 patients with kidney failure (52±15 years;41.5% women), there were 1,992 (66±12 years;34.8% women) and 996 (65±13 years;45.1% women) incident myocardial infarctions and strokes between 01/01/1996 and 12/31/2016. The age-standardized incidence of myocardial infarction per 100,000 decreased in men (from 4,376 [95% confidence interval [CI] 3,998-4,785] to 1,835 [95%CI 1,692-1,988]) and women (from 3,268 [95%CI 2,982-3,593] to 1,369 [95%CI 1,257-1,491]). The age-standardized incidence of stroke per 100,000 also decreased in men (from 1,978 [95%CI 1,795-2,175] to 799 [95%CI 729-875]) and women (from 2,234 [95%CI 2,031-2,468] to 903 [95%CI 824-990]). Compared to the general population, the incidence of myocardial infarction was 4-8-fold higher in patients with kidney failure, whilst for stroke it was 2-4-fold higher. The use of evidence-based cardioprotective treatment increased and the predicted probability of 1-year cardiovascular death following myocardial infarction for a 66-year-old patient with kidney failure (mean age of cohort) fell in men (76.6% to 38.6%) and women (76.8% to 38.8%), and also decreased in both sexes following stroke (men: 63.5% to 41.4%; women: 67.6% to 45.8%).

Conclusions: The incidence of myocardial infarction and stroke has halved in patients with kidney failure over the past 20 years but remains significantly higher than in the general population. Despite improvements in treatment, the prognosis of these high-risk patients remains poor.

TH-PO236

Trends of Blood Pressure Control in CKD Among US Adults: Findings from the National Health and Nutrition Examination Survey 2011-2020

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Background: Hypertension contributes to kidney disease progression, cardiovascular disease, and death in patients with chronic kidney disease (CKD). The evidence and clinical guidelines support lowering blood pressure (BP) goals in this patient population. We evaluated if BP control improved among US adults with CKD.

Methods: In the National Health and Nutrition Examination Survey (NHANES) for the periods 2011-2014, 2015-2016, and 2017-2020, we identified individuals with CKD defined as estimated glomerular filtration rate 20-59 mL/min/1.73 m² or urinary albumin/creatinine ratio ≥30 mg/g. The following systolic BP categories were evaluated: <120, 120-129, 130-139, and ≥140 mm Hg. All measures were tested for differences between year groups accounting for sample strata, clusters, and weights.

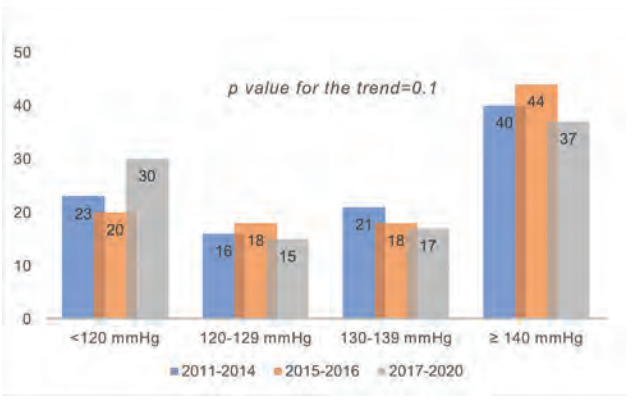
Results: During the periods of 2011-2014, 2015-2016, and 2017-2020, the prevalence of CKD was stable at 14, 13, and 13%, respectively (p value=0.4) and among those with CKD, the % of individuals with self-reported hypertension or taking BP medications was 66, 69, and 86%, respectively (p value<.0001). Although the number of BP medications prescribed increased significantly across time (**Table**), a significant % of individuals with CKD and hypertension had systolic BP 130-139 mm Hg (17%) or ≥140 mm Hg (37%) during the period 2017-2020 (**Figure**).

Conclusions: The number of individuals with CKD noted to have hypertension has increased significantly over time. Although there has been a significant increase in the number of BP medications prescribed, a considerable number of individuals with CKD still did not meet their BP goal.

Funding: Other NIH Support - NHLBI

Table: Number of individuals with CKD receiving BP medications

Number of BP medications	2011-2014	2015-2016	2017-2020	p value
0	13,240,309 (45)	13,283,274 (45)	6,974,905 (18)	<.0001
1	8,185,798 (28)	8,043,510 (27)	13,346,186 (35)	
2	5,304,534 (18)	6,290,783 (21)	11,389,885 (30)	
3+	2,764,304 (9)	2,130,880 (7)	6,620,570 (17)	



% in systolic BP categories over time

TH-PO237

An Interesting Presentation of Unilateral Renal Artery Stenosis

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Introduction: Renal artery stenosis is uncommon, however, the prevalence increase in the presence of hypokalaemia and severe hypertension. We report a spontaneous dissection of the renal artery resulting in unilateral ischaemic nephropathy and secondary hyperaldosteronism.

Case Description: A 52-year-old Chinese Male was referred for the evaluation of hypertension and symptomatic hypokalemia (2.4mmol/L). 24-hour urine potassium (K+) was 74mmol/day suggestive of urinary loss. There was no history of diuretic use. Cortisol post 1mg ONDST was 25nmol/L, excluding Cushing's syndrome. Serum aldosterone was elevated (29 ng/dL (<21)) and plasma renin activity was not suppressed (5.4 ng/ml/h (2.9-10.8)), suggesting secondary hyperaldosteronism. Doppler ultrasonography of the renal arteries showed an atrophied left kidney with poor visualization of the proximal segment of the left renal artery with tardus parvus waveform. CT angiography showed near complete occlusion at the origin of the dominant left renal artery with significantly reduced opacification distally and an atrophic left kidney suggesting chronic dissection with thrombosis. The right renal artery was normal. DMSA scan showed left kidney contributes to 5% and the right kidney contributes to 95% of the total kidney function. He was started on Valsartan 40mg OD and spironolactone 12.5mg OD later. His blood pressure is well controlled. Potassium supplementation was reduced from 3.6g/day to 0.6g/day while maintaining normal K+, stable serum creatinine of 119umol/L, eGFR 58ml/min/1.73m² and urine albumin/creatinine ratio of 2.7mg/mmol.

Discussion: We present an interesting case of unilateral RAS, likely from a chronic dissection of the left renal artery causing secondary hyperaldosteronism. Common etiologies of renovascular hypertension include atherosclerosis or fibromuscular dysplasia. Upon reviewing his medical history, we noted that he presented with left flank pain a year ago, and was treated for pyelonephritis. CT KUB then revealed normal-sized kidneys. We postulate that the spontaneous dissection could have happened then, resulting in left renal artery stenosis and secondary hyperaldosteronism. Initiation of RAAS blockade resulted in the reversal of the effects of hyperaldosteronism and glomerular hyperfiltration, as evidenced by the reduction in potassium supplementation, albuminuria, and BP control.

TH-PO238

Resistant Hypertension with Recurrent Flash Pulmonary Edema in the Setting of Bilateral Renal Artery Occlusion

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Introduction: Resistant hypertension is defined as elevated blood pressure despite three different classes of anti-hypertensives and warrants thorough investigation to rule out underlying secondary causes. Renal artery occlusion is an uncommon pathology, which can lead to severe kidney damage and can present with non-specific symptoms such as hematuria, acute kidney injury, uncontrolled hypertension.

Case Description: 49-year-old male with past medical history of unprovoked pulmonary embolism, recurrent flash pulmonary edema, hypertension, stage 4 chronic kidney disease with nephrotic range proteinuria who presented with shortness of breath, back pain and claudication symptoms. On presentation, he was found to have hypertensive emergency with flash pulmonary edema, requiring nicardipine infusion and mechanical ventilation. Initial laboratory tests were remarkable for hypokalemia, elevated creatinine, 4 g/g proteinuria on dipstick and microscopic hematuria. Anti-PLA2r, ANA, serum and urine electrophoresis, ANCA, serum and urine metanephrines were unrevealing. Patient had prior renal biopsy showing collapsing glomerulopathy with chronic renal thrombotic angiopathy. As the patient was hemodynamically stabilized, secondary causes for hypertension were investigated. Renal doppler ultrasound was performed, showing abdominal aorta thrombosis at the level of juxtarenal to infrarenal segments with bilateral occlusion of renal arteries. These findings furthermore confirmed with MR-Angiogram and renal nuclear scans. Given the life debilitating claudication symptoms, the patient underwent right axillobifemoral bypass.

Discussion: Recurrent flash pulmonary edema and resistant hypertension should raise suspect for renovascular hypertension and potentially renal artery occlusion. Renal artery occlusion is a rare finding and can be seen in patients with trauma, endovascular interventions, atherosclerosis, thromboembolic events and possibly underlying hypercoagulability. After ruling out lupus anticoagulants, antiphospholipid panel, Factor Leiden V, homocysteine, trauma and we concluded that the renal artery occlusion was due to atherosclerotic plaque proved by pathology. While the treatment is on case-on-case basis, revascularization was pursued for our patient with resolution of claudication symptoms but no significant improvement of kidney functions.

TH-PO239

Primary Hyperaldosteronism Secondary to Right Adrenal Hyperplasia with Nonfunctioning Left Adrenal Adenoma Elucidated by Adrenal Vein Sampling

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Introduction: Primary hyperaldosteronism includes two main subtypes namely idiopathic hyperaldosteronism(also termed bilateral adrenal hyperplasia) and unilateral aldosterone-producing adenoma, managed with aldosterone antagonists or adrenalectomy, respectively. Aldosterone renin ratio (ARR) has emerged as a significant parameter as compared to plasma aldosterone concentration (PAC), thus identifying need for adrenal vein sampling (AVS) or further exclusionary tests including imaging, the solitary utility of which without AVS may result in unwarranted adrenalectomy. Our case demonstrates the importance of AVS and elaborates the context that needs to be applied to plasma renin and aldosterone levels.

Case Description: A 68-year-old male with history of type 2 diabetes, coronary artery disease status post stenting 15 years ago, hyperlipidemia, and GERD, was referred for refractory hypertension, requiring carvedilol 25mg twice a day, doxazosin 2mg twice a day, hydrochlorothiazide 50mg daily, isosorbide mononitrate 30mg daily, losartan 100mg daily and spironolactone 50mg daily. Workup revealed microalbuminuria, normal serum potassium, bicarbonate, free metanephrines, renin, elevated aldosterone level of 40.1ng/dL, and elevated ARR of 44.6. Renal duplex ultrasound negative for renal artery stenosis. Noncontrast CT revealed 13x11mm left adrenal adenoma and bilateral adrenal gland thickening likely secondary to hyperplasia; adrenal vein sampling confirmed right adrenal vein aldosterone of 4880ng/dL, cortisol of 1158nmol/L(ratio 4.2), with left aldosterone 146ng/dL, cortisol 495nmol/L(ratio 0.3), and cortisol-corrected PAC laterization ratio of 14. He underwent laparoscopic right adrenalectomy with pathology confirming adrenocortical adenoma. Postoperative followup showed significant improvement in hypertension on fewer agents, decreased aldosterone of 7.8ng/dL, and ARR of 15.6.

Discussion: PAC may be challenging to interpret due to many influencing factors, hence, ARR is emerging as a beneficial parameter to delineate the initial diagnosis of primary hyperaldosteronism. Our case also emphasizes the utility of cortisol corrected PAC laterization ratio in these cases. While adrenal vein sampling may appear counterintuitive, it is prudent to consider AVS for confirmation prior to adrenalectomy.

TH-PO240

Lessons Learned in Determining Unilateral vs. Bilateral Intervention in Bilateral Renal Artery Stenosis

Amanda Abi Doumet, Ruchir D. Trivedi. *UConn Health, Farmington, CT.*

Introduction: Renal artery stenosis (RAS) is defined as a narrowing of one or both renal arteries. It is most frequently caused by atherosclerosis and less frequently by Fibromuscular Dysplasia (FMD) and other vascular abnormalities. Although RAS due to FMD is successfully treated with balloon angioplasty, such intervention is not as promising in atherosclerotic RAS. We present a case of a patient with bilateral RAS with successful balloon angioplasty of only the Left renal artery.

Case Description: A 46-year-old male with a history of hypertension and CKD stage IIIb presented with headaches and blurry vision. His BP was severely elevated at 209/153. His creatinine was elevated at 2.1 (baseline of 1.7). He was admitted for hypertensive emergency and underwent a workup for secondary causes of hypertension. Aldosterone/Renin ratio was 11.8/8.5 (1.4). Renal ultrasound duplex revealed a right kidney of 8.5 cm and left kidney of 11.4 cm, ostium of the right kidney was unable to be visualized and left renal artery systolic velocities were elevated. Renal angiography revealed critical mid-segment left RAS and right ostial RAS. A stent was placed in the left renal artery and the patient was started on Aspirin and Clopidogrel. Kidney function and blood pressure improved thereafter.

Discussion: RAS has many cardiovascular implications including resistant hypertension, CKD, and cardiac destabilization syndromes to name a few. Although the mainstay of treatment is medical therapy, some patients do benefit from stenting, such as those with hemodynamically significant atherosclerotic RAS and recurrent heart failure, refractory ACS, refractory hypertension, or progressive CKD due to bilateral or solitary ARAS. Although our patient had evidence of bilateral RAS, we concluded that the hemodynamically significant stenosis was that of the left renal artery. Since the left kidney was larger, we theorized that the primary stenosis was in the right kidney which led to compensatory hypertrophy of the left kidney and points to the relatively acute development of left RAS, explaining the patient's acute presentation. Improvement in kidney function and BP after stenting the left renal artery further supports that conclusion. More studies are needed to identify which patients will benefit most from stenting, based on clinical presentation and assessment of hemodynamic significance of RAS.

TH-PO241

Preeclampsia Superimposed on Secondary Hypertension in the Setting of Fibromuscular Dysplasia

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Introduction: Fibromuscular dysplasia (FMD) is a noninflammatory, nonatherosclerotic disorder of medium-sized vessels that leads to arterial stenosis. Most affected vessels are the renal and internal carotid arteries. When to pursue endovascular treatment is not always clear.

Case Description: The patient is an 18-year-old female who had recently given birth presented to the nephrology clinic for evaluation of uncontrolled hypertension possibly related to fibromuscular dysplasia. The patient was first seen to have hypertension at an emergency department when she was 10 weeks 4 days pregnant. At that time, her blood pressure was 176/82 mmHg. She was discharged home on labetalol 100 mg three times a day and referred for obstetric evaluation. At the obstetric clinic, work-up for secondary causes of hypertension was initiated. Renal ultrasound only showed involvement of the right renal artery with 60% stenosis. At 32 weeks 3 days, protein was detected for the first time in the urine and protein-creatinine ratio was 19.4, which represents at least 5000 mg of protein/day. As her blood pressure continued to be difficult to control, nifedipine was added to labetalol. At 32 weeks 5 days, labor had to be induced due to preeclampsia with severe features that included systolic blood pressures raging from 180-200 mmHg and fetal growth restriction. Creatinine remained within normal range throughout the entire pregnancy and afterwards. After leaving the hospital post-delivery, CT angiogram of abdomen/pelvis with and without contrast demonstrated left renal artery stenosis possibly related to FMD. At that time, protein-creatinine ratio had dropped to 0.22. Since then, losartan was added to the previous 2 antihypertensive and her blood pressure is still not well controlled.

Discussion: This patient had hypertension before 20 weeks gestation and proteinuria was first detected at 32 weeks 3 days, making this case one of chronic hypertension that progressed to preeclampsia with severe features. This patient meets criteria for angioplasty since she appears to have bilateral FMD and her blood pressure is not well controlled on as many as 3 antihypertensives. Cure rate of endovascular treatment appears to fall markedly with age. Curing hypertension in her case is preferable in view of her history of preeclampsia with severe features and the patient's desire to become pregnant again.

TH-PO242

Sex Differences in the Risk of Uncontrolled Hypertension: Variation over the Life Course

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Background: Recent studies suggest that sex differences in uncontrolled hypertension (HTN) may vary by age.

Methods: We evaluated the prevalence of HTN and uncontrolled HTN in middle-aged (visit 2) and older-aged (visit 5) men and women of the Atherosclerosis Risk in Communities (ARIC) Study, assessing the associated risk of death and kidney function decline (defined as a 40% decline in eGFR). We looked at whether sex differences in older age could be explained by differences in chronic kidney disease (CKD), coronary heart disease (CHD), obesity, or by anti-HTN medication prescription patterns or adherence.

Results: Among 14,261 participants attending visit 2 (mean age 57), the prevalence of hypertension was 36% in both men and women. Among those with hypertension, the prevalence of uncontrolled hypertension (defined as systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg) was higher in men (51%) than in women (44%). Among 6398 participants attending visit 5 (mean age 76), the prevalence of hypertension was similar in both men and women (76% and 74% respectively). Among those with hypertension, the prevalence of uncontrolled hypertension was higher in women (41%) than in men (33%). Both controlled HTN and uncontrolled HTN were risk factors for mortality for visit 2 participants (HR 1.3, 95% CI [0.08, 1.3] and HR 1.5 [1.3, 1.6], respectively), with higher risk associated with uncontrolled HTN in women compared with men (p=6.8E-03). Both controlled HTN and uncontrolled HTN were risk factors for kidney function decline (HR 1.2 [1.0, 1.5] and HR 1.6 [1.4, 1.9], respectively), with no difference by sex. Among visit 5 participants, controlled HTN and uncontrolled HTN were not significantly associated with mortality, but were strong risk factors for kidney function decline (HR 2.1 [1.2, 4.0] and HR 3.4 [1.8, 6.5], respectively) with no sex difference. Differences in uncontrolled HTN by sex at visit 5 was not explained by differences in CKD prevalence, CHD, obesity, anti-HTN medication prescription patterns (prescription, classes, and number), or anti-HTN medication adherence (defined as having at least one detectable anti-HTN medication metabolite in urine).

Conclusions: Uncontrolled HTN shows sex differences which vary by age, with implications for mortality and kidney function decline.

Funding: NIDDK Support

TH-PO243

Trends in Hypertension Recognition, Treatment, and Control Between 2011 and 2019 Among Adults with CKD in the Veterans Health Administration

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Background: Hypertension frequently accompanies chronic kidney disease (CKD) as etiology and sequela. We examined contemporary trends in hypertension treatment and control in a national sample of adults with CKD.

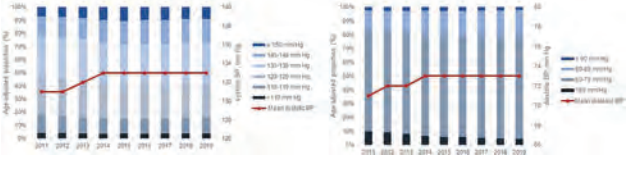
Methods: We evaluated serial 5% cross-sectional samples of adults with CKD between 2011 and 2019 in the Veterans Health Administration (VA). We defined CKD as a sustained estimated glomerular filtration rate (eGFR) value <60 ml/min/1.73m² or a urine albumin-creatinine ratio (UACR) ≥30 mg/g.

Results: We examined 238,748 adults with a mean age of 72 years, 96% of whom were male. The age-adjusted proportion of adults with controlled BP declined from 78.0% in 2011 to 72.9% in 2019 (p-value for linear trend <0.001). Between 2011 and 2019, among adults with BP above goal, the age-adjusted proportion with a diagnosis of hypertension declined from 97.1% to 94.3% (p-value for linear trend <0.001), the age-adjusted proportion who did not receive antihypertensive treatment increased from 18.8% to 21.6% (p-value for linear trend <0.001), while the age-adjusted proportion who received three or more antihypertensive medications decreased from 41.8% to 36.3% (p-value for linear trend <0.001). The age-adjusted proportion of adults who received angiotensin converting enzyme inhibitors or angiotensin receptor blockers declined from 65.0% to 59.7% (p-value for linear trend <0.001); the age-adjusted proportion of adults who received thiazide-type diuretics declined from 24.1% to 20.0% (p-value for linear trend <0.001).

Conclusions: Among adults with CKD treated in the VA, the proportion with controlled BP has declined over time, coinciding with fewer prescriptions for antihypertensive medications.

Funding: NIDDK Support

Figure. Age-adjusted systolic and diastolic blood pressure distribution among adults with chronic kidney disease in the Veterans Health Administration from 2011 to 2019



TH-PO244

Proteomics of Myocardial Fibrosis in Advanced CKD

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Background: We used a large-scale, high-throughput DNA aptamer-based discovery proteomic platform to identify circulating biomarkers of myocardial fibrosis (MF) in advanced chronic kidney disease (CKD).

Methods: We evaluated 26 living kidney transplant (KT) recipients (age 53±16 years, 44% women, dialysis vintage 24.3±20 months) and 21 KT waitlisted participants (age 55±13 years, 38% women, dialysis vintage 23.2±17 months) who underwent proteomic profiling (SomaScan v.4.1) at study baseline. Living KT group had MF assessed by non-contrast cardiac magnetic resonance T1 maps prior to and 9 months post KT. Waitlisted group had T1 maps at baseline and 9 months follow-up. Plasma levels of 6472 proteins were related to baseline and change in T1 maps using DESeq2, adjusted linear regression, spike and slab regression, and Firth's bias-reduced logistic regression models. PathfindR and STRING-db v11.5 enrichment analyses were used to explore pathways.

Results: Among 126 proteins associated with baseline T1 maps, 43 remained significant after adjusting for clinical covariates (false discovery rate [FDR] adjusted p<0.05). Of these, 10 proteins were consistently selected across a large proportion of resampling iterations (>60%), with macrophage colony stimulating factor-1 (M-CSF1), displaying the greatest retest reproducibility (80%). Compared to waitlisted, KT recipients had a significant reduction in T1 maps at 9 months (79.2% vs 38.9% participants, p=0.003). Though FDR adjustment attenuated the association, greater baseline M-CSF1 was associated with decreased T1 maps in KT recipients (OR 2.53, 95%CI: 0.85, 14.11) and lower baseline M-CSF1 associated with increased T1 maps in waitlisted participants (OR 0.35, 95%CI: 0.07, 1.08). Plasma M-CSF1 levels by ELISA highly correlated with SomaScan values, and confirmed the inverse correlation with T1 maps.

Conclusions: Kidney transplantion was associated with a reduction in myocardial fibrosis measured by T1 maps. Plasma M-CSF1 was inversely associated with T1 maps and may serve as prognostic, and potentially mechanistic biomarker, conferring a protective effect against myocardial fibrosis in advanced CKD.

Funding: Other NIH Support - NHLBI

TH-PO245

Relative Blood Volume Monitoring Using Crit-Line and Hospital Admissions: A Retrospective Analysis of over 25,000 Patients Across 330 Dialysis Clinics

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Background: Relative blood volume (RBV) monitoring may help guide fluid management, but real-world data on its use and potential impact on hospital admissions in chronic hemodialysis is limited. We aimed to compare hospital admissions among Fresenius Kidney Care (FKC) clinics with high utilization of RBV and propensity score matched (PSM) clinics not using RBV.

Methods: All data was retrospective, de-identified, and collected as part of routine clinical care and spanned 7/1/22-12/31/2022. RBV was conducted using Crit-Line (CLiC; Crit-Line in a Clip) devices integrated into 2008T dialysis machines. 165 FKC clinics with high utilization of RBV (HI-RBV; >90% of HD treatments used RBV) were PSM to 165 clinics not using RBV (NO-RBV) based on the following: pt census, age, gender, race, primary insurance, diabetes, catheter use, and ESRD network. Hospital admission rates (all-cause and fluid-related), hospital days, and 30-day readmissions were calculated and compared as rate ratios (RR), rate differences (RD), and proportions along with 95% confidence intervals and p-values.

Results: Outcomes for HI-RBV clinic pts (n=11,845) compared to NO-RBV clinic pts (n=13,238) are shown in Table. We observed an 8% lower rate of hospital admissions (p<0.0001) and 14% lower rate of fluid-related hospital admissions (p=0.0002) comparing HI-RBV to NO-RBV. There were 13 and 4 fewer hospital admissions per 100 person years (py) for all-cause and fluid related, respectively, along with 113 fewer hospital days per 100 py comparing HI-RBV to NO-RBV (p<0.0001). We can estimate an additional 48 missed treatments per 100 py in NO-RBV clinics due to these excess hospital days. There was a trend toward lower 30-day readmissions among HI-RBV vs NO-RBV (25.5% vs 27.3%, p=0.049).

Conclusions: Clinics with high utilization of RBV experienced fewer all-cause (8%) and fluid-related (14%) hospital admissions and hospital days (113 days per 100 py) when compared to PSM clinics without RBV.

Funding: Commercial Support - Fresenius Medical Care

	Incident Rate ppy		Rate Ratio	Rate difference ppy	p-value
	HI-RBV	NO-RBV	HI-RBV vs NO-RBV	HI-RBV vs NO-RBV	HI-RBV vs NO-RBV
All-cause hospital admissions	1.55 (1.51,1.59)	1.68 (1.64,1.72)	0.92 (0.89,0.95)	-0.13 (-0.18,-0.08)	<0.0001
Hospital days	9.75 (9.66,9.85)	10.89 (10.79,10.98)	0.90 (0.88,0.91)	-1.13 (-1.27,-1.00)	<0.0001
Fluid- related hospital admissions	0.27 (0.26,0.29)	0.32 (0.30,0.33)	0.86 (0.80,0.93)	-0.04 (-0.07,-0.02)	0.0002

TH-PO246

New Approach for Intradialytic Estimation of Absolute Blood Volume During Ultrafiltration

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Background: Managing blood and fluid volumes in chronic kidney disease (CKD) patients plays an essential role in dialysis therapy to replace kidney function. The study aims to develop an estimation approach to provide predictable information on blood and fluid volumes during a regular dialysis routine.

Methods: The method utilizes a nonlinear fluid volume model, a mathematical optimization technique, and the Unscented Kalman Filter (UKF). The method relies on anthropometric patient information (pre-dialysis weight, assumed dry weight), bounded parameter assumptions, and actual, on-line treatment information (UF-rate and hematocrit (H) or related measures of hemoconcentration). The method does not require a specific UF-rate or volume infusion protocols. Data collected were used where UF was varied to examine intravascular volume dynamics.

Results: The method was applied to 20 data sets of ten patients and provided comparable results compared to a previous method. Average blood volumes of 5.3±0.55L, plasma volumes of 4.1±0.64L, interstitial fluid volumes of 17.3±3.3L, and red blood cell volumes of 1.2±0.14L were estimated. We show that by implementing the estimated parameters, the measured H can be precisely predicted.

Conclusions: The method is comparable with a previous method and uses a short data segment for estimation.

Funding: Government Support - Non-U.S.

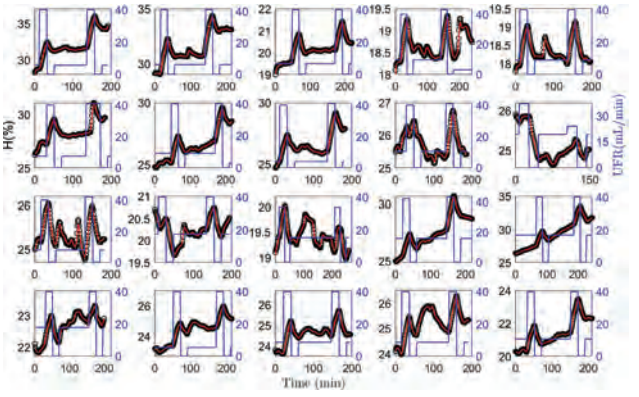
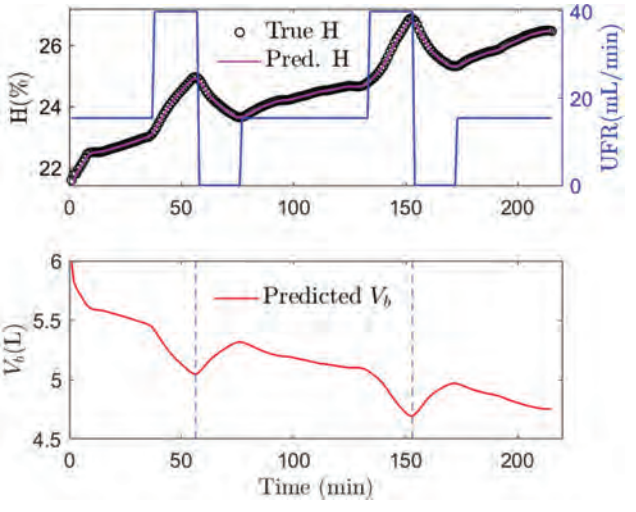


Figure 1. Predicted H trajectories (red lines) for measured profiles (black circles) during 20 treatments for 10 patients.



Modeled vs actual H measurements (black circles) with UF rates; estimated blood volume (Vb) estimations.

TH-PO247

Estimation of Absolute Blood Volume in Hemodialysis Patients Using Bioimpedance Spectroscopy

Fansan Zhu,[1] Jochen G. Raimann,[1] Ulrich Moissl,[2] Samer R. Abbas,[1] Paul W. Chamney,[3] Stephan Thijssen,[1] Peter Kotanko.[1,4] *[1]Renal Research Institute, New York, NY; [2]Fresenius SE & Co KGaA, Bad Homburg, Germany; [3]Fresenius Medical Care (UK) Ltd, Huthwaite, United Kingdom; [4]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: Measurement of absolute blood volume (ABV) during hemodialysis is essential to understand the relationship between the rates of vascular refilling and ultrafiltration. However, ABV is usually measured with dilution methods that are impractical in clinical routine. We evaluated whole body bioimpedance spectroscopy (wBIS) as an alternative approach.

Methods: Extracellular (ECV) and intracellular (ICV) volume were estimated using published equations (Moissl, Physiol Meas 27:921-933, 2006) based on wBIS measurements (Hydra 4200). Lean tissue mass (LTM) and adipose tissue mass (ATM) were calculated by a body composition model (BCM) (Chamney, Am J Clin Nutr 85:80 –89,2007). Reference blood volume (ABV_Dax) was measured by tracer dilution (Daxor BVA-100 analyzer, Daxor Corp., New York, NY, USA). Multiple regression and Bland-Altman analyses were used to determine the relationship of ABV with BCM and wBIS models, respectively.

Results: Data from 12 subjects (3 females, 53.8±15.2 years, pre-HD weight 85.6±19.7 kg) were analyzed. Pre-HD ECV (19.01±3.62L), ICV (23.02±5.96L), LTM (46.78±13.97kg) and ATM (36.86±18.53 kg) were calculated, while ABV_Dax (5.58±1.20 L) was measured before HD. The BCM model (ABV_BCM=1.028+0.023*ATM+0.079*LTM) comprised LTM and ATM as independent variables (Fig. 1). The wBIS model (ABV_wBIS=0.711+0.141*ICV+0.085*ECV) comprised ECV and ICV as independent variables (Fig.2). ABV_Dax correlated with ABV_BCM (R^2=0.84, p<0.0001; bias = -0.01±0.5 L) and with ABV_wBIS (R^2=0.84, p<0.0001; bias=0.00±0.49 L). Since the head and parts of the feet and hands had not been measured by wBIS, the y-intercept in both regression models conceptually represents an estimate of the blood in these body parts.

Conclusions: Estimation of ABV by both ABV_BCM and ABV_wBIS models correlate with the reference method. Despite the small sample size, utilizing such simple models may provide an approach using wBIS to estimate ABV and, in conjunction with relative blood volume measurements, to monitor ABV during HD.

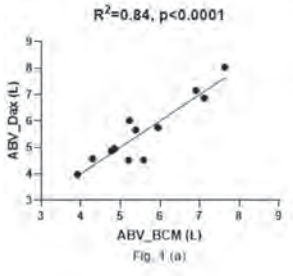


Fig. 1 (a)

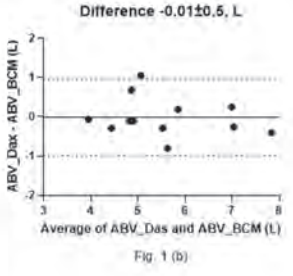


Fig. 1 (b)

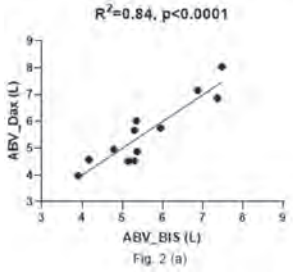


Fig. 2 (a)

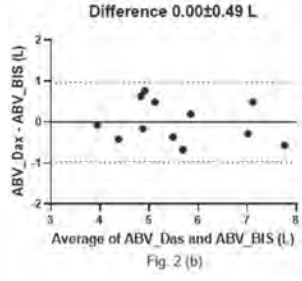


Fig. 2 (b)

TH-PO248

Estimation of Fluid Overload in Hemodialysis Patients Using Leg Bioimpedance

Fansan Zhu,[1] Peter Kotanko.[1,2] *[1]Renal Research Institute, New York, NY; [2]Icahn School of Medicine at Mount Sinai, New York, NY.*

Background: While 8-point bioimpedance provides a simple and convenient technique to measure segmental and whole body extracellular (ECV) and intracellular volume (ICV), it cannot quantitate fluid overload (FO). The aim of this study was to evaluate whether FO in hemodialysis patients can be estimated with a leg bioimpedance model.

Methods: Leg resistances were measured with four metal electrodes built into the footplate (Fig.1). Leg extracellular resistance (R_L; at 1 kHz frequency) and volume (ECV_L) were measured. ECV_{2L} represents ECV of both legs combined. Body height (H), pre-HD weight (Wt) and ultrafiltration volume (UFV) were recorded. Leg hydration index (α, Ω/cm) was defined as R_L/H in healthy subjects (HS; $\alpha_{HS}= R_{LHS}/H_{HS}$) and patients ($\alpha_P= R_{LP}/H_P$), respectively. The difference between average α_{HS} (α'_{HS}) in the HS and patients ($\Delta\alpha=\alpha'_{HS} - \alpha_P$) reflects the degree of leg FO. $\Delta\alpha*ECV_{2L}$ and body mass index ($BMI=Wt/H^2$) were considered as independent variables in a regression model that was built to explore the relationship between UFV and FO.

Results: Sixteen HS (age 34.8±7.6 years, H 168.7±9.5 cm, Wt 72.7±17.3 kg) and thirteen HD patients (age 47±16 years, H 169.5±4.5 cm, Wt 83.9±5.4 kg) were studied pre-HD. Leg resistance (R_L) was 217.3±55.3 Ω pre-HD, UFV was 3862±1320 mL. Average α_{HS} (α'_{HS}), defined as the standard index of leg normal hydration, was 1.8±0.3 Ω/cm. Δα was 0.24±0.37 Ω/cm in the HD patients. FO [in mL] was estimated as 534 + $0.36*\Delta\alpha*ECV_{2L}$ + 70.24*BMI. UFV was highly correlated with estimated FO (R^2= 0.82, p<0.0001). Bland-Altman analysis showed a bias of 0.15±394 mL (Fig.2).

Conclusions: Estimated leg hydration correlates well with FO in hemodialysis patients. A model with leg resistance and BMI as independent variables can predict FO in HD patients.

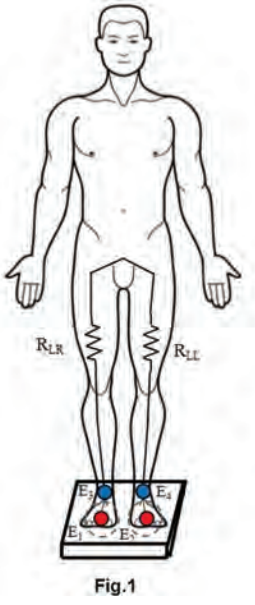


Fig.1

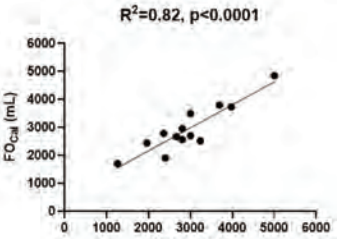


Fig.2 (a)

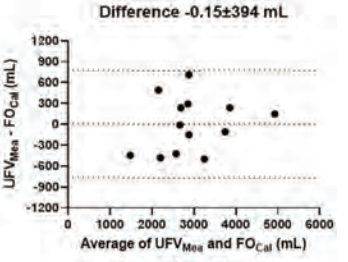


Fig.2 (b)

TH-PO249

Pulmonary Congestion Management Guided by Lung Echography in Hemodialysis: When and How?

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Background: Assessment of pulmonary congestion (PC) by lung ultrasound (LUS) may help its management in hemodialysis (HD) patients, and better defining the dry weight (DW). We inspected the best moment to perform LUS in HD, and then applied a LUS guided DW adjustment approach.

Methods: Prospective randomized study: 18 HD patients, preceded by an observational phase: B-lines score (BLS: 8-sites method) and echocardiography were obtained before and after the first 2 HD sessions of the week. Total body volume using Bio-electrical Impedance Analysis (BIA) was measured besides serum NT-pro BNP levels. Circulating markers of inflammation (soluble urokinase Plasminogen Activator Receptor [suPAR] and soluble Suppression of Tumorigenicity 2 [sST2]) were measured. Patients were then randomized into: an active group where DW was reduced by 500 g in case of BLS > 0.54/zone measured after HD2 (every 2 weeks), and a control group where DW was modified only according to standard of care. Same measurements were repeated a month later.

Results: BLS pre-HD1 (16 ± 5.53) and post-HD1 (15.3 ± 6.63) were elevated as pre-HD2 (16.2 ± 5.26) and post-HD2 (13.6 ± 5.83). BLS was not affected by inter-dialysis interval (68h vs 44h). BIA was correlated to BLS only before HD2 (P= 0.007). BLS and the systolic cardiac function (left ventricular ejection fraction) were correlated only after HD2 (P=0.046). NT-ProBNP levels and BLS were correlated before both sessions (P=0.004, P=0.001). Cardiac diastolic function was correlated to BLS before HD1 (P=0.002) and after HD2 (P=0.034). Mean levels (± SD, ng/ml) of suPAR (7.88 ± 3.07 and 7.78 ± 3.02) remained high (N< 4 ng/ml), while sST2 levels reached 2-fold the upper normal value (27.4 ± 17.8). At day 30, a significant reduction in BLS was obtained before (17.4 *vs* 8.5, P <0.0001) and after (13.3 *vs* 5.0, P<0.001) HD in the active group, whereas no difference was found in controls.

Conclusions: Pulmonary congestion is common in HD patients even after reaching their dry weightand is not systematically correlated to volume status or cardiac function. Chronic inflammation may be involved in PC pathophysiology. The best moment to estimate pulmonary congestion degree by lung ultrasound is after the 2nd HD session of the week, and a step by step DW adjustment guided by LUS may significantly and safely reduce PC.

Funding: Government Support - Non-U.S.

TH-PO250

Legacy Effect of a Lung-Ultrasound Intervention on the Risk for Death and Cardiovascular Events in Dialysis Patients

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Background: In the "LUng water by Ultra-Sound Guided Treatment (LUST) to Prevent Death and Cardiovascular Complications in High Risk ESRD Patients with Cardiomyopathy" trial (NCT02310061)", this treatment strategy was not more effective than a usual care strategy in improving the primary end point of the study over two years. Since robust long-term effects of intensive haemodialsyis in the frequent haemodialysis trial, we designed a post-trial, observational analysis extended up to 4.4 years.

Methods: We included in this analysis 315 HD patients. In patients in the active arm of the trial (n=157) ultrafiltration prescription was guided by lung US, while in the control arm (n=158) ultrafiltration was prescribed on the basis of standard clinical criteria. After the trial, patients were followed-up for 2 additional years, but no intervention was applied (observational phase). Since fluid volume is higher in men than in women, by protocol we tested the effect modification of male sex on the response to the lung-US intervention.

Results: Among the 315 HD patients, 223 (71%) were males. During the long-term observation (up to 4.4 years), the combined event occurred in 88 patients (56%) in the active arm and 100 (63%) in the control arm. Like in the LUST trial, the 16% risk reduction registered in the observational extension of the trial failed to achieve significance (HR: 0.84, 95% CI: 0.63-1.12, P=0.23). Sex emerged as a robust modifier [P for effect modification 0.02] of the effect of the lung US intervention on the combined end-point. Indeed, the intervention produced a 35% risk reduction in men [HRmen: 0.65, 95%CI: 0.46-0.93, P=0.02] but not in women [HRwomen: 1.40, 95%CI: 0.84-2.34, P=0.20].

Conclusions: In an observational extension to 4.4 years of the LUST trial, the treatment strategy guided by lung-US was associated with a 35% reduction of the risk of the combined end-point of the trial in men while no such an effect emerged in women. These results are in keeping with biological knowledge indicating that in the hemodialysis population, men have higher fluid volume and cardiovascular risk than women.

TH-PO251

Volume Status Assessed by Physical Examination Correlates with Lung Ultrasound Findings in Patients with CKD

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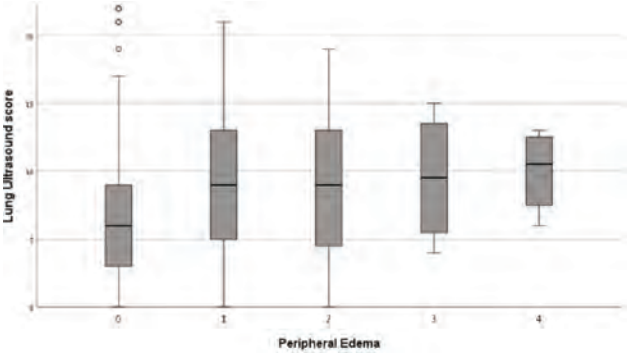
Background: Volume overload is common in patients with chronic kidney disease (CKD), predominantly in dialysis patients. Volume assessment by physical examination (PE) may be subjective, therefore more accurate methods are necessary. Lung ultrasound (LUS) is one method used to accurately diagnose dry weight in dialysis patients. We aimed to assess LUS accuracy compared to PE in the range of CKD stages.

Methods: A prospective single center study. Hemodialysis (HD), peritoneal dialysis (PD) and CKD 1-5 patients were enrolled. PE was performed prior to LUS to evaluate signs of volume overload. Lung findings (crackles, pleural effusion) were reported as present or not, peripheral edema was graded 0-4[1]. HD patients were examined twice, pre and post dialysis. LUS was performed by inspection of 12-zones. Each zone was assigned 0 points for less than 2 separated B-lines, 1 point if more than 3 B-lines were observed, 2 points when multiple B-lines with coalescing lines were documented and 3 points in cases of pulmonary consolidation. Accordingly, exam scores could range from 0, indicating a normal exam, to 36, indicating worst congestion possible. Results of PE and LUS were compared.

Results: Among 175 participants, 112 were HD patients, 18 PD and 45 CKD 1-5ND patients. Higher LUS scores correlated with presence of lung crackles (OR=1.16 (1.10-1.23) p<0.01) and pleural effusion (OR=1.17 (1.11-1.23) p<0.01). There was a significant correlation between LUS score and peripheral edema (Figure 1), and an inverse correlation between room air saturation and LUS score (r=-0.143, p=0.017). In HD patients weight differences before and after dialysis (delta weight) were compared with LUS score difference before and after dialysis (delta score). There was a linear correlation between delta weight and delta score (r=0.225, p=0.013).

Conclusions: LUS correlates significantly with PE findings in volume overload assessment in a broad spectrum of CKD patients.

Funding: Private Foundation Support



(r=0.27, p<0.001)

TH-PO252

Temporal Trend of Direct Oral Anticoagulant vs. Vitamin K Antagonist Usage in Dialysis Patients

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Background: Many dialysis patients take anticoagulation for various indications such as stroke prevention in atrial fibrillation, DVT and/or PE. Vitamin K antagonist (VKA) has been used for decades and Direct Oral Anticoagulants (DOAC) have gradually replaced VKA in the general population due to its ease of use. However, due to its safety issue in dialysis patients, the adoption of DOAC has been slow, until the approval of Apixaban by FDA in advanced CKD patients. In this study, we examined the temporal trend of anticoagulant usage in dialysis patients in an integrated health care system.

Methods: This is a retrospective cohort study performed within Kaiser Permanente Northern California (KPNC) from 2013-2021. Pharmacy records and ICD codes identified patients on dialysis (hemodialysis or peritoneal dialysis) who are taking oral anticoagulants to determine the percentage of dialysis patients on anticoagulants. Next, we determined the percent of patients on VKA and a DOAC. The percentage of patients on these two anticoagulants were determined every year.

Results: We identified 1688 dialysis patients on anticoagulants in the study period, representing 16.5% of dialysis populations (10242). In this population, mean age was 68.3 (SD 12.7), 40% female, 41% white, 21% Asian, 18% Hispanic, 15% Black and 6% others. There is an increase in the prescribing trends of DOAC with concurrent decrease in prescribing of VKAs (apixaban increased from 0 % in 2013 to 5.4 % in 2021 while warfarin decreased from 14.5% in 2013 to 9.8% in 2021 (figure). If a patient was to be switched off anticoagulation, they were more likely to be switched off VKA rather than apixaban.

Conclusions: This study revealed a diverging trend in the prescribing of VKA and DOAC over the past 9 years. Prescribers were more likely to switch from VKA to DOAC. Study is ongoing comparing the efficacy, safety, and cost.

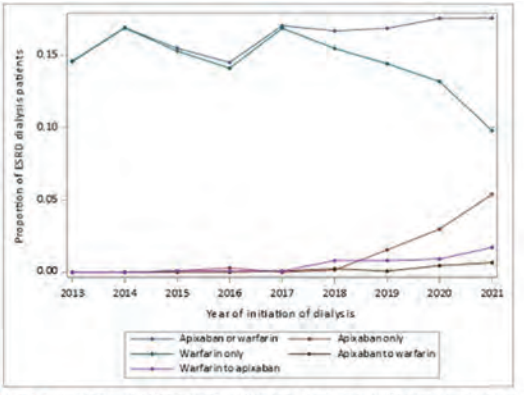

Figure 2. Illustrates prescribing trends of Warfarin, Apixaban over the course of 8 years. The top line is either Warfarin or Apixaban (blue), the second from top line is warfarin only (green), 3rd from top in red is Apixaban only (red). Then the 4th from top in magenta id the trend of switching warfarin to apixaban and bottom line in brown is trend from switching Apixaban to warfarin which occurred the least over the course of the study period.

TH-PO253

Absolute Iron Deficiency, Coronary Artery Calcification, and Mortality in Dialysis Patients

Sonoo Mizuiri,[1] Yoshiko Nishizawa,[1] Toshiki Doi,[1,3] Aiko Okubo,[1,3] Kenichi Morii,[1,3] Kazuomi Yamashita,[1] Koji Usui,[2] Kenichiro Shigemoto,[1] Takao Masaki.[3] *[1]Iryo Hojin Ichiyokai Harada Byoin, Hiroshima, Japan; [2]Iryohojin Ichiyokai Ichiyokai Clinic, Hiroshima, Japan; [3]Hiroshima Daigaku Byoin, Hiroshima, Japan.*

Background: It is reported that iron-deficiency is associated with hypercoagulability and stroke by upregulating transferrin (Tang X. Circ Res. 2020;127:651). We studied the associations among iron deficiency, coronary artery calcification and mortality in patients on dialysis.

Methods: We included 230 patients with predilution online hemodiafiltration and 76 on hemodialysis. The Agatston coronary artery calcium score (CACS) and clinical data, such as transferrin saturation (TSAT), ferritin, hemoglobin, mean corpuscular hemoglobin (MCH), serum albumin and C-reactive protein (CRP) at baseline, were assessed. Kaplan–Meier survival analyses and Cox proportional hazard models were used to assess patients' survival. Logistic regression analyses were used to determine related factors for absolute iron deficiency (TSAT ≤20% and ferritin concentrations ≤100 ng/mL).

Results: In all patients (n=306), age, dialysis duration and diabetes prevalence were 65±12 years, 76 (38–142) months and 42.5%, respectively. During 3 years, 52 all-cause deaths and 34 cardiovascular (CV) deaths occurred. Patients with absolute iron deficiency (n=102) showed significantly lower TSAT (13%±4% vs 30%±10%) and ferritin (34±23 vs 109±96 ng/mL) and MCH (28±3 vs 32±2 pg) concentrations, but significantly higher CRP concentrations than patients without absolute iron deficiency (n=204) (P<0.05). Age, sex, dialysis duration, prevalence of diabetes and serum albumin concentrations were not significantly different according to the presence of absolute iron deficiency. Absolute iron deficiency was significantly related to the CACS (P<0.05). Patients with absolute iron deficiency had a significantly lower Kaplan–Meier survival rate for 3-year CV death than patients without absolute iron deficiency (82.2% vs 90.9%; log-rank test, *P*<0.05). However, there was no significant difference in survival for 3-year all-cause death between the two groups. After adjusting for age, sex, diabetes, dialysis duration, serum albumin, C-reactive protein and hemoglobin, absolute iron deficiency was a significant predictor for 3-year CV mortality (hazard ratio: 2.08, P<0.05), but not for 3-year all-cause mortality.

Conclusions: Absolute iron deficiency is a significant predictor for the CACS and CV mortality, but not for all-cause mortality in patients on dialysis.

Funding: Private Foundation Support

TH-PO254

Coronary Artery Calcification Is Associated with Low Kt/Vurea and Extracellular Fluid Excess in Patients on Hemodialysis

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Background: An insufficient dialysis dose and extracellular fluid excess are independent predictors of cardiovascular morbidity in patients on hemodialysis. We studied the associations among coronary artery calcification, Kt/Vurea, and body composition in patients on hemodialysis.

Methods: The Agatston coronary artery calcium score (CACS), postdialysis body composition using bioelectrical impedance device, and clinical data including Kt/Vurea and predialysis β2-microglobulin (β2M) at enrollment, were assessed in patients on hemodialysis. The patients were classified into two groups according to a CACS ≥400 or a CACS <400, and intergroup differences were analyzed using the Wilcoxon test or the x^2 test, as appropriate. Linear regression analyses were performed to identify the risk factors for CACS.

Results: In all patients (n=324), age, the dialysis duration, the diabetes prevalence, and the CACS were 69±12 years, 116±105 months, 133/324 (41.0%), and 763 (155–2491), respectively. Patients with a CACS ≥400 (n=208) were older (72±11 vs. 66±14 years), had a longer dialysis duration (123±109 vs. 104±98 months), had a higher diabetes prevalence (46.6 vs. 31.0 %), serum phosphate concentrations (5.5±1.5 vs. 5.1±1.3 mg/dL), extracellular water/total body water (ECW/TBW) (0.49±0.03 vs. 0.47±0.03), and overhydration (OH) (1.2±1.5 vs. 0.7±1.1 L), and had lower Kt/Vurea (1.43±0.24 vs. 1.64±0.54) than patients with a CACS <400 (n=116), (*P*<0.05). Serum albumin, magnesium, C-reactive protein, and albumin-adjusted calcium levels were not significantly different between the two groups. In simple linear regression analyses, age, dialysis duration, diabetes, smoking, serum phosphate, ECW/TBW, and OH were significantly associated with the CACS (all *P*<0.05), and β2M showed marginal significance (*P*=0.06). Multiple linear regression analysis adjusted for age, dialysis duration, and diabetes showed that Kt/Vurea, β2M, and ECW/TBW were risk factors for CACS (all *P*<0.05). After additional adjustment for serum phosphate and smoking, only Kt/Vurea (β: −0.16) and ECW/TBW (β: 0.12) were significant predictors for CACS (both *P*<0.05).

Conclusions: Lower Kt/Vurea and extracellular fluid excess are independently associated with coronary artery calcification in patients on hemodialysis.

Funding: Private Foundation Support

TH-PO255

Association Between Magnesium, Erythropoietin Resistance, and Mortality: The Japanese Dialysis Outcome and Practice Pattern Study (J-DOPPS) Study

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Background: Limited data are now available to evaluate the relationship between serum magnesium level, anemia, and mortality in the dialysis population.

Methods: Using data from the Japanese Dialysis Outcomes and Practice Patterns Study (J-DOPPS) phases 5 and 6, we analyzed the association between serum magnesium (s-Mg) levels and the erythropoietin resistance index (ERI) as the primary outcome. To estimate the longitudinal relationship, a mixed-effect model was used with ERI at each 4-month period as the dependent variable, quintiles of s-Mg at the previous 4-month period as the independent variable. We also examined the all-cause and cardiovascular disease (CVD)-related deaths as secondary outcomes by Cox regression with quintiles of s-Mg at baseline.

Results: Of the 4776 participants in J-DOPPS, 1650 were included in the analysis. The median of s-Mg at baseline was 2.5 mg/dL. A significant linear association of s-Mg with ERI (p for trend < 0.001) was revealed (Figure). The highest quintile of s-Mg was significantly associated with lower incidence of all-cause mortality (Table) and deaths due to CVD events compared to the middle (reference) quintile.

Conclusions: We observed that lower s-Mg levels subsequently induced higher ERI and that mild higher s-Mg levels predicted good rather than poor outcomes in Japanese hemodialysis patients. Adjustment of s-Mg levels may be proposed as a new strategy at low cost and risk to reduce the risk of premature mortality.

Funding: Commercial Support - Kyowa Kirin Co, Ltd.

Relationship between the all-cause deaths and serum magnesium.

Outcome	Mg quintiles (mg/dL)	Incident rate (/100 PYs)	Crude analysis HR (95%CI)	Adjusted analysis HR (95%CI)
All-cause deaths	Q1 (≤2.1)	5.1	0.9 (0.6. 1.5)	0.6 (0.4. 1.1)
	Q2 (2.2 - 2.3)	6.3	1.2 (0.8. 1.8)	1.2 (0.8. 1.8)
	Q3 (2.4 - 2.5)	5.4	Reference	Reference
	Q4 (2.6 - 2.7)	4.1	0.8 (0.5. 1.2)	0.8 (0.5. 1.4)
	Q5 (2.8 ≤)	2.8	0.8 (0.5. 1.2)	0.6 (0.4. 1.0)

Mg, magnesium; Pys, person-years; HR, hazard ratio; CI, confidence interval.

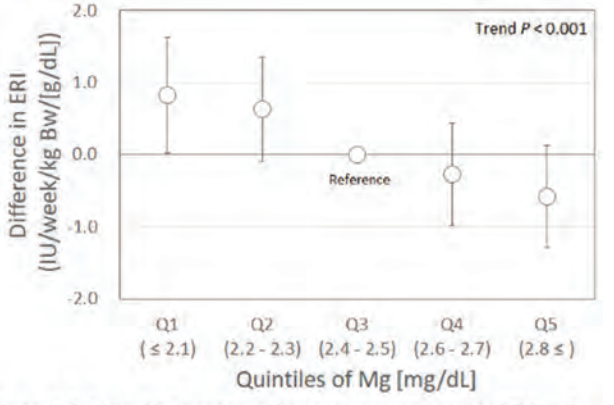

Figure 1. Relationship between erythropoietin resistance index (ERI) and quintiles of serum magnesium (Mg). Point estimates and 95% confidence intervals of between-group difference with Q3 as the reference are presented.

TH-PO256

Anticoagulant and Antiplatelet Use and Risk of Serious Bleeding Events Among PDOPPS and DOPPS Patients Receiving Peritoneal or Hemodialysis, 2009-2022

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Background: Risk of serious bleeds among patients receiving dialysis is higher than the general population and may increase with the use of oral anticoagulant (OAC) and antiplatelet therapies (APT). The rate of bleeding in patients on OAC and APT between dialysis modalities are not well reported.

Methods: Using data from the Dialysis Outcomes and Practice Patterns Study (DOPPS; 2009-2022) and Peritoneal DOPPS (PDOPPS; 2014-2022), we describe OAC and APT use among patients receiving hemodialysis (HD) or peritoneal dialysis (PD) and present event rates of bleeding events that led to death or inpatient hospitalization, per 100 person-years, stratified by dialysis type, and use of OAC or APT.

Results: Overall, 27,612 received HD and 5,288 PD. OAC (9% vs. 4%) and APT (10% vs. 7%) use was higher among patients receiving HD vs. PD, and >99% of all OAC use was warfarin. In both modalities, the rates of non-fatal, fatal bleeding events and hospitalizations due to any bleed or GI bleed were higher for patients prescribed (vs. not) OAC and APT (Table). First hospitalization bleeding rates occurred 2 and 3 times more often among HD patients and PD patients using OACs (compared to not), respectively. Those using APTs were observed to have a 25% (HD) and 40% (PD) increase (compared to not) in first hospitalization rate. The same trend was observed for recurrent hospitalizations due to any bleed and fatal bleeds.

Conclusions: OAC and APT use was ≤10% in both populations. Serious bleeding rates were higher among patients prescribed OAC and APT regardless of dialysis modality and differences in bleeding rates between treatment groups were larger among PD patients. Results underscore the need for strategies to reduce bleeding in patients on dialysis requiring anticoagulation, including novel agents with improved safety profiles.

Funding: Commercial Support - Merck and Co., Inc.

Rate of serious bleeding event types by anticoagulant or antiplatelet use among patients with ESKD receiving peritoneal or hemodialysis in DOPPS (2009-2022) and PDOPPS (2014-2020)

Bleeding Event Rate (per 100 person-years)	Hemodialysis		Peritoneal Dialysis		Hemodialysis		Peritoneal Dialysis	
	Anticoagulant Use				Antiplatelet Use			
	No	Yes	No	Yes	No	Yes	No	Yes
	24997 (91%)	2615 (9%)	5082 (96%)	205 (4%)	24941 (90%)	2671 (10%)	4931 (93%)	357 (7%)
First hospitalization due to any bleed type	8.86	7.93	9.78	11.59	8.13	5.09	3.94	5.62
First hospitalization due to GI bleed	2.10	4.71	1.72	6.10	2.26	3.09	1.68	4.66
Recurrent hospitalizations due to any bleed type	4.66	9.36	5.54	14.17	4.94	6.87	5.70	7.89
Recurrent hospitalizations due to GI bleed	2.66	5.47	2.45	7.09	2.77	4.22	2.33	6.76
Death due to any bleed type	0.64	1.08	0.48	1.69	0.67	0.83	0.52	0.58

TH-PO257

Hemoglobin (Hgb) Variability and Target Range in Hemodialysis (HD) Patients

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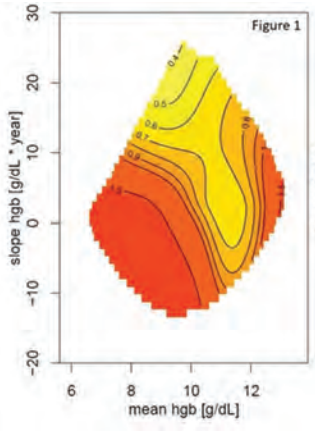
Background: Based on randomized controlled trials in CKD patients (pts), in the US, a hgb target range between 10 to 11 g/dL is the mandated. Retrospective studies have shown lower hospitalization and death rates with higher hgb, and a higher risk of death with increased hgb variability. We investigated in this retrospective cohort study of incident HD pts receiving erythropoietin stimulating agent (ESA), the association between all-cause mortality hazard ratio (HR), hgb variability and level.

Methods: We studied a cohort of incident HD pts initiated with a long-acting ESA (Mircera; Vifor) within the first 90 days. In pts with at least twelve hgb values over the 6-months baseline period we quantified mean hgb and variability, as either standard deviation (sd) or slope of a linear model, as metrices. We built proportional hazard models including both mean and variability metrices to predict HR over the following 18 months, adjusted for race, sex, age, diabetes, serum albumin and phosphorus. We then built spline functions to depict HR in a bivariate fashion as a function of baseline mean hgb level and variability.

Results: We studied 64,042 pts out of 517,860 pts in Fresenius Kidney Care clinics. A range between 10.5 and 12.5 g/dL associated with the lowest HR when accounting for variability of hgb during the baseline period (**Figure 1** and **2**). An increasing slope and increased variability seem to associate with improved survival at low hgb levels.

Conclusions: A wider and upwards shifted hgb target range is associated with favorable mortality outcomes, independent of variability or systematic trends. Hgb variability, possibly a resultant of responsiveness to therapy, confers a survival advantage at lower and higher levels of mean hgb Limitations of retrospective research apply. Adequately powered and designed experimental studies are needed.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd



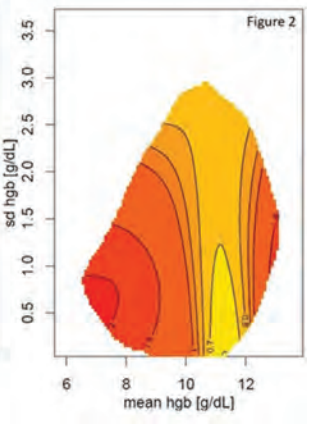


Figure 1: HR as a function of baseline hgb mean and slope. **Figure 2:** HR as a function of baseline hgb mean and sd.

TH-PO258

Using Machine Learning to Construct a Predictive Model for Hemoglobin in Maintenance Hemodialysis Patients

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Background: Constructing prediction models of hemoglobin concentration by machine learning method, to assist clinicians to make clinical decisions in order to achieve individualized and precise treatment for maintenance hemodialysis (MHD) patients with renal anemia.

Methods: The medical records of maintenance hemodialysis patients from January 1, 2021 to January 1, 2023 in Sichuan Provincial People's Hospital were included. Demographic characteristics, test results, medication orders were included to constructed the prediction models. Selection of characteristic variables were mainly based on previous published articles, and all medical data were derived after desensitization. Data were randomly divided into training set (80%) and test set (20%) after desensitization, filling, deletion and other preprocessing. Ten machine learning methods (Linear Regression, K Neighbors Regressor, Support Vactor Regression, Ridge Regression, Lasso Regression, eXtreme Gradient Boosting Regressor, Random Forest Regressor, AdaBoost Regressor, Gradient Boosting Regressor, Bagging Regressor) were used to construct prediction models. Model performance was assessed by assessing the difference between predicted and true values and by fitting with internal validation.

Results: The medical records of 495 patients were finally included. The study included 56% male with a median age of 60 years old. The patients' dry weight was 58.7±11.3 kg and their weight before dialysis was 61.3±11.6 kg. In terms of laboratory results, the patients had a hemoglobin level of 109(96~118) g/L, serum albumin level of 40.8 (38.1~43.9)g/L, serum ferritin of 210.3(130.0~359.4)ng/mL and an average transferrin saturation level of 26.2±17.3 %. The patients' median dose of intravenous iron supplements was 500 mg/month, and their median dose of erythropoiesis-stimulating agents was 5 (4 to 6.25)×10^4 U/month. Ten machine learning models were used for modeling, Random Forest showed better prediction performance compared with other models, with an RMSE of 9.41 and a coefficient of determination R^2 of 0.65 for the training set.

Conclusions: The machine learning-based hemoglobin prediction model of MHD patients can be used to predict hemoglobin concentration to a certain extent, which can contribute to the individualized and precise management of anemia in maintenance hemodialysis patients.

Funding: Clinical Revenue Support

TH-PO259

Dynamic Predictions of All-Cause Mortality in Incident Hemodialysis Patients with Extended Joint Models Adjusting for Albumin Trajectory and Competing Risks

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Background: Joint models (JM) provide individual patient dynamic risk predictions based on the association between longitudinal biomarkers and mortality. We explore extensions to JM methodology performed for the first time with hemodialysis (HD) clinical trial data.

Methods: We evaluated the association of albumin with all-cause mortality in incident HD patients followed over 8 years in the Initiating Dialysis Early And Late trial. To account for skewness/outliers in albumin, novel JM with mixed effects sub-model with skew-normal, *t* and skew-*t* errors were compared with conventional JM under normal distribution. Furthermore, we adjusted for the competing event of transplantation using Weibull cause-specific hazards. The dataset (N=315 patients) was randomly split into training dataset (3/4, N=236) for model fitting and validation dataset (1/4, N=78) to infer predictive performance. We obtained 12-month individual patient survival predictions from all JM at cut-offs 1, 1.5 and 2 years utilizing albumin trajectory and baseline risk factors.

Results: A median of 12 albumin records per patient with 24% and 19% event rates for death and transplantation ensured convergence of all 12 joint models. Albumin hazard ratio of death remained robust (0.89 to 0.90), suggesting significant inverse relationship between albumin and death adjusted for baseline confounders and the competing event of transplantation. JM presented excellent survival prediction accuracy in the validation dataset which improved with longer follow-up. JM with competing event outperformed JM with survival only (area under the curve (AUC) ranges at 1, 1.5 and 2 years: 0.80-0.84 vs 0.79-0.83, 0.86-0.90 vs 0.84-0.88, 0.96-0.97 vs 0.96-0.97), across all distributional models for albumin. Prediction performance of all JM surpassed classical Cox model with baseline albumin (AUC = 0.71, 0.77, 0.93). Results were confirmed by a simulation study.

Conclusions: Our first comprehensive study of JM extensions in incident HD patients indicates its great potential for dynamic personalized survival prediction. Robustness of estimates to deviations from normality and higher predictive accuracy when adjusting competing events contribute to JM superiority over the classical Cox approach.

Funding: Commercial Support - Baxter Healthcare Corporation

TH-PO260

Real-Time Dual Prediction of Intradialytic Hypotension and Hypertension Using an Explainable Deep Learning Model

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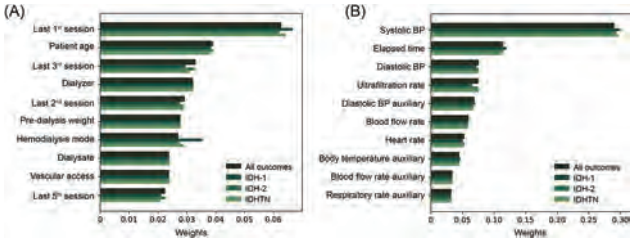
Background: Intradialytic hypotension (IDH) and hypertension (IDHTN) are associated with poor outcomes in hemodialysis patients. However, there is currently no real-time predictive model for dual outcomes. This study aims to develop an explainable deep learning model using a sequence-to-sequence-based attention network to simultaneously predict IDH and IDHTN.

Methods: Electronic health records of 11,110 hemodialysis patients were utilized, comprising 302,774 sessions. The data was divided into training (70%), validation (10%), and test (20%) sets using randomization. IDH-1 was defined as nadir systolic blood pressure (BP) <90 mmHg, IDH-2 as a decrease in systolic BP ≥20 mmHg and/or a decrease in mean arterial pressure ≥10 mmHg, and IDHTN as an increase in systolic BP ≥10 mmHg within 1 hour. The temporal fusion transformer (TFT)-based model was developed and compared with other machine learning models, including recurrent neural network, light gradient boosting machine, random forest, and logistic regression, in terms of model performance measured by receiver operating characteristic curve (AUROC) and area under the precision-recall curves (AUPRC).

Results: The TFT-based model outperformed other models with AUROCs of 0.953 (0.952–0.954), 0.892 (0.891–0.893), and 0.889 (0.888–0.890) for predicting IDH-1, IDH-2, and IDHTN, respectively. The AUPRCs of the TFT-based model for the outcomes were higher compared to other models. Key predictors included age, previous session, systolic BP, and elapsed time.

Conclusions: The developed TFT-based model enables real-time prediction of both IDH and IDHTN while providing explainable variable importance.



Mean weights of time-invariant and time-varying features from the attention module in the model. (A), Weights of time-invariant features. (B), Weights of time-varying features. BP, blood pressure.

TH-PO261

Effect of Antioxidants on Oxidative Stress, Endothelial Dysfunction, Inflammatory Markers, and Carotid Intima Media Thickness in Maintenance Hemodialysis and Renal Transplant Patients

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Background: Cardiovascular disease (CVD) is a major cause of morbidity and mortality in dialysis patients. Various non-traditional factors have been proposed for the increased incidence of CVD. N-acetylcysteine (NAC) serves as an antioxidant, acts on atherosclerosis and also improves the endothelial functions. This study was designed to assess the effects of three months of NAC therapy on oxidative stress, endothelial dysfunction, inflammatory markers and carotid intima media thickness in maintenance hemodialysis and renal transplant patients.

Methods: Doppler was done to assess endothelial function by flow mediated dilatation (FMD) of the brachial artery and carotid arterial intima media thickness (CIMT). Brachial artery was imaged during reactive hyperemia (endothelium-dependent, flow-mediated dilatation, FMD) and during nitroglycerine-mediated dilatation (NMD, endothelium-independent). Oxidants (Melondialdehyde, MDA) and antioxidants (Total Antioxidant Status) were measured. NAC 1200 mg was given in two divided doses for three months. Parameters were repeated after three months of NAC therapy.

Results: 220 hemodialysis, 135 renal transplant patients were enrolled. Hemodialysis patients had higher serum homocysteine level which was significantly reduced after three months of NAC (25.7±3.86 vs 13.9±3.01 µmol/L after NAC, p<0.001). At baseline they had a high hsCRP (05.6±1.01 mg/dl) which reduced significantly (02.1±0.43 mg/dl, p<0.001) after NAC. CIMT was significantly reduced after three months of NAC (0.49±0.12mm). FMD of brachial artery endothelium was impaired at baseline (0.34±0.07mm, 0.69±2.11%), significant improvement after 3 months of NAC (0.41±0.11mm, 10.12±2.86%, p<0.001). Elevated baseline oxidative stress markers (MDA) compared to levels after NAC (16.21±10.34 vs 09.31±4.34 nmol/ml, p<0.001). Antioxidant status was significantly low at baseline (1.03±0.21 mmol/l) compared to antioxidant status after NAC (1.41±0.24 mmol/l, p=0.01). Similar findings were seen in the post renal transplant patients.

Conclusions: CKD patients have endothelial dysfunction and oxidative stress which begins early, progresses during dialysis and persists after renal transplantation. With three months of therapy, NAC significantly reduces the oxidative stress, inflammatory markers and improves the endothelial function.

TH-PO262

Experience Comparing the Use of Citric Acid Solution (CD) with L-Ascorbic Acid (Vitamin C) to Simple Citric Solution in Patients with ESRD Under Hemodialysis (HD)

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Background: The purpose of the study is to record the experience of comparing the use of CD solution with Vitamin-C in relation to the use of pure CD solution in patients with ESRD under HD.

Methods: 45 patients with ESRD under HD (40 new entrants) receiving CD solution with vitamin-C (2g/lt) for a period of 12 months were compared with 26 patients (18 new entrants) of the same weight who received plain CD solution. Changes in heparin dose as well as the anemia profile of the patients were recorded.

Results: In the vitamin C solution the initial cumulative dose of heparin 1818±659.28 iu (24 iu/kgrBW) to 3323.52±1467.79 iu (44 iu/kgr/BW) at 12 months. With no observed thrombotic events or bleeding tendency, the heparin dose was significantly reduced from classically recommended doses (loading dose 30-50 IU/kgBW and then 10 IU/kgBW/hour). A corresponding observation was also noted in pure CD (29 iu/kgrBW beginning-39 iu/kgrBW end). Hb and Hct increased significantly (10.63±1.55 start-11.79±0.91 end, p<0.05, 32.25±4.45 start-36.5±2.92 end, p<0.05) with constant weekly dose of erythropoietin (14000±9500 iu start-14000±10000 iu end, p=NS) and constant ferritin levels (526.73±498.72 iu start-690.44±470.32 iu end, p=NS). The above notice was combined with a significant reduction in monthly iron administration (200 mg monthly final dose). In CD without Vitamin-C we had corresponding observations with a consistently significantly higher dose of monthly iron administration (400-500 mg final dose).

Conclusions: Our findings suggest that the use of both solutions provides anticoagulation with a significant decrease in heparin while simultaneously increasing hemoglobin with a fixed dose of erythropoietin. The addition of vitamin C is associated with reduced monthly iron intake.

TH-PO263

Comparison of Citrate Dialysate in Pre- and Post-Dilution Online Hemodiafiltration: Effect on Clot Formation and Adequacy of Dialysis in Hemodialysis Patients

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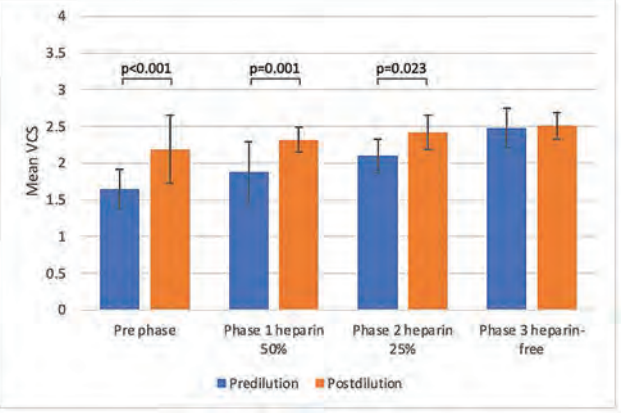
Background: Citrate dialysate (CD) has been used successfully in conventional hemodialysis and continuous renal replacement therapy but has never been compared between pre- and post-dilution online hemodiafiltration (oL-HDF). Therefore, we investigated the efficacy, metabolic changes, and quality of life of citrate anticoagulation for oL-HDF in the maintenance of hemodialysis patients in both modes.

Methods: Eight dialysis patients were treated with CD for 4 weeks in each phase. The visual clotting scores were investigated as the primary endpoints. The adequacy of dialysis, laboratory parameters, and quality of life were measured as secondary objectives.

Results: The mean clotting scores in the pre-dilution mode were significantly lower than in the post-dilution and all phases except in the heparin-free phase ($P < 0.001$ in baseline phase, $P = 0.001$ in phase 1, and $P = 0.023$ in phase 2). The quality of life related to physical in the post-dilution mode was significantly higher than in the pre-dilution mode in baseline and phase 1 ($P = 0.014$ and 0.004 at baseline and phase 1, respectively). The metabolic changes were not different in both modes.

Conclusions: Citrate dialysate allows decrease or discontinuation of anticoagulation in both the pre- and post-dilution mode of oL-HDF without significant side effects.

Funding: Government Support - Non-U.S.



TH-PO264

Citrate-Acidified Dialysate Requires Less Heparin Use Without Affecting Mineral Metabolism Negatively

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Background: Heparin is used to prevent clotting in hemodialysis, but may cause bleeding, thrombocytopenia, and skeletal complications. Citrate-acidified dialysate (CAD) compared to acetate-acidified dialysate (AAD) may improve hemodynamic stability and reduce inflammation. Citrate has calcium complexing properties in regional anticoagulation, yet its use may affect mineral metabolism negatively. We studied the effect of a dialysis bath with low concentrations of citrate on heparin use and mineral metabolism.

Methods: 207 prevalent ESRD pts. (182 with high flux dialysis (HD), 25 with post dilution hemodiafiltration (HDF)) were followed for 48 weeks after switching from AAD (3mmol/l acetate) to CAD (0.8 mmol/l citrate, 0.3 mmol/l acetate; MTN, Germany). We monitored heparin consumption, KT/V, CRP, iPTH, phosphate, magnesium, and calcium as well as side effects.

Results: The cohort comprised 127 males and 81 females, mean age 71.6 years (range 25 – 95). Mean treatment time was 254 minutes per session (range 180– 00) and mean blood flow at baseline 360 mL/min (range 250 -420) vs. 254 minutes (range 180–300) and 370 ml/min (range 240-420) at 48 weeks. Mean initial heparin dosing per session was 5171 IU (95%CI 4836-5507) in HD and 6720 IU (95%CI 5920-7520) in HDF. This could be reduced step by step to a mean of 2985 IU (95%CI 2723-3246) in HD and 3375 IU 95%CI 2867-3883) in HDF (after 48 weeks ($p \leq 0.05$) in HD pts. than in HDF pts. at start. It increased during the observation in HD (8.0 vs. 15.0, n.s. after 48 weeks), but not in HDF (CRP start 2.7mg/l vs. 4.2mg/l after 48 weeks, n.s.). In neither group magnesium, calcium, phosphate, iPTH nor KT/V changed significantly. During the observation period 7 pts. (3.4%) were intolerable to CAD, 11 withdraw for unknown reasons (5.3%), 11 pts. (5.3%) left the clinic, 1 patient switched to CAPD (0.5%), 3 (1.4%) were transplanted and 32 died (15.38%).

Conclusions: Under CAD heparin-dosing could be reduced markedly. This may be beneficial for the patient and reduce treatment costs. Long-term treatment with a low-concentration CAD was well tolerated and did not exacerbate secondary hyperparathyroidism. Further long-term studies are ongoing to assess effects on calcification, morbidity, and mortality.

TH-PO265

To Study the Clinical and Biochemical Outcomes of Citrate-Based Dialysate in Hemodialysis Compared with Bicarbonate-Based Dialysate in a Tertiary Care Hospital

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Background: The study to compare the effects of Citrate-based dialysate with Bicarbonate-based dialysate on systemic haemodynamics, dialysis efficiency, serum calcium, phosphate and bicarbonate levels.

Methods: The study was conducted in 25 ESRD patients undergoing HD with bicarbonate dialysate initially for period of 3 months followed by citrate dialysate for 3 months. Parameters were recorded at start, 3 months of HD with bicarbonate dialysate and HD with citrate dialysate at 6 months. Predialytic, intradialytic and postdialytic BP was recorded at each HD session. The mean of all BP readings was calculated for both groups. The clinical and lab parameters Kt/v, calcium, phosphate and bicarbonate levels were compared among both groups

Results: The mean Predialytic SBP in bicarbonate is 153.84 ± 16.80 mmhg, in Citrate dialysate is 140.24 ± 16.63 mmhg($p<0.001$), mean Predialytic DBP in bicarbonate is 87.16 ± 10.75 mmhg, in citrate dialysate is 79.96± 8.63 mmhg ($p<0.001$). The Intradialytic SBP and DBP were lower in pts.undergoing citrate vs bicarbonate. The mean Intradialytic SBP in bicarbonate is 148.56 ± 15.50 mmhg vs 135.92 ± 15.29 in citrate($p=0.0053$). The mean Intradialytic DBP in bicarbonate is 84.12 ± 12.02 mmhg vs 75.92 ± 8.94 mmhg in citrate($p=0.0086$). The mean Postdialytic SBP in bicarbonate is 143.56 ± 17.50 mmhg vs 129.24 ± 15.46 in citrate($p=0.0035$). The mean Postdialytic DBP in bicarbonate is 82.40 ± 10.07 mmhg vs74.20 ± 7.04 mmhg in citrate(p value=0.0016). The mean Kt/v in bicarbonate is 1.2 ± 0.06 vs 1.33± 0.06 in citrate (p value<0.001). The mean calcium level in bicarbonate is 9.03 ± 1.03 mg/dl vs 8.51 ± 0.97 mg/dl in citrate($p=0.07$), the phosphate in bicarbonate dialysate is 5.53 ± 1.04 vs 4.76 ± 1.72 in citrate (p value=0.06). The mean HCO3 level in bicarbonate dialysate is 16.08 ± 1.39 vs 17.75 ± 1.34 in citrate group(p value<0.001)

Conclusions: Citrate dialysate can be good alternative for the standard bicarbonate based dialysate as it provides significant advantages in improvement in Pre, Intra And Postdialytic BP, better dialysis efficiency, improved acid base balance and lower phosphate levels.

TH-PO266

The Association of Dialysate Bicarbonate with Cardiac Arrhythmia in the Monitoring in Dialysis (MiD) Study

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Background: Sudden death accounts for half of all cardiovascular-related mortality among patients receiving maintenance hemodialysis (HD) and occurs more frequently on days that patients undergo HD. Higher dialysate bicarbonate (D_{BIC}) may predispose to alkalemia and arrhythmogenesis. We tested if higher D_{BIC} is associated with cardiac arrhythmia, and if this is modified by serum bicarbonate (S_{BIC}).

Methods: Using data from the Monitoring in Dialysis study, we analyzed session-level data over a 12-month period from 66 patients with implantable loop recorders (ILR). We fit logistic regression and negative binomial mixed effects regression models to assess the association of D_{BIC} with the presence and frequency of reviewer confirmed arrhythmia (RCA) events (ILR identified or patient marked event in which a manual review of the stored ECG tracing confirmed the presence of atrial fibrillation, supraventricular tachycardia, sinus tachycardia with rate >130 beats per minute, ventricular tachycardia, asystole, or bradycardia) in the intra- and inter-dialytic period.

Results: Mean age was 56 ± 12 years, 70% were male, 53% were Black, and 35% were Asian. There were 9,718 RCA events over 3,655 HD sessions. There were fewer RCA episodes associated with D_{BIC} >35 compared to 35 mEq/L in unadjusted and adjusted models (IRR 0.45 (0.27, 0.75) and aIRR 0.54 (0.30, 0.97), respectively). Otherwise no associations between D_{BIC} and arrhythmia were identified. No results were modified by the inclusion of S_{BIC} in the model.

Conclusions: We observed a lower frequency of RCA with higher D_{BIC}, contrary to our original hypothesis. Within RCA, a majority of events were atrial arrhythmia. Validation of these findings in larger studies is required, with further need for interventional studies to explore the optimal D_{BIC} level.

Funding: NIDDK Support

Table: Association of dialysate bicarbonate with arrhythmia – session to session models (repeated measures negative binomial regression). Adjusted for age, sex, race, dialysis vintage, vascular access, and pre-dialysis serum bicarbonate.

Arrhythmia Subtype	Dialysate Bicarbonate (mEq/L)			
	<35 vs ≥35 aIRR (95% CI) n/N p-value[2]	>35 vs ≥35 aIRR (95% CI) n/N p-value[2]	<35 vs >35 aIRR (95% CI) n/N p-value[2]	n/N p-value[1]
Reviewer Confirmed Arrhythmia	0.43 (0.08, 2.29) 585/249 vs. 1221/549 0.32	0.54 (0.30, 0.97) 1250/388 vs. 1221/549 0.04	0.79 (0.14, 4.36) 585/249 vs. 1250/388 0.79	3036/1186 0.09
Reviewer Confirmed Arrhythmia Subtypes				
Reviewer Confirmed Atrial Arrhythmia	0.49 (0.08, 2.83) 342/249 vs. 862/549 0.43	0.47 (0.20, 1.13) 547/388 vs. 862/549 0.09	1.03 (0.16, 6.72) 342/249 vs. 547/388 0.98	1751/1186 0.21
Reviewer Confirmed Ventricular Arrhythmia	2.30 (0.91, 5.83) 72/249 vs. 58/549 0.08	2.60 (0.97, 6.93) 114/388 vs. 58/549 0.06	0.89 (0.32, 2.47) 72/249 vs. 114/388 0.82	244/1186 0.09

Abbreviations: aIRR = adjusted incidence rate ratio; n/N = number of events / number of sessions.
[1]Overall p-value from repeated measures model F test.
[2]Pairwise comparison p-values from t-tests (not adjusted for multiple comparisons).

TH-PO267

Dialysate Buffer in Hemodialysis: Effect of Practice Patterns on Serum PTH

Pablo A. Urena Torres, Pascal Seris, Anne Kolko-Labadens, Charles Chazot. *Aura Paris, Paris, France.*

Background: We report the analysis of 3 dialysate (D) acidic buffers on serum PTH in 4 dialysis units in Paris (France) area.

Methods: Data from prevalent hemodialysis (HD) patients (pts) treated in 4 units were collected in the 4th quarter 2022 and analyzed with Kruskal-Wallis and stepwise logistic regression tests. The biology lab is common to the 4 units. PTH was assessed using the Architect Intact PTH assay®.

Results: The 529 pts were 64 y.o. with 35% females, dialysis vintage: 47 months, Charlson index: 10. The acidic buffers were acetate (30.7%), hydrochloric acid (HCl) (35.7%) and citric acid (citrate) (33.6%). Pts on acetate were significantly younger (59 years) versus 67.5 and 66 years on HCl and citrate ($p=0.001$), with a lower Charlson index (9 versus 10 (0.001). Pts on HCl had significantly lower serum PTH levels; serum magnesium was significantly lower in citrate group; calcium, phosphate, native vitamin D were not different (Table 1). Muscle cramps during the dialysis were found in 10.2% (citrate), 8.5% (HCl) and 6.2% (acetate, $p=0.027$). The D calcium is reported in Table 1. The proportion of pts on calcimimetics and active vitamin D did not differ between groups. Factors associated with a PTH >612 pg/ml were age (-0.012, $p<0.04$), acetate buffer (0.065, $p<0.001$) and calcimimetic prescription (0.76; $p<0.001$). Conversely, only dialysis vintage was associated with a PTH < 130pg/ml (0.07; $p=0.0066$).

Conclusions: The use of citrate D in this cohort was not associated with a higher PTH compared to pts on acetate or HCl. The large prescription of D calcium at 1,65 mmoles/l in the citrate group may have helped to avoid low ionized calcium. Higher muscle cramps and lower magnesium were findings already reported with the use of citrate D and confirmed in this cohort. Dialysis with citrate or HCl are possible alternatives when avoiding acetate buffer is wanted. Increasing D magnesium to avoid cramps remains to be studied.

	Acetate	Citrate	HCl	p
n	162	186	176	
Calcium (mmol/l)	2,20 (2,13-2,29)	2,19 (2.12-2,26)	2,10 (2,12-2,27)	NS
Phosphate (mmol/l)	1,31 (1,06-1,59)	1,315 (1,13-1,55)	1,30(1,15-1,545)	NS
Magnesium (mmol/l)	0.90 (0,83-0;97)	0.86 (0,77-0;93)	0.88 (0,805-0,95)	< 0.001
PTH (pg/ml)	526 (324-861)	421 (226-671)	318 (189-582)	< 0.001
25OHD (ng/ml)	39,5 (29,5-50,28)	40,54 (33,37-49,67)	39,90 (34,37-42,22)	NS
Bone-specific alkaline phosphatase (ng/ml)	28.9 (20.3-49.1)	23.0 (17.4-35.1)	26.6 (18.1-40.7)	NS
Calcium dialysate (mmol/l)	-	-	-	
1.25	0.6 %	0.6 %	1.1 %	
1.50	75.9 %	0 %	65.5 %	
1.65	0 %	72.9 %	0 %	
1.75	23.5 %	26.6 %	33.5 %	

TH-PO268

Asymptomatic Heartbeat Irregularities (AHbI) During Hemodialysis (HD) Are Associated with Decreased Short-Term Survival

Dan Sapoznikov, Rebecca Backenroth, Michal Dranitzki Elhalel, Dvora Rubinger. *Hadassah University Medical Center, Jerusalem, Israel.*

Background: Intradialytic AHbI are not well defined and are of unknown significance.

Methods: Beat-to-beat systolic blood pressure (SBP) and interbeat interval (IBI) were monitored during regular HD sessions in 83 age-matched patients (Pt). AHbI were defined as ≥10 irregular beats on a 4hr recording. Hemodynamic variability indices were assessed using Finometer device and Beatscope software.

Results: AHbI were detected in 25 Pt (AHbI (+)). The representative clinical, laboratory and hemodynamic data in AHbI (+) and in Pt with regular beats (AHbI(-)) are listed in Table 1. There were no statistically significant differences between groups regarding the proportion of diabetes, hypertension, ischemic heart disease, SBP, intradialytic hypotension, PTH level or ultrafiltration rate. Kaplan-Meier analysis showed a significnant decreased survival at 2y in AHbI(+) (Figure 1).

Conclusions: 1.Intradialytic AHbI are associated with cardiovascular risk factors and a higher plasma phosphate level, suggesting a link between mineral metabolism and heart disease. 2. In AHbI (+), diminished post HD plasma potassium change combined with decreased IBI and increased sdCO suggest a tendency to hemodynamic instability leading to higher mortality. The nature and the long term effects of the AHbI remain to be further explored.

Table 1.

	AHbI (+) (n=25) Age 65±9 y	AHbI (-) (n=58) Age 66±10 y	p
Male gender (n)	22	34	0.009
History of smoking (n,%)	17 (68)	19 (33)	0.003
Left ventricular systolic dysfunction (n,%)	13 (54)	13 (24)	0.008
Peripheral vascular disease (n,%)	18 (72)	28 (48)	0.046
Plasma calcium (mmo/L)* ^	2.25±0.17	2.27±0.17	NS
Plasma phosphate (mmol/L)* ^	1.69±0.37	1.46±0.31	0.004
Plasma potassium decrease after HD (mmol/L)^	1.24±0.56	1.54±0.61	0.039
IBI (msec)**	839 (122)	891 (234)	0.010
sdDBP (mmHg)^^ **	3.7 (0.9)	2.9 (1.3)	0.003
sdCO (L/min)^^ **	0.57 (0.25)	0.44 (0.21)	0.001

* Predialysis: ^mean±SD; **Median (interquartile range); ^^ sd (standard deviation); DBP: diastolic blood pressure; CO: cardiac output.

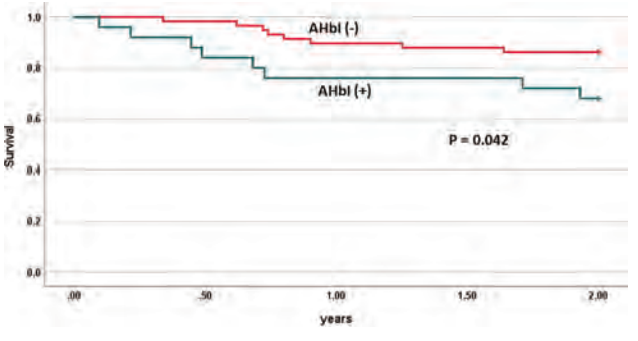


Figure 1.

TH-PO269

Platelet Count Has a U-Shaped Association with Mortality in Hemodialysis Patients: A Multinational Analysis of DOPPS

Xinju Zhao,[1] Li Zuo,[1] Angelo Karaboyas,[3] Roberto Pecoits-Filho.[2] [1]*Peking University People's Hospital, Beijing, China;* [2]*Arbor Research Collaborative for Health, Ann Arbor, MI;* [3]*Arbor Research Collaborative for Health, Ann Arbor, MI.*

Background: Based on the role of platelets in coagulation, clot formation, and systemic inflammation, we utilized data from a very large international cohort study to explore the association of platelet counts with mortality and cardiovascular (CV) death in hemodialysis (HD) patients.

Methods: International data from 13,631 patients enrolled in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phase 5 (2012-2015) were analyzed. Participants were divided into 3 groups according to their platelet counts (low: <100, normal: 100-300, high: >300*10^9). Associations between platelet counts and all-cause and CV mortality were analyzed using Cox regression, adjusted for confounders.

Results: Mean platelet count was 205*10^9/L overall and ranged from 173 *10^9/L in China to 227 *10^9/L in Sweden (figure 1). Overall, 2,463 (18 %) patients died and 948 (7%) died from CV disease. Both low (HR=1.5, 95% CI: 1.2, 1.8) and high (HR=1.2; 95% CI: 1.0, 1.4) platelet counts were associated with higher all-cause mortality after adjustment for covariates (Figure 2); results for CV death were consistent.

Conclusions: Platelet count has a U-shaped association with all-cause and CV mortality in HD patients, and thus may be used as an outcome predictor that is readily available among HD patients.

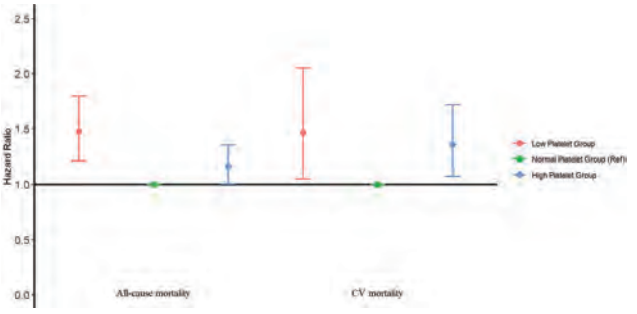


Figure 1. Patients in normal, low, and high platelet groups from 15 countries and areas, A/NZ is for Australia and New Zealand; GCC is for Gulf Cooperation Council (6 countries)

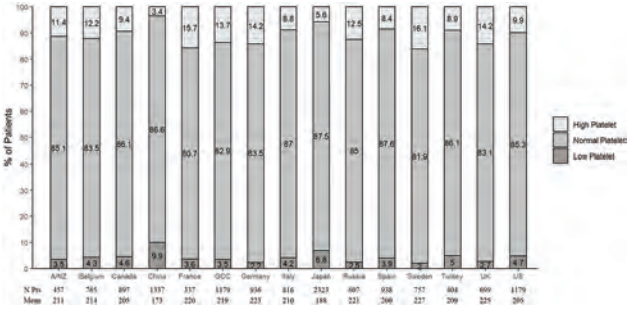


Figure 2. Associations between the platelet counts and all-cause/CV mortality in COX regression model (adjusted for age, gender, BMI, vintage, comorbidities, lab data, Intradialytic weight loss, fistula, primary kidney disease, standard kt/v, urine output < 200 ml/d)

TH-PO270

Clinical Burden and Management of Hyperkalemia in Hemodialysis Centers in China: A Multicenter Retrospective Study (Visualize-HD)

Xinju Zhao, Li Zuo. For the Visualize-HD Study Group. *Peking University People's Hospital, Beijing, China.*

Background: Hyperkalemia (HK) is associated with sudden cardiac death in patients on maintenance hemodialysis (mHD). We aimed to examine HK prevalence, serum potassium (sK) management practices, and mortality data in Chinese HD centers.

Methods: Visualize-HD (NCT05020717) was a retrospective survey conducted in 31 Chinese administrative divisions. Patients aged ≥18 years who were on mHD for ≥3 months were eligible. HD centers were grouped as having high or low HK (sK >5.0 mmol/L) prevalence based on median values. Outcomes were analyzed over 3 years. The primary outcome was risk factors associated with HK prevalence. Secondary outcomes included HK prevalence, sK management practices, and risk factors associated with mortality.

Results: A total of 50,983 patients from 231 centers were included. The age groups 18–44, 45–64, 65–74, and ≥75 years accounted for 18.7%, 46.5%, 23.0%, and 11.8% of patients, respectively; 59.2% were male. Most patients had a dialysis vintage of <5 years (62.2%), used 2.0 mmol/L dialysate potassium (91.8%), were on three times weekly dialysis (68.0%), and had a sK test once every three months (53.9%). Over half of the cohort (55.2%) received renin-angiotensin-aldosterone system inhibitors and 7.7% received potassium-binding drugs. HK occurred in 40.8% of patients; 20.4%, 8.7%, and 3.2% had sK >5.5, >6.0, and >6.5 mmol/L, respectively. Higher HK prevalence was associated with a higher proportion of patients with hyperphosphatemia and lower proportions of elderly patients and those with hypoalbuminemia at the HD center level (all P < 0.05). The 3-year cumulative mortality rate was 21.3%. Over one-third of deceased patients (36.7%) had HK based on their last sK tests. Centers with high vs low HK prevalence had higher mortalities (all-cause: 21.9% vs 20.7%; cardiovascular: 13.5% vs 11.5%, both P < 0.05).

Conclusions: HK is prevalent in Chinese HD centers and is associated with risk factors. Chinese HD centers with higher HK prevalence had increased mortality rates. Long-term sK control is important for improving survival in patients on mHD. Yet, potassium-binding drugs are underused.

Funding: Commercial Support - AstraZeneca

TH-PO271

Readmission After Gastrointestinal Bleeding Hospitalization in Dialysis Patients

Yue Jiao,[1] Belen Alejos,[2] Melanie Wolf,[2] John W. Larkin,[1] Anke Winter,[2] Sheetal Chaudhuri,[1] Manuela Stauss-Grabo,[2] Len A. Usvyat,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux,[6] David C. Wheeler,[3] Peter Stenvinkel,[4] Jürgen Floege.[5] On Behalf of the INSPIRE Core Group. *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]University College London, London, United Kingdom; [4]Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [5]University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany; [6]Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany*.

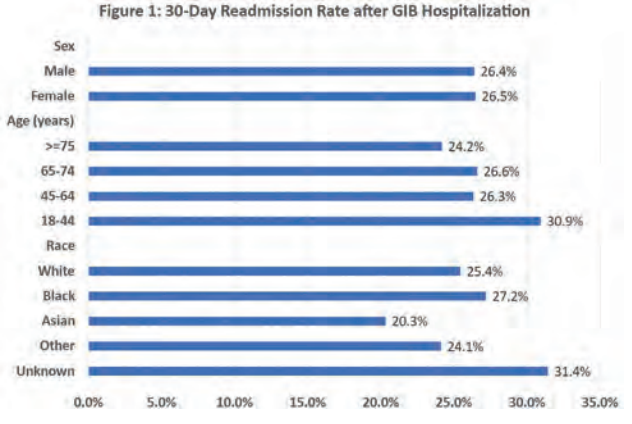
Background: Gastrointestinal bleeding (GIB) is the most common bleeding event in patients on chronic dialysis, and oftentimes leads to hospitalization. The outcomes associated with hospitalization for a GIB are unknown. The INSPIRE collaborative group assessed all-cause hospital readmission rates after a GIB hospitalization among a nationally representative sample of dialysis patients in the United States.

Methods: We used data from adult dialysis patients who had a GIB hospitalization between Jan-2018 to Mar-2021. GIB hospitalizations were defined from primary, secondary, or tertiary discharge diagnosis codes (Zhao et al., AHRQ 2006). All-cause readmission rate considered hospitalizations within 30 days from an index GIB hospitalization.

Results: Among a population of 405,530 patients, there were 19,663 GIB hospitalizations during follow up and 5,196 all-cause readmissions (26.4%) within 30 days of the index GIB hospitalization. On average readmissions occurred within 16.3 days of the index GIB hospitalization. Patients with a GIB hospitalization typically had one readmission event (n=4,365), yet a small proportion of patients had multiple readmissions during follow-up. Readmission rates after a GIB hospitalization were highest for younger patients between 18-44 years old, and those with an unknown or black race (**Figure 1**).

Conclusions: The 30-day all-cause readmission rate after a GIB hospitalization was 26%, and appeared to be highest among younger patients of a black race or those who were missing data on race. These findings act as a benchmark for the nephrology community. Future adjusted analyses are warranted to confirm the results and should consider modality and competing events of death within 30 days of an index GIB hospitalization.

Funding: Commercial Support - Fresenius Medical Care



TH-PO272

Left Ventricular Global Longitudinal Strain in Stable Stage 5 CKD Patients with Preserved Ejection Fraction Predicts Cardiovascular Events and Mortality After Dialysis Commencement

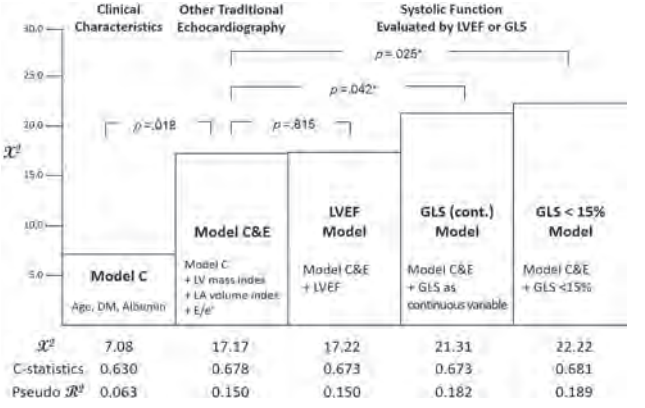
Chih-Hen Yu, Li Wenhuang, Yen-wen Liu, Junne-Ming Sung. *National Cheng Kung University College of Medicine, Tainan, Taiwan*.

Background: Early detection of subclinical cardiac dysfunction offers opportunity of timely intervention, especially before vulnerable transition from advanced CKD to ESKD. We previously found absolute left ventricular global longitudinal strain (GLS) <15% is predictive to mortality in dialysis patients with preserved ejection fraction (EF), while it's still inconclusive whether the systolic function evaluated by GLS before hemodialysis commencement (HDC) is applicable to predict post-dialysis outcome in clincial stable CKD5 patients.

Methods: In this longitudinal prospective observation across HDC, we aimed to predict the post-dialysis cardiovascular outcome with pre-dialysis GLS. The CKD5 patients who had long-term HDC before 2020 were enrolled to post-dialysis outcome follow-up. Inclusions were EF>50% and eligible GLS within 2 years before HDC; main exclusion was frequent admission. The primary outcomes were post-dialysis major adverse cardiovascular cerebral events(MACCE), and secondary outcome was all-cause mortality(ACM).

Results: 201 among 242 stable CKD5 patients reached HDC, and 108 with eligible GLS were enrolled. Median duration from examination to HDC was 5.39 months. Median follow-up was 1458 days. GLS<15% is independent predictor of MACCE (HR 2.34[1.11-4.91]p=.025*) and ACM(HR 2.97[1.18-7.49]p=.021*). GLS as continuous variable is independent predictor of MACCE(HR 0.90[0.82-1.00]p=.040*) and ACM(HR 0.84[0.73-0.95]p=.007**). The incremental diagnostic values contributed from GLS<15%(p=.025*) or GLS(p=.042*) were significant in nested Cox models but LVEF (Figure).

Conclusions: LV subclinical systolic dysfunction, assessed by GLS<15% within previous 2 years before HDC, predictedpost-dialysis MACCE and ACM in clinically stable patients having their HDC.



GLS and GLS<15% increase predicting value of Cox models of MACCE; colums represent chi-square value in -2 log likelihood test

TH-PO273

Effectiveness of Heart Rate Variability for Predicting Intradialytic Hypotension in Chronic Hemodialysis Patients

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Background: Intradialytic hypotension(IDH) is a common complication during hemodialysis reported to occur in 20–30% of hemodialysis sessions. According to a recent meta-analysis, IDH based on nadir 90 criterion was reported to have the highest association with the patient survival rates. The heart rate variability(HRV) test is a non-invasive and simple method to measure autonomic nervous system activity. To date, no studies have demonstrated the usefulness of the HRV test in predicting IDH based on nadir 90 criterion. This study was aimed to elucidate the usefulness of the HRV test in predicting the occurrence of IDH.

Methods: This study was a multi-center prospective observational study. A total of 70 patients were enrolled in this study. Blood tests, echocardiography, and body composition measurement results were collected, and HRV test was performed for 24 hours during non-hemodialysis period. And then, a total 12 hemodialysis sessions were monitored. The patients were divided into the IDH group and non-IDH group. HRV index model was developed by a multivariate logistic regression analysis. The predictive value of IDH occurrence was analyzed through area under the receiver operating characteristic curve(AuROC) value.

Results: According to the nadir 90 criterion, 37 patients were placed in the IDH group, and 33 patients in the non-IDH group. Considering that the HRV test is affected by the lifestyle, data of night-time(00:00~04:00) was used. Standard deviation of normal-to-normal interval(SDNN), root-mean-square of successive differences(RMSSD), normal-to-normal interval>50ms(NN50) count, percentage of NN50 count(pNN50), total power(TP), very low frequency(VLF), low frequency(LF), high frequency(HF), and LF/HF ratio, which are parameters of the HRV test, were analyzed to develop a HRV index model. The AuROC value for IDH occurrence (even in one session) of the developed HRV index model was 0.776. The AuROC value for frequent IDH occurrence (in more than 10% of sessions) was 0.803. A high HRV index(>0.544) was observed as an independent risk factor after adjusting for several other confounding factors(odds ratio 6.137, P=0.011).

Conclusions: The HRV test can be used as a useful tool to predict IDH. This is the first study to demonstrate the usefulness of the HRV test in prediction of the IDH occurrence according to the nadir 90 criterion.

TH-PO274

Changes of Hemodynamic Parameters over a Single Treatment Week in Patients Undergoing Chronic Intermittent Hemodialysis

Bernhard N. Bohnert, David König, Ferruh Artunc. *Eberhard-Karls-Universitat Tubingen Medizinische Fakultat, Tubingen, Germany*.

Background: Using ultrasound dilution, hemodynamic parameters such as access flow or cardiac output can be measured non-invasively and repeatedly during hemodialysis (HD). No data are available on the changes of these parameters within one week of treatment with long and short dialysis intervals.

Methods: In a prospective cohort study, various hemodynamic parameters were determined in n=44 prevalent HD patients during a 4-hour HD using the HD03 monitor (Transonic). Measurements were taken hourly on the first HD day of the week, on the

second and third day at the beginning and end of HD. Access flow (AF, L/min), cardiac index (CI, L/min/m2 body surface area), central blood volume index (CBVI, mL/kg body weight), total cardiac ejection fraction (TEF, %) and total cardiac end-diastolic volume index (TEDVI, mL/kg) were recorded.

Results: The median AF was 1.1 L/min (interquartile range 0.8-1.7) at the beginning of the first HD of the week and did not change during HD. The values were unchanged on the following HD days. The median CI was 3.2 (2.7-3.9) L/min/m2 body surface area at the beginning of the first HD and CI continuously decreased to 85% of the baseline value during the HD ($p<0.001$). The CI recovered to baseline by the second HD and decreased to a median of 83% of baseline at the end of the second HD ($p<0.001$). The same pattern was found at the third HD. Median TEF was 53% (46-64) at the start of the first HD of the week and remained constant across all HD treatments. Medians of the central hydration parameters CBVI and TEDVI were 19 (16-25) and 10 (8-12) ml/kg body weight, respectively, at the beginning of the first HD and were lowered significant by 13% and 9%, respectively, at the end of the first HD. The course was similar to that of the CI, with a re-increase until the beginning and a reduction at the end of the second and third HD, respectively. The TEDVI and the CBVI were significantly lower before the beginning of the third HD than before the first HD. Systolic and diastolic blood pressure as well as heart rate showed a course parallel to that of the CI.

Conclusions: HD treatment compromises cardiac index that recurs regularly and reversibly within the treatment week. Central overhydration is highest after the long interval and decreases as the week progresses.

TH-PO275

Risk Factors for Inpatient Mortality in Patients with CKD Hospitalized with Infections due to Multidrug-Resistant Organisms: A Nationally Representative Study

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Background: The CKD population, especially those with end-stage kidney disease (ESKD) on hemodialysis (HD), has higher rates of infections and more exposure to multidrug-resistant organisms (MDRO). However, few studies have evaluated the risk factors for mortality among CKD patients hospitalized with MDRO infections.

Methods: We extracted data from the 2020 national inpatient sample, the largest nationwide inpatient database in the US, for adults (age ≥18 years) with diagnosis of CKD (non-dialysis dependent CKD) and ESKD (on HD) with MDRO infections (methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, multidrug-resistant gram-negative bacilli and *Clostridioides difficile*) by ICD 10 codes. The primary outcome was inpatient mortality. We compared the baseline characteristics and constructed multivariable logistic regression models adjusted for socio-demographics, comorbidities, and hospital characteristics to determine the risk factors for inpatient mortality.

Results: There were 49,624 and 15,075 admissions with MDRO infections among patients with CKD and ESKD, respectively. The mean age was 72.5 vs. 63.3 years, females 49.1% vs 47.2%, and White patient accounted for 73.0% vs. 48.9% in CKD vs ESKD group, respectively. Inpatient mortality was higher in ESKD patients compared to CKD patients (9.5% vs.12.1%). Older age and worse comorbidity scores were associated with increased risk of death in both groups. Black patients had higher risk of inpatient mortality compared to White patients (OR 1.40; 95% CI 1.14-1.71) in the CKD but not ESKD group. In the CKD group, hospital characteristics including large bed size, Northeast location, and government ownership were associated with higher risk of death; while in ESRD group, private-investor hospitals had higher mortality.

Conclusions: Inpatient mortality is higher in ESKD compared to CKD patients hospitalized with MDROs. Risk factors for mortality were older age, more comorbidities, and among those with CKD, Black race. Hospital-level risk factors include size, region, and ownership. Further studies should investigate structural, social, and dialysis-related factors on risk of inpatient mortality in CKD and ESKD patients hospitalized with MDRO infections.

TH-PO276

Factors Influencing Pre- and Post-Dialysis Central and Peripheral Blood Pressure in Dialysis-Dependent Veterans: A Single-Center Study

Abdul Hannan A. Rasheed,[1,2] Anuradha Wadhwa,[1,2] Holly J. Kramer,[1,2] Kavitha Vellanki.[1,2] *[1]Edward Hines Junior VA Hospital, Hines, IL; [2]Loyola University Health System, Maywood, IL.*

Background: Central aortic blood pressure (BP) is more reflective of cardiovascular health than peripheral BP. While it is hypothesized, central BP monitoring which detects minute changes in vessels is not suitable for dialysis patients due to stiff vessels, data on pre and post dialysis variations between central and peripheral BP is non-existent. We aimed to study the differences between pre and post dialysis central and brachial BP in patients and identify factors influencing any differences.

Methods: All patients receiving hemodialysis at Hines VA Hospital were approached between December 2021 and March 2022. Pre and post dialysis central aortic and brachial BP were obtained using ACTOR technology. Data collected included demographic characteristics, prescribed dialysis time and achieved ultrafiltration (UF). Mixed effects model was used for statistical analysis.

Results: A total of 51 patients participated in the study. Baseline characteristics are shown in Fig 1. Average difference of 2.6 mmHg is noted between pre and post dialysis brachial and central aortic systolic BP readings, post dialysis readings being higher than pre dialysis readings (Fig 2) after controlling for age, BMI, ethnicity, history of smoking, diabetes, peripheral vascular disease and coronary artery disease. Every 1 liter increase in UF is associated with a 1.35 mmHg difference in brachial vs. central aortic systolic BP.

Conclusions: In our single center study of veteran male dialysis population, for every liter of UF achieved, a 1.35 mmHg difference is noted in post dialysis brachial and central aortic systolic BP.

Variable	Mean	S.D	Min	Max
Age (Years)	69.3	10.2	50	89
Weight (kg)	93.6	23.2	54	164
BMI	29.5	6.7	18.3	47.9
Brachial Systolic (mmHg)	142.5	27.5	69	201
Brachial Diastolic (mmHg)	70.7	14.3	43	111
Central Systolic (mmHg)	128.6	24.8	65	189
Central Diastolic (mmHg)	72.5	14.5	45	115
Ultrafiltrate (Liter)	2.3	1.1	-0.4	4.4

Fig 1: Baseline Characterisitics

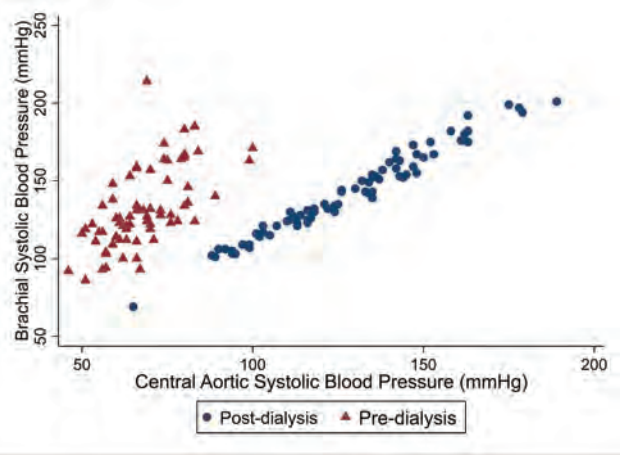


Fig 2: Pre and Post Dialysis BP

TH-PO277

Exposure to Elevated Temperature Is Associated with Elevated Risk for Cardiovascular Disease (CVD) Outcomes and Mortality Among Hemodialysis Patients in the United States

Yuzhi Xi,[1,2] Zachary S. Wettstein,[3] Abhijit V. Kshirsagar,[4] Yang Liu,[1] Danlu Zhang,[1] Yun Hang,[1] Ana G. Rappold.[5] *[1]Emory University, Atlanta, GA; [2]ORISE Fellow at US EPA, Chapel Hill, NC; [3]University of Washington, Seattle, WA; [4]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [5]United States Environmental Protection Agency, Washington, DC.*

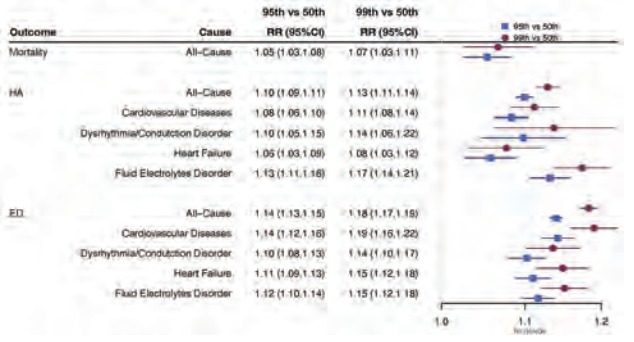
Background: Ambient temperatures have increased due to climate change in many parts of the world. Adaptation and resilience to changing conditions is particularly concerning among individuals with chronic kidney disease, due to loss of renal function which impacts regulation of thermoregulatory mechanisms. The aim of this study is to assess the effect of heat on mortality and health care utilization among US hemodialysis patients.

Methods: We conducted a retrospective time-series analysis (2011-2016) of daily mortality, hospital admission, and emergency department visits identified in the United States Renal Data System. Daily ambient temperature was estimated on a 1 km grid and assigned to ZIP-code. Conditional-Poisson models were used to assess the risk of developing adverse health outcomes associated with temperature exposure.

Results: Overall, daily ambient temperature increase is associated with elevated risk for both mortality and health care utilization among hemodialysis patients. The rate ratios for all-cause mortality and daily temperature was 1.07 (95% CI: 1.03-1.11), 1.17 (1.14-1.21) for fluid disorder-related hospital admissions, and 1.19 (1.16-1.22) for cardiovascular event-related emergency department visits, comparing 99th percentile vs. 50th percentile daily temperatures. Larger effects were observed for cumulative lagged exposure three-days prior to the outcome and for Southwest and Northwest climate regions.

Conclusions: Heat exposure is associated with elevated risk for mortality and health care utilization among this vulnerable population. Furthermore, the effect appears to be potentially cumulative in the short-term, and varies geographically. Disclammer: this abstract does not represent EPA policy nor USRDS position.

Figure 1. Same day effect (Rate Ratios (RR) and 95% Confidence Interval) of exposure to daily ambient temperature on mortality and health care utilization among hemodialysis patients in the contiguous United States 2011-2016



TH-PO278

Predictors of Hospitalization in Adolescents and Young Adults with ESKD

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Background: Treatments for end-stage kidney disease (ESKD) include in-center dialysis, home dialysis, and transplant. Adolescents and young adults (AYA) are at increased risk for difficult disease course. Identification of risk factors for hospitalization may lead to changes in management.

Methods: We performed a secondary analysis of data in the US Renal Data System (USRDS). Included subjects were 16-24 years old at dialysis start 2010-2015 and had no previous history of kidney transplant. The combined outcome is time to first hospitalization. Analysis was by Cox proportional hazard modeling.

Results: Of the 4658 eligible subjects, 57% were male, 65% were white, and they had a mean age of 20.7 years (Table 1). Participants were followed for a median of 2.7 (2.6, 2.9) years during which there were 1963 hospitalizations. Multivariable Cox proportional hazards showed female sex, non-Hispanic ethnicity, dialysis catheter use, diabetic kidney disease, and lack of insurance were associated with increased risk of first hospitalization (Table 2).

Conclusions: Both demographic and potentially modifiable dialysis-related factors are associated with increased risk of hospitalization in AYA with ESKD.

	N = 4,665[1]
AGE	20.6 ± 2.5
MALE SEX	2,674 (57%)
RACE	
WHITE	3,046 (65%)
BLACK	1,234 (26%)
NATIVE AMERICAN	19 (0.4%)
ASIAN	269 (5.8%)
PACIFIC ISLANDER	63 (1.4%)
OTHER/UNKNOWN	34 (0.7%)
HISPANIC	1,456 (31%)
ESKD ETIOLOGY	
DIABETES	157 (3.4%)
HYPERTENSION	751 (16%)
GLOMERULONEPHRITIS	2,269 (49%)
CYSTIC KIDNEY	122 (2.6%)
OTHER UROLOGIC	312 (6.7%)
OTHER/UNKNOWN CAUSE	1054 (23%)
DIALYSIS MODALITY	
HEMO	3,650 (78%)
CAPD	375 (8.0%)
CCPD	637 (14%)
OTHER	3 (<0.1%)
AV ACCESS (HD ONLY; N = 3650)	
AVF	364 (10.0%)
AVG	40 (1.1%)
CATHETER	3,242 (89%)
OTHER	10 (0.3%)
INSURANCESTATUS	
NO INSURANCE	719 (15%)
COMMERCIAL	1,463 (31%)
MEDICAID/DUAL ELIGIBLE/MANAGED MEDICAID	1,735 (37%)
OTHER	574 (12%)
MEDICARE/MANAGED MEDICARE	174 (3.7%)

Table 1. Baseline Characteristics

	HR[1]	95% CI[1]	p-value
Age	0.98	0.96, 1.01	0.2
Female Sex	1.20	1.09, 1.34	**<0.001**
Race			
White	—	—	
Black	0.76	0.67, 0.86	**<0.001**
Native American	1.13	0.60, 2.12	0.7
Asian	0.56	0.43, 0.72	**<0.001**
Pacific Islander	0.59	0.36, 0.96	**0.035**
Other	1.59	0.90, 2.79	0.11
Unknown			
Non-Hispanic race	1.95	1.71, 2.23	**<0.001**
ESKD etiology			
Diabetes	—	—	
Hypertension	0.60	0.44, 0.80	**<0.001**
Glomerulonephritis	0.70	0.53, 0.93	**0.013**
Cystic kidney	0.74	0.49, 1.13	0.2
Other urologic	0.64	0.45, 0.90	**0.009**
Other cause	0.64	0.47, 0.87	**0.004**
Unknown cause	0.54	0.38, 0.75	**<0.001**
Dialysis Modality			
HD	—	—	
CAPD	1.64	0.23, 11.7	0.6
CCPD	2.59	0.91, 7.35	0.075
Other	2.30	0.32, 16.4	0.4
Arteriovenous Access (HD only; n = 3653)			
AVF	—	—	
AVG	1.02	0.55, 1.89	>0.9
Catheter	1.29	1.07, 1.54	**0.006**
Other	3.21	1.62, 6.38	**<0.001**
INSURANCE STATUS			
No insurance	—	—	
Commercial	0.65	0.55, 0.77	**<0.001**
Medicaid/Dual eligible/Managed Medicaid	1.05	0.91, 1.22	0.5
Other	0.82	0.68, 1.00	**0.048**
Medicare/managed Medicare	1.30	0.98, 1.72	0.069

[1]HR = Hazard Ratio, CI = Confidence Interval

Table 2. Multivariable Hazard Ratios.

TH-PO279

Optimal Caloric Requirements of Critically Ill Patients on Chronic Hemodialysis (CHD)

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Background: The KDOQI 2020 nutrition guidelines do not address the energy requirements of critically ill CHD patients (pts). This study determined the actual caloric needs of critically ill CHD pts.

Methods: This was a single-center, single-blinded, randomized control trial of 11 critically ill intubated pts admitted to the ICU. A Puritan Bennet Indirect calorimeter was used for the data collection on nondialysis days or before starting hemodialysis while NPO or on enteral feeding or TPN matched for protein, fat & carbohydrates after reaching a steady state. All pts were randomized to either a 28 kcal/kg/day or a 38 kcal/kg/day after baseline NPO data was obtained the prior day. The data collected by the calorimeter were 8 hr machine averages and included VO2, VCO2, respiratory quotient, and energy expenditure. In addition, time-averaged glucose obtained every 4 hours was calculated. Finally, statistics were performed utilizing the Student's T-test & ANOVA for paired data.

Results: A total of 11 pts were included, seven males & four females. The pts had a mean age of 39 ± 7 years. 8 out of the 11 patients completed all three days of the study. Four patients were under 60 years, two males and two females. two females and five males comprised the over-60 age group. The baseline REE for patients <60 years was 26.0 ± 4 kcal/kg/day, and for patients >60 years was 22.0 ± 2 kcal/kg/day despite sepsis in two patients in each group. REE for all NPO patients was 23.5 ± 4 kcal/kg/day and only 24.5 ± 4 kcal/kg/day, and 26.0 ± 3 kcal/kg/day for TPN days with 28 or 38 kcal/kg/day ($p>0.05$). Time-averaged glucose increased to a clinically significant level with both diets; 162 ± 30 mg/dL ($p<0.05$) for pts receiving a 28 kcal/kg/day diet and 159 ± 25 mg/dL($p<0.05$) for a 38 kcal/kg/day diet.(Table1)

Conclusions: Current KDOQI nutrition recommendations overestimate the energy expenditure of critically ill HD patients. Critically ill CHD pts should be fed 24-26 kcal/kg/day or have their EE measured by indirect calorimetry to receive proper nutrition and avoid overfeeding.

Funding: Clinical Revenue Support

Table 1

	V02 (ml/min)	VCO2 (ml/min)	RQ	REE	Glucose
NPO	208±19	155±12	0.8	1426.5±125.2	106±15
28 kcal/kg/day	204±20	192±13*	0.95*	1454.9±131.8	162±30*
38 kcal/kg/day	214±24*	214±24*	0.95*	1676±214.3	159±25*

* $p<0.05$ compared to NPO. Increase in VCO2, RQ and glucose levels suggest CHO overfeeding and increased lipogenesis in the TPN, enteral feeding groups. No statistically significant difference was found between 28 kcal/kg/day and 38 kcal/kg/day groups in studied parameters.

TH-PO280

Mortality of Elderly Patients with AKI Undergoing Continuous Renal Replacement Therapy: Is Age a Risk Factor?

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Background: The incidence of elderly patients with acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is increasing. There is little evidence on the difference of mortality rates according to age in elderly patients. This study aimed to evaluate the age effect and predictors for mortality in elderly patients with AKI requiring CRRT.

Methods: A retrospective analysis was performed in elderly patients with AKI who underwent CRRT. A total of 480 patients aged ≥65 years were stratified into three groups according to age: youngest-old (age 65-74 years, n=205), middle-old (age 75-84 years, n=217), and oldest-old (age ≥85 years, n=58). The 28-day and 90-day survival rates were compared between three groups and predictors for mortality were analysed.

Results: The 28-day and 90-day survival rates were not different between three age groups (P=0.156 and P=0.189, respectively). The oldest-old group did not show an inferior survival rate to other two groups. For 28-day mortality, prothrombin time [hazard ratio (HR) = 1.37, 95% confidence interval (CI) = 1.01 – 1.88, P = 0.046] and urine output at the start of CRRT (HR = 0.999, 95% CI = 0.998 – 1.000, P=0.012) and CRRT duration (HR = 0.89, 95% CI = 0.83 – 0.95, P=0.001) were predictors. For 90-day mortality, mean arterial pressure (HR = 1.02, 95% CI = 1.00 – 1.05, P=0.019), admission duration (HR = 0.97, 95% CI = 0.95 – 0.99, P<0.001) and CRRT duration (HR = 0.96, 95% CI = 0.91 – 0.99, P=0.036) were predictors. The middle-old group or the oldest-old group did not exhibit higher risk compared to the youngest-old group for 28-day and 90-day mortality.

Conclusions: An older age was not a risk factor for mortality in elderly patients with AKI undergoing CRRT. This implicates the importance of active management and application of CRRT in critically ill elderly patients with AKI.

TH-PO281

Intradialytic Hypotension and Worse Outcome in Patients with AKI Requiring Intermittent Hemodialysis

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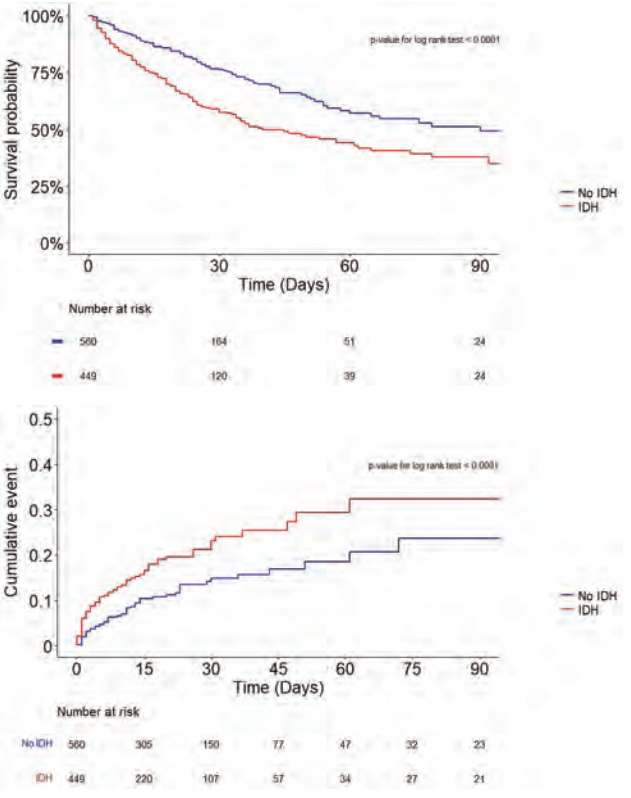
Background: Intradialytic hypotension (IDH) is a critical complication related with worse outcomes in patients undergoing maintenance hemodialysis. Herein, we addressed impact of IDH on death and other outcomes in patients with severe acute kidney injury (AKI) requiring intermittent hemodialysis.

Methods: We retrospectively reviewed 1,009 patients who underwent intermittent hemodialysis due to severe AKI. IDH was defined as a decrease in systolic blood pressure (SBP) of ≥30 mmHg, with or without a nadir SBP of <90 mmHg during the first session. The primary outcome was all-cause death, and transfer to the intensive care unit due to unstable status was additionally analyzed. Hazard ratios (HRs) of outcomes were calculated using a Cox regression model after adjusting for multiple variables. Risk factor of IDH was evaluated using a logistic regression model.

Results: IDH occurred in 449 (44%) patients during the first hemodialysis session. Patients with IDH had higher death rate (39.6%) than those without IDH (23%) (HR, 1.39 [1.09–1.78]). The rate of ICU transfer was higher in patients experiencing IDH (17%) than those without IDH (11%) (HR 1.46 [1.02–2.09]). Factors, such as old age, high SBP, high pulse rate, active cancer, cirrhosis, anemia, and hypoalbuminemia, were associated with an increased risk of IDH episode.

Conclusions: The occurrence of IDH is associated with worse outcomes in patients with AKI requiring intermittent hemodialysis. Therefore, careful monitoring of IDH is necessary in this patient subset.



TH-PO282

Antibiotics Dosing in Four-Hour Sustained Low-Efficiency Dialysis: A Retrospective Data Review

Husien Almarawi, Alaa Rahhal, Amer Aljundi, Mohamed M. Kasem, Ahmed S. Mahfouz, Khaled M. Mahmoud. *Hamad Medical Corporation, Doha, Qatar*.

Background: Sustained Low-Efficiency Dialysis (SLED) is characterized by a slower blood flow rate than intermittent hemodialysis (IHD). SLED is usually done over 6-12 hours and a shorter duration of 4-hour might spare more time for procedures in critical care units (ICU). However, antibiotics dosing is not well established in 4-hour SLED, and clinicians might prescribe antibiotics using IHD dosing in view of the shorter duration.

Methods: In this single-center study, we assessed the dosing practices and clinical outcomes of antibiotics among recipients of 4-hour SLED. In-hospital mortality and recovery from sepsis were compared between those who received SLED dosing versus IHD dosing, using Cox regression and Kaplan-Meier curves. P-value <0.05 was set to represent statistical significance.

Results: A total of 107 patients who underwent 4-hour SLED and received at least one broad-spectrum antibiotic were identified between 1/06/2016 to 1/06/2020. Among them, 68% were male with a mean age of 68 ± 12 years. The majority of patients were from the Middle East (81%). Around 20% had positive urine cultures, 19% had positive blood cultures, and 10% had positive sputum cultures. The majority of 4-hour SLED recipients (84%) were prescribed antibiotics according to IHD dosing, while only 16% were prescribed SLED dosing regimens. The use of SLED-based recommended dosing in 4-hour SLED resulted in significantly higher sepsis recovery [76% vs. 42%, HR= 2.02, 95 CI (1.07-3.82), p=0.030]. Interestingly, the in-hospital mortality didn't differ between the two groups.

Conclusions: Our findings suggest that patients undergoing 4-hour SLED are more likely to get prescribed antibiotics using IHD-recommended dosing, which resulted in worse clinical outcomes. These findings would encourage using SLED-recommended dosing for 4-hour SLED and might serve as the basis for future larger studies.

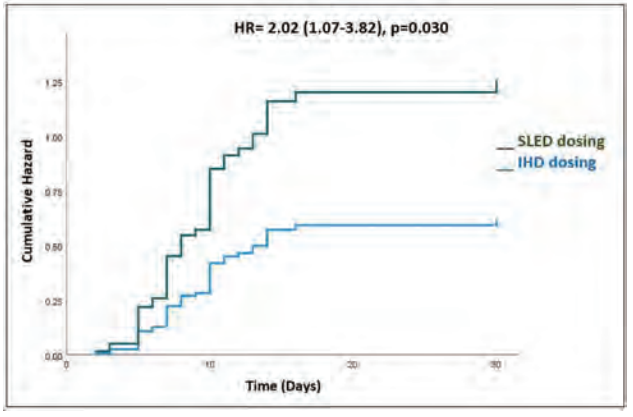


Figure 1. Kaplan-Meier curve of recovery from sepsis

TH-PO283

Clinical Factors Affecting Continuous Renal Replacement Therapy Circuit Survival

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Background: Continuous renal replacement therapy (CRRT) is an effective treatment for critically ill patients with acute kidney injury (AKI). However, CRRT circuit is frequently clotted despite anticoagulation resulting in blood loss and reduced dialysis efficacy. We aim to investigate the clinical factors affecting CRRT circuit survival.

Methods: A total of 117 CRRT circuit cases from 102 patients were reviewed retrospectively. We collected clinical data and investigated the factors affecting (1) the time from CRRT start to first dialysis circuit clotting or (2) frequency of circuit exchange during CRRT operation.

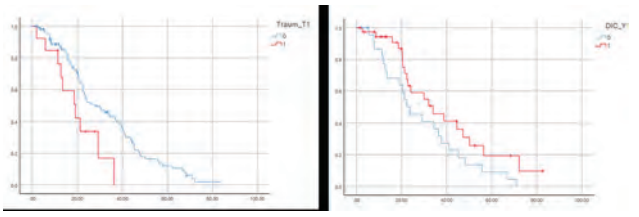
Results: The average time to 1st clotting was 26.1 hours. In Kaplan-Meier estimation, AKI due to trauma was related to shorter CRRT circuit survival (p=0.016), while DIC condition was related to longer survival (p=0.061) (Figure 1). In multivariate Cox-regression analysis, it was confirmed that the higher filtration fraction (FF) is associated with the shorter circuit lifespan, while the higher DIC score or corrected calcium level were associated with the longer circuit survival (Table 1). The average number of circuit exchange was 1.46. In multivariate linear regression test adjusted for age, FF, DIC score and RBC transfusion, it was shown that FF had the positive correlation with frequent circuit exchanges (β=0.272, p=0.026), while DIC score had the negative correlation (β= - 0.287, p=0.019).

Conclusions: The study indicates CRRT circuit survival depends on factors related to intra-dialyzer condition such as FF or clotting tendency rather than clinical severity of patients. Interestingly, our results suggest that consumptive coagulopathy due to DIC rather prevents circuit clotting. Low corrected calcium is also thought to be due to consumption as a clotting factor and therefore predict early CRRT circuit clotting.

Table 1. Clinical factors contributing to early CRRT circuit clotting

Variable	Adjusted HR (95% CI)*	*P* value
FF	1.16 (1.04, 1.28)	0.005
DIC score	0.68 (0.52, 0.89)	0.005
Corrected Ca	0.72 (0.55, 0.93)	0.011

HR: Hazard ratio; CI: confidence interval; DIC: diffuse intravascular coagulation; FF: filtration fraction; Ca: calcium
*Adjusted for age, hemodialysis catheter access, SOFA score.



TH-PO284

Continuous Renal Replacement Therapy vs. Intermittent Hemodialysis: Outcomes of Critically Ill Patients with AKI

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Background: Acute kidney injury (AKI) is a commonly diagnosed condition in critically ill patients, which poses a significant risk of chronic kidney disease, end-stage renal disease, and dialysis dependence (DD). Renal replacement therapies, including continuous renal replacement therapy (CRRT) and intermittent hemodialysis (iHD), are often used to support AKI patients. Although each modality has benefits, results from studies of outcomes associated with each modality remain inconclusive.

Methods: This retrospective multicenter cohort study utilized the TriNetX, a global federated health research network, to access deidentified electronic medical records from multiple large healthcare organizations. The primary objective was to investigate the outcomes of critically ill patients with AKI who received either CRRT or iHD after propensity score matching. The study identified and compared a total of 1024 propensity score-matched AKI patients in each group from Jan 2012, assessing them for 30-day mortality and DD using odds ratio (OR), 95% confidence interval (CI), hazard ratio (HR), log-rank test, and Kaplan-Meier survival analysis. Additionally, the study identified and compared a propensity-matched subgroup of 195 patients on mechanical ventilation in each group, with platelet count < 100/mL and bilirubin > 6 mg/dL and assessed these outcomes.

Results: The study was conducted on two groups, CRRT versus iHD, each consisting of 1024 patients. The 30-day mortality rate was 537 patients in the iHD group, and 672 patients in the CRRT group [OR: 0.578; 95% CI: 0.743-0.860; HR: 0.692; 95% CI: 0.617-0.775; p=0.637]. DD was observed in 114 and 93 patients in the iHD and CRRT groups, respectively [OR:1.254; 95% CI: 0.940-1.674; HR:1.125; 95% CI: 0.855-1.480; p=0.150]. In subgroup analysis 30-day mortality was reported in 100 and 110 patients and survival probability of 47.61% and 41.76% in the iHD and CRRT groups respectively, [HR: 0.851; 95% CI: 0.649-1.115; p=0.790]. DD was observed in 25 patients in both cohorts.

Conclusions: In the cohort of critically ill patients with acute kidney injury who were admitted to the intensive care unit and required renal replacement therapy, the choice of renal replacement therapy modality did not have a significant impact on either 30-day mortality or the development of dialysis dependence.

TH-PO285

Timing of Continuous Renal Replacement Therapy in Critically Ill Patients on Extracorporeal Membrane Oxygenation

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Background: To investigate the timing for continuous renal replacement therapy (CRRT) in critically ill patients undergoing extracorporeal membrane oxygenation (ECMO).

Methods: Clinical data were collected of critically ill patients who received ECMO combined with CRRT in the Intensive Care Unit (ICU) of Henan Provincial People's Hospital from January 2017 to June 2021. According to the time to start CRRT after ECMO application, they were divided into early CRRT group or late CRRT group. The differences in baseline clinical data and mortality between the two groups were compared. Kaplan-Meier curves obtained with the Log-rank test were plotted to demonstrate the differences in patients' survival between the two groups. Cox regression analysis was used to explore the risk factors of death.

Results: A total of 122 patients were enrolled, while 96 patients (78.69%) died. The early CRRT group and late CRRT group included 100 cases (81.97%),22 cases (18.03%),respectively. Compared with the late CRRT group, the early CRRT group had higher proportion of receiving ECMO treatment due to respiratory and cardiac arrest, proportion of ECMO with venous-arterial mode, APACHEII score, and SOFA score (all $P<0.05$). In contrast, ICU stay time, The mechanical ventilation time and ECMO application time were shorter (all $P<0.05$). Kaplan-Meier curve showed that there was no significant difference in cumulative survival between the two group ($\chi 2=3.397$, $P=0.065$). Time-Dependent Cox Regression Model showed that Early CRRT was a risk influencing factor for patient death {HR=Exp[3.642+1.177×ln(t)], 95% CI 3.225~451.394, $P=0.004$}. Multivariate Cox regression analysis showed that early CRRT {HR=Exp[3.499+1.162×ln(t)], 95% CI 2.123~516.029, $P=0.013$}, ECMO weaning failed (HR=3.470, 95%CI 1.986~6.061, $P<0.001$), high APACHEII score (HR=1.042, 95% CI 1.001~1.085, $P=0.044$) were risk factors for in-hospital death.

Conclusions: Early CRRT after ECMO treatment may have a greater effect on mortality in critically ill patients than the late CRRT. Failure of ECMO weaning and high APACHEII score were risk factors for in-hospital death.

Funding: Government Support - Non-U.S.

TH-PO286

The Timing of Renal Replacement Therapy in Patients with Venoarterial Extracorporeal Membrane Oxygenation (VA-ECMO): A Nationwide Observational Cohort Study in Japan

Tomonori Takeuchi,[1,2] Toshihiro Kubo,[2] Norihiko Inoue,[2] Ashita J. Tolwani,[1] Keith M. Wille,[1] Kenji Wakabayashi,[2] Javier A. Neyra,[1] Kiyohide Fushimi.[2] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]Tokyo Ika Shika Daigaku Daigakin Ishigaku Sogo Kenkyuka, Bunkyo-ku, Japan.*

Background: Acute kidney injury is a common complication in patients on VA ECMO, thus fluid management plays a crucial role during VA ECMO. Renal replacement therapy (RRT) enables precise fluid management, but early initiation of RRT has not shown benefits in general critically ill populations. We hypothesized that early initiation of tight fluid control with RRT would be beneficial for VA ECMO patients. In this study, we aimed to determine the association of early initiation of RRT with clinical outcomes in patients on VA ECMO, using the Diagnosis Procedure Combination database, a nationwide claims database in Japan.

Methods: This is a cohort study of adult patients who underwent VA ECMO during hospitalization between 4/2018 and 3/2022. We excluded patients who initiated RRT before starting VA ECMO and patients with end-stage kidney disease. We used propensity-score-based inverse probability weighting (IPW) to balance the baseline factors and to compare outcomes between two groups: patients who initiated RRT within 48h of VA ECMO initiation (Early RRT group) and those who did not (Late RRT group). The primary outcome was in-hospital mortality and the secondary outcome was RRT dependence at discharge in survivors.

Results: Of 1,181 VA ECMO patients, 336 were in the Early and 845 were in the Late RRT groups. After IPW, the clinical factors between the groups were well balanced, including the prevalence of cardiovascular disease (96.7 vs 97.8%), the total SOFA scores on the day of VA ECMO initiation (10.4 vs 10.4), and its renal component (0.9 vs 0.9). The median time to initiate RRT from the start of VA ECMO was 0 (IQR 0–1) days in the Early and 5 (IQR 2–11) days in the Late RRT groups. Early RRT initiation was associated with increased in-hospital mortality (66.5 vs 53.6%; OR 1.7, 95%CI 1.3 – 2.3) and increased RRT dependence at discharge in survivors (12.7 vs 2.0%; OR 5.6, 95%CI 2.2 – 14.0).

Conclusions: In adult patients with VA ECMO, early RRT initiation was associated with increased in-hospital mortality and RRT dependence at discharge in survivors, suggesting that early RRT initiation may not provide advantages for this population. Further investigation is needed to explore causal inference and identify specific subpopulations that may benefit from early initiation of RRT.

TH-PO287

Treatment Time Loss and Its Association with Fluid Balance Gap and Hospital Mortality in Critically Ill Adult Patients Receiving Continuous Renal Replacement Therapy

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Background: Even with CRRT, fluid balance goals are not always achieved. Recent studies showed that fluid balance gap (prescribed vs. achieved) is independently associated with hospital mortality. It has also been suggested that CRRT downtime can impair fluid management. Herein, we aimed to examine patient-related risk factors for treatment time loss and its association with hospital mortality and fluid balance gap.

Methods: Retrospective cohort study of critically ill adults receiving CRRT. Percent fluid balance gap (%FBgap) was calculated as the percentage difference between fluid balance goal and fluid balance achieved, divided by fluid balance goal. Percent treatment time loss (%TTL) was defined as the percentage of CRRT downtime in relation to the total CRRT time. We performed a linear regression model with %TTL as the dependent variable and age, sex, SOFA score at ICU admission and start of CRRT, Charlson comorbidity index, and %FBgap as independent variables. Adjusting for these clinical parameters, we further conducted a logistic regression model to determine the independent association of %TTL with hospital mortality. The correlation and interaction between %FBgap and %TTL were also examined.

Results: We included 591 patients with a median age of 60 years [IQR 50-68] and median SOFA score of 11 [IQR 7-14] at ICU admission and 13 [IQR 10-15] at start of CRRT. The median CRRT duration was 72.3h [IQR 30.7–141.4] (total of 61,718h). On average, treatment downtime per patient was 4.7h, accounting for 4.5% of total CRRT. There was no significant correlation between %FBgap and %TTL (r= -0.011, p=0.78). The multivariable model did not identify any patient-specific clinical parameters associated with %TTL. In the adjusted model, %TTL was not independently associated with hospital mortality (OR 1.02, 95%CI: 0.99–1.04) and there was no interaction between %FBgap and %TTL with hospital mortality (p interaction =0.92).

Conclusions: In this cohort of critically ill adult patients undergoing CRRT, treatment downtime only accounted for 4.5% of total CRRT time. %TTL was not independently associated with hospital mortality or significantly correlated with %FBgap. Other factors beyond %TTL need to be investigated to optimize fluid management with CRRT.

Funding: NIDDK Support

TH-PO288

Interactions Between Intradialytic Central Venous Oxygen Saturation, Ultrafiltration Rate, and All-Cause Mortality in Maintenance Hemodialysis Patients

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Background: In hemodialysis patients, low central venous oxygen saturation ($ScvO_2$) and high ultrafiltration rate (UFR) have been associated with adverse outcomes. Here we explore the interactions between $ScvO_2$ and UFR in relation to all-cause mortality.

Methods: We conducted a retrospective study in maintenance hemodialysis patients with central venous catheters as vascular access. During a 6-month baseline period, Crit-Line (Fresenius Medical Care, Waltham, MA) was used to measure continuously intradialytic $ScvO_2$. We defined four groups by median $ScvO_2$ and median UFR. The follow-up period was 3 years. We constructed a Cox proportional hazards model with adjustment for age, diabetes, and dialysis vintage to assess the association between $ScvO_2$ and UFR and all-cause mortality during follow-up.

Results: Baseline comprised 5,231 dialysis sessions in 216 patients. The median $ScvO_2$ was 58.8% and median UFR was 6.8 mL/kg/h. During follow-up, 44 patients (20.4%) died. Kaplan-Meier analysis (**Figure 1A)** showed that worst survival was observed in patients with lower ScvO2 combined with higher UFR (group 4). The same result was observed in univariate Cox analysis. In multivariate analysis with adjustment for age, diabetes, and vintage, this association was mitigated (**Figure 1 B**).

Conclusions: Intradialytic $ScvO_2$ is an important effect modifier that should be considered when interpreting the relationship between UFR and outcomes. In patients with higher intradialytic $ScvO_2$, high UFR may be better tolerated, and fluid overload can be prevented easier while imposing high UFR in patients with low intradialytic $ScvO_2$ may lead to worse outcomes.

Funding: Commercial Support - Renal Research Institute

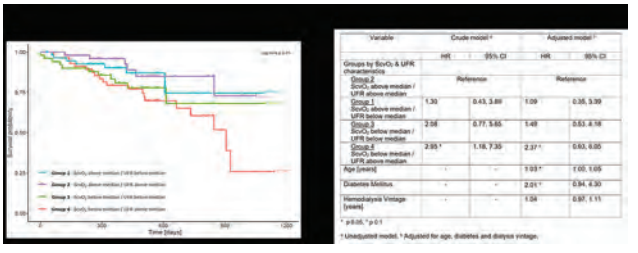

Figure 1A. Kaplan-Meier analysis of survival probabilities in the four subgroups of patients based on the level of $ScvO_2$ and UFR above and below the median of 58.8% and 6.8 mL/kg/h, respectively.

Figure 1B. Crude and adjusted hazard ratios (HR) for all-cause mortality associated with $ScvO_2$ and UFR levels below or above the median population. CI, confidence interval.

TH-PO289

Parathyroid Hormone Decrease During Sepsis Predicts Re-Hospitalization in Hemodialysis Patients

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Background: Hemodialysis patients are at significant risk for infections. Given our clinical observation of decreased Parathyroid hormone (PTH) levels during sepsis among hemodialysis patients suffering from secondary hyperparathyroidism, we aim to characterize PTH levels before and during infection and explore its clinical significance.

Methods: A retrospective observational study conducted in the nephrology department at the Galilee Medical Center, Israel, between 2020-2022. Hemodialysis patients suffering from sepsis were included. PTH levels at different time points were analyzed using Wilcoxon signed rank test. Multivariable logistic regression analyses were conducted to identify risk factors for rehospitalization and mortality (median follow-up: 12.3 months, range:1.9-35.5). Model 1 included Age≥65 years, gender, dialysis vintage≥4 years and diabetes. Model 2: Similar to model 1 plus C reactive Protein (CRP), neutrophil/lymphocyte ratio (NLR) and albumin during hospitalization. Model 3: Similar to model 2 plus partial PTH decrease compared to baseline PTH.

Results: 72 hemodialysis patients were included in this study. The median duration of hospitalization was 9 days (IQR 7-15). 74% were re-hospitalized after discharge while 50% were re-hospitalized within 1.8 months (IQR 0.5-5.8). Infection was the most common rehospitalization diagnosis. The mortality rate during follow-up period was 17% (median survival time: 7.7 months (IQR 3.7-11.9). As hypothesized, PTH levels significantly decreased during sepsis compared to baseline (p<0.001), with partial decrease of 29% (IQR 8%-49%). In the final model of the multivariable logistic regression analyses, several traditional risk factors were associated with re-hospitalization risk: Age≥65 years: OR 5.3, p=0.034 and dialysis vintage≥4 years: OR 5.5, p=0.045. Interestingly, partial PTH decrease during infection was the most significant risk factor for re-hospitalization (OR 12.6, p=0.013). In the final model of the multivariable logistic regression analyses for mortality, only diabetes had a borderline significance (OR 8.6, p=0.065).

Conclusions: In this hemodialysis cohort a significant decrease in PTH levels during infection had the highest OR for re-hospitalization. Further multicenter, prospective studies are needed to validate and explore this association, mechanism, and clinical implications.

TH-PO290

Association Between Sleep Quality and Cardiovascular Disease in Maintenance Hemodialysis Patients

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Background: Most patients on maintenance hemodialysis (MHD) have sleep disorders. Studies have shown that poor sleep quality is associated with a variety of diseases, such as diabetes, cardiovascular disease (CVD), and depression. However, few studies have investigated sleep quality in the population of Chinese patients on hemodialysis. This study aimed to analyze sleep quality in patients on maintenance hemodialysis (MHD), and assess the impact of sleep quality on their prognosis.

Methods: A total of 601 patients on MHD were prospectively included in this cohort study. Pittsburgh sleep quality index (PSQI) was used to evaluate the sleep quality of patients. The global PSQI score > 7 indicates that a person with poor sleep quality. Follow-up was conducted until December 31 2022, with all-cause death and major adverse cardiovascular events (MACEs) as the endpoint events. Correlations between sleep quality and incidences of endpoint events were analyzed using Cox risk regression models.

Results: Of the 601 patients, 595 completed the PSQI assessment, with 278 (46.7%) having poor sleep quality. Patients in the PSQI>7 group were older (p<0.001) and had a higher proportion of comorbid cardiovascular disease (CVD, p<0.001) and diabetes (p=0.002). Years of education (p=0.028), diastolic blood pressure (p=0.002), and heart rate (p=0.005) were lower in the PSQI>7 group than in the PSQI≤7 group. The 595 patients were followed up for 3 (2.5-3.7) years, during which 116 (19.4%) died, 415 (69.8%) survived, 64 (10.8%) were lost to follow-up, and 115 (19.3%) experienced MACEs. After adjusting for confounding factors such as age, gender, dialysis age, and previous cardiovascular disease, the risk of MACE in patients with poor sleep quality was twice that of patients with good sleep quality (HR=2.037 (1.339, 3.097), p=0.001). There was no significant difference in the risk of all-cause death between the two groups (HR=0.851 (0.584,1.240), p=0.4).

Conclusions: The prevalence of poor sleep quality in patients on MHD was 46.7%. Poor sleep quality was independent risk factor for MACEs in patients on MHD.

Funding: Government Support - Non-U.S.

TH-PO291

Comparison of Utilities Consumption Between Different Modalities of In-Center Haemodialysis

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Background: Water is scarce in different parts of the world, including the Kingdom of Saudi Arabia (KSA). Water consumption during hemodialysis (HD) is about 360 liters/patient/week. Online hemodiafiltration (HDF) requires more water consumption (dialysate and replacement fluid) than HD/patient/week. Electricity production is interconnected with water usage. In KSA, Dialysis incidence is expected to increase on average by 5% yearly. This study quantifies local KSA utilities costs associated with in-center HD (ICHD; including High-Flux HD [HF-HD], Expanded HD [HDx], & online HDF).

Methods: Under laboratory conditions and a set treatment protocol, consumptions were recorded for power (Watt-hours, Wh) & water (Liters, L). We gathered cost data from available resources; KSA National Water Company (NWC) & Saudi Electricity Company (SEC). The results were tabulated in Microsoft Excel comparing HD modalities (HF-HD, HDF & HDx). We used single & double-pump dialysis machines (Baxter, Deerfield, IL, USA). Protocols for HF-HD, HDx, & HDF were derived from local expert opinion based on local practice. The cost of consumables & session provision per modality is assumed the same. The analysis considered the perspective of a single center with 30 dialysis beds running two shifts/day over 6 days/week at 100% capacity, caring for 120 patients/year.

Results: HDx water consumption is 3 million (m) liters and electricity consumption is 50.4m Wh/ center/year (same results for HF-HD). The total for HDF is 4.1m L & 60.2m Wh/year, respectively. HF-HD and HDx will reduce the consumption of water and electricity by 1.1m L and 9.8m Wh/year, respectively. For HF-HD and for HDx, the total cost of water & electricity consumption in US Dollars $ (USD)/center/year was $16,002.33 (USD $1 = 3.75 Saudi Riyal [SAR]). When providing HDF, water and electricity cost/center/year was $21,297.20.

Conclusions: In a typical dialysis center in Saudi Arabia, choosing to provide HDx may reduce water and electricity consumptions by $5,294.87 /year versus HDF. This significant cost savings together with the clinical benefits and ease of delivery of the HDx modality may help in favoring this therapeutic modality and strengthening economic data available to policymakers and providers.

Funding: Commercial Support - Baxter AG

TH-PO292

Does Online Hemodiafiltration Improve Clinical Outcomes and Quality of Life in Dialysis Patients Compared to Conventional Hemodialysis?

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Background: The field of dialytic renal replacement modalities has seen advancements; however, interventional studies have produced dismal outcomes. The debate regarding the most beneficial outcome between hemodiafiltration (OL-HDF) and hemodialysis (HD) for dialysis patients remains open. This study aimed to compare clinical, biochemical, and quality of life (QoL) data between patients receiving HD and OL-HDF over a six-month follow-up period.

Methods: A prospective observational study was conducted involving 70 dialysis patients. The inclusion criteria included stable patients with a dialysis Kt/Vurea greater than 1.2 who had received either HDF or HD three times per week for at least three months. Patients who had undergone renal transplantation, exhibited severe noncompliance, or had a life expectancy of less than three months due to conditions unrelated to kidney illness were excluded. QoL was assessed using the dialysis symptom score over the six-month period, along with clinical and biochemical parameters. Both modalities had an intended HD treatment duration of 240 minutes, with a blood flow rate between 250-400 mL/min and a dialysate flow rate of 500 mL/min for both groups.

Results: Out of the 70 dialysis patients, 35 (19 males) were in the HD group, with an average age of 50.05±15.31 (range 41-60) years, and 35 (19 males) were in the OL-HDF group, with an average age of 50.31±11.44 years. Compared to the HD group, the HDF group showed significantly lower levels of inflammatory markers such as Beta 2-microglobulin ($p < 0.001$) and hs-CRP ($p < 0.002$), lower levels of phosphorus ($p < 0.001$), and higher hemoglobin ($p < 0.001$) over the six-month follow-up period. Patients in the HD group had higher mean symptom severity scores compared to those in the HDF group (40.97±12.24 vs. 24.11±5.03, $p < 0.001$). Single pool dialysis Kt/V, calcium, blood pressure control, and the amount of anti-hypertensive drugs required were similar in both groups.

Conclusions: Online hemodiafiltration may be a preferable option over conventional HD due to reduced inflammation, improved anemia control, better phosphorus control, and improved dialysis tolerance with fewer symptoms. Further research is needed to determine the long-term effects of mortality and morbidity in dialysis.

TH-PO293

Predialysis Serum Albumin and Hemoglobin and the Risk of Intradialytic Hypotension

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Background: Intravascular hypovolemia may predispose to intra-dialytic hypotension (IDH), a common occurrence among patients receiving maintenance hemodialysis (HD), which is associated with adverse outcomes. Whether higher pre-HD serum albumin and hemoglobin (Hb), which may reflect hemoconcentration, could serve as biomarkers to predict IDH during an HD session warrants further investigation.

Methods: We analyzed data from a prospective cohort study of patients included in the DaVita Biorepository (N=950). Pre-HD serum albumin, hemoglobin, and complete blood pressure (BP) data were available for n=938 patients and n=11,460 sessions. Random-effects Poisson regression models (adjusting for age, sex, race, access type, pre-HD systolic BP (SBP), session length, ultrafiltration, post-HD weight, diabetes mellitus, heart failure, ischemic heart disease, peripheral vascular disease, lung disease) were fit to examine the association of serum albumin and hemoglobin with IDH (defined as minimum SBP <100 if pre-SBP ≥160 or minimum SBP <90 if pre-SBP<160 mmHg).

Results: At baseline, mean age was 58 ±14 years and 44% were female. The mean pre-HD albumin and hemoglobin were 3.5 ±0.5 g/dL and 10.8 ±1.6 g/dL, respectively. A total of 1,606 (14%) sessions were complicated by IDH. Higher pre-HD serum albumin was associated with a 17% higher adjusted risk of IDH (IRR 1.17; 95%CI 1.00, 1.37). Higher Hb (per g/dL) was associated with 6% higher risk of IDH (IRR 1.06; 95%CI 1.02,1.11). When both were considered in the same model, only hemoglobin retained significance (IRR 1.05; 95%CI 1.01, 1.10).

Conclusions: Higher pre-HD serum albumin and hemoglobin were each independently associated with IDH, but only hemoglobin retained significance in a joint-model. Higher hemoglobin may thus serve as a widely-available biomarker to predict IDH at an individual HD-session level.

TH-PO294

Impact of Dialysate Calcium Concentration on Bone Metabolism in Relation to Different Calcimimetics

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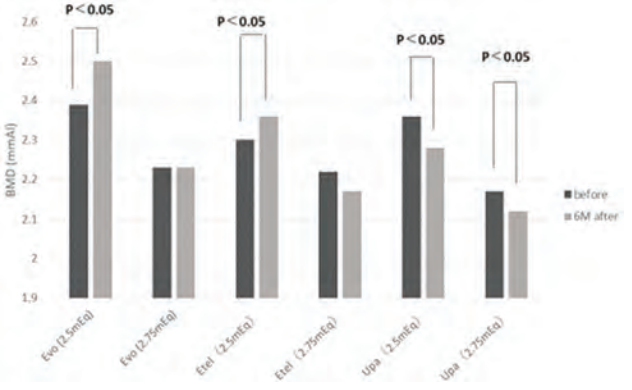
Background: In Japan, three types of calcimimetics are currently approved to treat secondary hyperparathyroidism. However, the specific impact of these drugs on bone metabolism remains unknown. Furthermore, limited research is available on the potential influence of different dialysate calcium concentrations used during hemodialysis on the

bone-related effects of these calcimimetics. This study aimed to examine the influence of dialysate calcium concentration on bone metabolism associated with different calcimimetics.

Methods: Ninety patients undergoing hemodialysis with a dialysate containing either a calcium concentration of 2.75 mEq/mL or 2.5 mEq/mL and having secondary hyperparathyroidism with an intact parathyroid hormone (i-PTH) level ranging from 50–400 pg/mL were included in the study. These participants had been taking calcimimetics for more than a year. Six groups were established by combining two dialysate calcium concentrations and three types of calcimimetic preparations. Changes in bone mineral density were assessed over six months using the Dual-Energy X-ray Absorptiometry (DEXA) Imaging Protocol.

Results: In patients with a calcium concentration of 2.5 mEq/L dialysate, evocalcet and etelcalcetide resulted in an increase in bone mineral density by 4.4% and 1.3%, respectively. Conversely, upacicalcet showed a decrease in bone mineral content by 3.3%. Among patients receiving dialysate with a calcium concentration of 2.75 mEq/L, only upacicalcet resulted in a significant reduction of 2.3% in bone mineral density when comparing pre- and post-medication measurements. (Figure)

Conclusions: Calcimimetics exert significant effects on bone metabolism in addition to their ability to lower iPTH levels. However, this effect may vary depending on the concentration of calcium in the dialysate.



TH-PO295

Loss of Residual Kidney Function at One Year in Diabetic and Non-Diabetic Incident Patients Treated with Incremental Hemodialysis

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Background: Residual kidney function (RKF) is better preserved with incremental haemodialysis (I-HD) as compared to conventional thrice-weekly HD (TW-HD). Presence of diabetes is associated with a faster decline of RKF in TW-HD. We aimed to analyze the RKF decline at one-year in diabetic versus non-diabetic patients initiating dialysis with I-HD.

Methods: We conducted an analysis of a prospectively assembled cohort in a single university centre including all adults initiating I-HD from January 2013 to December 2021. Outcomes were maintenance of incremental dialysis at one year and RKF decline at one year (or transition to TW-HD) according to the presence of diabetes.

Results: Of 264 patients who started hemodialysis, 93 initiated dialysis with I-HD of whom 30 were diabetics. At dialysis initiation, age, eGFR, comorbidity score, daily diuresis and urea clearance (KrU) were similar between non-diabetic and diabetic patients. Transition to TW-HD occurred after a mean duration of 16 +/- 15 months and 11+/- 10 months in non-diabetic and diabetic patients respectively (p= 0.07). At one year, the percentages of non-diabetic patients and diabetic patients still on I-HD were 51% and 37% respectively. At one-year, non-diabetic and diabetic patients had a daily diuresis decline of 32 and 37 % (p= 0.07) and a KrU decline of 34 and 46 % (p< 0.01) respectively.

Conclusions: RKF decline is more rapid in incident diabetic patients versus non-diabetic patients treated with I-HD and its duration before transition to TW-HD is shorter in patients with diabetes. Nephrologists should be aware that transition to TW-HD could be faster in diabetic patients.

TH-PO296

Patiromer Efficacy to Reduce Episodic Hyperkalemia in ESRD Patients: The PEARL-HD Study

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Background: Patients who have end-stage kidney disease (ESKD) maintained on hemodialysis (HD) are exposed to a high risk of cardiac arrhythmias, and this risk is augmented by periodic exposures to hyperkalemia (HK). Use of dialysate with a low potassium concentration may increase the risk of sudden cardiac death. Furthermore, HD patients carry a high pill burden, and it is unclear if prescription of an additional oral medication will reduce the frequency of episodic HK. The purpose of the study is to determine whether patiromer (P) administered daily will effectively reduce episodes of HK in ESKD patients who receive HD, and to explore whether P administration reduces the number of significant arrhythmia events.

Methods: This is a prospective, randomized, open-label trial. Eligible ESKD patients who were on thrice-weekly HD were screened from health records. A total of 33 patients were randomized 1:1 to P vs usual care. Patients randomized to P were administered the medication daily with breakfast or lunch in place of their prescribed phosphate binder, and the dose was titrated based on pre-HD serum potassium concentrations at start of weeks 1, 2, and 3. All participants received 7-day continuous cardiac monitors (CCM) at baseline and at week 4. A Mann-Whitney test was used to compare median number of HK episodes across groups. Fisher's exact test was used to compare the probability of at least 1 HK episode.

Results: Of those randomized, one withdrew due to adverse symptoms, and one withdrew due to pregnancy. The mean age of randomized patients was 57 y, 50% were male, 79% were Black, 11% were Hispanic/Latino, and mean HD vintage was 6 y. The P group had significantly lower median HK episodes compared to the control group (0 vs 3, p=0.002). Those in the P group were significantly less likely to have at least one HK episode compared to the control group (21% vs 71%; p=0.021). On the week 4 CCMs, 5 participants had > 1000/24 hr premature ventricular contractions, 4 had ventricular tachycardia events, 3 had atrial fibrillation, and 0 had bradycardia events, with no differences between the groups.

Conclusions: Patiromer administered orally once a day effectively reduces frequency of HK in ESKD patients who receive thrice-weekly HD. Larger studies are needed to determine whether patiromer reduces significant cardiac events.

Funding: Commercial Support - Vifor

TH-PO297

Incidence and Concurrence of Hyperkalemia and Hyperphosphatemia in a Single Outpatient Dialysis Setting: Long vs. Short Interdialytic Interval

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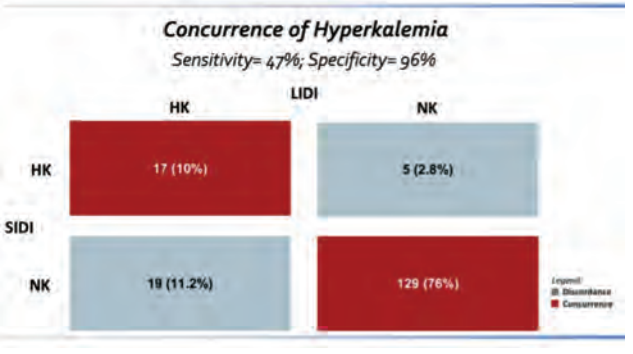
Background: Predialysis hyperkalemia is a common finding in patients receiving intermittent hemodialysis, more common following the long interdialytic interval (LIDI). Monthly laboratory assessments are most often done mid-week, following a short interdialytic interval (SIDI). We examined the occurrence and concurrence of hyperkalemia and hyperphosphatemia in individual patients, SIDI vs. LIDI to determine the sensitivity and specificity of detecting these electrolyte abnormalities following short vs. long intervals.

Methods: Serum potassium and phosphorus were measured predialysis after a LIDI which followed a previous mid-week SIDI. We performed a retrospective observational cohort study in this single outpatient dialysis center treating 174 patients aged ≥ 18 receiving dialysis 3 times weekly for at least 3 months. Hypokalemic patients were excluded. Patients were categorized into two groups depending on severity of serum potassium: NK=Normal and mild (3.5-5.4 mEq/L) and HK=Moderate and Severe (≥ 5.5mEq/L). Phosphorus levels were grouped: NP= 2.4-6.5 mg/dL and HP ≥ 6.6 mg/dl. The incidence of these two electrolyte abnormalities and concurrence, with calculations of sensitivity and specificity for elevations noted in SIDI vs LIDI were evaluated.

Results: HK group was noted in 13% of patients (22/170) at SIDI and 21% (36/170) at LIDI, 1.6 times more likely. Only 17 of the 36 patients in the HK group were hyperkalemic at both SIDI and LIDI, 47% sensitivity. Similarly, the sensitivity for detection of hyperphosphatemia SIDI vs LIDI in the HP group was only 50%.

Conclusions: A clinically significant number of patients with predialysis hyperkalemia will go undiagnosed if routine monthly testing is only performed following a SIDI. In view of new, safe and effective potassium binders approved for treatment in adults with chronic hyperkalemia, monitoring of potassium following LIDI should be evaluated on a periodic basis.



TH-PO298

Favorable Outcome of Combined Antihypertensive Agents for Patients Undergoing Hemodialysis

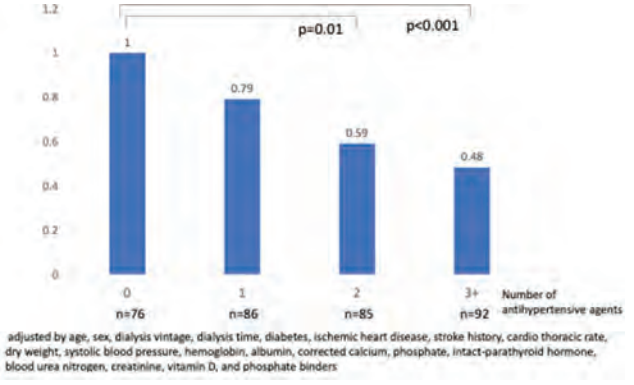
Emiko Otsuka,[1,2] Mineaki Kitamura,[2] Maiko Nakamura,[1] Hiro Inoue,[1] Satoshi Funakoshi,[1] Tomoya Nishino.[2] *[1]Nagasaki Renal Center, Nagasaki, Japan; [2]Nagasaki Daigaku, Nagasaki, Japan.*

Background: Various antihypertensive agents are currently available. Some of them, including angiotensin receptor blockers, not only lower blood pressure but also have a favorable effect on life prognosis. However, the pleiotropic effects of anti-hypertensive agents in patients undergoing hemodialysis remain unknown.

Methods: Patients undergoing hemodialysis during 2011 and 2012 at Nagasaki Renal Center were followed up until June 2021. Multivariate Cox regression analyses were conducted, including patients' demographic data, such as blood pressure and the number of antihypertensive agents received.

Results: A total of 339 patients (mean age: 67.3 years, 57% men, median dialysis vintage: 4.7 years) were included. The prescription ratios of angiotensin receptor blockers, beta-blockers, and calcium blockers were 41%, 19%, and 50%, respectively. According to the multivariable Cox regression analysis, angiotensin receptor blockers (Hazard ratio [HR]: 0.69, 95% confidential interval: 0.51–0.95, P=0.02) and calcium channel blockers (HR: 0.58, 95% confidential interval: 0.43–0.77, P<0.001] were associated with a better prognosis. Compared with patients who did not receive antihypertensive agents, patients who were prescribed one, two, and three or more antihypertensive agents showed an adjusted relative risks of death of 0.79, 0.59 (p=0.01), and 0.48 (p<0.001), respectively.

Conclusions: Our study showed that the number of antihypertensive agents received was negatively correlated with prognosis, indicating their pleiotropic effect. Therefore, physicians should combine antihypertensive agents to lower the blood pressure of patients undergoing hemodialysis to improve the prognosis.



TH-PO299

Association of Erythropoiesis-Stimulating Agents with Peri-Dialytic Blood Pressure Parameters

Anika T. Singh,[1,2] Timothy E. Yen,[3] Suraj Sarvode Mothi,[4] Sushrut S. Waikar,[5,6] Finnian R. McCausland.[1,2] *[1]Brigham and Women's Hospital Department of Medicine, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]The University of Mississippi Medical Center, Jackson, MS; [4]St Jude Children's Research Hospital, Memphis, TN; [5]Boston Medical Center, Boston, MA; [6]Boston University School of Medicine, Boston, MA.*

Background: Anemia is a common comorbid condition among patients with end-stage kidney disease (ESKD) requiring maintenance hemodialysis and is associated with morbidity and mortality. While recombinant human erythropoietin (rHuEPO) revolutionized anemia correction, concerns existed about the development or worsening of hypertension. This study aims to understand practice patterns of erythropoiesis-stimulating agent (ESA) use in outpatient hemodialysis and associations of ESA use with Hyper0 (any increase in systolic BP from pre- to post-HD) and peri-HD BP parameters.

Methods: ESA administration at individual HD sessions was assessed from the DaVita Biorepository (n=950), a prospective cohort study consisting of clinical data and biospecimen collection. Unadjusted and multivariable Poisson and linear random effects models adjusted for age, sex, race, access, pre-HD SBP, HD vintage, UFR, diabetes, heart failure, ischemic heart disease, peripheral vascular disease, and lung disease were fit. Exploratory models were fit including the prior variables with additional adjustment for hemoglobin (Hb) and endothelin-1 (ET-1).

Results: Mean age was 53 ±22 years, 44% were females, and 38% were Black. Mean pre-HD SBP was 152 ±28 mmHg. ESAs were administered at 97,172 of the 135,892 sessions (71.5%) sessions. Those with ESAs administered were younger, had higher UF volume and rate, longer HD sessions, higher pre-HD SBP, diabetes, PVD, and higher Hb and ET-1. In fully adjusted models, we observed a 9% higher rate of Hyper0 (IRR 1.09; 95%CI 1.06–1.12 mmHg.) In exploratory models adjusted for Hb + ET-1, this association was mildly attenuated (IRR 1.06; 95%CI 1.01–1.1 mmHg.) In fully adjusted models of peri-HD parameters, ESAs were associated with a higher nadir SBP (IRR 1.3; 95%CI 1.1–1.6 mmHg) with similar patterns of association noted for ESAs and post-HD SBP.

Conclusions: We observed an independent association between ESA administration and higher risk of Hyper0, and higher intradialytic SBP parameters. Future studies are warranted to better understand the mechanisms underlying these findings.

Funding: NIDDK Support

TH-PO300

Hypotension at the Start of Dialysis Is a Risk Factor of Cardiovascular Mortality

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Background: In recent studies on hemodialysis (HD) patients, The association of Blood pressure at the start of dialysis and cardiovascular disease (CVD) morbidity is controversial. In a retrospective study, we aimed to investigate whether the pre-hemodialysis blood pressure levels predict CVD-related death.

Methods: The patients were followed up for up to 4 years. At baseline, demographic data, comorbidity data, physical examination results, and laboratory data were recorded for each patient. Pre-dialysis fasting blood samples were collected from arterial blood lines at the beginning of a week. We divided the study patients into 4 groups according to their systolic blood pressure at the start of dialysis in an ascending order: from the bottom 25th percentile (Q 1) to the top 25th percentile (Q 4). The Cox proportional hazards model was used to assess the association between blood pressure and the risk of CVD related death.

Results: A total of 132 outpatients treated at the Kohsaikai Kamiooka Jinsei Clinic in Yokohama and the Soubudai Nieren Clinic in Kanagawa, Japan between December 2008 and July 2009 were enrolled. At the baseline, blood pressure at the start of dialysis was 147 ± 20 / 51 ± 5 mmHg. Among the 132 patients, there were 11 lethal events due to CVD. The risk of CVD death was significantly higher in the lowest systolic blood pressure patients (Q 1) than in highest blood pressure patients (Q 4) for 4 -years (Kaplan-Meier curve, log rank $P = 0.035$). In the multivariate Cox regression analysis, low systolic blood pressure was found to be independent risk factors for CVD mortality.

Conclusions: Hypotension at the start of dialysis is an independent risk factor of cardiovascular mortality.

TH-PO301

A Single-Center Study of the Appropriate Timing of Chest X-Rays in Hemodialysis Patients

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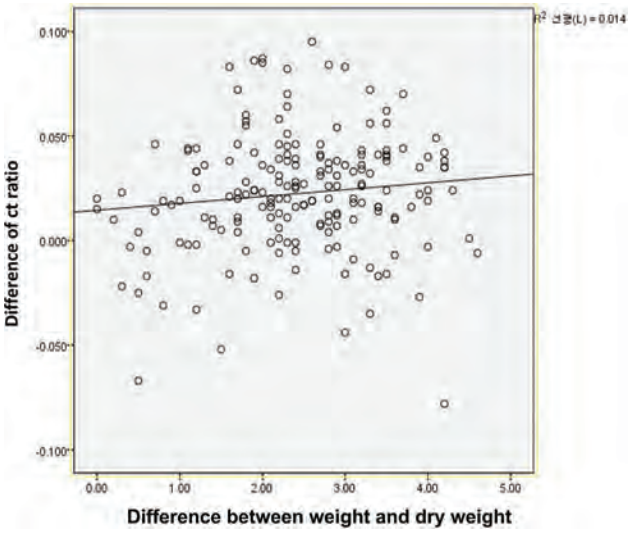
Background: To determine dry weight, the most commonly method is bioimpedance and relative plasma volume(RPV) monitoring. However the cardiothoracic ratio(ct ratio) of chest PA is still a common method of setting the dry weight. It is not clear when to perform chest PA. So chest PA is conducted at the convenience of patients and medical staff regardless of dialysis. We hypothesis that the ct ratio before dialysis would be different from that when the appropriate dry weight was reached.

Methods: We analyzed 211 hemodialysis patients at our hospital from December 1 to 10, 2022. We took chest PA in patients before hemodialysis on Monday or Tuesday, the beginning of the week(Pre-HD ct ratio). When our patients had been considered euvolemia and reached dry weight after hemodialysis during the week, we additionally performed a chest PA test and evaluated the ct ratio(Post-HD ct ratio). Using SPSS ver. 18, we compared the ct ratio of chest PA before and after dialysis. We analyzed the correlation between the difference in the ct ratio of chest PA and the difference between weight and dry weight at the time of the test.

Results: There was a significant difference between the Pre-HD ct ratio(0.513 ± 0.058) and the Post-HD ct ratio(0.491 ± 0.060, $P < 0.05$). The difference in the ct ratio of the chest PA was correlated with the difference between weight and dry weight. However, differences in ct ratio were not related to gender, age, primary disease, dialysis period, and previous RRT methods.

Conclusions: There was a difference in the ct ratio of chest PA before and after dialysis. As the patient's weight approached the dry weight, the ct raito of the chest PA decreased. We concluded that the appropriate time to administer chest PA was after the patient's weight reached dry weight.



TH-PO302

Transcatheter Aortic Valve Implantation Is Effective for Severe Aortic Valve Stenosis in Hemodialysis Patients

Kenji Harada. *Kokura Kinen Byoin, Kitakyushu, Japan.*

Background: In Japan, of the >340,000 chronic dialysis patients, approximately 60% have lifestyle-related diseases including diabetes and nephrosclerosis. Two-thirds of maintenance dialysis patients (age, ≥65 years) often develop aortic stenosis (AS) and other serious and complex systemic cardiovascular disease complications associated with chronic kidney disease mineral and bone disorder (CKD-MBD). Furthermore, renal function loss and a prolonged state of renal failure are observed requiring renal replacement therapy (RRT). AS in dialysis patients progresses quickly, and the frequency of hospitalized treatment for heart failure increases with the worsening condition, leading to ADL deterioration, which may subsequently cause dialysis hypotension/interruption. At our hospital, of the 420 maintenance dialysis patients who died during hospitalization in 5 years before 2020 (420/2,637=16%), 32 cases (8%) developed AS complications, which became their direct cause of death in 12 cases (3%), and aortic valve replacement (AVR) was performed in 5 cases (1%). Maintenance hemodialysis patients (HD) are at high risk group and have a poor prognosis for life. Previously, transcatheter aortic valve implantation (TAVI) was not indicated, but recently TAVI has been approved in Japan. Efficacy of TAVI for HD patients remains unclear, here we investigated several outcomes.

Methods: A total of 123 maintenance dialysis patients with severe AS were included in 2019-2021. We examined TAVI group and AVR group for length of hospital stay, hospitalization costs, life expectancy, and rates of complications such as occurrence of arrhythmias.

Results: Over a 3-year period, we performed TAVI for 58 maintenance dialysis patients (mean age, 81 years); their median duration of hospitalization was 14 days for a median cost of 6,259,350 JPY. The mean age was older than that of 66 patients who underwent open-heart AVR during the same period (mean age, 73 years; 35 days for 7,192,570 JPY); therefore, the cost was less, and the rate of complications, including vital prognosis and arrhythmia, was not inferior in hospitalization period.

Conclusions: In conclusion, TAVI is effective for elderly maintenance dialysis patients with severe AS and has a positive health care economics, ADL maintenance.

TH-PO303

Apollo DB: Characteristics of a Global Dialysis Database Across Major World Regions

Melanie Wolf,[1] Yue Jiao,[2] Kaitlyn Croft,[1] Maria Ines Diaz Bessone,[3] Marco Rancati,[4] Anke Winter,[1] Paola Carioni,[4] Sheetal Chaudhuri,[2] Luca Neri,[4] Kanti Singh,[2] Milind Nikam,[5] Stefano Stuard,[1] Adrian M. Guinsburg,[2] Jeffrey L. Hymes,[2] Len A. Usvyat,[2] John W. Larkin,[2] Franklin W. Maddux.[2] Apollo DB Team. *[1]Fresenius Medical Care, Bad Homburg, Germany; [2]Fresenius Medical Care, Waltham, MA; [3]Fresenius Medical Care, Buenos Aires, Argentina; [4]Fresenius Medical Care, Crema, Italy; [5]Fresenius Medical Care, Singapore, Singapore.*

Background: Large amounts of data are captured during dialysis. This data can be used for secondary purposes to understand and advance care models, yet data is often not available on a multinational level. Apollo DB is an anonymized dialysis database that combines and harmonizes data from a global provider for research and quality improvement activities.

Methods: Apollo DB captures data from 40 countries on demographics, laboratories, treatments, and outcomes. Data from different electronic systems is harmonized and anonymized based on logic established in a re-identification risk assessment. Data is consolidated and stored in a central cloud environment. The database contains data on 363 variables from Jan 2018-Mar 2021 and will be updated periodically.

Results: Apollo DB includes 543,169 patients, 4.6% Asia-Pacific (AP), 13.9% Europe, Middle East, & Africa (EMEA), 7.0% Latin America (LA), and 74.5% North America (NA). Select characteristics are shown by world region in **Figure 1**. Most patients are 45-64 years old (yo), yet more are 18-44 yo in AP & LA, while more are 65-74 & ≥75 yo in EMEA & NA. Hemodialysis is the most used modality, but peritoneal dialysis is common in LA (17.3%) and NA (13.2%). There were regional differences, such as higher urea removal in EMEA that commonly uses hemodiafiltration. The mean treatment time tends to be lower in NA and patients have a higher weight and are taller versus other regions.

Conclusions: In a first descriptive analysis, several regional differences were observed. These patient characteristics act as benchmarks for the nephrology community. Apollo DB offers opportunities for investigators to conduct global analytics and advance the state of the art.

Funding: Commercial Support - Fresenius Medical Care

Figure 1: Apollo DB Characteristics by World Region

Parameter		AP	EMEA	LA	NA
Patient n		25,231	75,396	38,147	404,395
Country n		12	22	5	1
Age at dialysis start	18-44	20.5%	16.7%	22.4%	15.6%
	45-64	46.0%	38.4%	43.4%	41.3%
	65-74	21.1%	25.3%	21.8%	24.6%
	≥75	12.3%	19.5%	12.4%	18.5%
Female		42.2%	40.0%	40.4%	42.3%
Height [cm]	<150	5.2%	4.2%	7.8%	2.4%
	150-159	27.1%	19.4%	25.8%	16.1%
	160-169	39.0%	36.6%	39.6%	31.5%
	170-179	21.6%	30.6%	21.8%	30.2%
	180-189	3.8%	8.2%	3.2%	16.0%
	190-199	0.2%	0.7%	0.2%	2.3%
	≥200	0.01%	0.05%	0.02%	0.12%
Dialysis treatments n		4,717,899	19,066,011	7,399,095	108,833,244
Patients	HD	87.6%	67.7%	87.6%	93.9%
	HDF	25.5%	67.7%	22.6%	0.0%
	PD	0.0%	3.2%	17.3%	13.2%
Pre-dialysis weight [kg]		69.5	76.8	71.3	85.4
Treatment time [min]		252.7	249.2	243.4	224.1
UFV [mL]		2580.7	2334.8	2416.5	2522.6
Pre-BUN [mg/dL]		53.7	40.4	55.3	56.5
Post-BUN [mg/dL]		13.2	10.5	13.9	14.9
Urine volume [mL]		796.4	888.9	1092.0	1000.9
PD volume/day [mL]		2000.0	1749.8	1928.5	4127.6
PD exchanges/day n		4.0	3.7	5.1	4.5

Data presented as counts (n), proportions (%), or mean values by major world region. BUN: blood urea nitrogen; HD: hemodialysis; HDF: hemodiafiltration; PD: peritoneal dialysis; UFV: ultrafiltration volume; AP: Asia Pacific; EMEA: Europe, Middle East, and Africa; LA: Latin America; NA: North America

TH-PO304

Characteristics of Global Dialysis Data from Multiple Providers in the New MONitoring Dialysis Outcomes (MONDO) Dataset

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Background: The **MON**itoring **D**ialysis **O**utcomes (**MONDO**) initiative is an academia-industry collaboration whereby providers can contribute data to an anonymized dataset used for joint research purposes. We present the characteristics of 20 years of longitudinal patient data contributed to the new MONDO dataset, which is now the most robust global dialysis dataset in the world.

Methods: Data from Jan 2000-Dec 2019 on 382 fields was captured longitudinally on a per patient per observation level (e.g., each lab, treatment, value) with a universal data structure. Detailed distribution statistics were used for re-identification risk assessment and confirmed the anonymization logic for providers to apply and provide acceptably low risk, consistent with international data privacy standards (e.g., GDPR, HIPAA). Final datasets were consolidated and hosted by the Renal Research Institute.

Results: Nine providers from 41 countries across six continents contributed to MONDO (289,715 patients across 20 years). Hemodialysis was the most used modality globally (**Table 1**). In Europe, Middle East & Africa, 63.2% of patients used hemodiafiltration (HDF) for ≥1 treatment. Peritoneal dialysis (PD) was used in 20% of patients in Latin America (LA) (20%) and 15% in North America (NA), yet ambulatory PD was more frequent in LA, while cycling PD was more frequent in NA. 11% of patients received a transplant. 42.5% died or stopped dialysis with some regional variability.

Conclusions: MONDO developed a new global research dataset to study dialysis outcomes, pathophysiology, and risk prediction. MONDO is open to collaboration and contributions without geographic restrictions.

Funding: Commercial Support - Fresenius Medical Care

Table 1. Characteristics of patients in the MONDO dataset

	APAC	EMEA	LATAM	NORTH AM
Patient n	100.0% (33862)	100.0% (138940)	100.0% (98178)	100.0% (18735)
Female	42.3% (14320)	40.0% (55599)	42.2% (41475)	41.9% (7844)
HD	89.6% (30339)	78.1% (108493)	87.3% (85741)	93.7% (17552)
HDF	31.2% (10556)	53.2% (87800)	10.0% (9810)	0.5% (91)
Mixed HD/HDF	0.4% (143)	0.5% (687)	<0.1% (49)	N/A
CAPD	0.2% (77)	2.7% (3768)	12.3% (12068)	6.3% (1181)
CCPD	<0.1% (8)	0.6% (884)	7.2% (7103)	8.7% (1623)
Kidney function recovered	2.1% (728)	3.1% (4239)	5.7% (5588)	4.1% (760)
Transplant	6.9% (2338)	13.1% (18192)	9.8% (9637)	10.0% (1880)
Died or Withdrawal	30.6% (10356)	42.4% (58938)	48.6% (47705)	33.4% (6250)

Data are shown as %(n). Modality data shows proportion and number of patients using the modality one or more times during the 20 years of follow up. Outcomes are based on crude counts that do not consider follow-up time. HD: hemodialysis; HDF: hemodiafiltration; CAPD: continuous ambulatory peritoneal dialysis; CCPD: continuous cyclic peritoneal dialysis APAC: Asia Pacific; EMEA: Europe, Middle East, Africa; LATAM: Latin America; NORTH AM: North America.

TH-PO305

Volumetric Accuracy Testing (VAT) of a Novel Patient-Centric Gravity-Based Automated Peritoneal Dialysis Cycler (GBC) vs. Conventional Pump-Based Cyclers (PBC)

James A. Sloand,[1,2] Steve J. Lindo,[2] Rick Pendergraft.[2] *[1]The George Washington University Milken Institute of Public Health, Washington, DC; [2]Simergent, Oklahoma City, OK.*

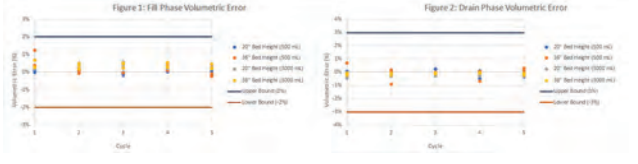
Background: Safe and effective APD cycler function requires volumetric accuracy of fill and drain (F/D) volumes to accurately calculate achieved ultrafiltration (UF) critical to clinical outcomes in PD. PD fluid volume measurement in most contemporary APD cyclers is now pump, rather than gravity-based, partly due to unreliability of GBC load cells. However, PBCs contribute to device noise/sleep disruption and drain pain (in up to 47% of patients) from high suction pressures. VAT of a low cost, novel, newly engineered GBC designed to provide reliable F/D volumes was performed and values compared with reported F/D accuracy of conventional PBCs and another recently marketed GBC. In a recent blinded study, features of the novel GBC were rated far more favorably by PD patients & RNs than those of conventional PBCs.

Methods: VAT was performed collecting volume from both a Sartorius laboratory scale ("actual") and the new GBC ("measured"). VAT was performed on 3 tubing sets with a patient bag at 2 bed heights (36" & 20") and 2 F/D volumes (500ml & 3000ml). For both Fill & Drain, 5 cycles of 500ml (total 30 F/D cycles) and 3 cycles of 3000ml (total 18 F/D cycles) were tested. VAT was calculated as (measured-actual/actual) x 100%.

Results: Figures 1 & 2 show VAT results for Fill and Drain for 500ml & 3000ml F/D cycles at described bed heights. All 500ml Fills were within the required accuracy bounds of ±2%; all Drains were within the required accuracy bounds of ±3%. VAT for 3000mL volumes for both F/D was within ±1% volumetric error at both bed heights. Published F/D accuracy for FMC Liberty, Baxter HomeChoice, and FMC Silencia (GBC) are ±2%/±3%, ±2/±2%, and <±5%, respectively.

Conclusions: The novel low cost GBC with enhanced load cell technology & features previously demonstrated to be preferred by PD patients & RNs achieved F/D volumetric accuracy comparable to conventional PBCs and better than that of another recently marketed GBC. The new GBC has potential to significantly reduce drain pain, device noise & cost while maintaining UF accuracy.

Funding: Commercial Support - Simergent LLC



TH-PO306

A Feasibility Study to Establish Dialysate Flow Characteristics in Peritoneal Dialysis to Associate Outflow Dysfunction

Nupur Gupta, Kathleen A. Lane, Yang Li, Brent W. Miller. *Indiana University School of Medicine, Indianapolis, IN.*

Background: Peritoneal dialysis (PD) catheter dysfunction is the second leading cause of technique failure in PD after peritonitis. Failure to recognize this complication early result in techinique failure. Dialysate flow characteristics have been measured in the past for modeling automated PD dwell and drain time for clearance of solute rather than catheter dysfunction. We hypothesize dialysate flow characteristics are associated with outflow dysfunction.

Methods: The study was a prospective observational study measuring dialysate flow characteristics in incident PD patients. Dialysate flow rates were measured by standardized method weighing the drained volumes every 5 minutes up to maximum of 30 min or complete drainage of fluid up to 3 times during Training. The catheter-related complications were recorded during the study visits and then monthly up to 6 months. Patient characteristics at study entry were summarized by mean ± SD and proportions. Repeated-measure Poisson regression was performed to analyze incidences rates during and after training.

Results: 21 patients were consented; 3 withdrew. 17/21 patients had completed flow records. The mean age at study entry was 53.3 ± 16.9 years, and 58.8% were men. Two out of three training visits were used for analysis. The mean drain time for training visits (both sitting and reclined) was 17.9 ±8.1 min. 52.9% and 64.7 % of patients reported catheter related complications in training and follow up visits respectively. Drain pain was the most reported complication during training while catheter dysfunction was most common during follow up visits. SThe sitting total time ≥ 10 minutes from first training visit was associated with 83% lower odd risk incidents rates of complications in training (incidents rates ratio (IRR) - 0.17, CI - 0.050-0.581, P= 0.005). Catheter dysfunction in training was associated with complications during monthly visits (IRR -1.66, CI-1.01-2.73, P= 0.0477).

Conclusions: Our study established feasibility of measuring dialysate flow characteristics and reports PD catheter complication rate. The drain time ≥ 10 min is associated with reduced catheter related complications in training due to early intervention by the clinical staff. Catheter dysfunction in training increases the odds of complications during monthly visits.

Funding: Clinical Revenue Support

TH-PO307

Dynamical Monitoring of "Intraperitoneal" Pressures by a Sensor Integrated into a Peritoneal Dialysis (PD) Cycler: Proof-of-Principle Bench Studies

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Background: We performed two bench studies utilizing a PD simulator. One evaluated the accuracy and precision of IPP measurements by a pressure sensor integrated in a PD cycler; the second assessed the relationship between IPP and intraperitoneal volume (IPV) during volume exchanges.

Methods: The first study was performed using a PD simulator filled with 2 liters of 2.5% dextrose dialysate (Fig.1). The IPP was monitored every 15 seconds by the Liberty Cycler (Fresenius Medical Care North America, Waltham, MA). The height (h) of the PD simulator was adjusted to increase in 6 steps and decrease in 5 steps. The height increment (Δh) was 5.08 cm; each step was maintained for 10 minutes. The change in pressure (ΔP) is calculated as ΔP=ρ*g*Δh, where ρ (density of dialysate) and g (acceleration of gravity) were kept constant. The coefficient of variation (CV% = 100*Mean/SD) of the IPP was obtained at each step. The second bench study kept the PD simulator at a constant height and IPP measurements were repeated 8 times. Regression analysis and Bland-Altman plots were performed to determine the relationship between calculated and measured IPP.

Results: Fig.2 shows the change in height (a) of the simulator and the concurrent increased and decreased in IPP (b) with the steps up and down. ΔIPP correlated (R^2=0.98, p<0.0001) with ΔP in each step (c). IPPs were accurately and precisely measured with a smaller bias (0.34±0.87 cmH_2O) and CV (2.5±1.9 %). IPP correlated with IPV (Fig.3) during filling (R^2=0.99, p<0.0001) and draining (R^2=0.86, p<0.0003) respectively.

Conclusions: This bench study shows that ΔIPP can be measured accurately and precisely by the pressure sensor integrated in the Liberty Cycler and that IPP measurements should be feasibly, non-invasively and automatically performed using a PD cycler equipped with a pressure sensor. Given the importance of IPP changes during a PD treatment, the technique could be a valuable tool to dynamically assess IPP.


Fig 1 Study setup

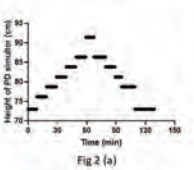

Fig 2 (a)

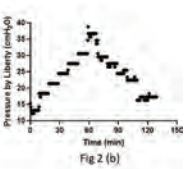

Fig 2 (b)

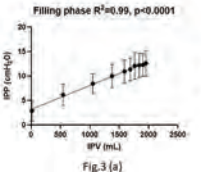

Fig.3 (a)

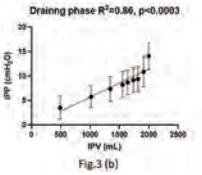

Fig.3 (b)

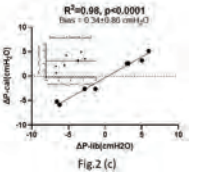

Fig.2 (c)

TH-PO308

A Prospective, Multi-Center, Open-Label Assessment of Efficacy and Safety of the Quanta Dialysis System for Home Hemodialysis

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Background: Hemodialysis (HD) treatments in the United States (US) are typically delivered in a dialysis center. Home hemodialysis (HHD) reduces costs to healthcare payors while providing more flexibility to patients with kidney failure. The Quanta™ Dialysis System (Quanta Dialysis System) is a modern, user-friendly HD device. Whether it is equally safe and effective when operated by patients and caregivers in the US at home vs. healthcare professionals at a center is unknown. The purpose of this study is to determine non-inferiority of efficacy and safety of the Quanta Dialysis System in self-care HHD vs. in-center HD.

Methods: This is a prospective study set in 12 sites in the US. Adult patients with kidney failure currently undergoing dialysis for ≥90 days were eligible. Enrollment began November 2021 and continued during the Omicron wave of the COVID-19 pandemic. Participants received HD at their respective HHD training centers for 4-8-weeks. While dialyzing, participants and caregivers trained to use the device at home. Once deemed competent by a nephrology care team, participants performed supervised HHD during a transition week, then performed HHD with a care partner for 8 weeks. The primary efficacy outcome is dialysis adequacy measured by mean standardized weekly Kt/V. The primary safety outcome is a composite of adverse events.

Results: As of April 2023, 23 patients were enrolled. The mean age was 55.5 ± 13.1 years, mean weight was 95.6 ± 20.4 kg, 10 (43.5%) participants were female, and 17 (73.9%) had a fistula or a graft for dialysis access. Only 4 (17.4%) participants have previously dialyzed with an HHD device. To date, 15 patients have transitioned from in-center HD to HHD, including 11 (73%) who achieved competency by the 5th week of training. Eight patients have completed the study.

Conclusions: Data on successful completion of training suggests the Quanta Dialysis System is easy to use for patients with kidney failure in the US. As the final participants are projected to complete the study by August 2023, complete safety and efficacy comparisons between use of the Quanta Dialysis System in HHD vs. in-center HD will be reported at the time of presentation.

Funding: Commercial Support - Quanta Dialysis Technologies

TH-PO309

Patient Reported Outcomes (PRO) Among Patients Receiving Home Hemodialysis (HHD) with the Tablo® Hemodialysis System

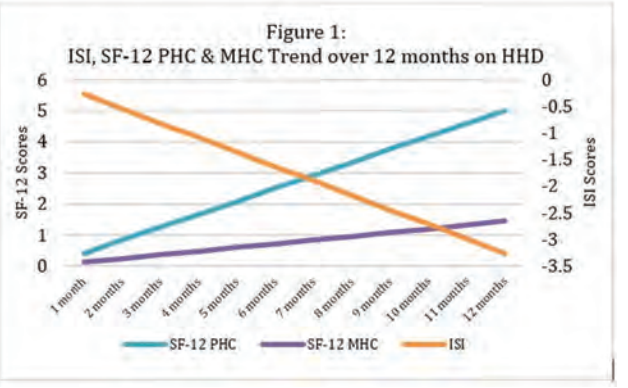
Jarnet H. Wazny,[1] Christie D. Holmes,[1] Cynthia J. D'Alessandri-Silva,[1] Glenn Chertow.[2] *[1]Outset Medical, San Jose, CA; [2]Stanford University School of Medicine, Stanford, CA.*

Background: The HOME Registry is an ongoing observational ("real world") study of patients with kidney failure utilizing the Tablo® Hemodialysis System (Tablo) for home hemodialysis (HHD). To date, relatively few studies have evaluated patient-reported outcomes among patients receiving HHD.

Methods: We evaluated the first 55 patients on Tablo HHD using an ePRO software at 1-, 3-, 6- and 12-month visits using: 1) Physical Health Composite (PHC) and 2) Mental Health Composite (MHC) scores from the Medical Outcomes Study Short Form 12 (SF-12) along with the 3) insomnia total score from the Insomnia Severity Index (ISI). We employed mixed effects regression for repeated measurements, using specific covariance matrix structures to allow for model convergence and to optimize model fit. We analyzed time (visit) as a fixed effect and age, designated race, education, employment, and care partner type as random effects.

Results: The mean patient age was 57.4 years old. The demographic composition was 76% men, 5.5% Black, 9% Hispanic/Latino, 39% with less than college degree attainment, 69% AV fistula, and 45% having transitioned from in-center HD. The SF-12 PHC and ISI had positive correlations with time, at p=0.046 and p=0.0035, respectively. Every 1 month increase in time was associated with a 0.417 increase in the SF-12 PHC and a 0.272 decrease in ISI score. There was no significant relation between time and the SF-12 MHC (p=0.19). Figure 1 shows modeled results for ISI and SF-12 PHC and MHC.

Conclusions: Preliminary results show favorable effects of Tablo-enabled HHD on self-reported physical health and symptoms of insomnia. Longer term follow-up in a larger patient sample will further elucidate the benefits of Tablo-enabled HHD on functional capacity, symptoms, and well-being.



TH-PO310

Characteristics of Tablo Home Hemodialysis Users in Medicare Fee-for-Service

Stephan C. Dunning,[1] Michael A. Aragon,[1] Cynthia J. D'Alessandri-Silva,[1] Eric D. Weinhandl.[2,3] *[1]Outset Medical, San Jose, CA; [2]University of Minnesota Twin Cities, Minneapolis, MN; [3]Satellite Healthcare, San Jose, CA.*

Background: The Tablo® Hemodialysis System was cleared for home hemodialysis (HHD) use in March 2020, offering dialysis patients the first novel technology for HHD since 2005. In the 2022 ESRD PPS Final Rule, the Centers for Medicare and Medicaid Services (CMS) designated Tablo a "substantial clinical improvement" over the incumbent technology based on increased treatment flexibility, higher treatment adherence, higher modality retention and improvement in patient quality of life. This designation made it eligible for Capital-Related Assets Transitional add-on Payment for Innovative Equipment and Supplies (CRA TPNIES).

Methods: Using CMS Medicare FFS Limited Data Sets, we identified Tablo HHD claims between Jan 1 and June 30, 2022, using HCPCS E1629, which was designated for billing the CRA TPNIES reimbursement. Importantly, TPNIES billing is not validated, so may under capture the true Tablo HHD population in Medicare FFS. We then summarized user characteristics, including age, sex, race/ethnicity, and concurrent Medicaid enrollment, as well as treatment characteristics.

Results: Between Jan 1 and June 30, 2022, there were 53 patients who collectively had 1,830 billed Tablo HHD treatments (Mean treatments per patient: 34.5, SD: 25.2). The mean (SD) age was 60.6 (15.5), with 51% age ≥65. Racial distribution was 28.3% Black, 49.1% White and 22.6% Other, and 34.4% of users had concurrent Medicaid enrollment. A summary of the billed treatments shows a mean (SD) weight of 82.9 (20.8) kg, and a mean (SD) hemoglobin of 9.8 (1.4) g/dL. Vascular access type in use was 42% Catheter, 58% Fistula. Based on billed Tablo HHD treatment volume, the total TPNIES add-on payments (assuming $25 per treatment) in the first half of 2022 are estimated to be $45,750.

Conclusions: This is a novel and early window into Tablo HHD users and treatments in the Medicare FFS population and a first estimate of the TPNIES add-on payment. Thus far, the population appears to be more elderly and diverse, and with greater catheter dependence than the broader HHD population. Additional research into Tablo HHD adoption, utilization and outcomes in the Medicare population will be important for understanding and advancing home dialysis growth overall.

Funding: Commercial Support - Outset Medical

TH-PO311

Characteristics of the First 500 Tablo Home Hemodialysis Users

Stephan C. Dunning, Hunter Kirk, Cynthia J. D'Alessandri-Silva, Michael A. Aragon. *Outset Medical, San Jose, CA.*

Background: The Tablo® Hemodialysis System was cleared for home hemodialysis (HHD) use in March 2020, offering dialysis patients the first novel technology for HHD since 2005. In the 2022 ESRD PPS Final Rule, the Centers for Medicare and Medicaid Services (CMS) designated Tablo a "substantial clinical improvement" over the incumbent technology based on increased treatment flexibility, higher treatment adherence, higher modality retention and improvement in patient quality of life. As adoption continues to grow, we sought to characterize the first 500 users in the Tablo HHD population.

Methods: We collected user-reported demographics and geographic information among the first 500 Tablo HHD users. Data include age, sex, race/ethnicity, employment status and Zip Code. Using Zip Code, we evaluated neighborhood characteristics such as Social Deprivation Index (SDI) and Rural status using RUCA 4+. Population characteristics are compared to similar data from the 2022 USRDS Annual Data Report, where feasible. The results are descriptive only using MS Excel. No statistical significance tests were performed.

Results: Across the basic demographics of age sex and race/ethnicity, the Tablo HHD population and USRDS HHD appear to have similar characteristics with several favorable trends. The first 500 Tablo HHD users versus USRDS HHD are: ● Slightly older: 35.2% vs 29.0%, Age 65+ respectively. ● Slightly more racially/ethnically diverse: 45.6% vs 52.8% White, 19.5% vs 30.6% Black, 11.5% vs 3.0% Asian and 18.1% vs 11.1% Hispanic, respectively. ● More unemployed, fewer retired: 33.5% vs 18.6% Unemployed,

38.8% vs 54.3% Retired, respectively. Socio-economic data show equitable adoption across strata, with SDI 1-33 (37.2%), SDI 34-66 (32.2%) and SDI 67-100 (30.6%). Rural and Urban status are 14.4% and 85.6%, respectively.

Conclusions: Continued improvement in equity across ethnic, racial and socio-economic status among all HHD patients is critical to successful expansion of home adoption in the US. The first 500 Tablo Home Hemodialysis users have similar characteristics to the overall HHD population reported by the USRDS with early favorable trends toward diverse and equitable adoption across racial and socio-economic groups.

Funding: Commercial Support - Outset Medical

TH-PO312

Utilization of Extended Training Decay Periods to Evaluate Training Effectiveness in Home Dialysis Devices

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Background: When conducting medical device usability testing, users perform tasks under representative use conditions. A "training decay" in the study is a defined time period between user training and user testing to allow for representative memory decay. FDA 2016 guidance emphasizes the training provided to test participants should approximate the training that actual users would receive including training decay. In practice, medical device manufacturers typically utilize a 1-hour training decay to simplify scheduling logistics. Real-world training decay for home hemodialysis (HHD) patients ranges from several hours up to nine days before their first-time independent use. Here we present the results of a usability validation study evaluating extended training decay on the safe and effective use of the Tablo Hemodialysis System.

Methods: A human factors (HF) protocol was implemented with recruitment of 16 patient/care partner pairs (PCP) and 17 health care professionals (HCP). The PCP arm included 10 pairs without any prior HHD experience, and the HCP arm was composed of dialysis nurses and technicians. Each participant completed standard Tablo training, after which they experienced extended training decay periods ranging from 1 to 4 weeks. All participants then performed a simulated dialysis treatment (treatment setup, monitoring, and tear down) on Tablo. Task performance (use errors, close calls, and difficulties), subjective interviews and knowledge task assessments were recorded.

Results: The training decay averaged 16 days (min = 9 days, max = 28 days) for HCPs and 13 days (min = 6 days, max = 25 days) for patient/care partner pairs. Participants were able to complete all necessary tasks with minimal use error rates (0.32% and 0.65%), for HCPs and PCPs, respectively. Post testing, 100% of participants reported confidence in being able to use Tablo safely and effectively.

Conclusions: Objective evidence of effective training through HF validation is critical to ensuring safe use of home dialysis devices. Task performance from this study demonstrates the effectiveness of standard Tablo training in scenarios of extended training decay including and beyond actual use (up to 28 days). These results extend prior data on the usability and ease of learning Tablo for patients performing home hemodialysis.

Funding: Commercial Support - Outset Medical

TH-PO313

Hybrid Dialysis in Peritoneal Dialysis Patients with Low Solute Clearance or Volume Overload: Two Years' Experience

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Background: ESRD patients on PD prefer this modality because it allows them greater flexibility related to timing, a better lifestyle, and fewer dietary restrictions compared to HD. With the reduction in residual renal functions, the largest applicable PD regimen might not be enough to achieve adequate solute clearance or fluid removal. In such circumstances, convincing some patients to shift completely to hemodialysis is usually difficult. We started a Hybrid Dialysis (HyD) prescription for these patients by keeping them on PD 6 days per week and an HD session once per week. The safety and efficacy of HyD were evaluated.

Methods: Identified all PD patients with either low solute clearance or inadequate ultrafiltration despite using the maximum applicable PD regimen. They were referred to vascular surgeons for hemodialysis access then arranged HD slots. We enrolled eighteen patients from May 2021 till April 2023. All of them were kept on once-weekly hemodialysis for 3-4 hours plus PD 6 days per week. We evaluated volume status clinically, Pre-HD urea, potassium, phosphorus, and bicarbonate as indicators of solute clearance, and Albumin level as an indicator of nutritional state. In addition, dialysis-related Emergency Department visits and dialysis access-related infection rates after starting hybrid dialysis were also observed.

Results: Volume status significantly improved associated with a reduction in mean systolic blood pressure, (169 ± 32 Vs 135± 15 mmHg, $p < 0.0001$) and around a 5 % drop in mean dry weight. All solute clearance indicators showed significant improvement with HyD, reductions in mean urea by 36.7% (27.5 ± 8 vs 18.4 ± 7 mmol/L) p-value < 0.001, mean potassium by 23.52% p-value <0.0001 and mean phosphorus reduction of 26.5 % p-value <0.01. The rise in mean bicarbonate was by 15.6 % p-value <0 .001. Improvement of mean serum albumin from 26 ± 6 gm/L to 30 ± 7 gm/L p-value < 0.05. No ED visits or dialysis access-related infections were reported.

Conclusions: Hybrid dialysis is a safe, effective, and reasonable dialysis modality in PD patients with either volume-overloaded or low solute clearance. associated with an improved nutritional state & better control of BP.

TH-PO314

Urgent Start Peritoneal Dialysis (PD) as a Safe and Effective Dialysis Modality to Reduce the Dropout of Patients on Peritoneal Dialysis

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Background: PD dropout became a major factor affecting the unitized PD program and created a new burden in the setting of limited HD slots. Our registry shows that almost 35-50 % yearly for the last 3 years of patients who choose PD as a permanent dialysis modality and started temporary HD through Permcath till the maturation of the PD catheter will change their mind and request to be kept on HD and removal of PD catheter even before starting PD training. Urgent start PD program started by keeping CKD 5 patients eligible to start PD on one vascular access (PD catheter) without Permcath insertion and start Peritoneal dialysis 48hrs post PD catheter insertion. The safety and efficacy of the program were evaluated through monitor any mechanical complications and patient satisfaction besides our regular parameters such as volume status and electrolytes.

Methods: Identified CKD-5 patients during ED visits with eithe an earlier plan for PD as a dialysis modality or having no plan. We evaluated the emergency and urgent need to start Renal replacement therapy. We created an Urgent Start PD pathway for those patients without the emergency need to start or who had an emergency need and became stable after starting HD through a temporary dialysis catheter. They were referred to vascular surgeons for PD catheter insertion after checking suitability and liability to Peritoneal dialysis. PD will start 48 hrs. after insertion. We enrolled sixteen patients from October 2022 till April 2023, all of them were started on APD but the final PD model is decided after completing both APD and CAPD training. Body surface area was the main factor that affected APD Prescription. Frequent PD clinic visits were arranged to readjust the PD regimen and monitor mechanical complications, patient satisfaction, volume status, and electrolytes.

Results: Almost all patients were discharged with satisfactory conditions & accepted electrolytes without any mechanical complications and with fewer dates of admission after starting the new program.

Conclusions: Urgent start PD seems to be a safe, effective, and reasonable way to reduce PD dropout in addition to reducing cost and total days of hospitalization. We need a larger number of patients and a longer duration to generalize the findings of these observations.

TH-PO315

Prevalence of Frailty and Symptom Burden in Patients on Staff-Assisted Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) is a preferred modality for patients with clinical or psychosocial consideration, but self-care can be challenging for some individuals. Staff-assisted PD offers support for patients to start or remain on PD. This study aims to evaluate the physical, cognitive, and emotional status of patients receiving staff-assisted PD.

Methods: Patients who received staff-assisted PD by April 2023 were included. Physical function was evaluated by the Clinical Frailty Scale (CFS; score >=5 indicating frailty), and the Katz Activities of Daily Living (ADL) surveys. Symptom burden (physical and emotional), cognition, and patient activation were evaluated using the Integrated Palliative Outcome Score (IPOS)-Renal survey, the Quick Mild Cognitive Impairment Screen (QMCI), and the Patient Activation Measures (PAM)-13-item survey, respectively. Surveys were completed after initiation of assistance. Descriptive analysis was performed on completed surveys.

Results: A total of 72 patients received staff-assisted PD. CFS, ADL, IPOS-Renal, QMCI, and PAM were completed by 72 (100%), 51(71%), 68(94%), 42 (58%), and 46 (64%) patients respectively. Frailty was identified by the CFS survey in 28% of patients, and 29% of ADL respondents were dependent in at least one activity. Of those who completed the IPOS-Renal survey, physical symptoms of moderate or worse severity were reported by 79% of patients, with weakness and poor mobility being the most common physical symptoms, while anxiety and depression at a moderate or worse severity was reported by 40% and 28% of the patients respectively. Mild cognitive impairment and dementia were identified in 15% and 28% respectively of those who completed the QMCI survey. Low activation (levels 1 and 2) was observed in 37% of patients.

Conclusions: Patients referred to staff-assisted PD experience significant physical and psychosocial challenges, underscoring the need for these programs to support home dialysis.

TH-PO316

Outcomes of Incident Peritoneal Dialysis Patients with Depressive Symptoms

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Background: In 2016, CMS introduced annual depression screening as a reporting measure under the QIP. For incident dialysis patients, screening surveys are typically administered by social workers in the fourth month of modality initiation. This study aimed to explore the outcomes related to depressive symptoms in a contemporary cohort of incident peritoneal dialysis (PD) patients.

Methods: A retrospective observational study was conducted on patients starting PD for the first time between January 2017 and December 2022 at dialysis units managed by a mid-sized U.S. non-profit dialysis provider. Those who completed the PHQ2 survey within 150 days after starting PD were followed for 365 days from the date of survey completion. A PHQ2 score equal to or greater than 3 was considered positive. Univariate and age- and sex-adjusted Fine-Gray models were used to examine the association between time to transfer to hemodialysis (HD) or death, and time to first hospitalization, while Poisson regression was used for rate ratios.

Results: A total of 2,215 patients were included. Mean age was 58.7 ± 15.9 years, with 38% being female. PHQ2 surveys were positive in 75 (3.4%) patients. During the follow-up period, 16.3% transferred to HD, 3.7% died, and 6.5% received a kidney transplant. Patients with a positive PHQ2 survey were found more likely to experience transfer to HD or death (hazard ratios (HR): 1.99; 95% CI: 1.33 – 2.97, and 2.02; 95% CI: 1.35 – 3.03 in the unadjusted and adjusted models respectively). The hospitalization event rate was 1.45 and 0.75 events per patient-year for those with positive and negative PHQ2 results, respectively (Rate Ratio (RR) 1.95, 95% CI: 1.53 – 2.45). Similarly, hospital days per year were 11.06 and 5.44 days per patient-year for the PHQ2 positive and negative patients, respectively (RR: 2.03, 95% CI: 1.87 – 2.20). Lastly, a higher hazard for time to first hospitalization was observed in those with a positive PHQ2 survey (HR 1.62, 95% CI: 1.14 – 2.31, and 1.62, 95% CI: 1.14 – 2.30).

Conclusions: Among incident peritoneal dialysis patients, depression symptoms are associated with increased risk of transfer to HD or death and of hospitalization. This represents a potentially addressable risk factor for poor clinical outcomes that may be amenable to intervention.

TH-PO317

Nurse-Assisted Home Hemodialysis with NxStage System One Portable Machine: An Experience in the Gulf Cooperation Council (GCC)

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Background: Home hemodialysis (HHD) is a renal replacement therapy applied to treat active, autonomous, and relatively, healthy dialysis patients. NxStage System One, portable dialysis machine suitable for home setting. NAHHD is an innovative modality for patients providing freedom choice in dialysis therapy. Indications for NAHHD in the GCC is due to Limited Mobility, CVA, Fractures, Morbid Obesity, Intolerance to conventional HD, Infections, Mental Retardation, Psychiatric disorder. Here, at NAHHD treating mostly debilitated and frail patients with comorbidities at home and long term care facilities. Presenting clinical outcomes of Home Hemodialysis treatment, at HHD, service provider in the GCC.

Methods: The study includes 566 patients undergoing HHD treatment, for atleast more than 3 months and thus one year report of the health outcomes with portable HD machine at home was done. Estimated the HD adequacy and key performance indicators. The frequency and length of session, fluid volume calculated by dose calculator by NxStage, with target standardised KT/V ≥2.1.

Results: The total number of 566 patients (X) on NxStage machine at home and at long term care facility were included in the study. Study group selected based on duration i.e., (X >3 months). Female- 52.65% and Male- 47.35%. The mean average age of the patients, 69.06 ± 14.63. The average comorbidities: 6.114 ± 3.45 (Min-2, Max-16). The vascular access: AVF- 25.27%, AVG- 3.53%, PC- 70.67%, AVF/PC- 0.53%. The yearly average of the biological parameters with HD adequacy are shown in Table 1. The annual mortality rate is 18.02%, as shown in Graph 1.

Conclusions: The results as shown states efficient and remarkable health outcomes. Moreover, the mortality rate of the HHD patients as comapred to the US Renal Data System, shows better quality of therapy and retention in patients.

TABLE 1: HD ADEQUACY & BIOLOGICAL OUTCOMES

HD ADEQUACY	YEARLY AVERAGE
Session Length (minutes)	222.75
Number of Sessions/Week	3.90
Filtration/Flow Fraction (FF%)	49.58
Dialysate Volume (L)	31.35
Post weight (Kg)	67.40
UF Volume (L)	1.96
HB (g/L)	107.39
Albumin (g/L)	36.77
Serum Calcium (mmol/L)	2.28
PO4 (mmol/L)	1.47
K (mmol/L)	4.98
PTH (pg/mL)	440.88
Std Kt/V	2.19

TH-PO318

Assisted Home Hemodialysis: A Game-Changer for Patients and Providers

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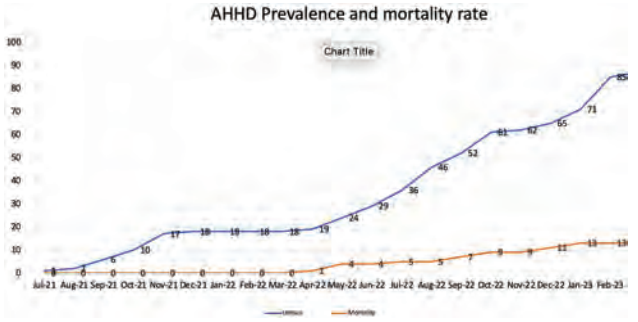
Background: Home hemodialysis HD (HHD) offers autonomy, cost benefits, and better quality of life. Uptake of HHD is limited by patient motivation and cognitive and physical barriers. Assisted HHD (AHHD) is a new concept where dialysis team provides HD at home but it is limited due to financial and logistics restriction. We are reporting success and outcomes of our AHHD program in the State of Qatar.

Methods: A Retrospective study of all HD patients who are enrolled in AHHD program between 7/2021 to 2/2023. Inclusion mainly for elderly patients requiring ambulance transportation to the dialysis center. Primary objective was effectiveness and safety of AHHD and secondary objectives were cost effectiveness and quality of life.

Results: 85 patients enrolled in our AHHD program during study period with a mean follow up of 7 months (total 5968 HD treatments). Age was 71+/-10 years with 45% males. 13 patients died and 2 patients returned to dialysis center. We had 8 incidents of HD catheter malfunction and 20 technical incidents resolved without affecting program flow. No reported significant access bleeding, falls or hypotension episodes. We found a significant decrease of 43% in hospitalization rates compared to 6-month pre-study period. The program proved to be cost-effective, resulting in a reduction of costs by 27%, primarily attributed to savings in ambulance transport expenses. Key performance indicators, including adequacy, anemia, and mineral and bone management were maintained. In a survey, patients and families expressed an extraordinary level of satisfaction, with rates exceeding 98% in all assessed categories.

Conclusions: We present our program for AHHD, designed for frailed dialysis population. This initiative has yielded exceptional outcomes, substantial cost savings, exemplary safety measures, remarkable enhancements in quality of life, and an extraordinary level of patient satisfaction.



AHHD prevalence and mortality rate

TH-PO319

Medication Management with Antihypertensive Agents and Associations with Peritoneal Dialysis Technique Failure in a Large, Retrospective Incident Cohort

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Background: The first 90 days of peritoneal dialysis (PD) have high rates of PD technique failure (TF). Although many factors determine patients' (pts) longevity on PD, only some are potentially modifiable. Proper management of antihypertensive medications (AH-M) is one modifiable factor that may help to control blood pressure and fluid balance. We aimed to assess the association between AH-M and PD TF at 90 days.

Methods: Adult, ESKD pts first prescribed PD at Fresenius Kidney Care (FKC) facilities between 2017-2019 were included. Deidentified data were extracted from the clinical data warehouse. Medication classification was conducted by clinical pharmacists. Case-mix adjusted Cox regression models were used to evaluate the associations between AH-M and PD TF. Subanalyses were conducted based on residual renal function (RRF).

Results: Pts included (n=22,908) were often treated with AH-M (91%). There was a trend toward any AH-M being protective of PD TF (HR: 0.85, p=0.06). However, certain AH-M subclasses had stronger associations than others (Table). Treatment with any diuretic (54% of pts) was associated with 17% lower technique failure rate (p=0.001) compared to no diuretic. Subclasses of diuretics were associated with lower TF (15% for loop diuretics and 18% for other diuretics). ACEi were associated with lower rates of PD TF (19%, p=0.0047), whereas remaining subclasses showed no association. There was no association with diuretics in the pts without RRF (Table).

Conclusions: In a large population of incident PD pts, we observed that several AH-M subclasses were associated with reduced rates of PD TF after controlling for many non-modifiable case-mix variables/confounders.

Funding: Commercial Support - Fresenius Medical Care

Concomitant Medications	Reference	N Patients	% Patients	Adjusted Model (Parameter + Base* Model)		
				Hazard Ratio	95% CI	P
Any hypertensive	No	2,141	9.4			
	Yes (vs no)	20,767	90.6	0.8560	0.7280 1.0070	0.0604
Any diuretics (loop + other)	No	10,483	45.8			
	Yes (vs no)	12,426	54.2	0.8280	0.7410 0.9270	0.0010
Loop diuretics	No	11,294	49.3			
	Yes (vs no)	11,614	50.7	0.8460	0.7550 0.9470	0.0036
Other diuretics	No	20,280	88.5			
	Yes (vs no)	2,628	11.5	0.8180	0.6740 0.9930	0.0426
ACE inhibitors	No	18,823	82.2			
	Yes (vs no)	4,085	17.8	0.8090	0.6990 0.9370	0.0047
ARBs	No	17,835	77.9			
	Yes (vs no)	5,073	22.1	0.9150	0.7990 1.0470	0.1960
Beta blockers	No	9,092	39.7			
	Yes (vs no)	13,816	60.3	0.9690	0.8840 1.1040	0.8273
CC Blockers	No	9,056	39.5			
	Yes (vs no)	13,852	60.5	1.0560	0.9560 1.1940	0.2423
Alpha Beta	No	14,953	65.3			
	Yes (vs no)	7,955	34.7	0.9660	0.8810 1.1030	0.8048
Central antagonists	No	22,768	99.4			
	Yes (vs no)	140	0.6	1.3700	0.7760 2.4190	0.2774
PATIENTS WITH RESIDUAL RENAL FUNCTION AT BASELINE						
Loop diuretics	No	9,078	47.3			
	Yes (vs no)	10,129	52.7	0.8840	0.7370 1.0600	0.1825
Other diuretics	No	16,866	87.8			
	Yes (vs no)	2,337	12.2	0.7150	0.5230 0.9780	0.0361
Any diuretics (loop + other)	No	8,358	43.5			
	Yes (vs no)	10,847	56.5	0.8230	0.6850 0.9880	0.0362
PATIENTS WITHOUT RESIDUAL RENAL FUNCTION AT BASELINE						
Loop diuretics	No	2,216	59.9			
	Yes (vs no)	1,485	40.1	1.017	0.876 1.181	0.8283
Other diuretics	No	3,412	92.1			
	Yes (vs no)	291	7.9	0.997	0.591 1.682	0.4372
Any diuretics (loop + other)	No	2,125	57.4			
	Yes (vs no)	1,578	42.6	1.057	0.912 1.226	0.4617

* controlling for age, CAPD/APD, dialysis vintage, gender, race, ethnicity, body surface area, residual renal function, charlston comorbidity index, diabetes, geographic region, PD program size, insurance, relationship status, employment, and primary language

TH-PO320

The Effect of Implementing a Dialysis Start Unit on Modality Decision Among Patients with Urgent Start Kidney Replacement Therapy

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Background: Many individuals start dialysis in an acute setting with suboptimal pre-dialysis education. The dialysis start unit (DSU) is a program performing in-center hemodialysis (HD) in a separate space while providing support and education on chronic kidney disease and treatment options in the initial weeks of kidney replacement therapy. We aimed to assess the uptake of home dialysis therapies between 2013-2021 among patients who started acute inpatient HD at University Health Network, Toronto and underwent dialysis at the DSU.

Methods: This is a retrospective observational cohort study based on prospectively collected data. Patients' demographics were obtained from electronic charts. In the DSU, all patients received dialysis modality education by a nurse educator, dedicated home dialysis nurses, and the allied health care team.

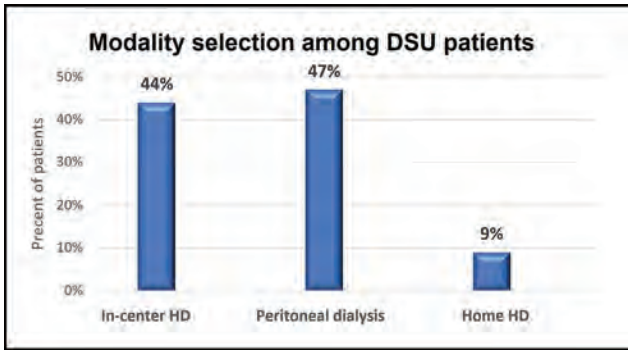
Results: During 2013-2021, 122 patients were dialyzed in the DSU and included in the study. Among those patients, 68 patients ultimately chose home dialysis (57 peritoneal dialysis and 11 home HD). Fifty-four patients continued in-center HD. Patients adopting home dialysis were less likely to have diabetes and hypertension as the etiology of kidney failure and more likely to have glomerulonephritis or vasculitis.

Conclusions: Dialysis modality education is implementable in advanced chronic kidney disease. Individualized education and care after urgent start dialysis can potentially enhance home dialysis choice and utilization.

	Home dialysis (n= 68)	In center hemodialysis (n=54)
Mean age at start of dialysis, years	52.9+/-23.5	56.7+/-17.8
Gender, male	36 (53%)	33 (61%)
Etiology of Kidney failure		
Diabetes / hypertension	12 (18%)	16 (30%)
Failed kidney transplant	9 (13%)	11 (20%)
Glomerulonephritis / vasculitis	21 (31%)	8 (15%)
Other	18 (26%)	12 (22%)
Unknown	8 (12%)	7 (13%)
Followed by nephrologist before admission		
No	27 (40%)	22 (41%)
General nephrology	12 (18%)	11 (20%)
Pre-dialysis clinic	25 (37%)	15 (28%)
Transplant clinic*	4 (6%)	6 (11%)

*as the only nephrology follow-up

Patients demographics and comorbidities



Modality selection among DSU patients

TH-PO321

Participation in a CKD Navigator Program Is Associated with Improved Quality of Dialysis Starts

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Background: Initiation of chronic dialysis is frequently accompanied by the use of central venous catheters, hospitalisation and need for in-center hemodialysis. Optimal start dialysis with a permanent access, in an oupatient setting and with the patient's choice of modality is suggested to improve patient quality of life as well as reduce complications and cost. Education, coaching and monitoring of patients as they approach End-Stage Kidney Disease (ESKD) are proposed to increase the probability of optimal starts.

Methods: The University of Vermont Medical Center (UVMMC) began enrolloing persons with an eGFR $\leq$ 20 ml/min/1.73m^2 in a CKD navigator program in November 2020. The program provides education, assessment, planning, coaching and monitoring. From November 2020 through April 2023, 270 patients were approached to participate, 180 agreed (67% engagement rate) and 127 had completed a plan for ESKD and were being monitored. During this same period, 141 UVMMC patients started dialysis, 33 of whom were followed in the navigator program. The 141 starts were assessed for a permanent access (PermAcc), outpatient location (OP) and whether they were in a home program (HOME) then grouped according to participation in the program (NAV) or not (NoNAV). Starts with the combinationof PermACC+OP and PermAcc+OP+Home were also compared. The significance of differences between groups was assessed by Chi Square analysis with Yates correction when appropriate.

Results: For numerical results see findings in Table. Patients participating in the navigator program were statisically more likely to start with a permanent access and in a home program. Combinations of these characteristics with an outpatient start also were statistically more common in navigator participants. Starting dialysis in an outpatient setting as a single finding was not different between groups.

Conclusions: Although lacking radomization, this observational study supports the proposal that patient participation in a CKD navigator program improves the quality of dialysis starts.

Funding: Private Foundation Support

	Characteristics of Dialysis Starts				
	PermAcc	OP	Home	Perm+OP	Perm+OP+Home
NAV n=33	15	23	7	13	6
	45.5%	69.7%	21.2%	39.4%	18.9%
NoNAV n=108	25	63	5	24	5
	23.1%	58.3%	4.6%	22.2%	4.6%
p value NAV vs NoNAV	0.02	0.42	<0.01	0.05	0.01

Characteristics at Dialysis Start

TH-PO322

Experience with Remote Monitoring of Automated Peritoneal Dialysis: The First 50 Patients in a Private Peritoneal Dialysis Program in Mexico

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Background: The benefits of remote monitoring (RM) of automated peritoneal dialysis (APD) have been established, the aim of this study is to describe the characteristics and outcome of the first 50 patients who were mantained in APD with RM, from November 2019 to February 2022 in a private peritoneal dialysis program in Mexico City. Also, we analyzed time and distance traveled savings for patients.

Methods: Retrospective cohort study. This was an observational study, describing the main clinical outcomes in our patients maintained in APD with RM.

Results: A total of 50 patients were admitted to the study. Their mean age was 62.5 years. Most patients lived in an urban setting. 2 patients were lost to follow-up. The main causes of end stage renal disease were diabetes mellitus (60%) and hypertension (20%). The basal frequency of clinic visits was 1 per month; During the study, 92% of the prescribed PD sessions were completed. Just 2% of prescribed sessions were interrupted, and 6% were missed treatments. The median lost dwelling time was 78 minutes per patient-month (range 0-366), the mean number of prescription changes was 3 (range 0-8). Among patients who had a change in prescription during the study, the main adjustment was an increase in infusion volume and time spent on treatment (57%). Icodextrin 7.5% was prescribed, 16% of the prescribed PD sessions. The leak rate was only 5%. Peritonitis rate was 0.36 episodes/patient-year, both episodes were caused by gram positive microorganisms. 1-year PD catheter migration rate was 30%, most catheters were placed by a variety of surgical techniques (65%). 1-year PD catheter patency rate was 75%. Weekly Kt/V mean was 1.60 (± 0.28). 1-year PD technique survival was 60 %, the main causes of PD technique failure were mechanical failure (35%) and infections (35%). Twelve patients died during the study, the main cause was infections 50% (COVID-19 25%). The distance traveled by patients was reduced by 534 km with a time saving of 804 min for patients.

Conclusions: APD with RM allows a better use of healthcare resources, helping to improve patients follow up and remote early prescription modification. The main outcomes rates were similar than previously reported in similars countries. It is important to consider the COVID-19 pandemic impact on these results.

TH-PO323

Machine Learning for Identification of Near-Term All-Cause and Cardiovascular Death Among Patients Undergoing Peritoneal Dialysis

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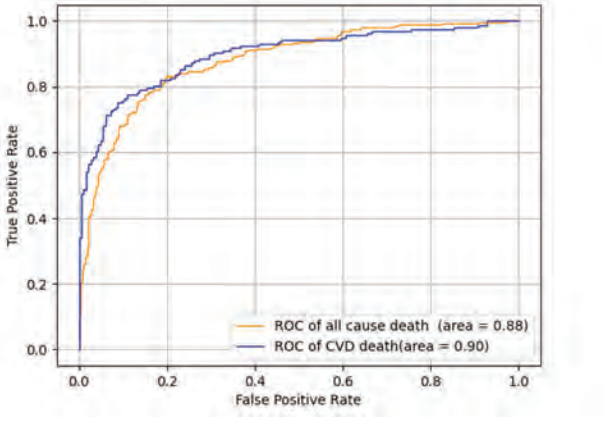
Background: Although more and more cardiovascular risk factors have been verified in peritoneal dialysis (PD) populations in different countries and regions, it is still difficult for clinicians to accurately predict who will have cardiovascular events and when the cardiovascular events will occur and cause death. We developed and validated machine learning-based models to predict near-term all-cause and cardiovascular death.

Methods: Machine learning models were developed on the Peritoneal Dialysis Telemedicine-assisted Platform Cohort (PDTAP) of 7539 PD patients enrolled between June 2016 and April 2019, which was randomly divided into a training set and an internal test set by 5 random shuffles of 5-fold cross-validation, to predict of 3-month cardiovascular death and all-cause death. We chose objectively collected markers such as patient demographics, clinical characteristics, and laboratory, and dialysis-related variables to inform the models and assessed the predictive performance using a range of common performance metrics, such as precision, accuracy, and area under the curve (AUC).

Results: CVDformer model was used to predict 3-month cardiovascular death of PD patients. In the test set, CVDformer model had a precision of 87.96% - 89.45% and an accuracy of 86.10% - 88.74%. best than the LSTM model had 78.78% - 80.45% for precision and 76.53% - 79.12% for accuracy. The AUC was 0.88-0.90 in identifying the presence of near-term all-cause death and cardiovascular death using the CVDformer model.

Conclusions: We developed and used a novel combination of machine learning methods to assess the all-cause mortality risk and cardiovascular death risk in 3 months. The ability to identify the potential risks of all-cause and cardiovascular death with an inexpensive, widely available, and automatic procedure has important practical implications, particularly for the management of dialysis patients.



TH-PO324

Computational Models of Peritoneal Dialysis

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Background: *In silico* models may play a vital role in improving patient-specific kidney replacement therapies. Recent advances in mathematical modeling include models of kidney physiology (e.g. regarding sex-specific differences, solute, drug and toxin transport and their interactions). Various models have been generated for peritoneal dialysis (PD) as well, but what lacks is a benchmarking of the different models on the same (pre-) clinical dataset. Here, we look at previously published models of PD and benchmark the efficiency of the models in predicting time-dependent evolution dialysate concentrations of six solutes.

Methods: Two mechanistic models (Graff, Öberg (modified for static dwells; this model is also modular and has been applied to automated PD and continuous flow PD)) and two analytical models used in clinical practice and research (Garred, Waniewski) were chosen. The four models, in combination, encompass various mechanisms that are essential to PD (diffusion, convection, lymphatics). The dataset consisted of data from multiple static dwells (n = 16) in uremic pigs. Each model was trained by fitting the dialysate solute concentrations (in a subset of the dwells) to predict the mass transfer area coefficient (MTAC) of each solute. With the fitted MTAC, we predicted the dialysate solute concentrations in the remaining dwells.

Results: The (modified) model by Öberg appears to be the optimal model in terms of low error in solute concentration predictions, applicability of the model to multiple datasets (with different initial dialysate concentration), physiological MTAC values and reasonable ultrafiltration values in pigs. Applying the modified Öberg model to the data obtained in the uremic pig experiments showed a good predictive accuracy (Figure 1). Notably, this model accurately predicted the effects of sodium sieving, whereas other models did not.

Conclusions: The modified Öberg model provided an accurate prediction of solute concentrations throughout a static dwell in uremic pigs.

Funding: Private Foundation Support

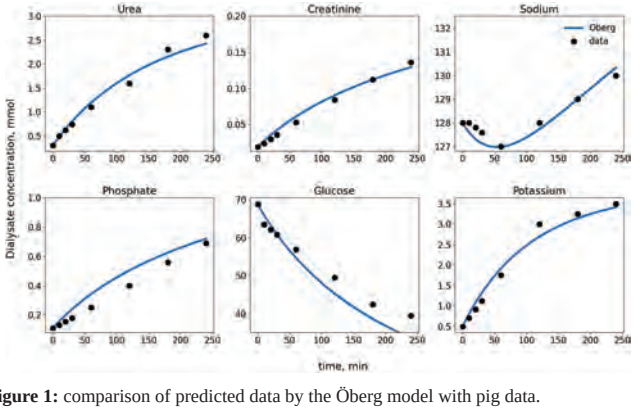

Figure 1: comparison of predicted data by the Öberg model with pig data.

TH-PO325

Robust Joint Models of Albumin and All-Cause Mortality in Incident Peritoneal Dialysis Patients: A Dynamic Predictions Perspective Adjusting for Competing Risks

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Background: Joint models (JM) allow investigation of association between longitudinal biomarkers and mortality in patients on peritoneal dialysis (PD) and provide individual patient dynamic risk predictions. Yet, deviations from JM assumptions in dialysis trial data and consideration of competing events remain unexplored.

Methods: We evaluated the association of albumin with all-cause mortality in incident PD patients followed over 8 years in the Initiating Dialysis Early And Late trial. To account for skewness/outliers in albumin, novel JM with mixed effects sub-model with skew-normal, t and skew-t errors were compared with conventional JM under normal distribution. Furthermore, we adjusted for the competing events of transfer to hemodialysis and transplantation using Weibull cause-specific hazards. The dataset (N=314 patients) was randomly split into training dataset (3/4, N=236) for model fitting and validation dataset (1/4, N=78) to infer predictive performance. We obtained 6-month individual patient survival predictions from all JM at cut-offs 1, 1.5 and 2 years utilizing albumin trajectory and baseline risk factors.

Results: A median of 9 albumin records per patient and a 35% death rate with median time-to-event of 4.5 years ensured convergence of all 16 joint models. Albumin hazard ratio of death remained robust (0.78 to 0.81), suggesting significant inverse relationship between albumin and death across all models. Longer follow-up improved the prediction accuracy of all JM in the validation dataset. JM with competing events outperformed JM with survival only (area under the curve (AUC) ranges at 1, 1.5 and 2-years: 0.53-0.57 vs 0.52-0.55, 0.75-0.80 vs 0.75-0.77, 0.84-0.90 vs 0.82-0.88), regardless of the distribution assumption for albumin. Prediction performance of all JM surpassed classical Cox model with baseline albumin (AUC = 0.46, 0.70, 0.75). Results were confirmed by two simulation studies.

Conclusions: This first comprehensive JM in dialysis patients demonstrates utility for dynamic personalized survival prediction, with robustness of estimates to deviations from normality and higher predictive accuracy when adjusting for competing risks, and marked superiority to the classical Cox approach.

Funding: Commercial Support - Baxter Healthcare Corporation

TH-PO326

Random Forest Can Accurately Predict the Technique Failure of Peritoneal Dialysis-Associated Peritonitis Patients

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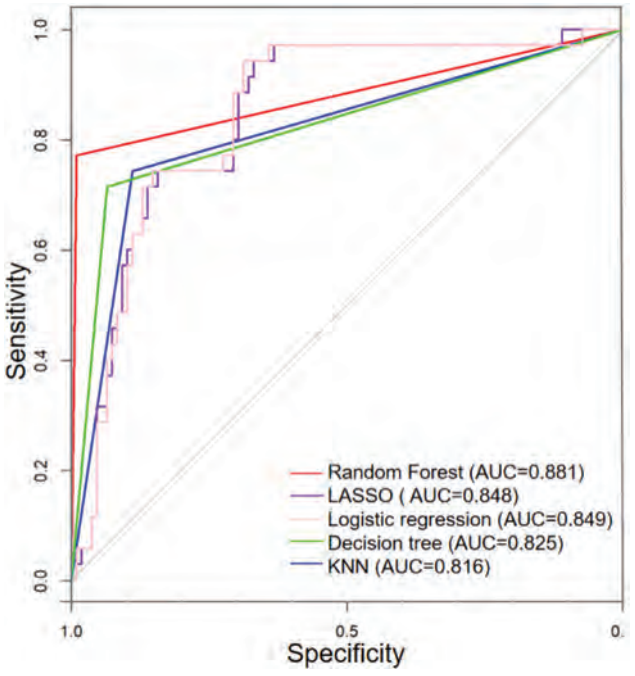
Background: Peritoneal dialysis associated peritonitis (PDAP) is a major cause of technique failure in peritoneal dialysis (PD) patients globally. The purpose of this study is to construct a risk prediction model which could accurately predict the technique failure in PDAP patients.

Methods: This retrospective cohort study included maintenance PD patients in our center from January 1, 2010 to December 31, 2021. Technique failure was defined as catheter removal, transfer to hemodialysis (HD) or peritonitis-related death. The risk prediction models for technique failure in PDAP patients were constructed based on five machine learning algorithms: random forest (RF), the least absolute shrinkage and selection operator (LASSO), decision tree, k nearest neighbor (KNN), and logistic regression (LR). And the internal validation was conducted in the test cohort.

Results: A total of 574 episodes of peritonitis during the 12 years were included in this study. The technique failure accounted for 23.69%, and the mortality rate was 4.00%. There were significant statistical differences between the technique failure group and the technique survival group in multiple baseline characteristics. The RF prediction model is the best able to predict the technique failure in PDAP patients, with the accuracy of 93.75% and AUC of 0.881. And the model had sensitivity and specificity of 77.14% and 99.08%, respectively.

Conclusions: RF prediction model could accurately predict the technique failure of PDAP patients, which demonstrated excellent predictive performance and assist in clinical decision making.



ROC curves of prediction models based on machine learning algorithms

TH-PO327

Modifiable Physical Factors that Influence Physical Function for People Receiving Peritoneal Dialysis

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Background: People receiving peritoneal dialysis experience physical function decline, impairing their ability to complete everyday activities, leading to poorer quality of life. Physical factors including cardiorespiratory fitness, muscle strength, physical activity and sedentary behaviour are associated with physical function, and considered modifiable, as they can be altered through intervention. However, little is known about the interrelationship between the factors and physical function or how these factors change over time in this cohort. This study aimed to explore modifiable physical factors that are associated with physical function, identifying which has the strongest influence, and explore temporal changes.

Methods: Adults receiving peritoneal dialysis underwent assessments for objective (Short Physical Performance Battery) and self-report (Short Form-36 Physical Function) physical function, cardiorespiratory fitness (six-minute walk), muscle strength (quadricep, bicep, abdominal, hand-grip strength), physical activity (accelerometry) and sedentary behaviour (inclinometery) on three occasions over a 12-month period (baseline, 6-months, 12-months).

Results: Eighty-two participants (mean age 61.4 years) underwent assessments. All modifiable physical factors were predominantly moderate to strongly associated with physical function at baseline. Through the observation period, cardiorespiratory fitness had the strongest and most consistent influence with every metre conferring a 0.08-unit ($p < 0.01$) and 0.01-unit ($p < 0.05$) increase in self-report and objective physical function score, respectively. Temporal changes were observed for modifiable physical factors with significant mean changes in cardiorespiratory fitness (-9.8%), quadricep strength (-5%), moderate-vigorous (-25.9%) and total (-16.2%) physical activity, and sedentary behaviour (+7.1%).

Conclusions: The results of this study indicate that cardiorespiratory fitness could be routinely monitored to detect risk of physical function decline and targeted through intervention to enhance physical function for people receiving peritoneal dialysis. Nevertheless, all factors should be considered when designing interventions to mitigate temporal changes and induce the numerous health benefits offered.

TH-PO328

Home Therapy New Patient Experience Survey Assessment for New Home Dialysis Patients

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Background: Home hemodialysis (HHD) and peritoneal dialysis (PD) patients with an email receive a Home Therapy New Patient Experience Survey (PES) 21 days after initiating treatment. Feedback gathered from the survey is used to identify and address problems early and patients are referred for clinical support as needed. The aim is to listen and respond to patient feedback early in their journey, improve experience and clinical and health outcomes, thereby increasing home dialysis retention rates. The purpose of this study is to assess these aims.

Methods: 11,793 PD and 2,156 HHD patients who received a PES between 5/1/19 and 2/28/21 are compared to matched patients of the same modality who did not receive a survey. Controls were chosen using propensity score matching with confounders including month of first order occurrence, age, gender, race, ethnicity, state, urban/rural, BMI, residual kidney function, vintage, vascular access type, comorbidities, and primary insurance. Outcomes include 1 year follow-up status (maintained modality, in-center HD [ICHD], other home modality, transfer, transplant, or death), and hospitalizations. Analysis included Cox proportional hazards model and bootstrap methods with =0.05.

Results: PD: Compared to controls, PES patients were 15% less likely to switch to ICHD, 25% more likely to have a transplant, and had fewer hospitalizations. Not statistically significant but directionally positive, survey patients were 21% more likely to switch to HHD, 16% less likely to transfer to a non-Fresenius clinic, and had fewer days hospitalized. **HHD:** Compared to controls, survey patients were 49% less likely to switch to ICHD, 71% less likely to switch to PD, 48% less likely to transfer to a non-Fresenius clinic and had fewer frequency and duration of hospitalizations. Not statistically significant but directionally positive, survey patients were 34% more likely to have a transplant.

Conclusions: This study provided evidence that proactively and consistently listening to patients to understand their experience on home dialysis and taking action based on their feedback, often in real-time, can help prevent issues escalating, improve patients' overall health outcomes, increase patient retention on home and their overall loyalty to Fresenius Kidney Care as a dialysis provider.

TH-PO329

Patient-Reported Experience Measure of Home Haemodialysis Dialysis at Imperial College Renal and Transplant Centre

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Background: There is a drive to expand home dialysis in the United Kingdom. Instruments to explore patient reported experience measures (PREM) are vital to identifying barriers to home dialysis. In 2021, Rivera et al developed the first English language instrument which incorporates aspects of service widely recognised as key components of high-quality home dialysis care.

Methods: An observation study of patient experience of home haemodialysis (HHD) in West London Renal and Transplant Centre. In June 2022, with permission from Rivera et al, we approached all patients on HHD with an adapted questionnaire.

Results: 29 of 37 patients responded. Table 1 lists demographics. 20 patients had been on HHD for 1 to 5 years, and 4 patients for more than 5 years. One patient had been on HHD for ≤ 3 months, hence excluded in further analysis. 24 patients rated their overall mental or emotional health as either 'Good', 'Very good' or 'Excellent'. 9 reported of difficulty doing errands alone, such as visiting a doctor's office or shopping. 24 patients reported 'Usually' or 'Always' staff spent enough time with them. 21 patients felt the staff were 'Usually' or 'Always' able to help with problems encountered during HHD. 26 patients felt involved in treatment decision and 27 reported their HHD team made sure their dialysis plan worked for them. All 28 patients reported confidence in caring for their dialysis access and performing their dialysis safely at home.

Conclusions: This is a diverse cohort with bias towards patients with higher educational attainment, functional independence and reduced burden of comorbidities. Approachability of staff, structured guidance and an individualised treatment plan aid sustainability of HHD. To reassess in June 2023, for continuing development.

Table 1. Patient demographics

	n	
Age range		
18 to 24	1	3 %
25 to 34	2	7 %
35 to 44	2	7 %
45 to 54	9	31 %
55 to 64	10	34 %
65 to 74	2	7 %
75 to 84	2	7 %
85 or older	1	3 %
Gender		
Female	16	55 %
Male	13	45%
Ethnicity		
Black	12	41 %
White	8	28 %
Asian	7	24 %
Other	2	7 %
Education		
Bachelor's degree or higher	13	45 %
Technical/ Vocational training	3	10 %
Diploma or equivalent	6	21 %
Completed high school	3	10 %
Not completed school	4	14 %
Current employment status		
Employed for wages	9	31 %
Self-employed	1	3 %
Out of work due to health issues	8	28 %
Out of work due to other reason	3	10 %
Student	1	3 %
Retired	7	24 %
Comorbid status		
Diabetes or high sugar	9	31 %
Heart disease	6	21 %
Significant hearing difficulty	1	3 %
Significant visual impairment	2	7 %
Difficulty walking of climbing stairs	12	41 %
Difficulty dressing or bathing	7	24 %

TH-PO330

Patient and Care Partner Perspectives of Psychosocial Issues While on Home Dialysis

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Background: Home dialysis has many advantages but requires initiative from patients and care partners. Without proper support, patients run the risk of burning out. We sought to explore patients' and care partners' perspectives and experiences of the psychosocial factors that make home dialysis challenging, contribute to burnout, and ultimately lead to transfer to in-center hemodialysis (ICHD).

Methods: We conducted 5 focus groups and 3 semi-structured interviews of 18 adult English-speaking patients and 11 care partners with experience with home dialysis, 16 who had transferred to ICHD, and 13 who were identified as high risk for transfer to ICHD. Transcripts were thematically analyzed.

Results: We identified three themes: 1) being overwhelmed by the reality of dialysis, 2) the exhausting monotony of treatment, and 3) ongoing psychosocial impacts. Participants found it overwhelming to depend on a lifesaving therapy, manage comorbid conditions and deal with machine issues. The exhausting monotony of treatment entailed the burden of time and responsibility required for home dialysis and continually planning/storing dialysis equipment and supplies. Psychosocial impacts included feeling isolated, fear of making a fatal mistake, feeling dependent on others, dealing with body disfigurement issues, and negatively impacting relationships.

Conclusions: Performing home dialysis can be a daunting task for patients and care partners. Care teams need to identify and understand the psychosocial struggles to implement effective support strategies for patients and care partners.

Illustrative Quotes

Theme	Subtheme	Quotes
Overwhelmed by reality of dialysis	Concurrent management of co-morbidities	"Yeah because of her diabetes and the fact that the dextrose in the [dialysis] bags makes her sugars worse."
	Frustration at ongoing machine issues	"It started out pretty rough and that was due to equipment failure. It's a complicated machine, but those failures are draining on me."
	Burden of time required	"The first phrase that comes to my mind, I think about dialysis is that it takes time."
Exhausting monotony of treatment	Drowning in responsibility	"It's just a hell of a responsibility with everything or even just with a partner. It's just a lot, a lot to do."
	Continual Logistics and storage management	"I guess it really didn't hit me until all of the supplies started showing up the machine. Just all these little fine details that you really don't think of."
	Feelings of isolation	"You feel like you're on an island by yourself, like you just don't have anywhere to turn."
Ongoing psychosocial impacts	Negatively impacting relationships	"To be honest, we would take it at each other a lot of times, like his stress would be taken out on me and vice versa."
	Fear of making a fatal error	"You know, like the horror stories you would hear about if air got in so he would panic."
	Crippling dependence on others	"First of all, if they were by themselves, I don't know how you do it."

TH-PO331

A Survey on the Prevalence of Burnout Among Peritoneal Dialysis Patients and Caregivers in Performing Peritoneal Dialysis

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Background: PD patients or their caregivers should regularly perform PD fluids exchanges 1-4 times per day. Some PD patients are still unable to accept their kidney damage and require dialysis to keep their lives. Previous studies have shown that emotional and social deficits are the major causes of burnout of PD patients. The study's aim is to survey the prevalence and risk factor of burnout in PD patients and their caregivers in performing PD.

Methods: We used two questionnaires the Maslach Burnout Inventory (MBI) and the State-Trait Anxiety Inventory (STAI) to investigate PD patients and caregivers who were the primary operator performing PD. The MBI questionnaire includes three main dimensions (emotional exhaustion, depersonalization, and reduced sense of personal accomplishment), 22 items, and a scale of 0-6 to indicate the severity of symptoms. The definition of burnout in MBI is high emotional exhaustion(cutoff score=7.78) and high depersonalization (cutoff score=22.36). The STAI questionnaire consists of state anxiety and trait anxiety, each containing 20 items, and each item is rated on a scale of 1-4.

Results: A total of 107 PD operators including PD patients and their caregivers, were enrolled for our study from April 2023. One of them withdrew due to peritonitis in the past 3 months, and 5 refused to participate due to lack of interest. In the final sample of 101 patients, mean age was 54 years old, and 49.5% were female. Ninety (89%) participants were patients and the remainder were caregivers. Median PD vintage were 3.5 years. In the MBI questionnaire survey, 22 patients (21.8%) had a high exhaustion score; 9 cases (8.9%) had a high score of cynicism (>22.36); 63 patients (62.4%) had a high Professional Efficacy (>28.2). On the STAI questionnaire, the mean score for state anxiety was 35.5, and 24 patients (23.8%) reported severe anxiety; the average score for trait anxiety was 38.3, and 31 cases (30.7%) met severe anxiety.

Conclusions: In our PD patients, there was a high incidence of emotional exhaustion and severe anxiety but a high personal efficacy. However, after adjusting for PD operators, age, PD vintage, there was no significant correlation between these parameters and the scores in each questionnaire.

TH-PO332

The Effects of Negotiation on Discordant Home Hemodialysis Patients

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Background: Home hemodialysis (HHD) has demonstrated superior clinical outcomes, improved quality of life and enhanced treatment flexibility in comparison to 3days/week incenter HDs.Nonetheless, some patients are discordant to their dialysis prescription and require a negotiation program to maintain their normal lifestyle and ameliorate their illness behavior.

Methods: Retrospective single center observational study of all prevalent HHD patients at UHN (2018-2022). Demographic and clinical data were extracted from clinical charts. Negotiation was defined as weekly contact between nurses and patients by phone, email or clinical visit to discuss the importance of being concordant to treatment and adapting the length and schedule of dialysis to avoid clinical complications. Patients were defined as concordant, concordant with agreement with at least 75%of dialysis prescription and discordant for those skipping/shortening HHD sessions without prior agreement with the clinical team.

Results: From 94patients, 33(35%) required negotiation:15(16%) were concordant patients with agreement and 18(19%) discordant patient. There were no demographic differences between groups. Patients requiring negotiation presents higher median time on HHD (7.6years vs 4.3years for concordant patients). Discordant patients tended to be younger and were less likely to be listed for kidney transplant(figure 1). There were no differences in hospitalisation/technique complications amongst the 3groups.

Conclusions: A third of HHD patients require negotiation to maintain their lifestyle and safety. Those patients requiring negotiation did not present with more hospitalisation or technique complications than concordant patients. We speculate that a negotiation

program should be implemented in HHD centers to ameliorate patient concordance and mitigate attrition.

	Total (n = 94)	Concordant (n= 61)	Concordant with agreement at least 75% of dialysis prescription (n = 15)	Discordant (n = 18)	p value
Gender (male), n (%)	59 (63)	38 (62)	8 (53)	13 (72)	0.519
Age, years; median [IQR]	50 [36.6-60.3]	51 [37-61]	53 [47-61]	46 [35-54]	0.102
Patient living alone, n (%)	12 (13)	8 (13)	1 (7)	3 (17)	0.739
Dependant living at home, n (%)	27 (29)	18 (30)	6 (40)	3 (17)	0.334
Assisted home dialysis, n (%)	9 (10)	8 (13)	0 (0)	1 (6)	0.246
Hypertension, n (%)	72 (77)	49 (80)	9 (60)	14 (79)	0.286
Diabetes mellitus, n (%)	15 (16)	13 (21)	1 (7)	1 (6)	0.219
Access type, n (%)					0.370
AVF	39 (46)	28 (46)	7 (47)	4 (22)	
Catheter	49 (52)	29 (48)	7 (47)	13 (72)	
Graft	6 (6)	4 (7)	1 (7)	1 (6)	
Previous dialysis treatment, n (%)					0.282
No	31 (33)	22 (36)	4 (27)	5 (27.8)	
Peritoneal dialysis	22 (23)	15 (25)	1 (7)	6 (33.3)	
In center hemodialysis	41 (44)	24 (40)	10 (67)	7 (38.9)	
Previous renal transplant, n (%)	35 (37)	19 (31)	8 (53)	8 (44)	0.220
Listed for renal transplant, n (%)	31 (33)	21 (34)	7 (47)	3 (17)	0.174
Hospitalized last 5 years, n (%)	64 (68)	38 (62)	11 (73)	15 (83)	0.244
Technique survival, years; median [IQR]	4.3 [1.9-11]	3 [1.5-10]	7.6 [3-11]	7.6 [2.2-11]	0.145

TH-PO333

Measuring Mindset: Validation of the Health Mindset Scale (HMS) in Peritoneal Dialysis (PD) Patients

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Background: Many patients who start peritoneal dialysis (PD) transition to hemodialysis after complications. Patient psychological factors may influence long-term PD success. Fixed mindset is the belief that ability cannot change, and growth mindset is the belief that knowledge and ability can grow and improve. Patient mindset may influence PD training, patient dialysis task execution at home, patient response to peritonitis, and modality persistence. The purpose of this study is to examine validity of the Health Mindset Scale (HMS) among adult PD patients.

Methods: Home dialysis units at two academic medical centers in the US are participating. The Health Mindset Scale (HMS), a 3-item Likert-based survey [scored 3-18, higher number indicates greater growth mindset], was administered at baseline, and then repeated for test-retest reliability. Instruments for resilience, depression, and health mindset specific to peritonitis were also administered at baseline. Spearman's rank correlation coefficients assessed correlations, and Cronbach's alpha assessed internal consistency.

Results: Mean age of 52 enrolled participants was 52yo [SD 16], with 48% male, 28% black, 40% with diabetes, and 87% with hypertension. Mean vintage was 628 days [SD 631]. Mean albumin was 3.9 gm/dL [SD 0.44]. Mean HMS score was 11.8 [SD 4.9] at baseline, and 13.7 [SD 3.5] at follow-up. HMS test-retest correlation was 0.43 [95% CI 0.05, 0.70]. Correlations between HMS and peritonitis mindset score, resilience, and depression were 0.64 [95% CI 0.41, 0.79], 0.26 [95% CI -0.03, 0.50], and 0.13 [95% CI -0.16, 0.40], respectively. Cronbach's alphas for baseline HMS, peritonitis mindset, depression, and resilience were 0.88, 0.83, 0.69, and 0.93, respectively.

Conclusions: Results results suggest good internal consistency of instruments for health mindset and peritonitis mindset, depression, and resilience in this sample of adult PD patients. Mindset variation suggests that an intervention to support growth mindset may be an important target to maintain PD as the ESKD treatment option.

Funding: Private Foundation Support

TH-PO334

Time Trends and Causes of Infectious Mortality Among Patients Starting Dialysis in Finland

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Background: Infections are the second most common cause of death among dialysis patients. Still, there is very scarce information on recent trends and causes of infectious mortality among dialysis patients. Our aim was to evaluate the development of mortality caused by infectious diseases during the past decades in the dialysis population in Finland.

Methods: All adult patients who started chronic dialysis treatment in Finland during 2000–2019 were included. The patients were identified from the Finnish Registry for Kidney Diseases, and followed until kidney transplantation, death, five years from start of dialysis or end of 2019. Cumulative incidence of death caused by infections was calculated and deaths due to other causes were accounted for as competing risk events. Hazard ratios of infectious death were calculated according to time periods of dialysis start using Cox regression with adjustment for age, sex, primary kidney disease, and comorbidities.

Results: Altogether 9671 patients started dialysis of whom 75% commenced hemodialysis and 25% peritoneal dialysis. During the 5-year follow-up, 2956 (31%) patients received a kidney transplant, and 3692 (38%) dialysis patients died of whom 866 (23%) due to infections. The crude cumulative incidence of infectious death decreased steadily over five-year time periods during 2000–2019 (Figure). The hazard ratio of infectious death decreased continuously and was 0.50 (95% CI 0.39–0.61) for patients who started dialysis in 2015–2019 compared to 2000–2004. The most common causes of infectious death were septicemia (38%), pulmonary infection (36%), and peritonitis (8%). Invasive fungal, viral, or opportunistic infections rarely caused death.

Conclusions: Dialysis patients' risk of dying due to infections has dropped by half since the beginning of the millennia. The reason for this development will need further studies.

Funding: Private Foundation Support

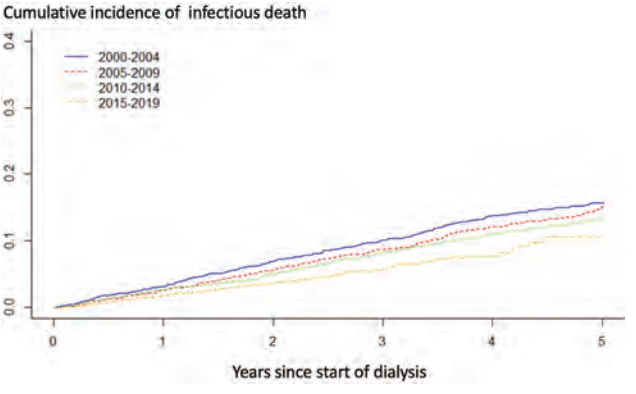

Figure. Cumulative incidence of death due to infection according to time period of start of dialysis.

TH-PO335

Impact of Glycemic Control on Technique Failure in Incident Peritoneal Dialysis with Diabetes: Focusing on Volume Overload

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Background: To date, diabetes mellitus (DM) has been regarded as a risk factor for ultrafiltration failure in peritoneal dialysis (PD). This study is aim to delineate whether glycemic control could contribute to the technique failure in PD patients with DM, especially in terms of volume overload.

Methods: We retrospectively analyzed data from 84 incident PD patients with DM. The study population consisted of 71 males and 13 females, with mean age 51.1 ±1.3 years. Median follow-up duration was 34.5 ± 2.4 months. We divided the patients into two groups based on the time-average HbA1c values : HbA1c 8.0%≤ (n=17) and HbA1c 8.0%>(n=67). We used multivariate Cox proportional regression models to assess the relationship between the degree of glycemic control and the occurrence of volume overload-associated technique failure.

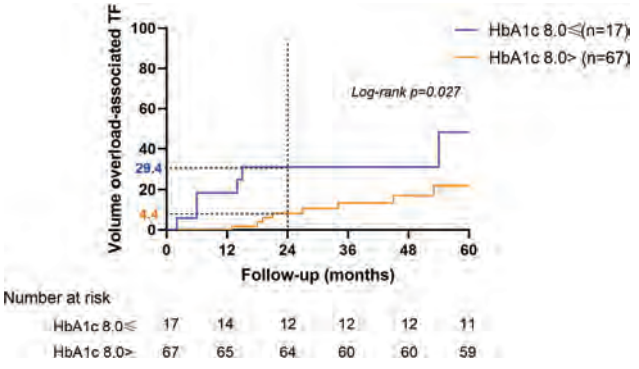
Results: Multivariate Cox regression analysis revealed that patients with a HbA1c level 8.0≤ had a significantly higher risk of volume overload associated technique failure (HR 3.741, 95%CI 1.166-11.908, P=0.026) compared to counterparts particularly within the first 2-years (HR 6.760, 95%CI 1.413-32.331, P=0.017). Additionally, hypertension was found to be significantly associated with an increased risk of volume overload-associated technique failure (HR 10.021, 95%CI 1.236-81.260, P=0.033).

Conclusions: Inadequate glycemic control (HbA1c 8.0≤) particularly during the first 2-years, and hypertension were found to be related with a volume overload-associated technique failure in DM patients undergoing PD.

Funding: Veterans Affairs Support

Cox Regression Analysis for volume overload-associated technique failure

	Univariate model			Multivariate model		
variable	HR	95% CI	p	HR	95% CI	p
Age (60<)	0.309	0.040-2.366	0.258	0.333	0.039-2.812	0.336
Gender (male)	0.888	0.278-2.840	0.842	1.215	0.301-4.904	0.784
Time average A1c 8.0≤	3.160	1.096-9.113	0.033	3.741	1.166-11.908	0.026
PD modality (APD vs. CAPD)	0.869	0.301-2.506	0.795	0.496	0.127-1.931	0.312
Exposure to High concentrate glucose	0.557	0.184-1.681	0.583	0.504	0.108-2.357	0.658
Use of Icodextrin	1.012	0.339-3.024	0.983	1.179	0.348-3.997	0.881
Hypertension	6.255	0.917-47.885	0.077	0.517	0.119-1.668	0.377
Cardiovascular disease	0.389	0.121-1.252	0.113	0.430	0.111-1.668	0.222



TH-PO336

Impact of Hypokalemia on Peritonitis in Peritoneal Dialysis Patients: A Multicenter Study

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Background: The association between peritoneal dialysis (PD) related peritonitis and hypokalemia is not well recognized. We examined their relationship and outcome of peritonitis in three PD centres of the southern region of Malaysia.

Methods: A total of 99 adult patients in Johor state who had undergone Tenchkoff catheter insertion for PD from 1st January 2017 to 31st December 2019 were analysed. Demography, lab results and medical data were obtained from medical records. Serial outpatient readings of serum potassium levels were analysed to define into two groups: hypokalemia (HK) and normokalemia (NK). Subjects with peritonitis will only have preceding 6 months of potassium readings analysed while subjects without peritonitis, have a maximum of 24 months study period. HK was defined as an average serum potassium level <3.5mmol/l, while NK ≥3.5mmol/L. Demographic factors are analysed using chi-square test. Association of potassium status and other related factors with peritonitis were analysed using univariate and multivariate logistic regression.

Results: Among 99 eligible PD patients, mean age (±SD) was 52.68 (±27.99) years old. 59.6% were females and 50.5% were diabetes mellitus. 17 (17.2%) belonged to HK group. Univariate and multivariate logistic regression (table 1) showed only hypokalemia status positively associated with peritonitis: unadjusted odds ratio 3.452 (CI 95% 1.176-10.132, p=0.024) versus adjusted odds ratio 3.224 (CI 95% 1.000–10.395, p=0.050). Among patients who developed peritonitis, HK subjects had lower mean serum albumin level (g/L) than those with NK (25.50±4.06 vs 29.16±5.94). HK subjects had higher CRP levels (mg/L) as compared to those with NK (151.47±94.91 vs 138.29±99.63). Peritonitis-associated catheter removal rate was higher in NK group compared to HK group (45.8% vs 10%, p=0.046).

Conclusions: PD patients with hypokalemia is positively associated with occurrence of peritonitis. Larger sample size and further studies are needed to understand its mechanisms. Correction of hypokalemia is therefore important to prevent such events.

Funding: Government Support - Non-U.S.

TH-PO337

Peritoneal Dialysis Outcomes in Severely Obese Patients: Single-Center Experience

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Background: Peritoneal dialysis (PD) has been increasingly performed in obese end stage kidney disease patients (ESKD) with the rising prevalence of obesity. However, PD is still viewed as a relative contraindication in severe obesity and experience in this group is sparse.

Methods: In a retrospective study, we identified patients with body mass index (BMI)>40 kg/m^2 from patients who initiated PD between 2014 and 2020 (n=99) at the University Hospital Home Dialysis Center. Charts were reviewed for clinical and laboratory variables to assess PD adequacy, technique, and patient survival. Date of last evaluation was March 2023.

Results: A total of nine patients (9%) had severe obesity with mean BMI 43.2±2.9 kg/m^2, age 47.8±12.6 years, and 44% were female. The cause of ESKD was Diabetes Mellitus in eight and IgA nephropathy in one patient. PD catheter was placed percutaneously in six and surgically in three patients. None of the patients had pericatheter leak or poor healing. PD training was initiated within 7.4±11.4 days after catheter placement. The initial prescription involved on average 4±0.5 cycles over 8.7±1.1 hr at night, total volume 9.0±1.2 lt and three patients had a last fill of 1.67±0.24 lt. Adequacy (both clinical and weekly kt/v>1.7 using actual/adjusted weight) was achieved in every patient using incremental PD. After an average of 17.7±6.8 months on PD, three patients transferred to hemodialysis (1 burnout, 1 prolonged hospitalization after cardiac surgery, 1 peritonitis with leak in the tunnel) and one moved to another PD facility. The remaining five patients continue to be on PD with a mean duration of 27.8±4.5 months. The latest prescription was 4.3±0.7 cycles over 9.2±1.2 hr at night, total volume of 11.1±2.6 lt and six had a last fill of 1.9±0.08 lt. Seven patients maintained the residual kidney function by the end of follow up. Peritonitis rate was 0.28 episode/pt-yr. Two patients had issues with slow drain and one with omental wrapping. Mean HbA1c was 7.8±2.3% and 7.1±1.3% at PD initiation and end of follow up, respectively.

Conclusions: Our experience demonstrates that PD is a viable option for long term therapy in patients with severe obesity. Further studies in a large population are needed to confirm our findings.

TH-PO338

Association Between Prediabetes and Cardiovascular Mortality in Patients Treated with Peritoneal Dialysis: A Retrospective Study from Southern China

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Background: The term prediabetes is used for individuals who have impaired glucose metabolism but the levels of glucose or HbA1c are not yet high enough to be diagnosed as diabetes. Prediabetes may already be associated with an increased risk of chronic diabetes-related complications in the general population. The present study was aimed to investigate the clinical impact of prediabetes on cardiovascular mortality in a population from southern of China who received peritoneal dialysis(PD) treatment.

Methods: Patients who received PD treatment above 3 months between January 2004 and December 2021 from four center were enrolled. The clinical record from last time before PD treatment were collected as baseline data. Prediabetes was defined as impaired fasting plasm glucose (FPG) according to the definition of the World Health Organization (WHO-prediabetes:6.1-6.9mmol/L). The association of baseline prediabets with cardiovascular mortality was evalued with multivariable Cox proportiona hazard analyses. We further performed subgroup analysis stratified by baseline characteristics including age(<47,≥47year), sex, smoking, hypertension status, PD vintage(<42,≥42months), hemoglobin(<83,≥83g/L), albumin(<36,≥36g/L), serum potassium(<2.0,≥2.0mmol/L).

Results: A total of 2045 PD patients were enrolled in this study. Of them, 545 were (26.7%) diagnosed as diabetes, 165(8.1%) were diagnosed as prediabetes according to IFG-WHO. During a median follow-up period of 42months, 178(8.7%) patients occurred cardiovascular mortality, of which 95 of1335(7.1%) patients in the non-prediabetes group and 20 of 165(12.1%) patients in the WHO-prediabetes group. Adjusted Cox regression models showed that compared with non-prediabetes, patients diagnosed as WHO-prediabetes was associated with an increased risk of cardiovascular mortality(HR 1.80,95% CI,1.12-2.88) after adjusted for age, sex, smoking, hypertension status, PD vintage, hemoglobin, albumin etc. The inverse association between the prediabetes with cardiovascular mortality was stronger in patients without hypertension (P for interaction=0.013).

Conclusions: WHO-prediabetes is an independent risk factor for cardiovascular mortality in patients receiving PD treatment.

TH-PO339

Clinical Outcomes of Peritoneal Dialysis in Patients with Chronic Liver and Kidney Failure: A Single-Center Experience

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Background: Patients with Chronic Liver and Kidney Failure (CLKF) face severe complications and high mortality. Simultaneous Liver-Kidney Transplant (SLKT) is the ideal therapeutic option, but the dearth of organs leaves most patients dialysis-dependent. PD is often overlooked due to concern for elevated peritonitis risk, hypoalbuminemia, and poor transplant candidacy. However, HD is often poorly tolerated due to exacerbation of pre-existing hemodynamic problems. We present a single-center experience to provide evidence that PD should be recommended in CLKF patients.

Methods: In this retrospective observational study, we included all patients with CLKF who initiated PD from 01/2006 to 03/2023. Medical charts were reviewed, and demographic/clinical data was retrieved. The primary clinical outcomes included mortality, PD complications, hospitalization rates, change in serum albumin from baseline, and SLKT candidacy. Censoring events were study period end, death, transfer to HD or to a different PD center, and SLKT.

Results: Twenty-six patients with CLKF and mean age of 58 years initiated PD during the study period. The mean time on PD was 38.3 months. There were 18 episodes of peritonitis with a rate of 0.2 episodes per year. Nine patients died with annualized mortality of 10.9%. Hospitalization rate was 0.95 per patient per year. Six patients received SLKT, 5 remain active on the waitlist. Four patients had technique failure with a permanent switch to HD. Mean serum albumin at the end of the observation period was 2.8g/dL, a 12% decline from baseline ($p=0.06$). No patient needed therapeutic paracentesis for ascites while on PD.

Conclusions: To our knowledge, this is the largest single-center study on PD with CLKF patients. Our patients had mortality, hospitalization, and peritonitis rates lower than the general PD population. Peritonitis episodes were more commonly from non-enteric pathogens suggesting a failure of aseptic PD technique rather than cirrhosis-related spontaneous bacterial peritonitis. The decline in serum albumin from baseline was not statistically significant. Six patients received SLKT and 5 are active on the list, demonstrating PD can be a successful bridge to SLKT. Given excellent outcomes and effectiveness in ascites management, we propose PD as a first-line kidney replacement therapy option in patients with CLKF.

TH-PO340

The Effects of Objective Structured Clinical Examination on Home Hemodialysis Transition

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Background: Home hemodialysis (HHD) augments quality of life and improves several clinical outcomes in patients with end-stage kidney disease. However, patients are required to learn a complex medical task and are obligated to demonstrate competency of training. We hypothesize that Objective Structured Clinical Examination (OSCE) is a feasible strategy to enhance training and improve patient and provider confidence.

Methods: From 2017 to 2021, 58 patients completed HHD training at University Health Network. Each patient completed an OSCE for formative assessment and a final OSCE for summative evaluation. The OSCE comprised of 94 or 85 items, depending on vascular access. Targeted training was provided after the first OSCE on identified areas of improvement. 25 of 58 consented and completed an optional Likert Scale survey (1 to 10) assessing confidence in seven categories, as seen in Figure 1. These include three routine practices of ultrafiltration (UF) target, HHD access, and machine set up followed by three advanced actions of alarm and complication management, and safety. A final item, readiness to go home, served as a global assessment. Patients and training nurses completed the surveys, scoring from 1 to 10, before and after each OSCE. Within subject differences were assessed by paired Student t test.

Results: The mean OSCE score increased from 96.2 (+/- 5.7) after the first OSCE to 98.2 (+/- 3.1) % after the second OSCE ($p > 0.05$). The patient mean score for home readiness increased from 8.0 (+/- 1.8) after the first OSCE to 9.5 (+/- 1.0) after the final OSCE ($p < 0.05$). Similar trends were observed from the nurse trainers, with their mean home readiness score increased from 6.6 (+/- 1.8) to 8.9 (+/- 1.1) ($p < 0.05$) after the OSCE process. Individually, there was an increase in patient confidence in all categories. Confidence in ultrafiltration target, dialysis access, and machine setup improved by 0.68, 0.40, and 0.36 respectively ($p < 0.05$). Confidence in advanced components including alarm troubleshooting, complication management, and safety increased by 0.84, 1.04, and 0.72 respectively ($p < 0.05$).

Conclusions: We demonstrated that OSCE is an implementable training strategy, which is associated with augmented home readiness and confidence scores in our patients and nurse trainers. We speculate that assurance of training may reduce patient burnout.

	Patient		Nurse	
	After OSCE 1	After OSCE 2	After OSCE 1	After OSCE 2
Ultrafiltration Target	9.2	9.9	8.4	9.0
Dialysis Access	9.3	9.7	8.4	9.0
Machine Setup	9.6	9.9	8.7	9.2
Alarm Troubleshooting	8.3	9.1	7.4	8.4
Complications Management	8.0	9.1	7.3	8.4
Safety	8.8	9.6	7.3	8.7
Readiness for Home	8.0	9.5	6.6	8.9

Figure 1. Patient and nursing reported confidence scores.

TH-PO341

Tumoral Calcinosis in a Patient with ESKD on Peritoneal Dialysis: A Diagnostic Dilemma

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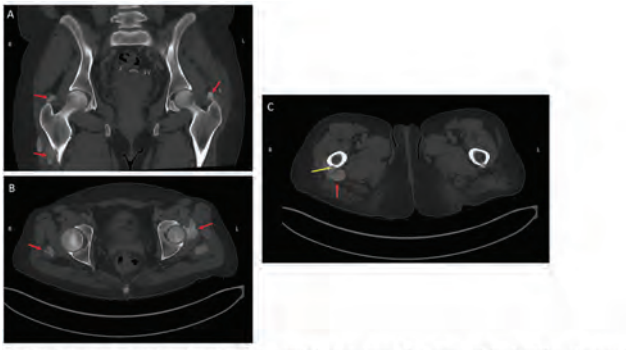
Introduction: Tumoral calcinosis is an uncommon complication of secondary hyperparathyroidism related to end-stage kidney disease (ESKD) with calcium and phosphate deposition in soft tissues, which is different from calciphylaxis characterized by microvascular calcification resulting in painful skin ulcers.

Case Description: A 42-year-old woman with history of ESKD on peritoneal dialysis (PD) for 6 years presented with severe multiple joint pains for 2-week duration. Home medications included losartan, cinacalcet and calcium acetate. Labs revealed phosphorus of 11 mg/dl (2.5 - 4.8 mg/dl); parathyroid hormone (PTH) of 1061 pg/ml (15-65 pg/ml). She was anuric and her most recent Kt/V was 2.3. On examination, she had tenderness in multiple proximal and distal interphalangeal joints on her hands, bilateral hip, and knee joints. Computed tomography (CT) pelvis with contrast showed calcified masses in soft tissue and periarticular region in bilateral hip consistent with tumoral calcinosis (Figure A, B and C – red arrows); direct extrinsic erosion of the right posterior proximal femoral diaphyseal cortex (Figure C – yellow arrow) and left hip acetabulum. Given the severity of symptoms, she was transitioned to intermittent hemodialysis and received sodium thiosulfate infusions. Calcium acetate was switched to sevalamer. She received a kidney transplant 3 months later. On 10 month follow up, her symptoms resolved.

Discussion: The timeline for tumoral calcinosis can range from 17 - 84 months in PD patients. Treatment includes low phosphorus diet, noncalcium-based phosphorus binders, calcimimetics, sodium thiosulfate and surgical options are parathyroidectomy for secondary or tertiary hyperparathyroidism. Nephrologists should be aware of this rare entity to provide appropriate care including patient education on medication adherence, if needed switching dialysis modalities to intensive hemodialysis (5 times per week) and surgical management. Studies have shown complete resolution of tumoral calcinosis after kidney transplant.



CT pelvis with contrast: A – Coronal view shows bilateral hip tumoral calcinosis (red arrow); B - Cross sectional view shows bilateral hip tumoral calcinosis (arrows); C – Cross sectional view shows tumoral calcinosis (red arrow) causing erosion of right posterior proximal femoral diaphyseal cortex (yellow arrow)

TH-PO342

Pantoea dispersa Peritonitis in a Patient on Peritoneal Dialysis

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Introduction: *Pantoea dispersa*, a gram-negative bacterium belonging to the genus Pantoea, is commonly found in natural environments, including plants, soil, and water. While traditionally regarded as a plant pathogen, certain species have emerged as significant pathogens in humans, particularly in immunocompromised individuals. Here, we report a rare occurrence of *Pantoea dispersa* peritonitis in a patient on peritoneal dialysis (PD).

Case Description: A male in his mid-60s with end-stage kidney disease on PD presented with a two-day history of progressively worsening diffuse abdominal pain and cloudy dialysis effluent. Additional symptoms included chills, nausea, emesis, and diarrhea. Analysis of PD fluid revealed an elevated WBC (9749 cells/mm^3) with neutrophil predominance (98%). We initiated empirical intraperitoneal (IP) antibiotic therapy using vancomycin and cefepime. PD fluid culture grew *Pantoea dispersa* from tow separate samples. Susceptibility testing showed low minimum inhibitory concentrations (MIC) to all tested antibiotics including aminoglycosides, trimethoprim/sulfamethoxazole, fluoroquinolones, and cephalosporins (cefoxitin was intermediate). Hence, the IP antibiotic regimen was changed to ceftazidime monotherapy. The patient reported significant improvement in abdominal pain by day 3, and repeat analysis of PD fluid on day 4 confirmed an excellent response to antibiotic therapy (WBC 113 cells/mm^3). He was discharged with a plan to complete a 3-week course of IP ceftriaxone as outpatient.

Discussion: This case sheds light on the emerging significance of *Pantoea dispersa* as a pathogen in human infections, particularly in immunocompromised hosts including patients with end-stage kidney disease. *Pantoea dispersa* often exhibits multidrug resistance, emphasizing the importance of susceptibility testing for optimal management. Notably, *Pantoea agglomerans*, a related species, has been reported as a rare cause of peritonitis in PD patients, with documented complications including ultrafiltration failure and encapsulating peritoneal sclerosis. However, the consequences of *Pantoea dispersa* peritonitis remain unclear. By presenting this case, we hope to enhance clinicians' understanding and awareness of the potential pathogenicity of *Pantoea dispersa*, facilitating the establishment of effective management in similar clinical scenarios.

TH-PO343

Comprehensive Approach to Renal Education and Support: Methods and Outcomes

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Introduction: The 2019 Advancing American Kidney Health Initiative aims to increase home dialysis utilization and improve access to kidney transplantation. In our approach to achieve these goals, we designed a quality initiative to provide comprehensive, patient-centered nephrology care for patients with high risk of disease progression.

Case Description: This QI project started January 2021. High risk patients were identified via EMR registry. Inclusion criteria was GFR < 30 ml/min or KFRE score > 20% at 2 years. Patients were contacted and offered enhanced education and support regarding modality choices & CKD progression. Patients were sequentially scheduled with an experienced nephrology NP, Social Worker, dietician and home dialysis nurse, with an additional NP follow up visit to determine further education, resource needs, ESRD decision plan and tracking. Patient modality choices were subsequently relayed to primary nephrologists and documented in the EMR. Patient progress and gaps in coordination were discussed during quarterly list management meetings.

Discussion: Our cohort included 42 patients (Average age; 65 years, GFR 16 ml/min, KFRE 53%).35% patients completed all 5 comprehensive visits.78% made decisions on preferred modality (33% iHD, 40% PD, 21% undecided). 20 patients (47%) progressed to ESRD, with incident rates of PD 25% and iHD 75%. 7% patients died prior to ESRD progression. 9 patients (45% of ESRD group) initiated hemodialysis as in-hospital starts. 36% (n=8) of patients without progression to ESRD are with AVF/AVG placement, awaiting RRT initiation. Transplant status include 2 patients on the active, 10 inactive transplant lists. 23 referrals were closed due to patient ineligibility whereas 1 patient received a pre-emptive transplant. Development of a multidisciplinary high-risk nephrology care clinic at our institution resulted in attainment of improved rates of incident PD utilization, which surpassed rnational benchmarks. Significant number of our patietns without ESRD progression are expected to have optimal start RRT with functioning AV access. Despite advanced care planning, 45% of our ESRD starts initiated RRT in hospital, demonstrating high complexity of care/disease burden of advanced CKD patients. Adoption of comprehensive care models for patients at increased risk for development of ESRD may lead to improved patient outcomes while also meeting national quality metrics.

TH-PO344

Mycobacterium Exit Site Infection in a Peritoneal Dialysis Patient

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Introduction: Mycobacterium Fortuitum (*M.Fortuitum*) is a rare form of nontuberculous infection that uncommonly affects peritoneal dialysis (PD) patients. Mycobacterial peritonitis has a high rate of morbidity and mortality. We present a case of a patient with Mycobacterium exit site infection which led to PD catheter removal, transition to intermittent hemodialysis, eradication of infection and reinsertion of PD catheter to successfully reinitiate PD.

Case Description: A 41-year-old man with end stage kidney disease on PD (catheter placed 2021), hypertension, and diabetes mellitus, presented to outpatient PD clinic in July 2022 with purulent drainage from the PD catheter exit site. Prior to this in April 2022 he was treated for coagulase negative staphylococcus peritonitis with intraperitoneal cefazolin and fungal prophylaxis. In July 2022, exit site culture was positive for AFB with speciation to *M. Fortuitum*. Peritoneal fluid cultures were negative. He was initiated on ciprofloxacin, clarithromycin and fungal prophylaxis. Due to ongoing purulent drainage, he underwent surgical evaluation with PD catheter revision and exit site debridement. He was also referred to Infectious Disease. Exit site culture again grew *M. Fortuitum* that was macrolide resistant. He was switched to doxycycline and ciprofloxacin. CAT scan showed no drainable fluid collection. Due to sustained exit site infection, he underwent PD catheter removal and transitioned to intermittent hemodialysis via tunneled dialysis catheter. After 4 months of antibiotic therapy post-PD catheter removal, CAT scan confirmed no evidence of fluid collection, at which time antibiotics were concluded. A month after he was infection free, he underwent new PD catheter placement and transitioned back to PD, with plan for re-activation on the transplant list.

Discussion: Our patient had resolution of exit site infection and restarted PD after a long course of antibiotics and removal of the initial PD catheter. This case not only advocates for early removal of PD catheter and foregoing exit site revision, but also illustrates the importance of dual therapy for mycobacterial infection treatment. Fortunately, this patient never progressed to mycobacterial peritonitis. Lastly, this case demonstrates the importance of multidisciplinary collaboration between nephrology, infectious disease, and surgery to safely and quickly eradicate infection.

TH-PO345

Valacyclovir Neurotoxicity: A Case Comparison of Peritoneal Dialysis and Hemodialysis

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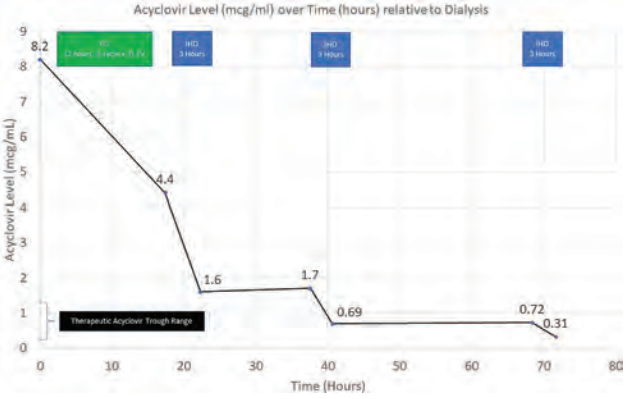
Introduction: The standard treatment for acyclovir neurotoxicity in ESRD is hemodialysis (HD) as it eliminates roughly one-third of acyclovir per session. However, there are various reports of success with peritoneal dialysis (PD) intensification. We report an ESRD patient with acyclovir neurotoxicity given both PD and, after persistent symptoms, HD. This offers the unique opportunity to compare therapeutic effects.

Case Description: An 87-year-old man with ESRD on PD was hospitalized with confusion, ataxia, and visual hallucinations. Prior to admit, the patient had shingles and got valacyclovir 1gm q8 hours (ESRD max recommended dose = 500mg q24-48 hours). Neurologic symptoms began after his 3rd dose. He was adherent to home PD. Total KT/V 1 month prior was 2.09 with little residual GFR (KT/Vr = 0.06). On admit, he was afebrile with left flank vesicular rash, slurred speech, slow motor skills, and imbalance. BMP had BUN 60 mg/dl, creatinine 11.7 mg/dl. CBC, cultures, toxicology, and CT head were negative. Acyclovir neurotoxicity was diagnosed. Dialysis was performed and acyclovir levels were drawn (Figure). Patient declined initial recommendation of temporary HD. Yet, after no clinical change with 12 hours intense PD, he had HD, improving after each HD, and eventual neurotoxic resolution.

Discussion: Valacyclovir, a prodrug of acyclovir, is efficacious in treating herpes zoster. We have a unique neurotoxic acyclovir overdose treated with PD and HD sequentially. Despite 12 hours of intervening PD, our patient's acyclovir level took ~18 hours to reduce in half. In normal renal function, the elimination half-life of acyclovir is ~3 hours, yet in ESRD this increases to ~14 hours. Based on ESRD half-life, this suggests intense PD was not effective for acyclovir toxicity. In contrast, the acyclovir level dropped rapidly with each HD along with clinical improvement. In our patient, HD was the superior modality and should be considered first to avoid potential long-term neurotoxic injury in patients with minimal residual kidney function.



TH-PO346

A Case of Hyperprolactinemia in a Dialysis Patient

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Introduction: The prolactin levels are elevated in the CKD population, up to nearly 65% in the ESKD population, but symptoms like galactorrhea may not be present generally. We present a case of hyperprolactinemia in a CKD patient significant enough to cause symptom

Case Description: A 23-year-old female with a history of obesity, Caroli's disease, BPD, ESKD secondary to nephronophthisis, currently on Home hemodialysis, history of deceased donor kidney transplant 2008 with graft failure 2022, presented with bilateral breast enlargement, pain, and milky discharge for a year, associated with oligomenorrhea. She denied any visual disturbances. Labs notably showed elevated prolactin levels of 92.7; TSH, ACTH, IGF, FSH, LH, and testosterone levels were within normal limits. Head CT with and without contrast were done which showed no masses or lesions, and an unremarkable sella turcica. Initially, she had been on Abilify for BPD, and despite a lowered dosage symptoms persisted. Subsequently despite being off Abilify for two months symptoms persisted. She has been started on cabergoline with the improvement of symptoms.

Discussion: Hyperprolactinemia in CKD is thought to be secondary to a reduction in metabolism and reduced availability of dopamine-stimulating prolactin. While the patient was on Abilify, which may cause elevated prolactin levels, being off of it, the symptoms persisted, therefore was unlikely the cause. CT head was unremarkable, suggesting against prolactinoma, and the hyperprolactinemia attributed to ESKD. Hyperprolactinemia is common, but galactorrhea is rarely seen and could be appropriately treated with cabergoline.

TH-PO347

Dialysis-Associated Ascites: Leave No Stone Unturned

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Introduction: Dialysis-associated ascites (DAA) is a rare complication of ESRD, with a pathogenesis that is poorly understood. Here, we present a case of DAA that developed in a patient after starting home hemodialysis.

Case Description: A 54-year-old man with a rare genetic renal-limited neoplasm eventually had all kidney tissue removed and went on HHD using NxStage via an AVF. Shortly thereafter, he developed large ascites that required paracentesis (~8 L) every 6-8 weeks, and also developed sexual dysfunction and restless leg syndrome (RLS). Cardiac function and hepatic synthetic function remained normal and he had no edema. The ascites was exudative with a serum:ascites albumin gradient less than 1.1. Cytology was always negative. After 4 years on HHD, he received a kidney transplant that had to have a ureteral stone removed just prior to transplant. Within 48 hours of transplant, his DAA completely resolved and over the next 6 weeks his sexual dysfunction and RLS also resolved. In the 8 years since his transplant, he has never developed nephrolithiasis and continues to enjoy essentially normal kidney function.

Discussion: DAA is said to carry a poor prognosis with a mortality rate of 45% over 15 months. The pathogenesis is unclear, but hypoalbuminemia is thought to be a contributing factor. Patients usually present with severe, worsening and recurrent ascites, and cachexia. It is considered generally refractory to the usual treatment modalities and remains largely a diagnosis of exclusion. Kidney transplantation is the only definitive treatment with resolution of the ascites usually occurring over 6 weeks. In our patient, who was anephric due to a very rare renal-limited neoplasm, the ascites was mobilized immediately and resolved in 48 hours, and his other symptoms resolved within 6 weeks.

Although his transplant kidney came from a stone-former, he is not a stone former and has never had nephrolithiasis. We conclude that although being anephric may increase the risk of DAA, it can rapidly resolve with transplantation so the prognosis may not be as grave if transplant can be expedited.

TH-PO348

A Case of Cellulosimicrobium Peritonitis Associated with Peritoneal Dialysis

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Introduction: While peritoneal dialysis (PD) associated peritonitis is common, isolation of an uncommon organism can pose a clinical challenge. We present a case of PD peritonitis caused by the organism *Cellulosimicrobium*. A review from 2019 by Rivero et al found only 43 described cases of infection due to *Cellulosimicrobium*. Two-thirds of described cases were associated with an indwelling medical foreign body, and only 5 cases described associated with PD.[1]

Case Description: A 71-year-old male presented with acute coronary syndrome and hypervolemia. Nephrology was consulted for PD management. During evaluation for coronary artery bypass graft (CABG) patient was transitioned from PD to Continuous Hemodiafiltration, requiring aggressive ultrafiltration. CABG was complicated by protracted cardiogenic shock. Unresolving shock and leukocytosis raised concern for concurrent sepsis, broad-spectrum antibiotics (vancomycin and cefepime IV) and infectious workup were pursued. PD fluids were consistent with peritonitis and cultures were positive for *Cellulosimicrobium*. Despite 10 days of vancomycin cultures remained positive. Persistent clinical instability delayed removal of PD catheter, which was removed on day 20. Patient was successfully transitioned to hemodialysis and remained without evidence of persistent infection at discharge.

Discussion: Despite vancomycin sensitivity in all previously described cases of infection attributed to this organism, two weeks of IV administration failed to clear the infection in our case.[1] This is consistent with the five published cases of *Cellulosimicrobium* described in the literature (fig 1), where three out of five cases were considered antibiotic failure and required PD catheter removal. Depending on the clinical context, removal of PD catheter should be considered early in the treatment course of *Cellulosimicrobium* peritonitis given high rate of treatment failure.

Year Author	Patient Demographics	Antibiotics Regimen	Required PD catheter removal?
1990 Rihs et al.[2]	71-year-old Female	Vanc (IP) +Genta (IM and IP)	Yes
1996 Borra and Kleinfeld[3]	59-year-old Female	Vanco (IP)+ tobra (IM)→ Doxycycline (PO)	No
1999 Lujan-Zilberman et al[4]	13-year-old Female	Vancomycin (IP)	No
2010 Betancourt et al[5]	62-year-old Male	Vanco (IP)+ Genta (IP)+ciprofloxacin→ Vanco (IP) + TMP-SMX→ Vanco (IP)+ GENT (IV) +TMP-SMX	Yes
2015 Sug et al[6]	50-year-old Female	Ceftazidime (IP)+ Cefazolin (IP) → Ceftazidime (IP)+ Tobra (IP) → Ceftazidime (IP)+Tobra (IP)+Vanco (IP)	Yes

Figure 1: Published Cases of Cellulosimicrobium PD Peritonitis: Vanco- vancomycin. Genta-gentamycin. Tobra- tobramycin. TMP-SMX- trimethoprim-sulfamethoxazole IP- intraperitoneal, IM- intramuscular

TH-PO349

Delayed "Sweet" Hydrothorax Associated with Peritoneal Dialysis

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Introduction: Hydrothorax in Peritoneal Dialysis (PD) patients is diagnostically challenging, often attributed to volume overload, uremic effusion, or parapneumonic effusion. A pleuro-peritoneal leak is a rare complication, usually presenting within 30 days of PD initiation, predominantly in females. We present a case of delayed pleuro-peritoneal leak three years after PD initiation.

Case Description: A 48-year-old man with end-stage renal disease from PLA2R-associated membranous nephropathy on automated peritoneal dialysis for 3 years presented with progressive dyspnea over 2 weeks. He had a recent admission for PD peritonitis 3 months ago. Examination revealed decreased breath sounds on the right side, crackles on the left lower lung fields, and pitting edema in both legs. A chest radiograph indicated a large right pleural effusion. Labs showed glucose of 69 mg/dL, elevated creatinine (21 mg/dL), elevated blood urea nitrogen (81 mg/dL), and elevated B-natriuretic peptide (1101 pg/mL), suggesting possible non-compliance with PD or PD failure. However, analysis of the pleural fluid sample revealed a protein concentration of 2.6 g/dL, creatinine of 22.1 mg/dL, glucose of 80 mg/dL, and lactate dehydrogenase of 162 IU/L, similar in composition to the dialysate fluid, consistent with a pleuro-peritoneal leak. Symptoms resolved upon discontinuing PD and switching to hemodialysis.

Discussion: Pleuro-peritoneal leak, also known as "sweet hydrothorax," is a rare complication of PD and classically occurs within a month of initiating PD due to increased intra-abdominal pressure during PD fluid administration in patients with diaphragmatic defects. Our patient's delayed presentation is unique and may be linked to prior peritonitis and weakened diaphragmatic tissue. Prompt identification is crucial, as treating other causes of hydrothorax can worsen the leak. A pleural fluid to serum glucose ratio >1.0 and elevated creatinine levels close to dialysate composition indicate a leak, confirmable with Peritoneal Scintigraphy or CT/MR Peritoneography. Temporary transfer to hemodialysis often promotes healing, while chemical pleurodesis, surgical repair, or permanent transfer to hemodialysis are options if conservative measures fail. Our case highlights the possibility of delayed presentation after peritonitis and underscores the importance of timely identification.

TH-PO350

Diagnosing Scrotal Wall Edema in a Patient Undergoing Peritoneal Dialysis

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Introduction: Acute genital edema is a well-documented complication of peritoneal dialysis (PD) and is seen in 4-10 % of patients. While most incidents occur via obvious defects in the peritoneal membrane, we present a case of acute scrotal wall edema thought to be due to microtears in the peritoneal membrane.

Case Description: A 46 year old male on PD for the past 20 months presented with complaints of acute scrotal swelling. Shortly after his first dwell via continuous cycling peritoneal dialysis (CCPD), he suffered a severe coughing bout while supine. He awoke the following day with diffuse, bilateral, nonreducible and nontender scrotal swelling. CCDP was temporarily held and swelling improved, but immediately re-occurred after resumption of CCPD. CT of the abdomen and pelvis did not show a patent processus vaginalis, inguinal hernia or other obvious peritoneal membrane defect. Scrotal ultrasound did not show a fluid collection but showed diffuse scrotal wall edema. To confirm that this edema was of PD origin, we added 30 mL of gastrograffin into 1 liter of PD fluid and let this dwell for 3 hours after which repeat CT abdomen and pelvis showed a contrast-enhanced scrotum (Figure 1). CCPD was discontinued and patient was transitioned to intermittent hemodialysis with complete resolution of his edema within 7 days.

Discussion: While scrotal edema is not uncommon in patients on PD, the mechanism for development is usually related to an obvious defect, such as an inguinal hernia or patent processus vaginalis. In our patient however, we hypothesize that microtears in his peritoneal membrane caused by the acute coughing episode may have been the culprit. To our knowledge, there is no gold-standard test for diagnosing peritoneal microtears in PD, however our method of instilling 30 mL of gastrograffin in 1 liter of peritoneal dialysis fluid may be beneficial in aiding diagnosis. Moreover, we hypothesize that serial imaging done at one, two and three hour intervals may provide additional information regarding the location of such microtears.

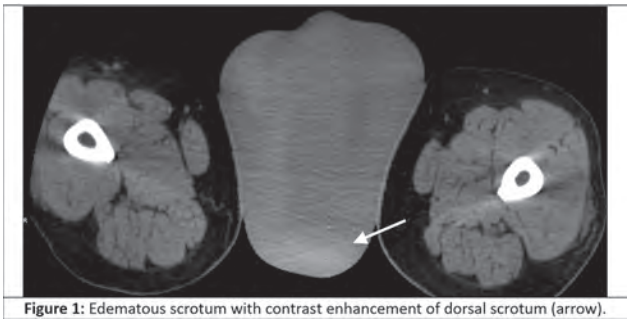

Figure 1: Edematous scrotum with contrast enhancement of dorsal scrotum (arrow).

TH-PO351

Neisseria zoodegmatis: An Interesting Cause of Peritoneal Dialysis (PD)-Related Peritonitis

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Introduction: Neisseria zoodegmatis is a zoonotic pathogen that has typically been associated with cats and dogs. In humans, infection with this organism is usually through cat or dog bites. It was originally termed Eugonic Fermenter(EF)-4b by the Centers for Disease Control, however has since been renamed as Neisseria zoodegmatis [1]. To the best of our knowledge, we present the second reported case of PD-related peritonitis due to Neisseria zoodegmatis [2].

Case Description: A 35 year old female with ESRD due to ADPKD, on peritoneal dialysis (PD) presented to our Emergency Department for abdominal pain. She had recently started on PD three months ago, and had not had any issues with her dialysis. She denied any cloudy effluent or peritonitis in the past. Preliminary workup revealed a potassium of 3.3 mmol/L, BUN of 48 mg/dL, serum creatinine of 6.98 mg/dL, calcium of 8.0 mg/dL, phosphorus of 4.4 mg/dL and albumin of 3.8g/dL. Contrasted imaging of the abdomen revealed enlarged kidneys with numerous cysts due to ADPKD as well as pneumoperitoneum likely due to the PD catheter. Upon further discussion, the patient mentioned that her cat chewed her PD tubing two weeks prior to presentation. Peritoneal fluid analysis revealed turbid yellow fluid along with 300 RBCs/uL, 14625 total nucleated cells/uL with 92% polymorphonuclear neutrophils and 2% lymphocytes. Anaerobic culture was negative however aerobic culture was significant for Neisseria zoodegmatis (formerly CDC group EF-4b). The infectious disease service was consulted, who recommended intraperitoneal (IP) ceftriaxone. As ceftriaxone dosing >2 grams in

PD patients has not been well tested, we planned for ceftriaxone 1 gram during a long, daytime dwell. Patient was discharged on a course of IP ceftriaxone with resolution of her symptoms.

Discussion: In this case, the patient's history was key to raising a high clinical suspicion for an unusual pathogen. Neisseria zoodegmatis is often misidentified as Pasteurella, dismissed as skin contaminant or not recognized at all [3]. We were able to identify this microbe and promptly treat with appropriate antibiotic with resolution of infection. Neisseria zoodegmatis is a pathogen that can cause peritonitis, especially in patients with household pets. Patient education regarding maintenance of PD equipment and exercising extreme caution when pets are near should be of utmost importance.

TH-PO352

The Phantom of the Peritoneum

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Introduction: Patients in urgent need of dialysis are commonly started on hemodialysis (HD) via a central venous catheter. More recently, acute to urgent start peritoneal dialysis (PD) is becoming an alternative. Studies have shown that the incidence of acute and chronic pancreatitis in PD patients was higher compared to HD patients and the general population. Most studies looked at patients on chronic PD. Here, we present a case of urgent start PD complicated by acute pancreatitis.

Case Description: A 58-year-old woman with a past medical history pertinent for ischemic stroke and CKD stage V with loss to follow up for months, and a one-week-old PD catheter presented to the emergency department with tonic-clonic seizures. She was given lorazepam with no response, so she was transferred to a tertiary care hospital. Labs showed a BUN of 117 mg/dL, similar to her BUN for the past month (94-112mg/dL), Cr 15.2 mg/dL, eGFR of 2 mL/min/1.73 m2, potassium of 5.5, lactic acid of 0.6 mmol/L, bicarbonate 15 mg/dL, creatinine kinase 347. CT head was unremarkable. EEG showed no evidence of seizure activity. She was started on PD with low volume runs of 500ml, which she tolerated and gradually increased to 1L. She was eventually extubated successfully. However, while into her fourth run, she started complaining of severe abdominal pain, nausea and vomiting. The PD was stopped. Lipase level came back elevated at 3000. CT abdomen pelvis showed pancreatic and peripancreatic edema with surrounding fluid consistent with acute pancreatitis. PD was held, and the patient was switched to HD. She improved and was discharged home with an outpatient dialysis unit. Her seizure was thought to be due to her old stroke per neurology. She was transitioned back to PD 8 weeks later and has tolerated it well.

Discussion: The majority of ESKD patients are started on in-center HD via a central venous catheter. The use of PD has been increasing in the last decade. Unplanned hemodialysis via a CVC is associated with higher rates of infection and reduced rates of survival compared to PD. Ideally, all patients with CKD should start dialysis in a planned elective manner rather than urgently. The evidence with regard to pancreatitis while on PD is controversial. Some studies report a higher incidence, while others do not. This case is the first to report acute pancreatitis in an urgent start of PD.

TH-PO353

A Peculiar Case of Pica in Peritoneal Dialysis (PD) Peritonitis

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Introduction: Anemia is found in majority of patients with CKD. It is associated with an increased risk of cardiovascular disease, morbidity and mortality in patients dependent on dialysis. Iron supplementation is usually advised to help improve symptoms and quality of life as well as reduce cardiovascular risk.

Case Description: Our patient is a 30 year old woman with history of ESRD secondary to anti-GBM disease on peritoneal dialysis with history of recurrent PD related peritonitis who presented to the emergency room due to abdominal pain, fevers, chills, nausea, and vomiting. She was hemodynamically stable with no leukocytosis but borderline left shift. CT of abdomen showed small bowel wall thickening. PD effluent samples were collected for gram stain and culture. Analysis showed turbidity and a WBC count of 58k with 80% neutrophils. She was started on broad spectrum antibiotics. Culture eventually grew *Acinetobacter pitti*. On further investigation, she reported eating dirt and clay for weeks. Bacteria of the genus *Acinetobacter* are ubiquitously distributed in nature, found in various types of soils. Iron panel showed low iron, low TIBC, and low ferritin. Iron was not given during admission due to active infection. Acinetobacter has a tendency to form biofilms which can cause recurrence of infection. The decision was made to keep the PD catheter in and she was sent home on a course of PO Cipro. Weeks later, she presented again with similar symptoms. During this admission, PD catheter was removed and she was transitioned to HD.

Discussion: Our case is a reminder of the surprising prevalence of pica in the ESRD population. Pica can go unrecognized until metabolic abnormalities or complications arise. Physicians do not routinely investigate pica due to underreporting and lack of information as well as guilt and fear of judgement from patients. CKD is a key player for major stress and can trigger pica. A common co-morbid condition associated with pica is anemia. Patients can have metabolic derangements such as alkalosis, hypoalbuminemia, ascorbic acid deficiency and zinc deficiency. Soil pica can affect certain electrolytes (potassium, phosphate and calcium) depending on soil composition and these electrolytes are further exacerbated in ESRD patients. Pica has extreme significance in the nutritional status of patients with kidney disease and should not be neglected in its implications on these patients.

TH-PO354

Alternatives to Daytime In-Center Hemodialysis and Employment in Patients with Kidney Failure

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Background: Maintaining employment is a priority for many patients with kidney failure. Yet, many working aged patients in the U.S. stop working with the onset of kidney failure. Access to a dialysis treatment schedule outside of working hours may help patients to remain employed.

Methods: We analyzed data from the US National Dialysis Registry to determine whether access to nearby facilities offering evening dialysis shifts and home dialysis increases the likelihood that patients are able to continue working after they start dialysis. Our cross-sectional analysis included working-aged patients (ages 18-54) receiving dialysis in US facilities in 2016. In a negative binomial regression model, we examined the associations among exposures of interest (the presence of facilities offering home dialysis or evening dialysis shifts in a patient's locality) and the number of employed working-aged adults at each dialysis facility. The multivariable model adjusted for observed patient, dialysis facility, and geographic characteristics, including information about individual patient employment at the onset of dialysis.

Results: We identified 4,860 US dialysis facilities with information about patient employment in 2016. Median employment among working-aged adults at these facilities was 17.9% (interquartile range 8.8% to 28.6%). In fully adjusted regression models, the presence of at least one facility offering an evening dialysis shift in a county was associated with a 5% increase in the relative rate of maintaining employment among working-aged patients receiving dialysis in the county (risk ratio (rr) 1.05; 95% Confidence Interval (CI) 1.01 to 1.09; p=0.02). The presence of at least one facility offering home dialysis in a county was associated with a 26% increase in the relative rate of maintaining employment (rr 1.26; 95% CI 1.18 to 1.34; p<0.001). The likelihood of employment did not increase with additional facilities in a county offering home dialysis.

Conclusions: Access to dialysis schedules outside of regular working hours – evening dialysis shifts and home dialysis – is associated with increased employment among patients with kidney failure. Efforts to increase access to these alternative dialysis treatments could help patients to continue working.

TH-PO355

REVOLUTIONIZE III: Consequences of Recurrent Hyperkalemia on Healthcare Resource Utilization and Cost

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Background: Hyperkalemia (HK) is associated with increased healthcare resource utilization (HRU) and costs, but there are limited data on the impact of HK recurrence on these in patients (pts) with chronic kidney disease (CKD). This real-world study describes all-cause medical costs and HRU in pts with recurrent HK (rHK), non-recurrent HK (nrHK) and normokalemia (NK).

Methods: Pts aged ≥18 years with stage 3/4 CKD were identified from Optum's de-identified Market Clarity data; HK was classified as rHK or nrHK by a claims-based algorithm. Pts with rHK were 1:1 exact and propensity-score matched with separate cohorts of pts with NK and nrHK. Index dates were the date of the first event of the index pair of HK diagnosis with ≥1 serum K^+ value >5.0 mEq within 7 days (rHK and nrHK cohorts) or a randomly-selected serum K^+ lab value of 3.5–5.0 mmol/L (NK cohort). Continuous insurance was required for 12 months before and after the index date. Study outcomes were all-cause medical costs and HRU over 12 months.

Results: There were 4549 matched pairs in the rHK vs NK analysis and 1599 matched pairs in the rHK vs nrHK analysis. The rHK cohorts had significantly higher mean per-pt all-cause medical costs than the NK cohort ($34,163 vs $15,175) and nrHK cohort ($52,290 vs $38,233) over 12 months (**Table**); HRU rates were also significantly higher for the rHK cohorts. The increased costs were driven by increased inpatient medical costs with rHK vs NK and rHK vs nrHK.

Conclusions: Large increases in all-cause medical costs and HRU after HK recurrence illustrate the unmet need for chronic management of HK in pts with stage 3/4 CKD, such as through long-term novel potassium binder therapies.

Funding: Commercial Support - AstraZeneca

	Normokalemia (N = 4549)	Recurrent HK (N = 4549)	P-value	Non-recurrent HK (N = 1599)	Recurrent HK (N = 1599)	P-value
All-cause medical cost per patient, $						
Any setting	15,175 (33,634)	34,163 (63,556)	<0.001	38,233 (57,321)	52,290 (86,368)	<0.001
IP	7392 (27,690)	21,250 (54,737)	<0.001	23,663 (48,994)	35,637 (75,559)	<0.001
ED	961 (3431)	2191 (8491)	<0.001	2533 (6572)	2870 (12,643)	0.34
OP	4591 (7708)	7412 (11,301)	<0.001	7890 (11,866)	9193 (11,967)	<0.01
All-cause HRU, number of admissions or visits per patient						
Any setting	23.0 (27.3)	34.1 (30.7)	<0.001	36.0 (34.8)	40.3 (34.9)	<0.001
IP admission	0.3 (1.2)	0.8 (2.1)	<0.001	0.9 (1.8)	1.3 (2.6)	<0.001
ED visit	0.3 (0.8)	0.6 (1.5)	<0.001	0.6 (1.5)	0.7 (2.0)	0.55
OP visit	13.8 (20.6)	21.0 (24.8)	<0.001	22.3 (29.3)	25.3 (28.5)	<0.01

Costs and HRU are reported as mean (SD) per patient during 12 months' follow-up. Costs were adjusted for inflation to 2022 US dollars.

Abbreviations: CKD, chronic kidney disease; ED, emergency department; HK, hyperkalemia; HRU, healthcare resource utilization; IP, inpatient; OP, outpatient; SD, standard deviation.

All-cause medical costs and HRU in patients with stage 3/4 CKD with or without HK

TH-PO356

Baseline Characteristics of Early Enrollees in TRACK, a Prospective Study of Hyperkalemia Management Decision-Making

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Background: The TRACK study is a prospective, observational, implementation science study designed to address the evidence gap regarding healthcare provider decision-making and management of patients with hyperkalemia (HK).

Methods: The study will enroll 1250 patients with HK in the US and Europe and record management decisions, treatment objectives and outcomes, HK recurrence and attainment of target renin-angiotensin-aldosterone system inhibitor (RAASi) dose during 12 months following an index episode of HK. The planned sample size provides a margin of error <3% to estimate endpoints of interest such as attainment of target doses of RAASi therapies at month 12. Eligible participants are adults with serum K^+ >5.0 mmol/L collected during standard of care within 14 days prior to informed consent. Baseline characteristics of early enrollees are presented descriptively.

Results: Baseline characteristics and initial HK management approach are shown for the first 62 enrollees. Chronic kidney disease (CKD) and/or heart failure was present in 90%. Mineralocorticoid receptor antagonist use was reported by 7% and other RAASi by 53%. RAASi downtitration and discontinuation during the qualifying HK episode was reported for (18%). Median K^+ was 5.4 mmol/L (IQR 5.2-5.6); eGFR 26 mL/min/1.73m^2 (IQR 15, 35). The most common initial management strategies for the index episode of HK, apart from monitoring serum K^+, were prescription of a low K^+ diet and use of K^+ binders (Table). We anticipate enrolling approximately half of the planned 1250 participants for presentation at Kidney Week.

Conclusions: TRACK will characterize contemporary provider decision-making in patients with HK and its impact on HK recurrence across a broad range of patient types in a variety of practice settings in the US and Europe.

Funding: Commercial Support - AstraZeneca

Table. Baseline characteristics and initial management strategy in patients with hyperkalemia

	Overall	Germany	Spain	UK	US
N	62	2	5	21	34
Age, years	68 (14)	73 (3)	68 (11)	64 (14)	67 (15)
Female	19 (31)	1 (50)	1 (20)	8 (38)	9 (27)
CKD without heart failure*	44/59 (75)	0	4 (80)	15/20 (71)	25/32 (78)
Kidney failure on dialysis	2	0	0	1	1
Heart failure without CKD*	3/59 (5)	1 (50)	0	2/20 (10)	0
Heart failure and CKD*	6/59 (10)	1 (50)	1 (20)	2/20 (10)	2/32 (6)
ACEI/ARB/ARNI	33 (53)	1 (50)	5 (100)	9 (43)	18 (53)
MRA	4 (7)	1 (50)	1 (20)	1 (5)	1 (3)
Number with initial management reported (Patients may appear in more than 1 row)	50	2	5	20	23
No treatment	5 (10)	0	0	5 (25)	0
Monitor K^+ level	37 (74)	1 (50)	5 (100)	12 (60)	19 (83)
Low K^+ diet	26 (52)	0	5 (100)	6 (30)	15 (65)
Start or increase dose of non-K-sparing diuretic	3 (6)	0	2 (40)	0	1 (4)
Down-titrate or discontinue ACEI/ARB/ARNI	6(12)	0	0	3 (15)	3 (13)
Down-titrate or discontinue MRA	3 (6)	1 (50)	1 (20)	0	1 (4)
Start or increase dose of potassium binder	12 (24)	0	4 (80)	2 (10)	6 (26)
Change dialysis prescription	0 (0)	0	0	0	0
Unscheduled dialysis	0	0	0	0	0

Mean (standard deviation) or n (%). *denominator reflects missing data. Angiotensin converting enzyme inhibitor (ACEi), angiotensin receptor blocker (ARB), angiotensin receptor/neprilysin inhibitor (ARNI), mineralocorticoid receptor antagonist (MRA)

TH-PO357

Thyrotoxic Periodic Paralysis Complicated by Severe Rebound Hyperkalemia

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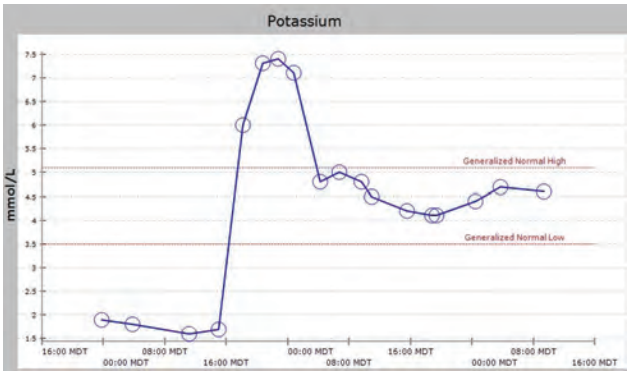
Introduction: Thyrotoxic periodic paralysis (TPP) is a rare, acquired subtype of periodic paralysis in which muscle weakness develops from profound hypokalemia in the setting of hyperthyroidism. We present a case of TPP complicated by severe rebound hyperkalemia.

Case Description: A 31-year-old Hispanic man without medical history presented with severe generalized weakness. His physical exam was notable for proptosis and tremor. Initial labs included hypokalemia (serum potassium 1.6 mEq/L), undetectable thyroid-stimulating hormone (TSH), free T4 2.3 ng/dL, and urine potassium 5 mEq/L. He was admitted to intensive care with a diagnosis of TPP and treated with methimazole, propranolol, and aggressive potassium replacement (100 mEq IV + 220 mEq PO in 24 hours). His weakness improved, but he subsequently developed severe hyperkalemia with peak serum potassium of 7.4 mEq/L (Figure 1). His hyperkalemia resolved with medical therapy. He was diagnosed with Graves' disease based on a positive TSH receptor antibody, and he was discharged home on methimazole and propranolol.

Discussion: TPP is a potentially fatal complication of hyperthyroidism characterized by episodes of sudden paralysis and hypokalemia, classically triggered by carbohydrate intake or exercise and often predating overt clinical hyperthyroidism. Though common in East Asian men, other non-white minorities, including Hispanics, appear to be at increased risk. Rather than potassium depletion, the primary cause of acute hypokalemia in TPP is transcellular shift caused by a hyperadrenergic state. As such, aggressive potassium repletion — particularly as the underlying hyperthyroidism abates with treatment — carries a risk of rebound hyperkalemia which can be lethal. Thus, initial treatment for TPP must focus on the underlying hyperthyroidism with antithyroid therapy and non-selective beta-blockade, with recommended potassium replacement limited to ≤90 mEq PO in 24 hours.



TH-PO358

Contemporary Use of Guideline-Directed Medical Therapy and Associated Outcomes in Cardiorenal Patients with Hyperkalemia: An Observational Multi-Country Study

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Background: International guidelines recommend renin-angiotensin-aldosterone system inhibitor (RAASi) therapy at the maximal tolerated dose to optimize treatment benefits in chronic kidney disease (CKD) and heart failure (HF). However, RAASi therapy increases the risk of hyperkalemia (HK), which is a barrier to achieving guideline-directed RAASi therapy. Novel oral anti-HK treatments, e.g., sodium zirconium cyclosilicate (SZC), are recommended to manage HK and allow the maintenance of RAASi therapy. This ongoing observational study investigates contemporary use of guideline-concordant RAASi and SZC therapy and associated outcomes in cardiorenal patients (pts) with HK in 3 geographic regions.

Methods: This analysis includes data from hospital records and claims from the US (Optum Clinformatics Data Mart), Japan (Medical Data Vision) and Spain (Big-Pac), and evaluates adults with CKD and/or HF who have an HK episode (ICD-10 code E87.5) or initiate outpatient SZC therapy while treated with RAASi. The observation period started when SZC became available in the respective country (July 2019 [US], May 2020 [Japan], June 2021 [Spain]). Across countries, use of guideline-directed medical therapy (GDMT) and associated outcomes will be assessed in terms of maintained/reduced RAASi therapy, SZC treatment, and HK- and cardiorenal-related hospitalizations.

Results: The US dataset includes 125,632 cardiorenal pts (mean age, 74 years; 50% male) who had an HK episode. CKD was present in 83% of pts and HF in 56%. The 3648 pts who initiated SZC were younger (72 years), more often male (54%), and more often had CKD (96%) compared with the overall HK cohort. Data from Japan and Spain will be available for analyses during Q2 2023. Results from analyses of RAASi therapy and SZC treatment patterns and associated outcomes across countries will be presented at the ASN congress.

Conclusions: This study provides contemporary insights into the characteristics of cardiorenal pts with HK and use of GDMT in clinical practice across 3 geographic regions which, together with the associated outcomes, may guide treatment optimization and improve patient prognosis.

Funding: Commercial Support - AstraZeneca

TH-PO359

Evaluation of Efficacy, Safety, and Treatment Patterns of Sodium Zirconium Cyclosilicate in Management of Hyperkalemia in China: An Interim Analysis (Actualize)

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Background: Sodium zirconium cyclosilicate (SZC), a novel highly selective potassium binder is approved in China for the treatment of hyperkalemia (HK), a potential life-threatening electrolyte imbalance condition. This interim analysis from an ongoing multi-center, prospective, non-interventional study evaluated the efficacy, safety and treatment patterns of SZC in Chinese HK patients under real-world settings (NCT05271266).

Methods: This study included patients ≥18 years with documented HK from 40 sites in China, taking/willing to take SZC treatment. The interim analysis included patients who have completed 1 month follow-up. As per Chinese label, SZC treatment was categorized into correction phase (FAS-P1) and maintenance phase (FAS-P2); the treatment was discontinued as per HK threshold (5.3/5.5 mmol/L in most sites under real-world settings). The study evaluated changes in serum K^+ (sK^+) levels and incidence of adverse events (AEs).

Results: A total of 193 patients and 354 patients were enrolled in FAS-P1 and FAS-P2, respectively. With an SZC mean daily dose of 11.5g in FAS-P1, the sK+ levels reduced significantly from baseline, 5.9 mmol/L to 5.0 mmol/L (ΔsK^+ -0.9 mmol/L), after correction phase, 51.3% and 77.8% patients showed sK+ levels between 3.5-5.0 mmol/L and 3.5-5.5 mmol/L. With an SZC median daily dose of 5g in FAS-P2, the mean sK^+ levels were 5.1 mmol/L during the maintenance treatment. SZC was well tolerated with only 1.5% and 0.5% patients in FAS-P1 and FAS-P2, respectively reporting AEs with rarely severe AEs and treatment discontinuations (Table 1).

Conclusions: From the interim analysis, SZC was effective and safe in treating HK. Hence, SZC can be considered a standard treatment for acute and chronic HK in China.

Funding: Commercial Support - AstraZeneca Investment China, Shanghai, China

Table 1 Summary of AE with SZC

Incidence Rate, per 100 person-days	FAS-P1(%)	FAS-P2(%)
Any AE	1.5	0.5
Any SAE	0	0.2
Any AE leading to permanent drug discontinuation	0	0
Any specific AE		
Oedema	0	0
Hypokalemia	0.1	0

AE, adverse events; SAE, severe adverse events

TH-PO360

Association Between Hyperkalemia and Cardiovascular Outcomes in Patients with Stage 3b/4 CKD: REVOLUTIONIZE II Study

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Background: Hyperkalemia (HK) is a common complication of moderate to advanced chronic kidney disease (CKD). The impact of HK (defined here as serum K+ >5.0 mEq and diagnosis code in any setting) on the time to cardiovascular (CV) outcomes among patients (pts) with CKD has not been well studied. Here we report cardiovascular (CV) outcome analyses from the REVOLUTIONIZE II study.

Methods: This observational study compared propensity score matched adult pts with stage 3b/4 CKD, with and without HK (HK and non-HK cohorts), in Optum's de-identified Market Clarity database. Index dates were the first CKD stage 3b/4 diagnosis date after ≥1 HK diagnosis in the 12 months (mo) prior (HK cohort) and a randomly selected CKD stage 3b/4 diagnosis date (non-HK cohort). Continuous insurance coverage was required for 12 mo before the index date. CV outcomes were major adverse CV events (MACE; all-cause mortality or inpatient [IP] admission with myocardial infarction or stroke), MACE+ (MACE or IP admission with heart failure), and IP admission with arrhythmia, analyzed in 3 matched subsets.

Results: Of 6619 matched pairs overall, CV analysis subsets included 5949 pairs for MACE, 5301 for MACE+, and 5564 for IP arrhythmia. Baseline variables were balanced between the two cohorts in all subsets. In each subset, the HK cohort had significantly higher rates of CV outcomes than the non-HK cohort during follow-up (P<0.001 for each CV subset; **Table**).

Conclusions: Among pts with stage 3b/4 CKD, rates of MACE, MACE+, and IP arrhythmia are significantly higher for pts with HK than those without HK. This reveals an unmet need for long-term outpatient treatment of HK.

Funding: Commercial Support - AstraZeneca

Cohorts for CV subset	Pts with CV outcome	HR, HK vs Non-HK (95% CI)	Pts with CV outcome, % Year 1	Year 2	Year 3	Year 4	Year 5	Follow-up, years Median (IQR)
MACE								
HK n=5949	1888	1.18 (1.11, 1.26)	18.3	28.6	36.8	43.2	48.4	2.1 (0.9, 3.3)
Non-HK n=5949	1639	P<0.001	15.8	24.9	32.2	38.1	42.9	2.1 (0.9, 3.3)
MACE+								
HK n=5301	1906	1.32 (1.23, 1.40)	21.9	33.1	41.8	48.5	52.6	2.2 (1.0, 3.3)
Non-HK n=5301	1530	P<0.001	17.1	26.3	33.7	39.6	43.3	2.2 (1.0, 3.4)
IP HF in the MACE+ cohort								
HK n=5301	1027	1.69 (1.53, 1.86)	12.9	19.4	24.5	28.4	31.6	2.2 (1.0, 3.3)
Non-HK n=5301	635	P<0.001	7.8	12.0	15.3	17.9	20.1	2.2 (1.0, 3.4)
IP arrhythmia								
HK n=5564	1039	1.59 (1.44, 1.75)	12.2	18.4	23.7	28.0	31.1	2.2 (1.0, 3.3)
Non-HK n=5564	678	P<0.001	7.9	12.0	15.7	18.7	20.9	2.2 (0.9, 3.4)

Abbreviations: CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; HF, heart failure; HK, hyperkalemia; HR, hazard ratio; IP, inpatient; IQR, interquartile range; MACE, major adverse cardiovascular event; pts, patients.

CV outcomes in pts with stage 3b/4 CKD

TH-PO361

Rates of Emergency Temporary Central Venous Access and Emergency Haemodialysis in the Advent of Lokelma: A Retrospective Case Series in a Tertiary Renal Unit

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Background: The value of Lokelma (sodium zirconium cyclosilicate) in the emergency treatment of hyperkalaemia is yet to be proven. We hypothesised that its use would be associated with a reduction in emergency temporary central venous access (CVC) and emergency haemodialysis (HD).

Methods: We conducted a retrospective case series of patients admitted to our unit with hyperkalaemia, comparing before (Jan 2018 – Dec 2019) and after (Apr 2021 – Sept 2022) Lokelma was available. All patients with a potassium >5.5 mmol/L treated with at least one ≥10g dose of Lokelma were analysed (post-Lokelma period). Patients treated with alternative potassium binders in the post-Lokelma period were excluded. A random number generator selected a comparator group of patients admitted with a serum potassium >5.5 mmol/L (pre-Lokelma period). Multivariable-adjusted logistic regression models determined likelihood of emergency temporary CVC and emergency HD.

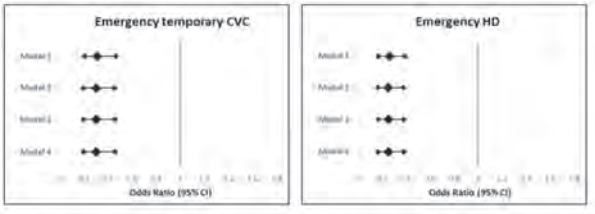
Results: Of the 1668 patients admitted in the post-Lokelma period, 271 were suitable for analysis. 265 patients were selected from the pre-Lokelma period. Participants in both periods were well matched (Figure 1). In the post-Lokelma period, patients were 69% less likely to require emergency temporary CVC (OR 0.31; CI 0.21 – 0.47) and 73% less likely to need emergency HD (OR 0.27; CI 0.18 to 0.40). These results were consistent after sequential adjustment for potential explanatory variables (Figure 2).

Conclusions: Lokelma was associated with a signification reduction in emergency temporary CVC and emergency HD in patients presenting to a tertiary renal unit with hyperkalaemia.

Figure 1 – Baseline characteristics of patients

	Pre-Lokelma period	Post-Lokelma period	p
N	265	271	
Age (years): mean (SD)	67.02 (13.84)	66.19 (14.65)	0.500
Male sex: n (%)	149 (56.2)	160 (59.0)	0.567
eGFR (mL/min/1.73m^2): n (%)			0.013
>= 50	84 (31.7)	72 (26.6)	
>=30 - <50	22 (8.3)	48 (17.7)	
>=15 - <30	52 (19.6)	47 (17.3)	
<15	107 (40.4)	104 (38.4)	
Dialysis-dependent: n (%)	83 (31.3)	72 (26.6)	0.264
Dialysis access: n (%)			0.097
Arteriovenous fistula	48 (51.1)	38 (50.7)	
Arteriovenous graft	10 (11.1)	12 (16.0)	
Peritoneal dialysis catheter	2 (2.2)	7 (9.3)	
Tunnelled central venous catheter	32 (35.6)	18 (24.0)	
Renal transplant recipient: n (%)	35 (13.2)	26 (9.6)	0.238
Diabetic nephropathy: n (%)	61 (23.0)	60 (22.1)	0.889
Hyperkalaemia-inducing medications: n (%)	94 (35.5)	98 (36.2)	0.939
Peak potassium (mmol/L): mean (SD)	6.30 (0.81)	6.28 (0.61)	0.674

Figure 2 – Odds ratios with 95% CI for emergency temporary CVC (left) and emergency HD (right) following sequential adjustment using models 1-4 (see footer)



Model 1 – No adj

Model 2 – Adj. for age, sex

Model 3 – Adj. for model 2, baseline eGFR, dialysis - dependent

Model 4 – Adj. for model 2, model 3, diabetic nephropathy, hyperkalaemia – inducing medications

TH-PO362

The Beneficial Effect of Sodium Zirconium Cyclosilicate on the Continuity of Renin-Angiotensin-Aldosterone System Inhibitors in the Management of Hyperkalemia: A Retrospective Observational Study

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Background: Sodium zirconium cyclosilicate (SZC), a non-absorbed non-polymer zirconium silicate, is a new potassium binder for hyperkalemia. A previous report showed that the administration of SZC in patients with hyperkalemia allows a higher continuation rate of renin-angiotensin-aldosterone system inhibitors (RAASi). However, few comparative studies have focused on the clinical utility between SZC and existing potassium binders. The purpose of this study was to evaluate the effect of SZC on the continuation of angiotensin-converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs) in patients with hyperkalemia compared to that of calcium polystyrene sulfonate (CPS).

Methods: Patients treated with ACEIs/ARBs, who were newly prescribed SZC or CPS for hyperkalemia at a tertiary referral hospital between August 2020 and April 2022, were enrolled in this single-center, retrospective observational study. The primary outcome measure was ACEIs/ARBs prescription three months after the initiation of potassium binders.

Results: A total of 174 patients on ACEIs/ARBs who were newly administered SZC (n=62) or CPS (n=112) were analyzed. The prescription rate of ACEIs/ARBs at three months was significantly higher in the SZC group than in the CPS group (89% vs. 72%). Multivariate logistic regression models showed that SZC was independently associated with the primary outcome (odds ratio 2.66, 95% confidence interval 1.05-7.43). The propensity score-matched comparison also showed a significant association between SZC and the primary outcome.

Conclusions: The current study demonstrated that the administration of SZC in patients with hyperkalemia allows for a higher continuation rate of ACEIs/ARBs than CPS. These findings suggest that SZC have potential benefits for patients with hyperkalemia receiving RAASi.

TH-PO363

A Paralyzing Consequence: Succinylcholine-Induced Hyperkalemia, A Rare but Dangerous Side Effect

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Introduction: Succinylcholine is a depolarizing neuromuscular blockade agent used during general anesthesia. Succinylcholine use can cause hyperkalemia and cardiovascular instability in certain susceptible patients. Here we describe a case of succinylcholine-induced hyperkalemia with cardiac arrest.

Case Description: A 27-year-old male with a medical history of alcohol use disorder was admitted to the ICU for rhabdomyolysis and septic shock due to MRSA pneumonia requiring mechanical ventilation. Following successful extubation, the patient had immobility due to profound weakness with an EMG demonstrating subacute sensory motor axonal polyneuropathy. He had also developed post-intubation dysphonia and laryngoscopy was recommended. Prior to laryngoscopy, his serum potassium level was 3.9 mEq/L. Upon administration of succinylcholine for intubation, he had a cardiac arrest. Immediate repeat labs revealed a serum potassium level of 9.2 mEq/L. Nephrology was contacted for emergent dialysis. In the interim, temporizing measures were given, including insulin with dextrose and calcium gluconate. A repeat serum potassium level was then 6.4 mEq/L with another level 30 minutes later being 3.3 mEq/L. The patient recovered without needing dialysis and was eventually discharged to an acute rehabilitation facility.

Discussion: Succinylcholine causes intracellular potassium efflux when binding to acetylcholine receptors. Several pathologic states cause an upregulation of acetylcholine receptors and predispose patients to a higher risk of critical hyperkalemia. These states include severe infections, rhabdomyolysis, diffuse atrophy, immobilization, denervation injury or diseases, and trauma. Identifying these conditions prior to using succinylcholine is vital. If succinylcholine use is required, close monitoring of the potassium level and cardiac status are necessary. The optimal treatment for patients with succinylcholine-induced hyperkalemia includes those treatments that redistribute potassium back inside cells. Dialysis has a limited role in treatment and poses a greater risk and delayed time to treatment. Succinylcholine-induced hyperkalemia is a rare, life-threatening condition, and practitioners should be aware of predisposing factors and appropriate treatment.

TH-PO364

Impact of Sodium Zirconium Cyclosilicate on Serum Potassium and Bicarbonate in Patients with Hyperkalemia and Metabolic Acidosis Associated with CKD: NEUTRALIZE Study

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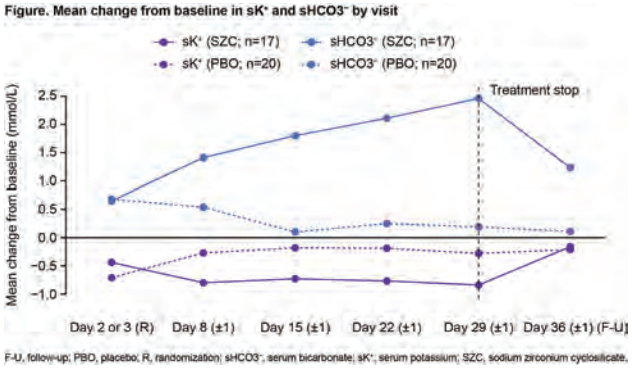
Background: Acidosis and hyperkalemia are common in CKD. The dual effect of sodium zirconium cyclosilicate (SZC), a selective binder of potassium (K^+) and ammonium, on serum K^+ (sK^+) and serum bicarbonate ($sHCO3^-$) was evaluated in CKD patients with hyperkalemia (HK) and metabolic acidosis.

Methods: In the NEUTRALIZE study (NCT04727528), patients with CKD (Stage 3–5) not on dialysis with HK (sK^+ >5.1 to ≤5.9 mmol/L) and metabolic acidosis ($sHCO3^-$ 16–20 mmol/L) received open-label SZC 10 g TID for ≤48 h. Patients achieving normokalemia (NK; sK^+ 3.5–5.0 mmol/L) were randomized 1:1 to SZC 10 g QD or placebo (PBO) for 4 weeks. Primary endpoint was patients (%) maintaining NK at end of treatment (EOT) without rescue. Key secondary endpoints were patients (%) with NK with ≥3 mmol/L increase in $sHCO3^-$ without rescue, and change in $sHCO3^-$ from baseline (BL) to EOT.

Results: Patients (n=229) were screened and 37 were randomized and received treatment (SZC n=17; PBO n=20: high screen failure rate and slow enrolment led to early study termination). Mean age was 63.3y, 68% male, and 87% White. Mean sK^+ (mmol/L) at BL was 5.4 (SZC) and 5.5 (PBO) and for $sHCO3^-$ (mmol/L) 16.1 (SZC) and 15.6 (PBO). At EOT, patients maintaining NK was 88.2% for SZC and 20.0% for PBO (OR, SZC vs PBO, 56.2; P=0.001). Due to small patient number, P-values for secondary endpoints are nominal. $sHCO3^-$ (mmol/L) at EOT was 18.2 for SZC vs 16.5 for PBO (P=0.050). Patients maintaining NK and ≥3 mmol/L increase in $sHCO3^-$ without rescue was 35.3% (SZC) and 5.0% (PBO; P<0.05). For SZC, trends were seen towards a decrease in sK^+ and an increase in $sHCO3^-$ (**Figure**). No safety concerns were reported.

Conclusions: SZC effectively lowered sK^+ and maintained NK during treatment. Despite low patient number, trends towards significance were seen for the increase in $sHCO3^-$ with SZC.

Funding: Commercial Support - AstraZeneca



TH-PO365

Prevalence, Recurrence, and Prognosis of Hyperkalemia in Real-World Patients in China

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Background: Hyperkalemia is a common and life-threatening electrolyte disorder. However, data on hyperkalemia burden in China especially its relationship to clinical outcome in real-world patients remain limited. We conducted a retrospective cohort study to investigate the prevalence, recurrence and prognosis of hyperkalemia in a large tetertiary hospital in China.

Methods: Patients aged ≥18 years who had at least one serum potassium measurement from January 2018 to December 2021 in a large tetertiary hospital in China were enrolled and followed up until April 2022. The primary endpoint was the proportion of patients who experienced a hyperkalemia event (serum potassium [sK] >5.0 mmol/L). Secondary endpoints included the proportion of patients who experienced hyperkalemia recurrence and all-cause mortality rate in patients with hyperkalemia. Risk factors associated with all-cause death in patients with hyperkalemia were analyzed using logistic regression (exploratory).

Results: A total of 55,288 patients were enrolled (median age: 54.0 years; 44.0% were male). Overall, 1131 patients(2.1%) experienced hyperkalemia (428 [0.8%] had sK >5.5 mmol/L and 167 [0.3%] had sK >6.0 mmol/L). 73.2% of patients with hyperkalemia were first diagnosed in the emergency department. Besides, hyperkalemia recurrence occurred in 12.4% patients during the 30 days follow-up, among them 6.6% patients recurred in 7 days. The 1-, 2-, 3- and 4-year all-cause mortality rates in patients with hyperkalemia were 18.5%, 19.5%, 19.9% and 20.2%. Risk factors for all-cause death were serum potassium level(per 1 mmol/L increase) [HR: 1.328, 95%CI:1.033-1.078,p=0.027] and hemoglobin lever(per 1g/dL) [HR:2.027, 95%CI: 1.460-2.815,p<0.01].

Conclusions: Hyperkalemia was common in real-world patients in China with relatively high recurrence and poor prognosis. In fact, hyperkalemia is not only considered as an occasional one-time critical event, but also affects long-term outcome and required continuous management.

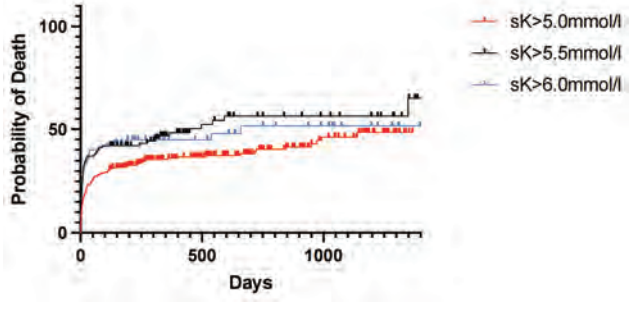

Figure 1. The all-cause mortality rates in patients with hyperkalemia.

TH-PO366

Predictors of EKG Changes in Hyperkalemia

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Background: Hyperkalemia can be potentially life-threatening in patients and calls for urgent intervention in a hospitalized setting. Typically, hyperkalemia is defined as serum potassium greater than 5 to 5.5 mEq/L. The incidence of hyperkalemia in hospitalized patients ranges from 1% to 10%. Studies have shown that the probability of electrocardiogram (ECG) changes increases with increasing serum potassium levels. ECG changes are also more common with acute, rapid changes of serum potassium and the concomitant presence of hypocalcemia and/or acidemia. In experimental settings, there appears to be a clear association between hyperkalemia and typical ECG abnormalities. However, in actual clinical practice, the relationship between potassium levels and ECG manifestations is less clear.

Methods: A partial database search and retrospective review of medical charts at Staten Island University Hospital between the years 2019-2022 was performed evaluating patients with hyperkalemia with potassium levels > 6.5 mEq/L. ECGs were reviewed to identify changes related to hyperkalemia. The presence or absence of certain variables, including demographics, electrolyte abnormalities, medications, and other co-morbidities were compared between the patients that had ECG changes and those that did not. We excluded patients with hemolyzed potassium samples and patients with baseline ECG changes. Univariate chi-square analysis and multivariate analysis were performed.

Results: One hundred forty-nine patients were identified that had admissions for non-hemolyzed hyperkalemia with serum potassium levels greater than 6.5 mEq/L, of which only 38 patients presented with EKG changes. There was no significant difference between patients with the presence or absence of CKD, ESRD, CHF, diabetes potassium-sparing diuretics, ACEs or ARBS, or patients admitted for rhabdomyolysis or acute coronary syndrome.

Conclusions: No significant predictors of ECG changes were identified in patients that had presented with hyperkalemia greater than 6.5 mEq/L between 2019-2022 at SIUH. The study may have been limited by the patient population. A larger patient population size may help identify predictors of ECG changes when hospitalized patients are admitted with hyperkalemia. Identifying these factors may potentially guide future treatment of hyperkalemia in the clinical setting.

TH-PO367

Real-World Experience with Sodium Zirconium Cyclosilicate for Hyperkalemia in the Acute Inpatient Setting

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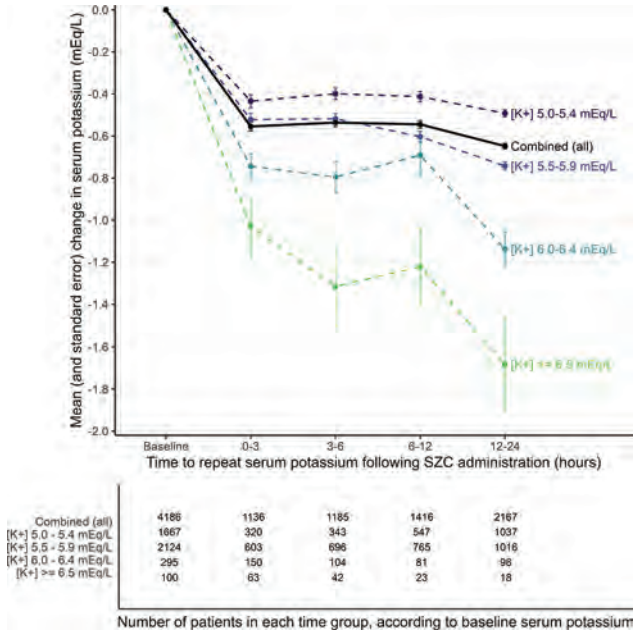
Background: The potassium binder sodium zirconium cyclosilicate (SZC) is often used for hyperkalemia treatment in the hospital. Its utility in this setting remains unknown, having been studied largely among outpatients and patients on dialysis. We sought to evaluate the real-world efficacy of SZC monotherapy for acute hyperkalemia in a large health system with a diverse patient population.

Methods: We included all adult (≥18) patients admitted to emergency departments or hospitals of Northwell Health in 2021-22; who received SZC due to a serum potassium (K) ≥5 mEq/L; and received no concomitant K-lowering therapy (loop diuretics, bicarbonate, insulin, albuterol, potassium binders, dialysis). Only the first SZC dose per patient was analyzed, and K was evaluated for up to 24 hours. We examined the mean reduction in K overall and by predefined hyperkalemia severity stratifications.

Results: Among 4186 patients, mean (SD) age was 71.3 (15.3) years with 55.3% men. Mean (SD) K was 5.6 (0.35) mEq/L. The proportion of patients with K 5-5.4, 5.5-5.9, 6-6.4, and ≥6.5 mEq/L were 39.8%, 50.7%, 7.0%, and 2.4%, respectively. SZC resulted in mean (SD) K decrease 0.56 (0.71) mEq/L within 3 hours, with greater reductions at higher baseline K levels (Figure). By 24 hours, 58.9% of patients had a decline in K of ≥0.5 mEq/L and 77.4% had K <5.5 mEq/L.

Conclusions: In the largest real-world study of SZC monotherapy in the acute setting, we found SZC to be effective for moderately severe acute hyperkalemia. Treatment efficacy was achieved after administration, and most patients had a clinically meaningful response. Further studies could help define the role of SZC with more severe hyperkalemia and when used with other therapeutic agents.



Mean (SE) change in K at intervals by baseline K and overall, and number of patients

TH-PO368

Minimizing Hypoglycemia Associated with Insulin Use for the Treatment of Hyperkalemia in the Inpatient Setting

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Background: Insulin use for hyperkalemia has been linked to hypoglycemia, especially with the commonly used 10 Units of Regular Insulin. However, studies have shown that a lower insulin dose of 5 units is just as effective in reducing potassium levels, with fewer incidences of hypoglycemia. Our Quality Improvement Project aims to establish a standardized Insulin protocol for hyperkalemia treatment across our Health System.

Methods: We searched our hospital's Electronic Health Record database to assess uses of the inbuilt "Hyperkalemia Order Set" within 30 days before and after the intervention. Our analysis considered lab data, Insulin usage, and finger stick glucose (FSG) after Insulin administration. The intervention involved: (A) educating the providers and (B) modifying the Hyperkalemia Order Set to default to 5 Units of Insulin, with up to 10 Units allowed at the provider's discretion. An alert was included with the Insulin order, reminding the provider to adjust the dose for renal impairment.

Results: During the 30-day observation phase, 48 orders were identified for intravenous (IV) Regular Insulin (with IV Dextrose 25 grams, per protocol) in patients with a mean pre-treatment serum potassium of 6.0 Meq/L. Among these orders, 69% prescribed 10 Units of Insulin while 31% prescribed 5-8 units of Insulin. We found 6 documented cases of hypoglycemia (FSG < 60) accounting for 12.5% of all orders. These patients were more likely to have received a higher dose of Insulin (mean Insulin dose = 10.2 Units) and have impaired renal function. In the post-intervention analysis, 37 orders were identified for IV Regular Insulin over a 30-day period. The mean pre-treatment potassium level was 6.5 Meq/L. Of these orders, 15.7% prescribed 10 Units of Insulin while the remaining 84.3% prescribed 5 units of insulin or less. Notably, three cases of severe hyperkalemia (mean potassium = 7.3 Meq/L) were successfully treated stepwise with 5 Units of Insulin followed by an additional 5 units given after repeating the potassium and glucose level. No cases of hypoglycemia were identified in the post-intervention phase.

Conclusions: Institutions need to have consistent protocols in place for managing hyperkalemia. Lower doses of insulin can effectively treat hyperkalemia while minimizing the risk of hypoglycemia.

TH-PO369

A Case of Severe Hyperkalemia: How High Can You Go?

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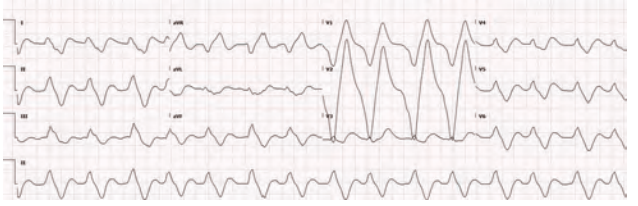
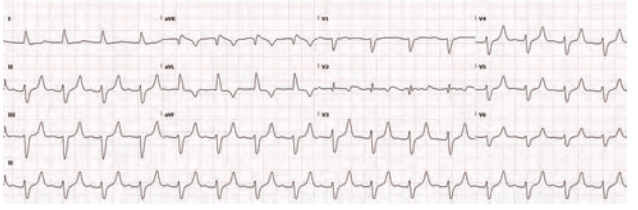
Introduction: Hyperkalemia is a common complication of both acute kidney injury (AKI) as well as chronic kidney disease (CKD). In severe cases, it can result in fatal arrhythmias and cardiovascular complications. Extremely elevated values may be mistaken for lab error due to hemolysis which can delay treatment and lead to preventable complications.

Case Description: A 46-year-old female with HTN and DM who presents to the emergency room with abdominal pain and found to have AKI with creatinine 8.9 mg/dl, BUN 75 mg/dl, CO2 9 mmol/L and severe hyperkalemia K 10 meq/L. There was no available baseline creatinine or history of prior CKD. Initial ECG at 22:07 showed QRS widening which was near a sinusoidal wave pattern. Patient was temporized with calcium gluconate, insulin/D50, fluids and received loop diuretic and zirconium. Dialysis access was quickly obtained, and dialysis initiated with 2K bath for the first hour followed by 1K bath for the second hour. Follow up ECG at 22:25 showed improvement of QRS after temporization and ECG had complete resolution with normal sinus rhythm and narrow QRS complex post dialysis. Etiology of AKI was presumed due to severe hypovolemia from poor oral intake in setting of Covid infection. There was no evidence of rhabdomyolysis, hemolysis, or urinary obstruction. Patient only required 1 dialysis session and creatinine improved to 3.4 on discharge 3 days later and 1.9 mg// dl 10 days after.

Discussion: Patients with advanced CKD and especially those on dialysis can usually tolerate higher levels of serum potassium due to higher intracellular stores and consequently a lower degree of membrane potential differential. In contrast patients with AKI usually do not have that buffer and have a higher likelihood of morbidity and mortality with severe hyperkalemia. ECG is a valuable tool to assess, confirm and monitor hyperkalemia in order to avoid delays in treatment and prevent cardiac arrest.



ECG at 22:07



ECG at 22:25

TH-PO370

Life-Threatening Hypokalemia: Incidence, Risk Factors, and Clinical Outcomes

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Background: Hypokalemia is one of the most common electrolyte disturbances encountered in clinical practice, and it can be fatal. Extremely low potassium levels (less than 2.5 mmol/L) can cause muscle necrosis, paralysis, cardiac arrhythmias, respiratory failure, and sudden death. In addition to decreased intake and trans-cellular shifts, the most common etiological factors in clinical practice are medication use, renal and gastrointestinal losses. To prevent serious complications, it is essential to conduct a thorough evaluation to determine the cause, correct it rapidly and closely monitor the patient's serum potassium levels.

Methods: In this retrospective analysis, we aimed to determine the incidence, risk factors, clinical manifestations, and outcomes of life-threatening hypokalemia in patients admitted to Beaumont Hospital between January 2018 and December 2023. A serum potassium concentration of less than 2.0 mmol/L was defined as life-threatening hypokalemia. The information was extracted from the laboratory information system, electronic patient records and medical charts.

Results: A total of 2,058,608 samples were analyzed for potassium during the study period. Among these, 208 (<0.01%) instances demonstrated life-threatening hypokalemia in an aggregate of 53 patients. Mean age at presentation (+SD) was 63 ± 21 years, with the majority (35/53, 66.3%) being females. Non-surgical causes were the most prevalent primary diagnosis, in which gastrointestinal and renal losses accounted for 35% of the cases in the setting of sepsis as a prevalent precipitating etiology in 18.9%. Long-standing gastrointestinal conditions such as Ulcerative colitis, Crohn's disease, and Gastritis [23% (n=12)], chronic alcohol use [21%], and chronic kidney diseases [9% (n=5)] are important risk factors. In approximately 2% of the cases, hypokalemia was caused by medication. Majority of patients required intravenous potassium replacement to a maximum of 560mmols, under close monitoring in ICU or CCU. In 4% of patients, life-threatening hypokalemia precipitated cardiac arrest. Over all, in-hospital mortality was observed in 17% of patients.

Conclusions: Severe life-threatening hypokalemia is uncommon, but associated with significant morbidity, and can be fatal. Gastrointestinal and renal losses are significant contributors.

TH-PO371

Hypokalemia: An Enigma

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Introduction: Hypokalemia is common, but *severe hypokalemia* (K < 2.5 mmol/L) is rare, with a narrower differential. This unique case presents a patient whose interminable hypokalemia was an enigma and whose labs were significantly discordant with presentation.

Case Description: A 47y/o man with diabetic CKD II presented to the ER with global weakness and paresthesias for two days. He denied diarrhea, nausea, or vomiting, but admitted to taking homeopathic OTC supplements from his home country with unknown contents. P/E including vitals was benign except for diminished strength across all muscle groups. Labs showed severe hypokalemia <1.5mEq/L, AKI, hypocalcemia, and combined HAGMA and NAGMA. Other electrolytes were normal. EKG revealed sinus rhythm. He was admitted to the ICU and started on oral and parenteral potassium supplementation. HAGMA resolved on day 2, but NAGMA persisted. After investigation, all causes of HAGMA proved negative and its origin remained unclear. Due to resolute NAGMA and hypokalemia, RTA was considered due to a negative diarrhea workup. Urine studies revealed a mixed picture - negative urine anion gap but high pH consistent during hospitalization. His family brought his OTC medications on the day of discharge, which contained phenolphthalein (PH), which was discontinued. Despite dramatic corrective measures, potassium levels improved marginally; it took five days of hospitalization to normalize.

Discussion: PH, a stimulant-laxative and OTC weight loss supplement, is banned in most countries due to carcinogenic effects, but still available in developing countries, and studies show harmful impact on kidneys due to toxicity and electrolyte imbalances. Although the patient did not experience diarrhea, PH, mainly eliminated by his kidneys, led to his lab anomalies. Persistent NAGMA, hypokalemia, and no diarrhea suggested RTA, but urinary studies indicated neither proximal nor distal RTA. Studies relay urinary pH is less reliable than anion gap as an indicator of RTA type. Chronic diarrhea mimics proximal RTA with a negative anion gap but variable pH which depends on hydration, and thus the urine sodium delivered to the collecting duct. Several cases of PH-induced hypokalemia were reported, having similarly mild symptoms relative to the degree of hypokalemia, likely due to the chronicity of use as in this patient. Thus, chronic PH use may result in milder symptoms for severe hypokalemia than expected.

TH-PO372

Hypokalemic Rhabdomyolysis as an Unusual Consequence of Cryptosporidium-Associated Diarrhea in an Immunocompromised Host: A Case Report

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Introduction: Hypokalemic rhabdomyolysis is rare and frequently overlooked. While most case reports associate it with renal potassium wasting, gastrointestinal losses leading to rhabdomyolysis have been sparsely reported. We report a case of an immunocompromised individual with cryptosporidium-associated diarrhea resulting to hypokalemic rhabdomyolysis.

Case Description: A 38-year-old Filipino male with a two-month history of anorexia, weight loss, and diarrhea presented to our institution with bilateral lower extremity weakness. Pertinent findings include hypotonia, decreased muscle strength in both lower extremities, and diminished deep tendon reflexes. Workup revealed a positive HIV test, serum creatinine 1.38 mg/dL (eGFR 64.40 mL/min/1.73m^2), blood urea nitrogen 21.07 mg/dL, and potassium 1.4 mmol/L. The complete blood count, electrocardiogram, thyroid function tests, and other serum electrolytes were unremarkable. The calculated urine potassium-creatinine ratio of 0.9, transtubular potassium gradient of 3.1, normal anion gap metabolic acidosis, and a negative urine anion gap were all consistent with lower gastrointestinal potassium loss. Rhabdomyolysis was confirmed with positive urine myoglobin and elevated serum creatinine kinase (15,573 U/L). Upon further investigation into the diarrhea, he was diagnosed with cryptosporidiosis. He received potassium supplementation and adequate hydration and eventually started on anti-retroviral drugs with the eventual resolution of symptoms.

Discussion: Potassium release into the interstitial fluid is crucial in regulating muscle blood flow during skeletal muscle contraction. Severe hypokalemia, whether renal or extrarenal in origin, attenuates this physiologic vasodilation resulting in relative ischemia and muscle necrosis. Hypokalemia caused by lower gastrointestinal losses only occurs if the diarrhea is persistent, as observed in this patient with cryptosporidiosis, or if accompanied by significant volume loss. This case underscores the significance of excluding rhabdomyolysis in patients with profound symptomatic hypokalemia. Thorough evaluation and clinical suspicion can aid in accurate diagnosis and prompt treatment.

TH-PO373

An Unusual Electrolyte Disturbance in Iron Man Athlete

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Introduction: Endurance athletes are at risk for developing numerous electrolyte disorders during competition, famously hyponatremia. The incidence ranges from 0 to 18% in marathoners and triathletes and may be as high as 51% in longer endurance events. Other disturbances with potassium and acid base balance may also be present. The healthcare and performance industries continue to try optimize this balance.

Case Description: A 38 year old male participating in the Ironman World Championship developed exhaustion, tingling in his extremities and swelling. Unable to finish the race, initial medical evaluation revealed a venous pH of 7.64, PCO2 of 57.7, HCO3 level of 62.2. Sodium of 128, potassium of 2.3, chloride less than 65. He received two liters of normal saline and 40mEq of potassium chloride with rapid improvement in his symptoms. Due to prior episodes of hyponatremia and nausea while training, this patient had sought consultation with a company focused on sweat and solute replacement. Testing illustrated a sweat rate of 2.5 L per hour and over 2 g of sodium per liter. He noted improvement in his performance with a concentrated electrolyte mix of sodium and potassium, as well as a dedicated water replacement strategy. However, for this race he used a strictly sodium citrate solution, delivering 25 grams of sodium citrate.

Discussion: The case represents a unique presentation of citrate toxicity in a high endurance athlete. The patient had been supplementing his electrolytes during this race, using sodium citrate alone with a focus on mitigating sodium loss. He consumed 25 g of sodium citrate over four hours and developed citrate toxicity which contributed to his metabolic alkalosis and hypokalemia. The case demonstrates the importance of maintaining a high index of suspicion for electrolyte abnormalities in athletes. It highlights the role of Nephrology in optimizing fluids and electrolytes for high performance athletes, thereby avoiding hazard and improving performance. Finally, it serves as a reminder to monitor the contents and concentrations of supplements for our patients, itself a burgeoning industry.

TH-PO374

Urinary Potassium Excretion Rate in Hypokalemic Periodic Paralysis: Spot vs. 24-Hour Urine

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Background: Hypokalemic periodic paralysis (HypoKPP) with acute hypokalemia and muscle paralysis is a potentially life-threatening emergency requiring rapid diagnosis and management. The role of timely spot versus 24 hour urine for urine K^+ excretion rate in the diagnostic and therapeutic value of HypoKPP have not well evaluated.

Methods: HypoKPP patients with the exclusion of other non-HypoKPP causes and incomplete urine collection were consecutively enrolled over 5 years. Spot and 24 hour urine collection for urine K^+ and other electrolytes excretion rate, and clinical characteristics including K^+ supplementation to achieve recovery were examined. Spot urine K^+ excretion was calculated by transtubular potassium concentration gradient (TTKG) and potassium-creatinine ratio (K^+/Cr). Balanced K^+ was defined as (supplemental K^+-24 hour urine K^+ excretion). Patients with K^+ deficit was defined as positive balanced K^+.

Results: Sixty-two HypoKPP patients (age 35.5 ± 10.4 year-old) including thyrotoxic periodic paralysis (TPP) (n=50), sporadic periodic paralysis (SPP) (n=9), and others (n=3) had hypokalemia (serum K^+ 2.2 ± 0.5 mmol/L) and received K^+ supplementation (77.0±45.3 mmol) to achieve recovery. All of them had a higher 24 hour urine K^+ excretion (61.7 ± 34.2 mmol/day > 20 mmol/day), but their TTKG (< 3, 64% of them) or K^+/Cr (< 0.18 mmol/L/mg/dl, 84% of them) were often lower. Despite acute hypokalemia without K^+ deficit, thirty-eight patients (61%) with a positive balanced K^+ balance had significantly lower serum K^+ (2.1±0.5 vs 2.4±0.4 mmol/dL, p=0.013), needed more supplemental K^+ (96.1±43.6 vs 46.7±28.8 mEq, p<0.001), and exhibited a slower increase in serum K^+ concentration during K^+ supplementation than those without K^+ deficit (n=24).

Conclusions: To evaluate urine K^+ excretion rate, timely spot urine is superior to 24 hour urine, which helps reveal the underlying subclinical K^+ deficit in HypoKPP patients.

TH-PO375

Newly Diagnosed Graves Disease in a Young Patient with Lower Extremity Weakness

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Introduction: The differential diagnosis for myositis and myopathy is broad and includes medication side effects, auto-immune myositis, infectious myositis, neuromuscular junction disease, metabolic diseases, and electrolyte abnormalities.

Case Description: A 32-year-old male with osteoarthritis presents to the emergency department with acute lower extremity weakness that developed over the course of the day. He had a similar episode 3 months ago that self-resolved, however on this occasion, the weakness progressed to lower extremity paralysis, prompting his presentation. His labs were notable for a potassium of 2.2 mEq/dL, an undetectable TSH, total T3 of 311 (high), and a T4 of 1.6 (high). Thyroid receptor antibodies were elevated to 21.3. He was diagnosed with thyrotoxic periodic paralysis (TPP) due to Graves disease. His potassium was repleted, and he was started on methimazole with rapid improvement in his symptoms.

Discussion: TPP is a skeletal muscle channelopathy associated with hyperthyroidism - most often secondary to Graves disease. Besides hypokalemia, differentiating factors from other forms of periodic paralysis include elevated T4, low T3, hypophosphatemia, hypomagnesemia, and often presents after the second decade of life. Thyrotoxicosis increases the activity and transcription of the Na-K ATPase, enhances sensitivity to catecholamines, and inhibits potassium leak channels leading to intracellular potassium

shifts. This leads to cellular hyperpolarization and subsequent paralysis. Treatment of TPP should be directed at correcting hypokalemia. Those treated with intravenous potassium tend to recover more quickly than those receiving oral supplementation. Lifestyle modifications such as avoiding heavy exercise, high-carbohydrate meals, and alcohol are crucial. Definitive treatment is achieved by restoring euthyroidism either through medications, radioactive iodine ablation, or surgery. It is vital to maintain a high index of suspicion of TPP in patients presenting with hypokalemia and abrupt paralysis.

TH-PO376

An Unexpected Cause of Hypokalemia and Metabolic Alkalosis

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Introduction: Ectopic ACTH syndrome (EAS) is a rare cause of Cushing's syndrome and is often linked with cancer, particularly neuroendocrine tumors, among which bronchial carcinoids are the most common. ACTH-secreting pulmonary carcinoids are often small and pose diagnostic/therapeutic challenges.

Case Description: A 21-year-old man presented to the hospital with psychosis symptoms. His BP was 140/90 mmHg. Laboratory test results are listed in Figure 1A. Further workup revealed low serum levels of renin < 0.1 ng/ml/hour and aldosterone 3.1 ng/dL. AM serum cortisol, 24-hour urine cortisol, and ACTH levels were elevated at 49.5 mcg/dL, 5,904 ug/g Cr, and 258 pg/ml, respectively. Brain MRI showed a 5mm pituitary adenoma (Fig 1B). High-dose dexamethasone suppression test resulted in less than 50% suppression of serum cortisol, indicating a potential source of ectopic ACTH secretion. Inferior petrosal sinus sampling resulted in non-functional pituitary adenoma. A CT scan of the chest/abdomen/pelvis was performed but failed to identify the source of ACTH secretion. Eventually, a PET radiotracer (Gallium-68 dotatate) scan showed a left lung perihilar nodule with somatostatin receptor positivity (Fig 2A). Lung nodule resection confirmed a carcinoid tumor labeled immunohistochemically with ACTH and resulted in the resolution of hypokalemia and hypertension.

Discussion: 11β-HSD2 enzyme inactivates cortisol to cortisone. High levels of circulating cortisol oversaturate the activity of 11β-HSD2, leading to a mineralocorticoid effect on the collecting ducts, causing sodium resorption and potassium excretion (fig 2B). Clinical manifestations of hypercortisolism include hypertension, hypokalemia, metabolic alkalosis, low serum renin, and low aldosterone levels.

Figure 1A

Tests	Results	Normal range
Sodium	143 mmol/L	132-148 mmol/L
Potassium	2.5 mmol/L	3.5-5 mmol/L
Chloride	99 mmol/L	98-111 mmol/L
Bicarbonate	34 mmol/L	23-32 mmol/L
Blood Urea Nitrogen	15 mg/dL	10-25 mg/dL
Creatinine	0.77 mg/dL	0.7-1.4 mg/dL
Calcium	9.0 mg/dL	8.4-10.5 mg/dL
Albumin	4.1 g/dL	3.5-5.0 g/dL
Glucose	127 mg/dL	65-100 mg/dL
Magnesium	2.5 mg/dL	1.6-2.6 mg/dL
ABG		
Ph	7.55	7.35-7.45
PaCO2	49 mmHg	35-45 mmHg
PaO2	95 mmHg	75-100 mmHg
HCO3-	42 mmol/L	18-23 mmol/L
Random urine chloride	35 mmol/L	30-26 mmol/L
Random urine potassium	27 mmol/L	17-99 mmol/L
Random urine creatinine	62.6 mg/dL	40-278 mg/dL
24 hour urine potassium	275 mmol/24 hour	75-125 mmol/24 hour

Figure 1B

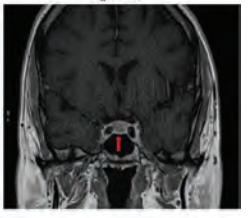


Figure 2A

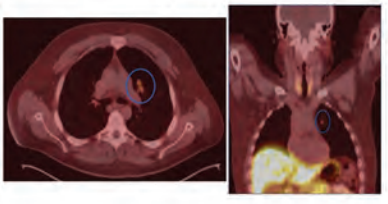
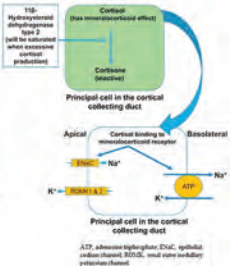


Figure 2B



TH-PO377

Severe, Symptomatic, and Resistant Hypokalemia in Peritoneal Dialysis

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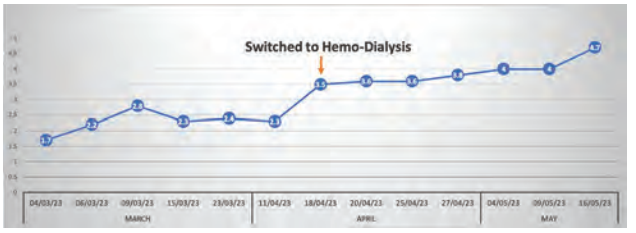
Introduction: Hypokalemia is common in peritoneal dialysis (PD) patients and it affects a third of all PD patients. According to the Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS), the prevalence of hypokalemia in PD patients ranges from 3% to 47%. The reason can be poor intake, increased losses from sweat, urine, stool or dialysis and intracellular shift. Hypokalemia is associated with an increased risk of arrythmia and cardiovascular mortality.

Case Description: A 53-year-old female ESRD patient with a history of diabetes, hypertension and dyslipidemia on peritoneal dialysis presented with bilateral leg weakness. She had hypokalemia that was resistent to potassium chloride, ACE inhibitors and spironolactone. Magnessium level was low and was replaced. Her medication list included potassium chloride 80 mg BID, lantus insulin, lisinopril and spironolactone. Her aldosterone level was 5 ng/dl (4 - 31). Dialysate effluent potassium was only 1.7 mmol/L. The patient was discharged home hypokalemic but symptom free. A month later, she was readmitted with persistent bilateral leg weakness and pain. She had severe hypokalemia despite high dose oral potassium, ACE inhibitors and spironolactone. She was switched to hemodialysis and insulin dose decreased. Her potassium levels normalized on a standard bath of 2K (2 mEq/L). She is off potassium and spironolactone. Her symptoms improved dramatically.

Discussion: Hypokalemia is very common in peritoneal dialysis patients and can leed to fatal cardiac arrhythmia. In most cases it is amenable to treatment with potassium supplements or addition of ACE inhibitors or spironolactone. In our patient, we failed to treat her hypokalemia while on PD. The normal distribution of potassium between cells and the extracellular fluid is maintained by the Na-K-ATPase pump in the cell membrane. In our case, we believe that it was disrupted due to presence of insulin resulting in hypokalemia from increased potassium entry into cells. We are not aware of any other means to maintain normokalemia and have not encountered any case that needed a change in modality due to hypokalemia.



Persistent Hypokalemia in Peritoneal Dialysis

TH-PO378

Flaccid Paralysis due to Nafcillin-Induced Pseudo-Gitelman Syndrome

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Introduction: Mild hypokalemia is a known side effect of the penicillin antibiotic Nafcillin. However, severe hypokalemia (i.e., serum potassium of <2.5 mmol/L) after starting penicillin-type antimicrobials is rare. Severe hypokalemia can be associated with weakness, cramps, arrythmias, and increased risk of mortality. Hypomagnesemia is a well-known cause of hypokalemia. In hospitalized patients, most cases of hypokalemia are asymptomatic or mild.

Case Description: We present the case of a 69-year-old woman with a history of methicillin-sensitive *Staphylococcus aureus* bacteremia. She was started on Nafcillin 12 g/day during a prior hospitalization, which was continued as an outpatient. The patient had intermittent hypokalemia at that time. However, her magnesium and potassium levels were normal at discharge. She was readmitted to the hospital 10 days later with chief complaints of nausea, diarrhea, body aches, weakness, flaccid paralysis, muscle spasms, and numbness. Upon arrival to the emergency department, she was noted to have low potassium (1.6 mEq/L) and magnesium (1.0 mEq/L) levels. Her vital signs were stable and physical exam was unremarkable besides diffuse flaccid paralysis. She received IV and oral potassium chloride with aggressive magnesium replacement. Despite attempts at repleting both electrolytes, her hypokalemia and hypomagnesemia persisted. Her urinary fractional excretion of potassium and magnesium were elevated, suggesting renal potassium and magnesium wasting. Nafcillin was replaced with daptomycin after consultation with Infectious Disease, and her potassium level and magnesium levels normalized within 24 hours. Her potassium at discharge was 4.3 mEq/L and magnesium was 2.0 mEq/L.

Discussion: Nafcillin-induced hypokalemia is rare. Nafcillin is a non-reabsorbable anion that causes increased sodium absorption in the collecting duct and makes the urinary lumen more negative, which facilitates potassium excretion. In this case, Nafcillin also contributed to hypomagnesemia, resulting in renal magnesium wasting.

TH-PO379

Too Much of a Good Thing Can Be Deadly

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Introduction: The treatment of megaloblastic anemia from vitamin B12 deficiency results in an increase in hematopoietic cell production leading to potassium uptake into the cells. This has been reported to cause hypokalemia. It is rare for this to cause arrhythmias leading to cardiac arrest. We present a case of hypokalemia following vitamin B12 administration which resulted in cardiac arrest.

Case Description: A 29 y/o G1P0 female was found to have anemia with workup revealing low vitamin B12 level. She was started on oral B12 which was escalated to IM injections at 33 weeks gestation. She received weekly doses of IM B12 1,000mcg x 4 doses. Serum potassium 4 months prior was 3.9 mmol/L and was not repeated. Ten days after her final dose, at 37 weeks gestation she suffered a cardiac arrest with achievement of ROSC. Workup at the hospital revealed a serum potassium of 2.1 mmol/L which required intensive IV potassium repletion. Along with that she had features of pre-eclampsia. Blood pressure ranged from systolic readings of 110 to 150 mmHg, with serum creatinine ranging from 0.3-0.7 mg/dL, and spot UPCR of 350mg/g. She had spontaneous vaginal birth at 37 weeks gestation. Cardiac workup showed no coronary disease and no evident etiology for the cardiac arrest. Workup for hypokalemia was initiated and no other cause was identified including no endocrinology or genetic conditions. Discharged in stable condition

on potassium supplementation with external defibrillator. She was taken off potassium supplementation as outpatient with stable potassium levels and no other cardiac event.

Discussion: In normal pregnancy, vitamin B12 levels can decline by as much as 30% by the third trimester. Typically recommendations are to replete if symptomatic or with macrocytic anemia. Dangerously low levels of potassium leading to cardiac arrest are possible following vitamin B12 replacement therapy. This is mentioned by the manufacturer. No cases were described in pregnancy. However in a more recent experience, this was found not to be clinically significant. Potassium levels are not routinely checked during parenteral vitamin B12 administration. This raises the question if we should check potassium levels in certain circumstances. Ordering providers should be aware of hypokalemia after vitamin B12 supplementation with consideration of following potassium level after administration especially in pregnancy.

TH-PO380

Refractory Hypokalemia in a Patient with Ectopic Adrenocorticotropic Hormone (ACTH) Secretion

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Introduction: Due to similarities in structure, aldosterone and cortisol bind to mineralocorticoid receptors with similar affinity. The enzyme 11ß-hydroxysteroid dehydrogenase (11ß-HSD) limits the effect of cortisol at this receptor by converting cortisol to cortisone which is inactive at this site. Deficiency in 11ß-HSD allows for unopposed cortisol stimulation at this receptor which mimics a state of mineralocorticoid excess. This condition manifests clinically with hypertension, hypokalemia, and metabolic alkalosis. We report a case of mineralocorticoid excess from ectopic production of ACTH leading to profound, refractory hypokalemia.

Case Description: A 56-year-old female with a history of COPD and large cell neuroendocrine carcinoma presented with one day of dyspnea, chills, and bilateral lower extremity edema. Lab work was remarkable for creatinine 1.4 mg/dL (baseline creatinine 0.7), tCO_2 > 40 mmol/L, potassium of 2.2 mEq/L, and WBC 11.3 x 10^9/L with 87% neutrophils. CT angiography chest showed LLL subsegmental PE and multifocal pneumonia. The patient was admitted for management of pneumonia and started on IV fluids, broad-spectrum antibiotics, subcutaneous enoxaparin, and oral and IV potassium supplementation. She was noted to have worsening hypokalemia to 1.6 mEq/L despite aggressive repletion. A comprehensive chart review revealed nine months of intermittent episodes of moderate to severe hypokalemia and metabolic alkalosis starting one month after her neuroendocrine lung cancer diagnosis. A VBG showed pH 7.48, CO_2 77 mmHg, and HCO_3 56 mmol/L, suggestive of a primary metabolic alkalosis. 24-hour urine potassium was 68 mEq which confirmed inappropriately elevated urine potassium losses in the setting of severe hypokalemia. ACTH was elevated at 183 pg/mL (normal: 9-46), suggesting ectopic production of this hormone. 24-hour urine cortisol was 2086 mcg (normal: 4-50), confirming the suspicion of ectopic secretion of ACTH causing an apparent mineraloid corticoid excess picture. The patient was started on spironolactone and standing oral potassium replacement with subsequent improvement of her hypokalemia.

Discussion: This case emphasizes the importance of thoroughly working up persistent hypokalemia. Ectopic ACTH production leading to mineralocorticoid excess in patients with malignancy is a rare occurrence. Without establishing a diagnosis, appropriate management cannot be sought.

TH-PO381

The Dual Diagnosis: Hypokalemic Rhabdomyolysis Unveils an Adrenal Nodule

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Introduction: The occurrence of rhabdomyolysis as the initial manifestation of primary hyperaldosteronism (PHA), accompanied by severe hypokalemia is uncommon. We present a distinctive case where a patient with hypertension experiences myalgia, revealing severe hypokalemia causing rhabdomyolysis, ultimately leading to the identification of adrenal nodule.

Case Description: 61 year old female with past medical history of hypertension presented to the hospital evaluation of weakness and myalgias ongoing for 2 weeks. She denied drug abuse, diuretics or liquorice use. No significant family history. Blood pressure (BP) 165/102 mm Hg and tenderness to palpation of thighs bilaterally. Labwork (table 1) revealed Hypokalemia and elevated CK levels. EKG demonstrated elongated QT interval and U wave. Rhabdomyolysis and severe Hypokalemia were established as first diagnosis. She was treated with supplemental IV/oral potassium and fluids. Labs (Table 1) suggested low plasma renin activity (PRA) and elevated Aldosterone/PRA ratio raising suspicion for PHA. Patient was started on amlodipine, telmisartan, aldactone with oral potassium. A CT adrenal protocol revealed 2 cm right adrenal nodule, possibly an aldosteronoma. Patient was referred for lapraroscopic adrenelectomy.

Discussion: Severe hypokalemia (potassium < 2.0 mmol/L), can lead to decreased blood flow and muscle perfusion, triggering rhabdomyolysis. While there are limited documented cases in the literature, PHA has been identified as a potential cause of hypokalemia-induced rhabdomyolysis. Other factors associated with this condition include licorice ingestion, laxative abuse, and diuretic use. Diagnosing PHA can be challenging when rhabdomyolysis and severe hypokalemia manifest as initial symptoms. A high level of suspicion is crucial in hypertensive patients, where the occurrence of rhabdomyolysis and hypokalemia necessitates considering primary hyperaldosteronism as a potential cause.

Sodium	135 - 146 mmol/L	144
Potassium	3.5 - 5.1 mmol/L	1.6
Chloride	98 - 107 mmol/L	98
CO2	22 - 32 mmol/L	36
BUN	6 - 20 mg/dL	7
Creatinine	0.5 - 1.0 mg/dL	0.7
Estimated Glomerular Filtration Rate	>=60 mL/min	>90
Anion Gap	7 - 15 mmol/L	10
Glucose	70 - 120 mg/dL	135
Calcium	8.4 - 10.2 mg/dL	8.8
Magnesium	1.5 - 2.6 mg/dL	2.5
Phosphorus	2.5 - 4.8 mg/dL	1.9
CK	26 - 192 U/L	5,788
Cortisol, Free, 24 HR Urine	4.0 - 50.0 mcg/24 h	13.1
Cortisol	2.5 - 19.5 ug/dL	10.7
Potassium, 24 Hour Urine	25.0 - 120.0 mmol/24 hours	62.3
Aldosterone, LC/MS/MS *** ng/dL		38
PRA, LC/MS/MS 0.25 - 5.82 ng/mL/h		0.07
PRA, LC/MS/MS		0.13
ALDO/PRA Ratio 0.9 - 28.9 Ratio		542.9

Table 1

TH-PO382

Renal Replacement Therapy in Treatment of Adult-Onset Ornithine Transcarbamylase Deficiency

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Introduction: Hyperammonemia is a relatively common disorder that has a spectrum of presentations ranging from confusion to coma. The less common etiology of hyperammonemia is related to urea cycle disorders such as ornithine transcarbamoylase deficiency (OTCD). This X-linked enzymatic disorder results in an accumulation of ornithine, orotic acid and urea with incomplete penetrance. The majority of cases occur as congenital enzyme disorders that may present with severe, development effects and high mortality in the pediatric population. However, the enzyme deficiency may also be inherited with incomplete penetrance such that the disorder is triggered by high protein catabolism states at later life stages.

Case Description: Here presented is a case of a 61 year old female without prior medical history who presented with somnolence after initiation of corticosteroids for acute back pain. No evidence of infection, hemodynamically stable and serum ammonia was 233 mcg/dL. The patient had no hepatic dysfunction and was evaluated for urea cycle disorder. Intermittent hemodialysis (IHD) was used for rapid lowering of serum ammonia levels. Following IHD ammonia improved to 118 mcg/dL. However, within 24h ammonia increased to 223 mcg/dL. The patient received a second session of IHD followed by initiation of CVVH to prevent rebound accumulation. CVVH was continued for approximately 24h to allow for administration of nitrogen scavengers (benzoate and phenylacetate). The patient was initiated on intravenous nitrogen scavengers, low protein/high glucose/high fat diet until mental status improved. Genetic testing identified X-linked hemizygous variant for OTCD.

Discussion: This case report explores the tandem use of large surface area dialyzer via IHD and continuous veno-venous hemofiltration (CVVH) for rapid ammonia filtration. Rapid withdrawal of IHD prior to maintenance therapy with nitrogen scavengers has been associated with rapid reaccumulation of ammonia if the urea cycle co-factors are not replaced. This is a method that has been previously studied in the pediatric population with limited application to the adult population due to its rarity (1 in 56000 births). However, we applied these principles to an adult with success and improvement in clinical outcome.

TH-PO383

Urinary Response to Consumption of Plant-Based Meat Alternatives: Secondary Analysis of the SWAP-MEAT Trial

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Background: Consumption of excess animal meat can exacerbate kidney disorders such as urinary stone disease and chronic kidney disease. Plant-based meat alternatives, "plant-meat", have entered the commercial market. It is not known whether plant-meat confers the same health benefits as whole vegetables because plant-meat is highly processed food. We hypothesized that consumption of plant-meat reduces dietary load of acid, phosphorus, and nitrogen compared with consumption of animal-meat.

Methods: SWAP-MEAT was a randomized crossover trial in which participants consumed ≥2 servings/day of either plant-meat or animal-meat for 8 weeks each, while keeping all other foods and beverages similar. We analyzed fasting spot urine samples from participants at baseline and after each phase of plant-meat or animal-meat. We used a linear mixed-effects model to investigate if the change in urine indices was different between baseline and at the end of each phase, adjusting for urine creatinine

concentration, the fixed effect of diet order, phase, and the random effect of correlated observations. Primary outcomes included differences between baseline and after plant-meat or animal-meat phase for urine sulfate, urine ammonium, urine phosphorus, urine urea nitrogen, and urine pH.

Results: Differences in mean concentration for urine sulfate, urine ammonium, urine phosphorus, and urine urea nitrogen were significantly lower after plant-meat compared with animal-meat. Difference in mean urine pH was significantly higher after plant-meat compared with animal-meat.

Conclusions: Consumption of plant-meat was associated with lower dietary load of acid, phosphorus, and nitrogen compared with consumption of animal-meat. Plant-based meat products could support persons who wish to reduce dietary acid load in a manner that does not increase dietary phosphorus or nitrogen, which may benefit patients with urinary stone disease or chronic kidney disease.

Funding: NIDDK Support

Mixed Effects Linear Regression Model: adjusted for urine creatinine (mg/dL)

Plant-meat	Estimate	95% Confidence Interval
Urine sulfate (mEq/L)	-6.68	-10.96, -2.4
Urine ammonium (mmol/L)	-4.15	-8.2, -0.07
Urine phosphorus (mg/dL)	-9.01	-17.5, -0.5
Urine urea nitrogen (mg/dL)	-124.8	-226.9, -22.6
Urine pH	+0.32	+0.18, +0.46

Reference: Animal-meat

TH-PO384

SGLT2 Inhibitors as a Treatment for Fanconi-Bickel Syndrome: A Case Report

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Introduction: Fanconi-Bickel syndrome is an ultra-rare genetic disease characterized by SLC2A2 mutation encoding for the basolateral glucose transporter (GLUT2) in the proximal tubule of the nephron. This defective transport ultimately leads to accumulation of glycogen and dysfunction of proximal tubule cells. This manifests clinically as the renal Fanconi syndrome and eventually kidney failure. Systemic complications of proximal tubule injury include metabolic acidosis, bone demineralization and, for some not completely elucidated reasons, dysglycemia.

Case Description: We present the case of a 43-year-old man who was diagnosed with Fanconi-Bickel syndrome (homozygous splice site mutation in SLC2A2). He had a history of infantile-onset renal Fanconi syndrome, hypercalciuria and bilateral nephrolithiasis, osteoporosis, bilateral sensorineural deafness and non-insulin dependent type 2 diabetes. At referral the patient presented with CKD G2, non-anion gap metabolic acidosis, slightly elevated serum calcium, decreased serum phosphate, supressed PTH and hypercalciuria, despite oral supplementation of phosphate, bicarbonate and vitamin D. We hypothesized that SGLT2i in this patient may halt the progressive proximal tubule injury by preventive glucose uptake and help the management of diabetes. Fractional excretion of phosphate (FE_{PO4}) and urinary retinol-binding protein (RBP)-creatinine ratio, two markers of proximal tubular injury, were stable after 2 months of SGLT2i therapy.

Discussion: To date, Fanconi-Bickel syndrome does not have a specific treatment. Standard of care includes supplements of fluids and electrolytes to counterbalance proximal tubular injury and management of complications such as diabetes. SGLT2i use has been described in a mouse model of another glycogen storage disease (GSD1b), whose underlying defect is different from that of Fanconi-Bickel but presents with a similar phenotype. Data showed that gliflozins prevents glycogen accumulation and restores proximal tubule cells' function. Using the same rationale, the administration of SGLT2i in adult patients with Fanconi-Bickel syndrome may prevent further proximal damage and slow the progression towards end-stage kidney disease. In conclusion, we hypothesize a potential benefit of SGLT2i in adult patients affected by Fanconi-Bickel syndrome.

TH-PO385

A Hidden Challenge: Metabolic Acidosis After Neobladder Surgery

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Introduction: Neobladder construction is a surgical procedure involving the creation of a new bladder using intestinal segments. One complication is hyperchloremic metabolic acidosis, which occurs due to the continued exchange of electrolytes by the neobladder lumen. This complication is uncommon and may not be promptly identified by primary physicians.

Case Description: A 70-year-old man with urothelial cancer who underwent transurethral resection of bladder tumor, radical cystoprostatectomy, and neobladder construction. The patient experienced postoperative complications, including pneumonia and fungemia. One month later, he presented with weakness and a humming sensation in his ears. His medical history included hypertension and type 2 diabetes mellitus, and he was taking metformin and losartan. He denied experiencing diarrhea, using non-steroidal anti-inflammatory drugs, or having a prior history of renal disease. Vital signs showed blood pressure of 115/75 mmHg, heart rate 100 beats per minute, respiratory rate 19, oxygen saturation 98% at room air, and temperature 37°C. Physical examination revealed an acutely ill male in no distress, with dry oral mucosa and decreased skin turgor. Initial laboratory results revealed creatinine level 1.76 mg/dL (baseline creatinine 0.8 mg/dL), BUN level 62.0 mg/dL, chloride level 116 mmol/L, bicarbonate level 8.1 mmol/L, potassium level 5.54 mmol/L. Arterial blood gas values of pH 7.255, pCO2 14 mmHg, and pO2 100 mmHg. Normal anion gap metabolic acidosis with an anion gap of 9. The urinary anion gap was +23. The patient was initially treated with a bicarbonate drip, which was later transitioned to oral bicarbonate. Renal function improved, and the metabolic acidosis resolved. The patient was discharged with oral buffer therapy and scheduled for follow-up at the clinics.

Discussion: Hyperchloremic metabolic acidosis is a rare complication of neobladder reconstruction. The apical Cl-/HCO3- exchanger plays a key role in the development of acidosis. Although this can be transient, delayed diagnosis can lead to significant morbidity. Early identification allows for effective treatment with sodium bicarbonate. It is crucial to provide detailed and clear post-operative discharge documentation to ensure early recognition of such complications.

TH-PO386

Nonsteroidal Anti-Inflammatory Drug-Induced Type I (Distal) Renal Tubular Acidosis

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Introduction: Acute kidney injury (AKI) is the most recognized kidney toxicity of non-steroidal anti-inflammatory drugs (NSAID), but NSAIDs have also been linked to the development of acid-base disorders. Here, we present a patient with a history of frequent ibuprofen consumption resulting in the manifestation of a type I renal tubular acidosis (RTA).

Case Description: A 38-year-old man with a history of C6-C7 spinal injury due to a snow-boarding accident causing spastic paraplegia presented to an emergency department with new-onset agitation and confusion. His medications included ibuprofen 800mg every 6-8 hours and oxycodone. Brain imaging and blood and urine cultures were unremarkable. Urine toxicology was positive for his prescribed agent. Laboratory investigations were notable for an ammonia of 74 mcmol/L (normal range: 16 – 60), albumin of 4.4 g/dL (3.2 - 5.2), potassium of 2.8 mmol/L (3.5 – 5.0), venous pH of 7.22 (7.32 – 7.42), venous pCO2 of 36 mmHg (41 – 51), serum bicarbonate of 15 mmol/L (22 – 31), anion gap (AG) of 16, creatinine of 0.97 mg/dL (0.80 – 1.50) correlating to eGFR or 102 mL/min/1.73m2 via CKD-EPI, and glucose of 58 mg/dL (65 – 199). He was administered Dextrose 10% @100 mL/h and lactulose enema with improvement in encephalopathy. Post treatment labs demonstrated a venous pH of 7.26, venous pCO2 of 30 mmHg, serum bicarbonate of 13 mmol/L, AG of 12, urine pH of 7.5, and a urine anion gap at 29 (Urine Na(97mmol/L) + Urine K(32mmol/L) - Urine Cl(100mmol/L)). Acetaminophen, salicylate, ethanol, creatinine-kinase and lactate were all normal/negative. Ibuprofen was discontinued and sodium citrate-citric acid 30mL twice daily was provided. At outpatient follow up, his acid-base disorder had resolved and his mentation normalized.

Discussion: This case adds to several reports illustrating the association of ibuprofen with type I RTA in setting of preserved renal function. Ibuprofen is postulated to inhibit carbonic anhydrase (CA) II yielding impaired urinary acidification and luminal retention of bicarbonate. Hypokalemia is associated with type I RTA and are potent stimulators of ammoniagenesis. Although impairment of CA is usually associated with proximal (type 2) RTA, impairment of CAII can cause a distal RTA.

TH-PO387

Unveiling the Enigma: Hypokalemic Paralysis in Sjögren-Associated Renal Tubular Acidosis

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Introduction: Hypokalemic Paralysis (HP) is a rare life-threatening disorder presenting as muscle weakness and low serum potassium levels. This case series focuses on two female patients with Sjögren's syndrome-associated renal tubular acidosis (SS-RTA) who developed HP. SS-RTA is a form of distal renal tubular acidosis where the kidneys are unable to adequately acidify urine and reabsorb bicarbonate, resulting in an acid-base imbalance. The SS-RTA is thought to occur due to inflammation caused by Sjögren's syndrome-associated autoantibodies. Although distal renal tubular acidosis causes hypokalemia, HP is rare. The important differential diagnoses include Hypokalemic Periodic Paralysis and Thyrotoxic Periodic Paralysis. The cases illustrate the association between SS-RTA and HP.

Case Description: Case 1: A 26-year-old female with intellectual impairment presented with vomiting, weakness, altered sensorium, and hypercapnic respiratory failure requiring intubation and mechanical ventilation. Investigations confirmed hypokalemia, normal anion gap metabolic acidosis (NAGMA), and SS-RTA. Treatment included intravenous (IV) potassium and sodium bicarbonate. Follow-up was done on an outpatient basis for correction of hypokalemia and NAGMA. Case 2: A 47-year-old female had progressive limb weakness, slurred speech, reduced muscle power and absent reflexes. On investigations low serum potassium and positive serology for Primary Sjögren syndrome (PSS) were found, and renal biopsy findings of Membranoproliferative glomerulonephritis with chronic tubulointerstitial inflammation. Treatment involved IV potassium and IV fluids. She was readmitted for recurrence of hypokalemia.

Discussion: Hypokalemic Paralysis is characterized by muscle weakness and low serum potassium levels. SS-RTA leads to hypokalemia, triggering HP. Low magnesium and potassium levels and high creatine kinase levels are risk factors for severe paralysis in HP. The diagnosis is based on clinical, laboratory, and imaging findings. Management involves correcting acidosis, normalizing potassium, and addressing the underlying cause. Recognizing SS-RTA as a possible cause of hypokalemia in periodic paralysis,

especially in Sjögren's syndrome, is essential. Early diagnosis and treatment are crucial for better outcomes. Further research is needed for delineating genotypes and phenotypes of PSS predisposing to HP.

TH-PO388

Rare Presentation of Primary Sjögren Syndrome, Hypokalemic Paralysis: A Case Report

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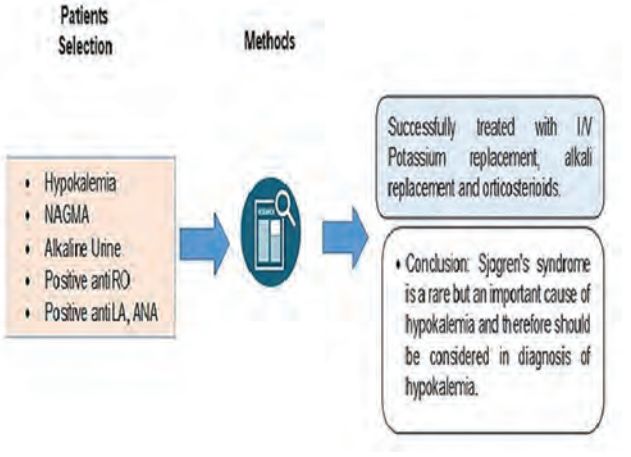
Introduction: Sjogren's Syndrome is a multisystem autoimmune disorder characterized by chronic inflammation of exocrine glands, sicca syndrome. Among extra glandular manifestations renal involvement occurs as tubulointerstitial nephritis (TIN) and glomerular damage. Distal renal tubular acidosis (dRTA) is the most common presentation of TIN. However, dRTA may rarely be severe enough to present as hypokalemic paralysis. Also, Sjogren's syndrome presenting for the first time with hypokalemic paralysis secondary to dRTA without other glandular manifestations is also very rare. Our patient had severe hypokalemic paralysis secondary to dRTA as the first manifestation of primary Sjogren's syndrome.

Case Description: Methodology: We report a case of 45 years old lady, recently diagnosed as depressive illness with no other pre-morbid, who presented to us with acute onset of severe weakness in all four limbs for last 4 days. There was no other complaint. Clinical examination revealed hyporeflexia in four limbs with no other positive findings. Laboratory workup revealed severe hypokalemia, normal anion gap metabolic acidosis, alkaline urine and strongly positive serological markers of Sjogren's syndrome, (anti-RO, anti-LA, ANA). Results: We treated that patient by intravascular replacement of potassium, oral, alkali, replacement and corticosteroids. Patient showed an excellent response to this treatment. She will be followed up for the recurrence of tubular dysfunction and other systemic manifestations of Sjogren's syndrome.

Discussion: This report highlights that Sjogren's syndrome is a rare but an important cause of hypokalemia and therefore should be considered in diagnosis of hypokalemia.



TH-PO389

Distal Renal Tubular Acidosis as the Initial Manifestation of Hashimoto Thyroiditis

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Introduction: Distal renal tubular acidosis (dRTA) is a rare disorder, characterized by inadequate proton secretion in the distal tubule and collecting duct in the presence of metabolic acidosis. In adults, the most common cause of dRTA is autoimmune disease, and the association with Hashimoto thyroiditis (HT) has rarely been studied.

Case Description: A 25-year-old female diagnosed with nephrolithiasis 2 years prior presented to the emergency room complaining of weakness, loss of coordination and strength, pain and paresthesias. On examination, her arms showed decreases in speed, range of motion and deep tendon reflexes. Labs revealed severe hypokalemia (2.0 mEq/L), together with increase in CPK (3412 U/L), hyperchloremic metabolic acidosis (anion gap 9) and urinary pH of 8.5. Intravenous potassium and bicarbonate were started in the with gradual symptom improvement. On day 4 she was discharged on oral potassium citrate (40 mEq/d) and sodium bicarbonate (6 g/d). On follow-up, there was complete symptom resolution, normalization of potassium (4.3 mEq/L) and improved bicarbonate (20 mEq/L), but thyroid hormones were altered (TSH = 73.58, T4 < 0.42). We started levothyroxine at 25 μg/d. The patient tested positive for anti-TSH receptor antibody (1.95 IU/L) and anti-thyroid peroxidase antibody (> 900 IU/ml), thus confirming the diagnosis of HT. The levothyroxine dose was increased to 100 μg/d due to persistence of the hormonal alteration (TSH = 51, T4 = 0.48).

Discussion: In this case, the dRTA might have been due to a reduction in the number or function of H^+- and H^+/K^+-ATPases. To our knowledge, this is the sixth reported case of dRTA secondary to HT, which may be underdiagnosed.

Variable	Normal range	Admission (01/31/23)	Follow-up (08/02/23)
pH	(7.35-7.45)	7.24	7.3
Bicarbonate (mEq/L)	(22-28)	11.1	20.0
Base excess	(10 ± 2)	−14.7	−4.2
Anion gap	(8-12)	9	6
Sodium (mEq/L)	(135-145)	141	140
Potassium (mEq/L)	(3.5-5.0)	2.4	4.3
Chloride (mEq/L)	(98-106)	121	114
Ionized calcium (mmol/L)	(4.49-5.29)	5.41	4.68
Magnesium (mg/dl)	(1.6-2.6)	3.1	2.5

TH-PO390

A Varied Presentation of Fanconi Syndrome Following AKI in COVID-19 Infection

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Introduction: Renal pathology in COVID-19 may manifest as glomerulopathies, tubular injuries, acute kidney injury (AKI), and CKD. One such pathology is generalized proximal convoluted tubular (PCT) dysfunction, referred to as Fanconi's syndrome. We present a case of COVID-19 infection associated with AKI followed by Fanconi syndrome, characterized by persistent electrolyte abnormalities and metabolic acidosis. Incomplete Fanconi's syndrome in COVID has occurred before the onset of AKI, but here our patient develops it after the resolution of the AKI.

Case Description: A 60-year-old female was admitted for severe COVID-19 infection and intubated due to respiratory failure. She eventually developed AKI which resolved quickly with fluids. Labs showed persistent normal anion gap metabolic acidosis (NAGMA) even after AKI resolution, along with hyponatremia, hypokalemia, hypophosphatemia, hypocalcemia, and hypomagnesemia. Nephrology was consulted for the persistent electrolyte disturbances despite adequate replacement and hyperchloremic NAGMA. Urine studies showed mild renal tubular acidosis but negative for proteinuria and glycosuria. Post-COVID Fanconi syndrome was suspected, and electrolyte monitoring with replacement was continued. Eventually, she was extubated and with the recovery of her respiratory status - electrolyte disturbances, and metabolic acidosis also slowly normalized. The patient was discharged on electrolyte supplements and had stable renal function and electrolytes at the follow-up.

Discussion: Tubulopathies can be explained by the direct toxic effect of the virus via the ACE2 ligand, expressed on proximal and distal tubular cells. Incomplete Fanconi's in COVID-19 infection has been described based on 4 specific PCT abnormalities (proteinuria, renal phosphate wasting, hyperuricosuria, and glycosuria). But this case presented differently with varied electrolyte disturbances and acidosis. Fanconi's in COVID usually precedes AKI, possibly acting as a predictor of AKI or can occur alone. But here, it evolved after the resolution of AKI, questioning its utility as such a predictor. It is important to acknowledge this significant association between COVID-19 and tubulopathies to explain some persistent electrolyte and acid-base abnormalities in such patients. This case also emphasizes that there might be more unique ramifications of COVID-19 to be expected in every organ system.

TH-PO391

Is Diabetic Ketoacidosis Synonymous with Death in Patients on Enfortumab Vedotin for Urothelial Carcinoma?

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Introduction: Enfortumab vedotin (EV), is a novel breakthrough therapy which received accelerated FDA approval in 2019 for the treatment of metastatic urothelial carcinoma in patients who have failed other lines of treatment. The characteristics of its adverse effects especially diabetic ketoacidosis (DKA) are not well understood.

Case Description: A 57-year-old male with no history of diabetes, diagnosed with urothelial carcinoma two years prior, failed several lines of treatment including platinum-based chemotherapy and immune checkpoint inhibitors. He developed metastasis and was started on EV. After his second dose of EV, he was admitted to the ICU for diabetic ketoacidosis (DKA) with a high anion gap metabolic acidosis, serum bicarbonate of 12 mEq/L, blood Ph 7.2, hyperglycemia to 450 mg/dL, positive ketones in urine, an elevated C-peptide, with an initial hemoglobin A1C of 7.7%. He was in shock requiring multiple pressors and developed oliguric AKI (serum creatinine 1.5 mg/dL, baseline 0.7 mg/dL). He was intubated for airway protection and started on continuous renal replacement therapy. Despite aggressive treatment, the patient died on hospital day 2.

Discussion: EV is an antibody-drug conjugate which joins an antibody directed against the cell adhesion molecule, nectin-4, which is highly expressed in urothelial carcinoma, with monomethyl auristatin E, an inducer of cell cycle arrest and apoptosis. Just 2 cases of DKA due to EV have been reported since its approval for use in metastatic urothelial carcinoma (One at the 2020 American Thoracic Society Conference and the other at the 2021 American Society of Nephrology Conference). The precise mechanism for the development of DKA is yet unidentified. An elevated C-peptide, noted in one of the reported cases, suggests insulin resistance, but the very rapid progression of the acidosis and death within three days in all the cases suggests some other effects of the drug on glucose metabolism still to be elucidated. There is an FDA warning on its use in patients with glucose over 250 mg/dl, but this was insufficient to prevent DKA in the

reported patients. Our patient had an elevated A1C on admission. Therefore, we strongly suggest screening for diabetes in every patient considered for EV, and to avoid it if A1C is greater than 7%.

TH-PO392

Continuous Renal Replacement Therapy (CRRT) Worsening Acidosis

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Introduction: Euglycemic ketoacidosis (EDKA) is an uncommon cause of high anion gap metabolic acidosis (HAGMA) and should be suspected in diabetics with normal blood glucose (BG) who develop HAGMA. EDKA can complicate continuous renal replacement therapy (CRRT) when poor intake is accompanied by dialysate caloric losses. We describe a patient with EDKA on CRRT following peritonitis from perforated diverticulitis.

Case Description: A 52-year-old AA male with a history of HTN, T2DM, obesity and ESRD on HD presented with diarrhea, left lower quadrant (LLQ) pain and 2 episodes of emesis. On exam, he had LLQ tenderness and leukocytosis with left shift. Imaging showed diverticulitis with multiple fistulas and organizing collection suspicious of abscess. Initially, managed conservatively, but later had signs of peritonitis with free fluid and pneumoperitoneum on imaging, requiring sigmoidectomy. Post-op he was in septic shock, requiring vasopressor support and switched to CRRT from HD. He remained NPO, first awaiting ostomy creation and later due to poor mentation. He continued CVVHDF with Phoxillium and Primasol solutions (both glucose-free dialysate and replacement fluid), however had worsening HAGMA without diarrhea or hyperlactatemia. His BG remained <200 mg/dL. Starvation ketoacidosis was suspected and confirmed with serum Beta hydroxy butyrate (BHB) levels of 7.6. He was started on TPN and transitioned to tube feeds with subsequent resolution of acidosis. Within 2 days of feeding his Hco3 levels normalized in parallel with a decrease BHB levels.

Discussion: Euglycemic ketosis is driven by insulin deficiency and insulin resistance, starvation, and an excess of counter-regulatory hormones. In absence of external nutrition, glucose content of replacement fluid, especially phosphate-containing fluid can cause negative caloric balance with glucose loss of > 80g in the effluent which is more than SGLT2, a known cause of EDKA. In our patient, the day of ketonemia detection, metabolic acidosis had worsened despite appropriately dosed CRRT with minimal lactatemia, while not on insulin and the use of phosphate-containing replacement fluid providing a perfect storm to develop euglycemic ketoacidosis while being on CRRT. This case highlights the need to consider EDKA in the differential diagnosis of high anion gap metabolic acidosis in patients on CRRT.

TH-PO393

Unraveling the Enigma: Deciphering Recurrent Metabolic Acidosis and the Elusive Kabadi Syndrome

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Introduction: This case report explores the diagnostic challenges posed by rare metabolic acidosis conditions. It focuses on Kabadi syndrome (KBS), accompanied by carnitine deficiency. Understanding and managing KBS remains difficult due to its rarity and limited knowledge of the condition. In highlighting the complexity of such cases, we emphasize the need for thorough investigation into rare etiologies.

Case Description: A 65-year-old female with idiopathic chronic pancreatitis with recurrent life-threatening severe anion gap metabolic acidosis (AGMA) over three years, requiring frequent admissions to the intensive care unit. She presented with respiratory distress, altered mental status, and abdominal pain. Laboratory findings consistently showed severe acidemia, low bicarbonate, and elevated anion gap. Glucose levels were normal, with positive ketones. Workup revealed consistently elevated lipase levels with normal liver function tests. Genetic testing was inconclusive, except for low carnitine levels. Imaging indicated chronic pancreatitis. Management involved insulin therapy, hydration, correction of acidosis, pancreatic enzymes, and carnitine supplementation, leading to resolution; ultimately, medication non-compliance led to readmissions.

Discussion: KBS, or pancreatic ketoacidosis, is a rare condition characterized by euglycemic ketoacidosis. It is triggered by elevated pancreatic lipase levels, resulting in fat necrosis and ketone production. The pathophysiology involves the release of free fatty acids, converting them into ketone bodies and causing metabolic acidosis. Carnitine deficiency further impairs ketone clearance and contributes to acidemia. In this patient, the combination of KBS and carnitine deficiency adds complexity. Carnitine supplementation may protect against recurrence; especially as cognitive impairments associated with carnitine deficiency may explain medication non-compliance. This case underscores the importance of comprehensive investigations, genetic testing, and innovative thinking in unraveling rare etiologies. The multidimensional treatment approach includes fluid management, acidosis correction, pain management, pancreatic enzyme replacement therapy, nutritional support, and carnitine supplementation. This report highlights the complexity of rare AGMA etiologies, emphasizing perseverance, innovative investigations, and personalized approaches.

TH-PO394

An Unusual Case of Metabolic Acidosis

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Introduction: Metabolic acidosis is common in hospitalized patients, and more than half the patients admitted to intensive care units have metabolic acidosis. The cause of acidosis is usually apparent from the clinical setting, but in rare instances, a methodical workup is needed to decipher the underlying cause. We present an unusual cause of metabolic acidosis.

Case Description: A 40 yr. woman with Mitochondrial Encephalomyopathy with Lactic Acidosis and Stroke-like episodes (MELAS), presented with sudden worsening of chronic right-sided weakness. An initial work up ruled out acute stroke, and patient was started on intravenous L-Arginine for MELAS. On day five, she developed acute encephalopathy and severe acidosis (Figure-1). The severe non-gap metabolic acidosis was thought to be from L-arginine. Following discontinuation of IV L-arginine and initiation of bicarbonate supplementation, the patient's acidosis improved rapidly.

Discussion: Metabolic acidosis has been reported with prolonged use of L-arginine, particularly in high doses. The mechanisms by which L-arginine causes metabolic acidosis remains unclear. While arginine is administered as arginine hydrochloride, the number of protons added is not significant enough to cause severe acidosis. Although the urine anion gap was negative in our patient, possibly due to exogenous bicarbonate, the urine osmolar gap indicated a renal tubular acidosis. This was confirmed by generalized aminoaciduria and low levels of directly measured ammonia. There was no evidence of phosphaturia or hypophosphatemia. Interestingly, in the isolated perfused tubule exposure to L-arginine causes inhibition of bicarbonate reabsorption in the proximal tubules. Metabolic acidosis could augment L-arginine absorption in the intestine worsening acidosis. Our case highlights that L-arginine can be an unusual cause of severe metabolic acidosis. The physiology underlying this clinical observation requires further studies.

Lab	On admission	Day 1 of IV Arginine	IV Arginine discontinued (s/p day 5)	Prior to discharge
Sodium	134	132	129	138
Potassium	3.8	6.0	5.9	3.8
Chloride	100	108	107	101
Carbon Dioxide	19	13	8	26
Glucose	251	240	277	102
Calcium	10.4	9.7	10.6	
BUN	28	34	42	16
Creatinine	0.67	0.79	0.86	0.58
Albumin	4.6	4.1	4.7	3.6
Lactic acid	3.2			
Anion gap	15	11	14	11
Urine chemistry	pH: 5 Na: 81 K: 40 Cl: 150 Glu: 150 AG: -29 Osm:.632 OG:106			
Other urine studies (nmol/mg C)	Ammonia:12 Arginine: 166 Ornithine: 181 Cysteine:375 Lysine:117			
VBG	pH:7.16 CO2:36 HCO3:12.8			

TH-PO395

Factitious Lactate Elevation: A Clue for Ethylene Glycol Poisoning

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Introduction: Ethylene glycol poisoning is a medical emergency, and an early diagnosis is imperative for proper treatment. In most of the institutions the turnaround time for a direct measurement takes a few hours. Severe metabolic acidosis with an elevated osmolar gap can give a clue in the appropriate clinical setting. We describe a case of factitious lactic acid elevation using blood gas analyzers (point of care) in this group of patients. This could be an additional indicator to support a diagnosis of ethylene glycol poisoning.

Case Description: 50 yr old lady was found by family in bed, unresponsive, and with labored respirations. She was intubated in the field for airway protection given her poor GCS, and transported to the emergency department. She was afebrile but hypertensive and initially needed nicardipine drip for BP control. Labs were significant for leucocytosis of 34000, anion gap 30, serum bicarbonate 5, lactate 15 (obtained on blood gas analyzer), pH 6.90. Sodium 148, Chloride 113, blood glucose 185. Creatine Kinase 47. Initial Creatinine 2.4 and Blood Urea Nitrogen 16. Measured osmolarity was 357 with osmolal gap of 44. Simultaneous lactic acid done in the central laboratory was normal at 0.9. Ethylene Glycol level was significantly increased and was 46. Patient started on sodium bicarb, fomepizole, thiamine and folinic acid and pyridoxine, monitoring BMP and VBG every 4 hours. Patient underwent hemodialysis. Eventually her acidosis improved, and she was extubated.

Discussion: Ethylene glycol gets metabolized in liver and form glycolic acid and glyoxylic acid. These compounds cross react with L-lactate oxidase used in point of care blood gas analyzers and release hydrogen peroxide that is measured as a surrogate for the level of lactate. This results in a false elevation of lactate. A concurrent lactate level performed in the central laboratory using ion selective electrodes was normal. There is usually a very good correlation between point of care analyzers and the central laboratory in measuring lactic acid in various clinical situations. This discrepancy and a factitious elevation of lactic acid can be an important clue for the diagnosis of ethylene glycol poisoning.

TH-PO396

Patent Foramen Ovale Causing Lactic Acidosis

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Introduction: Lactic acidosis is secondary to the accumulation of protons and lactate in body fluids and is associated with poor clinical outcomes and increased mortality. Hypoxemia leads to increased anaerobic glycolysis causing excess generation of lactate. Congenital cyanotic heart diseases are associated with an increased risk for lactic acidosis, which is also rarely seen in acyanotic heart disease. Here we present a case of a patient with patent foramen ovale (PFO) causing lactic acidosis, which resolved after its closure.

Case Description: A 70-year-old white male with a history of hypertension, and remote smoking presented with worsening shortness of breath for a few hours. He had hypoxemia with oxygen saturation between 83% to 88%; his heart rate ranged from 100 to 110 beats per minute, and his respiratory rate ranged from 22 to 30 breaths per minute. Initial blood gas showed a pH of 7.53, pCO2 of 24.8 mm Hg, and PO2 of 48.7 mm Hg on room air. His initial chemistry showed a sodium level of 139 mmol/l, potassium of 4.0 mmol/l, bicarb level of 12 mmol/l, chloride level of 101 mmol/l, anion gap of 26 mmol/l, BUN of 34 mg/dl, creatinine of 0.98 mg/dl, serum albumin level was 4.1 gr/dl. He had normal pro-BNP and lactic acid of 4.8 mmol/l. Chest X-ray was negative for any signs of volume overload or infiltrate. Common etiologies of lactic acidosis were considered and ruled out. The patient never had hypotension, and pan cultures were negative. The lactic acid level remained elevated even after tachypnea had improved. Pulmonary / Cardiac shunting was suspected, and the patient underwent an echocardiogram with an agitated saline contrast study, which showed a right-to-left shunt. The patient underwent transesophageal echocardiography, which was suggestive of mild-to-moderate pulmonary hypertension, right ventricular systolic pressure was 40 mmHg, and 6 mm PFO with a right-to-left shunt. The patient underwent percutaneous closure of the PFO, leading to the resolution of hypoxemia and normalization of the lactic acid and anion gap. Significant right to left shunting through the PFO contributed to his hypoxemia, which likely worsened recently, contributing to Type A lactic acidosis.

Discussion: After excluding common etiologies, nephrologists should consider cardiac and pulmonary shunts in the differential diagnosis when evaluating patients with elevated anion gap metabolic acidosis with lactic acidosis.

TH-PO397

Mind the Gap: Pyroglutamic Acidosis as a Not-so-Rare Cause of High Anion Gap Metabolic Acidosis (HAGMA)

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Introduction: In addition to the common causes of high-anion gap metabolic acdiosis (such as lactic acidosis, ketoacidosis, and toxic alcohol ingestion), pyroglutamic acidosis can also result in HAGMA. This case report illustrates a patient in which otherwise unexplained metabolic acidosis was attributed to 5-oxoproline accumulation in the setting of chronic acetaminophen exposure and malnutrition.

Case Description: A 39-year-old man with a history of paraplegia, malnutrition, and prior PEG tube placement was admitted for management of a gastro-cutaneous fistula involving abdominal wall takedown and partial omentectomy. His post-operative course was complicated by pneumonia, septic shock, and AKI-D requiring two sessions of iHD on hospital days 8 and 10. Following HD treatments, he recovered renal function with appropriate urine output and stable electrolytes. During this period, he was started on scheduled acetaminophen 4 g daily for pain control. Over the course of subsequent hospital days 11–13, he developed worsening AGMA with a peak anion gap of 26. After initial respiratory compensation, he ultimately required intubation for tachypnea and worsening hypercarbia. The workup for common causes of AGMA was non-revealing with normal lactate, D-lactate, alcohol, and beta-hydroxybuterate levels. Organic acid analysis of urine showed significantly elevated levels of 5-oxoproline excretion (6797 mmol/mol Cr., reference range: <62). Acetaminophen was discontinued, with subsequent resolution of metabolic acidosis over the next 3 days.

Discussion: This case demonstrates the development of HAGMA in a malnourished patient after several days of acetaminophen ingestion where the workup for common causes of HAGMA was non-revealing. In these situations, the accumulation of 5-oxoproline (pyroglutamic acid) is an important consideration. This rare condition can occur due to chronic acetaminophen exposure and subsequent glutathione depletion, particularly in the setting of poor nutritional status and a malfunctioning intestine.

Acidosis Trend

Hospital Day	HCO3-	Anion Gap
Day 10 (last iHD)	21	18
Day 11	18	22
Day 12	15	23
Day 13 (Acetaminophen stopped)	10	26
Day 14	15	21
Day 15	21	14

TH-PO398

Severe ICU-Acquired Metabolic Acidosis due to Pyroglutamic Acidosis (5-Oxoprolinuria)

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Introduction: Anion gap metabolic acidosis (AGMA) is an acid-base disturbance frequently encountered in the intensive care unit (ICU). However, pyroglutamic acidosis (PGA) is a rare cause of ICU-acquired metabolic acidosis.

Case Description: A 56-year-old woman with a recent large stroke requiring craniectomy with abdominal bone flap was readmitted for septic shock from an abdominal abscess. Her course was complicated by new intracranial hemorrhage, persistent encephalopathy requiring prolonged mechanical ventilation via tracheostomy, malnutrition requiring tube feeds, and multiple episodes of acute kidney injury (AKI). A month after readmission, she developed AGMA of unclear etiology, with arterial pH 7.31, arterial PCO_2 16 mmHg, bicarbonate 9 mEq/L (down from 21-31), anion gap 17 mEq/L (up from <6-8), albumin 1.2 g/dL, creatinine 1.5 mg/dL, lactic acid 2.5 mmol/L, and beta-hydroxybutyrate 0.1 mmol/L. Notably, since admit she had received scheduled acetaminophen 500-650 mg four times daily, which was stopped upon nephrology consult. She received N-acetylcysteine 600 mg twice daily for five days. She required continuous renal replacement therapy (CRRT) for one day for transient oliguria and worsening AKI (peak SCr 1.9 mg/dL) from recurrent septic shock, with sustained resolution of her acid-base disturbance. However, a urine sample sent for organic acids prior to CRRT initiation ultimately revealed elevated pyroglutamic acid.

Discussion: Acetaminophen normally undergoes cytochrome metabolism to N-acetyl-p-benzoquinone imine (NAPQI), a highly reactive oxidation product that is detoxified by glutathione. In glutathione deficiency, a buildup of the organic anion pyroglutamic acid (5-oxoproline) can occur. In predisposed patients – classically older malnourished women – chronic therapeutic acetaminophen use can induce acquired glutathione deficiency and PGA, which likely explains the severe AGMA out of proportion to renal dysfunction in our case. As most labs do not measure 5-oxoproline locally, PGA is likely underrecognized and underreported, though it features in the modern GOLDMARK mnemonic for AGMA (glycols, 5-oxoproline, L- and D-lactate, methanol, aspirin, renal failure, ketosis). Moreover, though this is one of only a few prior published cases of ICU-acquired PGA, this case illustrates that PGA must be considered on the differential diagnosis of unexplained ICU-acquired AGMA.

TH-PO399

Amiloride vs. Furosemide for the Treatment of Edema in Nephrotic Syndrome (AMILOR): A Pilot Study

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Background: According to findings from nephrotic mouse models, edema formation in nephrotic syndrome (NS) is caused by sodium retention through activation of the epithelial sodium channel ENaC. In these models, edema formation could be prevented by ENaC blockade with amiloride. The monocentric randomized controlled AMILOR study investigated the anti-edematous effect of the ENaC blocker amiloride in nephrotic patients in comparison to standard therapy with the loop diuretic furosemide.

Methods: Patients with acute NS (n=10 per arm, etiology MCD n=6, MN n=8, FSGS n=2, amyloidosis n=1, IgAN n=1, other n=2; age 53 [interquartile range 38–61], male/female 13/7) and eGFR (CKD-EPI)>30 ml/min/1,73m2 were randomized to treatment with amiloride (start 5mg/d, max.15mg/d) or furosemide (40mg/d, max.120mg/d) over 16 days. Overhydration (OH) was measured by bioimpedance spectroscopy (Body Composition Monitor, Fresenius). Depending on the course of OH, the dose was adjusted on days 2,5,8,12 and 16 and, if necessary, HCT was added on d8 (start 12.5mg/d, max. 25mg/d). The primary endpoint was the decrease in OH on d8. The study was terminated prematurely due to insufficient recruitment and low statistical power due to a low actual effect size.

Results: Median baseline OH was 5.3 L /1.73m2 (26 [18-34]% of extracellular water [ECW]) in the amiloride arm and 6.2 L/1.73m2 (28 [24-29]% ECW) in the furosemide arm. On d8, OH decreased to 3.7 L/1.73m2 (19 [16-27]% ECW) in the amiloride arm and to 4.5L/1.73m2 (21 [13-28]% ECW) in the furosemide arm. Till d16, OH decreased significantly to 60 [29-93]% or 2.2 L/1.73m2 (12 [9-24]% ECW) in the amiloride arm and to 69 [57-85]% or 3.4 L/1.73m2 (17 [14-27]% ECW) in the furosemide arm. The decrease in OH on d8 and d16 was not significantly different between both arms. Hyperkalemia>5.3 mM (max. 5.7 mM) occurred in n=3 patients taking amiloride (all GFR according to CKD-EPI-Cys <40mL/min/1.73m2).

Conclusions: The AMILOR study is the first randomized controlled pilot study on the use of diuretics in NS demonstrating an antiedematous effect of the ENaC blocker amiloride without a significant difference to furosemide. Thus, amiloride emerges as an alternative to the standard therapy with furosemide. The knowledge gained lays the foundation for the design of a larger multi-centre study with greater statistical power.

TH-PO400

Correlation Between Conventional Ultrasound and Microchip Technology Ultrasound in Evaluating Pulmonary and Inferior Vena Cava in AKI Patients Undergoing Renal Replacement Therapy

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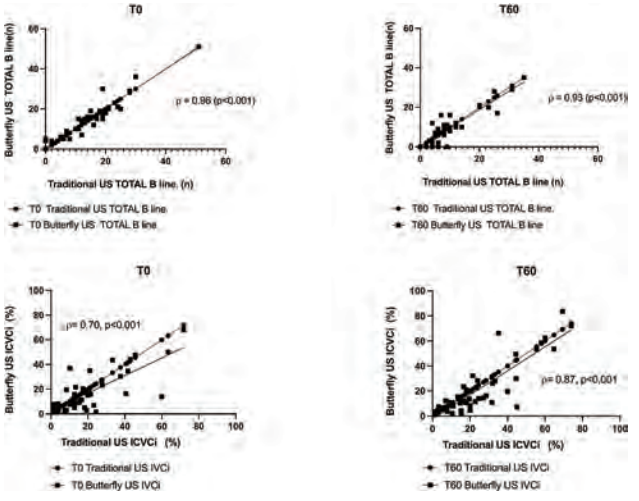
Background: Point of care ultrasonography is an essential tool in nephrologists physical examination. Ultraportable ultrasound with microchip technology-Butterfly IQ is a recent technological advance and should be compared with the traditional piezoelectric. So the study aims to compare both technologies, in the analysis of two extravascular volume parameters: B-lines and Inferior venous collapsibility index (IVCi) in patients with acute kidney injury (AKI) in the ICU receiving renal replacement therapy (RRT).

Methods: We conducted a study on fifty sedated, mechanically ventilated patients with AKI requiring RRT in two hospitals. Exclusions included individuals under 18 years, pregnant women, cancer patients with no further treatment options, and patients receiving high-dose norepinephrine or any dose of vasopressin. We evaluated B lines and IVCi using both technologies at two-time points. Correlation tests were performed.

Results: A total of 200 exams were done with a mean age of 73.5±13, including 20 male patients (39%). Conventional HD was performed in 27.5% of cases, with a mean prescribed ultrafiltration of 1.6 ± 0.8 L. The correlation between the piezoelectric and microchip technologies for evaluating pulmonary B-lines was strongly positive, with correlation coefficients 0.96 and 0.93 at the beginning and 1st hour, respectively (P=0.001). Similarly, the correlation coefficients of tIVCi were 0.70 and 0.87 at the beginning and 1st hour, respectively (P=0.001), indicating a moderate correlation.

Conclusions: On AKI patients under RRT USG by Butterfly IQ microchip has an excellent correlation with traditional piezoeletric technology and combines advantages related to portability, easy handling and low cost with reliability in obtaining parameters for volume assessment obtained at the bedside.



TH-PO401

Chronology of Cyst Epithelium Transformation to Renal Cell Carcinoma Through scRNA-seq

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Background: We have described a mouse model suitable for studying the progression of renal cell carcinoma (RCC). Upon deletion of a single gene (*Tsc1*) by a kidney-specific Cre (*KspCre*) in specific segments of the nephron, the mTORC1-dependent downregulation of polycystin-1 initially triggers the establishment of an overt cystic phenotype. Mutated epithelial cells then transform into cancerous lesions. The slow progression of the phenotype allows to dissect between mechanisms driving cyst formation, and the ones supporting epithelium malignant transformation. However, mutant cells lose epithelial markers, making it difficult to follow the next steps of transformation.

Methods: Our RCC model (*Tsc1;kKO*) was crossed with *mTmG* strain, ubiquitously expressing membrane Tomato (mT) marker that recombines to mGFP (mG) upon KspCre expression, allowing to discriminate mutated cells over time. Mutant kidneys were characterized by histological and immunofluorescence analysis. Kidney single cell suspension was characterized by flow cytometry. Chromium 10x single cell RNA sequencing (scRNA-seq) was performed on 20 000 cells from P80 mutant and ctrl kidneys.

Results: *mTmG;Tsc1;kKO* mutants were comparable to our previous RCC model, with the epithelium lining the cysts progressively transforming to papillae (P20), cystadenomas (P50), and carcinomas (P80). All the structures identified were mG^+, allowing following the mutated cells during transformation. Indeed, flow cytometric analysis confirmed the expansion of the mG^+ population at P80, consistent with the reported prominent proliferation of *Tsc1* KO cells. scRNA-seq identified clusters of cells from all the segments of the nephron, both in mutant and ctrl kidneys. Cells deriving from the distal tubule and collecting duct were identified by *Egfp* transcript. This uniquely defined the *Tsc1* KO cells and their expansion in the mutated kidney. Interestingly, we identified sub-clusters of mG^+ cells with a proliferative and de-differentiated profile, and we observed the expansion of different immune populations in mutated kidneys, potentially supporting the RCC progression.

Conclusions: We generated a model of RCC through which we can dissect between driving events of cystogenesis and mechanisms supporting epithelial transformation to cancerous lesions. scRNA-seq represents a valuable approach to deciphering key mechanisms and new populations in RCC.

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TH-PO402

Selective V2 Vasopressin Receptor Blockade Increases Urinary Exosome Pendrin Expression in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Tolvaptan, a selective V2 vasopressin receptor (V2R) antagonist, has shown to improve kidney function and acid retention biomarkers in ADPKD-treated patients. However, the underlying mechanisms of this association remain unclear. Here we investigated the effect of Tolvaptan on renal acid-base handling in ADPKD by analyzing the abundance in urinary exosomes of Pendrin and the B1 subunit of V-ATPase, which regulate HCO_3^- and H^+ transport in the collecting ducts.

Methods: In this prospective study, 24 ADPKD patients were enrolled from the Bern ADPKD registry. Patients were allocated with a 1:1 ratio in the Tolvaptan and no-Tolvaptan groups. All patients performed baseline and 2-year follow-up visits. Net acid excretion (NAE) and net gastrointestinal alkali absorption (NGIA), markers of acid and alkali intake, were calculated from 24h urines. Second morning spot urine samples with freshly added protease inhibitors and immediately frozen at –80 °C were used to isolate urinary exosome proteins with an already established differential centrifugation method. Primary polyclonal anti-rabbit antibodies for Pendrin and the B1 subunit of V-ATPase were used for immunoblotting. Changes in urinary exosome abundance were normalized by Alix (exosome housekeeping protein).

Results: 19 patients (9 with and 10 without Tolvaptan) were included in the final analysis. 5 patients were excluded because Alix was not detectable. Compared to baseline, urinary exosome Pendrin abundance increased by 134.4% only in Tolvaptan-treated patients ($p < 0.01$) after two years. Pendrin abundance strongly and directly correlated with NGIA (rho 0.75, $p < 0.01$) at baseline, and inversely with NAE (rho –0.51, $p = 0.03$) during follow-up. Urinary HCO_3^- excretion was associated with Pendrin expression over time (rho 0.73, $p < 0.01$). Ultimately, changes in urinary exosomal Pendrin were inversely associated with plasma potassium (rho –0.71, $p = 0.03$) only in the Tolvaptan group.

Conclusions: Urinary exosome Pendrin expression is sensitive to subtle changes in the acid-base status of ADPKD patients. Tolvaptan increases the expression of Pendrin in urinary exosomes, supporting the hypothesis that selective V2R blockade exerts an effect on systemic acid-base status of ADPKD patients.

TH-PO403

Automated Detection and Quantification of Individual Collagen Fibers Indicates Collagen Dynamics Underlying Increased Fibrotic Index in ADPKD

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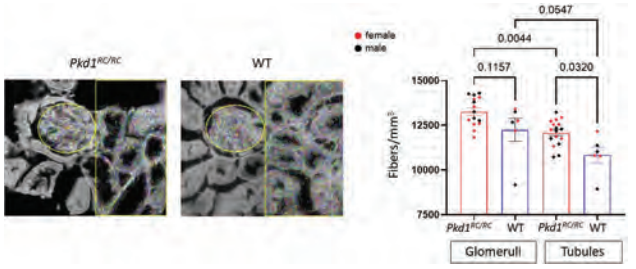
Background: Autosomal dominant polycystic kidney disease (ADPKD) is the fourth leading cause of kidney failure. While cysts are the most obvious phenotype, accumulating evidence indicates the involvement of the extracellular matrix in in the kidney and other organs. The most abundant protein in this matrix is collagen, which is encoded by 44 genes comprising supramolecular assemblies making up 28 collagen types. As such, histological methods to assess overall collagen are valuable and routinely used in ADPKD research, yet they are limited by variability and insensitivity. We used CT-FIRE software that automatically detects individual collagen fibers to determine fiber density in glomeruli and tubules in an ADPKD mouse model.

Methods: Four-month-old *Pkd1*$^{RC/RC}$ mice were compared to WT. All mice were F1 progeny from a 129/C57BL6J cross. Kidneys were fixed, cryosectioned, and stained with Sirius red. Tissue area and fibrotic index were determined using ImageJ and collagen fibers were automatically detected using CT-FIRE fiber detection software (LOCI; Madison, WI). Statistical measurements were obtained using PRISM (GraphPad Software, Inc.).

Results: Standard brightfield imaging trended toward a higher fibrotic index in *Pkd1*$^{RC/RC}$ than WT, and individual fibers showed an increase in fiber density overall in *Pkd1*$^{RC/RC}$. Comparison of glomeruli vs tubules showed a higher density of fibers in glomeruli for both *Pkd1*$^{RC/RC}$ and WT. Fiber density did not differ in glomeruli of *Pkd1*$^{RC/RC}$ vs WT but was higher in *Pkd1*$^{RC/RC}$ tubules (see figure). There were no differences in fiber width, length, or straightness in either glomeruli or tubules between *Pkd1*$^{RC/RC}$ and WT.

Conclusions: These data demonstrate the potential of CT-FIRE software to provide more objective, higher resolution information about collagen in ADPKD. Mice used here had already developed cysts, but additional studies are needed to determine whether this approach can provide new insight into earlier-stage ADPKD.

Funding: NIDDK Support, Private Foundation Support



TH-PO404

Correction of PKD by Gene Transfer into Pkd1-Null Mouse Model

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Background: Autosomal dominant polycystic kidney disease(ADPKD) causes renal cysts and insufficiency due mainly to PKD1 mutations. Since microscopic cysts in ADPKD kidneys are likely formed *in utero,* we re-expressed wild-type *Pkd1*/*Pc1* protein in *Pkd1*$^{-/-}$ mouse via germ line by series of complementary gene transfer to assess for long-term cure of severe cystogenesis and neonatal death.

Methods: Pc1 re-expression in the most severe mouse model *Pkd1*$^{-/-}$ was assessed by 3 strategies using genomic *Pkd1* under its own regulatory elements (*Pkd1*^{wt}), driven by kidney specific regulatory elements (900nt SB, ^{SB}*Pkd1*) or *Pkd1*^{Minigene}. Renal molecular (qPCR, IB), tubular (stainings, IF, RNAscope) and functional (BUN, hct) analyses were performed.

Results: *Pkd1*$^{-/-}$ mice targeted with 2 distinct *Pkd1*^{wt} gene transfers, of ~8-fold overexpression and intense RNAscope signal over all tubular segments and glomeruli similarly to endogenous cell profile, fully rescued PKD phenotype. ^{SB}*Pkd1* one- and high-copy gene transfers conveyed 0.6- or 7-fold *Pkd1* endogenous levels respectively. One-copy ^{SB}*Pkd1* transfer initiates cysts after birth ~P3 and confer sufficient *Pkd1* expression during maturation to correct proximal tubules and glomeruli, to minimize distal cyst and to postpone but not prevent cyst in collecting ducts. This transfer extended *Pkd1*$^{-/-}$ life survival by 4-fold. High-copy ^{SB}*Pkd1* transfer provide proper targeting and expression levels for complete rescue during renal maturation, and significantly retard cyst in proximal and collecting tubules at post-maturation but is insufficient to prevent distal cysts. This transfer increased lifespan by 25-fold. ^{SB}*Pkd1* transfers show that collecting tubules require higher *Pkd1* expression during maturation and that SB regulatory elements appreciably overlap with those of the endogenous promoter. High-copy renal *Pkd1*^{Mini} transfer resulted in similar expression to endogenous *Pkd1* with widespread and homogeneous weak *Pkd1* cellular signal, partially rescuing glomeruli and all cystic tubular segments during maturation and attained therapeutic levels with increased lifespan by 4-fold.

Conclusions: Our study determined that *Pkd1* intragenic sequences not only control levels of expression but alike the upstream sequences, also regulate spatio-temporal expression pattern. One-copy ^{SB}*Pkd1* is sufficient to substantially delay cystogenesis. Pc1 re-expression can considerably extend lifespan or eliminate PKD.

Funding: Government Support - Non-U.S.

TH-PO405

Delivering Nucleic Acids to ADPKD Cystic Cells via a Nucleic Acid Binding and Cell-Penetrating Antibody

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Background: Mutations in *PKD1*, which encodes polycystin-1 (PC1), cause ~78% of autosomal dominant polycystic kidney disease (ADPKD) cases. We have shown that transgenic expression of the 200-aa PC1 C-terminal tail (CTT) in the Pkd1$^{fl/fl}$;Pax8^{rtTA};TetO-Cre (*Pkd1*-KO) mouse model of ADPKD suppresses cystic phenotype and preserves renal function. To overcome the challenge of delivering CTT-encoding cDNA or mRNA to cystic epithelia we used the lupus-derived antibody 3E10-D31N and its humanized version, V66. These cell-penetrating antibodies non-covalently bind and deliver nucleic acids to tumors by targeting the nucleoside transporter ENT2. Specific targeting of tumors occurs due to increased ENT2 expression in proliferative tissues.

Methods: Trial #1: one 200μg dose of 3E10-D31N labeled with fluorochrome IR700, administered to 11-week *Pkd1*-KO mice. Trial #2: 3 doses of V66 (100μg/dose) combined with mRNA encoding GFP (20μg/dose), administered 24 hours apart to 13-week *Pkd1*-KO mice. In vivo imaging system (IVIS) and immunofluorescence microscopy (IF) were used to assess treatment results.

Results: IVIS imaging of Trial #1 kidneys revealed absence of fluorescently labeled 3E10-D31N in untreated controls, suggesting specificity of the total radiant efficiency (TRE) observed in treated WT and pre-cystic mice. Interestingly, treated pre-cystic mice showed an ~ 50% increase in TRE relative to treated WT, suggesting that this approach can successfully target highly proliferative ADPKD tissue. IVIS imaging of kidneys from Trial #2 revealed GFP fluorescence only in cystic kidneys from mice that were treated with V66/GFP mRNA, and not in cystic tissue from mice that received GFP mRNA alone or untreated mice. Interestingly, a positive correlation was observed between kidney size and TRE levels. Finally, IF studies revealed GFP present in a punctate cytoplasmic pattern in cystic epithelial cells of animals that received V66/GFP mRNA and not in controls.

Conclusions: 3E10-D31N/V66 targets cystic epithelia and delivers GFP mRNA that drives protein expression *in vivo.* We will next deliver CTT mRNA and assess protein expression and potential impacts of this intervention on the development of cystic phenotype. This strategy could support the delivery of other potentially therapeutic mRNAs or cDNAs in the context of other renal diseases.

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

TH-PO406

Obesity and PKD: Mechanistic Studies Using the Pkd1RC/RC Model

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Background: Obesity is a covariate of more rapid kidney cyst growth in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD). Murine studies suggest that immune cell function and metabolic defects influence disease progression; both of which are altered in obesity. Caloric restriction (CR), in turn, slows PKD progression in mice.

Methods: Using the C57Bl/6J *Pkd1* p.R3277C (*Pkd1*$^{RC/RC}$) mouse, we established a diet-induced obesity model of ADPKD by *ad libitum* feeding a high fat diet (HFD, 42% calories from fat) from 4 weeks to 7 months of age; control diet (CD, 13% calories from fat, matched composition). PKD severity, fat mass (quantitative magnetic resonance), and kidney immune- (flow cytometry) and metabolic- (LC-MS/MS) state were assessed at study end.

Results: Compared to consumption of CD, HFD caused a 1.2-fold ($p<0.01$) increase in body weight in males (M)/females (F) and a 2.4-fold in M ($p<0.05$) and 1.8-fold in F ($p<0.05$) increase in fat mass. Interestingly, PKD severity only significantly worsened in females on HFD vs CD not males: increased kidney weight/femur length (1.4-fold, $p<0.01$), cyst- (1.98-fold, $p<0.01$) and fibrotic- volume (2-fold, $p<0.05$). Kidney metabolomics revealed significant dysregulation of the kynurenine pathway, which we recently identified as key modifier of PKD progression and immunosuppression, e.g., kynurenic acid (KA) increased by 3.1-fold (F) ($p<0.001$) and 1.28-fold (M) in mice on HFD vs CD. Of note, CR resulted in a 3-fold reduction in KA ($p<0.05$) in a separate age/sex matched study of *Pkd1*$^{RC/RC}$ mice. Correlatively, the kidney immune landscape of *Pkd1*$^{RC/RC}$ mice on HFD significantly shifted towards immunosuppression with increased numbers of M2-like infiltrating macrophages (1.45-fold, <0.01), $CD4^+$ T_{Regs} (1.96-fold, $p<0.05$), and T cell PD-1 expression (1.8-fold, <0.01).

Conclusions: We established a model of ADPKD that mimics clinical findings of patients with ADPKD and high adiposity, although the sex dimorphism needs further investigation. We also outline kynurenines/immunosuppression as a potential mechanistic link. The model will allow evaluation of novel therapeutic/nutritional avenues to reduce adiposity and slow PKD progression as well as adiposity-linked mechanisms driving kidney cyst growth.

TH-PO407

A Novel Kidney-Selective AMPK Activator Slows Renal Cystic Disease and Fibrosis in PKD Mice

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Background: ADPKD is characterized by progressive enlargement of fluid-filled cysts, leading to inflammation and fibrosis, and a decline in kidney function. Metformin, the only FDA-approved AMPK activator and most commonly used drug for the treatment of type 2 diabetes, reduced mTOR-mediated cell proliferation and CFTR-mediated ion transport in *Pkd1* mutant cells and inhibited cyst growth of rapid PKD models. However, metformin-associated lactic acidosis, a potentially lethal side effect, raises concerns about its application for long-term treatment of ADPKD. Metformin is a biguanide that requires an organic cation transporter (OCT) to be taken up by cells and is transported into the kidneys *via* OCT2; however, it is not a substract for OCTN1/2 and is eliminated in urine. In collaboration with Pano Therapeutics, we tested biguanides with improved potency for AMPK, OCT2, and OCTN1/2. PAN1021 was 38× more potent for OCT2 and >100× more potent of OCTN1/2 than metformin, thus reducing renal elimination. Previously, PAN1021 decreased mTOR signaling, proliferation, anion secretion, and *in vitro* cyst formation of human ADPKD cells. Here, we compared effects of PAN1021 and metformin on cyst disease, inflammation, and fibrosis in an orthologous PKD mouse model.

Methods: PAN1021 (100mg/kg) or metformin (300mg/kg) was delivered to *Pkd1*$^{RC/RC}$*;Pkd2*$^{+/-}$ mice, an early onset PKD model, by daily gavage from 5 to 20 wk. Mice were killed 3 h after the last treatment, and blood and kidneys were collected for analysis.

Results: PAN1021 had no effect on body weight, appearance, or behavior of the PKD mice, indicating that the drug was safe, and it caused a significant decrease in kidney weight (%body weight; KW/BW). By contrast, the metformin response was variable and half of the mice showed an increase in KW/BW. Both drugs reduced renal fibrosis and BUN. PAN1021 reduced P-S6/S6, a component of mTOR signaling, and PCNA, a proliferation marker. It potently reduced TNF-α and F480, inflammation markers, and α-SMA and collagen 1A1, fibrosis markers, and restored the levels of PPARα, a regulator of fatty acid oxidation.

Conclusions: A novel kidney-selective AMPK activator PAN1021 inhibits renal mTOR, cell proliferation, cyst growth, tissue inflammation, and fibrosis in PKD mice. PAN1021 has an OCT profile anticipated to reduce the risk of lactic acidosis in ADPKD patients.

Funding: NIDDK Support

TH-PO408

The Effect of Lowering Uric Acid with a Xanthine Oxidase Inhibitor on PKD in Mice

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Background: In rodents uricase converts uric acid (UA) to allantoin and uricase inhibition with oxonic acid (OXO) raises serum UA. The aim of the study was to determine the effects of lowering UA with the xanthine oxidase inhibitor, oxypurinol (Oxy), in a mouse model of PKD.

Methods: Pkd1$^{RC/RC}$ (RC) mice, a hypomorphic Pkd1 gene model. OXO (300 mg/kg) or Oxy (24 mg/kg) +L-arginine (increases solubility of Oxy) treatment from day 50 to 120 of age. UA measured by LC/MS-MS. Males+females analyzed together. Caspase-1 protein measured by immunoblot. Cyst index (% of kidney cystic) cyst number and cyst area determined on cross sections by a computerized algorithm.

Results: See Table. Pharmacokinetic studies in normal rodents showed a 5 -fold increase in serum UA 2 hrs after OXO dosing. Oxy did not affect PKD in mice likely because baseline UA levels were low in rodents (0.35 mg/dL) due to uricase. So, the effect of OXO that increases UA in mice was determined. In RC mice, OXO resulted in a significant increase in serum UA, 2 kidney/body weight ratio (2K/BW) (%) and cyst indices. Mechanisms of increased PKD caused by UA were investigated: OXO resulted in a 50% increase in serum UA and an increase in pro-inflammatory cytokines/chemokines in the kidney: IL-5, IL-6, CXCL1. On polarized light UA crystals were not seen and caspase-1, a marker of the inflammasome, was not increased in OXO-treated kidneys. Oxy resulted in a 300% decrease in serum UA and significantly decreased the increase in 2K/BW and cyst indices caused by increasing UA with OXO.

Conclusions: Increasing serum UA by inhibiting uricase with OXO results in an increase in kidney weight and cyst indices. The combination of OXO + Oxy decreased the increase in kidney weight and cyst indices induced by OXO. A potential mechanisms of how OXO causes increased cyst growth in RC mice is induction of a pro-inflammatory cytokine storm in the PKD kidney in the absence of UA crystalluria or inflammasome activation.

Funding: Commercial Support - XORTX Pharmaceuticals

	Veh	Oxy	Veh	OXO	OXO	OXO+Oxy
2K/BW(%)	2.1	2.2	1.8	2.1*	2.01	1.77*
Cyst index (%)	9.5	10	6	10*	14	10.8*
Cyst No	124	150	134	185*	95	74
Cyst size μm^2	6990	6251	6421	6442	10491	7440*
Caspase-1/GAPDH			0.6	0.6	0.7	0.7
IL-5/IL-6/CXCL1 (pg/mL)			0.1/3.4/12	0.3/10.7/19 All=*		

*P<0.05. RDU=relative densitometry units, N=8-16 per group

TH-PO409

Therapeutic Blocking of IL-17A Binding to IL-17RA Diminishes PD-L1 Expression Is a Novel Therapeutic Approach for ADPKD

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Background: Interleukin (IL) - 17A is a critical pro-inflammatory determinant that has been demonstrated to expedite cell proliferation and inflammatory responses in the disease microenvironment. Howbeit, its role in ADPKD has not yet been reported.

Methods: To verify the role of IL-17A in ADPKD, we administered cyanidin, a small molecule flavonoid that disrupts IL-17A/IL-17RA interaction, to *Pkd1* mutant mouse models. To determine the molecular basis of IL-17A/IL-17RA signaling inhibition, we performed western blotting, qRT-PCR and knockdown studies in *Pkd1* mutant renal epithelial cells and tissues. We also determined the relationship of IL-17A/IL-17RA signaling with PD-L1 immune-checkpoint molecule via co-IP and siRNA knockdown studies. Flow cytometry analysis was carried out to determine CD8 and CD4 Th17 cell population.

Results: We found that disruption of IL-17A/IL-17RA interaction by cyanidin significantly impeded cyst growth as well as the recruitment of macrophages via decreased levels of MCP-1 secretion into the cystic microenvironment in *Pkd1* mutant mouse kidneys. Mechanistically, ablation of IL-17A/IL-17RA signaling blunted the activation of PKD associated signaling pathways (AKT, MAPK, NF-κB) to reduce cyst growth and inflammatory responses in *Pkd1* mutant cells and kidneys. In essence, the therapeutic utility of IL-17A signaling blockade in inhibiting cyst proliferation was mediated via decrease in mitochondrial fragmentation in *Pkd1* mutant cells. Interruption of IL-17A binding to IL-17RA also reduced the expression of TGF-β and then abrogated renal fibrosis and collagen deposition in *Pkd1* mutant kidneys. We further found that - 1) disruption the interaction of IL-17A/IL-17RA with cyanidin and knockdown of IL-17RA decreased the expression of PD-L1 immune checkpoint molecule, and 2) IL-17RA interacted with PD-L1 to alter its activity. As a result, the adaptive immune response was tempered via dramatic rise in CD8+ T cells infiltration and reduction in the CD4+ Th17 population due to lowering of the levels of CCL-20.

Conclusions: This study elucidates the roles of IL-17A/IL-17RA signaling and its novel relationship with PD-L1 in ADPKD, suggesting that disruption of IL-17 signaling either alone or in combination with anti-PD-L1 immunotherapy can be a viable powerful strategy in ADPKD treatment.

Funding: NIDDK Support

TH-PO410

Targeting ALDH1A1 with Nanoparticle-Based Immunotherapy on Kidney PD-L1 Synergistically Delays Cyst Growth

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Background: ALDH1A1 is responsible for oxidation of acetaldehyde in mammals, which is upregulated in various cancers to drive cancer growth. ALDH1A1 is associated with tumor immunity by regulating the ratio of effector T cells to Treg cells within tumor tissues. However, the role of ALDH1A1 and its relationship with PD-L1 as well as the PD-L1 mediated immune response in ADPKD remains elusive.

Methods: To investigate the role of ALDH1A1 and its relationship with PD-L1 in ADPKD, we treated Pkd1 mutant mouse models with the ALDH1A1 inhibitor DSF either alone or together with nanoparticles carrying PD-L1 antibody and evaluated their effect on cyst growth, immune response and fibrosis as well as on specific PKD associated signaling pathways by immunostaining, Western blot, qRT-PCR and flow cytometry analysis. To increase kidney specificity, nanoparticles were conjugated with PD-L1 and kidney specific cadherin-16 (CDH16) antibodies.

Results: ALDH1A1 was upregulated in cyst lining epithelial cells in *Pkd1* mutant kidneys. Targeting ALDH1A1 with its specific inhibitor DSF decreased cyst growth as seen by the decrease of cystic index, KW/BW ratio and BUN levels in *Pkd1$^{RC/RC}$* kidneys as well as cyst lining epithelial cell proliferation by the decrease of the activation of AURKA, AKT, S6 and STAT3. In addition, treatment with DSF decreased the expression of PD-L1 and activated the immune response characterized by the increase of CD8+ T cells as examined by flow cytometry analysis, and decrease the recruitment of macrophages. Our CHIP assay indicated that ALDH1A1 bound with the promoter of *PD-L1* to regulate its transcription. Treatment with DSF induced cystic renal epithelial cell death which should be mediated by the downregulation of PD-L1 and the activation of CD8+ T cells in *Pkd1$^{RC/RC}$* kidneys. ALDH1A1 can also bind with the promoter of *CCL2* to regulate its transcription, which is responsible for the recruitment of macrophages. Treatment with DSF and mesoporous silica nanoparticles (MSN) conjugated with PD-L1 and CDH16 antibodies has a synergistic effect on cyst growth.

Conclusions: ALDH1A1 is a novel transcription factor which binds the promoters of specific genes, such as *PD-L1*, *CCL2* and fibrotic genes. Targeting ALDH1A1 with its inhibitor either alone or in combination with nanoparticle-mediated PD-L1 antibody is a novel therapeutic strategy for ADPKD.

TH-PO411

New Therapy for Early-Stage Polycystic Kidney Disease: Combination of Difelikefalin and Tolvaptan

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Background: We have reported that difelikefalin, a partial agonist of kappa opioid receptors, produces a centrally mediated water diuresis presumably by inhibiting the central release of vasopressin (AVP). Since plasma AVP is elevated and participates in mediating polycystic kidney disease (PKD), we tested the hypothesis that difelikefalin would be superior to the V2 AVP antagonist, tolvaptan, in slowing progression of early-stage PKD.

Methods: Three-month old PKD mice were divided into 4 groups and were treated daily (dose titrated to decrease urine osmolality) for 3-months with either difelikefalin, tolvaptan, combination of difelikefalin and tolvaptan (D+T), or vehicle. Glomeruli filtration rate (GFR; beginning, midterm, endpoint) and total kidney volume (TKV, calculated as length, width, and depth of kidneys after mice were sacrificed) were measured in each group. Metabolic studies were also performed to measure 24-hour urine output and water intake.

Results: The results demonstrated that in contrast to vehicle treatment, difelikefalin, tolvaptan, and D+T each prevented a significant decline in GFR during the 3-month PKD disease progression. However, at the termination of study only D+T markedly reduced TKV compared with vehicle treated PKD mice (188 ± 12 vs 228 ±10 mm^3, resp.). In other studies, it was shown that the same age PKD mice treated for 3-months with difelikefalin combined with a half dose of tolvaptan (D+1/2T) was as efficacious in preventing a decline in GFR and suppressing an increase in TKV as D+T. Compared to baseline levels, water intake and urine output were significantly elevated in PKD mice treated with tolvaptan and D+T. Importantly, PKD mice treated with D+1/2T had significantly reduced urine output and water intake than PKD mice treated with tolvaptan alone or D+T.

Conclusions: Together, these findings suggest that difelikefalin not only potentiates the effect of tolvaptan but also allows a reduced dose of tolvaptan to achieve the same protection of renal function and kidney size, but with less polyuria and polydipsia. Thus, the combination of half-dose tolvaptan and difelikefalin is superior to tolvaptan alone in maintaining GFR and TKV and causes fewer side effects. (Funding DoD W81XWH-22-1-0046)

Funding: Other U.S. Government Support

TH-PO412

First-in-Human Study of an mTORC1-Selective Inhibitor for the Treatment of ADPKD

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Background: There are no disease modifying therapies currently available for patients with autosomal dominant polycystic kidney disease (ADPKD). The mechanistic target of rapamycin complex 1 (mTORC1) is a protein kinase complex and key regulator of cellular metabolism and proliferation that promotes cyst formation and growth. We are developing a mTORC1-selective inhibitor to slow kidney disease progression in patients with ADPKD while reducing the incidence of mTORC2-associated toxicities that have limited other rapalogs in ADPKD clinical trials. In addition to demonstrating selectivity for mTORC1 inhibition over mTORC2 inhibition, our compound has previously been demonstrated to reduce disease burden in ADPKD animal models. The objective of this first-in-human study was to assess the safety, tolerability and pharmacokinetics of single ascending doses of our compound in healthy adult volunteers.

Methods: In this double-blind, single ascending dose (SAD) study, we enrolled healthy adult volunteers into 4 sequential ascending dose cohorts. Subjects were randomized to receive our compound or placebo. Safety, tolerability and pharmacokinetics were assessed at baseline and at multiple timepoints after dosing.

Results: In this SAD study, our compound was safe and well tolerated at all dose levels examined. All adverse events related to our compound were mild. Concentrations of our compound increased with increasing doses.

Conclusions: Our compound was safe and well tolerated after a single dose in healthy volunteers. A planned phase 1b, multiple ascending dose study in patients with ADPKD will evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics with repeated doses of our compound.

Funding: Commercial Support - Janssen R&D

TH-PO413

Hypoxia-Inducible Factor-Prolyl Hydroxylase (HIF-PHD) Inhibitor Accelerates Liver Cyst Growth in Autosomal Dominant Polycystic Kidney Disease

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Background: It has been reported that hypoxia-inducible factor prolyl hydroxylase (HIF-PHD) inhibitor promotes renal cyst formation due to activation of HIF. However, the effect on liver cysts is unclear. In this study, we will analyze the effects of HIF-PHD inhibitor on liver cysts and their mechanisms.

Methods: We used *Pkd1* conditional knockout mice (*Pkd1*$^{flox/flox}$ *Mx-1-Cre* mice). Mice were injected with polyinosinic-polycytidylic acid for 6 consecutive days at 5 days of age to inactivate *Pkd1*. Both cystic and non-cystic mice were randomly assigned to vehicle-only and enarodustat-treated groups (non-Cystic (CT), non-Cystic (Ena), Cystic (CT) and Cystic (Ena) group). Enarodustat was mixed in feed. Mice were sacrificed at 8 weeks of age. We analyzed the phenotype of cystic livers by liver/body weight ratio (LV/BW), and cystic index (CI) which was defined as the percentage of areas occupied by cysts. For evaluation of cell proliferation, immunohistochemical staining for proliferating cell nuclear antigen (PCNA) was performed. We also performed western blotting of signaling pathway of cyst growth by using whole liver.

Results: There was no significant difference in body weight among 4 groups. Mice treated with enarodustat exhibited a significant high level of hematocrit in both non-Cystic (CT) and Cystic (Ena) groups ($p<0.01$). There was no significant difference in LW/BW, but the Cystic Index (CI) of liver was significantly elevated in Cystic (Ena) group (30.8±8.5%) than in Cystic (CT) group (18.0±5.9%; $p<0.05$). Masson-Trichrome staining showed accelerated liver fibrosis in the Cystic (Ena) group. PCNA positive cells in the cystic epithelial cells was higher in the Cystic (Ena) group than in the Cystic (CT) group ($p=0.02$). In immunohistochemical staining of glucose transporter 1, the positive area rate was significantly higher in the Cystic group than in the non-Cystic group and was significantly expressed in the Cystic (Ena) group. Western blotting showed that phosphorylated Erk and phosphorylated p70S6K tended to be upregulated in the Cystic (Ena) group.

Conclusions: HIF-PHD inhibitor accelerated liver cyst formation via proliferation of cyst lining cells by activating the MAPK pathway and mTOR pathway.

TH-PO414

Time-Restricted Feeding and Autosomal Dominant Polycystic Kidney Disease: A Pilot, Randomized Clinical Trial

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most commonly inherited progressive kidney disease leading to cyst growth. Time-restricted feeding (TRF) is a novel fasting regimen that restricts eating to a particular window (typically 8 hrs/day) which could slow cyst growth based on preclinical models.

Methods: A 12-month, randomized controlled, single-blind, behavioral dietary intervention was utilized to compare TRF vs. a healthy eating advice without TRF control group (HE). Participants underwent baseline and 12-month measurements, including adherence via meal logging (primary outcome), anthropometric measures, blood/urine sampling, and magnetic resonance imaging (MRI) to determine height adjusted total kidney volume (htTKV) and abdominal adiposity (exploratory outcomes). The behavioral intervention sessions were taught by a registered dietician via zoom with classes held weekly for the 1st month and then monthly. Independent t-tests and Pearson's bivariate correlations were performed.

Results: Twenty-nine participants were randomized (TRF n=14, HE n=15) including (23 females (F) 48±9 yrs of age (mean±s.d.), body mass index (BMI) 32.0 ±5 kg/m^2, estimated glomerular filtration rate 75±24 ml/min/1.73m^{2,} and htTKV 710 [334,1018] ml/m (median [IQR]). 71% (n=10) of TRF and 87% (n=13) of HE participants completed the intervention. The eating window was 9.5±0.2 hours for TRF (60% achieving the 8-hour window) and 12.1±0.1(mean±s.d.) for HE groups ($p=0.07$). Likelihood to adhere to TRF at 12 months was 8±2 points (10-point likert scale). Both groups lost weight: -3.7 [-8.1,2.6] % and -3.6 [-8.1,-0.4] % (median[IQR]) in the TRF and HE group, respectively. Annual percent change in htTKV was 2.8 [0.8,4.3] % and 4.0 [-2.4,11.5] % in the TRF and HE groups, respectively. Both change in weight ($r=0.674$, $p=0.0002$) and change in visceral adipose volume ($r=0.54$, $p=0.009$) were positively correlated with change in htTKV.

Conclusions: Both TRF and HE groups lost modest weight after the 12-month intervention. The 8-hour eating window appeared to be difficult to adhere to in the TRF group, although satisfaction of adherence was high. Weight and adiposity loss may be more important drivers of kidney growth than timing of eating.

Funding: NIDDK Support, Private Foundation Support

TH-PO415

Development of a Clinical Trial Enrichment (CTE) Tool for Autosomal Dominant Polycystic Kidney Disease

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Background: Despite the regulatory advances in ADPKD including the qualification of total kidney volume (TKV) as a prognostic enrichment biomarker and its designation by the FDA as a reasonably likely surrogate endpoint, the clinical development paradigms for PKD remain challenging.

Methods: Registry (Mayo, Emory, Colorado), longitudinal (CRISP), and RCT data (HALT) were curated and mapped to Clinical Data Interchange Standards Consortium Study Data Tabulation Model (CDISC SDTM) standards. Model-Informed Drug Development (MIDD) approaches to predict time to end-stage renal disease (ESRD) were employed with estimated glomerular filtration rate (eGFR) decline and total kidney volume (TKV) as longitudinal markers. The data was divided with 80% for training and 20% for validation. To build the joint model, we identified the appropriate longitudinal progression model, the appropriate time to event ESRD model, and incorporated the impact of longitudinal markers on event hazard.

Results: Two base models that captured the overall trend of TKV and eGFR were examined and the one with a lower Akaike Information Criteria (AIC) score was chosen. Covariates were: Age of diagnosis, baseline age, baseline eGFR, and baseline log(TKV) as continuous covariates Race, sex, and presence of hypertension at baseline as categorical covariates Age of diagnosis, baseline age, baseline TKV, and sex as covariates for the TKV longitudinal model Baseline age, baseline eGFR, race and baseline TKV as covariates for the eGFR longitudinal model For the time-to-event model, the Weibull distribution was selected based on the lowest AIC (best fit) before incorporating longitudinal markers. A graphical user interface (GUI) for the CTE tool was constructed for the creation of virtual simulations of disease progression. The tool models different trial durations, population sizes, and hypothetical magnitude of drug effects on TKV/eGFR progression and predict their impact on ESRD.

Conclusions: A quantitative tool can be utilized to model disease progression trajectories in defined ADPKD subpopulations and potentially simulate impact on ESRD based on theoretical drug effects on TKV/eGFR progression. The tool may be beneficial in clinical trial design to ultimately benefit ADPKD patients.

Funding: Other U.S. Government Support, Commercial Support - Sanofi, Private Foundation Support

TH-PO416

Kynurenines and Change in Body Mass Index in Autosomal Dominant Polycystic Kidney Disease

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Background: We have previously described that overweight and obesity are associated with kidney disease progression in individuals with early-stage autosomal dominant polycystic kidney disease (ADPKD). We have also reported dysregulated kynurenine metabolism, which associated with kidney disease severity, in early-stage patients with ADPKD. As the tryptophan-kynurenine pathway has been reported to be dysregulated in obesity, and kynurenines can induce and potentiate oxidative stress and

inflammation, we hypothesized that baseline kynurenine circulating concentrations would associate with change in BMI patients with ADPKD.

Methods: 357 participants with ADPKD and estimated glomerular filtration rate (eGFR) >60 ml/min/1.73m^2 who participated in HALT Study A and had repeated measurements of kynurenines, BMI, and covariates were included. Twelve key tryptophan metabolites were previously measured in plasma using a validated liquid chromatography-mass spectrometry assay. The time-varying associations between kynurenines (individual mean and mean change over time) and change in BMI over 48-months were assessed using linear mixed effects regression models.

Results: Mean±s.d. age was 38±8 years, eGFR was 90±17 ml/min/1.73m^2, and height-adjusted total kidney volume was 724±413 ml/m^2, baseline BMI was 27.0±4.8 kg/m^2. Greater individual log-transformed mean concentrations of kynurenic acid (b-estimate 1.71 [0.41, 3.01]), and quinolinic acid (β-estimate 2.13 [0.00, 4.25) and a lower log-transformed mean change in picolinic acid over time (β-estimate -0.52 [-0.13, -0.95]) were associated with greater increase in BMI after adjustment for demographics, study randomization, eGFR, baseline height-adjusted kidney volume, and genotype.

Conclusions: Several kynurenines were associated with change in BMI in ADPKD patients. Further research should evaluate whether kynurenines could serve as a biomarker of obesity-associated kidney growth in patients with ADPKD.

Funding: NIDDK Support

TH-PO417

Assessing Formoterol Treatment in a Mouse Model of Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a disease caused by mutations in the genes PKD1 and PKD2 that results in cyst growth within the kidney and over time leads to renal failure. Tolvaptan is currently the only drug approved for treating ADPKD, but it is only modestly effective and has significant side effects. ADPKD is associated with metabolic dysfunction. Treating the metabolic dysfunction in ADPKD may be therapeutic. A metabolic modulator, formoterol, is a beta-2 adrenergic receptor agonist commonly prescribed for chronic obstructive pulmonary disease. Our previous research has demonstrated the effectiveness of formoterol in treating some forms of chronic kidney disease (CKD). Metabolic dysfunction is thought to be corrected by formoterol's ability to stimulate mitochondrial biogenesis. We hypothesize that formoterol treatment in a mouse model of ADPKD will be therapeutic in reversing, stopping, or slowing disease progression.

Methods: RC/RC mice, a model of ADPKD generated using mutations in PKD1 from a human family, will be treated using osmotic mini pumps filled with formoterol for six months at 1 mg/kg body weight/day after they reach the age of three months. Pumps will be exchanged 4-6 times over the course of treatment with blood and urine collections at each surgery for further analysis. Cohorts of 12 males and 12 females will be treated to address any sex differences in treatment; 6 mice treated and 6 mice untreated/receiving vehicle (DMSO) in each cohort. Mice will be weighed weekly. MRIs will be performed at three months and at end of the experiment on a representative sample of the mice to assess cyst burden. After six months of treatment the mice will be sacrificed, and the kidney, liver, heart, and spleen will be harvested for histological, protein, and nucleic acid-based analyses. Formoterol will also be tested in the PCK rat model of PKD.

Results: Mice Males: To date, a trend toward lower kidney/body weight (p=0.28) and liver/body weight (p=0.07) ratios is observed in the formoterol-treated compared to the vehicle-treated mice, which may indicate decreased cystogenesis. Females: In progress **Rats** In progress.

Conclusions: Preliminary data suggest that formoterol may have an effect on cyst growth, though additional cohorts of treated and untreated mice need to be studied.

Funding: Veterans Affairs Support, Private Foundation Support

TH-PO418

Validation of the Mayo Imaging Classification System for Predicting Renal Outcome in ADPKD

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Background: The Mayo Imaging Classification is used to predict the rate of disease progression in patients with autosomal dominant polycystic kidney disease (ADPKD). The goal of this study was to validate its ability to predict renal prognosis in a large cohort of patients with ADPKD.

Methods: Included were ADPKD patients with 'typical' disease, at least one height-adjusted total kidney volume (HtTKV) measurement, ≥3 eGFR estimates and ≥1 year follow-up. The stability of the classification, kidney growth rate and eGFR decline rate were calculated for each Mayo HtTKV class at various timepoints. The observed eGFR decline rate at these timepoints were compared to the values predicted by the Mayo Clinic formula for future eGFR. Kaplan-Meier survival analysis was performed to predict end stage kidney disease (ESKD) using Mayo HtTKV class as a predictor variable.

Results: We included 619 patients with a mean age of 47 ± 11 years and an eGFR of 63 ± 25 ml/min/1.73m^2 at baseline. The majority of patients (70.0 - 88.9%) remained in their baseline Mayo HtTKV class after 6 years of follow-up. The mean eGFR decline and TKV growth rates during a mean follow-up duration of 5.0 ± 2.2 years were -3.26 ± 2.49 ml/min/1.73m^2/year and 5.29 ± 3.97 %/year, respectively. There was considerable variation in kidney growth and eGFR decline rates within each Mayo HtTKV class. The observed eGFR decline at follow-up was not significantly different from the predicted values for Mayo HtTKV classes 1A, 1B, 1C and 1D. However, the observed eGFR decline of Mayo HtTKV class 1E was less than predicted. This was also observed in patients aged <40 years at baseline and in patients with *PKD2* mutations. The classification was a strong predictor for ESKD.

Conclusions: The Mayo Imaging Classification demonstrates acceptable stability over time and is predictive of the rate of eGFR decline albeit with wide inter-individual variations. The ability to predict future eGFR decline for individual patients might be improved by developing equations that include additional prognostic covariates.

TH-PO419

Applicability of Mayo's Autosomal Dominant Polycystic Kidney Disease Prognostic Tool in the Southeast Asian ADPKD Population

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Background: Mayo autosomal dominant polycystic kidney disease (ADPKD) prognostic tool revolved around the height-adjusted total kidney volume ($HtTKV_0$) measurement using MRI at a single point of time adjusted with age_0 and it was recognized as a strong predictor for kidney disease progression in patients with ADPKD. This study reports 24-month prospective longitudinal studies examining the applicability of the Mayo ADPKD prognostic tool in the Southeast Asian cohort in a tertiary center in Malaysia.

Methods: Convenience sampling was completed on March 2021. Patients were subjected to a single non-contrasted T2W-MRI kidney scan using the ellipsoid method with subsequent yearly blood samples collected for analysis. Total kidney $volume_0$ (TKV_0) was measured by 2 radiologists and the average of 2 results was recorded. Correlation of glomerular filtration rate generated from the Mayo ADPKD prognostic tool ($eGFR_{Mayo}$) and serum estimated glomerular filtration rate of patients according to 2009 $CKD\text{-}EPI_{creatinine}$ ($eGFR_{2009CKD\text{-}EPI}$) were tested with Spearman correlation coefficient and Bland-Altman analysis.

Results: A total of 50 patients were enrolled with a median age of 39.5 years (33.5, 58.0) and predominantly female (54%), and of Chinese (60%) ethnicity. Median TKV_0 was 1233.8cm^3 (697.2, 1995.8) and $HtTKV_0$ was 727.9ml/m (447.0, 1180.9). Three patients dropped out at month 24. $eGFR_{Mayo}$ correlated very strongly with $eGFR_{2009CKD\text{-}EPI}$ during the 24 months study with R_{S0}=1.000 (bias of -0.196, precision=0.395), R_{S12}=0.972 (bias of -0.204, precision=8.300), and R_{S24}=0.952 (bias of 4.670, precision=10.930) respectively, p<0.001. $eGFR_{Mayo}$ demonstrated an accuracy of 42.6 – 98% within 10mls/min/1.73m^2 of serum $eGFR_{2009CKD\text{-}EPI}$.

Conclusions: Mayo's ADPKD prognostic tool demonstrated its applicability to the Southeast Asian ADPKD population with a very strong correlation to $eGFR_{2009CKD\text{-}EPI}$, low bias, and high precision. Long-term data with a larger sample size needs to be evaluated in future studies.

Funding: Government Support - Non-U.S.

Spearman correlation coefficient & Bland-Altman analysis

Variables	Sample size, n	Spearman's correlation coefficient (Rs)	p-value	Bias (Mean difference)	Precision (±1.96SD of Mean Difference)	Accuracy (P10),%
eGFR Mayo* vs eGFR 2009CKD-EPI at 0 month	50	1.000	0.000	-0.196	0.395	98
eGFR Mayo* vs eGFR 2009CKD-EPI at 12 months	50	0.972	0.000	-0.204	8.300	58
eGFR Mayo* vs eGFR 2009CKD-EPI at 24 months	47	0.952	0.000	4.670	10.930	42.6

*Web app by Mayo Foundation & Medical Education & Research

TH-PO420

Tolvaptan Use and Prescribing Patterns in Patients with Autosomal Dominant Polycystic Kidney Disease: A Multicenter Real-World Experience

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common genetic disease leading to End Stage Kidney Disease. Tolvaptan was approved and is being used to treat patients with rapidly progressing disease. In this study we describe the real-world experience of Tolvaptan use among patients with ADPKD.

Methods: We retrospectively identified adult patients with ADPKD enrolled in the Risk Evaluation and Mitigation Strategy (REMS) program and treated with Tolvaptan at the University of Kansas Medical Center (KUMC) and University of Iowa Hospitals and Clinics (UIHC) from 2018 to 2023. The investigators abstracted data and treating physicians reviewed and confirmed the data. We performed descriptive analysis of the patients' demographics, baseline labs, Tolvaptan prescribing trends, reasons for stopping treatment, and frequency of imaging surveillance.

Results: The study includes 134 patients, 115 from KUMC and 19 from UIHC. The average age of start of Tolvaptan treatment was 42.67 and 36.17 years respectively for KUMC and UIHC. Male to female ratio was approximately 1:1 for KUMC and 1:2 for UIHC. In the KUMC cohort, 87% were Caucasian, and the remaining 13% comprised of African American and Hispanic ethnic groups. In the UIHC cohort, 95% were Caucasian. By March 2023, 63% and 58% remained on Tolvaptan and of the KUMC and UIHC

cohorts respectively. The two major reasons for discontinuing Tolvaptan included intolerance of polyuria and polydipsia (26% in KUMC and 50% in UIHC) and renal transplantation (17% in KUMC and 13% in UIHC). The average fluid intake was 5.23 and 3.36 Liters respectively in the KUMC and UIHC cohorts. The starting dose combination of 45 mg (AM)/15 mg (PM) was prescribed to most patients at both KUMC (90%) and UIHC (89%). For many patients, prescribing physicians had to considerably titrate Tolvaptan doses to moderate side effects.

Conclusions: The findings of this descriptive study provide valuable insights into the real-world use of Tolvaptan in treating patients with ADPKD. A higher percentage of patients with ADPKD are discontinuing Tolvaptan compared to trials findings due to polyuria and polydipsia. The study also highlights the need for considerable titration of Tolvaptan dose to manage symptoms.

TH-PO421

Kidney Function Decline in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Patients: Assessment of Real-World Effectiveness of Tolvaptan

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Background: In clinical trials, tolvaptan led to a slower decline in kidney function (vs placebo) among ADPKD patients at risk of rapid progression. The objective of the current study is to evaluate real-world effectiveness of tolvaptan by comparing annual rate of change in kidney function, as measured by eGFR, in adult ADPKD patients treated with and without tolvaptan.

Methods: From May 2019 to September 2022, 57 US nephrologists completed a web-based survey using medical records of ADPKD patients treated with tolvaptan for ≥2 year (cases). A cohort of ADPKD patients in Mayo class 1C to 1E not treated with tolvaptan was obtained from CRISP, HALT-PKD (data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases) and OVERTURE studies (controls). Cases and controls were matched 1:1 on baseline age, gender and chronic kidney disease (CKD) stage. Kidney function decline was compared between cases and controls using mixed models, which included treatment, time, and a treatment-by-time interaction as fixed effects and patient-specific intercepts and slopes (for time) as random effects.

Results: Of the 149 cases treated with tolvaptan, controls matched for age, sex and CKD stage were identified for 110 cases. Among these 110 matched pairs, the majority were male (60%), aged 43 (SD: 10.1) years on average, and 76% were in CKD stage 3a or earlier. Mean eGFR at baseline was 60 mL/min/1.73m^2 among cases and 63 mL/min/1.73m^2 among controls. The annual change in eGFR was -2.23 mL/min/1.73m^2 among cases vs -3.62 mL/min/1.73m^2 among controls with a statistically significant difference of 1.40 mL/min/1.73m^2 per year (95% CI: 0.05, 2.74, p =0.042). A second analysis, whereby cases and controls were matched on baseline age, gender and eGFR resulted in 98 matched pairs. In comparison of the 98 matched pairs tolvaptan was associated with a trend in reduction of decline rate by 1.18 mL/min/1.73m^2 per year (95% CI: -0.22, 2.58, p =0.097).

Conclusions: In the current analysis, tolvaptan showed real world effectiveness in slowing decline in eGFR when compared to matched historical controls, consistent with its efficacy in clinical trials.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

TH-PO422

Liver Safety of Tolvaptan in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD): Interim Data from a European Union Post-Authorization Safety Study (EUPASS)

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Background: After risk of drug-induced liver injury was detected during tolvaptan clinical development for the treatment of ADPKD, a real-world pharmacovigilance study was required as a condition of EU regulatory approval. We provide an interim-analysis of 6-years of liver safety data from EUPASS.

Methods: This is an interim analysis from a prospective, observational study enrolling patients prescribed tolvaptan for ADPKD in everyday clinical practice. Data are obtained through physician records collected as part of regular standard of care. Per the prescribing label, liver enzymes are monitored monthly for the first 18 months of treatment and once every 3 months thereafter, and patients and providers are required to report adverse events suggestive of liver injury. The data collection period was Oct 2016–Apr 2022. An independent hepatic adjudication committee (HAC) evaluates all DILI cases in EUPASS.

Results: At data cutoff, 2,074 patients had received at least one dose of tolvaptan (median follow-up, 528 days). Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) levels ≥3 times upper limit of normal (ULN) were found for 65 patients (3.1%). Among these patients, 35 (1.7%) had elevation of ALT/AST > 3 to ≤ 5 times ULN, 21 (1.0 %) had elevation of > 5 to ≤ 10 times ULN, 9 (0.4 %) > 10 times ULN. Tolvaptan was interrupted or withdrawn in 59/65 (90.8%) participants with confirmed ALT/AST ≥3 times ULN, with most transaminase elevations and adverse events resolved or resolving at data cutoff. No laboratory results met criteria for high-risk liver injury (Hy's Law). As per the assessment of HAC, there was no dose-response relationship.

Conclusions: Regular monitoring facilitates prompt detection of liver adverse events and intervention to reduce risk of severe injury. Data from interim analysis indicate that monitoring and risk minimization measures are effectively mitigating the risk of liver injury. No Hy's law cases/deaths have been reported.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc., Princeton, NJ, USA

TH-PO423

Integrating Multi-Omics for Precision Medicine: Identification of Drug Targets and Biomarkers for ADPKD from Large Patient Cohorts

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of kidney failure. There is an unmet medical need for biomarkers (early diagnosis, reliable prognosis) and for effective and safe therapy. Especially research on the molecular drivers of ADPKD progression is challenging due to the lack of available biopsies. An integrative approach utilizing patient samples and ADPKD models can bridge this gap.

Methods: Blood samples from NURTuRE-CKD participants (200 ADPKD, 2,000 other CKD) were subjected to genotyping and deep mRNA-Seq. Selected serum and urine samples were analyzed by proteomics and metabolomics. Whole-exome sequencing (WES) data were provided by the NURTuRE consortium. Cyst-forming renal organoids were differentiated from human iPSCs carrying a loss-of-function mutation in PKD1 and subjected to snRNA-Seq.

Results: In NURTuRE omics data we observed that: (1) ADPKD patients' blood transcriptomes constitute a cluster that is distinct from age-, sex- and eGFR-matched non-ADPKD samples (other CKD), (2) several proteins are differentially abundant in ADPKD vs. other CKD urine proteomics, (3) among NURTuRE-CKD patients, WES revealed carriers of PKD1 and PKD2 pathogenic mutations who had previously not been diagnosed with PKD and may represent early or pre-onset cases of ADPKD. To provide more insight into early disease mechanisms, we performed snRNA-Seq of human iPSC-derived cyst-forming renal organoids. To leverage their combined power, we used these datasets reflecting different aspects of the disease to build a multi-layered similarity network while maintaining source information. This network was incorporated into a larger graph database, which allows for the expansion of feature information and the generation of embeddings for biological interpretation facilitated by machine learning.

Conclusions: Our integrated multi-omics analysis framework utilizes patient samples and cyst-forming organoids to enable the analysis of molecular mechanisms underpinning ADPKD, especially in early disease stages. This will facilitate the discovery of diagnostic or prognostic biomarkers and novel targets.

TH-PO424

Effects of Salt and Protein Intake on Polyuria in Tolvaptan-Treated ADPKD Patients: A Randomized Controlled Trial

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Background: The only renoprotective treatment in Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a vasopressin V2-receptor antagonist (V2RA). However, aquaresis-associated side effects limit tolerability. We investigated whether salt and protein intake influence urine volume and aquaresis-related endpoints in V2RA-treated ADPKD patients.

Methods: In this randomized, controlled, double-blind, crossover trial, ADPKD patients treated with a maximally tolerated dose of a V2RA were included. While on a low salt (≈6 g/24h) and low protein (≈0.8 g/kg/24h) diet, patients were given additional salt and protein during a baseline study period to mimic regular intake, which was replaced by placebo during four 2-week periods: low salt/low protein, low salt/regular protein, low protein/regular salt and regular protein/regular salt intake in random order. Primary endpoint was change in 24h urine volume. Secondary endpoints were change in quality of life, measured glomerular filtration rate (mGFR), blood pressure and copeptin level.

Results: Twelve patients (49±8 years, 25.0% male, mGFR 59±23 mL/min/1.73m^2) were included. Baseline salt- and protein intake was 10.8±1.3 g/24h and 1.2±0.2 g/kg/24h. During the low salt and low protein treatment periods, intake significantly decreased to 5.8±1.6 g/24h and 0.8±0.1 g/kg/24h respectively. Baseline 24h urine volume (5.9±1.2 L) diminished to 5.2±1.1 L (-11%, p=0.004) on the low salt & low protein and to 5.4±0.9 L (-8%, p=0.04) on the low salt intake. Reduction in 24h urine volume tended to be greater in patients with lower urine osmolality (-16 vs -7%, p=0.1). Polyuria QoL scores improved with changes in urine volume. mGFR decreased on the low salt & low protein intake, while mean arterial pressure did not change during the study periods. Plasma copeptin decreased significantly during low salt and low protein periods.

Conclusions: Changes in intake of salt and protein have only a minor effect on urine volume in V2RA-treated ADPKD patients. In subjects with most complete vasopressin blockade, i.e. those with the lowest baseline urine osmolarity, this antipolyuric effect tended to be most pronounced. Reduction of osmolar intake decreased plasma copeptin and might therefore improve the renoprotective effect of a V2RA.

Funding: Private Foundation Support

TH-PO425

Eight Years of Canadian Real-World Assessment of Tolvaptan in ADPKD: C-MAJOR Study and Safety Monitoring and Distribution Program

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Background: Tolvaptan is approved in Canada for slowing renal function decline and kidney enlargement in patient with ADPKD. As required by Health Canada, a patient registry study evaluating long-term clinical outcomes (C-MAJOR) and a hepatic safety monitoring and distribution program (HSMDP) to mitigate risk of liver injury were implemented. The aim of this interim analysis is to describe patient characteristics at tolvaptan initiation from the C-MAJOR study and to report on liver transaminase elevation rates and treatment persistence through the HSMDP.

Methods: C-MAJOR is a non-interventional, observational, multi-centre study of ADPKD patients treated with tolvaptan. HSMDP ensures tolvaptan is dispensed under controlled liver function monitoring.

Results: As of February 2023, 469 patients were enrolled in C-MAJOR. At baseline, 51% were female, with a mean (SD) age of 45 (12) years, BP 129 (13)/83 (10) mmHg and eGFR 64 (28) mL/min/1.73 m². Overall, 68% were in early CKD stages 1, 2 and 3a. Total kidney volume was 1963 (1538) mL, 80% had a family history of ADPKD, 38% had a family history of early end-stage kidney disease, and 91% were at high risk of disease progression (Mayo Imaging Class 1C-D-E). The most common clinical manifestations were hypertension (84%), hepatic cysts (71%) and kidney pain (24%). From the HSMDP, 82 (3.4%) of the 2418 patients who initiated tolvaptan reported an elevation of transaminases (>3x ULN), with 11 (0.45%) meeting guidelines for permanent discontinuation. No cases of drug-induced liver injury were reported. Occurrence of ALT/AST levels greater than 3x ULN were seen up to 81 months post tolvaptan initiation and of these, 32% of the episodes occurred following the first 18 months of treatment. Treatment persistence rates at 12, 24 and 36 months were 84%, 77% and 72%, respectively.

Conclusions: This analysis provides Canadian real-world evidence that most ADPKD patients treated with tolvaptan are at high-risk of disease progression and three-year treatment persistence is similar to phase III study data. The HSMDP in Canada has been effective at avoiding the incidence of drug-induced liver injury associated with tolvaptan.

Funding: Commercial Support - Otsuka Canada

TH-PO426

Development Program of 2-deoxy-D-glucose (2DG) for the Treatment of ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by the growth of fluid-filled kidney cysts due to abnormal epithelial proliferation. We have demonstrated that ADPKD cyst epithelial cells undergo metabolic reprogramming with increased aerobic glycolysis (Warburg effect) and so are exclusively dependent on glucose for energy production. This can be exploited to treat ADPKD using an analog of glucose, 2-deoxy-D-glucose (2-DG), that inhibits glycolysis. We have shown that 2DG is effective at slowing cyst growth in both rapid and slowly progressive mouse PKD models. 2DG has previously been tested in over 200 normal human volunteers and cancer patients in both single and continuous daily dosing for up to 3 months and shown to be safe and well tolerated at doses up to 45 mg/kg/day.

Methods: We now present a new development program to advance 2DG for treatment of ADPKD. Preclinical investigational new drug (IND)-enabling activities are underway or will begin soon, including refinement of the dose-response relationship, chronic GLP toxicology studies in rodent/non-rodent species, synthesis of GMP-grade batches of drug product, and discussions with regulatory authorities.

Results: Our first-in-human study is proposed to be a multicenter Phase 1B uncontrolled, multiple ascending dose clinical trial. ADPKD patients aged 18–60 yr with eGFR >60 mL/min/1.73 m² will be enrolled in cohorts of 3 and administered single daily oral doses of 2DG for 2 weeks. The primary objective will be to assess the safety and tolerability of 2DG in ADPKD patients and to determine a recommended Phase 2 dose. The secondary objectives will be to determine the pharmacokinetics of 2DG and to identify candidate metabolic response biomarkers in patient blood and urine.

Conclusions: The results of this study will determine whether it is justified to proceed to a clinical proof-of concept study, and will also inform the design of such a trial.

Funding: Other U.S. Government Support

TH-PO427

Prognostic Model for Progression of Autosomal Dominant Polycystic Kidney Disease to Kidney Failure

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a hereditary disease that leads to kidney failure (ESKD), typically in the fifth decade of life. Given the variability between individuals in the rate of progression to ESKD there is significant unmet need for an accurate prognostic model that can predict the course of disease early in individual patients. CRISP IV is the longest extant ADPKD cohort (21 years), providing a unique opportunity to determine the association between clinical observations early in the disease and hard clinical outcomes.

Methods: Data collected from participants in the CRISP and HALT-A studies between 2001 and 2022 were modeled using multivariable Cox proportional hazards. The outcome was a composite of kidney failure (dialysis or kidney transplant) and eGFR <15 mL/min/1.73 m². Candidate dependent variables were picked on the basis of face validity, and selected for inclusion in the model by iterative forward selection.

Results: Of 759 included participants with a median follow-up of 8.2 years, 123 (16.2%) reached the composite endpoint. A prognostic model was built using 5 essential variables. Four clinical variables (serum CO_2, hemoglobin, BMI, diastolic BP) were found to add independently to this model.

Conclusions: We have developed a prognostic model that can predict kidney failure in an ADPKD patient over a time horizon of 15 years. The next step is to validate this in an external ADPKD registry cohort and create a risk calculator.

Funding: NIDDK Support

Variable	Hazard ratio	95% CI	p-value
Age – yr	1.11	[1.07;1.15]	<0.01
Sex – Male	Ref		
– Female	0.94	[0.54;1.61]	0.811
Serum creatinine (mg/dL)	19.99	[5.87;68.03]	<0.01
Mayo Imaging Class			< 0.01
1A	0.34	[0.05;2.55]	
1B	0.5	[0.26;0.97]	
1C	Ref		
1D	1.74	[1.08;2.79]	
1E	5.05	[2.72;9.36]	
Genotype – PKD2	Ref		
– PKD1	6.55	[2.02;21.29]	<0.01
Serum carbon dioxide – mmol/L	0.85	[0.78;0.93]	<0.01
Hemoglobin – g/dL	0.76	[0.63;0.92]	<0.01
Diastolic BP – mm Hg	1.02	[1.00;1.04]	0.023
Body mass index – kg/m2	1.04	[1.01;1.07]	0.022

Table. Multivariable model showing hazard ratios for the outcome of kidney failure or eGFR <15 mL/min/1.73 m2

TH-PO428

Baseline Characteristics of Participants in Statin Therapy in Patients with Early-Stage ADPKD Clinical Trial

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Background: At present tolvaptan is the only agency approved therapy to slow kidney disease in patients with faster progressing autosomal dominant polycystic kidney disease (ADPKD). However, aquaretic side effects limit use for some patients, underscoring the need for identification of additional ADPKD therapies. We previously showed that pravastatin treatment slowed kidney cystic disease progression in children and young adults with ADPKD. In order to assess whether pravastatin slows disease progression in an adult population with ADPKD we designed a randomized double blind placebo-controlled trial (NCT03273413).

Methods: 150 subjects with an ADPKD diagnosis and early stage kidney disease (eGFR ≥ 60 ml/min/1.73m²) were included in the study. Subjects were recruited nationally and study visits were conducted at the University of Colorado Renal Research Clinic. Baseline visits were ongoing between 2017 and 2022. All participants were randomized to receive either study drug, 40 mg of pravastatin or matching placebo each day for a 2-year period. Baseline assessments included demographics, medical history, total kidney volume (TKV) and renal blood flow (RBF) by magnetic resonance imaging, Glofil-125

(Iothalamate-125) nuclear medicine assessment of measured GFR (mGFR) and routine blood chemistries including creatinine for eGFR by CKD-Epi equation.

Results: Participant mean age and standard deviation was 40 ± 10 years and 65% of subjects were female. There was good agreement between baseline eGFR (90 ± 20 ml/min/1.73m^2) and mGFR (92 ± 20 ml/min/1.73m^2) r = 0.7, P< 0.0001. Renal blood flow (682 ± 193 ml/min/1.73m^2) was positively correlated with both eGFR (P<0.0001) and mGFR (P<0.0001) and negatively correlated with natural log height corrected TKV (P< 0.004) Median height corrected TKV ml/m (IQR) 687 (468,1026).

Conclusions: The target goal for subject recruitment was attained. Subject recruitment spanned a longer than expected period due to travel and University restrictions related to the COVID-19 epidemic. The clinical trial is currently ongoing with the last participant scheduled to complete the end-of-study 2-year visit in March 2024.

Funding: Other U.S. Government Support

TH-PO429

How Well Do Risk Assessment Guidelines Perform for ADPKD?

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Background: The approval of Tolvaptan for treatment of ADPKD heralds a new era when mechanism-based therapy is now possible. However, Tolvaptan is an expensive drug associated with potentially serious side-effects and is currently reserved for patients at high-risk for progression to ESKD. Two sets of risk assessment guidelines for ADPKD are now available based on the consensus of two panels of nephrologists from Canada and Europe. However, how well do these guidelines perform in risk assessment has not been formally assessed.

Methods: We conducted a prospective study in 474 patients with typical imaging pattern of ADPKD by MRI who also had detailed clinical and laboratory data. We used age- and height-adjusted total kidney volume to derive the Mayo Clinic Imaging Class as a "gold-standard" for risk assessment (i.e. low-risk: 1A-1B; high-risk: 1C-1E). We then applied the revised Canadian guidelines (Can J Kidney Health Dis. 2018) and the updated European guidelines (NDT 2022) to our patient cohort to assess their performance.

Results: The study cohort consisted of 286/474 (60%) high-risk patients with MCIC 1C-1E. Applying the updated Canadian risk assessment algorithm resulted in exclusion of 245/474 (52%) patients including 86/286 (30%) of the high-risk patients. The resultant cohort (229/474) was enriched with 88% high-risk patients but also included 12% of low-risk patients. The updated European guidelines provide a 3-step hierarchal algorithm, when applied resulted in exclusion of 55% (157/286) of high-risk patients. During the last step, 122 patients could not be classified due to a lack of eGFR slope information. The resultant cohort (180/474) was enriched with 72% high-risk patients but also included 28%(51/180) of low-risk patients.

Conclusions: Risk assessment in ADPKD is evolving process that needs to be redefined by new clinical data and test technologies. Clinical guidelines should be evaluated using real-life data and those that enrich high-risk patients while minimize low-risk patients have most clinical utility.

Funding: Government Support - Non-U.S.

TH-PO430

Identification and Characterization of Biomarkers from Cell-Free DNA Methylation in ADPKD Patients

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Background: ADPKD is caused by mutations of PKD1/PKD2. However, there is no proper biomarker for this disease. Recently, circulating cell-free (cf) DNA has attracted attention as biomarkers in the context of prediction, prognostication, and monitoring of drug response in human diseases.

Methods: We isolated cfDNA from plasma and urine and performed EM-Sequencing to identify cfDNA methylation signatures and the differential methylation regions (DMRs) with 5% methylation difference between the pediatric ADPKD patients and age-matched healthy individuals. The DMRs associated signaling pathways were analyzed with gene set enrichment analysis (GSEA).

Results: We identified 2,054 and 30,511 DMRs in cfDNA from plasma and urine, in which 1,409 (69%) and 24,707 (81%) DMRs were aligned to protein-coding genes, 43 (3%) and 7453 (30%) DMRs were located on the promoters of those protein-coding genes, and 26 of 43 (60%) and 7365 of 7453 (99%) DMRs were hypomethylated in ADPKD patients. The criteria used to identify DMRs as biomarkers include that, 1) their methylation is three times more than the initial 5% differential methylation in ADPKD patients versus healthy controls in either plasma or urine; 2) they are located to the promoter regions of protein-coding genes; and/or 3) they are constantly hypo- or hyper-methylated in both plasma and urine. We identified 7 hypo- and 5 hyper-methylated DMRs in plasma only, and 1754 hypo- and 55 hypermethylated DMRs in urine only, and those DMRs only matched criteria 1 and 2. Importantly, we identified 19 DMRs in both plasma and urine, and 10 of these 19 DMRs matched all three criteria. These 10 DMRs associated protein-coding genes encode inflammatory cytokine (CD70), metabolic related proteins (PON1, LOXL1, CERS3, ENOSF1), neurological synapse related factor (SDK1), epigenetic regulators (PRDM8, CMTR2) and transcriptional regulators (CIZ1, NBL1), which were all hypomethylated and their mRNA levels were increased in *Pkd1* mutant mouse kidneys. The diverse function of these 10 proteins/factors and the associated pathways supports the roles in regulation of cyst growth in ADPKD.

Conclusions: This study identifies cfDNA methylation signatures and the differential methylation regions in ADPKD patients, and the 10 candidate DMRs and the associated genes and pathways are potential biomarkers and novel mechanisms for ADPKD progression.

Funding: NIDDK Support

TH-PO431

Evaluation of Tolvaptan Effect in Autosomal Dominant Polycystic Kidney Disease (ADPKD) Using Inverse Probability of Censoring Weighting for Long-Term Extension Data

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Background: In long-term extension (LTE) clinical trials switching treatment arms is common among placebo participants. Inverse Probability of Censoring Weighting (IPCW) was invented to recreate balanced treatment arms by assigning weights to patients without switching. Another possible issue is no comparators exist during LTE trials, leading to bias in comparisons between treatments when including LTE data. In this research, we aim to create a control group for treatment comparison and determine whether IPCW decreases bias raised from crossover in LTE data.

Methods: Using data from TEMPO 3:4 trial and its LTE TEMPO 4:4, we created a control group for placebo druing LTE, calculated weights using IPCW, and conducted analyses: 1) estimation of time to end stage kidney disease (ESKD) using Cox regression models; (2) estimation of average decline in eGFR between placebo and tolvaptan using mixed-effects models.

Results: IPCW method performed well in reducing errors from unbalanced treatment arms and determining effectiveness of tolvaptan with a decreased hazard ratio(HR) in Model 1(0.17 with 95% CI (0.05, 0.54)) compared to HRs estimated in Model 2, which ignored crossover and analyzed as intention-to-treat (ITT) (0.38 with 95% CI (0.20, 0.75)) and Model 3, a time-varying Cox regression model (0.22 with 95% CI (0.09, 0.56)) (Table 1). Cox regression models were adjusted by baseline age, eGFR, creatinine, sex, race, PKD diagnosed before age 35, and TKVs over time. It also adjusted biases well in Model 4 (-4.22 ml/min/1.73 m^2 per year for placebo; -2.93 ml/min/1.73 m^2 per year for tolvaptan) on average eGFR decline, compared to Model 5, which excluded placebo patients from LTE and longer years were used to estimate tolvaptan effects, and Model 6 using ITT method mentioned in Model 2 (Table 2). Mixed-effects models were used without adjustment.

Conclusions: In Cox regression and mixed-effects models, IPCW reduced bias in estimating long-term effects from crossover after creating a control group for placebo patients.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Table 1. Hazard Ratios for time to ESRD with matched LTE.

Model	Treatment	Hazard Ratio (95% CI)
Model 1 (IPCW)	Tolvaptan	0.17 (0.05, 0.54)
Model 2 (ITT)	Tolvaptan	0.38 (0.20, 0.75)
Model 3 (Time-varying)	Tolvaptan	0.22 (0.09, 0.56)

Table 2: Average declines on eGFR between placebo and tolvaptan.

Model	Treatment	n	Slope/year (95% CI)
Method 4(IPCW)	Tolvaptan	920	-2.93 (-3.95, -1.91)
	Placebo	478	-4.22 (-5.62, -2.83)
Method 5 (No Placebo in LTE)	Tolvaptan	920	-3.27 (-3.42, -3.11)
	Placebo	478	-3.66 (-3.96, -3.37)
Method 6 (ITT)	Tolvaptan	920	-3.26 (-3.42, -3.11)
	Placebo	478	-4.28 (-4.51, -4.05)

TH-PO432

Computable Phenotype to Identify ADPKD Patients, A Validation Study

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common inherited kidney disease. Patients with ADPKD are at high risk of end-stage kidney disease as the disease lacks a cure. It is important to facilitate the recruitment of ADPKD patients in clinical trials. Here, we sought to validate a computable phenotype based on the ICD-9/10 codes for ADPKD in the electronic medical record (EMR).

Methods: We retrospectively identified 495 patients with ICD-9/10 for ADPKD or renal cysts and were following up at the University of Iowa Hospitals and Clinics (UIHC). We conducted a chart review to verify if they had ADPKD. We stratified patients into four groups: Group A, following in the nephrology clinic with ICD-9/10 codes of ADPKD; Group B, following in the nephrology clinic with ICD-9/10 codes for renal cysts; Group C, following in the non-nephrology clinic with ICD-9/10 codes for ADPKD; and Group D, following in the non-nephrology clinic with ICD-9/10 codes for renal cysts.

Results: Of the 495 patients, 134 (27%) patients were evaluated in the nephrology clinic and 360 (73%) in the non-nephrology clinic. A total of 117 patients had ICD-9/10 codes for ADPKD, where 108 (92%) had confirmed ADPKD and 9 (8%) didn't have ADPKD. A total of 377 had ICD-9/10 codes for renal cysts, where only 1 (0.3%) had

ADPKD, while 376 (99.7%) didn't have ADPKD. The overall sensitivity of the ICD-9/10 codes for ADPKD was 92.3% and the specificity was 99.7%. In the nephrology clinic, the sensitivity was 94.6% and the specificity was 100%. In the non-nephrology clinic, the sensitivity was 88.4% and the specificity was 99.7% (Figure.1).

Conclusions: Utilizing ICD-9/10 to identify patients with ADPKD is of excellent overall sensitivity, specificity, PPV, and NPP. The sensitivity tends to be higher in the nephrology clinic Vs non-nephrology clinic.

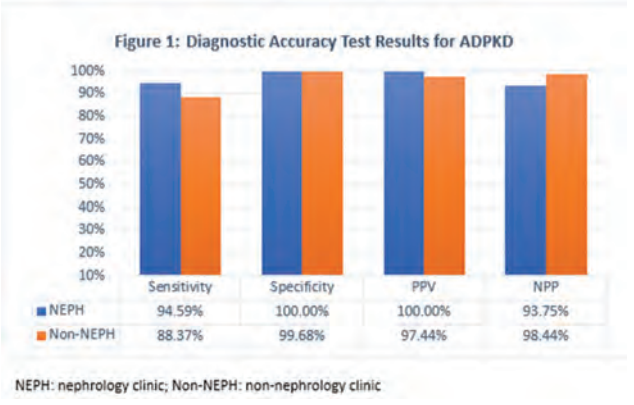

Figure 1: Diagnostic Accuracy Test Results For ADPKD

TH-PO433

Omics Profiling of Tolvaptan-Treated Autosomal Dominant Polycystic Kidney Disease Patients

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a life-threatening genetic kidney disease and the fourth leading cause of kidney failure. Dialysis or transplant are current treatments for end-stage ADPKD patients, and no other ideal efficient therapeutic strategy exists. The selective vasopressin V2-receptor antagonist, Tolvaptan, was used to treat hyponatremia in heart failure but was approved by FDA for ADPKD treatment in 2018; however, there are limitations for ADPKD patients to receive Tolvaptan treatment and its significant side effects severely affect patient's life quality. In this study, we use omics tools to discover potential therapeutic targets with fewer side effects for ADPKD patients.

Methods: Tolvaptan was started with the 45-0-15 dose, then titrated to 60-0-30 after two months. Blood and urine were collected before Tolvaptan treatment and 2, 3, 6, 9, and 12 months after treatment. Omics profiling was performed using SureSelect XT HS2 mRNA Library Preparation kit (Agilent, USA) and sequenced on Nextseq. Differential expression analysis was performed using StringTie and DEseq2 with Welgene Biotech's in-house pipeline. Genes with p-value < 0.05 and > 2.0-fold changes were considered significantly differentially expressed. Functional enrichment assay was performed using cluster Profiler v3.6.

Results: Our data indicate that cytoskeleton-regulating proteins and junctional proteins: NBPF10, RGPD2, MYH1, NPIPB9, SLC9B1P1, and TUBB7P were involved in the regulation of cystogenesis in Tolvaptan-treated ADPKD patients. In addition, the downstream junctional and cytoskeleton regulating genes of the above proteins (Log2 ratio: CRB3, 11.01; CLDN10,10.09; MAPK10, 7.34; FGF17, 9.47; MYH14, 7.04) were significantly ($p<0.05$) preserved after Tolvaptan treatment that may be involved in the regulation of calcium, Rho GTPases, and PAK Pathway signaling. Furthermore, Hypoxanthine, Creatine, L-a-aminobutyric acid, and Trimethylamine N-oxide were significantly decreased in our metabolomics data analysis, showing paracellular transportation in kidney cells was inhibited.

Conclusions: Our data shows Tolvaptan treatment regulates the integrity of tight junctions and paracellular transportation of kidney cells. It elucidates the possible targets in inhibiting side effects and provides novel therapeutic targets that may be served in ADPKD treatments with fewer side effects.

Funding: Private Foundation Support

TH-PO434

Association Between PKD1 Truncating Mutations and Accelerated eGFR Decline in ADPKD Patients: Implications for Early Identification and Intervention

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Background: ADPKD severity varies due to allelic and genic heterogeneity. Identifying patients at risk of rapid disease progression may improve outcomes. This study aims to explore the association between PKD1 types (truncating vs. non-truncating) mutations & rate of eGFR decline in ADPKD patients.

Methods: This study followed up 42 PKD1-ADPKD patients with clinically & genetically confirmed diagnoses for an average of 6.6±3.8 years. Renal function tests were performed annually, and eGFR was calculated using the CKD-EPI Creatinine Equation (2021).

Results: Patients with PKD1 truncating mutations had a more rapid rate of eGFR decline per year (-4.7 ml/min/1.73 m2 per year) compared to patients with PKD1 non-truncating mutations (-3.5 ml/min/1.73 m2 per year) ($P<0.001$).

Conclusions: This study highlights the association between PKD1 truncating mutations & a more rapid rate of eGFR decline in ADPKD patients. Identifying patients with potential rapid disease progression may aid in early intervention & better disease management to improve outcomes.

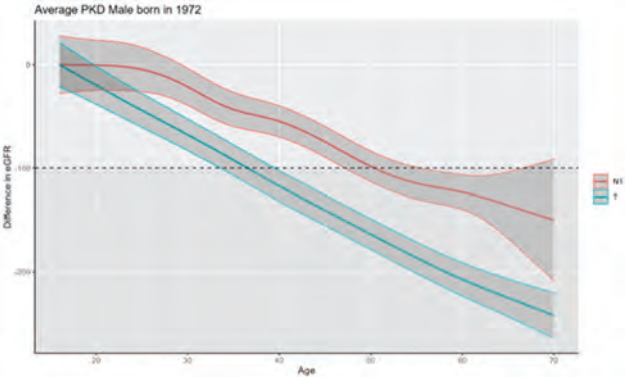
Funding: Government Support - Non-U.S.

Analysis of ADPKD progression per PKD1 mutation type

	Effect Estimate	95% CI	P
Truncated vs. Non-Truncated (a)			
Creatinine (mmol/L)	184.6	57.1 - 312.1	0.007
Urea (mmol/L)	5.9	1.0, 10.7	0.022
eGFR (ml/min/1.73 m2)	-19.2	-38.9, 0.42	0.063
Rate of eGFR (ml/min/1.73 m2) decline per year (b)			
PKD1 Truncating mutation	-4.7	-5.0, -4.4	<0.001
PKD1 Non-truncating mutation	-3.5	-4.0,-3.1	<0.001

a estimated from mixed effects model adjusted for sex, age at visit, and birth year

b estimated from stratified mixed effects models adjusted for sex and birth year. P-value of interaction was obtained from an interaction term.



A non-linear estimation of eGFR change through a smooth interaction between age at visit and mutation type.

TH-PO435

Comparison of the Total Kidney Volumes Using the Ellipsoid Equation and Manual Segmentation in ADPKD

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Background: Total kidney volume (TKV) is an important prognostic biomarker of disease progression in autosomal dominant polycystic kidney disease (ADPKD). The gold standard of manual segmentation TKV (mTKV) is time and labour-intensive. The ellipsoid equation TKV (eTKV) is commonly used in clinical practice, but assumes uniform growth of the kidneys. Our study examined the correlation between the eTKV and mTKV and we examined cases individually where there was misclassification.

Methods: We analyzed coronal T2-weighted MRI slices for 143 patients with ADPKD from a single centre. eTKV was determined using standard orthogonal measurements. The ground truth mTKV was performed by a single trained individual. Pearson's correlation coefficient was calculated and a Bland-Altman analysis was performed. A confusion matrix was generated to illustrate the misclassification in the Mayo Imaging Classification (MIC) between the two approaches. We explored cyst imaging features where the difference in TKV methods was ≥20%.

Results: The mean age of the cohort was 45 (SD 15), 46% were male, hypertension prevalence was 71%, the median eGFR was 76 ml/min/1.73m^2 (IQR 46-107), height-adjusted TKV was 865 mL/m (IQR 490-1307), and tolvaptan use was 45%. The correlation coefficient between both TKV measures was 0.96. The Bland-Altman analysis showed wide limits of agreement [-40.43%, 25.15%], and 24 patients were reclassified by one MIC risk category. Of the 25 patients (17%) who exhibited ≥20% difference between the two measures, 23 patients were characterized as having large exophytic cysts.

Conclusions: The eTKV is efficient and generally reliable for calculating TKV, but it may lose accuracy in patients with large exophytic cysts. Further study should explore the association of exophytic cysts with kidney disease progression. Understanding whether exophytic cysts should be included in the TKV estimation may aid in risk stratification.

Confusion Matrix of Mayo Imaging Class Determined By Total Kidney Volume Using Ellipsoid Equation (eTKV) and Manual Segmentation (mTKV)

		eTKV					
		1A	1B	1C	1D	1E	2
mTKV	1A	11	0	0	0	0	0
	1B	3	24	0	0	0	0
	1C	0	8	46	2	0	0
	1D	0	0	8	23	1	0
	1E	0	0	0	2	13	0
	2	0	0	0	0	0	2

TH-PO436

Prognosis of Polycystic Kidney Disease: FinnGen Study

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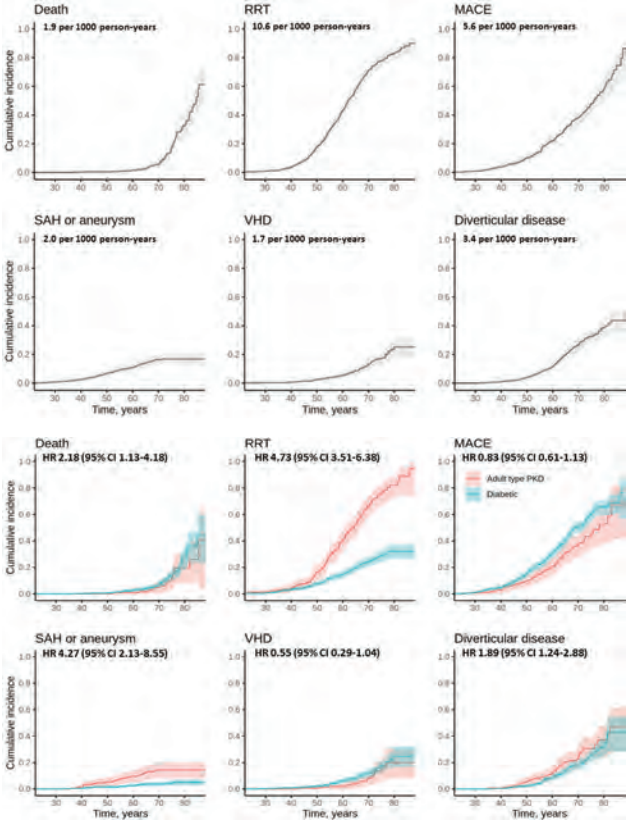
Background: The extra-renal complication risk and progression rate of autosomal dominant polycystic kidney disease (PKD) are incompletely understood. We assessed the clinical outcomes of PKD in the FinnGen study, which covers nearly 10% of the Finnish population (N=473681).

Methods: PKD patients and clinical outcomes were identified using ICD diagnosis codes. The outcomes of interest were death, start of dialysis or transplantation (RRT), major adverse cardiovascular events (MACE), subarachnoid hemorrhage (SAH) or cerebral aneurysms, valvular heart disease (VHD, defined as valvular regurgitation), or diverticular disease. In a smaller sample with data available for estimated glomerular filtration rate (eGFR), we compared the risk of adverse outcomes and kidney function decline in PKD patients and controls (diabetes mellitus [DM] patients) using multivariable-adjusted Cox regression and repeated linear mixed models. The cases and controls were matched with a ratio of 1:4 by age, sex and eGFR.

Results: The study sample included 674 PKD patients. The incidence of clinical outcomes in these patients is reported in Figure 1. The risk of adverse outcomes in PKD patients (N=173) compared to DM patients (N=692) is reported in Figure 2. The risk of death, RRT, SAH or cerebral aneurysms, and diverticular disease was greater in PKD patients compared to DM patients ($p<0.02$ for all). The eGFR decreased more rapidly in PKD patients compared to DM patients (-2.31 [95% CI, -2.41 to -2.22] vs -1.62 [95% CI, -1.67 to -1.56] ml/min/1.73 m^2 per year, $p<1x10^{-16}$).

Conclusions: In this large register study, PKD patients demonstrated a greater risk for most adverse outcomes and a more rapid kidney function decline compared to DM patients.



TH-PO437

A Serum Proteomic Study Identifies Novel Biomarkers for Autosomal Dominant Polycystic Kidney Disease

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Background: ADPKD is a genetic disorder characterized by cyst growth and expansion, and inflammation and renal fibrosis leading to kidney failure. The disease course of ADPKD is highly variable depending on the gene, mutation, and other factors. Better methods to measure disease progression, such as serum biomarkers, are urgently needed in ADPKD to complement total kidney volume data.

Methods: The level of 1500 circulating proteins in serum samples from 45 ADPKD patients with an eGFR ≥ 15 ml/min/1.73m^2 (4 subgroups based on eGFR, CKD1-4) and 12 healthy individuals were measured using the SOMAscan proteomics platform. Differentially expressed proteins (DEPs) were analyzed by Go and KEGG enrichment analyses. Differentially expressed genes in kidneys of *Pkd1$^{flox/flox}$:Pkhd1-Cre* mice were identified by RNA-seq.

Results: A total of 155 proteins were upregulated and 49 proteins downregulated in patients with ADPKD and CKD3 compared to healthy individuals ($p < 0.05$). DEPs were associated with several signaling pathways, including cytokine-cytokine receptor interactions, TGF-β signaling, complement and coagulation cascades, TNF signaling, cancer, lipid regulation, and atherosclerosis. Potential individual serum biomarkers were identified by the following criteria: 1) more than >20% increase in CKD2 versus healthy control; 2) more than two-fold increase in CKD4 versus healthy control; and 3) the change of protein level was associated with a decline of eGFR. A total of 31 proteins were identified, including the inflammatory biomarkers (MIC-1, TNFR-I, TNFR-II, TNFRSF21, IGFBP-6, and TGF-bRIII), fibrosis biomarkers (MMP-7, MMP-3, Edostatin, WFDC2), and other biomarkers (Resistin, EPHB4, EFNB2, and CAD17). Specifically, the level of MMP-7 was increased 1.8-, 3.2-, 6-, and 8.2-fold in ADPKD patients with CKD1-4, respectively. Among the 155 upregulated and 49 downregulated proteins, the mRNA levels of 55 and 11 genes were similarly increased or decreased in mouse PKD kidneys. These results suggest that these specific upregulated and downregulated proteins are altered in the kidney and can also be tested as urinary biomarkers.

Conclusions: Our study identified several potential diagnostic biomarkers in ADPKD. The TNFR-I, TNFR-II, MMP-7, and WFDC2 have been reported as prognostic biomarkers in CKD, but the other inflammatory and fibrotic biomarkers are novel for ADPKD.

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TH-PO438

Changes in Tubular Biomarkers with Dietary Intervention and Metformin in Patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: Tubular biomarkers, which reflect tubular dysfunction or injury, are associated with incident chronic kidney disease and kidney function decline. Several tubular biomarkers have also been implicated in progression of ADPKD. We evaluated changes in tubular biomarkers in four groups of patients with ADPKD who participated in one of two clinical trials (metformin therapy and diet-induced weight loss), based on evidence suggesting that such interventions could reduce tubule injury.

Methods: 66 participants (26M/40F) with ADPKD and estimated glomerular filtration rate (eGFR) >30 ml/min/1.73m^2 who participated in either a 12-month metformin clinical trial (n=22 metformin [max dose 2,000 mg/d]; n=23 placebo) or 12-month dietary weight loss study (n=10 daily caloric restriction [DCR; 34% restriction]; n=11 intermittent fasting [IMF]; 3x/wk) were included in assessments of urinary tubular biomarkers (kidney injury molecule-1 [KIM-1], fatty-acid binding protein [FABP], interleukin-18 [IL-18], monocyte chemoattractant protein-1 [MCP-1], neutrophil gelatinase-associated lipocalin [NGAL], clusterin, and human cartilage glycoprotein-40 [YKL-40]; normalized to urine creatinine), at baseline and 12 months. The association of baseline levels with change in height-adjusted total kidney volume (htTKV) and eGFR, with covariate adjustment, was also assessed.

Results: Mean±s.d. age was 48±8 years, eGFR was 71±16 ml/min/1.73m^2, and baseline BMI was 30.5±5.9 kg/m^2. None of the tubular biomarkers changed with any intervention as compared to placebo. Tubular biomarkers were not associated with change in eGFR or htTKV over one year, after adjustments for demographics, group assignment, and clinical characteristics (Table).

Conclusions: In this cohort of patients with ADPKD, tubular biomarkers did not change with dietary-induced weight loss or metformin, nor did they associate with kidney disease progression.

Funding: NIDDK Support

Tubular Biomarker (log-adjusted)	Adjusted association with change in htTKV (B-estimate [95% CI])	Adjusted association with change in eGFR (B-estimate [95% CI])
KIM-1	4.3 (-1.1, 9.6)	2.1 (-6.4, 10.6)
FABP4	0.52 (-3.2, 4.3)	-2.3 (-7.5, 2.9)
IL-18	0.14 (-7.4, 7.8)	-7.5 (-17.0, 2.0)
MCP-1	2.7 (-4.5, 9.8)	-3.5 (-38.5, 21.5)
NGAL	1.2 (-2.4, 4.8)	-1.3 (-6.2, 3.6)
Clusterin	2.6 (-4.1, 9.2)	1.7 (-4.7, 8.1)
YKL-40	-0.36 (-3.3, 2.6)	-0.10 (-4.3, 4.1)

TH-PO439

Evaluation of the Predictive Ability and Concordance of Prognostic Scores for Rapid Progression in ADPKD: A Multicenter Cohort

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Background: ADPKD is characterized by the progressive development of bilateral renal cysts, resulting in enlargement of the kidney volume and ESKD. ERK-NET assessed Tolvaptan indications according to 3 algorithmic criteria: total kidney volume (HtTKV) and Mayo Clinic Imaging Class (MCIC), rate of decline in eGFR, and the Predicting Renal Outcome in Polycystic Kidney Disease (PROPKD) score. These scores are alternatively used to define rapid progressor (RP) patients. The aim of this study is to evaluate and improve the concordance of sensitivity and specificity of MCIC and PROPKD predictive abilities for rapid disease progression.

Methods: Data from 3 centers (Bologna, Dublin, Berlin/Leipzig) were assessed. We defined RP with: eGFR slope ≥3 mL/min/1.73m^2/ yearly over 4 years, or MCIC classes 1C-D-E, or PROPKD score (7-9). Descriptive statistics were used to summarize clinical parameters. The concordance between MCIC and PROPKD was assessed using Kappa statistics. In *PKD1* missense variants, the REVEL score was obtained and treated as a continuous variable; score greater than 0.65 were considered 'pathogenic' and regarded as *PKD1*-truncating variants for PROPKD score calculation.

Results: We evaluated 298 ADPKD patients, demographic and clinical data are summarized in Tab 1. After 4 yr of follow-up, MCIC (p 0,041), HBP (p 0,031), and urological events (p<0.001) result were statistically significant on multivariate analysis (Tab 1). Assessment of RP using PROPKD and MCIC scores yielded Kappa Cohen of 0,149; 47.9% (*n*=143) were concordant, 49,32 % (*n*=148) patients identified as RP for MCIC were non- RP for PROPKD, while 2.3% (*n*=7) of PROPKD score considered RP using PROPKD score were considered non-RP using MCIC classes. Following the reclassification of *PKD1* missense variants by REVEL score, K of Cohen improved to 0.174, and PROPKD becomes predictive of RP also at multivariate (p 0.010).

Conclusions: Concordance between scores results low (K of Cohen 0,149). PROPKD is more selective compared to the Mayo. Nevertheless, PROPKD allows the identification of some RP patients excluded from MCIC. The combined use of scoring may increase the ability to identify progressive patients. REVEL score could improve the agreement.

TH-PO440

Impact of the 2021 Glomerular Filtration Rate Estimation Equation in a Cohort of White Polycystic Kidney Disease Patients

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Background: New estimated glomerular filtration rate (eGFR) equations removed race adjustment, but the impact of this removal on prediction of chronic kidney disease (CKD) staging for autosomal dominant Polycystic Kidney Disease (ADPKD) patients is unknown. We aimed to investigate the impact of new eGFR equations on CKD staging and their associations with clinical characteristics in ADPKD patients.

Methods: We examined data for 288 consecutive White patients with ADPKD [mean age 53±16; 158 (54.9%) women, 130 (45.1%) man] through chart review between 2000-2013 with a median 9-yr follow-up (IQR, 6-12 yrs). We computed changes in eGFR resulting from substituting the CKD-EPI 2009 equation for the 2021 equation and the consequent reclassification into different CKD Stages according to KDIGO 2012 classification. Correlates of eGFR changes during follow up are also studied.

Results: Compared to the 2009 equation, CKD-EPI 2021 yielded a higher baseline eGFR, with a median of 2.67 mL/min/1.73 m^2 (IQR 1.43-3.43) and higher last visit eGFR with a median 2.64 mL/min/1.73 m^2 (IQR 1.24-3.65). Among the cohort of ADPKD patients, 9% (n=26) were reclassified into a higher category of eGFR, as were the following proportions by baseline (2009 equation) stage: from CKD stage 2, 9.1% (n=6) from CKD stage 3, 9.4% (n=3) from stage 4 and 12.8% (n=6) from stage 5. No patient was re-classified into a more severe CKD stage. Based on last visit eGFR, CKD stage was also reclassified into a higher category in 13.3% (n=6) from CKD stage 2, 12.5% (n=6) from stage 3, 10% (n=2) from stage 4 and 7.9% (n=3) from stage 5. The median change in eGFR over median 9 years (follow-up - baseline value) calculated by CKD-EPI 2009 and CKD-EPI 2021 was -8.5 mL/min/1.73 m^2 (IQR 0.5-22.1) and -7.9 mL/min/1.73 m^2 (IQR 0.5-22.7), respectively. Among the baseline clinical characteristics, smoking was significantly correlated with eGFR decline during follow up (CKD-EPI 2009, r=0.0186, p=0.016; CKD-EPI 2021, r=0.186, p=0.018).

Conclusions: Implementing the CKD-EPI 2021 equation in a Caucasian ADPKD population, would increase eGFR by a modest amount. A significant proportion of the population would be re-classified into a higher eGFR category, with a consequent decrease in the prevalence of stage 5 CKD.

TH-PO441

Impact of the COVID-19 Pandemic on Health Care Utilization and Behaviors in Adults with ADPKD

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Background: The impact of the COVID-19 pandemic on those with chronic diseases was pervasive, affecting healthcare seeking behaviors, and medication and access to care. The impact of COVID-19 on adults with ADPKD is uncertain.

Methods: Participants were recruited from 223 adult ADPKD patients without ESRD in a study at the University of Maryland. N=66 patients participated in a questionnaire from July 2022-December 2022 about PKD-related complications, COVID infections, healthcare seeking behaviors, and care avoidance before and after March 2020.

Results: N=34(51.5%) of participants reported a positive COVID-19 test result. N=29(44%) reported frequent concern about contracting COVID-19. Those who avoided medical care at least once (n = 17, 26%) had similar demographics and PKD severity to those who did not but reported greater telehealth utilization and use of non-prescribed medication for COVID-19 prevention. They were also more likely to have contracted COVID-19 (Table). Among the N=53 who reported very good or excellent PKD disease management pre-pandemic, N=47(94%) reported no significant change during the pandemic.

Conclusions: Among a sample of ADPKD patients with well-managed disease, there was no significant decline in self-reported PKD management during the pandemic. However, more than 1 in 4 reported avoidance of care and were more likely to have utilized telehealth and been infected with COVID-19. Future studies should investigate care avoidance in PKD patients whose care is not as easily transitioned to telehealth.

Funding: NIDDK Support

Characteristics of Participants with and without new avoidance of healthcare during COVID pandemic

	No avoidance (n=49)	Healthcare avoidance (N=17)	p-value
Age (yrs)	45.5 (14.0)	47.8 (11.4)	0.5
Male	22 (45%)	7 (41%)	0.99
White	44 (90%)	16 (94%)	0.99
College Education	40 (82%)	15 (88%)	0.7
eGFR (ml/min/1.73m2)	77.9 (32.4)	67.6 (31.2)	0.3
htTKV (cc/m)	670 [439, 1279]	838.6 [658.2, 1108.9]	0.3
Flank Pain	21 (43%)	9 (53%)	0.6
UTIs	24 (49%)	12 (71%)	0.3
Often or Always Concerned about COVID	21 (43%)	8 (47%)	0.8
Use of non-prescribed meds for COVID prevention	4 (8%)	6 (35%)	0.01*
COVID infection during pandemic	21 (43%)	13 (77%)	0.02*
Telehealth Use during pandemic	21 (43%)	13 (77%)	0.002*

Cell values represent mean(SD), median[IQR], or N(%)

TH-PO442

Evaluation of Autonomic Modulation in Normotensive Autosomal Dominant Polycystic Kidney Disease Patients

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Background: Autonomic cardiovascular dysregulation has been described among Autosomal Dominant Polycystic Kidney Disease (APDKD) patients exhibiting hypertension and reduced kidney function. The present study aimed to evaluate the involvement of the sympathetic nervous system (SNS) preceding the onset of hypertension and kidney dysfunction.

Methods: We measured resting Heart Rate Variability (HRV) and systolic and diastolic arterial blood pressure (sBP and dBP) for five minutes in *Finapres*® device and cardiovascular reactivity after sympathoexcitatory stimuli: Stroop colored word test (SCWT), cold pressor test (CPT), and isometric handgrip (HG). Baroreflex sensitivity (BRS) was analyzed through the Valsalva maneuver (VM). Thirteen (13) ADPKD normotensive patients (5M/ 8F, 25.9±5.7 years old) and 13 healthy subjects (HS, 6M/7F, 26.1±4.6 yrs), eGFR of 104.8±18.6 and 104.9±11.0 mL/min/1.73m2, respectively, were included.

Results: Mean values of HR, BP, and HRV parameters at resting were not statistically different between groups. Although resting systolic BP (sBP) was similar for both groups, mean peak-phase-II-sBP and nadir-phase-III-sBP during VM were significantly higher in ADPKD versus HS (165.9±20.1 vs 142.5±19.7 and 140.2±11.7 vs 116.9±15.8 mmHg, p<0.05, respectively). Absolute differences between mean values of HR before and during CPT (at 2 minutes) were bigger in the ADPKD group (8.7±5.3 vs 2.9±5.6 bpm, p<0.05). Absolute differences between mean values of sBP and dBP before and during HG test (at 2 minutes) were smaller in ADPKD group than HS for sBP (11.8±8.1 vs 21.6±13.9 mmHg, p<0.05) and dBP (8.1±7.9 vs 14.7±8.1 mmHg, p<0.05). Absolute differences between mean values of HR during HG test and at 2 minutes of the recovery period were smaller in ADPKD than HS (-3.4±5.6 vs -10.5±9.0 bpm, p<0.05). Responses of HR and BP to SCWT did not differ between groups.

Conclusions: Preliminary data from VM and CPT as well as the delay in BP and HR returning to basal values observed in HG test suggested an increase in sympathetic drive in ADPKD normotensive patients. An additional number of patients need to be further evaluated to confirm present findings.

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TH-PO443

A Diagnosis of Depression/Anxiety Is Associated with More Rapid eGFR Decline in Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the leading genetic cause of kidney failure. 22-60% of patients with ADPKD are diagnosed with depression, which is associated with worse physical health and decreased dietary compliance with ADPKD guidelines. Depression in chronic kidney disease patients is associated with increased all-cause mortality, but the impact of mental health on ADPKD progression has not been assessed.

Methods: We identified ADPKD patients seen at Yale Nephrology from 2016 to 2021 and retrospectively collected demographic, medical history, and clinical data through automated query and manual chart review. Patients were separated into two groups, those diagnosed with depression and/or anxiety (DA), and those without a diagnosis of depression and/or anxiety (NDA). Estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD EPI Creatinine equation. Differences between groups were assessed through chi-squared and Student's T-test, and the impact of DA on kidney function decline, represented by average change in eGFR, was assessed through simple and multiple linear regression.

Results: There were 49 (26%) patients with DA, and 140 (74%) patients without. DA patients were more likely to be female (p=0.0044), younger (p=0.044), have higher body mass index (BMI) (p=0.021), and be diagnosed with obstructive sleep apnea (p=0.046). There were no differences between Mayo Imaging Classification (MIC) or genotype between the groups, though tolvaptan use was more common in the NDA group (p=0.021). DA diagnosis was not linked to more rapid eGFR decline (p=0.672) with simple linear regression. However, DA was a significant predictor for rapid eGFR decline (p=0.019) on multivariable regression when controlling for factors linked to disease progression, including ADPKD genotype, MIC, kidney stones, hypertension, and diabetes, as well as age, sex, and BMI.

Conclusions: DA is significantly correlated with rapid eGFR decline in ADPKD patients in addition to traditional risk factors such as genotype, age and MIC. Future investigations may help determine if the impact of DA on eGFR decline is through a clinical, psychological, and/or behavioral mechanism.

Funding: Clinical Revenue Support

TH-PO444

Pregnancy and Its Association with Total Kidney Volume in Nulliparous Women with Autosomal Dominant Polycystic Kidney Disease

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Background: There is mounting evidence of metabolic dysregulation contributing to polycystic kidney disease (PKD) progression. The maternal metabolic changes during pregnancies are well described, but the relationship between pregnancy and changes in total kidney volume in women with PKD is unclear. In this study, we tested the hypothesis that a pregnancy carried to live delivery in nulliparous PKD women is associated with a greater increase in total kidney volume than in non-pregnant PKD women.

Methods: Using data from the University of Colorado PKD registry from 1985 to 2004, a total of 6 nulliparous PKD women with pre and post-kidney ultrasound measurements for their first pregnancy met the inclusion criteria for the study (cases). Using a pool of 172 women with PKD but without pregnancy, we selected 6 for matches for the PKD women with pregnancies (controls). These women were matched 1:1 by age, race, and eGFR (calculated by the MDRD equation). A two-sample T-test was performed to compare the yearly change in height-adjusted total kidney volume (htTKV), calculated by ellipsoid formula, between cases and controls. Analyses were further adjusted for history of hypertension.

Results: Of the PKD women with pregnancies, the mean (SD) age and mean (SD) eGFR before pregnancy was 26±3 yrs and 79±22 mL/min/1.73m^2, respectively. The median (IQR) htTKV for cases and controls were 288 [248-366] and 350 [240-515]ml/m^2, respectively. The follow-up median duration was 7.00 [2.1-9.5] yrs, for women with and without pregnancies. The yearly percent change (median; IQR) in htTKV in PKD women with and without pregnancies was 14.2 [7.1-15.8] and 7.1 [1.4-8.6]%, respectively (p=0.11). Results remained unchanged after adjustment for history of hypertension.

Conclusions: Nulliparous PKD women demonstrated a faster increase in htTKV after pregnancy than non-pregnant PKD participants; however, it was not statistically significant. Further studies looking at the effect of pregnancy on PKD progression are needed.

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TH-PO445

Deciphering the Chronology of Cystogenesis and Metabolic Reprogramming

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Background: ADPKD is among the most prevalent monogenic diseases. Multiple relevant orthologous animal models were generated over the years and helped defining mechanism of disease progression and identifying therapies able to retard end-stage-kidney-disease. However, the initial stages of renal cystogenesis have been poorly defined. Identification of the cellular alterations occurring at the onset of cystogenesis would provide important information on mechanism of disease and possibly help designing better therapies targeting initiating events and being more effective.

Methods: Mutant kidneys have been characterized by IHC and IF analysis. Single cell dissociation was performed pairing mechanical and enzymatic approaches. PARSE single cell combinatorial barcoding RNA sequencing was performed on 10k cells from P54 control kidneys, with a depth of 50k reads/cell

Results: We have developed a tamoxifen-inducible *Pkd1* animal model (TmKspCrePkd1fl/fl) carrying a fluorescent switch cassette (mT/mG) that allows identification of cells in which the Cre recombinase has been activated to study the initiating events in cystogenesis. Induction by 3 low dose injections of Tamoxifen resulted in full penetrance (cyst formation) within two weeks. 5 days after the last injection we identified renal tubules completely green, but not cystic, while 8 days post injection green cells started to form cysts. A pilot scRNA-seq of WT cells confirmed the capability to capture and distinguish induced from non-induced cells as well as the higher sequencing depth and reduced contamination of the combinatorial scRNA-seq approach.

Conclusions: Our inducible Pkd1 KO model enables the determination and characterization of both pre-cystic and cystic time windows, as well as the selection of low abundant pre-cystic mutant cells due to our colorSwitch reporter cassette. Comparison of mutant cells involved in cyst initiation and expansion will permit the exact determination of new mechanisms as well as therapeutic windows that allow tailoring of treatments to the corresponding metabolic stage of each cell-type. The experimental analysis is ongoing.

TH-PO446

Financial Implications of Genetic Testing in Nephrology: A Real-Life Evaluation of the Costs Related to Podocytopathy and Collagenopathy Diagnosis

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Background: Collagenopathies and podocytopathies significantly contribute to CKD. Despite concerted efforts to enhance genetic testing guidelines, a data vacuum persists concerning the economic burden for diagnosis these diseases impose on healthcare systems. This study aims to shed light on healthcare resources utilization and the accompanying financial burden attributable to diagnosing these diseases, using real-world data. Moreover, we sought to evaluate the potential cost savings associated with using early genetic testing in diagnostic trajectories.

Methods: In this multicentric, retrospective study we enrolled all patients with a conclusive genetic diagnosis of podocytopathy and collagenopathy, from our tertiary hospital from Jun 2014 to Dec 2022, as previously described. Direct medical costs from clinical onset to conclusive genetic diagnosis, including medication use, in-hospital visits, invasive procedures, blood sampling, imaging studies, hospital admissions, and genetic tests, were recorded from patient clinical records. These costs were subsequently compared to those anticipated under a 'exome first' approach, involving a basic panel of tests followed immediately by genetic testing within a one-year follow-up period.

Results: The study included 43 patients (23 female), with 22 diagnoses of podocytopathies and 21 of collagenopathies. Over a median follow-up period of 3.5 years; patients required a wide range of resources consumption. Overall, the direct medical costs totaled 98,252 euros for medications, 4,125 euros for in-hospital visits, 68,138 euros for biopsies, 68,926 euros for blood tests, 2,560 euros for urinalysis, 9,023 euros for imaging, and 146,000 euros for genetic testing. Remarkably, the annual cost per patient averaged 3,897 euros, aligning closely with the cost of adopting the 'exome first' approach.

Conclusions: Our study underscores the significant unnecessary treatments and costs associated with the existing diagnostic approach for collagenopathies and podocytopathies. By adopting an early genetic testing strategy, we can mitigate this burden and reallocate resources more efficiently, providing valuable insights for healthcare policymakers.

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TH-PO447

Large-Scale Case-Control Exome-Wide Association Study Identifies Known and Novel Susceptibility Genes for Idiopathic Nephrotic Syndrome

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Background: The genetic causes of idiopathic nephrotic syndrome (INS) have traditionally been studies using family-based approaches and comprehensive association studies across the age of onset, response to therapy, and ancestries are lacking.

Methods: We conducted an exome sequencing (ES) study on 5,262 children and adult cases with INS caused by focal segmental glomerulosclerosis or minimal change disease, including 1,998 steroid sensitive cases (SSNS) and 3,264 cases that were not known to be responsive to steroids (either steroid resistant or untreated/unknown). Per-gene burden of rare coding variants was assessed by exome-wide collapsing analysis comparing the above 5,262 cases and 28,637 population controls with ES data under dominant and recessive models. Analyses were conducted on the entire dataset and then again after removal of cases harboring diagnostic/pathogenic Mendelian mutations in known FSGS genes and *APOL1* high-risk genotypes.

Results: In the analysis on the entire cohort, we identified and retrieved association for many of the known FSGS genes, including *WT1* (best $P = 1.09 \times 10^{-23}$; OR= 15.64), *COL4A5* (best $P = 2.37 \times 10^{-17}$; OR= 9.83), *INF2* (best $P = 1.87 \times 10^{-11}$; OR= 12.22), and several others, under dominant models, and *NPHS1* (best $P = 1.56 \times 10^{-21}$; OR= 25.18), *NPHS2* (best $P = 3.93 \times 10^{-15}$; OR= 30.58), *SMARCAL1* (best $P = 9.91$ x 10-9; OR= 31.97) and several others, under a recessive model. This analysis re-classified *CD2AP* as an autosomal recessive cause of INS, and points to mutations in *CLN5* and *OCRL* as common causes of FSGS phenocopies. Removal of solved cases and re-analysis prioritized 5 novel genes that exceeded the 5% false discovery rate (FDR), one gene that represented a phenotypic expansion of a known Mendelian neurodevelopmental disease, and three genes for which mouse models of the orthologues display glomerulopathy. Three of them are novel candidates for steroid resistant NS and two for SSNS.

Conclusions: These findings expand our understanding of the genetic underpinning of INS, identify novel candidate genes, and highlight the high genetic heterogeneity of disease. Genetic and functional validation studies of these results are ongoing.

TH-PO448

Genotype-First Analysis in an Unselected Health System-Based Population Reveals Variable Penetrance of COL4A5 Variants

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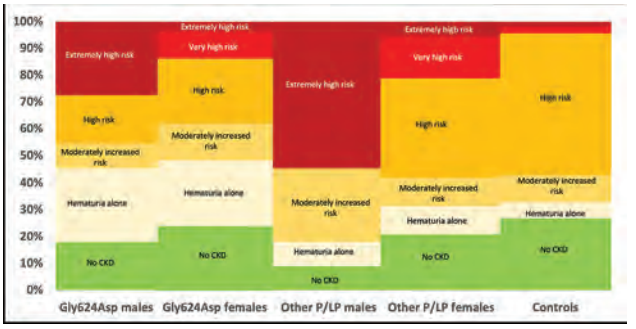
Background: Current literature suggests that nearly all hemizygous males with *COL4A5* mutations (i.e. X-linked Alport Syndrome [AS]) progress to end-stage kidney disease (ESKD) though most data come from selected cohorts.

Methods: We used exome sequencing data from the Geisinger MyCode DiscovEHR study, an unselected health system-based cohort with exome sequencing and electronic health record data to identify patients with *COL4A5* variants reported as pathogenic (P) or likely pathogenic (LP) in ClinVar. Phenotypic data sources included the United States Renal Data System (USRDS), ICD codes, blood and urinalysis data. Patients were categorized into Kidney Disease Improving Global Outcomes (KDIGO) risk categories using estimated glomerular filtration rate (eGFR) and albuminuria (preferentially) or urine dipstick protein data.

Results: Out of 174,418 participants, there were 24 hemizygous males (mean age 53.8 [SD 19.5] years) and 55 heterozygous females (mean age 59.8 [SD 17.6]) with a P/LP *COL4A5* variant, including Gly624Asp (n=48) and 9 missense and 4 protein truncating variants. Overall, 41% of males had KDIGO severely increased risk category and 4% of females had severely increased risk category with lower severity for Gly624Asp than other variants **(Figure)**. In logistic regression analyses adjusted for age, sex, and race, hemizygous males and heterozygous females were at increased risk of ESKD (females: OR 5.2, 95% CI: 1.2, 21.3; males: OR 36.1, 95% CI: 14.5, 89.7). Few had been diagnosed with Alport Syndrome (21% of males, 9% of females). Only 45% of individuals had completed albuminuria screening, and ~1/3 were taking renin angiotensin aldosterone system (RAAS) inhibitors.

Conclusions: In an unselected cohort, we demonstrate a wider spectrum of kidney severity in men and women than has been described previously with variability by genotype. Future studies are needed to determine whether early genetic diagnosis can improve outcomes in Alport Syndrome.

Funding: NIDDK Support



TH-PO449

Small but Clinically Relevant Contribution of Copy Number Variations (CNVs) to Idiopathic Nephrotic Syndrome

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Background: Idiopathic Nephrotic Syndrome (INS) is a frequent cause of kidney failure. The utility of genetic diagnostics within the context of rare variants affecting Mendelian NS-associated genes have been demonstrated on patients with various kidney disease. Nevertheless, genetic studies have overwhelmingly assessed the contribution of single nucleotide variants while the contribution of rare Copy Number Variations (CNV) to INS remains poorly understood.

Methods: We conducted chromosomal DNA microarray (CMA) genotyping on a multi-ethnic cohort of 3,600 INS patients across ages of onset and response to immunosuppressive therapy. An interim analysis of 2,230 INS cases was conducted. To extract CNVs, we used PennCNV with default parameters. Predicted CNVs were annotated against the CNV start and stop boundaries of 221 known Genomic Disorders (GD) and a curated list of 126 genes that, when mutated, are known to cause INS/FSGS or a phenocopy of it. A subgroup analysis will be conducted after the removal of solved cases via exome sequencing, partitioning by age of onset, response to therapy, and genetic ancestry.

Results: 18 of 2,230 INS individuals (0.8%) carried a GD-CNV without significant enrichment for a particular subcategory. Notably, we identified 6 (0.3%) individuals with smaller deletions that encompassed INS-associated genes for which a loss-of-function mechanism of disease determination is known: *NPHS1* (N=2), *FRAS1*, *HNF1B*, *LMX1B*, and *WDR73*.

Conclusions: This interim analysis showed that the overall CNV diagnostic rate for INS is relatively low, (< 2%), but should not be overlooked since these variants add to the overall genetic diagnostic workup and have direct implications in clinical management for NS (ex steroid avoidance) and risk stratification for extra-urinary complications associated to these variants.

Funding: NIDDK Support

TH-PO450

The Polygenic Burden of Rare Variants Predicts Onset of CKD in the UK Biobank

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Background: Genetic contributors to chronic kidney disease (CKD) have been explored through monogenic mechanisms by rare mutations and polygenic mechanisms through the aggregate impact of many small-effect common variants. In this work, we test whether a polygenic burden of rare variants across numerous genes contributes to CKD by constructing a rare variant polygenic risk score (rvPRS).

Methods: We first conducted a discovery exome-wide association study (ExWAS) of rare protein-truncating variants with a calculated severe CKD phenotype based on eGFR below 30 ml/min/1.73m2 using a discovery set of 834 cases and 147,855 British European controls in the UK Biobank (UKB). After excluding known Mendelian CKD genes, an rvPRS was constructed of 124 nominally significant ($P<0.05$) *risk* genes associated with severe CKD. As such, the effect conferred through rvPRS124 would not be driven through underlying monogenic mechanisms. We then tested the predictive power of rvPRS124 using a validation set consisting of 688 independent CKD events in the UKB.

Results: In the validation set, rvPRS124 conferred a 21% increase in hazard for incident CKD onset with one rare protein-truncating allele (HR=1.21; 95%CI, 1.01-1.46; P=0.045) after adjusting for age, sex, the first 5 principal components of ancestry, and pertinent clinical risk factors including obesity, myocardial infarction, and smoking. Individuals with 2 or more rvPRS124 alleles (N=1,352) had a 10-fold increase in hazard

for CKD onset compared to individuals with no rvPRS124 variants (HR=10.0, 95% CI, 2.5-39.4; P=1.3 x 10-3). No single gene in rvPRS124 replicated an association with CKD after adjusting for multiple hypothesis testing (P<4x10-4; 0.05/124), which emphasizes the importance of rare variant polygenic mechanisms underlying CKD. Lastly, through 1000 permutations of random gene sets, we show that the association of rvPRS124 with CKD was specific to the selected genes used to construct the score and not solely due to the gene count (P<0.05).

Conclusions: Using the UKB, we demonstrate a cumulative impact of rare protein-truncating variants in genes not known to have monogenic effects on CKD. An omnigenic score, incorporating established clinical risk factors and both Monogenic and common variant polygenic effects, should also include the polygenic burden of rare variants in non-Mendelian CKD-related genes.

TH-PO451

Unraveling the Unknown: A Few Illustrative Examples of the Utility of Genetic Testing for CKD

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Introduction: Genetic testing can offer critical insight into diagnosing disease states that were previously challenging to identify. In the context of CKD, genetic testing using commercially available panels can provide valuable information to guide personalized treatment decisions. We highlight three cases seen in our clinic over the past six months that illustrate the value of genetic testing for CKD.

Case Description: Case 1: 75- year-old self-identified Black male presented to the clinic with elevated creatinine and significant history of treatment-resistant hypertension and hypokalemia. Subsequent workup was consistent with Primary Hyperaldosteronism (plasma aldosterone-renin ratio, 58). Genetic testing, pursued initially to identify glucocorticoid remediable hyperaldosteronism, revealed a CACNA1H mutation, consistent with Type 4 Familial Hyperaldosteronism. Case 2: 56-year-old self-identified Black male with a history of ischemic cardiomyopathy and orthotopic heart transplant seven years ago was evaluated for worsening creatinine. A renal biopsy showed secondary focal segmental glomerulosclerosis and hypertensive arteriosclerosis attributed to calcineurin inhibitors. Genetic testing revealed APOL1 homozygosity with G1/G1alleles. Case 3: 41-year-old self-identified Black female was evaluated for persistent albuminuria and intermittent hematuria over several years with stable serum creatinine. She had no significant medical co-morbidities or family history. Genetic testing revealed COL4A3 mutation, seen with Alport's syndrome without sensorineural hearing loss.

Discussion: In summary, these cases highlight the tremendous clinical utility of genetic testing in a CKD clinic. As genetic testing technologies continue to advance and emerge for specific renal diseases, such as APOL1-mediated CKD, routine genetic testing for patients with CKD is worth considering.

TH-PO452

Reclassification of Genetic Diagnoses: Need for Structure in Re-Evaluation of Genetic Findings

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Introduction: Constant advances and emerging data in genomic medicine causes classification of genetic findings to be dynamic. In kidney disease (KD) alone, the number of single gene disorders are increasing, with over 600 genes described thus far. Genetic variant pathogenicity is classified according to the American College of Medical Genetics (ACMG) guidelines. Although the ACMG guidelines provide a classification with >95% certainty, variants of unknown significance (VUS), which do not have enough information to classify, may be reclassified when more information becomes available. The ACMG guidelines suggest that all new data should be incorporated into the genetic evaluation as it becomes available. This includes, but is not limited to, any new patient specific clinical information, family data, and population and case data in the literature. Currently, there are no protocols guiding when and how often to reevaluate genomic data. We present a case which highlights the importance of periodic genetic re-evaluation in a living donor post kidney donation.

Case Description: A 45-year-old female donated her left kidney as a non-directed altruistic donor. At the time of donor assessment, her creatinine was normal (60-70mmol/L), however, she had persistent microscopic hematuria. Given a positive family history of KD in a maternal uncle, genetic testing was performed. This revealed a variant of unknown significance (VUS) in COL4A4 c.3307G>A, p.G1103R. Since a VUS is not considered a clinically actionable finding, she elected to proceed with donation. Unfortunately, 5-years post-donation, she had progressive rise in creatinine (125 umol/L). An updated pedigree analysis now revealed that two of her children had developed KD and hearing impairment, prompting reanalysis. New clinical data and additional data in literature supported pathogenicity of this variant warranting reclassification to pathogenic, supporting a familial diagnosis of Alport Syndrome.

Discussion: We show that reevaluation of patient genomics can lead to reclassification of previously identified variants, which can have significant clinical implications for the patient and at-risk family members. This case highlights both the importance of re-analysis of genomic data and the clinical implications of establishing a genetic diagnosis for family screening and decision making for transplants.

TH-PO453

The Role of Whole-Exome Sequencing in Diagnosis of Genetic Disorders: A Case Report of a Novel Mutation in the Fibrinogen A-Alpha Chain Gene

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Introduction: Hereditary fibrinogen amyloidosis (AFib) was first characterized in 1993 in a Peruvian kindred. Patients with AFib present with renal disease and typically progress to ESRD. We describe a case of Afib with a novel mutation in the FGA gene identified by whole-exome sequencing (WES).

Case Description: A 51-year-old male patient presented to the nephrology clinic for the evaluation of a nephrotic range-proteinuria (5.4 g/day) and decreased eGFR (35 ml/min/1.73m^2). His family history was notable for stage V CKD of unknown cause (patient's mother). His past medical history is remarkable for a ruptured spleen and splenectomy following a minor trauma, two years prior to current evaluation. The initial work-up was negative for autoimmune disorders, hepatitis serology, malignancy screening, monoclonal gammopathy. The kidney biopsy revealed severe amyloid deposition with striking glomerular enlargement and almost complete obliteration of the normal architecture, without vascular or interstitial involvement. The reevaluation of splenic tissue did also reveal extensive amiloyd deposition. The bone marrow biopsy was negative and the patient didn't have any prior history of a chronic inflammatory process (serum amyloid A protein was slightly increased, 19 mg/L). Typing of amyloid by immunohistochemistry (IHC) could not reliably differentiate between AA amyloidosis and AFib. Because the initial genetic testing for hereditary amyloidosis (including testing for SAA1 promoter gene) was negative, a WES was further performed. The patients was identified to be heterozygous for two variants of uncertain significance (VUS) of FGA gene, c.1676A>T, p. (Glu559Val) and c. 967C>G, p. (Pro323Ala).

Discussion: This case report illustrates the limitations of amyloid typing by IHC and the role of WES in identifying novel mutations in hereditary amyloidosis. The patient was heterozygous for two VUS of FGA gene, of which the c.1676A>T, p. (Glu559Val) has been previously reported in two German sisters with AFib, while the c. 967C>G, p. (Pro323Ala) has not been reported in the medical literature. Despite that both variants were reported to be VUS, the correlation with the patient's family history and the severity of renal and splenic involvement further outlines that these variants are clinically significant.

TH-PO454

An Unusual Genetic Etiology for Adult-Onset FSGS

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Introduction: Focal segmental glomerulosclerosis (FSGS) is a histological pattern that is commonly associated with nephrotic syndrome and characterized by damage to the podocyte cytoskeleton. Genetic FSGS results from mutations in genes encoding podocyte proteins, particularly those predominantly expressed in the slit diaphragm. Here we discuss a case of genetic FSGS associated with mutation of a gene predominantly expressed in the proximal tubules.

Case Description: A 31-year-old African American male was referred to the renal clinic for evaluation of stage IV chronic kidney disease (CKD) and nephrotic range proteinuria. He had a history of well-controlled hypertension (not on any antihypertensives) and non-obstructive nephrolithiasis. Given proteinuria of more than 3 grams, suggesting glomerular disease and uncertain etiology of his CKD, a renal biopsy was performed. Biopsy revealed focal segmental glomerulosclerosis and severe interstitial fibrosis with tubular atrophy. Given the patient's age and the unclear etiology of his FSGS, genetic testing was conducted, which revealed a homozygous mutation in the CLCN5 gene, consistent with Dent Disease type 1.

Discussion: Dent Disease type-1 is a rare X-linked recessive disease due to mutations in the CLCN5 gene that encodes for the electrogenic Cl-/H+ exchanger. It usually manifests with proximal tubular dysfunction including low-molecular-weight proteinuria, hypercalciuria, nephrolithiasis, and progressive CKD. A novel mutation (L521F) in the CLCN5 gene has been reported to cause defects in podocyte transport and FSGS. However, the L521F mutation is usually not associated with hypercalciuria or nephrolithiasis. Our patient had evidence of both glomerular and tubular involvement. Our case demonstrates the value of genetic testing in patients with CKD of uncertain etiology, particularly in younger patients or those with unusual presentations. Understanding the genetic basis of kidney disease can lead to novel discoveries in renal physiology.

TH-PO455

Monogenic Causes Identified in 30.70% of Children with Steroid-Resistant Nephrotic Syndrome: A Single-Centre Study

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Background: Steroid resistant nephrotic syndrome (SRNS) is the second most common cause of end-stage kidney disease in children, mostly associated with focal segmental glomerulosclerosis (FSGS). Advances in genomic science have enabled the identification of causative variants in 20 – 30% of SRNS patients.

Methods: We used whole exome sequencing (WES) to explore the genetic causes of SRNS in children. Totally 101 patients with SRNS, and 13 patients with subnephrotic proteinuria and FSGS were retrospectively enrolled in our hospital between 2018 and 2022. For the known monogenic causes analysis, we generated a known SRNS gene list of 71 genes through reviewing the OMIM database and literature.

Results: Causative variants were identified in 30.70% of our cohort, and the most frequently mutated genes in our cohort were WT1 (7/33), NPHS1 (3/33), ADCK4(3/33), TRPC6(3/33) and ANLN (3/33). Five patients carried variants in phenocopy genes, including MYH9, MAFB, TTC21B, AGRN, and FAT4. The variant detection rate was the highest in the two subtype groups with congenital nephrotic syndrome and syndromic SRNS. In total 68.75% of variants we identified were novel, and have not been previously reported in literature.

Conclusions: Comprehensive genetic analysis is key to realizing the clinical benefits of a genetic diagnosis. We suggest that all children with SRNS undergo genetic testing, especially those with early onset and extrarenal phenotypes.

TH-PO456

Genetic Causes of Focal Segmental Glomerulosclerosis in Koreans

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Background: Focal segmental glomerulosclerosis (FSGS) is a relatively common pathologic findings of nephrotic syndrome or chronic kidney disease (CKD) presenting proteinuria. Genetic FSGS, usually not responding to immunosuppressive medications, is more common in younger patients and those who have a family history of kidney disease. Common genetic causes of FSGS include mutations reported COL4A mutations in families, but those of Korean population have not been well investigated.

Methods: The Korean Genetic Kidney Disease Cohort study is enrolling patients with kidney diseases of presumably genetic origin since 2021. Clinical characteristics of the cases were collected by the referring physicians and the genomic DNA of the enrolled cases were sequenced by multiple parallel sequencing of whole exome sequencing. Pathogenicity of variants were interpretated according to the American College of Medical Genetics (ACMG) guideline referring the resources of gnomAD (genome Aggregation Database), ClinVar (National Center for Biotechnology Information ClinVar Database), VarSome and other in silico prediction tools.

Results: Of a total 453 prospective cases of the our cohort, 124 cases (27.4%, Male:Female 64:60, mean age of diagnosis 20.8 year (range 0-78.7 years)) had pathological diagnosis of FSGS. Among them, 20.9% had a positive family history. Genetic diagnosis was obtained in 40.3% (n=50), among which COL4A3-5 (n=8) were the most commonly found causative gene, followed by NPHS1 (n=6), PAX2 (n=5), WT1 (n=4), COQ6/8B (n=4), NUP107 (n=3), TRPC6 (n=3), LAMA5 (n=2), MYH9 (n=2), MAFB (n=1). Gene testing changed the diagnosis in 8 (FSGS to Alport syndrome (AS)), lead to extrarenal manifestation screening in 8 (AS, PAX2, MYH9, and MAFB), and provided information on potential treatment (coenzyme Q10) in 4 with COQ6/8b mutations.

Conclusions: We found that proportions of causative genes in Korean FSGS are different from previous results of Western countries. Similar to the literature, gene testing was useful in obtaining more precise diagnosis and guiding management.

TH-PO457

Getting the Full Picture: Identifying Cases with Multiple Genetic Diagnoses Using Comprehensive Renal Gene Testing

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Background: Comprehensive genetic testing can provide genetic diagnoses for kidney disease of unknown etiology and those with unexpected phenotypes due to multiple genetic causes.

Methods: Analysis of 42,221 samples tested with the Renasight™ test was performed to identify cases with diagnostic findings in ≥ 2 genes. The cases were categorized based on: 1) disease penetrance: high (variants are expected to cause the condition) or susceptible (variants provide risk for disease development) and/or 2) disease phenotypic presentation: a) distinct phenotypes (2 conditions with dissimilar symptoms), b) same phenotype (2 distinct conditions with the same symptoms), c) combined phenotype (2 distinct genes that interact to cause the same disease (Digenic)).

Results: A total of 818 cases with multiple positive results spanning 130 genes (787 dual and 31 triple) were found, accounting for 7.7% of all tests with a positive result. Of the 369 different gene combinations identified, 274 occurred only once. The most common positive gene result was *APOL1* (344, 42.1%), among which, additional positive findings included: high penetrance genes with expected distinct phenotypes (28.9%), *TTR* (associated with cardiac amyloidosis; 9.5%) and other susceptibility genes (1.2%). Multiple positive findings among the non-*APOL1* cases (56.4%) included those with 2 high penetrance genes that cause distinct phenotypes (35.3%), cases with both a high penetrance gene and a susceptibility gene (8.91%), and cases with a *TTR* finding and a second high penetrance gene (7.2%). Digenic findings comprised 3.8% of all multiple positive cases and those with two separate gene findings that independently cause the same phenotype comprised 1.2% (Table).

Conclusions: We found that 7.7% of patients with genetic kidney disease had multiple etiologies that encompassed a wide range of genes and combinations demonstrating that comprehensive genetic testing is crucial for identifying the full range of genetic causes of kidney diseases that may be missed by traditional testing methods.

	Result Category	Number of Cases (%)
Triple positives		31 (3.8%)
Dual positives	**APOL+**	**325 (39.7%)**
	a. *APOL1* + high penetrance gene (e.g. *COL4A3, PKD*)	237 (28.9%)
	b. *APOL1* + *TTR*	78 (9.5%)
	c. *APOL1* + susceptibility gene	10 (1.2%)
	Non-*APOL*	**462 (56.4%)**
	a. 2 high penetrance genes, separate phenotypes	289 (35.3%)
	b. Susceptibility (e.g. *ABCC8*, complement) + high penetrance gene (e.g. *COL4A3, PKD, HBB*)	73 (8.9%)
	c. *TTR* + high penetrance gene (e.g. *COL4A3, PKD, HBB*)	59 (7.2%)
	d. Digenic (e.g *COL4A3* + *COL4A4*)Genes that cause same phenotype (e.g. *PKD1/PKD2*)	31 (3.8%)

Table: Summary of the dual and triple positive findings results

TH-PO458

Genome-Wide DNA Methylation Association Study Identifies DNA Methylation Associated with ESRD

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Background: Kidney disease is a progressive condition afflicting >10% of the general population worldwide, of which progression to end-stage renal disease (ESRD) caused poor quality of life and significant premature mortality. Defining DNA methylation biomarkers and understanding their roles in ESRD may help develop preventive and therapeutic strategies for kidney disease progression.

Methods: We conduct a blood-based genome-wide DNA methylation association study of ESRD in 2 independent cohorts (consisting of 1924 samples) from China and Singapore. Two-sample summary-level Mendelian randomization analysis was performed to evaluate the causality of the associations between methylation at DMP and kidney function (eGFR/eGFR decline). We also attempted to identify the candidates of ESRD-related genes underlying the significant associations by integrating the regulatory information from multiple public and published datasets. Using publicly available tools, we analyzed drug candidates for prevention or treatment of CKD progression based on ESRD-related genes.

Results: We identified a total of 922 differentially methylated positions (DMPs) at genome-wide significance ($P < 9e-8$). Regulatory function analysis of these DMPs have implicated 1255 candidate ESRD-related genes, which are enriched for biological processes related to immunity, GTPase activator activity, and signal complex assembly. All the candidate genes were enriched in key regulatory elements for gene function, including accessible chromatin elements. Of these candidate ESRD-related genes, some are the targets of investigational or approved drugs. Mendelian randomization revealed some causal association between DMPs and kidney function (eGFR/eGFR decline).

Conclusions: Our study demonstrated that DNA methylation play a significant role in the progression of kidney disease. Our study has not only identified DMPs as potential biomarkers for predicting renal progression and further implicated genes as potential therapeutic targets for ESRD treatment.

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TH-PO459

Aberrant Splicing Caused by Intronic Variants Positioned at Third to Fifth Nucleotides in COL4A5

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Introduction: Alport syndrome is an inherited kidney disease caused by the variants of *COL4A3, COL4A4,* or *COL4A5*, which encode type IV collagen. Among them, approximately 80% of cases have X-chromosome-linked pathogenic variants of *COL4A5*. According to recent advances in genetic analysis, a number of novel variants have been detected in Alport syndrome. It has been already known that single nucleotide substitutions in the introns positioned at 1st and 2nd from the last nucleotide of exons always cause aberrant splicing in general.

Case Description: Methods: We extracted intronic 11 variants positioned at 3rd, 4th, and 5th from the last nucleotide of exons in *COL4A5*, in our Alport syndrome cohort from January 2006 to July 2022. We performed minigene in-vitro splicing assays, and if available, we also performed messenger RNA (mRNA) sequences obtained from patients' samples. Results: The variants' positions are as follows; 3rd in three, 4th in two, and 5th in six patients. All 11 patients had hematuria, and at least 9 of them had also proteinuria. The minigene splicing assay revealed aberrant splicing, particularly upstream entire exon skipping in all variants. Moreover, the results of mRNA sequences in six cases were consistent with those of the minigene splicing assay results.

Discussion: This study revealed that the intronic variants positioned at 3rd, 4th, and 5th from the last nucleotide of exons in *COL4A5* are highly likely to cause aberrant splicing. It is also revealed that the hybrid minigene splicing assay may be useful, especially when patients' samples were not available for mRNA sequences. Intronic variants close to the exons are likely to be pathogenic and when those intronic variants are detected pathogenicities need to be evaluated.

TH-PO460

Monogenic Disease Variants in the Swiss Kidney Stone Cohort and Stone-Free Controls

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Background: With a lifetime prevalence of 10%, kidney stones (KS) are among the most common diseases. KS disease (KSD) has a complex pathogenesis influenced by a variety of factors, including dietary intake, fluid consumption, metabolic abnormalities, and a genetic predisposition. A thorough understanding of both the genetic and biochemical factors is crucial for a better diagnosis, therapy and prevention. However, data from larger cohorts with KSD with detailed profiling are scare.

Methods: The Swiss Kidney Stone Cohort (SKSC) is a multicenter longitudinal observational study consisting of two distinct groups: Kidney stone formers (KSF) and matching non-KSF (NKSF; status confirmed by low-dose CT scan). Blood and urine samples were collected at baseline (KSF, NKSF) and periodically over a 3-year period (KSF). Exome sequencing was performed in all participants, and variants in established KSD genes were assessed according to the ACMG/AMP criteria with subsequent genotype/phenotype analysis for KSF and NKSF.

Results: 731 KSF and 201 NKSF were included. A diagnosis of monogenic KSD was established in 10.1% of KSF. (Likely) pathogenic variants were predominantly located in genes encoding proteins involved in phosphate/calcium metabolism (*SLC34A1*, *SLC34A3*, *ALPL*, *CYP24A1*) or cystinuria (*SLC3A1*, *SLC7A9*). Of note, 4.5% of NKSFs also carried (likely) pathogenic variants in KSD genes and displayed matching biochemical parameters (e.g., NKSF with *SLC34A1* variants had comparable reduction of TmP/GFR). In addition, our longitudinal follow-up revealed that among KSFs, patients with monogenic KSD showed a significantly steeper decrease in eGFR over a 36-month period (ΔeGFR -4.9 vs. -2.0 mL/min/1.73 m^2, p=0.027).

Conclusions: The SKSC is the hitherto largest genetically analyzed KS cohort, accompanied by a control group of confirmed NKSF. The comparison with NKSFs, who also carried (likely) pathogenic variants in KS genes, suggests that KS occurrence may depend on additional factors that may be either genetic (additional rare or common variants) or environmental. Additionally, the results from genetic analysis in KS genes can help identify patients at higher risk for a faster decline in kidney function.

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TH-PO461

Mayo Clinic Experience with TRPC6 Mutations Using Clinical Whole Exome Sequencing

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Background: Integration of genomic and research testing and multidisciplinary evaluation in a nephrology cohort with CKD of unknown etiology or suspected monogenic disease provides a diagnosis in approximately a third of families in our center. The TRPC6 gene, a member of the transient receptor potential (TRP) superfamily of cation-selective ion channels, encodes the slit diaphragm-associated canonical TRP cation channel C6 protein expressed in podocytes. Around 20 missense mutations have been reported, including nine gain-of-function and five loss-of-function mutations that affect TRPC6 channel activity. We present our experience at the Mayo Nephrology Clinic with cases of proteinuric chronic kidney disease found to have TRPC6 variants.

Methods: Testing utilized kidney/nephrotic disease panels, single gene analysis, or analysis of kidney-related genes from exome sequencing. The Nephrology Genomics Board, composed of nephrologists, geneticists, and pathologists, interpreted the patients' clinical and genetic data. Kidney biopsy was performed for most patients. Variant classification followed the 2015 guidelines from the American College of Medical Genetics and Genomics and the Association for Molecular Pathology.

Results: Eight probands, all adults, were identified with TRPC6 variants and proteinuric CKD. All variants clustered in Exons 1, 2, and 13. We provided a definitive genetic diagnosis for three probands with pathogenic or likely pathogenic variants, one of which has not been reported previously. In addition, five cases had variants of interest, and among them, three had other first-degree family members with CKD as well. One of the cases with a positive family history had a sibling who was accepted for kidney donation after the donor tested negative for TRPC6 variants.

Conclusions: In summary, TRPC6-related CKD diagnoses have diagnostic and prognostic implications, enabling a more precise diagnosis and changes in management, including the evaluation of safety for living kidney donation. Furthermore, further studies on the functional analysis of TRPC6 variants may provide new insights into diagnostic precision and the mechanisms of the disease.

Age of genetic testing	c. change	p. change	Allele frequency (GNOMAD)	Functional evidence	ESRD	Pathogenicity	Family history
29	c.75 C>T	p.(R25=)	0.0074% (2)	None	CKD2. Proteinuria	VUS	n/a
36	c.432G>C	p.E144D	Not present	None	CKD1. Proteinuria >9/day	VUS	Brother. Mother. Uncle. Maternal grandfather (ESRD)
45	c.325 G>A	p.G109S	Not present	None	FSGS. ESRD. TMA. IgA	LP	Father with CKD
44	c.2699_T>A	p.Y899N	Not present	n/a	FSGS	LP	Mother
66	c.2611 C>T	p.Q871*	Not present	Premature STOP codon	ESKD	LP	n/a
74	c.2695C>T	p.Leu899Phe	Not present	n/a	CKD3. Proteinuria	VUS	Mother. Maternal great uncle
31	c.1594G>C	p.V532Leu	n/a	Highly conserved AA	CKD1	VUS	Mother. Sister
29	c.2683 C>T	p.R895C	Not Present	Activates channel	CKD2. Proteinuria	P	Father (ESRD). Uncle. Grandfather

LP: Likely pathogenic; VUS: Variant of undetermined significance

TH-PO462

TRPC6 Nephropathy: An International Registry of Prevalence and Outcome

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Background: Monogenic forms of focal segmental glomerulosclerosis(FSGS) represent an important subset of patients with nephrotic syndrome. They often have an ominous clinical course reaching end-stage renal disease(ESRD) at a young age. Variants in *TRPC6*(a non-selective calcium channel) have been described to cause autosomal dominant ESRD. Most have been described as "activating"variants, resulting in increased influx of calcium into the podocyte, precipitating the sclerosing process.*TRPC6* is a rare disease with many cases reported to date arising from a large New Zealand kindred. Recently, a compound targeting*TRPC6*has entered clinical trial-making understanding the natural history all the more important.

Methods: We established a*TRPC6*collaborative research group&developed a questionnaire focusing on natural history, variability in phenotype&gene variants. This has been circulated internationally to professionals involved in inherited kidney disease, nephrologists worldwide&those who have previously published on*TRPC6*.

Results: To date, we have received responses involving38patients worldwide(Europe, UK, Asia, Australia, New Zealand, North America and Africa) from 21 families, identifying 17 variants. The majority are missense, with commonest variants located on exons 2&13. Average age of genetic testing-32 years old. All but three patients experienced symptoms before the age of 40(six were 10 years old or younger). Presentation varied from microalbuminuria to anasarca&pre-eclampsia;most presenting with nephrotic syndrome, six presented with ESRD. Four patients were found to have hearing impairment.18patients underwent renal biopsy, 14(78%) demonstrated FSGS. 19patients progressed to ESRD-median age of 29 years old.12 patients have undergone transplantation(10 of which are still functioning). Three patients have had recurrence of nephrotic syndrome, two of which still have graft function. The third patient lost graft function after two years, aged 28. One patient died from complications related to dialysis. To the best of our knowledge the remaining are alive with self-supporting renal function&varying degrees of CKD.

Conclusions: *TRPC6* is a rare cause of monogenic ESRD presenting with nephrotic syndrome. The condition shows considerable variability in disease progression. New treatments are becoming available in effort to reduce immunosuppression burden.

TH-PO463

The Natural History and Genetics of TRPC6-Associated Podocytopathy

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Background: Pathogenic variants in TRPC6 account for a small but significant proportion of inherited podocytopathy. TRPC6 podocytopathy is caused mainly by gain-of-function mutations increasing the open probability of the encoded channel, making it potentially amenable to inhibitory drug therapy. Understanding the natural history and spectrum of genetic variation is therefore of considerable importance. Here, we report on the outcome data and mutational spectrum of a large cohort of patients with TRPC6-associated podocytopathy.

Methods: A cohort of 86 patients with TRPC6 variants and proteinuric kidney disease from 51 families was assembled. All patients underwent exome/genome sequencing and targeted Sanger sequencing. Affected regions of the TRPC6 protein were visualized using the cBioPortal mutation mapper, and predicted effects of mutations on the TRPC6 protein were generated using several validated in silico scoring systems (REVEL, CADD, PrimateAI, and Polyphen-2). Clinical data were collected and used for genetic correlations.

Results: 33 independent TRPC6 variants were identified. The majority of variants had high pathogenicity scores, though only 45% of them have existing ClinVar annotation. Variants were clustered in 3 regions, with one cluster in the early ankyrin repeat, a second in the transient receptor ion channel (TRP_2) domain, and a third at the C-terminal end. Within the cohort, age of onset of kidney disease ranged from <1 year to 53 years, with a median of 19 years. Data regarding progression to ESRD were available for 65% of patients; of these, 68% developed ESRD, with a median age of 31 years (ranging from 1 to 57 years).

Conclusions: TRPC6-associated podocytopathy is a rare cause of genetic FSGS. We have assembled a large cohort of patients, demonstrating high intra- and inter-familial variability in age at presentation and outcomes, and that the resulting kidney disease is progressive and frequently results in ESRD. Granular clinical genetic and kidney pathology correlations are ongoing.

Funding: NIDDK Support, Commercial Support - Actio Biosciences

TH-PO464

Five Cases with MAFB Variants

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Introduction: The pathogenic variants in *MAFB* gene cause multicentric carpal tarsal osteolysis syndrome (MCTO) (OMIM: # 166300), an N-terminal variant characterized by progressive destruction of the bones, and Duane retraction syndrome (DRS) (OMIM: # 617041), a C-terminal variant characterized by congenital eye movement abnormalities, whose inheritance pattern is autosomal dominant. Nephropathy have been reported in about half of the patients with MCTO and in five patients in three families with DRS. Only one case with DRS family history of nephropathy without extrarenal manifestations (isolated-FSGS) has been reported in the past.

Case Description: Five cases with pathogenic variants in *MAFB* were diagnosed in our department, four with MCTO and one with isolated-FSGS. Among four cases with MCTO, case1 showed congenital nephrotic syndrome (CNS), case 2 nephrotic syndrome, case 3 persistent proteinuria, and case 4 bone lesions, respectively. Genetic analysis revealed heterozygous missense variants in all four cases with MCTO (case 1 and 2: c. 212 C > T, p. (Pro 71 Leu), case 3: c. 188 C > A, p. (Pro 63 Gln), and case 4: c. 188 C > G, p. (Pro 63 Arg)), all of which were de novo variants and N-terminal side. Case 1, case 2, and case 3 developed nephropathy at the ages of 0 months, 1 year 11 months, and 3 years, and led to end-stage kidney disease (ESKD) at the ages of 6 months, 3 years and 20 years, respectively. On the other hand, the isolated-FSGS patient has developed persistent proteinuria since12 years old, but his renal function was still normal at the age of 19. Genetic analysis revealed a novel heterozygous missense variant at c. 755 C > G, p. (Ala 252 Gly) which was a de novo variant and C-terminal side.

Discussion: Case 1 was the youngest case of developing ESKD and the first case manifesting CNS. In case 5, who was the isolated-FSGS case, a variant near the DRS hotspot was identified, but no eye movement abnormalities were observed. This case is the second case showing isolated nephropathy among cases with *MAFB* variants. MCTO should be included in the differential diagnosis as a cause of CNS disease. Isolated-FSGS may be a new phenotype of *MAFB* abnormalities different from MCTO and DRS.

TH-PO465

RAAS Inhibition Delays Onset of Nephrotic Syndrome due to TRPC6-Mediated FSGS: A Case Report of a Sibling Pair

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Introduction: Transient receptor potential channel (TRPC6) is a slit diaphragm protein located on the podocyte, and a known genetic cause of focal segmental glomerulosclerosis (FSGS). Upregulation of TRPC6 channel activity is proposed to disturb podocyte structure, leading to proteinuria. ACE inhibitors (ACEi) demonstrate reno-protective benefits, reduction in proteinuria, and are commonly used to reduce proteinuria in FSGS. Here we describe progression to symptomatic nephrotic syndrome in a sibling pair with TRPC6 mediated steroid resistant FSGS as a function of early vs. late initiation of ACEi.

Case Description: Sibling A, the older of the two affected siblings, presented to care at 3 years of age with generalized edema, hypoalbuminemia (1.6g/dL), and nephrotic range proteinuria (UPCR 35mg/mg). Family history revealed that the child's father had end stage kidney disease of unclear etiology at the age of 3 years. Genetic testing of the child and parents demonstrated an autosomal dominant mutation in TRPC6 ((c.523C>T) [p.R175W]). Sibling A was unresponsive to steroids and cyclosporine and progressed to dialysis dependence due to fluid overload and pulmonary edema. Sibling A underwent kidney transplantation without recurrence of proteinuria. Sibling B, whose genetic diagnosis was made shortly after birth, was immediately started on RAAS inhibition, which was then maximally up-titrated (0.6mg/kg) as tolerated by blood pressure. He eventually underwent unilateral nephrectomy at age 4 to aid with proteinuria reduction. At age 5, nephrectomy of the remaining kidney was pursued with transition to peritoneal dialysis and preparation for kidney transplant. The age at dialysis dependence was 3 years in Sibling A and 5.5 years in Sibling B.

Discussion: In summary, this report describes delay in progression to symptomatic nephrotic syndrome in a child with TRPC6 mutation due to early exposure to ACEi. The reno-protective mechanisms of ACEi are not fully understood and include proteinuria reduction and anti-fibrotic effects. Angiotensin II has been described to cause upregulation of TRPC6, thus aggressive blockade of this pathway may be a unique benefit to patients with TRPC6 mutations. A comparison of the siblings reported here would suggest that ACEi may significantly delay symptomatic nephrotic syndrome when started early and dosed maximally.

TH-PO466

Clinical and Genetic Characteristics of INF2-Related Monogenic FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is a histological lesion with diverse aetiologies. Although monogenic forms of FSGS are characterized by a grim clinical course, resulting in early end-stage renal disease (ESRD), they often remain underdiagnosed. Disease-causing variants in INF2 (inverted formin 2), which encodes an essential actin regulatory protein, have been identified as the most common cause of dominantly inherited FSGS; however, the disease has a highly heterogeneous clinical presentation and progression.

Methods: To describe the natural history of *INF2*-related FSGS, we established a *INF2* research group and produced an e-survey describing the clinical outcomes (age at presentation, disease trajectory, histological diagnosis) and genetic data (exon location, and functional domains).

Results: We have received responses from 9 European centers and collected data from 53 patients (21 families), 22 (41.5%) of these cases have not previously been published. The age of initial presentation was 26.3 ± 12.8 years, with the majority of patients presenting with proteinuria and/or edema. Among the 25 patients (47.2%) who underwent kidney biopsy, FSGS accounted for 64% of the histopathologic diagnoses. Of the available data, 18 had reached end-stage kidney disease with a mean time to ESKD of 7.8 years from the presentation. Ten patients have undergone transplantation, and 8 patients had associated Charcot-Marie Tooth Neuropathy. Most families [19/22; 86.4%] had missense variants spanning exons 2 to 4 that localize to a diaphanous inhibitory domain.

Conclusions: *INF2* is an increasingly recognized cause of monogenic kidney disease that can lead to ESKD and has an important impact on responses to treatment. Continued efforts are required to determine phenotype variability and disease severity of *INF2*-related FSGS globally.

TH-PO467

Novel Double-Dominant Mutations of COL4A4 Gene Causing Alport Syndrome in a Hispanic Family

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Introduction: Autosomal recessive (AR) and Autosomal dominant (AD) disease account for 10-15% and 20-30% respectively of patients with Alport syndrome due to genetic defects in either the COL4A3 or COL4A4 genes. Here we report family of four patients with microscopic hematuria and proteinuria caused by 2 novel mutations of COL4A4 gene.

Case Description: We present a 13-year-old male patient who was presented with microscopic hematuria and proteinuria since the age of 4. Patient had normal audiology and ophthalmologic examination and normal renal function including serum creatinine. His brother, mother, and father had microscopic hematuria but no other symptoms. Genetic testing was performed for all four individuals using Next Generation Sequencing (NGS, Illumina) and confirmed COL4A4 gene mutation with 2 novel variants that is predicted to disrupt the canonical splice acceptor site for exon 9 and 29. The first intronic variant, *NM_000092.5:c.559-2A>T,* is predicted to abolish canonical splice acceptor activity while the second intronic variant, *NM_000092.4:c.2545+2T>G,* alters the highly conserved splice donor site for exon 29 and is predicted by all four splice site prediction tools queried to abolish canonical splice donor activity. Both variants are expected to result in altered function of the COL4A4 gene product as a result of aberrant splicing. Of these mutations, our patient has bi-paternally inherited variants with compound heterozygosity, while the rest of his family showed only one pathogenic variant, which can explain the severity of his microscopic hematuria and proteinuria.

Discussion: Here we report unusual double dominant inheritance pattern in a 13 year old boy who has inherited defective genes from both affected parents. These type of patients may have worst prognosis than other forms of Alport syndrome. Current classification needs to be revised in view of newer genetic information.

Clinical features and genetic findings in a family with Alport syndrome

Subject	I (index case)	II (brother)	III (father)	IV (mother)
Sex	M	M	M	F
Age	13	23	54	52
Genotype	Heterozygous	Heterozygous	Heterozygous	Heterozygous
Variants	c.559-2A>T (p.?) c.2545+2T>G (p.?)	c.2545+2T>G (p.?)	c.2545+2T>G (p.?)	c.559-2A>T (p.?)
Classification	Likely pathogenic	Likely pathogenic	Likely pathogenic	Likely pathogenic
Microscopic hematuria	3+	1+	1+	1+
Urine protein/creatinine ratio	1.4	<0.2	<0.2	<0.2

TH-PO468

Therapeutic Strategies for PodR138Q Nephrotic Syndrome

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Background: The most common missense mutation in podocin, Pod^{R138Q}, results in steroid-resistant nephrotic syndrome. Pod^{R138Q} causes the podocin to be trafficked incorrectly resulting in it being trapped in ER and degraded leading to aberrant function of the slit diaphragm. Understanding the mechanism of this mis-trafficking and degradation may lead to new therapeutic strategies for treating this disease.

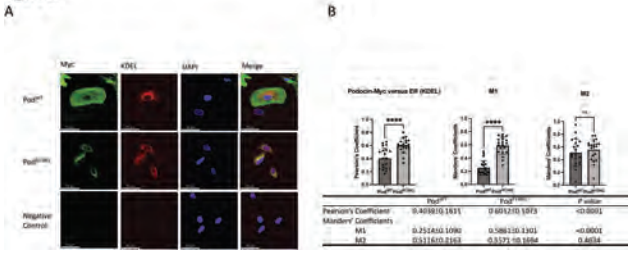
Methods: Both Pod^{WT} and Pod^{R138Q} were overexpressed in immortalized human podocytes. These cells were treated with MG132 (proteosome inhibitor), bafilomycin A1 (lysosome inhibitor), and kifunensine (Kif) (ER mannosidase I inhibitor). Podocin localization/tyrafficking was analyzed by western blotting and immunofluorescence.

Results: Pod^{R138Q} had higher co-localization coefficients with ER than Pod^{WT} (Fig 1). Pod^{WT} was mainly degraded by the lysosome, and Pod^{R138Q} degraded only by the proteosome (Fig 2A, 2B). Blocking podocin proteosomal degradation with MG132 resulted in Pod^{R138Q} being localized to plasma membrane lipid rafts (Fig 2C). Kif leads to the accumulation of high mannose N-glycan podocin (Fig 2B). High mannose N-glycan Pod^{R138Q} had affinity to calnexin (Fig 2D), and this implies that Pod^{R138Q} is degraded via ER-associated degradation (ERAD).

Conclusions: Pod^{WT} is mainly degraded by the lysosome whereas Pod^{R138Q} undergoes ERAD. By using a proteasome inhibitor, Pod^{R138Q} can be rescued correctly trafficked to lipid rafts. This finding could suggest a new therapeutic target for medical intervention for Pod^{R138Q} nephrotic syndrome.

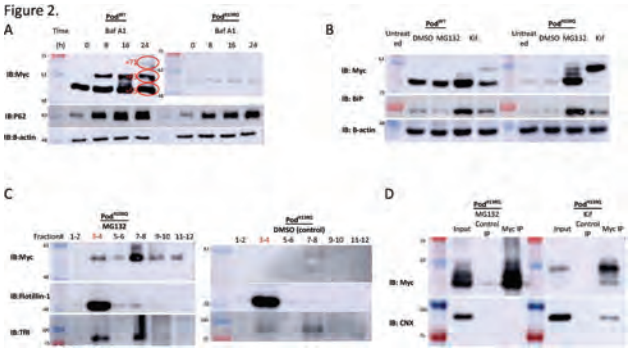
Funding: Private Foundation Support

Figure 1.



The colocalization coefficients between podocin and ER.

Figure 2.



Podocin treated by bafilomycin A1, MG132, and Kif (2A, 2B). Sucrose gradient centrifugation showed MG132 treated Pod^{R138Q} in lipid rafts (2C). Co-IP showed high mannose Pod^{R138Q} interacting with calnexin (2D).

TH-PO469

Efficacy and Mechanism of Dapagliflozin in Alport Syndrome

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Background: Alport syndrome(AS) is a hereditary kidney disease caused by *COL4A3/4/5* mutation. Currently, the standard therapy is merely RAASi, thus new treatment for AS is urgently needed. SGLT2 inhibitor has been approved for the treatment of diabetic nephropathy and chronic kidney disease, while its therapeutic effect on AS is unknown.

Methods: We conducted an observational, single-arm, prospective study based on AS patients with heterozygous mutations of COL4A3/A4/A5 from May 1, 2021, to August 1, 2022, in Shanghai Ruijin Hospital. Participants were treated with dapagliflozin 10mg per day. Proteinuria and serum creatinine were assessed every 3 to 6 months. We also investigated the effect of dapagliflozin on AS mice. *Col4a3* p.C1615Y homozygous mutant mice were used as an AS model. Mutant and wild-type mice(16-17-week -old) were administered with dapagliflozin (10mg/kg), or vehicle in drinking water, and the blood, urine, and kidney samples were collected after 28 days of treatment.

Results: Nine AS patients with heterozygous mutations of COL4A3/A4/A5 were included in this study. There are five males and four females, the average age was 40 years, and all patients were followed up 12 (11.5-17.0) months. The urine protein was 1.66 (1.06-1.90) g at baseline and 0.70 (0.50-2.21) g at the last follow-up time, with a 58% decrease from baseline. The eGFR at last time was 72.5 (61.7-80.1) ml/min/1.73$m^{2.}$ no statistical significance was shown compared with the baseline 66.3 (55.7-101.5) ml/min/1.73m^2. No adverse events were observed in these patients. Consistent with the observational study, the animal study also showed that Dapagliflozin significantly alleviated proteinuria (urinary albumin creatinine ratio). We also observed that mutant mice treated with dapagliflozin exhibited significantly reduced transcript levels of renal proinflammatory cytokines and fibrotic markers, including Ccl2, Ccl5, Cxcl10, Vimentin, and Col1a1 as compared to vehicle-treated mutant mice. These data were also supported by H&E and F4/80 IHC staining showing decreased immune cell infiltration in kidney tissues of dapagliflozin-treated mutant mice.

Conclusions: Altogether, these results suggest that dapagliflozin is a promising treatment for AS patients, and further studies are required to elucidate the precise mechanism of SGLT2 inhibitors on retarding AS progression.

Funding: NIDDK Support

TH-PO470

Phenotypic Spectrum Analysis and Molecular Mechanism Study of PAX2 Variants in the Chinese Population

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Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) is the leading cause of renal failure in children. Dysfunction of transcription factors can cause human and mouse CAKUT. Variants in *PAX2* gene are widely reported to cause CAKUT with or without optic nerve abnormalities (Renal coloboma syndrome, RCS). Interestingly, heterozygous variants in *PAX2* gene were also reported to cause Focal Segmental Glomerulosclerosis (FSGS). However, the mechanism is not well studied.

Methods: Variants in *PAX2* gene and phenotypic spectrum from 16 individuals were summarized. Functional effects of different *PAX2* variants were confirmed by constructing wild-type and mutant *PAX2* overexpression plasmids. Minigene splicing assay was performed to test function of splicing variants. The plasmid of mutant *PAX2* gene associated with FSGS was also transfected into human podocytes. Meanwhile, we further performed RNA-seq to analysis the different signaling between different phenotype.

Results: A total of 16 individuals with 12 different variants *PAX2* variants were included in this study. Among them, nonsense mutations (5/16, 31%) were the main type of variation. One variant caused FSGS phenotype. In vitro study, nonsense mutations produces truncated proteins and damaging the protein stability. Different *PAX2* gene variant proteins all significantly reduced the expression level of *PRS4*-luc. Both c.43+1G>A and c.213-2A>G in *PAX2* gene demonstrated abnormal splicing of mRNA. The FSGS phenotype-associated *PAX2* gene variant c.975C>A mainly shows damage to podocytes dominated by mitochondrial dysfunction. Furthermore, by RNA-seq, we showed *PAX2* gene mutations associated with CAKUT phenotype, mainly involved in PI3K-Akt signaling pathway, neural development, extracellular matrix and other factors, while FSGS phenotype-associated *PAX2* gene variants, mainly involved in cell adhesion, actin cytoskeleton related to podocyte development.

Conclusions: Our study showed different *PAX2* gene variants cause different phenotype. Functional study showed *PAX2* gene mutations associated with CAKUT phenotype are mainly involved in PI3K-Akt molecular pathways, neural development and other factors, while *PAX2* gene mutations associated with FSGS phenotype are mainly involved in cell adhesion, actin cytoskeleton and the development of podocytes.

TH-PO471

A New BMP-4 Gene Mutation Associated with Adult Focal Segmental Glomerulosclerosis (FSGS)

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Introduction: FSGS has been associated with numerous gene defects in children, adolescents & adults. We describe a new BMP-4 gene mutation associated with adult onset FSGS treated successfully with combined supratherapeutic ACE inhibitors with an ARB.

Case Description: In 1994 a 40 year(yr) old non-smoking obese man developed nephrotic syndrome & hypertension. His daily urine protein excretion was 3.6 gms, iothalamate gfr 81 ml/min, s creatinine 1.2 mg/dl, s albumin 3.0 gm/dl & cholesterol 400 mg/dl. He had no signs of systemic diseases. C3 & C4 complements, ANA, ANCA, immunofixation, hepatitis A, B & C were normal. A renal biopsy showed: Light: 3/16 glomeruli with focal glomerular sclerosis & moderate tubular & interstitial sclerosis. IF: completely negative. EM: increased measangial matrix with focal foot process fusion, thickened basement membranes & no immune deposits. A Dx of FSGS. NOS possibly due to obeisty was made. He was treated with supratherapeutic lisinopril 40 mg bid and valsartan 160 mg a day for 30 years despite retraction of the Lancet COOPERATE trial in 2012. His decrease in gfr over 29 yrs was only 1.8 ml/mim/yr. His urine protein decreased to 1 gm after 6 yrs & was only 1 gm/d until 2015 when it increased to 1.5 gm/d, & then to 2.2 gm in 2022. His gfr gradually declined to 65 ml /min in 2000, 50 ml/min in 2010, 36 ml/min in 2015 & 29 ml/min in 2023. A Renasight gene panel (Natera, Austin, TX) showed: a c 124G>C (pAla 42 Pro) mutation, codon 42 missense on exon 3 guanine for cytosine.

Discussion: Loss of function mutations in BMP-4 are associated with CAKUT. A BMP-4 gain of function mutation in animal studies shows increased SMAD which inhibits podocyte VEGF leading to shrinkage & immature glomeruli (H.Euda, JASN

19:685, 2008). In addition Iv and intravitreal VEGF inhibitors in humans can cause FSGS (CC Estrada JASN 30:187, 2019). We conclude that the BMP-4 mutation in our pt could lead to inhibition of intraglomerular VEGF inducing FSGS. Supratherapeutic ACE inhibitors with an ARB may slow the loss of gfr in FSGS & could be used as a control for a study against sparsentan for FSGS.

TH-PO472

ADCK4 Nephropathy in Identical Siblings

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Introduction: *ADCK* mutations are recently documented cause of coenzyme Q10 (CoQ10) nephropathy, which emerges during adolescence and progresses to end-stage renal disease in early adulthood. Here, we present the identical twin sisters who were diagnosed with ADCK nephropathy, exhibiting divergent clinical severity.

Case Description: The elder twin displayed proteinuria (0.5 g/day), and kidney biopsy revealed focal segmental glomerulosclerosis (FSGS) during her mid-10s. During initial pregnancy, urinary qualitative tests yielded results ranging from 0 to 2+. During subsequent pregnancy, in late 20s, proteinuria gradually escalated to 3 to 4+. Six months post-delivery, the lab results were as follows: albumin 4.3 g/dL, estimated glomerular filtration rate (eGFR) 126 ml/min/1.73, and urine protein-to-creatinine ratio (UPCR) 3.0 g/gCr. Kidney biopsy demonstrated FSGS (NOS variant) along with mitochondrial accumulation within the podocyte. Despite the initiation of steroid, including pulse steroid therapy, and cyclosporine, proteinuria persisted. Four years later, immunosuppression was discontinued. In late 30s, UPCR increased to 3.6 g/gCr, prompting the reintroduction of steroid, cyclosporine, and rituximab. Although UPCR gradually declined to 1.0 g/gCr, eGFR decreased to 50 ml/min/1.73. Due to steroid-resistant proteinuria, progressive renal dysfunction, pathological findings, and a familial history of FSGS, genetic analysis was conducted, revealing a homozygous pathogenic mutation in *ADCK4*. Administration of CoQ10 resulted in complete remission of proteinuria (UPCR < 0.3 g/gCr) and restoration of renal function (eGFR 71 ml/min/1.73). The younger twin also exhibited proteinuria (0.4 g/day), and kidney biopsy demonstrated FSGS during her mid-10s. She had no history of pregnancy, delivery, or comorbidities. At the age of 39, her renal function remained preserved, with an eGFR of 92 ml/min/1.73 and UPCR of 0.23 g/gCr.

Discussion: ADCK4 nephropathy represents a renal-limited subtype of CoQ10 nephropathy, exhibiting a favorable response to CoQ10 supplementation. Therefore, it is crucial to comprehend the clinical characteristics to facilitate genetic testing in appropriate instances. Our case study vividly illustrates a wide spectrum of clinical severity, even in identical twins, thus emphasizing the influence of environmental factors on the exacerbation of ADCK4 nephropathy.

TH-PO473

Colocalization of Genetic Associations with Plasma and Urine Proteins Provide Insights into Renal Protein Handling and Related Clinical Outcomes

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Background: Genetic mechanisms underlying tubular handling of proteins in the kidney can provide valuable insights into the pathogenesis of kidney-related diseases. We generated urine proteomics data and integrated it with large-scale proteomics, genomics, and biobank data to test whether genetic influences on protein levels are shared between plasma and urine, hypothesizing that shared signals represent filtered or tissue-shared proteins secreted into the urinary tract.

Methods: We employed genome-wide association study (GWAS) results of 364 plasma proteins measured in 35,559 Icelanders with significant ($p<2e-9$) associations in 2,279 genomic regions. We extracted respective regions from GWAS of 353 proteins measured in urine of 754 participants of the German Chronic Kidney Disease study and conducted genetic colocalization analyses for plasma-urine protein pairs. To link the results with clinical outcomes, we additionally incorporated genetic associations with 1,419 medical conditions from the UK Biobank (N=400,000).

Results: Strong evidence for colocalization was detected for 105 of 2,371 plasma-urine pairs, suggesting a single causal genetic variant affecting both plasma and urine protein levels. The proportion of pairs consisting of the same protein was significantly higher among the colocalizing pairs (23/105, 21.9%) than among all pairs (54/2371, 2.3%; p=5e-13), and included known and emerging biomarkers such as GDF15 for adverse kidney outcomes. We further detected 3,001 colocalized pairs of plasma protein and clinical outcome (out of 37,030), entailing kidney diseases, of which 1,141 (38%) enlisted plasma proteins that also colocalized with urine proteins. Interesting examples encompassed a shared genetic basis for urine and plasma levels of Kidney Injury Molecule-1 (HAVCR1), hypertension and kidney stones, as well as for prostate-specific microseminoprotein beta in urine and plasma and prostate cancer.

Conclusions: We report colocalizing proteins that share genetic architecture in plasma and urine, additionally linking them to medical conditions. The generated resource can reveal circulating biomarkers of diseases that are also informative when quantified in urine, and will facilitate a deeper understanding of renal protein handling and its link to kidney diseases.

Funding: Government Support - Non-U.S.

TH-PO474

Molecular Mechanisms of Novel NPHS2 Pathogenic Variants and Proposed Therapeutic Interventions

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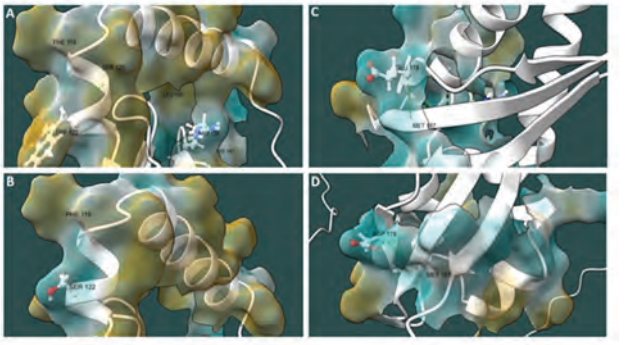
Background: The human *NPHS2* gene encodes podocin protein, an essential component of GBM. Mutations in *NPHS2* causes steroid-resistant FSGS/nephrotic syndrome. Podocin signaling is essential to the structure and function of glomerular podocytes. Defining the molecular dysfunctions of this novel *NPHS2* mutations is imperative to improving our understanding of the dynamic roles of podocin protein and potential therapeutic interventions.

Methods: We study the molecular and biochemical properties of the *NPHS2* pathogenic variants and podocin protein using patient-derived induced pluripotent stem cell (piPSC) and reprogrammed podocytes. To further study the implications of the W122S mutation, *in silico* analysis was performed. ColabFold was used to predict the structure of wild-type podocin and W122S mutated podocin.

Results: Try122 is located in podocin's transmembrane region, where the protein inserts itself into the inner leaflet of the plasma membrane. It is here where podocin recruits nephrin and CD2AP into lipid rafts, forming a multiprotein signaling complex. This complex was found to be integral in the formation of the podocyte's actin cytoskeleton. Given its predicted location on the outer surface of the transmembrane region of podocin, Try122 supports podocin's ability to embed itself in the plasma membrane.

Conclusions: Distinct differences in lipophilicity and structure of the transmembrane domain are revealed. Further work using our patient's derived stem cell will allow us to understand the signaling cascade and therapies.



Structure prediction results of wild type podocin residues and their respective mutations. Visualized with hydrophobicity maps on surfaces and contacted residues. A. Transmembrane tryptophan 122 contacting Ser120 and Phe119. B. Podocin mutant W122S contacting Phe119 and losing contact with Ser120. Distinct differences in lipophilicity and structure of the transmembrane domain are visible. C. Glutamic acid 178 protrudes from PHB domain and contacts Met187. D. E178D mutant shows a similar structure to wild type form and maintains contact with Met187.

TH-PO475

Molecular Mechanisms of Neonatal-Onset WT1-Related Glomerulopathy

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Background: Human mutations in *WT1*, or *Wilms' tumor 1*, lead to severe, progressive glomerulopathy marked by heavy proteinuria and progression to end-stage renal disease (ESRD). A subset of patients with *WT1* variants present at birth with rapid progression to renal failure. We sought to determine the genotypic spectrum and molecular mechanisms causing neonatal onset *WT1*-related disease.

Methods: We performed a systematic literature review of neonatal-onset (<1 month of age) *WT1*-related glomerulopathy and of all cases with the *WT1* p.Arg467Trp or p.Arg467Gln variants. Cell biological techniques were utilized to assess the cellular localization, DNA binding, and transcriptional activity of wild type and mutant WT1 proteins.

Results: We identified 21 cases with pathogenic *WT1* variants who had disease onset by 1 month of age and ESRD by 6 months. 17/21 (80%) cases had mutations at one of two DNA-binding residues: p.Arg439 (n=10) and p.Arg467 (n=7). Notably, there was enrichment for the p.Arg467Gln variant (n=6) and no cases with the p.Arg467Trp variant, which is a common mutational hot-spot. We found that nearly all individuals with the p.Arg467Gln variant developed early onset renal failure (median age at ESRD 1.2 months, n=15), while those with the p.Arg467Trp variant had a more variable disease course (median age at ESRD 21.6 months, n=40). *In vitro* studies showed that the wild type WT1 protein (in the -KTS isoform) localized diffusely within the cell nucleus, while both the p.Arg467Gln and p.Arg467Trp mutant proteins (in the -KTS isoform) localized to nuclear subdomains and failed to activate transcription. The p.Arg467Gln and p.Arg467Trp mutant proteins also have significantly reduced DNA binding, suggesting that these mutations do not function in a dominant manner via activation of aberrant transcriptional pathways.

Conclusions: *WT1* mutations at the p.Arg439 and p.Arg467 loci are associated with neonatal-onset disease and early progression to ESRD. The p.Arg467Gln variant leads to more severe disease than the p.Arg467Trp variant but there was no functional difference between the two mutant proteins with regards to cellular localization or DNA binding. Further studies will be needed to better elucidate the mechanisms of neonatal-onset WT1-related glomerulopathy.

Funding: NIDDK Support, Other NIH Support - National Institutes of Health, Cancer Prevention and Research Institute of Texas

TH-PO476

Rescue Mechanism for Glomerular Endothelial Lipid Metabolic Dysfunction in Alport Syndrome

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Background: Glomerular endothelial dysfunction plays a key role in the development of chronic kidney disease (CKD). In Alport syndrome (AS, caused by mutations in collagen IVα3α4α5) damage to the glomerular endothelial cells (GEC) occurs before onset of heavy proteinuria and is characterized by altered fenestration size and glycocalyx deposition. Despite this evidence, the role of GEC in Alport progression is poorly understood. Here, we elucidate the role of lipids in GEC injury in an animal model of AS, and the potential of using amniotic fluid stem cell (AFSC) derived extracellular vesicles (EVs) as a rescue strategy to restore glomerular homeostasis.

Methods: The phasor approach to FLIM (fluorescent lifetime imaging microscopy) was applied to evaluate the metabolic changes in the kidneys (and particularly in the glomeruli and GEC) of AS and WT mice. GEC isolated by FACS from tdTomato-reporter AS and WT mice at 4-months of age were compared by bulk RNA-seq and lipidomics. In vitro, silencing experiments on primary human GEC were performed to study the role of fatty acid synthase (FASN) in GEC metabolic dysfunction. FASN-carrying AFSC-EVs and control nanoparticles were applied both *in vitro* and *in vivo* to restore lipid homeostasis in GEC.

Results: In AS mice, RNAseq analysis of GEC revealed changes in the metabolic genes, (including FASN) and pathways associated with uptake, synthesis and oxidation of fatty acids. FLIM studies showed that changes in the metabolic fingerprint of the GEC correlated with increasing age and severety of disease in AS mice. Lipidome analysis found high abundance of triglycerides in GEC isolated from AS. We confirmed accumulation of lipid droplets in the glomeruli of AS mice, as well as in FASN KO human primary GEC, *in vitro*. These results suggest potential mitochondrial dysfunction in GEC. AFSC-EVs treatment restored lipid homeostasis in GEC, both *in vitro* and *in vivo*.

Conclusions: We report for the first time a lipid metabolic dysfunction in Alport GEC, and the ability of AFSC-EVs to rescue this phenotype. Therefore, better understanding of the role of GEC in AS could lead to the development of targeted new therapies for the treatment of this and other forms of CKD.

Funding: Private Foundation Support

TH-PO477

Apolipoprotein M Treatment Restores Kidney Function in Mouse Model of Alport Syndrome

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Background: Studies suggest that altered Apolipoprotein M (APOM) expression is associated with dyslipoproteinemia, atherosclerosis and possibly diabetes, obesity, and inflammation. However, little is known about the role of APOM in the kidney. We previously reported decreased glomerular APOM expression in glomerular diseases. ApoM is a protein linking cholesterol and sphingolipid metabolism, which are both important players in the development of glomerular injury in Alport Syndrome (AS) among other glomerular disorders. Here we test the hypothesis that systemic replacement of ApoM in AS protects from the development of kidney failure.

Methods: To study the role of APOM in the kidney, we analyzed renal APOM expression in a mouse model of progressive renal disease associated with Alport Syndrome (Col4a3 KO mice). We found reduced mRNA and protein expression of APOM in the kidneys of Col4a3 KO mice. To investigate if APOM replenishment would improve renal function in this mouse model, we injected Col4a3 KO mice with recombinant human APOM (rh-APOM). Three groups of mice were studied: (1) Col4a3 +/+ (WT) + vehicle, (2) Col4a3 -/- (KO) + vehicle, and (3) Col4a3 -/- (KO) + rh-ApoM. rh-APOM was administered by weekly intraperitoneal injection starting at 4 weeks of age and until sacrifice at 8 weeks of age.

Results: APOM mRNA and protein expression were markedly reduced in glomeruli and podocytes from Col4a3 KO mice compared to WT mice. Treatment of Col4a3 KO mice with rh-APOM normalized renal APOM levels and prevented the development of renal failure (serum BUN and creatinine), proteinuria (urinary albumin/creatinine ratio), and protected from the development of glomerulosclerosis, tubular atrophy and dilation.

Conclusions: Our results suggest that restoring renal APOM levels in an experimental model of AS protect from renal failure and that treatment with rh-APOM may represent a novel therapeutic strategy for the treatment of glomerular diseases.

Funding: NIDDK Support

TH-PO478

Exploring the Molecular Basis of Ramipril-Induced Nephroprotection in Alport Syndrome

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Background: Renin-angiotensin system inhibitors such as angiotensin-converting enzyme Inhibitors (ACEi) play a central role in the treatment of CKD, and they are known to reduce proteinuria and extend kidney survival in Alport syndrome. This beneficial effect has been explained by the reduction of intraglomerular pressure and the inhibition of inflammation and subsequent fibrosis. However, the actual molecular changes induced by ACEi in the kidneys are yet elucidated.

Methods: The ACEi ramipril was administered orally (n=10 each) to a mouse model of Alport syndrome (Col4a5 knockout). Treatment was initiated at five weeks (early treatment group) or ten weeks (late treatment group) and continued until 16 weeks of age, with comprehensive evaluation including functional studies, imaging and mass spectrometry-based proteomic analysis kidney tissue.

Results: The mean urinary albumin-creatinine ratio ± SEM was significantly lower ($p<0.01$) in both the early treatment group (1417±470.3) and the late treatment group (2984±1116) compared to the no-treatment group (8902±1320). No significant differences were observed between the early and late treatment groups. Although serum BUN was not significantly different between the no-treatment and treatment groups, light microscopy showed that the early-treatment group had less cellular infiltration of the interstitial area than the no-treatment and the late-treatment group. Proteomic analysis revealed distinct proteomic profiles not only between Alport mice and wild-type mice but also between ACEi-treated Alport mice and non-treated Alport mice. With pathway enrichment analysis, we found significant enrichment for terms associated with chaperonin-mediated protein folding, extracellular matrix organisation and glycosaminoglycan metabolism in ACEi-treated mice compared to untreated mice.

Conclusions: The present study indicates that the molecular mechanisms of the nephroprotective effects of ACEi, such as the reduction of proteinuria and improved histological findings in the Alport mouse, involve proteins related to chaperonin-mediated protein folding, extracellular matrix organisation and glycosaminoglycan metabolism pathways in the kidney.

TH-PO479

Adult Male Patient of C1q Nephropathy with Heterozygous Pathogenic COL4A4 Variant

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Introduction: Autosomal dominant Alport syndrome (ADAS) is a disease with heterozygous pathogenic *COL4A3* or *COL4A4* variants. ADAS is considered to have a better renal prognosis than X-linked Alport syndrome and less likely to develop focal and segmental glomerulosclerosis. However, ADAS could predispose to IgA glomerulonephritis (IgAN). We report an adult male patient of C1q nephropathy with ADAS.

Case Description: A 47-year-old man admitted our hospital for renal biopsy. He had hematuria and proteinuria since childhood. Six years before admission, he had hypertension and chronic kidney disease (serum Cr was around 2.5 mg/dL). His maternal grandmother, maternal aunt, son, and daughter had hematuria. No one, including him, suffered from hearing loss. One year before admission, his renal function deteriorated (Cr 3.37 mg/dL) and severe proteinuria appeared (5–7 g/day). Renal biopsy showed that 25% of glomeruli had global sclerosis and 60% had segmental glomerulosclerosis. Immunofluorescence shows global granular mesangial staining for C1q and IgM. Electron microscope revealed diffuse intra-membranous deposits with GBM thickening. Genetic analysis showed that he had heterozygous pathogenic variant in *COL4A4* (c.2510G>C: p.Gly837Ala). We diagnosed him as C1q nephropathy with ADAS and started 1 mg/kg of corticosteroid for C1q nephropathy. We added cyclosporine after 1 month of treatment due to refractory proteinuria. However, because cyclosporine worsened renal function and he suffered from avascular necrosis of femoral head, immunosuppressive therapy was tapered.

Discussion: As far as we know, this is the first case of C1q nephropathy with ADAS. ADAS may also predispose to glomerulonephritis other than IgAN. Additionally, concomitant glomerulonephritis could worsen renal prognosis in ADAS patients.

TH-PO480

Genotype-Phenotype Correlations in Alport Syndrome: A Single-Center Experience

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Background: Alport syndrome is a common and heterogeneous genetic kidney disease, oftentimes leading to end-stage kidney disease (ESKD). Due to the growing availability of genetic testing, understanding the interplay between genetic and clinical features has become essential for individualized prognostication.

Methods: This is a single-center, retrospective study that included 36 adults with type IV collagen mutations. Our scope was to describe how genetic features influence renal survival, i.e., the age at renal replacement therapy initiation.

Results: A total of 28 different mutations were identified, out of which 8 had not been previously described. Mutations affecting each of the type IV collagen α chains were equally prevalent (33.3%). Six patients had multiple mutations. One patient had mutations involving all α chains. Five patients also had mutations involving podocyte and glomerular basement membrane proteins, but with no significant differences regarding proteinuria and renal survival. Most patients had a family history of kidney disease (71%). The most prevalent clinical picture was nephritic syndrome (64%), followed by isolated hematuria (24%). One third of the subjects had extrarenal manifestations, such as hearing loss (28.6%) and eye abnormalities (7.1%). There were no significant differences in laboratory findings at diagnosis between patients with COL4A3, COL4A4 and COL4A5 mutations. Eighteen patients presented with (41.6%) or later developed (8.3%) ESKD at a median age of 25.5 years old (IQR, 21.5-37.25). Six patients underwent kidney transplant. Overall kidney survival was 40.55 years (95% CI, 35.55-45.55). COL4A4 group displayed a significantly better renal survival when compared to COL4A3 (p=0.027). Hearing loss was associated with a significantly poorer renal prognosis (p<0.001). For a subgroup where follow-up data were available (44.4%), the 5-year renal survival was 68.6% and in patients with multiple mutations, a lower renal survival at 27 months was noticed (p=0.014).

Conclusions: In our study, COL4A3 mutations, presence of multiple mutations and a personal history of hearing loss were associated with a poorer renal prognosis.

TH-PO481

The NOX Inhibitor Setanaxib Combined with Ramipril Reduces Glomerular Function Decline and Fibrosis in a Mouse Model of Alport Syndrome

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Background: Alport syndrome is a rare genetic disorder, which presents in childhood or adolescence. It is caused by genetic variants affecting type IV collagen, leading to progressive kidney damage. Setanaxib, an NADPH oxidase (NOX) inhibitor, has been shown in preclinical models to reduce inflammation and fibrosis – mechanisms known to play a role in Alport syndrome disease progression. In this study, we assessed the therapeutic potential of setanaxib in a mouse model of Alport syndrome.

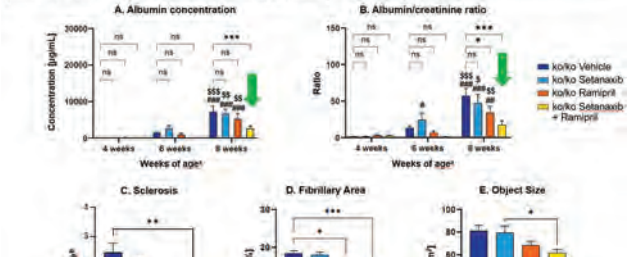
Methods: Four-week-old *Col4a3* -/- mice on 129/SvJ background (n=10 per group) were given 10 mg/kg ramipril (an ACE inhibitor [ACEi]) in drinking water, 60 mg/kg setanaxib once daily by gavage, setanaxib and ramipril combined, or vehicle, over 4 weeks. At the end of the study, kidneys were analyzed by imaging and proteomics.

Results: Urinary albumin levels and albumin/creatinine ratio were reduced at 6 and 8 weeks of age in mice receiving ramipril alone, with a further reduction seen in mice receiving setanaxib and ramipril combined (Fig. 1A,B). Histologic analysis indicated that setanaxib and ramipril combined also significantly decreased glomerular sclerosis (scored by a pathologist) and overall fibrosis (Fig. 1C-E). Proteomic and *in silico* analyses also reported increased detection of glomerular basement membrane and collagen proteins with setanaxib and ramipril combined.

Conclusions: These results indicate that setanaxib, when combined with the standard of care ACEi, induced mechanisms that reduced the decline in glomerular function and fibrosis in a well-established mouse model of Alport syndrome.

Funding: Commercial Support - Calliditas Therapeutics

Figure 1. (A) Urinary albumin concentration and (B) albumin/creatinine ratios according to treatment at 4, 6, and 8 weeks of age. (C) Periodic acid Schiff staining and pathologist's score indicating glomerular sclerosis. Sirius red staining and quantification indicating mainly interstitial fibrosis by (D) fibrillary area and (E) object size.



¹Treatment started at 4 weeks.
²The pathologist conducting the scoring was blinded to treatment.
*p<0.05, **p<0.01, ***p<0.001; $p<0.05, $$p<0.01, $$$p<0.001 (6 or 8 weeks vs 4 weeks); ##p<0.01, ###p<0.001 (8 weeks vs 6 weeks)
two-way ANOVA with Bonferroni *post hoc* test.
ANOVA, analysis of variance; ko, knockout; ns, not significant.

TH-PO482

Beyond COL4A: Combined Renal Histopathology and Genetic Testing Reveals the Genetic Complexity of Thin Glomerular Basement Membrane Disease

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Background: Improved access to genetic testing is changing the diagnostic landscape of chronic kidney disease (CKD). While renal histopathology represents the current gold standard in the differential diagnosis of CKD, the incremental diagnostic yield of genetic testing remains unknown. We aim to investigate the combined diagnostic yield of histopathology and genetic testing, and we seek to identify novel correlations between genotypes and histopathologic phenotypes.

Methods: We identified 114 patients from two academic medical centers in Boston, MA, who underwent both, kidney biopsy and kidney panel genetic testing between 1/1/2020 and 5/1/2023. We assessed pathologic diagnosis and quantifiable ultrastructural phenotypes. We then analyzed corresponding genotypes for diagnostic variants and variants of uncertain significance (VUS). Variants were grouped by genes associated with CAKUT and podocytopathy (or steroid resistant nephrotic syndrome, SRNS).

Results: Glomerular basement membrane thinning was found in 47/114 patients, representing the most common ultrastructural abnormality. We found 16 COL4A variants in 14 patients with GBM abnormalities (8 diagnostic variants, 8 VUS). The remaining patients with GBM abnormalities had variants in dominant CAKUT genes (14 variants in 12 patients) and dominant SRNS genes (15 variants in 13 patients). 4 patients had exclusively recessive SRNS variants identified. In 8 patients, GBM abnormalities did not correlate with any variant of the above categories. 12/18 patients with COL4 variants had ultrastructural evidence of segmental or diffuse podocyte foot process effacement, and 5/18 had a diagnosis of primary FSGS.

Conclusions: In our retrospective cohort of patients who underwent kidney biopsy and genetic testing, thin glomerular basement membranes represented the most common ultrastructural finding. In only one third of these patients, a COL4A variant was found. Variants in dominant CAKUT and SRNS genes were the next most common findings, reflecting the genetic complexity of TBMD beyond COL4A mutations, and suggesting alternative mechanisms of disease causation. Genetic testing for COL4A variants alone would have missed the diagnosis of TBMD in 68.9% of cases, while 3.5% of test results were found to be false positive.

Funding: NIDDK Support

TH-PO483

Diagnostic Utility of Characterizing Glomerular Basement Membrane (GBM) Collagen IV Changes by Quantitative Immunofluorescence in Paraffin Sections from FSGS Patients Carrying COL4A3/4/5 Variants

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Background: Variants in COL4A3/4/5 genes are the most common genetic abnormalities associated with FSGS patients without typical Alport syndrome (AS), linking glomerular basement membrane (GBM) collagen IV (colIV) aberrations and podocytopathy. However, variant pathogenicity is often unclear.

Methods: We developed a new method of immunofluorescence staining for collagen α5(IV) and α1/2(IV) on kidney paraffin sections and used Airyscan confocal microscopy to assess colIV levels in 17 idiopathic FSGS patients with pathogenic/likely pathogenic (P/LP) variants, variants of uncertain significance (VUS), and likely benign (LB) variants in *COL4A3/4/5* genes, respectively. Samples from 2 nephrectomies, 3 transplant surveillance biopsies, and 6 biopsies from FSGS patients without *COL4A* variants were used as controls.

Results: Our approach demonstrated collagen α3α4α5(IV) and α1α1α2(IV) in the GBM as two distinct layers, which enabled quantitative comparisons (Figure 1). The ratios of the mean fluorescence intensities of collagen α5(IV) to α1/2(IV) (α5:α1/2 FI ratios) and the ratios of the thicknesses of α5(IV) to α1/2(IV) (α5:α1/2 thickness ratio) were calculated to represent the level of collagen α3α4α5(IV) in relation to α1α1α2(IV). α5:α1/2 FI and thickness ratios were comparable across the control samples (mean ratios 1.36±0.9 and 1.97±0.63, respectively), while both ratios were drastically decreased in all patients with P/LP variants (mean ratios 0.19±0.08 and 0.94±0.48, respectively) confirming the validity of the approach. We then identified 3 VUS patients with significantly reduced α5:α1/2 FI and thickness ratios, suggesting these variants could in fact be pathogenic.

Conclusions: Our approach can serve as a new diagnostic tool to identify the subgroup of FSGS patients with underlying pathogenic *COL4A* variants, which can be confirmed with genetic testing. This may help guide immunosuppressive therapy for FSGS.

Funding: NIDDK Support

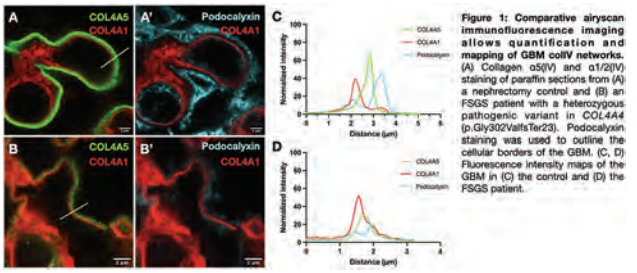

Figure 1: Comparative airyscan immunofluorescence imaging allows quantification and mapping of GBM collV networks. (A) Collagen α5(IV) and α1/2(IV) staining of paraffin sections from (A) a nephrectomy control and (B) an FSGS patient with a heterozygous pathogenic variant in *COL4A4* (p.Gly302ValfsTer23). Podocalyxin staining was used to outline the cellular borders of the GBM. (C, D) Fluorescence intensity maps of the GBM in (C) the control and (D) the FSGS patient.

TH-PO484

Sex Differences in Glomerular Protein Expression in Mice with Autosomal Recessive Alport Syndrome

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Background: Alport syndrome (AS) is a monogenic disorder that leads to progressive kidney disease, ear, and ocular abnormalities. It is caused by pathogenic variants in *COL4A3*, *COL4A4*, or *COL4A5*, which encode the α3, α4, and α5 chains of type IV collagen. *COL4A3* and *COL4A4* reside on chromosome 2q36, while *COL4A5* is on the X chromosome. We evaluated for sex differences in mice with autosomal recessive AS.

Methods: We compared differences in global protein expression in isolated glomeruli between 1-day old male and female *Col4a3* knockout (KO) and wildtype (WT) mice with mass spectrometry (MS). MaxQuant was used for analysis and statistical tests were done on Perseus. Pathway analysis was performed using Gene Ontology.

Results: At postnatal day 1 (P1), we observed more severe disease in male compared to female *Col4a3* KO mice, as evidenced by higher urine albumin-creatinine ratios (uACR) (1088 mg/mmol vs. 875.6 mg/mmol, p=0.4). 309 significantly differentially expressed proteins in the glomerulus were identified, of which 208 were downregulated and 101 were upregulated in male *Col4a3* KO mice. We also compared P1 WT male and female mice and no differentially expressed protein was detected at baseline. Interestingly, the well-known podocyte apical surface transmembrane sialoglycoprotein, podocalyxin, was upregulated in males compared to female *Col4a3* KO mice. Pathway analysis showed that *Col4a3* KO male mice also had decreased biological processes suggestive of impaired glomerular structure maintenance such as actin filament bundle assembly, cell morphogenesis involved in differentiation and endoplasmic reticulum-nucleus signaling pathway. By contrast, pathways including peptide biosynthetic process and ATP biosynthetic process were found to be increased in male *Col4a3* KO mice, possibly due to increased compensatory mechanisms.

Conclusions: One day old male compared to female *Col4a3* KO mice display more severe disease. Podocalyxin has been reported to be excreted in urine due to podocyte loss and we postulate that its upregulation in male *Col4a3* KO mice may represent compensation. Overall, glomerular proteomic comparison highlights biological pathways that can explain phenotypic differences between male and female mice with autosomal recessive AS, though its mechanistic drivers are unclear.

Funding: Private Foundation Support

TH-PO485

Frequency of Diagnostic Variants of Kidney Disease in Diabetic Kidney Disease Patients: A Single-Center Investigation

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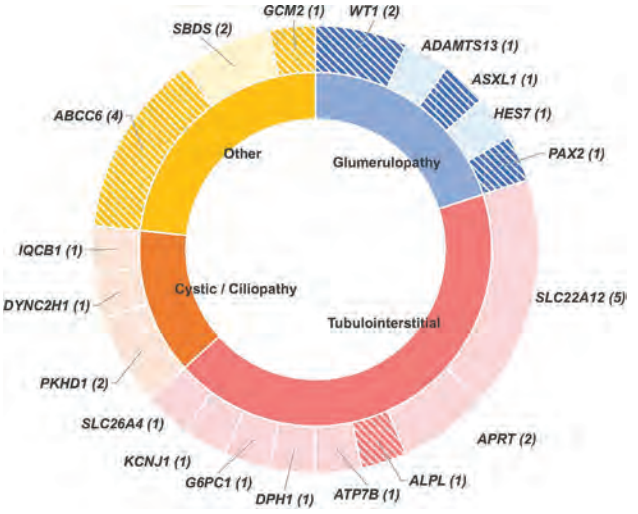
Background: Involvement of rare variants in the pathogenesis of lifestyle diseases has not been investigated in detail. The past research showed that diagnostic variants were detected only in 1.6% of cases with diabetic kidney diseases (DKD) (NEJM, 2019), but there was no mention of which cases should be genetically tested. Therefore, we performed a whole genome sequence (WGS) based analysis of pathogenic single nucleotide variants (SNVs) of DKD patients to extract the characteristics of cases with pathogenic SNVs.

Methods: We performed WGS for Japanese patients with clinically diagnosed-DKD. Variants were processed with GATK Best Practices. We defined target variants as those included in the 625 genes associated with Mendelian nephropathy and genitourinary diseases (same as analyzed genes in NEJM 2019) and classified as pathogenic or likely pathogenic by ACMG criteria. Target variants were classified into four categories: glomerulopathy, tubulointerstitial, cystic/ciliopathy, and others.

Results: Of the 79 participants, 66 (84%) were males, 70.3±0.8 ages, and 9 (11%) had a family history of kidney diseases. A total of 25 patients (32%) had the target variants, all heterozygously. There were no significant differences in clinical information such as level of albuminuria between cases with and without the target variants. There were 10 cases with the variants in genes *WT1*, *ASXL1*, *PAX2*, *ALPL*, *ABCC6*, and *GCM2*, which reportedly show an autosomal dominant (AD) manner of inheritance. Only 2 of these 10 cases had a family history of kidney disease.

Conclusions: Among clinically diagnosed Japanese DKD patients, a considerable number had kidney-related pathologic variants, which were unexpectedly large compared to the previous report. It was difficult to determine from clinical presentation or family history which cases had the target variants.



Gene names of the detected target variants are shown along with their category classification and the number of persons with them. Stripes indicate AD pattern of inheritance.

TH-PO486

Mouse and Human Studies Support DSTYK Loss of Function as a Low Penetrance and Variable Expressivity Risk Factor for Urinary Tract Anomalies and Movement Disorders

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Background: Previous work identified rare variant in *DSTYK* in humans with congenital anomalies of the kidney and urinary tract (CAKUT). *DSTYK* coding variants exist at low frequency in the general population, complicating genetic interpretation. Mouse and human studies were used to clarify the association, penetrance and expressivity of *DSTYK* variants.

Methods: We phenotypically characterized *Dstyk* knockout mice on 3 genetic backgrounds (C57BL/6J, FVB/NJ and C3H/HeJ). We expanded, characterized and re-sequenced the original family segregating the *DSTYK c*.654+1G>A splice-site variant (referred to "splice variant" below). *DSTYK* loss-of-function (LOF) and the splice-site variants were annotated in individuals across different phenotypes: a) CAKUT, b) Epilepsy, and c) amyotrophic lateral sclerosis (ALS) vs. controls. PheWAS analysis was performed using UKBB data.

Results: C57BL/6J *Dstyk*$^{-/-}$ mice exhibited a 23% penetrance of obstructive uropathy (OU). FVB/NJ *Dstyk*$^{-/-}$ mice showed a similarly low penetrance, but with added phenotypes of hypoplasia and partial duplication of the kidney and proximal ureter. C3H/HeJ mutants showed a 40% penetrance of OU, but with mild-to-moderate severity. Expansion, re-analysis and re-sequencing of the original family segregating the rare splice-site variant showed low penetrance and no alternative genetic causes for CAKUT. LOF *DSTYK* variant burden showed significant excess for CAKUT (OR=9.13, P=6.50x10^{-3}), and Epilepsy (OR=6.20, P=1.35x10^{-2}), vs. controls. Enrichment analysis for the splice variant was significant for epilepsy (OR= 6.04, P=1.72x10^{-2}). Literature review and exploratory PheWAS supported association with neurological disorders.

Conclusions: Mouse and human data support causality for *DSTYK* LoF variants. Large sequencing studies (e.g. >200,000 cases) are required to fully assess the contribution of *DSTYK* rare variants to lowly-penetrant underlying traits with relatively common population prevalence such as obstructive uropathy. Therefore, while *DSTYK* LoF variants should not be used to ascertain diagnosis or risk stratification, they may be used in clinical settings when coupled with inheritance information and clinical plausibility.

Funding: NIDDK Support

TH-PO487

Tofacitinib Suppresses JAK/STAT Pathway Hyperactivity Ex Vivo in Pediatric Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) accounts for approximately 20% of cases of pediatric nephrotic syndrome and is the leading cause of end-stage renal disease among glomerular disorders in the US. Primary FSGS is thought to be caused by a circulating factor which causes podocyte, glomerular and endothelial injury, and presumably immune dysregulation. There is growing evidence that the JAK/STAT pathway is involved in various kidney diseases, however, its role in FSGS has not been thoroughly studied. We recently identified JAK1 gain-of-function mutation in a pediatric patient with membranous nephropathy and multisystem immune dysregulation, which was successfully treated with a JAK inhibitor. We hypothesized that JAK/STAT pathway hyperactivity may play a role in the pathogenesis of pediatric primary FSGS, and may be suppressed by *ex vivo* JAK inhibition.

Methods: We recruited eleven individuals age 2-18yr with primary FSGS and ten age- and sex-matched healthy controls. Mass cytometry (CyTOF) with antibodies against STAT proteins was performed on heparinized whole blood samples to characterize JAK/STAT pathway activity in immune cell subsets. Multiplex immunoassay was performed on plasma samples to quantify circulating cytokine levels. Plasma from patients were added to healthy control peripheral blood mononuclear cells (PBMCs) and treated with or without tofacitinib for 4 hours, followed by CyTOF.

Results: The JAK/STAT pathway is overactive in 60% patients despite immunosuppression, predominantly showing increased phosphorylated STAT3 (pSTAT3) activity in T cell subsets. The level of STAT3 phosphorylation in T cells predicts lower kidney function, lower serum albumin, and increased proteinuria 1 year later. IL6 and IL17 which stimulate STAT3 phosphorylation are increased in patient plasma. Tofacitinib treatment of healthy control PBMCs incubated with patient plasma leads to reduction in pSTAT3 activity in T cell subsets, particularly in CD4+ T cells.

Conclusions: JAK/STAT pathway overactivity is present in pediatric patients with primary FSGS and predicts future severity of disease. JAK/STAT hyperactivity is likely driven by cytokine signaling and may be targeted by JAK inhibition.

TH-PO488

Validation of Multiple Office Blood Pressure Measurement: A Novel Tool for Evaluating Blood Pressure in Children

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Background: Blood pressure measurement (BPM) is a common procedure in clinical practice, but it can be challenging to obtain reliable values in children. Casual office BPM (gold standard) is all but accurate and ABPM may be difficult to perform or even misleading. Multiple Office Blood Pressure Measurement (mOBPM) was developed at our Center in 2010 for evaluating BP with serial and automated measurements (≥10 in at least 30 min) using standard oscillometric devices. BP values were uploaded in a software and coefficient of variation (CV) was calculated after excluding outlier values (<5th and & >95th centile of the recorded values).

Methods: The present study compares results obtained with mOBPM vs ABPM in children addressed to our Center for suspected arterial hypertension (AH). Given that children develop myocardial hypertrophy soon after the development of AH, Cardiac Mass Index (CMI) was used as gold standard to categorize patients as hypertensive or normotensive.

Results: Twenty-five children were enrolled. AH was confirmed by increased CMI in 5 (20%) of them. ABPM identified 11 (44%) hypertensive children vs 12 (48%) identified by mOBPM. Sensitivity and specificity were 60% and 60% using ABPM vs 100% and 65% using mOBPM. PPV and PNV were 27% and 86% vs 42% and 100%, respectively.

Conclusions: The present analysis shows that mOBPM is more reliable than ABPM in the diagnosis of AH in children. We recommend the routine use of mOBPM for measuring BP since ABPM may lead to wrongful diagnosis, can provide misleading results because of children discomfort and is more time-consuming.

TH-PO489

Evaluating Pediatric Hypertension According to Different Guidelines Using a Multi-Institutional Electronic Health Record Database

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Background: Childhood hypertension is associated with cardiovascular morbidity and adult mortality. However, the burden of pediatric hypertension in Taiwan remains unclear.

Methods: We conducted a cross-sectional study using outpatient blood pressure (OBP) measurements obtained in routine care visits from the Chang Gung Research Database between 2009 and 2018 to evaluate guideline defined hypertension and patient-related factors of pediatric hypertension. Additionally, we examined the agreement on hypertension between the 2017 American Academy of Pediatrics Guidelines and the 2004 Fourth Report.

Results: In total, 12,469 children and adolescents who underwent three separate >= 3 OBP measurements over 33,369 person-years with a total of 95,608 BP measurements in an outpatient setting were analyzed. According to the 2017 American Academy of Pediatrics (AAP) guidelines, the rate of pediatric hypertension in the study setting ranged from 0.78–5.95 per 1000 persons between 1 and 17 years of age. Perfect agreement existed between the thresholds of the two guidelines for defining hypertension in 1-7, 8-12 and 13-17 years of age groups (all k static >=0.85), but the use of AAP threshold classified more children as having hypertension. Children and adolescents with hypertension often had complex chronic diseases and required substantial healthcare services in outpatient, emergency, and inpatient settings.

Conclusions: The present study provides evidence of guideline-based pediatric hypertension. The study results highlight the importance of regular blood pressure monitoring to identify and management of hypertension in children and adolescents. Further research is required to investigate the effect of new thresholds on the identification of target organ damage in pediatric age.

Funding: Private Foundation Support

Comparison of pediatric hypertension defined by 2004 and 2017 versions of guidelines in three age groups

Age group, year	Number of participant	2004 Fourth Report		2017 AAP guideline		Differences	
		Number of case	Event rate / 1000 persons	Number of case	Event rate / 1000 persons	Kappa (95% CI)*	Agreement (%)**
1-7	495,962	375	0.76	387	0.78	0.98 (0.97-0.99)	99.58
8-12	255,615	523	2.05	573	2.24	0.94 (0.94-0.96)	99.11
13-17	218,368	1185	5.43	1300	5.95	0.85 (0.84-0.87)	97.44

American Academy of Pediatrics (AAP)

*Cohen's Kappa estimate >0.8 indicates perfect agreement

** Agreement (%) between two guidelines was calculated with as (number of cases + number of non-cases agreed in both guidelines/total participants)

TH-PO490

Hypertension Associated with Hyper-Reninemic Hyperaldosteronism After COVID-19 Infection in a Pediatric Patient

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Introduction: COVID-19 was a leading cause of death among children and adolescents from Aug 2021 through Jul 2022, ranking 8th for all causes and 1st for infectious causes **[Kompaniyets, 2022][1]**. Children and adolescents are at risk for certain post-COVID complications. **[Tadeo, 2023][2] [Flaxman, 2023][3]**. In a prospective multicenter study in Turkey, 28% of the children ages 10-18 yrs had abnormal blood pressure 8 weeks after a mild COVID-19 infection, of whom 39.2% had stage 1 HTN **[Uysal, 2022][4]**. The pathophysiology of SARS-CoV-2 associated hypertension (HTN) remains unclear **[Kukarni, 2022][5]**.

Case Description: A 13-yr-old male with no significant past medical history presents to the pediatric nephrology clinic for evaluation of HTN. He had COVID infection 9 mths ago and was noted to be hypertensive since then. He was asymptomatic. Vitals notable for BP 142/87 mmHg, BMI 31 kg/m^2. Exam was normal. Labs revealed normal CBC, urinalysis, lytes, creatinine, TSH, serum metanephrine levels. Renin [4.2ng/mL/h] and aldosterone [37.6 ng/dL] levels were elevated. Renal US with doppler was unremarkable. MRA abdomen was negative for renal artery stenosis. 24-hour ABPM showed a daily average 135/70 mmHg and night average 140/73 mmHg. He was started on lisinopril with improvement in BP.

Discussion: Angiotensin converting enzyme 2 (ACE2), which is utilized by SARS-CoV-2 for entry into host cells, is widely expressed in the lungs, kidneys, testes, gut, adipose tissue, and brain. Infection within host cells mediates RAS overactivation. One hypothesis is that the increased activity of the ACE/AngII/AT1R axis or the decreased activity of the ACE2/Ang-(1–7)/Mas Receptor axis generates pulmonary and neurogenic HTN **[3]**. We were able to rule out secondary causes in our patient with hyper-renninemic hyperaldosteronism and clinical response to lisinopril further supports this proposed mechanism. In a retrospective and prospective cohort study of adult patients, 21.6% patients had uncontrolled HTN requiring treatment, 23 days post-discharge from the hospital or ER for COVID infection **[Wrona, 2022][6]**. In a cross-sectional study in Korea, an increase in the prevalence of HTN was observed among youths during the pandemic **[Song, 2019][7]**. There are limited studies available in pediatric patients in comparison to adults assessing prevalence and risk factors for HTN post COVID infection.

TH-PO491

Melorheostosis and Renal Artery Stenosis in Solitary Kidney: A Pediatric Case

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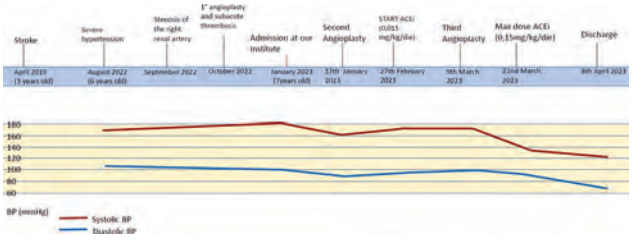
Introduction: Melorheostosis is a rare bone dysplasia characterized by irregular hyperostosis of bones, diagnosed by typical radiological signs. Additionally, soft tissue changes have been described. We present a patient with melorheostosis and severe hypertension due to angioplasty-resistant renal artery stenosis (RAS) of the solitary kidney.

Case Description: A 7-years-old girl presented with severe hypertension. She had a history of stroke, absence of left kidney and scoliosis. In 2022, due to severe RAS she underwent percutaneous cutting balloon angioplasty with improvement on blood pressure control. Few days later the occurrence of subacute thrombosis was treated by drug eluting stent. MRI imaging of the spine revealed evidence of bony aspects compatible with melorheostosis. She was considered not suitable for vascular surgery and proposed to our Institution for nephrectomy or renal transplant. In our Institute she was treated with 9 antihypertensive drugs without reaching pressure control. Kidney ultrasound demonstrated in-stent fracture with severe restenosis. Two additional percutaneous angioplasties were attempted with no significant improvement. Then we introduced ACE inhibitor (ACEi) titrated to benefit on blood pressure control without compromising kidney function. Her blood pressure is now acceptable.

Discussion: Melorheostosis is associated with different malformation of soft tissue: we present the first case of melorheostosis with RAS in solitary kidney patient. RAS causes activation of RAAs to increase renal blood flow, leading to high blood pressure. The use of ACEi in patients with RAS is controversial: it acts directly on the causative mechanism of hypertension, but it leads to a reduction in the kidney blood flow, with the risk of developing acute kidney damage. Given the poor response to several angioplasties, we started with Ramipril at very low dose progressively increased until 0.11 mg/kg/die. She is treated now with 5 antihypertensive drugs, with better pressure control.



TH-PO492

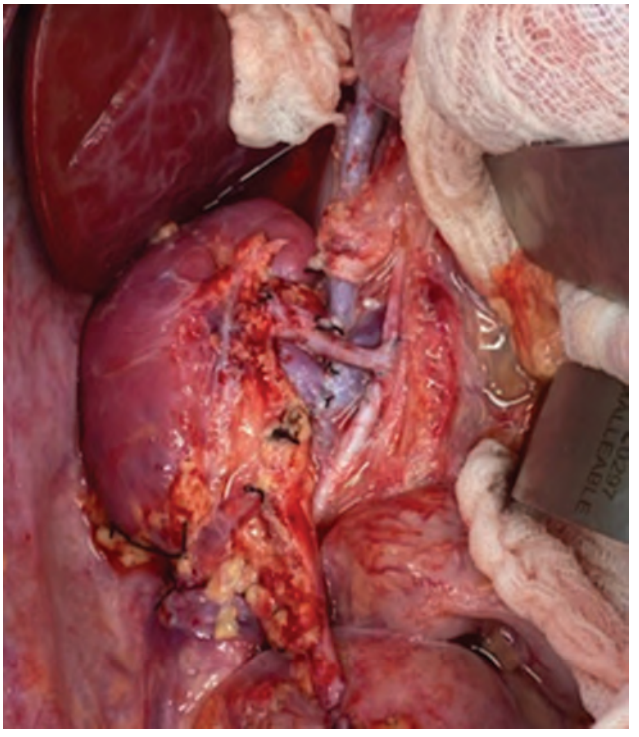
Renal Autotransplant in a Pediatric Patient with Neurofibromatosis Type 1 (NF1) and Renal Artery Stenosis (RAS)

Morgan E. Beebe, Samantha J. Wala, Mahmoud Kallash, Jaimie D. Nathan, Sara K. Rasmussen. *Nationwide Children's Hospital, Columbus, OH.*

Introduction: Patients with NF1 are at increased risk for developing HTN, with RAS being the most common etiology. When medication fails, surgery may be indicated. We present a case of a 6-year-old boy with NF1 and RAS whose HTN was refractory to medical therapy and balloon dilation, but successfully treated with renal autotransplant.

Case Description: A 6-year-old boy with NF1 presented to our nephrology clinic with HTN. While his laboratory findings were unrevealing, computed tomography angiography (CTA) of the renal vessels revealed high-grade stenosis of the proximal right renal artery. He subsequently underwent arterial dilation and balloon angioplasty performed with IR. Following this, he presented in hypertensive urgency on dual-medical therapy. Repeat CTA redemonstrated severe right-sided stenosis; IR deemed the patient inappropriate for re-intervention. With 45% function of the right kidney on MAG-3 scan, our surgical colleagues offered renal autotransplant for consideration, which the family accepted. Six months postoperatively, his antihypertensive burden decreased from four-drug therapy to amlodipine monotherapy, with home blood pressures averaging 100/60 mmHg.

Discussion: Patients with NF1 are at increased risk of developing HTN. In those with RAS, a stepwise treatment approach from least-to-most invasive is preferred. If multidrug therapy and endovascular interventions fail, nephrectomy is then considered. Because stenosis may recur in the remaining kidney, renal autotransplant can be a preferred intervention for the treatment of refractory HTN with RAS in patients with preserved renal function. While more technically challenging in pediatric patients, this intervention confers the benefit of retaining the native kidney.



Graft *in situ*

TH-PO493

Clinical Characteristics of Korean Pediatric Renovascular Hypertension According to Underlying Diseases

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Background: Previously, Moyamoya disease (MMD) has been suggested as the most common cause of renovascular hypertension (RVH) in Korean children. The *ring finger protein 213* (*RNF213*) has also been reported to be a causative gene of systemic vasculopathy in East Asia which results in MMD and RVH. This study aimed to evaluate the clinical characteristics of RVH and to compare the outcomes according to underlying diseases in Korean children.

Methods: A retrospective study was performed in patients who were diagnosed RVH at age under 18 years in Samsung Medical Center from 2010 to 2022. Medical records including sex, age, gene study, location of vascular lesion, treatment modalities and response to treatment were reviewed. *RNF213*-related vasculopathy designates systemic vasculopathy involving intracranial, renal, and pulmonary arteries with defined *RNF213* mutation. According to underlying diseases, patients were grouped as *RNF213*-related vasculopathy (group 1, n=17), atypical vasculopathy (group 2, n=14), and others including congenital anomalies of kidney and urinary tract (CAKUT) and solid tumor (group 3, n=10).

Results: A total of 41 pediatric patients (19 males and 22 females, mean age of 10.1±4.8 years) were included. The mean value of initial blood pressure (BP) was 162/96 mmHg. Twenty five children were incidentally detected hypertension without symptoms while 15 patients showed neurological symptoms. Five patients were diagnosed RVH prior to MMD. Twenty patients underwent percutaneous transluminal angioplasty (PTA), 3 patients received bypass surgery, and 3 patients were done nephrectomy. Target organ damage was found in 15 patients (36.6%). Ostial vascular involvement was notably prevalent in group 1. For response to treatment, BP and stenotic lesions were poorly controlled in group 1 and 2 while overall outcome was relatively favorable in group 3. However, no statistical differences were revealed for the location and level of stenosis, treatment modalities, and outcomes between 3 groups.

Conclusions: The *RNF213*-related vasculopathy including MMD is the most common cause of RVH in Korean children in association with ostial vascular lesions. PTA and bypass surgery are mostly performed for patients with *RNF213*-related or atypical vasculopathy and clinical outcomes are relatively poor in these patients compared to other underlying diseases such as CAKUT or solid tumor.

TH-PO494

Blood Pressure Control in Pediatric Hemodialysis: Data from the SCOPE Collaborative

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Background: The Standardizing Care to Improve Outcomes in Pediatric End Stage Kidney Disease (SCOPE) Collaborative is a quality improvement initiative focused on improving care of children on dialysis. Accurate blood pressure (BP) measurement is a focus of SCOPE as hypertension and cardiovascular disease is a leading cause of morbidity and mortality for children on dialysis.

Methods: Twenty centers collected two post-hemodialysis (HD) BP measurements per week for two weeks of each month using a standardized procedure (BP measurement bundle) to characterize the BP of children on HD from 4/1/2019-3/31/2022. The measurements were conducted via either oscillometric or manual methods. Hypertension was classified using the 2017 AAP hypertension guidelines.

Results: A total of 2,390 BP evaluation forms from 294 HD patients ≥3 years of age have been submitted to date. There were 4,713 weekly BP measurements. 1,457 (31%) measurements were from patients aged 3-12 years and 3,256 (69%) measurements were from patients aged 13 years and older. BP medications were prescribed at the time of 56% of measurements. Overall, 2,432 (52%) of the BP readings were abnormal. The majority (58.5%) of measurements in the 3-12 year olds were consistent with either Elevated, Stage I or Stage II hypertension. In the patients 13 years and older, 48.5% of measurements were abnormal, with 35% of the readings in Stage I/II hypertension. More than 70% of the abnormal readings were based only on oscillometric measurement. 891 (18.9%) of all BP measurements were manual. In 41% of instances when a manual BP was repeated after an oscillometric reading, the BP classification changed, in 33% there was an increase in the BP classification, while the classification improved in 67% of cases.

Conclusions: The prevalence of elevated BP/hypertension is high amongst pediatric HD patients in the SCOPE collaborative when using a standardized BP measurement procedure and despite the use of antihypertensive therapy. While most of the BP classifications were based on oscillometric measurements instead of manual readings, the latter may help inform treatment decisions. Additional efforts by SCOPE will help to further define a clinically practical strategy for BP assessment in children on HD as a prelude to addressing therapeutic BP management.

TH-PO495

Prevalence of Masked Hypertension and Its Association with Target Organ Damage in Children: A Systematic Review and Meta-Analysis

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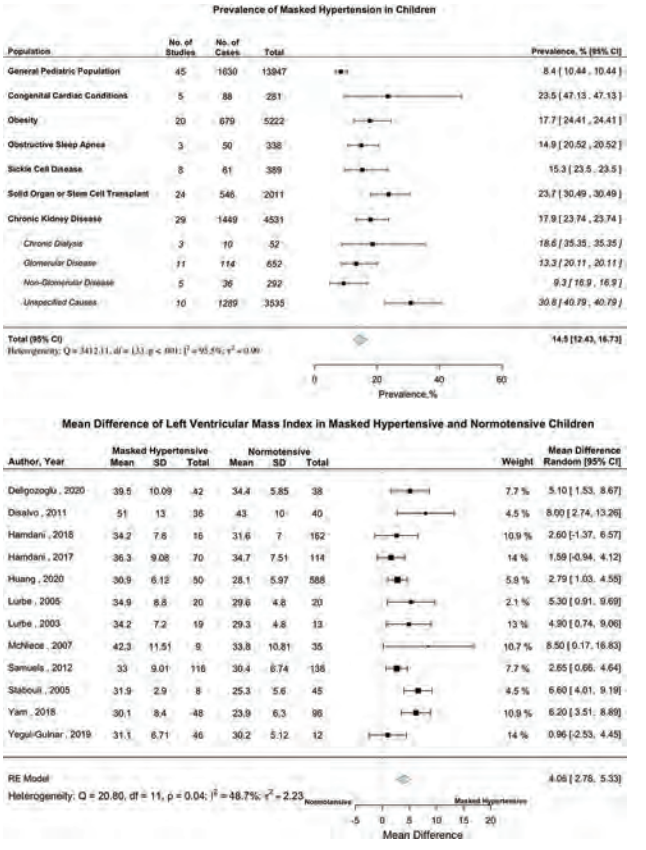
Background: We investigate the prevalence of pediatric masked hypertension (MH) in children with various comorbid conditions and compare the risk of target organ damage in children with MH and normotensive children.

Methods: A systematic literature search on nine databases included English publications from 1974-2023. MH was defined based on ambulatory blood pressure monitoring. LVMI was indexed to subject height and body surface area (g/m$^{2.7}$). LVH was defined by the 95th percentile pediatric reference range, or a pediatric or adult cut-off. Correlation coefficients were transformed and pooled using a random effects model.

Results: Of 8996 screened studies, 12 studies and 2028 children were included. MH prevalence was highest among those with chronic kidney disease (CKD) (18%), congenital cardiac conditions (24%), obesity (18%), and solid-organ or stem-cell transplant (24%). LVMI was elevated in the MH group (mean=35.48 g/m$^{2.7}$) compared to the normotensive group (mean=31.10 g/m$^{2.7}$), with a mean difference of LVMI was 4.06 g/m$^{2.7}$ (95% CI:2.78-5.33) (fig). MH children were at 2.37 (95% CI: 1.41, 3.97) increased odds of LVH compared to normotensive children.

Conclusions: MH is common among children with congenital cardiac conditions, solid organ or stem-cell transplant, CKD, and obesity, and is associated with increased risk of LVH. These findings emphasize the importance of early screening, diagnosis, and treatment of hypertension in these high-risk children.



TH-PO496

Risk of Target Organ Damage in Pediatric CKD Patients with Ambulatory Hypertension: A Systematic Review and Meta-Analysis

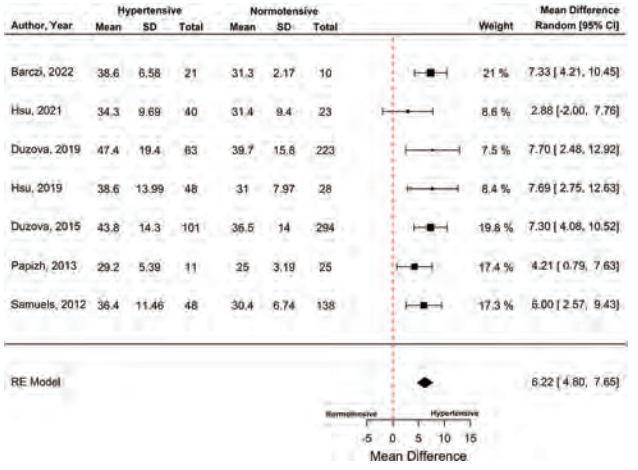
Jason Chung,[1] Cal Robinson,[2] Andrew Yu,[3] Lauren Sheffield,[4] Manish Sinha,[5] Janis M. Dionne,[6] Mark Mitsnefes,[7] Andrew M. South,[8] Rulan S. Parekh,[9] Myanca D. Rodrigues,[10] Damien G. Noone,[2] Rahul Chanchlani.[11] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]The Hospital for Sick Children, Toronto, ON, Canada; [3]University of Alberta, Edmonton, AB, Canada; [4]McMaster University, Hamilton, ON, Canada; [5]Evelina London Children's Hospital, London, United Kingdom; [6]BC Children's Hospital, Vancouver, BC, Canada; [7]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [8]Wake Forest University School of Medicine, Winston-Salem, NC; [9]Women's College Hospital, Toronto, ON, Canada; [10]McMaster University, Hamilton, ON, Canada; [11]McMaster Children's Hospital, Hamilton, ON, Canada.*

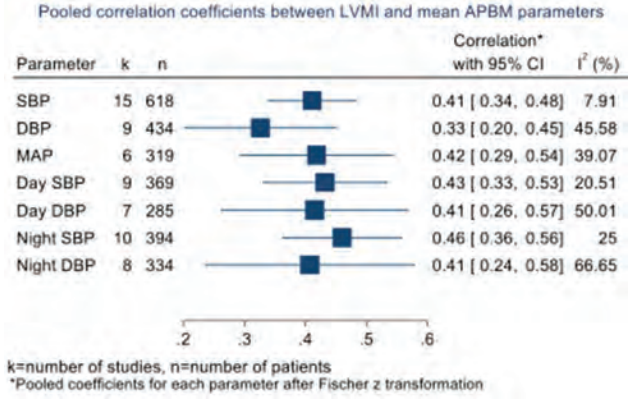
Background: The objective of this systematic review is to determine the association between ambulatory hypertension and left ventricular mass index (LVMI) as well as ambulatory blood pressure monitoring (ABPM) parameters in youth with CKD.

Methods: A systematic literature search on 9 databases included English publications from 1974-2022. LVMI was indexed to subject height and body surface area (g/m$^{2.7}$). Correlation coefficients were transformed and pooled using a random effects model.

Results: Of 1,128 screened studies, 16 studies and 2,254 children and adolescents were included. LVMI was elevated in the hypertensive group compared to the normotensive group (mean difference: 6.22 g/m$^{2.7}$, 95% CI: 4.80-7.65). Hypertensive children were at 3.34 (95% CI: 2.38-4.68) increased odds of left ventricular hypertrophy compared to normotensive children. Estimates of pooled correlation coefficients demonstrated nighttime systolic (r=0.46, 95%CI: 0.36, 0.56) and daytime systolic (r=0.43, 95%CI: 0.33-0.53) BP to have the strongest positive linear relationship to LVMI.

Conclusions: Pediatric CKD patients with ambulatory hypertension especially during nighttime are at significant risk of increased LVMI. Adequate blood pressure control among children with CKD is imperative to avoid the risk of target organ damage and future cardiovascular disease.





TH-PO497

Association of Isolated Nocturnal Hypertension (INH) and Target Organ Damage in Light of the 2022 American Heart Association (AHA) Pediatric Ambulatory Blood Pressure Monitoring (ABPM) Guidelines

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Background: Pediatric INH, previously defined by the 2014 guidelines as sleep blood pressure (BP) >95th%ile for sex and height, is associated with increased risk of target organ damage (TOD). In 2022, AHA guidelines lowered sleep BP thresholds to 110/65mmHg. The aim was to determine the association of INH and TOD according to the new guidelines.

Methods: A retrospective chart review of ABPMs from adolescents 13-21 years old between 2015-2022 was performed. ABPM phenotypes were normotension, INH, isolated daytime hypertension (HTN), and sustained day-night HTN. The primary exposure was INH, defined as sleep BPs ≥110/65mmHg with wake BPs <130/80mmHg. Echocs performed within 6 months of ABPM were reviewed. The primary outcome was left ventricular hypertrophy (LVH), defined as LVMI >95th%ile. Pearson's chi-squared, Wilcoxon rank-sum, and logistic regression were utilized as appropriate.

Results: Of 353 ABPM reports (median age 16, 73% male), 25% (N=89) classified as INH by 2014 guidelines, while 45% (N=115) classified as INH by 2022 guidelines. Hypertensive sleep BPs bordered the 110/65mmHg cutoff; median systolic BP was 116mmHg [IQR 112,122] and median diastolic BP was 62mmHg [58,68] (Table 1). Echos were available for 60% of the cohort (N=154) and 57% (N=65) of INH. LVH prevalence according to ABPM phenotype was 40% (26/65) of INH, 33% (2/6) of isolated daytime HTN, and 46% (38/83) of sustained day-night HTN. Any HTN was associated with >2x increased odds of LVH [OR=2.5 95%CI(1.2-5.2)], but there was no association of INH with LVH as compared to normotension.

Conclusions: Lack of association between INH and LVH may reflect the increased sensitivity of 2022 AHA guidelines to diagnose nocturnal HTN. LVH was less prevalent among INH as compared to other hypertensive phenotypes. While the cohort was small, these findings may inform future studies of how clinicians should manage INH.

ABPM Phenotypes					
Variables*†	Normotension (N=98)	Isolated Nocturnal Hypertension (N=115)	Isolated Daytime Hypertension (N=9)	Sustained Day-Night Hypertension (N=131)	P-Value
Age – years	16 [15, 17]	16 [15, 17]	14 [14, 16]	16 [14, 17]	0.35
Male sex (n%)	58 (74.4)	79 (76.7)	8 (100)	78 (67.2)	0.13
BMI percentile	0.91 [0.69, 0.98]	0.94 [0.78, 0.97]	0.96 [0.88, 0.99]	0.86 [0.62, 0.96]	0.041
24h systolic BP	113 [108, 118]	120 [117, 125]	123 [120, 127]	132 [128, 136]	<0.001
24h diastolic BP	65 [62, 67]	68 [63, 72]	75 [73, 76]	75 [69, 81]	<0.001
Wake systolic BP	117 [111, 124]	123 [118, 126]	132 [125, 134]	135 [131, 139]	<0.001
Wake diastolic BP	69 [65, 73]	69 [64, 74]	80 [79, 83]	78 [73, 84]	<0.001
Sleep systolic BP	103 [98, 106]	116 [112, 122]	105 [104, 106]	122 [116, 131]	<0.001
Sleep diastolic BP	56 [52, 59]	62 [58, 68]	59 [58, 61]	66 [60, 74]	<0.001
LVMI > 95th percentile (n%)	12 (20.0)	26 (35.1)	2 (28.6)	38 (43.7)	0.024
LVMI > 51 (n%)	1 (1.7)	7 (9.5)	0 (0)	12 (13.8)	0.065

Table 1: Demographics and Cardiovascular Outcomes of Hypertensive Phenotypes
*All continuous variable represented as median [IQR]
†All BPs using units of mmHg

TH-PO498

Sleep-Disordered Breathing, Risk of Target Organ Injury, and Role of Obesity in Youth Referred for Hypertension Disorders

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Background: Sleep-disordered breathing (SDB) has adverse consequences on blood pressure regulation in adults, but its relationship with target organ injury (TOI), especially in youth, is less clear. Our objective was to determine if SDB is associated with higher risk for TOI in youth referred for hypertension disorders and if obesity magnified this risk.

Methods: Interim cross-sectional analysis of baseline data from the multisite Study of the Epidemiology of Pediatric Hypertension Registry (SUPERHERO) which retrospectively collects electronic health records data using biomedical informatics scripts. Inclusion criteria were initial visit for hypertension disorder based on ICD-10 codes between 1/1/2015 and 12/31/2022 and age <19 years. Exclusion criteria were kidney transplant, dialysis, or pregnancy per ICD-10 codes at the index visit. Exposures were ICD-10 code-defined SDB, and obesity by body mass index percentile was our effect modifier. Outcomes were ICD-10 code-defined heart and kidney TOI at the index visit. We used unadjusted generalized linear models.

Results: In this analysis of 11,580 participants, mean age was 12.0 ± 5 years, 52% had obesity, 4% has SDB, and 8 % had TOI (Table). Compared to participants without SDB, those with SDB had a 57% lower risk of TOI (RR 0.43, 95% CL 0.26 to 0.69). Obesity was associated with a lower magnitude of association, though not significantly (interaction *p*-value 0.08).

Conclusions: In a large multisite registry of youth referred for hypertension disorders, participants with an ICD-10 code for SDB at baseline had a lower risk of TOI by ICD-10 code. Next steps include better defining our exposure and outcome. Further studies are needed to determine if clinical interventions that impact sleep health can mitigate future cardiovascular risk in youth.

Funding: Other NIH Support - NIH K23-HL-148394, L40-HL148910, UL1-TR001420

Participant characteristics, BP severity, and target organ injury by SDB status

	Total N=11580	No SDB codes n=11084 (96%)	SDB codes n=496 (4%)
Age (years)	12.0 (5.0)	12.0 (5.1)	12.4 (3.9)
Female	4549 (39%)	4387 (40%)	162 (33%)
Race			
White or Caucasian	6508 (56%)	6183 (56%)	325 (66%)
Black or African American	3114 (27%)	3006 (27%)	108 (22%)
Multiracial, other, unknown, or refused	1958 (17%)	1895 (17%)	63 (13%)
Hispanic or Latino ethnicity	2715 (23%)	2562 (23%)	153 (31%)
Payor/insurance status			
Public (government-sponsored insurance)	6715 (58%)	6386 (58%)	329 (66%)
Private/Self-pay/Other	4793 (41%)	4634 (42%)	159 (32%)
Unknown	72 (1%)	64 (1%)	8 (2%)
Department			
Nephrology	8867 (77%)	8624 (78%)	243 (49%)
Cardiology	962 (8%)	956 (9%)	6 (1%)
Other/Unknown	1751 (15%)	1504 (14%)	247 (50%)
Obesity	6030 (52%)	5577 (50%)	453 (91%)
Age ≥ 13 years, n=6220	6220 (54%)	5970 (54%)	250 (50%)
Systolic blood pressure (mmHg)	125.9 (16.0)	125.9 (16.1)	126.2 (12.1)
Diastolic blood pressure (mmHg)	72.9 (12.6)	72.8 (12.7)	73.7 (9.0)
Age < 13 years, n=5360	5360 (46%)	5114 (46%)	246 (50%)
Systolic blood pressure z-score	1.7 (0.9)	1.7 (0.9)	1.6 (0.8)
Diastolic blood pressure z-score	1.0 (0.9)	1.0 (1.0)	1.0 (0.8)
Blood pressure severity, n=8850 (77%)			
Stage 2 hypertension	2663 (23%)	2576 (23%)	87 (18%)
Stage 1 hypertension	4092 (35%)	3880 (35%)	212 (43%)
Elevated blood pressure	2104 (18%)	1988 (18%)	116 (23%)
High blood pressure*	9190 (79%)	8754 (79%)	436 (88%)
Target organ injury by ICD-10 codes	905 (8%)	888 (8%)	17 (3%)

N (%), mean (*SD*). Percentages may not add to 100% due to rounding. Obesity defined by body mass index or weight-for-length-based CDC or WHO criteria depending upon age ≥ 2 or < 2 years.
*Includes those who met high blood pressure criteria but unable to further classify.

TH-PO499

Urinary Biomarkers in Neonates Born to Mothers with Preeclampsia

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Background: Effects of preeclampsia on renal development or function in newborns are unknown. We hypothesized that the circulating factors causing endothelial dysfunction and impaired renal function in mothers with preeclampsia may adversely affect fetal kidneys.

Methods: All newborns with gestational age ≥32 weeks were eligible. Moms with known renal abnormalities on function or structure on prenatal ultrasound, nephrotoxic medication exposure as well as babies born with low APGAR scores, fetal distress were excluded. Bag urine samples were stored at -70° C and assayed using commercially available ELISA kits for Cystatin C,Nephrin, KIM – 1 and Klotho. Urinary creatinine and protein contents were measured using standard techniques. Comparisons between the groups were made using t-tests or Wilcoxon Rank Sum Test. For categorical variables, Chi-square or Fisher's exact analyses were used.

Results: The baseline characteristics of 68 mothers and their newborns were comparable to each other. Urine protein and creatinine were significantly higher (Table1) while Klotho levels were significantly lower in study group. Urinary Nephrin was higher in study infants but the difference was not statistically significant (p value 0.053). There was no correlation between maternal urinary protein/creatinine ratio and levels of urinary biomarkers in their infants.

Conclusions: This cross-sectional study on urinary biomarkers among infants born to preeclampsia mothers has shown high urinary protein in the study group over control. Urinary klotho levels were also significantly lower in the study infants mirroring the existing knowledge of low klotho levels with acute renal injury and advanced CKD. Levels of urinary nephrin urinary KIM-1 and cystatin C level were not statistically different between the two groups. Further prospective studies tracking renal function, proteinuria and blood pressure measurement can provide clues to the significance of these urinary biomarkers as early screening tools for CKD in infants born to mothers with preeclampsia.

Urinary biomarkers

Biomarker	Mother Preeclampsia + (%) N = 34	Mother Preeclampsia - (%) N =34	P value
Total Protein (mg/dl) Median (IQR)	37.1 (14.4 to 53.5)	20.3 (7.5 to 30.0)	0.04
Creatinine (mg/dl) Median (IQR)	63.4 (25.2 to 96.6)	24.8 (19.8 to 44.2)	0.008
Cystatin C (ng/ml) Median (IQR)	2.4 (1.2 to 6.2)	7.59 (1.1 to 33.8)	0.12
KIM-1 (ng/ml) Median (IQR)	0.035 (0.0045 to 0.20)	0.074 (0.0045 to 0.30)	0.16
Nephrin (µg/ml) Median (IQR)	0.56 (0.06 to 1.90)	0.15 (0.066 to 0.53)	0.053
Klotho (pg/ml) Median (IQR)	3.08 (3.08 to 21.28)	17.03 (3.08 to 92.36)	0.0032

TH-PO500

Association Between Birth Weight Z-Score and Blood Pressure in 9- to 10-Year-Old Icelandic Children

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Background: Low birth weight has been associated with adverse cardiovascular outcomes, including an increased risk of hypertension later in life. The aim of this study was to examine the association between birth weight (BW) indices and blood pressure (BP) in a cohort of healthy 9-to 10-year-old Icelandic school children.

Methods: Icelandic children aged 9-10 years underwent 4 seated BP measurements in 2009. BP percentiles and z-scores were calculated from the average of the 4 measurements. Height and weight were measured, and information on birth weight and gestational age was obtained from the Icelandic Birth Registry. Birth weight z-score was calculated based on a standardized growth chart by Niklasson & Albertsson-Wikland. Pearson correlation coefficient and multivariable linear regression were used for statistical analysis.

Results: Of 892 children with complete data, 458 were girls (51.3%). The mean BP in girls was 111/63 mm Hg and 112/64 mm Hg in boys. The mean BW was 3688 ± 586 g for girls and 3750 ± 644 g for boys. A significant negative correlation was observed between BW and systolic BP z-score (r= -0.09, p=0.001), and between BW z-score and systolic BP z-score (r= -0.09, p=0.006). There was a negative correlation between the diastolic BP z-score and both BW and BW z-score (r= -0.09, p=0.005, and r= -0.10, p=0.003). The relationship was stronger in girls for both BW and z-score (r= -0.11, p=0.024 and r= -0.10, p=0.036) than in boys (r= -0.07, p=0.14 and r=-0.08, p=0.11). When adjusted for body mass index (BMI) z-score, there was a significant association between BW z-score and systolic BP z-score (beta= -0.12, p<0.001) and diastolic BP z-score (beta= -0.08, p<0.001) in girls. In boys the adjusted association was significant for BW z-score and systolic BP z-score (beta= -0.07, p=0.024), but the association with diastolic BP z-score was of borderline significance (beta= -0.04, p=0.05). Neither BW nor the BW z-score significantly correlated to absolute blood pressure values in children.

Conclusions: This study suggests that low birth weight may be an important predictor of elevated BP in children and indicates the importance of BP follow-up of low-birth-weight infants.

TH-PO501

Association of Psychosocial and Neurocognitive Dysfunction in Pediatric Hypertension

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Background: Pediatric hypertension (HTN) is a significant problem, with incidence of elevated BP increasing over time. Cardiac end organ damage of HTN is well-documented but only recently has attention turned to its neurocognitive effects. Researchers have previously demonstrated significantly lower performance on neurocognitive testing in children with primary HTN compared to normotensive controls and have reviewed the effects of HTN on attention and anxiety/depression. The goal of this study is to further identify the common neuropsychological concerns that are prevalent in children with HTN, and to clarify the neuropsychological factors associated with HTN concerns.

Methods: This is a retrospective chart review of outpatient pediatric nephrology patients (n=197) who received an ambulatory blood pressure monitor and neuropsychological screening measures between 6/2020 and 8/2021.

Results: The study included 197 subjects who completed ABPM placement and neuropsychological screening. There was no specific correlation between ABPM data and clinical levels of anxiety, depression, or ADHD hyperactivity symptoms. HTN and ADHD inattentive symptoms were significantly associated. Elevated systolic BP load, elevated diastolic BP load, and mean arterial pressure were all associated with areas of executive functioning and learning concerns, inclusive of working memory and mathematics skills (all p's <0.05). Systolic BP load was also associated with problems in factual memory, sequential processing, and problem-solving.

Conclusions: This study highlights the relation between pediatric HTN and neurocognitive concerns, but does not clarify concerns for psychological symptoms. The findings assert the potential need to implement behavioral health and neurocognitive screenings when concerns for elevated BP are present to activate immediate and effective intervention for BP management. Further analysis will continue to characterize specific aspects of HTN, patient demographics, and neuro/psychological symptom elevations.

TH-PO502

Prematurity and Low Birth Weight Associate with Adolescent Hypertension in a Large Nationwide Cohort

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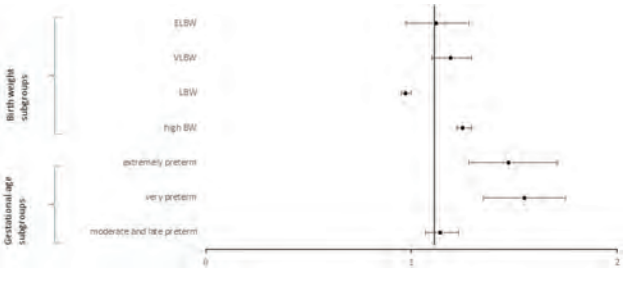
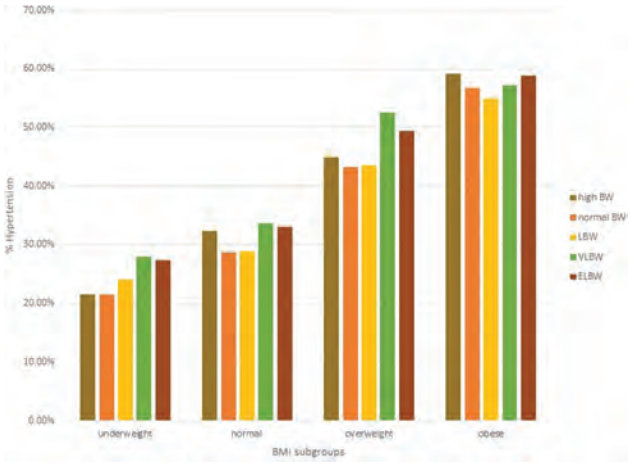
Background: prematurity is a global burden occuring in ~ 11% of total deliveries. Chronic kidney disease (CKD), due to incomplete nephrogenesis and acute kidney injury episodes, can be a long term complication of prematurity. The aim of this study is to explore the risk of having hypertension or proteinuria, as CKD manifestations, in adolescents born prematurely or small for gestational age in a large nationwide cohort.

Methods: Study population included potential recruits that were examined in an Israel Defence Forces (IDF) medical facility between November 2005 and October 2018. Clinical, demographic and anthropometric data were retrieved from the IDF medical files electronic system. Data regarding gestational age at delivery, retrieved from the Israeli Ministry of Health database, was available for adolescents born between January 1993 to December 2000.

Results: Study cohort included 513,802 participants, aged 17.3±0.9 years. 48,994 individuals had data regarding gestational age at birth (38.8 ± 2.99 weeks). Adolescents born as very- and extremely preterm infants had 55% and 47% greater risk for having hypertension, respectively. Being born with very or extremely low birth weights have an OR of 1.19 and 1.12 for adolescent hypertension, respectively (figure 1). Within the overweight and obese adolescents, comparison between different birth weight groups revealed higher hypertension prevalence in adolescents born as low, very low and extremely low birth weights (figure 2).

Conclusions: Our study demonstrated a higher trend for adolescent hypertension in very premature infants and in infants born with very and extremely low birth weight. These adolescents should be monitored for signs of CKD in order to treat and delay its progression.





TH-PO503

Association Between Epigenetic Age Acceleration at Extremely Preterm Birth and Systolic Blood Pressure in Adolescence

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Background: Epigenetic age deviation from chronologic age is associated with poor cardiovascular (CV) outcomes in adults. No studies have evaluated this association in children born preterm, who are at risk for advanced epigenetic gestational age (eGA) and poor CV outcomes. Our objective was to examine the association between epigenetic gestational age acceleration (eGAA) and adolescent systolic blood pressure (SBP) in individuals born extremely preterm.

Methods: This is a secondary analysis of the Extremely Low Gestational Age Newborn study. Participants were born <28 weeks' gestation and had placental DNA quantification at birth and 3 manual blood pressures measured during follow up at 15-17 years old. eGA was estimated using the Robust Placental Clock (RPC). eGAA was calculated as residuals from a linear regression of predicted RPC eGA on chronologic gestational age (GA). Mixed effects models were fit to assess association between eGAA and average adolescent SBP. A minimally sufficient adjustment set, identified using a directed acyclic graph, included maternal factors (health insurance, years of education, marital status, prenatal smoking, pre-pregnancy body mass index (BMI) > 30 kg/m^2, diabetes, hypertension) and birth weight for GA.

Results: 202 study participants had data for eGA and adolescent SBP. 34% had elevated SBP > 120mmHg, and 52.6% were male. 67% with elevated SBP were male, 27.8% had mothers with hypertension, and 25% had mothers with BMI > 30 kg/m^2. In the overall sample, we found no association between eGAA and adolescent SBP (p=0.539). When stratified by sex, for every 1 week acceleration in eGA, adolescent males had an increase of 3.32mmHg in SBP (p=0.04; Table 1).

Conclusions: Epigenetic gestational age acceleration at birth is associated with significant increase in SBP in adolescent males but not females who were born extremely preterm. The kidney is key in regulating blood pressure, so future research includes evaluating kidney-specific epigenetic changes at preterm birth and CV outcomes.

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Table 1. Association between eGAA and adolescent SBP by sex

	Coefficient	95% CI
Males, unadjusted	2.296	-0.71, 5.303
Males, adjusted	3.320	0.197, 6.444
Females, unadjusted	-1.122	-3.186, 0.943
Females, adjusted	-1.002	-3.068, 1.006

TH-PO504

Disparities in Medication Fill Duration in Pediatric Hypertension

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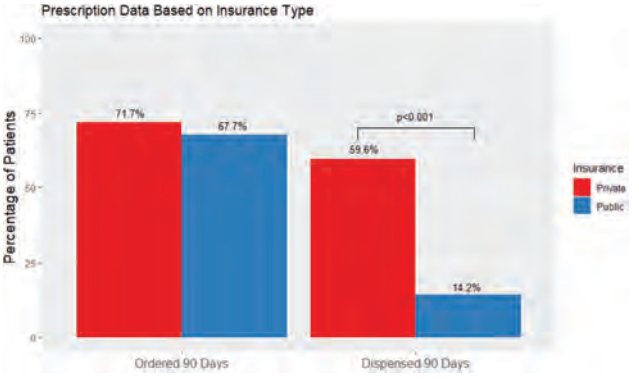
Background: Medication nonadherence is a barrier to blood pressure control. The CDC recommends prescribing 90-day fills for maintenance medications yet antihypertensives are often dispensed as 30-day fills due to insurance limits. This increases the burden of pharmacy visits, a contributor to nonadherence. We observed how often antihypertensives are dispensed as a 30-day supply despite a prescription for longer duration and the impact of 30-day vs 90-day fills on adherence.

Methods: This retrospective cohort study included patients with hypertension (HTN) seen in our Pediatric Nephrology Clinic over a 3 year period. For each patient, antihypertensive medication days prescribed was compared to days dispensed using pharmacy refill and insurance claim data. Proportion of days covered (PDC) was calculated to estimate medication adherence.

Results: A total of 449 patients (61% primary HTN, 39% secondary HTN) had 4,492 prescription orders and 8,800 dispenses over the 3-year period. While 36% of prescriptions were ordered for ≥90 days only 12% were dispensed for ≥90 days and 70% of patients had at least one prescription for ≥90 days but only 37% of patients had at least one dispense for ≥90 days. In addition, 35% of patients had a fill discrepancy (prescribed but never received a 90-day fill). There was no difference in likelihood of being prescribed a 90-day fill by insurance type (public vs private, OR = 0.82, p = 0.35) but patients with public insurance were less likely to be dispensed a 90-day fill (OR = 0.126, p <0.001) and more likely to have a fill discrepancy (OR = 6.02, p <0.001). Patients who received at least one 90-day fill had better adherence rates (median PDC, 77.5% vs 58.1%, p <0.001).

Conclusions: Longer fill duration is associated with better adherence with antihypertensive medication in pediatric patients. However, patients are often dispensed only 30-day fills despite a 90-day prescription. Patients with public insurance are markedly less likely to be dispensed 90-day fills, a modifiable barrier to improving adherence in disadvantaged youth.



TH-PO505

A Systematic Review of Efficacy and Safety of Dialysis Modalities in Neonates/Children with Inborn Errors of Metabolism

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Background: Inborn errors of Metabolism (IEM) are due to mutations that involve aberrations in the metabolism of macromolecules and synthesis of essential compounds, especially hyperammonia. Treatment of IEM typically involves RRT initiation. Our systematic review in neonates and children investigates survival rates and ammonia level reduction in varying RRT modalities (CRRT, HD, PD).

Methods: The literature search was conducted through PubMed, Web of Science, and Embase. The search terms included 'neonates' and 'pediatric' linked with 'IEM' and the varying RRT modalities. The studies included entailed survival rate and ammonia level data in patients with IEM with an intervention of RRT. Analysis variables included efficacy outcomes [% reduction in ammonia (RIA) from pre-dialysis to post-dialysis and time to 50% RIA] and mortality among neonates with IEM on different dialysis modalities. The data was analyzed using R version 3.1.0.

Results: A total of 38 studies were included, with a total sample size of 697. The mortality was observed to be lower among neonates with IEM receiving CRRT vs. PD or HD. The pooled proportion (95% CI) of mortality of those who got CRRT was 25.4% (21.26% - 29.91%) [I^2: 44.6%; p=0.0117. Those who received PD was 36.64% (30% - 43.6%) [I^2: 39.5%; p=0.0579; And those who received HD was 35.9 % (26.5% - 46.2%) [I^2: 18.0%; p=0.2876. The mean (SD) time to 50% RIA level was seen to be higher with CAVHD or CVVHD vs. HD [3.4 (4.1) or 4.3 (3.5) vs. 1.6 (0.4)] hrs. The time to 50% ammonia reduction was significantly lower with CVVHDF vs. PD [median (IQR): 6 (6–9.5) vs. 14 (6–30) hrs; p=0.01, CVVH vs. PD [mean (SD): 4.4 (1.5) vs. 16.3 (10.9) hrs; p=0.042] and CVVHD vs. PD [4.7 (2.5) vs. 13.5 (6.2) hrs; p<0.0001. Likewise, the mean (SD) time to 50% decline in plasma ammonia or leucine levels with CVVHD (n=7) vs. PD (n=5) [7.1 (4.1) vs. 17.9 (12.4) hrs; p<0.02.

Conclusions: Results indicate that the efficacy of the mean % RIA is superior in CRRT. Comparing time to 50% RIA levels, CRRT is superior to PD, while HD appears slightly superior to CRRT. Findings show lower mortality among patients with IEM who received CRRT vs. PD or HD. In conclusion, PD has been shown to be less effective compared to HD and CRRT. The ability to reduce ammonia quicker by HD is also associated with a greater risk of mortality than CRRT.

TH-PO506

Abstract Withdrawn

TH-PO507

Phosphate-Containing vs. Phosphate-Free Solutions in Pediatric Continuous Renal Replacement Therapy: A WE-ROCK Study

Faizeen Zafar,[1] Katja M. Gist,[1] Javier A. Neyra,[2] David T. Selewski,[3] Huaiyu Zang,[1] Nicholas J. Ollberding,[1] Shina Menon.[4] *[1]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [2]The University of Alabama at Birmingham, Birmingham, AL; [3]Medical University of South Carolina, Charleston, SC; [4]Seattle Children's Hospital, Seattle, WA.*

Background: Hypophosphatemia is common in patients on continuous renal replacement therapy (CRRT), and is associated with adverse outcomes (prolonged mechanical ventilation (MV) and longer ICU stay). We aimed to compare outcomes between commercially available phosphate-containing (1 mmol/L, PHOS+) and phosphate-free (PHOS-) solutions in pediatric CRRT patients.

Methods: The Worldwide Exploration of Renal Replacement Outcomes Collaborative in Kidney Disease (WE-ROCK) is a 32-center registry of patients aged 0-25 years treated with CRRT for acute kidney injury or fluid overload (FO). This analysis excluded patients with incomplete CRRT fluid data or those receiving pharmacy-compounded solutions with variable phosphate concentrations. Primary outcomes were 28-day MV- and ICU-free days. Multivariable regression analyses were conducted for outcome comparisons.

Results: We included 410 patients; median age 8.2 years (IQR 1.6-14.1y). Of these, 43.4% (178/410) received PHOS+. The PHOS+ group had a higher %FO (7.2% vs. 5.4%, p=0.009) and lower MV rate at CRRT initiation (64% vs. 82%, p<0.001). There was no difference in PELOD and vasoactive inotropic score between the groups. Both groups received a similar dose of CRRT (42 vs 48 ml/kg/h, p=0.4) although the duration was longer for the PHOS+ group (7 vs 4d, p<0.001). The PHOS+ group had less incident hypophosphatemia (<2.5 mg/dl) during CRRT compared to the PHOS- group (20% vs. 33%, p=0.007). However, there were no differences in 28-day MV- and ICU-free days and 90-day mortality between the 2 groups in unadjusted and adjusted analyses (Table).

Conclusions: PHOS+ (1 mmol/L) CRRT solutions reduced incident hypophosphatemia in this pediatric cohort but did not associate with reduction in 90-day mortality or less ventilator or ICU resource utilization.

Table. Multivariable analysis for 28-day ventilator- and ICU-free days*

Variable	ICU-free days** OR (95% CI)	Ventilator-free days** OR (95% CI)
Age	0.81 (0.59-1.11)	1.09 (0.71-1.68)
Sepsis†	1.20 (0.82-1.77)	0.97 (0.67-1.40)
PELOD-2 score†	**0.30 (0.16-0.55)**	**0.31 (0.21-0.48)**
% Fluid overload†	**0.57 (0.41-0.78)**	0.96 (0.84-1.10)
VIS†	0.92 (0.71-1.20)	0.89 (0.74-1.07)
CRRT dose, mL/kg/hr	1.01 (0.95-1.07)	0.98 (0.93-1.03)
CRRT duration, days	**0.27 (0.15-0.49)**	0.82 (0.69-0.98)
Hospital size, small vs. medium	0.68 (0.31-1.49)	1.23 (0.51-2.99)
Hospital size, small vs. large	2.01 (0.81-4.97)	0.89 (0.49-1.62)
Phosphate-free vs. phosphate-containing CRRT solution	1.11 (0.49-2.54)	0.98 (0.71-1.35)

CI, confidence interval; CRRT, continuous renal replacement therapy; ICU, intensive care unit; OR, odds ratio; PELOD-2, pediatric logistic organ dysfunction-2 score; VIS, vasoactive inotropic score.

*OR and 95% CI were obtained by semiparametric ordinal regression accounting for nesting of patients within centers via the Huber-While cluster sandwich estimator of variance, where OR <1 indicated association with a worse clinical outcome (i.e., increased healthcare utilization). The model adjusted for all the listed covariates. For continuous predictors such as age, the OR was computed by comparing the 75th percentile to the 25th percentile of the variable.

†Determined at CRRT initiation

**Significant predictors marked in bold

Multivariable analysis for 28-day ventilator- and ICU-free days

TH-PO508

Regional Citrate Anticoagulation in Continuous Renal Replacement Therapy in Children: Opportunities for Optimization

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Background: Regional citrate anticoagulation (RCA) is based on blood citrate concentration of 3-4 mmol/L to reach post filter ionized calcium (Cai) of 0,25-0,40 mmol/L in continuous hemodiafiltration (CVVHDF). However, it can lead to metabolic complications of citrate accumulation.

Methods: From May 2019 to Dec 2022, 5,5% (109/1970) of patients admitted in a PICU were submitted to CVVHDF using RCA with 2,2% citrate. 25 patients were excluded for CVVHDF <24h, and 3 others for prior CVVHDF. Data related to minimum magnesemia was analyzed to sensitize the results.

Results: From the 81 patients included, 56,8% were girls, the age was 4.2 years (1.1-12.8) and the weight 13 kg (8,1-36,3). Organic dysfunctions were cardiovascular in 64,2%, pulmonary in 70,4% and hepatic in 65,4%, and the mortality rate was 51.9%. Hypomagnesemia (Mg<1,7mg/dL) was observed in 64% of patients, and the minimum magnesemia was 1,6mg/dL (1,4-1,8), where blood flow rate was 6ml/kg/min (3,4-7,5), the replacement+dialisate fluid rate of 65 ml/kg/h (47-92), blood citrate concentration of 1,7 mmol/L (1,4-2,6), citrate dosage of 0,6mmol/kg/h (0,35-0,85), reaching CaT/Cai (citrate GAP) of 2,01 (1,89-2,03). Only 4 patients presented citrate acummulation (citrate GAP >2,5). Patients <1 years of age reached larger blood flow rate [7,7 (6,7-11,7) vs 4,8 (3-6,5), p<0,001], smaller blood citrate concentration [1,5 (1,4-1,9) vs 1,9 (1,4-2,80), p=0,048], larger citrate dosage [0,75 (0,64-1,09) vs 0,53 (0,32-0,77), p=0,008], and larger citrate GAP [2,14 (1,96-2,33) vs 1,96 (1,79-2,09), p=0,035]. Blood citrate concentration tended to be smaller in the circuits with <36 horas of duration (48,7%), [1,7mmol/L (1,3-2,0) vs 1,9 (1,4-2,8) vs p=0,062], and no difference was observed in the citrate dose (p=0,117) or post filter Cai (p=0,385).

Conclusions: The low circuit patency obtained is probably associated with the low blood citrate concentration used. Children <1 year of age presented good tolerance to high doses of citrate, with a low rate of citrate accumulation. It is possible that children tolerate citrate dosages of 0,6-0,85 mmol/kg/h, reaching blood citrate concentration of 3mmol/L by adjusting the blood flow rate to 2-5 ml/kg/min, improving circuits patency without major metabolic consequences.

TH-PO509

Longitudinal Trends in Pediatric Hospitalizations Complicated by AKI in the United States

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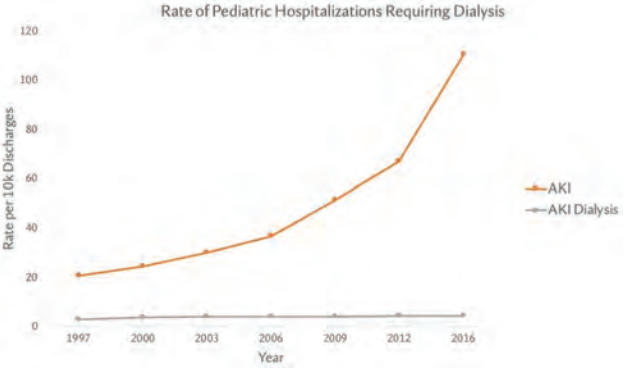
Background: There are limited national data describing longitudinal trends of pediatric acute kidney injury (AKI) and AKI requiring dialysis (AKI-D) We aimed to characterize rates of pediatric AKI and AKI-D across the United States over a 20-year period.

Methods: We analyzed data from the Kids Inpatient Database (KID) from 1997 to 2016. AKI was identified using International Classification of Diseases Clinical Modification (ICD-CM) codes, 9th Revision (1997-2012) and 10th Revision (2016). Use of dialysis during hospitalization was assessed using procedure codes. We excluded pediatric hospitalization for uncomplicated, term newborn birth. Weighted data was used to estimate national yearly incidence totals and rates.

Results: Over the study period, there was a weighted total of 49,228,048 pediatric discharges, 22,059,242 of which were included in the final analysis. Nationwide, the yearly incidence of AKI and AKI-D increased from 1997 (AKI**:** 8340 cases/year, AKI-D: 1049 cases/year) to 2016 (AKI: 43,053 cases/year, AKI-D: 1656 cases/year). The rates of hospitalizations with AKI and AKI-D also increased from 1997 (cases/10k discharges [95%CI]: AKI: 20.7 [20.2, 21.1], AKI-D: 2.6 [2.4,2.8]) to 2016 (AKI: 111 [110, 112], AKI-D: 4.2 [4.0, 4.5]) (**Figure 1**).

Conclusions: This analysis of KID shows an increase in the absolute number, and the rate of pediatric hospitalizations complicated by AKI and AKI-D 1997 to 2016. While some of the increase may be explained by an increase in awareness and documentation, there is a near 3-fold increase in rates of AKI-D. More detailed analysis are needed to evaluate the reasons behind this. Given our understanding of the long-term impact of AKI, it is important to assess for preventable causes and to optimize care of those with AKI and AKI-D.



TH-PO510

Long-Term Outcomes After Pediatric Non-Dialysis-Treated AKI: A Population-Based Cohort Study

Cal Robinson,[1] Nivethika Jeyakumar,[2] David J. Askenazi,[3] Akash Deep,[4] Amit X. Garg,[2] Stuart Goldstein,[5] Jason H. Greenberg,[6] Cherry Mammen,[7] Danielle M. Nash,[8] Rulan S. Parekh,[1,9] Samuel A. Silver,[10] Ron Wald,[11] Michael Zappitelli,[1] Rahul Chanchlani.[12] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]ICES Western, London, ON, Canada; [3]The University of Alabama at Birmingham, Birmingham, AL; [4]King's College London, London, United Kingdom; [5]Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [6]Yale University, New Haven, CT; [7]BC Children's Hospital, Vancouver, BC, Canada; [8]London Health Sciences Centre, London, ON, Canada; [9]Women's College Hospital, Toronto, ON, Canada; [10]Queen's University, Kingston, ON, Canada; [11]St Michael's Hospital, Toronto, ON, Canada; [12]McMaster Children's Hospital, Hamilton, ON, Canada.*

Background: Acute kidney injury (AKI) is common in hospitalized children. Dialysis-treated pediatric AKI is associated with long-term chronic kidney disease (CKD), hypertension, and death. We aim to evaluate the outcomes after non-dialysis-treated AKI, which are uncertain.

Methods: Retrospective cohort study of all hospitalized children (0-18yr) surviving non-dialysis-treated AKI from 1996-2020 in Ontario, identified via provincial administrative health databases. Children with prior kidney replacement therapy (KRT; dialysis or transplant), CKD, or AKI were excluded. Cases were matched with up to four hospitalized controls without AKI by age, neonatal status, sex, index year, ICU admission, cardiac surgery, malignancy, hypertension, and a propensity score for AKI. Children were followed until death (2.9%), provincial emigration (5.3%), or March 2021 (91.8%). The primary outcome was major adverse kidney events (MAKE; composite of death, chronic KRT, or *de novo* CKD).

Results: A total of 4173 pediatric AKI survivors were matched to 16,337 hospitalized controls. Baseline covariates were well-balanced after propensity score matching. Median age was 8yr (IQR 1-15); 706 (16.9%) AKI cases were neonates. During median 9.7-year follow-up, 17.6% of AKI survivors developed MAKE vs 4.6% of controls (HR 4.3, 95%CI 3.9-4.8, p<0.001). AKI cases had higher rates of chronic KRT (2.2% vs 0.2%; HR 12.8, 95%CI 8.5-19.4), CKD (15.9% vs 2.0%; HR 8.8, 95%CI 7.7-10.0), hypertension (16.8% vs 7.7%; HR 2.4, 95%CI 2.2-2.7), and subsequent AKI (5.7% vs 1.5%; HR 4.0, 95%CI 3.4-4.8), but no mortality difference (2.7% vs 2.9%; HR 1.0, 95%CI 0.78-1.16).

Conclusions: Children with non-dialysis-treated AKI are at increased long-term risk of CKD, chronic KRT, hypertension, and subsequent AKI vs hospitalized controls.

Funding: Private Foundation Support

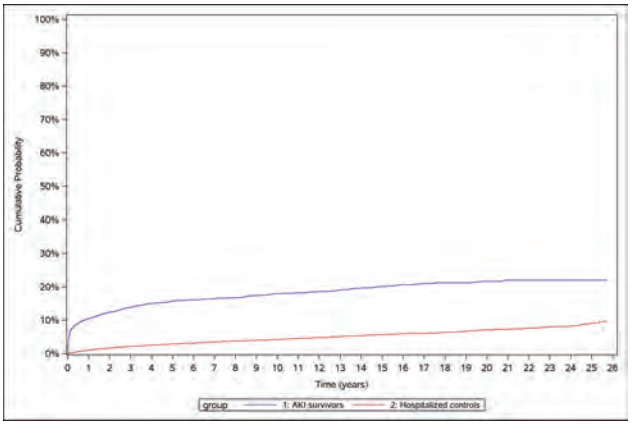


Figure. Cumulative incidence of MAKE

TH-PO511

Reducing AKI in Critically Ill Pediatric Patients: An Improvement Project Targeting Nephrotoxic Medication Exposures

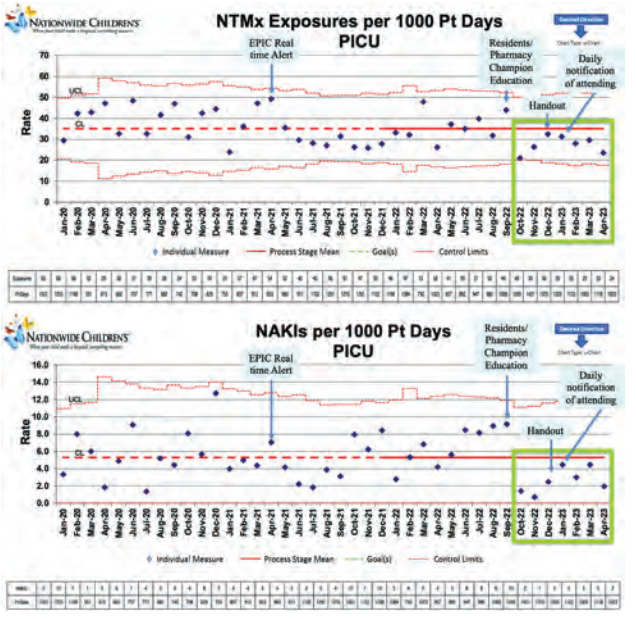
Natalie R. Capretta,[1] W. Joshua Frazier,[1,2] Jeffrey Lutmer,[1,2] Cheryl Sargel,[1] Lindsay Kalata,[1] Robert J. Gajarski,[1,2] Diana Zepeda-Orozco.[1,2] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University, Columbus, OH.*

Background: Acute kidney injury (AKI) occurs commonly in critically ill hospitalized pediatric patients, is associated with nephrotoxic medication exposure and is independently associated with worse clinical outcomes. Our pediatric intensive care unit (PICU) utilized the multicenter Nephrotoxic AKI (NAKI) quality improvement project to increase awareness of nephrotoxic medication exposures, develop interventions, and reduce NAKI.

Methods: A multi-phased approach was used to increase education and recognition surrounding nephrotoxic medication exposures in the PICU and their role in subsequent AKI. Monthly resident physician education was provided by our unit-based clinical pharmacist, and an informational handout was created and reviewed monthly during resident PICU orientation. A third phase included a clinical pharmacist notification to attending physicians of patients meeting exposure criteria with acceptable alternatives to nephrotoxic drugs and suggestions for AKI monitoring.

Results: Our cohort included 39,181 patient days admitted to the PICU at our institution between October 1st 2022 and April 30th 2023. A total of 225 unique patients met nephrotoxic exposure criteria leading to 21 AKI episodes. We reduced nephrotoxic medication exposure rates by 25% from 36.73 to 27.39 per 1000 patient days and NAKIs by 51% from 5.43 to 2.64 per 1000 patient days.

Conclusions: Interventions to decrease AKI successfully in critically ill patients required a multi-phased approach including recurrent education efforts and pharmacy-driven daily physician alerts. Organizational implementation of these interventions is ongoing.



TH-PO512

GUIDANCE: Primary Results of a Prospective, Observational Clinical Study Evaluating the Performance of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) in the Risk Assessment of AKI in Pediatric ICU Patients

Stuart Goldstein,[1] Shina Menon,[2] Katja M. Gist,[3] Megan Soohoo,[3] Natasha Afonso,[4] David M. Kwiatkowski,[5] Christopher W. Mastropietro,[6] David J. Askenazi,[7] Hostensia M. Beng,[8] Sarah J. Kizilbash,[9] Abby M. Basalely,[10] Avi Traum,[11] Julie C. Fitzgerald.[12] The GUIDANCE Investigators. *[1]Cincinnati Children's Hospital, Cincinnati, OH; [2]Seattle Children's Hospital, Seattle, WA; [3]Children's Hospital of Colorado, Aurora, CO; [4]Texas Children's Hospital, Houston, TX; [5]Lucile Packard Children's Hospital School, Palo Alto, CA; [6]Riley Hospital for Children at Indiana University Health, Indianapolis, IN; [7]Children's of Alabama, University of Alabama at Birmingham, Birmingham, AL; [8]East Carolina University Brody School of Medicine, Greenville, NC; [9]University of Minnesota Children's Hospital, Minneapolis, MN; [10]Cohen Children's Medical Center, Queens, NY; [11]Boston Children's Hospital, Boston, MA; [12]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: Acute kidney injury (AKI) has been associated with prolonged hospital stays, future progression to chronic kidney disease, and a 25-80% risk of in-hospital death in critically ill patients. Our ability to treat this condition is lacking, partially due to our inability to detect AKI early. We sought to validate the clinical cut-off value for neutrophil gelatinase-associated lipocalin (NGAL) in pediatric patients. Here, we report the clinical performance of NGAL as a risk assessment marker for AKI in GUIDANCE, a validation study completed in support of an FDA submission.

Methods: Children (aged ≥ 90d to 22 yr) admitted to an intensive care unit (ICU) with a urine sample collected within 24 hours of admission were eligible. Eligible patients must have had either mechanical ventilation, vasoactive medication administration, solid organ or bone marrow transplantation, OR hypotension within 24 hours of admission. Urine NGAL was measured using a particle-enhanced, turbidimetric, NGAL assay. Serum creatinine (SCr) was measured on days 1, 2, and 3 to determine stage 2 or 3 SCr-AKI per KDIGO guidelines. Independent adjudication by three clinical experts assessed for AKI within 48-72 hours using SCr measurements and clinical information but did not have access to NGAL results. NGAL positivity was defined as a urine concentration ≥125 ng/mL based on a prior derivation study.

Results: Six hundred sixty patients were screened, and 514 were evaluable per the study protocol. Forty-seven patients (9.1%) developed stage 2 or 3 AKI; 36 of these patients were NGAL-positive. The sensitivity, specificity, negative predictive value, and positive predictive value for the NGAL test ≥125 ng/mL was 76.6% (36/47), 86.8% (406/468), 97.6% (406/416), 36.7% (36/98), respectively. The diagnostic performance of NGAL as demonstrated by an area under the ROC was 0.86 (95%CI, 0.80-0.92).

Conclusions: These data demonstrate that a particle-enhanced, turbidimetric, NGAL assay performs well early in ICU course to aid in risk assessment for stage 2 or 3 AKI in critically ill children.

Funding: Commercial Support - BioPorto Diagnostics

TH-PO513

Does Kidney Echogenicity Correlate to eGFR in Pediatric AKI?

Shrea Goswami, Michelle C. Starr, Daniel Cater, Andrew L. Schwaderer.
Indiana University School of Medicine, Indianapolis, IN.

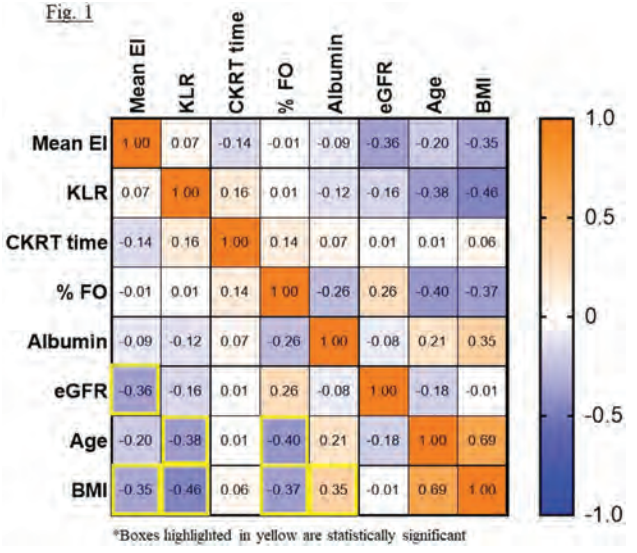
Background: Kidney ultrasound echogenicity is a subjective finding reported by radiologists however it may be more clinically useful if quantified. The objective is to investigate if ultrasonographic parameters of the kidney correlates to estimated glomerular filtration rate (eGFR) in pediatric AKI.

Methods: Retrospective study in a tertiary children's hospital. Ultrasounds of 35 subjects were identified with AKI at the time of CKRT initiation. Three distinct areas of the kidney cortex and liver were cropped. Using Adobe Photoshop software a gray scale pixel density value was quantified. An inverse ratio of the kidney to liver mean pixel densities was the quantified echogenicity index (EI). The kidney lengths, age, weight, height, race/ethnicity, percent fluid overload (%FO), seurm albumin and time on CKRT were entered into a multivariate calculator. The difference between the mean measured and predicted right and left kidney lengths was the kidney length ratio (KLR).

Results: 35 subjects were analyzed. The median age was 10 years (range 2-16) and 54% were male. Heatmap correlation analysis revealed statistically significant negative correlations for mean EI with eGFR and BMI (r = -0.36 [p-value 0.03]: and -0.35[p-value 0.04], respectively). KLR showed negative correlation with BMI and age (r= -0.46 [p-value 0.005] and r = -0.38[p-value 0.0025], respectively). The % of FO significantly correlated with decreasing size and BMI. The AUC for EI with eGFR <90ml/min/1.73m^2 and <60ml/min/1.73m^2 was 0.7 (p-value 0.08 and 0.02, respectively). EI < 1.17 predicted eGFR < 90 with sensitivity of 46.2% (95% CI 29%-65%) and specificity of 88.9% (CI 57%-99%). Similarly, for eGFR <60 with sensitivity of 55.0%(CI 34%-74%) and specificty of 86.7%(CI 62%-98%). AUC for KLR was 0.6 and statistically insignificant.

Conclusions: Increased kidney echogenicity appears to be a more accurate correlate with decreased kidney function than increased kidney size.

Fig. 1



Correlation plot for data. Significant values highlighted in yellow.

TH-PO514

Is Kidney Echogenicity an Early Indicator of AKI Recovery?

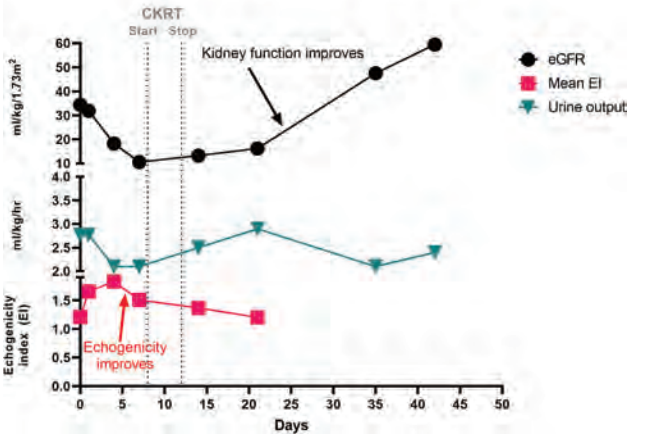
Shrea Goswami, Michelle C. Starr, Daniel Cater, Andrew L. Schwaderer.
Indiana University School of Medicine, Indianapolis, IN.

Introduction: Kidney ultrasound echogenicity is a subjective finding reported by radiologists however it may be more clinically useful if quantified. We present a case report of a 15-year-old girl with acute kidney injury (AKI).

Case Description: 15-year-old girl was diagnosed with AML requiring treatment with a tyrosine kinase inhibitor, gilteritinib. Within two weeks of receipt of this agent she developed severe non-oliguric AKI, likely from medication induced thrombotic microangiopathy. Her baseline serum creatinine was 0.40 mg/dL with a peak of 6.83mg/dL, necessitating CKRT for 5 days. She was receiving serial abdominal ultrasounds for concerns for venous occlusive disease at the same time. Mean echogenicity (EI) was obtained by quantifying the grey scale pixel density of value of the right kidney cortex compared to the liver using adobe photoshop software. Serial echogenicity index (mean EI) of the kidney cortex, weekly urine output (ml/kg/hour) and estimated glomerular filtration rate (eGFR) was collected during hospitalization. It appears that mean EI peaked on day 4 while eGFR was the lowest. Subsequently EI improved on day 7 while the eGFR had sustained improvement between days 21-42.

Discussion: To our knowledge we are not aware of any reports studying kidney echogenicity as a marker for kidney recovery and raises the possibility that it may improve before other markers. EI as an early indicator of kidney recovery needs to be prospectively evaluated compared to other markers such as urine NGAL and, in oliguric patients, increasing urine output.

Fig. 1: Mean EI, urine output and eGFR during hospitalization



Clinical timeline of key parameters relevant to kidney recovery.

TH-PO515

Epidemiology and Outcome of AKI in Hospitalised Children in Australia

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Background: Available estimates of the burden of acute kidney injury (AKI) in hospitalised children are inconsistent and the prognostic implications of its severity, duration, and frequency are poorly understood. Additionally, lack of hospital data on AKI impacts service provision and planning.

Methods: We used our electronic medical record to capture the epidemiology and outcome of AKI in a cohort of children aged between 1 month and 18 years who were hospitalised for at least 24 hours at a quaternary paediatric centre in Melbourne, Australia, between 1 January 2017 and 31 December 2021. AKI was examined according to phenotype in terms of KDIGO stage, duration (transient <48 h, persistent 48 h to 7 d, or acute kidney disease), and frequency. The primary outcome was 30-day mortality. Secondary outcomes included resource utilisation, hospital outcome, and major adverse kidney events at 30 days (MAKE30).

Results: A total of 4,214 AKI episodes occurred, involving 3,134 admissions for 1,540 children (incidence 16%; 17.77 episodes per 1000 patient-days). Most AKI was stage 1, transient, and occurred as a single episode. AKI was associated with an increased risk of 30-day mortality (aOR 3.93, 95% CI 2.77 to 5.58). Compared to children without AKI, children with AKI had a higher odds of ICU admission (aOR 3.40, 95% CI 3.13 to 3.69), mechanical ventilation (aOR 2.05, 95% CI 1.76 to 2.41), vasoactive drugs (aOR 3.76, 95% CI 3.28 to 4.30), and extracorporeal membrane oxygenation (aOR 32.37, 95% CI 15.73 to 66.60). Children with AKI were also more likely to die in hospital (aOR 5.98, 95% CI 4.29 to 8.35), be discharged to rehabilitation (aOR 2.03, 95% CI 1.66 to 2.47), or develop a MAKE30 (aOR 40.35, 95% CI 29.63 to 54.94) compared to children without AKI, when adjusted for ICU status and age. Most adverse events had a graded association with AKI stage and AKI duration; the association between AKI frequency and outcome is less clear.

Conclusions: AKI occurs commonly in hospitalised children and is associated with increased mortality and, among survivors, greater hospital resource utilisation. There was a graded increase in the magnitude of the association with increasing AKI severity and duration. This analysis could be automated and repeated over time to measure the impact of interventions to detect and reduce AKI.

TH-PO516

Predictors for the Development of CKD Stage 2 or Higher in Repeat Pediatric Heart Transplant Recipients

Melvin Chan. *University of Colorado, Denver, CO.*

Background: There is little data on the risk factors for developing chronic kidney disease (CKD) in repeat pediatric heart transplant recipients.

Methods: All repeat heart transplants (RT) at our center from 1995-2021 were reviewed. Renal function was determined by estimated glomerular filtration rate (eGFR) derived from CKiD U25 calculator using creatinine at each hospital and clinic visit.

The stages of acute kidney injury (AKI) were in accordance with the Kidney Disease: Improving Global Outcomes (KDIGO) serum creatinine criteria. Independent samples t-test was conducted on the development of CKD stage 2 or higher and the following variables: pre-transplant eGFR; post-transplant eGFR at 1-3 months; ages at first heart transplant (FT) and RT; time between transplants; gestational age; weight category prior to transplant; and number of AKIs between FT and RT. Multivariate logistical regression was performed for significant variables.

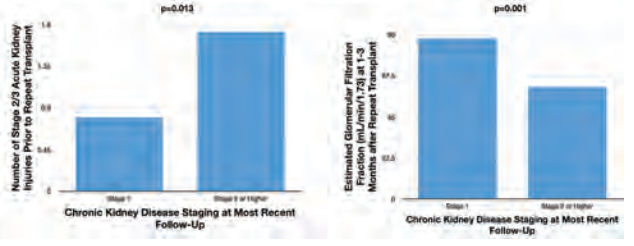
Results: A total of 43 RT were included in this cohort, with a majority being Caucasian and mean age of 14 years old. Median follow-up time was 3 years. Univariate analysis showed significant associations between development of CKD stage 2 or higher and the following variables: pre-transplant eGFR, post-transplant eGFR at 1-3 months, the number of stage 2 and 3 AKIs between FT and RT. Multivariate logistic regression showed that post-transplant eGFR at 1-3 months (OR 0.92) and number of stage 2 and 3 AKIs (OR 21.5) remained significant, with an AUC of 0.91, sensitivity of 0.97, and specificity of 0.60.

Conclusions: Our preliminary data shows the post-transplant eGFR at 1-3 months and number of stage 2 and 3 AKIs are predictors for the development of chronic kidney disease stage 2 or higher. More research is needed to look at predictors for development of advanced chronic kidney disease to inform transplant teams when a repeat heart transplant or a dual heart and kidney transplant can be done.

Table 1. Predictors for Development of Chronic Kidney Disease Stage 2 or Higher

Variables	Univariate Analysis	Multivariate Analysis	
	p-value	OR	p-value
Pre-transplant eGFR	0.002		
Post-transplant eGFR at 1-3 months	0.001	0.92	0.031
Number of stage 2 and 3 AKIs	0.013	21.5	0.015

Figure 1: Univariate Predictors of Developing Chronic Kidney Disease, Stage 2 or Higher



TH-PO517

AKI in Pediatric Heart Transplant Patients with a Ventricular Assist Device (VAD)

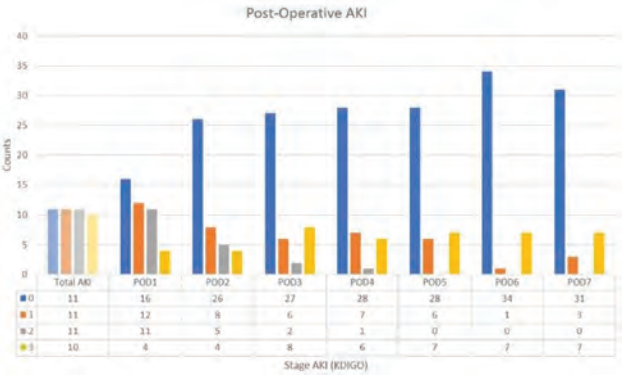
Deirdre Bartlett,[1,2] Jamie Penk,[1] Brian Madden,[1] Alexander J. Kula.[1] *[1]Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [2]Stanley Manne Children's Research Institute, Chicago, IL.*

Background: Acute kidney injury (AKI) is common and an independent risk factor for prolonged hospitalization, development of CKD, and mortality in critically ill children undergoing cardiac surgery. AKI following heart transplant (HTxp) has not been as well studied, and even less is known in patients bridged with ventricular assist device. The VAD population warrants further attention given unique risk factors of prolonged mechanical circulatory support, multiple surgeries requiring cardiopulmonary bypass, and nephrotoxic treatments pre- and post- HTxp including diuretics and immunosuppression. Our study aimed to address this knowledge-gap by describing rates of AKI following HTxp in VAD dependent pediatric patients at time of surgery.

Methods: We performed an observational, retrospective study. Included patients met the following criteria: received HTxp at our institution during the past 5 years, age <18 years, use of VAD at time of HTxp, and at least 1 creatinine value in the first 7 postoperative days. GFR estimated using bedside Schwartz equation. AKI stages defined by KDIGO creatinine criteria. Primary outcome was incidence of AKI in the first week following HTxp.

Results: Out of 140 HTxp performed, 43 (31%) met inclusion criteria. Mean pre-Txp GFR was 142 mL/min/1.73m2. 11% (5/43) had CKD not requiring dialysis and 4.7% (2/43) were on dialysis entering transplant. During the first 7 post-operative days, 74.42% (32/43) developed any AKI, 48.84% (21/43) developed severe AKI (stage 2-3) and 16.27% (7/43) required dialysis. Multivariate analysis will be performed to determine significantly associated risk factors.

Conclusions: Our study demonstrates pediatric HTxp recipients with VADs may have a high burden of AKI and severe AKI. The incidence of AKI in our cohort was much higher compared to previously published rates in other pediatric cardiac surgeries. Kidney care may need to be prioritized in VAD patients following HTxp. We plan to work to identify modifiable risk factors for post-transplant AKI in VAD patients in ongoing research.



TH-PO518

Outcomes of Simultaneous Heart-Kidney vs. Sequential Heart-Kidney Transplantation in Children

Ruchi Mahajan, Michael D. Evans, Sarah J. Kizilbash. *University of Minnesota Twin Cities, Minneapolis, MN.*

Background: Heart transplant (HTx) recipients frequently require kidney transplantation for concomitant advanced chronic kidney disease. Data on simultaneous (HTx and Kidney Transplant (KTx) at the same time) versus sequential {HTx performed before KTx} HTx and KTx in children are limited. Herein, we compare KTx outcomes between the two groups.

Methods: We used the Scientific Registry of Transplant Recipients (SRTR) to identify all pediatric (age < 21 years) Htx recipients who also received a KTx within 10 years of the HTx. We divided the study cohort into two: simultaneous heart/kidney and sequential heart/kidney recipients. We compared continuous and categorical variables using the Wilcoxon rank sum test and chi-square test. We compared patient and death-censored graft survival between simultaneous and sequential KTx recipients using the Cox regression, adjusting for age at the KTx, sex, race, pretransplant dialysis, donor type, and prior KTx. All analyses were performed in R, and a p-value of < 0.05 was considered statistically significant.

Results: Our analysis cohort included 165 recipients (79 for sequential and 86 for simultaneous). Table 1 is baseline characteristics of the cohort. We found no difference in patient survival (aHR: 0.97; 95% CI: 0.39, 2.41; p = 0.95) but better death-censored graft survival in sequential heart/kidney recipients compared with simultaneous heart/kidney recipients (aHR: 4.26; 95% CI: 1.21, 14.9; p = 0.02).

Conclusions: Pediatric HTx/KTx recipients who receive the KTx after their HTx have a better death-censored kidney allograft survival compared with those who receive KTx simultaneously with the heart transplant. Children with less significant kidney dysfunction at the time of HTx evaluation should be considered for a sequential heart/kidney transplant.

Baseline Characteristics of Patients undergoing Sequential versus Simultaneous Heart Kidney Transplantation.

Demographic Characteristics	Sequential heart and kidney transplant N = 79	Simultaneous heart and kidney transplant N = 86	p Value
Median Age at kidney Tx (years)	17.00 [13.00, 21.00]	16.00 [12.00, 18.75]	0.015
Female	35 (44.3)	44 (51.2)	0.47
Race : Asian Black Multi Native White	0 (0.0) 16 (20.3) 2 (2.5) 0 (0.0) 61 (77.2)	4 (4.7) 35 (40.7) 0 (0.0) 1 (1.2) 46 (53.5)	0.003
Pretransplant dialysis :N Y	13 (17.1) 63 (82.9)	37 (44.6) 46 (55.4)	<0.001
Donor Type : Deceased Living	34 (43.0) 45 (56.0)	86 (100.0) 0	<0.001
Delayed graft function (%): N Y	72 (92.3) 6 (7.7)	66(77.6) 19(22.4)	0.017
eGFR at Heart Transplant (ml/min/1.73m2) Median (IQR)	53.76 [37.16, 83.60]	28.49 [17.18, 45.81]	<0.001
Cause of ESKD (%): Focal Segmental Glomerulosclerosis (FSGS) Nephritis Hypoplasia/dysplasia/Agenesis Acute Tubular Necrosis Calcineurin Inhibitor Therapy Congenital Obstructive uropathy Other	3 (3.8) 1 (1.3) 1 (1.3) 1 (1.3) 42 (53.2) 1 (1.3) 30 (37.9)	9 (10.6) 3 (3.5) 3 (3.5) 2 (2.4) 20 (23.5) 0 (0.0) 49 (56.9)	0.072

TH-PO519

New Treatments, New Challenges: Nephrotoxicity-Associated Naxitamab in Pediatric Patients with High-Risk Neuroblastoma

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Background: Neuroblastoma is the most common extracranial solid tumor in pediatrics, having a poor survival in high- risk (HR) tumors. Naxitamab(hu3F8) is a humanized monoclonal antibody anti-dysialoganglioside (GD2) approved for treatment

of > 1 year-old and adults with refractory/relapsed HR-neuroblastoma limited to bone or bone marrow. Our hospital has been the first center (2017) worldwide use it (clinical trials/compassionate use), obtaining excellent results.

Methods: Retrospective descriptive study including 244 patients (41% female-101-and 59% male-143-) using Naxitamab (monotherapy and/or associated with chemotherapy) from June 2017 to current day (6 years) in whom renal involvement and/or hypertension (HT) was evaluated.

Results: Mean age was 8 years, presenting nephrotoxicity of some type up to 26.6%(65):HT(11.9%/29), acute renal damage(ARD10.2%/25) and proteinuria(5.3%/13), developing all of them during the infusion or the first 3 cycles. In case of HT, only in 6 patients an ABPM was performed, observing:2 nocturnal-HT,2 diurnal-HT without specific-pattern and 2 disautonomic-pattern, not previously observed. Among the ARD, all cases were tubular except for one patient who presented clinical-analytical pattern of acute tubule- interstitial nephritis(AIN). Eight of them(32%) presented possible confounding factors in the development of(previous chemotherapy, ibuprofen or radiotherapy). Among patients with proteinuria(none nephrotic range): 38% tubular, 38% glomerular and 23% mixed.2 patients presented ARD+AHT and 3 a combination of AHT+ARD+proteinuria. Of these last, all of them received prior chemotherapy, leaving 2 of them with chronic renal damage(CKD stage 2 and 3).67 patients(27.4%) died due to progression of their underlying disease.

Conclusions: Management of HR-neuroblastoma remains a daily challenge. Naxitamab is an emerging therapy in this type of tumors, although there are few studies describing its AE. Previous studies of our group in mice explain the involvement of the myelin sheaths of the autonomic nervous system with this drug, which could explain, among others, the dysautonomic pattern of blood pressure presented. Short- and long-term follow-up, the systematic performance of ABPM and the use of early markers of renal damage, could lead to a more efficient management of complications derived from this new treatment.

TH-PO520

Incidence of Nephromegaly Following Hematopoietic Stem Cell Transplantation in Children and Young Adults

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Background: Hematopoietic stem cell transplantation (HSCT) is an effective treatment for a variety of malignancies, metabolic and autoimmune diseases. Complications of HSCT include infections, veno-occlusive disease, mucositis, hemorrhagic cystitis, and graft-versus-host disease. Nephromegaly, along with other abdominal organomegaly, has been reported in the literature but the incidence and clinical significance is unknown.

Methods: Children and young adults (age ≤ 19 years) who underwent HSCT over a 10-year period (2011 to 2021) were screened for the study. Patients were included if they underwent a kidney ultrasound pre-HSCT and within 3 months post-HSCT. We retrospectively collected data that included demographics, type of HSCT, conditioning regimen and primary diagnosis. Data extracted from ultrasound reports included kidney length, presence, and severity of hydronephrosis and other renal anomalies. Other data points collected included HSCT source, conditioning regimen, and concurrent renal anomalies. The primary outcome of the study was the kidney length percentile for patient's age as measured by ultrasound before and within 3 months after the HSCT. Paired t-test was used for comparison of continuous data and Chi-Square test for comparing proportions.

Results: Twenty-seven patients met the inclusion criteria for the study. Median age was 7 years (20 months to 19 years) with 41% females. The kidney length percentile was significantly increased post-HSCT (79.3, IQR 71.5 - 98.7) as compared to pre-HSCT (72.4, IQR 44.9 - 97.2, p = 0.03). The percentage of patients with unilateral nephromegaly was 51.8% pre and 59.3% post HSCT (p = 0.58). The percentage of patients with bilateral nephromegaly was 14.8% pre and 29.6% post-HSCT (p = 0.19). No statistically significant differences were detected when groups were stratified by age, sex, primary diagnosis, HSCT source, conditioning regimen, and presence of other renal anomalies.

Conclusions: In this cohort of children and young adults, kidney length percentiles for age significantly increased post-HSCT. The mechanism and clinical significance of this increase requires further investigation.

TH-PO521

Epidemiology and Outcomes of AKI and Dialysis After Bone Marrow Transplant in Pediatric Patients

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Background: Acute kidney injury (AKI) is a common post-operative complication of bone marrow transplantation (BMT) in pediatric patients, with high mortality and morbidity. However, little is known about the epidemiologic characteristics. We assessed the characteristics, risk factors, and outcomes of BMT-induced AKI and the incidence, prevalence, and mortality of dialysis in the pediatric population.

Methods: Using patient data from TriNetX, a platform of health record data from 101 healthcare organizations, two cohorts were identified using ICD-10/lab/procedure/prescription codes: <18y/o patients with AKI within 30 days of BMT, and <18y/o patients who underwent BMT excluding AKI. Cohorts were 1:1 propensity matched for age, sex, and race. Outcomes assessed were: characteristics, risk factors, and clinical outcomes (hospitalization, emergency department [ED] visit, intensive care unit [ICU] admit, and mortality) after 6 and 12 months and incidence, prevalence, and mortality of dialysis patients post-AKI. Risk ratio (RR) and hazard ratio (HR) with 95% confidence intervals (95% CI) and Kaplan-Meier analysis were conducted.

Results: After matching, 524 pediatric patients were included. Characteristics, risk factors, and outcomes are in **Table 1**. Patients with AKI had higher rates of all clinical outcomes and greater mortality risk: 12.8% reduction in survival probability at 6 months and 14.6% at 1 year, **Figure 1**. The incidence of dialysis post-BMT and AKI was 4.3% at 1 year and 10.6% at 5 years, while the prevalence was 12.8% at 1 year and 14.6% at 5 years. Survival probability was 11.9% below the control cohort.

Conclusions: We found BMT-induced AKI and dialysis led to worse clinical outcomes in child patients. Further research is needed to develop preventive/management strategies for this high-risk population.

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Baseline characteristics	*AKI, No. (%) n=524*	*Control, No. (%) n=4,225*	*p-value*
Age (Mean ± SD)	7 ± 4.9	6 ± 4.5	p<0.001
Male	295 (56.3)	2,467 (58.4)	p=0.336
White	277 (52.9)	2,196 (52)	p=0.655
BMI	19.2±4.9	17.9±4.34	p<0.001
Diabetes Mellitus	34 (6.5)	79 (1.9)	p<0.001
Creatinine	0.61±0.48	0.32±0.24	p<0.001
Risk Factors n=524, after matching			*Risk Ratio (95% CI); p-value*
Hypertension	315 (60.1)	140 (26.7)	2.25 (1.92-2.64); p<0.001
Dialysis	59 (11.3)	10 (1.9)	5.90 (3.05-11.41); p<0.001
Veno-occlusive disease	41 (7.8)	13 (2.5)	3.15 (1.71-5.82); p<0.001
Graft versus host disease	225 (42.9)	96 (18.3)	2.34 (1.91-2.88); p<0.001
Sepsis	92 (17.6)	19 (3.6)	4.84 (3.70-7.82); p<0.001
Jaundice	22 (4.2)	10 (1.9)	2.20 (1.05-4.60); p=0.031
Amphotericin B	25 (4.7)	17 (3.2)	1.47 (0.80-2.69); p=0.208
Aminoglycosides	77 (14.7)	35 (6.7)	2.20 (1.50-3.22); p<0.001
Calcineurin inhibitors	140 (26.7)	97 (18.5)	1.47 (1.17-1.86); p=0.002
Intravenous immunoglobulins (IVIG)	136 (26.0)	93 (17.7)	1.46 (1.16-1.85); p=0.002
Clinical Outcomes n=524, after matching			*Hazard Ratio (95% CI); p-value*
Hospitalization	283 (54.1)	168 (32.1)	1.98 (1.64-2.40); p<0.001
Emergency Department Visit	169 (32.3)	123 (23.5)	1.62 (1.28-2.04); p<0.001
Intensive Care Unit Admission	93 (17.8)	28 (5.4)	3.70 (2.42-5.65); p<0.001
All-Cause Mortality	90 (17.2)	25 (4.8)	3.84 (2.47-5.99); p<0.001

Table 1: Baseline characteristics, risk factors, and clinical outcomes of AKI and control patients after 12 months.

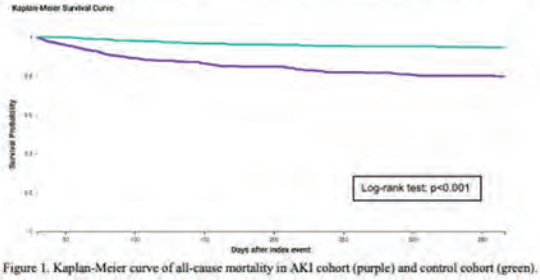

Figure 1. Kaplan-Meier curve of all-cause mortality in AKI cohort (purple) and control cohort (green).

TH-PO522

Long-Term Kidney Outcomes of Pediatric Acute Lymphoblastic Leukemia Survivors

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Background: Hypertension (HTN) and chronic kidney disease (CKD) have been described in pediatric cancer survivors but renal outcomes following childhood acute lymphoblastic leukemia (cALL), the most frequent pediatric cancer, remain poorly defined. We aimed to determine the prevalence of abnormal estimated glomerular filtration rate (eGFR) and HTN among cALL survivors in the short- and long-term and assess potential associations with clinical characteristics prior to end of treatment.

Methods: This is a retrospective cohort study of 237 cALL survivors with no prior kidney disease. Clinical, imaging, and laboratory data were documented from cALL diagnosis to end of treatment (1987-2010) and at study follow-up (2013-2015). Logistic regression models were used to examine relationships between clinical characteristics and kidney outcomes.

Results: 49.8% of the cohort were males and median age at diagnosis was 4.8 (IQR = 3.0-9.8) years. By end of treatment, HTN and acute kidney injury (AKI) were diagnosed in 15.3% and 34.2% of patients respectively. Stage 1 AKI represented 77.8% of all AKI episodes. Initial ultrasound findings suggestive of leukemic kidney infiltration (LKI) and tumor lysis syndrome (TLS) were associated with higher AKI risk. HTN risk was higher among children younger than 5 years old (OR 2.3; 95% CI 1.1-4.8), those with LKI (3.5; 1.5-7.9), and who had AKI (2.5; 1.2-5.2). Median length of follow-up was 15.0 (11.6-19.7) years, with median age of 21.4 (16.8-25.9) years old. High blood pressure values suggesting HTN were recorded in 11.5% of patients. Mean eGFR was 100.3±15.7 ml/min/1.73m^2, with no difference between patients who had previous severe AKI episodes versus not. 27.1% of the cohort met criteria for stage 2 CKD (eGFR < 90 ml/min/1.73 m^2). CKD at long-term follow-up was not associated with number of AKI episodes, AKI severity, nor HTN prior to end of treatment. Prior severe AKI episodes were associated with high blood pressure at follow-up (5.1; 1.7-15.2).

Conclusions: Attention may be warranted for patients with ultrasound findings suggestive of LKI and TLS prior to end of treatment. cALL survivors who had severe AKI would benefit from long-term blood pressure monitoring. All cALL survivors should have their kidney function monitored as over 1 in 4 had stage 2 CKD by early adulthood, regardless of previous AKI or HTN diagnoses.

TH-PO523

Severe AKI and CKD Are Common in Children with Veno-Occlusive Disease Following Bone Marrow Transplantation

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Background: Veno-occlusive disease (VOD) is a life-threatening complication occuring after bone marrow transplantation (BMT). The prevalence and severity of short and intermediate kidney outcomes is unknown.

Methods: Single center retrospective cohort of children with VOD following BMT from 2010-2020 (N=44). Primary outcome was treatment with kidney replacement therapy (KRT). Secondary outcomes included severe AKI and CKD at 1 year post BMT.

Results: Severe AKI developed in 35 (80%) of children with VOD and KRT was used in 21 (48%). Childen receiving KRT were younger (p=.041) and had lower pre-BMT eGFR (p=.032). Children receiving tacrolimus for GVHD prophylaxis (p<.001), shorter time to VOD diagnosis (p=.021), and more fluid overload (p=.001) were more likely to require KRT (**Table**). 33 (75%) survived to discharge. Of those receiving KRT, 13 (62%) survived to discharge. One year following BMT, 19 patients (43%) had died. Of those alive at 1 year, 9 (36%) had CKD and 9 (36%) had hypertension (**Figure**).

Conclusions: Despite high mortality, severe AKI and KRT in children with VOD is no longer universally fatal. In those that survive, CKD is common. We describe patient and treatment factors associated with KRT. Further study is needed to assess the causality, such as fluid overload and target interventions, such as diuretic therapy and individualized fluid management, in this high-risk patient population.

	Cohort	KRT	No KRT	p-value
N	44	21	23	
Male, n (%)	22 (50)	8 (38)	14 (61)	.13
Age at transplant (years), median, IQR	3.9 (9.2)	3.8 (10.5)	4.0 (10.7)	.041
Race, n (%)				.86
Caucasian	35 (80)	16 (76)	19 (83)	
African American	7 (16)	4 (19)	3 (13)	
Asian	2 (4)	1 (5)	1 (4)	
Hispanic Ethnicity, n (%)	7 (16)	1 (5)	6 (26)	.06
Diagnosis, n (%)				.22
Oncologic	33 (75)	14 (67)	19 (83)	
Non-Oncologic	11 (25)	7 (33)	4 (17)	
Conditioning regimen, n (%)				.59
MAC	33 (75)	15 (71)	18 (78)	
NMA/RIC	5 (12)	2 (10)	3 (13)	
Other/None	6 (13)	4 (19)	2 (9)	
Stem cell source, n (%)				.47
Bone Marrow	19 (44)	11 (52)	8 (35)	
Peripheral Blood	10 (23)	4 (19)	7 (30)	
Cord Blood	14 (33)	6 (29)	8 (35)	
Donor Type, n (%)				.77
Autologous	8 (18)	3 (14)	5 (22)	
Allogenic related	13 (30)	6 (29)	7 (30)	
Allogenic unrelated	23 (52)	12 (57)	11 (48)	
GFR at admission, n (%)	136 (40)	126 (64)	138 (35)	.032
GVHD Prophylaxis, n (%)				
Tacrolimus	20 (46)	14 (67)	6 (26)	<.001
Sirolimus	3 (7)	2 (10)	1 (4)	.80
Cyclophosphamide	26 (59)	12 (57)	14 (61)	.39
Methotrexate	12 (27)	7 (33)	5 (22)	.54
Days to VOD Diagnosis (Median, IQR)	16 (10)	15 (9)	19 (12)	.021
GVHD, n (%)	10 (23)	7 (33)	3 (13)	.11
TMA, n (%)	10 (23)	6 (29)	4 (17)	.47
ICU Admission, n (%)	32 (73)	21 (100)	11 (48)	NA
Peak Fluid Overload (Median, IQR)	10.8 (11.8)	18.8 (23.8)	2.5 (5.36)	<.001
Fluid Overload at ICU Admission (Median, IQR)	10.7 (9.8)	10.7 (13.7)	8.3 (9.7)	.001
Nephrology Consult, n (%)	32 (73)	21 (100)	11 (48)	NA

Table: Clinical Characteristics of Children with VOD by Kidney Replacement Therapy (KRT) status

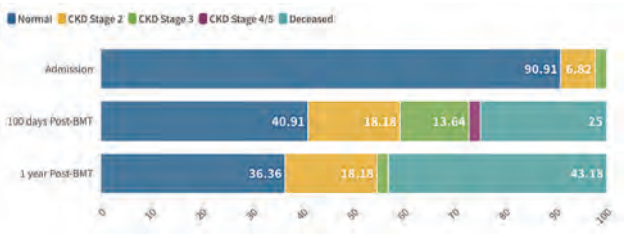

Figure: Chronic Kidney Disease in Children with VOD following BMT

TH-PO524

Renal Vein Thromboses: A 10-Year Review of a Tertiary Pediatric Center Practice

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Background: Renal vein thrombosis (RVT) is a rare diagnosis predominantly affecting neonates. Although uncommon, there is long-term risk of hypertension (HTN) and chronic kidney disease (CKD). RVT tends to be unilateral (70% of cases) but extension of thrombosis is common (52% of cases). There are many risk factors predisposing to RVT including genetic thrombophilia mutations. Current management is based solely on expert opinion or small observational studies with no consensus. The choice and length of anticoagulation, if used, is variable and recommendations vary.

Methods: We reviewed our practice of RVT at a single tertiary pediatric nephrology center in the United Kingdom. We carried out a retrospective review of RVT cases over the past 10 years to evaluate our practice and develop local consensus on management.

Results: 18 patients were screened, with 14 patients eligible for inclusion. Nearly all patients identified were neonates, diagnosed with RVT at a median age of 3 days. Our review found a higher proportion of cases having bilateral RVT (57%) compared to unilateral (43%), with associated thromboses occurring in 71% of cases. 86% of cases received anticoagulation initially with low molecular weight heparin (LMWH)/enoxaparin (50%), unfractionated heparin (42%) or alteplase (8%). Long term anticoagulation was predominantly LMWH (62.5%) with others receiving warfarin (25%) and one case receiving rivaroxaban. Duration of anticoagulation varied between 1 week to 6 months. Most children (79%) were investigated with a thrombophilia screen, and 45% of those investigated had a gene mutation identified (2 with prothrombin mutation and 3 with factor V Leiden mutation). Mortality was high (21%) with long term outcomes of HTN (50% of cases) and CKD (43% of cases) being common at 3 and 6 month follow up.

Conclusions: Our review, although small, highlighted the variability in RVT presentation and management. There were more cases of bilateral RVT with a high index of associated thrombus formation in our population. Most cases received anticoagulation, but we recognise the variation in practice and length of therapy. We highlight the need for thrombophilia screening as well as monitoring for long-term sequalae like HTN and CKD. We recommend that larger international studies or an RVT registry are needed to achieve consensus on management between pediatric haematology and nephrology.

TH-PO525

Congenital Single Kidney, Inferior Vena Cava Abnormality, and Bilateral Ileo-Femoral Deep Vein Thrombosis: A Case of KILT Syndrome

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Introduction: KILT (kidney and inferior vena cava (IVC) abnormalities with leg thrombosis) syndrome is a rare condition comprising of renal defects, IVC abnormalities and venous thrombosis. There is limited knowledge about its pattern of presentation, management, and prognosis.

Case Description: We present a 30-year old lady who was referred to us with microscopic haematuria, single kidney on recent imaging and normal renal function. She later developed bilateral ileo-femoral DVT. In 2016, she presented to her General Practitioner with bilateral loin pain and positive urine dip. Computed tomography (CT) urogram was performed due to pyelonephritis revealing a solitary left hypertrophied kidney, hence referred to our renal clinic. She had normal renal function, no proteinuria or hypertension so renal biopsy was not clinically indicated. Renal function and urine parameters were therefore monitored annually. She presented to the Accident & Emergency department in August 2022 with pelvic inflammatory disease then developed a rigid left calf. Ultrasound Doppler demonstrated extensive DVT involving the popliteal femoral axis and anti-coagulation was commenced. Haematology screen was negative. She re-presented with right thigh pain in September 2022. CT abdomen-pelvis showed bilateral DVTs extending into the iliac veins and IVC as well as an IVC anatomical variant. In view of her having a single kidney, IVC abnormality and leg thrombosis a diagnosis of KILT syndrome was made. She has since developed a pulmonary embolism despite oral anti-coagulation.

Discussion: Most reported cases present with leg thrombosis and are later found to have absent/hypoplastic kidney. Our patient presented with a single kidney and no known history of thrombosis. The presentation therefore seems to be varied and a high degree of clinical suspicion is necessary. Could we have prevented DVT if we had imaged her

IVC anatomy as workup for the single kidney? Perhaps. We feel KILT syndrome should be included in the differential diagnosis of young patients with renal defects to prompt consideration of CT imaging of the IVC. Early detection may prevent renal hypoplasia with vascular intervention. There is no consensus of prevention or management of DVTs in KILT syndrome. Therefore, long-term anticoagulation and more follow up is required.

TH-PO526

Res(e)t and Relaxation: Intractable Hypernatremia

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Introduction: Sodium and water homeostasis is regulated by vasopressin (AVP) release from the anterior pituitary and its antidiuretic action on the kidney. Osmoreceptors detect changes in plasma tonicity. The osmotic threshold (or osmostat) for AVP release is ~285 mOsmol/kg H_20.

Case Description: A 3-y boy with global developmental delay, cerebral palsy and G-tube dependence presented with pneumonia. The plasma sodium (PNa) improved from 154mmol/L to 151mmol/L with increased water intake. On follow up, PNa was 157mmol/L: he was admitted for further investigations. There was persistent sialorrhea and diaphoresis, but no medication changes, excess water losses or increased salt intake. He had stable vitals, 100g drop in weight and unremarkable examination. With no intervention, repeat bloodwork showed PNa 150mmol/L, plasma osmolality (POsm) 309 mOsm/kg H20, urine osmolality (UOsm) 1019 mOsm/kg and FeNa 0.5%. All other serum electrolytes and renal indices were unremarkable. Active increase in free water intake above his usual total fluid intake resulted in a PNa nadir of 146mmol/L, with urine osmolality of 187 mOsm/kg. These data show evidence of free water loss while still hypernatremic. After returning to his TFI, PNa settled around 151 mmol/L, with UOsm 600 mOsm/kg, and has remained stably high ever since.

Discussion: We describe a case of hypertonic hypernatremia and concomitant highly concentrated urine, indicating excellent urinary concentrating ability and adequate ADH production, effectively ruling out diabetes insipidus. Once PNa dropped below 150mmol/L (but never less than 146), enhanced free water excretion was invariably observed. We hypothesized that these findings are in keeping with an osmostat that is reset at a higher POsm to trigger ADH release: a rarer form of reset osmostat (RO), which is more commonly associated with hyponatremia (type C SIADH). We estimate that the threshold is ~150mmol/L instead of the usual 145. The etiology remains unclear with no hypothalamic lesion and no evidence of anterior pituitary dysfunction, and perhaps long term hypodipsia contributed. An overview of published literature on reset osmostat hypernatremia will be discussed. RO should be considered when dealing with a patient with an unusually difficult-to-control dysnatremia, when there is evidence of normal kidney function, and intact urine diluting and concentrating ability.

TH-PO527

Prediction of Ionized Hypocalcemia by Anion Gap and Its Components in Children Admitted to the Intensive Care Unit: A Retrospective Cohort Study

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Background: The diagnosis of ionized hypocalcemia based on total serum calcium can be misleading. Correction of total calcium for hypoalbuminemia may be erroneous because calcium binds to other anions outside of the serum albumin. In this study, we tested the hypothesis that a correction of total serum calcium for anion gap and its components would improve the accuracy of a non-invasive diagnosis of ionized hypocalcemia in pediatric patients admitted to the ICU.

Methods: This is a retrospective study of patients aged 1 month to 21 years who were admitted to PICU at SUNY Downstate Medical Center between 2016-2020. All patients who had measurements of basic metabolic panel and blood gas analysis respectively taken within 60 minutes of each other were included. Logistic regression analysis for the prediction of ionized hypocalcemia using either the anion gap (AG model), its ion components (Na, Cl, and CO2; ion model), total serum calcium, and serum albumin as independent variables were performed.

Results: Compared with the AG model, the ion model was a better predictor of ionized hypocalcemia. The value of area-under-the-curve (ROC) was 0.85 ($p < 0.005$) for AG model and 0.9 ($p < 0.005$) for the ion model (Figure 1). Both parameters were more predictive of ionized hypocalcemia than the albumin-adjusted calcium method with the value of the ROC of only 0.8 ($p < 0.05$), Figure-1.

Conclusions: A correction of the total serum calcium for the anion gap and its components [sodium, chloride, and CO2] respectively improved the ability to diagnose ionized hypocalcemia non-invasively in pediatric patients admitted to ICU.

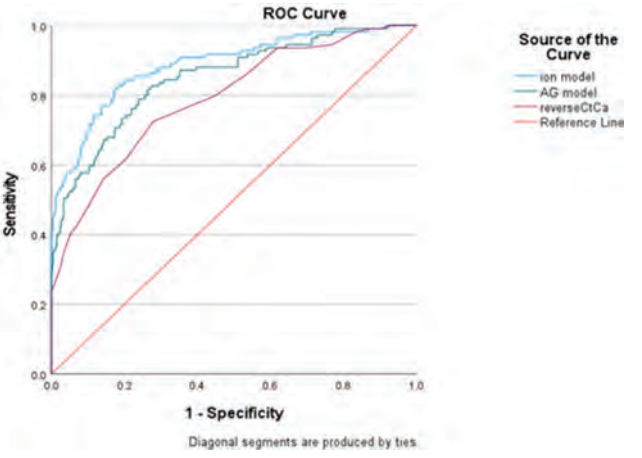

Figure-1

TH-PO528

Clinical Features of Cystinosis and Practice Patterns: A Report of the NAPRTCS Cystinosis Registry

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Background: The NAPRTCS Cystinosis Registry was established to describe the clinical features of cystinosis in children and young adults and the associated practice patterns of providers.

Methods: Subjects ≤ 25 yrs of age with cystinosis at any NAPRTCS center are eligible for enrollment. Demographic and clinical data from time of diagnosis, time of registry enrollment, and every 6 months thereafter are collected.

Results: To date, data from 91 subjects from 30 centers diagnosed between 12/1999 and 8/2022 are available. Patient demographics and clinical features are shown in Table 1. Reported medications at diagnosis included cystine lowering medications (81.3%), cysteamine eye drops (35.2%), and phosphorus and potassium supplementation (42.9%, 40.7%) (Table 2). Procysbi use progressively increased following FDA approval in 2013. Median creatinine at registry entry and 36 months post enrollment was 0.64 mg/dL (eGFR 76.4 ml/min/1.73m^2) and 0.79 mg/dL (66.1 ml/min/1.73m^2), respectively. At registry entry, almost half the patients (48.9%) had a g-tube and photophobia was reported in 25.3%. Over 90% of patients were at grade level with 34.1% receiving special services. The most common subspecialty visits were ophthalmology (28.9%), endocrinology (25.6%), and GI (17.8%).

Conclusions: Children with cystinosis present early in life with the majority diagnosed before 2 years of age. Patients typically experience 5 months of symptoms prior to diagnosis, with failure to thrive present in more than 50%. Children and young adults with cystinosis have complex care needs which are often met through multispecialty care providers.

Funding: Commercial Support - Horizon, Leadiant

Table 1. Cohort demographics and clinical characteristics

	n=91 Median (IQR) or %
Age at diagnosis	18 months (12, 36)
Age at registry entry	9 years (6, 13)
Male	49 (53.8%)
White	71 (78.0%)
Median duration of symptoms	5.5 months (2.0, 10.0)
Clinical features at diagnosis	
Failure to thrive	49 (53.8%)
Vomiting	37 (40.7%)
Corneal crystals	30 (33.0%)
Labs	
WBC cystine level by assay	
Granulocyte (n=35)	5.10 nmol/mg protein (2.7, 9.0)
Leukocyte (n=22)	3.31 nmol/mg protein (2.1, 5.8)
Genetic analysis	22 (24.2%)
Distance from center (n=62)	
<20 miles	20 (22.0%)
20-50 miles	17 (18.7%)
>50 miles	28 (30.8%)

Table 2. Medication utilization

	At diagnosis (N=91)	Registry Entry (N=90)	6 Months (N=78)	12 Months (N=73)	24 Months (N=49)	36 Months (N=26)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cystagon	50 (54.9%)	27 (30.0)	24 (30.8)	17 (23.3)	11 (22.4)	4 (15.4)
Procysbi	24 (26.4%)	54 (60.0)	49 (62.8)	54 (74.0)	41 (83.7)	20 (76.9)
Cysteamine eye drops	32 (35.2%)	66 (73.3)	60 (76.9)	59 (80.8)	41 (83.7)	21 (80.8)
Potassium	37 (40.7%)	55 (61.1)	46 (59.0)	41 (56.2)	27 (55.1)	15 (57.7)
Phosphorus	39 (42.9%)	43 (47.8)	33 (42.3)	29 (39.7)	18 (36.7)	10 (38.5)
Sodium bicarbonate	17 (18.7%)	24 (26.7)	17 (21.8)	17 (23.3)	14 (28.6)	10 (38.5)
Sodium chloride	4 (4.4%)	6 (6.7)	8 (10.3)	5 (6.8)	4 (8.2)	3 (11.5)
Carnitine	23 (25.3%)	40 (44.4)	32 (41.0)	35 (47.9)	24 (49.0)	15 (57.7)
Indomethacin	5 (5.5%)	12 (13.3)	6 (7.7)	7 (9.6)	3 (6.1)	-

TH-PO529

Updates on Renal Amyloidosis in Children and Adolescents

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Background: Amyloidosis affects individuals with eastern Mediterranean ethnicity; however, worldwide manifestation is frequent because of worldwide human migration. Although renal amyloidosis (RA) is a potentially fatal disease, it is relatively rare in children and adolescents. Its early manifestation as nephrotic syndrome may be mistaken for a minimal change disease. Familiarity with its geographical spread and pattern of presentation may enhance diagnostic awareness. For this purpose, we embarked on a PubMed search for articles on pediatric RA.

Methods: We searched the PubMed and Embase databases from 1960 to 2022 for relevant original articles including case reports and case series on RA in children and adolescents.

Results: RA occurred (n = 679) commonly among a population affected by familial Mediterranean fever (FMF) (n = 2812) who are mostly residents of Turkey (n = 1907) and Armenia (n = 836). The second most common cause of RA was idiopathic juvenile arthritis (JIA) (n = 139). Other reported causes were tuberculosis (TB) (n = 10) and epidermolysis bullosa (EB) (n = 13). In general, there was often renal remission following early diagnosis and treatment of FMF, JIA, and TB. The poor response to treatment in EB frequently resulted in end-stage kidney disease and fatal outcomes. There were only 6 cases of hereditary RA, three of which were due to ALys amyloid deposition. There was a single report of ALECT2 disease.

Conclusions: Most cases of pediatric RA were due to auto-inflammatory syndrome. Acquired causes were mostly due to JIA. Early treatment frequently resulted in renal remission. Finally, resources for modern genetic diagnosis most likely influenced the prevalence and geographical spread of the disease. Ref Picken MM. Current Understanding of Systemic Amyloidosis and Underlying Disease Mechanisms. Am J Cardiol. 2022;185: S2-S10.

Summary Data of Renal Amyloidosis (RA) from Original articles (OA), Case reports (CR), and Case series (CS) in Children and Adolescents.

Primary pathology/ type of amyloidosis	Gender ratio	Mean age (yrs.)	Publication types (n = no. of subjects with RA)
Tuberculosis	3M 3F 4NR	12.8	5CR, 1CS (n = 10)
Neutropenia	0M 6F	13.5	6CR (n = 6)
Hodgkin's Lymphoma	2M 2F	9.5	4CR (n = 4)
Recessive dystrophic Epidermolysis bullosa	9M 4F	14.3	7CR (n = 10)
Juvenile Idiopathic Arthritis	25M 24F 90NR	8.9	3OA, 2CS, 14CR (n = 139)
Inflammatory bowel disease	2M 1F	12.6	3CR (n = 3)
Chronic granulomatous disease	2M 1NR	15	3CR (n = 3)
Tumor Necrosis Factor Receptor Periodic Syndrome.	19M 16F	8.4; mean age RA = 35	1OA, 4CR, 1CS (n = 35)
Familial Mediterranean fever (FMF)	442M 368F	10.7	13CR 9OA, 4CS (FMF n = 2812; RA n = 679)
Mevalonate kinase deficiency (MKD)	64M 63F	8.2	9CR, 3CS, 1OA (MKD n = 149; RA n = 13)
Hereditary amyloidosis (3ALys; 3AFib)	4M 2F	14.1	6CR (n = 6)

TH-PO530

Elevated Serum Gd-IgA1/s.IgA Levels and Not Serum Gd-IgA1 Alone Is an Independent Risk Factor for Composite Outcome in South Asian IgA Nephropathy (IgAN)

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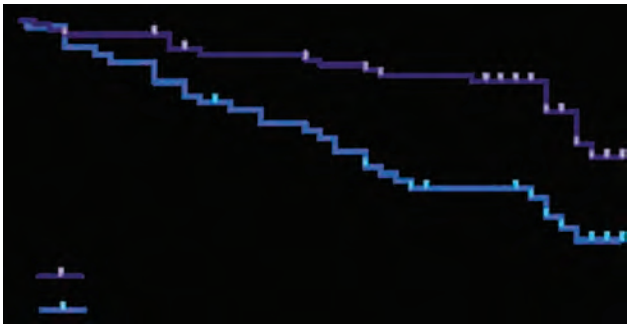
Background: The role of serum Gd-IgA1 in a prospective longitudinal South Asian IgAN cohort **(GRACE-IgANI)** and the impact of immunosuppression is not known.

Methods: We measured serum galactose-deficient IgA1 (s.Gd-IgA1) levels in 170 IgAN patients, 40 disease controls, and 27 healthy controls by KM55 ELISA (IBL international GmBH, Germany) at baseline. Longitudinal measurements were made at 1 year and 2 years in a subgroup of 117 IgAN patients who received a short course of immunosuppression. The baseline associations and the usefulness of s.Gd-IgA1 as a diagnostic and prognostic biomarker was assessed.

Results: s.Gd-IgA1 had significant positive correlation with serum immunoglobulin A (s.IgA) (r=0.6, n=170, p<0.001). Neither s.Gd-IgA1 nor s.Gd-IgA1/s.IgA ratio was a diagnostic marker for IgAN. s.Gd-IgA1/s.IgA ratio had stronger baseline and longitudinal associations than s.Gd-IgA1 alone. Elevated s.Gd-IgA1/s.IgA ratio was significantly associated with baseline clinical and histopathological indices of activity and chronicity. In the subgroup that received immunosuppression, there was significant decrease in both s.Gd-IgA1 and s.IgA at 1 year. The mean time to the composite outcome was significantly shorter for each quartile increase in s.Gd-IgA1/s.IgA ratio by Kaplan-Meier survival analysis [<1.3: vs. 1.3-1.7 HR 3.3 (95% CI 1.2-9.1), 1.7-2.3 HR 4.3 (95% CI 1.6-11.9), >2.3 HR 6.2 (95% CI 2.4-16.2), p<0.001]. Higher median s.Gd-IgA1/s.IgA ratio was as an independent predictor for composite outcome by Cox proportional-hazards (HR 2.3, 95% C.I. 1.2-4.5, p=0.01) model and outperformed 24-hour urine protein.

Conclusions: We have shown for the first time in IgAN with South Asian ethnicity, the relevance of proportion of s.Gd-IgA1 to total serum IgA for risk stratification, its association with prognosis and its longitudinal changes with immunosuppression. The results need to be externally validated.

Funding: Government Support - Non-U.S.



TH-PO531

Claudin-1 Is a Therapeutic Target for Crescentic Glomerulonephritis

Geoffrey Teixeira,[1] Jean-Daniel Delbet,[2] Vincent Anquetil,[1] Alberto Toso,[1] Stephen Toovey,[1] Luigi Manenti,[1] Roberto Iacone,[1] Jesper Kers,[3,4] Ton J. Rabelink,[3] Kevin Saitoski,[2] Thomas F. Baumert,[5,6] Ariela Benigni,[7] Susanna Tomasoni,[7] Giuseppe Remuzzi,[7] Thomas Cagarelli,[8] Marco Prunotto,[9] Solange Moll,[8] Pierre-Louis Tharaux.[2] *[1]Alentis Therapeutics, Allschwil, Switzerland; [2]Paris Centre de Recherche Cardiovasculaire, Paris, France; [3]Leids Universitair Medisch Centrum, Leiden, Netherlands; [4]Amsterdam UMC Locatie AMC, Amsterdam, Netherlands; [5]Universite de Strasbourg, Strasbourg, France; [6]Institut Universitaire de France, Paris, France; [7]Istituto di Ricerche Farmacologiche Mario Negri, Milano, Italy; [8]Hopitaux Universitaires Geneve, Geneve, Switzerland; [9]Universite de Geneve Section des Sciences Pharmaceutiques, Geneve, Switzerland.*

Background: Crescentic glomerulonephritis (CGN), encompasses a large spectrum of kidney diseases characterized by extensive epithelial cell proliferation forming crescents and renal fibrosis. Current therapies for CGN do not directly target the deleterious response of resident kidney cells. Claudin-1 (CLDN1), a transmembrane protein involved in epithelial tight junctions, can, in pathological conditions, be exposed outside the tight junctions and mediate pro-fibrotic pathways and extracellular matrix (ECM) remodelling. We have developed ALE.F02, a first-in-class monoclonal antibody (mAb) highly specific in targeting CLDN1 exposed outside the tight junctions. ALE.F02 exhibited an excellent safety profile with evidence of on-target biological activity in first-in-human clinical trial. This study investigated the functional role of CLDN1 in proliferative glomerular parietal epithelial cells (PEC) as a therapeutic target for ANCA-associated vasculitis (AAV), Lupus Nephritis (LN) and crescentic IgA nephropathy (IgAN).

Methods: CLDN1 expression in renal tissues of CGN patients was analyzed using immunohistochemistry, immunofluorescence and spatial transcriptomics. Correlations between CLDN1 expression, disease biomarkers and crescent evolution were studied. Spatially resolved molecular roadmap from CLDN1+ crescentic glomeruli were conducted. Proof-of-concept studies using anti-CLDN1 mAb were performed in preclinical models of CGN.

Results: In tissues (n=100+) of CGN patients, exposed CLDN1 was highly expressed by cellular and fibro-cellular crescents. Multi-color immunofluorescence of CGN patients revealed up-regulated CLDN1 expression by activated PEC. CLDN1 upregulation was associated with high plasma levels of renal disease biomarkers (CD44, CXCL12, MMP7). Spatial transcriptomics analysis highlighted the association between CLDN1+ crescentic glomeruli and ECM proteins. Proof-of-concept studies in CGN mouse models showed that treatment with anti-CLDN1 mAb reduced proteinuria and fibrosis biomarkers.

Conclusions: Our results suggest a functional role for CLDN1 in the pathogenesis of CGN, providing preclinical proof-of-concept for ALE.F02 as a novel therapeutic approach in patients with CGN.

TH-PO532

Elevated Levels of IL-6 in IgA Nephropathy Patients Are Induced by an Epigenetically Driven Mechanism Modulated by Viral and Bacterial RNA

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Background: Immunoglobulin A nephropathy (IgAN) is the most frequent primary glomerulonephritis characterized by the presence of IgA immune complexes in the glomeruli. Newly, the role of IL-6 in pathogenesis is becoming increasingly important but reason why levels of IL-6 are elevated in IgAN patients is not well understood. One attainable hypothesis comes out from our recent whole genome DNA methylation screening in IgAN patients, that identified, among others, a hypermethylated region comprising Vault RNA 2-1 (VTRNA2-1), a non-coding RNA.

Methods: Total RNA were isolated from PBMCs of IgAN patients, transplanted IgAN patients (TP-IgAN), non-IgAN transplanted patients (TP) and healthy subjects (HS). VTRNA2-1, CREB and PKR transcripts were evaluated by RT-PCR. Total and phosphorylated PKR, CREB and Il-6 proteins were evaluated by ELISA. Poly (I:C), a synthetic analogue of dsRNA, and Pfizer-BioNTech COVID-19 vaccine were used to transfect patient PBMCs. PKR inhibitor imoxin (C16) 1 μM was used to stimulate patient PBMCs.

Results: Here we confirm that VTRNA2-1 is low expressed in IgAN subjects compared to HS and we found that also in transplanted IgAN patients (TP-IgAN), compared to non-IgAN transplanted patients (TP), the VTRNA2-1 transcript was expressed at level very low. We found that in IgAN patients with downregulated VTRNA2-1, PKR is overactivated, coherently with the role of the VTRNA2-1 that binds to PKR and inhibits its phosphorylation. The loss of the VTRNA2-1 natural restrain caused the activation of CREB by PKR, a classical cAMP-inducible CRE-binding factor interacting with a region of the IL-6 promoter and leading to IL-6 production, both in IgAN and in TP-IgAN patients. PKR is normally activated by bacterial and viral RNA and we found that both the RNA poly(I:C) and the COVID-19 vaccine stimulation significantly increase the IL-6 levels in PBMCs from HS but had an opposite effect in those from IgAN patients.

Conclusions: In conclusion, the discovery of the upregulated VTRNA2-1/PKR/CREB/IL-6 pathway in IgAN patients may provide novel approach to treat the disease and may be useful for development of precision nephrology and personalized therapy, possibly by checking the VTRNA2-1 methylation level in IgAN patients.

Funding: Private Foundation Support

TH-PO533

Topological Analysis of High-Resolution Spatial Transcriptomics Reveals Immune Glomerular Architecture of Lupus Nephritis

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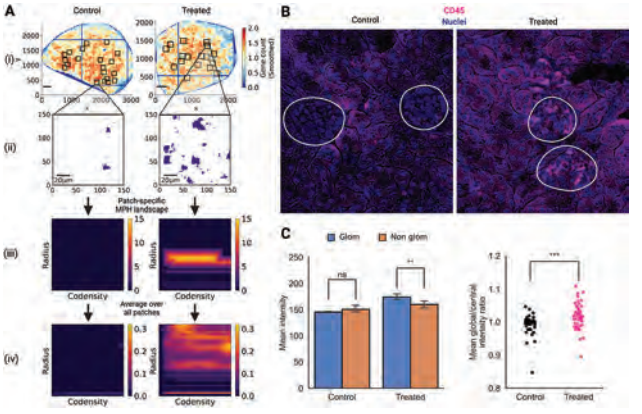
Background: To develop targeted treatments for immune complex diseases such as lupus nephritis (LN) we need to understand immune and renal cell interactions. The advent of spatial sub-cellular resolution whole transcriptome technologies offers the potential to study cell distribution within glomeruli, but requires new mathematical approaches. Conventional 'fixed-window' approaches bin data across spots, discarding the granularity of a high-resolution platform and missing small or rare cells such as immune infiltrates.

Methods: Murine kidneys treated with topical imiquimod or vehicle were prepared for single nuclei RNA sequencing (snRNA-Seq, 10x Genomics) and 200nm spot spatial transcriptomics (STOmics, Beijing Genomics Institute) and analysed (Seurat, RCTD). We developed topological automatic cell type identification (TopACT), combined with multiparameter persistent homology (MPH) to quantify multiscale spatial cell organization. TopACT independently classifies and annotates spot level cell type using a dynamic local neighbourhood.

Results: On synthetic data imputed from renal snRNA-Seq, TopACT produced high accuracy spot-level cell type annotations in comparison to fixed-window approaches. In murine kidney, TopACT spatially resolved individual immune cells in LN, enriched within glomeruli, where the average MPH landscape indicated large loops of immune cells (Fig 1A). This leads to the prediction, driven by spatial data, and confirmed by CD45 immunofluorescence, of a peripheral ring structure of glomerular immune cells in LN (Fig 1B and C).

Conclusions: Our multiscale method for topological automatic cell classification improves accuracy of cell-type information for subcellular resolution spatial transcriptomics, and detects the spatial arrangement of glomerular immune cells in LN. TopACT is generalisable, flexible and has potential for further application to 3D or spatiotemporal data.

Funding: Commercial Support - Funding from UKRI/ Medical Research Council and Kidney Research UK. Beijing Genomics Institute collaborated on the research - no direct financial support /funding to research team., Government Support - Non-U.S.



TH-PO534

ACE in Granulocytes Has a Protective Role in Crescentic Glomerulonephritis via Complement Lectin Pathway Independent of Angiotensin II

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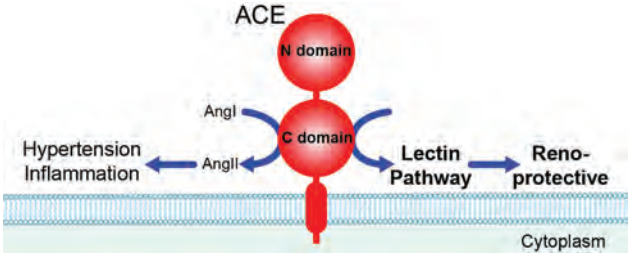
Background: ACE is a well-known enzyme to regulate blood pressure and inflammation, and structurally having two enzymatic domains: N-domain and C-domain. Its C-domain regulates blood pressure by producing angiotensin II in renin-angiotensin system. We recently reported a novel function of ACE: ACE overexpressed neutrophils have a protective role in immune complex (IC)-mediated crescentic glomerulonephritis (GN) via complement C3b-CR1/2 axis, efficiently removing IC deposits. Here, we show that ACE C-terminal catalytic domain is responsible for the renoprotective role in myeloid cells in crescentic GN via lectin pathway.

Methods: We induced the nephrotoxic serum nephritis (NTN) in C57Bl/6 (WT), Jwt mice that overexpressing ACE in myeloid cells (neutrophils and monocytes/macrophages), Jcko mice that overexpressing C-domain knockout ACE in myeloid cells, and Jnko mice that overexpressing N-domain knockout ACE in myeloid cells, and evaluated renal function and histology (crescent formation and fibrinoid necrosis). In addition, we examined complement pathway activation in vitro and blood angiotensin II level.

Results: 7 days after induction of NTN, Jwt mice showed less severe proteinuria and mild histological glomerular damages, showing overexpressed ACE in neutrophils and monocytes/macrophages has the protective role in IC-mediated crescentic GN. When we induced NTN in Jcko mice and Jnko mice, Jcko mice lost the renoprotective effects and Jnko mice still showed the severe glomerular damage. These data clearly showed that ACE C-domain, but not N-domain, has the renoprotective role. Regarding complement activation, recombinant ACE activated lectin pathway, but not classical and alternative pathways. Given the normal blood pressure level and the normal plasma angiotensin II level in all these mouse strains, the ACE C-domain mediated renoprotective effect is independent of angiotensin II.

Conclusions: ACE C-domain in granulocytes has a protective role in crescentic glomerulonephritis via complement lectin pathway independent of Angiotensin II.



Dual effects of ACE C-domain in kidney disease

TH-PO535

Integrin β6 Regulates Tubuloglomerular Feedback Through the NKCC2-COX2/nNOS Pathway

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Background: Integrin β6 (β6) is a protein expressed in some tubules and macula densa cells, which activates transforming growth factor-β (TGF-β). Our previous studies showed that $\beta6^{-/-}$ mice exhibit milder tubulointerstitial fibrosis but more severe glomerulosclerosis than wild type (WT) after 5/6 nephrectomy. This study aimed to explore the involvement of macula densa integrin β6 in the dysfunction of tubuloglomerular feedback.

Methods: We first knocked down β6 in mouse macula densa cells (MMDD1) and exposed them to high salt. The expression of Oxidative Stress Responsive Kinase 1 (OXSR1), a regulator of NKCC2 activity, was assessed by qPCR. The protein

expressions of NKCC2, COX2, and nNOS were analyzed by western blot. We then measured renal clearance before and after acute volume expansion in $\beta6^{-/-}$ and WT mice.

Results: Immunostaining showed that integrin β6 and NKCC2 colocalized on the cell membrane of MMDD1. Knockdown of β6 significantly increased the expression of OXSR1 and NKCC2 and induced more nNOS and less COX2 compared to WT cells. High salt reduced COX2 and increased nNOS protein expression in WT, which was not changed in β6 knockdown cells. In vivo, following acute volume expansion with 3% of body weight volume of isotonic saline over 5 min, blood pressure decreased minimally and similarly in both groups at 15 min and recovered to the baseline level at 30 min after volume expansion. GFR of WT mice increased at 30 minutes and returned to baseline at 90 min. In contrast, integrin β6 knockout mice reached peak GFR at 60 min, but ultimately returned to baseline at 90 min.

Conclusions: These findings suggest that integrin β6 regulates tubuloglomerular feedback through the NKCC2-COX2/nNOS pathway. The dysfunction of tubuloglomerular feedback induced by β6 knockout on macula densa cells may contribute to the observed mismatch in tubulointerstitial fibrosis and glomerulosclerosis in $\beta6^{-/-}$ mice after 5/6 nephrectomy.

Funding: NIDDK Support

TH-PO536

Lambda Light Chain Predominance Links C1q Deposition to Endocapillary Hypercellularity in IgA Nephropathy

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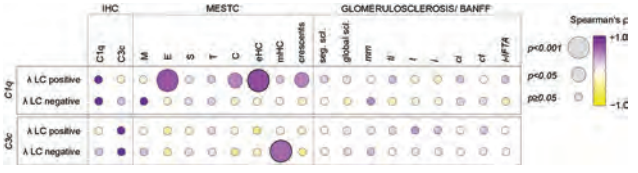
Background: Involvement of the complement system is a key driver of immune complex-mediated nephritogenicity in immunoglobulin A nephropathy (IgAN), being the most prevalent primary glomerulopathy worldwide. Despite growing insights on the pathophysiological relevance of lambda (λ) light chain (LC) predominance in IgAN, implications of glomerular complement deposition remain largely elusive. Therefore, we here aimed to systematically assess the correlative pattern of clinicopathological findings and glomerular complement C1q and C3c deposits in λ-LC predominant biopsy-proven IgAN.

Methods: A total of 37 patients with biopsy-proven IgAN obtained between 2016 and 2021 were retrospectively included in a single center observational study. Clinical data assessment comprised age, sex, serum creatinine levels, blood urea nitrogen, eGFR, complement C3/ C4 and proteinuria. Oxford-scored lesions mesangial (M) and endocapillary hypercellularity (E), segmental sclerosis (S), tubular atrophy (T), crescentic formations (C), and other lesions scored analogous to the Banff classification were evaluated. Immune histochemistry-detected glomerular deposits of complement factors C1q/ C3c and kappa (κ)/ λ LCs were semiquantitatively scored. Two groups were formed according to the λ-LC status: λ-LC positive (*n=20*) and λ-LC negative (*n=17*). Clinicopathological correlations were analyzed in both groups regarding glomerular C1q and C3c deposits by means of multivariable linear regression.

Results: Enrolled patients featured a median creatinine level of 1.5 mg/dL. C1q and C3c deposition featured no significant association with serum parameters indicative of kidney injury or proteinuria. We identified endocapillary hypercellularity to feature the strongest association with glomerular C1q deposition in the λ-LC positive group (ρ=0.7; β=0.745, *p<0.001*). In the λ-LC negative group, a significant correlation of C3c deposition and mesangial hypercellularity was identified (ρ=0.6; β=0.762, *p<0.001).*

Conclusions: We here show a correlative pattern of λ LC-associated deposition of complement factors C1q and C3c in distinct histopathological features of IgAN implying an involvement of the classical pathway in the preset of λ-LC predominance.



TH-PO537

Classical Monocyte-Derived and Lipid-Associated TREM2+ Macrophages Orchestrate Inflammatory and Fibrotic Processes in ANCA-Associated Glomerulonephritis

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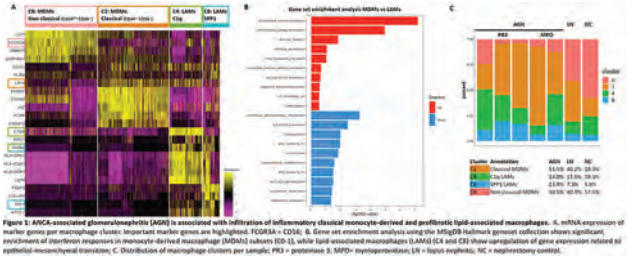
Background: ANCA-associated glomerulonephritis (AGN) associates with a high risk of end-stage kidney disease. Kidney macrophage infiltration is one of the main histological hallmarks of vasculitic lesions and is strongly linked to disease activity. The role of kidney macrophages in local inflammation remains unclear. Here we investigate kidney macrophage diversity and function.

Methods: Single cell transcriptome analysis of $CD45^+$ immune cells from freshly retrieved kidney biopsies of 5 AGN patients, 1 disease-control with class 2 lupus nephritis (LN), and 1 nephrectomy control (NC) was performed using 10X Genomics technology. Myeloid cells were selected and subsequently reclustered to identify disease-specific macrophage subtypes and functionality was assessed by a gene set enrichment analysis (GSEA). Validation studies were performed using flow cytometry and immunohistochemistry.

Results: Focused analysis identified 2 monocyte-derived macrophage (MDMs) clusters and 2 new $TREM2^+$ lipid-associated macrophage (LAMs) subtypes, $C1Q^+$ and $SPP1^+$/Osteopontin$^+$ LAMs **(panel A)**. GSEA revealed increased interferon responses in MDMs compared to LAMs **(panel B)**, and increased TNFa signaling via NFkB in classical MDMs compared to non-classical MDMs. $SPP1^+$ LAMs showed upregulation of gene sets related to fibrosis and cell cycle. Evaluating kidney macrophage subsets between diseases revealed increased % classical MDMs and LAMs in AGN (respectively, 52% and 38%) compared to NC tissue (18% and 24%) **(panel C)**. Flow cytometric analysis identified a similar increase in peripheral blood classical monocytes during active disease (P<0.0001).

Conclusions: Classical MDMs and LAMs are the main kidney macrophage subsets present in AGN. Classical MDMs drive inflammation, whereas $SPP1^+$ $TREM2^+$ LAMs orchestrate fibrosis. Targeting these specific macrophage subsets may potentially reduce acute kidney injury and long-term fibrosis.



TH-PO538

Evaluation of Intrarenal Plasmacytoid Dendritic Cells in Active Lupus Nephritis

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Background: Interferon-alpha (IFNα)-responsive genet expression is highly upregulated in the kidneys of patients with active lupus nephritis (LN). Infiltrating plasmacytoid dendritic cells (pDCs) have been postulated to be a source of intrarenal IFNα. In this study we quantified intrarenal pDCs in patients with LN and correlated infiltration with histologic activity and chronicity.

Methods: Immunohistochemistry (IHC) for BDCA-2, a marker of pDCs and a subset of dendritic cells was used to visualize intrarenal pDCs. All pDCs within a biopsy were counted and the average number of glomerular pDCs and the number of tubulointerstitial pDCs per unit area were determined. The NIH activity and chronicity indices were calculated. IHC for MX1, an IFNα-inducible protein was used to characterize the interferon response.

Results: We studied 18 patients with proliferative (70% (n=12)) or proliferative + membranous LN (30%, n=6), 60% (n=11) of whom were de novo diagnoses and 40% (n=7) carried an LN diagnosis for 1-6 years. Patients were biopsied for suspected LN flare. pDCs were found mainly as individual cells within the tubulointerstitium in these kidney biopsies, and were seldom seen within glomeruli. In some biopsies, aggregations of pDCs were found in areas of tubulointerstitial inflammation or surrounding glomeruli. A median (range) of 0 (0-0.82) pDCs/glomerulus and 2.7 (0.77-49) pDC/mm^2 of tubulointerstitium were found. There was no evidence of an association between tubulointerstitial pDCs and serum creatinine, proteinuria, activity index, or chronicity index. MX1 immunoreactivity was found in abundance throughout the kidney, including glomerular and tubular epithelial cells, glomerular and tubulointerstitial endothelial cells, vascular wall smooth muscle cells, and infiltrating inflammatory cells.

Conclusions: pDCs are thought to be the major source of IFNα in the kidneys of patients with LN. If this is true, our data suggest that very few infiltrating pDCs are needed to initiate a robust IFNα response within the kidneys.

Funding: Commercial Support - Biogen

TH-PO539

The Balance Between STAT3 and Glutathione Metabolism Is Required for Parietal Cell Activation and Proliferation in Proliferative Glomerulopathies

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Background: STAT3 signaling is activated in podocytes and parietal epithelial cells (PECs) in murine models of proliferative glomerulopathy and in human RPGN and subtypes of FSGS. We previously showed that podocyte-specific loss of STAT3 preserves podocyte loss and attenuates PEC activation. However, the mechanism by which STAT3 activation triggers PEC activation, proliferation, and crescent formation and whether its inhibition as a therapeutic target in proliferative glomerulopathies remains poorly understood.

Methods: PECs were treated with increasing doses of IL-6 (5, 10, 20, 40ng/ml) to explore the role of STAT3 activation in cell viability. We generated mouse PECs with deletion of STAT3 using Crispr/Cas9. MTT assay was performed on Cas9 (wildtype) and STAT3 knockout (STAT3-/-) PECs. Cell migration of Cas9 and C7 cells were measured using a scratch assay. Mitochondrial respiration, glycolytic rate, and ATP production were performed using seahorse analyzer. Glutathione, superoxide, and reactive oxygen species (ROS) levels were measured. RNA sequencing was conducted in the Cas9 and STAT3-/- PECs. PEC-specific STAT3-/- mice were generated as well as STAT3 inhibitor treatment in mice post-nephrotoxic serum (NTS) administration.

Results: STAT3-/- PECs exhibited reduced cell proliferation, activation, oxygen consumption, and ATP production. RNAseq demonstrated a downregulation of differential expressed genes (DEGs) involved in glutathione metabolism with an upregulation in focal adhesion DEGs. STAT3-/- PECs had reduced cellular glutathione pool leading to increased levels of superoxide levels leading to increased oxidative stress and DHE expression. In silico analysis showed that pSTAT3 occupies the promoter region of key glutathione synthesis genes, suggesting potential direct regulation. PEC-specific STAT3-/- mice or treatment with STAT3 inhibitor reduced proteinuria, PEC activation (CD44, Akap12), crescent formation with increased oxidative stress (8-oxo-G, OGG1) as compared to their respective controls post-NTS treatment.

Conclusions: To date, this is the first study to demonstrate the mechanism by which STAT3 activation in PECs enhances glutathione metabolism to maintain a balance in ROS and exacerbate PEC activation and crescent formation in proliferative glomerulopathies.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO540

Association of a New Variant of Complement Regulator FHR2 with C3 Glomerulopathy

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Background: C3 glomerulopathy (C3G) is caused by a dysregulation of the complement system leading to C3 deposition and formation of glomerular deposits. Several C3G patients harbor mutations or copy number variations in the human Factor H (*FH*) and/or Factor H-Related (*FHRs*) genes. Therefore, FH and FHRs are emerging immune targets for inhibition of the complement cascade, as well as markers to monitor patients on complement regulatory drugs to test their efficiency.

Methods: Here, we focused our study on FHR2, known to inhibit *in vitro* formation of the terminal complement complex. We identified new variants for the *FHR2* gene in a cohort of C3G patients and performed detailed functional studies on the novel variant FHR2$_{L46}$, which has the Pro at position 46 replaced by Leu. Patients with FHR2$_{L46}$ variant presented increased FHR2 plasma level, as compared to controls and displayed FHR2 deposits in glomeruli. We generated a recombinant FHR2$_{L46}$ mutant protein to gain insight into the effect of this novel FHR2 variant on complement regulation.

Results: As the amino acid exchange occurred in the first short consensus repeat (SCR1), we first tested if the Leu at position 46 altered FHR2 homodimerization and heterodimerization of FHR2 with FHR1 and FHR5. We observed that FHR2$_{L46}$ binds significantly less to FHR2 and FHR1 but more to FHR5. Furthermore, FHR2$_{46L}$ acquired the capacity to bind to cell surfaces by interacting with glycosaminoglycans heparin and malondialdehyde (MDA)-modified amino group (MAA) epitopes. FHR2$_{L46}$ also bound substantially more to necrotic cells compared to wild-type FHR2 (FHR2$_{WT}$). In contrast, no difference was observed between FHR2$_{L46}$ and FHR2 WT binding to C3 and C5.

Conclusions: Taken together, the present study identified a novel FHR2$_{L46}$ variant in a C3G patient and suggests that the FHR2$_{L46}$ mutant forms stable oligomers with FHR5 and enhances complement activation.

TH-PO541

An Integrated Proteome-Transcriptome Organoid Atlas Illuminates Core Concepts of Kidney Disease

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Background: The use of kidney organoids as a model for studying kidney disease shows great promise, but their potential is limited by our limited understanding of the proteins they express and their functional profiles. In this study, we aimed to address this limitation by examining the proteome and transcriptome of organoids throughout their culture period and in response to TNFα, a cytokine stressor.

Methods: In our study, we employed proteomic analysis to compare kidney organoids with other established model systems and native tissues, including native glomeruli and cultured podocytes. We examined the developmental trajectory of organoids and explored their innate immune responses, thereby expanding the applicability of organoids as a valuable model system in the field of nephrology. Additionally, we performed a comprehensive comparison of our proteomic data with both bulk and single-cell transcriptomics data, providing a more comprehensive understanding of the molecular landscape of kidney organoids.

Results: We found that older organoids displayed increased accumulation of extracellular matrix while showing decreased expression of glomerular proteins. By integrating single-cell transcriptome data, we discovered that most changes in the proteome were localized to podocytes, tubular cells, and stromal cells. Treatment of the organoids with TNFα resulted in the differential expression of 322 proteins, including cytokines and complement components. Importantly, the transcript expression of these 322 proteins was significantly higher in individuals with poorer clinical outcomes in proteinuric kidney disease. Notably, key proteins associated with TNFα (C3 and VCAM1) were found to be increased in both human tubular and organoid kidney cell populations, indicating the potential of organoids to advance the development of biomarkers. VCAM1 was localized to the descending thin limb (DTL) of proteinuric patients with kidney disease.

Conclusions: By integrating various “omic” layers of kidney organoids, incorporating a relevant cytokine stressor, and comparing with human data, we highlight the significance of kidney organoid modeling in understanding and studying complex human kidney disease.

Funding: NIDDK Support, Other NIH Support - The Nephrotic Syndrome Study Network (NEPTUNE) is part of the Rare Diseases Clinical Research Network (RDCRN), which is funded by the National Institutes of Health (NIH) and led by the National Center for Advancing Translational Sciences (NCATS) through its Division of Rare Diseases Research Innovation (DRDRI)., Government Support - Non-U.S.

TH-PO542

Identification of Conserved Gene Expression Changes Across Common Glomerular Diseases by Spatial Transcriptomics

Jeongmin Cho,[1] Sehoon Park,[1] Jung Hun Koh,[1] Yaerim Kim,[2] Hajeong Lee,[1] Seung Seok Han,[1] Dong Ki Kim.[1] *[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Keimyung University Daegu Dongsan Hospital, Daegu, Republic of Korea*.

Background: Glomerular diseases encompass a group of kidney diseases that may share common gene expression pathways. We aimed to analyze glomerular-specific gene expression profiles across various glomerular diseases.

Methods: We performed spatial transcriptomic profiling using formalin-fixed paraffin-embedded kidney biopsy specimens of controls and patients with five types of glomerular diseases using the GeoMx Digital Spatial Profiler. We identified common differentially expressed genes (DEGs) across glomerular diseases and performed Gene Ontology (GO) annotation using the ToppGene suite.

Results: A total of 35 DEGs were consistently downregulated in glomeruli across the disease compared to the control, while none of the DEGs were consistently upregulated. Twelve of 35 downregulated DEGs, including the two hub genes FOS and JUN, were annotated with molecular function GO terms related to DNA-binding transcription factor activity. The annotated biological process GO terms included response to lipid-related (17/35 DEGs), response to steroid hormone (12/35 DEGs), or cell cycle regulation (10/35 DEGs).

Conclusions: Identifying common DEGs by spatial transcriptomic analysis provides insights into underlying molecular mechanisms of glomerular diseases and may lead to novel assessment or therapeutic strategies.

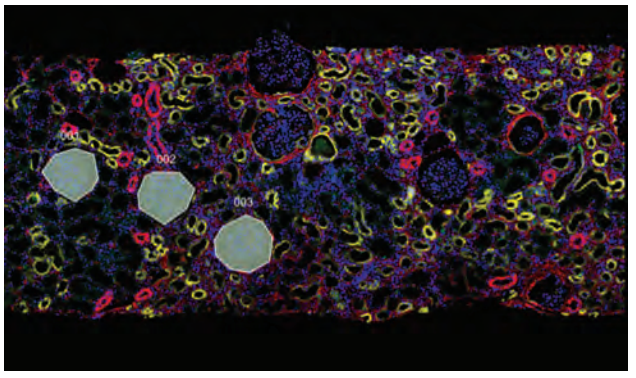

Figure 1. Glomerular region-of-interest (ROI) scan for digital spatial profiling

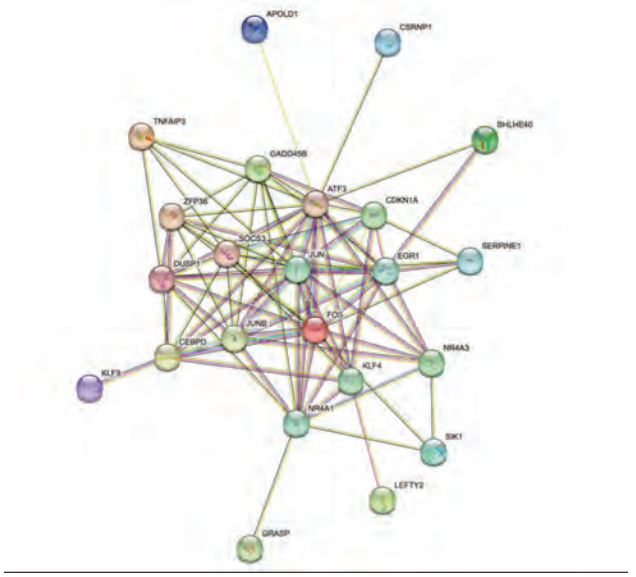

Figure 2. Gene association network analysis

TH-PO543

Generation of CX3CR1-Expressing T Regulatory Cells Using Retroviral Transduction

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Background: T cells play a central role in the pathogenesis of acute glomerulonephritis. Studies in rodent models as well as observations in patients suggest an imbalance of pro-inflammatory T effector cells and anti-inflammatory T regulatory cells (Treg), resulting in autoimmune-mediated glomerular injury. Increasing the numbers of T regulatory cells in the inflamed kidney might restore the T cell balance and, thus, attenuate disease. This could be achieved by transfusion of Tregs equipped with specific chemokine receptors to increase their migration into the inflamed kidney. In this regards, the CX3CR1-CX3CL1 axis represents a promising target, as it has been implicated in a variety of inflammatory diseases in the kidney.

Methods: The nephrotoxic nephritis model (NTN) is used to assess the distribution of CX3CL1 in the kidney using IHC stainings. The expression of CX3CR1 on renal and splenic immune cells during homeostasis and NTN is analysed using flow cytometry. Standard cloning techniques are used to design a retroviral vector for transduction of naïve murine T cells.

Results: Flow cytometry analysis after 7 days of nephrotoxic nephritis reveal CX3CR1 expression mostly on macrophages and classical dendritic cells Type 2 in the kidney and spleen. Renal and splenic T cells, on the other hand, express less CX3CR1, with about 20% of cytotoxic T cells and 10-15% of Tregs and Th17 cells expressing the receptor. Immunohistochemistry reveals increased Fractalkine expression in nephritic kidneys compared to healthy controls. To generate induced Tregs expressing CX3CR1, the protein coding sequences for CX3CR1 or eGFP were linked with a P2A site to the sequence for FOXP3 and introduced into a MSCV retroviral vector system. This vector will be used for transfection of the Pheonix-Eco packaging cell line to produce virions for subsequent transduction.

Conclusions: The expression of CX3CL1 is upregulated in nephritic kidneys and might therefore represent a promising point of action to increase renal migration of ex vivo induced T regulatory cells. A viral vector was successfully cloned to generate CX3CR1 expressing Tregs. Future experiments will validate the suppressive function of these Tregs in vitro and in vivo. Ultimately, the therapeutic potential in attenuating NTN will be assessed.

TH-PO544

Comparing Different Pathogenic Patterns Between Immunoglobulin A Nephropathy and Lupus Nephritis Using Integrated Bioinformatics Analysis

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Background: Immunoglobulin A nephropathy **(**IgAN) and lupus nephritis (LN) are the most common primary and secondary glomerular diseases, respectively, sharing several similarities in clinical presentations. Common pathogenic mechanisms in IgAN and LN have been well established by previous studies. However, it is confusing how these two independent diseases carrying distinct pathological features are manifested considering the similarities between them. Therefore, different mechanisms of the pathogenesis between IgAN and LN were compared in this study.

Methods: Glomerular gene expression profiling data were acquired from the Gene Expression Omnibus (GEO) database. R packages were used for the data processing. Least Absolute Selection and Shrinkage Operator (LASSO) regression analysis and multivariate logistic regression analysis were used to construct models predicting IgAN and LN. Cibersort processed the analysis of immune cell infiltration in IgAN and LN. RT-qPCR was used to validate the gene expression in the human renal mesangial cells (HRMC).

Results: In the regressing predicting models based on differentially expressed genes (DEG) and weighted correlation network analysis (WACNA), retinoic acid receptor γ (RARG) and prolactin releasing hormone (PRLH) were independent risk factors for IgAN, and HECT domain and RCC1-like domain-containing protein 5 (HERC5) and interferon stimulated exonuclease gene 20 (ISG20) were independent risk factors for LN. GO analysis revealed that DEGs mostly correlated to IgAN in the "salmon" module in WGCNA were enriched in ligand-receptor activity induced cellular growth and development, and DEGs mostly correlated to LN in the "red" module were enriched in nucleic acid/nucleotide binding-induced type I interferon related activity and response to virus infection. Immune infiltration analysis showed CD4+ T-cells and M2 macrophage abundance in the glomerular compartment in IgAN and LN, respectively. The expression of RARG in HRMC was significantly elevated after stimulation of immune complexes (IC) from IgAN patients, staphylococcus aureus cell protein C (SAC) and interleukin 6 (IL-6).

Conclusions: IgAN and LN carry distinct molecular patterns in the pathogenesis, in which overexpression of RARG might be responsible for mesangial proliferation in IgAN.

TH-PO545

Characterization of Cell Surface Glycophenotypes of IgA1-Secreting Cells Reveals Distinct Subpopulations and Correlation with Glycosylation of Galactose-Deficient IgA1 in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is an autoimmune disease in which the autoantigen, IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1), is recognized by IgG autoantibodies, and some of the resultant immune complexes deposit in the glomeruli to induce kidney injury. Elevated levels of Gd-IgA1 in the circulation of IgAN patients predict worse outcomes. However, Gd-IgA1 represents only a small portion of total circulatory IgA1. We hypothesize that specific subpopulations of IgA1-secreting cells produce most of the Gd-IgA1. Here, we report that certain cell-surface glycophenotypes correlate with Gd-IgA1 production.

Methods: Immortalized IgA1-producing cells derived from peripheral-blood cells of IgAN patients and healthy controls were live-sorted for IgA^+ populations and separated into PNA-low and high subpopulations (PNA lectin is specific for galactose(Gal)-b1,3*N*-acetylgalactosamine(GalNAc) disaccharide of glycoconjugates). These subpopulations were then incubated for 48 h with a mixture of pro-inflammatory cytokines (IL-4, IL-6, IL-21, CD40L; 50 ng/mL each). Live cells were treated with sialidase (to remove sialic acid that may be attached to Gal, GalNAc, or both), then stained with PNA, HPA (lectin specific for GalNAc), and antibody specific for IgA, followed by flow cytometry analysis. Amounts of IgA1 and Gd-IgA1 secreted into the cell-culture medium were determined by ELISA.

Results: Cell-surface glycosylation of $IgA1^+$ sorted cells was dynamic after expansion of subpopulations. IgA cell-surface expression also changed after the expansion of cells. The frequency of IgA^- cells correlated with Gd-IgA1, irrespective of IgA1 sialylation or IgA production ($p<0.01$; $n = 5$). Additionally, cell-surface HPA reactivity of PNA-high cells exclusively increased after treatment with sialidase, and negatively correlated with degree of sialylation of secreted Gd-IgA1 ($p<0.01$; $n=5$).

Conclusions: We found an inverse correlation of cell-surface GalNAc sialylation with Gd-IgA1 sialylation in PNA-high cells. This observation suggests that some glycosyltransferase pathways are regulated by distinct mechanisms with different impact on cell-surface glycophenotypes and IgA1-glycosylation.

Funding: NIDDK Support

TH-PO546

Nucleotide-Sensing TLR9/TLR7 System Is a Potential Therapeutic Target for IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis worldwide. Galactose-deficient IgA1 (Gd-IgA1) is a key effector molecule in the pathogenesis of IgAN. Previous reports indicated that toll-like receptor (TLR)9 and TLR7 are involved in synthesizing Gd-IgA1. TLR9 and TLR7 recognize microbial DNA and RNA, respectively. Several clinical trials suggested hydroxychloroquine (HCQ), known to suppress TLR9/TLR7, might effectively treat IgAN. The present study aimed to clarify whether TLR9/TLR7 could be the therapeutic targets for IgAN.

Methods: First, we divided the ddY mice, the spontaneous IgAN model, into the control group, HCQ administered group, CpG-ODN (ligand of TLR9) nasally administered group, CpG-ODN + HCQ group, Imiquimod (ligand of TLR7) nasally administered group, and Imiquimod + HCQ group, respectively. We analyzed the serum aberrantly-glycosylated IgA, IgG-IgA immune complexes (IC), proteinuria, and renal pathology. Next, we cultured the splenocytes of ddY mice with CpG-ODN or Imiquimod. We analyzed the effect on the synthesis of aberrantly-glycosylated IgA. Finally, we cultured tonsillar mononuclear cells (TMCs) from IgAN patients with CpG-ODN or Imiquimod. We analyzed the cellular expression of C1GaLT1, an enzyme involved in IgA1 glycosylation, and the supernatant Gd-IgA1 levels.

Results: The mice administered with CpG-ODN or Imiquimod showed elevated serum levels of aberrantly-glycosylated IgA and IgG-IgA IC. Furthermore, these mice showed aggravated proteinuria. Renal pathological findings further confirmed glomerular mesangial proliferation accompanied by significant IgA/IgG/C3 depositions. The mice co-administered with HCQ did not show the changes that CpG-ODN or Imiquimod induced. The splenocytes of ddY mice significantly elevated IL-6, known to affect IgA glycosylation, and promoted aberrantly-glycosylated IgA when stimulated by CpG-ODN or Imiquimod. In the human studies, stimulation with CpG-ODN or Imiquimod let the cultured TMCs promote IL-6 synthesis, downregulated C1GaLT1 and consequently enhanced the production of Gd-IgA1.

Conclusions: Present data suggested that nucleotide-sensing TLR9/TLR7 are involved in the pathogenesis of IgAN and might be the candidates for disease-specific therapeutic targets.

TH-PO547

Differentiating Lupus Nephritis Classes Using Peripheral Blood DNA Methylation

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Background: Approximately 60% of patients with systemic lupus erythematosus (SLE) develop nephritis. Histologically-determined disease classification provides clinically actionable information including administration of kidney-specific immunosuppression. Given the pivotal role of autoimmunity in SLE, we hypothesized that DNA methylation patterns of immune cells could distinguish between the different lupus nephritis classes.

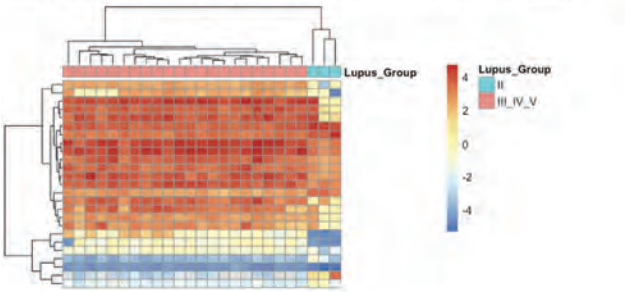
Methods: We identified 25 participants from the Yale Kidney Biobank with biopsy-confirmed lupus nephritis. DNA was extracted from blood buffy coat. DNA methylation was analyzed using Illumina MethylationEPIC V2.0, surveying > 935,000 CpG loci. β-values (percent methylation) were derived using the R Sesame package. KEGG pathway enrichment and differential methylation analyses were performed, comparing class II participants to those with more advanced nephritis (III, IV, V).

Results: We identified 3 participants with class II disease, and 22 participants with classes III, IV, or V disease. Enrichment analysis identified differential methylation in Rap1 signaling, focal adhesion, and MAPK signaling pathways between the two groups (q-values < 0.001). Participants with advanced lupus nephritis exhibited *ERK* hypermethylation and *RAP1* hypomethylation compared to those with class II. We identified 5 CpG loci that were differentially methylated between the two groups (adjusted p-values < 0.05). Unbiased hierarchical clustering based on the top 25 differentially methylated loci revealed that those with class II nephritis have distinct methylation profiles as compared to those with more advanced nephritis (Figure 1).

Conclusions: Our findings suggest that DNA methylation patterns in immune cells may distinguish between lupus nephritis classes, potentially guiding the decision to conduct a kidney biopsy. The observed methylation differences in ERK and RAP1 pathways, which have been implicated in SLE pathophysiology, among advanced lupus nephritis classes may provide valuable insights into disease pathogenesis.

Funding: NIDDK Support, Private Foundation Support

Figure 1. Heatmap demonstrating hierarchical clustering of samples based on top 25 differentially methylated loci between participants with class II vs. those with class III, IV, or V nephritis.



TH-PO548

Deciphering the Contribution of Inflammatory Macrophages to Focal Segmental Glomerulosclerosis

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Background: Focal segmental glomerulosclerosis (FSGS) refers to a histologic pattern of glomerular injury that can result from heterogenous disease entitites, which in turn respond differently to therapeutic regimens. Causes for FSGS include immunological diseases that respond to immunosuppressive treatments. Modern biotechnological tools allow us to characterize diseases resulting in an FSGS pattern in detail with the prospect of providing pathophysiology-based precision medicine for the patients.

Methods: We used a genetic model (heterozygous compound mutations in *Nphs2)* that causes a slowly progressive FSGS phenotype with a strong intraglomerular immune cell infiltrate. In order to characterize these immune cells in depth and to identify glomerular communication patterns, we employed bulk and single nucleus RNA sequencing of glomerular isolates, flow cytometry, and immunohistochemistry.

Results: We identified myeloid cells to be the most abundant immune cells in diseased glomeruli. A macrophage subpopulation with an M2-like, tissue-remodeling transcriptomic signature significantly expanded over time, which correlates with proteinuria. We confirmed such intraglomerular infiltration of macrophages by immunohistochemistry, and detected macrophages in the tubulointerstitium at a later stage of the disease. snRNAseq-based ligand-receptor-target gene network analysis indicated progressively altered signaling between glomerular cells resulting in a pro-fibrotic inflammatory milieu characterized by strong signaling activity of the TGFb-superfamily and upregulation of CC-chemokines and matrix metalloproteinases. Intriguingly, fractalkine (CX3CL1), a macrophage recruiting chemokine, was strongly upregulated at an early stage of the disease. Immuno-staining localized fractalkine to glomerular endothelial cells while flow cytometry showed significant upregulation of its receptor CX3CR1 on macrophages.

Conclusions: In this model, a mutation in a slit-diaphragm protein results in a glomerular fibro-inflammatory phenotype with strong macrophage infiltration that may be linked to fractalkine. Based on these results, our project might provide the rationale for new therapeutic approaches in FSGS.

Funding: Government Support - Non-U.S.

TH-PO549

Identifying Targetable Renal Immune Pathways in Lupus Nephritis

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Background: Lupus Nephritis (LN) is characterised by renal immune-complex (IC) deposition, how these deposits trigger inflammatory mediators, and signalling between resident and recruited cells is unclear. Mouse lupus models share clinical features of human disease including renal involvement. Using single nuclei RNA sequencing (snRNA-seq), we compare two models of early LN, to identify disease drivers, potential therapeutic targets, and to establish an approach translatable to human kidney.

Methods: Kidney sections from autoimmune MRL/lpr mice aged 15-weeks, or Balb/c mice treated for 8 weeks with topical TLR7 agonist (IMQ) and respective controls, were processed for histology, immunofluorescence (IF), flow cytometry and snRNA-seq (10x genomics).

Results: IMQ kidneys showed IC deposition, mesangial expansion, and endothelial proliferation consistent with class-II LN. MRL/lpr mice additionally developed crescents, and class-III LN. Transcriptomic data from 92k nuclei identified clusters corresponding to resident and immune populations. Early S1/S2 proximal tubule segments were identified as interferon (IFN) susceptible targets in both models. Intrarenal T, B, and myeloid cells were enriched in diseased mice. MRL/lpr mice had the largest immune infiltrate, including NK and CD8 T cells expressing markers of cytotoxicity and exhaustion (Gzma, Pdcd1). Integrated analysis with human immune renal LN single cell data (Arazi et al., 2019), showed overlap with MRL/lpr phenotype with cytotoxicity and exhaustion

signatures (GZMA, PDCD1) identified in the NK and CD8 T cell clusters. Shared disease phenotypes across models included increased CD11b^{hi} renal resident macrophage populations, expressing genes implicated in phagocytosis, efferocytosis (Mertk, Lrp1) and IFN responses (Stat1), with trajectory analysis suggesting these arise from increased patrolling non-classical monocytes, and highlighting targets to inhibit monocyte infiltration.

Conclusions: Integrated kidney snRNA-seq in two LN models delineates a shared immune signature, with interactions with stromal, tubular, and glomerular cells important in early disease perpetuation and damage. Our comprehensive kidney single nuclei approach is generalisable, suggests candidate genes for rescue experiments and can be applied to human renal tissue.

TH-PO550

Urinary Extracellular Vesicles Reveal Distinct Biological Effects of Voclosporin in the Treatment of Lupus Nephritis

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Background: In the Phase 2 AURA-LV and Phase 3 AURORA 1 trials the novel calcineurin inhibitor voclosporin significantly increased complete renal response rates compared to placebo, both including mycophenolate mofetil and low-dose steroids. We further explore this treatment response by analyzing urinary extracellular vesicles (uEV), which are secreted by kidney cells and have the potential to provide a non-invasive read-out of cellular processes.

Methods: We isolated uEV from biobanked spot urine samples collected from patients with active lupus nephritis (LN) treated with voclosporin or placebo in AURORA 1 (n=60 per arm). uEVs were isolated at baseline and at the end of treatment using a differential ultracentrifugation protocol. Proteomes were quantified by tandem mass spectrometry on a Thermo Exploris480 with a data-independent acquisition strategy. Data was analyzed with Spectronaut and proteins with a log2-fold change >1 and q-value <0.05 considered significant. Pathway analysis was performed using the Reactome database.

Results: We identified 3708 proteins in uEV. At baseline 545 proteins were different in patients who responded to voclosporin. Pathway analysis linked these proteins to neutrophil degranulation, selenoamino acid metabolism, and Robo-receptors. Previous work on Robo-signaling showed it controls leukocyte infiltration and podocyte function in kidney injury and is increased in LN, while selenoamino acids are key to cellular antioxidant defenses and control Akt signaling through calcineurin. 732 proteins significantly changed in the patients who responded to voclosporin. Pathway analysis for voclosporin-altered proteins showed enrichment of the complement C2 and C4 pathways, while Fc-gamma receptor phagocytosis and tyrosine kinase signaling changed in patients responding to placebo. Neutrophil degranulation was changed by both voclosporin (61 proteins) and placebo (52 proteins), but involved different proteins (15 shared).

Conclusions: Using mass spectrometry of uEV we identified potential non-invasive biomarkers for treatment response to voclosporin in patients with LN. In addition, we were able to characterize the altered processes in the patients responding to voclosporin, which included complement and a specific change in neutrophil-associated proteins.

Funding: Commercial Support - Aurinia Pharmaceuticals

TH-PO551

Active CD11b Targets TLR7-Driven Inflammation to Reduce suPAR Levels and Kidney Damage in Lupus Nephritis

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Background: Lupus nephritis (LN) is a common end-organ injury resulting from systemic lupus erythematosus (SLE). CD11b heterodimerizes with b2 integrin to form the CD11b/CD18 receptor on surface of leukocytes that is essential for their normal functions. Genome-wide association studies revealed a number of single nucleotide polymorphisms (SNPs) in the ITGAM gene, that codes for CD11b, associate with SLE and LN. Prior studies have shown that several coding SNPs in CD11b reduce integrin function and increase Toll like receptor (TLR)-dependent inflammatory signaling. However, it is not clear if ITGAM SNPs also correlate with various kidney disease biomarkers, such as suPAR, and what the underlying mechanism could be. Additionally, it is not known if activation of CD11b would be able to reduce these biomarkers and kidney injury in vivo.

Methods: We used a combination of in vitro and in vivo assays. A macrophage cell line as well as primary macrophages were utilized and treated with TLR7 agonists. Two orthogonal approaches, genetic and pharmacologic, were utilized to activate CD11b and measure its effect on TLR7-dependent inflammatory signaling in myeloid cells in vitro and in LN models in vivo. Additionally, we utilized the MRL/lpr mice, a genetic model which shares many features and organ pathology with SLE, and a newly developed humanized mouse model of LN to mechanistically define role of CD11b activation in disease control.

Results: TLR7-stimulation increased suPAR levels in wild type cells in vitro and in vivo. Absence of CD11b (using CD11b knock out) exacerbated response. Conversely, CD11b activation using an oral agonist or a genetic mutation in CD11b significantly reduced suPAR and reduced proteinuria and LN pathology. CD11b activation also reduced splenomegaly and infiltration of CD11b+ inflammatory cells in the kidney. Mechanistically, CD11b activation reduced TLR7-dependent activation of NFkB to suppress suPAR generation.

Conclusions: We demonstrate that CD11b activation reduced TLR7-dependent suPAR levels in models of LN. These studies provide further support for CD11b activation as a therapeutic strategy for LN.

Funding: NIDDK Support

TH-PO552

In Vitro Expansion of Regulatory T Cells Restores Functional Capacity in ANCA Vasculitis

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Background: ANCA vasculitis is an autoimmune disease characterized by loss of tolerance to one of two main ANCA autoantigens, myeloperoxidase or proteinase 3. Broad immune system dysfunction is exhibited within relapses of disease which includes regulatory T cell (Treg) dysfunction. Previously, our group and others have demonstrated that Tregs are functionally deficient and unable to restrain effector T cell proliferation and cytokine production in ANCA vasculitis.

Methods: Tregs defined as CD4+, CD127low, CD25high, and CD45RA+ were sterile sorted from cryopreserved peripheral blood mononuclear cells. Sorted Tregs were then expanded in vitro with combinations of supplemental IL-2 and stimulation from CD3/CD28 Dynabeads for 14 days. After the 14 day expansion, Tregs were analyzed for phenotype and function was assessed by in vitro suppression assays.

Results: After 14 day expansion, Tregs from both healthy controls and patients with ANCA vasculitis expanded between 500-2000 fold over day 0 starting material. Expanded Tregs maintained >95% FOXP3+ protein expression and surface markers of CD25high, CD127low. Healthy control Tregs had potent suppressive capacity with >90% suppression of effector T cells. Expanded Tregs from ANCA vasculitis patients varied in their suppressive capacity from 30% suppression to >60% suppression of effector T cells. Variances in degrees of suppression may be due to clinical activity status and/or medication regimen at time of sample.

Conclusions: Tregs taken directly ex vivo from ANCA vasculitis patients fail to suppress effector T cell function. We have utilized a Treg expansion protocol that yields highly pure Tregs with 500-2000 fold expansion of numbers of Treg cells. Importantly, these expanded Tregs are functionally able to suppress autologous and allogeneic effector T cell proliferation. These studies are foundational for future trials of Treg expansion to maintain remission in ANCA vasculitis.

Funding: NIDDK Support

TH-PO553

Autoantibodies Against Laminin-521 Are Pathogenic in Anti-Glomerular Basement Membrane Disease

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Background: We previously demonstrated that laminin-521 is a novel autoantigen within the GBM and that antibodies to laminin-521 are present in about one-third of patients. However, definitive evidence for a pathogenic role of these antibodies has been lacking.

Methods: In this study, a rare case of atypical anti-GBM disease whose serum was negative for anti-a3(IV)NC1 antibody prompted us to investigate the possible presence of autoantibodies binding to laminin-521. Additionally, WKY rats were immunized with recombinant human laminin-521 to test the pathogenicity of antibodies to laminin-521 *in vivo*. Disease control and negative control rats were immunized with recombinant human α3(IV)NC1 and phosphate-buffered saline, respectively.

Results: The patient was diagnosed with a kidney biopsy. Circulating autoantibodies reactive exclusively to laminin-521 were confirmed in this patient. Immunoblot results reveal circulating IgG from this patient binds α5 and γ1 chains. A decrease in antibody levels was observed and was associated with improved clinical presentation after plasmapheresis. In rats immunized with laminin-521, but not in negative controls, severe proteinuria, crescentic glomerulonephritis, IgG deposits, complement activation, and infiltration of T cells and macrophages were observed. Lung hemorrhage occurred in 75.0% (6/8) of rats. Besides, sera and kidney elutes from laminin-521 immunization rats demonstrated a high level of IgG binding to laminin-521 but not to human α3(IV)NC1, while the opposite was observed in human α3(IV)NC1-immunized rats.

Conclusions: Patient data and animal studies imply a causative role of autoantibodies against laminin-521 in the development of anti-GBM disease and aid in the understanding of its etiology.

TH-PO554

Galectin-3 Involved in the Development of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common type of glomerulonephritis that frequently progresses to end-stage renal disease. However, the molecular pathogenesis underlying IgAN remains largely unknown. This study investigated the role of galectin-3 (Gal-3), a galactoside-binding protein in IgAN pathogenesis.

Methods: Two complementary mouse IgAN models, a model induced with TEPC-15 hybridoma using Gal-3 knockout (KO) mice, and a spontaneous IgAN model of "grouped" ddY (gddY) mice were employed.

Results: Gal-3 expression increased with disease severity in the glomeruli, peri-glomerular regions, and some renal tubules in both the inducible and spontaneous IgAN models. Gal-3 KO in the TEPC-15 hybridoma-induced IgAN mice significantly improved proteinuria and renal function and reduced severity of renal pathology, including neutrophil infiltration and decreased differentiation of Th17 cells from renal-draining lymph nodes, despite increased percentages of regulatory T cells. Gal-3 KO also inhibited the NLRP3 inflammasome, yet it enhanced autophagy and improved renal inflammation and fibrosis. Moreover, administration of 6-de-O-sulfated, N-acetylated low-molecular-weight heparin, a competitive Gal-3 binding inhibitor, restored renal function and improved renal lesions in passive IgAN mice.

Conclusions: These results suggest that Gal-3 is critically involved in IgAN pathogenesis by activating the NLRP3 inflammasome and promoting Th17 cell differentiation. Therefore, targeting Gal-3 action may represent a new therapeutic strategy for treatment of this renal disease.

TH-PO555

Mice with a Pax2 Missense Variant Are Susceptible to Experimental FSGS and Display Impaired Glomerular Repair

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Background: FSGS is a form of chronic kidney disease characterized by podocyte loss. Our team previously reported that *PAX2* pathogenic missense variants account for 4% of adults with FSGS. PAX2 regulates glomerular development and its expression persists in adult parietal epithelial cells (PECs), postulated to serve as a reservoir for cells including podocytes. We hypothesize that in humans and mice with pathogenic *PAX2* missense variants, PEC-mediated podocyte regeneration is impaired.

Methods: FSGS induced by Adriamycin was performed on wildtype mice and mice with a *Pax2* missense variant (termed *Pax2*^{MV}). Kidney tissue were analyzed by histology and immunostaining. Glomeruli were isolated and subjected to mass spectrometry (MS), analyzed by Gene Ontology (GO) Enrichment Analysis. Kidney tissue from relatives with *PAX2*-associated FSGS was also analyzed.

Results: At embryonic day 16.5, mouse wildtype kidneys showed overlapping expression of PAX2 and WT-1 in the condensed mesenchymal cells until PEC and podocyte differentiation, supporting a close lineage relationship. *Pax2*^{MV} had reduced nephron number but displayed only minor differences in glomerular function at baseline. Adriamycin-injured *Pax2*^{MV}mice showed more severe FSGS compared to wildtype, including decreased podocyte numbers and increased albuminuria. Adriamycin-injured *Pax2*^{MV}mice showed PAX2-expressing glomerular tuft cells, which were rarely observed in injured wildtype and were similar to histological findings from *PAX2*-associated FSGS patients, suggesting a role of these ectopic *PAX2*-expressing cells in pathogenesis. GO processes obtained from isolated glomeruli demonstrated maladaptive repair in *Pax2*^{MV}, including increased epithelial cell migration, decreased cell adhesion, de-regulated actin cytoskeleton dynamics, and in-utero embryonic development; while GO terms of normal repair mechanisms including regulation of cell morphogenesis, cell adhesion, cell-cell junction assembly, and actin cytoskeleton organization were enriched in wildtype.

Conclusions: Our findings support decreased glomerular regeneration in *Pax2*^{MV} mice compared to wildtype. We are next pursuing glomerular single-cell RNA sequencing to characterize the role of PECs in this process.

Funding: Government Support - Non-U.S.

TH-PO556

Molecular Imaging of Kidney C3d Deposits to Monitor Lupus Nephritis

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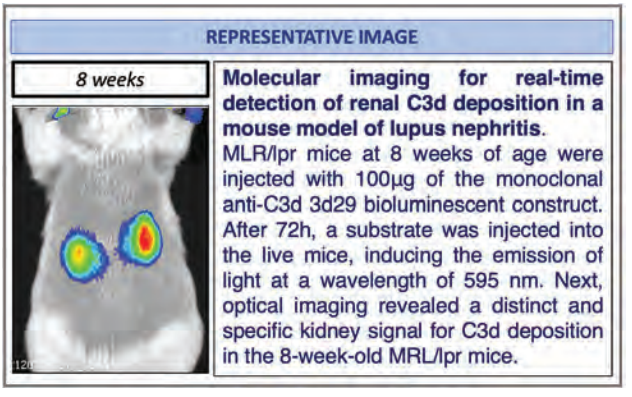
Background: Early identification of lupus nephritis (LN) is crucial in managing inflammation that could lead to chronic injury and kidney failure, but clinical signs and laboratory tests don't reliably predict histology in LN. Our work focused on using molecular imaging of renal C3d deposition to detect LN at an early stage.

Methods: Biopsy reports were retrospectively analyzed from LN patients to study the link between C3 staining intensity and histology. We also created a monoclonal antibody (mAb 3d29) against human C3d, that cross-reacts with mouse but doesn't bind intact C3. Next, we stained kidney tissue from LN patients and MRL/lpr mice (a model of LN). Lastly, we generated imaging probes from the mAb 3d29 to quantify C3d deposits by optical and positron emission tomography (PET) imaging in live mice.

Results: In LN biopsies, the intensity of C3 deposition correlated with histology. By immunostaining, our mAb 3d29 detected glomerular C3d in kidney samples from MRL/lpr mice and LN patients. In MRL/lpr mice, glomerular C3d deposits were seen at 8 weeks when mice had no histological/functional signs of kidney disease. C3d deposition stepwise increased at 12, 16, and 20 weeks, but showed a decrease at 24 weeks. Next, we performed optical imaging using the 3d29 mAb in *Cfh*-/- mice, a model of C3 glomerulopathy. Imaging demonstrated high intensities in their kidneys, whereas low signal or only background was detected in wild-type and *C3*-/- mice. As C3d deposition is an early disease event in MRL/lpr mice, we tested if early C3d imaging could predict future disease severity. Preliminary experiments in MRL/lpr mice suggested that renal C3d deposition detected by imaging at 8 weeks correlated with increased disease activity at 16 weeks. PET imaging in MRL/lpr and control mice with the radiolabeled 3d29 mAb showed similar results.

Conclusions: Renal C3d deposition seems a biomarker of disease activity in LN, and molecular imaging of C3d could be helpful to monitor disease activity in LN patients.

Funding: Private Foundation Support



TH-PO557

Enhanced Growth of Gut Bacteria Muribaculaceae Reduces Inflammation and Kidney Injury in an Experimental Model of Anti-Neutrophil Cytoplasmic Antibody Vasculitis

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Background: The gut microbiome is a critical factor influencing immune homeostasis. Reduced microbial diversity in the gut has been associated with the increasing prevalence of autoimmune diseases. Notably, the family *Muribaculaceae* has declined within the human microbiome in the industrialised world, and studies have linked its reduced abundance to disease. We investigated the role of the declining *Muribaculaceae* family in ANCA-associated vasculitis (AAV). We hypothesized that dietary supplementation with resistant starch (RS) a fermentable substrate for gut bacteria would enhance the growth of anti-inflammatory short chain fatty acid (SCFA) producing bacteria (including *Muribaculaceae)* which would mitigate neutrophil activation and ameliorate kidney inflammation in AAV.

Methods: Using an experimental model of ANCA vasculitis, we assigned mice to treatment groups receiving a diet supplemented with 15% RS (n=8) or a calorie-matched control diet (n=8). Additionally, another cohort of mice was randomized to receive either a control vehicle (n=8), or SCFAs acetate (n=8), butyrate (n=8), or propionate (n=8) orally.

Results: 16S rRNA analysis (Illumina miseq) analysis of the caecal contents revealed that the RS diet induced significant alterations in the gut microbiota consortium, characterized by a notable expansion of SCFA-producing bacteria from the *Bacteroidaceae* and *Muribaculaceae* families. The ratio of firmicutes/bacteriodota an indication of gut dysbiosis was reversed in the mice on the RS diet. RS treated mice all had significant diminution of inflammation, with a reduction in glomerular injury, neutrophil, macrophage and CD4 T cell recruitment. Mice in the RS treatment group had significantly reduced dendritic cell activation in the draining lymph nodes with a decrease in MHCII and CD80 expression. Albuminuria was significantly decreased in the RS group ($p < 0.05$). SCFAs alone were not as efficient as RS supplementation in reducing glomerular injury and leukocyte infiltration.

Conclusions: Our findings highlight the therapeutic potential of SCFA production through RS fermentation or direct administration of SCFAs in ANCA vasculitis. These interventions represent possible novel adjunct therapies for reducing inflammation in vasculitis.

Funding: Government Support - Non-U.S.

TH-PO558

Targeting Tissue-Specific T Cell Plasticity by Pooled Single-Cell CRISPR Screening in Preclinical Mouse Models

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Background: Treatment of autoimmune diseases demands a shift from unspecific immunosuppression towards targeted therapies. This could be achieved by turning pro-inflammatory T helper cells into anti-inflammatory subsets. However, the molecular

pathways involved in T cell plasticity and stability are not fully understood. Single cell CRISPR-screens are a powerful tool to simultaneously analyze the impact of multiple genes on cellular phenotypes.

Methods: By combining single cell gene expression analysis and T cell receptor sequencing, we uncover Th17 to Th1 cell plasticity in the human kidney in renal autoimmunity. To investigate the molecules involved in T cell plasticity in disease settings, we established *in vivo* single cell CRISPR droplet sequencing (iCROP-seq).

Results: By applying this technique to *in vivo* models of inflammatory diseases in the kidney and intestine, we demonstrate that CRISPR-induced alterations in T cell polarization can be identified and ranked according to corresponding transcriptional perturbations. In particular, we targeted pro-inflammatory Th17 cells in models of immune-mediated diseases and quantified polarization biases into Th1 and regulatory T cells.

Conclusions: iCROP-seq will facilitate the identification of therapeutic targets by highly efficient functional stratification of genes and pathways in a disease- and tissue-specific manner.

Funding: Government Support - Non-U.S.

TH-PO559

Proliferative Glomerulonephritis with Monotypic Immunoglobulin Deposits (PGNMID) and Preeclampsia

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Introduction: We report the case of a pregnant woman presenting with hypertension, nephrotic range proteinuria and hematuria. Kidney biopsy revealed glomerular thrombotic microangiopathy (TMA) and underlying PGNMID with IgG1-k deposits.

Case Description: A 33-year-old woman presented at 21 weeks' gestation with new-onset hypertension. She had a history of prior preterm preeclampsia and obesity s/p gastric sleeve surgery. Physical exam was normal except for blood pressure 141/111 mmHg. Kidney function was normal. UA showed hematuria and proteinuria, with UPCR of 3.7 g/day. Fetal ultrasound showed severe fetal growth restriction (FGR). ANA, Anti-dsDNA, Anti-PLA2R Ab were negative, and complements were normal. She had persistent proteinuria and microscopic hematuria on multiple UAs from 5 years prior to pregnancy. Kidney biopsy was done at 23 weeks' gestation to evaluate for glomerular disease vs. preeclampsia. Light microscopy showed glomerular endotheliosis with a membranoproliferative pattern, consistent with preeclampsia. IF showed mesangial and segmental glomerular capillary wall staining for IgG1 and k with negative λ, consistent with proliferative glomerulonephritis with monotypic IgG-k deposits (PGNMID). SPEP and immunofixation was negative for a monoclonal protein. Testing for HBV, HCV, and HIV was negative. At 24 weeks, labor was induced for worsening transaminitis. Due to severe FGR, neonatal resuscitation was not attempted. At 3 weeks postpartum, her BP and proteinuria improved (UPCR 1.3g/day). Kidney function remained normal.

Discussion: To our knowledge, this is the first reported case of PGNMID with preeclampsia. There is 1 report of PGNMID in pregnancy, but without preeclampsia. As in our case, IF showed IgG1- k, and there was no monoclonal protein detected. PGNMID was first described in 2004 as an endocapillary proliferative or membranoproliferative glomerulonephritis related to monoclonal IgG deposition. Most (70%) patients with PGNMID do not have a detectable circulating monoclonal protein in the serum or urine. In such cases, treatment directed at a hypothesized underlying clone may still be considered. In our patient, preeclampsia complicated the clinical presentation and obscured the pathologic findings of PGNMID. Kidney biopsy assisted in confirming the diagnosis of preeclampsia, allowing appropriate management when preeclampsia progressed.

TH-PO560

Gross Hematuria and Proteinuria in Myelofibrosis: A Curious Case of Myelofibrosis-Related Glomerulopathy

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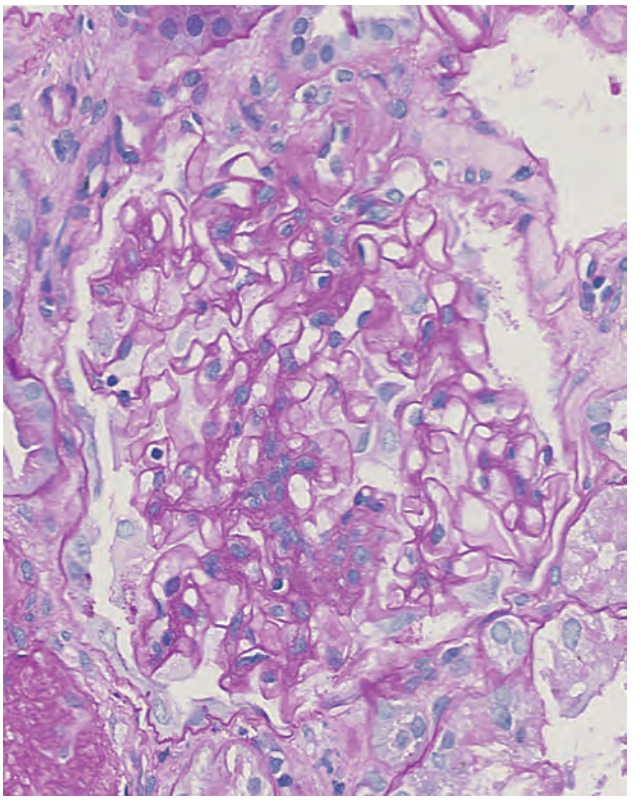
Introduction: Renal involvement in myeloproliferative disease is rare and presents with proteinuria, nephrotic syndrome, and renal insufficiency. Renal damage can be due to renal extramedullary hematopoiesis (EMH) and glomerulopathy. Renal EMH presents as infiltration of the interstitial, functional damage of parenchyma and vessels and sclerosing mass-like lesions causing hydronephrosis and renal insufficiency.

Case Description: 69 year old male patient with JAK2 mutated Polycythemia Vera progression to Myelofibrosis; admitted for respiratory failure with lobar pneumonia. Patient was on Ruxolitinib for 7 years. Baseline creatinine was 1.43mg/dL. Patient had an AKI with creatinine of 4 mg/dL attributed to contrast use and hypotension. During the hospital course, the patient developed an acute onset colicky flank pain associated with frank hematuria. CT imaging and renal duplex ultrasound were normal except for hepatosplenomegaly. Additional testing showed proteinuria (3.7g/g). Numerous dysmorphic RBCs and muddy brown casts present on microscopy. Serology for proteinuria were non-revealing. Renal biopsy showed diffuse moderate acute tubular injury, glomerulopathy with mesangial expansion, thickened glomerular capillary walls and megakaryocytes consistent with myeloproliferative neoplasm related glomerulopathy. The patient did not require dialysis. His hematuria and creatinine improved to 1.6 mg/dL. Patient remains on Ruxolitinib and received splenic radiation for symptomatic splenomegaly.

Discussion: Patient with myeloproliferative disease presenting with AKI, proteinuria, hematuria and acute abdominal colicky pain should raise suspicion of myeloproliferative related glomerulopathy.



Mesangial expansion and hypercellularity on light microscopy on Periodic Acid-Schiff stain.

TH-PO561

Scleroderma-Associated Kidney Disease: A Case Series

Tara O'Sullivan,[1,2] Darragh O'Donoghue,[1,2] Andrew J. Redmond,[1,2] John G. Ryan,[1,2] Sarah M. Moran,[1,2] James Gleeson,[1,2] Adeel R. Ahmed.[1,2] [1]*University College Cork, Cork, Ireland;* [2]*Cork University Hospital, Cork, Ireland.*

Introduction: Scleroderma is a rare multisystem disorder categorised into limited and diffuse subtypes. Recognised renal manifestations of scleroderma include renal crisis (SRC) and ANCA associated vasculitis. We present three differing cases of scleroderma associated renal disease.

Case Description: Case 1: 64 year old normotensive female with systemic sclerosis developed AKI and microangiopathic haemolytic anaemia. ANCA and ANA were negative. IgG Kappa paraprotein detected (9.7g/L). Bone marrow biopsy showed 7.2% plasma cells. Renal biopsy demonstrated intraglomerular thrombotic microangiopathy, without onion-skinning or involvement of interlobular or arcuate arteries. Treatment was targeted at the plasma cell clone. **Case 2:** 53 year old female with CREST presented with hypertension (BP 231/124mmHg) and developed AKIN3. She was anti-centromere positive. Renal biopsy demonstrated thrombotic microangiopathy, with onion-skin appearance of arterioles. She was treated as SRC with captopril, leading to improvement in renal function. **Case 3:** 75 year old female with limited systemic sclerosis admitted with nephrotic syndrome. She was hypertensive but did not tolerate RAAS inhibition. Urinary PCR was 873.6mg/mmol. Renal biopsy demonstrated a cellular form of focal segmental glomerulosclerosis, without tip lesions. Corticosteroids were avoided due to risk of precipitating SRC. She was treated with tacrolimus, which reduced proteinuria to the sub-nephrotic range.

Discussion: These cases demonstrate three different presentations of scleroderma associated renal disease. The intraglomerular distribution of TMA in Case 1 is more consistent with MGRS rather than SRC, in the context of a paraprotein. While there is one published case of SRC in a patient with concurrent scleroderma and monoclonal gammopathy, SRC is less frequent in seronegative scleroderma. SRC presenting in CREST, as in case 2, is unusual as it is more commonly reported with diffuse scleroderma, and anti-centromere antibodies have a negative association. In the final case, primary FSGS is a highly atypical manifestation of limited systemic sclerosis. The contrasting pathologies highlight the diagnostic value of kidney biopsy in scleroderma patients presenting with renal impairment, and its importance in guiding treatment.

TH-PO562

Unique Case of Silicosis Leading to Several Autoimmunities: Rheumatoid Arthritis and Membranous Lupus Nephritis

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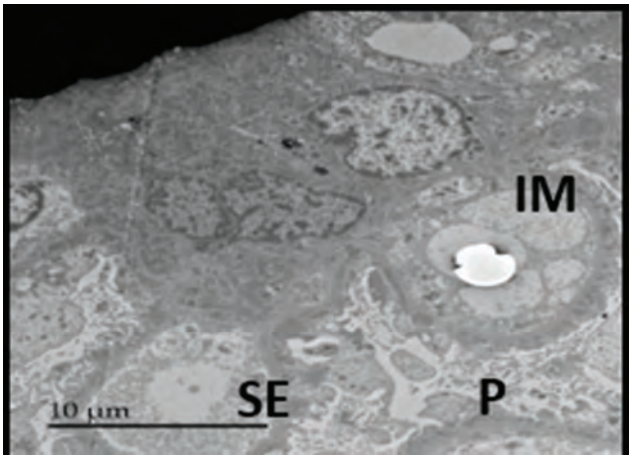
Introduction: Silicosis is a fibrotic lung disease caused by the inhalation of free crystalline silica, and is the oldest pulmonary occupational hazard known. Silica exposure has been linked to several other conditions including infections, malignancies and autoimmunity.

Case Description: A 41-year-old male, marble factory worker, lung silicosis diagnosed by biopsy on 2012. ANA, dsDNA, anti-Smith and RF were all negative than. in 2017 due to symmetrical arthritis and newly positive RF rheumatoid arthritis was diagnosed, and he was treated with steroids, hydroxychloroquine and methotrexate. Patient currently presented with arthralgia, peripheral edema, and almost 10 Kg gain during a month. He was not taking any medical treatment at that time. lab results indicated normal renal function, a low serum albumin (23g/L), and nephrotic range proteinuria (7.4 g/g). ANA, anti-Smith, anti-SSA were positive, and C3 was low. Renal biopsy revealed rigid glomerular capillary walls with tiny discreate deposits in the outer aspect of the GBM, a "full house" pattern immunofluorescence, and increased mesangial matrix (M) with numerous electron dense deposits, intramembranous (IM) and subepithelial deposits (SE) interposition of glomerular basement membrane material (spikes), and effacement of foot processes (P) were seen at EM(figure), compatible with membranous pattern injury of SLE. Patient received steroids hydroxychloroquine and MMF treatment.

Discussion: Silicosis is associated with impaired immune system, high risk for pulmonary infections malignancies and more. It is also associated with inflammatory diseases such as RA, scleroderma and mixed connective tissue disease. Autoantibodies as anti-DNA and anti-SSA/B occur in a higher frequency in individuals exposed to silica than general population. Renal involvement secondary to silica has been seen in the past, however this is the first description of membranous lupus nephritis after silica exposure.



TH-PO563

Unusual Presentation of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID)

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is a recent entity of monoclonal gammopathy of renal significance (MGRS) due to monoclonal immunoglobulin (mIg) deposits in the glomerulus leading to kidney injury. However, clinical or laboratory evidence of cryoglobulinemia needs to be ruled out. We describe a unique case of PGNMID with pathologically similar to infection related GN but with laboratory evidence of positive type II cryoglobulinemia and anti-smooth muscle antibodies.

Case Description: A 29-year-old obese male with hypertension and type 2 DM was admitted for AKI in the setting of nausea, vomiting, diarrhea & NSAID use. Creatinine (Cr) was 2.5 mg/dl with a baseline of 0.9 mg/dl. He received IV hydration and Cr improved to 1.8-1.9 mg/dl. However, further work up revealed microscopic hematuria & nephrotic syndrome with UPCR of 10 g/g. Serologic workup revealed positive ANA (1: 160). SPEP did not show monoclonal protein spike. Type II cryoglobulin with monoclonal IgG lambda and polyclonal IgG with a titer of 20 mg/dL was detected. Kidney biopsy showed PGNMID with monotypic IgG3-lambda shaped subepithelial deposits concerning for "infection-related glomerulonephritis". Extensive infectious workup was negative. Hematologic evaluation did not reveal an underlying lymphoproliferative disorder. Rheumatologic workup showed elevated anti smooth muscle antibody (1:320). After 2 weeks, proteinuria improved significantly to 1.9 g/g but Cr increased to 2.3 mg/dl with persistent microscopic hematuria. Patient was then started on Prednisone 1 mg/kg. Cr improved to 2.0 mg/dl and UPCR 0.6 g/g after about 1 week of high dose steroids. He is doing better clinically but microscopic hematuria persists.

Discussion: We describe a unique case with pathologic evidence of PGNMID with subepithelial hump deposits suggestive of infection, monotypic composition of the deposits (IgG3-lambda) suggestive of possible underlying dysproteinemia but also with laboratory evidence of mixed cryoglobulinemia which also raises the possibility of an unusual pattern of cryoglobulinemic GN. Interestingly, anti-smooth muscle antibodies are also positive which raises a suspicion of sub clinical autoimmune hepatitis which can be associated with mixed cryoglobulinemia. This case emphasizes the importance of a thorough serologic workup, despite having biopsy results.

TH-PO564

Semaglutide (Ozempic), a Possible Cause of Focal Segmental Glomerulosclerosis (FSGS)

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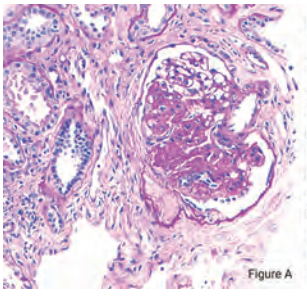
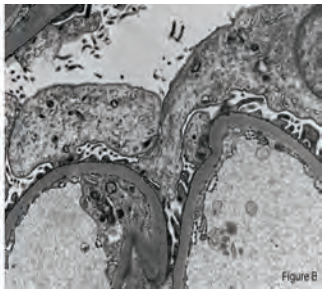
Introduction: Semaglutide use has been increasing rapidly because of its beneficial effects on diabetes control, cardiovascular protection, and weight loss. Adverse renal events are rare. We present a case of semaglutide-associated FSGS.

Case Description: A 55-year-old nondiabetic female with history of end stage kidney disease secondary to IgA nephropathy treated by kidney transplantation 3 years earlier. Her baseline serum creatinine was 1.2 mg/dL and she had no proteinuria. She was initiated on Semglutide for weight loss. Soon after starting. 0.5 mg weekly, she developed proteinuria; UPC (urine protein to creatinine ratio) =400 mg/mg. The association was not suspected and so her dose was increased to 1.0 and then 2.0 mg weekly. The increases in Semaglutide dose coincided with worsening UPC 3300 mg at 2 months and 9 g/g at 4 months. She was subsequently admitted due to progressive edema and dyspnea; her 24 hour urine protein was 16 g/g now. Her serum creatinine remained at 1.2-1.5 mg/dL while her albumin and LDL levels were 1.7 and 303 mg/dL, respectively. She remained on Tacrolimus, Mycophenolate and Prednisone throughout. Blood tests for HIV, hepatitis, drug use and APOL1 gene were negative. A kidney biopsy showed FSGS on light microscopy (figure A), moderate to marked segmental foot process effacement by electron microscopy (figure B).

Discussion: To the best of our knowledge, this is the first case of FSGS that appears to be associated with the Semaglutide use. While we did not establish causality, the time course and progression of proteinuria raise the possibility that Semaglutide was the trigger. The mechanism is unknown but Semaglutide therapy is known to induce formation of anti-Semaglutide antibodies in up to 1% of patients. The clinical significance of this immune response is unknown but raises the possibility that it could have led to the formation of a circulating glomerular permeability factor that caused the FSGS. Identification of more cases may allow for further investigations into the potential causality and mechanisms of Semaglutide-associated FSGS.





TH-PO565

Type II Cryoglobulinemic Glomerulonephritis in a Patient with Marginal Zone Lymphoma

Devyani Sivakumar, Senin Shah, Manini Vishwanath. *Brown University, Providence, RI.*

Introduction: Cryoglobulinemia is rare and clinically significant in about 1 in 100,000. Renal involvement is seen in 30-60% cases and is especially associated with type II cryoglobulinemia. In a study of 80 patients with noninfectious biopsy proven mixed cryoglobulinemic glomerulonephritis, 7 patients had marginal zone lymphoma.

Case Description: A 76-year-old female with history of marginal zone lymphoma since 2019, managed conservatively, presented to the hospital with dyspnea on exertion, fatigue, 20 lbs weight gain and leg edema for 2 months. She had 3 recent hospitalizations for similar complaints and had been managed with diuretics and antibiotics, with no improvement. She was hypertensive to 167/86 mmHg, exam showed bilateral cervical lymphadenopathy and 2+ pitting pedal edema up to the groin. Labs revealed Cr 1.51 mg/dl [baseline 0.6-0.9 mg/dl]. UA positive for protein, albumin 2.4 g/dl and UPCR 9 g. Low complements with C3 at 33 mg/dl and C4 <3 mg/dl. Serology revealed ANA reactive [1:5120] and anti dsDNA negative. HIV, Hepatitis B and C were non-reactive. Kappa/Lambda ratio 1.68 with IF positive for monoclonal IgM kappa and potential monoclonal lambda free light chain. Immunoglobulin levels notable for elevated IgM at 1349 mg/dl. Cryoglobulin positive at 790 UL cryo/mL with isotype positive for weak monoclonal IgM kappa. Kidney biopsy showed membranoproliferative glomerular injury pattern with immune complexes which stained for IgM [3+], IgG [2+], C3 [2+], C1q [2+], kappa [2+], lambda light chains [1+]. A diagnosis of paraneoplastic

type II cryoglobulinemia related to marginal zone lymphoma was made. She started treatment with rituximab, cyclophosphamide and dexamethasone and responded well with improvement in symptoms and renal function.

Discussion: Noninfectious type II cryoglobulinemic glomerulonephritis associated with marginal zone lymphoma is uncommon. In a retrospective multicenter survey of 242 cases of noninfectious mixed cryoglobulinemic vasculitis, 22 cases had marginal zone lymphoma and renal involvement was seen in 84 cases. Management and prognosis is dependent on disease severity and involves treatment of underlying cancer. Although our patient responded well to treatment, there was a 2 month delay in diagnosis despite recurrent hospitalizations. It is important to highlight this association and the clinical presentation.

TH-PO566

ANCA-Associated Pulmonary Renal Syndrome with Immune Complex Deposition

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Introduction: Pulmonary renal syndrome (PRS) is a highly morbid condition in which rapid identification and empiric therapy is critical.

Case Description: A 55 year old female with a past medical history of hypertension, rheumatoid arthritis not on any active therapy, and CKD3 diagnosed 6 months ago, presented to the ED for 2 days of hemoptysis and hematuria. She denied any recent upper respiratory symptoms or fevers. She also developed constant, non radiating, epigastric pain with 2 episodes of blood streaked emesis. She denied any new medications. Because her symptoms were unremitting and she became dyspneic, she presented to the ED. On arrival, she was tachypneic at 34 respirations per minute and hypoxic to 84%. She had a hemoglobin of 6.4. Her creatinine was 8.96 with a baseline of 1.5. On urinalysis, she had 3+ protein, 3+ blood, 6-9 WBCs, >100 RBCs, no casts or dysmorphic RBCs were noted. A chest x-ray showed severe, diffuse pulmonary infiltrates. Given concern for acute glomerulonephritis (GN) with associated PRS, she was started on empiric pulse dose steroids with 1 gram of methylprednisolone IV daily for 3 days as well as plasmapheresis with FFP and cyclophosphamide. Subsequent workup showed a positive MPO-ANCA serology. Complement c3 and c4 levels were low. Anti-GBM was negative. ANA was positive at 1:1280 with a speckled, nuclear pattern. Anti-DS DNA was not detected. Anti streptolysin O antibodies were in the normal range. Serologies for HIV and hepatitis were unremarkable. Kidney biopsy revealed diffuse sclerosing and focal proliferative GN with 30 percent crescents and severe interstitial inflammation. There was also immune complex deposition.

Discussion: ANCA associated GN is most often pauci immune and concurrent immune complex GN is unusual but has been reported in 5-14 percent of patients with ANCA positive GN. When ANCA associated GN presents with immune complex deposition, vasculitis involvement is most often exclusively renal. In our case, the patient had both pulmonary and renal involvement. Recognition of MPO ANCA associated GN with concomitant immune complex deposition is important as it has been associated with worse renal outcomes. Moreover, while a link between ANCA positivity and rheumatoid arthritis has previously been established, RA related renal dysfunction is typically not rapidly progressive.

TH-PO567

A Case of ANCA-Associated Vasculitis with IgG4-Related Disease Treated with the C5a Receptor Inhibitor Avacopan

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Introduction: Complement is important in the immune system against infection but complement hyperactivation can cause complement-related disease, such as systemic lupus erythematosus. Recently, the C5a inhibitor avacopan was developed for treating antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). IgG4-related disease (IgG4-RD) is often associated with hypocomplementemia. C5a inhibitors may be effective in treating IgG4-RD, but this not been reported. We report the first case of AAV with IgG4-RD treated with avacopan.

Case Description: A 69-year-old man was admitted to our hospital because of fever, weight loss, anemia and urinalysis abnormalities. A blood test showed mild kidney dysfunction and elevated CRP, MPO-ANCA and serum IgG4 levels. An enhanced computed tomography (CT) scan showed bilateral renal swelling and multiple low-density lesions in the renal cortex. A renal biopsy showed pauci-immune type crescentic nephritis with necrotizing vasculitis. There was also prominent infiltration of IgG4-positive plasma cells with interstitial fibrosis called “storiform fibrosis,” which led to the diagnosis of coexistence of AAV and IgG4-RD. Remission induction therapy with glucocorticoids (GCs) and rituximab was followed by maintenance therapy with avacopan. One month later, the Birmingham vasculitis activity score (BVAS) improved from 15 to 0. Six months later, the renal low-density lesions on CT scan disappeared. GCs were tapered early with concomitant use of avacopan, and remission was maintained.

Discussion: Avacopan is a selective C5a receptor antagonist that blocks the inflammatory neutrophil response, including degranulation and release of reactive oxygen species. In the ADVOCATE study, avacopan was noninferior in the treatment response compared with GCs, and superior in reducing relapse and GC toxicity. GCs are the first-line treatment for IgG-RD, but the optimal treatment is unclear. Serum C5a levels in IgG4-RD were reported to be significantly higher than those in healthy donors and decreased at remission. These data suggest that avacopan may have been effective for not only AAV, but also for IgG4-RD, in our case.

TH-PO568

Infection-Related Glomerulonephritis (IRGN) due to Gordonia Bacteremia in an Immunocompetent Patient with a Femoral Catheter

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Introduction: Gordonia species rarely cause human infection, though cases of bacteremia in immunocompromised patients with endovascular devices have been reported. These may be under-recognized as blood cultures (BC) can be negative until 4 or more days after incubation. We report a case of IRGN secondary to Gordonia bacteremia in an immunocompetent patient with a chronic femoral catheter.

Case Description: A 61-year-old woman with complex regional pain syndrome on buprenorphine infusion via femoral catheter presented to our hospital with AKI on outpatient labs. She had been hospitalized 1 year prior with a diffuse macular rash while on Bactrim for cellulitis. At that time, she was febrile with negative BC and low C3/C4. Skin biopsy showed leukocytoclastic vasculitis (LCV), presumed to be drug-induced. Rash resolved with broad-spectrum antibiotics (Abx). At the current presentation, creatinine was 5.37mg/dL. UA showed 1+ protein and innumerable RBCs. C3 was low and rheumatoid factor (RF) was elevated. Renal biopsy showed diffuse proliferative crescentic immune-complex GN with full house staining pattern suspicious for lupus nephritis, though all serologies (except RF) returned negative. She developed fever after routine femoral catheter exchange and BC were sent. Steroid therapy was started for suspected autoimmune GN when BC were negative for 2 days. Unfortunately, after a sneezing spell she developed a spontaneous left subdural hematoma (SDH) with active bleeding requiring craniotomy. By then, BC (2 sets) grew Gordonia polyisoprenivorans at 3 days. Abx were started. Steroids were stopped. She briefly required hemodialysis but had rapid renal recovery with Abx. Unfortunately, she had further intracranial complications including transtentorial herniation and persistent comatose state. Family elected to continue all care. She was discharged to a nursing facility.

Discussion: The patient’s AKI and biopsy findings were attributed to IRGN. There was suspicion her spontaneous SDH was secondary to vascular mycotic infection from Gordonia bacteremia, and prior LCV may have been a manifestation of chronic bacteremia. Clinicians should have a high index of suspicion for slow-growing bacterial infections as an etiology of IRGN in unexplained glomerular disease, especially in patients with indwelling central catheters.

TH-PO569

Wunderlich Syndrome with Polyangiitis Overlap: A Diagnostic Challenge

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Introduction: Spontaneous renal hemorrhage, called “Wunderlich syndrome”, is a rare complication of vasculitides, especially polyarteritis nodosa (PAN). We present a patient with spontaneous renal hemorrhage with polyangiitis overlap syndrome.

Case Description: A white male in his 70s presented with leg pain, weakness, and oliguria. He noted worsening bilateral hearing loss and recurrent sinusitis over 6 months and involuntary 30 lb. weight loss over 3 months. Serum BUN/creatinine were 168 mg/dl/11.2 mg/dl and hemodialysis was started. Initial CT scan of abdomen was negative. He developed new onset left sided abdominal pain after 3 days. Repeat CT scan of abdomen showed bilateral renal hematomas (Fig. A) and multiple left renal aneurysms concerning for PAN (Fig. B) on CT angiogram. pANCA titer was 1:320 (<1:20) with anti-MPO titer of 134 AU/ml (0-19). He met classification criteria for both PAN and Microscopic Polyangiitis (MPA) (Table 1). Kidney biopsy was deferred due to high bleeding risk. Hearing improved after pulse methyl prednisone followed by oral prednisone, cyclophosphamide, and plasma exchange but he remains dialysis dependent six months after discharge.

Discussion: We describe a challenging case with features of both PAN and MPA with bilateral spontaneous renal hemorrhages which precluded tissue diagnosis. This clinical presentation is most consistent with “polyangiitis overlap syndrome” which has not been previously described in association with Wunderlich syndrome. Renal hemorrhage should be considered in patients with ANCA associated vasculitides or polyangiitis overlap syndromes with acute abdominal pain.

1990 ACR Criteria for Classification as PAN (least 3 of 10 criteria)	2022 ACR/EULAR Criteria for Classification as MPA, (total score ≥5)
Unexplained weight loss > 4kg	pANCA or anti-MPO antibodies positive (+6)
Myalgias (excluding shoulder or hip girdles), muscle weakness	
BUN >40 mg/dL or serum creatinine >1.5 mg/dL	
Characteristic arteriographic abnormalities not from noninflammatory disease processes	

Table 1

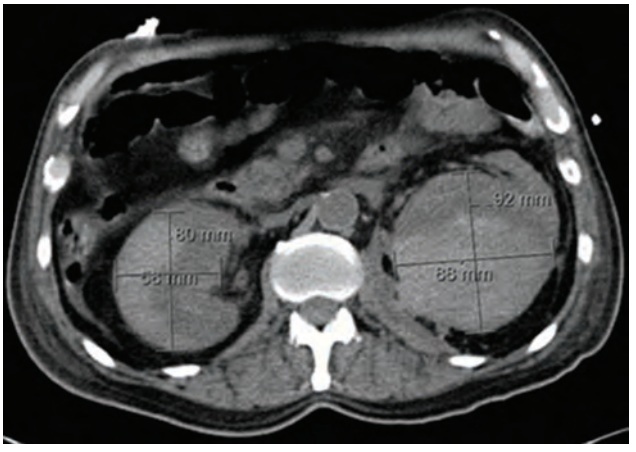

Fig. A

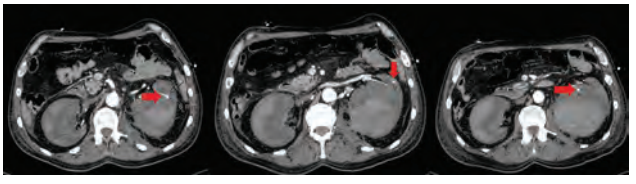

Fig. B

TH-PO570

A Rare Feature of Myeloperoxidase (MPO)-Positive Crescentic Glomerulonephritis (GN) and Neural Epidermal Growth Factor-Like 1 (NELL-1) Protein Positive Membranous Nephropathy (MN) in Mantle Cell Lymphoma (MCL)

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Introduction: MCL is a B-cell non-Hodgkin's lymphoma that can have renal involvement via infiltration, immune complex (IC), or complement-mediated (CM) GN. Typical IC-positive GN lesions include proliferative GN with monoclonal IgG deposits (PGNMD), C3GN, and MN. Antineutrophilic Cytoplasmic Antibody (ANCA) associated GN is now recognized to link with preceding or concurrent malignancy. Our case features a rare presentation of acute kidney injury (AKI) caused by MCL infiltration, coexisting MPO-ANCA associated crescentic GN, and NELL-1 positive MN.

Case Description: 61-year-old previously healthy male presented with intermittent fever, night sweats, maculopapular rash with bullae, anasarca and a 30 lbs weight loss. He was hypertensive and labs revealed anemia, thrombocytopenia, Strep. Agalactiae bacteremia, active urine sediment and severe AKI needing dialysis. Also notable was hypoalbuminemia 1.9 g/dL with proteinuria 9 g/g. Imaging revealed splenomegaly, diffuse lymphadenopathy, and normal-sized kidneys. Nephritic labs showed positive ANCA with MPO antibody specificity, low C3 and C4 levels, and normal kappa lambda light chain ratio. Bone marrow biopsy confirmed MCL with blastoid features. Renal biopsy showed crescentic GN, polyclonal IgG, C3, C1q, Kappa and Lambda along the tubular basement membrane, positive NELL-1 staining, and lymphomatous infiltration. Steroids and Rituximab were used as induction therapy without plasmapheresis. Rituximab continued as part of MCL chemotherapy. His renal function improved and dialysis was stopped. At 8 months creatinine was 2.9 g/dl with partial nephrosis remission (UPCR 1.3 g/g and albumin 3.3 g/dL).

Discussion: We describe a rare AKI in lymphoma presentation with MCL infiltration, MPO positive crescentic GN, and NELL-1 associated MN. To our knowledge no such case has been reported. The association between NELL-1 and malignancy is established, but it's unclear if this association with MPO ANCA is coincidental. Early identification through kidney biopsy and initiation of cancer treatment may alter the renal and patient overall prognosis. Our patient responded well to Rituximab and steroids, but the success of standard guideline therapy and the possibility of complete remission require further investigation.

TH-PO571

Idiopathic Multicentric Castleman's Disease (iMCD)-TAFRO Syndrome with Atypical Renal Biopsy Findings

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Introduction: Idiopathic Multicentric Castleman's Disease (iMCD) is a rare lymphoproliferative disorder characterized by enlarged lymph nodes in HHV-8 negative patients. It is associated with fevers, weight loss, hepatosplenomegaly, cell line dyscrasias, and organ dysfunction. One subtype of iMCD is TAFRO syndrome, characterized by the presence of thrombocytopenia, anasarca, myelofibrosis, renal dysfunction, and organomegaly. We report a patient who presented with a seronegative proliferative glomerulonephritis and was subsequently diagnosed with iMCD-TAFRO syndrome.

Case Description: A 47-year-old male with no past medical history presented to the hospital with non-specific lab abnormalities. Vital signs showed new hypertension, tachycardia, and intermittent fevers. Physical exam noted diffuse anasarca. Laboratory investigation revealed elevated inflammatory markers, new anemia, and acute renal injury. He did not have nephrotic syndrome per urine protein quantification. Urine microscopy revealed microscopic hematuria with hyaline and granular casts. Glomerulonephritis serologic evaluation was negative. Rapidly progressive renal failure necessitated initiation of renal replacement therapy and pulse dose steroids. Renal biopsy revealed a proliferative glomerulonephritis without crescents or segmental necrosis. Immunofluorescence demonstrated trace focal mesangial granular deposits of IgM and C3. Electron microscopy showed moderate foot process effacement without subendothelial or mesangial deposits. Other evaluations included a PET/CT scan, bone marrow biopsy, and cervical lymph node biopsy. Pending lymph node biopsy results, IV cyclophosphamide was started for presumed seronegative ANCA vasculitis. Results from the cervical lymph node biopsy were consistent with iMCD. The patient was transitioned to siltuximab with a prednisone taper.

Discussion: iMCD-TAFRO syndrome can present with proliferative glomerulonephritis. While this patient presented with common clinical findings of iMCD, renal biopsy results were atypical relative to prior reports of a MPGN or TMA-like histopathology. iMCD-TAFRO syndrome may not always conform to typically seen patterns. Diagnosis requires a high index of suspicion and should be considered for glomerulonephritis with non-specific biopsy findings in the context of a systemic inflammatory disease.

TH-PO572

Bacterial Endocarditis with Strongly Positive Anti-PR3 ANCA

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Introduction: ANCA-associated rapidly progressive glomerulonephritis (GN) should be identified and treated promptly. There are however infectious mimickers of ANCA-associated GN that may present only as a lack of complete pauci-immunity on biopsy. When lack of pauci-immunity is present, it should alert the clinician to a careful search for a causative infectious agent and to reconsider immunosuppressive therapy.

Case Description: A 64-year-old man with a mechanical mitral valve presented with dyspnea and acute kidney injury preceded by months of fatigue and weight loss. He was treated as decompensated heart failure. His first blood culture was negative. Subsequently, microscopic urinalysis showed dysmorphic red blood cells. Serological testing resulted with anti-PR-3 antibody at 955 AU/cc, anti-MPO within the reference range. Renal biopsy was consistent with crescentic GN, but lacking was complete pauci-immunity with mesangial staining for IgG (trace), IgM (1+), C3 (2-3+), C1q (2+). It was thought that he had a PR-3 associated RPGN. HCV, HBV, Anti-GBM antibodies and HIV serologies were negative. He began steroids, rituximab and cyclophosphamide. Subsequently, mixed cryoglobulin testing returned positively. The components C3 and C4 were low. Immunosuppression was discontinued and further infectious workup was repeated. Quantiferon GOLD testing was negative. Four of four blood cultures grew Staph. epidermidis. As he's a cat owner, Bartonella and Coxiella serologies were sent. Bartonella henselae IgM and IgG were both strongly positive, while Q-Fever IgM was less so. Echocardiogram demonstrated a mitral valve vegetation and CT of the abdomen showed splenic infarction (initial Echo and CT negative). He was started on treatment for S. epidermidis bacteremia and B. henselae, both of which could have been the causative agent of endocarditis. He eventually developed uremia and started kidney replacement therapy. He remains dialysis dependent.

Discussion: The decision to initiate immunosuppression is not light. Bartonella henselae has been shown to present as a rapidly progressive GN that mimics ANCA-associated GN through concomitantly elevated PR3-ANCA antibodies. Coxiella burnetii is a documented causative agent of mixed cryoglobulinemia. A level of suspicion for infectious disease should be maintained when pauci-immunity is absent despite clinically rapidly progressive GN in the setting of strong ANCA serological positivity.

TH-PO573

A Vexing Case

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Introduction: In 2020, somatic mutations in UBA1, an X-linked gene that encodes enzyme E1 necessary for ubiquitination, were described in patients with an adult-onset inflammatory syndrome called VEXAS (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, and Somatic). It has diverse systemic presentations and kidney manifestations are not well-characterized. We describe a patient who developed proliferative crescentic glomerulonephritis (GN) with deposits coincident with diagnosis of VEXAS.

Case Description: A 75-year-old male with hypertension and alcohol use disorder was admitted for worsening pancytopenia and acute kidney injury. 2 months prior he reported otitis externa and biopsy-proven atopic dermatitis responsive to steroids. Workup for pancytopenia including prior bone marrow biopsy (BM) was negative. Physical exam: BP 142/88 mmHg, normal heart, lung, abdomen and skin exam. Labs on admission: WBC 5200/μL, Hb 6.9g/dL, Platelets 133000/μL, Cr 1.96 mg/dL (baseline 0.8 mg/dL). Urinalysis: 2+ protein, 3+ blood, pyuria. Urine protein creatinine ratio 3.77. Serologies for complement, cryoglobulins, and ANCA were negative. Kidney biopsy

displayed proliferative necrotizing and crescentic GN with subendothelial deposits and lymphoplasmacytic infiltrate. IF staining: 3+ IgM, 3+ IgA, 1+ IgG, 1+ lambda. Review of prior BM biopsy showed cytoplasmic vacuoles in erythroid and myeloid precursors. Genetic screen positive for somatic UBA1c mutation. He was treated with steroids, mycophelonate and tocilizumab with partial response of declining creatinine and proteinuria.

Discussion: Limited data on kidney manifestations in VEXAS include MPO-positive necrotizing and crescentic GN, acute tubulointerstitial nephritis, and isolated interstitial infiltrate with MPO-positive and CD68+ myeloid cells. The present case adds to this data in describing a serology-negative necrotizing and crescentic GN. VEXAS syndrome represents dysregulated immune activation that leads to auto-immune organ injury. The kidney-specific pathological mechanisms of VEXAS syndrome are unknown but proposed theories include: cytokine-mediated tubular injury activating endothelial cells, recruitment of myeloid cells leading to further inflammation, and dysregulated neutrophil extracellular traps. Further research into how VEXAS syndrome involves the kidney is critical to targeted therapies for kidney disease in patients with this multi-system inflammatory syndrome.

TH-PO574

Hepatic Glomerulopathy After Liver Transplant: An Unexplored Clinical Entity

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Introduction: Hepatic glomerulopathy, also known as hepatic glomerulosclerosis is a secondary glomerular process that occurs in the context of liver failure and cirrhosis. Pathogenesis involves acquired LCAT (Lecithin–Cholesterol Acyltransferase) deficiency as the enzyme is mainly synthesized in the liver. Deposition of lipid particles in glomerular basement membrane (GBM) similar to those seen in congenital LCAT deficiency is pathognomonic. Here, we present a unique case of persistent hepatic glomerulopathy post liver transplant.

Case Description: A 58-year-old man s/p liver transplant with prior h/o alcoholic cirrhosis complicated by hepatocellular carcinoma presented to nephrology clinic for evaluation of persistent proteinuria post liver transplant. His immunosuppression includes tacrolimus and mycophenolate and BP is well controlled. Work up revealed nephrotic range proteinuria (approx. 4 gm/gm creatinine), rest is shown in Table 1. Kidney biopsy revealed deposition of lipid particles in glomerular basement membrane and metastatic micro-calcifications (Image 1).

Discussion: Hepatic glomerulopathy is an unexplored clinical entity which is characterized by deposition of small, irregular partially electro-lucent lipid particles in the subepithelial, intramembranous, subendothelial and mesangial regions as seen in our patient. The prevalence of hepatic glomerulopathy in liver disease is not known, nor is the clinical course post liver transplantation. To our knowledge, our case is the first to be reported in literature of persistent findings post liver transplantation. We believe raising awareness of the disease entity will help in understanding the clinical course and exploring treatment options.

Lab	Patient values	Reference range	Lab	Patient values	Reference range
Na	139	136-144 mmol/l	Albumin	3.7	3.6-5.0 g/dl
K	4.4	3.3-5.1 mmol/l	Cholesterol	233	<200 mg/dl
Urea	18	7-22 mg/dl	LDL	152	<100 mg/dl
Creatinine	0.98	0.6-1.4 mg/dl	HDL	43	>39 mg/dl
Calcium	9.4	8.9-10.3 mg/dl	Triglyceride	236	<150 mg/dl
C3	88.3	90-180 mg/dl	C4	9.2	10-40 mg/dl
Serology					
ANA 1:320	DsDNA neg	SSA/SSB neg	ANCA neg	Anti-PLA2R neg	HIV,HBV,HCV neg
SPEP negative for monoclonal gammopathy					

Table 1

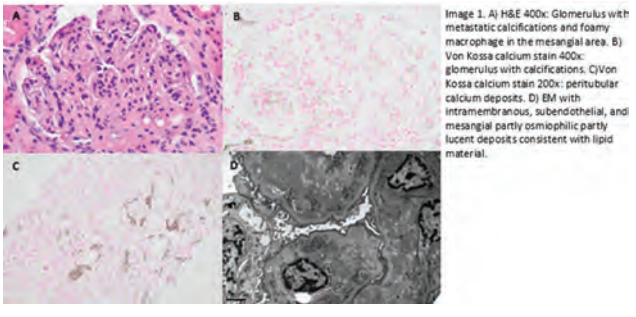

Image 1. A) H&E 400x: Glomerulus with metastatic calcifications and foamy macrophage in the mesangial area. B) Von Kossa calcium stain 400x: glomerulus with calcifications. C)Von Kossa calcium stain 200x: peritubular calcium deposits. D) EM with intramembranous, subendothelial, and mesangial partly osmiophilic partly lucent deposits consistent with lipid material.

Image 1.

TH-PO575

Mycobacterium simiae: A Rare Cause of Renal AA Amyloidosis

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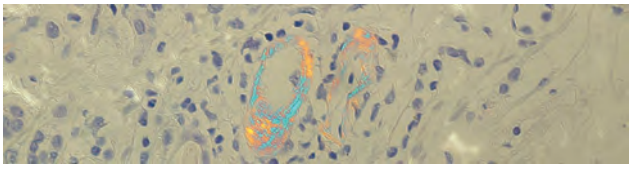
Introduction: *Mycobacterium Simiae* is a prevalent nontuberculous mycobacterium (NTM) that can become pathogenic to immunocompetent individuals with underlying lung disease. Rarely, untreated chronic NTM infections can result in AA amyloidosis.

Case Description: 74-year-old male with COPD presented with weight loss, nocturnal fever, elevated ESR and anemia. Cultures, serology tests, and GeneXpert for tuberculosis were negative. Normal FLC ratio. Borderline paraprotein detected only in serum. PET-CT showed increased uptake in upper right lung, small mediastinal and hilar lymph nodes. He was treated pneumonia. M. simiae grew in two sputum cultures after 4 weeks, repeated cultures were advised but not done. 5 months later patient presented with severe nephrotic syndrome, albumin <20 g/L and protein/creatinine ratio 20.8 g/g. Borderline paraprotein reported only in urine. Normal FLC ratio. Kidney biopsy was consistent with renal AA amyloidosis by immunostaining and lack of light chain restriction. PET CT revealed consolidations in right lower lobe and cavitations in both lower lobes. BM biopsy exposed dysplastic changes. Diagnosis of systemic AA Amyloidosis due to untreated M. simiae infection was made. He was treated with azithromycin, ciprofloxacin, cotrimoxazole but succumbed to his disease.

Discussion: NTM rarely cause amyloidosis with 5-8 years interval between NTM diagnosis and amyloidosis development after which mean survival time is 10 months. We believe that M. *simiae* caused amyloidosis in this case because of longstanding inflammation and negative extensive workup for other causes. We found only one case of AA amyloidosis associated with M. *simiae* lung infection with renal involvement but no nephrotic syndrome described. We present a rare case of nephrotic syndrome due to AA amyloidosis associated with *M. simiae* infection. Despite prolonged inflammation, M. simiae was diagnosed 5 months prior to AA amyloidosis diagnosis. Treatment was started late in the course of the disease and despite that he died within few weeks. This highlights the importance of early diagnosis and treatment of active M. *simiae* infection.



Congophilic amyloid deposits under polarized light showing apple-green birefringence

TH-PO576

Looking at ANCA Vasculitis

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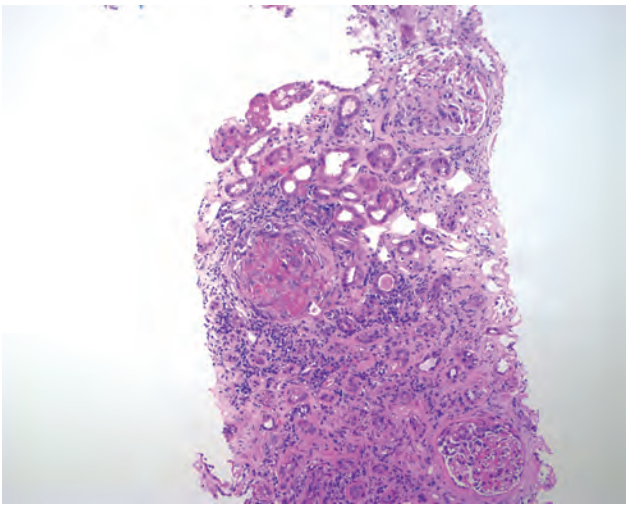
Introduction: Anti-neutrophilic cytoplasmic antibody (ANCA) associated vasculitis is a group of autoimmune diseases that can cause inflammation and damage to small blood vessels throughout the body. Inflammatory eye disease is described in 50% to 60% of patients with ANCA-positive vasculitis, and for 8% to 16% of patients, it is an initial manifestation.

Case Description: A 74-year-old man with a history of gout, chronic sinusitis, and chronic kidney disease (G3a) presented to the clinic with worsening kidney function and proteinuria without hematuria. He was seen by Ophthalmology a few months prior for scleritis and was treated with a short course of NSAIDs, with the improvement of his symptoms. The initial workup was unremarkable. Kidney biopsy showed a lesion of focal segmental sclerosis with obliteration of the capillary lumen, mild interstitial fibrosis, and tubular atrophy, immunofluorescence was negative and electron microscopy with rare small dense deposits. The patient was started on SGLT-2 inhibitors. Renal function continued to deteriorate. The patient's condition was complicated by acute bronchitis, diffuse anterior scleritis, and acute kidney injury, laboratory work was significant for positive ANCA antibodies with elevated PR3 antibodies. A repeat kidney biopsy revealed necrotizing crescentic glomerulonephritis. He was treated with IV steroids, rituximab and ultimately required dialysis.

Discussion: Renal involvement is a significant feature of ANCA vasculitis and can lead to acute kidney injury or chronic renal failure if left untreated. Clinicians should consider ANCA vasculitis in the differential diagnosis of patients presenting with scleritis, especially in those with renal dysfunction even with partial or complete resolution in ocular symptoms. Early diagnosis and treatment are essential in preventing irreversible organ damage and improving patient outcomes.



Biopsy with PAS stain showing crescent formation consistent with ANCA vasculitis

TH-PO577

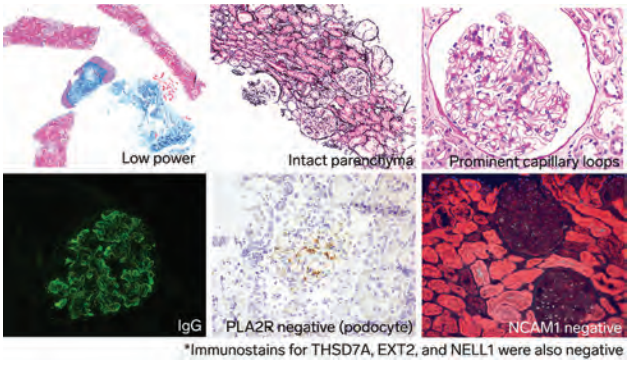
Membranous Nephropathy Associated with Alemtuzumab

Raja Ravender,[1] Chaitanya A. Pal,[1] Chandra Kumar Mallick Kodavanti,[1] Saeed K. Shaffi,[1] Darren W. Schmidt,[1] J. Pedro Teixeira,[1] Tiffany Caza,[2] Pablo Garcia.[1] UNMH/Arkana Team. *[1]The University of New Mexico, Albuquerque, NM; [2]Arkana Laboratories, Little Rock, AR.*

Introduction: Alemtuzumab is a humanized anti-CD52 monoclonal antibody approved for multiple sclerosis. We present a case of membranous nephropathy associated with alemtuzumab use.

Case Description: A 20-year-old woman with a seven-year history of multiple sclerosis was referred to nephrology due to new-onset nephrotic range proteinuria nine months after receiving her first cycle of alemtuzumab. She took no other medications. Vitals were stable with trace lower extremity edema. Spot urine protein- and albumin- to creatinine ratios were 4.63 g/g and 3481 mg/g, respectively. Serum creatinine was 0.4 mg/dL with serum albumin 2.1 g/dL. Hepatitis B and C, HIV, C3 and C4 complement, kappa/lambda ratio, anti-GBM antibody, rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibody, and anti-phospholipase A2 receptor (PLA2R) antibody were all negative. Renal biopsy revealed membranous nephropathy, with negative immunohistochemical stains for PLA2R, thrombospondin type-1 domain-containing 7A, exostosin 2, and neural epidermal growth factor-like 1. Alemtuzumab was held. Rituximab was initiated as it is effective for membranous nephropathy or multiple sclerosis, and we await the renal and neurologic response.

Discussion: Alemtuzumab depletes B and T lymphocytes and can produce side effects associated with immune reconstitution, with thyroid toxicity seen in up to 30% of patients. However, nephrotoxicity is rare (5/1485 patients, 0.3%). Mechanisms underlying kidney-related side effects from alemtuzumab use are not fully understood but may be linked to the anti-CD52 immunomodulatory effect on B and T cell lymphocytes. The autoimmune diseases observed after administering alemtuzumab are predominantly antibody-mediated and appear to respond to B-cell depletion, suggesting that rituximab may be a potentially effective therapy.



TH-PO578

Crescenteric Glomerulonephritis Leading to Diagnosis of Culture Negative Endocarditis

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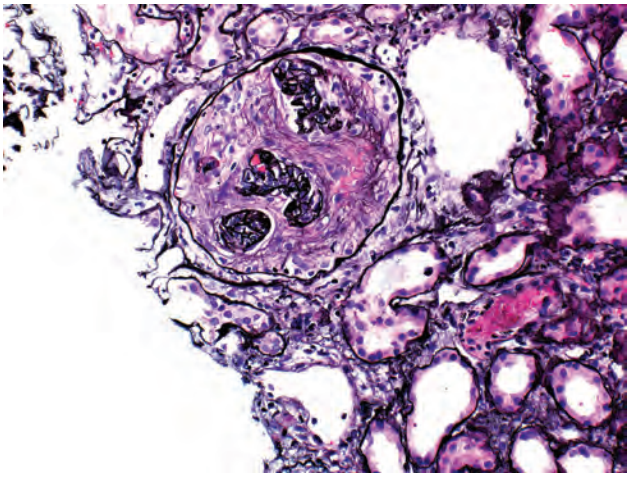
Introduction: Infective endocarditis-associated glomerulonephritis (IEAGN) as the initial presentation leading to diagnosis of afebrile, culture negative and negative serologic workup endocarditis.

Case Description: A 64-year-old male with history of CAD s/p remote CABG and hypertension presented with cough, dyspnea and worsening lower extremity edema. He was found to have a serum creatinine of 2.27mg/dL, hematuria and nephrotic range proteinuria 4.1g raising concerns for glomerular etiologies. Serologic workup showed mildly positive ANA 1:80, normal C3 and C4, ANCA, MPO, PR3, SPEP, and K/L ratio all negative, and no Bence Jones proteins. Hep B and C studies were negative. Outpatient kidney biopsy was obtained and demonstrated crescenteric glomerulonephritis on light microscopy with C3 dominant deposits on immunofluorescence favoring infection-associated glomerulonephritis and raising question for endocarditis. Patient readmitted for further inpatient workup. TEE showed evidence of vegetation on right coronary cusp. Blood culture negative. Histoplasmosis, Bartonella, and Q fever, Antistrep O, HIV, mycoplasma, and legionella were all negative. The patient was treated with six weeks of intravenous ceftriaxone followed with prednisone taper. Patient had improvement of symptoms and improvement of renal function.

Discussion: IEAGN develops as sequalae of acute or subacute endocarditis. In literature there has not been a case with acute renal injury with proteinuria and hematuria as the initial presentation of endocarditis. This case highlights the importance of renal biopsy in guidance of treatment of cresenteric glomerulitis in a case of culture negative, serology negative endocarditis.



Necrotizing cresenteric glomerulonephritis seen with Jones silver stain. Active crescents involve 55-60% of non-obsolescent glomeruli sampled for light microscopy.

TH-PO579

Truly a Catastrophe: A Case of Severe Anti-Phospholipid Syndrome in the Setting of Lupus

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Introduction: Antiphospholipid syndrome(APS) is characterized by venous or arterial thrombosis in the presence of antiphospholipid antibodies. It can occur as a primary vs secondary condition in which its associated with inflammatory disorders like systemic lupus erythematosus(SLE). APS related kidney disease can manifests itself in various ways from non-inflammatory occlusive diseases with arterial and venous thrombosis, TMA as well as glomerular diseases. Lupus can affect kidneys in the form of glomerulopathies in addition to TMA. It is important to distinguish inflammatory versus thrombotic lesions in order to ensure timely diagnosis and initiation of emergent management.

Case Description: 49-year-old female with a history of SLE not on any immunosuppression was admitted due to diarrhea and was found to have severe acute renal failure with a creatinine of 13. Serologies demonstrated low C3 and C4, Positive ANA, double-stranded DNA, cardiolipin IgG antibody, beta-2 glycoprotein IgG and c-ANCA. Duplex was negative for renal artery stenosis or renal vein thrombosis. She was initiated on hemodialysis secondary to volume overload. Anticoagulation was also initiated due to new diagnosis of bilateral upper extremity deep vein thrombosis. Kidney biopsy performed demonstrating chronic TMA in the glomeruli, negative for acute thrombi, crescents/features of lupus or a full house pattern on immunofluorescence. MR angio was also obtained in the setting of concern for APS showing complete intraluminal thrombus occlusion of aorta at the level of renal arteries down to the bifurcation, with occlusion of the right renal artery and narrowing of left renal artery. Due to concern for catastrophic APS she was promptly started on plasmapheresis and steroids. She remained

dialysis dependent and had recurrent hospitalizations for pulmonary edema secondary to hypertension, and eventually underwent aortoiliac bypass with improvment of hypertension and remained dialysis dependent.

Discussion: Renal prognosis remains poor in patients affected by SLE in the presence of aPLs and may lead to ESRD. Prompt initiation of anticoagulation, Immunosuppression and plasmapheresis remains the mainstay of treatment. Having a high index of suspicion is very important to diagnose thrombotic lesions as it affects not only kidney outcomes but also contributes to overall morbidity and mortality.

TH-PO580

Association of Preterm Birth with Adverse Outcomes of Glomerular Disease in Children and Adults in the CureGN Cohort

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Background: While some studies of children with nephrotic syndrome have demonstrated worse outcomes in those born preterm vs. term, there is little data on associations of preterm birth with kidney and cardiovascular outcomes in adult-onset glomerular disease.

Methods: We performed a cross-sectional and longitudinal survival analysis of participants in the Cure Glomerulonephropathy (CureGN) cohort with birth history data. Preterm (<37 weeks gestation) was compared to term (≥37 weeks gestation). Baseline characteristics and cardiovascular outcomes were compared using Chi-square and Mann Whitney testing. A survival analysis and adjusted Cox proportional hazards model was used to examine a composite outcome of 40% decline in estimated glomerular filtration rate (eGFR) or progression to End Stage Kidney Disease (ESKD). An adjusted logistic regression model was used to examine remission of proteinuria.

Results: More pediatric than adult participants in CureGN were born preterm: 12.8% (118/919) vs. 7.69% (117/1521) (p<0.001). Adults born preterm had a higher prevalence of Focal Segmental Glomerulosclerosis (FSGS) (35% vs. 25%, p=0.01) and *APOL1* high risk genotype (9.4% vs 4.2%, p=0.01) as compared to adults born term. Pediatric participants born preterm were more likely to have hypertension at enrollment (p=0.001). While there was no difference in eGFR at enrollment, participants born preterm had a shorter time interval to a 40% eGFR decline/developing ESKD after biopsy (p=0.001). In adjusted analysis, preterm participants were 28% more likely to develop 40% eGFR decline/ESKD (p=0.008) and 38% less likely to attain complete remission of proteinuria (p=0.006). There was no statistically significant difference in ever having hypertension or other cardiovascular events between the two groups.

Conclusions: Preterm birth was a risk factor for adverse outcomes in this heterogenous cohort of children and adults with glomerular disease. Children born preterm were more likely to have baseline hypertension while adults born preterm were more likely to have an *APOL1* high risk genotype and FSGS. Even in analyses adjusted for FSGS and *APOL1* risk status, there was a faster progression of chronic kidney disease in those born preterm. Low nephron endowment and other perinatal exposures may account for these differences.

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TH-PO581

Inpatient and Outpatient Service Review of a Greek Reference Centre for Glomerular Diseases

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Background: The glomerulonephritis (GN) is a rare and complicated disease with high demand of hospital resources while the chronic kidney disease and end-stage renal disease present increased prevalence in these patients.

Methods: We retrospectively assessed the inpatient and outpatient service for patients with GN, who have been followed-up at a Greek reference centre for GN, during the pre-Covid-19 period 2018-2020.

Results: 267 patients (median age 65±23 years) included. All patients underwent a kidney biopsy by the nephrologist without complications. ANCA associated GN (18%), Focal Segmental Glomerulosclerosis/Minimal Change Disease (17.5%), IgA nephropathy (17%), Membranous Nephropathy (12.6%), Lupus Nephritis (5%), Membranoproliferative GN (3%), Fibrillary GN (3%), Monoclonal Gammopathy of Renal Significance (3.3%) and IgG4-related disease (2%.) were encompassed. We reported median 75 new patients per year. Regarding the inpatient service, we observed an increasing trend to the hospitalizations during this period (274, 452, 461 hospitalizations in 2018, 2019, 2020 respectively). The AAV was the most common disease of hospitalizations through this period (53% in 2018, 33% in 2019, 39% in 2020), whereas the second most common was the FSGS/MCD (28% in 2018, 13% in 2019, 23.8% in 2020). The outpatient's service review also revealed an increasing number of visits per person per year (279, 456 and 464 total visits in 2018, 2019 and 2020 respectively). The disease with the highest number of visits per person was reported the AAV (median 3.25 visits per patient per year). All the patients treated in collaboration with a multidisciplinary team, consisting of nephrologist, rheumatologist, cardiologist, and pathologist. Finally, we reported complete response at 76% of the patients and in terms of renal improvement, 46% presented eGFR≥60ml/min/1.73m^2, 45% eGFR<60ml/min/1.73m^2 and only 9% progressed to ESRD after the first year of treatment.

Conclusions: The patients with GN present an increased need for hospitalization and regular outpatient visits. In addition to the medical treatment, the favourable outcome depends on a well-organized inpatient and outpatient service provided by a multidisciplinary team.

TH-PO582

Histopathology Findings and Outcomes of Non-Nephrotic Range Proteinuria in Adults and Children

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Background: While there are clinical practice recommendations for nephrotic syndrome (NS), the approach to diagnosis and management of non-nephrotic range proteinuria (NNP) is not well defined. We hypothesized that histopathologic diagnosis would differ between subjects with NNP compared to NS, and that renin-angiotensin aldosterone system (RAAS) blockers would be associated with complete or partial remission in subjects with NNP.

Methods: This is a secondary analysis of the Nephrotic Syndrome Study Network (NEPTUNE) cohort. We included adult and pediatric NEPTUNE participants who did not receive treatment for NS prior to screening, and who presented with urine protein creatinine ratio (UPCR) ≧ 0.5 g/g up to < 2 g/g in children and < 3 g/g in adults at the time of screening. A NS comparison group was identified using clinical diagnoses of NS and/or UPC ≧ 2 g/g in children and untreated adults with UPC ≧ 3 g/g at screening. Histopathologic diagnoses were compared by Chi-Square test between NNP and NS cohorts. In longitudinal analyses, we examined the associations of covariates with complete or partial remission and eGFR decline during the follow up period in NNP using generalized estimating equation.

Results: More than half of adult and children presenting with NNP were classified as overweight/obese and had high blood pressure. Subjects presenting with NNP were more likely to have FSGS than those presenting with NS [In adults, 37.1% in NNP vs 29.3 % in NS (p=0.002). In children, 41.2% in NNP vs 18.1% in NS (p<0.0001).] In those with NNP, histopathology diagnosis of FSGS (vs diagnosis of other) [OR=3.27, p=0.03] and/or high blood pressure at baseline [OR=0.51, p=0.02] predicted decrease rate of remission. In those with NNP, histopathology diagnosis of IgAN (vs FSGS) and/or overweight/obesity at baseline predicted faster eGFR decline [-8.63 ml/min/year (p=0.038), -7.04 ml/min/year (p=0.021) respectively]. While this study had a limited sample size, RAAS therapy was not statistically significantly associated with either remission or eGFR in this cohort.

Conclusions: This study supports the need for kidney biopsy in subjects presenting with NNP. Further study/clinical trials are needed to identify the effective therapies for subjects with NNP.

TH-PO583

Edema and the Risk of Thromboembolic Complications in Nephrotic Syndrome: A Cohort Study

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Background: Nephrotic syndrome (NS) is defined by severe albuminuria, hypoalbuminemia, and edema; however, the prevalence of edema with nephrotic range albuminuria and the associated risk of complications is unclear. We examined edema prevalence and the association between edema, mortality, and thromboembolic events (TE) in a cohort of NS patients.

Methods: A cohort study including patients being hospitalized or treated in outpatient clinics with a urine albumin-creatinine ratio (uACR) > 2,200 mg/g and plasma-albumin < 30 g/L in the Central Denmark Region between 2015-2022. Patients were identified from the central laboratory database by screening all recorded uACR and p-albumin measurements. We further collected demographics and outcomes and reviewed all medical records to examine if edema was present at time of NS diagnosis. Patients were followed until death or end of study.

Results: Among 806 included patients with nephrotic range albuminuria, 459 (61.4%) had edema at time of diagnosis. A total of 34 (4.2%) arterial TE (ATE) and 23 (2.6%) venous TE (VTE) were observed during follow-up (Table 1). Patients with edema

had a lower incidence rate of ATE compared to those without edema (10 vs 28 per 1000 person-years), while the incidence rate of VTE did not differ between groups. All-cause one-year mortality was higher in the edema group (33.7% vs 25.7%).

Conclusions: Edema was prevalent at the time of diagnosis and was associated with an increased all-cause one-year mortality despite lower risk of ATE. Additional analyses are needed to explore this association and to determine the prognostic relevance of edema in the diagnosis of NS.

Funding: Private Foundation Support

Table 1. Characteristics of patients with nephrotic range albuminuria with and without edema at diagnosis.

	All patients (n=806)	Edema (n=495)	Non-edema (n=311)
Male, n (%)	478 (59.3)	284 (57.4)	194 (62.4)
Age, yr. median (IQR*)	65.4 (52.7-74.8)	66.1 (54.3-75.5)	64.7 (48.2-74.6)
Family history of cardiovascular disease, n (%)			
Arterial thrombosis	146 (18.1)	104 (21.0)	42 (13.5)
Venous thrombosis	13 (1.6)	7 (1.4)	6 (1.9)
History of smoking and Alcohol, n (%)			
Ever smoked	518 (64.3)	317 (64.0)	201 (64.6)
>7/14 units per week	58 (7.2)	42 (8.5)	16 (5.1)
Comorbidities, n (%)			
Diabetes	264 (32.8)	170 (34.3)	94 (30.2)
Hypertension	275 (34.1)	169 (34.1)	106 (34.1)
Hypercholesterolemia	86 (10.7)	58 (11.7)	28 (9.0)
Congestive heart failure	65 (8.1)	45 (9.1)	20 (6.4)
Atrial fibrillation/Atrial flutter	80 (9.9)	51 (10.3)	29 (9.3)
Liver disease	20 (2.5)	17 (3.4)	3 (1.0)
Non-Hematological cancer	76 (9.4)	53 (10.7)	23 (7.4)
Hematological cancer	31 (3.8)	20 (4.0)	11 (3.5)
Previous ATE	81 (10.0)	44 (8.9)	37 (1.9)
Previous VTE	27 (3.3)	17 (3.4)	10 (3.2)
Renal biopsy, n (%)			
Minimal Change Disease	52 (6.5)	33 (6.7)	19 (6.1)
Focal segmental glomerulosclerosis	20 (2.5)	12 (2.4)	8 (2.6)
Membranous nephropathy	53 (6.6)	35 (7.1)	18 (5.8)
Mesangial proliferative GN	29 (3.6)	13 (2.6)	16 (5.1)
Membranoproliferative GN	10 (1.2)	10 (2.0)	0 (0)
Biochemical characteristics, median (IQR)			
eGFR** (mL/min/1.73m^2)	34 (17-65)	34 (16-62)	34 (18-70)
Plasma-Albumin (g/L)	27 (24-29)	27 (23-29)	28 (25-29)
uACR*** (mg/g)	3778 (2688-5300)	3996 (2925-5524)	3372 (2512-4896
Medication, n (%)			
Direct Oral Anticoagulant Drugs	56 (6.9)	35 (7.1)	19 (6.1)
Warfarin	54 (6.7)	36 (7.3)	18 (5.8)
Antiplatelet drugs	232 (28.8)	142 (28.7)	90 (28.9)
Angiotensin-converting enzyme inhibitor	207 (25.7)	129 (26.1)	78 (25.1)
Angiotensin II receptor blocker	200 (24.8)	126 (25.1)	74 (23.8)
Diuretics	345 (42.8)	220 (44.4)	125 (40.2)
Thromboembolic events after inclusion, n (%)			
Arterial Thromboembolic Event	34 (4.2)	12 (2.4)	22 (7.1)
ATE Incidence Rate per 1,000 person-yr. (95% CI)	17 (12-24)	10 (6-18)	28 (18-42)
Venous Thromboembolic Event	23 (2.6)	15 (3.0)	8 (2.6)
VTE Incidence Rate per 1,000 person-yr. (95% CI)	12 (8-17)	13 (8-21)	10 (5-20)
Follow up			
Median follow-up time, months (IQR)	23.9 (10.1-46.5)	22.5 (8.7-46.0)	25.7 (11.9-48.8)
All-cause one-year mortality	232 (28.8)	152 (33.7)	80 (25.7)

*IQR: Interquartile range
**eGFR: estimated Glomerular Filtration Rate
***uACR: urine Albumin-Creatinine Ratio

TH-PO584

Corticosteroid Dose and Risk of Infection in Children and Adults with Glomerular Disease: An Analysis of the CureGN Study

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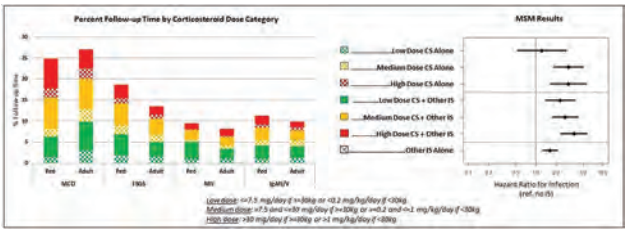
Background: Corticosteroid (CS) exposure is associated with risk of infection leading to increased morbidity and mortality in patients with glomerular disease (GD). We describe longitudinal CS exposure and measure its association with risk of infection in the Cure Glomerulonephropathy (CureGN) study.

Methods: CureGN is a prospective cohort study of patients with biopsy-proven primary GD. CS dose and duration were abstracted from participant medical records at interval study visits and harmonized to prednisone (oral) and methylprednisolone (IV) dose equivalents. Marginal structural models (MSM) were used to estimate effects of CS dose (see Figure), with or without other IS exposure, on hazards of first infection-related hospitalization or ED visit, adjusting for baseline age, race, sex, ethnicity, GD subtype, comorbid conditions, and time-varying markers of disease activity [eGFR, UPCR, and serum albumin].

Results: Of 2568 participants (43% female, 35% <18 years), 446 (17%) experienced a first infection over a median follow-up of 58 months (IQR 32-77). Children and adults were exposed to CS for 14% and 9% of their follow-up time, respectively. Median daily exposure to oral and intravenous CS was 13 mg (IQR 5-32) and 65 mg (IQR 40-500) in children and 10 mg (IQR 5-22) and 125 mg (IQR 125-125) in adults. In a multivariable MSM model, low, medium, and high dose CS exposure was associated with 1.22 (95% CI 0.53-2.84), 3.06 (95% CI 1.84-5.10), and 3.03 (95% CI 1.64-5.59) times higher hazards of infection without concurrent IS, and 2.30 (95% CI 1.40-3.77), 2.71 (95% CI 1.75-4.21), and 3.66 (95% CI 2.35-5.71) times higher hazards of infection with concurrent IS, compared to no IS exposure.

Conclusions: Medium and high dose CS independently increase risk of infection when used alone. When used in combination with other IS, all doses of CS increase risk of infection. These results can inform clinical care and highlight the importance of CS sparing medication regimens for patients with GD.

Funding: NIDDK Support, Other NIH Support - NIAID



TH-PO585

Influenza Vaccine Administration and Effectiveness Among Patients with Glomerular Disease

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Background: Influenza contributes to excess healthcare utilization and morbidity in individuals with glomerular disease (GD). Immune responses to influenza vaccination in individuals with GD may be attenuated by immune dysregulation and immunosuppressant use. We evaluated the effectiveness of influenza vaccination among patients with GD.

Methods: Individuals with primary GD were identified within the Merative MarketScan Claims & Encounters database and followed across annual influenza seasons until disenrollment or 2020. Influenza vaccination, influenza and influenza-like infections, and covariates were ascertained using ICD-9/10-CM-based definitions from medical and prescription claims. Influenza seasons (2010-2019) were analyzed individually by comparing the incidence rates of infection in vaccinated and unvaccinated individuals. Propensity score weighting was used to balance the distribution of potential confounders across vaccination status. Cox proportional hazards models were used to estimate vaccine effectiveness (VE=1-hazard ratio). We then compared years with a close match between vaccine composition and circulating influenza strains (2010-2013, 2015-2018), with a mismatched "control" season (2014). We used a weighted Cox model with an interaction term between vaccination status and vaccine match grouping to estimate the relative VE in matched vs. mismatched seasons.

Results: 46,010 influenza person-seasons were analyzed from 17,219 individuals (mean age 45 years (SD 17), 43% female), including 10,535 and 35,475 person-seasons from vaccinated and unvaccinated individuals, respectively. The mean proportion of individuals vaccinated per season was 23% (range 19-25%). VE estimates for individual seasons ranged from -74 to 66% for influenza and -58 to 29% for influenza-like infection. In the pooled analysis comparing matched vs. mismatched seasons, vaccination was modestly protective for both influenza (VE 17%, 95% CI -38 to 50) and influenza-like infection (VE 14%, 95% CI -24 to 41%).

Conclusions: Rates of influenza vaccination are suboptimal among patients with GD. Despite potential confounding by indication and uncaptured vaccinations and infections, these data suggest that protection from influenza after vaccination may be poor, leading to excess infection-related morbidity in this vulnerable population.

Funding: Other NIH Support - NIAID

TH-PO586

Patterns of Disease Progression Among Children and Adults with IgA Nephropathy/Vasculitis in CureGN

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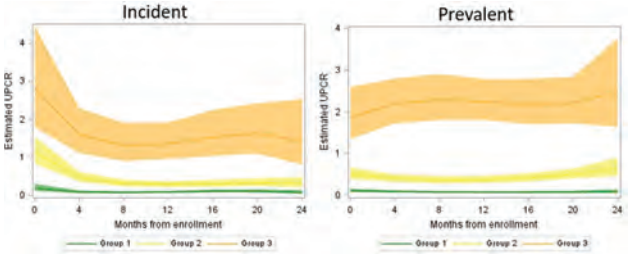
Background: IgA nephropathy (IgAN) is the most common glomerular disease world-wide. Identifying demographic and clinical characteristics that place patients at increased risk for disease progression is critical for optimizing therapeutic interventions and targeting clinical trials.

Methods: CureGN is a multi-center cohort study of children and adults with biopsy-proven glomerular disease, including 823 patients with IgA nephropathy/vasculitis with nephritis (IgAN/IgAVN). We used latent class analysis to segregate 316 incident and prevalent patients, with at least 4 UPCR measurements within the first 2 years of their follow-up, into 3 groups based on longitudinal UPCR trajectories over 2 years. Using Cox proportional hazard models, we then modeled disease progression, defined as the composite outcome of 40% eGFR decline or kidney failure (initiation of dialysis, transplant, or 2 eGFRs <15ml/min/1.73m^2), as a function of UPCR trajectory group while adjusting for age, eGFR at enrollment, use of immunosuppression, RAAS blockade, and IgAN/IgAVN status.

Results: 149 incident and 167 prevalent patients (enrolled <6 months and > 6 months from biopsy (max 5 years), respectively) were followed for a median of 6.1 (IQR 4.5,6.9) years. Three groups were identified based on UPCR trajectories (Figure). Among incident patients, those with the highest UPCR (group 3) demonstrated faster eGFR decline (median (IQR) decline -4.0 (-7.3,-0.1) ml/min/1.73m^2/year compared to +1.3 (-2.0,+3.1) in group 1 and -0.9 (-3.9,+1.7) in group 2) and had 5.4-times higher hazard of progressing to the composite outcome compared to Groups 1+2 combined (p=0.0016). Among prevalent patients, those with the highest UPCR (Group 3) had 3.9-times higher hazard of progressing to the composite outcome (p=0.0049). No association between immunosuppression use and the composite outcome was detected.

Conclusions: In both incident and prevalent IgAN/IgAVN cohorts proteinuria trajectories define patients into distinct clinical groups and are a strong independent predictor of disease progression.

Funding: NIDDK Support



TH-PO587

Frequency and Risk Factors for Glucocorticoid-Induced Diabetes Mellitus: The Japan Nephrotic Syndrome Cohort Study

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Background: Glucocorticoid (GC)-induced diabetes mellitus (GIDM) is one of the major complications of glucocorticoid treatments. The study aims is to examine the incidence and risk factors for GIDM among patients (pts) with primary nephrotic syndrome in Japan.

Methods: We conducted a *post-hoc* analysis of the Japanese Syndrome Cohort Study (JNSCS), a nationwide prospective study of primary nephrotic syndrome. 374 pts who received renal biopsy between 2009 to 2010 were enrolled in JNSCS. After excluding 151 pts (no data for baseline HbA1c, no GC use, and already diabetes at baseline), 223 pts (104 male) were included. GIDM was defined when pts started diabetes medication within 6 months of GC treatment.

Results: Baseline clinical data were as follows: mean age 54.6±20.0 years, mean body mass index 23.4±3.6, eGFR 65.6±37.2 ml/min/1.73m^2, and HbA1c 5.2±0.4%. GIDM was developed in 50 pts (22.4%) in 223 total pts, 14 pts (14.2%) in 98 minimal change diseases pts, 27 pts (30.3%) in 89 membranous nephropathy pts, 9 (33,3%) in 27 focal segmental glomerulosclerosis pts, and 0 pts (0%) in 9 other diseases pts. Multiple logistic regression analysis revealed age≥65 years and HbA1c≥5.6% before treatment are risk factors for the development of GIDM (Figure). Among 43 GIDM pts whose data were available, 15 pts (34.9%) discontinued diabetes medications within 2 years. There were no significant differences for adverse events (death, infections, vascular thrombosis, cardiovascular) and renal outcomes (complete remission, relapse, renal function deterioration) between patients with or without GIDM during 2 years after treatment.

Conclusions: About 20% of patients developed GIDM during the treatment of primary nephrotic syndrome in Japan. Older age and higher HbA1c levels at baseline are the risk factors for GIDM. One-third of GIDM patients could discontinue diabetes medications during 2 years after treatment.

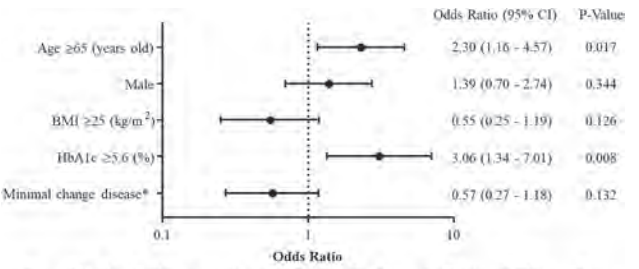

Figure 1 Results of multivariate analysis on risk factors for glucocorticoid-induced diabetes mellitus

* vs. other renal diseases (membranous nephropathy, focal segmental glomerulosclerosis, etc)

TH-PO588

Mood Changes Associated with High-Dose Corticosteroids in Adults with Glomerular Disease

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Background: Glomerulonephritis (GN) can be caused by a variety of underlying conditions, many of which are treated with high dose corticosteroids. There is a paucity of knowledge regarding the frequency, severity, and predictors of neuropsychiatric toxicity from high-dose corticosteroids in adults with glomerular diseases.

Methods: We conducted a prospective, survey-based study of adults with newly diagnosed or relapsing biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy (IgAN), and membranous nephropathy (MN). Institutional ethical approval was granted. Three identical questionnaires were provided for self-completion at enrolment, 2- & 12-weeks post-enrolment. The questionnaire was adapted from two existing surveys, developed and validated to measure mania (Altman Self-Rating Mania Scale) and depression (Patient Health Questionnaire – 9).

Results: 30 patients were enrolled. Biopsy diagnoses included: MN (10), MCD (9), FSGS (4) and IgAN (7). 60% (18) were new diagnoses. 43% (13) had a prior psychiatric diagnosis (depression (8), anxiety (4), post traumatic stress disorder (1)) The median age was 54 years. There was no significant difference between groups in proteinuria or GFR at baseline level, however serum albumin was lower in the steroid treated group (25g/L vs 32g/L). 47% (14) of participants received corticosteroids, while the remainder(non-exposed: n=16) received no form of immunosuppressive therapy during their 12-weeks of enrolment. *Mania:* ASRM scores at 2-weeks were significantly higher in the corticosteroid-exposed group compared to the immunosuppressant-naïve control group (p <0.001). Patients treated with corticosteroids experienced a mean ASRM score increase from baseline of 9 (standard deviation = 4.2) at 2-weeks, whereas their non-exposed counterparts experienced a negligible change. *Depression:* A significant between-group difference in PHQ-9 (depression) scores at 12-weeks was observed with the corticosteroid group recording higher scores (p < 0.001).

Conclusions: Patients with glomerular disease treated with corticosteroids experienced significant increases in mania scores at early stages of their treatment course, while depression predominated at later stages of treatment course.

Funding: Clinical Revenue Support

TH-PO589

Humanization and Telehealth for Improving Patient-Reported Outcomes in Glomerular Diseases: The Human-C Project

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Background: Glomerular diseases (GD) encompass rare diseases that predominantly affect young and working-age individuals, often requiring off-label therapies. These conditions necessitate personalized and ongoing monitoring, which can impact patients' quality of life (QoL). The implementation of telehealth should be tailored to individual patient profiles, while nurse coaching support can identify patients' personal and occupational needs, and reinforce effective communication. This study reports the outcomes of implementing telehealth and nurse coaching support (Humanization Coaching Project: Human-C Project) in a glomerular disease unit.

Methods: Objective: Evaluate the effect of the Human-C Project on patient-reported outcomes (PROMs) and patient-reported experience measures (PREMs) in GD patients, including during the COVID-19 pandemic. Telehealth via WhatsApp and nurse coaching support were introduced in November 2019, incorporating virtual visits. A nurse conducted interviews using Promis-29 and SF-36 questionnaires. In February 2023, an online survey with 15 items (including questions from Promis-29, SF-36, and nurse coaching) was administered to 233 patients.

Results: In 2019, 2,432 visits were recorded, reducing by 7% in 2020 (2,251 visits), with 37% being virtual. Eighty-nine patients responded to the questionnaire. The questionnaire covered domains such as employment status, disease knowledge, social

function, psychological health, medical appointments, and therapy preferences. Key findings included: working-age patients (87%), inadequate disease knowledge (16%), fatigue (53%), sleep issues (50%), dissatisfaction with work performance (40%), and reduced activity due to emotional problems (34%). Following the Human-C Project, 85% reported adequate healthcare team access during the pandemic, and 72% reported improved QoL.

Conclusions: Glomerular disease patients face QoL challenges, but the Human-C Project, along with telehealth, provides specific care perspectives and improves QoL. These findings have important implications for healthcare systems, even in crises like the COVID-19 pandemic.

TH-PO590

Adverse Educational Outcomes in Glomerular Disease

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Background: Research on kidney disease's cognitive impacts in youth has largely focused on CAKUT patients due to the extent of brain development in the first 5 years of life. Our prior research found decreased high school diploma/GED attainment in those with adolescent Glomerular Disease (GD) onset. However, school impacts range beyond diploma attainment. No studies have analyzed the likelihood of patients with renal disease onset solely after age 5 reporting any adverse educational impact. Objective: Determine the prevalence of any educational impact on GD patients diagnosed between ages 5-19 and which factors might contribute.

Methods: CureGN prospective cohort study participants with Minimal Change Disease(MCD), Focal Segmental Glomerulosclerosis(FSGS), Membranous Nephropathy(MN), or IgA Nephropathy(IgAN) diagnosed between ages 5-19(n= 817) were included in the analysis, with the outcome defined as any self reported educational impact. Odds ratios(OR) based on General Estimating Equations were used to determine predictors of educational impact. Predictors of interest included race-ethnicity, child (5-12) vs adolescents (13-19) GD onset, parental education, adherence, APOL1 high risk allele, disease type, sex, and number of coexisting conditions.

Results: 43%(348/817) reported GD ever impacted their education. Table 1 shows OR of the educational impact of predictors.

Conclusions: GD impacts a high percent of patients' educations, even with onset after age 5. Having coexisting conditions and Black race(reference White) increased the likelihood while IgAN(reference MCD) decreased the likelihood of reporting an educational impact. The racial disparity in educational outcomes and the underlying causes of GD's adverse educational outcomes warrant more research.

Variable	OR (CI)	p-value
Onset Age (reference: 13-19)		
5-12	1.18 (0.88,1.58)	0.2783
Ethnicity (reference: not Hispanic)		
Hispanic	1.24 (0.81,1.90)	0.3157
Race (reference: White)		
Black	**1.66 (1.10,2.49)**	0.0148
Other	1.05 (0.69,1.59)	0.8117
Maternal education (reference: High School diploma/GED)		
Less than High School	0.81 (0.50,1.31)	0.3928
2 or 4 year degree	0.88 (0.64,1.20)	0.4156
Graduate Degree	0.67 (0.39,1.16)	0.1535
BMI category at diagnosis (reference: healthy weight)		
Underweight	2.09 (0.78,5.61)	0.1452
Overweight	1.16 (0.82,1.66)	0.3975
Obese	1.07 (0.77,1.49)	0.6908
Glomerular Disease Diagnosis (reference: MCD)		
FSGS	0.93 (0.65,1.34)	0.6931
IgAN	**0.51 (0.35,0.74)**	0.0004
MN	0.85 (0.46,1.57)	0.6098
Medication Adherence (reference: non-adherent)		
Adherent	0.72 (0.33,1.56)	0.4006
Number of coexisting conditions (reference: no coexisting conditions)		
At least 1 coexisting conditions	**2.16 (1.54,3.02)**	<0.0001
APOL1 risk (Reference: Low risk)		
High Risk	1.09 (0.57,2.09)	0.8036
Unknown Risk	1.16 (0.86,1.56)	0.3457

TH-PO591

Assessment of Medication Adherence Among Adults with Glomerular Disease

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Background: Patients with glomerular disease (GD) face challenges taking complex and potentially toxic medication regimens. This study assessed medication adherence in adults with GD and associations with demographic, socioeconomic and disease-related factors.

Methods: CureGN is a multinational prospective cohort study of prevalent patients with biopsy proven GD. Nonadherence is assessed at enrollment and follow-up visits. We compared patient and disease characteristics at enrollment and probability of nonadherence during follow-up across self-reported racial and ethnic groups. We used multivariable mixed effects logistic regression models to explore associations between race and ethnicity and odds of nonadherence, serially adjusting for potential confounders.

Results: In 1,550 adults with GD (66% White, 15% Black, 10% Asian, 9% Hispanic, 56% male, median age 42 years; 64% privately insured (US); at enrollment, median estimated glomerular filtration rate 73.2mL/min/1.73m2, median urine protein-to-creatinine 1.5g/g), 914 (59%) reported at least one non-adherence response over a median 53 (28, 72) months follow-up time where a median 4 (2, 6) surveys were completed. Odds of non-adherence were higher for Black vs. White adults (OR 1.70, 95% CI 1.24-2.33), for public insurance (US) (OR 1.45, 95% CI 1.06-1.98), and for moderate or greater edema (OR 1.45, 95% CI 1.13-1.86). While forgetfulness was the most common stated reason for medication non-adherence (60%), Black adults were most likely to cite side effects (23% for Black adults vs 17% for overall cohort), cost (7% vs 3%), and feeling well (12% vs 8%) as reasons for non-adherence.

Conclusions: Non-adherence to medication is common in adults with GD. Black compared to White adults had higher odds of non-adherence, with side effects, cost, and feeling well all more commonly indicated as reasons. Interventions to target these reasons across racial and ethnic groups may help improve medication adherence.

Funding: NIDDK Support

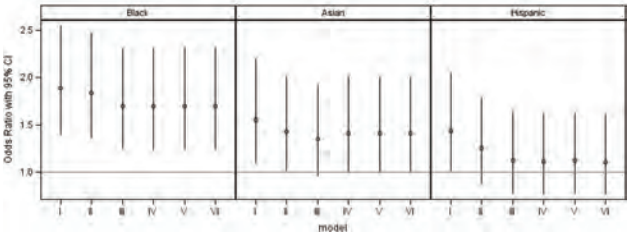

Figure: Odds ratios with 95% CI bars compared to White adults with sequential adjustment for confounders

TH-PO592

A New Mexico-Based Kidney Biopsy Registry Data Analysis

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Background: The frequency of biopsy-proven renal parenchymal diseases in the U.S. Southwest is unknown which is summarized in this study.

Methods: The University of New Mexico Kidney biopsy registry is a data repository from 2002 to 2019. We abstracted the primary diagnoses from the biopsy report with natural language processing and reviewed them to ensure data accuracy. We reported the initial primary diagnosis if the subsequent diagnoses were congruent in patients with multiple biopsies. Continuous and categorical data were reported as median (IQR) and n (%). We plotted time trends for each diagnosis.

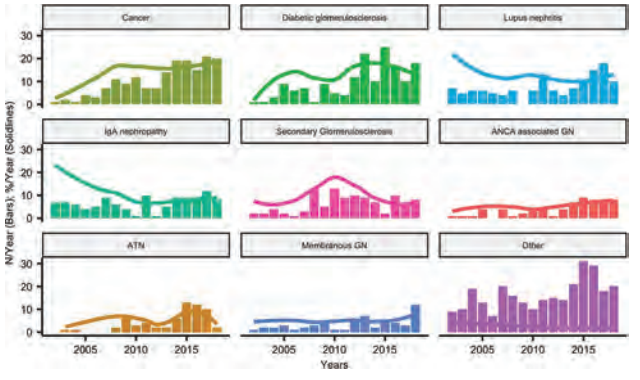
Results: Of the 1204 unique native kidney biopsies, cancer and diabetic glomerulosclerosis were the most frequent diagnoses (Figure 1). The majority self-identified as Hispanic or American Indian. Biopsy frequency increased with time. Patients with cancer were the oldest at the time of biopsy while those with lupus nephritis were the youngest ($p < 0.001$). A higher frequency of cancer and diabetic glomerulosclerosis was noted with time (Figure 2).

Conclusions: We used natural language processing to analyze kidney biopsy registry data in a predominantly Hispanic or American Indian cohort and identified disease frequency. This registry will facilitate the study of renal parenchymal disease's natural history and outcomes.

	N = 1,204[1]
Primary Diagnosis	
Other	287 (24%)
Cancer	179 (15%)
Diabetic glomerulosclerosis	179 (15%)
Lupus nephritis	131 (11%)
IgA nephropathy	120 (10.0%)
Secondary glomerulosclerosis	107 (8.9%)
ANCA associated GN	73 (6.1%)
Acute tubular necrosis	68 (5.6%)
Membranous GN	60 (5.0%)
Age at Biopsy (Years)	48 (27, 61)
Ethnicity & Race	
Hispanic/Latino	550 (46%)
Non-Hispanic-White	215 (18%)
American Indian	202 (17%)
Other	106 (8.8%)
Unknown-White	86 (7.1%)
Unavailable	45 (3.7%)

[1] n (%); Median (IQR)

Demographic and clinical data at biopsy



Yearly N (Bars) and % (LOESS smoothed solidlines) of biopsies stratified on the primary diagnosis

TH-PO593

Development of a Patient-Reported Outcome for Older Children and Adults with Nephrotic Syndrome as Part of "Preparing a Clinical Outcomes Set for Nephrotic Syndrome" (Prepare-NS)

Eloise Salmon,[1] Kayla Sifre,[1] Courtney N. Hurt,[2] Rebecca Scherr,[1] Patrick H. Nachman,[4] David T. Selewski,[3] Noelle E. Carlozzi,[1] Jin-Shei Lai,[2] John D. Peipert.[2] *[1]University of Michigan, Ann Arbor, MI; [2]Northwestern University Feinberg School of Medicine, Chicago, IL; [3]Medical University of South Carolina, Charleston, SC; [4]University of Minnesota Twin Cities School of Medicine, Minneapolis, MN.*

Background: Individuals with nephrotic syndrome (NS) experience fluid overload (FO) which can impact health-related quality of life (HRQOL). In partnership with the Food and Drug Administration (FDA), Prepare-NS aims to create and validate clinical outcome assessments (COAs) of FO in NS for use in drug development.

Methods: Context of use includes the following NS diagnoses: FSGS, minimal change disease, childhood-onset (not biopsied), membranous nephropathy, and IgM nephropathy. Participants with swelling in the past 90 days and not on dialysis volunteered via study website to complete an interview and consent (parental for participants under 18) was obtained. Concept elicitation interviews occurred via Zoom or phone and discussed how NS impacts functioning. Interview transcripts were coded in NVivo by two independent raters according to established standards for qualitative analysis. Recurring themes informed the conceptual model.

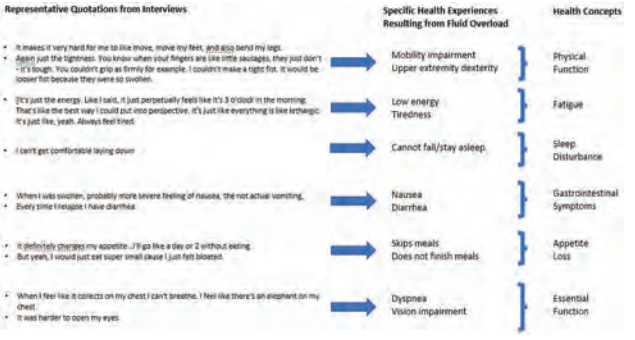
Results: To date, 25 participants have completed interviews. Image 1 shows participant demographics. Themes overall were consistent among age, sex, race, and diagnostic subgroups. Image 2 shows the conceptual model.

Conclusions: FO impacts HRQOL in the domains of physical function, fatigue, pain, sleep disturbance, gastrointestinal symptoms, appetite loss, and other essential functions. The next phase of Prepare-NS will be to develop the PRO inclusive of items to assess the impact of FO that is likely to be modifiable in NS disease modifying drug development.

Funding: Other U.S. Government Support

Variable	FSGS (n = 9)	MCD (n = 8)	Childhood [not biopsied] (n=1)	MN (n=6)	IgM (n=1)	Combined (N = 25)
Age - n (%)						
Child (<18)	2 (22)	2 (25)	1 (100)	0	0	5 (20)
Adult (≥18)	7 (78)	6 (75)	0	6 (100)	1 (100)	20 (80)
Female - n (%)	7 (78)	5 (63)	0	5 (83)	1 (100)	18 (72)
Race - n (%)						
Caucasian	7 (78)	6 (75)	1 (100)	4 (67)	1 (100)	19 (76)
African American	1 (11)	0	0	1 (17)	0	2 (8)
American Indian	0	0	0	0	0	0
Asian	1 (11)	2 (25)	0	1 (17)	0	4 (16)
Hispanic - n (%)	0	2 (29)	0	2 (40)	0	4 (16)
Days since most recent swelling episode	4.3	19.2	0	11.2	15	9.9

Participant demographics



Health concepts (with representative quotations) elicited during qualitative interviews on the impact of FO in NS

TH-PO594

Patterns of Acute Care Utilization and Health-Related Quality of Life in Primary Glomerulonephropathy Patients

Chien-Wen Yang,[1] Qian Liu,[2] Dorey A. Glenn,[3] Michelle Denburg,[4] Jarcy Zee.[1,2] *[1]University of Pennsylvania, Philadelphia, PA; [2]The Children's Hospital of Philadelphia Research Institute, Philadelphia, PA; [3]The University of North Carolina at Chapel Hill School of Medicine, Chapel Hill, NC; [4]The Children's Hospital of Philadelphia, Philadelphia, PA.*

Background: The relationship between acute care utilization and health-related quality of life (HRQOL) in patients with GN is unclear. We hypothesize that the number of acute care events (ACE) will be associated with worse HRQOL among adults and children in CureGN.

Methods: CureGN is a prospective observational cohort of primary GN including minimal change disease, IgA nephropathy/vasculitis, focal segmental glomerulosclerosis, and membranous nephropathy. Linear mixed effect models were used to explore the association between HRQOL and the number of ACE (hospitalizations and emergency room visits) within the prior 3 months. HRQOL was self-reported for adults and children ≥8 years old and reported by parent proxy for children <11 using the PROMIS instrument. Models were adjusted for potential confounders, including HRQOL measures before the 3-month ACE period, comorbidities, socioeconomic factors, and medication exposure.

Results: Among 2393 patients, 1282 experienced at least one ACE with an incidence of 75 events per 100 person-years. Infection, gastrointestinal and cardiovascular events were the most common diagnoses (15, 9, and 6 events per 100 person-years, respectively). Among adults and children ≥8, a greater number of ACE was associated with worse fatigue ($p<0.001$), general physical health ($p<0.001$), mobility ($p=0.001$), and global health ($p=0.005$). Among proxy-reported PROMIS measures, a greater number of ACE was associated with worse fatigue ($p=0.001$), mobility ($p<0.001$), and global health ($p<0.001$).

Conclusions: Having more ACE was associated with worse HRQOL in several physical health domains among patients with GN. Our study reinforces the healthcare burden of GN and helps identify risk factors for deterioration in the patient experience.

Funding: Other NIH Support - pharmacoepidemiology T32

Table. A Summary Table of the Association Between Number of 3-Month Acute Care Events and Each Domain of PROMIS Scores.

PROMIS Domain	β Coefficient (95%CI)	p value
Self-reported		
Anxiety	0.11 (-0.35, 0.57)	0.629
Fatigue	1.09 (0.51, 1.67)	<0.001
Sleep impairment	-0.09 (-0.77, 0.58)	0.790
General mental health	-0.42 (-1.02, 0.18)	0.168
General physical health	-1.24 (-1.81, 0.68)	<0.001
Mobility	-1.73 (-2.72, 0.75)	0.001
Global health	-1.52 (-2.58, -0.45)	0.005
Proxy-reported		
Fatigue	1.81 (0.76, 2.86)	0.001
Mobility	-1.64 (-2.38, -0.90)	<0.001
Global health	-1.85 (-2.82, -0.88)	<0.001

*The coefficient represents the change in the PROMIS score for each one count increase in ACE.
*Adjusted for age, sex, level of education, insurance type, country of residence, time from biopsy to enrollment, prior PROMIS scores, years from time of biopsy, student-employment status, number of comorbidities, edema status, weight status, eGFR, urine protein creatinine ratio, serum albumin and immunosuppressant exposures.

TH-PO595

Health-Related Quality of Life (HRQoL) in Adults with Primary Glomerular Diseases in India

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Background: There is paucity of information about the health-related quality of life (HRQOL) of patients with glomerular diseases.

Methods: We used PROMIS 29 v2.1 (Patient-Reported Outcomes Measurement Information System) tool to assess the HRQoL impact of primary glomerular diseases in adult patients, under the following domains: physical function, anxiety, fatigue, depression, sleep disturbance, ability to participate in social roles and activities, and pain interference in daily activities. A composite score representing the patient's global HRQoL was calculated using T scores (mean=50, standard deviation=10) of individual domains derived from patient responses. Multivariable linear regression models were evaluated for all domains and composite scores independently.

Results: 301 patients were recruited (100 minimal change disease/focal segmental glomerulosclerosis, 75 membranous nephropathy, 109 IgA nephropathy, and 17 membrano-proliferative glomerulonephritis). Mean T-scores were: physical function - 48 (47.6-49.9), fatigue - 48.7 (47.6-49.9), anxiety - 51.4 (50.3-52.6), sleep impairment - 44 (42.9-45), depression - 50.1 (49-51.2), ability to participate in social roles and activities - 55.6 (54.5-56.7), hindrance in daily activities due to pain - 51 (50-52). Worse physical function was significantly associated with female sex (β=3.28), low eGFR (<60ml/min/1.73m^2) (β=2.45), unemployed status (β=2.12), obesity (BMI>30) (β=4.4), and edema (β=2.71); fatigue with female sex (β=4.9), low eGFR (β=3.51) and obesity (β=7.41); anxiety with recent steroid use (β=2.61), female sex (β=3.74), and low eGFR (β=2.74) and sleep impairment with recent steroid use (β=3.46), female sex (β=2.56), lower eGFR (β=3.37) and edema (β=4.02). Depression was higher with obesity (β=5.0) and low eGFR (β=2.4) and pain interference with female gender (β=5.95), low eGFR (β=2.38), and obesity (β=4.0). Decreased ability to perform social roles was seen in females (β=4.6), and obese individuals (β=2.58). Lower composite scores (worse global quality of life) were associated with female sex (β= 3.65), lower eGFR (β= 3.14), and obesity (β=4.02).

Conclusions: Glomerular diseases adversely impact quality of life. Female sex, lower renal function, obesity, clinically apparent edema, and recent steroid use correlate with higher morbidity.

TH-PO596

Association Between Social Vulnerability, Environmental Burden, and Kidney Outcomes Among Individuals with Glomerular Disease: Results from the Cure Glomerulopathy Network (CureGN)

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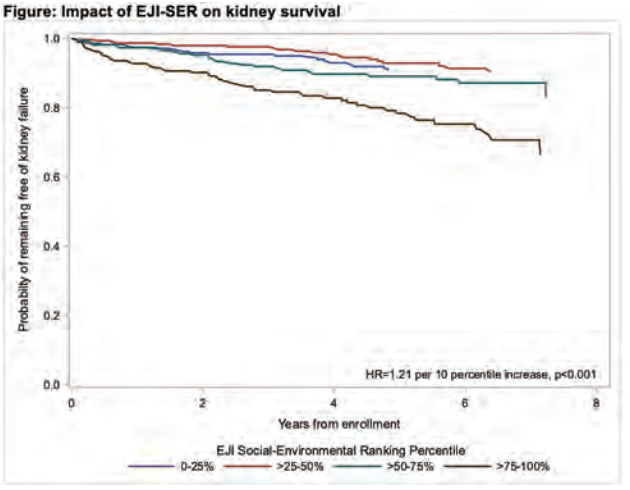
Background: The CDC Environmental Justice Index Social-Environmental Ranking (EJI-SER) combines a Social Vulnerability Module (SV) with an Environmental Burden Module (EB) to characterize cumulative environmental and social burden at the census tract level. With this analysis, we evaluate the association between EJI-SER and kidney outcomes in patients with glomerular disease (GD).

Methods: CureGN is an observational cohort study of adults and children with biopsy-proven GD. EJI-SER is percentile ranking by census tract, with higher score indicating more severe SV and EB burden. Associations between EJI-SER and its components with kidney failure (initiation of kidney replacement therapy, transplant, or 2 eGFRs <15ml/min/1.73m^2) and longitudinal eGFR were tested using multivariable Cox regression and linear mixed models, respectively, adjusted for demographics, histologic diagnosis, eGFR and urine protein to creatinine ratio at enrollment, and time from biopsy to enrollment.

Results: Among 1,131 participants with census tract data, median follow-up was 5.1 years (IQR 3.0-6.6) and median age at biopsy was 24 with 5% Asian, 18% Black, and 70% White. Median EJI-SER was 0.49 (IQR 0.26-0.75). EJI-SER was associated with higher hazard of kidney failure (adjusted HR 1.12 per 10 percentile increase [95% CI, 1.04-1.20]) and lower eGFR (mean eGFR 9.3 ml/min/1.73m^2 lower for EJI-SER >75th versus ≤25th percentile, p<0.001).

Conclusions: As captured by EJI-SER, higher environmental and social burden are associated with lower eGFR and higher risk of kidney failure in the CureGN cohort. This first use of the EJI-SER in GD demonstrates the need for additional investigation into drivers of disparities in GD and policies and resources that address these structural inequities.

Figure: Impact of EJI-SER on kidney survival



TH-PO597

Humanistic Burden of Rare Kidney Diseases: Understanding the Impact of IgA Nephropathy (IgAN) and FSGS on Patients and Care Partners Study (HONUS): Preliminary Results for FSGS in the United States (US)

Justyna Szklarzewicz,[1] Mark E. Bensink.[2] On Behalf of HONUS Advisory and Study Team Members. *[1]University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; [2]Travere Therapeutics Inc, San Diego, CA.*

Background: FSGS is known to cause significant clinical and economic burden, however, less is known about the humanistic burden associated with the disease. HONUS is a multi-national, cross-sectional survey study to evaluate humanistic burden of rare kidney diseases, including FSGS.

Methods: The study recruited adult patients with their care-partners, and parents of youth (8-17 years) with FSGS or IgAN. The survey collects data on demographic/clinical characteristics, health-related quality of life (HRQoL, 12-Item Short Form Survey [SF-12], PedsQL) and disease impact on employment (Work Productivity and Activity Impairment [WPAI]). This preliminary analysis uses US data collected from FSGS adult patients, their care-partners, and parents of youth with FSGS by April 2023. Data were evaluated descriptively.

Results: The analysis included 76 adult FSGS patients and their care-partners, and 29 parents of youth with FSGS (proxy for pediatric patients). Most patients were Caucasian (adults, 68%; pediatric, 69%) and female (adults, 76%; pediatric, 59%), with a mean age of 44 years (adults) and 12 years (pediatric). Most adult patients were in CKD stages 3-5 (3, 26%; 4, 4%; 5, 25%); 13% had received transplant. For adult patients, mean SF-12 physical and mental component scores (PCS, MCS) were 41.5 and 44.5, respectively, lower (reflecting worse HRQoL) than previously published mean scores (MCS and PCS of 50) for the US general population. Parents of pediatric patients reported a mean total PedsQL (parent proxy) score of 65.8, lower (reflecting worse HRQoL) than previously published scores (parent proxy range: 82-88) for healthy US pediatric populations. Adult patients reported 39% activity impairment and 28% overall work productivity loss due to FSGS-related reasons, while care-partners/parents of adult and pediatric patients reported overall work productivity loss of 15% and 31%, respectively, due to FSGS-related reasons.

Conclusions: Both adult and pediatric patients with FSGS experience impaired HRQoL compared to the US general population, impacting adult work productivity and that of care-partners and parents.

Funding: Commercial Support - Travere Therapeutics, Inc.

TH-PO598

Kidney Diseases Associated with Inflammatory Bowel Disease

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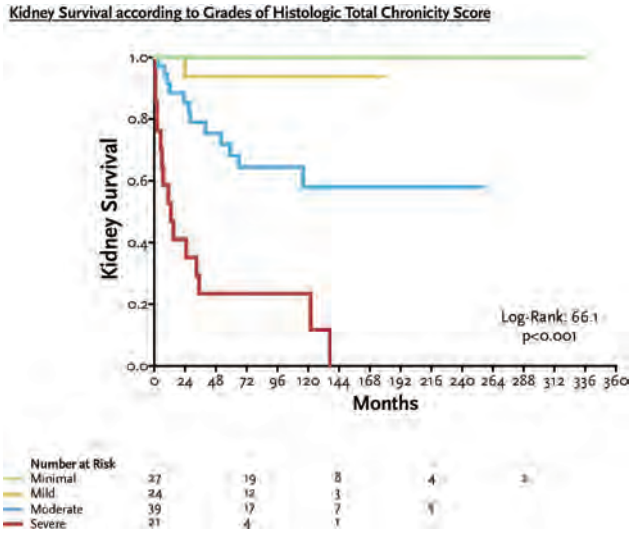
Background: Kidney disease is a well-known extra-intestinal manifestation associated with intestinal bowel disease (IBD), with different underlying etiologies. Little is known about the overall outcomes and predictors.

Methods: Retrospective, observational, cohort study. Patients with previous diagnosis of IBD in whom a kidney biopsy was performed at Mayo Clinic between 1994–2022, were included. Kidney transplant patients were excluded. The main outcomes were kidney failure (defined as eGFR<15 ml/min/1.73m²) and kidney function recovery at last follow-up (categorized as ≥75%, 25–75%, <25% of baseline eGFR).

Results: From a total cohort of 318 patients, 111 patients with IBD and long-term follow-up available were selected (45 ulcerative colitis and 66 Crohn's disease), with a mean age 48±17 years (40% females). Sixty-eight (61%) were under treatment with 5-ASA. IgA nephropathy, chronic interstitial nephritis and acute interstitial nephritis were the most common diagnoses (22%, 19%, 13%). Median eGFR at presentation was 30 [IQR17–54] ml/min/1.73m² and urinary protein-to-creatinine ratio 0.8 [0.3–3.4] g/g, with no differences between type of IBD. During a median follow-up of 59 (12–109) months, 29 (26%) patients progress to end-stage kidney disease (ESKD). By multivariable Cox regression analysis, the main predictors of kidney failure were age (HR: 1.04; p=0.002), baseline eGFR (HR: 0.94; p=0.003) and histologic total chronicity score (HR: 4.01; p<0.001). 26 (24%), 19 (17%), and 66 (59%) achieved complete, partial or no remission/recovery of kidney function, respectively. Global survival (ESKD+death) was significantly better in patients who achieved complete/partial recovery of kidney function.

Conclusions: One-fourth of patients with kidney disease associated with IBD progress to ESKD, and the main determinants of this outcome is age, baseline eGFR and degree of chronicity in kidney biopsy.



TH-PO599

Kidney Disease Outcomes in Patients with Inflammatory Bowel Disease

Manish K. Saha,[1] Duvuru Geetha,[2] Louis-Philippe Laurin,[3] Simon Leclerc,[3] Ronald Falk,[1] Susan L. Hogan,[1] Amy K. Mottl,[1] Yichun Hu,[1] Vimal K. Derebail.[1] *[1]University of North Carolina, Chapel Hill, NC; [2]Johns Hopkins University, Baltimore, MD; [3]Universite de Montreal, Montreal, QC, Canada.*

Background: Patients with inflammatory bowel diseases (IBD), Crohn's disease (CD) and ulcerative colitis (UC) may have extra-intestinal manifestations (EIM). The prevalence of histologic patterns of kidney disease seen in IBD patients is known, but clinical characteristics and long-term kidney outcomes remain ill-defined.

Methods: We performed a multi-center, retrospective, study of IBD patients who had a kidney biopsy across 3 centers. Inclusion criteria were: (i) IBD diagnosis based on clinical/histological characteristics and (ii) kidney biopsy with pathology report available. Baseline clinical data were analyzed for the whole cohort while outcomes were evaluated in those with available follow-up. Between groups, comparisons for continuous variables were made using Wilcoxon two-sample test and Fisher's exact test for categorical values.

Results: The frequency of various glomerular (GN), tubulointerstitial (TIN), and vascular (VD) processes are listed in Table 1. Patients with VD were older compared to other groups. At presentation, proteinuria was higher in patients with GN compared to those with TIN [2.13 (0.84, 4.07) vs. 0.30 (0.25, 1.25) p<0.05] and kidney function was worse in those with TIN compared to GN (3.10 [1.98, 4.50] vs. 2.10 [1.20, 3.11], p=0.05]). TIN occurred in 3 treatment naïve patients. In median follow-up of >3 years, 6 of 35 (17%) GN patients, 1 of 8 (12.5%) TIN, and 2 of 4 (50%) VD patients developed ESKD.

Conclusions: Patients with IBD may have varying forms of CKD including GN, and routine monitoring of kidney function is essential for early diagnosis and treatment. TIN may occur as an EIM independent of sulfasalzine therapy. Future studies are required to understand plausible shared immunopathogenesis.

Table 1 Frequency of various kidney diseases in patients with IBD

	CD+UC+IBD@ n=96	CD n=56	UC n=36
IgAN	18	11	6
FSGS	10	6	3
Amyloidosis-MGRS	8	5	3
ANCA-vasculitis	8	3	5
Other GN	12	5	7
TIN	14	8	5
VD	12	8	4
Others	9	6	3

@IBD - 4 patients had IBD without distinctive features of CD/UC -- 1 each had IgAN, FSGS, TIN, ATN

4 patients in CD and 1 in UC group had only ATN; MGRS=monoclonal gammopathy of renal significance, ANCA=Anti-neutrophil cytoplasmic antibody; Others: neoplasm, non-specific interstitial fibrosis

TH-PO600

Frequency of Adverse Events and Risk of Relapse Following SARS-CoV-2 Vaccination in Patients with Glomerular Diseases: A Multicentre Retrospective Study

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Background: Sars-cov2 vaccination has altered the natural course of COVID-19. We aimed to explore the frequency of adverse events of vaccination in patients with glomerular diseases (GD) including the risk of GD relapse afterwards.

Methods: Patients were included if they had biopsy-proven GD and received at least one dose of sars-cov2 vaccine. Patients who ended up in ESKD prior to vaccination or received a GD diagnosis after vaccination were excluded. We recorded demographics, histopathological diagnosis, immunosuppressive regimens, GD outcome before and after vaccination, and adverse events associated with the vaccine. Outcomes of GD included remission, relapse, treatment resistance, ESKD, and death. The rate of GD relapse post vaccination was estimated among patients who had achieved remission.

Results: 315 patients with biopsy-proven GD prior to sars-cov2 vaccination were included, with a mean age of 51(36-63) years at the time of diagnostic biopsy, of whom 142(45.1%) were males. Patients received a median of 3(3-4) vaccine doses. The median time from the diagnostic kidney biopsy to the 1st vaccine dose was 48.9(19.8-106.2) months. Among 255 patients with known GD status at vaccination, 139 (44.1%) were on immunosuppressive therapy, 224(87.8%) were on remission and 31(12.2%) were still active. 66(21.0%) patients reported systemic side effects (fever, arthralgias, myalgias) and 122(38.7%) local side effects (pain, swelling, itching, edema) associated with the vaccination. Renal function and 24-hour proteinuria remained stable after vaccination. Among patients in GD remission at vaccination, 23(9.0%) experienced a relapse during a follow up time of 18.2(15.5-20.1) months. Of those, 8 (7.8%) were on immunosuppression and 15 (18.1%) were not (p=0.058). The mean time to GD relapse following vaccination was 2.5(1.2-6.4) months.

Conclusions: According to the findings from this cohort, vaccination against sars-cov2 appears safe for patients with GD, with no significant impact in renal function or the probability for relapse.

Funding: Government Support - Non-U.S.

TH-PO601

Outcomes of COVID-19 Infection in Patients with ANCA-Associated Vasculitis Receiving Avacopan Therapy

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Background: The complement C5a-C5aR signaling axis plays a crucial role in the pathogenesis of ANCA-associated vasculitis (AAV) and COVID-19 infection. Avacopan, a C5aR antagonist is approved as an adjunct therapy for remission induction in AAV. Vilobelimab, a C5a antibody was granted Emergency Use Authorization by the FDA for severe COVID-19 infection. In AAV, COVID-19 infection poses an increased mortality risk. Additionally, the risk of severe COVID-19 infection is increased in patients receiving rituximab and glucocorticosteroids.

Methods: We performed an observational, retrospective study examining outcomes of patients with AAV treated with avacopan and who had COVID-19 infection. Data on ANCA type, immunosuppressive treatment, COVID-19 course, and COVID-19 vaccination status were retrieved after a review of the electronic medical records.

Results: A total of 7 patients were included. The mean (SD) age was 65.1 (±17.5) years old. Four patients had MPO-AAV and 3 patients had PR3-AAV. Two patients had a relapsing disease, and the rest had a new diagnosis of AAV. Six patients received at least 3 COVID-19 vaccines and a single patient received two COVID-19 vaccines. Five patients received a combination of rituximab, cyclophosphamide, glucocorticoids, and avacopan, whereas 2 patients received rituximab, glucocorticoids, and avacopan. The mean (SD) time from the date of initiation of induction immunosuppression to avacopan initiation was 20 (±21.5) days. The mean (SD) time from avacopan initiation to COVID-19 infection was 110 (±62) days. At the time of COVID-19 infection, all patients remained on rituximab therapy. The mean (SD) time between the last rituximab dose and the onset of COVID-19 infection was 63.8 (±57.1) days. Avacopan was continued in all patients. COVID-19 treatment included Paxlovid (n=3), Bebtelovimab (n=1), Molnupiravir (n=1), remdesivir and dexamethasone (n=1), and no treatment (n=1). All patients had mild symptoms except one patient who was hospitalized and died from severe COVID-19 infection.

Conclusions: COVID-19 clinical course appears to be mild in the majority AAV patients treated with avacopan, with a single patient experiencing severe COVID-19 infection and death. More studies are needed to explore the interplay between C5a blockade and infectious complications from SARS-CoV-2.

TH-PO602

Analysis of Clinical Features in ANCA-Associated Rapidly Progressive Glomerulonephritis Treated with Avacopan: A Single-Center Experience in Japan

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Background: Although avacopan (AVA) has recently become available as an induction therapy of ANCA-associated vasculitis, but the use of corticosteroid has not been established. Therefore, we conducted a retrospective analysis of the clinical database of ANCA-associated rapidly progressive glomerulonephritis (ANCA-RPGN)-patients in our hospital with a reduced regimen of corticosteroids.

Methods: All patients met the CHCC classification criteria for MPA and GPA at disease onset. Seven patients [3(43%) females)] followed for at least 12 weeks since Aug 2022 (up to Apr 2023) were analyzed for clinical course, including remission rates. Remission was defined as Birmingham Vasculitis Activity Score (BVAS) 0. GC Pulse, RTX, and AVA were used for induction therapy. PSL was begun at a dose of 0.4-1.0 mg/kg/day and then tapered off at 12 weeks.

Results: AVA was used in 12 patients with AAV, of whom 7 presented with RPGN. Of the 7 patients with renal involvement (4 MPO-MPA, 2 MPO-GPA and 1 PR3-GPA), 6 newly diagnosed and 1 relapsing disease received a remission induction. The mean age was 70.0±12.1 years, mean BVAS was 16.4±3.1, prednisolone (PSL) was 52.1±17.8 mg/day. At the start of AVA, s-Cr was 2.3±1.1 mg/dL, eGFR was 25.0±11.8 ml/min/1.73m^2, CRP was 1.9±3.1 mg/dL and the dose of PSL was 37.1±17.0 mg/day. At week 12 and 24, percentages of participants who could discontinue PSL were 43%, 60% and remission rates were 100%, 80%, respectively. There were no serious adverse events and no patients requiring maintenance dialysis. At week 12 and 24, doses of PSL were 3.6±4.5/1.5±2.2 mg/day, s-Cr were 1.6±0.6 /1.7±0.7 mg/dL, eGFR were 34.2±14.2 /35.6±17.7 ml/min/1.73m^2 and CRP were 2.7±6.7/0.11±0.09 mg/dl, respectively.

Conclusions: These results showed that AVA may be effective and have acceptable safety profiles in relatively elder AAV-RPGN patients in daily practice in Japan.

TH-PO603

Treatment, Relapse, and Complications of Myeloperoxidase (MPO) and PR3 ANCA-Associated Glomerulonephritis: Report from an Australian Centre

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Background: ANCA-associated vasculitis is a group of autoimmune vasculitides of unknown aetiology, with different phenotypic manifestations. Myeloperoxidase (MPO) and Proteinase 3 (PR3) have emerged as two main serological subtypes and growing evidence reported differences between their disease characteristics. We investigate the disease manifestation, progression and complications in patients with biopsy-confirmed ANCA-associated glomerulonephritis (AAGN).

Methods: This retrospective study was performed at the Royal Brisbane and Women's Hospital, a major tertiary hospital with a population catchment of approximately 1,030,006 people in North Brisbane, Australia. Patients with pauci-immune glomerulonephritis confirmed on kidney biopsy between 1st January 2005 to 1st October 2021 were identified. Clinical data were collected via medical records.

Results: A total of 1,433 kidney biopsy results were reviewed. 80 cases of pauci-immune AAGNs were identified. Majority were MPO-positive AAGN (53/80), as opposed to PR3-positive disease (21/80). 5/80 were ANCA negative and 1/80 did not have ANCA serology available. Pulmonary involvement rates in PR3 and MPO AAGN were similar at 29% (6/21) and 30% (16/53) respectively. Majority patients (58/73) had induction treatment with cyclophosphamide. More patients on cyclophosphamide developed malignancy compared to the patients on alternative therapy (14% (8/58) vs 5% (1/22), p=0.43). Approximately one in five (17/80) patients had a relapse over the study period. More relapses occurred in PR3 than MPO disease (38% (8/21) vs 13% (7/53), p=0.02). Most relapses (12/17 cases) occurred within 2 years of diagnosis. The longest time to relapse was 12 years. Numerous AAGN cases developed deep vein thrombosis or pulmonary embolism (8/80). The risks were higher in PR3 compared to the MPO group (3/21 vs 4/53, RR 1.89). Malignancy was common (16/80). No difference was observed between MPO and PR3 subgroups (21% vs 24%). 56% (9/16) of malignancies were diagnosed after AAGN diagnosis.

Conclusions: This is the first study in Australia that reports on AAGN outcomes and disease associations. Both, MPO and PR3 AAGN are associated with pulmonary involvement. PR3 AAGN is associated with a significantly higher relapse rate compared to MPO disease, this finding is consistent with other cohort studies in Europe.

TH-PO604

Burden of Infection-Related Hospitalization and the Impact of Multidisciplinary Care in ANCA-Associated Vasculitis: A Retrospective Cohort

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Background: ANCA associated vasculitis (AAV) is managed with combination immunosuppression. Infections are the most common cause of excess morbidity and mortality. Multidisciplinary clinics have improved outcomes in several chronic diseases but have not been evaluated in AAV.

Methods: A retrospective cohort study was performed of patients diagnosed with AAV at Monash Health in Melbourne, Australia between January 1, 2000 and February 28, 2018, excluding children and those with EGPA. Hospitalization rate was calculated as number of hospitalized patients out of those at risk excluding day admissions. Survival analysis was performed, with subjects entering analysis at diagnosis.

Results: Of 165 patients, 22 were hospitalized for infection within the first 12 months of AAV diagnosis with a hospitalization rate of 15 per 100 person-years. Median length of stay was 9.4 days. Hospitalization rate for infection did not change with vasculitis clinic establishment in 2014 (18 per 100 person-years pre vs. 8 per 100 person-years post, p=0.10). After infection, kidney disease (excluding routine dialysis), cardiovascular disease, and disease relapse accounted for the greatest burden of hospital days. Hospitalization rate for any cause reduced from 70 per 100 person-years before clinic establishment to 51 per 100 person-years after (p=0.02). Those with MPA were at comparable risk of death to those with GPA (HR 1.22, 95% CI 0.53-2.80). Where known, the most common cause of death was infection, followed by kidney failure (dialysis non-commencement for medical or social reasons), and malignancy within the first 12 months of AAV diagnosis.

Conclusions: Establishment of a multidisciplinary vasculitis clinic was associated with a significant reduction in hospitalization rate for any cause, with a trend toward a reduction in hospitalization rate for infection. Infection was the most common cause of death.

Table 1: Demographics & Characteristics of Included Patients

	MPA n=112	GPA n=53	p-value
Age*	63.4 (60.7-66.0)	54.7 (50.0-59.3)	<0.001
Male	59 (52.7)	36 (67.9)	<0.001
System involvement			
Renal	104 (92.8)	38 (71.7)	0.001
Dialysis	49 (43.8)	16 (30.2)	0.001
ESKD**	37 (33.0)	11 (20.8)	0.001
Ear/Nose/Throat	12 (10.7)	27 (50.9)	0.001
Lung	39 (34.8)	33 (62.3)	0.001
Eye	2 (1.8)	9 (17.0)	0.001
Arthritis	13 (11.6)	13 (24.5)	0.04
Neurological	8 (7.1)	5 (9.4)	0.85
Gastrointestinal	6 (5.4)	4 (7.5)	0.25
Skin	11 (9.8)	8 (15.1)	0.05
Subglottic stenosis	0 (0)	0 (0)	

Note: values are mean (95% CI) or number (%)
No Aboriginal/Torres Strait Islander patients in the cohort
*Age at AAV diagnosis in years
**ESKD defined as requiring dialysis for >/= 90 days

TH-PO605

Changing Phenotypes and Clinical Outcomes over Time in Microscopic Polyangiitis

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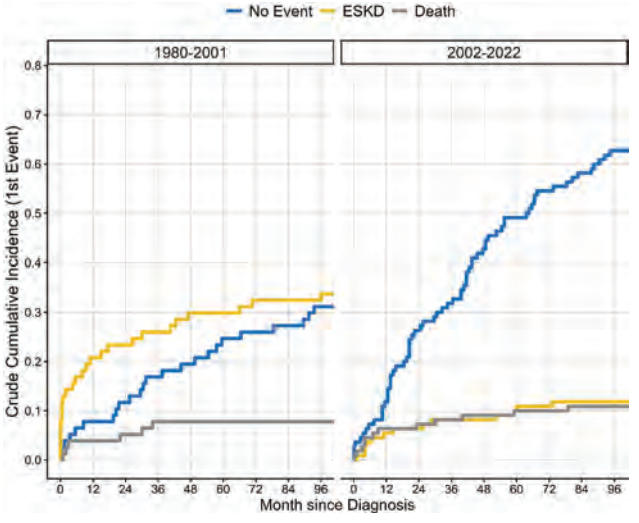
Background: Diagnosis and management of Microscopic Polyangiitis (MPA) have evolved considerably over the last decades, but it is unknown whether clinical, histological presentation and patient and renal outcomes have changed accordingly.

Methods: We compared clinical-histopathological characteristic at diagnosis, and the risk of death and of end stage kidney disease (ESKD) in patients diagnosed with MPA between 1980 and 2022, after grouping them in two periods (p): p1980–2001 and p2002–2022. We compared the mortality rate between the two periods using Kaplan-Meier estimator and Cox-regression and competing risks of ESKD and death using the Aalen-Johansen estimator, Fine-Gray multiple regression and multi-state models.

Results: Out of 187 patients, 77 were in p1980-2001, and 110 in p2002-2022. Patients in p2002-2022 were older (66.2(14.0) vs 57.7(15.8); P<0.001), had a better kidney function (eGFR 25.9(24.8) vs 21.5(28.2) mL/min/1.73m^2; P=0.011) and a lower prevalence of the Berden sclerotic class (4.8 vs 18.2%; P=0.006). Despite a similar crude and adjusted patient survival, the risk of ESKD decreased during p2002-2022, compared to p1980-2001 (0.30 [95%CI:0.16-0.57; P<0.001]) (**Figure**). The result remained significant after accounting for death after ESKD in multistate models and after adjusting for potential confounders (0.33 [95%CI:0.18-0.63; P<0.001]).

Conclusions: Clinical presentation of MPA has become less severe over the last decades, leading to a reduced risk of ESKD, despite a comparable risk of death. Older age, changing clinical patterns and better kidney function at the time of diagnosis do not fully account for the reduction in ESKD, which may be instead related to new induction and maintenance therapies as well as to a greater awareness of the disease.



TH-PO606

Non-Lupus Full House Nephropathy: A Debatable Entity

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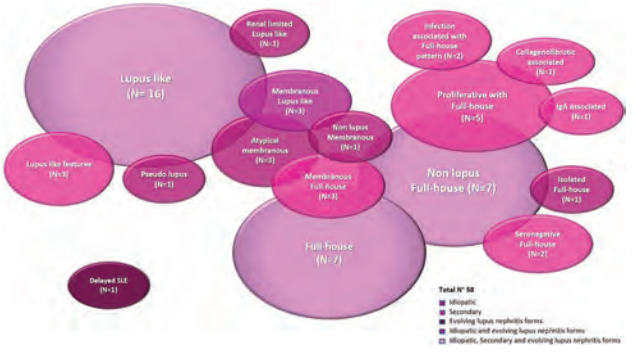
Background: Lupus nephritis (LN) is characterized by a variety of light microscopic findings on kidney biopsy and a full house (FH) pattern at immunofluorescence/immunohistochemistry. A FH pattern and lesions consistent with LN, in a patient without clinical and laboratory features of SLE have led to the descriptive term non-lupus full house nephropathy (NLFHN). We performed a systematic review focussing on NLFHN nomenclature, clinical findings and outcome.

Methods: In a reiterative process, all identified terms for NLFHN and other MeSH terms were searched in PubMed. 346 records were screened according to inclusion and exclusion criteria. The 58 records identified were published between 1982 and 2022 and 60.3% were case reports. The available clinical data of patients from different reports were collected and analysed.

Results: NLFHN was addressed with 22 different names: the same name used by different authors could refer to different entities (Figure 1). We identified 148 patients: 75(50.7%) were males; median age 35(23-58) years. Creatinine and proteinuria at onset were 1.4(0.8-2.5) mg/dL and 5.7(2.7-8.8) g/day. Less than 1/3 of patients achieved complete renal response (CRR). A clear causative agent was identified in 50 patients, mainly infective (50%). Secondary NLFHN were acute, non-relapsing diseases with lower renal function at onset compared to the idiopathic ones (P=0.001). Among the 57 patients with idiopathic NLFHN, CRR was comparable between patients treated with immunosuppression (IS) and supportive therapy; however, proteinuria and creatinine at onset were higher in patients treated with IS (P=0.089 and P=0.066). Only 8 patients developed SLE after a median follow-up of 5.0(1.9-9.0) years.

Conclusions: Despite increasing interest, the place of NLFHN among glomerular diseases is still uncertain, which complicates treatment decisions. Confusion arises by the lack of high-quality evidence and the lack of consensus on nomenclature. The description of three pathogenic categories is a step forward towards a shared framework of this rare entity.



TH-PO607

The Clinical Value of Monoclonal Protein in ANCA-Associated Vasculitis with Renal Involvement

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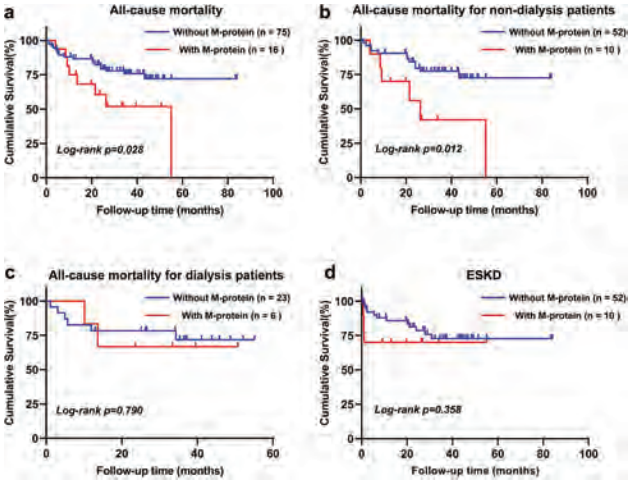
Background: The value of monoclonal protein (M-protein) in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) patients with renal involvement has not been investigated.

Methods: We analyzed AAV patients with renal involvement from 2013 to 2019 in our center. Patients with immunofixation electrophoresis were divided into M-protein positive group and M-protein negative group. The clinicopathological features and outcomes of the two groups were compared.

Results: Ninety-one AAV patients with renal involvement were enrolled for analysis, and 16 patients (17.6%) had a positive test for M-protein. Compared with M-protein negative patients, M-protein positive patients had lower hemoglobin (77.6 *vs.* 88.4 g/L, $p = 0.016$), MCHC (313 *vs.* 323 g/L, $p = 0.002$), serum albumin (29.4 *vs.* 32.5 g/L, $p = 0.026$) and complement 3 (C3) (0.66 *vs.* 0.81 g/L, $p = 0.047$), while higher platelets (252 *vs.* 201 10^9/L, $p = 0.048$) and incidence of pulmonary infection (62.5% *vs.* 33.3%, $p = 0.029$). However, renal pathological features between the two groups had no significant difference. In addition, during a median follow-up of 33 months, Kaplan-Meier survival analysis showed that, compared with M-protein negative patients, M-protein positive patients had a higher risk of all-cause mortality (log-rank test, $p = 0.028$), especially for patients who were not dialysis-dependent at the time of admission (log-rank test, $p = 0.012$).

Conclusions: Our results indicate that M-protein is associated with different clinicopathological features and increased all-cause mortality in AAV patients with renal involvement. Testing M-protein and rigorous diagnosing of the significance of the presence of M-protein may be helpful for assessing the survival of AAV patients with renal involvement.



TH-PO608

Impact of Sex in Clinical Presentation and Outcomes of Patients with ANCA-Associated Vasculitis with Severe Kidney Diseases

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Background: The impact of sex in the clinical presentation and outcomes of patients with anti-neutrophil cytoplasmic antibodies (ANCA) associated vasculitis (AAV) with glomerulonephritis (AAV-GN) has not been studied, particularly in patients with severe kidney involvement (eGFR<15mL/min/1.73m^2).

Methods: A retrospective cohort study on MPO-or PR3-ANCA patients with AAV (MPA or GPA) and eGFR<15 ml/min/1.73 m^2 or ESKD at presentation. Clinical presentation and outcomes were analyzed according with sex.

Results: We analyzed 166 patients with biopsy proven active AAV-GN and eGFR<15mL/min/1.73m^2 at diagnosis:78(47%) females and 88(53%) males. Arterial hypertension was more frequent in males (85.2%vs.70.5%,p=0.022). Median serum creatinine (SCr) was higher in males when compared with females (5.2[IQR 4.2-7.4]vs.3.6[IQR 2.8-5.1]mg/dL, p<0.001) but there were no differences in eGFR at presentation (9.9vs.12.1 mL/min/1.73m^2, p=0.053). There were no differences between groups in age at diagnosis, GPAvs.MPA, ANCA specificity, frequency of alveolar hemorrhage, BVAS score, chronicity score or crescentic features on kidney biopsy. Males received IV methylprednisolone more frequently (84.1%vs.69.2%,p=0.023), but other therapies were similar. Most patients who started dialysis within 4 weeks were males(53.4%vs.30.8%,p=0.003), however the rate of progression to ESKD at 12 months between groups was similar(p=0.186). When analyzing only the 71 patients that started dialysis within 4 weeks, infections at 12 months were more common in females (75.0%vs.36.2%,p=0.017). Rate of dialysis initiation or progression to ESKD was not different between males(n=61.7%) vs. females (n=62.5%) being on dialysis at 12 months. By multivariable logistic regression, factors related with dialysis initiation within 4 weeks in our cohort were SCr(OR1.478,[95%CI1.231-1.776],p<0.001), alveolar hemorrhage(OR2.726,[95%CI 1.099-6.763],p=0.031) and PR3-ANCA(OR3.155,[95%CI 1.485-6.702],p=0.003) adjusted to sex.

Conclusions: In our cohort, males presented with higher SCr, and dialysis was started within 4 weeks more frequently but outcomes were not different. Females had increased frequency of infections at 12 months.

TH-PO609

A Retrospective Observational Study of the ANCA-Negative Renal Vasculitis Cohort in the National Rare Kidney Disease Registry

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Background: A recent single centre study reported that ANCA-negative pauci-immune glomerulonephritis (PIGN) presents in younger patients, with higher end-stage kidney disease (ESKD) risk, despite lacking differences in histopathology. Fewer extra-renal manifestations were observed. The aim of this study was to review ANCA negative vasculitis PIGN outcomes in the Irish Rare Kidney Disease Registry.

Methods: Of 616 patients with PIGN in the registry, 13 were ANCA-negative (defined as negative on anti-MPO and anti-PR3 immunofluorescence / ELISA), with PIGN confirmed on kidney biopsy. Data collection included demographics, biopsy results, management, and outcomes.

Results: The mean age was 56.8 years (SD 12.85). 4 patients had renal limited disease. Most common other symptom/ system involved included: constitutional (n=4) and ENT (n=4), muco-cutaneous/ophthalmic (n=2), chest (n=2), neurological (n=1), abdominal (n=1). The mean estimated glomerular filtration rate (eGFR) at diagnosis was 19.4ml/min/1.73m (SD 19.9). Mean creatinine was 423µmol/L (SD 259.9). 8 patients had UPCR documented, with the mean UPCR recorded as 543.2 (SD 747.3). Applying the Berden score to 11 participants: 6 focal, 3 mixed, 1 crescentic, 1 sclerosed were observed. 10 of 13 patients received immunosuppression. Induction treatment included Methylprednisolone (n=7), Cyclophosphamide (n=7), Rituximab (n=2), oral prednisolone (n=3), and PLEX treatment (n=1). 9 patients were continued on maintenance treatment: oral prednisolone (n=6), Azathioprine (n=5), Mycophenolate Mofetil (n=3), Cyclophosphamide (n=1), Rituximab (n=1). 4 patients were on renal replacement therapy (RRT) at diagnosis, 1 patient developed end-stage kidney disease (ESKD). 10 patients achieved remission, 1 did not. 3 had documented relapse. 1 patient died within 5-years of diagnosis.

Conclusions: ANCA-negative vasculitis with renal involvement requires early detection and treatment to prevent kidney disease progression. Renal disease may occur as a single manifestation or as part of a multi--systemic presentation, underscoring the importance of organ surveillance. Further elucidation of the pathogenesis and prognostic markers of relapse in ANCA negative vasculitis, will play a key role in improving outcomes.

TH-PO610

Impact of Reclassification by the 2022 ACR/EULAR Classification Criteria on the ANCA-Associated Vasculitis Study Population

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Background: In 2022 the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) presented new classification criteria for the three subsets of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV): granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and Eosinophilic Granulomatosis with Polyangiitis (EGPA). Our aim was to assess the impact of the new 2022 ACR/EULAR classification criteria on future GPA, MPA and EGPA studies.

Methods: An established, single center cohort of patients with a clinical AAV diagnosis in a tertiary academic hospital was used as source population. Clinical diagnosis and disease characteristics at time of diagnosis were collected by manual review and matched to the novel 2022 ACR/EULAR classification criteria for GPA, MPA or EGPA. Patients with an unspecified AAV diagnosis and patients with insufficient clinical data for the time of diagnosis were excluded.

Results: We included 183 GPA, 54 MPA and 27 EGPA patients. In total 32/264 (12%) patients were reclassified. 22/183 (12%) clinical GPA patients were reclassified: 11 (6%) as MPA and 11 (6%) were unclassified. 3/54 (9%) MPA patients were reclassified: 1 (2%) as GPA and 2 (4%) were unclassified. 7/27 (25%) EGPA patients were reclassified: 3 (11%) as GPA and 4 (15%) patients were unclassified. One clinical GPA patient could be classified as both GPA and MPA. After reclassification, PR3+ patients remain predominantly GPA (from 97 to 99%), MPO+ patients are more often considered MPA (from 64% to 75%) and ANCA- patients can often not be classified (29%). Focusing on risk factors for relapse, an often used endpoint in clinical trials, we identified an enrichment of PR3 positivity in GPA patients (+12%) and of pulmonary involvement in MPA patients (+10%) after reclassification.

Conclusions: With 12% reclassification the 2022 ACR/EULAR classification criteria will impact inclusion in future studies. Reclassification is often based on ANCA serology and impacts the distribution of typical risk factors for disease relapse in MPA and GPA subgroups.

TH-PO611

Canadian Society of Nephrology Commentary on the 2021 KDIGO Glomerulonephritis Guidelines and 2023 ANCA/Lupus Updates

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Background: The Canadian Society of Nephrology (CSN) completes commentary on published Kidney Disease Improving Global Outcomes (KDIGO) Guidelines. In 2021, KDIGO published Glomerulonephritis (GN) guidelines with recent 2023 guideline updates. KDIGO guidelines includes Recommendations and practice points (PP), which are used when there is insufficient evidence for a Recommendation. In this article we describe the process and highlight findings of the CSN commentary on the KDIGO GN guidelines.

Methods: The CSN established a working group including adult and pediatric nephrologists, pharmacists, pediatricians, pathologists, and patient partners with expertise in GN across Canada. The working group aimed to review guideline's relevance and applicability to the Canadian context when caring for patients with GN. Recommendations from the KDIGO 2021 GN guidelines (including 2023 lupus and ANCA updates) were assessed with a standardized survey assessing whether working group members agreed or not with the Recommendation with focus on highlighting specific Canadian context that may impact the recommendation. Recommendations attaining <80% consensus or

those with comments pertaining to important considerations to the Canadian context were specifically discussed. Practice points were discussed amongst working group members and relevant PP were highlighted.

Results: This commentary highlights the impact of the KDIGO GN guideline Recommendations and PP on GN care in Canada. In general, the CSN working group agrees with most of the guideline statements by KDIGO. This commentary highlights the uptake of certain PP including lack of evidence, practice variation, and areas of controversy. Health equity and virtual medical care were important issues impacting GN care in Canada.

Conclusions: Canadian Society of Nephrology GN working group generally agrees with the KDIGO GN guidelines and recent lupus nephritis and ANCA updates, and highlights areas relevant to the Canadian healthcare for patients with GN.

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TH-PO612

Prevalence and Outcomes of Anti-Glomerular Basement Membrane Disease with and Without Secondary Glomerular Pathologies

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Background: Anti-glomerular basement membrane (Anti-GBM) disease is a rare but devastating autoimmune kidney disease. Anti-GBM disease can co-exist with several other glomerular pathologies, but little is known about the frequency of these associated pathologies and patients' renal outcomes compared to patients who have anti-GBM disease alone.

Methods: We retrospectively evaluated Mayo Clinic Renal Pathology Database and included patients (age ≥ 18 years) with a diagnosis of anti-GBM disease on a native kidney biopsy who were treated at the Mayo Clinic from 2000 to 2021. Detailed pathological findings were collected from renal pathology reports. Clinical characteristics and outcomes were collected from review of medical records.

Results: Total of 209 anti-GBM cases were identified and of these, 49 cases (23.4%) were treated at Mayo Clinic (internal), whereas 160 cases (76.6%) only had their biopsy reviewed at Mayo Clinic but were treated elsewhere (external). Of 209, 191 were typical anti-GBM (91.4%) and 18 (8.6%) were atypical anti-GBM. Of typical anti GBM cases (n=191), 119 (62.3%) had no other glomerular pathology, 53 cases (27.8%) also had anti-neutrophilic cytoplasmic antibody (ANCA)-associated glomerulonephritis (GN), 10 cases (5.2%) had membranous nephropathy (MN), 6 cases (3.1%) had IgA nephropathy, 3 cases (1.6%) had thrombotic microangiopathy (TMA) and 1 case (0.5%) had fibrillary glomerulonephritis). ANCA-GN patients were significantly older than patients with anti-GBM alone and had significantly higher serum creatinine (SCr) compared to patients with associated MN. Those with MN had significantly higher urinary protein compared to those with anti-GBM alone and those with ANCA-GN. Patients with ANCA-GN had the highest degree of sclerosis compared to other pathologies. Of the 49 internal cases, 32 (65.3%) required dialysis upon presentation and 91.7% survived at 1 year. Of those who required dialysis, only 9.1% discontinued dialysis. There were no different in the outcomes between groups.

Conclusions: Concomitant glomerular pathology is common among patients with anti-GBM disease and can occur in up to 40% of patients. ANCA-GN accounts for over 70% of those co-existing pathologies. Clinical characteristics may potentially serve as clues to look for secondary pathologies in patients who present with anti-GBM disease.

TH-PO613

Clinical Courses in IgA Vasculitis with Nephritis Underwent Tonsillectomy

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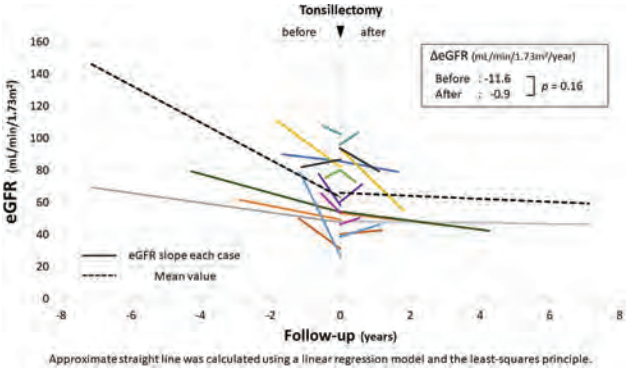
Background: Adult-onset IgA vasculitis (IgAV) frequently presents with kidney involvement and is often associated with unfavorable clinical courses. There is no established treatment in IgAV with nephritis (IgAVN) other than renin-angiotensin-aldosterone inhibitors and corticosteroids. Although tonsillectomy is one of the treatment options in primary IgA nephropathy, the efficacy of tonsillectomy in IgAVN has not been determined to date.

Methods: Adult patients with biopsy-proven IgAVN who received tonsillectomy at 6 hospitals in Japan from 2015 to 2022 were recruited. Changes in hematuria, time-averaged urine protein-to-creatinine ratio (UPCR), estimated glomerular filtration rate (eGFR), and serum IgA were evaluated before and after tonsillectomy. Hematuria remission and proteinuria remission were defined as three consecutive urinary RBC<5/HPF and UPCR<0.3g/g for at least 6 months, respectively.

Results: A total of 12 patients with IgAVN who underwent tonsillectomy were identified. The median observation periods before and after tonsillectomy were 20.7 months and 48.6 months, respectively. Corticosteroids were prescribed before and after the tonsillectomy in 5 (42%) and 7 (58%) patients, respectively. After the tonsillectomy, both hematuria score (median 4.25 versus 2.5) and time-averaged UPCR (median 0.63 versus 0.28 g/g) decreased. Five patients achieved hematuria remission and nine patients achieved proteinuria remission and only one patient showed a recurrent urine abnormality. The eGFR slope was changed from mean -11.6 to -0.9 mL/min/1.73m^2/year before and after tonsillectomy. Serum IgA after tonsillectomy also changed compared with before (median 394 versus 296 mg/dL).

Conclusions: Adult IgAVN patients who underwent tonsillectomy had relatively favorable clinical courses with improved urinary findings and eGFR slopes. The prospective controlled trial is needed to confirm the efficacy of tonsillectomy in IgAVN.



TH-PO614

Predictors of Major Adverse Kidney Disease Events in a Real-World Population with IgA Nephropathy

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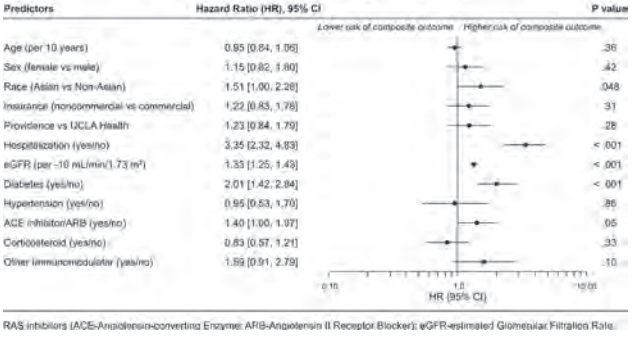
Background: IgA nephropathy (IgAN) is a glomerular disease that may progress to kidney failure. While albuminuria or proteinuria and reduced kidney function are associated with greater risk, other predictors are less clear. The study aim was to use a real-world population to assess clinical predictors of major adverse kidney disease events (MAKDE) in IgAN.

Methods: The study population was derived from electronic health records data in the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry at Providence and UCLA Health systems. Demographics, clinical characteristics, and prescriptions were obtained for adults ≥18 years old with a diagnosis code for IgAN in 2016-2020. Kaplan Meier survival analysis and Cox proportional hazards models evaluated MAKDE: 40% eGFR decline, eGFR <15 mL/min/1.73 m^2, and administrative codes for kidney failure, dialysis, or transplant.

Results: Patients with IgAN (N=1,099) were 50% women (n=554) and 55±18 (mean±SD) years old. At baseline, mean eGFR was 77±28 mL/min/1.73 m^2 (Chronic Kidney Disease Epidemiologic equation 2021); median urine albumin/creatinine ratio (UACR) and urine protein/creatinine ratio (UPCR) were 119 (interquartile range 30-518) mg/g and 0.7 (0.3-1.9) g/g. Renin angiotensin system (RAS) inhibitors and corticosteroids were prescribed to 49% (n=538) and 25% (n=278), respectively. MAKDE occurred in 13% (n=144) by 3 years. Predictors of MAKDE were Asian race, hospitalization, diabetes, RAS inhibitor use, and lower baseline eGFR (**Figure**). In a sensitivity analysis model including baseline UACR or UPCR measurements (n=335), levels above versus below the median had an adjusted hazard ratio of 2.10 (95% confidence interval 1.07-4.11).

Conclusions: MAKDE were common in patients with IgAN. Asian race and illness severity reflected by hospitalization, diabetes, and RAS inhibitor use, as well as reduced kidney function and albuminuria or proteinuria, predicted these events.

Funding: Commercial Support - Travere Therapeutics



TH-PO615

ESKD and CKD Progression Among a Diverse Immunoglobulin A Nephropathy (IgAN) Population

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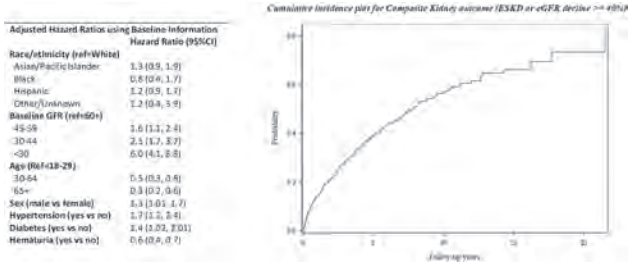
Background: IgAN is the most common glomerulonephritis and a leading cause of ESKD but real-world data on natural history of the disease are sparse. This study evaluated kidney outcomes among a diverse IgAN population in an integrated US health system.

Methods: Longitudinal cohort study (1/1/2000-12/31/2021) was performed within Kaiser Permanente Southern California members with biopsy proven primary IgAN. Secondary IgAN was excluded. Kidney outcome was a composite of ESKD (dialysis or transplant) and/or CKD progression. Patients were followed from index biopsy until kidney outcome and censored for mortality, disenrollment, or end of study. Multivariable Cox regression was used to estimate hazard ratios (HR).

Results: Among 687 patients with IgAN, mean age was 45.5 (SD 14.7) yrs. with 52% males, 40% Hispanic/Latino, 30% Asian/Pacific Islander, 24% White, 3% Black, and 39% with eGFR<45). At biopsy, mean eGFR was 58 and mean urine protein creatinine ratio (uPCR) was 2.5 g/g. A total of 270 (39%) had a kidney outcome (39 ESKD, 231 CKD progression) with median time to outcome of 1.3 years (2.4 years among eGFR>30 patients). Median time to ESKD was 2.6 years (4.7 years among eGFR>30 patients). The composite kidney outcome rate was 96.8 (per 1,000 person-years) without significant influence of race/ethnicity. ESKD incidence rate was 56.1 (per 1,000 person-years), also without significant influence of race/ethnicity over the median follow-up duration of 3.4 years. Baseline eGFR, male sex, hypertension, diabetes, hematuria, and age>65, were identified as predictors of ESKD and CKD progression.

Conclusions: Among a diverse IgAN population within a real-world environment, we observed a high rate of kidney outcomes in patients with lower eGFR and hypertension, but no difference across race/ethnic groups. Additional analysis evaluating effect of uPCR and treatment on kidney outcomes is ongoing.



TH-PO616

Clinical Burden of IgA Nephropathy (IgAN) in the United States: A Retrospective Electronic Medical Record (EMR) and Claims Analysis

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Background: IgAN is a complement-mediated kidney disease with a highly variable risk of disease progression; some patients already exhibit loss of kidney function at diagnosis. This analysis described the demographic and clinical characteristics of patients with IgAN in the US and estimated the proportion of patients at high risk of IgAN progression despite treatment with supportive care.

Methods: This was a retrospective cohort study of patients with IgAN aged ≥12 years using the HealthVerity database comprised of EMR, claims and lab data between 01-01-2016 and 09-30-2022. Demographic and clinical characteristics of patients who had been in the database for ≥12 months continuously before the date of their first IgAN SNOMED diagnosis code (index date) were examined. Patients at high risk of IgAN progression were defined as having proteinuria ≥1.0 g/g despite receiving supportive care (defined as ≥1 record of ACE inhibitors and/or ARBs within 12 months of the index date), and/or SGLT-2 inhibitors.

Results: Among 1,541 patients with IgAN included in the final analysis, mean ± SD age was 43.8±14.5 years and 53% were male. Of 918 patients with available data, 62.1% had stage ≥3 CKD at index. Mean ± SD eGFR was 67±33 mL/min/1.73m^2 and mean ± SD proteinuria was 1.9±1.9 g/g. Overall, 1.8% of patients had previously undergone a kidney transplant. Comorbidities were common, including hypertension (62.5%) and Type 2 diabetes (13.8%). Overall, 814/1,541 patients (52.8%) were treated with ACE inhibitors or ARBs (with or without SGLT-2 inhibitors) within 12 months post-index. Of patients with proteinuria data, the proportion of patients at high risk of IgAN progression despite supportive care at 6 months (±3 months) post-index was 46/109 (42.2%); at 12 months (±3 months) post-index, this proportion was 32/95 (33.7%).

Conclusions: In a cohort of patients with IgAN using real-world EMR and administrative claims data, comorbidities and advanced kidney disease were common. About half of these patients were receiving ACE inhibitors or ARBs (with or without SGLT-2 inhibitors) within 12 months after diagnosis, and half remained at high risk of progression at 6 months. These data highlight the need for novel therapies in IgAN.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

TH-PO617

Design and Rationale for PERFORM Patient Registry™: An Observational Cohort of Patients Utilizing TARPEYO® for Immunoglobulin A Nephropathy (IgAN) in the United States

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Background: Immunoglobulin A Nephropathy (IgAN) is a rare autoimmune disease characterized by the deposition of galactose-deficient IgA1 in the mesangial area of the glomeruli. Up to 50% of patients with IgAN are at risk of developing ESRD within ten to twenty years of diagnosis with poor survival outcomes. TARPEYO® (budesonide) was the first US FDA approved treatment (accelerated approval granted in December 2021) to reduce proteinuria in adults with primary IgAN at risk of rapid disease progression, generally a urine protein:creatinine ratio (UPCR) ≥1.5 g/g. Given the rarity and progressiveness of IgAN, an understanding of real-world treatment patterns and patient outcomes is warranted. The PERFORM Patient Registry™ uses a novel direct-to-patient approach to capture electronic health data and patient-reported data in real-world patients with IgAN who are utilizing TARPEYO.

Methods: Adult participants (≥ 18 years) with at least one dispensed prescription of TARPEYO will self- enroll in the registry online via the IQVIA Integrated Health Platform study application. This approach includes participant consent to sharing of their electronic health data (electronic medical records [EMR], TARPEYO dispensing claims) and collection of electronic participant-reported data (including the participant reported outcome [ePRO] of EQ-5D-5L). Participants will be followed up for a minimum of 36 months, until their withdrawal of consent or the end of the registry, whichever occurs first.

Results: This study will describe data obtained via the online study application for eligible participants. Additional exploratory analyses include characterization of the IgAN-treated participant population in terms of demographic and clinical characteristics, patterns of TARPEYO treatment utilization and clinical management of the disease over time.

Conclusions: This is the first direct to patient real-world registry of patients with IgAN utilizing TARPEYO. Patient recruitment via Version 1.0 of the registry began in December 2022 and the full registry Version 2.0 is expected to launch in May 2023.

Funding: Commercial Support - Calliditas NA Enterprises Inc.

TH-PO618

Levels of Socioeconomic Deprivation Are Associated with Worse Kidney Outcomes in Patients with IgA Nephropathy: Data from UK RaDaR

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Background: The UK National Registry of Rare Kidney Diseases (RaDaR) recruits adults and children with biopsy-proven primary IgA nephropathy (IgAN) and eGFR <60 mL/min/1.73m^2 or proteinuria ≥0.5g/24h from 107 adult and paediatric kidney units across the UK, including retrospective and prospective data. Given the well established gradient between greater socioeconomic deprivation and worse health, in this study we aimed to determine whether socioeconomic deprivation influenced the risk of developing kidney failure in IgAN.

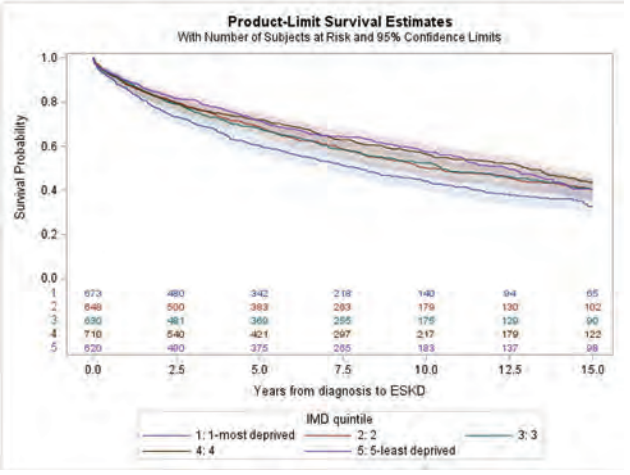
Methods: Deprivation quintile was derived using patient postcodes matched to Index of Multiple Deprivation (IMD) scores. Kidney survival from diagnosis was analysed using Kaplan Meier methods and Cox regression. The event was initiation of kidney replacement therapy, censored for death.

Results: The characteristics of 4,127 IgAN patients in RaDaR by IMD quintiles are shown in the **Table**. There was a clear association between risk of development of kidney failure and deprivation quintile (**Figure**) with the most deprived IgAN patient group exhibiting significantly faster progression. HR for kidney failure after adjustment for age, eGFR at diagnosis and gender for IMD1 vs 3 quintile: 1.46 (1.15-1.84), p=0.0017.

Conclusions: Outcomes in this large IgAN cohort have been published and shown to be poor with few patients expected to avoid kidney failure in their lifetime. This analysis demonstrates even worse outcomes if more socioeconomically deprived & highlights the need to develop strategies to ensure equity of access not only to early diagnosis but also to the new therapies that are showing promise in preventing kidney failure in IgAN.

IMD Quintiles	Age at diagnosis (median, 25th & 75th pctl)	Gender (M/F) (% IMD quintile)	White/ non-White (%)	eGFR at diagnosis (median, 25th & 75th pctl)	Time to kidney failure (median, 95% CI)
1- most deprived	38.9 (28.4, 51.2)	67.3/32.7	75.2/25.8	38 (21, 69)	7.9 (6.9, 9.3)
3	41.0 (29.4, 51.9)	69.9/30.1	86.2/13.8	39 (22, 70)	10.4 (9.0, 12.6)
5- least deprived	41.6 (30.6, 55.0)	74.3/25.7	88.5/11.5	37 (22, 68)	12.4 (11.1, 13.5)

Figure: Kaplan Meier plot showing time from diagnosis to ESKD, censoring for death



TH-PO619

Long-Term Renal Survival in Patients with IgA Nephropathy: A Systematic Review and Meta-Analysis

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Background: IgA nephropathy (IgAN), a primary glomerular disease named more than 50 years ago, is still one of the main causes of end-stage renal disease (ESRD) worldwide. Patients with ESRD incurred higher yearly costs and bear great financial pressure. Assessment of trends in renal survival could indicate whether changes in treatment strategies have resulted in improved long-term renal outcomes.

Methods: We searched the PubMed, Embase and Cochrane Database for cohort studies and clinical trials on renal survival with IgAN from their inceptions to November 2021. The outcome was defined as a composite of any of the following: doubling of serum creatinine level, 50% decline in estimated GFR (eGFR), or end-stage renal disease (ESRD). We extracted data on 3-year, 5-year, and 10-year renal survival in IgAN. Besides, we separately analyzed studies from developed countries and developing countries. We also analyzed the effect of proteinuria on long-term renal survival.

Results: We included 146 articles that reported on 98,334 patients from 1988 to 2021. The 3-year, 5-year and 10-year renal survival were 94.12% [95% confidence interval (CI) 94.08% to 94.16%], 88.64% (95% CI: 88.58% to 88.70%) and 77.46% (95% CI: 77.34% to 77.59%), respectively. In the past few decades, there have been no significant changes in 3-year and 5-year renal survival in IgAN patients. However, the 10-year renal survival of IgAN had gradually decreased since the late 1990s. Survival in developed countries was higher than in developing countries and fluctuate less. Furthermore, when proteinuria was < 1.0 g/24h, renal survival was improved.

Conclusions: We found that long-term renal survival was not increased over the years in IgAN. And the renal survival was lower in developing countries than in developed countries. The proteinuria was crucial in long-term prognosis of IgAN. When proteinuria was < 1g/24h, long-term renal survival was significantly improved. These results could be used to counsel patients on long-term renal survival and know the trend of survival in developed and developing countries.

Funding: Government Support - Non-U.S.

TH-PO620

Characteristics and Outcomes of IgA Nephropathy in the Canadian Province of Manitoba

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Background: Immunoglobin A (IgA) nephropathy is a common primary glomerulonephritis with variable clinical presentation. The aim of the current study was to characterize the population of patients with IgA nephropathy in the Canadian province of Manitoba.

Methods: In this retrospective, population-based cohort study, we identified all patients with biopsy-proven IgA nephropathy in the province of Manitoba, Canada between July 1, 2002 and December 31, 2019. Natural-language processing software was used for data extraction from pathology reports, which was then linked to administrative data via the Manitoba Centre for Health Policy. Descriptive statistics are presented to describe the patient population.

Results: We identified 366 patients (mean age at biopsy 43.2 years, 39.6% females). Mean estimated glomerular filtration rate (eGFR) at biopsy was 50 mL/min/1.73m^2, and mean urine albumin-to-creatinine ratio was 167.7 mg/mmol. Of the 122 patients with Oxford scores, 29 (23.8%) had M1, 46 (37.7%) had E1, 107 (87.7%) had S1, 29 (23.9%) and 43 (35.3%) had T1 and T2, respectively, while 33 (27%) had either C1 or C2. When stratifying by income quintiles, 31.7% of patients were in the lowest income quintile versus 9.6% in the highest. Comparing eras (2002-2010 versus 2011-2019), receipt of disease-modifying treatment within 6 months of biopsy remained stable for renin-angiotensin system inhibitors (69.6 vs 69.7%), anti-blood pressure medications (57.8 vs 60.6%) and glucocorticoids (23.0 vs 20.4%). Statin use increased significantly between periods (13.3% vs 29.0%, p<0.001). Patients were more likely to receive glucocorticoids if they had Oxford scores M1 versus M0 (41.4 vs 18.3%, p=0.01), E1 versus E0 (37.0 vs 15.8%, p=0.0078), or C1+2 versus C0 (51.5 vs 13.5%, p<0.0001). Over a median of 5.6 years of follow-up, 163 (44.5%) patients developed kidney failure and 69 (18.9%) patients died.

Conclusions: In this cohort, IgA nephropathy was associated with substantial risk of kidney failure and mortality. This study demonstrated the feasibility of using natural language processing as a data extraction technique, and will facilitate further epidemiologic research in this cohort. The study was limited by small sample size, incomplete Oxford scoring and lack of blood pressure data.

Funding: Government Support - Non-U.S.

TH-PO621

Analysis of the Real-World Management of IgA Nephropathy (IgAN) Patients in Five European Countries

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Background: Immunoglobulin A nephropathy (IgAN) is the most common form of primary glomerulonephritis worldwide. Current treatment strategies focus on controlling blood pressure and minimising proteinuria. This study investigated the real-world management of IgAN in five European countries through a physician questionnaire and patient chart review.

Methods: From 21 Dec 2022 to 6 Feb 2023, physicians from France, Germany, Italy, Spain and the UK completed a questionnaire on IgAN management, and patient charts from their centres were analysed. Physicians had to have ≥50 CKD stage 1–4 patients under their management, including ≥4 IgAN patients not on dialysis. Patients had to be ≥12 years, diagnosed with IgAN, not be on dialysis and have an eGFR ≥15 mL/min/1.73m^2.

Results: Participating physicians (N=261) each saw a mean of 30 IgAN patients in the past year. Patients audited as part of the study (N=473) were mostly male (71%), 78% were Caucasian, mean age was 47 years and 57% were in CKD stage 3. The mean time since referral to their current physician was 4.2 years. Proteinuria was >1 g/day in 66% of patients at referral and in 50% of patients at the current assessment (N=403 with both referral and current values). This was despite 92% of patients currently taking an ACE inhibitor and/or ARB, 43% taking an SGLT2 inhibitor and 16% taking a steroid. Physicians considered rate of eGFR decline to be moderate in 19% and fast in 6% of patients. However, among patients with eGFR values over 2 years (N=293), rate of eGFR decline was 3 mL/year in 12%, 4–5 mL/year in 16% and ≥6 mL/year in 19% of patients. Relapse occurred at least once in 54% of patients; steroid therapy was used to control the most recent relapse episode in 60% of patients. Most physicians (78%) agreed that they would prefer to administer therapies specifically approved for IgAN and 66% agreed that there is a lack of non-immunosuppressive treatments for IgAN.

Conclusions: Many patients with IgAN continue to have persistent proteinuria despite ACE inhibitor/ARB treatment, and progressive disease is common. Overall, this study indicates that there is a need for more effective treatment strategies to reduce proteinuria and disease progression in patients with IgAN.

Funding: Commercial Support - CSL Vifor

TH-PO622

Comparing Proteinuria and Kidney Survival in FSGS and IgA Nephropathy (IgAN): A NEPTUNE Analysis

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Background: Changes in disease activity markers are important outcomes for clinical trials in rare proteinuric kidney disease. While novel therapies may be effective in multiple etiologies, the relationship between proteinuria and kidney survival has not been directly compared across diseases.

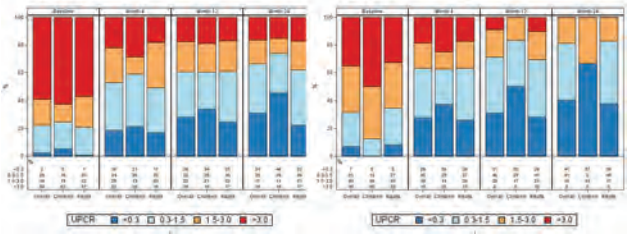
Methods: We studied children and adults with FSGS or IgAN enrolled in Nephrotic Syndrome Study Network (NEPTUNE) at the time of clinically indicated biopsy and followed prospectively with proteinuria and eGFR at each study visit. We tested the association between lowest proteinuria within 12 months (mo) after biopsy and the time to composite of ESKD/40% eGFR decline using Kaplan-Meier method.

Results: 211 FSGS and 58 IgAN patients were included. Compared to IgAN, FSGS patients had higher baseline eGFR, UPCR and obesity rates, but similar age and blood pressure. Relative change in proteinuria was -42% vs -39% by 12mo and -42% vs -63% by 24mo in FSGS and IgAN, respectively, but a significant proportion with either diagnosis did not achieve complete remission (Fig 1). Associations between higher protieinuria in 12mo and shorter kidney survival time were similar across diseases (Fig 2).

Conclusions: Lower proteinuria by 12mo after biopsy was associated with similar improvement in kidney survival in FSGS and IgAN. A substantial proportion of patients under usual care have high proteinuria at 24mo, highlighting unmet need for new treatments.

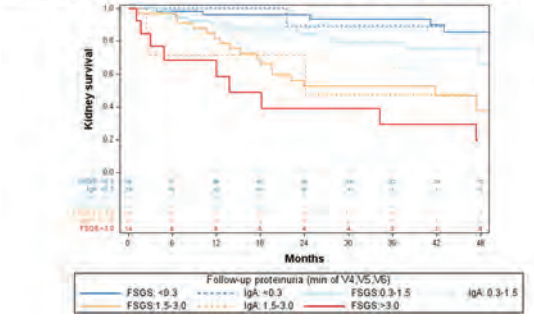
Funding: NIDDK Support, Other NIH Support - NCATS, Commercial Support - Travere Therapeutics

Figure 1: Proportion of patients reaching proteinuria thresholds over 24 months of follow-up, by pediatric and adult subgroups



Proportion of patients reaching proteinuria thresholds over 24 months of follow-up, by pediatric & adult subgroups

Figure 2: K-M survival for composite of 40% decline in eGFR or Kidney Failure, comparing FSGS to IgA by lowest proteinuria achieved in initial 12 months follow-up post-biopsy.



K-M survival for composite of 40% eGFR decline or ESKD, comparing FSGS to IgA by lowest proteinuria achieved in 12 months follow-up post-biopsy

TH-PO623

Sex Differences in Lupus Nephritis: A Meta-Regression Analysis

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Background: More frequent and severe lupus nephritis (LN) has been reported in men compared to women, but data are limited and inconsistent. We performed a meta-analysis to compare the histopathologic findings and outcomes between men and women with biopsy-proven LN (BPLN).

Methods: We conducted a systematic search of electronic databases through 2021 using the terms "lupus nephritis" and "sex/gender". Screening was limited to studies of adult patients with BPLN. We compared the biopsy findings and outcomes between the sexes. Pooled odds ratios (OR) with 95% confidence intervals (CI) were generated, and meta-regression performed to assess the impact of several covariates, using random-effects models.

Results: 25 studies were included (1210 men and 6635 women). 20 studies reported kidney histopathology, 11 kidney outcomes and 8 mortality rates. Men had a higher OR for class IV±V LN (1.26, 95% CI: 1.01-1.56) and the composite kidney outcome (doubling serum creatinine, kidney replacement therapy or eGFR<15 ml/min) (2.20, 95% CI: 1.59-3.06) and a lower OR for complete remission (0.52, 95% CI: 0.39-0.68) (Fig. 1). Meta-regression did not reveal statistically significant study-level relationships between sex differences in any of the covariates and the composite kidney outcome (Table 1).

Conclusions: Our analysis confirms the association between male sex and increased LN severity as well as worse kidney outcomes. Larger prospective studies are needed to validate this association and inform treatment strategies that may hold unique value for this high-risk population.

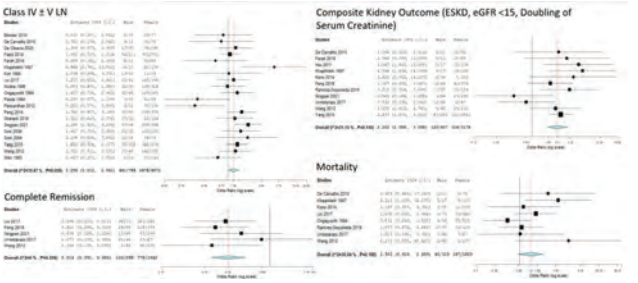

Figure 1. Forest plots showing the estimated OR with 95% CI for men with BPLN compared to women.

Characteristic	exp (β_1)	95% CI	p-value	Sample Size
Mean Difference in Age, years	1.02	0.91, 1.14	0.8	10
Mean Difference in Baseline Creatinine	3.00	0.64, 14.1	0.2	7
Mean Difference in Proteinuria	1.28	0.91, 1.80	0.2	7
Mean Difference in Activity Index	1.08	0.73, 1.57	0.7	6
Mean Difference in Chronicity Index	1.33	0.53, 3.34	0.5	6
Mean Difference in LN disease duration, months	1.01	0.93, 1.10	0.9	4
OR Diffuse Proliferative LN (class IV ± V)	1.15	0.92, 1.44	0.2	6
OR Complete Remission	0.13	0.01, 1.24	0.076	4
OR Hypocomplementemia (Low C3 or C4)	1.29	0.93, 1.80	0.13	4
OR Cyclophosphamide use	1.08	0.96, 1.21	0.2	5

Table 1. Meta-regression analysis for the effect of sex differences on the composite kidney outcome.

TH-PO624

Factors Predictive of Infections over Time in Lupus Nephritis Patients: Data from a Single-Center Retrospective Cohort

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Background: Infection is a common complication among patients with lupus nephritis (LN) who started treatment. Previous studies have shown that infection has become the leading cause of death in patients with LN. Therefore, early identification of risk factors for infection in LN patients is of great significance for complication prevention and improvement of prognosis. The aim of this study was to explore the clinical predictors of infection in patients with LN.

Methods: Patients who were diagnosed with LN and treated with immunosuppressive therapy at Guangdong Provincial People's Hospital from 2000 to 2020 were enrolled. Demographics, laboratory data, glucocorticoid dosage, antimalarial usage, immunosuppressive agents and infection details were included. Cox regression model was adopted to identify risk factors of infection. Both Univariable and multivariable analyses were performed.

Results: 1. A total of 374 LN patients were enrolled, of which 85.3% (n=319) were female. The average age was 30±12 years and the age ranged from 5 to 81 years. The mean of height was 1.58±0.99m and weight was 51.62±9.87kg. 219 patients (58.6%) with LN developed infection during follow-up, of which 111 (29.7%) were severe infection. 2. In order to compare changes of variables from 3 months, 6months and 12months after treatment, our study conducted cox regression analysis. We also conducted ROC and showed the AUC respectively (0.798, 0.700 and 0.521). Multivariable analysis demonstrated that IgM (HR=1.288,95%Cl : 1.074-1.544,p=0.006) and free light chain λ (HR=1.783,95%Cl : 1.000-3.177,p=0.050) were predictive factors of infection while after 3month treatment, anti-dsDNA reduction(HR=0.728,95%Cl : 0.563-0.924,p=0.016) and hemoglobin increase(HR=0.790,95%Cl : 0.652-0.958,p=0.017) were protective.

Conclusions: Our study showed that the incidence of infection in LN patients during treatment was high. Changes of variables in 3months after treatment had the most significant influence on infection and severe infection. High levels of IgM and serum free light chain λbefore treatment increase the risk of infection and dsDNA antibodies decreased and hemoglobin increased at the third month of treatment, were protective

Funding: NIDDK Support

TH-PO625

Cardiovascular and Renal Risks of Tacrolimus in Lupus Nephritis: A Long-Term Retrospective Cohort Study

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Background: Systemic lupus erythematosus is associated with an increased risk of cardiovascular disease. Tacrolimus is a calcineurin inhibitor that finds its origin in solid organ transplantation, but is also effectively used in lupus nephritis. In a transplant setting,

tacrolimus is associated with an increased cardiovascular risk, including nephrotoxicity, hypertension, dyslipidemia and hyperglycemia. In lupus nephritis the use of tacrolimus is off-label, and since head-to-head comparisons and long-term evaluations are lacking, its safety profile is less well-defined. Our objective was to investigate the long-term effects of tacrolimus on cardiovascular and renal outcomes in lupus nephritis patients.

Methods: In a retrospective, single-center cohort study, all adult lupus nephritis patients treated in the Leiden University Medical Center between 2004 and 2023 were investigated and dichotomized based on the prescription of systemic tacrolimus. We evaluated the Framingham risk score and the occurrence of cardiovascular events, diabetes, dyslipidemia, and change in kidney function.

Results: Of 223 patients that were enrolled in the study, 45 (20.2%) were ever prescribed tacrolimus. The remaining 178 patients had never been prescribed calcineurin inhibitors and were assigned to the control group. There was an equal incidence of cardiovascular events in both groups. The 10-year risk of coronary heart disease was significantly lower in the tacrolimus group, although this could largely be contributed to the age difference between the groups. Tacrolimus use was an independent predictor of eGFR decline, but this did not result in larger incidence of end-stage kidney disease during the follow-up period. There was no difference in the occurrence of diabetes or dyslipidemia between the groups, although there was a significant increase in HbA1c in the tacrolimus group.

Conclusions: Tacrolimus may have nephrotoxic and modest diabetogenic effects in lupus nephritis patients. Caution when prescribing tacrolimus and vigilance towards these possible side effects when continuing tacrolimus treatment as maintenance treatment is advised. However, further prospective studies in larger cohorts are necessary to confirm these findings and further assess the side-effects of tacrolimus in lupus nephritis patients.

TH-PO626

Exostosin 1-/Exostosin 2-Positive Membranous Lupus Nephritis Is Associated with a Favorable Kidney Prognosis

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Background: 30-35% of patients with membranous lupus nephritis (MLN) are positive for the exostosin 1/2 (EXT1/2) staining. Previous studies have suggested that positive EXT1/2 stain is associated with better response to therapy, kidney prognosis, and low rates of transition to proliferative nephritis. We evaluated the prevalence of EXT1/2 staining in our cohort of pure MLN and its association with response to therapy and long-term kidney outcomes.

Methods: Retrospective cohort study. From 100 patients with membranous nephropathy we evaluated 53 patients with pure MLN and follow-up >5 years. EXT1/2 was detected by immunohistochemistry. We compared the clinical and histopathological presentation of EXT1/2 positive and negative patients. The kidney outcomes of response to therapy, 40% decline in eGFR, doubling of serum creatinine, and kidney failure were assessed by survival analyses.

Results: Fourteen (26%) MLN patients had positive EXT1/2 staining. Patients with positive EXT1/2 staining were younger and had a higher eGFR at presentation. There were no differences in complete or partial response between both groups (log-rank p=0.118 and p=0.412, respectively). Over a median follow-up of 118 months (IQR 73-172), none of the EXT1/2 positive and 9 of the EXT1/2 negative patients progressed to 40% decline of the eGFR with 5- and 10-year 40% eGFR decline rates of 0% and 0%, and 16% and 26%, respectively (log-rank p=0.046, Figure 1). No differences were observed in progression to doubling of serum creatinine or kidney failure. All patients were alive at the last date of follow-up.

Conclusions: EXT1/2 positive MLN is associated with similar response to therapy than EXT1/2 negative MLN, but better long-term kidney prognosis.

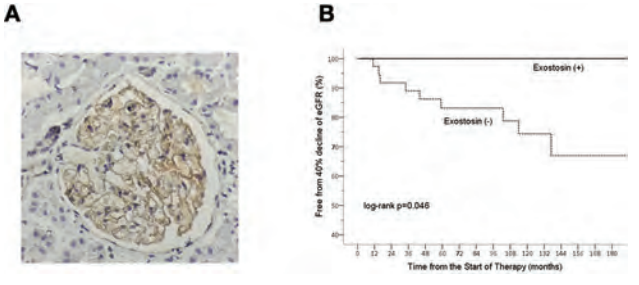

Figura 1. Glomerular EXT1/2 immunohistochemistry (A) and kidney outcome of 40% decline in eGFR according to EXT1/2 staining.

TH-PO627

The Impact of Late Renal Biopsy on Renal Survival in Patients with Lupus Nephritis

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Background: Brazil is the American country with the highest African ancestry. In lupus nephritis (LN) it is possible to observe differences in incidence and even severity according to the location and characteristics of the population studied. This study aims to describe the clinical-epidemiological profile and the influence of late diagnosis in patients with LN at the Nephrology Service of the Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, between the period from 1999 to 2015.

Methods: Retrospective descriptive observational study of patients diagnosed with LN and biopsied before six months of the onset of LN symptoms compared to those biopsied after six months or more than of the onset of symptoms.

Results: The total sample size was 398 patients. FAN was positive in 94.1% of patients, anti-DNA in 77.7% and anticardiolipin in 27.1%. The full-house pattern was observed in 124 patients (33.7%). Considering the time from the onset of LN-related symptoms until the kidney biopsy, in 47.5% this time was less than 6 months (early group) and in 52.5% this time was greater than or equal to 6 months (late group). The chronicity index was lower in the group biopsied less than 6 months, 2(1-4) vs 3(2-5), p= 0.003, with a higher activity index in this same group (5 (3-8) vs 4 (3-6), p= 0.006). The chronicity index had a positive correlation with initial, 3-month, 6-month and 5-year creatinine after renal biopsy, with r=0.56 and p< 0.0001, r=0.51 and p<0.0001, r=0.51 and p<0.0001 and r=0.38 and p<0.0001, respectively. Fifty-three patients progressed on dialysis over five years of follow-up and in uni and multivariate analysis late renal biopsy and chronicity index starting at 4 were independent factors for this worse outcome.

Conclusions: This study showed that renal outcomes in renal replacement therapy or chronic kidney disease were associated with delayed renal biopsy and higher chronicity index at diagnosis. Late biopsy comes from a delay in referral to a tertiary hospital nephrologist and therefore a delay in diagnosis and initiation of appropriate treatment for that patient.

TH-PO628

Comparison of Renal Outcomes Between Primary Membranous Nephropathy and Membranous Lupus Nephritis: A Prospective Multicenter Study

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Background: Primary membranous nephropathy (PMN) and membranous lupus nephritis (MLN) are autoimmune disorders characterized by immune complex deposit in the glomerular basement membrane. The optimal immunosuppressive regimen for these conditions remains undefined, and limited research exists on their renal outcomes.

Methods: This study included 108 patients with PMN and 43 patients with MLN (23 Class V only, 20 Class V + III or IV) diagnosed through renal biopsy at eight South Korean hospitals from September 2015 to April 2022. All patients received standard immunosuppressive therapy, including glucocorticoids with additional agents such as calcineurin inhibitors, mycophenolate mofetil, or cyclophosphamide. Renal outcome was assessed by comparing serum creatinine levels at baseline and one year, adjusted to baseline levels. The response rate was defined as CR (<0.5g/g reduction in proteinuria), PR (≥50% reduction in proteinuria), and TF (failure to achieve CR or PR). Median follow-up period for was 11 months in both PMN and MLN.

Results: PMN patients exhibited older age (57.5±12.9 vs 37.4±14.1, p<0.001), higher male proportion (86.1% vs 37.0%, p<0.001), higher BMI (26.0±4.6 vs 23.0±5.1, p=0.002), increased prevalence of hypertension (50% vs 16.3%, p<0.001), higher serum creatinine (0.9±0.4 vs 0.7±0.3, p=0.03), decreased albumin (2.6±0.7 vs 2.9±0.7, p=0.041), and increased urine protein creatinine ratio (6.1±3.6 vs 4.4±4.8, p=0.015) compared to MLN patients. After one year, in multivariated regression analysis, PMN patients showed that the increase rate of serum creatinine was higher than MLN patients (22.4% vs 11.7%, p=0.027), indicating worse renal function in the PMN group, while the reduction rate of proteinuria was similar in both groups (57.6% vs 61.7%, p=0.306). Response rates (CR+PR) and treatment failure rates (TF) did not significantly differ between the two groups (PMN: CR+PR=77.8%, TF=22.2%; MLN: CR+PR=76.7%, TF=23.3%; p=0.891).

Conclusions: This study showed the comparable response rate between PMN and MLN patients after treatment with immunosuppression. However, PMN patients had more deteriorated renal function compared to MLN patients during the median follow-up period of 11 months. Further evaluation with longer follow-up is necessary to gain comprehensive insights into renal outcomes in these patient groups.

TH-PO629

Clinical Outcome of NELL1-Associated Membranous Nephropathy

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Background: Neural epidermal growth factor-like 1 -associated membranous nephropathy (NELL1 MN) is related to multiple secondary causes, including malignancy and intake of complementary and alternative medicines. The association of CAM intake to NELL1 MN is well-reported in India. However, the outcome of the NELL1 MN remains to be determined.

Methods: We analysed retrospectively clinicopathologic features of NELL1 MN and compared them to non-M-type Phospholipase A2 receptor (PLA2R)/NELL1 MN from our PGIMER-primary MN registry and LTMC, Mumbai. We express the data as numbers, percentages, mean ± standard deviation (range) for normally distributed variables and median and interquartile range, otherwise.

Results: A total of 21 patients had NELL1 MN; the median age, proteinuria, creatinine, and albumin were 37 (26.5,55.5) years, 6.7(3.9,10.5) g/day, 1 (0.7,1.4) mg/dl and 2.4 (1.9,2.7) g/dl, respectively. 14(67%) patients received a modified Ponticelli regimen. For comparison, we included 21 consecutive patients of non-PLA2R/NELL1 MN. The median age, proteinuria, creatinine and albumin were 41 (30,54) years, 5.3 (2.7,8.7) g/day, 1 (0.7,1.3) mg/dl and 2.4 (1.9,3.0) g/dl, respectively. 14 (67%) had a history of CAM intake in the NELL1 MN group, which was higher than the non-PLA2R/NELL1 MN group (p<0.001); the malignancy work-up was negative in all the cases. The requirement for immunosuppressive therapy was higher in the NELL1 MN group compared to the non-PLA2R/NELL1 MN group (p=0.04). In the NELL1 MN group, we lost two patients to follow-up after a median follow-up of 18 (10,28) months; 15 (79%) patients achieved remission. Two patients died due to infectious complications. 78% and 65% of the patients in the NELL1 and non-PLA2R/NELL1 MN achieved remission (p=0.48).

Conclusions: The present report highlights the association of NELL1 MN with CAM intake compared to non-PLA2R/NELL1 MN. Three-fourths of the NELL1 MN responded to in-sighting drug withdrawal/ immunosuppressive therapy.

Funding: Government Support - Non-U.S.

TH-PO630

Kidney Outcomes in Self-Reported Black Patients with Primary Membranous Nephropathy in the Cure Glomerulonephropathy Study (CureGN)

Margaret Helmuth,[1] Salem Almaani,[2] Isabelle Ayoub,[2] Dhruti P. Chen,[3] Leonela A. Villegas,[4] Cynthia C. Nast,[5] Bruce M. Robinson,[6] Vimal K. Derebail,[3] Andrew S. Bomback,[7] Louis-Philippe Laurin.[8,9] Cure Glomerulonephropathy Study. *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]The Ohio State University Wexner Medical Center, Columbus, OH; [3]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]Connecticut Children's Medical Center, Hartford, CT; [5]Cedars-Sinai Medical Center, Los Angeles, CA; [6]University of Michigan, Ann Arbor, MI; [7]Columbia University, New York, NY; [8]Hopital Maisonneuve-Rosemont, Montreal, QC, Canada; [9]Universite de Montreal, Montreal, QC, Canada.*

Background: Primary membranous nephropathy (pMN) is a common cause of nephrotic syndrome in adults. Disease progression in Black versus non-Black patients with pMN remains to be fully characterized.

Methods: CureGN is an ongoing multi-center prospective, observational cohort of children and adults with biopsy-proven pMN or 3 other primary glomerular diseases. First diagnostic biopsies were performed between 2010 and 2023. For this analysis, we report baseline clinical data at enrollment, proportion of time on immunosuppression during follow-up, and incident rates for kidney failure and 40% eGFR decline. Time to kidney outcomes was estimated using adjusted Cox proportional hazards models.

Results: As of May 2023, 608 pMN patients were enrolled (580 with available follow-up data). Of those, 93 were self-reported Black/African American race: median age 52 (IQR, 37-64); 39% female; and median follow-up time of 4.4 yrs. Among 444 pMN patients genetically sequenced, 12 (3%) had 2-high risk APOL1 alleles; of the 73 pMN patients with self-reported Black/African American race who were sequenced, 11 (15%) had 2-high risk APOL1 alleles.

Conclusions: In patients with pMN, self-reported Black race appears to be strongly associated with worse kidney outcomes despite having similar eGFR at enrollment. Additional analyses including assessment of genetic factors are underway to gain understanding of determinants of this observed association.

Funding: NIDDK Support

	Black (N=93)	Non-Black (N=515)
Median eGFR at enrollment (mL/min/1.73m^2) (IQR)	76.5 (51.2-103.9)	78.4 (52.6-101.0)
Median urine protein to creatinine ratio at enrollment (IQR)	4.3 (1.5-8.2)	2.7 (0.7-6.3)
Proportion of time on any immunosuppression during study follow up (%)	27	28
Kidney failure rate (per participant year)	0.053	0.016
eGFR decline >40% rate (per participant year)	0.082	0.033
Kidney outcomes (Black vs. Non-Black)	**HR (95% CI)**	**p-value**
Kidney Failure	3.3 (1.6-6.6)	0.0008
Kidney Failure & eGFR decline >40%	2.4 (1.4-3.9)	0.0007
Complete Remission*	0.7 (0.4-1.1)	0.1

All models are adjusted for sex, age at biopsy, immunosuppression use prior to biopsy, UPCR at enrollment, eGFR at enrollment and time from biopsy to enrollment. *Among those who entered the study not in complete remission. eGFR = estimated glomerular filtration rate (per CKiD-U25 if age <25 years or CKD-EPI-2021).

TH-PO631

Membranous Nephropathy Outcomes Among Children and Adults: Cure Glomerulonephropathy Study (CureGN)

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Background: Membranous nephropathy (MN) is a rare entity in children, whereas it's one of the most common causes of primary nephrotic syndrome in adults. There are limited data on disease progression in children, as well as uncertainty about differences between childhood vs adult-onset MN.

Methods: CureGN is a multi-center prospective, observational cohort of individuals with biopsy-proven glomerular diseases. For this analysis, baseline clinical data and proportion of time on immunosuppression (IS) across study follow up were reported. Cox proportional hazard models were used to estimate time to kidney outcomes, and linear mixed models to assess estimated glomerular filtration rate (eGFR) trajectories. Models were adjusted for sex, age at biopsy, IS prior to biopsy, urine protein to creatinine ratio (UPCR), eGFR, and time from biopsy to enrollment.

Results: Among 608 MN participants (580 with ≥1 follow-up visit), 54 (9%) had childhood-onset MN (age <18 at time of biopsy) with characteristics including: 48% female, median age 14 years (IQR, 12-17), and 15% self-identify as Black. Overall, childhood-onset MN had an increased risk of end stage kidney disease (HR, 5.1; 95% CI, 1.45-18) in comparison to adults. The eGFR decline was steeper in children (-3.75 (±0.87) ml/min/1.73m2 per year) than adults (-0.14 (±0.78) ml/min/1.73m2 per year) (p<0.0001).

Conclusions: Despite potential for remission, children with MN had steeper eGFR decline and faster time to kidney failure than adults. Additional data are needed to extend our understanding of determinants of disease and outcomes to guide therapies and inform practice guidelines.

Funding: NIDDK Support

	Children (n=54)	Adults (n=554)
Enrollment		
Median eGFR (ml/min/1.73m2, IQR)*	107 (91-122)	77 (50-98)
Median UPCR (mg/mg, IQR)	1.5 (0.4-5.3)	2.9 (0.9-6.6)
Follow-up		
Follow-up time (years, IQR)	4.7 (3.0-6.4)	4.4 (2.4-6.0)
Proportion of time off IS (%)	57	74

*CKiD-U25 if age <25 year, CKD-EPI-2021 if age ≥ 25 years

Outcomes	Children		Adults		HR (95% CI)	P-value
	N	%	N	%		
Kidney Failure	8	15	43	8	5.1 (1.5-18)	0.011
Composite Endpoint: Kidney Failure or eGFR decline >40%	13	24	98	18	3.3 (1.6-6.9)	0.001
Complete Remission*	21/26	81	103/156	66	2.2 (1.3-3.7)	0.005

*Among participants who entered the study not in complete remission

TH-PO632

The Epidemiology of Primary Membranous Nephropathy: A Single-Centre Study over Two Decades

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Background: Membranous nephropathy is the commonest cause of nephrotic syndrome in non-diabetic White adults over the age of 40, and can be either primary (pMN) or secondary. Management aims to induce remission- spontaneously with supportive care, or with immunosuppression (IS). Here, we describe the natural history of this condition in a large tertiary centre in the UK.

Methods: 178 patients with pMN were identified over 2 decades. We collected data on demographics, baseline laboratory values, treatment received and outcomes including progression to renal replacement therapy (RRT) and mortality. Analysis was performed on the whole cohort and specific subgroups.

Results: Median age was 58.3 years with 63.5% male. Median baseline eGFR was 76.7mls/min/1.73m^2 and urine protein-creatinine ratio 664g/mol. Remission (partial or complete) was achieved in 134 (75.3%), either spontaneous in 60 (33.7%) or after treatment with IS in 74 (41.6%), and of these 57 (42.5%) relapsed. Progression to RRT was seen in 10.1% with mortality in 29.8%. Those who went into remission had improved outcomes compared to those who did not (less progression to RRT [4.5% vs 28%] and death [20.1% vs 67%]). Those classified as high risk as per KDIGO also had worse outcomes than those at low risk (mortality seen in 52.6% vs 10.8%, p<0.001).

Conclusions: We provide a comprehensive epidemiologic analysis of pMN at a large tertiary UK centre. Only 10.1% progressed to RRT (much lower than classically reported). For novelty, the KDIGO risk classification was linked to outcomes, highlighting its utility for identifying patients most likely to progress. The Salford glomerulonephritis research group was supported by an unrestricted project grant from CSL Vifor.

Funding: Commercial Support - CSL Vifor

Variable		Total (n= 178)
Age at time of biopsy, years (IQR)		58.3 (44.2-67.1)
Male, *n* (%)		113 (63.5)
Caucasian, n (%)		158 (88.8)
Diabetes *n (%)*		19 (10.7)
Hypertension, *n* (%)		97 (54.5)
Cardiovascular disease, *n* (%)		28 (15.7)
SBP, mmHg (IQR)		135 (122-148)
DBP, mmHg (IQR)		79 (70-85)
Haemoglobin, g/L (IQR)		130 (119-143)
Albumin, g/L (IQR)		28 (22.3-32.8)
Corrected Calcium, mmol/L (IQR)		2.38 (2.28-2.48)
Phosphate, mmol/L, (IQR)		1.21 (1.04-1.35)
anti-PLA2R positive, *n* (% of those with result available)		34 (59.6)
anti-PLA2R, U/ml (IQR)		122 (25.6-190)
eGFR, mls/min/1.73 m^2, (IQR)		76.7 (51.7-90)
Creatinine, µmol/L (IQR)		89.5 (70-122)
uPCR, g/mol (IQR)		664 (393-1007)
Remission, *n* (%)	Spontaneous	60 (33.7)
	After treatment	74 (41.6)
	Total	134 (75.3)
Relapse, *n* (% of those who went into remission)		57 (42.5)
Received ACEi/ARB, *n (%)*		167 (93.8)
Progressed to RRT, *n* (%)		18 (10.1)
Death, *n* (%)		53 (29.8)
Follow up duration, months (IQR)		

Baseline demographics, laboratory values and major outcomes for the total cohort.

TH-PO633

Characteristics of Membranous Nephropathy Patients Presenting with an Arterial or Venous Thromboembolism: A Retrospective Cohort Study

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Background: Membranous nephropathy (MN) is associated with a very high risk for developing arterial (ATE) or venous (VTE) thromboembolism. A previous study suggested an association between high PLA2Rab titers and ATE/VTE risk. We aimed at comparing MN patients with ATE/VTE at presentation versus MN patients without.

Methods: A total of 508 incident nephrotic MN patients were enrolled in this study. Nephrotic patients with ATE/VTE from six months prior and up to two weeks after the diagnosis of MN were defined as cases. Controls were MN patients without ATE/VTE. Differences in baseline data and outcome were studied.

Results: Twenty-five patients (5%) with ATE (n=6) or VTE (n=19) at presentation were compared to 483 patients without ATE/VTE. Baseline characteristics are presented in table 1. Approximately 75% of patients were PLA2Rab positive. There were no differences in PLA2Rab titer nor in severity of nephrotic syndrome between patients with or without ATE/VTE (Table). During follow-up (median 28.5 [11.7 – 66.4] months), 64% in the VTE/ATE group was treated with immunosuppressive therapy, compared to 58% in the control group (p = .713). Spontaneous remissions occurred in three patients in the ATE/VTE group.

Conclusions: We could not confirm the association between higher PLA2Rab levels and presentation with ATE/VTE. All patients were severely nephrotic, likely explaining the futility of serum albumin. Better biomarkers of thrombotic risk are needed.

Table 1. Baseline characteristics of the studied MN patients with and without an ATE or VTE at presentation

Baseline characteristics	With ATE/VTE (n=25)	Without ATE/VTE (n=483)	p Value
Gender (male, n (%))	20 (80)	336 (70)	0.375
Age (years)	55 ± 13	55 ± 15	0.999
PLA2R-related M (n, %)	20 (80)	358 (74)	0.673
sCreatinine (umol/l)	102 [81-149]	91 [77-113]	0.263
sAlbumine (g/L)	18 [14-24]	20 [16-24]	0.187
UPCR (g/10 mmol)	8.0 [5.9-9.9]	6.9 [5.0-10.3]	0.269
PLA2R-ab titer (RU/ml)*	91 [50-153]	87 [22-218]	0.604

*aPLA2R titers at presentation were available for 16 and 360 patients in the cases and control groups respectively.

TH-PO634

A Nomogram Prediction Model for Treatment Failure in Primary Membranous Nephropathy

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Background: The natural course of primary membranous nephropathy (PMN) is heterogeneous. Immunosuppressive therapy is recommended to PMN patients at risk for renal function deterioration. Prediction model for treatment failure of PMN has been rarely reported.

Methods: This study retrospectively included PMN patients diagnosed by renal biopsy in Sichuan Provincial People's Hospital from January 2017 to December 2020. Information of clinical characteristics, laboratory test, pathological examination, and treatment was collected. The outcome was treatment failure at the end of twelve months. Simple logistic regression was used to identify candidate predictive variables. Forced-entry stepwise multivariable logistic regression was used to develop the prediction model, of which the performance was evaluated using AUC, calibration plot, and DCA analysis. Internal validation was performed using bootstrapping method.

Results: A total of 310 patients were recruited in this study. The comorbidity rates of hypertension and diabetes were 37% (112/310) and 11% (33/310), respectively. At renal biopsy, the medium levels of eGFR, serum creatinine, serum albumin, proteinuria and PLA_2R antibody were 102.3 ml/min/1.73m^2, 70.1 µmol/L, 24.3 g/L, 5.9 g, and 35.48 RU/ml. 116 patients achieved the outcome. Forced-entry stepwise multivariable logistic regression indicated that PLA_2R antibody (OR=1.002, 95%CI: 1.001-1.003, P=0.002), renal interstitial inflammatory cells infiltration (OR=1.935, 95%CI: 1.393-2.478, P=0.017), and C3 deposit on immunofluorescence (OR=0.294, 95%CI: -0.928-1.515, P=0.049) were the three independent risk factors for treatment failure of PMN. The final prediction model has an AUC (95% CI) of 0.653(0.590-0.717) and a net benefit in the range of 23%-77%.

Conclusions: PLA_2R antibody, renal interstitial inflammatory cells infiltration, and C3 deposit on immunofluorescence were the three independent risk factors for treatment failure at 12 months in PMN. Our prediction model may help to identify patients with risk of treatment failure thus avoid unnecessary drug exposure and side effects.

TH-PO635

Interim Analysis of Dapagliflozin in Inactive Lupus Nephritis Cross-Over Randomized Trial

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Background: Clinical trials with sodium-glucose co-transporter 2 (SGLT2) inhibitors have demonstrated to slow the progression of CKD but excluded Lupus Nephritis (LN) patients. This study will assess efficacy and safety of dapagliflozin in inactive LN with residual proteinuria.

Methods: The present cross-over RCT(RBR-3vcg568) is including adults with chronic LN class III or IV(+/-V), proteinuria >500mg/24h and eGFR ≥20ml/min in maintenance therapy. RAASi should be stable >4w. We exclude patients with recurrent urinary infections; biopsy with active LN (AI>2) and use of induction therapy in the last 12mo, including CNI; and prednisone ≥20mg/d. Patients are randomized to receive dapagliflozin 10mg on top of standard of care (SoC) therapy or not. After 24w the groups are switched off. Primary endpoint is reduction of proteinuria compared to baseline at 6 and 12mo. Secondary endpoints are changes in weight and blood pressure and number of infections. The sample size was calculated for 28 patients enrolled for 80% power to detect a 25% relative risk reduction in proteinuria (α=0.05).

Results: From 87 screened class III or V(+/-V) LN patients in maintenance therapy, we excluded 67 due to active LN, low proteinuria or low eGFR. We have included 20 patients that were randomized 1:1. There were 18 (90%) women, mean age was 39.5y (±11.1), 1 (5%) had diabetes, median eGFR was 49.5ml/min (40.8-113.8), median proteinuria was 1133mg/24h (833.8-1749), 1 (5.5%) had low C3 or C4, all patients had SLEDAI ≤6 and used MMF≤2g/day. We analysed 6 and 7 patients from initial dapa and 6 and 4 patients from initial SoC after 3 and 6mo, respectively. Although the sample was not powered to compare the groups, initial results showed lower proteinuria in both groups at 3 and 6mo compared to baseline but did not show differences between them. Dapagliflozin was well tolerated, there were no infection episodes during the follow-up,

no weight and blood pressure changes, but 5 (45.4%) patients with dapagliflozin had symptoms of hypotension.

Conclusions: We expect that the complete results of this trial will help to evaluate whether the SGLT2 inhibitor, added to LN maintenance therapy, could safely reduce the residual proteinuria of inactive LN patients.

Funding: Government Support - Non-U.S.

TH-PO636

Current Status of Treatments for IgA Nephropathy in Japan: A Descriptive Study Using Claims Database

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Background: Several questionnaire-based studies have clarified the current status of treatment for IgA nephropathy (IgAN) in Japan. However, there have been few studies on based on the medical claims records. The aim of this study is to clarify the current treatment status for IgAN using the medical claims database in Japan.

Methods: Medical claims data were retrieved from JMDC (Tokyo, Japan). To interpret the medical claims data, we used the International Classification of Diseases, Tenth Revision codes (ICD-10) for disease, Anatomical Therapeutic Chemical (ATC) codes for drugs, names of the medical practice for treatment procedure, respectively. First, we extracted the claims who had disease code of IgAN from April 2014 to October 2020 (31282 patients, 469173 receipts). Then, we included the patients aged between 18 and 80 years at the index date with confirmed IgAN diagnosis at least 6 months of continuous insurance coverage/enrollment after the index date. We defined the newly diagnosed IgAN patients as those who underwent renal biopsy and confirmed IgAN more than twice (at least once as the "main disease"). Treatment patterns were categorized by ATC codes and names of the medical practice. Patient who occurred in severe infectious disease was defined as recorded the sequential organ failure assessment score in hospital record.

Results: Among the 4554 included patients, 2200 patients (48.3%) received the corticosteroids. Of those, severe infectious disease occurred in only 8 patients (0.17%). Renin-angiotensin system inhibitors (RAS-I) were used in 2682 patients (58.9%). Women aged 18-29 years had a lower prescription rate of RAS-I (30.2%) than other groups. Of the 805 patients were newly diagnosed IgAN (49.6% men; mean age 44.9), 396 patients (49.2%) underwent the tonsillectomy and 684 patients (85.0%) underwent the corticosteroid therapy including the oral corticosteroid alone respectively. Tonsillectomy with corticosteroid pulse therapy was the most commonly chosen initial treatment procedure (358 patients: 44.5%).

Conclusions: Tonsillectomy with corticosteroid pulse therapy was the standard treatment in Japan.

TH-PO637

Clinical Manifestation and Prognosis of Membranous Nephropathy in Patients with Primary Sjögren Syndrome

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Background: Glomerulonephropathy (GN) in primary Sjögren's syndrome (pSS) was rare. We aimed to compare the clinical features and prognosis between patients with membranous nephropathy and pSS (pSS-MN) and idiopathic MN (iMN) patients.

Methods: From January 1993 to September 2022, at Peking Union Medical College Hospital, we enrolled 96 pSS-MN patients diagnosed with renal pathology and the revised version of the American-European Consensus Group. The control group was 150 iMN patients diagnosed with renal pathology and positive serum anti-M-type phospholipase A2 receptor (PLA2R) antibody.

Results: Compared to the iMN patients, the pSS-MN patients were older, predominantly females (80.2% vs. 44.7%, $P < 0.05$), with lower 24h urine proteins, higher serum IgG levels, more anemia, and hypocomplementemia. pSS-MN patients had lower ratios of positive serum anti-PLA2R antibody (34.0% vs. 59.1%) and positive tissue PLA2R antigen (65% vs. 87.3%) (both $P < 0.05$). During the median time of 22 months, treated with a combination of glucocorticoids, immunosuppressive agents (cyclophosphamide, calcineurin inhibitors, tripterygium glycosides), or rituximab, the patient's eGFR remained normal. Moreover, the 24h urine proteins decreased from 3.1 g/d to 0.8 g/d.

Conclusions: We reported the largest cohort of pSS-MN patients displayed more pronounced immunological anomalies, with a lower prevalence of positive serum anti-PLA2R antibody and tissue PLA2R antigen than the iMN patients, and responded well to the treatment with stable eGFR.

Funding: Government Support - Non-U.S.

TH-PO638

Membranous Nephropathy: A Retrospective Observational Study in a Single Renal Unit

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Background: Membranous Nephropathy (MN) is a common cause of nephrotic syndrome in adults. The diagnosis and treatment paradigms for MN have evolved with the identification of PLA2R autoantibodies and evidence for the use of Rituximab. We aim to retrospectively examine the treatments and outcomes of all adults diagnosed with MN in a single renal centre, March 2013 to March 2023.

Methods: Patients' demographics, clinical presentation, treatments, full remission (FR), partial remission (PR), relapse, renal outcome and complications were collected via electronic health records.

Results: In total, 75 patients were identified with 13 diagnosed as secondary MN. Of the 58 patients with primary MN, their mean age was 57 (SD=14) years with 72% male and 35% positive serum anti-PLA2R. At diagnosis, their mean eGFR was 68 (SD=27) ml/min, uPCR 781 (SD=557) mg/mmol, serum albumin 20 (SD 6) g/L. 98% received RAAS inhibitor. Ten patients (17%) achieved FR or PR without further need of immunosuppressive therapy (IS). Of the 48 patients, the median time from diagnosis to start of IS was 2 (IQR 4) months. The majority (63%) received oral cyclophosphamide and prednisolone (CYP) as first line IS, whilst 19%, 15% and 4% received calcineurin inhibitor (CNI), prednisolone only and Rituximab, respectively. After first IS, 26% and 24% achieved FR and PR. 23 patients (47%) required second course of IS whilst 11 and 5 patients required third and fourth courses of IS, respectively. Relapses occurred in 29% of the patients. Overall, the mean eGFR at 6 months, 12 months, 2 years and 5 years was 64, 61, 62, 56 ml/min, two progressed to kidney failure and five died. The FR and PR rates were 41%, 37% following CYP, 47%, 11% following CNI and 27%, 64% following Rituximab. Pancytopenia (n=1), deranged liver function test (n=2), recurrent or opportunistic infections (n=3) and malignancies (n=4) were reported amongst those who received CYP. No significant complications were reported with Rituximab since its first use in October 2020.

Conclusions: In this cohort of MN, their overall long-term renal outcome was favourable. Although the FR rate was < 50%, progression to kidney failure was rare. Relapses remain a challenge. IS is complicated by infection and neoplasia. Biologics and diagnostics may refine therapy options in the future.

TH-PO639

The Natural History of Focal and Segmental Glomerulosclerosis (FSGS)

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Background: FSGS is the tissue manifestation of various kidney diseases that ultimately lead to end-stage kidney disease in most patients. Their rare and heterogeneous presentations and unpredictable responses to therapies pose a tremendous challenge. Here we report on one of the most extensive natural history studies of patients with a biopsy diagnosis of FSGS.

Methods: Nine collaborating sites are enrolling 800 patients with primary, genetic, or FSGS of unknown cause (Fig. 1A) diagnosed between Jan. 1, 2000, and Aug. 1, 2021. The time of the first kidney biopsy is the index date, flanked by pre-biopsy baseline patient characteristics and longitudinal follow-up data of outcomes of interest (Fig. 2B & C).

Results: We have collaboratively created a decentralized registry with 366 data elements for patients with glomerular diseases, secured regulatory approval for deidentified data sharing, and enrolled 103 eligible patients to date.

Conclusions: Large retrospective studies of rare diseases face difficult-to-overcome challenges, including variability in data, uniform definitions, and a need for a regulatory framework for data sharing. Here, we have leveraged a decentralized registry to exchange deidentified patient information, creating a large multi-site retrospective study for patients with FSGS across highly diverse populations and healthcare settings.

Funding: Commercial Support - Travere Therapeutics

Adult patients (age ≥18 years) with a tissue diagnosis of FSGS based on a native kidney biopsy performed during the study period who have a minimum of one-year clinical follow-up data.

Inclusion criteria:

- A tissue diagnosis of FSGS (native kidney biopsy report), with any degree of foot process effacement that is suspected to be due to "primary FSGS"
- A tissue diagnosis of FSGS (native kidney biopsy report), suspected to be "secondary FSGS," however without any apparent histological or clinical evidence of a secondary cause.
- Genetic podocytopathies

Exclusion criteria:

- Type 1 DM or uncontrolled DM2 (HbA1c >8% or 64mmol/mol) at time of kidney biopsy
- History of HIV, HepB, or HepC infection
- Presence of any systemic autoimmune disorders such as lupus, IgA, ANCA GN, MGRS, etc.
- Presence of any secondary cause such as morbid obesity (BMI>40 kg/m2), COVID19 associated FSGS, inherited basement membrane disorders, drug-induced FSGS (including but not limited to bisphosphonates, cocaine, heroin, and anabolic steroids)
- Collapsing FSGS

Figure 1. Study population inclusion criteria

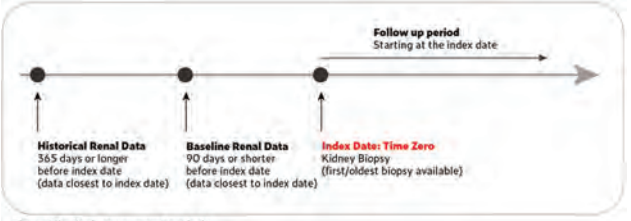

Figure 2A. Study assessment periods

Outcome	Definition
eGFR	Percent change in eGFR from baseline at years one, three, and five. eGFR is calculated using the new creatinine-based equation to estimate GFR without race
Slope of eGFR	Slope of eGFR assessed at years one, three, and five.
Proteinuria	Percent change in proteinuria from baseline at years one, three, and five, post biopsy.
Time to partial remission	The probability of achieving a UPCR ≤1.5 g/g and a >40% reduction from baseline in UPCR at years one, three, and five.
Time to complete remission	The probability of achieving no proteinuria (UPCR <0.2 g/g or ACR < 30, or dipstick trace or negative for protein) at years one, three, and five.
Time to MAKE (Major Adverse Kidney Events)	The probability reaching a confirmed 40% change in eGFR, end-stage renal disease (ESRD), or death. (ESRD is defined as initiation of renal replacement therapy [RRT], kidney transplantation, or eGFR <15 mL/min/1.73 m2 at years one, three, and five from the index date
eGFR decline	The probability reaching a confirmed 40% change in eGFR
End-stage renal disease (ESRD)	ESRD is defined as initiation of renal replacement therapy [RRT], kidney transplantation, or eGFR <15 mL/min/1.73 m2 at years one, three, and five from the index date
Renal death	Deaths that result from renal failure and immediate sequalae of this, such as uremia, hyperkalemia leading to cardiac arrest, acute kidney injury.
Time to MACE	The probability of major adverse cardio-vascular events defined as nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death at years one, three, and five from the index date.
Hospitalizations	Frequency and duration of hospitalizations
Cardiovascular death	Deaths that result from an MI, sudden cardiac death, death due to heart failure, death due to stroke, death due to cardiovascular procedures, death due to cardiovascular hemorrhage, and death due to other cardiovascular causes
All cause death. Time to event.	Any death. Mortality risk at years one, three, and five from the index date.

Figure 2B. Outcomes of interest.

TH-PO640

Incidence Rates of Primary Focal Segmental Glomerulosclerosis (FSGS) Within a Diverse Adult Southern California Population, 2010-2021

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Background: FSGS is a leading cause of end-stage kidney disease. However, little epidemiologic data exist exploring the specific FSGS subtypes that increases the importance of understanding this rare disease and subsequent management strategies. The goal of this study was to estimate the incidence of FSGS and primary FSGS among a large diverse population in the United States.

Methods: A retrospective cohort study within Kaiser Permanente Southern California was performed among patients (age ≥18yrs) with renal biopsy-proven FSGS between 2010-2021. Presumed primary FSGS consisted of biopsies with FSGS as the principal diagnosis. Manual chart reviews were then performed to confirm primary FSGS with extensive foot process effacement (FPE) of ≥80%. Patient demographics were assessed during the 1 year prior to date of biopsy (index date). Annual incidence rates (per 100,000 person-years) were calculated after adjusting to 2020 US census.

Results: Among 7,115,249 unique persons, we identified 3,839 patients with biopsy-proven FSGS. Of 1,509 presumed primary FSGS, 640 (42.4%) were confirmed primary FSGS (mean age [SD] 55.5 years [17.9], 56.4% male, 35.8% Hispanic/Latino, 28.8% White, 17.8% Asian/Pacific Islander, 15.9% Black). The adjusted annual incidence rates of primary FSGS ranged from 1.3 – 2.4 per 100,000 person-years (Table 1). The highest mean primary FSGS incidence rates per 100,000 person-years were among Black (3.4), Asian (2.7), and Pacific Islander (2.8) patients (Table 2).

Conclusions: Among a racially/ethnically diverse population, primary FSGS accounted for 16.7% of all biopsy-proven FSGS. Our findings suggest that primary FSGS remains a rare disease but varies across race/ethnicity. Proper identification of primary FSGS in patients may help facilitate tailoring therapeutic options.

Funding: Commercial Support - Otsuka Pharmaceutical Development & Commercialization, Inc.

Table 1. Incidence rate per 100,000 person-years

Year	Biopsy-Proven FSGS	Standardized* (95%CI)	Presumed Primary FSGS	Standardized* (95%CI)	Primary FSGS	Standardized* (95%CI)
2010	228	8.9 (7.8, 10.2)	100	4.5 (3.7, 5.4)	56	2.4 (1.9, 3.1)
2011	261	9.2 (8.1, 10.4)	115	4.4 (3.6, 5.3)	41	1.5 (1.1, 2.0)
2012	289	10.0 (8.9, 11.3)	101	3.7 (3.1, 4.6)	55	2.0 (1.5, 2.6)
2013	300	10.7 (9.5, 12)	120	4.6 (3.8, 5.5)	40	1.5 (1.1, 2.1)
2014	343	10.9 (9.8, 12.1)	134	4.3 (3.6, 5.1)	54	1.8 (1.3, 2.3)
2015	363	11.1 (10.0, 12.3)	146	4.5 (3.8, 5.3)	70	2.1 (1.7, 2.7)
2016	317	9.6 (8.6, 10.8)	128	3.9 (3.3, 4.6)	57	1.7 (1.3, 2.2)
2017	347	9.7 (8.7, 10.7)	152	4.1 (3.5, 4.8)	61	1.7 (1.3, 2.2)
2018	381	10.2 (9.2, 11.3)	147	3.9 (3.3, 4.6)	56	1.7 (1.3, 2.2)
2019	348	8.7 (7.8, 9.6)	127	3.3 (2.8, 3.9)	50	1.3 (1.0, 1.8)
2020	283	6.8 (6.1, 7.7)	107	2.8 (2.4, 3.4)	49	1.4 (1.0, 1.8)
2021	317	10.0 (9.0, 11.1)	132	3.8 (3.2, 4.5)	54	1.7 (1.3, 2.2)
Average		9.6 (7.0, 12.3)		4.0 (2.7, 5.3)		1.7 (0.9, 2.6)

*Standardized by age, sex and race/ethnicity based on US population of 2020 ACS estimates

Table 2. Primary FSGS incidence rate per 100,000 person-year, stratified by race/ethnicity

	White		Black		Hispanic		Asian and Pacific Islander		Other/Unknown	
Year	Cases	Incidence Rate	Cases	Incidence Rate	Cases	Incidence Rate	Cases	Incidence Rate	Cases	Incidence Rate
2010	18	1.9	13	5.6	20	2.4	6	2.4	1	0.5
2011	12	1.2	5	2.1	19	2.1	6	2.2	0	0.0
2012	14	1.4	11	4.4	18	1.9	11	3.8	0	0.0
2013	13	1.3	9	3.6	14	1.4	4	1.3	0	0.0
2014	16	1.5	8	3.1	22	2.1	8	2.6	0	0.0
2015	17	1.5	12	4.5	30	2.6	11	3.2	0	0.0
2016	14	1.2	10	3.6	19	1.5	14	3.8	0	0.0
2017	12	1.0	14	5.0	24	1.8	10	2.6	1	0.5
2018	19	1.5	9	2.8	16	1.2	11	2.7	3	1.2
2019	14	1.2	6	2.1	18	1.1	13	3.1	1	0.4
2020	14	1.2	6	2.1	18	1.3	9	2.1	2	0.7
2021	23	2.0	4	1.4	16	1.1	10	2.3	1	0.3
Average		1.4		3.4		1.7		2.7		0.3

TH-PO641

Demographic, Clinical Characteristics, and Treatment Outcomes of C3 Glomerulopathy in China: A Nationwide Retrospective Cohort Study

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Background: As a rare glomerular disease, there is limited data on the demographic, clinical characteristics, and treatment outcomes of C3 glomerulopathy (C3G) in China.

Methods: Patient medical records were retrospectively collected from 24 regional central hospitals across China, from 2013 to 2021. Descriptive analysis was performed on clinical characteristics, treatment, and outcomes. χ^2 test was performed to analyze the difference between children and adult groups.

Results: 470,000 patients with chronic kidney disease (CKD) were enrolled, of which 102 patients were C3G confirmed by renal biopsy. Among them, 9 were diagnosed with dense deposit disease and 93 were diagnosed with C3 glomerulonephritis. At the time of diagnosis, 46.2% of C3G patients had an eGFR<60 ml/min/1.73m^2, 47.1% had low serum complement C3, 48.8% had low serum C4, 22.5% had abnormal blood/urine protein electrophoresis, and 3% had elevated serum globulin. Besides C3 deposition, 4.9% and 12.7% of patients combined IgA and IgG deposition in pathological immunofluorescence, respectively. Compared to children, adult patients tended to present severe symptoms at diagnosis (Table 1). 55 patients (53.9%) received treatment with RASI, while 48 (47.1%) patients received glucocorticoids and 24 patients combined glucocorticoids with other immunosuppressants (cyclosporine, etc.). 16 patients were followed up for more than one year. Among them, 2 patients showed ≥40% decrease in eGFR from baseline, and 3 patients developed end stage renal disease (ESRD) within one year.

Conclusions: C3G has heterogeneous clinical characteristics, and adult patients presented more serious symptoms at diagnosis. Gaps are identified for C3G patients standardized treatment in China, and targeted therapy is urgently needed.

Funding: Commercial Support - Beijing Novartis Pharma. Co. Ltd.

Characteristics	Children (N=43)	Adult (N=59)	P
Demography			
Age	8.9 (6.1-11.2)	42.1 (29.4-53.8)	<0.001
Male, n (%)	24 (55.8)	29 (49.2)	0.642
Clinical symptoms			
Hypertension, n (%)	1 (2.3)	18 (30.5)	0.001
Proteinuria, n (%)	25 (58.1)	45 (76.3)	0.083
Massive proteinuria*, n (%)	12 (27.9)	32 (54.2)	0.014
Hematuria, n (%)	17 (39.5)	8 (13.6)	0.005
Laboratory tests			
Creatinine(μmol/L)	40.5 (34.0-56.0)	101.0 (78.5-180.8)	<0.001
eGFR (ml/min/1.73m^2)	164.1 (147.4-178.1)	66.0 (33.9-95.6)	<0.001
24-hour urine protein quantification (g)	0.27 (0.09-0.75)	2.14 (0.59-4.53)	<0.001
Serology detection-C3 (g/L)	0.76 (0.57-0.98)	0.76 (0.52-0.86)	0.367
Serology detection-C4(g/L)	0.18 (0.14-0.27)	0.22 (0.16-0.27)	0.146
Treatment			
Renin-angiotensin system inhibitor, n (%)	19 (44.2)	36 (61.0)	0.138
Glucocorticoid, n (%)	25 (58.1)	23 (39.0)	0.087
Heparin Disaccharides, n (%)	17 (39.5)	7 (11.9)	0.003

eGFR, estimated glomerular filtration rate.

*Massive proteinuria defined as urinary protein qualitative ≥3+ or UACR >300mg/g or 24-hour urinary protein qualitative >3.5g.

Baseline characteristics of patients with C3G stratified by age.

TH-PO642

Characteristics of Patients with Complement 3 Glomerulopathy (C3G) in a US Multi-Center Assessment

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Background: C3G is characterized by C3 deposition in the glomeruli caused by abnormal activation of the alternative complement pathway. There are no approved therapies for C3G. Despite supportive care, C3G remains a progressive form of kidney disease, with novel treatments needed to improve outcomes. Contemporary datasets on the clinical burden of patients with C3G are limited. Using real-world evidence from electronic medical records, this study describes the characteristics of patients diagnosed with C3G in the US.

Methods: This was a retrospective cohort study of patients included in the US Optum Life Science clinical electronic health record database who were aged ≥12 years at C3G diagnosis (per ICD-10 or SNOMED; index date) between 01/2015 and 06/2022. Patients had continuous clinical activity ≥12 months before (baseline) and ≥6 months after (follow-up) index date, and were followed until death or data end. Patient and clinical characteristics at index date were evaluated using descriptive statistics.

Results: Of 284 patients in the final sample, 78% were White, 11% African American, 2% Asian, and 10% other/unknown. Mean age ± SD was 49 ± 21 years, 50% were male, and 136/228 (60%) had stage ≥3 CKD at index. At baseline, mean Charlson Comorbidity Index (CCI) score ± SD was 2.3 ± 2.7. Of comorbidities included in the CCI, the most common included chronic pulmonary disease (25%) and diabetes without chronic complication (20%). At baseline, hypertension (65%) was the most common C3G-related comorbidity; 10% of patients had undergone dialysis and 12% kidney transplant. Obesity (BMI ≥30) was recorded in 100/249 patients (40%). Common C3G-related treatments at baseline included corticosteroids (54%), ACE inhibitors (41%), ARBs (26%) and immunosuppressants (21%). At baseline, proteinuria was assessed in 126 patients (44%); mean protein/creatinine ratio ± SD was 2.9 ± 3.9 g/g. Of 100 patients (35%) with available data, 34% had complement C3 level <77 mg/dl.

Conclusions: This contemporary assessment of patients with C3G from a national US cohort identified a population that presented with multiple comorbidities and advanced kidney disease around the time of diagnosis.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

TH-PO643

CKD Progression in Patients with Complement 3 Glomerulopathy (C3G) in a US Multi-Center Assessment

Briana C. Ndife,[1] Carolina A. Aldworth,[1] Kathleen Murphy,[1] Jennifer Nguyen,[1] Irina Pivneva,[2] Marie Louise Edwards,[2] Annika Anderson,[2] James Signorovitch,[2] Pietro A. Canetta.[3] *[1]Novartis Pharmaceuticals Corporation, East Hanover, NJ; [2]Analysis Group Inc Boston, Boston, MA; [3]Columbia University Irving Medical Center, New York, NY.*

Background: Patients with C3G have high rates of progression despite treatment. Using electronic medical record data, this study characterized disease progression in a US cohort of patients with C3G.

Methods: This was a retrospective cohort study of de-identified patients within the US Optum Life Science clinical electronic health record database, aged ≥12 years at C3G diagnosis (per ICD-10 or SNOMED) between Jan 2015–Jun 2022. Index date was the date of diagnosis. Patients had continuous clinical activity ≥12 months before (baseline) and ≥6 months after (follow-up) index. Patients were followed until death or data end. Patient and clinical characteristics were assessed using descriptive statistics, and time to CKD progression using Kaplan–Meier analyses.

Results: Of 284 patients in the final sample, mean age ± SD was 49 years ± 21; 136/228 (60%) had stage ≥3 CKD at index. During follow-up, 115/188 patients (61%) progressed to a higher CKD stage than at index, and/or to kidney failure; median time to progression was 12.6 months (95% CI: 9.4, 17.7). At 6 and 12 months, 38% and 48% of patients, respectively, had a progression of CKD stage. In progressors (n=115), mean age was 54 years and mean Charlson Comorbidity Index (CCI) score was 2.8; in non-progressors (n=73), mean age was 48 years and mean CCI score was 1.8. Among progressors and non-progressors, 14% and 6% of patients, respectively, were African American, had hypertension (79% and 55%), and had prior kidney transplant (10% and 3%) at baseline. At index, 68/115 (59%) of progressors and 28/73 (38%) of non-progressors had CKD stage ≥3. Within 90 days of index, a higher proportion of progressors relative to non-progressors were treated with ACE inhibitors (31% and 22%) or ARBs (23% and 14%). Up to 90 days after index, mean ± SD protein:creatinine ratio was 2.3 ± 2.6 g/g in 21 assessed non-progressors and 3.7 ± 5.0 g/g in 53 assessed progressors. The proportion of patients with complement C3 level <77 mg/dL at baseline was 15/47 (32%) among progressors and 9/24 (38%) among non-progressors.

Conclusions: Patients with C3G progress rapidly despite supportive care. Noted differences between progressors and non-progressors warrant further investigation.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

TH-PO644

Qualitative Analysis Reveals Insights to Meet the Needs of Patients with C3 Glomerulopathy (C3G)

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Background: C3 glomerulopathy (C3G), a rare condition characterized by abnormal regulation of the alternative complement pathway, results in kidney function impairment that can progress to end-stage renal disease. Published evidence of the patient experience in managing this rare condition is scarce. Therefore, the American Kidney Fund (AKF) sought to gain insight into the unique needs and challenges of people affected by C3G by convening a focus group of patients and caregivers.

Methods: Through convenience sampling via a C3G social media page, 8 participants were recruited for a virtual, 60-minute focus group. Six participants were adults diagnosed with C3G and two were caregivers of children with C3G. The focus group was recorded and transcribed, then analyzed for key themes using thematic analyses.

Results: Findings revealed 3 overarching themes: limited C3G awareness among health care providers, a lack of patient-friendly C3G education material, and a need to stay connected to the community. Participants faced challenges identifying health care providers knowledgeable about C3G and with experience treating patients with C3G leading several to travel far for their care. Many also discussed their struggle with finding accessible educational information and having to navigate complex scientific literature to learn more about their condition and treatment options. Social support needs were also identified including connecting with others with this rare condition and seeing progress being made with advancements in treatments and ongoing trials.

Conclusions: C3G educational resources written in plain language, especially targeted at newly-diagnosed patients, are needed. Additionally, increased HCP education and better avenues for identifying HCPs well-versed in C3G will help patients feel more confident in their care and management plans. Lastly, finding avenues to connect patients and share insights from clinical trials and ongoing advancements will help to relieve the emotional burden felt by patients and caregivers. As part of this effort, AKF is developing a C3G education campaign centered around tackling these barriers. Gathering patient input is imperative to ensure educational resources are meaningfully tailored to patient needs and values to improve health outcomes.

Funding: Commercial Support - Novartis Pharmaceuticals

TH-PO645

Patient Characteristics and Renal Outcomes of C3 Glomerulopathy (C3G) and Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN) in the UK: A Retrospective Analysis of 287 Patients in the UK National Registry of Rare Kidney Diseases (RaDaR)

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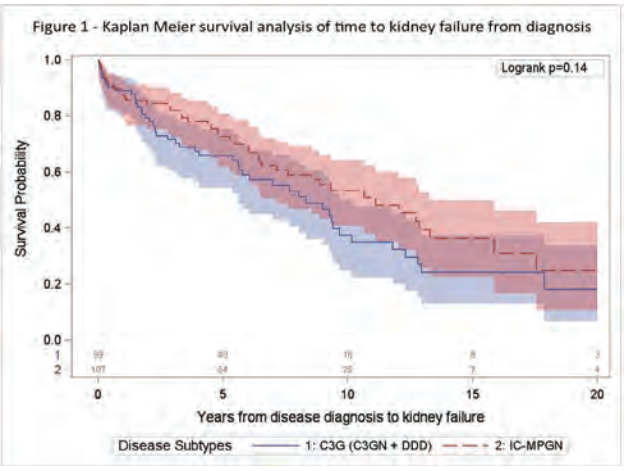
Background: Membranoproliferative glomerulonephritis (MPGN) is a rare, chronic kidney condition that encompasses immune-complex MPGN (IC-MPGN) and C3 glomerulopathy (C3G). There is limited literature on treatments and outcomes in MPGN.

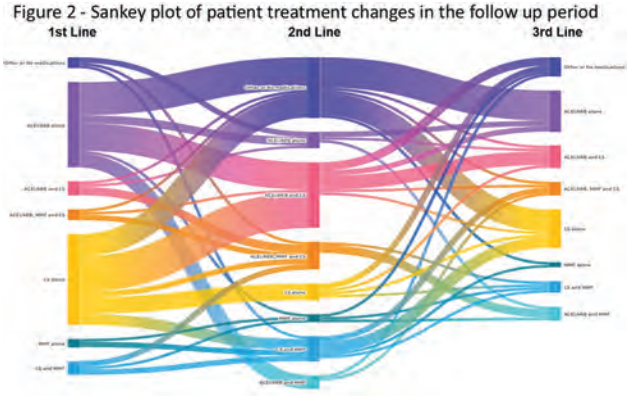
Methods: This is a descriptive, retrospective study of patients recruited to RaDaR with C3G or IC-MPGN confirmed on biopsy or clinical records. Kaplan-Meier analysis and logrank statistic were used to investigate time to kidney failure and linear mixed effects models to investigate annual estimated glomerular filtration rate (eGFR) slope by disease subtype.

Results: 287 patients were included in these analyses: 135 (47%) had confirmed C3G and 152 (53%) IC-MPGN. Median age at diagnosis was 14 years for C3G patients and 23 years for IC-MPGN patients. The majority of patients in the C3G and IC-MPGN cohorts were white (74% and 79% respectively). 53% of the IC-MPGN cohort and 45% of the C3G cohort were male. C3G patients had faster annual eGFR decline compared to IC-MPGN patients (5.1 vs 3.4 mL/min/1.73m2/year), although no significant difference was found in the time from diagnosis to kidney failure (median time to kidney failure 8.3 vs 11.1 years for C3G and IC-MPGN respectively, p-value 0.14, Figure 1). Of 141 patients with medication data, 51 (36%) were adult and 90 (64%) were paediatric at diagnosis. 58% of these patients were given RAS blockade (ACE-I/ARBs), and 46% were given corticosteroids as their initial treatment (Figure 2).

Conclusions: RaDaR is a large and robust data source allowing investigation into C3G/IC-MPGN natural history. We found heterogeneity of current treatment approaches in this cohort and rapid progression to kidney failure despite current treatments.

Funding: Commercial Support - Novartis





TH-PO646

Persistence of Signs and Symptoms in Treated Patients with C3 Glomerulopathy (C3G): Evidence from Real-World Data

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G is associated with a high risk of disease progression; approximately 50% of patients reach kidney failure within 10 years of diagnosis. This analysis aimed to describe C3G signs and symptoms (S&S) in treated patients.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a cross-sectional survey of C3G-treating nephrologists in US, EU5 (France, Germany, Italy, Spain, UK), China and Japan between August 2022 and April 2023. Nephrologists completed structured forms for consecutive patients presenting with C3G. The forms included demographics, C3G treatment history and clinical information including S&S.

Results: 111 nephrologists completed records for 385 C3G patients (US 100, EU5 189, China 60, Japan 36). Of the 288 receiving treatment at time of survey, median patient age was 41.0, 60% were men, 83% had C3 glomerulonephritis and 16% had dense deposit disease. 60% (173) of patients had been on treatment for <1 year, 21% (61) between 1-2 years and 19% (54) >2 years, median treatment duration was 43.2 weeks. Despite currently receiving treatment, most patients had S&S at time of survey. This was consistent in patients with a longer treatment duration. Common S&S experienced were proteinuria, hypertension, fatigue, and hematuria (**Table 1**). Around one third of patients had a CKD stage between 3b and 5, regardless of number of years on treatment. Of those patients treated for >2 years, 44% had ≥1g proteinuria/day where reported.

Conclusions: Despite treatment, C3G S&S persist in the majority of patients. Proteinuria remains high in many patients, increasing risk of progression to kidney failure. This shows a need for targeted treatments for C3G.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Table 1: Treated C3G patient current signs and symptoms by number of years on treatment

Time since treatment initiation (Years)	All with treatment n=288	<1y n=173	1-2y n=61	>2 y n=54
Number of signs & symptoms Mean (SD)	2.4 (1.8)	2.6 (1.8)	2.4 (1.7)	2.0 (1.5)
% Currently symptomatic	89%	94%	84%	80%
Top 5 S&S				
Proteinuria	66%	67%	70%	57%
Hypertension (140/90mmHg)	34%	40%	26%	24%
Fatigue	28%	33%	23%	17%
Hematuria	24%	21%	28%	28%
Edema	16%	15%	23%	9%
CKD Stage				
Base	n=274	n=163	n=58	n=53
CKD Stages 1-3a (GFR ≥45 mL/min/1.73 m2)	178 (65%)	104 (64%)	39 (67%)	35 (66%)
CKD Stages 3b-5 (GFR <45 mL/min/1.73 m2)	96 (35%)	59 (36%)	19 (33%)	18 (34%)
Protein Creatinine Ratio (PCR) (g/24hr)				
Base	n=263	n=160	n=53	n=50
<1g/day	99 (38%)	51 (32%)	20 (38%)	28 (56%)
≥1g/day	164 (62%)	109 (68%)	33 (62%)	22 (44%)

Table 1: Current therapy and proteinuria levels by region

TH-PO647

Real-World Time to Diagnosis in C3 Glomerulopathy (C3G)

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G is associated with a high risk of disease progression, approximately 50% of patients reach kidney failure within 10 years of diagnosis (Dx). Delayed dx may lead to poor prognosis. This analysis aims to better understand the diagnostic pathway in C3G.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a cross-sectional survey of C3G-treating nephrologists in US, France, Germany, Italy, Spain, UK (EU5), China and Japan between August 2022 and April 2023. Nephrologists completed forms for consecutive patients presenting with C3G. The forms included demographics, clinical information and reasons for diagnostic delay.

Results: 111 nephrologists completed records for 385 C3G patients (EU5 189, US 100, CN 60, JP 36). Median patient age at time of Dx was 38.8, and 59% were male. Median time from symptom onset to the patient's first physician consultation was reported for 78% of patients. In the EU5 (n=150) this was 4.1 weeks (IQR: 0.3-8.7), in the US (n=63) and China (n=59) this was 4.4 weeks (IQR US: 1.3-6.4, IQR CN: 1.3-12.4), and Japan (n=30) 6.8 weeks (IQR: 4.1-17.6). Median time from first physician consultation to confirmed C3G Dx was reported for 85% of patients. Half of the patients received Dx within 4.6 weeks, 10% experienced a much longer period (**table 1**). Reasons for a delay >4 weeks between first consultation and Dx were reported for 54% of patients (n=206). Waiting to conduct biopsy (39% EU5, 38% US, 27% China and 45% Japan) and waiting for biopsy results (33% EU5, 20% US, 38% China and 32% Japan) were the most common causes. When (e)GFR was recorded at Dx (84%), 43% of patients were at CKD stages 3b-5 (GFR <45 mL/min/1.73 m2).

Conclusions: While half of patients with C3G receive a diagnosis within 4-6 weeks of presentation, 1 in 10 wait over 21 weeks. During this time patients may progress to later stages of CKD. Accelerating Dx may improve prognosis for some patients.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Time from 1st consultation to C3G Dx (weeks)	All patients with both an initial consultation date and a Dx date (n=328)	EU5 (n=159)	US (n=77)	CN (n=59)	JP (n=33)
25th percentile	2.9	3.0	2.1	1.4	4.4
Median	4.6	5.0	4.6	3.9	8.4
75th percentile	10.4	9.9	13.0	9.4	10.8
90th percentile	21.9	21.4	35.0	14.1	32.8
(e)GFR at Dx	All patients with an (e)GFR value at Dx (n=325)	EU5 (n=172)	US (n=68)	CN (n=54)	JP (n=31)
CKD stage 3b-5	43%	52%	41%	20%	32%

Table 1: C3G Dx delay and (e)GFR

TH-PO648

The Idiopathic Hypocryoglobulinemia as an Emerging Membranoprolipherative Glomerulonephritis

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Background: A considerable number of patients with high clinical suspicion for cryoglobulinaemic vasculitis either show negative results for the detection of cryoglobulins or show only trace amounts which cannot be characterized for composition. We aimed at establishing whether the failure to detect or the detection of trace amounts of cryoglobulin with conventional methods either identifies a peculiar subset of low level cryoglobulinaemia (from now on hypocryoglobulinaemia) or represents a separate entity.

Methods: Using a modified precipitation technique in hypo-ionic medium, we prospectively identified between 2008 and 2021 237 patients (median age 60.8 years [22-97], 137 females) having <0.5% cryocrit and clinical suspicion of autoimmune disorder.

Results: 54 out of 237 patients (22.7%) had a history of HCV infection. 169 out of 237 patients (71%) had an established underlying disease, while 68 patients (28.6%) (median age 62.9 years [29-93], 35 females) did not show either laboratory markers or clinical symptoms consonant with an underlying aetiology. These 68 cases with only trace amounts of cryoglobulins were defined as having a putatively idiopathic hypocryoglobulinaemia. Nineteen of these 68 patients (27.9%) had a history of HCV infection. Twenty-four patients out of 68 (35.3%) were positive for rheumatoid factor (RF), while 25 (36.7%) patients had signs of complement consumption, and 36 (52.9%) had increased inflammatory indexes. Seven patients only had arthralgia and constitutional symptoms while 61 out of 68 (89.7%) presented with at least one of the three cardinal signs of cryoglobulinaemic vasculitis including skin lesions, peripheral nerve involvement, and glomerulonephritis. Seventy-five percent of the subjects had type III hypocryoglobulins. In patients with hypocryoglobulinaemia the histologic features of glomerulonephritis (also examined by electron microscopy) resembled those of mixed cryoglobulinaemia-associated glomerulonephritis.

Conclusions: In conclusion, hypocryoglobulins are often polyclonal and are mainly unrelated to HCV infection. Patients who present high clinical suspicion for vasculitis, especially glomerulonephritis and yet test negative for cryoglobulinaemia detected by standard techniques, could require deeper investigation even in the absence of HCV infection, RF activity or signs of complement consumption.

TH-PO649

Prognostic Factors and Outcomes of a Large Brazilian Retrospective Cohort of Renal Amyloidosis

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Background: To date, no large studies have characterized the epidemiology and outcomes of the main types of renal amyloidosis in Brazil or Latin America.

Methods: This retrospective cohort study evaluated 81 patients with biopsy-proven renal amyloidosis, diagnosed from January 1999 to December 2022. Follow-up started at kidney disease presentation and ended at death or December 2022. Clinical presentation, including age, serum creatinine, proteinuria and amyloid type, as well as survival and prognostic factors were analyzed.

Results: From the initial 81 patients, 76 had definite biopsy-proven renal amyloidosis and were analyzed. AL amyloidosis was the most frequent type (68.4%). AA amyloidosis was present in 14.5% and was mainly related to rheumatological diseases (7/11) and familial Mediterranean fever (2/11). Hereditary forms accounted for 11.8% of cases (10.5% AFibE545V, 1.3% ATTRV30M), and the type was inconclusive in 5.3%. The etiologic type was classified as confirmed in 43.1% and probable in 56.9%. AL was associated with lower serum albumin and higher degree of proteinuria compared to the other types. Patients with AL amyloidosis almost always presented with nephrotic syndrome, unlike patients with the AFib amyloidosis, who most often presented with isolated proteinuria and hypertension. The diagnosis of AA was frequently established before 40 years of age (45.5%) and more often displayed glomerular detection of C3 (70.0% in AA, 22.9% in AL and 11.1% in AFib/ATTR). During follow-up, 67.3% of AL, 54.5% of AA and 66.7% of AFib+ATTR progressed to ESKD, and 57.7% of AL, 36.3% of AA, and 22.2% of AFib+ATTR died; median kidney survival was 10 (1-154), 21.5 (1-117) and 56 (10-146) months, respectively (p=0.024). eGFR<60mL/min/1.73m^2 at diagnosis (HR 6.50 [95% CI, 1.73-24.40]) and shorter time from symptoms to diagnosis (HR 1.07 [95% CI, 1.01-1.13]) were identified as risk factors for progression to ESKD.

Conclusions: Our data broadly characterized the types of renal amyloidosis in this large cohort and revealed that most cases were AL amyloidosis, which was associated with worse kidney and overall survival. Our findings suggest that clinical presenting features can often distinguish the types. Hereditary forms should be considered when confirmation of AL cannot be obtained and a chronic inflammatory disease is not diagnosed.

Funding: Government Support - Non-U.S.

TH-PO650

Fibrinogen A Alpha-Chain Amyloidosis: A Brazilian Reality

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Background: Fibrinogen A α-chain amyloidosis (AFib amyloidosis) results from mutations in the fibrinogen A α-chain gene (*FGA*) and is the most common form of hereditary renal amyloidosis.

Methods: We characterized the natural history and long-term outcomes of AFibE545V amyloidosis in patients diagnosed by clinical presentation, renal biopsy and/or genetic testing at the University of São Paulo Medical Center from 2014 to 2022.

Results: A total of 47 patients from 15 unrelated families with AFib amyloidosis were diagnosed by genetic testing, all heterozygous for the p.E545V variant: 31 (66%) with clinical manifestation and 16 (34%) with no clinical manifestation. During the follow-up, 31 developed kidney disease at a mean age of 55.0±10.4 years. Clinical presentation consisted of proteinuria (67.7%), hypertension (84%), and kidney failure (39.3%). Nineteen (61.3%) patients progressed to end-stage kidney disease (ESKD) at a mean of 62.0±10.7 years, with a mean kidney survival of 45.5±38,7 months. The rate of estimated glomerular filtration rate (eGFR) decline was 8.45±6.41 mL/min/1.73m^2/year. Multivariate analysis showed that eGFR <60 mL/min/1.73m^2 at diagnosis was an independent risk fator for progression to ESKD (HR 5.45 [95% CI, 1.04-28.68]). 11.5% of the patients underwent chemotherapy treatment, even without evidence of plasma cell disorder. Only 9 (60%) of the unrelated probands had a family history of CKD or amyloidosis. Differences in penetrance rate were observed according to the age of the patients: 77.4% (>50 years) vs 22.6% (<50 years), p=0.028.

Conclusions: AFibE545V amyloidosis showed significantly variable penetrance according to age range. In patients with hypertension, proteinuria, and progressive renal impairment, one should consider this diagnosis to carry out targeted genetic testing for AFib, particularly for the p.E545V variant, especially in family members of identified cases. This procedure would avoid inappropriate treatment.

Funding: Government Support - Non-U.S.

TH-PO651

The Clinico-Pathologic Characteristics of Patients with Fibrillary Glomerulonephritis

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Background: Fibrillary glomerulonephritis (FGN) is a rare glomerular disease with lack of sufficient understanding of the disease pathogenesis. As a result, there is a lack of good evidence to guide therapy.

Methods: We identified patients with FGN from the Cleveland Clinic Kidney Biopsy Epidemiology Project from January 2015 to March 2023. Retrospective chart review was performed to obtain demographic and clinical characteristics.

Results: From 45 patients with FGN, 30 patients had sufficient data. 70% were female and 86% self-reported as white. The median age was 64 years. Clinical features at kidney biopsy were: hypertension (100%), acute or chronic kidney disease (100%), hematuria (76%), proteinuria (60%), nephrotic syndrome (48%). Hypocomplementemia was identified in one case. Work up for secondary associations revealed, M protein (20%), Hepatitis C virus infection (16%), autoimmune conditions (23%) and solid tumor malignancy (10%). Mean serum creatinine and proteinuria at biopsy were 2.7mg/dl (0.7-10) and 3.6 gm/dl (0.1-8.7) respectively. Regarding pathology, pure mesangial (90%) followed by endocapillary hypercellularity (6.7%) were the most common patterns of injury. The majority of patients (76%) had moderate to severe interstitial fibrosis and tubular atrophy and 13% had crescents. DNAJB9 was tested on 2 samples, both were positive. 86% of patients had positive IF staining for IgG/C3/K/L with the majority of IgG staining being described as a smudgy pattern. EM showed mesangial pattern deposition and GBM thickening in more than 80% of patients. Regarding treatment and outcomes, most patients were treated with non-immuno-modulatory antiproteinuric agents. Of 7 patients treated with immunosuppressive therapy, 5 patients received Rituximab. During an average of 24 months (0-70) follow up for 13 patients with data, 23% had partial remission (proteinuria reduction > 50% with stable eGFR), 23% had persistent disease, and 53% (7) progressed to ESKD. Aside from a positive correlation between creatinine during biopsy and ESRD, no predictive variables were identified on univariate and multivariable analysis.

Conclusions: FGN is a rare glomerular disease with poor renal outcomes. Treatment strategies vary. Prospective, multicenter studies are necessary to better understand the disease pathogenesis and identify appropriate therapy.

Funding: Private Foundation Support

TH-PO652

Post-Transplant Recurrence of Glomerular Diseases: Analysis of the CureGN Database

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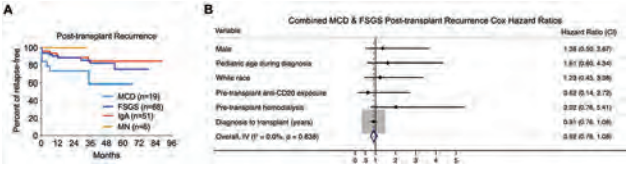
Background: Post-transplant recurrence of glomerular diseases is one of the leading causes of kidney graft failure. Identification of risk factors and predictive biomarkers are needed to guide management.

Methods: CureGN is a prospective multicenter international consortium of patients with biopsy-proven minimal change disease (MCD), focal segmental glomerulosclerosis (FSGS), IgA nephropathy/vasculitis (IgAN), and membranous nephropathy (MN). We included pediatric and adult patients from CureGN who underwent deceased or living kidney transplantation. The primary outcome was the risk of post-transplant recurrence. Recurrences were evaluated using a log-rank test. For secondary outcomes, clinical features of recurrent and non-recurrent patients were compared by t-test, Mann-Whitney, or Fisher's exact test. Risk factors of post-transplant recurrence were analyzed by Cox regression.

Results: A total of 144 patients were enrolled, including 19 MCD, 68 FSGS, 51 IgAN, and 6 MN. Overall, the mean age was 29.7±18.8, 46 (32%) were pediatric, 87 (60%) were male, and 88 (61%) were White. During a mean follow-up of 31.9±20.7 months, post-transplant recurrence occurred in 32%, 15%, and 12% of MCD, FSGS, and IgAN patients, respectively. None of the MN patients had a recurrence. In MCD and FSGS, the mean time to recurrence was 7.8±13.5 and 14.7±18.6 months, respectively **(Fig.1A)**. In the combined analysis of MCD and FSGS, none of the variables were associated with increased risk of recurrence (**Fig.1B**). All of the recurrent patients had dialysis pre-transplant, while 64% in the non-recurrent group (P = 0.002). For IgAN, the mean time to recurrence was 10.9±12.6 months and there was a tendency toward less White and more pre-transplant dialysis in the recurrent group. Overall, having a recurrence was associated with decreased post-transplantation eGFR in FSGS (HR 15.1, CI 13-17.3) and IgAN (HR 27, CI 22.4-31.7) in linear regression after adjusting for time.

Conclusions: In the diverse CureGN cohort, post-transplant recurrence was most common in MCD, followed by FSGS and IgAN. The recurrence of FSGS and IgAN was associated with reduced kidney graft function.



TH-PO653

Clinical Characteristics and Risk Factors Analysis on a Cluster of Patients with Acquired Solitary Kidney

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Background: Patients with acquired solitary kidney (ASK), including those who underwent unilateral nephrectomy and those presented with non-functional unilateral kidney atrophy due to acquired causes. While the long term outcome of ASK patients remains an issue of debate. The aim of this study was to observe the clinical characteristics of ASK patients and identify the risk factors for poor prognosis.

Methods: We performed a retrospective analysis on a case series of ASK patients once hospitalized in Renmin Hospital of Wuhan University, China, from January, 2011 to November, 2022. Preoperative and postoperative clinical and demographic data were collected until last admission, Univariate and multivariate Logistic regression models were used to analyze the risk factors for patients with postoperative eGFR <60 mL/min. Kaplan–Meier cumulative prevalence curves were used to compare the incidence of ESRD in different groups of ASK patients.

Results: 1. We enrolled 336 ASK patients in this study. Among them, 220 (65.5%) cases underwent unilateral nephrectomy due to hydronephrosis126 (37.5%) or renal cancer 94 (28.0%), the rest 116 (34.5%) patients were with unknown causes. The median age at diagnosis was 51.50 years old (IQR 42.02, 62.00), and after the median follow-up time of 6 years (IQR 3,12.75), the prevalence of hypertension, diabetes, anemia, hyperuricemia, hematuria and proteinuria were 43.8%, 15.7%, 40.8%, 37.8%, 71.1% and 44.3%, respectively. 2. K-M survival curve showed that ASK patients with hypertension, hyperuricemia, anemia, age at diagnosis ≥60 years, U-TP>2g/d were more likely to progress to ESRD. 3. Multivariate logistic regression analysis showed the risk factors which independently associated with the decreased eGFR including the age at diagnosis ≥60 years, follow-up time >10 years, hypertension, anemia, hyperuricemia, U-TP>2g/d, contralateral kidney operation history.

Conclusions: In conclusion, the ASK patients with underlying comorbidities, appears to be more susceptible in the long-term. It is particularly significant to have a strict and routine follow-up for ASK patients in high-risk.

TH-PO654

Belimumab for Recurrent Lupus Nephritis After Kidney Transplant

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Introduction: A 31-year-old woman with a history of end stage kidney disease (ESKD) due to systemic lupus erythematosus (SLE) glomerulonephritis (Class IV/V) underwent deceased donor pediatric en bloc kidney transplant. Nine months after transplant, she developed proteinuria with 2.2 g/g on a spot urine protein to creatinine ratio. Serum creatinine was stable at 1.3 mg/dl and she was maintained on tacrolimus 4 mg twice daily, mycophenolate mofetil 360 mg twice daily and prednisone 5 mg daily. She had no prior history of rejection.

Case Description: Renal biopsy was performed and showed focal, active nephritis with mesangial hypercellularity and inflammatory cells in the endocapillary space, consistent with class III+V lupus nephritis with an activity score of 3/24. Given the recurrence of SLE nephritis despite treatment with immunosuppression, treatment with belimumab was initiated at 200 mcg weekly given subcutaneously. Six months after starting treatment, proteinuria had decreased to 0.2 g/g with stable kidney function. Repeat kidney biopsy revealed class II and class V lupus nephritis with improvement in activity index to 0/24.

Discussion: Recurrence of SLE nephritis after transplant has been shown to increase the risk of graft loss[1]. Management of recurrence varies by provider but can involve steroids and alteration of the immunosuppressive regimen[2]. Belimumab is a fully human IgG1λ recombinant monoclonal antibody directed against B-lymphocyte Stimulator (BlyS) that binds to endogenous B-cell activating factor, leading to B-cell apoptosis and diminished autoantibody production. Use has been shown to reduce disease activity and flares in patients with SLE[3]. When added to standard therapy for lupus nephritis, belimumab has been shown to improve the chances of a renal response[4]. The addition of belimumab should be considered in patients with recurrent lupus nephritis after kidney transplant. 1 Contreras G, et al. Recurrence of lupus nephritis after kidney transplantation. J Am Soc Neph. 2010 Jul;21(7):1200-7. 2 Chadban SJ. Glomerulonephritis recurrence in the renal graft. J Am Soc Neph. 2001 Feb;12(2):394-402. 3 Furie R, et al; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab. Arthritis Rheum. 2011 Dec;63(12):3918-30. 4 Furie R, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. N Engl J Med. 2020 Sep 17;383(12):1117-1128.

TH-PO655

Belimumab-Induced Delirium and Behavioral Changes in a Patient with Lupus Nephritis: A Case Report

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Introduction: Belimumab is a monoclonal antibody against B-lymphocyte stimulator, approved by the United States Food and Drug Administration in 2011 for patients with active systemic lupus erythematosus or active lupus nephritis who are receiving standard therapy. Here, we describe a rare case of a patient developing delirium and behavioral changes after subcutaneous (SC) belimumab initiation.

Case Description: A 65-year-old female with lupus nephritis Class IIIC was started on SC belimumab due to progressive proteinuria while taking prednisone 40 mg daily, mycophenolic acid 180 mg twice daily and hydroxychloroquine 200 mg twice daily. After starting SC belimumab, the patient developed intermittent confusion, forgetfulness and aggressive behavior e.g., inability to recognize her daughter, yelling at others without reason, refusal to go to church despite being an active and regular member previously, and inability to recognize and use common household items. After she threatened to jump out of a moving car when her demands were not met, her husband took her to the emergency room. In the ER, initial laboratory workup and intracranial imaging were unremarkable. Patient was advised to discontinue belimumab and was discharged home. The symptoms resolved completely one to two days after discontinuing SC belimumab. The patient continues to take prior immunosuppressive therapy.

Discussion: Based on the timing of symptom onset, negative head imaging, unremarkable laboratory workup and immediate resolution after discontinuing belimumab, the symptoms were most likely caused by SC belimumab. She has tolerated both oral and intravenous pulse steroids without any adverse effects, thus ruling out steroids as a possible cause. Literature review showed that intravenous belimumab has been associated with depression, anxiety and suicidality, however, SC belimumab resulted in less psychiatric events than placebo (1). We believe this is the first case of SC belimumab induced delirium and behavioral changes with immediate resolution after cessation. It is important to educate patients and caregivers about such symptoms. This should be verified in post-marketing surveillance of belimumab as well as specific surveillance during clinical trial follow up.

TH-PO656

The Effect of Voclosporin as Monotherapy in Treating Lupus Nephritis

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Introduction: The current standard of care for lupus nephritis typically involves the use of combination therapy with immunosuppressive medications, such as mycophenolate mofetil (MMF) or cyclophosphamide, along with low-dose corticosteroids. While these medications can be effective in treating lupus nephritis, they are also associated with a range of potential side effects. We present a case of a young female patient who had multiple recurrent infections while on MMF which prompted conversion to voclosporin monotherapy with success in maintaining complete remission.

Case Description: We present a case of a 21 year old African American female with a past medical history of systemic lupus erythematosus (SLE), diagnosed at the age of 18, complicated by lupus nephritis (LN) class III. The patient was initially treated with a combination of mycophenolate mofetil (MMF), low-dose corticosteroids and hydroxychloroquine. Despite achieving partial remission with this treatment, the dose of MMF had to be reduced due to recurrent infections and persistent leukopenia. Voclosporin was eventually added to the regimen with the aim of achieving complete remission. However, MMF was eventually discontinued as the patient continued to have complications. The patient was continued on voclosporin monotherapy with low-dose prednisone for a total of 12 months, during which she achieved complete remission of her LN, with a stable serum creatinine and undetectable proteinuria.

Discussion: Lupus nephritis is a serious complication of SLE, and its treatment often requires the use of immunosuppressive medications, such as MMF and cyclophosphamide which bring with them a wide range of side effects including infections and myelosuppression. Voclosporin is a novel calcineurin inhibitor that has shown promise as a potential treatment for LN. It has been shown to be effective and well-tolerated in combination with MMF and low-dose corticosteroids in the AURA-LV and Aurora 1 trials. This case report demonstrates that voclosporin monotherapy may be an effective and safe treatment option for LN along with low-dose prednisone for LN in patients who are unable to tolerate or have contraindications to other immunosuppressive medications.

TH-PO657

A Rare Complication of Prolonged Immunosuppression in Lupus Nephritis

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Introduction: Epstein-Barr virus (EBV) is a well-recognized virus associated with lymphoproliferative disease (LD). Immunodeficiency and immunosuppression can lead to the reactivation and replication of the virus, increasing the likelihood of malignancy. We present a case of a patient with Lupus nephritis (LN) patient on long-term immunosuppression presenting with non-transplant-associated central nervous system (CNS) LD.

Case Description: A 35-year-old woman with frequently relapsing LN Class IV on mycophenolate mofetil (MMF), Plaquenil and prednisone for 15 years presented with numbness and weakness in the left side of her face and arm. MRI head showed bilateral supratentorial enhancing lesions (Fig 1). Positive dsDNA Ab, reduced C3, normal C4, EBV positive in cerebrospinal fluid, blood viral load <750 units/ml. CNS lesion biopsy confirmed iatrogenic EBV-associated LD (Fig 2). MMF was discontinued. Rituximab was started for the management of LD with resolution of the symptomatology. To date, lupus nephritis has remained quiescent on Rituximab.

Discussion: EBV-associated LD is influenced by the level of immune suppression and reduced surveillance by T cells. Certain medications can impede the proliferation of lymphoblastoid cell lines, and others affect T-cell function. In vitro and animal model studies have shown that prolonged use of MMF was associated with diminished recovery of Vδ2+ T cells and increased occurrence of EBV reactivation. MMF, commonly used in autoimmune diseases, may unmask an inherent susceptibility of the CNS for immunosuppression-related LD. While LD is frequently considered after organ transplantation, it is less often considered in non-transplant immunosuppressed patients. A high index of suspicion is needed when caring for non-transplant immunosuppressed patients presenting with primary CNS symptoms. Prompt evaluation is necessary to distinguish between lupus cerebritis and LD to individualize care and improve patient outcomes.

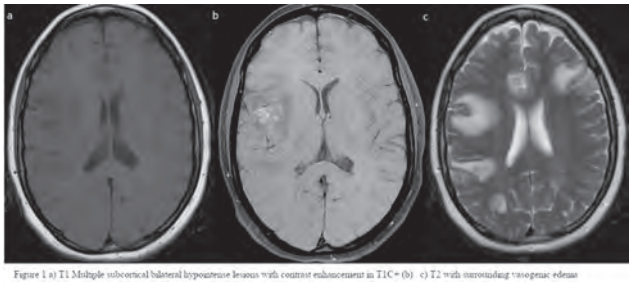

Figure 1 a) T1 Multiple subcortical bilateral hypointense lesions with contrast enhancement in T1C+ (b) c) T2 with surrounding vasogenic edema

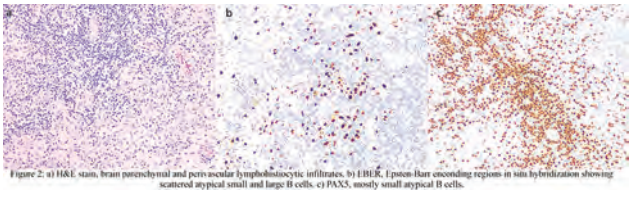

Figure 2: a) H&E stain, brain parenchymal and perivascular lymphohistiocytic infiltrates. b) EBER, Epstein-Barr encoding regions in situ hybridization showing scattered atypical small and large B cells. c) PAX5, mostly small atypical B cells.

TH-PO658

Combined Diagnosis of Proliferative Lupus Nephritis and Tuberculosis Infection: A Treatment Dilemma

Francis N. Atemnkeng,[1] Michelle L. Kirk,[1] James M. Pullman,[2] Michael D. Klein,[1] Savneek S. Chugh,[1] Sanjeev Gupta.[1] *[1]Westchester Medical Center, Valhalla, NY; [2]Montefiore Medical Center, New York, NY.*

Introduction: The treatment of tuberculosis (TB) infection (previously termed latent TB) during the induction phase of treatment for proliferative lupus nephritis (LN) is challenging. The use of high dose immunosuppression (IS) can cause TB disease. Rifamycin-based treatment for TB infection can also lead to major drug-drug interaction as rifampin can reduce the serum levels of mycophenolate mofetil (MMF), hence the level of IS.

Case Description: A 38-years-old Mexican male who presented with lower limb edema. Initial labs showed leukocytosis and acute kidney injury with nephrotic syndrome. Blood cultures grew Streptococcus pyogenes. Workup for glomerulonephritis (GN) revealed a positive ANA and hypocomplementemia, consistent with immune complex mediated GN. He received antibiotics for a total of 14 days. The urine protein/creatinine ratio (UPCr) one week later increased to 36.9 g/g from 3.2 g/g. Kidney biopsy demonstrated class III+V LN with 5/22 globally sclerosed glomeruli, 4 with segmental endocapillary hypercellularity with 2 cellular crescents on light microscopy and full house staining on immunofluorescence. Electron microscopy demonstrated mesangial, intramembranous, and sup-epithelial electron dense deposits and extensively effaced foot processes. The patient was discharged on conservative anti proteinuric therapy, as well as MMF. Routine TB screening with Quantiferon was positive, so he was started on rifampin and isoniazid. Follow-up 1 month later demonstrated UPCr of 1.76 g/g with no signs of TB disease.

Discussion: The term latent TB was changed to TB infection because these patients are infected with viable mycobacteria in various stages of containment by the host immune system. Therefore, during the induction phase of treatment of LN, with use of high dose IS, the presence of TB infection presents a high risk of progression to TB disease. We found no case reports of simultaneous diagnosis of proliferative LN and TB infection. Treatment literature is obtained from transplant patients diagnosed with TB infection, where rifampin was found to lower the level of MMF. Therefore, we suggest close follow-up of these patients to rule out TB disease and non-response to LN treatment during each visit.

TH-PO659

A 35-Year History of Lupus Nephritis Without Renal Fibrosis or Scarring: How Is This Possible? Exostosin 2

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Introduction: Recently, Exostosin 1/Exostosin 2 (EXT1/2) was identified as a novel antigen in membranous nephropathy associated with autoimmune disease, particularly lupus nephritis (LN). These patients have distinct clinical features, notably favorable outcomes despite high proteinuria. Current guidelines provide treatment recommendations for patients with LN. However, whether these represent the best approach to the subgroup of patients with EXT1/2+ LN remains elusive.

Case Description: A 54-year-old female with a 35-year history of class IV & V LN presented with proteinuria/hematuria along with hair loss and rash. The patient was not on any immunosuppressive drugs and was taken off hydroxychloroquine 2 years prior for retinal toxicity. History was significant for HTN, osteoporosis hypovitaminosis D, AVN of hips and knees, nephrolithiasis, HLD, glaucoma, and hysterectomy for uterine fibroids. Serology showed negative ANA (previously positive), positive anti-dsDNA, low C3, and low C4. Kidney biopsy revealed membranous LN Class V with EXT2+, PLA_2R-, THSD7A-, NELL1- staining. Notably, a near total lack of fibrosis or glomerulosclerosis was observed. Treatment was reinitiated with mycophenolate mofetil and tacrolimus for nephrotic syndrome, and losartan for HTN.

Discussion: Our patient has a long history of recurrent LN, with a notable lack of renal fibrosis or sclerosis. Further investigations revealed EXT2 positivity. Despite evidence demonstrating a favorable renal prognosis associated with EXT1/2+ LN, it is unclear whether these patients remain susceptible to other diseases, as persistent proteinuria can affect other clinical outcomes. Our patient had a recurrence of disease in the context of no immunosuppressive therapy. Without further evidence, we favor a standard approach to immunosuppressive therapy (as in EXT1/2 negative counterparts). We believe EXT1/2 immunohistochemical phenotyping of patients with LN should be performed to aid in our understanding of this subgroup. There are many outstanding questions regarding EXT1/2 and this case underscores the need for more research to help guide treatment practices.

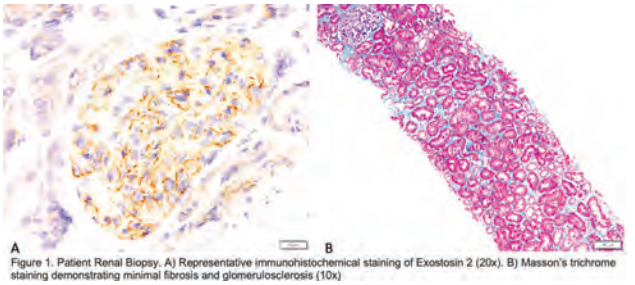

Figure 1. Patient Renal Biopsy. A) Representative immunohistochemical staining of Exostosin 2 (20x). B) Masson's trichrome staining demonstrating minimal fibrosis and glomerulosclerosis (10x)

TH-PO660

DNAJB9-Associated Fibrillary Glomerulonephritis with Systemic Lupus Erythematosus: A Case Series

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease with DNAJB9 positivity. We report 2 cases with lupus nephritis and FGN.

Case Description: Case 1: A 53-year-old woman with history of systemic lupus erythematosus (SLE), hypertension and depression presented severe proteinuria. The patient was diagnosed with SLE 20 years ago, her last lupus flare was 5 years ago. Over the course, her proteinuria worsened with spot urine protein-creatinine ratio (UPCR) was elevated at 3.54 with serum creatinine stable at 0.47mg/dl. Hep B and C, HIV, ANCA and PLA2R antibodies are negative. SLE serologies were not active. Serum C3 (148mg/dl) and C4 (42mg/dl) were in range. The serum light chain kappa/ lambda ratio was 1.05. She was on MMF and hydroxychloroquine. A kidney biopsy confirmed lupus

nephritis membranous type/ class V and glomerular dense fibrillary deposits suggestive of fibrillary glomerulonephritis. DNAJB9 antibody staining was positive. Patient received rituximab infusion therapy (1gm X 2 doses). Two months of follow up showed improvement in UPCR (0.9) with stable serum creatinine at 0.41mg/dl. One year out, the patient remains in remission. Case 2: A 65-year-old female with SLE (diagnosed ~40 years ago), hypertension and arthritis who presented with rising serum creatinine at 2.4 mg/dl. Her UPCR was stable at 0.3. Serological work up was negative. Serum C3 complement levels were mildly low (74mg/dl) and serum C4 complement levels were in range (18mg/dl). The Serum light chain kappa/ lambda ratio was 1.86. The patient was on MMF. Her BP was elevated, and lower extremity edema was present on exam. Kidney biopsy showed fibrillary glomerulonephritis with mesangioproliferative pattern and abundant electron dense material with fibrillary substructure infiltrating mesangium and glomerular basement membranes. mmunohistochemical staining of DNAJB9 was positive in glomeruli. Patient received rituximab infusion therapy. 9 months follow up showed stable UPCR (0.2) with elevated but stable serum creatinine at 1.86mg/dl. Her BP improved without any medications and clinically lower extremity edema disappeared. There was no progression of disease.

Discussion: The association between SLE and DNAJBP associated FGN is unclear. Rituximab may serve as a potential treatment strategy.

TH-PO661

Is It Rhabdomyolysis or Is It Lupus? A Case of Dual Presentation of New-Onset Lupus

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Introduction: Acute kidney injury in unconscious patients has a wide range of differential diagnoses; rhabdomyolysis is a common consequence. However, acute lupus nephritis is rarely the most common presentation of an unconscious patient. Here we report diagnosis of lupus nephritis with severe rhabdomyolysis.

Case Description: A 40-year-old male with no medical history presents after being found down. Per a friend, for past few weeks, patient had been feeling ill with several Urgent Care visits for fever, prescribed multiple rounds of antibiotics with no improvement. On admission his speech was slurred, and he had bruising over his arms, dry mouth and lips, with blue extremities. Social history was noted for smoking 20 pack years, occasional marijuana uses and micro-dosing mushrooms. Physical exam was significant for bilateral lower extremity reticular rash and severe cyanosis of fingers and toes. Admissions labs had severe electrolyte abnormalities: Na 116 mmol/L, K 6.2 mmol/L, Cl 79 mmol/L, HCO3 16 mmol/L, BUN 105 mg/dL and Cr 3.26 mg/dL, calcium 6.8 mg/dL, albumin 1.9 g/dL, PO4 10.0 mg/dL, CPK 6533 IU/L, uric acid 12.3 mg/dL, urinalysis with large blood, 1 RBC, 100 protein, trace LE, negative nitrites and 1 WBC, urine Pr/Cr 0.41 g/dL and negative urine culture. Urine drug screen was positive for cannabinoids only. Blood gas showed pH 7.17, pCO2 46.1 mmHg, pO2 33 mmHg and HCO3 17 mEq/L. US revealed bilateral DVTs. CT was grossly unremarkable. Due to worsening electrolytes and creatinine, renal replacement therapy was started. Additional labs including C3, C4, ANA, anti-dsDNA, SM/RNP Ab and chromatin Ab were consistent with Lupus. Pulse dose steroids were initiated, and renal biopsy results revealed acute tubular injury with myoglobin casts and class II lupus nephritis. After pulse dose steroids and 2 weeks of intermittent hemodialysis, kidney function improved substantially. Due to severe digit necrosis, patient required fingertip amputations. The patient was started on low dose mycophenolate and discharged with close outpatient follow-up.

Discussion: Rhabdomyolysis is known to occur in unconscious patients with severe AKI (1). Few case reports diagnose new-onset lupus with concomitant rhabdomyolysis with renal failure requiring dialysis. Additionally, the widespread skin involvement and digit amputation made diagnosis and management for this case difficult and thought provoking.

TH-PO662

Not All Lupus Nephritis Is "Complement"-ary

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Introduction: Lupus nephritis (LN) is a common but serious manifestation of Systemic Lupus Erythematous (SLE) that can lead to high morbidity and mortality, ultimately affecting up to 50% of patients with SLE. Typically, LN presents early in the clinical course of SLE, often within the first 3 years after diagnosis. Although the clinical manifestations of LN vary greatly, from nearly asymptomatic to rapidly progressive glomerulonephritis (RPGN), the typical presentation of LN includes edema, hypertension, proteinuria, and microscopic hematuria in patients with known SLE. We present a case with a classical presentation of lupus nephritis that did not follow the typical serologic findings.

Case Description: A 19-year-old white female with no significant past medical history presented to her primary care with 6-month history of intermittent bilateral itching leg pain and a 20lb weight gain. She initially attributed her leg pain to a high level of physical activity. Pain was worse between her knees and ankles and only temporarily alleviated with rest, massage, and ice. Over the past month, she developed new bilateral swelling in her legs. She denied history of recent illness, chest pain, SOB, congestion, malar rash, photosensitivity, oral ulcers, joint pains, or any history of kidney disease. Initial labs were significant for elevated lipid panel, ESR, and TSH with hypoalbuminemia. Urine analysis showed 3+ proteinuria with micro positive for >50% dysmorphic RBC and acanthocytes. Complements were normal suggesting against lupus nephritis. However, subsequent ANA came back positive with dsDNA 36 and anti-chromatin. The patient underwent a kidney biopsy and was diagnosed with Class IV +V lupus nephritis.

Discussion: In the work up of Nephritic syndrome we classically teach a targeted approach to serologic testing to avoid unnecessary (and potentially costly) labs. Complements are often used in the initial lab work up to assist in limiting serologic labs as a differentiating factor between complement mediated/immune complex mediated glomerulonephritis. In the above case, we initially had a lower suspicion for lupus nephritis due to normal complements. We were later surprised to find + ANA and biopsy confirmed class IV +V lupus nephritis. This case highlights the need to keep a broad differential diagnosis in the work up of Nephritic syndrome, and the limitations of Complement.

TH-PO663

A Rare Case of "Lupus-Like" Glomerulonephritis Presenting as Pulmonary Renal Syndrome (PRS)

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Introduction: PRS is a life-threatening condition characterized by rapidly progressive glomerulonephritis (RPGN) and diffuse alveolar hemorrhage (DAH). The main causes of PRS include ANCA associated vasculitis (AAV), anti-GBM disease, or immune complex-mediated glomerulonephritis (GN). Herein, we present a rare case of PRS with positive P-ANCA, but a "full house" crescentic GN on renal biopsy, with a negative ANA panel.

Case Description: A 59-year-old female with history of osteoarthritis presented with productive cough and dyspnea for two days. CT chest showed bibasilar ground glass opacities. Extensive infectious workup was negative. On the third day, she developed fever, hemoptysis, and rapidly progressive dyspnea necessitating intubation. Bronchoscopy revealed DAH. Her creatinine increased from 2.2 mg/dl on admission (baseline Cr 0.93 mg/dl) to 4.5 mg/dl within one week. Urinalysis revealed significant proteinuria (300 mg/dl) and RBC 40-60/HPF. Serologic workup revealed a high P-ANCA titer (> 1:640) and an elevated myeloperoxidase (MPO) antibody of 13. Anti-GBM, ANA, and anti-dsDNA were negative. Complements were normal. Kidney biopsy showed 19/69 glomeruli with cellular/fibrocellular crescent formation. Immunofluorescence (IF) revealed an intense "full house" staining. She was treated with plasmapheresis, steroid, and cyclophosphamide, resulting in the resolution of respiratory failure and improvement in Cr to 2.7 mg/dl upon discharge.

Discussion: Our patient's clinical picture supports a diagnosis of AAV with renal involvement, which typically presents as a pauci-immune crescentic GN with negative IF on biopsy. The presence of a "full house" IF pattern, suggestive of Lupus nephritis, was unexpected in this case. While P-ANCA can be found in 10% of patients with SLE, the absence of ANA excludes the patient from meeting the new EULEAR/ACR criteria for SLE diagnosis. SLE/AAV overlap syndrome has been reported as a rare entity, with biopsy features of both diseases. In such cases, the presence of ANCA antibody is often associated with more active lupus disease, higher ds DNA antibody levels, and worse renal function. Our case suggests the potential for AAV to overlap with other autoimmune syndromes, highlighting the importance of further studies to validate this association and develop a treatment strategy.

TH-PO664

Diagnostic Challenges in Lupus: Systemic Lupus Erythematosus Initially Presenting as Unicentric Castleman Disease

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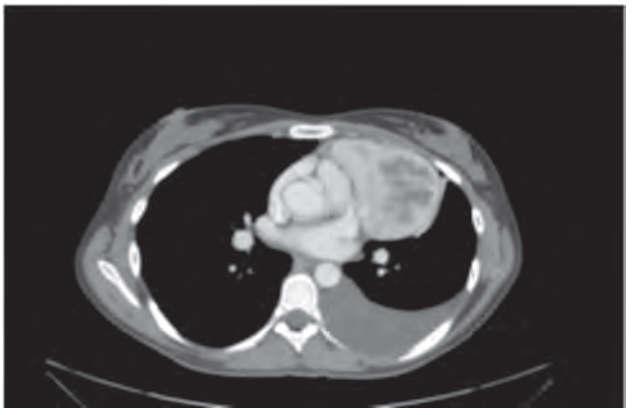
Introduction: Multiple conditions mimic Castleman Disease (CD), a group of lymphoproliferative disorders, including infection, neoplams and autoimmune disease. There is well-described clinical overlap between systemic lupus erythematosus (SLE) and CD as both can manifest with lymphadenopathy, proteinuria and positive anti-nuclear antibody (ANA) serology. Distinguishing between these two entities can be a vexing process and requires a multidisciplinary approach to care.

Case Description: A 23 year-old woman presented with dyspnea. Chest imaging revealed a large mediastinal mass and pleural effusion (Figure 1). The mass was resected and the patient was diagnosed with HHV-8 and EBV-negative CD. A clinician noted persistent hypoalbuminemia and discovered 8.2 grams per day of proteinuria despite surgical management. Work up included a kidney biopsy that showed a "full house" immune complex-mediated glomerulonephritis with focal activity, endocapillary hypercellularity and large subendothelial deposits. Serologic testing revealed positive ANA, anti-double-stranded DNA antibody and hypocomplementemia. The patient's final diagnosis was revised to SLE and she achieved remission with immunosuppressive therapy.

Discussion: To our knowledge, this is the first reported case of unicentric CD mimicking SLE in a patient with nephrotic syndrome. Because unicentric CD is managed with surgery alone, this report highlights the need for a broad diagnostic workup to rule out similarly presenting diseases with vastly different treatments. In this patient, workup for nephrotic syndrome prompted kidney biopsy and serologic testing that was essential for establishing the correct diagnosis and management.



TH-PO665

Guillain-Barre Syndrome Presenting Alongside Lupus Nephritis: Case and Management

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Introduction: Systemic Lupus erythematosus (SLE) can affect any organ system including the nervous system. However, peripheral nervous system involvement occurs in less than 10% of cases. We present here a case of Guillain-Barre syndrome (GBS) coexisting in a patient with undiagnosed new onset lupus nephritis.

Case Description: The patient is a 21-year-old female with past medical history of well controlled skin-limited SLE treated with hydroxychloroquine who presented with two weeks of ascending bilateral muscle weakness and the inability to ambulate in the setting of a recent gastrointestinal infection. Due to high suspicion for Guillain-Barre syndrome (GBS), she was started on plasmapheresis (PLEX) and pulse dose steroids. Despite completing 5 sessions of PLEX, her condition worsened and required mechanical ventilation due to respiratory muscle involvement. She further developed locked-in-syndrome. She, then completed 5 days of IVIG without any improvement. On day 13, she was noted to have acute kidney injury (AKI) with nephrotic range proteinuria, along with rare dysmorphic RBCs on urine sediment. Serology was positive for an SLE flare including hypocomplementemia, elevated ANA titer, and a positive dsDNA antibody. A kidney biopsy demonstrated full house immunofluorescence, with electron microscopy revealing subepithelial deposits and mesangial dense deposits, consistent with lupus nephritis, class V. Despite treatment with steroids, she quickly developed non-oliguric AKI, requiring hemodialysis. She was started on mycophenolate mofetil along with prednisone, resulting in recovery of kidney function within one month of initiating immunosuppression. However, she had much slower recovery in GBS symptoms, resolving 6 months after initial presentation.

Discussion: It is difficult to speculate which came first: GBS or lupus nephritis, since we know GBS can be initial presentation for lupus nephritis, however, GBS can trigger lupus nephritis as well through aberrant immune activation. However, when GBS coexists with lupus nephritis, its treatment is controversial, with standard treatment (PLEX +/- IVIG) being less effective. Currently no specific guidelines exist to treat GBS in such situations, however, cyclophosphamide with corticosteroids is considered first line of treatment, with mycophenolate mofetil, as in this case, an alternative treatment option.

TH-PO666

Cardiac Failure in Fibrillary Glomerulopathy Associated with Systemic Lupus Erythematosus

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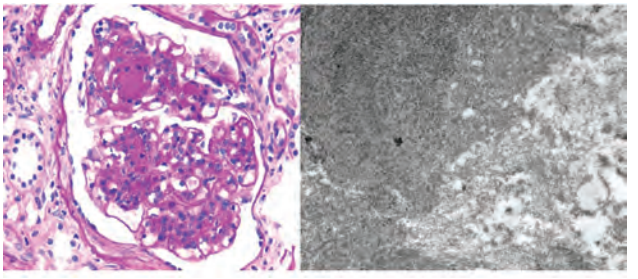
Introduction: SLE involves the kidneys in a large percentage of cases, and less frequently, there is the presence of myocardial damage with a prevalence of 8-25%.

Case Description: This is a 42-year-old male with a past medical history of pleural tuberculosis diagnosed three years ago, presenting with refractory exudative left pleural effusion, dyspnea, and pleuritic pain. He also has a three-year history of type 2 diabetes mellitus. His current symptoms as the same previously additional bilateral pleural effusion (transudate), intolerance to lying down, no peripheral edema, no retinopathy on fundoscopy. Laboratory findings included Hb of 11.7 g/dL, normo-normo anemia, eGFR by CKD-EPI of 28 mL/min/1.73m2, proteinuria of 8.9 g/24hrs with an inverted albumin/globulin ratio. Echocardiogram showed an ejection fraction of 23%. Only ANAs (1:640) and anti-U1-RNP (>200) antibodies were positive. C3 and C4 were normal. Renal biopsy showed negative staining with Congo red, indicating glomerulonephritis due to immune complexes with a membranoproliferative and nodular pattern. Immunofluorescence revealed a diffuse, global, and granular full house pattern, electron microscopy revealed fibrillary deposits measuring 10-20 nm.

Discussion: The presence of antibodies anti-U1-RNP and the occurrence of myocarditis are related to autoimmune activity against striated muscle. Myocarditis occurs in 5% to 10% of patients with SLE and most cases are asymptomatic and it can progress to heart failure. Atypical serology, unusual clinical presentation, and nodular biopsy make the diagnosis challenging, requiring electron microscopy for the diagnosis.



The mesangium shows diffuse expansion of the matrix with predominantly global proliferation, which gives some glomeruli a hiperlobulated appearance with the presence of acellular nodules.There are subendothelial and mesangial deposits of fibrils measuring 10-20 nm.

TH-PO667

Lupus Nephritis Complicated by Atypical Hemolytic Uremic Syndrome and Heterozygous Deletion in CFHR1-CFHR3 Successfully Treated with Ravulizumab

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Introduction: Atypical hemolytic uremic syndrome (aHUS) involves unchecked activation of the alternative pathway leading to deleterious action of complement on the endothelium. Failure to control complement activation is often due to inherited or acquired deficiencies of complement regulatory proteins, including Factor I, Factor H, Membrane Cofactor Protein, and CD46.

Case Description: 21 year old female with history of SLE presented with acute kidney injury (AKI) with an active urine sediment. Kidney biopsy showed diffuse lupus nephritis class IV and thrombotic microangiopathy (TMA). She was started on mycophenylate (MMF) 1g bid which she received for 2 wk, but was off for 4 wk, as she was not able to fill her medications, leading to admission for worsening AKI. Laboratory: hemoglobin 6.1gm/dl, platelet 185,000/ul, serum creatinine 7.25 mg/dl, UPCR 3.5 g/g, low C3 (57mg/dl), LDH 472 IU/l, haptoglobin 36 mg/dl, 2-3 schistocytes noted on blood smear. She was Induced with solumedrol and Myfortic 720 mg BID. Five sessions of plasmapheresis (PLEX) were done due to TMA biopsy findings. She developed microangiopathic hemolytic anemia (MAHA), severe thrombocytopenia, tonic-clonic seizures, and required hemodialysis. ADAMTS 13 level was normal and anti-phospholipid studies were negative. Given the high suspicion of atypical HUS, ravulizumab was added to her regimen. Hemoglobin and platelet count normalized after 2 weeks. She remained dialysis dependent for 6 weeks. Renal function improved and serum creatinine has remained stable at 3.0 mg/dl off dialysis. Genetic testing revealed compound heterozygosity for exon 2-6 deletion in CFHR1 and exon 1-6 deletion on CFHR3.

Discussion: The coexistence of atypical HUS with mutations in complement regulatory proteins and lupus nephritis is rare. Our patient had a successful outcome with addition of ravulizumab. Initial treatment with plasma exchange and conventional therapy with MMF and glucocorticoids did not improve MAHA, thrombocytopenia, or kidney function.

TH-PO668

A Do-Not-Miss Diagnosis: Thrombotic Thrombocytopenic Purpura in Systemic Lupus Erythematosus

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Introduction: Thrombotic thrombocytopenic purpura (TTP) is a rare complication of systemic lupus erythematosus (SLE) associated with high mortality. We report the case of a patient with SLE complicated by the development of fatal TTP.

Case Description: A 42-year-old male with history of SLE presented to an outside hospital endorsing three days of hematuria, hematemesis, dysarthria, malaise, and cutaneous changes for one week. His objective data there was pertinent for platelets (PLT) of 2 k/uL, creatinine of 2.38 mg/dL (baseline 0.8), and CT evidence of perinephric stranding. On arrival to our hospital, he was tachycardic, tachypneic, afebrile, and normotensive. Examination revealed jaundice with diffuse ecchymoses, and a normal neurological status. Laboratory studies on arrival were pertinent for undetectably low PLT count, hemoglobin 8.4 g/dL, creatinine 2.55 mg/dL, total bilirubin 3.6 mg/dL (direct 1.0), haptoglobin 20 mg/dL (ref 30-200), schistocytes on blood smear, LDH 3,433 U/L, D-dimer 38.5 ug/mL, fibrinogen 603 mg/dL, PT of 15.2 s, PTT of 34 s, and a normal vitamin B12. The patient's mental status rapidly worsened in the ensuing hours, and he developed hypoxic respiratory failure with a serum lactate of 12 mmol/L. He was moved to the intensive care unit to start empiric therapeutic plasma exchange (TPE). His ADAMTS13 activity level resulted at <5% (ref >61%) and notably the ADAMTS13 inhibitor activity was elevated. Prior to initiation of TPE, however, the patient was found unresponsive and in cardiac arrest. After forty minutes of advanced cardiovascular life

support effort, the patient was pronounced deceased just twelve hours after admission. Autopsy showed platelet-rich microthrombi in multiple organs, severe thrombocytopenia, and no deep vein thrombi most consistent with TTP.

Discussion: Thrombotic microangiopathies (TMA) are rare clinical syndromes characterized by thrombocytopenia, microangiopathic hemolytic anemia, and microvascular thrombus formation leading to end-organ damage. TTP is a rare and often lethal complication of SLE (sTTP) and its diagnosis is challenging due to the significant overlap in signs and symptoms. As illustrated by this case, severe thrombocytopenia in a patient with SLE should raise concern for sTTP as any delay in its diagnosis can be fatal. Early diagnosis and prompt initiation of treatment including therapeutic plasma exchange is crucial.

TH-PO669

Effective Treatment of Renal Thrombotic Angiopathy due to Idiopathic Multicentric Castleman Disease with Rituximab

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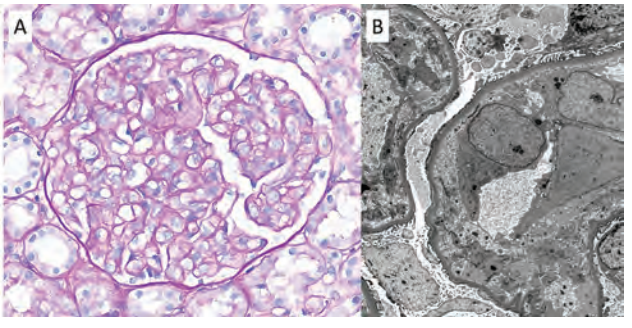
Introduction: Idiopathic multicentric Castleman disease (iMCD) is a rare, benign lymphoproliferative disorder. Renal involvement in iMCD is uncommon but is usually associated with thrombotic microangiopathy, and effective therapies have not been rigorously studied. First-line therapy includes steroids and monoclonal antibodies targeting IL-6. We present a case of iMCD with renal involvement unresponsive to siltuximab but responsive to rituximab.

Case Description: A 36-year-old gentleman presented with shortness of breath, edema, lymphadenopathy, and fevers and was found to have a serum creatinine (sCr) of 2.5 mg/dL. Urine sediment showed muddy brown casts and he had subnephrotic range proteinuria. A renal biopsy showed acute microangiopathy with diffuse glomerular endotheliosis and minimal fibrosis. A subsequent inguinal lymph node biopsy showed reactive lymphoid hyperplasia with some changes suggestive of Castleman disease. He was initiated on steroids and sCr improved to 0.94 mg/dL. One year after the initial presentation, he was re-admitted with dyspnea and acute kidney injury (AKI). A repeat renal biopsy showed chronic angiopathic changes accompanied by scattered endotheliosis and mild fibrosis, and he was placed on a prednisone taper with improvement in his renal function. Given his recurrent disease, he was started on siltuximab and received 3 doses. He failed to respond to this and was transitioned to rituximab with subsequent resolution of his AKI, proteinuria, and lymphadenopathy.

Discussion: Renal involvement in severe cases of iMCD is rare but is usually associated with microangiopathy and endothelial injury; however, little is known about the most effective treatment. Siltuximab is often the first-line therapy, but there is limited data for patients who do not respond. Second-line therapies include chemotherapy, immunomodulators, and immunosuppressants. Our case demonstrates improvement in renal function and resolution of proteinuria with rituximab.



TH-PO670

Atypical Hemolytic Uremic Syndrome with Normal Complement Studies in a Patient with Complement Factor I Deficiency

Brian Monk, Danielle C. Foster, Mohammad Atari, Mohamed Hassanein. *The University of Mississippi Medical Center, Jackson, MS.*

Introduction: Atypical hemolytic uremic syndrome (AHUS) is a type of thrombotic microangiopathy (TMA) that presents with organ dysfunction, particularly involving the kidney. AHUS occurs due to dysfunction in the alternative complement pathway and occurs sporadically, secondary to malignancy, drugs, or autoimmune diseases, or can be inherited. We present a rare case of AHUS due to a genetic mutation in complement factor I (CFI) and normal complement studies.

Case Description: A 27-year-old female with uncontrolled hypertension (HTN) was admitted for hypertensive emergency (blood pressure 211/119) and acute kidney injury (Cr 15.4 mg/dL, baseline 3 mg/ dL). Further workup showed hemoglobin 8.2 g/dL (ref: 11.2-15.7 g/dL), platelets 78 K/uL (ref: 182-369 K/uL), low haptoglobin, and elevated LDH. Infectious and autoimmune processes were ruled out. Compliment levels C3 and C4 were normal. While awaiting an AHUS complement panel, she required dialysis and underwent a kidney biopsy which showed TMA with 40% interstitial fibrosis and 60% acute tubular injury. Eculizumab therapy was initiated for suspicion of AHUS based on biopsy findings. A few days later, AHUS panel came back showing no abnormalities in the alternative complement pathway, except elevated C5b-9. After discharge, she was found to have a heterozygous mutation of the CFI gene which has been associated with autosomal dominant AHUS. Eculizumab therapy was continued and the patient was monitored closely outpatient.

Discussion: In the setting of normal complement studies, one cannot rule out AHUS as the primary cause of TMA. If the index of suspicion is high, it is recommended to start empirical Eculizumab and send off genetic studies to rule out a genetic cause of the AHUS, which may prevent unnecessary cessation or delay in Eculizumab therapy, and hence improve outcomes.

TH-PO671

Unusual Presentation of ANCA-Associated Vasculitis with Full-House Pattern Immunostaining

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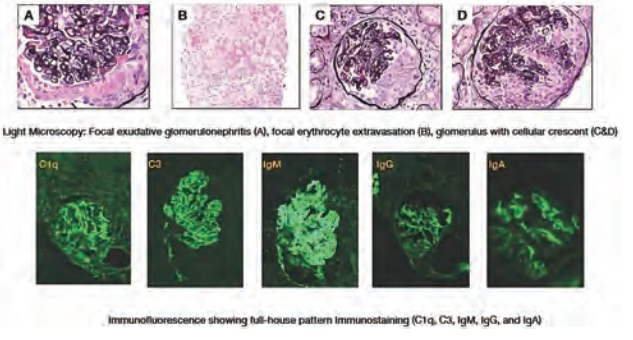
Introduction: Pauci-immune glomerulonephritis is the most common cause of rapidly progressive glomerulonephritis (RPGN) mainly secondary to antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Typically, renal involvement lacks the presence of immune deposits. Here we present a case of AAV-induced RPGN with a full-house pattern immunofluorescence (IF).

Case Description: A 35-year-old male with a history of uncorrected congenital heart disease presented to the hospital with lower extremitiy edema. Evaluation revealed AKI with serum creatinine 5.43 mg/dL, urine analysis with >100 RBCs (0-4), +50 protein with sub-nephrotic range proteinuria. Autoimmune workup was positive for ANA 1:160 (speckled pattern), low C3 70mg/dL (90-180 mg/dL), positive PR3-ANCA >8U (<0.4U), and P-ANCA, but negative MPO-ANCA and C-ANCA. Anti-dsDNA, anti-histone antibodies, anti-smith, anti-GBM, viral panel, and protein electrophoresis all were normal. Kidney biopsy showed necrotizing crescentic glomerulonephritis with variable para-medullary inflammation strongly suggesting ANCA vasculitis. IF showed a full-house pattern (IgG, IgM, IgA, C3, C1q, kappa, and lambda). Treatment with Rituximab and pulse steroids followed by steroids taper was initiated. Unfortunately, the patient passed away.

Discussion: Renal involvement by AAV typically has no or few immune deposits. Full-house immunofluorescence has been rarely reported in the setting of ANCA vasculitis and it is unusual. Although histopathology in our patient is suggestive of AAV, the presence of full house pattern on IF with positive serum ANA is concerning for possible overlap syndrome where lupus and ANCA vasculitis accompany. Despite the absence of anti-dsDNA and anti-smith, still, lupus cannot be ruled out. This case is one of a few reported cases having AAV with RPGN presentation and concomitant full-house pattern in kidney biopsy, possibly representing lupus/AAV overlap.



TH-PO672

Thrombotic Microangiopathy Associated with Exostosin-1-Associated Membranous Nephropathy: Case Report

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Introduction: Thrombotic Microangiopathy (TMA) is characterized by the association of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, associated to target organ damage. Its association with Membranous Nephropathy (MN) is rarely described. We report an atypical case of TMA with Exostosin 1-associated MN.

Case Description: A previously healthy 15-years-old woman presented with vomiting and seizures associated with MAHA, thrombocytopenia, hematuria and creatinine (sCr) 2.2 mg/dL. She had low serum complement level and negative viral serologies, ANA and anti-DNAds. PLASMIC score was five. Due to moderate suspicion of Thrombotic Thrombocytopenic Purpura (TTP), the patient was treated with Methylprednisolone 1g/day for three days, followed by Prednisone 1mg/Kg/day and Rituximab (500mg/wk - 4 weeks), in addition to plasmapheresis. On the 4th day of hospitalization, she developed refractory hypervolemia and worsening of renal function, requiring hemodialysis during 4 weeks. She has improved renal function and MAHA, but remained with nephrotic syndrome (peripheral edema, albumin 3.3g/dL, proteinuria 6.1g/day) associated to hematuria. A renal biopsy was performed showing subacute TMA associated with stage II MN, with granular deposits of IgG (3+/3+) and C3 (traces) in the glomerular basement membrane. Immunohistochemistry of the renal tissue was PLA2R-negative and

positive for Exostosin-1, IgG1, IgG2 and IgG4. On further investigation, she had positive p-ANCA and Anti-DNA, but negative ANA and APS antibodies. ADAMTS13 activity (4 weeks after Rituximab) was normal. The patient progressively decreased proteinuria and sCr, but after 4 months, she relapsed with peripheral edema, proteinuria 8.0 g/day and albumin 3.4 g/dL. Due to her previous good response to Rituximab, a new cycle of medication was scheduled.

Discussion: Despite MN being a frequent cause of nephrotic syndrome, few cases are reported in association with TMA. Auto-immune secondary causes of MN should be screened in young ladies. Since both conditions can be mediated by immune complexes, it is possible that autoantibodies caused the deposition of subepithelial immune complexes as well as the complement activation and endothelial injury which are responsible for TMA in our patient.

TH-PO673

Thrombotic Microangiopathy Secondary to Acute Pancreatitis: A Rare Association

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Introduction: Thrombotic microangiopathy (TMA) due to acute pancreatitis is rare with only 35 cases reported since 1978. The diagnosis requires a high index of suspicion and if not managed timely, can lead to severe morbidity and mortality. Here we report a case of TMA due to acute pancreatitis that was promptly recognized and successfully treated with Eculizumab.

Case Description: A 58-yo woman presented with one-day history of abdominal pain, nausea and vomiting after ingesting seafood. She was Jehovah's witness. Labs on admission showed an elevated lipase, 1900 U/L (13-60 U/L). Serum creatinine was at baseline (1.7 mg/dl). Treatment for acute pancreatitis was initiated. Two days later, serum creatinine increased to 8 mg/dl. Labs also showed features of microangiopathic hemolytic anemia and thrombocytopenia (Hgb 4 g/dl, platelet 46 K/uL, haptoglobin < 10 mg/dl, lactate dehydrogenase 2424 U/L). Schistocytes (>10/hpf) were present on peripheral smear. ADAMTS13 activity was normal. C3 was low normal at 99 mg/dl (normal range, 90-180 mg/dl) and C4 was normal. TMA was suspected and eculizumab started on day 7. Two days after starting eculizumab, platelet count improved to 128 K/uL, hemoglobin to 7 g/dl, LDH was 800 U/l and haptoglobin normalized. She remained dialysis dependent on discharge but 4 weeks later renal function recovered and she came off dialysis. Serum creatinine 6 weeks later is 3.6mg/dl. She remains on eculizumab. Genetic testing did not show any pathogenic mutations.

Discussion: Pancreatitis can occur in 2% of cases due to TMA, but pancreatitis causing TMA is exceedingly rare. In cases where TMA causes acute pancreatitis, it precedes the onset of pancreatitis, whereas, when acute pancreatitis causes TMA, it manifests typically 2-3 days after the pancreatitis (as in our case). The etiology of TMA after pancreatitis is speculated to be due to inflammatory mediators causing vascular endothelial injury, transient complement activation and ADAMTS13 inhibition. Eculizumab has been shown to shorten renal and hematological recovery but only reported in 3 of 35 cases. Most patients can stop the drug after 3-6 months. Importantly, in our case, we treated with eculizumab since she was Jehovah's witness and refused plasma exchange. AKI in acute pancreatitis can have a broad differential but early recognition of TMA-induced AKI can be lifesaving.

TH-PO674

A Rare Presentation of Genetic Complement-Mediated Thrombotic Microangiopathy

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Introduction: Complement genetics has recently gained prominence in understanding the pathogenesis of complement mediated thrombotic microangiopathy (CM-TMA) and the development of a specific therapy that is potentially lifesaving. We present a rare case of ischemic cortical infarcts concurrently with CM-TMA, successfully treated with eculizumab.

Case Description: A 46-year-old male with a history of hypertension and chronic type B aortic dissection presented to the hospital for evaluation of presyncope and paraparesis. Labs showed profound renal failure with serum creatinine (sCr) of 14 mg/dl (baseline 1.14 mg/dl about 4 years before his presentation). A urinalysis showed > 300 mg of proteins, urine Pr/Cr of 8.0, and > 25 non dysmorphic RBCs/HPF. The patient was started on hemodialysis for worsening uremia, and shortly he developed ischemic stroke symptoms. MRI of the brain showed acute multifocal ischemic infarcts. Additional testing showed anemia, thrombocytopenia, elevated lactate dehydrogenase, low haptoglobin, and schistocytes in the peripheral smear. ADAMTS13 was normal. Further workup and serologies for possible infectious or autoimmune diseases were negative. SPEP was normal. A kidney biopsy showed thrombotic microangiopathy with negative immunofluorescence. Additional testing of complement factors showed elevated factor H, C3a, and C5a, with a normal CH50, and factor B, supporting CM-TMA diagnosis. The patient was started on an induction dose of eculizumab and remained on a maintenance dose every two weeks. Genetic testing showed homozygous deletion of CFHR1, supporting the long-term use of a C5 inhibitor. The patient started to show signs of renal recovery. Hemodialysis was discontinued 6 weeks after initiation, and sCr improved and remained stable around 2.4 mg/dl while on eculizumab. Over a 2-year follow-up, hemoglobin and platelets normalized, and neurologic recovery was full.

Discussion: CM-TMA is caused by dysregulation of the alternative pathway. Eculizumab, a humanized anti-C5 monoclonal antibody, is effective in terminating the microangiopathic hemolytic activity in patients with CM-TMA. Early identification and treatment of this disease can be life-saving. We also highlight the importance of genetic testing as it can guide long-term treatment plans. Patients with high-risk variants and severe disease manifestations may need a prolonged treatment period.

TH-PO675

Avelumab-Induced Thrombotic Microangiopathy: A Case Report

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Introduction: Monoclonal antibodies against programmed cell death 1 (PD-1) can improve outcomes in many advanced cancers, including ovarian carcinoma. Despite such advantages, these agents are associated with various immune-related adverse events. We report a case of TMA after chemotherapy using Avelumab.

Case Description: A 56-year-old female, with a medical history of stage 3 ovarian cancer and hypertension was referred by her oncologist due to worsening kidney function. Her cancer was initially treated with carboplatin, paclitaxel, and veliparib for a total of 6 cycles. Therapy was changed to bevacizumab due to worsening disease but was suspended when the patient developed secondary hypertension. Subsequently, Avelumab was initiated. A slow rise in creatinine was noted two months after starting Avelumab. A renal biopsy showed acute on chronic thrombotic microangiopathy. Although there was anemia, no hemolysis or thrombocytopenia was noted. Supplementary work up including ADAMS 13, APLA, and autoimmune workup were normal. In the setting of possible atypical HUS secondary to PD 1 inhibitor exposure, eculizumab was initiated. In the most recent follow-up, kidney function has been steadily improving reaching a range between 1.7-2.0 mg/dl.

Discussion: Although TTP associated with Avelumab is reported, HUS associated with Avelumab has not been reported so far. Possible mechanisms of kidney injury that have been proposed: include excessive inflammatory cytokine production, and enhancing complement-mediated inflammation. Prompt discontinuation of the offending agents along wth initiation of complement inhibitory therapy is key to the successful management.

TH-PO676

ANCA Glomerulonephritis: Uncommon Presentation as Renal Masses

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Introduction: Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) can manifest with diverse systemic symptoms and commonly affects the kidneys, causing necrotizing glomerulonephritis (GN). Here, we report a rare case of AAV presenting as renal cortical masses.

Case Description: A 70-year-old male presented with fatigue, loss of appetite, and a 50-lb weight loss over six months. Initial laboratory workup was unremarkable including normal serum creatinine and urinalysis. CT scan showed non-specific bilateral pulmonary nodules and a 'rind' of abnormal soft tissue surrounding the abdominal aorta. Three months later, follow-up CT scan revealed worsening peri-aortic soft tissue thickening (max 3 cm) and the development of bilateral renal cortical masses (largest measuring 2.5 cm). Further workup showed positive p-ANCA with elevated MPO levels (>8.0 U; ref. <0.4 U), CRP (72 mg/dL; ref. <0.5 mg/dL), and mildly elevated IgG4 (137 mg/dL, ref. 2.4–121 mg/dL). Two kidney biopsies were obtained. The standard core biopsy showed plasma cell-rich infiltrates without IgG4 positivity, while the fine needle aspiration (FNA) to a renal mass showed focal necrotizing and crescentic GN with granulomatous vasculitis. Induction therapy with high-dose steroids and rituximab was initiated. Steroid dosage was tapered over a year, and maintenance rituximab doses were adjusted based on CD19+/CD20+ cell counts and MPO-ANCA titers. The patient has remained in clinical remission, without hematuria, proteinuria, or elevated serum creatinine over 4 years.

Discussion: AAV can form inflammatory masses in various organs, including kidneys, pancreas, orbit, and peri-aortic soft tissue, akin to IgG4-related disease. In a recent case series, patients with ANCA-associated renal masses often had elevated serum IgG4 levels or increased tissue IgG4+ plasma cells. Few cases had normal urinalysis and serum creatinine despite biopsy findings of crescentic GN, as in our case. Our case is particularly unique: (1) repeated CT scans confirmed rapid development and progression of renal masses and peri-aortic soft tissue thickening; and (2) crescentic GN was detected in FNA of the renal mass but not in the core biopsy. In patients with suspected AAV and renal masses, kidney biopsy is essential to establish the diagnosis and rule out cancer and infection before starting immunosuppression.

TH-PO677

ANCA-Negative Vasculitis Leading to Intrauterine Fetal Demise

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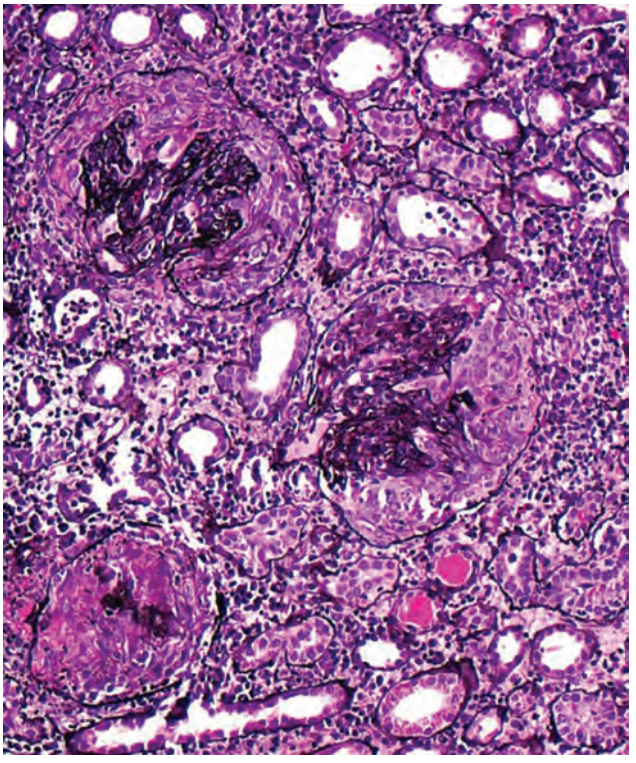
Introduction: ANCA-negative pauci immune crescentic glomerulonephritis is a relatively rare subtype of RPGN, accounting for ~10-30% of cases. ANCA-negative vasculitis complicating a pregnancy course is even more rare. We present an interesting case where fetal demise at 20 weeks was the first manifestation of ANCA vasculitis.

Case Description: A previously healthy 16-year-old, G1P0 at 20 weeks of gestation, presented with vaginal bleeding and lower limb edema of 3-4 days duration. No further

PMH except a recently completed antibiotic course 3 weeks ago for a URI. She was afebrile, HR 116/min, BP 158/110mmHg, SpO2 97% on RA. Lab workup WBC 8.4, Hgb 7.0, platelets 207, Na 136, K 4.4, HCO3 17, BUN 76, Cr 9.4 mg/dl (no baseline), and albumin 2.6 g/dl. UA: microscopic hematuria, 3+ protein. UPCR 6.3 g/g. UDS negative. Autoimmune workup was all negative including PR3/MPO. Trans-abdominal US showed fetal demise for which she underwent emergent vaginal delivery. From a kidney standpoint, the patient required hemodialysis on admission for volume overload. Given her severe anuric AKI, she underwent a kidney biopsy that showed: Diffuse necrotizing and crescentic glomerulonephritis, pauci immune, 23/24 glomeruli with cellular crescents and fibrinoid necrosis. The patient was treated with pulse steroids, rituximab 1 gram x 2, and plasmapheresis every other day for total of 7 sessions. She became non-oliguric; however, remained dialysis-dependent at the time of transfer to a pediatric hospital.

Discussion: We present a challenging case of ANCA-negative vasculitis complicating pregnancy leading to fetal demise. Our patient was managed similarly to an ANCA-positive vasculitis. We wonder if adding aserum creatinine to the routine urinalysis as part of first-trimester screening would have led to earlier diagnosis and changed this unfortunate outcome.



Cellular crescents

TH-PO678

Where Have All the Eos Gone? Long Time Passing or in the Heart? ANCA-Associated Crescentic Glomerulonephritis Presenting with Eosinophilic Myocarditis

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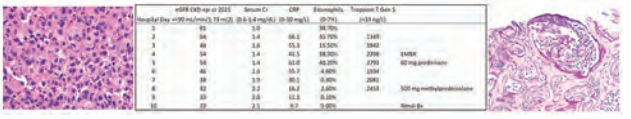
Introduction: Eosinophilic granulomatosis with polyangiitis (EGPA) may be diagnosed from other small vessel vasculitides by clinical criteria. Its rare presentation as an acute coronary syndrome in a community setting makes this an unfamiliar entity. New therapies in IL-5 and complement pathways are recent tools to reduce immunosuppression but trials have mixed results or must be used "off-label" for EGPA due to its variable presentation. We present a case of EGPA in which avacopan was initiated for compassionate use.

Case Description: A 69 year old male with history of asthma presented to his PCP with 3 days of constant left sided chest pain radiating to the back. Transfer to our institution showed cardiac MR consistent with subendocardial infarct and suspicion for eosinophilic myocarditis as peripheral eosinophilia was elevated to 38.7% (absolute eosinophils 2250/mm^3). Endomyocardial biopsy was performed showing sheet-like histiocytic cell proliferation with abundant eosinophilic inflammation (Figure 1). Methylprednisolone 500 mg was initiated for presumed eosinophilic myocarditis. Urinalysis was notable for 51-100 rbc and renal biopsy was performed. A diagnosis consistent with pauci-immune necrotising crescentic glomerulonephritis was made but eosinophils were absent. cANCA was positive at 1:320. The patient received rituximab and discharged with steroid taper but was rehospitalized for Klebsiella and Pseudomonas pneumonia and severely reduced eGFR of 9 mL/min/1.73 m^2. Cyclophosphamide was initiated with another round of high dose steroids but dialysis was started by week 9 of his original presentation. On day 58, the patient started avacopan 30 mg BID. Although he eventually became dialysis independent he continued to experience complications from infections and entered hospice 8 months after the diagnosis of EGPA.

Discussion: EGPA may affect multiple organs and therefore requires rapid recognition with aggressive treatment and coordination from specialists. However, complications often occur with sustained immunosuppression as our case demonstrates. The use of new agents for this rare cause of ANCA associated glomerulonephritis must further be studied.



TH-PO679

Avacopan and ANCA

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Introduction: ANCA-negative vasculitis, although rare, is associated with increased morbidity and mortality. In this case report, we present a patient with ANCA-negative vasculitis and highlight the use of the novel agent Avocopan.

Case Description: A seventy-four-year-old male with a medical history of hypertension, insulin-dependent diabetes, and coronary arterial disease presented to urgent care with symptoms of shortness of breath, cough, lower extremity swelling, and a rash on his buttocks. He was thought to have multifocal pneumonia and heart failure. Despite initial treatment, his edema worsened, and subsequent laboratory tests showed an increase in serum creatinine from 1.7 mg/dL to 3.75 mg/dL. Urinalysis revealed microscopic hematuria and proteinuria quantified at 8.89 g/day. Concerns arose regarding rapidly progressive glomerulonephritis, and a secondary serological workup yielded largely negative results, including ANCA. A kidney biopsy was performed, revealing pauci-immune crescentic glomerulonephritis of the focal necrotizing type with moderate activity and minimal chronicity. The patient underwent Rituximab induction therapy along with steroids for maintenance. However, due to worsening edema, hypertension, hyperglycemia, and weight gain a decision was made to switch the patient to Avacopan. At six months follow up, the patient's serum creatinine reduced to 1.89 mg/dL, and proteinuria decreased to 0.81 g.

Discussion: The standard approach to ANCA-mediated vasculitis has involved the use of glucocorticoids in combination with Rituximab or cyclophosphamide. However, a novel agent called Avacopan has emerged as a promising alternative. Avacopan specifically targets the alternative complement pathway, which is believed to play a role in the pathogenesis of ANCA vasculitis. In our case of ANCA-negative vasculitis the patient responded well to Avacopan therapy, achieving remission with minimal proteinuria. References: Jayne et Al. Avacopan for the Treatment of ANCA-Associated Vasculitis. NEJM 2021 Feb 18 384:599-609. Jennette JC, Nachman PH. ANCA Glomerulonephritis and Vasculitis. Clin J Am Soc Nephrol. 2017 Oct 6;12(10):1680-1691.

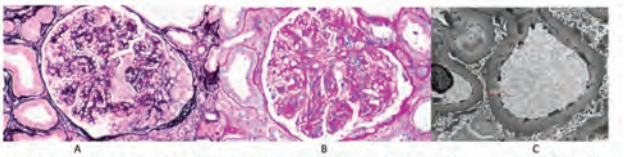

Figure A. Glomerulus with fibrocelilular crescent and glomerular basement membrane break (Jones silver stain 400x). Figure B. Glomerulus with (a) diabetic nodular sclerosis. Figure C. thickened glomerular basement membranes (PAS stain 400x and electron micrograph).

TH-PO680

ANCA Vasculitis in a Patient with Significant Silica Exposure

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Introduction: Exposure to free crystalline silica (silicon dioxide) is classically associated with an array of lung diseases. It has also been associated with ANCA vasculitis. Here we describe a case of ANCA vasculitis attributed to silicosis, a diagnosis that occurred through multi-disciplinary involvement.

Case Description: A 37-year-old male with no past medical history presents with one year of cough and hemoptysis. For the past 20 years, he has worked as a granite cutter, installing counter tops; he smokes 2-3 cigarettes per day. He was found to have a creatinine of 2.5 mg/dL (0.8 mg/dL eight months ago). Labs were notable for nephrotic range proteinuria of 5 g/g creatinine and 3+ hemoglobinuria with 13 RBCs/HPF but normal complements and negative rheumatoid factor, HIV, and anti-HCV. He had positive MPO/P-ANCA, dsDNA, and ANA. CT chest without contrast showed numerous nodules. After discussion between nephrology, rheumatology, infectious disease, and pulmonology, he was admitted for expedited kidney biopsy and bronchoscopy. Kidney biopsy revealed glomerulonephritis with 30% active crescents and both IgG and C3 deposition, not entirely typical for lupus or ANCA vasculitis but concerning for drug-induced or infection-associated ANCA. Bronchoscopy showed hemosiderin laden-macrophages but BAL was inconsistent with diffuse alveolar hemorrhage and negative for tuberculosis through AFB stain and culture. Since his quantiferon was positive and he had immigrated from a TB-endemic region, concern for miliary tuberculosis was high, so he underwent VATS lung biopsy which was consistent with silicosis based on pathology demonstrating nodular aggregates of dust-laden macrophages, fibrosis, and birefringent particles. A diagnosis of ANCA vasculitis associated with silicosis was made. He received

rituximab but experienced a severe infusion reaction so treatment was changed to cyclophosphamide and high-dose steroids with improvement in his creatinine although without return to baseline. He is also receiving treatment for latent tuberculosis.

Discussion: Silica exposure has been described in the literature to cause a variety of autoimmune conditions including ANCA vasculitis and lupus although the mechanism is unclear. Our patient's occupational exposure and biopsies support this diagnosis. This case highlights the importance of a thorough exposure history and multi-disciplinary engagement to arrive at a diagnosis.

TH-PO681

Obinutuzumab in Combination with Avacopan in Rituximab-Resistant ANCA-Associated Vasculitis (AAV)

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Introduction: Rituximab (RTX) is now considered the standard for induction (along with glucocorticoid) and maintenance therapy of patients with AAV. We report 2 patients with AAV who had active disease despite RTX therapy and were successfully treated with combination of Obinutuzumab (OBZ) (a type II anti-CD20) and Avacopan (C5aR antagonist).

Case Description: Patient 1: 80-year old female with a 10-year history of microscopic polyangiitis treated with mycophenolate (MPA) (for 6 years) and prednisone (PRED). She relapsed after being off immunosuppression for 2 years and was re-initiated on MPA therapy. Due to lack of response, she was switched to RTX induction 1g x 2 doses 2 weeks apart with PRED. At the time of RTX induction, serum creatinine (Scr) was 1.5 with MPO-ANCA titers > 8.0 U and hematuria (3-10 RBC/HPF). She was continued on RTX maintenance therapy (1g) every 6-months. However, despite RTX therapy (18 months) and CD20+ B cell of zero, she had rising Scr 2.1 mg/dL with persistent hematuria and MPO titers > 8.0 U. Repeat biopsy showed active necrotizing glomerulonephritis (GN). Therefore, she received OBZ 1g x 2 doses 2weeks apart with Avacopan 30 mg twice daily. At last follow up (9 months after OBZ), her Scr is stable at 2.0 mg/dL, hematuria completely resolved and MPO is down to 1.1 U. She has not experienced any adverse events. Patient 2: 47-year-old female was diagnosed with AAV after presenting with a Scr of 2.6, hematuria (3-10 RBC/HPF), MPO titers > 8.0 U and a biopsy that showed pauci-immune necrotizing GN. She was initially treated with RTX 375 mg/m^2 weekly for 4 doses and PRED. She was continued on RTX (1g) every 6 months. Although her Scr initially improved to 1.5 mg/dL, her MPO remained persistently > 8.0. Subsequently, she was noted to have a worsening Scr that peaked at 2.4 mg/dL with hematuria (100/HPF) and MPO > 8.0 U despite therapy with RTX. CD20+ B cells were zero. A repeat kidney biopsy showed active necrotizing GN. She received 1 dose of OBZ 1g, Avacopan 30 mg twice daily and prednisone. Six months following OBZ, Scr is stable at 2.2 mg/dL, hematuria resolved and MPO titers are down to 5.8 U.

Discussion: OBZ with Avacopan can be an effective strategy in AAV patients resistant to RTX. The efficacy of this combination should be evaluated through a randomized clinical trial to determine outcomes and adverse effects.

TH-PO682

Infection-Related ANCA-Negative Pauci-Immune Glomerulonephritis

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Introduction: Infection-related glomerulonephritis (IRGN) is typically an immune-complex mediated disease characterized by a diffuse proliferative process with mesangial, subendothelial and subepithelial deposits comprised of various combinations of IgM, IgG, IgA and C3. However, other forms of IRGN have also been reported, including those with a pauci-immune crescentic pattern of injury. The overwhelming majority of pauci-immune GN cases are associated with the presence of anti-neutrophil cytoplasmic antibodies (ANCA). However, approximately 2-10% of these patients may be ANCA negative, and here, we present two cases of IRGN, which were ANCA-negative, and demonstrated a pauci-immune crescentic pattern of injury.

Case Description: Table 1 describes the clinical characteristics, histologic features and outcomes for two patients who initially presented with acute kidney injury, were subsequently diagnosed with ANCA-negative pauci-immune crescentic GN on kidney biopsy and after further evaluation for secondary causes of pauci-immune GN, were found to have bacterial aortic/mitral valve endocarditis.

Discussion: This case series depicts two patients who developed ANCA-negative pauci-immune GN in association with bacterial endocarditis. The largest case series of 74 patients with ANCA-negative pauci-immune GN included 9 cases that were infection-related. 54% of these patients had extra-renal involvement and 23% of them required dialysis at diagnosis. The diverse glomerular presentations in association with infections have significant clinical implications since the prompt recognition of an underlying systemic infection is crucial to avoid inadvertent immunosuppressive therapy. It is imperative for clinicians to screen for occult infections not only when an immune-complex GN is seen, but also when a pauci-immune process is identified on a kidney biopsy.

Table 1

Clinical Characteristics	Case 1	Case 2
Age (Years) / Sex	69 / Female	59 / Female
Clinical Manifestations	Exertional Dyspnea and Lower Extremity Edema	Progressive Weight Gain, Exertional Dyspnea and Lower Extremity Non-Blanching Petechial Rash
Serum Creatinine on Initial Presentation (Baseline Creatinine) (mg/dL)	4.1 (1.0)	3.0 (0.6)
Urinalysis Urine Protein/Creatinine Ratio (mg/mg)	Microscopic Hematuria (>25 RBCs/HPF) (Dysmorphic RBCs) 0.45	Microscopic Hematuria: (>25 RBCs/HPF) (Dysmorphic RBCs) 0.95
Available Serologic Testing	ANA Negative ANCA Negative Low Serum C3 (71 mg/dL) Low Serum C4 (7 mg/dL)	Polyclonal IgG Type 3 Cryoglobulinemia IgM Lambda M-Protein ANA Negative ANCA Negative Low C3 (79 mg/dL) Normal C4 (24 mg/dL)
Blood Cultures Echocardiogram Findings	Streptococcus Mutans Mitral/Aortic Valve Vegetations	Streptococcus Mitis Mitral Valve Regurgitation Mitral/Aortic Valve Vegetations
Histologic Features on Kidney Biopsy	Pauci-Immune GN Endocapillary Hypercellularity Cellular/Fibrous Crescents with Necrosis Moderate IFTA	Pauci-Immune GN with Trace IgA, C3 and C1q Endocapillary Hypercellularity Cellular Crescents Severe IFTA
Clinical Outcomes	S/P Mitral and Aortic Valve Replacement Initiated KRT at the time of kidney biopsy Repeat kidney biopsy 1 month later showed focal global glomerulosclerosis without ongoing proliferative activity Last Follow-Up: remains KRT-dependent 4 months following valvular surgery	S/P Mitral Valve Replacement and Aortic Valve Repair Initiated KRT immediately after valvular surgery Subsequent kidney recovery with cessation of KRT one week after initiation Last Follow-Up: remains liberated from KRT with serum creatinine 1.23 mg/dL 3 months following valvular surgery

Interstitial Fibrosis and Tubular Atrophy (IFTA); Kidney Replacement Therapy (KRT)

TH-PO683

An Unusual Case of ANCA Vasculitis Coexisting with Membranous Nephropathy due to Cocaine Use

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Introduction: Membranous nephropathy (MN) is one of the leading entities causing nephrotic syndrome. Cocaine is associated with leukocytoclastic vasculitis, rhabdomyolysis, and ANCA-associated vasculitis (AAV) with pauci-immune necrotizing glomerulonephritis**.** We are reporting a rare case of a patient with rapidly progressive focal necrotizing & crescentic and sclerosing glomerulonephritis coexisting with MN in the setting of cocaine use.

Case Description: 51 yo male with Heart Failure reduced EF 30%, ANCA-associated MPA with focal segmental pauciimmune glomerulonephritis, Rheumatoid arthritis, polysubstance use (cocaine, alcohol) presents with dyspnea and lower extremity edema. BP 149/110, HR 100 beats/min, RR 18 respirations/min, T 97.7 Fahrenheit, O2 96% on room air Blood work showed macrocytic anemia of 8.1k with MCV 97.3, platelets: 256k, sodium: 139 mg/dL, potassium: 5.1 mg/dL, bicarbonate: 16, serum creatinine: 2.8 mg/dL, albumin: 1.9. BNP: 6992. UA >500 protein, moderate blood and RBCs 9, total protein creatinine ratio 3.88 g. Urine toxicology positive for cocaine and marihuana. C4 low 4, C3 low 68, ANA negative, RF negative, DsDNA: <1, P-ANCA 1:640, Myeloperoxidase ab elevated. Patient was admitted due to HF exacerbation and started on intravenous furosemide. Kidney biopsy showed Membranous, focal necrotizing crescentic and sclerosing glomerulonephritis. Treatment with steroids and immunosuppressive therapy with Rituximab and cyclophosphamide which he completed and discharged home. Returned to the ED 2 weeks later with clinical signs of fluid overload, anemia, and worsening kidney function requiring blood transfusion and subsequently started on dialysis. Hospital course was complicated with sepsis due to pneumonia and 7.5 cm abscess-like fluid collection posterior the bladder, abdominal tap positive for resistant Enterococcus faecium and ESBL positive, cyclophosphamide was discontinued and started on IV broad spectrum antibiotics. Ultimately patient succumbed to the disease.

Discussion: Coexistence of ANCA vasculitis with MN due to cocaine use is not frequently reported in the literature, effect of cocaine in the kidney has multiple pathophysiological mechanisms, causing AKI but very few includes MN intention of this abstract is to make physicians aware of this for the future and warrant further investigation.

TH-PO684

Late-Onset Hydralazine-Associated Immune-Complex Glomerulonephritis with Overlap ANCA and Lupus Nephritis Features

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Introduction: Hydralazine is one medication that has been long associated with drug-induced lupus and also antinuclear cytoplasmic antibodies (ANCA) vasculitis. We present an unusual case of an 83-year-old patient with hydralazine-associated glomerulonephritis (GN) with overlap features of ANCA vasculitis and lupus nephritis.

Case Description: The patient presented with hemoptysis with blood clot and estimated half a cup of red blood. She has history of hypertension and atrial fibrillation. Patient has had dyspnea on exertion, cough, nausea, and fatigue for 3 months. CT chest showed bronchial opacification, airspace disease, and mild fibrosis. Patient had remote 20 pack-year history of smoking. Her medications include hydralazine 50 mg 3 times a day for more than 10 years. Hemoglobin (Hgb) was 6.4 g/dL (down from 9.3 g/dL 1 month prior). Serum creatinine (Cr) was 2.3 mg/dL up from 1.4 one month prior and 0.7 six months prior. C3 and C4 70 and <8 mg/dL. Urinalysis showed 6-10 WBC and 50-100

RBC/hpf with dysmorphic RBCs and RBC casts. Urine protein/Cr ratio was 0.62 g/g. ANA 1:640, anti-dsDNA indeterminate, p-ANCA 1:640, MPO Ab 7.2 AI, PR-3 Ab >8.0 AI, anti-histone Ab 4.4 U. Kidney biopsy showed mild mesangial hypercellularity on light microscopy and mild mesangial deposits on electron microscopy. Immunofluorescence showed 1-2+ IgA, IgM, C3 diffuse granular deposits. Patient was given pulse IV methylprednisolone for 3 days, followed by slow taper prednisone. Cr peaked at 3.3 mg/dL and improved to 2.1 mg/dL upon discharge.

Discussion: Patient's presentation of pulmonary renal syndrome is common in ANCA vasculitis, supported by the high p-ANCA, MPO Ab, and PR-3 Ab However, the classical findings of ANCA vasculitis with purely pauci-immune necrotizing and/or crescentic GN were not found. Instead, glomeruli showed mild IgA-predominant deposits. Low complements and elevated ANA and anti-histone Ab suggest hydralazine-induced GN. Ten years of hydralazine use confers a high cumulative dose, in contrast to a review of 12 cases of hydralazine-associated ANCA vasculitis showed median drug duration of 22 months. In a review of 7 cases of drug-induced lupus nephritis, the duration was >12 months for most patients. In summary, this case may be an atypical hydralazine-induced GN with overlapping lupus and ANCA serology but with dominant IgA deposits.

TH-PO685

"Atypical" Atypical Anti-Glomerular Basement Disease

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Introduction: Anti-glomerular basement membrane (anti-GBM) disease frequently presents as rapidly progressive glomerulonephritis due to autoantibodies directed toward the alpha 3 NC 1 domain of type IV collagen, found in the glomerular and alveolar basement membrane. In atypical anti-GBM disease, serum antibodies are negative, but the biopsy shows linear IgG staining. Clinically, it presents with an indolent renal limited course and good prognosis.

Case Description: A 36-year-old woman with a history of HIV, hypertension, diabetes mellitus type 2, asthma, obesity, and fatty liver presented with elevated creatinine, hematuria, and proteinuria. She developed foamy and dark urine six months before referral. HIV was stable with an undetectable viral load, CD 4 count 190 cells/mm^3 on dolutegravir-rilpivirine. Physical examination was unremarkable. Presentation labs were BUN 34, sCr 1.91 mg/dL, urinalysis with 3+ blood, 100 protein, albuminuria 3087mg/g. C3 143mg/dl, C4 28 mg/dl, and serologies included negative ANCA, MPO, PR3, and anti-GBM. Kidney biopsy demonstrated an active necrotizing and crescentic glomerulonephritis involving 36% of the sampled glomeruli, as well as older fibrous crescents in 27% of the glomeruli. There was patchy interstitial nephritis and mild interstitial fibrosis and tubular atrophy. Direct immunofluorescence demonstrated linear staining of the GBMs for IgG (3+) and kappa (2-3+) and lambda (3+) light chains. There were no electron-dense deposits by electron microscopy. The patient was started on treatment with solumedrol and cyclophosphamide. After the development of diffuse alveolar hemorrhage, 6 sessions of plasmapheresis were performed. sCr peaked at 3.6 with improvement to 2.2 since. ESR/CRP were used as surrogates of disease activity, owing to the lack of ability to monitor antibody titers.

Discussion: Atypical GBM was thought to have an indolent disease course without crescent formation on light microscopy, but more recent literature has shown crescents in pathology and progression to ESKD. Diffuse alveolar hemorrhage has not been reported to our knowledge. Management of atypical anti-GBM is complicated, owing to the lack of ability to monitor serum levels of antibodies. It is important for treating clinicians to be aware of the evolving landscape of this entity and of the difficulties in treatment including decisions regarding plasmapheresis and methods to monitor disease activity.

TH-PO686

Pulmonary Renal Syndrome Caused by Seronegative Anti-Glomerular Basement Membrane (GBM) Disease

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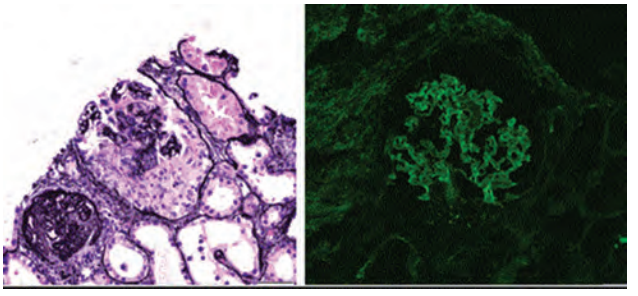
Introduction: Anti-GBM disease is a common cause of crescentic RPGN with or without pulmonary hemorrhage. We present an unusual case of pulmonary renal syndrome caused by biopsy proven anti-GBM disease without serum anti-GBM antibodies (Ab).

Case Description: A 50 YO F with history of asthma and suspected PE on apixaban presented with dyspnea and found to have hypoxia with bilateral lung opacities and AKI (SCr 1.7, baseline 0.6) Urinalysis showed hematuria and nephrotic-range proteinuria of 3.8 gm/gm. Initial serologic workup for infectious and autoimmune etiologies was negative, particularly ANCA <1:20 and anti-GBM Ab 0.5 units (normal range: 0.0-0.9). A renal biopsy showed diffuse necrotizing crescentic GN involving 50% of glomeruli with linear IgG deposits along the GBM. Prompt treatment with high dose steroids, cyclophosphamide and plasmapheresis was initiated along with supportive care. Clinical course was complicated by severe hemoptysis leading to hypoxia and cardiac arrest that necessitated VV ECMO support and CRRT after ROSC. Bronchoscopy showed blood in the airway but no active hemorrhage and repeated anti-GBM Ab remained within reference range. Given severe hypoxemia, 13 additional TPE sessions were done along with CYC and steroids. Later on, pulmonary function improved significantly allowing for ECMO decannulation. However, RRT-requiring AKI persisted without renal recovery.

Discussion: We present a rare case of pulmonary renal syndrome caused by seronegative anti-GBM disease occur in only 2-3% of cases. The diagnosis relies on the detection of anti-GBM Ab along with biopsy-proven crescentic necrotizing GN and/or alveolitis but serum Ab can be negative in rare cases due to low test sensitivity, antibodies to atypical GBM epitopes, or non-IgG anti-GBM Ab. The absence of alveolar hemorrhage on initial presentation with negative serology makes the diagnosis challenging, thus kidney biopsy becomes critical for early diagnosis and salvage treatment. Given the rarity of seronegative anti-GBM disease, there is no data on management and prognosis and the renal outcome of this case is undetermined.



Biopsy

TH-PO687

Ureteral Obstruction as a Risk Factor for Anti-Glomerular Basement Membrane (GBM) Disease

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Introduction: Anti-glomerular basement membrane (anti-GBM) disease has an incidence of 0.5–1 per million population; possible triggering factors including smoking & hydrocarbon exposure. Limited data also suggests a link between obstructive uropathy & the development of anti-GBM antibodies. We present a case of a 77-year-old male with chronic bilateral hydroureteronephrosis who subsequently developed anti-GBM disease & was successfully treated with a combination of steroids, cyclophosphamide, & plasmapheresis.

Case Description: A 77-year-old male with history of Chronic Kidney Disease Stage 3a presented for a routine outpatient evaluation; he was asymptomatic at time of presentation. Laboratory evaluation was notable for a serum creatinine of 4.42 mg/dL that had increased from 1.31 mg/dL seven months earlier. Urine microscopy showed numerous dysmorphic RBCs/HPF raising concern for a rapidly progressive glomerulonephritis (RPGN) prompting inpatient admission. CT imaging studies were notable for chronic bilateral hydroureteronephrosis dating back for at least two years. His serologic evaluation was negative with the exception of anti-GBM antibody that was positive at 1.8 U. Repeat imaging showed continued bilateral hydronephrosis initially delaying kidney biopsy however NM MAG3 scan did not reveal a high-grade urodynamic obstruction. After urologic evaluation, the patient underwent a native kidney biopsy confirming anti-GBM disease. He received pulse dose steroids, followed by cyclophosphamide, Prednisone taper, & 14 sessions of plasmapheresis. His serum creatinine has nadired at 2.6 mg/dL & anti-GBM antibodies are now undetectable.

Discussion: Anti-GBM antibodies target a cryptic α3 antigen of the non-collagenous 1 domain of type IV collagen. It is hypothesized that disruption of this domain, exposing the α-3 chain, is required for anti-GBM antibodies to develop. While several environmental triggers have been implicated in this process, ureteral obstruction & hydronephrosis remain an under-recognized & poorly understood trigger. Although challenging due to the rare nature of this disease process, further studies are needed to elucidate the nature of this relationship.

TH-PO688

Clinical Characterization and Outcomes of Lupus Nephritis in the Colombian Caribbean: Data from the Lupus Nephritis Register (RENELUP)

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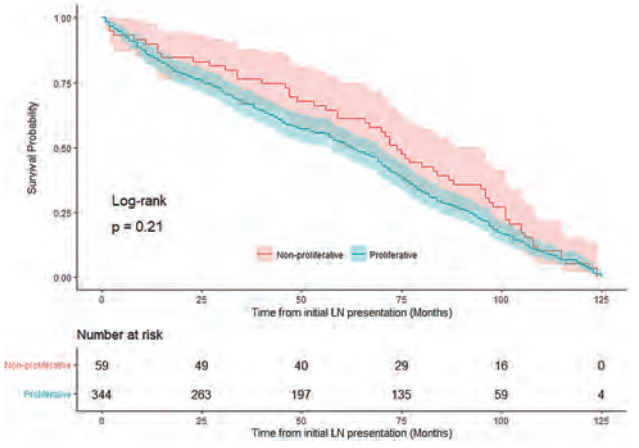
Background: LN is a severe manifestation of SLE, impacting outcomes directly and indirectly through therapy. LN varies across populations. Registries are crucial for understanding LN and assessing therapies. This study evaluates LN in RENELUP to assess its status in the Colombian Caribbean.

Methods: A multicenter cohort of 579 LN patients enrolled from 2008 to 2023. RENELUP, a JAVA-based web app, recorded demographic data, severity, outcomes, treatments, and mortality. Patients were grouped into Proliferative (Class III-IV) and Non-Proliferative (Class I-II-V) LN using ISN/RPS criteria. Chi-square/Mann-Whitney U tests evaluated renal survival using Kaplan-Meier estimator.

Results: Most patients were female (87%). Mean age was 41.1±13.1 years. Proliferative LN class IV was the main profile (62%). Proliferative LN had higher serum creatinine, proteinuria, activity index compared to Non-Proliferative LN ($p<0.05$). Hematuria, chronicity, low C3/C4, and clinical response were similar between LN classes. Overall SLEDAI-2K was 15.4±2.5. MMF (64%) was used as main induction therapy. Renal survival comparable based on serum creatinine at first presentation ($p>0.05$).

Conclusions: Our study provides insights into LN in the Colombian Caribbean. Predominant proliferative LN Class IV with significant renal involvement was observed. Moderate disease activity and MMF as main induction therapy highlight clinical management in this population, emphasizing the importance of patient registries for monitoring disease and treatment outcomes.



TH-PO689

Vitamin D Levels on Lupus Nephritis: Profile of a Large Brazilian Academic Center

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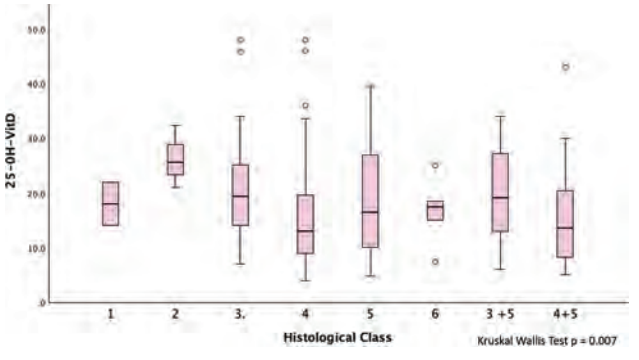
Background: Lupus nephritis is present in most patients with lupus. It is believed that the imbalance between pro-inflammatory and anti-inflammatory factors is responsible for its manifestation. Vitamin D is known for its anti-inflammatory activity and plays a regulatory role in cytokine production. Therefore, we tested the association between the level of 25-OH-Vitamin D, histological class, activity index and degree of proteinuria in patients from a large Brazilian academic center.

Methods: Patients diagnosed with lupus nephritis between January 2012 and December 2018 were included. Variables evaluated were age, gender, creatinine, estimated glomerular filtration rate (eGFR) by CKD-EPI, proteinuria, histological class and serum level of 25-OH-Vitamin D at the time of kidney biopsies.

Results: 253 kidney biopsies were performed during this period, 86% in women. The mean age was 31 years (13-70), creatinine 1.3 mg/dL (0.32-8.04), eGFR of 57.9 mL/min (6.2-165.3), proteinuria of 2.7g (0.07-10.7) and level of 25-OH-Vitamin-D 17 (4-48). Spearman's correlation between Vitamin D levels and proteinuria was -0.338 with $p<0.001$. The association between levels of vitamin D, histological class of lupus nephritis and activity index > 9 was significant ($p= 0.007$ and p 0.003, respectively), with the lowest median found in class IV. We didn't find associations between vitamin D levels and thrombotic microangiopathy.

Conclusions: Low levels of vitamin D were found in patients with more severe histological class, higher activity index and higher proteinuria, which may be involved as a risk factor for the inflammatory imbalance present in lupus and disease activity.



TH-PO690

Incidence of Primary Immunoglobulin A Nephropathy (IgAN) Among a Diverse Population in the United States

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Background: IgAN is a leading cause of primary glomerular disease and end stage kidney disease (ESKD) with a 10-year risk of chronic kidney disease (CKD) progression of up to 40%. Global incidence is estimated at 2-5 cases per 100,000 people. US data suggest lower rates but varies by race/ethnicity. We examined incidence of primary IgAN, leveraging a diverse, contemporary cohort from a single integrated health system in California.

Methods: A retrospective cohort was studied (1/1/2010-12/31/2021) of Kaiser Permanente members with biopsy proven IgAN, excluding secondary IgAN. Annual IgAN incidence rates were standardized by age, sex, and race/ethnicity according to the 2020 US Census using the American Community Survey (ACS). Primary IgAN rate was calculated for 2010-2021 and stratified by race/ethnicity. We estimated IgAN prevalence by using mean annual incidence x estimated disease duration.

Results: A total of 606 primary IgAN patients were identified with mean age (SD) of 46 years (15.0) with males (51.2%), Hispanic/Latinos (38.6%), Asian/Pacific Islanders (30.4%), Whites (25.6%), and Blacks (3.1%). The average annual incidence rate (per 100,000 person-years) of primary IgAN was 4.5, 1.7, 1.2, and 0.6 among Asian/Pacific Islanders, Hispanic/Latino, Whites, and Blacks, respectively. The mean annual IgAN incidence of 1.4 per 100,000 person-years equates to an adjusted IgAN prevalence estimate of 40 per 100,000 persons (incidence x estimated disease duration of 28.5 years for IgAN patients).

Conclusions: Our findings show a mean annual IgAN incidence of 1.4 per 100,000 person-years. Asian/Pacific Islander and Hispanic/Latino had the highest incidence rate of IgAN. Whether the clinical course and response to treatment for IgAN patients varies by race/ethnicity warrants further investigation.

Funding: Commercial Support - Otsuka Pharmaceuticals

Table 1: Prevalence Rate of Primary IgAN by Race/Ethnicity (2010-2021)

Race/Ethnicity	Total patients	Number of Patients	Rate per 100,000	2020 US Census Adjusted
	7128506	606	8.5	
White	2210545	155	7	
Black	499249	19	3.8	
Hispanic	2519144	234	9.3	
Asian/Pacific Islander	716038	184	25.7	
Other/Unknown	1183530	14	1.2	
Overall, 2010-2021	7128506	606	8.5	8.1

Calculated as number of IgAN patients divided by members during 2010-2021, and then standardized by age, sex and race/ethnicity according to the 2020 US Census data.

Table 2: Incidence Rate of Primary IgAN (2010-2021)

			Primary IgAN		
Year	Number of Patients	Person-year	Incident cases	Crude rate (95% CI)	Standardized* Rate (95% CI)
2010	2784574	2440317	48	2 (1.5, 2.6)	1.8 (1.3, 2.4)
2011	2904383	2568616	42	1.6 (1.2, 2.2)	1.6 (1.2, 2.1)
2012	3006453	2658714	59	2.2 (1.7, 2.9)	1.8 (1.4, 2.3)
2013	3086408	2719321	42	1.5 (1.1, 2.1)	1.4 (1.1, 1.9)
2014	3264155	2839294	49	1.7 (1.3, 2.3)	1.7 (1.3, 2.2)
2015	3493355	3051452	61	2 (1.6, 2.6)	1.7 (1.3, 2.2)
2016	3654039	3202685	42	1.3 (1, 1.8)	1.1 (0.8, 1.5)
2017	3806869	3348480	49	1.5 (1.1, 1.9)	1.4 (1, 1.8)
2018	3949125	3473261	48	1.4 (1, 1.8)	1.0 (0.8, 1.3)
2019	4015034	3536364	60	1.7 (1.3, 2.2)	1.4 (1.1, 1.8)
2020	4073571	3616949	47	1.3 (1, 1.7)	1.1 (0.9, 1.5)
2021	4140133	3654803	59	1.6 (1.3, 2.1)	1.5 (1.1, 1.9)
Average 2010-2021				1.7 (0.9, 2.4)	1.4 (0.8, 2.0)

*Standardized by age, sex and race/ethnicity based on US population of 2020 ACS estimates. Note: Incidence rate per 100,000 person-year

TH-PO691

The Epidemiology of ANCA-Associated Vasculitis over Two Decades at a Large Tertiary Centre

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Background: ANCA-associated vasculitis (AAV) is a systemic condition affecting small blood vessels and commonly causes kidney disease. It has a reported incidence of around 20-25 per million per year. Here we aimed to describe its epidemiology at our renal centre over a 23-year period and to compare granulmatosis with polyangiitis (GPA) and miroscopic polyangiitis (MPA).

Methods: We identified all patients with AAV between January 2000 and December 2022 through our biopsy database and electronic patient record (EPR). The cohort after exclusions totalled 278. We collected baseline demographic data, baseline laboratory values, treatment received and outcomes including progression to renal replacement therapy (RRT), relapse rates and mortality.

Results: Median age of the cohort was 63.5 years, 52.5% were male and 92.4% White. GPA was seen in 49.3% and MPA in 42.1%. Median eGFR at presentation was 18mls/min/1.73m^2. RRT at presentation occurred in 19.4%. Relapse occurred in 23%, progression to RRT in 26.6% and 1-year mortality was 3.2%. Median follow up duration was 54 months. Those with GPA were younger, had higher incidence of ENT disease at presentation, were more likely to relapse and had greater 1- and 5- year survival. Mortality rate per hundred person years improved from 2010 onwards.

Conclusions: This is one of the largest retrospective observational studies conducted on AAV, which reports real world epidemiology of this rare condition. AAV presents with advanced renal disease and there remain important differences in presentation and outcomes between GPA and MPA. The Salford glomerulonephritis research group was supported by an unrestricted project grant from CSL Vifor.

Funding: Commercial Support - CSL Vifor

Variable		Total cohort, n=278	GPA (n=137)	MPA (n=117)	P-value
Baseline demographics					
Age, years (IQR)		63.5 (51.8-72)	60 (58.5-68)	67 (57.5-75)	<0.001
Male gender (%)		146 (52.5)	83 (60.6)	50 (42.7)	0.005
White ethnicity (%)		257 (92.4)	129 (94.2)	104 (88.9)	0.128
Hypertension (%)		177 (63.7)	86 (62.8)	78 (66.7)	0.518
Cardiovascular disease (%)		50 (18)	22 (19.0)	23 (19.7)	0.893
Diabetes (%)		28 (10.1)	12 (8.8)	15 (12.8)	0.295
Presence of ENT disease (%)		64 (23.0)	45 (32.8)	13 (11.1)	<0.001
RRT at presentation (%)		54 (19.4)	24 (17.5)	25 (21.4)	0.438
Laboratory results					
Creatinine, µmol/L (IQR)		233 (130-396)	160 (102-240)	246 (141-379)	0.262
eGFR, mls/min/1.73m^2 (IQR)		18 (9-38)	28 (17-53)	18 (10-34)	0.184
ESR, mm/hr (IQR)		33 (14-67)	37 (18.5-69)	23.5 (12-52)	0.287
uPCR, mg/mmol (IQR)		120 (45-272)	115 (51.5-259)	116 (42-262)	0.458
PR3 antibody (%)		127 (45.7)	125 (91.9)	1 (0.9)	<0.001
MPO antibody (%)		120 (43.2)	9 (6.6)	110 (94.0)	<0.001
Outcomes					
Cardiovascular/ thromboembolic events after diagnosis (%)		60 (21.6)	30 (21.9)	23 (19.7)	0.661
Relapse (total) (%)		64 (23.0)	46 (33.6)	16 (13.7)	<0.001
Time to first relapse, months (IQR)		37.5 (24-68.8)	40.5 (25.5-70.0)	24.5 (10.0-65.0)	0.116
Adverse events (%)	BM suppression	46 (16.5)	24 (17.5)	21 (17.9)	0.929
	Infection	40 (14.4)	17 (12.4)	21 (17.9)	0.217
	Malignancy	40 (14.4)	24 (17.5)	15 (12.8)	0.301
Progression to RRT (%)		74 (26.6)	34 (24.8)	33 (28.2)	0.541
Mortality (%)	Total	111 (39.9)	47 (34.3)	51 (43.6)	0.130
	1 year	9 (3.2)	3 (2.2)	5 (4.3)	0.349
	5 year	54 (19.4)	25 (16.8)	26 (22.2)	0.274

P-value by Chi-squared test for categorical variables and Mann-Whitney U for continuous variables.

Demographics, laboratory results and major outcomes for the total cohort, those with GPA and those with MPA.

TH-PO692

Ofatumumab: A Therapeutic Option for Secondary Membranous Nephropathy in Adults

Monarch Shah, Lalida Kunaprayoon, Corey J. Cavanaugh. *University of Virginia, Charlottesville, VA.*

Introduction: B-cell targeting therapies like cyclophosphamide and rituximab are integral in treating many glomerulopathies like FSGS, lupus nephritis, and high-risk membranous nephropathy (MN). Newer B cell targeting therapies like ofatumumab has infrequently been used in MN, although trials are ongoing. Much less is known about their use in secondary MN. We describe the use of ofatumumab in two cases of secondary MN.

Case Description: We retrospectively analyzed two cases of MN treated with ofatumumab. The first case was a 53-year-old woman with nephrotic syndrome and a history of biopsy-proven MN with kappa predominance staining on immunofluorescence and a co-occurring MGUS (IgG Kappa) with a B-cell lymphocytosis with a kappa restricted B-cell. She was thus diagnosed with monoclonal gammopathy of renal significance and treated with 3 cycles of Cyclophosphamide after insurance denied her rituximab. Unfortunately, she relapsed 1 year later and was treated with ofatumumab, 300mg day 1, and 700mg day 14. Her proteinuria responded from 3.32g to 0.44 grams proteinuria 2 months after infusion. Case 2 was a 48-year-old female with profound nephrotic syndrome (56g/24-hour urine collection, serum albumin 1g/dL) refractory to cyclophosphamide combined with steroids and rituximab. She then developed anaphylaxis to rituximab on subsequent infusions and was switched to ofatumumab. She received 100 mg on day 1, 700mg on day 21, and 700 mg on day 35 for cycle 1, then 300 mg weekly for 1 month on cycle two (6 months after cycle 1). Patient 1 saw complete renal remission and patient 2 had a partial response with a reduction from 10.8 grams proteinuria to 3.6 g pr/cr ratio with normalization of serum albumin.

Discussion: This case series has shown that ofatumumab is a viable option for patients with secondary MN. The novel anti-CD20 monoclonal antibody like ofatumumab can become another option for patients who have refractory disease despite completing historical therapies like rituximab and cyclophosphamide. It also provides an agent for patients who have allergies to rituximab. More options for novel B-cell targeting therapies should be explored for secondary MN. Future clinical trials would be helpful to establish its efficacy and safety profile.

TH-PO693

Obinutuzumab with Tacrolimus as a Bridge for Membranous Nephropathy

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Introduction: Treatment of Membranous Nephropathy (MN) has been improving over the past several years. Obinutuzumab, a monoclonal antibody that targets CD20 on B-cells, is another potential therapeutic approach under investigation. Currently, Obinutuzumab is approved for the treatment of specific tumors such chronic lymphocytic leukemia.

Case Description: We describe a 64-year-old male with a history of benign essential hypertension, stage 3a chronic kidney disease presenting with worsening proteinuria. Eight years prior to presentation, he was diagnosed with MN, and at that time, he was anti-Phospholipase A2 Receptor (PLA2R) antibody negative with 4gm of proteinuria. He was started on tacrolimus and got 1 year of treatment leading to remission. He relapsed months after stopping tacrolimus and his PLA2R antibody titers rose to 11 RU/mL with worsening proteinuria. He was started on cyclosporine and continued it for over 7 years and was discontinued a year before presentation. At the time of presentation, he had 3gm of proteinuria and was started on dapagliflozin and two infusions of rituximab with 1gm each two weeks apart with some initial allergic reaction but then completed the infusions without complications. A year later, he relapsed and PLA2R antibodies rose to 23.5 RU/mL and proteinuria of 11gm. He was given two infusions of Obinutuzumab with 1gm each two weeks apart given his sub-optimal prior response to rituximab and allergic reaction to the drug along with a tacrolimus bridge. His proteinuria improved to 2gm with serum a creatinine of 1.2mg/dL. He was taken off tacrolimus few months post Obinutuzumab treatment. He continues SGLT2i and ARB therapy as well.

Discussion: Obinutuzumab is a more potent anti B cell agent that may be a promising therapy for MN. Using Obinutuzumab along with tacrolimus as a bridge to get the response of MN may serve as a potential long-term therapy for MN.

TH-PO694

EXT-1 Membranous Glomerulonephropathy

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Introduction: Membranous nephropathy is one of the most common causes of nephrotic syndrome in adults. The most common etiology is autoimmune condition and identification of pertinent antigens could help in the management of the disease.

Case Description: This is the case of a 33y/o male with past medical history of chronic inflammatory demyelinating polyneuropathy and recurrent pulmonary embolism on apixaban. Patient presented to emergency department complaining of worsening pleuritic chest pain and shortness of breath of one day of evolution. He was also tachycardic, tachypneic and had bilateral lower extremity edema. Laboratory evaluation was remarkable for >600protein and 0-3RBCs on urine dipstick. Renal panel showed creatinine of 1.27mg/dL and albumin of 1.7g/dL. The patient was admitted for recurrent unprovoked pulmonary embolism despite being on anticoagulation therapy and nephrotic syndrome. Initial workup for nephrotic syndrome reported 24-hour urine protein of 20,570mg. Further work up was negative for diabetic disease, hepatitis panel, HIV panel, complements, PLA2R antibodies and lupus nephritis. However, serologic markers ANA, RNP70 Ab and U1 RNP Ab were positive consistent with mixed connective tissue disease. During hospitalization, the patient developed an acute kidney injury with creatinine elevated to 2.65mg/dL, and renal biopsy was performed. Kidney biopsy showed acute tubular injury and exostosin-1 associated membranous glomerulopathy. The patient was treated with two doses of 1g rituximab, prednisone, and losartan. At subsequent clinic follow up, patient's spot urine protein-creatinine ratio was improved to 3.4g. Renal function is stable with creatinine of 1.13mg/dL and albumin improved to 2.3g/dL.

Discussion: Exostosin 1 and 2 are novel proteins seen in secondary membranous nephropathy associated with autoimmune diseases, especially lupus nephritis. Our patient's case is unique as his serology is positive for mixed connective tissue disease with no extra-renal manifestations and this is the first case reported of the association of MN with mixed connective tissue disease. Due to rarity of disease and lack of standard therapy we have opted for rituximab treatment based on literature review. After the initial course of rituximab treatment, our patient showed significant improvement in proteinuria to sub-nephrotic range. He is currently on medical management with losartan.

TH-PO695

Membranous Nephropathy in Kimura Disease: A Case Report and Literature Review

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Introduction: Kimura disease (KD) is a chronic benign granulomatous disease characterized by the formation of indistinct masses in the subcutaneous soft tissues and lymph nodes of the head and neck region. Approximately 20% of patients with KD have renal disease, with 60-80% reportedly having nephrotic syndrome. Membranous nephropathy (MN) is one of the major pathologies of renal diseases in KD; however, the underlying mechanism remains unknown.

Case Description: We herein present a 28-year-old male diagnosed with KD after biopsy of a left lower eyelid mass 11 years earlier. Two months before his presentation, proteinuria was noted for the first time. He visited our hospital with edema in the lower legs and scrotum. A blood test showed a serum creatinine level of 0.95 mg/dL and serum

albumin level of 0.9 g/dL. Urinalysis showed heavy proteinuria (7.22 g/gCr) without hematuria. Renal biopsy revealed spike formation by PAM staining and granular deposits of IgG and C3 in the glomerular basement membrane by direct immunofluorescence microscopy (IF). Electron microscopy showed subepithelial electron dense deposits (EDD). The serum anti-phospholipase A2 receptor (PLA2R) antibody was negative, while IF staining for PLA2R was positive in the glomerular basement membrane. The patient was diagnosed with PLA2R-associated MN.

Discussion: Target antigens in MN, such as PLA2R, were recently identified in both primary and secondary MN. Our literature review on MN in KD including 14 cases revealed that most cases showed subepithelial EDD without subendothelial EDD (Table). This result strongly suggests the involvement of autoantibodies on the surface of podocytes in its pathogenesis. In the present case, PLA2R staining was positive on the glomerular basement membrane. A literature review revealed that PLA2R staining was only performed on 3 out of the 14 cases investigated, and was positive in 2. Further studies on the antigens responsible are needed to elucidate the underlying pathogenesis.

Case No.	Sex	Age (years)	U-pro (g/day)	Serum anti-PLA2R Ab	Glomerular PLA2R Ag	EDD	
						Subepithelial	Subendothelial
1	M	48	20.0	NA	NA	+	NA
2	M	57	0.89	NA	NA	+	NA
3	M	71	3.80	NA	NA	+	-
4	M	68	4.00	NA	NA	+	-
5	M	36	14.1	NA	NA	+	-
6	M	48	5.27	NA	NA	+	-
7	M	15	2.10	NA	NA	+	-
8	F	33	16.6*	NA	NA	+	-
9	M	22	21.0*	Negative	Positive	+	-
10	F	56	13.4	NA	NA	+	-
11	F	42	0.37	NA	Negative	+	NA
12	M	50	NA	Negative	NA	+	NA
13	M	30	13.5	Negative	NA	+	-
14	M	47	7.1	Negative	Positive	+	-

Table. Patient characteristics. *Proteinuria indicated by the urinary protein-to-creatinine ratio.

TH-PO696

An Interesting case of Membranous Nephropathy in a Patient with Diffuse Alveolar Hemorrhage and Cocaine Use: A Case Report

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Introduction: Membranous nephropathy (MN) is a common cause of nephrotic syndrome in adults. 70-80% of the cases are primary. We present a case of primary membranous nephropathy in a patient with cocaine use disorder presenting with diffuse alveolar hemorrhage and acute renal injury.

Case Description: A 60-year-old woman with a medical history of HTN, asthma, and cocaine use presented with left-sided chest pain after a mechanical fall following alcohol and cocaine consumption. Trauma work-up: no fracture. CT chest: multifocal pneumonia. Serum Cr: 3.25(baseline: 0.8-1.2), UA: mild proteinuria-30 mg/g, no casts. Her hospital course was complicated by severe ARDS requiring intubation, septic shock, and worsening renal function with oliguria. Repeat UA: proteins>300mg/g, no casts. Serum Cr: 2.25/BUN: 53/K+: 5.4/HCO3: 21. Hemodialysis(HD) was initiated for volume overload. Bronchoscopy showed diffuse alveolar hemorrhage. Serology: positive ANA(1:40), anti-RNP/Sm antibody(3.1). RF complement levels, anti-MPO, ANCA, lupus antibodies, lupus anticoagulant antibodies, Sjogren's antibodies, anti-JO-1, scleroderma, anti-proteinase-3 antibody, anti-DNAase, anti-smooth muscle, anti-GBM, cryoprecipitate, RPR test, IgG, IgM antibodies were negative. Hepatitis B core antibody, CMV DNA was positive. VATS biopsy demonstrated scattered hemorrhagic infarct with organizing pneumonia. Kidney biopsy revealed stage 3/4 membranous nephropathy with focal segmental sclerosis. Presence of co-dominant IgG1 and IgG3 subclass and IgG4 and PLA2R staining of the GBM immune deposits, and few mesangial immune complex deposits. CPK: normal. Anti-PLA2-R resulted in positive. Following high-dose steroids, she is now on steroid taper and on intermittent HD due to poor renal recovery.

Discussion: Diffuse alveolar hemorrhage and nephrotic range proteinuria prompted testing to rule out pulmonary-renal syndromes, which were unsatisfactory; a mildly positive ANA could be secondary to an acute illness. Electron microscopy and immunofluorescence findings of kidney biopsy were inconsistent. IgG1 and IgG3 subclass staining of the GBM immune deposits suggested lupus membranous nephropathy; IgG4 and PLA2R staining suggested primary membranous nephropathy. Despite risk factors for secondary MN(Hep B positive, levamisole with cocaine exposure) a positive Anti-PLA2-R made the diagnosis of primary MN.

TH-PO697

THSD7A-Related Membranous Nephropathy (MN) in a Patient with Prostate Adenocarcinoma

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Introduction: Thrombospondin type-1 domain- containing 7A (THSD7A) is a transmembrane protein expressed on the podocytes that serves as an auto-antigen in patients with membranous nephropathy. We report a case of kidney biopsy proven THSD7A associated MN in a 69-year-old Vietnamese male with history of metastatic prostate adenocarcinoma and chronic Hepatitis B.

Case Description: A 69-year-old male admitted for weight loss was found to have retroperitoneal lymphadenopathy, diffuse mixed sclerotic and lytic lesion, and enlarged prostate. He underwent EUS with FNA of retroperitoneal adenopathy which showed metastatic prostate cancer. Then two months later, patient presented with marked anasarca for two weeks. He was afebrile, normotensive and saturating well on RA. Labs notable for albumin 1.6, UA with >1000 mg/dL proteinuria, urine protein/creatinine 18.68, Hepatitis B surface antigen reactive, Hepatitis B core antibody reactive, and PSA 833. Phospholipase A2 Receptor (PLA2R) antibody was negative and THSD7A antibody was positive. Subsequently had a kidney biopsy which showed membranous nephropathy, grade I. He was initially suspected to have secondary MN due to cancer and untreated HBV, but kidney biopsy stain pattern more reflective of primary THSD7A MN likely related to his cancer. He was started on both Hepatitis B treatment (with Entecavir) and prostate cancer (with Lupron and Enzalutamide), Bumex, Metolazone and anticoagulation with Lovenox. While waiting for Rituximab approval, patient was started on Ponticelli regimen [Protocol: cyclophosphamide and alternate with prednisone for 6 months total (month 1, 3, 5, prednisone 0.5kg/day, then 2, 4, 6 cyclophosphamide 2mg/kg/day), with Bactrim prophylaxis]. Once the Rituximab was approved, Ponticelli regimen was stopped after the first month and prednisone was tapered. He has finished Rituximab induction therapy and currently on every 6 months maintenance. Current urine protein/Creatinine ratio remains elevated at 13. Hepatitis B is well-controlled and PSA is now 0.5.

Discussion: In a meta-analysis of 10 studies involving 4121 participants, the prevalence of THSD7A was on average 3% in all patients and higher at 10% in PLA2-R patients. Another study discovered that 8 of 40 patients developed a malignancy within a median time of 3 months from diagnosis of MN. Thus it is important to screen and monitor for malignancies in THSD7-A positive MN patients.

TH-PO698

A Case of Coexisting Primary Membranous Nephropathy and Dermatomyositis

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Introduction: Dermatomyositis (DM) is an inflammatory disorder of the skin and skeletal muscle characterized by cutaneous eruptions and myositis. DM is associated with malignancy, interstitial lung disease, esophageal dysmotility and cardiac complications. Unlike other connective tissue diseases, DM does not classically feature renal involvement, although several small case series and retrospective analyses have described a small minority of patients with DM who develop renal pathologies, including ATN in the setting of rhabdomyolysis as well as various glomerular diseases.

Case Description: A 56-year-old African American woman presented with one week of leg swelling. Vital signs were remarkable for hypertension to systolic BPs of 170s, and exam was remarkable for prominent facial edema and 3+ bilateral lower extremity edema, with skin hyperpigmentation on the face, neck, chest and upper arms. Creatinine was at her baseline of 0.7 mg/dL. U/A revealed 4+ blood and 4+ protein, quantified at 10.2 g/g. Urine microscopy revealed lipid casts and <1 isomorphic RBC/hpf. Nephrology and rheumatology were consulted and recommended workup as follows: C3 and C4 normal, SPEP negative, serum anti-PLA2R IgG negative, HIV and hepatitis B/C serologies negative, ANA positive 1:1280 nuclear fine speckled pattern. She had negative dsDNA, anti-Sm, centromere B, RNP, anti-SCL 70, anti-SS-A, anti-SS-B, anti-cardiolipin and anti-B2 glycoprotein antibodies. CPK was sent on account of 4+ blood on U/A with relative paucity of RBC on microscopy and was elevated at 1249 IU/L. Myositis panel was sent and returned positive for anti-MI2 alpha and beta antibodies, consistent with DM. A renal biopsy was performed and revealed membranous nephropathy (MN). Although serum anti-PLA2R IgG was negative, the biopsy stained positive for anti-PLA2R IgG, suggesting primary MN. Comprehensive malignancy evaluation was performed given the close association of both membranous nephropathy and dermatomyositis with cancers and was negative. The patient was started on rituximab for management of MN and prednisone for management of DM.

Discussion: To our knowledge, this is the third case report describing coexisting primary MN and DM in the absence of underlying malignancy. The biological basis for the coexistence of these two pathologies in a single patient remains to be elucidated, although can be presumed to result from a breakdown of immune tolerance.

TH-PO699

Not So "Golden": A Case of Mercury-Associated NELL-I-Positive Membranous Nephropathy

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Introduction: Mercury is a heavy metal that exists in various forms and can be encountered through multiple pathways of exposure. Inorganic mercury is associated with glomerular disease - particularly membranous nephropathy (MN) - as well as peripheral neuropathy. In recent years, inorganic mercury in skin lightening creams has been associated with neural epidermal growth factor-like 1 protein (NELL-1) positive MN; very few cases are reported from the United States. We report a case of skin lightening cream-associated mercury toxicity and NELL-1 positive MN.

Case Description: A 41-year-old female with type 2 diabetes who emigrated from Afghanistan 2 years prior presented with 6 months of progressive leg edema, worsening proteinuria, and long-standing peripheral neuropathy. Four months before presentation, albumin/creatinine ratio (ACR) was 6,050 mg/g; immediately before presentation, ACR was 17,862 mg/g. Subsequent 24-hour urine protein was measured at 37.1 grams. Serum creatinine was 0.6 mg/dL. On initial presentation, skin lightening cream use was queried;

the patient produced a container of "Golden Pearl" beauty cream, found by the FDA to contain 12,000 ppm mercury, which she regularly used. Her blood and urine mercury levels were found to be elevated. Serologic studies included multiple negative serologic studies including anti-phospholipase A2 receptor (PLA2R) antibodies. The patient was admitted to the hospital and treated with furosemide. A kidney biopsy was performed and was notable for MN, staining negative for anti-PLA2R and positive for NELL-1. Chelation with succimer was unable to be initiated due to cost; treatment with steroids is being arranged.

Discussion: Mercury-associated MN generally has a favorable prognosis with discontinuation of mercury use; steroids and chelation are the most common therapies utilized in the literature. Skin lightening creams may be used in the United States by immigrants from regions in which they are routinely used. In patients presenting with unexplained proteinuria from areas of the world where mercury-containing products are used, particularly with peripheral neuropathy, mercury toxicity should be considered and skin lightening cream use should be queried. Mercury-associated MN has an emerging association with NELL-1; mercury screening may be warranted in patients with NELL-1 positive MN.

TH-PO700

An Unusual Presentation of a Common Disease: Primary Membranous Glomerulopathy with Light-Chain Deposits: Case Report

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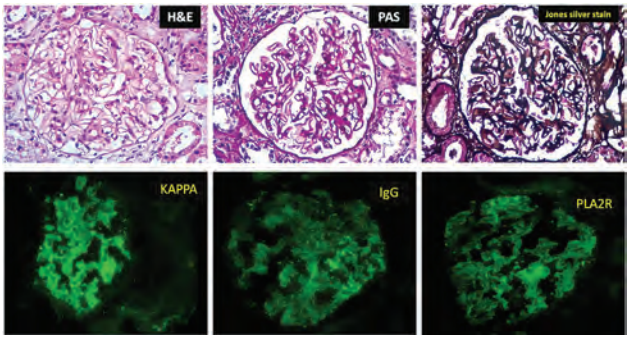
Introduction: Membranous glomerulopathy (MG) is a common cause of nephrotic syndrome (NS) caused by the formation of immune complexes along the subepithelial slope of the glomerular basement membrane (GBM) and considered as the main cause of idiopathic NS in adults. Deposits of light chain isotype are rarely seen.

Case Description: A 56-year-old Guatemalan male patient with a 3-month history of lower-limbs edema. No previous medical history. On first evaluation presented AKI with SCr of 1.58mg/dl associated with proteinuria (12.8gr/day), hematuria (5 RBC/HPF) and oval fatty bodies and fat droplets. Laboratories with hyperlipidemia (cholesterol 692mg/dl, triglycerides 396mg/dl), C3-C4 normal, FANA+ 1:80, ANCAs, HIV, HBV, HCV, rheumatoid factor were negatives and serum anti-PLA2R+ (353 RU/ml (positive >20)), serum and urine electrophoresis negative for monoclonal protein. Kidney biopsy was performed and reported homogenous thickening of the GBM with mesangial proliferation; Jones stain with pin hole pattern on the capillary wall. Negative for endocapillary or extra capillary hypercellularity, double contours or interstitial fibrosis IF: IgG (+), IgM (+), Kappa (++) and PLA2R (++) with granular pattern in GBM. The patient is on RAASi with losartan 100mg/day while decides to accept rituximab protocol. With improvement of SCr (1.04mg/dl) controls after 1-month but still with nephrotic range proteinuria.

Discussion: The pathophysiology of MG results from the formation of immune complexes, predominantly by polytypic deposits along the subepithelial slope of the GBM. Usually, these immune complexes are against PLA2R and HTSD7A but about 10% of patients with typical PMN are negative for both antibodies making it probable that more autoantibodies to podocyte antigens will be found such as light-chain deposits. Though, positive serum antiPLA2R suggest a primary etiology, the rarely seen deposition of single IgG subclass should prompt a clinical workup to exclude the presence of an underlying etiology.



TH-PO701

"Finding the Bright Side": A Case Series of Spontaneous Remission in NELL1 Membranous Nephropathy

Ion D. Bucaloiu, Lakshna Sankar, Kartik Kalra. *Geisinger Health, Danville, PA.*

Introduction: Neural tissue encoding protein with EGF- like repeats (NELL1) has been identified as a target antigen in membranous nephropathy (MN). It can be primary or associated with malignancies, stem cell transplant, de novo in kidney transplant, drugs, autoimmune diseases and infections.

Case Description: Four patients of Caucasian origin with age ranging from 50 - 71 years presented with nephrotic syndrome (Table 1). At presentation, all had urine protein creatinine ratios above 5 g/g creatinine. Immunological work up was negative. Kidney biopsy was positive for NELL1 associated MN. Infectious work up including hepatitis panel, human immunodeficiency virus (HIV) and rapid plasma regain (RPR) were negative. Screening for underlying malignancy including computed tomography (CT) of chest, abdomen and pelvis, pap smear, mammogram and colonoscopy was unremarkable. Careful review of home medications list showed no indigenous medications except for one patient who was on lipoic acid for a duration of 1 year which was stopped after the diagnosis of NELL1 MN. Supportive care such as renin-angiotensin blockade (RAAS) and diuretics were initiated with periodic monitoring of renal functions and proteinuria (Table 1). All 4 patients went into remission within 3 – 6 months.

Discussion: Spontaneous remission (30% of the patients) is a well-known characteristic of MN. Patients with persistent nephrotic range proteinuria are at risk of progression to end stage kidney disease and may require immunosuppression therapy. Several studies showed that a higher percentage of NELL1 MN cases are associated with malignancies (up to 30%) compared to MN associated with other antigens (PLA2R and THSD7A). Our case series suggests that NELL1 MN without underlying malignancy might experience spontaneous remission without need for immunosuppression. After excluding malignancy, a conservative strategy including maximizing RAAS blockade with serial monitoring of kidney function and proteinuria for 3-6 months may be appropriate in NELL1 MN.

Table 1: Clinical characteristics of NELL1 membranous nephropathy

Patients	Age, gender and demographics	Creatinine in mg/dL (reference range 0.5 – 1 mg/dL)	Proteinuria (Urine protein creatinine ratio in mg/g)	Albumin in g/dL (reference range 3.8 – 5 g/dL)	Serum PLA2R IFA (Immunofluorescence)	Renal biopsy	Supportive care (RAAS blockade +/- diuretics)	Time to remission Complete / Partial
Case 1	50-year-old Caucasian female	0.9	5200	3.5	Negative	Membranous glomerulopathy, NELL1 positive; PLA2R, THSD7A, EXT 2 were negative.	Lisinopril 30 mg daily, cessation of lipoic acid	6 months
Case 2	68-year-old Caucasian male	1.2	6235	3.2	Negative	Membranous glomerulopathy, NELL1 positive; PLA2R and THSD7A were negative.	Losartan 100 mg daily	2 months
Case 3	70-year-old Caucasian male	1.0	9124	2.7	Negative	Membranous glomerulopathy, NELL1 positive; PLA2R and THSD7A were negative.	Losartan 100 mg daily, Lasix 40 twice daily	3 months
Case 4	71-year-old Caucasian female	0.8	17,245	2.9	Negative	Membranous glomerulopathy, NELL1 positive; PLA2R, THSD7A, SEMA3B and EXT2 were negative.	Losartan 25 mg daily, Torsemide 20 mg daily	6 months

TH-PO702

I Am the Lucky Third: Spontaneous Resolution of High-Risk Membranous Nephropathy

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Introduction: The 2021 KDIGO guidelines for the treatment of high-risk and very high-risk membranous nephropathy (MN) involve angiotensin-converting enzyme inhibitors (ACEi) or angiotensin receptor blockers, and intense immunosuppression with rituximab or combination of cyclophosphamide and steroids. Typically, these immunosuppression regimens are initiated immediately in high-risk and very high-risk MM. Here we present a case of very high-risk MN nephropathy who achieved spontaneous with only conservative management.

Case Description: A 28-year-old male with no significant past medical history presented with acute onset of left flank pain and lower limb swelling for 3 weeks. Pertinent lab workup showed proteinuria of 28 grams/day, serum albumin of 1.1g/dL, and normal serum creatinine. CT angiogram showed bilateral renal veins thrombosis extending to the inferior vena cava. The serological workup for glomerulonephritis came back positive for anti-PLA2R antibodies, hence diagnosing him with primary MN. Renal biopsy further confirmed MN and PLA2R stain was diffusely positive The patient underwent an interventional radiology-guided thrombectomy. Given the severity of his clinical picture and following a detailed discussion of the risks versus benefits of different protocols of immunosuppressants, a pulsed dose of methylprednisolone was administered followed by oral prednisone for modified Ponticelli regimen, but the patient later refused cyclophosphamide due to the risk of infertility and agreed with initiating of rituximab. However, the prior authorization for rituximab was unsuccessful, and the patient was discharged on a tapered course of prednisone, lisinopril, and apixaban. At six-month follow-up, proteinuria was reduced to 1.6 g/d and renal function remained stable.

Discussion: Here we present a case of very high-risk MN in which the patient achieved spontaneous remission and remained in partial remission at the 6-month follow-up visit. Cases such as this highlight the fact that risk stratification in MN is based on criteria at the time of initial diagnosis, when in fact the disease may follow a dynamic and changing course over time. Just as low and moderate risk patients may ultimately progress to renal failure, here we present a case of very high risk MN that ultimately achieved remission without intensive immune suppression.

TH-PO703

An Unlikely Culprit: A Case of Membranous Nephropathy with Celiac Disease

Sneha M. Vaddadi, Katherine D. Wick, Kuang-Yu Jen, Niti Madan. *UC Davis Health, Sacramento, CA.*

Introduction: Membranous nephropathy is a cause of nephrotic syndrome, categorized as primary (e.g. anti-PLA2R-associated) or secondary (due to autoimmune conditions, malignancy). There are a few case reports demonstrating an association between membranous nephropathy and celiac disease, an autoimmune disorder affecting the small intestine with the ingestion of gluten, however, this association has not been well established. We present a case of secondary membranous nephropathy with celiac disease and subsequent complete remission with the treatment of the underlying disease.

Case Description: A 46-year-old female initially presented for evaluation of the nephrotic syndrome with a urine protein to creatinine ratio 8.6 g/g and serum albumin of 1.8 g/dL. Workup for viral, autoimmune and malignant etiology significant only for evidence of prior Hepatitis B infection and positive surface antibodies. A kidney biopsy demonstrated evidence of early-stage membranous nephropathy without secondary features. Tissue PLA2R staining and Anti-PLA2 antibody testing were negative. The patient was diagnosed with primary membranous nephropathy due to negative secondary workup. Cyclosporine and low-dose prednisone treatment for 1 year resulted in partial remission. The patient then got diagnosed with Celiac Disease. She transitioned to a gluten-free diet with continued conservative management with an angiotensin-converting enzyme (ACE) inhibitor resulting in complete remission of her disease.

Discussion: Celiac disease has been associated with IgA nephropathy; its presentation with IgG membranous nephropathy is not well-established. With an otherwise negative workup and despite biopsy results without secondary features, the etiology of the glomerular disease in this case was likely celiac disease given the complete remission only after dietary modification. This case demonstrates a potential novel association between the autoimmune condition celiac disease and secondary membranous nephropathy.

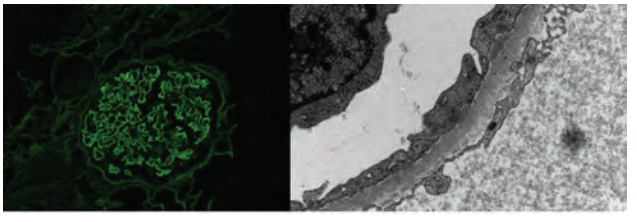

Figure 1: A. Immunofluorescence demonstrating IgG deposition along capillary loopsB. Subepithelial immune deposits on electron microscopy

TH-PO704

Unveiling a Novel Link: A Case of Secondary FSGS with Anti-MDA5 Amyopathic Dermatomyositis

Sneha M. Vaddadi, Shubha Ananthakrishnan, Niti Madan, Kuang-Yu Jen, Nasim Wiegley. *UC Davis Health, Sacramento, CA.*

Introduction: Amyopathic dermatomyositis is a cutaneous predominant form of dermatomyositis, characterized by the biomarker anti-MDA5 antibody. Extra-dermatologic involvement has been shown within the pulmonary, vascular, or articular systems. No known reports demonstrate an association between this rarer form of dermatomyositis and glomerular disease. We report a case of anti-MDA5 dermatomyositis associated focal and segmental glomerulosclerosis (FSGS), treated with immunosuppressive therapy targeting the underlying autoimmune condition.

Case Description: A 56-year-old Black man with confirmed anti-MDA5 positive amyopathic dermatomyositis diagnosed via skin biopsy and otherwise negative myositis panel presented for nephrotic syndrome and acute kidney injury evaluation. Labs showed serum creatinine of 2.04 mg/dL (baseline 0.8), urine protein to creatinine ratio >7 g/g, serum albumin of 2.6 g/dL, and urinalysis without cellular sediment. A native kidney biopsy was performed, showing features of FSGS on light microscopy (LM), negative immunofluorescence (IF), with segmental foot process effacement and the presence of tubuloreticular inclusions on electron microscopy (EM). Malignancy workup was negative. The patient was treated with high-dose prednisone and mycophenolate mofetil (MMF) for targeted treatment of both dermatomyositis and FSGS, with subsequent improvement to partial remission in the first 6 months.

Discussion: To our knowledge, this is the first reported case of kidney involvement with amyopathic dermatomyositis. With an otherwise negative workup for other viral or malignant causes, the likely etiology of secondary FSGS was this autoimmune condition. MMF, a common treatment for dermatomyositis, was utilized in this case for targeted treatment of both dermatomyositis and FSGS and resulted in improved proteinuria and partial remission of nephrotic syndrome.

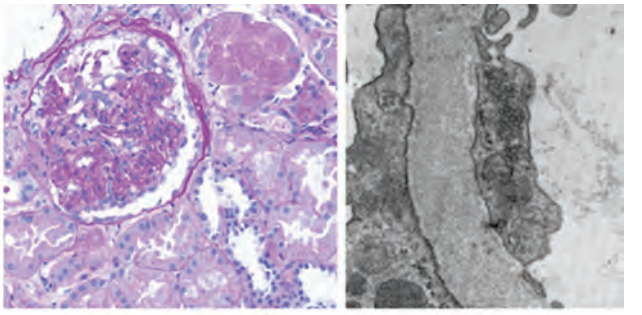

Figure 1: A. Periodic Acid Schiff stain showing segmental glomerulosclerosis.B. Tubuloreticular inclusion on Electron Microscopy

TH-PO705

Compressed and Concomitant Cyclophosphamide with Prednisone for Membranous Nephropathy: Low Doses for Very-High-Risk Patients

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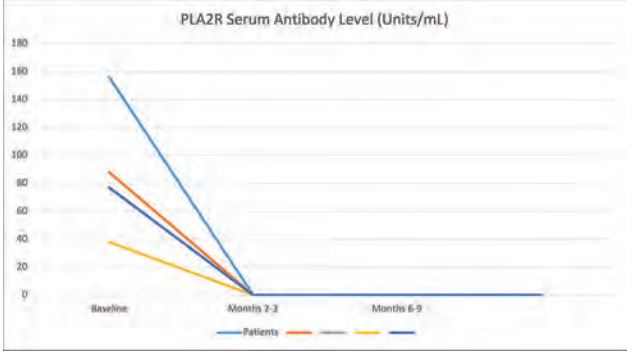
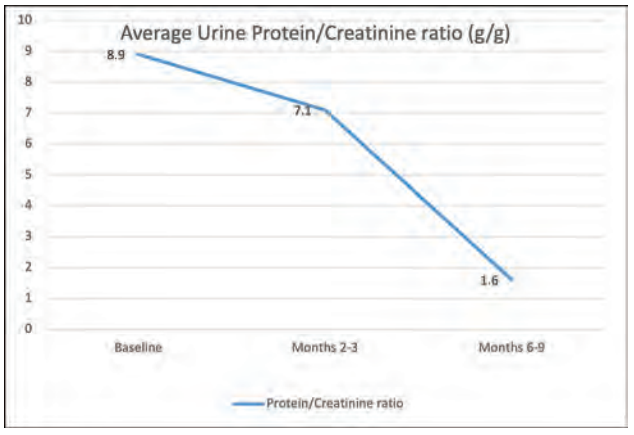
Introduction: Immunosuppressive therapy for primary membranous nephropathy (MN) has undergone significant change in the last 5 years. The "modified Ponticelli" regimen for MN is the recommended therapy for very high-risk MN according to KDIGO guidelines. The regimen consists of alternating cycles of cyclophosphamide and corticosteroids for a total of 6 months and comes with dose-dependent side effects such as cytopenias, infections, and malignancy. Here, we describe our experience with compressed and concomitant CYC/GC in very high-risk patients.

Case Description: We retrospectively analyzed 4 cases of PLA2R-positive membranous nephropathy with very high-risk features treated with concomitant prednisone 0.5mg/ kg tapered with oral cyclophosphamide 1.5-2mg/kg daily over 3-4 months. All patients were male between the ages 36-62. Clinical data, including serum PLA2R-AB levels and UPCR, were collected over the treatment period and 6 months after completion (Images 1 and 2). All patients had complete or partial remission at 9-12 months follow-up. No cytopenias or infections were observed. One patient developed steroid-related diabetes.

Discussion: Compared to the 24-week modified Ponticelli regimen, our doses of GC were lower, with a shorter duration of therapy and without any loss in efficacy (Table). A compressed and concomitant CYC/GC regimen in very high-risk patients with PLA2R membranous nephropathy is safe and effective in this limited case series.

	Compressed CYC/Pred	Modified Ponticelli (for a 60kg patient)
Average total CYC dose	11.21g	10.8-13.5g
Average total GC dose	1965mg	11.4g
Total duration of therapy	13.75 weeks	24 weeks





TH-PO706

FAT1 as an Antigen in Antibody-Mediated Rejection-Associated Membranous Nephropathy

Laith Al-Rabadi,[1] Tiffany Caza,[2] Christopher P. Larsen,[2] Laurence H. Beck.[3]
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Introduction: Membranous nephropathy can be a manifestation of antibody mediated rejection (ABMR). While recurrent membranous nephropathy has been mostly attributed to PLA2R, the targeted antigen in ABMR-associated membranous remains unknown. FAT1 has been recently found to be an antigen in post hematopoietic stem cell transplant but not in de novo membranous nephropathy related to ABMR.

Case Description: Patient has evidence of ABMR evidenced by presence of peritubular capillaritis, glomerulitis, and positive donor specific antibody (HLA DQ1 11,000). In addition to microcirculation inflammation, membranous nephropathy was identified on kidney biopsy. Serum from the patient with De novo membranous MN recognizes HGE at a high molecular weight band (higher than THSD7A and PLA2R). We sought to investigate whether FAT1 can be the targeted antigen given the high molecular weight on western blotting. Immunostaining revealed a granular pattern of FAT1 along the capillary wall.

Discussion: FAT1 can be the antigen implicated in membranous nephropathy related to ABMR. We are currently screening a larger cohort to validate our findings.

TH-PO707

Disseminated Nocardiosis in an Immunosuppressed Patient with Membranous Nephropathy

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Introduction: Nocardiosis is a rare life-threatening opportunistic infection which has been reported in association with immunosuppressed patients. The diagnosis is challenging because of the insidious onset of symptoms with a subacute course that progresses over several weeks. Misdiagnosis and late treatment can lead to fatal consequences. We report a new case of disseminated nocardiosis (lungs, brain, eyes and joints) in a patient diagnosed with membranous nephropathy. We also review the literature and analyze the clinical characteristics and modalities of treatment of nocardiosis.

Case Description: A 49-year-old Eritrean man diagnosed with nephrotic syndrome secondary to primary membranous nephropathy with high risk progression factors. He was started on immunosuppression along with general supportive measures. He presented to the Accidents & Emergency department with fever, fatigue, productive cough, red eyes and right knee swelling since the preceding week. He was found to have pneumonia, bilateral uveitis and right septic arthritis. He had arthroscopic drainage and washout of the knee. Cultures of sputum, blood and joint came back positive growing Nocardia otitidiscaviarum. CT brain imaging revealed left occipital ring enhancing lesions with surrounding edema without mass effect suggesting brain abscess. Patient was started on Trimethoprim/Sulfamehtoxazole based on sensitivity testing and this was continued for 12 months. Immunosuppression was also stopped once the diagnosis was made and he had shown signs of remission around the same time. Patient responded very well to antibiotics and fully recovered.

Discussion: Immunosuppression is the most important predisposing factor for systemic nocardiosis. Poor outcome is mostly found in immunocompromised patients which can be improved by early detection and administration of the correct antibiotic regimen. More studies on nocardiosis are required to better identify risk factors associated with morbidity /mortality and to develop effective methods of prevention of the disease.

TH-PO708

Primary Sjögren Syndrome (pSS) with PLA2R-Associated Membranous Nephropathy (MN)

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Introduction: pSS is an autoimmune disorder characterized by lymphocytic infiltration of exocrine glands. Renal involvement occurs in 5% of pSS cases. The prevalent renal pathology associated with pSS is tubulointerstitial nephritis, with less frequent glomerular manifestations, mainly membranoproliferative glomerulonephritis. pSS is also a recognized cause of secondary MN. Herein, we present a rare case of co-occurrence of pSS and primary MN with negative serum PLA2R antibody (Ab) but positive tissue PLA2R Ab.

Case Description: A 27-year-old female with a history of pSS on plaquenil was referred to a Nephrology clinic for subnephrotic proteinuria of 1.5 gm. Urinalysis revealed no microscopic hematuria. Her creatinine was 0.54 mg/dl with no evidence of renal tubular acidosis or nephrolithiasis. Immunological markers including ANA, dsDNA, and serum PLA2R Ab were negative. Complements were normal. HIV, HBV, and HCV tests were negative. Kidney biopsy showed MN with positive immunofluorescence for IgG, C3, and PLA2R. One year later, her proteinuria decreased to 0.47 gm with preserved renal function without treatment. Her serum PLA2R Ab remained negative.

Discussion: This case poses a diagnostic challenge as to whether the observed MN is primary or secondary to pSS. Serum PLA2R Ab is associated with MN development and has high sensitivity (78%) and specificity (99%) for primary MN. Although PLA2R Ab detection has been reported in secondary MN cases such as sarcoidosis (55%), it is largely absent in rheumatic disease-associated MN, especially lupus MN (<5%). The absence of serum PLA2R Ab in this case aligns with the "kidney as sink" hypothesis, proposing that early-stage disease may show negative serum levels due to high Ab affinity for tissue antigens. Despite having persistent negative serum PLA2R Ab levels, our patient demonstrated positive tissue PLA2R Ab staining. Moreover, PLA2R Ab levels are also indicative of disease prognosis. In our case, the patient, with persistently negative serum PLA2R Ab, exhibited a significant spontaneous reduction in proteinuria. Her remission occurred in the absence of any pSS therapy, suggesting a coincidental occurrence of MN and pSS. Our case highlights that primary MN can coexist with other autoimmune diseases, emphasizing the need to distinguish primary from secondary MN due to potential differences in management strategies, where PLA2R Ab detection can be insightful.

TH-PO709

A Case of Rapidly Progressive Glomerulonephritis due to Superimposed IgA Nephropathy on Collagenofibrotic Glomerulopathy

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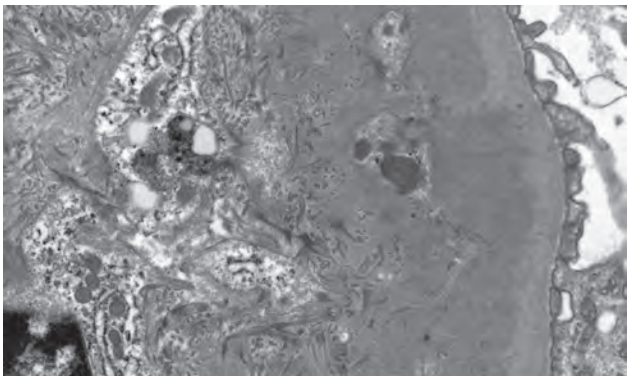
Introduction: Collagenofibrotic glomerulopathy (CFG) is a rare disease characterized by the accumulation of type III collagen in the glomerulus. CFG and IgA nephropathy (IgAN) may coexist coincidentally, but there have been no reports presenting rapidly progressive glomerulonephritis (RPGN). Here, we report the case that developed in RPGN and was diagnosed with active IgAN accompanied by CFG.

Case Description: A 69-year-old Japanese woman complained of new-onset fatigue and generalized edema lasting one month. She had a history of rheumatoid arthritis for about 20 years and had been administered etanercept, a TNFα inhibitor, for eight years. Her serum creatinine (SCr) level used to be around 1.5 mg/dL. On admission, She exhibited gross hematuria, an elevated SCr (5.8 mg/dL), a decreased serum albumin (2.63 g/dL), a weight gain (+10 kg), and was clinically diagnosed with RPGN and nephrotic syndrome. Histological examination revealed active IgAN with positive KM55(galactose deficient(Gd)-IgA1) and superimposed CFG. She temporarily needed hemodialysis, but with steroid pulse therapy and cyclophosphamide, her SCr improved to 2.66 mg/dL, and hematuria was also resolved.

Discussion: This is the first report of RPGN caused by IgAN superimposed on CFG. In IgAN, IgA deposition in the capillary wall have been reported to have a poor renal prognosis. In this case, the presence of type III collagen in the mesangial region promoted IgA deposition in the capillary wall and induced RPGN. Furthermore, this is the first case in which etanercept induced IgA nephropathy with Gd-IgA1. The mechanism of action of TNFα inhibitor-induced IgAN may be the generation of anti-drug antibodies to the glycan structures of the TNFα inhibitors. This cross-reacts with Gd-IgA1 and forms a large antigen-antibody complex, and then may have caused IgAN. Despite the rare and complex diseases, we believe the appropriate interpretation of renal biopsy findings contributed to effective treatment and favorable renal outcomes.



TH-PO710

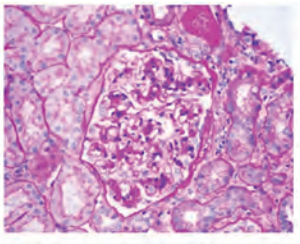
A Novel Case of IgA Nephropathy Relapse Secondary to Adalimumab

Christopher D. Naranjo,[1,2] Margarita D. Almeida,[1,2] Mary Sifain,[1,2] Chavely Valdes Sanchez,[1,2] Zachary Kornblum,[1,2] Marco A. Ladino Avellaneda.[1,2] University of Miami/Miami VAMC Fellowship Program. *[1]University of Miami School of Medicine, Miami, FL; [2]Miami VAMC, Miami, FL.*

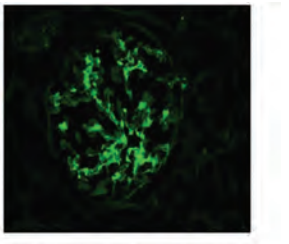
Introduction: IgA nephropathy is the most diagnosed glomerulonephritis worldwide. Biologic agents including tumor necrosis factor alpha (TNFa) inhibitors have been identified as a potential cause for IgAN and on our patient, recurrence.

Case Description: The patient is a 35 year old male with biopsy proven IgA nephropathy diagnosed 4 years prior to current presentation. Initially, the patient was found to have microscopic hematuria and proteinuria on routine urinalysis. Kidney biopsy was performed at that time and demonstrated focal fibrocellular and fibrous crescentic disease. He was treated with glucocorticoid therapy and RAAS blockade, leading to full remission. He had underlying uveitis managed with Rituximab and Methotrexate, then Adalimumab. On the current presentation, the patient reported an isolated episode of hematuria 2 months prior. Creatinine increased to 1.6 mg/dL from 1.1 mg/dL 4 months prior. A urinalysis demonstrated > 500 mg of albuminuria and 57 RBC/hpf. Spot urine protein to creatinine ratio was 526 mg/g. A second kidney biopsy showed light microscopy demonstrated mesangial hypercellularity. Electron microscopy revealed patchy effacement of podocyte foot processes.

Discussion: We report a case of IgA nephropathy, which was initially treated with glucocorticoid therapy, leading to a sustained remission. Later, the patient was started on Adalimumab due to uveitis. IgAN relapsed after taking Adalimumab for 6 months. On diagnosis, the patient was started on Mycophenolate Mofetil as a steroid sparing strategy. The patient deferred repeat treatment with glucocorticoid therapy. The patient was treated supportively with RAAS blockade and SGLT2i, with good anti-proteinuric response. This is a novel case of recurrence of IgA nephropathy, as there is scant literature available that studies IgA Nephropathy related to Adalimumab. Furthermore, physicians must be aware of this potential side effect when prescribing Adalimumab, particularly in patients with underlying IgA nephropathy.



Light microscopy (PAS stain): Mesangial hypercellularity and endocapillary hypercellularity.



Immunofluorescence: Granular mesangial staining for IgA.

TH-PO711

IgA Nephropathy and IgA Vasculitis, Two Sides of the Same Coin: A Rare Case of Rapidly Progressive IgA Nephropathy with IgA Vasculitis of the Skin

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Introduction: IgA Nephropathy (IgAN) is the most common type of primary glomerular disease worldwide. About 25-30% of IgAN patients develop end-stage kidney disease within 20-25 years. IgA vasculitis (IgAV) is a small-vessel vasculitis that affects multiple organs including the skin and kidneys. Renal involvement occurs in 45 to 85% of adults with IgAV. Despite the similarities between IgAN and IgAV, most IgAN trials excluded those with vasculitis. Here we report a case of rapidly progressive glomerulonephritis (RPGN) secondary to IgAN in a patient presenting with IgAV involving the skin.

Case Description: A 44-year-old Asian man with hypertension, gout, anemia, hypothyroidism and alcoholic cirrhosis presented with profuse epistaxis and pruritic skin rash. The physical examination was notable for palpable purpuric rash on all extremities. His blood urea nitrogen and serum creatinine were 90 and 4.8 mg/dL. His serology tests were negative. C3 was low at 50 mg/dL. He had microscopic hematuria and proteinuria. A skin biopsy showed superficial perivascular lymphohistiocytic infiltrate with perivascular fibrin and 2+ IgA staining. The patient received methylprednisolone and was initiated on hemodialysis. A kidney biopsy showed focal proliferative glomerulonephritis with approximately 18% active cellular crescents in conjunction with ubiquitous IgA mesangial deposits.

Discussion: The pathophysiology of both IgAN and IgAV is based on the multi-hit hypothesis involving galactosidase deficient IgA and complement pathways. The histologic differentiation between the two diseases remains impossible. Despite the possibility of secondary IgAN from cirrhosis, the evidence of IgAV in the skin of our patient suggested a primary systemic disease. The therapy for IgAN with RPGN is methylprednisolone followed by a combination of oral or intravenous cyclophosphamide and corticosteroids. Rituximab has been reported previously in treatment of IgAV. Due to concerns for cyclophosphamide hepatotoxicity and non-adherence, we recommended rituximab for our patient. He remained dialysis dependent at the date of this report. This report calls for the inclusion of IgAN with IgAV on future clinical trials and a more specific therapeutic guideline for this subgroup of patients.

TH-PO712

Minimal Change Nephrotic Syndrome in an Elderly Female with Acute Onset Type 1 Diabetes

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Introduction: Concurrent type 1 diabetes (T1D) and idiopathic nephrotic syndrome (NS) is rare, and most previously reported cases were in children. Recently, a younger adult who developed minimal change NS (MCN) several months after acute-onset of T1D was reported 1). Moreover, human leukocyte antigen (HLA) A24, Bw52, Bw61, DR2 and DR9 has been described to be associated with both T1D and renal disease 2).

Case Description: An Asian 78-year-old female with anti-glutamic acid decarboxylase (GAD) 65 antibody-positive acute onset T1D, anti-thyroperoxidase antibody-positive Hashimoto thyroiditis, and fatty liver disease, diagnosed them three years ago then treated with mdi insulin and po levothyroxine 3), was admitted again to our section due to bilateral leg edema as well as remarkable body weight gain. Her serum albumin was decreased to 1.8 mg/dL. Laboratory data show Hb 12.2 g/dL, TP 4.7 g/dL, Cr 1.11 mg/dL, eGFR 36.8 ml/min/1.73m^2, Na 132 mEq/L, K 5.7 mEq/L, Tchol 353 mg/dL, LDL-c 165 mg/dL, fT4 0.90 ng/dL, TSH 13.81 mU/L, HbA1c 6.9 %, normo-complement proteins, D-dimer 9.23 μg/mL**,** UACR < 30 mg/gCr, UP 7.9 g/gCr with selectivity index 0.18, β2-microglobulin 27 mg/L. Serum antibodies were positive in GAD 604 U/mL, TPO 168 IU/mL, Tg 123 IU/mL, whereas was negative in MPO/PR3-ANCA, GBM, nor staff as paraproteinemia. No deep vein thrombosis nor malignancy was shown in non-enhanced computed tomography imaging. Kidney biopsy detected minor glomerular abnormalities with 1/10 obsolescence glomeruli; No Kimmelstiel-Wilson nodule was shown. Diagnosis of MCN was made with incidence described above. Her HLA typing was A24, A26, B62, B54, and DR9. Given methylpredonisolone (mPSL) 500 mg/day intravenously for three days, then PSL 40 mg/day orally, CR was acheived but fastly relapsed twice so added po 75 mg cyclosporin A. Five weeks after admission, she discharged with po 25mg PSL plus 75 mg cyclosporin A, mdi 50 units/day insulin with po 50 mg SGLT2i ipraglifrozin, and 25 μg levothyroxin.

Discussion: The patient maintained remission with cyclosprin A; not required temporal hemodialysis 1)2) nor LDL-apheresis 1). HLA subtype was partially coincide in aged case 2) but not in young adult case 1). Th 1/2 predominance in T1D/MCN should have discussed 1)2). References. 1) Nishizono R, BMC Nephrol 2020;21:410. 2) Kagiyama S, Am J Nephrol 1999;19:369-72. 3) Koga S, 17th Intl Conf Endocr 2016 poster # PT04-02-17, program book p.203.

TH-PO713

Rituximab in the Treatment of Thymoma-Related Minimal Change Disease

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Introduction: Thymoma may cause autoimmune-related kidney disease. This article presents two cases of thymoma-related kidney disease treated with oral prednisone in combination with rituximab. Remission of proteinuria were achieved, and shrinkage of the thymoma mass was observed on the CT scan.

Case Description: Case 1: A 67y male was admitted because of foamy urine and edema. Lab tests revealed hypoalbuminemia and proteinuria. Scr increased progressively, while auto-immune antibodies were negative. Chest CT showed a mass in the anterior mediastinum. The patient underwent a right posterior hepatic lobectomy in 2020. The pathology revealed a thymoma type B2. Other past history includes hypertension and diabetes. Based on the patient's clinical manifestations, history of thymoma, and renal biopsy, the patient was diagnosed as thymoma-related minimal change disease, acute interstitial inflammation, diabetic nephropathy, and hypertensive kidney injury. Methylprednisolone was administered 240mg/d *3d, followed by prednisone 30mg/d and rituximab 375mg/m^2/week *4 weeks. Remission was achieved one month after completion of the RTX course. Surprisingly, the thymoma shrank on the CT scan. **Case 2**: A 67y male was admitted because of foamy urine and edema. Lab tests showed a 24h urine protein of 8.78g. Plasma albumin was 16.9g/L, eGFR was 53mL/min/1.73 m^2.

The patient claimed a history of thymoma, and underwent thymectomy in 2014. PET-CT showed left pleural, left phrenic angle and cardiophrenic angle lymph node, and anterior chest wall subcutaneous metastases. The patient claim a history of hypertension. The final diagnosis based on clinical manifestations and renal biopsy was thymoma-related MCD, hypertensive kidney injury, and AIN. Steroid therapy (methylprednisolone 120mg/d*3d, followed by prednisone 40mg/d) combined with RTX (375mg/m^2/week *4weeks) was administered. The patient's proteinuria gradually decreased two months after RTX treatment, the urine protein was 0.67 g/24h at the latest follow-up. In addition, there was remission of the patient's thymoma metastasis.

Discussion: Experience in treating thymoma-related nephropathy with RTX is limited, our cases report the effectiveness of RTX in both MCD and thymoma. This report provide a new approach for treating thymoma-related kidney disease, especially for those who are not suitable for surgery.

TH-PO714

Collapsing Focal Segmental Glomerulosclerosis in a Patient with Hemophagocytic Lymphohistiocytosis

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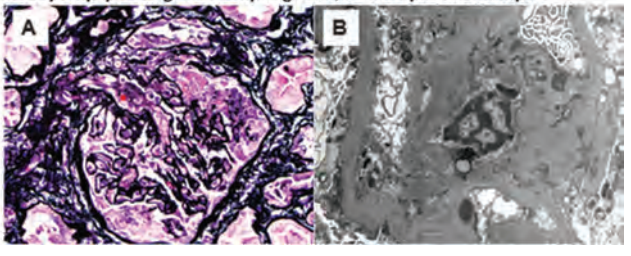
Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a systemic inflammatory disorder caused by the activation and proliferation of nonmalignant macrophages. HLH-associated podocytopathy is very rare. Here, we report a case of HLH-associated collapsing focal segmental glomerulosclerosis (FSGS).

Case Description: A 46-year-old black man with plasma cell leukemia presented to the hospital with a fever and dyspnea. CT scan showed bibasilar lung consolidation and antibiotics were started. He had anemia (hemoglobin 5 g/dl), thrombocytopenia (platelets 10,000 K/µl) and high ferritin (129,379 ng/ml), lactate dehydrogenase (3707 U/L), triglycerides (294 mg/dl), and soluble IL2 Receptor (2145 pg/ml). Based on these findings, a diagnosis of HLH was made. On admission, urine analysis showed 30 mg/dL protein; on hospital day #5, the urine-spot-protein-creatinine ratio (UPCR) was 60 g/g; urine albumin-creatinine-ratio was 25 g/g, and UPEP/IF revealed a monoclonal band with an M-spike of 8.3 mg/dl. Serum creatinine (SCr) rose to 3.8 mg/dl. One gram of solumedrol was administered daily for three days, followed by oral prednisone 60 mg daily. Kidney biopsy showed collapsing FSGS with rare sub-epithelial humps and no evidence of paraprotein disease. Blood cultures and tests for HIV, parvovirus, CMV, EBV, and SARS-CoV-2 were negative. Genotyping for APOL-1 risk alleles is pending. Two weeks following steroid initiation, UPCR improved to 1.5 g/g, and SCr was 1.2 mg/dl.

Discussion: Here, we report a case of HLH-associated collapsing FSGS with sub-epithelial humps. No infectious cause was identified, but the presence of sub-epithelial humps suggests an infectious trigger for HLH. HLH is characterized by cytokine release, which induces podocyte injury. HLH-associated collapsing FSGS occurs in black individuals with APOL-1 mutation. In a large case series of HLH-associated glomerular diseases[1], the mortality rate was 64%, and kidney recovery was rare. The rapid improvement in proteinuria and AKI in collapsing FSGS, as observed in this patient, is very rare. [1] Nephrotic syndrome associated with hemophagocytic syndrome. Kidney Int. 2006.

Kidney biopsy findings. A. Collapsing FSGS, B. Sub-epithelial humps



TH-PO715

Collapsing Glomerulopathy: A Case Series

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Introduction: Collapsing glomerulopathy (CG) is a rare variant of FSGS and is associated with rapid progression to ESRD. We present a series of three cases of CG.

Case Description: Case 1: A 32-year woman presented with acute pulmonary edema. She had tachycardia, stage II hypertension, and diffuse lung crepitations. On evaluation, she had global hypokinesia of left ventricle with ejection fraction of 25%, acute kidney injury (creatinine -3.6mg/dl) with a small right kidney (6.5cm). Her sputum culture grew multidrug-resistant Klebsiella pneumoniae. She was treated with Polymyxin B, diuretics, and three anti-hypertensives. There was no evidence of renal artery stenosis on doppler. Left renal biopsy was done, which showed collapsing glomerulopathy with IgA nephropathy, and was started on oral steroids. At 3 months, her BP is controlled on one drug, creatinine is 2.8mg/dl. Case 2: A 55-yr male presented with nephrotic syndrome. He had well-controlled diabetes and hypertensive. His creatinine worsened from 3.5 to 6.4mg/dl. Renal biopsy showed collapsing glomerulopathy with diabetic nephropathy, RPS class 3. He was treated with oral steroids but had no recovery and is dialysis dependent. Case 3: A 46-year-old man presented with umbilical hernia. He was found to have nephrotic syndrome, right renal mass, and renal failure. A well-defined lobulated heterogeneously enhancing lesion with cystic areas was seen arising from the lower pole of the right kidney, suggestive of renal cell carcinoma. Left renal biopsy showed collapsing glomerulopathy with diabetic nephropathy, RPS class III. He underwent right partial nephrectomy, which showed renal cell carcinoma–Clear cell variant. At 3 months, he has no edema, normal serum Albumin, and creatinine.

Discussion: We present a series of collapsing GN, with varying outcomes. Case 1 had partial recovery, case 2 had rapid progression, and case 3 had complete recovery. The etiology could be probably uncontrolled hypertension and IgA nephropathy in case 1, Case 2 was idiopathic, and Case 3 was malignancy related.

	Age (years) /Sex	Creatinine (mg/dl)	Outcome	Etiology	Histology
Case 1	32/F	3.6	Creatinine- 2.8	IgAN, HTN	Mesangial hypercellularity. Segmental sclerosis with adhesions to Bowmans capsule in one glomerulus, collapse of capillary tuft with hyperplasia of overlying podocytes in one glomerulus
Case 2	55/M	6.4	ESRD	Idiopathic	Kimmelstiel Wilson nodules are noted. Mesangiolysis and capillary tuft collapse with the overlying podocytes hyperplasia seen in two glomeruli. Microaneurysmal dilatation of capillaries is seen. 40-55% interstitial fibrosis and tubular atrophy. Diffuse lymphoplasmacytic infiltrate is seen in interstitium.
Case 3	46/M	2.1	Recovered	Renal Cell carcinoma	Diffuse and nodular mesangial matrix expansion. Occasional Kimmelstiel Wilson nodules. Segmental collapse of the capillary tuft with hyperplasia of overlying of podocytes in one glomerulus. There is microaneurysmal dilatation of some capillaries. 25-30% interstitial fibrosis and tubular atrophy.

TH-PO716

Membranoproliferative Glomerulonephritis Associated with Hemophilus parainflunezae Endocarditis: A Rare Presentation

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Introduction: We present a case of acute renal failure due to diffuse membranoproliferative glomerulonephritis in the setting of HACEK organism mitral valve infective endocarditis (IE).

Case Description: A 56-year-old with year old male with no significant past medical history was transferred to the ICU for renal failure, anemia and hypotension. He had a three month history of fevers, night sweats, reddish brown urine and 15 Ib weight loss. Physical exam was notable for confusion, respiratory distress on 14 liters oxygen, a pansystolic murmur over the mitral area and +2 bilateral pedal edema. He had profound microcytic anemia on initial presentation with a hemoglobin of 4 g/dL, alongside leukocytosis 29 10x9/L. Metabolic panel was notable for Creatinine 5.28, BUN 162, PO4 10.2 and albumin 2.6. He underwent continuous renal replacement therapy (CRRT) for uremic encephalopathy in the setting of hypotension. Further investigation revealed 2.5g proteinuria ove 24 hours and RBC casts in the urine analysis. C3 was 38.4 mg/dL, C4 was undetectable and rheumatoid factor was more than 115. Hepatitis C was not detected and other rheumatologic serologies were unremarkable. The patient was started on empiric plasmapheresis for concern of cryoglobulinemic glomerulonephritis (GN). A transthoracic echocardiogram showed a large mitral valve (MV) vegetation, severe MV regurgitation, and a small pericardial effusion. Blood cultures grew gram negative rods after 79 hours, which were finalized to Hemophilus parainfluenzae. Plasmapheresis was stopped. Due to persistent encephalopathy, MRI brain was obtained which showed septic emboli. His kidney biopsy revealed diffuse membranoproliferative GN with C3/IgM strongly positive. His final diagnosis was mixed cryoglobulinemia and MPGN in the setting of Hemophilus endocarditis. He was maintained on IV ceftriaxone and eventually underwent surgical mitral valve replacement.

Discussion: Acute renal failure related to IE-associated glomerulonephritis (IEAGN) has been reported in literature, with varying pathophysiological mechanisms, including one third of patients having anti-neutrophil cytoplasmic antibody (ANCA) positivity. To our knowledge, there are no reported cases of IE caused by HACEK organisms associated with MPGN. This case highlights a unique presentation that may be missed.

TH-PO717

Cryofibrinogen-Associated Membranoproliferative Glomerulonephritis

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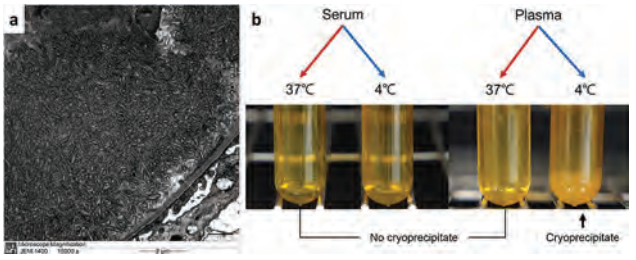
Introduction: Cryofibrinogenemia is a rare disorder caused by deposition of cryofibrinogen. Various clinical manifestations associated with cryofibrinogenemia. Although the kidney can be a target organ, but there are few reports. We describe a case of cryofibrinogen-associated glomerulonephritis in old man with prolonged diabetes.

Case Description: A 74-year-old man with diabetes mellitus visited the emergency department with generalized edema and weakness since 1 week. Serum creatinine level was 3.9 mg/dL (up from a baseline 6 mo earlier 1.2 mg/dl), and urinalysis revealed microscopic hematuria and nephrotic-range proteinuria (5.15 g/day in 24-h urine sample). Kidney biopsy, performed to ascertain the exact cause of acute kidney injury with nephrotic-range proteinuria, revealed basement membrane thickening, mesangial matrix prominence, marked inflammation, and endocapillary hypercellularity under light microscopy. Immunofluorescence microscopy showed no staining for immunoglobulin G. Electron microscopy revealed subendothelial and mesangial deposits with large-bore multilayered tubular structures (Figure 1a) that were further evaluated and comprised

an abnormal protein that precipitated when the plasma, but not serum, was stored at 4'C and redissolved at 37'C(Figure 1b). Liquid chromatography-tandem mass spectrometry revealed fibrinogen-α, -β, and -γ chains, and fibronectin. Despite adequate hydration, the patient's renal function did not improve, and prednisolone (1 mg/kg/day) therapy was initiated and continued for 3 months, whereby the serum creatinine decreased to 1.9 mg/dL. However, the renal function of the patient decreased gradually thereafter to eventual kidney failure that necessitated hemodialysis.

Discussion: Cryofibrinogenemia can induce several organ dysfunctions, manifesting as mostly dermatological symptoms, as well as kidney involvement. Distinctive ultrastructure findings of large microtubular structures on electron microscopy, plasma cryoprecipitates when cold, and proteomic analysis are crucial for diagnosing cryofibrinogen-associated glomerulonephritis.



a. Electron microscopy, b. Cryoprecipitates

TH-PO718

Unraveling the Mystery: A Case of Cryoglobulinemia

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Introduction: Cryoglobulinemia is a systemic inflammatory syndrome that generally involves small-to-medium vessel vasculitis due to cryoglobulin-containing immune complexes. The classification distinguishes three subtypes of cryoglobulinemic diseases. But at the same time, there are rare instances where there could be misleading classification of the disease due to the presence of two different underlying disorders. Here we report a case of type 2 cryoglobulinemic membranoproliferative glomerulonephritis with a detectable monoclonal IgM kappa in serum.

Case Description: A 70-year-old gentleman with a past medical history of chronic myelogenous leukemia presented with epigastric abdominal pain and melena. He was diagnosed with liver cirrhosis and spontaneous bacterial peritonitis. Additional workup revealed active hepatitis C infections, acute kidney injury with hematuria, sub-nephrotic proteinuria, active sediment on urine microscopy, elevated RF, serum immunofixation showing monoclonal gammopathy, IgM, kappa type and urine immunofixation with lambda light chain band. A kidney Biopsy was performed that showed cryoglobulinemic glomerulonephritis. Due to monoclonal gammopathy, hematology performed a bone marrow biopsy, which returned 2-3% plasma cells. The diagnosis was felt to be more consistent with mixed/Type 2 Cryoglobulinemia secondary to HCV infection. The monoclonal gammopathy and the presence of Kappa-restricted B cells were felt to be an association rather than the cause of cryoglobulinemia. Therefore, he was not treated further with plasma cell-directed therapy. He received treatment with Rituximab, plasmapheresis, and steroids.

Discussion: This case highlights the importance of differentiating between different types of cryoglobulinemia that determines appropriate therapy. Detectable monoclonal gammopathy can be found in the serum of patients with type II cryoglobulinemic glomerulonephritis. Although lymphoproliferative disorders are more closely related to type I cryoglobulinemia, it is essential to exclude monoclonal gammopathy in patients with mixed cryoglobulinemic glomerulonephritis to reveal hidden lymphoproliferative disease before the diagnosis of essential cryoglobulinemia can be made. This has implications for the management of such patients.

TH-PO719

Interstitial Inflammation and C3 Glomerulopathy Secondary to an Autoinflammatory Syndrome

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Introduction: Dual presence of histiocytic interstitial inflammation and C3 glomerulopathy (C3GN) are uncommon. We report a rare case of non-Langerhans cell histicoytosis associated acute kidney injury (AKI).

Case Description: A 71-yr-old male was admitted to the hospital with anasarca and generalized weakness. Laboratory data were significant for anemia, AKI, hypercalcemia, and trace monoclonal IgA lambda. Autoimmune and infectious workup was unrevealing. PET scan revealed hypermetabolic extensive infiltration of kidneys, perirenal space, and mild bilateral hydronephrosis. Bone marrow biopsy demonstrated hypercellular marrow without evidence of neoplasm. Vacuolization was not demonstrated in neutrophils. Kidney biopsy showed C3GN. Interestingly, a cluster of interstitial CD68-positive and Langerin-negative histiocytes was present. C3GN was thought to be inactive in the absence of active urine sediment. Biopsy of the perinephric mass showed fibroconnective tissue primarily composed of histiocytes, without evidence of neoplasm. IgG4 and EBV staining were negative. Further evaluation led to the identification of a pathogenic variant in the *UBA1* gene p.(M41) – a somatic variant which may result in promotion of pro-inflammatory gene expression, and implicated in the pathogenesis of VEXAS (Vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic mutation) syndrome, a recently described autoinflammatory disease. The patient's clinical presentation in the setting of a pathogenic *UBA1* variant was consistent with VEXAS syndrome. Speculatively, the alternate complement pathway, could have been activated by the inflammatory mediators or IgA lambda protein, leading to C3GN (C3 Nef antibody was negative, normal C3/C4). AKI was determined to be multifactorial and hypercalcemia was secondary to cytokine-mediated increased calcitriol synthesis by monocytes. This patient was treated with oral glucocorticoid and anti-IL-6 receptor monoclonal antibodies, with marked improvement in clinical status, inflammatory markers, kidney function, and metabolic uptake on follow-up PET scan.

Discussion: Acute interstitial inflammation with infiltration of non-Langerhans cell histiocytes due to VEXAS syndrome is a rare cause of AKI. A high degree of suspicion is required to diagnose VEXAS which carries significant mortality and morbidity without prompt treatment.

TH-PO720

Nephrotic Range Proteinuria with White, Cloudy Urine

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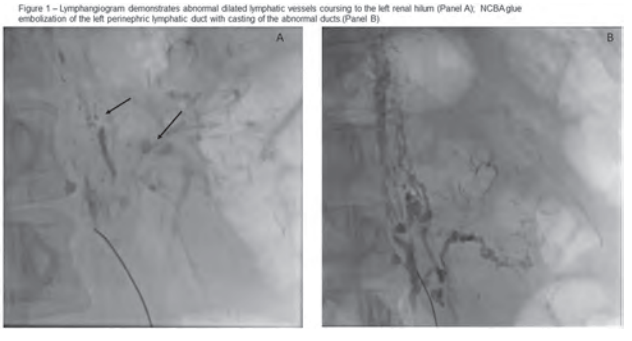
Introduction: Nephrotic range proteinuria may be due to a myriad of glomerular pathologies. While rare, non-glomerular etiologies can produce high grade proteinuria in the absence of significant glomerular pathology.

Case Description: A 30-year-old male was evaluated for nephrotic range proteinuria and hypoalbuminemia. Physical examination was unremarkable. Laboratory data showed Creatinine 1.1 mg/dl (eGFR 100 ml/min/1.73m^2), urine to protein creatinine (UPCR) ratio of 9 g/g, UACR at 183 ug/mg, serum albumin 2.7 g/dl. The urine was "cloudy," and sediment analysis demonstrated no acanthocytes or lipid-laden oval fat bodies. Kidney biopsy showed normal glomeruli by light microscopy with unremarkable immunofluorescence staining and no significant glomerular abnormalities by electron microscopy. Additional studies were performed in our research laboratory to determine the cause of urinary turbidity. Upon addition of ether (a fat solvent), clearing of "cloudy" centrifuged urine occurred with layering of fat globules at the bottom. With addition of Sudan III stain, a red-stained fatty layer accumulated upon centrifugation. Urine assessed in a clinical laboratory showed elevated levels of triglyerceride, cholesterol, and chylomicrons. Filariasis serologies were negative. The patient was diagnosed with chyluria based on the urine TG level and ether test. MR lympangiography showed abnormally dilated lymphatic channels in the left paraspinal region communicating with the left kidney. He underwent lymphangiogram with N-butyl cyanoacrylate glue embolization of the left perinephric lymphatic duct, and within 12 hours, the urine cleared to clear yellow.(Figure 1) Repeat labs 1 month after embolization showed UPCR of 0.07 g/g and serum albumin of 4.2 g/dl.

Discussion: Chyluria is a rare cause of nephrotic range proteinuria. Urine color and turbidity, absence of oval fat bodies, and non-selective proteinuria were early diagnostic clues, with urine TG confirming the diagnosis. Microscopic examination of the urine sediment is essential in evaluating patients with proteinuria.



TH-PO721

Compassionate Use of Pegcetacoplan in a Patient with C3 Glomerulopathy: A Case Report

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Introduction: Pegcetacoplan is a C3 complement inhibitor which is approved by the United States Food and Drug Administration for paroxysmal nocturnal hemoglobinuria and geographic atrophy secondary to macular degeneration. It is undergoing a phase III trial (Valiant trial, NCT05067127) which is assessing subcutaneous pegcetacoplan in patients with C3 glomerulopathy (C3G) or immune-complex mediated glomerulonephritis. Here, we discuss the case of a patient who did not qualify for the trial but was approved for compassionate use of pegcetacoplan.

Case Description: A 26-year-old female was diagnosed with biopsy proven C3G with negative genetic testing. Over the course of about one and a half year, her renal function had deteriorated from estimated glomerular filtration rate (eGFR) of 64 to 22 ml/min/m^2 , with proteinuria progressing from 1.5 to 2.7 gm/day, while being on prednisone and mycophenolic acid (MFA). Due to the inability to tolerate MFA (MFA induced colitis on colon biopsy), she was transitioned to tacrolimus and prednisone. The patient kept being hospitalized frequently due to acute kidney injuries (AKI), with five admissions over four months. Patient was not a candidate for the Valiant trial due to eGFR < 30 ml/min/m^2, 76% glomerular sclerosis (GS) and 60% interstitial fibrosis and tubular atrophy (IFTA) on the last biopsy. Therefore, a request for compassionate use of pegcetacoplan was submitted. It was approved after four months and started in September 2022. While being on pegcetacoplan for six months, the patient's renal function remained stable (eGFR 19-22 ml/min/m^2, proteinuria 0.5-0.7 gm/day) and she did not require any hospitalizations. The medication was well tolerated without any serious adverse effects. In March 2023, the patient progressed to end stage renal disease (ESRD) and was started on hemodialysis.

Discussion: There is currently no approved therapy for C3G. Our patient had frequent episodes of AKI, multiple hospitalizations and did not meet the criteria for Valiant trial due to her low GFR. We believe pegcetacoplan might have delayed her progression to ESRD, improved her quality of life by avoiding hospitalizations and allowed her time to get listed for transplant. Further studies are needed to evaluate the efficacy and safety of pegcetacoplan in advanced C3G.

TH-PO722

C3 Glomerulonephritis and Thrombotic Microangiopathy in a Patient with C3 Nephritic Factor

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Introduction: Complement-mediated kidney diseases include thrombotic microangiopathy (TMA), and C3 glomerulonephritis (C3GN). TMA can occur due to complement dysregulation manifesting as hemolytic anemia, thrombocytopenia and kidney dysfunction. C3GN develops due to mesangiocapillary C3 accumulation. We report a case where both conditions developed in the same patient.

Case Description: A 36-year-old woman presented with shortness of breath and generalised edema. She had a history of hepatitis C infection. Laboratory testing showed creatinine 2.1mg/dL (eGFR 30 mL/min/1.73m2) and albumin 19 g/L. Urinalysis showed hematuria and protein/creatinine ratio (uPCR) 1,100 g/mol. Hepatitis C viral load was 5.52 x 10^6 IU/m. Other viral, autoimmune, cryoglobulin and paraprotein tests were negative. C3 was low 0.22 g/L (0.9-1.8). C4 was normal. Kidney biopsy showed mesangial and endocapillary hypercellularity with double contours. IF showed granular C3 deposition in capillary and mesangium. EM showed subendothelial deposits, consistent with membranoproliferative glomerulonephritis. Renal parameters did not improve with hepatitis C treatment. C3 Nephritic Factor (C3NeF) was positive and Prednisolone and Mycophenolate were thus commenced with improvement of creatinine to 1.4 mg/dL and uPCR to 192 g/mol. One year later the patient presented with dyspnea, kidney failure (creatinine 14.1mg/dL) and features of TMA, with haemoglobin 63 g/L and platelets 133 x 109/L. Haptoglobin was low (0.26 g/L) and blood film showed schistocytes. ADAMTS13 level was normal. Hemodialysis commenced and Eculizumab was given with improvement in hematological parameters only. Complement genetic analysis (aHUS, C3GN) panel was negative. At four-year follow up, the patient remains dialysis-dependent.

Discussion: TMA and C3GN are disorders caused by complement defects, with the former from membrane-anchored complement activation and the latter from fluid-phase complement activation. C3NeF is a stabilizing antibody against the C3 convertase complex, a common step in multiple complement pathways, leading to complement-mediated disorders. Our patient had both TMA and C3GN. This illustrates the complexity and overlap of complement pathways.

TH-PO723

A Case of AKI Secondary to Toxocara-Induced C3 Glomerulonephritis

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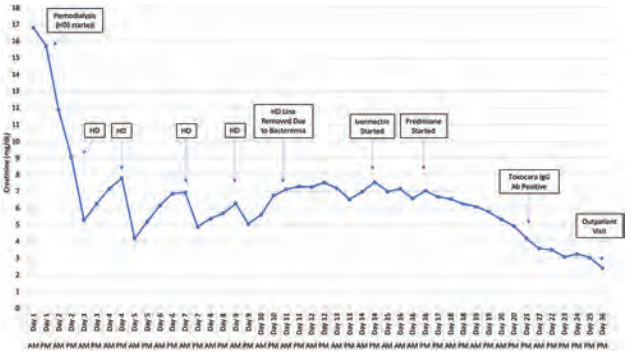
Introduction: C3 glomerulonephritis (C3GN) is a rare form of glomerulonephritis that can occur secondary to infection. We present a case of biopsy-confirmed C3GN in a patient with AKI requiring dialysis and positive Toxocara IgG Ab who achieved partial remission with steroids.

Case Description: A 59-year-old male with hypertension and diabetes mellitus presented with a week of anasarca and oliguria after a 3-month trip to Cuba. Physical exam was notable for bilateral 4+ pitting edema up to his hips. Labs demonstrated a Cr of 16.81 mg/dL (1.16 mg/dL 16 months prior) and eosinophilia 1.9K/cumm. Urinalysis revealed 3+ protein, 21-50 WBC/hpf, >50 RBC/hpf, and a 24-hour urine protein of 5.4 grams. Notable serologic workup included elevated DNASE B Ab, ANA 1:160, and low serum C3. Hemodialysis (HD) was started for diuretic resistant oliguric AKI. His course was complicated by MRSA bacteremia necessitating a line holiday, during which time his urine output improved and his Cr and azotemia spontaneously stabilized without further HD. A kidney biopsy showed C3GN, 2/10 globally sclerotic glomeruli, moderate interstitial fibrosis, 40% tubular atrophy, and moderate hyaline arteriosclerosis. Initial infectious workup was negative. Given the biopsy results and persistence of Cr ~7 mg/dL, oral prednisone 60mg daily was initiated. ID recommended 2 days of empiric Ivermectin while awaiting results of a parasitic workup. His Cr steadily decreased to ~3 mg/dL on steroids. Toxocara IgG Ab subsequently resulted positive. There were no acute signs of Toxocariasis, so albendazole was not started. His Cr continued to improve at discharge.

Discussion: Toxocariasis, a parasitic helminth infection, can cause eosinophilia and is important to consider when evaluating for C3GN, even without active signs of infection. It is typically diagnosed with an ELISA Ab assay and treated with albendazole. Prednisone may be added for severe systemic involvement. Patients without active Toxocariasis, significant sclerosis, or fibrosis on renal biopsy may have good renal recovery after prompt steroid treatment.



TH-PO724

A Case of AA Amyloidosis Associated with "Skin Popping" Heroin

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Introduction: The differential diagnosis for renal disease in patients with substance use disorder can be broad. Etiology can be related to the substance itself, a contaminant of the substance, or a transmitted disease. The renal complications can be acute or chronic and include glomerular, interstitial, and vascular diseases. This case highlights the importance of distinguishing by kidney biopsy between different etiologies in patients with substance abuse.

Case Description: A 62-year-old man with history of Hepatitis C (treated 8 months prior), treated latent TB, chronic left ankle ulcer, and substance use disorder presented to the emergency room with right calf pain for 4 days. Per patient, he used heroin via "skin popping" a couple of times since his pain was severe, but denied using for 15 years prior. Exam with hyperkeratotic plaques on right ulnar palm, left heel ulcer, and lower extremity edema. He was found to have a new deep vein thrombosis in the right popliteal and posterior tibial veins. His laboratory workup revealed a serum creatinine of 5.5 mg/dL from 1.0 mg/dL 5 months prior, urinalysis with 3+ protein and 2+ blood, and 14.8 grams of urine protein per 1 gram of urine creatinine. Hepatitis C viral load was undetectable. Other workup resulted during the hospitalization including HIV, Hep B, cryoglobulins, Anti-GBM, complements, ANCA, ANA, and dsDNA were negative. He had an abnormal SPEP and elevated free light chains ratio. Kidney biopsy revealed AA amyloidosis with preserved glomeruli and tubulointerstitial fibrosis less than 30%. Although serum creatinine did not significantly change during hospitalization, he remained with good urine output and did not develop indications to start dialysis.

Discussion: Given the broad differential diagnosis in patients with substance abuse, it is key to differentiate between them with a kidney biopsy. Renal amyloidosis should be considered in the differential diagnosis of heroin users when they present with proteinuria and renal impairment. Untreated skin and soft tissue infections can cause persistent inflammation that trigger AA amyloidosis. Unfortunately, injection drug users who develop AA amyloidosis are usually diagnosed late when the renal disease is advanced. There are no proven treatments currently. However, some have suggested that AA amyloidosis may be preventable and potentially reversible if the inflammatory stimulus is eliminated early.

TH-PO725

AL Kappa Amyloidosis with Rapidly Unfavorable Evolution: A Case of Renal, Hepatic, and Muscular Involvement with POEMS Syndrome and Unusual Autoantibody Activity

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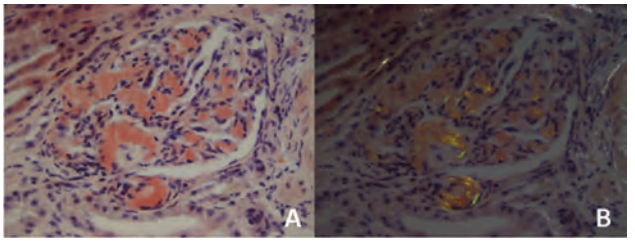
Introduction: AL amyloidosis arises in the setting of plasma cell discrasia, with deposition of amyloidogenic misfolded immunoglobulin-free light chains in peripheral tissues resulting in progressive organ dysfunction. Involved organs include kidneys, heart, liver, nervous system and gastrointestinal tract.

Case Description: We report the case of a 61-year-old man who presented with hypotension, alternating diarrhea and constipation, muscle pain, paraesthesias, and a monoclonal IgG kappa component with altered free light chain ratio, nephrotic syndrome and acute kidney injury requiring haemodialysis. After renal and bone marrow biopsies a diagnosis of AL k amyloidosis was reached **(Fig. 1)**. Evidence of persistently elevated levels of liver function tests and creatine phosphokinase led to consideration of amyloid infiltration in the liver and muscle, confirmed by biopsies. Clinical management was complicated by the presence of hypopituitarism associated with MRI changes consistent with hypophysitis. High-titer anti-cardiolipin IgG and anti-β2 glycoprotein IgG was

observed, despite the absence of thrombotic lesions on whole-body CT images. The patient was started on a cyclophosphamide-bortezomib-dexamethasone-daratumumab regimen, interrupted after four cycles, following the patient's death only one month after the onset of nephrotic syndrome.

Discussion: We described a rare case of systemic amyloidosis with a rapidly unfavorable outcome with abrupt disease onset, in which organ involvement has rapidly progressed to multiorgan failure. If we exclude central nervous system involvement, polyendocrinopathies may be explained by concomitant POEMS. The significance of autoantibody positivity in the absence of clinical autoimmunity remains unclear, and raises the suspicion of a false positivity due to molecular mimicry.



Kidney biopsy: (A) Glomerulus and arteriole with amorphous material in mesangial areas and the arteriolar wall respectively stains positive with Congo red and shows apple-green birefringence in polarized light, consistent with amyloid (B).

TH-PO726

Nephrotic Syndrome due to AA Amyloidosis Associated with Cystic Fibrosis: A Case Report

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Introduction: Cystic fibrosis (CF) is an autosomal recessive and multisystemic disease that predominantly involves the respiratory and digestive tracts. New drugs for treatment and early recognition have recently increased survival of the patients, leading to a chronic inflammation environment, introducing renal AA amyloidosis as a possible complication.

Case Description: A 28-year-old male with cystic fibrosis, mild malnutrition and recurrent pneumonia was admitted for treatment of infectious decompensation and investigation of anasarca that started 1 month earlier. He underwent antibiotic treatment with resolution of the infectious condition. Concerning the edemigenic syndrome, echocardiogram and abdominal ultrasound indicated normal results; spot urine revealed 6.41g of protein and no hematuria or pyuria. Urine protein-creatinine ratio in isolated sample was 7.5g/g; 24-hour proteinuria: 4.56g; serum albumin of 1.8g/dL; LDL 191mg/dL; triglycerides 248mg/dL. Serologies for hepatitis B, hepatitis C and HIV, and both FAN and ANCA resulted negative. Urinary protein electrophoresis showed no alteration. Renal biopsy presented mesangial expansion with amorphous eosinophilic pale material, PAS negative, with birefringence on analysis under polarized light in sections stained with Congo red (fig1). Amyloid A antigen test was performed, which resulted positive in arteriole walls. Gathering all of this information, the patient obtained a presumptive diagnosis of AA amyloidosis secondary to CF.

Discussion: CF may rarely complicate with AA amyloidosis. Amyloid deposits occur mainly in the liver, spleen and kidneys. This complication reflects a history of recurrent infections and successive inflammatory insults. AA amyloidosis presents itself as a poor prognostic factor and patients with CF and 24h-proteinuria > 1g or nephrotic syndrome should mandatorily perform a renal biopsy.

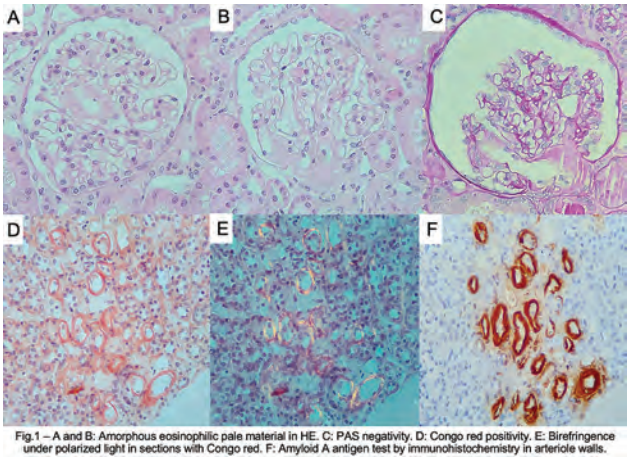

Fig.1 – A and B: Amorphous eosinophilic pale material in HE. C: PAS negativity. D: Congo red positivity. E: Birefringence under polarized light in sections with Congo red. F: Amyloid A antigen test by immunohistochemistry in arteriole walls.

TH-PO727

A Rare Case of Paraneoplastic Scleroderma Renal Crisis in a Patient with Squamous Cell Carcinoma of the Tongue

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Introduction: Scleroderma Renal Crisis (SRC) is a life-threatening emergency that presents with hypertension, Acute Kidney Injury (AKI) and Thrombotic Microangiopathy (TMA) in patients with Systemic Sclerosis (SSc). It is associated with 20% mortality at 6 months and 19-40% of patients requiring long term dialysis[1,2]. Paraneoplastic Scleroderma Renal crisis (PSRC) is a rare subset of SRC that has been reported previously[3]. We report a rare case of PSRC without history of SSc in a patient with squamous cell carcinoma of the tongue.

Case Description: 61-year-old male with history of squamous cell carcinoma of the tongue on radiotherapy presented for evaluation of decreased oral intake for few days. He was noted to have tachycardia and hypertension (BP167/109 mmHg). Labs showed anemia, thrombocytopenia and serum creatinine of 1.5mg/dL (baseline 1mg/dL). Urinalysis showed small blood and 30 mg/dL protein with granular casts. Renal ultrasound was unremarkable. The patient was treated initially for a presumed acute tubular injury (ATN) from prolonged pre-renal state. Due to worsening renal function with a creatinine 8.9 mg/dL the patient was initiated on hemodialysis. A renal biopsy was obtained revealing a widespread prominent mucoid intimal hyperplasia with severe occlusion and secondary changes of bloodless glomeruli. Mesangial lysis, acute tubular injury with focal ATN and minimal interstitial inflammation was seen. Repeat physical exam revealed thickening of the skin of the hands. Further testing revealed evidence of schistocytes, elevated LDH and positive RNA polymerase III. A diagnosis of PSRC was made and the patient was started on captopril. The patient continued to be dialysis dependent at the time of discharge.

Discussion: Paraneoplastic SCR has been reported in a few cases of lung, breast and abdominal cancers[3]. The pathogenesis is postulated to be related to cancer induced profibrotic cytokines and growth factors leading to renal vascular damage[3]. To our knowledge, there are no reported cases of squamous cell cancer associated PSCR. Our case adds to the literature of the rare PSCR in this patient population. This case highlights the importance of considering PSCR in the differential diagnosis of cancer patients presenting with AKI, TMA and higher than baseline blood pressure measurements.

TH-PO728

A Case of Fibrillary Glomerulonephritis Presenting as Rapidly Progression Glomerulonephritis in a Patient with Untreated Hepatitis C

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare progressive disease accounting for 0.5% to 1.4% of all native kidney biopsies. The diagnosis is established with renal biopsy demonstrating randomly oriented fibrils ranging 15-25 nm on electron microscopy, and negative Congo red staining. Recent discovery of DNAJB9 as a biomarker has been reliable for diagnosis, although its role in pathogenesis remains unclear. It is strongly associated with underlying malignancy, monoclonal gammopathy, autoimmune disease or infections. Prognosis remains poor with no established clinical guidelines to optimize therapy. Here, we describe a case of FGN presenting with rapidly progressive glomerulonephritis and crescents on biopsy in a patient with untreated Hepatitis C.

Case Description: A 64 yo. M with significant past medical history of hypertension, cirrhosis secondary to untreated Hepatitis C and methamphetamine who presented with dyspnea. Initial work up showed AKI with creatinine of 4.52 mg/dL. Urinalysis displayed hematuria and UPCR of 7.04 g/g, raising suspicion for an underlying GN. Serological work including anti-GBM, ANCA, Cryoglobulin, RF, HIV, Hepatitis A and B were negative. Hepatitis C antibody was positive, with quantitative RNA greater than 300,000 IU/mL. Electron microscopy from biopsy revealed randomly oriented fibrils of ~ 15nm in diameter throughout the glomeruli. IF revealed IgG, C3, kappa/lambda light chains in the mesangium and along the GBM. IHC analysis showed negative Congo red and positive DNAJB9. Of the 46 glomeruli analyzed, 7 demonstrated cellular and fibrocellular crescents. Biopsy findings were consistent with FGN. He was started on pulse dose steroids followed by a taper and cyclophosphamide. Due to worsening renal function and volume overloaded state, he required initiation of dialysis. Despite starting treatment for Hepatitis C, there has been no evidence of renal recovery.

Discussion: Overall prognosis for FGN remains poor with approximately 40-50% of patients progressing to ESRD. Our case highlights the challenges with recognition and management of FGN as a cause of RPGN since clinical presentation is similar to other recognized etiologies. Despite treatment of RPGN and Hepatitis C, our patient had progression of disease emphasizing need for further trials and novel therapies.

TH-PO729

An Atypical Case of IgG4-Related Disease (IgG4-RD) Manifesting as Extensive Abdominal Periarteritis and Membranous Nephropathy (MN): A Case Report and Literature Review

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Introduction: IgG4-RD is a progressive immune-mediated fibrotic disease characterized by tumor-like mass formation in many affected organs. Tubulointerstitial nephritis (TIN) with increased IgG4-positive plasma cells is the dominant feature of IgG4-related kidney disease. Here we present an atypical case of IgG4-RD, and a literature review of 18 cases on IgG4-related MN.

Case Description: A 71-year-old man with a peptic ulcer was admitted with acute-onset leg edema and nephrotic syndrome. The laboratory data revealed serum albumin 1.9 g/dL, creatinine 1.1 mg/dL, and urinary protein 9.3 g/gCr. The renal biopsy showed granular staining in the capillary walls for IgG (IgG1>4) and negative PLA2R staining, suggesting secondary MN. Computed tomography (CT) scans revealed extensive wall thickening around the iliac and splenic arteries, and superior and inferior mesenteric arteries with dilatation. The findings of periarteritis, high serum IgG4 and IgE levels, and numerous IgG4-positive cells infiltration to interstitium led to the diagnosis of IgG4-RD. Other etiologies causing vascular lesions such as lymphoma, and polyarteritis nodosa, were incompatible with the clinical findings. We chose low-dose prednisolone because this patient had a peptic ulcer and high doses of prednisolone may promote aneurysm formation in IgG4-related arteritis. After the initiation of prednisolone (10 mg) and ARB, he achieved partial remission of proteinuria. We successfully controlled IgG4-RD and avoided the recurrence of peptic ulcers.

Discussion: In this case, nephrotic syndrome and the absence of typical manifestations, such as pancreatitis and sialadenitis made the diagnosis of IgG4-RD challenging. It was also unique in that extensive arteritis was confined to a major branch of the abdominal aorta, not the aorta itself. These features suggest a new phenotype of IgG4-RD. Our literature review of 18 cases on IgG4-related MN, including 1 case with aortitis, demonstrated that 10 cases achieved complete remission, and 8 achieved partial remission of proteinuria with various treatments such as corticosteroids, cyclophosphamide, and rituximab. Although the number of affected organs had no relation with the response of proteinuria, the complication of TIN had an association with a good response.

TH-PO730

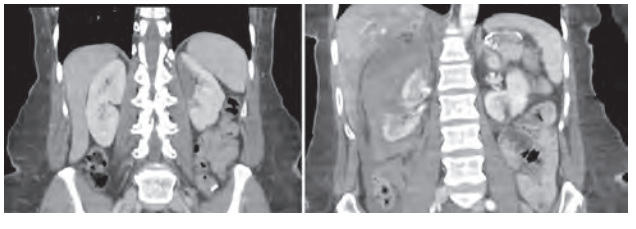
A Case of Renal Infarcts Followed by Renal Hematoma: The Importance of Angiography in the Diagnosis of Polyarteritis Nodosa

Erica Marnet, Kaltrina Sedaliu. *Bridgeport Hospital, Bridgeport, CT.*

Introduction: A renal infarct (RI) may go undiagnosed given its non specific symptoms; abdominal or flank pain, nausea and vomiting. Classically, it is attributable to cardiovascular causes, such as atrial fibrillation (AF), or to coagulopathies. Frequently, however, no underlying etiology is ascertained. Polyarteritis nodosa (PAN) is a medium vessel vasculitis not associated with antineutrophil cytoplasmic antibodies. Biopsy demonstrating necrotizing arteritis is the gold standard for diagnosis, and when it cannot be secured, angiography is an important tool to establish the diagnosis, exhibiting aneurysms or segmental stenosis of intraabdominal arteries.

Case Description: A 52-year old female, with a past medical history of abdominal pain with prior extensive work up, presents with acute on chronic abdominal pain, nausea, vomiting and 6 kg weight loss. Work up revealed a left RI. Telemetry was negative for AF, as a transesophageal echocardiogram for left ventricle thrombus. Her hospital stay was complicated by ongoing abdominal pain, repeated imaging showing a new large right RI. Hypercoagulable work up was negative. However, It was believed she was high risk for recurrent thrombosis, thus, initiated on Apixiban. After two weeks, she returns with abdominal pain and was discovered with a large right pericapsular hematoma with possible active bleeding. Given hemodynamic instability, she underwent a right renal angiogram that showed severe irregularity with multifocal areas of stenoses, dilatations and microaneurysms, also, large areas of devascularization, consistent with PAN. Hepatitis B sorology showed prior immunization. She was treated with pulse dose steroid therapy and IV cyclophosphamide (total of 5 infusions), followed by PO prednisone 1mg/kg. Her abdominal pain ultimately resolved and she experienced no further thrombotic events.

Discussion: The underlying etiology of RI requires compressive investigation. Proper treatment warrants an evidence based practice. PAN is a rare entity, however usually complicates with RI. This case highlights the importance of prompt recognition, appropriate diagnostic investigation, and timely treatment.



TH-PO731

Histiocytic Glomerulopathy

Marwa Ahmed,[1] Jason M. Kidd,[1] Samih H. Nasr,[2] Lihong Bu.[2] *[1]Virginia Commonwealth University Health System, Richmond, VA; [2]Mayo Clinic Minnesota, Rochester, MN.*

Introduction: Direct glomerular involvement by activated histiocytes is a rare histopathologic finding and may be associated with cryoglobulinemic glomerulonephritis, Langerhans cell histiocytosis (LCH) and hemophagocytic lymphohistiocytosis (HLH). We present a case of histiocytic glomerulopathy without a readily identifiable systemic cause.

Case Description: A 67-year female with recent cholecystectomy presented with abdominal pain and nausea. She was noted to have elevated alkaline phosphatase levels (1000 U/L) but with normal AST/ALT. She subsequently developed anasarca and anuric kidney failure requiring dialysis. Kidney biopsy showed diffuse macrophage foam cells positive for CD68 in glomeruli (image-1). Immunohistochemistry stains for CD1a and Langerin were negative making Langerhans cell histiocytosis unlikely. A bone marrow biopsy showed rare hemophagocytic macrophages. A broad serologic work up was performed and was mostly unremarkable. Although serology showed elevated IL-2 receptor alpha, hyperferritinemia, hypertriglyceridemia, and bone marrow with hemophagocytic macrophages; she did not meet full criteria for HLH. Due to concern for hypersensitivity reaction to metal clips placed during her cholecystectomy, she underwent laparoscopic removal. She was started on high dose methylprednisolone and then oral prednisone. Renal function improved and dialysis was discontinued.

Discussion: Histiocytic glomerulopathy is a rare entity categorized by the presence of macrophages in glomeruli. We present an idiopathic case which may have been triggered by a hypersensitivity reaction. Treatment options are limited and include steroids, plasmapheresis, and intravenous immunoglobulins (IVIG). Our patient responded to steroids in addition to removal of a potential underlying trigger. Six weeks after her initial presentation she remains off dialysis with excellent renal function.

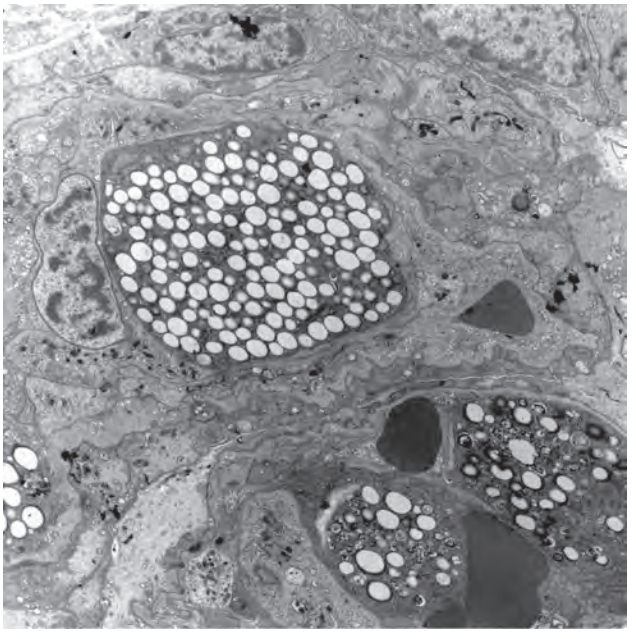


Image-1

TH-PO732

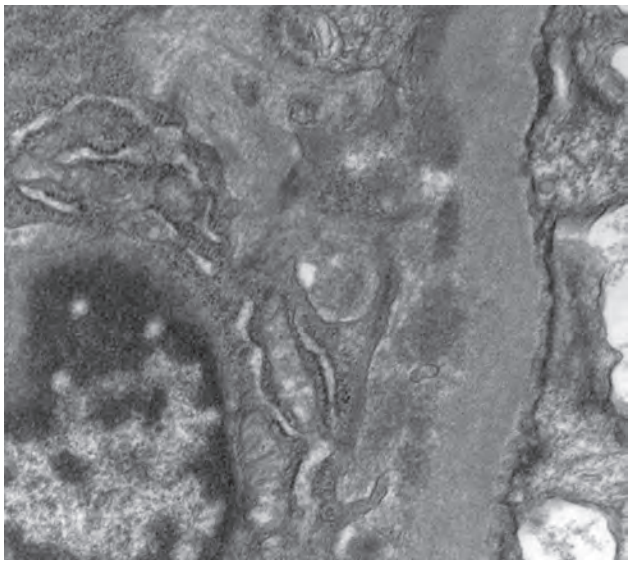
Tick-Borne Disease and Kidney

Ramandeep Kaur, Mushfique Choudhury, Jason R. Pettus, Thomas M. Kaneko, Clay A. Block. *Dartmouth Hitchcock Medical Center, Lebanon, NH.*

Introduction: A case of IgA nephropathy presenting coincidentally with Lyme disease.

Case Description: A previously healthy 41-year-old man presented with 5 days of chest pain, fever, erythematous skin rash, myalgias and painless gross hematuria. Laboratory data showed serum creatinine of 1.22 mg/dL (reference range 0.8-1.5) and CRP of 44.4 mg/L (reference range < 4.9). Urine microscopy showed 8 WBC/HPF and 20 RBC/HPF including acanthocytes. Urine protein-creatinine ratio was 0.8. Creatinine kinase, P-ANCA, C-ANCA, MPO Ab, and PR3 Ab were negative. Lyme IgG and IgM were positive and consistent with active infection with B. burgdorferi. A renal biopsy was performed for persistent microscopic hematuria. Light microscopy was normal, but immunoflorescence (IF) showed 4+ mesangial granular staining for IgA, 2+ kappa and 3+ lambda. C1q, IgG, fibrinogen, albumin were negative. Electron microscopy (EM) confirmed electron dense para-mesangial deposits. A diagnosis of IgA nephropathy was made. In addition to Doxycycline, he was treated with steroid taper and lisinopril. One year later, his urine protein-creatinine ratio is <0.1 and CRP is <3.0 mg/L.

Discussion: Lyme Disease can trigger IgA nephropathy and should be considered in tick exposure. Patients presenting with hematuria and/or proteinuria may be tested for acute Lyme disease.



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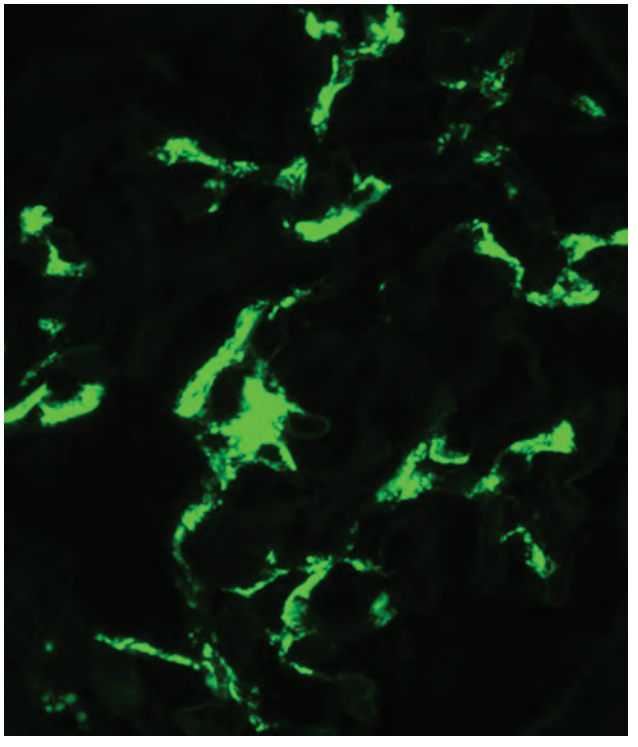

IF-IgA

TH-PO733

A Podocyte-Specific Injury Mouse Model with Inducible Yamanaka Factors

Katharina Lemberg, Selina Hölzel, Florian Buerger, Gijs A. Franken, Caroline M. Kolvenbach, Ken Saida, Daanya Salmanullah, Konstantin Deutsch, Friedhelm Hildebrandt. *Boston Children's Hospital, Boston, MA.*

Background: Ectopic expression of the *Yamanaka* transcription factors *Oct4, Klf4, c-Myc* and *Sox2* (OKMS) can reprogram somatic cells into pluripotent stem cells *in vitro* (Takahashi *Cell* 126, 2006). As shown recently for different tissues, *in vivo* expression of those factors can enhance regeneration and improve outcome after injury through partial cellular re-programming (Hishida *Cell Rep*. 39, 2022), even in non-mitotic cells (Lu *Nature* 588, 2020). In order to apply this approach to podocytes and examine effects of OKMS on podocyte regeneration, we employed a podocyte-specific injury model (Guo *J Am Soc Nephrol* 23, 2012) and crossed it with a conditional and inducible OKMS mouse model, thereby generating podocyte-specific expression of the *Yamanaka* factors.

Methods: We crossed the previously published inducible diphtheria toxin receptor-mouse (Buch *Nat Methods* 2, 2005) with a Podocin-Cre recombinase mouse (Moeller *Genesis* 35, 2003), and further with the ROSA26-rtTA(neo); OKMSCh250-mouse (JAX stock #031012). We induced OKMS-expression *in vitro* in extracted primary podocytes, as well as *in vivo* by 7-day application of doxycycline via drinking water. Furthermore, we determined urine albumin/creatinine ratios (ACR) and obtained histological samples to evaluate the extent of kidney injury after intraperitoneal diphtheria toxin (DT) injection in 5 different doses.

Results: To determine if OKMS can be induced, expression was first tested *in vitro.* Primary podocytes from $OKMS^{tg/WT}$; $rtTA^{fl/WT}$; Podocin-Cre^{+} - mice showed increasing *Oct4* and *Sox2* expression over time, but no expression of *Nanog* after 6 days and no decrease in podocyte-specific markers, whereas primary podocytes from a $OKMS^{tg/tg}$; $rtTA^{fl/WT}$; Podocin-Cre^{+} - mouse exhibited expression of *Nanog*, as well as a decrease of *Nphs1* and *Nphs2*, but an increase in *WT1*. *In vivo*, administration of 10 μg/kg and 7.5 μg/kg DT led to proteinuria with ACR levels over 50 g/g after 4 days as well as glomerulosclerosis and tubular casts on light microscopy after 4 weeks. Administration of 5 μg/kg, 2.5 μg/kg and 1.25 μg/kg showed later onset (d6), lower levels and, after 14 days, a reduction of proteinuria.

Conclusions: We, hereby, provide a suitable mouse model to study the effect of *Yamanaka*-expression in a podocyte-specific injury model.

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

TH-PO734

Deficiency of Melanocortin 5 Receptor Exacerbates Proteinuria and Podocytopathy upon Glomerular Injury

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Background: Converging evidence suggests that therapeutic targeting of nonsteroidogenic melanocortinergic pathways represents a novel strategy for treating proteinuric glomerulopathies. However, the type of melanocortin receptor (MCR) mediating this beneficial effect remains controversial and uncertain. Recent work indicates that MC5R is expressed in glomerular cells and MC5R signaling may be involved in glomerular pathobiology. This study examined the possible effect of MC5R ablation in nephrotoxic serum (NTS)-elicited podocytopathy.

Methods: NTS nephritis was induced in MC5R knockout (KO) mice and wild-type (WT) littermates. Additional WT mice received treatment with a highly selective MC5R agonist or vehicle before NTS injury. Proteinuria, podocyte injury and glomerular damage were evaluated early in the heterologous phase of NTS nephritis.

Results: Despite no discernible phenotypes under physiological conditions, KO mice sustained exacerbated glomerulopathy upon NTS injury, as shown by heavier albuminuria. This was associated with worsened glomerular pathology, characterized by glomerular hypercellularity, swelling of glomerular endothelial cells, and fibrinoid necrosis of glomerular capillary tufts, although glomerular depositions of the glomerular basement membrane-reactive heterologous rabbit IgG and the C5b-9 membrane attack complex along the glomerular capillary loops were found to be comparable between the WT and KO groups after NTS insult. In parallel, KO mice exhibited more severe podocytopenia than WT mice after NTS injury, as evidenced by reduced numbers of WT-1 positive cells in glomeruli, as well as worsened podocyte injury, marked by loss of glomerular expression of podocyte homeostatic proteins such as podocin and synaptopodin. Conversely, to test if activation of MC5R signaling is sufficient to protect against NTS-elicited podocytopathy, WT mice with NTS nephritis were subjected to MC5R agonism by using a peptidomimetic selective agonist. This resulted in an attenuated proteinuria and an improved podocyte injury, as evidenced by preserved expression of podocyte marker proteins.

Conclusions: Our findings suggest that MC5R-mediated melanocortinergic signaling protects against proteinuria and podocytopathy upon glomerular injury, and may be harnessed as an actionable target for treating proteinuric glomerulopathies.

Funding: NIDDK Support

TH-PO735

Lower NBL1 Increases Kidney Function in a Glomerular Damage Model

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Background: Increased serum levels of neuroblastoma suppressor of tumorigenicity 1 (NBL1) have been associated with a faster decline in kidney function in patients with diabetic nephropathy (DN), and *in vitro* experiments suggest higher NBL1 levels lead to podocyte apoptosis. We aim to test whether there is a causal relationship between NBL1 and CKD by manipulating *Nbl1* expression.

Methods: We generated an *Nbl1* heterozygous knockout (HET) model in the C57BL/6J background (homozygous knockout is not viable) and confirmed lower NBL1 levels in these mice. We tested two kidney damage models. In the first model, we induced tubular damage using a low-dose cisplatin protocol. In the second model, we induced glomerular damage by introducing a *Col4a5* mutation through breeding.

Results: In our tubular damage model, we did not find differences in renal phenotypes between the HET mice and wildtype (WT) littermates. Bulk RNA-seq also showed no differences between the two groups. However, in our glomerular damage model, HET mice have a higher glomerular filtration rate than their WT littermates. The kidneys show no difference in glomerular damage at the gross histological level, but a more detailed study of the podocytes is ongoing. In addition, bulk RNA-seq showed approximately 130 differentially expressed genes between the two groups, including *Jun, Junb, Fos, Fosb, Egr1, Egr2,* and *Egr3,* which encode transcription factors implicated in the pathogenesis of DN.

Conclusions: Our preliminary results suggest that NBL1 is causal for decreased kidney function only in the model defined by glomerular pathology. Our next steps aim to determine what drives increased NBL1 expression, and the source of serum NBL1.

TH-PO736

Podocyte-Specific NRF2 Activity Protects Against Adriamycin-Induced Kidney Injury

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Background: NRF2 is a key regulator of antioxidant and detoxification pathways in the kidney. KEAP1 is an endogenous inhibitor of NRF2. Various cellular stressors alter KEAP1 binding to NRF2, leading to NRF2 nuclear translocation and upregulation of target antioxidant and detoxification genes. Unexpectedly, NRF2 enhancers increased proteinuria in CKD clinical trials. Our prior work also demonstrated that global NRF2 enhancement exacerbates proteinuria in mouse models of glomerular disease. The kidney cell(s) mediating these effects are not known. Since podocytes are key cells maintaining the glomerular filtration barrier, we hypothesized that podocyte-specific NRF2 activity exacerbates proteinuria and glomerular injury.

Methods: We generated podocyte-specific KEAP1 knockout mice (Podo-KEAP1 KO) by crossing *Podocin-Cre* mice with *Keap1* floxed mice. These mice exhibit increased NRF2 activity only in podocytes. We subjected Podo-KEAP1 KO and control littermates to either adriamycin or chronic angiotensin II infusion to induce glomerular injury and proteinuria. Kidney injury was assessed by histologic, biochemical, and molecular indices.

Results: Contrary to our expectations, Podo-KEAP1 KO mice were protected against adriamycin-induced kidney injury, as demonstrated by lower levels of proteinuria, the injury marker NGAL, and fibrosis. Results from glomerular isolates reveal significantly increased antioxidant (*Nqo1* and *Cat*) and a trend to decreased inflammatory responses (*IL-1β*) that may protect Podo-KEAP1 KO mice from adriamycin injury. However, in the angiotensin II model there was neither improvement nor worsening of disease.

Conclusions: Although prior work demonstrated that global NRF2 enhancement worsens proteinuric CKD, we now show that podocyte-specific NRF2 enhancement protects against adriamycin-induced injury. This may be due to a specific effect of podocyte NRF2 activity to reduce glomerular oxidative stress in this model. Lack of effect in the angiotensin II model suggests a different mechanism of injury. Non-podocyte effects must also mediate CKD exacerbation in both models when NRF2 is globally enhanced. Future studies will determine the cell- and disease-specific effects of NRF2 in CKD and whether podocyte-specific NRF2 can be targeted therapeutically.

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TH-PO737

14-3-3 Proteins Stabilize Vimentin and Actin Filaments to Maintain Primary and Foot Processes in Podocyte

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Background: 14-3-3 proteins are a ubiquitously expressed family of adaptor proteins. Despite exhibiting high sequence homology, several 14-3-3 isoforms have isoform-specific binding partners and roles. We reported that 14-3-3β interacts with FKBP12, a binding protein of tacrolimus, and synaptopodin (Syp) to maintain the structure of actin fibers in podocytes (Yasuda et al., FASEB J, 2021). However, the functions of 14-3-3 proteins in podocyte are not fully elucidated. The precise localization and differential role of 14-3-3 isoforms in glomeruli are also unclear.

Methods: mRNA expression of 14-3-3s in kidneys was analyzed with RT-PCR, and their localization was investigated with immunohistochemical analyses. The interaction of 14-3-3s was analyzed by immunoprecipitation assay with the lysate of cultured podocytes and HEK-transfected cells. The effect of 14-3-3 isoform-specific siRNAs was analyzed in cultured podocytes. The expression of 14-3-3s in podocyte injury models was analyzed.

Results: 14-3-3β and 14-3-3σ were abundantly expressed in glomeruli. 14-3-3β in glomeruli was restricted in podocytes. 14-3-3σ in glomeruli was expressed in podocytes and mesangial cells. 14-3-3β was dominantly co-localized with FKBP12 in the foot processes, and a part of 14-3-3β was co-localized with Par3 at the slit diaphragm. 14-3-3β interacted with Par3, and the interaction was decreased by the transfection of FKBP12. The interaction of Par3-Par6 was enhanced by the treatment of 14-3-3β siRNA (3 times to normal, $p<0.05$). The structure of F-actin was deranged (score 1.8 vs. 3.1 of normal, $p<0.05$), and process formation was impaired (46.5% to normal, $p<0.005$) in the podocytes treated with 14-3-3β siRNA. 14-3-3β and Syp expression was decreased in podocyte injury models. 14-3-3σ in podocytes was expressed in the primary processes. 14-3-3σ interacted with vimentin but not with the actin-associated proteins FKBP12 and Syp. The structure of vimentin fibers was deranged (65.2% to normal, $p<0.05$), and process formation was impaired (40.1% to normal, $p<0.005$) in the podocytes with 14-3-3σ siRNA. 14-3-3σ and vimentin expression was increased in the early phase of podocyte injury but was decreased in the late stage.

Conclusions: 14-3-3 proteins play the roles in maintaining the primary and foot processes by stabilizing vimentin and actin filaments in podocyte.

Funding: Government Support - Non-U.S.

TH-PO738

COVID-19 Unmasking Concurrent IgA Nephropathy and Minimal Change Disease

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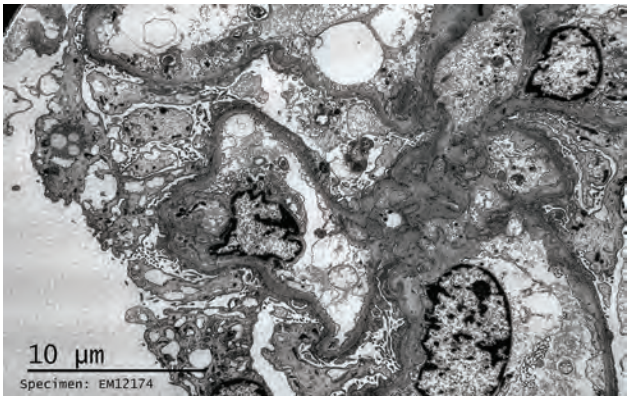
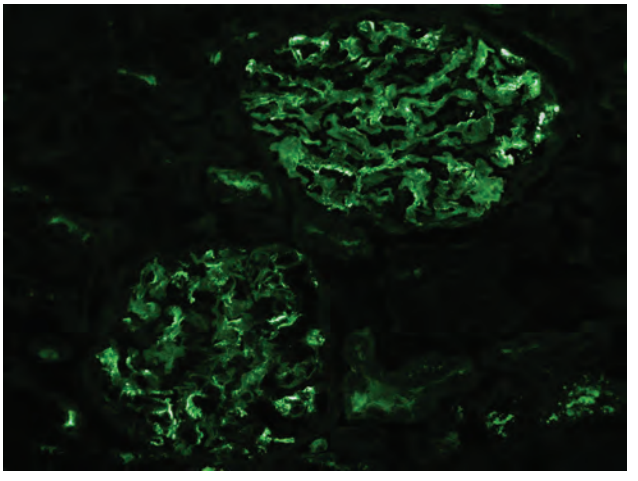
Introduction: The existence of concurrences of Minimal Change Disease (MCD) and IgA nephropathy (IgAN) is exceedingly rare. This is an unusual case of COVID-19 unmasking a dual glomerulopathy of MCD and IgAN.

Case Description: 54-year-old Asian female presented with flu-like symptoms, worsening anasarca, and bubbly urine. She was hemodynamically stable on room air. Exam was pertinent for lung crackles, edematous eyelids, and +2 lower extremities edema. Labs showed BUN 50mg/dL, creatinine (Cr) 2.9mg/dL, and albumin 0.8mg/dL. Baseline Cr was 0.61mg/dL. Urine analysis showed >300mg/dL proteins with large blood and dysmorphic RBC. A spot urine protein 5065.9 mg/dL and Cr 389 gm/dL. COVID-19 was positive. Glomerulonephritis panel was negative. Kidney biopsy under immunofluorescence microscopy showed diffuse segmental granular mesangial staining +2 IgA. Electron Microscopy showed extensive effacement of podocyte foot processes (> 90%) with dense deposits in the mesangium. Concurrence of IgAN and MCD was diagnosed and she was started on prednisone and lisinopril.

Discussion: This highlights the rarity of the co-existence of two glomerular diseases with COVID-19. We postulate the likelihood that our patient had long-standing IgAN given the disease's indolent course, followed by the development of MCD from COVID-19 infections. There have been similar cases showing the concurrence of the two diseases, but there has been no report with COVID-19 infection. After treating the patient with steroids for total of 3 months, our patient was able to successfully remain in remission.



Foot process effacement



IgA immune deposits

TH-PO739

Selected Renal Cells Express a Podocyte-Parietal Epithelial Cell Transcriptome

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Background: Selected renal cells (SRCs) express podocyte, ureteric bud and cap mesenchyme markers and in models of chronic kidney disease (CKD) their administration is associated with improved glomerular barrier function, renal filtration, and preservation of renal microarchitecture and glomerular integrity. We tested the hypothesis that SRCs

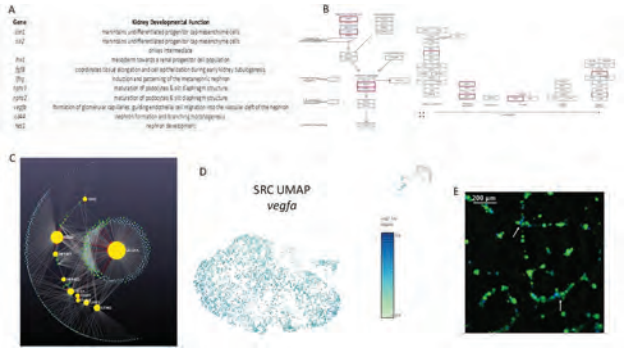
share a podocyte-parietal epithelial cell (PEC) transcriptome associated with renal repair and restoration.

Methods: The intersection set of podocyte-PEC genes (literature) and directionally aligned SRC genes were seeded into miRNet and Cytoscape for visualization of the shared transcriptome and identification of its functional attributes. Human SRCs (National Disease Research Interchange kidneys) were submitted to scRNA-seq to map gene expression and placed in culture and the supernatant queried for secreted vascular endothelial growth factor A (VEGFA) and its angiogenic activity using a human umbilical vein endothelial cell (HUVEC) tube formation assay.

Results: *osr1*, *six2*, *lhx1*, *fgf8*, *lfng*, *nphs1*, *nphs2*, *vegfa*, *cd44* and *hes1* are expressed by both podocyte-PEC and SRCs and involved in kidney developmental functions including maintenance of undifferentiated nephron precursors, tube and nephron formation, maturation of the glomerular barrier and formation of the glomerular capillary bed (A, B). *Vegfa* emerged as the hub gene within this network (C). SRCs expressed *vegfa* (D) and secreted VEGFA (0.75 to 3.02 ng/mL, mean=1.45 ng/mL) whose angiogenic activity was evidenced by HUVEC tube formation (E).

Conclusions: A *Vegfa* anchored podocyte-PEC transcriptome expressed by SRCs may recapitulate events associated with kidney development and mediate the preservation or improvement of glomerular integrity, renal microarchitecture and renal filtration observed in CKD models.

Funding: Commercial Support - ProKidney



(A, B) SRCs express podocyte-PEC genes involved in kidney development including glomerular development. (C) The shared podocyte-PEC and SRC transcriptome. (D) *Vegfa* is expressed by SRCs whose secreted gene product is associated with tube formation in HUVECs (E, arrows).

TH-PO740

Podocyte Density, Rather than Podocyte Number per Glomerulus, Is Associated with Kidney Outcomes in Obesity-Related Glomerulopathy

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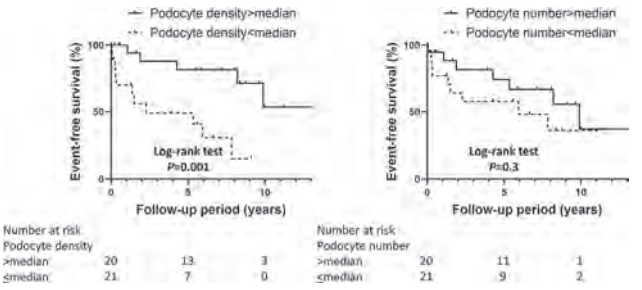
Background: Obesity-related glomerulopathy (ORG) is a slowly progressive glomerular disease occurring in obese individuals. Podocyte injury and subsequent podocyte depletion are regarded as key processes in ORG progression. However, no previous study has assessed the longitudinal association between podometrics and long-term kidney outcomes in ORG.

Methods: Podocyte number per glomerular volume (podocyte density) and podocyte number per glomerulus (podocyte number) in ORG patients were estimated using model-based stereology. The associations between these podometrics at the diagnostic biopsy and subsequent kidney outcomes (30% decline in eGFR) were examined by log-rank tests and Cox proportional hazard analyses.

Results: Forty-one ORG patients with median age of 47 years, eGFR 63 mL/min/1.73m^2 were analyzed. At biopsy diagnosis, ORG patients with podocyte density below the median value were older, predominantly male, and had larger body surface area, higher proteinuria, larger glomeruli, and lower podocyte number than ORG patients with higher podocyte density. During a median follow-up period of 3.9 years, 16 (39%) ORG patients reached a 30% decline in eGFR. Kidney survival in patients with lower podocyte density was significantly worse than in patients with higher podocyte density ($P = 0.001$), but there was no significant association between kidney survival and lower vs higher podocyte number ($P = 0.3$). Cox hazard analyses showed that podocyte density, but not podocyte number, was associated with kidney outcome after adjustment for clinical factors, including age, sex, proteinuria, and eGFR.

Conclusions: Our results indicate that lower podocyte density, rather than lower podocyte number, is a high-risk factor for progression of ORG. Confirmation in other ORG cohorts and potential generalizability to other glomerular diseases will require further studies.

Funding: Government Support - Non-U.S.



TH-PO741

Deletion of Neph1: Important for Renal Filtration but Critically Decisive for Patterning of the Enteric Nervous System

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Background: The immunoglobulin superfamily (IgSF) is a diverse group of proteins defined by the presence of one or more immunoglobulin domains. Nephrin (*NPHS1*) and Neph1 (*NEPH1*) are two well-known members of the IgSF in the kidney. They are expressed on podocytes where they form the slit diaphragm through homophilic interactions between neighboring foot processes. While many reported mutations for *NPHS1* cause early-onset albuminuria leading to kidney failure, only two *NEPH1* mutations have been reported, resulting in later-onset albuminuria progressing to chronic kidney disease. Knockout (ko) models for *Nphs1* and *Neph1* both show albuminuria and perinatal death. However, it is unclear whether death is caused by the kidney phenotype. Nephrin is expressed in podocytes, pancreas, and cerebellum, while Neph1 has a broader expression in podocytes, lung, brain, heart, skeletal muscle, liver, pancreas, and gut.

Methods: Podocyte specific conditional ko of *Nphs1* and *Neph1*, constitutive ko of *Nphs1* and *Neph1*, expression analysis using in-situ hybridization. Perinatal mice underwent μMRI analysis and examination of the olfactory bulb (OB) and enteric nervous system using immunofluorescence (IF) and 3D reconstruction.

Results: By utilizing podocyte specific conditional ko models of *Nphs1* and *Neph1*, we can demonstrate that while *Nphs1*^{Pod} mice die perinatally, *Neph1*^{Pod} mice are viable with a median survival of 4.5 months, indicating that the kidney phenotype is not the cause of perinatal death. We found increased expression of *Neph1* in the OB of mouse embryos. Shortly after birth, we found Neph1 at the axon terminals of primary olfactory sensory cells in the ventromedial zone of the OB. We used olfactory marker protein (OMP) as an indirect marker for disturbed axonal guiding and found a condensed layer of OMP with insufficient transport to the specific glomeruli in *Neph1*$^{-/-}$ mice. Furthermore, μMRI of perinatal *Neph1*$^{-/-}$ mice revealed widened, fluid filled bowels. Using IF, we found a much wider ganglion network of the enteric nervous system in ileum and colon of *Neph1*$^{-/-}$ mice, suggesting a disturbed regulation of peristalsis.

Conclusions: We believe, this offers a plausible rationale for the perinatal mortality observed in *Neph1*$^{-/-}$ mice, as well as the low occurrence and hypomorphic characteristics of NEPH1 variants found so far in humans.

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TH-PO742

Identification of Intercellular Communication Involved in the Progression of Tubulointerstitial Fibrosis Common to Podocyte Injury and Ischemia-Reperfusion Injury Models

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Background: Tubulointerstitial fibrosis (TF) is the final common pathway of progressive chronic kidney disease. The fibrogenic niche, a specialized microenvironment that triggers the differentiation of myofibroblasts (MF), is one of the critical therapeutic targets for TF. However, it remains uncertain what kind of intercellular communication shapes the fibrogenic niche.

Methods: Podocyte-specific *Tln1* knockout (*Tln1* KO) in C57BL/6J background mice (*Tln1*$^{fl/fl}$ *Nphs2*^{rtTA} *TetO - Cre*) and an ischemia-reperfusion injury (IRI) model on C57BL/6 wild-type mice were used as animal models for TF. *Tln1*$^{WT/WT}$ *Nphs2*^{rtTA} *TetO - Cre* mice and sham-operated mice served as the controls. Kidney samples were collected on day 10 and week 5 after initiation of doxycycline induction for *Tln1* KO mice and on days 2, 5, and 14 for the IRI model. The kidney samples were subjected to several analyses, including single-cell RNA sequencing (scRNA-seq).

Results: Histological examinations and real-time PCR analyses confirmed the development of TF lesions at week 5 in *Tln1* KO mice and at day 14 in the IRI model. scRNA-seq analyses of a combined dataset from the two animal models identified 21 cell clusters. As TF progressed, clusters of injured proximal tubules (Inj-PT), impaired Henle's loops, MFs, and inflammatory cells appeared in common in both animal models. CellChat analyses of the inter-cluster communication revealed the closest communication between the Inj-PT and MF clusters. The communication between these two clusters included *Spp1-Itgb1/5* and *Pdgfa/b-Pdgfrb*, *Mdk-Sdc1/2/4*, and *Bmp6-Acvr1* signaling. The Inj-PT cluster expressed high levels of *Havcr1* that encodes kidney injury molecule 1.

Conclusions: These results indicated that *Havcr1*-positive proximal tubular cells communicate strongly with myofibroblasts in both animal models. Although further experiments are required, these intercellular communications may contribute to developing a fibrogenic niche.

TH-PO743

Interleukin (IL)-27-Induced Podocyte Injury in Minimal Change Nephrotic Syndrome (MCNS)

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Background: We have previously demonstrated that relapse in MCNS was associated with decreased monocyte expression of CD14 and downregulation of proinflammatory cytokines in lipopolysaccharide-stimulated monocytes. This study aimed to identify the dysregulated monokines in disease relapse and subsequently to investigate the proteinuria-inducing mechanism in an experimental rat model and cultured human podocytes.

Methods: Monocytes were isolated from 5 MCNS patients in relapse (MCNSrelapse) and remission (MCNSrem) using monocyte isolation kit II. Monocyte transcription profile was performed using Illumina Human Ref8 chips. Plasma IL-27 levels were measured in 14 MCNS patients in relapse and remission and 20 healthy controls. Experimental rat model was created through electroporation of IL-27 plasmid DNA in Wistar rats. The role of IL-27 in human podocytes was examined through cell RhoA/Rac1 and STAT1/3 activities. Statistical analysis was done using Mann-Whitney test and Wilcoxon signed rank test for paired data.

Results: Monocyte transcriptome in MCNSrelapse involved regulation of IL-1 signaling, RhoGTPases regulation of actin cytoskeleton, toll-interleukin receptor (TIR)-domain-containing adapter-inducing interferon-β (TRIF) and IFN-induction pathways. Analysis of monokine gene expression showed 2.7-fold increase in *IL27* expression in MCNSrelapse. Plasma IL-27 levels were also significantly higher in MCNSrelapse (1.56±0.19ng/ml) compared to MCNSrem (0.95±0.13ng/ml) (P<0.05) and controls (0.89±0.14ng/ml) (P≤0.01). Similarly, in an IL-27 overexpression rat model, both 24-hour urine albumin excretion (409±34 *vs* 251±34μg/24h, P=0.005) and plasma triglyceride levels (36±2 *vs* 27±2mg/dL, P=0.02) were significantly higher at Day 70, compared to control rats. This was associated with upregulation of glomerular pSTAT3 expression in IL-27 transfected rats. Additionally, IL-27 stimulation in human podocytes resulted in phosphorylation of both STAT1 and STAT3 as well as 1.56-fold increase in activated Rac1 levels.

Conclusions: corroborated in the IL-27 overexpression rat model demonstrating podocyte injury possibly through activation of STAT3 and Rac1 as shown on podocyte culture experiments.

Funding: Government Support - Non-U.S.

TH-PO744

Disrupting Circadian Control of Autophagy Induces Podocyte Injury and Proteinuria

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage-renal disease. The decrease in podocyte number or density is associated with DKD progression. Currently, there is a lack of effective methods of protecting podocytes or improving damage. The circadian clock exists with a wide range of biological process and controls numerous aspects of physiology to adapt the daily environmental changes caused by Earth's rotation. The renal clock plays an important role in maintaining tubular function, but its effect on podocytes remains unclear.

Methods: Adult C57BL/6J mice and podocyte specific *Clock* knockout mice (podocyte-*Clock*$^{-/-}$) were used to construct the type II diabetes model in vivo. Primary podocytes were cultured in 30mM high glucose. Chromatin immunoprecipitation (CHIP) qPCR analysis and dual-luciferase reporter gene assay were used to elaborate association between *Clock* and autophagy.

Results: The rhythmic oscillations of *Clock* were disappeared in high glucose treated podocytes and in glomeruli from diabetic mice. The podocyte specific *Clock* knockout mice at age 3 months and 8 months showed deficient autophagy, loss of podocytes and increased albuminuria. Chromatin immunoprecipitation (CHIP) sequence and PCR analysis indicated *Clock* binding to the promoter regions of Becn1 and Atg12. ChIP-qpcr analysis also confirmed the binding of *Clock* and autophagy gene promoter reduced when exposed to high glucose. Deletion *Clock* in podocyte could aggravate podocyte injury and proteinuria in diabetic mice. The autophagy in podocyte-*clock*$^{-/-}$ diabetic mice was lower than that of control diabetic mice.

Conclusions: Our findings demonstrate that *clock*-dependent regulating autophagy is essential for podocyte survival. The loss of circadian control autophagy plays an important role of podocyte injury and proteinuria.

Funding: Government Support - Non-U.S.

TH-PO745

Reduced Glycolytic ATP Production Is Responsible for Irreversible Podocyte Injury in Nephrotic Syndrome

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Background: Energy metabolism is essential for cellular function and homeostasis, and the kidney is a high energy-consuming organ, making it susceptible to injury during aberrant energy metabolism. Podocyte energy metabolism is also critical for homeostasis under physiological condition, but its role in stress condition, especially in nephrotic syndrome involving circulatory permeability factors, is unclear. Therefore, to clarify the role of energy metabolism in injured podocytes, we examined changes in podocyte energy metabolism by circulating humoral factors of minimal change disease (MCD) or focal segmental glomerulosclerosis (FSGS).

Methods: Cultured human podocytes were treated with biopsy-proven MCD and FSGS patients' or healthy subjects' sera, analyzed for cell apoptosis by flow cytometry, and real-time ATP production rates in glycolysis and mitochondrial respiration using a Seahorse Extracellular Flux Analyzer. In addition, metabolomic analysis of serum-treated podocytes by GC-MS was performed to obtain an overview of energy metabolism. Isolated mouse glomeruli from Adriamycin nephropathy were also evaluated.

Results: FSGS patients' sera significantly induced apoptosis in human podocytes compared to MCD patients' or healthy subjects' sera. There was a correlation between decreased glycolytic ATP production and the rate of cell apoptosis in podocytes treated with FSGS patients' sera. In addition, treatment with low concentrations of glycolytic inhibitors further induced podocyte apoptosis, despite increased mitochondrial ATP production in podocytes treated with MCD patients' sera. Metabolomic analysis also showed that glycolytic metabolites were reduced in podocytes treated with FSGS patients' sera compared to MCD. Glycolytic enzymes were also decreased in mouse glomeruli isolated from Adriamycin nephropathy.

Conclusions: These data suggest that irreversible podocyte injury is associated with disruption of metabolic compensatory mechanisms, particularly reduced glycolytic ATP production.

Funding: Government Support - Non-U.S.

TH-PO746

STING Activation by Mitochondrial DNA Triggers Podocyte Injury in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) remains the most common cause of end stage kidney disease in the USA, and is characterized by mitochondrial dysfunction, increased circulating serum mtDNA levels, and activation of STING, a DNA-sensing innate immune adaptor, expressed in podocytes. Mitochondrial DNA (mtDNA) has been previously described to activate STING signaling in renal tubular cells in DKD, leading to autoinflammation. We hypothesize that loss of mitochondrial transcription factor A (TFAM) and impairment of PTEN-induced putative kinase 1 (PINK1) mediated mitophagy triggers mtDNA leakage and causes podocyte injury in DKD.

Methods: 16-week-old control (db/+) and diabetic (db/db) mice were used. Glomeruli were isolated to determine the expression of OXPHOS complex subunits, TFAM, PINK1 and TOM20, a biomarker for mitochondrial mass. Mitochondrial morphology was evaluated by TEM. Free mtDNA levels were measured in plasma, urine and cytosolic fractions from kidney cortex. Treatment with nuclear DNA (nDNA) or mtDNA was performed *in vitro*(10 ng, 30 min) using immortalized control human podocytes and *in vivo* (5 mg/kg, 24h) using control and STING knockout mice, followed by pSTING/STING expression and phenotypical analyses.

Results: We found that db/db mice have decreased glomerular TFAM expression and increased PINK1 expression in the mitochondrial fraction of db/db mice kidney cortices. Mitochondria morphology was indicative of dysfunction on TEM analysis, which was confirmed by increased expression of OXPHOS complex II (SDHA), and loss of mitochondrial mass marker TOM20. Db/db mice were also found to have increased mtDNA in the cytosol of kidney cortices, as well as in blood and urine. Treatment with mtDNA led to increases in pSTING expression *in vitro* and the development of albuminuria and foot process effacement *in vivo*, while STING -/- mice were protected from renal injury.

Conclusions: Our data suggest that loss of TFAM accumulation of PINK1 contribute to pathologic leakage of mtDNA into the circulation and cytosol causing albuminuria and podocyte injury.

Funding: NIDDK Support, Private Foundation Support

TH-PO747

RIPK3 Promotes Mitochondrial Fission and Dysfunction via PGAM5-Drp1 Signaling During Diabetic Podocyte Injury

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Background: Receptor-interacting protein kinase (RIPK)3 is an essential molecule for necroptosis and its role in kidney fibrosis has been investigated using various kidney injury models. However, the relevance and the underlying mechanisms of RIPK3 of podocyte injury in DKD are poorly understood. In this study, we investigated the role of RIPK3 in kidney injury of DKD and elucidated the underlying mechanism.

Methods: We evaluated the association of RIPK3 on clinical indices of DKD in the kidneys from diabetic patients and animals. To investigate the role of RIPK3 in glomerular damage of DKD, diabetes was induced by a high-fat diet in *Ripk3* knockout (KO) mice and cultured podocytes were stimulated with high glucose with or without RIPK3 inhibitor GSK872.

Results: RIPK3 level was upregulated in podocytes and plasma from human DKD cohort. Such upregulation was correlated with podocyte loss, albuminuria, and poor renal outcome. RIPK3 deficiency in DKD mice improved albuminuria, podocyte numbers, and renal histopathological features including foot process effacement and glomerular basement membrane (GBM) thickening. Increased mitochondrial fragmentation, upregulated mitochondrial fission-related proteins such as phosphoglycerate mutase family member 5 (PGAM5) and dynamin-related protein 1 (Drp1), and mitochondria dysfunction were decreased in RIPK3-depleted diabetic podocytes both *in vitro* and *in vivo*. By contrast, RIPK3 overexpression was sufficient to decrease oxygen consumption rate and increase PGAM5 expression and mitochondrial fragmentation due to mitochondrial translocation of Drp1.

Conclusions: RIPK3 is associated with diabetic podocytopathy, likely by regulating mitochondrial fission via PGAM5-Drp1 signaling. Targeting RIPK3 might be a promising therapeutic option for treating DKD.

Funding: Government Support - Non-U.S.

TH-PO748

Dapagliflozin Exerts Senomorphic Effects on Adriamycin-Induced Podocyte Injury via Modulation of Complosome

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Background: Recent clinical and experimental studies demonstrate that Sodium-glucose co-transporter 2 inhibitors (SGLT2i) exert reno- and cardiovascular protection independently of the hypoglycaemic effect. SGLT2i treatment rapidly reduces proteinuria preserving renal function in the long term. The mechanisms underlying the renal protection of SGLT2i are not fully understood. PODOs are the cornerstone of the glomerular filtration barrier, and podocytopathy is the principal cause of proteinuric glomerular diseases such as FSGS. In the present study, we attempt to verify if SGLT2i have a direct effect on Podocytes (PODO) after Adriamycin (ADR) injury investigating the underlying mechanisms.

Methods: Human-immortalized PODO and glomerular endothelial cells were used. Expression of SGLT2 Nephrin, Synaptopodin, p53, and $p21^{WAF1}$ on PODO was investigated with immunofluorescence (IF), Western Blotting (WB), and quantitative PCR (qPCR). After ADR damage, the SGLT2i (Dapagliflozin, Dapa) at 100 nM was used to treat PODO. The PODOs' actin cytoskeleton was evaluated. A PODO-endothelial cell co-culture device was used to test the albumin permeability (P_{alb}). Intracellular Complement activation (Complosome) was analysed by confocal microscopy.

Results: PODOs express SGLT2 receptor. Dapa significantly decreased P_{alb} provoked by ADR (ADR, 17%±5; ADR+Dapa, 2.5%±1, P<0.05) in vitro. Dapa repairs ADR-induced PODO injury by recovering of PODOs' F-actin, increasing Nephrin (mRNA: ADR, 0.04±0.01; ADR+Dapa, 0.29±0.13; P<0.05; protein: ADR, 0.21±0.02; ADR+Dapa, 0.57±0.3: P<0.05) and Synaptopodin (mRNA: ADR, 0.34±0.2; ADR+Dapa, 1.13±0.2; P<0.05; protein: ADR, 0.06±0.01; ADR+Dapa, 0.13±0.02; p<0.05). Importantly, Dapa down-regulates nuclear p53 (protein: ADR, 7.56; ADR+Dapa, 4.69) and $p21^{WAF1}$ (ADR, 1.93; ADR+Dapa, 0.76). Moreover, we found that ADR actives complosome with a significant increase in intracellular C5a but not C3a. Dapa can inhibit intracellular C5a activation, shifting from the intracellular compartment to the outer cellular membrane.

Conclusions: SGLT2i exerts senomorphic effects restoring ADR-induced PODO inflammation and counteract Podo senescence. The underlying mechanisms could be the inhibition of Complosome activation at the C5a level.

TH-PO749

The IgG Glycome Predicts Nephritis and Leads to Podocyte Injury in Systemic Lupus Erythematosus (SLE)

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Background: Lupus nephritis (LN) occurs in 50% of patients with systemic lupus erythematosus (SLE) for which we lack biomarkers, and an understanding of its pathogenesis. We have previously demonstrated that IgG in LN is aberrantly glycosylated and can injure podocytes.

Methods: We evaluated the IgG glycome by N-glycan profiling in a pediatric cohort of 40 children with SLE and 20 paired pre and post treatment LN samples using LS-MS Mass Spectrometery. We used enzymatic treatments to evaluate the role of glycans in podocyte injury. Data were analyzed using GEE analysis, Spearman test, t-test and regression analysis. Podocyte phenotype was evaluated by wound healing assay, cytoskeleton evaluation (F-actin) and podocyte specific proteins by RT-PCR and western blotting.

Results: We found that the overall glycosylation was reduced 6 months post treatment in patients with LN. Furthermore, those decorated with terminal galactose were increased while those with terminal sialic acid were reduced. In addition, neutral glycans were increased after treatment while negatively charged glycans were decreased. To evaluate whether these differences were due to treatment rather than LN activity, we analyzed the IgG glycome in SLE without LN, LN, LN in remission 6-month after treatment. We found that neutral glycans and negatively charged glycan chains changed with LN activity. Furthermore, the presence or absence of sialic acid and galactose correlated with parameters that influence active nephritis (renal SLEDAI, dsDNA, C3, cellular crescents and proteinuria). A switch from tri to bi -antennary complex type N-Glycans was noted in those with decling GFR. More interestingly, treatment of IgG with PNGase- F, which removes glycan chains, prevented cytoskeleton and motility changes in podocytes that were induced in LN. In addition, nephrin expression was preserved following PNG-ase treatment.

Conclusions: The IgG glycome in pediatric SLE patients is altered and is further aberrantly glycosylated in LN. The magnitude of change is associated with LN activity. More importantly, the glycans on IgG can lead to podocyte injury in LN. Our data shed light on the role of IgG glycosylation in the development of podocyte injury and propose the development of approaches using the IgG glycome to diagnose and monitor LN. Further, it highlights IgG glycosylation as an important pathogenic mechanism in LN.

Funding: Other NIH Support - NIAID K99 - 7K99AI162843-02, U54 GM104940

TH-PO750

Downregulation of TRPM4 and Consequent Increase in TRPC6 Activity Are Critical Initiation Events Leading to Podocyte Injury

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Background: TRPM4 was identified as a molecule downregulated in PAN nephropathy, a mimic of MCNS, by RNA-seq analysis. TRPM4, a member of TRP channels, is a monovalent cation channel, which facilitates Na+ influx, and consequently suppresses Ca2+ influx. We have reported that TRPM4 is restrictedly expressed at podocytes in glomeruli, and is mainly localized at the surface of the foot process just above the slit diaphragm. However, the function of TRPM4 in podocyte is not elucidated yet. TRPC6, a Ca2+ channel localized at the slit diaphragm, is also a member of TRP channels. It is accepted that increase in TRPC6 activity plays a critical role in several types of podocyte injury. However, no studies on the association of TRPM4 with TRPC6 have been reported.

Methods: Variants expression of TRPM4 was analyzed with RNA materials of human cultured podocyte. To analyze the relation between TRPM4 and TRPC6, gene silencing studies with siRNA were performed with cultured podocytes. The effect of 9-phenanthrol, a specific TRPM4 inhibitor on the expression of TRPC6 was analyzed. The kinetics of the expressions of TRPM4, TRPC6, and podocyte functional molecules were analyzed in cultured podocytes treated with adriamycin, a reagent that is capable of inducing FSGS-like podocyte injury by injection into rats.

Results: A unique TRPM4 variant, lacking exon 17, was expressed in podocytes. The expression of TRPC6 was altered in TRPM4-knockdowned podocytes, but TRPM4 expression was not altered in TRPC6-knockdowned podocytes. The 9-phenanthrol treatment clearly promoted the expression of TRPC6 (139.76% ± 5.49%, P < 0.05). TRPM4 was clearly downregulated (62.25% ± 7.74%, P < 0.01) and the expression of TRPC6 was increased (120.27 % ± 31.23%) at 14 hours after adriamycin treatment. At this time point, neither any morphological alterations nor altered expressions of podocyte functional molecules were detected yet.

Conclusions: The depletion assays with siRNAs suggested that TRPM4 is an upstream regulator of TRPC6. The study with 9-phenanthrol clearly showed that functional loss of TRPM4 promoted TRPC6 expression. It is conceivable that downregulation of TRPM4 and consequent increase in TRPC6 activity are critical initiation events leading to podocyte injury. TRPM4 is available as an early marker to detect podocyte injury.

TH-PO751

Nephrin, Podocin, and Neph1 Encoding mRNAs Are Dysregulated by Alternative Polyadenylation During Podocyte Injury

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Background: Podocyte injury and proteinuria are hallmark characteristics of glomerular disease. Nephrin, Podocin and Neph1 are critical regulators of the structure and function of podocytes and the glomerular filtration barrier. We hypothesized that these important components of the slit diaphragm could be dysregulated at the level of mRNA processing during podocyte injury and glomerular disease.

Methods: Glomerular alternative mRNA polyadenylation was detected using APATrap analyses of the RNASeq data from puromycin aminonucleoside (PAN) and adriamycin (ADR)-induced nephropathy models of podocyte injury and glomerular disease, mimicking human minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), respectively.

Results: *Nphs1* (encoding for Nephrin) mRNA presented with a significant shift from proximal to distal usage of the polyadenylation [p(A)] site in its 3' untranslated region (3' UTR) in both PAN (12.7% shift vs healthy control) and ADR (24% shift vs. healthy control) -induced glomerular disease models. The Nphs1 mRNA p(A) shift to distal site and lengthening of the 3'UTR during injury was also validated by 3' Rapid Amplification of cDNA Ends assay. In contrast, a reverse shift was detected on the *Nphs2* (encoding for Podocin) mRNA in the ADR-induced nephropathy model (9.2% shift vs healthy control) only. The p(A) shift in *Nphs1* mRNA to a more distal site during injury results in introduction of target sites for miRNAs (miR-376a-5p, miR-466c-5p and miR-466d), which might affect its localization, stability and translation. Neph1 mRNA also showed a shift to a more distal site (~13% shift vs healthy control) in both PAN and ADR -induced glomerular disease models, exposing additional 415 nucleotides to miRNA targeting. On the other hand, a shift in *Nphs2* p(A) site from distal to proximal during injury results in introduction of the p(A) site in its last coding exon upstream of the STOP codon, which might affect its stability by the mRNA non-STOP decay pathway.

Conclusions: Alternative mRNA polyadenylation of *Nphs1, Nphs2 and Kirrel* mRNAs during podocyte and glomerular injury could result in their altered levels or function, with potential implications towards the dysregulation of podocyte structure and function and disruption of glomerular filtration barrier.

Funding: Private Foundation Support

TH-PO752

Podocyte Injury in Human Primary Membranous Nephropathy: Evidence Supporting a Role for Complement

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Background: Primary membranous nephropathy (PMN) is the leading cause of nephrotic syndrome in adults and a common cause of end-stage kidney disease (ESKD). The Heymann's nephritis rat model of PMN shows that proteinuria is complement-mediated. However, the pathogenetic role of complement in human PMN remains unclear. We aim to demonstrate that complement activation can have both structural and functional effects on podocytes.

Methods: An in-vitro model of immortalized human podocytes (from Moin Saleem, Bristol, UK) was used for all the experiments. Cells were exposed to 25% serum of 19 PMN patients (from the Toronto Glomerulonephritis Registry). Complement deposition was detected by immunofluorescence (IF). As positive control, cells were pre-sensitized with anti-CD59 and exposed to 25% normal human serum (NHS) to induce complement activation. Changes in intracellular calcium were monitored using a fluorescent dye (Fluo 8-AM), acquiring images every 20 seconds (up to 10 minutes) by confocal microscopy. Calcium effects on mitochondrial membrane potential were measured by flow cytometry. Intracellular adenosine triphosphate (ATP) changes were analyzed by bioluminescence. Actin cytoskeleton re-arrangements were evaluated by IF. Wound healing assays were performed to study functional effects on cell migration.

Results: Incubation with 25% PMN serum led to deposition of both C3b and C5b9 on the cell surface, which was significantly higher compared to controls ($p < 0.05$). Complement activation induced a significant rise in the intracellular calcium levels. Loss of mitochondrial membrane potential was also observed, together with intracellular ATP decrease, disruption of the actin cytoskeleton and impaired cell migration. Effects of both structure and function of podocytes were reversed by inhibition of the terminal complement pathway.

Conclusions: Complement is active in PMN, leading to both structural and functional effects on podocytes. Effects can be reversed by inhibition of the terminal complement pathway. Further studies are needed to fully understand the consequences of complement activation on the podocyte energy machinery and the rationale for the use of complement inhibitors in PMN. Our research may identify novel molecular treatment targets with the potential of improved patient outcomes and quality of life.

TH-PO753

Podocyte Injury Marker EGR1 in Lupus Nephritis

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Background: We have discovered that early growth response 1 (EGR1) is expressed in injured podocytes from an early stage in animal studies. Additionally, we have observed that EGR1 expression in podocytes correlates with proteinuria, urinary nephrin/podocin mRNA levels, and glomerular podocin expression in patients with glomerular diseases. These findings suggest that EGR1 could potentially serve as a marker of podocyte injury. The objective of this study is to investigate the relationship between EGR1 expression in podocytes and the activity of lupus nephritis (LN).

Methods: We recruited patients diagnosed with LN by kidney biopsy at Jikei University Hospital, Tokyo, between January 2001 and March 2020. Patients under 20 years and those with fewer than 8 glomeruli were excluded. We collected the SLE disease activity index (SLEDAI), estimated glomerular filtration rate (eGFR), and urinary protein excretion (UPE) levels from the patients' medical records during kidney biopsy. We measured the percentages of glomeruli with podocytes expressing EGR1 (%EGR1glo), sclerotic glomeruli (%GS), glomeruli with endocapillary hypercellularity (%Endo), and glomeruli with cellular/fibrocellular crescents (%Cres), as well as tubulointerstitial damage from the kidney biopsy specimens. %EGR1glo was compared with these parameters using Spearman's rank correlation coefficient, and %EGR1glo between LN classes was compared using the Kruskal-Wallis test. Multiple comparison corrections were conducted using Holm-Bonferroni method.

Results: Seventy-five patients were included in this study (84% female, median age 38 [interquartile range 31–50] years, SLEDAI 17 [14–22], eGFR 86 [60–103] mL/min/1.73 m^2, UPE level 1.49 [0.57–3.23] g/d, and %EGR1glo 14.3 [8.8–28.6]%). LN classes were 4% Class I, 8% Class II, 44% Class III, 36% Class IV, and 8% Class V. %EGR1glo showed correlations with SLEDAI, eGFR and UPE level (rho = 0.419, -0.358, and 0.45; P = 0.003, 0.018, and <0.001, respectively). In the histological analysis, %EGR1 was significantly higher in Class IV than in the other classes (vs Class I + II, P <0.001; vs Class III, P <0.001: and vs Class V, P = 0.004). %EGR1glo correlated with %Endo and %Cres (rho = 0.566 and 0.586; P <0.001 and <0.001, respectively), but not with %GS or tubulointerstitial damage.

Conclusions: EGR1 expression in podocytes was associated with the activity of LN, especially with acute lesions.

Funding: Government Support - Non-U.S.

TH-PO754

Podocyte Injury Induces Rapid Collagen Degradation Within Mesangial Cells

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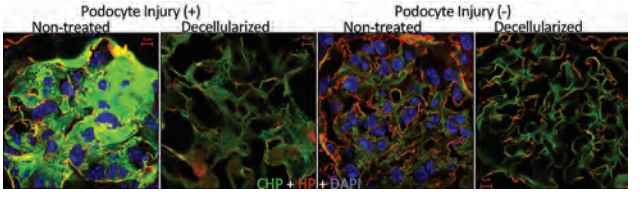
Background: Glomerulosclerosis, characterized by accumulation of extracellular matrix (ECM) proteins, is primarily caused by podocyte injury. In our investigation of mouse model of podocyte injury, we frequently observed mesangiolysis in sclerotic glomeruli. Our hypothesis is that mesangial collagen undergo degradation subsequent to podocyte injury. This study aimed to characterize the process of collagen degradation following podocyte injury.

Methods: Podocyte injury was induced in transgenic mice expressing hCD25 in podocytes through the injection of hCD25-directed immunotoxin, LMB2. Denatured collagen was visualized using Collagen hybridizing peptide (CHP), a specific binder of unfolded collagen chains, and imaged with LSM880. Collagenolytic activities was assessed by quenched fluorogenic DQ-Gelatin or DQ-Collagen IV.

Results: CHP staining was intensified in glomeruli seven days after the induction of podocyte injury preceding the establishment of sclerotic lesions. The intensity of glomerular CHP staining correlated with the severity of glomerular injury and was localized in mesangial cells labeled by Itga8. Notably, intense glomerular CHP staining was absent in decellularized sections, while hydroxyproline (HP) staining persisted (Figure). The primary CHP staining was partially co-localized with MEK1/2 or GAPDH, but not with LAMP1, a lysosome marker, or with ERp72, an ER marker, suggesting that CHP is present in the cytoplasm. Collagenolytic activity in glomeruli with podocyte injury was found to be elevated in parallel with CHP staining.

Conclusions: These findings indicate that podocyte injury triggers and promotes degradation of collagen and accumulation of denatured collagen within mesangial cells. Further investigation is required to elucidate the detailed process involved.

Funding: Government Support - Non-U.S.



Figure

TH-PO755

The Mouse Nephrotoxic Serum (NTS) Model to Screen Novel Drugs for Reversal of Podocyte Injury

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Background: Kidney podocyte drug targets are being studied for treatment of diabetic kidney disease (DKD) and chronic kidney disease (CKD), requiring screening models to triage agents for efficacy testing. Nephrotoxic serum (NTS) causes nephritis driven by immune complex-mediated inflammation of the kidneys. Methods of induction vary widely: kidney immunogen used, source of serum, presence of adjuvant or pre-immunization, dose of NTS, and/or mouse strain. A new batch of commercially available NTS (Probetex, San Antonio, TX) has been validated for rats but not mice. Characterization of this mouse model will facilitate rapid screening podocyte targeting agents for DKD/CKD.

Methods: An IV dose range of new Probetex NTS was tested in four strains of mice. Female C57Bl/6 and DBA/1 mice were chosen for more testing. Kidney injury model induction was tested using single or multiple sequential daily NTS injections. Disease model severity was assessed measuring serum creatinine, BUN, urine albumin to creatinine ratio (UACR) and Luminex Kidney Injury Panels. Upon establishing mouse strain sensitivity to NTS, the effect of clinically approved standard of care agents lisinopril or losartan to preserve kidney function was assessed.

Results: One dose of new NTS did not replicate reported body weight effects in mice; small UACR effects were noted but less than published literature. In contrast, two or three daily NTS injections caused an increase serum creatinine, BUN and UACR, with sensitivity of DBA1 mice being greater than C57 mice. Comparing fold-increase in UACR to PBS control mice, two doses of NTS induced 6.8±1.7 and 149±64 fold-increases, and three doses of NTS induced 217±36 and 292±117 fold-increases, in C57 and DBA1 mice respectively. Lisinopril or losartan treatment were both able to attenuate the NTS-induced kidney injury by over 65%, as assessed by UACR changes, in either 2- or 3-dose NTS injury paradigms in DBA1 mice, with a concomitant improvement in tissue histopathology.

Conclusions: The new Probetex NTS was validated for use in mice to generate a screening model for podocyte injury. The differential sensitivity of C57 vs DBA1 mice, and the ability to alter the disease severity in each model by modifying the NTS-injection protocol will permit tailoring the degree of injury relevant to the research question.

Funding: Commercial Support - Janssen Pharmaceutical Companies of J&J

TH-PO756

Nucleophosmin Translocation Detects Early Podocyte Injury

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Background: Podocyte loss is common in diverse glomerular diseases. However, the lack of injury markers limits elucidation of the pathophysiologic processes that cause podocyte loss. Nucleophosmin (NPM) mediates regulated kidney cell death, and its translocation from the nucleus to the cytosol is an early marker and trigger of ischemic injury in tubular epithelial cells. Based on these observations, we tested the hypothesis that NPM translocation reflects podocyte injury. In our preliminary study, we detected NPM translocation as a novel marker of podocyte injury in cell injury models, and in human glomerular disease.

Methods: In vitro, podocytes were exposed to diverse insults known to injure podocytes including oxidative stress, adriamycin, and hyper-osmolarity. NPM translocation was evaluated by immunofluorescence and immunoblotting of cytosolic podocyte extracts. To assess NPM translocation in humans, kidney biospy tissue from diabetic nephropathy patients was stained for NPM and established podocyte markers.

Results: NPM translocation was detected in cultured podocytes after oxidative stress, or exposure to either adriamycin, or hyper-osmolarity (Figure 1). Podocyte NPM translocation was also observed in patients with established diabetic kidney disease (Figure 2).

Conclusions: NPM translocation reflects acute podocyte injury in vitro and podocyte injury in diabetic glomerulopathy. Regulated cell death mediated by NPM may be a primary pathologic mechanism of podocyte loss. NPM is also a rational therapeutic target in glomerular diseases to reduce the dropout of the limited number of podocytes residing in the human kidney.

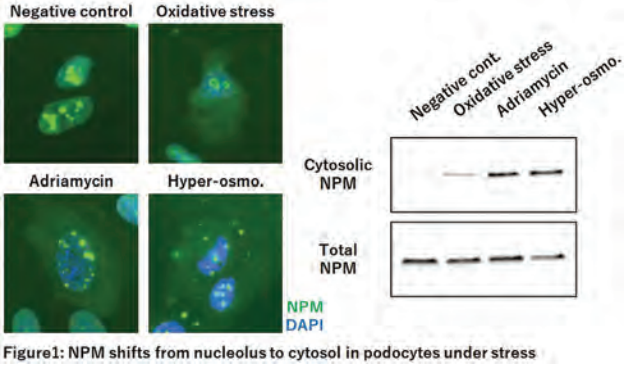

Figure1: NPM shifts from nucleolus to cytosol in podocytes under stress

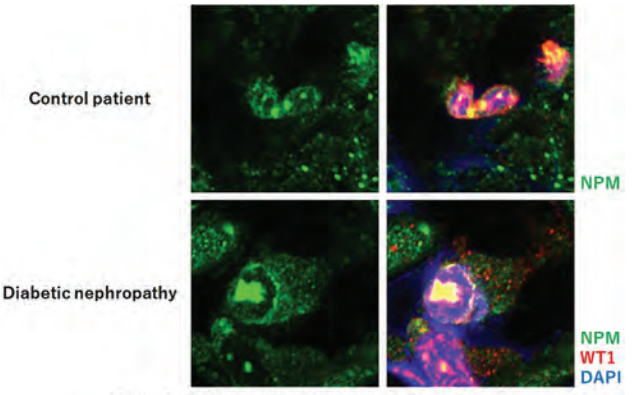

Figure 2: NPM translocation in diabetic nephrpathy

TH-PO757

Targeting Membrane Lipid Peroxidation Rescues Podocyte Dysfunction in Cystinosis

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Background: Cystinosis is a rare, incurable, autosomal recessive lysosomal storage disease caused by mutations in the *CTNS*$^{-/-}$ gene and leading to lysosomal cystine accumulation in all cells of the body. While cystinosis is considered as a prototype of proximal tubular dysfunction, the disease also affects glomerular podocytes and presents with increased podocyte losses into urine and glomerular proteinuria at early disease stages. Cysteamine, the current standard of care treatment, decreases lysosomal cystine accumulation but does not reverse podocyte injury. Thus, we aimed at investigating other pathogenic mechanisms than mere cystine accumulation involved in glomerular dysfunction in cystinosis.

Methods: Immortalized cystinosis patient-derived podocytes, healthy podocytes and *CTNS*$^{-/-}$ knockdown podocytes were used and the results were validated in our newly in-house developed fluorescent ctns$^{-/-}$ zebrafish larvae model (l-fabp:DBP-eGFP;CTNS). To understand the impaired podocyte functionality, static and dynamic permeability assay, tracer metabolomics analysis (LC-MS), flow cytometry, RT-qPCR, western blot, chemical and dynamic roGFP2 redox-sensing fluorescent probes were used.

Results: Cystinosis podocytes present decreased adhesion, increased permeability and enhanced ferroptosis cell death caused by an accumulation of mitochondrial ROS-driven lipid membrane peroxides. Moreover, these cells show fragmented mitochondrial network with impaired energy and TCA cycle metabolism and decreased expression of superoxide scavenging enzyme SOD2. Targeting mitochondrial ROS with MitoTEMPO in combination with cysteamine or lipid peroxidation with Liproxstatin-1 improved podocytes dysfunction *in vitro* and rescued proteinuria in cystinosis zebrafish larvae.

Conclusions: Mitochondrial dysfunction leading to increased ROS production and subsequent lipid peroxidation drive podocyte detachment and ferroptosis and plays a key role in podocyte injury in cystinosis. Targeting these mechanisms represents a new therapeutic prospective for nephropathic cystinosis.

TH-PO758

Exploring the Pathogenicity of an Anillin Coding Variant in Proteinuric Kidney Disease

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Background: Mutations in slit diaphragm proteins and regulators of actin dynamics are implicated in the pathogenesis of proteinuric kidney disease (protKD). Coding variants of Anillin (ANLN), a scaffolding protein found at slit diaphragms, have been associated with FSGS, but mechanisms are unknown. The aim of this study is to investigate the pathogenicity of ANLN coding variants identified in individuals with protKD.

Methods: Expression of ANLN relative to proteinuria was assessed in bulkRNAseq profiles of microdissected kidney tissues from NEPTUNE (n=238 glom, n=316 tub) and living donor (n=8, 10) cohorts. WGS data in NEPTUNE (n=620) were interrogated for ANLN coding variants; allele frequencies were compared to gnomeAD. Kidney organoids

(hKO) were generated from an iPSC line from a NEPTUNE participant harboring an ANLN coding variant and scRNA-seq (Sc) performed. Cell junction integrity and cytoskeletal dynamics were assessed by IF and live imaging in *Xenopus laevis* embryonic epithelial cells following morpholino knockdown of ANLN and replacement with ANLN WT or coding variant.

Results: Kidney tissue ANLN mRNA expression correlated with UPCR and negatively with eGFR. Ten previously uncharacterized variants of ANLN were found in 16 NEPTUNE individuals; 6 harbored one missense mutation (rs141247770) resulting in an I1109V substitution in the pleckstrin homology (PH) domain, which binds phospholipids. Sc profiling of hKO ANLN I1109V versus WT epithelial cells revealed perturbation of YAP and MAPK8 signaling pathways. Live imaging of *X. laevis* embryos expressing the ANLN variant revealed disrupted tight junction (ZO-1) integrity plus abnormalities in junctional F-actin and cell size and shape.

Conclusions: Our protKD cohort data are consistent with prior animal models showing that perturbed ANLN expression is associated with kidney disease. Functional studies in hKO and *Xenopus* models harboring the ANLN variant within the PH domain revealed disrupted cell-cell junction integrity, cytoskeletal dynamics, cytokinesis, and several dysregulated signaling pathways. Together, our findings reveal that alterations in both ANLN expression levels and function are critical in the pathogenicity of proteinuric kidney disease.

Funding: NIDDK Support, Other NIH Support - NCATS

TH-PO759

A Modular Intracellular Hierarchical-Responsive Nanocarrier Enables Dual Targeting for High Therapeutic Efficacy in Kidney Diseases

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Background: Single-drug nanocarriers that can improve targeting capability and reduce drug toxicity compared with free drugs demonstrate a promising strategy for disease treatment. However, due to cell heterogeneity during disease progression, dose-induced drug resistance, and instability of nanocarriers in the blood circulation, achieving dual targeting of different injured cell subsets while reducing drug dosage and maintaining treatment efficacy remains challenging. In addition, developing nanocarriers is a complex and time-consuming process; there is a desire for a universal nanocarrier for various diseases, especially complex diseases. Here, we have successfully designed a modular nanocarrier capable of co-delivering drugs with a reduced effective dosage of one-tenth that of single-drug nanocarriers.

Methods: The dual-drug targeting nanoparticles consist of three main modules: a PLGA nanoparticle, an antibody, and two drugs. We first constructed a 400 nm PLGA nanoparticle encapsulating drug A. Then, the podocyte-specific antibody Nephrin was modified onto the nanoparticle surface. Finally, drug B was coupled to the antibody. The dual-targeting dual-drug nanoparticles were injected into mice to evaluate their toxicity compared with free drugs. We explored the targeting of the nanoparticles using organ imaging and other methods. We established three kidney disease models in mice to compare the effects of dual-targeting nanoparticles at different concentrations.

Results: Dual-targeting nanoparticles loaded with different drugs demonstrated dual targeting of glomeruli and tubules. To treat acute kidney injury, the nanocarriers encapsulated rapamycin and dexamethasone acetate; for PAN, the drugs were rapamycin and captopril; and for the ccRCC model, gefitinib and glutathione were chosen as the targeted antitumor drugs. For different diseases, lesions were significantly treated with different drug combinations. We observed reduced tubular injury in the acute kidney injury model, recovered podocyte foot processes in the PAN model, and reduced cancer foci in the ccRCC model. These results show that dual-drug loaded nanomaterials have an excellent ability to address complex disease presentations.

Conclusions: The dual-drug delivery system can flexibly adapt to treating various diseases by modifying the particle size, surface antibodies, and drugs.

Funding: Clinical Revenue Support

TH-PO760

Oxysterol-Binding Protein-Like 7 Deficiency in CKD

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Background: OSBPs have been implicated in various processes such as cholesterol transfer from the endoplasmic reticulum to the Golgi, and cholesterol efflux. Previous studies have shown that OSBPL7 deficiency leads to decreased autophagy in other cell types, which may impact lipid trafficking and podocyte function. The purpose of this study is to investigate the role of OSBPL7 in chronic kidney disease and its potential as a therapeutic target. OSBPL7's involvement in autophagy and endoplasmic reticulum stress suggests that its deficiency may contribute to the development of CKD.

Methods: The study utilized immortalized mouse podocytes and a Tg[l-fabp: DBP:eGFP] zebrafish model to investigate the effects of OSBPL7 deficiency on the development of renal dysfunction in podocyte disease and measure the integrity of glomerular filtration. We determined OSBPL7 protein levels in metabolic and non-metabolic mouse models of CKD using western blot. OSBPL7 deficient podocytes and zebrafish were generated and the impact of OSBPL7 deficiency on ER stress markers, autophagy, lipid droplets, and proteinuria was analyzed.

Results: The results show that OSBPL7 protein levels were reduced in the renal cortex of metabolic and non-metabolic mouse models of CKD. OSBPL7 deficiency leads to an increase in apoptosis levels and ER stress markers in podocytes and a decrease in autophagic flux. Additionally, an increase in lipid droplet levels is observed in OSBPL7 deficient podocytes, but this increase was found to be cholesterol independent. Knocking down OSBPL7 expression in Tg[l-fabp:DBP:eGFP] zebrafish leads to increased proteinuria and a slight edema phenotype. The findings suggest that OSBPL7 plays a critical role in the regulation of autophagy and ER stress in podocytes and contributes to the progression of CKD.

Conclusions: This study sheds light on the important role of OSBPL7 in podocytes and its potential as a therapeutic target in CKD. The results indicate that OSBPL7 deficiency may lead to lipid accumulation inside the podocyte and contribute to the proteinuria observed in CKD. Further studies are needed to fully understand the mechanisms and to develop potential therapeutic strategies for treating CKD. In summary, this study provides new insights into the role of OSBPL7 in chronic kidney disease and directly implicated OSBPL7 deficiency to proteinuria in a zebrafish model.

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TH-PO761

Steroid-Dependent Minimal Change Disease in an Adult Responsive to Rituximab

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Introduction: The patient is a 30M diagnosed at age 27 with minimal change disease. His clinical course was complicated by multiple relapses following an initial treatment with full dose steroids (60mg per day) per clinical guidelines. He ultimately progressed to steroid dependent disease. Consequently, the patient was prescribed Rituximab, to which he showed a clinical and serologic response, with almost full remission of proteinuria.

Case Description: The patient was diagnosed with minimal change disease in 2019, and he was treated with a course of full dose steroids by his primary nephrologist. However, after steroids were tapered off, the patient suffered three more relapses of his minimal change disease over the course of the ensuing fourteen months. After the last relapse, steroids were unable to be weaned (remained on 5 mg PO daily). A CT scan of the chest returned unremarkable for lymphadenopathy or any findings suspicious for lymphoma. The patient sought a second opinion with a nephrologist at Westchester Medical Center. Upon initial evaluation in November 2020, urine protein to creatinine ratio (UPCR) was 3mg/g, with creatinine 1.06. He continued the aforementioned maintenance dose of prednisone 5mg PO daily. On follow-up in July 2021, the patient endorsed frothy urine, lower extremity swelling, and twenty pound weight gain. The patient had increased his dose of prednisone to 10mg PO daily prior to the appointment. Creatinine 0.86 and UPCR 4mg/g. Once again, he was started on full dose steroids for treatment, with subsequent improvement in proteinuria. However, by April 2022, the patient once again endorsed lower extremity swelling and frothy urine while on steroids. A repeat biopsy was performed that showed minimal change disease, with 40-89% effacement of the podocyte foot processes. The patient was subsequently given two doses of Rituximab 1gm IV for steroid dependent minimal change disease. Steroids were discontinued. Upon follow-up in February 2023, the patient's creatinine was 1.1 and UPCR 0.04mg/g.

Discussion: Minimal change disease is a rare clinical entity in adult patients. The patient in this case presented with relapsing minimal change disease (confirmed by two separate biopsies) that ultimately became steroid dependent. This case provides an example of successful response to Rituximab as an alternate agent for minimal change disease in treatment resistant cases.

TH-PO762

Uncovering the Role of Cyclin G-Associated Kinase (GAK) in Regulating the Podocyte Cytoskeleton

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Background: Podocytes are terminally differentiated epithelial cells that are integral components of the glomerular filtration barrier (GFB). These cells have specialized interdigitating structures called foot processes, characterized by an extensive network of actin filaments. Damage to podocytes leads to cytoskeletal reorganization and morphological changes, which ultimately result to foot process effacement and disruption of the GFB. In 2020, our group previously identified subsets of chronic kidney disease (CKD) patients with significantly reduced expression of cyclin G associated kinase (GAK).

Methods: We subsequently generated a podocyte specific *Gak* knockout mouse (*Gak*$^{fl/fl}$ *Pod-Cre-Dtr*^{fl}) mice, which developed foot processes effacement, progressive proteinuria, and profound glomerulosclerosis. To further interrogate the role of GAK in podocytes, we utilized a mouse model, which enables transgenic expression of a truncated GAK protein consisting only of the 62-kDa C-terminus end (*Gak*-C62$^{+/-}$). We then generated the C62/*Gak* KO mouse model by crossing the *Gak*-C62$^{+/-}$ mouse to our podocyte specific *Gak* KO mouse.

Results: Interestingly, our preliminary data showed that the C62/*Gak* KO mice rescued the proteinuria and glomerulosclerosis phenotypes, and podocyte foot processes were also maintained, suggesting a novel role of the C-terminal domains of GAK in cytoskeletal regulation in podocytes. Furthermore, *in vitro* analysis of cell morphology indicates disruption of cytoskeletal structure of *Gak* KO podocytes compared to wildtype controls. *Gak* KO podocytes form long spindles as opposed to the stellate shaped wildtype

podocytes. This morphological change in vitro was again rescued in podocytes isolated from the C62/*Gak* KO mouse. To elucidate the mechanism of rescue, we also performed a co-immunoprecipitation combined with shotgun proteomics experiment to identify potential binding partners of the C-terminus end of GAK. Remarkably, our results suggest a novel interaction between GAK and lymphocyte-specific protein 1 (LSP1), a known actin-binding partner, which was the top hit.

Conclusions: Together, these results further support the integral role of GAK, specifically its 62-kDa C-terminus in regulating actin dynamics in podocytes and may provide a novel target for treating CKD that specifically addresses podocyte dysfunction.

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TH-PO763

Soluble CD93 Contributes to Podocyte Activation in Minimal Change Disease

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Background: Minimal Change Disease (MCD) is considered a podocytopathy, but subtle endothelial injury may also be present. CD93, a protein primarily expressed in endothelium, mediates focal adhesion kinase (FAK) activation in endothelium and can be shed during inflammation. We tested the hypothesis that glomerular endothelium releases CD93 that in turn activates podocyte FAK in MCD.

Methods: We tested for CD93 in human kidney tissue (immunofluorescence), urine and sera (ELISA) from 27, 57 and 48 children, respectively, with MCD during relapse. Patients without glomerular disease served as controls (n=9 for kidney tissue, n=19 for soluble CD93). We cultured human glomerular endothelial cells (GEnC) with human sera and measured CD93 (extracellular domain) in cell lysates by western blot. Additionally, we exposed GEnC to human sera and, following washing steps, we measured CD93 (ELISA) in serum-free supernatants. By co-immunoprecipitation, we studied CD93 and podocyte β1 integrin interaction. Human podocytes were also treated with recombinant CD93 (rCD93) and human sera, with β1 integrin (Mab13) and CD93 blocking antibodies, respectively, and we assessed FAK activation by western blotting.

Results: Compared to controls, CD93 expression was higher in MCD glomeruli and colocalized with endothelium ($p<0.0001$). Soluble CD93 was higher in urine (~10 fold) and serum (~1.5 fold) from MCD patients in relapse compared to controls ($p<0.0001$ for both). MCD sera in relapse stimulated cultured human GEnC to release CD93. CD93 was higher in supernatants and lower in cell lysates from GEnC previously exposed to MCD sera in relapse compared to controls ($p<0.01$). rCD93 bound to podocyte β1 and medaited FAK activation (Figure 1a, $p<0.05$ at 6 hours). MCD sera in relapse caused podocyte FAK activation, which was mitigated by adding a CD93 antibody to sera (Figure 1b, $p=0.01$).

Conclusions: MCD sera trigger the release of soluble CD93 from GEnC and this, in turn, contributes to podocyte activation.

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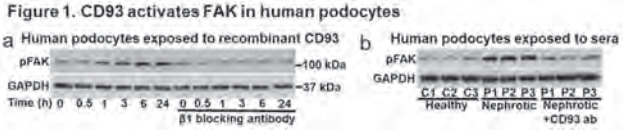

TH-PO764

The Direct Effect of Mycophenolate Mofetil on Podocytes in Nephrotoxic Serum Nephritis

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Background: Mycophenolate mofetil (MMF) is applied in proteinuric kidney diseases, but the exact mechanism of its effect on podocytes is still unknown. Our previous *in vitro* experiments suggested that MMF can ameliorate podocyte damage *via* restoration of the Ca^{2+}-actin cytoskeleton axis. The goal of this study was to characterize podocyte biology during MMF treatment in proteinuric glomerulopathy.

Methods: Nephrotoxic serum (NTS) nephritis (NTN) was induced in three-week old wild-type mice. On day 3, half of the mice were treated with MMF (100 mg/kgBW/d p.o.) for one week. On day 10, we performed proteomic analysis of glomeruli as well as super-resolution imaging of the slit diaphragm. For multiphoton imaging of Ca^{2+} concentration ($[Ca^{2+}]_i$), the experimental design was repeated in mice expressing podocyte-specific Ca^{2+} sensor.

Results: MMF ameliorated the proteinuria induced by NTS. We identified significant changes in the abundance of proteins involved in Ca^{2+} signaling and actin cytoskeleton regulation, which was further confirmed by direct $[Ca^{2+}]_i$ imaging in podocytes showing decreased Ca^{2+} levels after MMF treatment. This was associated with a tendency to restoration of podocyte foot process structure.

Conclusions: Here, we provide evidence that MMF has a substantial direct effect on podocytes. MMF contributes to improvement of $[Ca^{2+}]_i$ and amelioration of the disorganized actin cytoskeleton in podocytes. These data extend the knowledge of direct effects of immunosuppressants on podocytes that may contribute to a more effective treatment of proteinuric glomerulopathies with the least possible side effects.

TH-PO765

Loss of PRDM16 Aggravated Podocytopathies by Regulating Insulin Signaling

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Background: Podocytopathies are kidney diseases that are characterized by proteinuria or nephrotic syndrome due to direct or indirect podocyte injury. Our lab has investigated the effect of tubular PRDM16 on renal fibrosis. And we found that the expression of PRDM16 was abundant in healthy podocytes, however, decreased greatly in injured podocytes. In this study, we aim to clarify the function of PRDM16 on podocyte injury.

Methods: The expression of PRDM16 in the podocytes of podocytopathies patients and mice was detected by Western Blot, qPCR and Co-immunofluorescence staining. Podocyte-specific PRDM16 knockout mice were generated, and Streptozotocin-induced diabetic nephrology (DN) model was established. Kidneys, urine, and blood were collected. Lentivirus was used to overexpress PRDM16 in podocytes, and FSGS and DN animal models. Western Blot, qPCR, IHC, IF, electron microscope, urinary albumin to creatine ratio (ACR), Masson's staining, and PAS staining were used to verify the podocytes-protected role of PRDM16 in vivo and in vitro. RNA-sequencing, glucose intake assay, glycolysis detecting with seahorse bioanalyzer, ChIP, Co-IP, and luciferase assay were used to clarify the mechanism of PRDM16 on insulin signaling.

Results: The results showed PRDM16 was decreased markedly in the podocytes of Podocytopathies patients and mice. Renal injection with PRDM16 overexpression lentivirus decreased proteinuria and podocyte injury of Adriamycin nephropathy and DN mice. Podocyte-specific PRDM16 knockout diabetic mice showed more severe proteinuria and podocyte injury compared to $PRDM16^{fl/fl}$ diabetic mice. RNA-sequencing results revealed that insulin signaling changed obviously in PRDM16 overexpression podocytes. And we verified that PRDM16 promoted the transduction of insulin signaling and glucose metabolism by inhibiting the Ser307 phosphorylation of insulin receptor substrate-1(IRS-1) which was recognized and degraded by the ubiquitin-proteasome system. The mechanism of PRDM16 regulating the phosphorylation of IRS-1 was inhibiting the transcription of serine-threonine kinase, IKK-β.

Conclusions: Loss of PRDM16 in podocytes aggravated podocyte injury by inhibiting insulin signaling and successive glucose metabolism. Mechanistically, PRDM16 blocked the Ser307 phosphorylation of IRS-1 by downregulating the transcription of IKK-β.

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TH-PO766

PFKFB3 Downregulation Aggravates Angiotensin II-Induced Podocyte Detachment

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Background: Podocytes are known to play a critical role in the maintenance of normal glomerular filtration. However, the exact mechanism of podocyte loss remains unclear. Fructose-2,6-biphosphatase 3 (PFKFB3) is a bifunctional enzyme and has been demonstrated to play a crucial role not only in glycolysis, cell proliferation, and cell survival but also in cell adhesion. The purpose of this study is to evaluate the role of PFKFB3 in Angiotensin II (Ang II)-induced kidney injury.

Methods: Immunohistochemical staining and immunofluorescence double staining techniques were employed to determine the localization of PFKFB3 in podocytes. Western blot analysis was performed to assess the expression levels of PFKFB3, p-talin1, and ITGB1 in glomeruli. The adhesive capacity of podocytes was assessed using an adhesion assay. Western blot was conducted to evaluate the expression levels of p-talin1 and ITGB1 in podocytes. Flow cytometry was employed to assess the impact of PFKFB3 on podocyte apoptosis. To examine the impact of PFKFB3 on podocyte adhesion under Ang II treatment, pEnCMV-PFKFB3 plasmid and PFKFB3 siRNA were transfected into podocytes.

Results: PAS and HE staining of mouse kidney sections revealed significant glomerulosclerosis in the Ang II-infused mice. Urinary protein examination demonstrated that the angiotensin II-infused mouse model exhibited higher levels of proteinuria. Immunofluorescence staining and immunofluorescence double staining revealed that Ang II inhibited the PFKFB3 expression in both the cytoplasm and nucleus of cultured human podocytes. Western blot experiments further confirmed that Ang II inhibited PFKFB3, p-talin1, and ITGB1 expression in glomeruli. In vitro study, adhesion assay demonstrated that Ang II stimulation of podocytes resulted in decreased adhesion compared to the control groups. Inhibition of PFKFB3 further enhanced the suppression of p-talin1 and ITGB1 expression in podocytes induced by Ang II. Additionally, stimulation of podocytes with Ang II suppressed PFKFB3, leading to podocyte apoptosis. All these effects were significantly exacerbated following transfection with PFKFB3 siRNA. However, the overexpression of PFKFB3 alleviated these effects.

Conclusions: These findings suggest that Ang II leads to the decrease in podocyte adhesion by suppressing PFKFB3 expression and indicates a potential therapeutic target for podocyte injury in CKD.

TH-PO767

MHC Class I Molecules and Dendrin Are Upregulated in Primary FSGS Podocytes

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Background: The pathophysiology of primary focal segmental glomerulosclerosis (FSGS) is incompletely understood, and differentiation between FSGS subtypes remains challenging. We used single-cell transcriptomics to identify new pathways that are specifically deranged in primary FSGS podocytes.

Methods: We performed single-nucleus RNA-sequencing (10x Genomics Chromium) on cryopreserved kidney biopsy cores from patients with primary FSGS (n=9, all nephrotic), maladaptive FSGS (n=9, none nephrotic), proteinuric controls (PLA2R-positive membranous nephropathy, n=3), and healthy controls (pre-perfusion biopsies, n=4).

Results: We identified 194,594 nuclei, of which 3,660 were podocytes expressing canonical marker genes **(Figure 1A)**. Differential gene expression analysis between primary FSGS podocytes (n=1,635 nuclei) and all other podocytes (n=2,025 nuclei) showed significant upregulation of genes encoding major histocompatibility complex (MHC) class I proteins (*HLA-A, HLA-B, HLA-E, B2M*) and dendrin (*DDN*) (**Figure 1B-C**). Overexpression of MHC class I molecules has previously been observed in autoimmune diseases such as diabetes mellitus[1]. We hypothesize that presentation of self-antigens in primary FSGS podocytes via MHC class I proteins may either be an initiating event, triggering production of a pathogenic permeability factor, or alternatively an adaptive response to earlier podocyte injury. Dendrin, which interacts with slit diaphragm proteins, translocates to the nucleus in injured podocytes, triggering apoptosis in mouse models of FSGS[2], thereby making it a promising new target in human primary FSGS.

Conclusions: MHC class I molecules and dendrin represent two novel differentially expressed pathways that could aid in further distinguishing different FSGS subtypes.

References: 1: Russell, et al. Diabetes. 2019. 2: Empitu, et al. J Am Soc Nephrol. 2023.

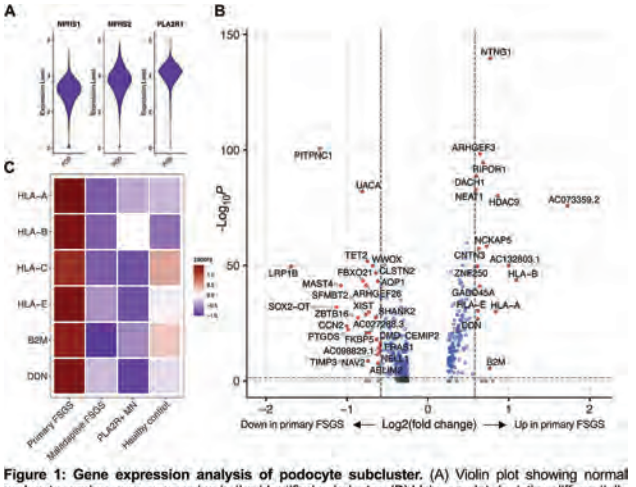

Figure 1: Gene expression analysis of podocyte subcluster. (A) Violin plot showing normal podocyte marker gene expression in the identified subcluster. (B) Volcano plot depicting differentially expressed genes (DEGs) between primary FSGS podocytes and other podocytes [red dots: p < 0,05 and absolute log2FC > 0.58 (right) or < -0.58 (left)]. (C) Heatmap of selected upregulated DEGs.

TH-PO768

Shear Stress on Podocyte Foot Processes Arising from Flow in Filtration Slits Studied by Numerical Flow Simulations

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Background: The glomerular filtration barrier is exposed to flow dynamic forces arising from filtration pressure (tensile stress) and filtrate flow (shear stress). Filtrate flow acts on podocyte cell bodies in Bowman's space and on foot processes (FPs) lining the filtration slit. Besides a previous estimate of 8 Pa (Endlich & Endlich, *Semin. Nephrol.* 2012), the magnitude of shear stress to FPs remains unknown.

Methods: We used numerical flow simulations to study forces arising from glomerular filtration. Simulations were run with a realistic model of a filtration unit and the corresponding filtration parameters of the rat kidney. The filtration unit consists of fenestrated endothelium, the GBM, and two opposing halves of FPs bridged by the slit diaphragm (SD). The GBM and SD were regarded as porous media.

Results: Modeling the GBM and SD as one homogenous porous medium, a peak wall shear stress of 65.2 Pa acting on FPs in the filtration slit was found; pressure dropped by 2.5 mm Hg across the SD. Increasing filtration slit width from 30 to 40 nm reduced peak wall shear stress by only 9% to 59.4 Pa. Modeling GBM and SD as two separate homogenous porous media with an increased viscous resistance of the SD further increased the pressure drop across the SD, but also wall shear stress on FPs. Two factors were revealed that may account for the high levels of wall shear stress: 1) convergence of filtrate flow out of the GBM into the filtration slit (similar to a nozzle), 2) transition from a porous medium (GBM, SD) with a rather uniform velocity profile into free flow (Bowman's space) with a developing parabolic velocity profile.

Conclusions: Our data demonstrate that FPs are likely to experience high levels of wall shear stress in the filtration slit that markedly exceed levels of endothelial wall shear stress. Shear stress on FPs represents the only flow dynamic force that directly tends to disconnect viable podocytes from the GBM—a hallmark of podocyte loss in many glomerular diseases.

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TH-PO769

YAP and TAZ in Podocytes: Twins Distinguished by Single-Nucleus Transcriptomic Analysis

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Background: Podocyte homeostasis and the maintenance of the filtration barrier relies on the balanced activity of YAP and TAZ, the two effectors of the Hippo signaling pathway. Previous studies showed an increase of YAP and TAZ during glomerular disease. Additionally, specific deletion of YAP and TAZ in adult podocytes increases susceptibility to induced injury, suggesting a protective role. However, the exact molecular mechanisms underlying these observations remain unclear. Here, we investigate the individual roles of YAP and TAZ in podocytes *in vivo*.

Methods: We generated genetic mouse models in which YAP, TAZ, or both were knocked out specifically in podocytes (pKO). The mice were deeply characterized including kidney function, slit diaphragm morphology and survival. To gain insights into pathomechanisms leading to podocyte disease and to differentiate processes unique for YAP or TAZ we performed single nuclei RNA Sequencing (snRNASeq) of isolated glomeruli of mice of different ages and stages of disease.

Results: YAP pKO mice present a heterogenous disease onset until 12 weeks old, with a phenotype resembling focal segmental glomerulosclerosis (FSGS) with proteinuria and reduced slit diaphragm length. TAZ pKO mice displayed a tendency towards a reduced slit diaphragm length without developing proteinuria. Notably, when breeding mice to obtain both YAP and TAZ knockout alleles, no viable offspring was produced with less than two of the four YAP/TAZ alleles, suggesting compensational mechanisms. Immunostainings supported this hypothesis. The snRNASeq analysis revealed similar patterns in the YAP and TAZ pKO mice, further confirming their overlapping functions. Subsequent cell communication network analysis provided first evidence on disturbed signaling pathways that could contribute to the phenotypic differences observed between YAP and TAZ pKO mice.

Conclusions: While YAP and TAZ have a high level of similarity and are considered homologous twins, their roles in podocytes are distinct, as only the specific deletion of YAP leads to FSGS. Strikingly, combined YAP/TAZ activity above a certain threshold is indispensable for podocyte homeostasis, as the combined knock out is not viable. With this study we apply snRNASeq to elucidate shared, unique and compensatory functions of YAP and TAZ in podocyte homeostasis and injury.

TH-PO770

Multi-Ethnic Genome-Wide Association Study (GWAS) for Idiopathic Nephrotic Syndrome Identifies Susceptibility Loci Across the Life Span, Response to Therapy, and Genetic Ancestry

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Background: Large-scale genetic association studies for idiopathic nephrotic syndrome cause by focal segmental glomerulosclerosis and minimal change disease are lacking, especially for forms of disease that are unresponsive to immunosuppressive treatment. To address this knowledge gap, we conducted a large-scale genome-wide association study (GWAS) for common variants with paired exome sequencing in order to assess the complex polygenic architecture of non-Mendelian INS.

Methods: This study consists of 5,600 INS cases across the life span, genetic ancestry, and response to therapy, compared to over 50,000 genetically matched controls. More than 80% of cases had paired exome or genome sequencing. GWAS was conducted first on the entire cohort and then in subgroups based on age of onset, ancestry, and response to therapy. Analyses were conducted again after removal of cases harboring diagnostic/pathogenic Mendelian mutations in known FSGS genes and *APOL1* high-risk genotypes. Ancestry specific GWAS were conducted using Regenie and Saige, metanalyses were conducted using Metal and TransMeta.

Results: Trans-ethnic metanalysis of all cases irrespective of age of onset and response to therapy showed the known association of *APOL1*, driven by individuals of recent African ancestry (OR= 2.67, P= 4.24 x 10^{-61}), association with the *HLA-DQA1* locus (OR=1.49, P= 5.91 x 10^{-24}) and with chromosome 4 (*LDB2*; OR=1.34, P= 4.48 x 10^{-9}). After removal of cases harboring pathogenic mutations causing Mendelian forms of

FSGS and *APOL1* HR genotypes, the strength for association to chromosome 4 increased and a novel locus on chromosome 15 reached genome-wide significance (*ADAMTSL3*; OR=1.53, P=2.73 x 10^{-08}). Ancestry-specific and sub-phenotype analyses according to the age of onset and response to glucocorticoid treatment resulted in validation and replication of loci for SSNS (*e.g. CALHM6, CLEC16A*), and several novel HLA loci (for adult SSNS and non-Mendelian SRNS).

Conclusions: Interim results demonstrate multiple novel loci for INS, including pleiotropic risk alleles that predispose to NS across different sub-phenotypes, and loci specific to ancestry, age of onset, and response to therapy.

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TH-PO771

Regulation of Podocyte Adhesion by SEL1L-HRD1 ERAD via Integrin

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Background: Podocytes are specialized epithelial cells crucial for the kidney glomerular filtration barrier. They form interdigitating foot processes with neighboring podocytes in the kidney glomerulus to filter the blood. Adhesion of podocytes to glomerular basement membrane (GBM) is key to the formation of foot process and filtration function. Impairment of this process causes podocyte detachment, proteinuria and glomerulosclerosis in humans. While homeostasis in the endoplasmic reticulum (ER) has been generally recognized as important for cellular function, our understanding of ER homeostasis in podocytes remains unclear. Endoplasmic reticulum-associated degradation (ERAD) is the primary mechanism for the clearance of misfolded ER proteins by cytosolic proteasomal degradation. The SEL1L-HRD1 protein complex represents the most conserved ERAD pathway. However, the role of SEL1L-HRD1 ERAD in podocyte function remains poorly understood.

Methods: The podocyte-specific SEL1L-deficient mice were generated. Mouse body weight and survival curve were recorded. Urine samples from mice at 1, 3, and 5 weeks of age were collected to assess the abundance of albumin and WT1. Kidneys from wild-type (WT) and SEL1L-deficient mice were collected for ultrastructure observation by scanning electron microscopy (SEM) and transmission electron microscopy (TEM), the abundance and cellular location of the integrin subunit ITGA3 by immunofluorescence staining and western blot.

Results: Compared with WT mice, SEL1L-deficient mice showed lower body weight and premature renal failure with a median lifespan of 14 weeks. More albumin and detached podocytes were observed in SEL1L-deficient mice. Moreover, SEL1L-deficient mice showed damaged glomeruli and severe foot process effacement based on SEM and TEM. In terms of molecular mechanism, ITGA3, an important podocyte adhesion receptor, was accumulated in the ER, not exit to podocyte membrane, in the absence of SEL1L-ERAD.

Conclusions: Our data demonstrate SEL1L-ERAD regulates podocyte attachment on the glomerular basement membrane via degrading misfolded integrin subunit, ITGA3.

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TH-PO772

Identification of Circular Dorsal Ruffles as Signal Platforms for the AKT Pathway in Glomerular Podocytes

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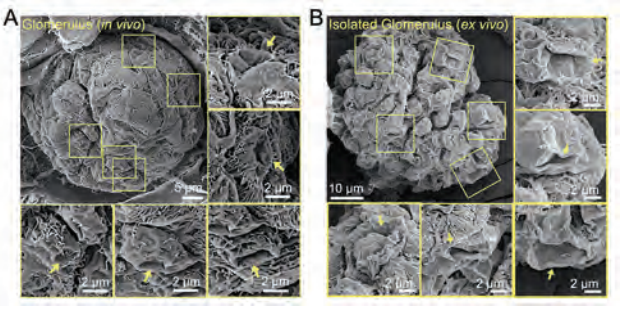
Background: Circular dorsal ruffles (CDRs) are rounded membrane ruffles induced by growth factors to function as precursors of the large-scale endocytosis called macropinocytosis. In addition to their role in cellular uptake, recent research using cell line systems has shown that CDRs/macropinocytosis regulate the canonical AKT/mTORC1 growth factor signaling pathway. However, as CDRs have not been observed in tissues, their physiological relevance has remained unclear. Here, we first report that CDRs are expressed in glomerular podocytes *ex vivo* and *in vivo*, and we visually captured the transformation process to macropinocytosis.

Methods: Ultra-high resolution scanning electron microscopy (SEM) and confocal microscopy were used to see if CDRs are expressed at the surface of mouse glomerulus and isolated glomeruli. Podocyte cell line MPC5 was used for further imaging analysis as well as biochemical assays to test if CDRs regulate the Akt/mTORC1 pathway.

Results: High-resolution SEM of mouse kidney tissue showed that glomerular podocytes displayed CDR-like structures *in vivo* (Fig. 1A, arrows). In total, 21 glomeruli from five mice were examined using SEM. CDR-like structures formed in 25.38% of the podocytes (n=528). Moreover, epidermal growth factor (EGF) and platelet-derived growth factor (PDGF) induced CDRs in MPC5 cells. Inhibition of CDRs significantly mitigated GF-induced AKT phosphorylation and attenuated mTORC1 activation in cells. Confocal microscopy showed that AKT signaling components localized to CDRs. Importantly, we utilized isolated mouse glomeruli for *ex vivo* experiments and found that podocytes express CDRs as macropinocytic cups after EGF stimulation (Fig. 1B, arrows), regulating the AKT pathway.

Conclusions: Our results demonstrate the physiological role of CDRs as signal platforms for the AKT/mTORC1 pathway in podocytes at the tissue level. As mTORC1 plays critical roles in podocyte metabolism and aberrant activation of mTORC1 triggers podocytopathies, the outputs from this study strongly suggest that targeting CDR formation could represent a potential therapeutic approach for these diseases.

Funding: Government Support - Non-U.S.



TH-PO773

Dual Deletion of Guanylyl Cyclase-A and p38 Mitogen-Activated Protein Kinase (MAPK) in Podocytes with Aldosterone Administration Causes Glomerular Intracapillary Thrombi

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Background: Previously, we demonstrated that podocyte-specific guanylyl cyclase-A (GC-A; natriuretic peptide receptor 1; NPR1) conditional KO (pod-GC-A cKO) mice with aldosterone exhibit podocyte injury, and that pharmacological inhibition of p38 MAPK ameliorates it. However, the effects of genetic deletion of p38 MAPK in podocytes have been unknown.

Methods: We generated podocyte-specific p38 MAPK and GC-A double cKO (pod-double cKO) mice, and treated them with aldosterone and high salt without nephrectomy (B-ALDO). Next, we focused on PAI-1 (SERPINE1) and administered PAI-1 neutralizing antibody to pod-double cKO mice. *In vitro*, we examined human podocytes in which p38 MAPK was deleted by CRISPR/Cas9 system and GC-A was suppressed by siRNA. Then, we cultured human p38 MAPK-null podocytes transfected with si-*NPR1* in the upper layer and wild-type glomerular endothelial cells (GE) in the lower layer, with PAI-1 inhibitor in the transwells.

Results: Unexpectedly, B-ALDO-treated pod-double cKO mice resulted in elevation of serum Cr, massive albuminuria and severe foot process effacement in addition to intracapillary fibrin thrombi indicating endothelial damage. PAI-1 was increased in podocytes and treatment with PAI-1 neutralizing antibody ameliorated intracapillary thrombus formation in B-ALDO-treated pod-double cKO mice. *In vitro*, knockout of p38 MAPK and suppression of GC-A in human cultured podocytes upregulated *SERPINE1*, *TGFB1*, and *FN1*. Deletion of p38 MAPK and inhibition of GC-A in podocytes in the upper layer upregulated *TGFB1* in the GE in the lower layer, indicating that some humoral factors derived from podocytes could work as cell-to-cell mediators. The treatment with PAI-1 inhibitor decreased *TGFB1* in both podocytes and GE.

Conclusions: Podocyte-specific deletion of p38 MAPK and GC-A exacerbated glomerular endothelial cell injury as well as podocyte damage which was ameliorated by PAI-1 neutralizing antibody. PAI-1 in podocytes is one factor that disrupts the podocyte-endothelial crosstalk, suggesting that p38 MAPK and GC-A play indispensable roles in podocytes.

TH-PO774

Podocyte Infolding Glomerulopathy: Insights from Proteomics by Laser Microdissection and Mass Spectrometry

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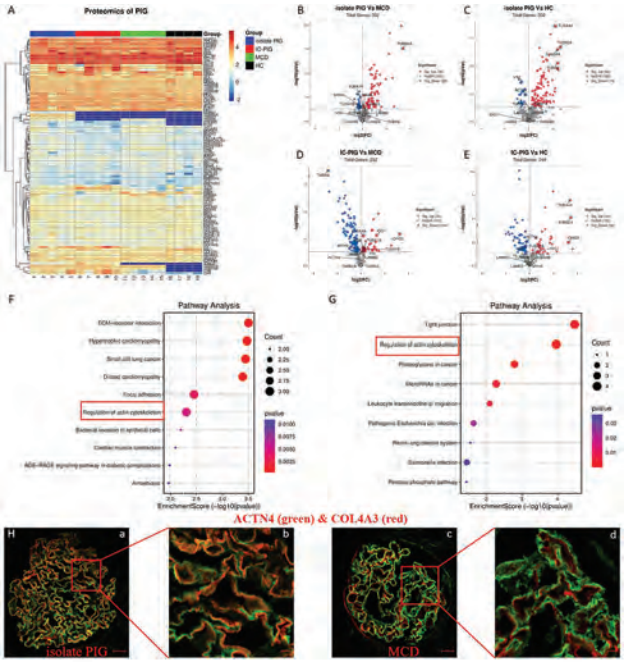
Background: Podocyte infolding glomerulopathy (PIG) is a newly recognized rare glomerular injury. The potential mechanism of this injury pattern remains unclear.

Methods: 10 cases diagnosed with PIG and 5 minimal change disease (MCD), 4 donor kidney biopsy specimens at Kingmed Diagnostics were analyzed by laser scanning microdissection and mass spectrometry (LMD/MS). The clinicopathological features, especially the ultrastructural changes were reviewed.

Results: 10 cases were divided into 2 groups according to immunofluorescence, IC-PIG (coexisting with immune-complex associated glomerulonephritis), and isolate PIG (without immunoglobulin or complement deposition). The underlying disease of IC-PIG included lupus nephritis in 4 cases, and membranous nephropathy in 1 case, while no known underlying disease was found in 5 cases of isolate PIG. Immunoglobulin gamma-1 heavy chain (IGG1) and Immunoglobulin heavy constant gamma 3 (IGHG3) showed significant differences in the IC-PIG group compared with the other two control groups. The differentially expressed protein, α-actinin4 (ACTN4), was detected by LMD/MS in 10 PIG glomeruli (P=0.005) compared with 9 controls, among the top 20 proteins. The displacement of ACTN4 into the GBM was confirmed by the confocal microscope. Interestingly, Tubulin Beta-4 Chain (TUBB4A) was only detected in the isolate group

compared with IC-PIG, normal donor kidney and MCD among the identified 302 proteins. Regulation of actin cytoskeleton signaling was screened out by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment.

Conclusions: PIG is a rare morphological change of podocyte injury with heterogeneous diseases. Podocyte cytoskeletal protein ACTN4 and TUBB4A were dysregulated which may involve in the mechanism of podocyte injury.



Mass spectrometry and confocal imaging.

TH-PO775

Single-Cell Transcriptional Analysis Reveals the Effect of Anti-PLA2R and Anti-THSD7A Sera on Human Glomerular Cells

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Background: Primary membranous nephropathy (MN) is a leading cause of nephrotic syndrome in adults due to the deposition of anti-podocyte antibodies in the glomerular subepithelial space. Several podocyte proteins have been identified as targets of these autoantibodies, with PLA2R and THSD7A the most prominent. We investigated the specific effect of anti-PLA2R and anti-THSD7A on glomerular cells using single cell transcriptomics on a human glomerulus-on-a-chip (GOAC) system.

Methods: GOACs were generated using human primary podocytes and glomerular endothelial cells and cultured with human serum from MN patient with anti-PLA2R or anti-THSD7A antibodies for 72 hours. Sera from healthy individuals were used as a control. Samples from three different individuals were used for each group. Albumin leakage assay was performed on GOAC to confirm injury. Single cell RNA-seq analysis (scRNA-seq) was performed on cells retrieved from the GOAC. Downstream analyses were done using UMAP, gene and pathway enrichment, and intra- and inter-cluster comparative transcriptomics.

Results: Exposure to anti-PLA2R and anti-THSD7A sera from MN patients induced injury on the GOAC as confirmed by albumin leakage. scRNA-seq analysis showed robust activation of the complement pathway in both cohorts. Preliminary analysis also suggested activation of podocyte injury pathways with changes in genes involved in slit diaphragm formation being more prominent in cells exposed to anti-THSD7A sera vs the anti-PLA2R. At the same time, GEC displayed an enrichment in genes involved in proliferation and metabolic changes under both conditions compared to healthy sera, suggesting a broader effect of MN sera that extends beyond direct podocyte damage.

Conclusions: The combined use of the GOAC and transcriptomics studies allows to investigate molecular and transcriptional changes affecting podocytes and GEC when both exposed to MN sera. This approach can help unraveling glomerular mechanisms of injury in MN, thus providing potential new targets for the treatment of nephropathies and other glomerular diseases.

Funding: NIDDK Support

TH-PO776

Multi-Institutional Study of Anti-Nephrin Autoantibodies in Post-Transplant Focal Segmental Glomerulosclerosis Recurrence

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Background: Post-transplant recurrence of focal segmental glomerulosclerosis (rFSGS) is a major challenge in kidney transplantation. Recently, we reported very early pathological changes in podocytes and possible roles of circulating anti-nephrin antibodies (abs) in a patient with rFSGS (Hattori et al, Am J Transplant, 2022). To confirm these preliminary results, we performed a multi-institutional study.

Methods: 14 Japanese kidney transplant recipients with childhood-onset primary FSGS who had stored plasma samples and graft biopsy specimens were analyzed. All patients underwent whole exome sequencing and no pathogenic variants in FSGS-related genes were identified. Circulating anti-nephrin abs were measured by ELISA and the cut off levels were defined as 231 U/mL, the maximum antibody levels among the controls (9 genetic FSGS patients, 13 membranous nephropathy patients, 4 lupus nephritis patients and 13 healthy controls). Dual immunofluorescence staining of nephrin and IgG or ShcA, an adaptor protein of phosphorylated nephrin, was performed using the structured illumination microscopy.

Results: There were 10 rFSGS and 4 non-recurrent (non-rFSGS) patients. In rFSGS patients, median (interquartile range) anti-nephrin abs before transplant or during a post-transplant recurrence were markedly high at 950 (839, 1323) U/mL. Graft biopsies showed punctate IgG deposition co-localizing with nephrin that showed altered localization and increased expressions of ShcA. Eight of 10 rFSGS patients achieved remission, and graft biopsies after remission showed normal nephrin expression and no signals for IgG and ShcA. Anti-nephrin abs decreased to 261 (121, 398) U/mL in 4 patients with available samples at remission. In non-rFSGS patients, anti-nephrin abs were comparable with the controls regardless of the timing of sample collection. Their graft biopsies showed normal nephrin expression and no signals for IgG and ShcA.

Conclusions: Our results suggest that anti-nephrin abs are associated with rFSGS via nephrin phosphorylation. Larger studies including other ethnicities are required to confirm this finding and to determine the prevalence and incidence of post-transplant FSGS recurrence associated with anti-nephrin abds.

Funding: Government Support - Non-U.S.

TH-PO777

Exosomes Play a Pivotal Role in Linking Proteinuria to Glomerulosclerosis by Mediating Podocyte-Mesangial Communication

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Background: Podocyte injury is the primary feature of the vast majority of glomerular diseases, while mesangial cell activation is the hallmark of glomerulosclerosis. How these two types of cells communicate in glomerular disease remains elusive. Exosomes act as membranous vesicle carriers and are involved in the pathogenesis of kidney disease by shuttling proteins and other materials between donor and recipient cells. Here, we tested whether exosomes play a role in mediating podocyte-mesangial communication in glomerular disease.

Methods: Exosomes secreted by injured podocytes were purified by differential centrifugation and characterized using nanoparticle tracking analysis and transmission electron microscopy. Differentially expressed proteins from podocyte-derived exosomes were analyzed by protein microarray, and sonic hedgehog (Shh) was identified as one of the most regulated proteins in the exosomes from injured podocytes. The potential role and mechanism by which exosomal-Shh mediates communication between podocytes and mesangial cells was investigated *in vitro* and *in vivo*.

Results: *In vitro*, we found an increased production of exosomes in mouse podocyte cells (MPC5) stimulated by angiotensin II (Ang II). Shh and activated N-Shh were encapsulated in exosomes isolated from Ang II-treated MPC5 cells (Ang II-Exo). The Ang II-Exo were able to induce the activation and proliferation of rat mesangial cells (RMC). In contrast, inhibition of exosome secretion with dimethyl amiloride, depletion of exosomes from conditioned medium or knockdown of Shh expression abolished the ability of Ang II-Exo to induce RMC activation. *In vivo*, the injection of podocyte-derived exosomes exacerbated glomerulosclerosis, which was negated by inhibitors of Shh signaling. Furthermore, blocking exosome secretion also ameliorated glomerulosclerosis following Ang II and adriamycin injury in mice.

Conclusions: Podocyte-derived exosomes play a critical role in mesangial cell activation and glomerulosclerosis by carrying Shh ligands. Therefore, strategies targeting exosomes may be a novel way to treat proteinuric kidney disease.

TH-PO778

Identification of Novel Small Molecules for Podocytopathies Using a High-Throughput Screen for KLF15 Agonists

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Background: Krüppel-Like Factor 15 (KLF15) is a glucocorticoid-responsive, zinc-finger transcription factor that is critical for maintenance of podocyte differentiation. Previous studies demonstrate that podocyte-specific induction of *KLF15* attenuated kidney injury and improved overall survival in proteinuric murine models. Here, we developed a high-throughput screen (HTS) to identify novel KLF15 agonists for podocytopathies.

Methods: We developed a HTS using human podocytes expressing a dual reporter, firefly luciferase reporter directed at the *KLF15* promoter and renilla luciferase, and tested the NCI small molecule library (2642 compounds). Hit-to-lead optimization was conducted using a Structure-Activity Relationship (SAR) study. Lead KLF15 agonists were tested in cultured human podocytes and the proteinuric murine models: LPS, Nephrotoxic Serum (NTS) Nephritis, and HIV-1 transgenic (Tg26) mice.

Results: HTS assay exhibited high reproducibility with low variability (signal to background ~ 3.22 and a low Z-score ~ 0.56). We identified 16 hits with > 2.5-fold change in *KLF15* reporter activity and an EC_{50} < 100nM. Based on cell viability and "lead likeness" of the hits, SAR study was conducted to synthesize novel leads with improved efficacy and low cell toxicity. The novel lead, BT503, demonstrated improved cell viability in cultured human podocytes and reduced proteinuria and podocyte effacement in mice treated with LPS. BT503 treatment in NTS and Tg26 mice also attenuated kidney injury (proteinuria, serum creatinine, urea nitrogen), podocyte and glomerular injury, and interstitial fibrosis. Concurrent treatment with BT503 in cultured human podocytes and mice also reduced the dexamethasone dose required to restore podocyte injury. Subsequent RNA-sequencing, in-silico drug-docking studies, and western blot analysis in cultured podocytes demonstrate that the salutary effects of BT503 and induction of KLF15 are mediated through NF-kB signaling.

Conclusions: To date, this is the first study to develop a KLF15 HTS using human podocytes to identify and optimize novel small molecules, and subsequently demonstrate their therapeutic efficacy in cultured podocytes and proteinuric murine models with a mechanism of action.

Funding: NIDDK Support, Veterans Affairs Support

TH-PO779

SGLT2 Inhibitor Suppresses Progression of Obesity-Related Nephropathy Induced by Podocyte Hypertrophic Stress

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Background: We recently reported that podocyte hypertrophic stress occurred relatively early during the onset of nephropathic progression in a rat model of type 2 diabetes-related nephropathy. In this study, we evaluated the progression of obesity-related nephropathy (ORN) caused by podocyte hypertrophic stress and the efficacy of an SGLT2 inhibitor (SGLT2i) in obese rat models.

Methods: To investigate the ORN progression, we used 8-week-old Zucker fatty (ZF) rats exhibited non-diabetic obesity model (n = 6), and Zucker lean (ZL) rats as a control model (n = 6). Kidney biopsies and urine samples were collected at 16, 24, and 32 weeks of age. Next, to investigate the effect of an SGLT2i, ZF rats were divided into two groups (SGLT2i: n = 6, non-treated: n = 6); beginning at 12 weeks of age, both groups were fed the same amount of diet. From 24 weeks of age, the SGLT2i group received canagliflozin 10 mg/kg/day for 8 weeks. Kidney tissues and urine samples were collected at 32 weeks of age. We measured urinary sediment podocin (U-sed pod) mRNA using qRT-PCR, glomerular volume (GV), podocyte volume (PV), and podocyte density (PD) to evaluate the podocyte injury.

Results: ZF rats were significantly heavier than ZL rats during the entire observation period. The urinary protein (UP) excretion level in ZF rats began to significantly increase at 16 weeks of age and became 20-fold greater than the level in ZL rats at 32 weeks of age. Significant increases in the GV, PV, and U-sed pod mRNA level, along with a decrease in PD, were observed in ZF rats from 16 to 32 weeks of age. Neither non-treated nor SGLT2i groups were hyperglycemic, and no changes in blood pressure occurred during the observation period. Compared with non-treated group, SGLT2i group exhibited significant weight loss, approximately 50% decrease in UP, significant reductions in the GV and PV, an increased PD ($p < 0.01$), and decreased U-sed pod mRNA ($p < 0.01$). SGLT2i group exhibited a significant increase in urinary sodium excretion ($p < 0.01$) and restored creatinine clearance to the level in control group.

Conclusions: Quantitative and morphological assessment of podocytes suggest that podocyte hypertrophic stress causes ORN progression. An SGLT2i may suppress podocyte hypertrophic stress by inhibiting glomerular hyperfiltration, and progression of ORN.

Funding: Government Support - Non-U.S.

TH-PO780

Cross-Talk of Injured Podocytes with Parietal Epithelial Cells Through Wnt4/β-Catenin Signaling

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Background: With changing demographics, chronic kidney disease (CKD) and its treatment have become a major public health concern. However, glomerulopathies such as FSGS have limited treatment options. Therefore, understanding the pathogenesis of these lesions, including gender differences, is critical to expanding therapeutic options.

Methods: Here we investigated podocyte injury and crosstalk with parietal epithelial cells (PECs) using both male and female transgenic rats expressing the human diphtheria toxin receptor (hDTR) in podocytes under the control of the podocin promoter. Podocyte injury was induced by injection of diphtheria toxin and disease progression/repair was assessed on days 3, 7, 14, 21. 28 and 42 by immunohistochemistry and real-time PCR. An in vitro podocyte injury model and PECs were used to further investigate the mechanisms of cellular crosstalk.

Results: After injection of diphtheria toxin into transgenic animals, we observed a loss of WT1-positive podocytes starting on day 7. The percentage of glomeruli with FSGS lesions and the number of Pax8-positive PECs on the glomerular tuft increased with time and correlated significantly ($r=0.927$, $p<0.001$). Interestingly, proteinuria at day 14 was approximately twice as high in males, and FSGS lesions and Pax8-positive cells on the tuft tended to be higher in males compared to females. From d14, both glomerular mRNA and protein expression of Wnt4 were increased, which was more pronounced in male animals. Wnt4 was localized in podocytes and beta-catenin in Pax8-positive lesions as shown by confocal microscopy. The Wnt4 target gene CD44 was strongly upregulated at d7 after model induction and then slowly increased after an initial decrease until the end of the experiment (d42). In cell culture, we confirmed that injured podocytes expressed and secreted Wnt4. Cell culture supernatants stimulated the expression of Wnt target genes Axin2 and beta-catenin in PECs but not in podocytes.

Conclusions: Taken together, these data suggest that the canonical Wnt/b-catenin axis plays a critical role in the crosstalk between PECs and injured podocytes and the subsequent migration of PECs onto the tuft. Furthermore, gender-specific differences in podocyte injury and regeneration appear to be, at least in part, Wnt4-mediated.

Funding: Government Support - Non-U.S.

TH-PO781

Association of Minimal Change Nephrotic Syndrome with Mitochondrial Dysfunction in a Rat Model

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Background: In recent years, it has been reported that mitochondrial dysfunction is associated with various renal diseases. However, the relationship between minimal-change nephrotic syndrome (MCNS) and mitochondrial dysfunction remains unclear. Here, using a rat model of MCNS, we examined changes in glomerular mitochondrial damage in response to increased urinary protein.

Methods: To prepare this MCNS model, male Wistar rats aged 6 weeks (n=18) each received a subcutaneous injection of 50 mg/kg puromycin aminonucleoside on day 1 and were euthanatized on days 4, 7, and 10 (n=6, respectively). Whole-day urine samples were collected from the rats on the day before euthanasia, and glomerulus and plasma samples were taken on days 4, 7, and 10 for measurement of protein, creatinine, markers of lipid peroxidation, and mitochondrial DNA content. The experimental protocol, including ethical aspects, was approved by the Osaka Medical and Pharmaceutical University Animal Care and Use Committee (approval number: 21096-A).

Results: Daily urinary protein excretion showed a gradual increase on days 3, 6, and 9 (median 18.1, 95.8, 279.1; interquartile range (IQR) 10.3-23.2, 74.3-103.0, 181.0-366.3 mg/dL, respectively; p=0.0006). The levels of plasma 4-hydroxynonenal were significantly lower on days 4 and 7 than on day 10 (median 0.73, 1.06, 3.29; IQR 0.48-1.12, 0.87-1.23, and 2.65-4.26 mg/mL; p=0.002). From day 4 to day 10, mitochondrial DNA levels decreased gradually (median 3278, 2867, 2369; IQR 3,200-3,360, 2,530-3,090, 2,068-2,937 pg/mL; p=0.01). There was a strong negative correlation between the amount of daily proteinuria and glomerular mitochondrial DNA content (r= -0.718, p= 0.008). Furthermore, glomerular mitochondrial damage was studied using transmission electron microscopy.

Conclusions: In this MCNS rat model, urinary protein excretion increased as glomerular mitochondrial dysfunction worsened. This suggests that glomerular mitochondrial dysfunction may be closely related to the pathogenesis of MCNS.

Funding: Government Support - Non-U.S.

TH-PO782

Ezetimibe Restores the Communication Between Lipid Droplets and Mitochondria via Modulation of Plin5

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Background: Podocyte lipid accumulation contributes to glomerular diseases such as diabetic kidney disease (DKD) and Alport Syndrome (AS). These excess lipids, such as cholesterol and fatty acids, are esterified and stored as cholesterol ester and triglyceride in lipid droplets. Excessive FFA catabolism resulting from excessive lipolysis of TG is a major contributor to cell lipotoxicity. Perilipin 5 (PLIN5) is an LD-related protein that plays a critical role in regulating TG lipase activity and the interactions between LD and mitochondria, where it protects mitochondria from excessive exposure to FFA. Here we test the hypothesis that PLIN5 expresses in podocytes and that PLIN5 deficiency in AS causes excessive TG breakdown and the loss of LD-mitochondrial contact, thus contributing to kidney failure.

Methods: *In vitro,* Immortalized AS podocytes and WT podocytes were established and characterized in our laboratory by breeding the Col4a3KO mice (Jackson Laboratory) to H-2kb-tsA58 transgenic mice (Charles River). PLIN5 expression was determined by RT-PCR and western blot analysis in podocytes from Col4a3KO mice when compared to controls. TG lipolysis and FFA quantification were determined and normalized to protein content. LD-Mitochondrial contact was determined by TEM analysis. PLIN5 expression was studied in kidney cortexes, and the effect of Ezetimibe on PLIN5 modulation, on LD-Mitochondrial contact, and on podocyte injury was studied *in vitro* and *in vivo*.

Results: We demonstrate that PLIN5 is expressed in podocytes, and the expression of PLIN5 is significantly decreased in AS podocytes compared to WT podocytes ($p<0.01$). AS podocytes also showed significantly increased rates of TG lipolysis ($p<0.05$), intracellular free fatty acids ($p<0.05$), and apoptosis ($p<0.01$) when compared to WT podocytes. AS podocytes had a reduced number of LD-mitochondrial contacts ($p<0.05$), implying apoptosis. Moreover, Ezetimibe, which restored LD-Mitochondrial contact *in vitro* ($p<0.05$) and improved kidney function *in vivo*, was found to restore PLIN5 expression *in vitro* and *in vivo* ($p<0.05$).

Conclusions: Our study suggests that podocyte PLIN5 deficiency causes podocyte injury in AS through excessive TG lipolysis and inefficient FA transfer from LD to Mitochondria. Ezetimibe improves LD-mitochondria communication by restoring PLIN5 expression.

Funding: NIDDK Support

TH-PO783

Expression Evaluation of TRPC6 and PODXL Genes in Podocyte Cell Culture After Albumin Overload with and Without Puromycin-Aminoglycoside Damage

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Background: Proteinuria is a prognostic marker for kidney disease and one of the main symptoms of podocytopathies. This study aimed to evaluate the relative expression of *TRPC6* and *PODXL* genes after albumin overload in podocytes *in vitro.*

Methods: Human podocyte cultures were exposed to progressive 0, 3, 20 and 40 mg/mL of albumin for 24h without and with 15 ug/uL exposure to puromycin aminoglycoside (PAN) for 12h. qPCR was performed with RPLP0 as endogenous control. The phenotype recovery was evaluated, either with gradual (removing 25% every 24h of total overload) or abrupt (removing all albumin in the first 24h) regression conditions. SDS-page and Western Blot were performed to evaluate protein expression. Statistical analysis was performed with ANOVA and Tukey's *a posteriori* test ($p<0.05$) (n=5).

Results: The rate of *PODXL* gene transcript was higher than control in 40 mg/mL of albumin without PAN and in 0, 20 and 40 mg/mL of albumin with PAN ($p<0.0001$). Phenotype recovery was observed after gradual removal of albumin overload at 20 mg/mL with PAN. Similar results were observed for protein expression, both in progressive and regressive conditions ($p<0.05$). For *TRPC6* gene, there was a decrease in expression after progressive albumin exposure with 3, 20 and 40 mg/mL without PAN ($p<0.0001$) and an increase expression in 20 and 40 mg/mL with PAN treatment ($p<0.0001$). Phenotype recovery was observed in gradual and abrupt regressive conditions.

Conclusions: When podocytes are injured, podocalyxin is released in vesicles that are excreted in the urine and used as an early glomerular disease biomarker. Therefore, we believe that this mechanism might explain why the phenotype was not recovered in the 40 mg/mL condition. Regarding *TRPC6*'s increased expression after PAN exposure, it might increase Ca^{+2} influx leading to apoptosis, aggravating podocyte damage after proteinuria insult.

Funding: Government Support - Non-U.S.

TH-PO784

Defects in CLVS1 Gene Increase Glycolytic Activity in Cultured Human Podocytes

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Background: Increased oxidative stress is a common feature of chronic kidney disease. We have shown that the homozygous H310Y variant in the gene encoding clavesin-1 (*CLVS1*) is a cause of steroid sensitive nephrotic syndrome and disrupts podocyte endocytosis as well as binding of clavesin-1 to an antioxidant transporter. Human podocyte cells lines with CLVS1 knockout (KO) and homozygous H310Y knockin (KI) displayed increased levels of reactive oxygen species (ROS) and apoptosis that could be rescued by treatment with corticosteroids as well as ROS inhibitors. However, the precise effects of CLVS1 deficiencies on the metabolic profile of podocytes is unknown.

Methods: To identify differences in podocyte metabolic function due to deficiencies in *CLVS1*, we used an Agilent Seahorse XF Analyzer to examine *CLVS1* KO, homozygous *CLVS1* H310Y KI, corticosteroid treated *CLVS1* H310Y KI, and control podocytes. Assays designed to measure ATP production, mitochondrial respiration, and glycolysis were used to examine differences between cell groups (N=15 for each).

Results: *CLVS1* KO and H310Y KI podocytes displayed a more energetic cell phenotype compared to controls that included a higher level of overall ATP production and increased glycolytic activity ($p<0.0001$ for each). An almost two-fold increase in glycolysis, glycolytic capacity and glycolytic reserves were observed in KO and KI podocytes compared to controls ($p<0.0001$ for each). These levels were unaffected by steroid treatment. Differences in mitochondrial respiration were relatively minimal between control and *CLVS1* KO or KI podocytes. However, increases in non-glycolytic acidification and non-mitochondrial oxygen consumption were observed in KO and KI podocytes ($p<0.0001$ for each), suggesting that additional physiological abnormalities may be present as well.

Conclusions: Defects in *CLVS1* increase glycolysis-mediated ATP production in podocytes. Glycolysis is a key component of podocyte metabolic activity, particularly in foot process regulation and elevated ROS levels can induce a shift towards increased glycolytic activity. However, further studies are required to determine if this altered metabolic activity contributes to podocyte dysfunction due to deficiencies in *CLVS1* or if it is a survival response to other cellular abnormalities including increased ROS levels.

Funding: Other NIH Support - NICHD

TH-PO785

Elucidation of the Molecular Mechanism of Albuminuria Improvement by Nonsteroidal Mineralocorticoid Receptor (MR) Antagonists Focusing on Podocyte Calcium (Ca2+) Dynamics

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Background: MR activation in podocytes has been linked to the progression of glomerular and podocyte injuries in diabetic kidney disease (DKD). In the FIDELIO-DKD study, non-steroidal MR inhibitors showed a significant reduction in the development of renal outcomes compared to placebo. However, there are still many unknown aspects regarding MR activation in DKD. Transient Receptor Potential Canonical (TRPC)s, a Ca^{2+} channel in podocytes, has been implicated in various kidney diseases, including hereditary nephrotic syndrome. We hypothesized that increased TRPC activity and expression due to MR activation in podocytes contribute to glomerular damage in DKD. We investigated the molecular mechanism of finerenone's effect on improving albuminuria in DKD.

Methods: C57BL/6 mice (control) and diabetic Akita mice (Akita) were used in the study. Four groups were created: Control-Nx (Nx; one nephrectomized), Control-Nx+HS (high salt diet), Akita-Nx+HS, and Akita-Nx+HS+finerenone. The mice were sacrificed at 17 weeks of age, and specimens and tissues were analyzed. In vivo imaging using a two-photon laser microscope was performed to confirm changes in albumin leakage from glomeruli. Additionally, cultured podocytes were used to assess the effect of aldosterone (Aldo) stimulation on TRPC5 expression, reactive oxygen species (ROS) production, Ca2+ influx, and actin rearrangement. Podocin-GCaMP5/tdTomato mice, which specifically express the calcium sensor protein GCaMP in podocytes, were used to study the effect of Aldo stimulation on Ca2+ influx.

Results: The Akita-Nx+HS group exhibited abnormal podocyte morphology and significantly increased albuminuria. Increased intraglomerular ROS production was observed, along with clear albumin leakage from glomeruli. In cultured podocytes, Aldo stimulation induced increased TRPC5 protein expression, ROS production, Ca2+ influx, and actin rearrangement. Similar Ca2+ influx was observed in Podocin-GCaMP5/tdTomato mice. These changes were ameliorated by MR and TRPC5 inhibitors.

Conclusions: The study demonstrated that MR activation in podocytes contributes to glomerular damage in DKD through increased TRPC5 channel expression and activity. MR inhibitors like finerenone improve podocyte Ca2+ dynamics and reduce damage in DKD.

Funding: Commercial Support - Bayer

TH-PO786

Multidimensional Characterization of Renal Biopsies Integrating Podocyte Morphology with Clinical and Histopathological Features

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Background: Podocyte foot process effacement and loss of glomerular filtration slits are common pathological changes observed in many chronic kidney diseases (CKD). Accurate measurement of podocyte morphology requires electron microscopy or advanced super-resolution light microscopy. Here, we used three-dimensional-structured illumination microscopy (3D-SIM) to quantify glomerular filtration slits in residual diagnostic biopsies of the NURTuRE CKD cohort. We integrated this measure of podocyte foot process morphology with other clinical and histopathological features to enable future precision diagnostics and patient stratification strategies.

Methods: Histological sections of formalin-fixed, paraffin-embedded kidney biopsies were stained for podocin and nephrin and analyzed using the 3D-SIM Podocyte Exact Morphology Measurement Procedure (PEMP). Filtration slit densities (FSD) and filtration slit lengths (FSL), which describe the density and extent of the glomerular filtration network, were derived from a median of 17 glomeruli per sample for 69 NURTuRE CKD patients of various etiologies.

Results: Quantification of podocyte morphology revealed different patterns of intra- and intersample variance with distinct, etiology-dependent distributions, likely reflecting common disease mechanisms. While samples from primary glomerular diseases showed a reduced median FSD and FSL with low intrasample variance, samples from secondary glomerular diseases showed high intrasample variance, suggesting distinct patterns of glomerular injury and disease progression. Moreover, podocyte morphology was strongly correlated with urinary protein and albumin creatinine ratios, but independent of other histopathological features, including glomerulosclerosis ratios and interstitial fibrosis and tubular atrophy scores.

Conclusions: Assessment of podocyte morphology in NURTuRE kidney biopsies supports FSD and FSL as independent and precise histopathological estimators of foot process effacement and glomerular integrity, revealing etiology-specific features of disease. Further integration of clinical time series and renal survival data, will uncover the potential of PEMP for kidney precision diagnostics and risk prediction.

Funding: Commercial Support - Evotec SE

TH-PO787

Role of Colony-Stimulating Factor-1 Receptor in Driving Parietal Epithelial Cell Activation in Focal Segmental Glomerulosclerosis

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Background: Parietal epithelial cells (PECs) are renal progenitor cells similar to bone marrow stem cell niches. In focal segmental glomerulosclerosis (FSGS), activated PECs contribute to extracellular matrix deposition. Colony stimulating factor-1 (CSF-1), a hematopoietic growth factor, acts through its specific receptor, CSF-1R, and has been implicated in various glomerular diseases. However, its role in PEC activation is still unknown. In this study, we studied the CSF-1/CSF-1R pathway in dysfunctional activation of PECs in FSGS.

Methods: CSF-1R expression was assessed in FSGS patient biopsies and in adriamycin (ADR)-induced FSGS mouse model. ADR-induced animals were further treated with specific CSF-1R inhibitors, GW2580 or Ki20227 (n=5-7). CSF-1R expression, localization in the glomerulus and its relevance to glomerulosclerosis were examined, as well as de novo CD44 formation and its correlation with the ERK1/2 pathway. Human kidney progenitor cells were treated with CSF-1 (n=6/group) to observe migration and proliferation changes and to identify potential key interactors of CSF-1 through RNAseq. Genes of interest were validated in the FSGS model.

Results: CSF-1R was upregulated in PECs and podocytes in FSGS biopsies. *In vitro*, results showed that PECs constitutively expressed CSF-1R. CSF-1 treatment induced CSF-1R upregulation and transcriptional changes in genes associated with PEC activation. CSF-1/CSF-1R activated the ERK1/2 pathway, upregulated CD44 while both ERK and CSF-1-R inhibitors reduced CD44 expression. CSF-1 promoted PEC proliferation and migration while suppressing podocyte differentiation. These results were validated in the ADR-induced FSGS model. Treatment with specific CSF-1R inhibitors demonstrated strong therapeutic effects. CSF-1 also promoted interferon (IFN)-related gene transcription in human PECs.

Conclusions: This study provides the first evidence of the involvement of the CSF-1/CSF-1R pathway in PEC activation in FSGS and suggests potential therapeutic use of CSF-1R inhibitors in FSGS treatment.

TH-PO788

AMPK Activation Ameliorates Angiotensin II-Induced Downregulation of Podocyte ZO-1

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Background: Angiotensin II (Ang II) promotes the development and progression of proteinuria and renal diseases and induces podocyte apoptosis. ZO-1 (zonular occludens-1) protein as a component of the slit diaphragm plays a pivotal role in glomerular permeability by connecting slit diaphragm structure and actin cytoskeleton. AMP-activated protein kinase (AMPK), as a sensor of cellular energy status, has been known to play an important role in the pathophysiology of metabolic diseases, including diabetes, and its renal complications. We investigated the role of AMPK on the changes of ZO-1 of podocyte induced by Ang II.

Methods: Mouse podocytes were incubated in media containing various concentrations of Ang II and AMPK-related agents. The changes of ZO-1 and permeability were observed by confocal imaging, western blotting, and permeability assay in the presence of Ang II.

Results: Ang II induced the fusion of microvilli and the gap pores on podocytes, which were improved by AICAR, an AMPK activator. Ang II also reduced and disrupted the intercellular ZO-1 staining, resulting in increased podocyte intercellular permeability. The intensities of fluorescences and bands of ZO-1 protein were decreased by Ang II in a dose-dependent manner by confocal microscopy and western blot analysis, respectively. AICAR and metformin, AMPK activators, ameliorated the abnormal distributional changes and the protein of ZO-1. Losartan, Ang II type I receptor blocker, also ameliorated the decrease of ZO-1 protein.

Conclusions: Our findings suggest that Ang II induces the relocation and suppression of podocyte ZO-1 via Ang II type 1 receptor which is ameliorated by AMPK-activating agents.

TH-PO789

Pre-Transplant Nephrin Autoantibodies Predict Post-Transplant Recurrent Focal Segmental Glomerulosclerosis (FSGS)

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Background: Recurrent Focal Segmental Glomerulosclerosis (FSGS) following renal transplant occurs commonly and can lead to early graft failure. Evidence supports a recipient derived circulating factor(s) that leads to early post-transplant recurrence however its identity has remained elusive. The recent discovery of nephrin autoantibodies in minimal change disease (MCD) lead us to hypothesize that nephrin autoantibodies pre-transplant may predict early recurrence in FSGS.

Methods: Single center retrospective study of 16 consecutive patients undergoing renal transplant for biopsy proven primary podocytopathy from the Centre Hospitalier Regional Universitaire de Lille between 2012 and 2019. Circulating anti-nephrin antibodies were evaluated pre-transplant by indirect ELISA. Recurrent FSGS was diagnosed on biopsy and the presence of nephrin antibodies was evaluated by immunofluorescence (IF).

Results: The median age of disease onset and transplant were 19 years (IQR 8.5-31.25) and 31 years (IQR 23.5-43.75) respectively. Disease recurrence was seen in half of the patients and occurred early, within 1 day, in 62.5% (n=5/8). One quarter (n=4/16) of the patients were serologically positive for nephrin autoantibodies at the time of transplant (Fig 1) and as expected, this was universally associated with disease recurrence (n=4/4) and constituted the majority, 80% (n=4/5) of those with early recurrence. There was complete concordance with anti-nephrin antibodies in the renal biopsies. Approximately one third (n=5/16) of the patients underwent pre-transplant plasma exchange (PE) and the majority (n=4/5) were serologically negative for nephrin autoantibodies. Post-transplant recurrence occurred in 2 of 5 patients and one of them was anti-nephrin antibody positive despite pre-emptive PE.

Conclusions: The presence of circulating nephrin autoantibodies at the time of transplant was universally associated with post- transplant early recurrence and were identified within the kidney disease. Our findings support an important role for nephrin autoantibodies in the pathogenesis of recurrent FSGS. In those patients undergoing pre-emptive PE this is would be an important biomarker to guide treatment as one patient who recurred despite PE has persistent circulating nephrin autoantibodies.

Funding: Private Foundation Support

TH-PO790

Characterization of a Novel Human Podocyte Cell Line as a Model for CKD Drug Development

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Background: Podocytes are terminally differentiated epithelial cells which act as a crucial component to form the glomerular filtration barrier. There are a number of challenges in working with human and mouse podocytes in culture for drug discovery programs as most cell lines do not present a typical podocyte morphology that is comparable with the in vivo situation, and some of the podocyte markers are not expressed in these cell lines. In this study, we characterized a novel human podocyte cell line

PODO/TERT 256 from Evercyte that has several advantages over long-standing SV40 T antigen immortalized podocytes. We completed further evaluation of this cell line as a potential tool for target validation and drug discovery.

Methods: The mRNA expression of podocyte markers was detected using qPCR and the protein expression was confirmed by western blotting and immunofluorescence staining of cultured podocytes. Comparative RNA profiling with other cell lines was assessed by RNA-seq. The effect of podocyte injury was assessed using puromycin aminonucleoside. The cell viability study and adhesion assay were quantified using CellTiter-Glo. The adhesion of podocytes was evaluated using Laminin, a ligand for Integrin $\alpha 3\beta 1$.

Results: We showed, that in PODO/TERT 256 cell line, the key podocyte markers *NPHS1, SYNPO, PODXL, WT-1, KIRREL, KIRREL3* were detectable by qPCR. Expression of the nephrin, podocin, synaptopodin and podocalyxin proteins were confirmed by western blotting. The localization to the cellular membrane for synaptopodin and nephrin was confirmed by immunofluorescent staining. RNA profiling study indicated that this cell line possesses podocyte characteristics. Nephrin expression was stimulated by 12-O-tetradecanoylphorbol-13-acetate (TPA) and suppressed by glucose. The cells demonstrated susceptibility to puromycin aminonucleoside (PAN) induced injury. Cell adhesion assays confirmed the suitability of this novel podocyte cell line for functional studies.

Conclusions: Characterization of novel podocyte cell line PODO/TERT 256 (Evercyte) confirmed expression of multiple podocyte-specific markers on RNA and protein levels. This new podocyte cell line will become a powerful tool for identification of the novel therapeutic targets and discovery of the new drugs for CKD.

Funding: Commercial Support - Janssen Research & Development

TH-PO791

Urinary Podocin Cell Count in Relation to Glomerular and Tubular Damage Markers in Patients with Primary Nephrotic Syndrome

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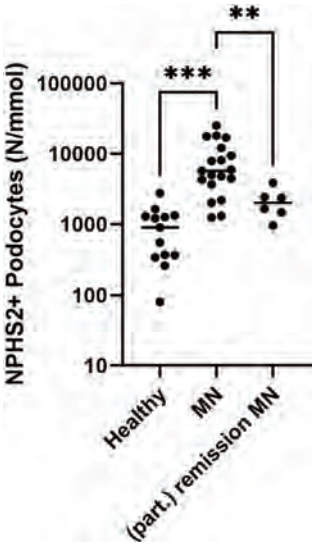
Background: Progressive renal failure in patients with glomerular disease is driven by podocyte depletion. Several methods have been proposed to monitor urinary podocyte loss. Here, we investigated the process of podocyte depletion in patients with primary membranous nephropathy (MN) by flow cytometric detection of Podocin-positive cells in urine.

Methods: We included 27 patients with MN. Urinary cell pellets were processed and stained for Podocin and subsequently counted using FACS. Urinary protein and creatinine levels were determined from the same portion of urine. Normal values of urinary Podocin-positive cells were obtained in urine samples of 13 healthy controls.

Results: Mean urinary podocyte count (Podocin-positive cells) was significantly higher in patients compared to healthy controls. Podocyte excretion showed significant correlations with urinary protein ($r = 0.71$), glomerular damage marker IgG ($r = 0.75$) and the tubular damage markers α1-microglobulin ($r = 0.66$) and β2-microglobulin ($r = 0.43$), all corrected for creatinine.

Conclusions: Urinary excretion of Podocin-positive podocytes was significantly increased in patients with MN, and correlated significantly with protein/creatinine ratios and glomerular and tubular damage markers. We conclude that this method can be used to monitor the process of podocyte depletion, and potentially the impact of treatment. We are planning prospective studies to evaluate the prognostic value of urinary Podocin$^+$ podocyte excretion in patients with PNS.

Funding: Government Support - Non-U.S.



TH-PO792

Value of Repeat Renal Biopsies in Lupus Nephritis in Two Large Inner-City Hospitals in New York

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Background: Class transition is common in lupus nephritis (LN) patients and may affect treatment. While the initial biopsy is indicated for the diagnosis, the role of repeat renal biopsies during renal flares is controversial. We retrospectively evaluated the histopathological and treatment changes associated with repeat renal biopsies in LN patients.

Methods: Fifty-six LN patients with at least 2 renal biopsies were included at Jacobi Medical Center and Montefiore Medical Center in Bronx, NY. Statistical analysis was performed using STATA 18 (StataCorp).

Results: The study cohort consisted of 80.4% (45/56) female, 48.2% (27/56) Black, and 42.8% (24/56) Hispanic patients, with a mean age of 26.4 ± 13.1 at the initial biopsy. The most common LN classes were proliferative, accounting for 62.9% and 80.8% of the identified classes in the 1st and 2nd biopsies respectively. There were no differences between the mean activity indices between the 1st and 2nd biopsies (1.89 ± 2.11 vs 2.10 ± 2.07, p =0.666). Mean chronicity indices were significantly higher in the 2nd vs. 1st biopsies (5.05 ± 2.60 vs 2.69 ± 2.19, p <0.001). Class switch occurred in 52% (26/50) of the repeat biopsies. Among the proliferative classes, 35% (11/31) had class switch within the proliferative categories (mixed class to III or IV or vice versa, or III to IV or vice versa), 6% (2/31) transitioned to class V, and 3% (1/31) to class II. Eighty percent (8/10) of the mixed III/IV+V class remained histologically unchanged in the repeat biopsies. Among non-proliferative classes, 75% (6/8) transitioned to proliferative classes (III, IV, or III/IV+V). Class switch during flares occurred more frequently in the non-proliferative classes compared to the proliferative classes (63% vs 45%, p=0.013). In the end, 64% of patients had escalation in their immunosuppression, 17% had de-escalation, and 19% had no change.

Conclusions: Repeat biopsies were found to be particularly important in those with non-proliferative class of LN at the initial biopsy since transition to proliferative class occurred in a majority of these cases. Further, a class switch occurred in more than half the patients and a majority of the patients had an escalation of therapy, suggesting the benefit of repeat biopsies during flare in our largely minority population.

TH-PO793

Identification of Unique Molecular "Fingerprints" of Systemic Lupus Erythematosus (SLE) and Evaluation of Kidney Function Using Urine Raman Spectroscopy and Chemometrics

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Background: SLE, a pan-systemic inflammatory disease, can have a deleterious effect on renal function. Timely detection and management of renal dysfunction is highly desirable, since many patients develop disease at an early age and inflammatory nephropathies can be relentlessly progressive.

Methods: We developed a Raman spectroscopic technology (Rametrix® molecular urinalysis) to detect SLE systemic/renal effects by analysis of patient urine. It is based on chemometric analysis of the Raman spectrum of urine and detects metabolomic differences. The technology is not designed specifically to detect cell degradation products (DP), such as nucleic acid DPs, but can be harnessed to probe and quantify these. We hypothesized that SLE would alter urine composition and that Rametrix® analysis could detect renal dysfunction via urine molecular 'fingerprinting'. We applied Rametrix® analysis on 587 urine specimens collected from 82 patients with biopsy-proven (80/82) and/or laboratory-validated SLE markers. Patients were 8-21 years of age (median age 14.5) and 77.5% female. Most patients were African-American (183/587), Latino (162/587) or Caucasian (129/587). Serial longitudinal urine samples were obtained on multiple individuals. A renal SLEDAI-2K score was correlated to Rametrix® findings. Using chemometric analysis of urine Raman spectra, we compared SLE urine spectra with urine spectra from urine of healthy controls (203), patients with CKD (20), COVID19 patients (118), bladder cancer patients (19) and Lyme disease patients (20).

Results: Rametrix® molecular urinalysis distinguished SLE-associated changes in urine composition with predictive metrics (accuracy, sensitivity, specificity, PPV, and NPV) ranging between 73-97%. A correlation between changes in urine Raman spectra and physician assessment of disease (SLEDAI-2K) was also found through computational analysis. Urine spectra from SLE and COVID19 patients showed notable Raman spectral similarities, suggesting common inflammatory pathways (interferonopathies).

Conclusions: Raman molecular urinalysis can be useful to detect and manage SLE and renal dysfunction.

Funding: Commercial Support - Rametrix Technologies, Inc.

TH-PO794

Establishment of Diagnostic Criteria for Tubulointerstitial Nephritis with IgM-Positive Plasma Cells (IgMPC-TIN)

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Background: We proposed the IgMPC-TIN disease concept in 2017, and this disease concept is gradually gaining recognition in Japan. However, there are no clear diagnostic criteria for diagnosing IgMPC-TIN. We attempted to develop diagnostic criteria for IgMPC-TIN from both clinical and histological parameters or from only clinical parameters using cases collected from multiple institutions.

Methods: A total of 118 renal biopsy samples were collected from 61 patients with suspected IgMPC-TIN and 57 patients with other interstitial lesions from our hospital and national collaborating centers, and we performed double staining (IgM and CD138) using the immunoenzymatic method. Patients with M protein in their blood or urine and patients with diabetes mellitus were established as exclusion criteria. Then several nephrologists classified each case that did not meet the exclusion criteria from +3 (typical IgMPC-TIN) to −3 (not IgMPC-TIN at all). Based on 49 cases judged as +3 and 56 cases judged as −3, a decision tree-based diagnostic algorithm was created in JMP. Finally, the sensitivity and specificity of the diagnostic criteria created were calculated.

Results: In the diagnostic criteria consisting of histological and clinical parameters, the most important requirement was a maximum IgMPC infiltration count of ≥20/high magnification field of view (7400 μm^2). The next most important requirement was the presence of urinary sugar, and the next requirement was the presence of primary biliary cholangitis (PBC). For diagnostic criteria consisting only of clinical parameters, the most important requirement was a serum IgM level of 267 or higher, followed by the presence of Fanconi syndrome. Sensitivity and specificity of each diagnostic criterion were 97.9 and 100% for histological and clinical parameters and only for clinical parameters. Although we consider diagnostic criteria that include histological parameters to be the gold standard, diagnostic criteria based solely on clinical parameters are also sufficiently accurate.

Conclusions: We analyze the clinical characteristics of IgMPC-TIN cases and develop criteria for the diagnosis of IgMPC-TIN based on histological and clinical parameters.

Funding: Government Support - Non-U.S.

TH-PO795

ANCA-Associated Kidney Disease in a Child with History of Presumed IgG4-Related Disease

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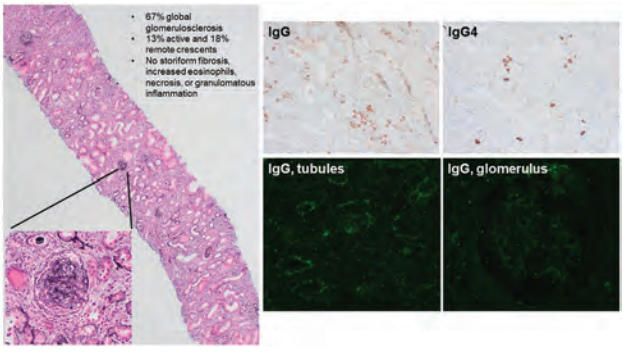
Introduction: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and IgG4-related disease (IgG4-RD) are immune disorders with distinctions in pathogenesis, prognosis, and management, that can share clinical and laboratory features. While ANCA positivity excludes IgG4-RD in the 2019 ACR/EULAR classification, this criterion is not uniformly applied, and AAV can form inflammatory masses in various organs and show increase in IgG4+ plasma cells, similar to IgG4-RD. This case highlights challenges in AAV and IgG4-RD diagnoses in a child.

Case Description: A 5-year-old female with previously normal kidney function presents with nausea, diarrhea and acute kidney injury with hematuria and proteinuria. Her only medical history is of a left orbital mass a year ago, diagnosed as IgG4-RD based on elevated serum IgG (1270 mg/dL) and biopsy with sclerosing fibrosis with IgG4+ plasma cells and eosinophils, and treated with steroids with complete mass resolution. On this admission, she has a positive MPO ANCA (1:80) with pertinent negatives of normal serum C3, C4, total IgG, and IgG4, and negative ANA and anti-dsDNA. A kidney biopsy shows chronic active pauci-immune crescentic glomerulonephritis and acute tubulointerstitial nephritis with up to 14 IgG4+ plasma cells/40X field, IgG4+/IgG+ plasma cell ratio up to 25%, and focal tubular basement membrane (TBM) deposits (Image). She is treated with pulse steroids and rituximab with no kidney function improvement, in contrast to most cases of IgG4-RD.

Discussion: Pauci-immune crescentic GN with positive ANCA are characteristic for kidney AAV, and in retrospect, suggest the orbital mass may have represented the initial manifestation of AAV despite orbital mass histology with increased IgG4+ plasma cells and elevated serum IgG4 at diagnosis. The additional features of TBM deposits and increased IgG4+ plasma cells in the kidney biopsy highlight further potential for confounding morphologic overlap between AAV and IgG4-RD, for which correlation with ANCA testing is essential.



TH-PO796

Interstitial ANCA-Associated Vasculitis Associates with Severe Kidney Injury Independent of Glomerulonephritis

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Background: Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a small vessel vasculitis affecting multiple organ systems, including the kidney. Although crescentic ANCA glomerulonephritis (GN) is a common histological finding reflecting glomerular small vessel vasculitis, it is reasonable that manifestation of AAV could also contribute to interstitial small vessel vasculitis. Therefore, we here aimed to expand our current knowledge focusing on interstitial vasculitis in ANCA GN by systematic histological scoring of vascular lesions analogous to Banff.

Methods: A total number of 49 kidney biopsies with confirmed renal involvement of AAV at the University Medical Center Göttingen were retrospectively included between 2015 till 2020. A renal pathologist evaluated all biopsies and was blinded to clinical data collection and analysis.

Results: Since previous studies established that crescentic ANCA GN associates with severe kidney injury and acute deterioration of kidney function in AAV, we first systematically scored interstitial vasculitis in association with requirement of renal replacement therapy (RRT). Among all active and chronic tubulointerstitial lesions analogous to the Banff scoring system, the only association between severe kidney injury requiring RRT was observed for interstitial vasculitis in AAV reflected by peritubular capillaritis (ptc, p=0.0002) and arteritis (v, p=0.0069), affecting 5/49 (10.2%) and 11/49 (22.4%) of renal biopsies, respectively. Interestingly, no association between interstitial vasculitis (ptc and v correlating with severe kidney injury) and any glomerular lesion in ANCA GN (also correlating with severe kidney injury) was observed, thereby confirming that interstitial vasculitis contributes to severe kidney injury independent of ANCA GN. By contrast, short-term renal recovery from RRT was equal in both groups, suggesting a distinct association with acute decline of kidney function at disease onset.

Conclusions: Taken together, by using the Banff scoring system we here expand our current knowledge of renal interstitial lesions in AAV revealing peritubular capillaritis and arteritis as important histological alterations associated with severe kidney injury in a considerable subset of AAV.

TH-PO797

Transthyretin Amyloidosis with Biopsy-Proven Renal Involvement

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Background: Systemic amyloidosis is a cluster of disorders characterized by tissue deposition of amyloid (highly ordered fibrils composed of low molecular weight subunits of a variety of proteins). Transthyretin (TTR) amyloidosis (ATTR) is either an autosomal dominant inherited condition (ATTRv, where v stands for "variant") or a non hereditary disease due to misfolding of wild-type TTR (ATTRwt). ATTR is likely underdiagnosed due to its clinical variability and lack of specific symptoms or biomarkers. The first aim of the study is to emphasise the importance of suspecting ATTR when facing certain clinical manifestations in association with renal impairment and urinary abnormalities. Furthermore, renal biopsy provides crucial information for a correct diagnosis and treatment approach.

Methods: We report 5 cases of biopsy-proven renal ATTR deposition in patients presenting with mild to moderate renal impairment and mild urinary abnormalities. The TTR precursor has been confirmed in kidney specimens by immunohistochemistry. Genotyping was carried out in every patient.

Results: The presence of amyloid was found in all patients, with different distribution (#1-3 pericapsular and vascular; #2 vascular; #4 mesangial, vascular, in tubular basement membrane and in the interstitium of cortex and medulla; #5 pericapsular, vascular and interstitial). On genetic analysis three patients were wild-type (#1-2-5), one carried the c.424G>A (p.(Val142Ile)) mutation (#3) and the last one the Val30Met mutation (#4).

Conclusions: Suspicion of ATTR should be considered in patients with increase in serum creatinine, mild proteinuria and cardiac and peripheral nerve symptoms. This can be of utmost importance in elderly patients in whom a monoclonal gammopathy of undetermined significance can co-exist and drive a wrong diagnosis of primary light chain amyloidosis (AL), that could lead the clinician to undertake inappropriate treatments. Renal biopsy and genetic sequencing are both critical in diagnosing ATTR. Finally, we suggest distinguishing in the context of the ATTR deposition disease an ATTR nephropathy characterized by mesangial accumulation of amyloid, that impacts functional and urinary assessment, from isolated deposition in small vessels without specific clinical consequences, albeit critical for ATTR diagnosis.

TH-PO798

Microplastics: First Proteomic Analysis on Kidney Tubular Cells

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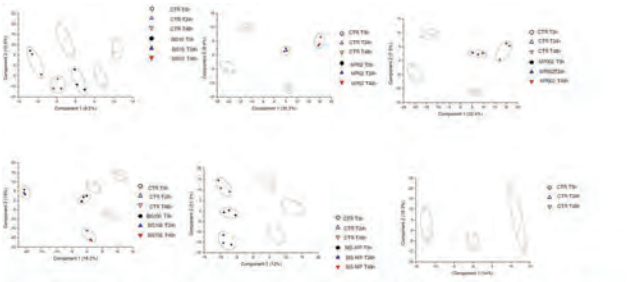
Background: Microplastics (fragments < 5 mm in diameter) and nanoplastics (< 1 μm) are ubiquitous in the environment. Microplastics (MPs) absorb environmental pollutants, such as bisphenol A (BPA), and release them into tissues increasing their toxicity. Their presence has been proved in human blood and human tissues, such as placenta and lung, and in cirrhotic liver. Biological effects of MPs are inflammation, oxidative stress and alteration of metabolic pathways. We performed proteomic analysis to evaluate the toxicity of polyethylene (PE) and bisphenol-A (BPA) MPs on renal tubular cells (HK2).

Methods: HK-2 cultures were exposed to BPA, PE Microspheres (PE-MP) and MP combined with BPA. We performed a proteomic analysis by mass spectrometry (MS). Analysis of data were performed using unsupervised hierarchical clustering using multidimensional scaling, non-linear support vector machine (SVM) learning, and partial least squares discriminant analysis. In SVM learning, a fourfold cross-validation approach was applied to estimate the prediction and classification accuracy.

Results: Analysis showed a clear differentiation of the HK2 proteome based on conditioning and identified a "core" of proteins, significant at ANOVA and above the 95th percentile for "fold increase" and significant at T-test compared with controls, highly discriminatory between groups. A final set of 5 proteins was selected to be validated for distinguishing features. PPIAL4C accelerate the folding of proteins. Nephronectin is involved in cellular adhesion. GDF15 is a markers of stress conditions. IGFBP7 is a biomarker of acute kidney damage. CDKN1C is a negative regulator of cell proliferation.

Conclusions: MP and BPA significantly modify the protein expression in renal tubular cells. These findings highlight the urgent need for additional research into the toxic effects of plastic debris on human kidneys and the eventual link to kidney diseases.



Multidimensional scaling. Highly performance discrimination of all the experimental groups, different conditions and times compared with controls

TH-PO799

Magnetic Resonance Imaging Contrast Agents: Confounded Exposures Matter

Brent Wagner,[1,2] G. P. Escobar,[1,3] Tamara A. Howard,[3,1] Abdul Mehdi S. Ali,[4,1] Joshua Deaguero,[1,3] Karol Dokladny.[1,3] Kidney Institute of New Mexico. *[1]Kidney Institute of New Mexico, Albuquerque, NM; [2]New Mexico VA Health Care System, Albuquerque, NM; [3]University of New Mexico Health Sciences Center, Albuquerque, NM; [4]University of New Mexico, Albuquerque, NM.*

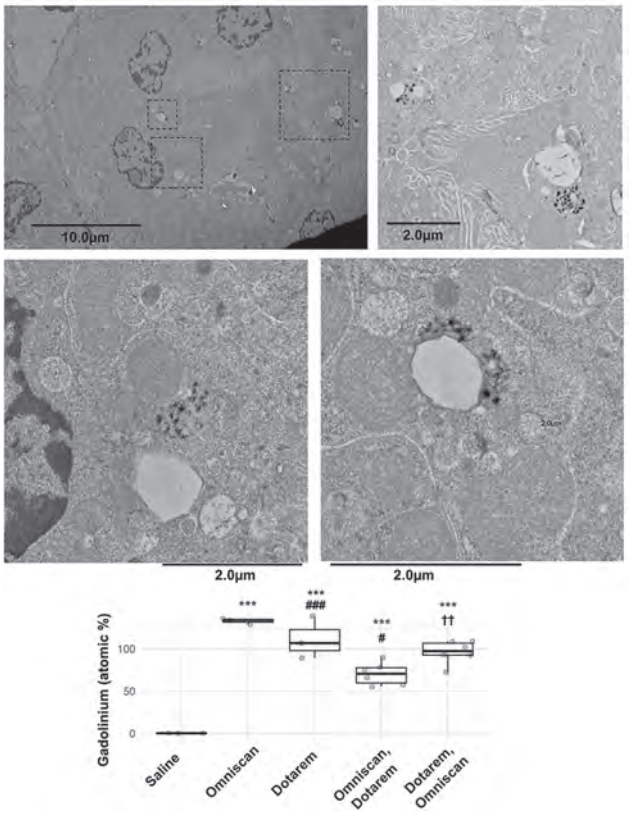
Background: Gadolinium-induced systemic fibrosis involves the monocyte chemoattractant protein-1/C-C chemokine receptor 2 pathway. Observational analyses measuring the risk of nephrogenic systemic fibrosis universally discounted exposures to multiple brands. The patients who contact the Kidney Institute of New Mexico report exposure to various brands or American College of Radiology Group 2 agents. Using our rodent model, we examined the pathology and metal retention of combined Group1/2 exposures.

Methods: We treated rodents for one week with Omniscan and three weeks of Dotarem (and vice versa) according to our standard, published protocols. Specimens were analyzed using conventional histology and electron microscopy. We quantified gadolinium with ICP-MS (Nexion 300D, Perkin-Elmer).

Results: Confounded treatments (Omniscan followed by Dotarem or vice versa) led to the formation of intracellular nanoparticles in the renal proximal tubules.

Conclusions: Measuring the incidences of gadolinium-induced complications has been artificially reduced by excluding confounded contrast agent exposures. Our results demonstrate that Le Chatellier's principle must be entertained in estimating the risk from magnetic resonance imaging contrast agents. Because routine magnetic resonance imaging contrast agent administration leads to gadolinium-rich nanoparticles in the brain and the kidney, defending particular brands is a fragile position.

Funding: NIDDK Support, Other NIH Support - UL1TR001449, Veterans Affairs Support, Private Foundation Support



Mixed exposures to class 1 and 2 magnetic resonance imaging contrast agents (Omnisan, Dotarem) led to intracellular gadolinium-rich nanoparticles in the renal proximal tubule. Transmission electron microscopy, Hitachi H7700. Kidney gadolinium levels were similarly elevated regardless of the magnetic resonance imaging contrast agent treatment group. *** P < 0.001, ANOVA, TukeyHSD.

TH-PO800

Intersectin 1 and Intersectin 2 Localize with IgG Deposition in Glomeruli

Naonori Kumagai, Tomomi Kondo, Yuji Matsumoto, Yohei Ikezumi. *Fujita Ika Daigaku, Toyoake, Japan.*

Background: Intersectin 1 (ITSN1) and intersectin 2 (ITSN2) are multifunctional proteins and are causative gene for steroid-sensitive nephrotic syndrome. However, their expression in glomeruli remains unclear. IgG deposition cause glomerular injury and play a pivotal role in glomerular diseases such as membranous nephropathy and lupus nephritis. However, the molecules associated with IgG deposition remain unclear.

Methods: ITSN, ITSN2, and IgG were co-stained with immunofluorescence staining for renal biopsy specimens of pediatric patients with glomerular diseases such as steroid sensitive nephrotic syndrome, steroid resistant nephrotic syndrome, IgA nephropathy, Henoch-Schonlein nephropathy, membranous nephropathy, and lupus nephritis.

Results: ITSN1 and ITSN2 stained at the same site and with the same intensity as IgG regardless of the type of disease. In membranous nephropathy and lupus nephritis, ITSN1 and ITSN2 stained strongly at the IgG stained site with the same intensity as IgG, especially in glomerular capillary. In other kidney diseases such as IgA nephropathy, Henoch-Schonlein nephropathy, steroid sensitive nephrotic syndrome, and steroid resistant nephrotic syndrome, ITSN1 and ITSN2 stained weakly at the IgG stained site with the same intensity as IgG.

Conclusions: ITSN1 and ITSN2 seem to express in glomeruli in response to IgG deposition, since they stain at the IgG stained site with the same intensity as IgG regardless of the type of disease. They are considered commonly associated with IgG deposition regardless of the type of disease, which cause glomerular injury. It remains to elucidate the pathophysiological role of ITSN1 and ITSN2 in glomerular injury caused by IgG deposition.

Funding: Government Support - Non-U.S.

TH-PO801

Fast Molecular Profiling of Kidney Biopsy Tissue by Gene Profiling from Biopsy Transport Medium

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Background: Molecular assessment by targeted gene profiling of kidney biopsy tissues is gaining traction in kidney pathology, particularly kidney transplant biopsies (e.g. with the Nanostring B-HOT panel). A critical downside of molecular assessment from FFPE tissues is its turnaround time and same-day diagnostics is currently not feasible. Timely and tailored treatment requires the support of faster and more sensitive molecular assessment and we therefore studied the use of biopsy transport medium (BTM) used to transfer kidney biopsies from the clinic to the pathology ward.

Methods: We utilized tumor-free tissues from complete nephrectomy to cut tissues into small strips, imitating the size of a renal biopsy. These biopsies were stored in PBS to mimic the process of biopsies transport at our department. We optimized RNA isolation by comparing different RNA isolation methods, centrifuge speeds, and storage times of the biopsies in the BTM. We checked the quantity and integrity of the RNA and performed qPCR with different biomarkers. We validate the reliability of BTM by comparing gene expression in BTM and frozen tissues from the same kidney. Finally, from a cohort of regular biopsies, RNA was isolated.

Results: Our results showed that different RNA isolation methods, centrifuge speeds, and different storage time up to 24 hours did not have a significant effect on RNA quality and yield. In a preliminary assessment, we were able to measure cell-specific genes by RT-PCR, representing T cells, B cells, macrophages, and even podocytes. The average RNA yield from regular biopsies was 165ng with RIN values around 7. As an example, CD68 expression of BTM correlated with the CD68 expression of tissue from their corresponding kidneys (N=5, r= 0.902, p<0.05).

Conclusions: Our results demonstrate that we can obtain relatively large amounts of RNA with sufficient quality from BTM, and that gene expression analysis from BTM is practically feasible as we were able to measure the expression levels of cell-specific genes within 5 hours after arrival. BTM represents an interesting new source for rapid molecular assessment and a potentially feasible alternative to molecular assessment on FFPE tissues without the need for an extra biopsy core. Further research should validate its potential in discriminating clinically relevant diagnosis and/or quantification of disease activity.

TH-PO802

Development and Validation of a Multilayer Segmentation Model to Quantify Chronic Changes on Kidney Biopsy

Muhammad Sohaib Asghar,[1] Lucas Stetzik,[2] Jaidip M. Jagtap,[1] Laura Barisoni,[3] Mariam P. Alexander,[1] Fadi E. Salem,[4] Maxwell L. Smith,[5] Andrew Janowczyk,[6,7] Aidan F. Mullan,[1] Aleksandar Denic,[1] Andrew D. Rule.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Aiforia Technologies, Cambridge, MA; [3]Duke University, Durham, NC; [4]Mayo Clinic in Florida, Jacksonville, FL; [5]Mayo Clinic Arizona, Scottsdale, AZ; [6]Emory University, Atlanta, GA; [7]Georgia Institute of Technology, Atlanta, GA.*

Background: Semiquantitative visual assessment of chronic structural changes is clinically relevant but has limited reproducibility. To better quantify chronicity, we developed a multilayer artificial intelligence (AI) model for the automated detection of glomerular, tubulointerstitial, and vascular chronic changes.

Methods: HistoQC was first applied to 1258 whole slide images (WSI) generated by multisite multi-scanner Aging Kidney Anatomy study to curate the dataset and to ensure representative variability. Aiforia Create, an AI-based interactive tool, was then used on 193 PAS-stained whole slide images (WSI) from 99 kidney tumor patients and 94 living kidney donor biopsies. This approach uses an iterative process to assign classes (semantic segmentation or object detection with instance segmentation) across nested layers. A total of 20,509 objects or regions were manually annotated to train the model. To validate the model, an independent test set of 10 WSIs (5 kidney tumor patients and 5 kidney donors) were annotated independently by 7 human validators and by the AI model. Then, for all 203 WSIs, the objects and regions detected by the AI model were used to calculate chronic changes. These were correlated with similar measures of chronic changes derived independently using human annotations.

Results: The final model assigned 20 classes across 9 nested layers (**Figure 1**). The F1 score for AI vs human was 95% and for human vs human was 96%. The correlation between AI model vs human measures was r=0.92 for glomerular volume, r=0.90 for cortex per glomerulus, r=0.92 for % globally sclerotic glomeruli, r=0.82 for AI % tubular atrophy vs. human % interstitial fibrosis/tubular atrophy, and r=0.72 for % artery stenosis from intimal thickening.

Conclusions: A multilayer AI model for the segmentation of 20 different classes on PAS-stained WSIs facilitate the quantification of kidney chronicity indices.

Funding: NIDDK Support

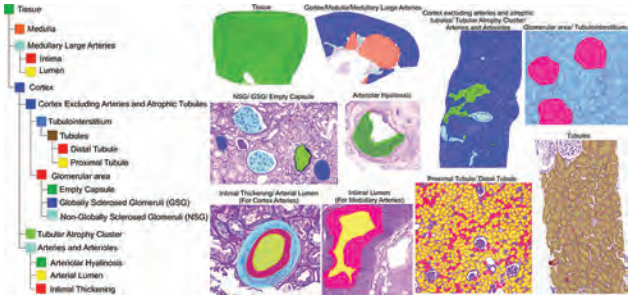

Figure 1. Layer tree of AI model with examples of performance in each class.

TH-PO803

On-Site Evaluation of Renal Biopsy Specimens: Impact on Diagnostic Yield in the Absence of Nephropathologists

Esra Ekiz, Tariq A. Mu'Amar, Suhaib A. Andrabi, Leroy Herbert. *Harlem Hospital Center, New York, NY.*

Background: Renal biopsy is a crucial procedure for diagnosing kidney diseases, and the quality of obtained tissue samples is essential for accurate diagnosis. On-site evaluation of biopsy specimens has been shown to increase the diagnostic yield. However, there is a trend of omitting on-site assessment when a nephropathologist is not readily available, leading to decreased yield. We hypothesized that evaluation of biopsy specimens by a nephrologist en-suite would improve specimen adequacy in the absence of a pathologist.

Methods: Electronic medical records of patients who underwent kidney biopsy from 2019 to 2022 were reviewed. Demographic, clinical, and biopsy-related data were collected. Biopsy specimens were evaluated by a nephrologist on-site, and the final pathology report was provided by different pathologists. Adequacy of the specimens was assessed based on the number of glomeruli observed under light microscopy, immunofluorescence, and electron microscopy.

Results: The average age of the study sample was 50, range between 20-72 years of age. 19 of all patients were women. 5 out of 30 biopsies were performed under CT-guidance. Adequate number of glomeruli were found in 27 biopsies; 2 of them had 6 glomeruli in LM, the other had a total of 3 glomeruli. A minimum of 1 glomerulus was available for IF and EM. 2 specimen were deemed adequate by ephrologist but inadequate by patholgist. 1 specimen was deemed inadequate by both nephrologist and pathologist. Average glomerular yield was 26. Median glomerular yield was 40 glomeruli total. The most common pathologic diagnoses were secondary FSGS and diabetic nodular glomerulosclerosis.

Conclusions: Adequate biopsy samples are crucial for accurate diagnosis and monitoring of kidney disorders. Previous studies have shown that on-site assessment of biopsy specimens improves yield outcomes. In this study, evaluation of specimens by a nephrologist en-suite showed nearly 100% correspondence with pathologists' assessments. Our findings suggest that nephrologists' evaluation of gross biopsy specimens can positively impact biopsy yield in institutions lacking nephropathologists. Further research with larger cohorts is needed to validate these findings and assess the generalizability of this approach.

TH-PO804

Biopsy Features of Initial KPMP Participants with CKD and Diabetes or Hypertension

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Background: The Kidney Precision Medicine Project (KPMP) is obtaining kidney biopsies in people with common causes of CKD and AKI for complete clinical, histopathological, and molecular characterization. Here we report findings from the first set of adjudicated CKD biopsies.

Methods: KPMP enrolled adults with CKD and diabetes or hypertension with eGFR 30-59ml/min/1.73m^2, UACR >30mg/g, or UPCR >150mg/g. Standardized clinicopathological adjudication by KPMP nephrologists and kidney pathologists was completed for 39 participants enrolled 2019-2022. Clinicians completed surveys to assess impacts of biopsy results on diagnosis and management.

Results: Participants' mean age was 59 years, 59% were female. Mean eGFR was 53ml/min/1.73m^2 and median UACR was 96mg/g. Among participants with diabetes and CKD (N=28), 15 (54%) had a primary diagnosis of diabetic nephropathy, 3 (11%) had vascular nephrosclerosis, 2 (7%) had other glomerular diseases, and 8 (29%) participants had non-specific biopsy findings for which no primary diagnosis could be determined. Among those enrolled with hypertension and CKD (N=11), 5 (46%) had vascular nephrosclerosis and 6 (55%) had non-specific findings. A range of glomerular, tubulointerstitial, and vascular findings was observed (**Table**). 26% of clinicians stated results were different than expected and 77% stated results affected prognostic discussions.

Conclusions: Kidney biopsies in people with common causes of CKD show a broad range of histopathology and may have clinical utility. Unexpected and non-specific findings precluding a definitive diagnosis are often present. Biopsies influenced prognostic discussions between participants and their providers.

Funding: NIDDK Support

Table. Laboratory and biopsy characteristics of KPMP CKD participants

Variable	Overall (n=39)	DKD (n=28)	HCKD (n=11)
Adjudicated diagnoses (N (%))			
Diabetic nephropathy	15 (38.5)	15 (53.6)	0 (0.0)
Vascular nephrosclerosis	8 (20.5)	3 (10.7)	5 (45.5)
Cannot determine	14 (35.9)	8 (28.6)	6 (54.5)
Other*	2 (5.2)	2 (0)	0 (0)
Laboratory measures			
eGFR, most recent (mean (SD))	53 (24)	57 (28)	44 (10)
UACR, mg/g Cr (median [IQR])	96 [4, 520]	204 [45, 887]	4 [2, 19]
UPCR, mg/g Cr (median [IQR])	26 [82, 900]	629 [158, 1,878]	75.5 [64, 155]
Biopsy features			
% Global glomerulosclerosis (mean (SD))	24.4 (16.0)	24.2 (15.4)	25.1 (18.1)
Diabetic changes (N (%))**			
0	17 (43.6)	6 (21.4)	11 (100.0)
I	2 (5.1)	2 (7.1)	0 (0)
IIa	7 (17.9)	7 (25.0)	0 (0)
IIb	3 (7.7)	3 (10.7)	0 (0)
III	10 (25.6)	10 (35.7)	0 (0)
Global glomerulosclerosis, exceeding age-expected (N (%))	27 (69.2)	20 (71.4)	7 (63.6)
Maximum GBM thickness nanometers (median [IQR])	900.0 [838.5, 1,180.0]	900.0 [838.5, 1,180.0]	NA
Tubular atrophy (N (%))			
0	2 (5.1)	1 (3.6)	1 (9.1)
1+	18 (46.2)	13 (46.4)	5 (45.5)
2+	16 (41.0)	11 (39.3)	5 (45.5)
3+	3 (7.7)	3 (10.7)	0 (0)
Tubulointerstitial fibrosis (N (%))			
0	2 (5.1)	1 (3.6)	1 (9.1)
1+	17 (43.6)	12 (42.9)	5 (45.5)
2+	17 (43.6)	12 (42.9)	5 (45.5)
3+	3 (7.7)	3 (10.7)	0 (0)
Tubulointerstitial inflammation, fibrotic areas (N (%))			
0	8 (20.5)	3 (10.7)	5 (45.5)
1+	24 (61.5)	19 (67.9)	5 (45.5)
2+	6 (15.4)	6 (21.4)	0 (0)
3+	1 (2.6)	0 (0)	1 (9.1)
Arteriosclerosis (N (%))			
0	3 (7.7)	3 (10.7)	0 (0)
1+	8 (20.5)	4 (14.3)	4 (36.4)
2+	16 (41.0)	12 (42.9)	4 (36.4)
3+	12 (30.8)	9 (32.1)	3 (27.3)
Arteriolar hyalinosis (N (%))			
0	11 (28.2)	5 (17.9)	6 (54.5)
1+	8 (20.5)	4 (14.3)	4 (36.4)
2+	8 (20.5)	7 (25.0)	1 (9.1)
3+	12 (30.8)	12 (42.9)	0 (0)

*Other diagnoses: N=1 fibrillary glomerulonephritis, N=1 IgA nephropathy; **Graded using the pathologic classification system for diabetic nephropathy developed by the Renal Pathology Society (2009); DKD = diabetic kidney disease (diabetes + CKD at enrollment); HCKD = hypertensive kidney disease (hypertension + CKD at enrollment)

TH-PO805

Automated Foot Process Width (FPW) Measurements Using a Deep Learning (DL) Model Are Interchangeable with Stereology and Correlate with Kidney Functional and Structural Variables

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Background: Increased FPW is a key measure of podocyte (PC) health and injury. Unbiased stereology, the current gold standard, is time consuming and not widely available. To address this, we developed a DL model for automated FPW measurement.

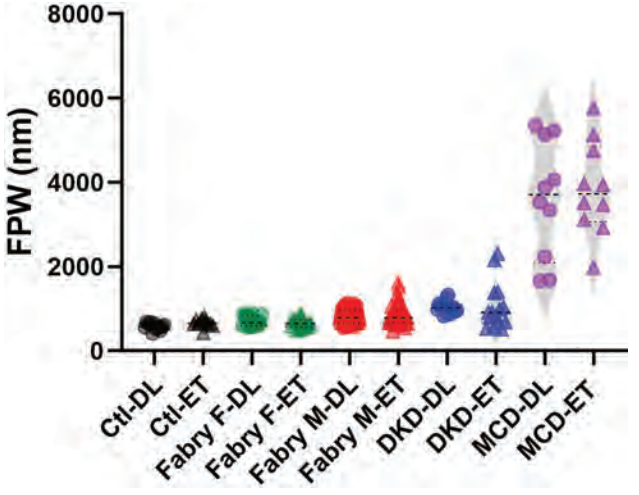
Methods: A U-Net variant model was trained to semantically segment the PC-glomerular basement membrane interface (PGBMI) and filtration slits. A cloud-based application was developed for users to upload systematic electron microscopy (EM) images, view and download the results. The model was applied to EM images of biopsies from Fabry disease (FD) patients (n=56), type 2 diabetes (T2D) (n=15), minimal change disease (n=10), and controls (n=17). The results were compared with unbiased stereology measurements by expert technologists (ET).

Results: DL and ET FPW measurements were correlated and not statistically different in all of the groups. Bland-Altman plot confirmed method interchangeability. FPW measurement time/biopsy was reduced from ~8 hours (ET) to <1 min (DL). In male (M) FD patients, both DL and ET measured FPW correlated directly with age, urine protein/creatinine (PCR), podocyte volume (VPC) and volume of FD inclusions per PC [V(Inc/PC)]; However, only DL FPW correlated inversely with PC numerical density. In female (F) FD patients, only DL FPW directly correlated with PCR, VPC and V(Inc/PC). In the T2D group, both DL and ET FPW correlated directly with fractional volume of mesangial matrix per glomerulus. However, only DL FPW directly correlated with urine

albumin/creatinine, and fractional volume of mesangium per glomerulus, and VPC, and inversely with glomerular filtration surface density.

Conclusions: Our novel and validated DL model for EM FPW measurements can make this important biomarker widely accessible for research and clinical applications.

Funding: NIDDK Support, Other NIH Support - NCATS



TH-PO806

Clinical Relevance of Computationally Derived Spatial Relationships Between Interstitial Fibrosis and Tubular Atrophy (IFTA) and Peritubular Capillary Features

Yijiang Chen,[1] Bangchen Wang,[2] Dawit S. Demeke,[3] Fan Fan,[1] Celine C. Berthier,[4] Jeffrey B. Hodgin,[3] Andrew Janowczyk,[5,8] Laura Barisoni,[2,6] Anant Madabhushi.[5,7] *[1]Case Western Reserve University Department of Biomedical Engineering, Cleveland, OH; [2]Duke University Department of Pathology, Durham, NC; [3]University of Michigan Department of Pathology, Ann Arbor, MI; [4]University of Michigan Department of Internal Medicine, Ann Arbor, MI; [5]Emory University, Atlanta, GA; [6]Duke University Department of Medicine, Durham, NC; [7]Atlanta Veterans Administration Medical Center, Atlanta, GA; [8]University Hospital of Geneva, Geneva, Switzerland.*

Background: The status of the tubulointerstitium and microvasculature is clinically relevant in glomerular diseases. While extent of interstitial fibrosis and tubular atrophy (IFTA) and peritubular capillaries (PTC) shape are independently associated with glomerular disease progression, the prognostic relevance of PTC shape features stratified by IFTA remains unknown.

Methods: N = 344 PAS-stained whole slide images (114 MCD/MCD-like, 132 FSGS, 61 MN and 37 IgAN) from the NEPTUNE/CureGN datasets were manually segmented for cortex and IFTA. A deep learning model was applied for PTC segmentation. The WSIs were split into training (S_t) and testing (S_v) datasets (1:1). 100 pathomic features quantifying cortical PTC shape were extracted from PTCs in IFTA and non-IFTA regions. Clinical outcome was defined as 40% eGFR decline or kidney failure. Lasso regression models were constructed on S_t, identifying top PTC shape features in IFTA and non-IFTA regions. The same features and model parameters were applied on S_v for independent validation. A prognostic model built with IFTA cortical density alone was created for comparison. Cox proportional hazards models and KM curves were used to evaluate prognostic relevance of the models.

Results: PTC shape features in IFTA regions were prognostic of disease progression, while PTC shape features in non-IFTA regions were not. The association between cortical IFTA density and disease progress was included for comparison (Figure 1). The top PTC shape features selected from IFTA regions are listed in Table 1.

Conclusions: IFTA density and PTC shape characteristics in IFTA regions are biomarkers of disease progression in patients with glomerular diseases. These results suggest that PTCs within IFTA regions tend to undergo morphologic changes, and these morphologic features are associated with kidney failure.

Funding: NIDDK Support, Other NIH Support - NIH-NCI

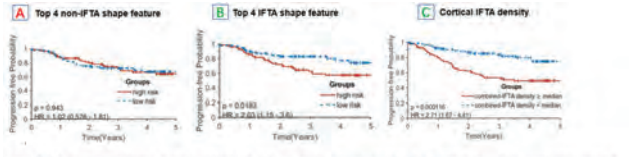
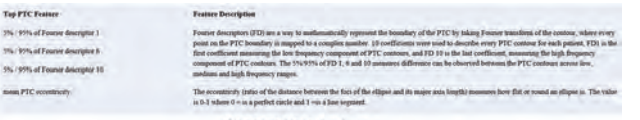


Figure 1: Cox Proportional Hazards model Visualized with KM Curves: (A) showing non-IFTA PTC shape model without significant association with disease progression ($p > 0.05$), (B) IFTA PTC shape feature based model and (C) Cortical IFTA density model showing significant association with disease progression ($p < 0.05$)



Top PTC Feature	Feature Description
5% / 95% of Fourier descriptor 1	Fourier descriptors (FD) are a way to mathematically represent the boundary of the PTC by taking Fourier transform of the contour, where every point on the PTC boundary is mapped to a complex number. 10 coefficients were used to describe every PTC contour for each patient. FD1 is the first coefficient measuring the low frequency component of PTC contours, and FD 10 is the last coefficient, measuring the high frequency component of PTC contours. The 5%/95% of FD 1, 6 and 10 measures difference can be observed between the PTC contours across low, medium and high frequency ranges.
5% / 95% of Fourier descriptor 6	
5% / 95% of Fourier descriptor 10	
mean PTC eccentricity	The eccentricity (ratio of the distance between the foci of the ellipse and its major axis length) measures how flat or round an ellipse is. The value is 0-1 where 0 = is a perfect circle and 1 =is a line segment.

Table 1: Top IFTA PTC shape feature descriptors

TH-PO807

A Comparison of Artificial Intelligence (AI) vs. Human-Derived Measures of Nephron Size

Jaidip M. Jagtap,[1] Andrew Janowczyk,[2] Aleksandar Denic,[1] Yijiang Chen,[4] Muhammad Sohaib Asghar,[1] Sumana Ramanathan,[1] Aidan F. Mullan,[1] Timothy L. Kline,[1] Bradley J. Erickson,[1] Laura Barisoni,[3] Andrew D. Rule.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Emory University, Atlanta, GA; [3]Duke University, Durham, NC; [4]Case Western Reserve University, Cleveland, OH.*

Background: Enlarged nephrons as detected by glomerular volume and cortex per glomerulus (reciprocal of glomerular density) on kidney biopsy are prognostic for progressive CKD but require stereological calculations based on tedious human annotations. We sought to compare clinical associations with nephron size as calculated by AI versus human.

Methods: PAS-stained wedge section whole slide images (WSI) from nephrectomies (N=932) were manually annotated for cortex and non-sclerosed glomeruli using ImageScope software. A previously developed AI model for glomerular segmentation (NEPTUNE study) was applied to the same WSI. A threshold of 2000 μm2 for the smallest glomerular profile excluded false positives with the AI model. Spatial intersection statistics were compared between AI and human derived segmentations. Clinical correlations and the risk of progressive CKD (kidney failure or a 40% decline in eGFR sustained for at least 3 months) was assessed using AI versus human derived glomerular volume and cortex per glomerulus.

Results: The intersection between AI and human annotations of glomeruli had a Dice of 96%, precision of 99%, and recall of 93%. Glomerular volume was larger by AI than human (.0030 vs .0027 mm3, p<0.001) as was cortex per glomerulus (.080 vs .077 mm3, p<0.001). There were 52 progressive CKD events. Correlation of clinical characteristics with AI vs human estimates of glomerular volume is shown in the Table. The risk of progressive CKD with glomerular volume (per SD) was 1.76 (95%CI 1.41-2.19) by AI and 1.89 (95%CI 1.61-2.23) by human and with cortex per glomerulus (per SD) was 1.82 (95%CI 1.49-2.21) by AI and 1.71 (95%CI 1.52-1.93) by human.

Conclusions: The AI approach provides efficient quantification of nephron size measures comparable to a human approach.

Funding: NIDDK Support

Characteristics correlated with glomerular volume

	Human r (p value)	AI r (p value)
Age	-.09 (.009)	-.13 (.0001)
Male	.23 (<.0001)	.23 (<.0001)
BMI	.31 (<.0001)	.32 (<.0001)
Hypertension	.15 (<.0001)	.13 (<.0001)
Diabetes	.14 (<.0001)	.14 (<.0001)
Smoker	.10 (.004)	.11 (.001)
eGFR	.00 (.90)	.04 (.26)
24hr protein	.18 (<.0001)	.15 (<.0001)

TH-PO808

Spatial Transcriptomic Analysis Reveals Altered Gene Expression in Glomerular Parietal Epithelial Cells Following Tubular Injury

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Background: In our previous study, we observed that acute tubular injury leads to the activation and transdifferentiation of parietal epithelial cells (PECs), resulting in a decrease in the ratio of columnar to flat PECs. In this study, our objective was to investigate the spatial transcriptomics of PECs following tubular injury.

Methods: We conducted experiments using wild-type (WT) mice and transgenic mice expressing the diphtheria toxin (DT) receptor in proximal tubular epithelial cells (PTECs). The mice were injected with DT at week 0 and week 1 and sacrificed after 6 weeks. Paraffin-embedded tissue sections were analyzed using the NanoString GeoMx DSP platform.

Results: Using fluorescent antibodies, we successfully isolated glomerular tuft and PECs and performed GeoMx spatial transcriptomics analysis. Principal component analysis (PCA) clearly distinguished tuft and PECs in both DT-treated and normal mice. In DT-treated PECs, we observed increased expression of 153 genes, including osteopontin (*OPN*), which showed enrichment in pathways related to actin cytoskeleton regulation, apelin signaling, the citric acid cycle, and respiratory electron transport. Immunostaining revealed that osteopontin was undetectable in PECs of WT mice, whereas its expression was significantly increased at week 3 and week 6 after tubular injury in DT-treated mice.

Conclusions: Our findings indicate that proximal tubular injury affects glomerular PECs, leading to their activation and altered gene expression. This study suggests potential pathways involved in the communication between tubular and glomerular compartments.

Funding: NIDDK Support

TH-PO809

Histopathological Description of Sickle Cell Nephropathy of the Arab-Indian Haplotype

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Background: Sickle cell disorders are a group of autosomal recessive disorders characterized by the presence of the hemoglobin S (HbS) variant, which leads to sickling and hemolysis of the red blood cells. The inheritance of one variant gene, sickle cell trait (SCT), leads to a carrier state and milder form of the disease while having 2 genes leads to the more aggressive state of sickle cell disease (SCD). The main variants of HbS genes are the haplotypes present in the African race and the Arab-Indian (AI) haplotype, found in Saudi Arabia and central India. Sickle Cell Nephropathy (SCN) has been well characterized in the population of African descent. However, the histopathological changes of SCN have not been described in the patients of AI haplotype.

Methods: This was a single-center retrospective analysis of all adult patients with sickle cell disorders (SCD/SCT) who underwent a kidney biopsy from January 2012 until May 2023. Histological specimens were retrieved and examined by a research histopathologist. Clinical and biochemical data were collected and analyzed at the time of biopsy and last follow-up.

Results: 22 kidney biopsies were identified, 5 of which were excluded due to active lupus nephritis leaving 17 biopsies (12 SCD and 5 SCT). The mean age was 44 +/- 10 years, 8 were females (47%). The main indications for biopsy were unexplained raised creatinine (4/17) and proteinuria (13/17). The median hemoglobin S in SCD and SCT was 81% and 26%, respectively. Changes suggestive of SCN were only observed in SCD; the main findings were tubular hemosiderosis (92%), global sclerosis (83%), glomerular hypertrophy (75%), sickled RBCs (58%), FSGS lesions (42%), and duplication of the glomerular basement membrane (33%). None of the findings from SCT biopsies were consistent with SCN changes (2 diabetic glomerulosclerosis, 1 chronic glomerulonephritis, 1 normal glomerular architecture, and 1 cortical necrosis).

Conclusions: In patients with Sickle cell disorder in Saudi Arabia, where the AI haplotype is predominant, the SCN histopathological changes were largely similar to the ones previously reported with the haplotypes in the African race. These changes were only present in SCD and are likely to reflect the nature of the repetitive damage.

TH-PO810

Influence of Hospital Practices on Native Glomerular Pathologic Patterns: Insights from the Largest Kidney Biopsy Cohort in Thailand

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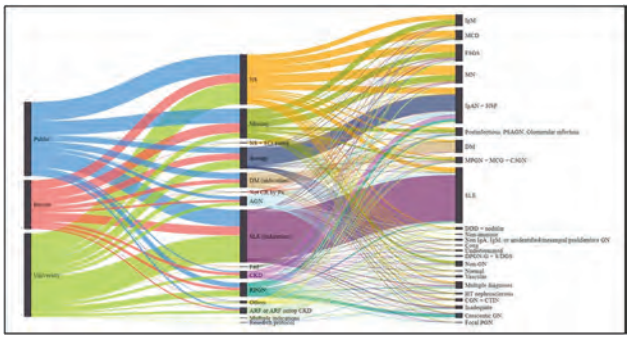
Background: We sought to explore the effects of kidney biopsy and glomerular pathologic patterns using the largest Thailand kidney biopsy registry.

Methods: Records of kidney biopsy registries from the Chulalongkorn University (one of the biggest university-based hospitals in Thailand) and the Kidney Center Bangkok Hospital (a center providing kidney pathologic diagnosis for all private and public hospitals in Thailand) between 2000 and 2014 were analyzed and classified into three groups: university practice (U), private practice (Pv), and public practice (Pb). Records from pediatric patients, kidney transplant recipients, repeated biopsies, and insufficient clinicopathologic diagnosis were excluded from the study**.** One-way ANOVA was conducted to compare continuous variables among hospital types while Chi-Squared test and Fisher's exact test were used for categorical variables.

Results: Out of 6,995 native kidney biopsies, 5,007 were eligible for analysis from 62 provinces covered all regions of Thailand over 15 years. University hospitals performed the highest number of kidney biopsies, followed by public and private hospitals. The three most common indications across all practice groups were nephrotic syndrome (NS), systemic lupus erythematosus (SLE, e.g., suspected lupus nephritis, morphologic diagnosis before making treatment decisions), and asymptomatic urinary abnormalities. U had a significantly higher proportion of biopsies due to SLE than the others (Image 1). In contrast, Pv performed biopsies with more indication of asymptomatic urinary abnormalities and unknown CKD than the others. Lupus nephritis was the most common pathological finding in U and Pb groups, while the Pv group was IgA nephropathy corresponding to the indications for biopsy.

Conclusions: The prevalence of pathologic diagnosis patterns is correlated well with the biopsy indication. Our findings highlight the influence of hospital practices on kidney biopsy indications and glomerular diagnoses.



TH-PO811

Unusual Pathogens in Usually Encountered Infections in ESRD

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Introduction: In this case series of ESRD patients, we aim to highlight serious infections caused by pathogens hitherto not commonly encountered in India.

Case Description: *Aeromonas hydrophila*, found in aquatic environment was isolated from biopsy of non healing leg wound (prior cultures being negative) in a transplant recipient, who responded only after an appropriate 6 week antibiotic course. *Serratia marcescens*, found in water and soil, was isolated from BAL of a transplant recipient with cavitatory pneumonia and from a tunnelled catheter in a HCV positive patient on MHD with CRBSI. Both patients did not exhibit positive cultures from prior samples and responded only to Meropenem (other higher antibiotics being resistant). *Morganella morganii*, part of normal flora in humans, was grown from tunnelled catheter of a patient on MHD with fever of unknown origin (other workup of FUO being inconclusive), needing catheter removal due to pan resistance. *Elizabethkingia meningoseptica*, a commensal in healthcare facilities, was isolated from non tunnelled HD catheter, and needed Colistin therapy as the only available choice. *Geotrichum species*, a contaminant of fruits & vegetables was finally isolated from tunnelled catheter of a patient with CRBSI with 2 negative blood cultures previously over 3 weeks. A 54/F patient needed CAPD catheter removal due to Candida tropicalis infection and 3 months later needed tunnelled catheter removal due to Candida parapsilosis (a common skin flora and a subungual proliferator) infection. Both above organisms were resistant to Azoles and Echinocandins.

Discussion: These unusual organisms residing in soil, water, disinfection solutions and surfaces in dialysis units need active surveillance and timely microbiological detection as they are likely to increase morbidity and mortality in ESRD. Tackling the double whammy of newer pathogens and depleting arsenal of sensitive antibiotics is a big challenge in developing countries. High index of clinical suspicion and state of the art diagnostic facilities for detecting causative pathogens is the need of the hour.

TH-PO812

Renal Malakoplakia: A Rare Disease Causing Acute Renal Failure

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Introduction: Malakoplakia is a rare chronic inflammatory condition characterized by granulomatous lesions, frequently involving the kidneys. We present a case of renal malakoplakia in the setting of Escherichia coli (E.coli) bacteremia leading to acute renal failure.

Case Description: A 36-year-old woman presented with vomiting and shortness of breath. Initial evaluation revealed hypotension, tachycardia, leukocytosis (22,000/μL), and acute kidney injury with elevated creatinine (6.4 mg/dL from a baseline of 0.6 mg/dL). Urinalysis showed blood, leukocytes, bacteria, and a urine protein/creatinine ratio of 31 mg/mg. Computed tomography scan indicated fatty hepatomegaly and globular nephromegaly. Urine and blood cultures grew E. coli. The patient was treated for septic shock with antibiotics and vasopressors. However, she developed oliguric acute renal failure and required continuous renal replacement therapy. A left kidney biopsy was pursued to evaluate the nephromegaly, which revealed multifocal microabscesses, parenchymal necrosis, fibrosis, calcifications, and an inflammatory infiltrate with histiocyte predominance, consistent with malakoplakia. Von Kossa stain confirmed the presence of numerous Michaelis-Gutmann bodies. Renal mercaptoacetyltriglycine 3 scan showed differential function of 25% in the left kidney and 75% in the right kidney. Despite prolonged antibiotic therapy, the patient continued to experience volume overload, persistent leukocytosis, bacteremia, and fungemia. Given the higher disease burden in the left kidney, she underwent a radical left nephrectomy for source control. Postoperatively, her clinical condition improved, and she was discharged on suppressive minocycline.

Discussion: The pathogenesis of malakoplakia involves impaired bactericidal capacity of macrophages. Michaelis-Gutmann bodies, characterized by calcium and iron deposits, are pathognomonic. Diagnosis is challenging due to variable clinical presentations and imaging findings resembling malignancy. Renal biopsy remains the gold standard for definitive diagnosis. Given its rarity, evidence-based treatment is limited; however, a general approach includes systemic antibiotics and surgical excision. Renal malakoplakia poses clinical challenges in differentiating from other infections and tumors. Early diagnosis through biopsy is crucial for prompt treatment and to prevent long-term morbidity and mortality.

TH-PO813

Infection as a Trigger of Acute, Transient Glomerular Deposition of Clonal Immunoglobulins

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Introduction: Glomerular deposition of clonal IgM, frequently in the form of intracapillary pseudothrombi, can be seen in Waldenström macroglobulinemia (WM) and type 1 cryoglobulinemia (CG). Both are typically associated with B-cell lymphomas, particularly lymphoplasmacytic lymphoma (LPL). While infection is a frequent trigger of mixed (type 2 and 3) CG, its association with type 1 CG is uncommon. We report two cases in which striking lambda-restricted IgM deposits and acute kidney injury (AKI) occurred in the setting of systemic infections, with prompt resolution on treatment of the infection.

Case Description: Patient 1 was a 57-year-old female who presented with AKI following bowel perforation, treated with resection and antibiotics. Serum protein electrophoresis (SPEP) showed IgG kappa and IgM lambda M-proteins, without history of lymphoma. Patient 2 was a 59-year-old female with a 9-year history of an untreated, quiescent mature B-cell lymphoma, who presented with AKI, nephrotic range proteinuria, and hematuria, alongside a recent sore throat, presumptively treated with antibiotics for a respiratory infection. Her lab findings showed hypocomplementemia and faint IgM-lambda M-protein on SPEP. Neither patient was tested for cryoglobulins. Renal biopsies for both patients revealed glomerular capillary loops distended by abundant amorphous, eosinophilic and PAS-positive material, which stained strongly for IgM and lambda light chain on immunofluorescence and was granular and lacked substructure by electron microscopy. These findings were initially interpreted as concerning for renal manifestations of WM. However, after further investigation, neither patient exhibited LPL, and both patients experienced recovery of renal function following treatment of their respective infections (patient 2 also received a short course of steroids). Notably, patient 1 was diagnosed with a diffuse large B-cell lymphoma several years later.

Discussion: While infection may not be the root cause of clonal immunoglobulin production, these two cases suggest that it may serve as a trigger for glomerular deposition of clonal IgM in patients predisposed by underlying lymphoma. WM was initially suspected in both patients; however, the rapid normalization of renal function after resolution of infection indicates that they had undiagnosed type 1 CG triggered by infection.

TH-PO814

Nephropathy of Prematurity and the Crucial Role of Kidney Biopsy

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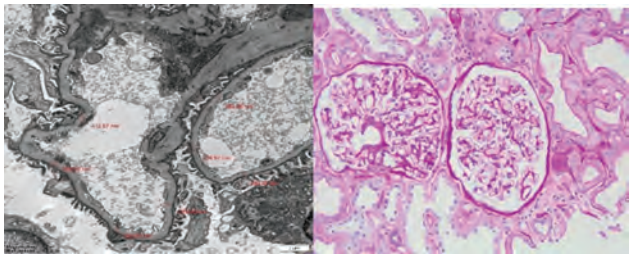
Introduction: Nephrogenesis, the creation of nephrons, typically concludes before birth, yet in preterm infants it can extend up to 40 days post-birth. Nevertheless, these late-forming nephrons mature prematurely and remain abnormal. The exact influence of premature birth on nephrogenesis remains unclear. In light of this, we share a case of a young woman with signs of nephropathy attributed to her premature birth.

Case Description: A 22-year-old female with migraines and high blood pressure (230/150 mmHg) presented at an emergency department. Initial tests revealed normal CBC and CMP, but with elevated BUN (62 mg/dL) and creatinine (2.8 mg/dL). Mild proteinuria and a few red blood cells were noted. A renal ultrasound only found a small cyst in the right kidney. No stenosis was found, leading to further diagnostic workup. By the 5th day, with improved kidney function and controlled blood pressure, a renal biopsy was performed due to unclear AKI cause. The biopsy findings indicated acute tubular injury and Glomerulomegaly with secondary focal global and segmental glomerular sclerosis (Figures 1, 2). As the patient had no history of drug abuse, the prospect of premature birth was considered, which she confirmed, leading to the diagnosis of Chronic Kidney Disease due to nephropathy of prematurity

Discussion: This case is unique due to hypertension and renal failure in a patient with a normal workup and kidney size. Nephropathy of prematurity should be considered in young adults presenting with renal failure and benign urinary findings. This case underlines the importance of vigilant follow-ups for early detection of renal diseases in young adults with proteinuria and high blood pressure but normal kidney size. The case raises the question of whether monitoring renal function in premature infants should be extended into adulthood. Kidney biopsy remains the definitive method for diagnosing unexplained CKD, emphasizing the role of vigilant follow-ups and consideration of underlying renal disease in young adults with proteinuria, high blood pressure, and normal kidney size.



Dilated flat tubules and glomerulomegaly. Rare focal scarringno electron-dense deposits.

TH-PO815

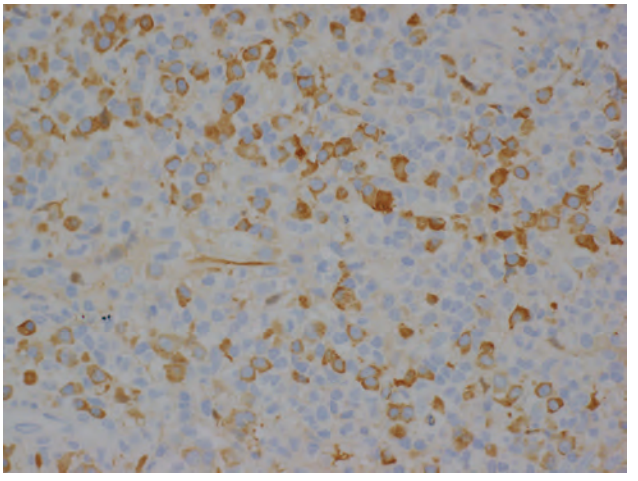
Systemic Immunoglobulin G4-Related Disease

Jacob R. Henderson, Karl B. Pembaur. *The Christ Hospital, Cincinnati, OH.*

Introduction: Immunoglobulin G4-Related Disease (IgG4-RD) is an autoimmune condition that can result in systemic fibrosis and organ damage. Clinical manifestations include lymphadenopathy, atopy like symptoms, and is often found incidentally on imaging with diffuse or focal organ lesions. Serological findings can include elevated levels of immunoglobulins and low complement levels. A tissue biopsy is needed for diagnosis revealing IgG4 lymphoplasmacytic infiltration with variable degrees of fibrosis.

Case Description: A 79 year-old male with a PMHx of HTN, biliary stricture, asthma, and BPH presented with generalized fatigue, pruritus, and difficulty initiating urination for one month. Labs revealed an AKI (Cr 5.19, BUN 47; UA - mild proteinuria), transaminitis (AST 322, ALT 460, ALP 796, TBili 4), and anemia (Hgb 11.2). MRCP revealed a biliary duct stricture, chronic pancreatitis, and soft tissue swelling representing retroperitoneal fibrosis. ERCP with biliary stent placement and biopsies were performed, revealing lymphoplasmacytic infiltration and diffuse fibrosis. Renal biopsy revealed diffuse interstitial inflammatory IgG4 lymphoplasmacytic infiltration with interstitial nephritis. Total protein and globulin levels were elevated. SPEP/IFE revealed increased gamma globulins (2.1) with no monoclonality. Immunoglobulin G4 was elevated at 266.2 (4-86), IgG1 was elevated at 1185 (282-395), and low C4 levels.

Discussion: The patient was diagnosed with IgG4-RD and started on immunosuppression with solumedrol and rituximab, complement levels were used to track responsiveness to treatment. Repeat serologic tests after immunosuppression revealed normalization of IgG4, IgG1 and complement levels, with a CD19/20 count of zero, showing that his IgG4-RD was in remission. Early recognition and treatment of IgG4-RD is of upmost importance due to a fibrotic transition that is poorly responsive to treatment with resultant end organ damage.



Renal biopsy demonstrating IgG4 plasma cells.

TH-PO816

Proliferative Glomerulonephritis with Monoclonal IgG1λ Deposits, Characterized by Intracapillary λ-Containing Macrophages Infiltration

Natsumi Kasahara,[1] Ryo Nishioka,[1] Daichi Kaikoi,[2] Anri Mori,[1] Hiromitsu Akamatsu,[1] Hiroaki Saito,[1] Hajime Sanada,[1] Yoshinori Takahashi,[1] Shunsuke Tsuge,[1] Satoshi Hara,[1] Kiyoaki Ito,[1] Ichiro Mizushima,[1] Mitsuhiro Kawano.[1] *[1]Kanazawa Daigaku Fuzoku Byoin, Kanazawa, Japan; [2]Toyama Kenritsu Chuo Byoin, Toyama, Japan.*

Introduction: Monoclonal gammopathy of renal significance (MGRS) encompasses kidney disorders caused by monoclonal proteins. We report a rare case of proliferative glomerulonephritis with monoclonal IgG1λ deposits (PGNMID) in a patient with monoclonal gammopathy of undetermined significance (MGUS). Notably, the case is characterized by the infiltration of intracapillary macrophages containing λ immunoglobulin.

Case Description: A 69-year-old Japanese female with MGUS presented with renal dysfunction and proteinuria. She had a history of persistent proteinuria (urinary protein 3.4 g/g Creatinine), microscopic hematuria, and kidney dysfunction (serum Creatinine 1.3 mg/dL) for the past 2 years. Due to refractory symptoms, she was admitted to our hospital. On admission, her urinary protein was 1.1 g/day, with microscopic hematuria, and serum Creatinine 1.9 mg/dL. Immunofixation analysis detected monoclonal IgGλ in both serum and urine, while cryoglobulins were absent. Renal biopsy revealed diffuse endocapillary proliferative glomerulonephritis with subendothelial deposition. Immunofluorescence demonstrated IgG1, C3, and λ deposition with an infringe pattern, confirming the diagnosis of PGNMID. Remarkably, the intracapillary cells exhibited a foamy appearance and showed double positivity for CD68 and λ. Electron microscopy confirmed electron dense deposits (EDD) in the subendothelial area, and intracapillary foam cells contained EDD. Due to the presence of other life-threatening factors, the patient received renal protection therapy without anti-tumor treatment. Over a four-year period, renal dysfunction progressively worsened, with a serum creatinine level of 2.9 mg/dL and persistent proteinuria.

Discussion: We present a rare case of PGNMID characterized by the infiltration of intracapillary monoclonal λ-containing macrophages. The underlying pathophysiology remains unknown, but it may share similarities with crystal-soring histiocytosis, where macrophages engulf monoclonal immunoglobulins. To our knowledge, only one similar case has been previously, suggesting that this histological finding could represent a novel manifestation of MGRS.

TH-PO817

How Factor H Deficiency Triggered Atypical Hemolytic Uremic Syndrome (aHUS) in a New Mother

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Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare form of thrombotic microangiopathy (TMA) causing dysregulation of the alternative complement system. aHUS presents with microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and organ damage, notably, renal failure requiring dialysis. Morbidity and mortality is preventable as treatments are now available. Yet, treatment is often delayed as aHUS is viewed as an exclusion diagnosis. Prior studies have shown that aHUS is associated with many genetic mutations of complement proteins. Of these, Factor H (CFH) were found in 25% of cases. We present an aHUS case of CFH deficiency in a postpartum patient.

Case Description: A 26 year old healthy female, who one week ago had a normal term vaginal delivery, presented with hypertensive emergency, MAHA, thrombocytopenia, and renal failure requiring dialysis. Initial labs showed deficient C3 levels and normal C4 levels. Plasmapheresis was started for suspicion of Thrombotic Thrombocytopenic Purpura. Therapy was stopped when her ADAMTS13 returned normal. She was screened for infections, drugs, and malignancy, all were negative. A renal biopsy showed TMA with 10% cortical necrosis. Results of her complement panel showed dysregulation of the alternative pathway: low CFH and low alternative pathway levels. She was diagnosed with aHUS and treated with a C5 Inhibitor, Eculizumab. Eculizumab was given weekly and after her third dose, her hemolytic labs improved. After her 4th dose, her renal function was near complete recovery and dialysis stopped. Her dose now was every two weeks for a minimum of six months.

Discussion: C5 inhibitors have hugely improved renal survival. Our patient received Eculizumab with promising renal recovery. A 2010 study of 100 females with aHUS showed that 48% of cases involved CFH mutations. Another study assessed 273 aHUS patients and 139 had CFH dysfunction. We are learning that the defect affects more than one area on the CFH gene. Thus, the location of dysfunction affects the severity and treatment response making aHUS much more challenging to standardize.

Genetic defect	Frequency	Response to short-term plasma therapy	Long-term outcome	Outcome after kidney transplantation
CFH	20–30%	Rate of remission: 60% (dose- and timing-dependent)	Rate of death or ESRD: 70–80%	Rate of recurrence: 80–90%
CFI	4–10%	Rate of remission: 30–40%	Rate of death or ESRD: 60–80%	Rate of recurrence: 80–90%
CFHR1 & 3 with CFH autoantibodies	6%	Rate of remission: 70–80%	Rate of death or ESRD: 30–40%	Rate of recurrence: 20%
MCP	10–15%	No indication for therapy	Rate of ESRD or death: <20%	Rate of recurrence: 15–20%
CFH	1–2%	Rate of remission: 30%	Rate of death or ESRD: 70%	Recurrence in one case
C3	5–10%	Rate of remission: 40–50%	Rate of death or ESRD: 60%	Rate of recurrence: 40–50%
THBD	5%	Rate of remission: 60%	Rate of death or ESRD: 60%	Recurrence in one case

Figure 1: Summary of Clinical Outcomes From Complement Genetic Defects in Atypical Hemolytic Uremic Syndrome

Waters, A. M., & Licht, C. (2011)

TH-PO818

Lanthanum Gastropathy in Gastrectomy Specimen: A Case Report

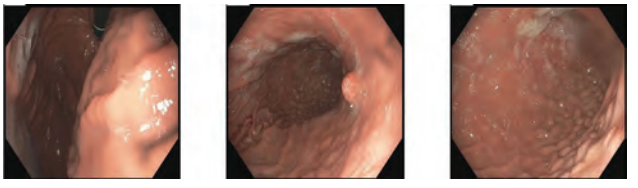
Erika M. Dorff, Sarah Y. Liu, Amer K. Abu Alfa, Wasef Abu- Jaish. *University of Vermont Medical Center, Burlington, VT.*

Introduction: Lanthanum carbonate is a non-calcemic phosphate binder that is used in end-stage renal disease (ESRD.) It has few adverse effects due to its poor systemic absorption. Gastrointestinal lanthanum deposition was first reported in 2015 and is likely due to alterations in epithelial permeability from inflammation in chronic kidney disease. Endoscopy findings include gastritis, erosions, ulcerations, and polyps, with a diffusely white mucosa and fine granular deposits. It is challenging to detect these findings in cases with minimal microscopic deposition and may be missed on biopsy.

Case Description: A 36-year-old with ESRD secondary to hypertension was started on lanthanum in 2017. She was evaluated by bariatric surgery in 2019 for sleeve gastrectomy and endoscopy was completed as part of the pre-operative workup. Findings were significant for gastritis and multiple gastric polyps. Biopsies demonstrated aggregates of histiocytes with granular eosinophilic material in the lamina propria. She underwent sleeve gastrectomy in 2022 in which the excised portion showed similar histiologic findings. There have been no further studies or adverse events reported since the surgery.

Discussion: This case allows for the evaluation of a gross specimen as there have been no reports to date describing lanthanum gastropathy in specimens larger than biopsy. Not all patients taking lanthanum undergo endoscopic and histologic evaluation, but studies have found deposits in 60-85% of those evaluated. One case report found concurrent neoplastic changes, though this is the only description of such. The findings in this case were not consistent with neoplasm despite prolonged lanthanum use, but further studies must be conducted to determine long-term effects in patients with ESRD.

Gastrectomy gross specimen



Endoscopic findings

TH-PO819

Development of a Predictive Model for Assessing the Risk of Severe Renal Fibrosis in Kidney Biopsy

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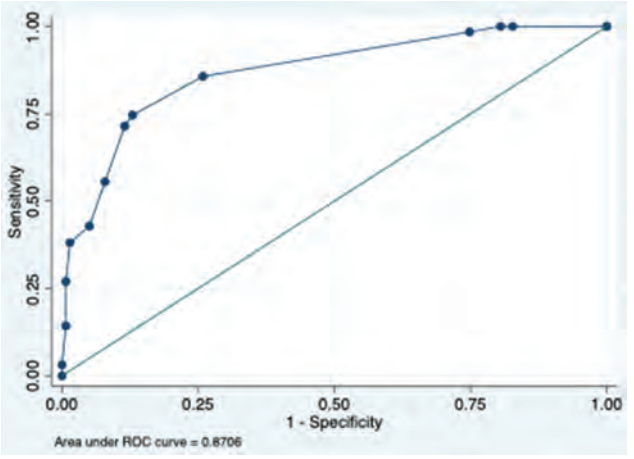
Background: Kidney biopsy is an essential diagnostic tool for various kidney diseases, but its clinical utility may be limited in cases of severe fibrosis, coupled with an increased risk of bleeding. Although several clinical parameters are used to predict the extent of renal fibrosis, a validated predictive model has not yet been established. This study aimed to construct a predictive model for assessing the risk of severe renal fibrosis.

Methods: Medical records of patients who underwent native kidney biopsies at Ramathibodi Hospital between January 2017 and December 2021 were reviewed. Severe renal fibrosis was defined as interstitial fibrosis and tubular atrophy (IFTA) greater than 50% or glomerulosclerosis greater than 50% on the pathology report. Clinical data, laboratory results, and ultrasonographic parameters were collected. Multivariable logistic regression analysis was performed to build the predictive model, and its discriminative performance was assessed using the receiver operating characteristic (ROC) curve. The internal validity of the model was evaluated through bootstrapping techniques.

Results: Among 202 patients, 31% exhibited severe renal fibrosis. The predictive model incorporated five significant predictors: nocturia, CKD, anemia, kidney length, and loss of corticomedullary differentiation. The model had an area under the ROC curve of 0.87 (95% CI: 0.818-0.923). The scoring model ranged from 0 to 18, with a score of 10 or higher indicating a positive likelihood ratio of 26 for severe fibrosis prediction. Internal validation using bootstrap resampling yielded an optimism of 0.024, with a shrinkage factor of 0.869.

Conclusions: The developed predictive model, utilizing routine clinical parameters, has demonstrated exceptional discriminative ability and ease of use in predicting renal fibrosis. It holds great potential in assisting clinicians with risk stratification and the planning of kidney biopsies.



TH-PO820

Left Ventricular Diastolic Dysfunction by Echocardiography Is a New Predictor of Delayed Graft Function

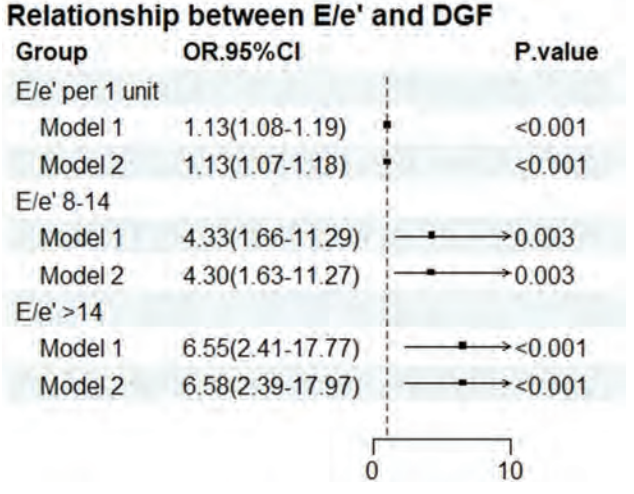
Linhui Huo, Hongli Jiang. *The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China.*

Background: Diastolic dysfunction (DD) is a common complication among end-stage renal disease (ESRD) patients. The ratio of early transmitral flow velocity (E) to early diastolic velocity (e') of the mitral annulus (E/e') is related to left ventricular (LV) diastolic dysfunction (LVDD). Delayed graft function (DGF) is a detrimental complication after kidney transplantation (KT). It is unclear whether increased E/e' predisposes a recipient to DGF.

Methods: A total of 574 patients were enrolled in this retrospective study. Two-dimensional echocardiography and Doppler imaging were performed. Multivariate logistic regression analyses were performed to calculate the OR (95%CI) for DGF. Model 1 included variables with P<0.05 in the multivariate logistic regression analyses. Model 2 was adjusted for demographic data (age and sex) and operation data (warm ischemia time and cold ischemia time). Model 3 (reference model) includes all the variables in Model 2 except E/e'. Discrimination was assessed by AUCs. Model performance was also evaluated by continuous net reclassification index (cNRI) and integrated discrimination improvement (IDI).

Results: 93 patients (16.25%) developed DGF. E/e' was higher in DGF patients(14.07±6.16 vs. 11.51±4.23, P<0.001). Per 1 unit E/e' increase (OR 1.16; 95%CI, 1.1-1.23) and higher E/e' categories (8≤E/e' ≤14 OR 6.51; 95%CI, 2.38-17.80; E/e' >14 OR 6.58; 95%CI, 2.39-17.97) were associated with DGF. After adjusting for other covariates, the relationship between E/e' and DGF remained significant (adjusted OR 1.13; 95%CI, 1.07-1.18). Compared with Model 3, Model 2 had better discrimination and reclassification (cNRI, 46.48%; 95% CI, 24.61%- 68.34%; IDI, 4.36%; 95% CI, 1.81%-6.91%).

Conclusions: Our study found that higher E/e' was an independent predictor of DGF. This may provide an important perspective on the management of waiting list patients. Our results recommend that clinicians should take measures to lower E/e' before transplantation to lower DGF risks.



TH-PO821

Pre-Transplant Daratumumab (Dara) and Kidney Transplant Rejection

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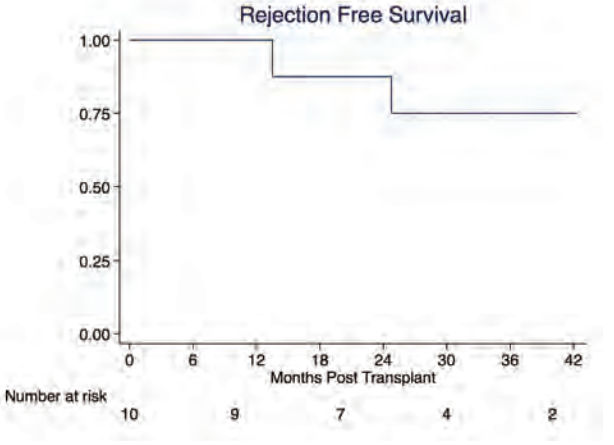
Background: This study examined the post-kidney transplant outcomes of patients who received Dara, a monoclonal antibody against CD38 positive cells, pre-transplant. Concerns exist that Dara may increase the risk of rejection.

Methods: We identified solitary kidney allograft recipients who received Dara within 180 days pre-transplant in our center. Clinical and laboratory data were abstracted from the chart. Protocol biopsies are routine in our practice.

Results: Ten patients met inclusion criteria. Mean age was 60 (±10) range 36-73 years, there were 7 males, and 7 received a living donor transplant. Induction was with Basiliximab in 7, Alemtuzumab in 2 & Anti-thymocyte globulin in 1. Maintenance immunosuppression consisted of ± corticosteroids, tacrolimus, mycophenolate mofetil in 9 patients, Belatacept replaced tacrolimus in one patient and in one patient sirolimus was substituted for tacrolimus 26 months post-transplant due to microangiopathy. Last dose of dara was 22 (16,30) days prior to transplant. Three patients resumed dara: 11, 24, and 244 days post-transplant. Follow-up was 32 (± 16) months. One patient did not undergo protocol biopsies due to systemic anticoagulation. The remainder had protocol biopsies at the predetermined time points. No graft losses occurred during follow-up. Two patients had subclinical borderline changes (i0, t1) at one year, and (i1, t3) on the two-year protocol biopsy. The latter, after reduction in immunosuppression due to CMV infection **(Fig1)**. Another patient developed severe BK nephropathy that required significant immunosuppression reduction.

Conclusions: In our series of 10 patients, we did not observe any clinical acute cellular rejections. Two patient had subclinical borderline changes, one- and two-years post-transplant. Daratumumab did not appear to increase the risk of rejection.



Rejection free (including borderline changes) kidney graft survival.

TH-PO822

Role of Angiopoietins in Cardiovascular Disease (CVD) Outcomes of Kidney Transplant Recipients

Liam Brown,[1] Natalie Gendy,[2] Mary Kate Staunton,[1] Kanika K. Garg,[1] Yu Yamamoto,[1] Wassim Obeid,[3] Andrew Bostom,[4] Sherry Mansour.[1] *[1]Yale School of Medicine, New Haven, CT; [2]Western University Schulich School of Medicine & Dentistry, London, ON, Canada; [3]Johns Hopkins University, Baltimore, MD; [4]Brown University, Providence, RI.*

Background: Kidney transplant recipients have 30 times the risk of dying from cardiovascular disease (CVD). We tested the role of 2 vascular biomarkers, angiopoietin-1 and angiopoietin-2 (angpt-1, -2), in the development of CVD in deceased donor kidney transplant recipients.

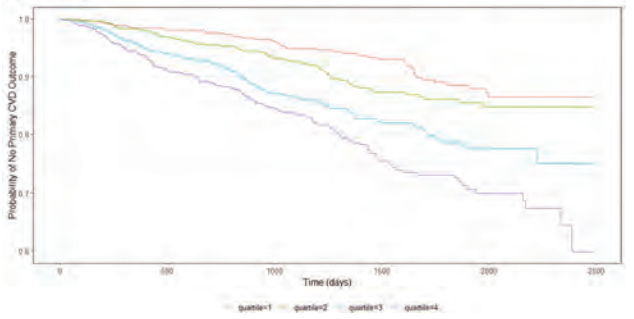
Methods: This is an ancillary analysis of the FAVORIT study, evaluating the associations between baseline levels of angpt-1 and angpt-2 in the development of CVD and the secondary outcomes of graft failure (GF) and death in 2000 recipients. We used a Cox regression analysis to test the associations between biomarker quartiles and outcomes.

Results: Median age of participants was 52 IQR [45, 59] years with 37% women and 73% identifying as white. Median time from transplantation to biomarker measurement was 3.99 IQR [1.58, 7.93] years. Median time to the development of CVD was 3.7 IQR [2.89-5.25] years. Angpt-1 was not significantly associated with outcomes. Higher levels of angpt-2 (quartile 4) as compared to quartile 1 had about 2 times the risk of CVD, GF and death [aHR 1.85 (1.25 - 2.73), *P*<.01; 2.24 (1.36 - 3.70), *P*<.01; 2.30 (1.48 - 3.58), *P*<.01, respectively, (Figure 1)].

Conclusions: Angpt-2 may identify high-risk kidney transplant recipients for the development of CVD. This may aid in tailoring follow-up after transplantation to reduce the risk of CVD.

Funding: NIDDK Support

Figure 1. Kaplan-Meier curve of the probability of not developing CVD stratified by Angpt-2 quartiles



The red line represents the probability of not developing CVD in patients with quartile 1 of angiopoietin-2 concentrations. Quartiles 2,3, and 4 are represented by the green, blue, and purple lines respectively. We adjusted for demographics (age, sex, race, and ethnicity); CVD related factors (hypertension, diabetes mellitus, body mass index, history of CVD, baseline estimated glomerular filtration rate); transplant-related variables (pancreas transplant, and graft vintage at randomization); medications (lipid lowering drugs, cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, and prednisone); and urine albumin-to-creatinine ratio and randomization status.

TH-PO823

Impact of Hyperparathyroidism and Its Different Subtypes on Long-Term Graft Outcome: A Single Transplant Center Cohort Study

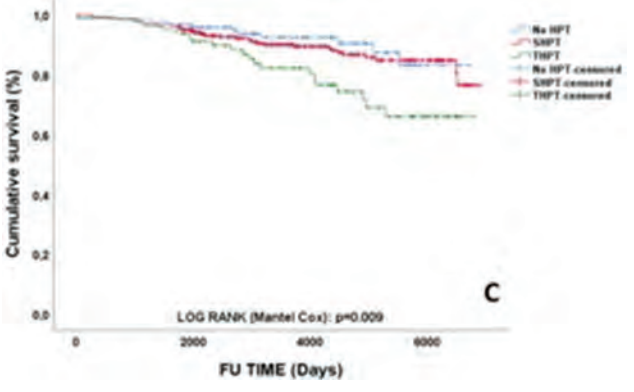
Carlo Alfieri,[1,2] Paolo Molinari,[1,2] Anna Regalia,[1] Anna Maria Pisacreta,[1,2] Elisa Cicero,[1,2] Giulia V. Re Sartò,[1,2] Giuseppe Castellano.[1,2] *[1]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [2]Universita degli Studi di Milano, Milano, Italy.*

Background: We studied the association between parathormone (PTH) levels and long-term graft loss in RTx patients (RTx-p).

Methods: We retrospectively evaluated 871 RTx-p, transplanted in our unit from Jan-2004 to Dec-2020 assessing renal function and mineral metabolism parameters at 1, 6 and 12 months after RTx. Graft loss and death with functioning graft during follow-up (FU, 8.3[5.4-11.4] years) were checked.

Results: At month-1, 79% had HPT, of which 63% with secondary HPT (SHPT) and 16% tertiary HPT (THPT); at month-6, HPT prevalence was 80% of which SHPT 64% and THPT 16%; at month-12 HPT prevalence was 77% of which SHPT 62% and THPT 15%. A strong significant correlation was found between HPT type, PTH levels and graft loss at every time point. Mean PTH exposure remained strongly and independently associated to long-term graft loss (OR 3.1 [1.4-7.1], p=0.008). THPT was independently associated with graft loss at month-1 when compared to HPT absence and at every time point when compared to SHPT. No correlation was found with RTx-p death. Discriminatory analyses identified the best mean PTH cut-off to predict long-term graft loss to be between 88.6 and 89.9 pg/ml (AUC=0.658). Cox regression analyses highlighted that THPT was strongly associated with shorter long-term graft survival at every time point considered (Figure 1, PTH status at 12-months after KTx).

Conclusions: High PTH levels, and especially tertiary HPT during 1st year of RTx seem to be associated with long-term graft loss.



Survival analyses of long-term graft outcomes according to PTH status at 12-months after KTx

TH-PO824

Acute Phosphate Nephropathy: A Preventable Cause of AKI Among Kidney Transplant Recipients

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Introduction: Acute Kidney Injury (AKI) after a kidney transplant is an extreme emergency. It is associated with allograft loss and increased morbidity. Prompt recognition of reversible causes of AKI is important to prevent graft loss. We present a case of a kidney transplant patient who developed AKI secondary to acute phosphate nephropathy.

Case Description: A 37-year-old male with end-stage renal disease secondary to hypertension underwent a deceased donor kidney transplant. His pre-operative laboratory results include calcium of 8.2 mg/dl, phosphorus of 6.6 mg/dl, PTH of 855 pg/ml, and 25-hydroxyvitamin D of 18.6 ng/ml. His phosphate binder Sevelamer was discontinued after the transplant. He had an immediate graft function and an uncomplicated post-operative course. He was discharged on hospital day 4 with a creatinine of 1.1 mg/dl and phosphorus of 2 mg/dl. His immunosuppressants include Tacrolimus 7 mg twice daily, Myfrotic 720mg twice daily, and Prednisone 5mg daily. On follow-up, his blood work showed stable renal function but worsening hypophosphatemia of 1.4 mg/dl. He was initiated on oral phosphate supplementation. Two weeks later, he has a progressive worsening of AKI with creatinine trending up to 3 mg/dl. Due to concern for acute rejection, a kidney biopsy was performed which showed acute tubular injury with focal tubular necrosis, focal tubular subepithelial tubular calcium phosphate deposition, and calcium phosphate casts. There was no evidence of T-cell or Anti-body mediated rejection. Phosphate supplementation was discontinued which subsequently improved the patient's allograft function with his creatinine reaching a nadir of 1.8 mg/dl 3 months later.

Discussion: Hypophosphatemia is commonly seen after kidney transplantation. This case highlights that acute phosphate nephropathy secondary to oral phosphate repletion may cause AKI among kidney transplant patients. Nephrologists should be vigilant in managing hypophosphatemia following a kidney transplant. Unless hypophosphatemia is life-threatening, we recommend conservative management including high dietary phosphate intake. Oral phosphate supplementation should only be considered in patients who are symptomatic with persistent severe hypophosphatemia and once a patient is initiated, careful monitoring of serum phosphate level and kidney function is recommended.

TH-PO825

Rapid Point-of-Care Capillary Blood Assays for Monitoring Cystatin C Levels in Kidney Transplant Recipients

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Background: Frequent monitoring of tacrolimus (TAC), an FDA-approved immunosuppressant, and estimated glomerular filtration rate (eGFR) in kidney transplant recipients (KTRs) are necessary to prevent allograft rejection and toxicity. We propose to use cystatin C (CysC) concentration as a marker for estimating eGFR for KTRs; CysC concentration is independent of age, sex, and muscle mass, making it a valuable predictor of nephrotoxic risks associated with TAC in KTRs. IOS has partnered with UCI Nephrology and WFIRM to develop a novel point-of-care (POC) enhanced lateral flow assay (ELFA) platform to determine levels of CysC from fingerstick capillary blood.

Methods: ELFA performance was assessed using standard calibration curves (SCCs) with spiked whole blood samples at various CysC levels. Method validation involved 17 KTRs, comparing ELFA measurements on fingerstick blood samples (n=3) to standard lab measurements of CysC from venous blood. Samples were collected from the same KTRs before their next TAC dose. A comparison of ELFA CysC and lab serum assumed a 50% hematocrit correction. Pearson correlation and Bland-Altman analysis determined the agreement between ELFA and clinical laboratory methods.

Results: SCCs indicated ELFA performs well in the 0-6 mg/L range for CysC. ELFA and standard lab measurements strongly correlated with r=0.88. Bland-Altman analysis showed a mean difference (bias) of 0.13 mg/L for CysC between the two methods.

Conclusions: The ELFA platform delivers minimally invasive, convenient sampling in a POC device using capillary fingerstick blood from KTRs, and provides accurate, rapid measurements of CysC that have demonstrated good repeatability and strong correlation with laboratory standard reference measurements.

Funding: Other U.S. Government Support

TH-PO826

Performance of GFR Estimating Equations in Kidney Transplant Recipients of Various Races

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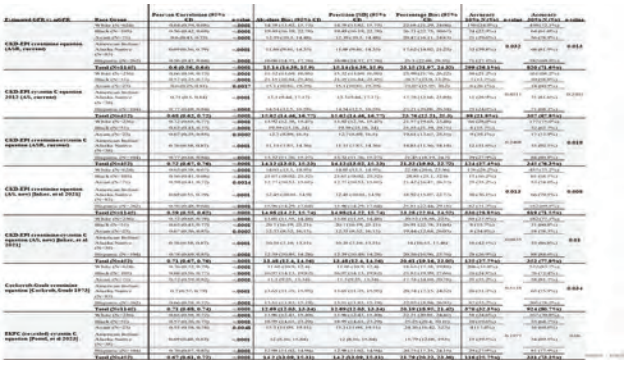
Background: We compared the performance of various estimated Glomerular filtration rate (eGFR) equations in kidney transplant recipients of different races.

Methods: This single-center study compares eGFR with measured GFR at 1-year post-transplant.

Results: There were 1145 subjects with 1-year eGFR and mGFR data. Whites made up 54%, followed by Hispanics (23%), Blacks (9%), Native Americans (7%), and Asians (6%). Among Whites, 2021 CKD-EPI creatinine cystatin C-based equations outperformed others [r=0.72, 95% CI (0.65, 0.78)]. The Cockcroft-Gault creatinine equation was the best correlated, least biased, and most accurate (83.7% A30). In Blacks, both 2009 CKD-EPI [r=0.56, 95% CI (0.42,0.68)] and 2021 CKD-EPI [r=0.56, 95% CI (0.41, 0.68)] had a weak correlation. The new EKFC (rescaled) cystatin C equation did not perform better in blacks than the 2021 CKD-EPI creatinine or 2012 CKD-EPI cystatin C-based equations. Cockcroft-Gault creatinine equation had the best correlation [r=0.68, 95% CI (0.56, 0.77)], followed by the 2021 CKD-EPI creatinine-cystatin C equation (0.63, 95% CI (0.43, 0.77). Among Hispanics, cystatin C and combined creatinine cystatin C-based equations were superior, with the 2021 CKD-EPI creatinine-cystatin C equation being the most accurate (84.6%) and highly correlated [r=0.78 (0.69, 0.85)]. In Native Americans, the creatinine-cystatin and EKFC cystatin c equations achieved the highest 30% accuracy (>85%).

Conclusions: The study suggests that combined equations of creatinine-cystatin C performed better than creatinine-based equations and the cystatin C-based equations in all races. EKFC rescaled cystatin equation performed better than 2021 CKD EPI. There was no substantial difference between the 2009 CKD EPI and the new 2021 CKD-EPI equation, which does not factor in race.



TH-PO827

eGFRcr, eGFRcys, Muscle Mass, and All-Cause Mortality in Kidney Transplant Recipients: Post-Hoc Analyses from a Randomized Controlled Trial

Gabriel A. Curran,[1] Jane D. Mcneilly,[2] Alastair J. Rankin,[2] Kaitlin J. Mayne,[1,3] Elbert Edy,[4] Patrick B. Mark,[1,2] Jennifer S. Lees.[1,2] *[1]University of Glasgow, Glasgow, United Kingdom; [2]NHS Greater Glasgow and Clyde, Glasgow, United Kingdom; [3]University of Oxford, Oxford, United Kingdom; [4]Manchester University NHS Foundation Trust, Manchester, United Kingdom.*

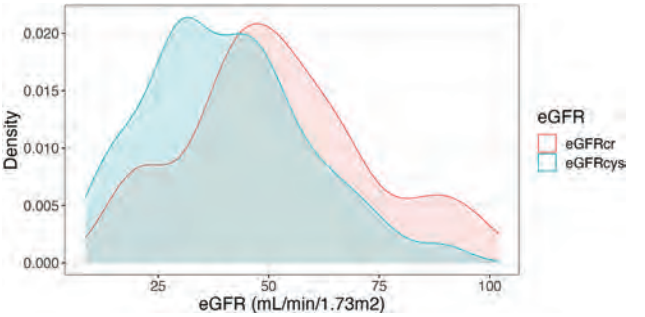
Background: We explored eGFRcr, eGFRcys and pectoral muscle cross-sectional area (PMA: a muscle mass surrogate) in kidney transplant recipients (KTR) and assessed relationships: i) between parameters and ii) with all-cause mortality.

Methods: Participants were from the ViKTORIES randomised controlled trial (ISRCTN22012044) in prevalent KTR. eGFRcr (2009) and eGFRcys (2012) were calculated from creatinine and cystatin C respectively at baseline. PMA was calculated as the mean pectoral muscle area from slice 1 (the first slice in which the full pectoral muscle became visible), 3 and 5 on non-contrast axial thoracic computed tomography (CT) scans taken at baseline. Follow-up data were extracted from the electronic record. Linear regression tested associations between eGFR measures and PMA. Cox proportional hazards models tested associations between eGFR measures, PMA and death.

Results: Of 90 ViKTORIES participants, 90 had available serum/plasma samples and 89 had CT data for analysis. Mean (±SD) age was 57.6 ± 9.6 years and 63 (70%) were male. The proportion with pre-existing cardiovascular disease (21.1%) and diabetes (22.2%) was lower than observed in UK KTR populations. Over median follow-up of 4.8 (IQR 4.5 - 5.1) years, there were 14 deaths. Mean eGFRcys (40.9 ± 18.3 mL/min/1.73m^2) was lower on average than eGFRcr (52.5 ± 21.0 mL/min/1.73m^2; Figure). PMA was inversely associated with eGFRcr (adjusted β per 1cm^2 increase in PMA: -0.326, p=0.007), but not eGFRcys (adjusted β: -0.172, p=0.165). eGFRcys (but not eGFRcr nor PMA) was significantly associated with death (aHR per 10mL/min/1.73m^2 decrease: 1.62, 95% CI 1.05-1.92).

Conclusions: In this population of KTR with lower-than-expected cardiometabolic comorbidity, eGFRcys was lower than eGFRcr, was not associated with muscle mass but was strongly associated with mortality. As seen in the general population, eGFRcys is a valuable marker to stratify risk of death in KTR.

Funding: Private Foundation Support



Density plots of eGFRcr and eGFRcys in the ViKTORIES trial

TH-PO828

Long-Term Outcome of Kidney Transplant Recipients with History of Complement-Mediated Thrombotic Microangiopathy

Kanza Haq,[1] Alana Dasgupta,[3] S.M. Bagnasco,[1] Umberto Maggiore,[2] Nada Alachkar.[1] *[1]Johns Hopkins University, Baltimore, MD; [2]Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; [3]The Ohio State University Wexner Medical Center, Columbus, OH.*

Background: The long-term outcome of kidney transplant recipients with history of complement-mediated thrombotic microangiopathy (cTMA) is unknown.

Methods: We retrospectively studied all kidney transplant recipients with TMA as primary disease or developed TMA post-transplant between Jan 2000 and Dec 2020 in our center. We estimated the crude survival probability via Kaplan-Meier methods starting at date of transplant until graft failure or death. The adjusted hazard ratio (aHR) associated with primary cTMA was estimated using Cox regression models with time-varying cTMA effect and biopsy diagnoses included as time-varying variables.

Results: We identified 129 patients (20 with cTMA as primary disease) who had 460 biopsies. After a mean follow-up of 4.5 years, 73 started dialysis and 22 died. Compared to others, patients with cTMA were younger both at cTMA diagnosis and at transplantation (age at diagnosis, 28.9±16.3. vs 46.5±16.0 years; P<0.001). Crude survival probability is reported in **Figure 1**. After adjusting for non-linear age, sex, ethnicity, biopsy diagnoses, cTMA was associated with 4-fold increase in the hazard of transplant failure shortly after transplant (adjusted hazard ratio (aHR): 3.97 [95%CI:1.52-10.38; P=0.005]); then, the aHR decreased by 0.87 (95%CI: 0.77-1.00; P=0.046) per year elapsed since transplantation (**Figure 2**). Banff diagnoses were all associated with increased hazard of transplant failure: grade 1 & 2 TCMR, borderline rejection, and CNI-toxicity (P<0.05), and ABMR (P=0.077), the strength of their association with transplant failure not being affected by cTMA history (P=0.38 for interaction).

Conclusions: Patients with cTMA have an increased risk of early transplant failure which vanishes with time elapsed since transplant when standard Banff diagnoses seem to take over cTMA history in determining transplant prognosis.

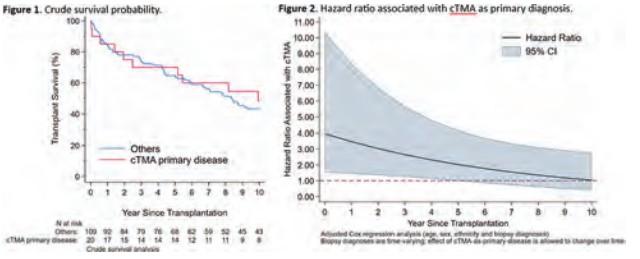


Figure 1. Crude survival probability. **Figure 2.** Hazard ratio associated with cTMA as primary diagnosis.

TH-PO829

Long-Term Outcomes Comparing Belatacept- vs. Tacrolimus-Based Maintenance Immunosuppression in Kidney Transplant Recipients: A UNOS Database Analysis

Adriana Montalvan,[1] Stalin I. Canizares Quisiguina,[1] Devin Eckhoff,[1] David D. Lee,[1] Kalathil K. Sureshkumar,[2] Bhavna Chopra.[1] *[1]Beth Israel Deaconess Medical Center, Boston, MA; [2]Allegheny Health Network, Pittsburgh, PA.*

Background: Calcineurin-inhibitors have been the mainstay of maintenance immunosuppression in kidney transplant recipients (KTRs), which is associated with nephrotoxic risks. Several immunosuppressants have been tried as nephron sparing agents but with limited success. We compared long-term outcomes of KTRs on tacrolimus (Tac) vs belatacept (Bela) based maintenance immunosuppression.

Methods: Using the UNOS Standard Transplant Analysis and Research (STAR) file to identify adult, first KTRs only from 2010 to 2022 who received induction therapy. Patients were categorized based on Tac or Bela based maintenance immunosuppression

at discharge. Multivariate cox regression models adjusting for several donor, transplant and recipient factors were used to compare graft, death-censored graft failure (DCGF) and patient death in all KTR and further stratified by donor type.

Results: A total of 194307 and 5152 patients on Tac and Bela were identified. Compared to patients discharged on Tac, subjects discharged on Bela were more likely to be older (53.5y vs 52.1y), African American (35.2% vs 27.3%), and diabetic (36.6% vs.34.5%), had greater time on dialysis (974d vs 913d), and received higher KDPI kidneys (36 vs 23) ($p<0.05$). Results of all KTRs and further stratified by donor type are shown in Table 1. Outcomes were similar in living donor KTRs; in deceased donor KTRs, Bela was associated with increased risk of death and DCGF.

Conclusions: Based on demographic and clinical data, patients discharged on Bela as maintenance therapy had higher comorbid burden. Our study found increased DCGF and patient death in the Bela group, which might be related to increased comorbidity, risk of early rejections despite the reduced nephrotoxic effects, and possibly increased viral and fungal infections associated with Bela. Retrospective nature and selection bias are major limitations of database study. Randomized controlled trials comparing Bela vs Tac are awaited.

Outcomes of all, deceased and living donor kidney recipients based on immunosuppression maintenance at discharge

	Patient Death HR (95%CI); p	Adjusted Overall Graft Failure HR (95%CI); p	Death Censored Graft Failure HR (95%CI); p
All patients Tac(n=194307) vs Bela(n=5152)	0.89 (0.82-0.97); 0.009	0.97 (0.90-1.05); 0.457	0.85 (0.78-0.94); 0.001
Deceased Donor Tac(n=3722) vs Bela(n=134583)	0.89 (0.82-0.97); 0.009	0.97 (0.90-1.05); 0.457	0.85 (0.78 - 0.94); 0.001
Living Donor Tac(n=59724) vs Bela(n=1430)	0.87 (0.74-1.03); 0.115	0.97 (0.82-1.14); 0.683	0.92 (0.75-1.12); 0.398

TH-PO830

Long-Term Outcomes Comparing Belatacept vs. Tacrolimus Stratified by Cytomegalovirus Risk in Kidney Transplant Recipients: A UNOS Database Analysis

Adriana Montalvan, Stalin I. Canizares Quisiguina, Devin Eckhoff, David D. Lee, Bhavna Chopra. *Beth Israel Deaconess Medical Center, Boston, MA.*

Background: Cytomegalovirus (CMV) infection is associated with increased risk of death and significant morbidity which can cause graft loss. Some studies have shown that Belatacept (Bela) may be associated with an increased risk of CMV reactivation and infection. We analyzed the UNOS database to compare long term patient and graft outcomes comparing Tacrolimus (Tac) vs Bela based maintenance immunosuppression (IS) in Kidney Transplant Recipients (KTR) stratified by CMV risk.

Methods: Using the UNOS Standard Transplant Analysis and Research (STAR) file, we identified adult, kidney-only transplant recipients from 2010 to 2022 who received (depleting/non-depleting) induction therapy and were discharged on Tac or Bela based maintenance IS. Multivariate cox regression models adjusting for several donor, transplant and recipient factors were used to compare Tac vs Bela maintenance in KTR stratified by CMV risk; CMV low (D-/R-), CMV intermediate (R+), and CMV high risk (D+/R-). Outcome measures included overall mortality, graft, and death-censored graft failure (DCGF).

Results: A total of 196785 KTR were identified where 5046 were on Bela and 191739 on Tac at discharge. The long-term outcomes comparing Tac vs. Bela were similar in CMV low risk group, worse (DCGF and Patient) for Bela in CMV intermediate risk and DCGF was nearing significance worse for Bela in high-risk group. Results are shown in Table 1.

Conclusions: When stratifying KTR based on CMV risk, it appears that patients on maintenance Bela IS may be at increased risk for DCGF when the CMV risk increases. Lack of granularity of data on CMV infection related details, retrospective design and selection bias are limitations of this study.

Outcomes on KTR according to immunosuppression maintenance at discharge stratified by CMV risk

	Adjusted Overall Graft Failure HR (95%CI); p	Death Censored Graft Failure HR (95%CI); p	Patient Death HR (95%CI); p
CMV Low Risk Tac (n=33035) vs Bela (n=866)	1.04 (0.82-1.31); 0.749	1.31 (0.93-1.83); 0.123	1.06 (0.82-1.37); 0.661
CMV Intermediate Risk Tac (n=124730) vs Bela (n=3423)	0.99 (0.91-1.01); 0.890	0.83 (0.74-0.92); 0.001	0.89 (0.80-0.98); 0.015
CMV High Risk Tac (n=33948) vs Bela (n=757)	0.86 (0.73 - 1.02); 0.091	0.81 (0.65-1.01); 0.058	0.87 (0.71-1.05); 0.149

pos: positive | neg: negative

TH-PO831

Renal Allograft Function Outcomes After Conversion from Conventional Immunosuppression to Belatacept Plus Low-Dose Conventional Drug Regimen

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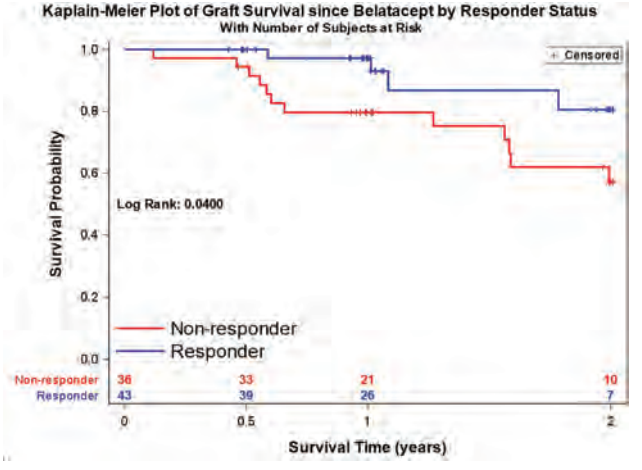
Background: Calcineurin Inhibitors (CNI) and Sirolimus have been traditionally used as immunosuppressants to prevent rejection in kidney transplant recipients but they are often associated with undesirable renal and metabolic adverse effects. Belatacept which is a selective T-cell costimulation blocker does not have the undesirable AE's. Data on using Belatacept and low dose CNI/Sirolimus combination is scant. At our institution, patients are switched to this regimen if they had Slow/delayed graft function, complications related to CNIs or graft rejection while on these drugs.

Methods: It is a retrospective chart review study. We included all patients >18 years of age at Indiana University Hospital who had a Kidney transplant and were switched from Tacrolimus, Sirolimus or Cyclosporine to a combination of Belatacept and lower dose CNI/Sirolimus. 'Response' (to the addition of belatacept) was defined as >10% change in the eGFR per year from baseline (pre-belatacept values) over 2 years. Logistic regression models were performed.

Results: N=79 Mean Age=53 years. History of deceased donor kidney transplant= 64 %. Response was observed in 54% of patients with improved eGFR by 6 months ($p= 0.003$) and sustained by 2 years eGFR of 49.1+/-19.5 vs. 35.3 +/-11.4 ($p = 0.04$). The mean duration of dialysis in responders vs. non responders was 32 and 52 months, respectively ($p= 0.057$) and there was no difference in tacrolimus levels post conversion. By univariate anlayses, non-response was significantly associated with retransplant (OR= 4.93) and higher level of proteinuria (OR= 1.51), and history of graft rejection before belatacept (OR= 3.45).

Conclusions: Belatacept in combination with low dose conventional immunosuppression appears to be a favorable option in patients with slow/delayed graft function or intolerance to conventional drugs at their therapeutic levels.



TH-PO832

Safety of Belatacept as a Maintenance Immunosuppressive Therapy in Kidney Transplantation: A Systematic Review and Meta-Analysis

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Background: Although calcineurin inhibitors (CNIs) are used as the standard maintenance immunosuppressive therapy after kidney transplantation, they are associated with nephrotoxicity and long-term renal allograft loss. Recent randomized controlled trials (RCTs) showed that using Belatacept (Bela) as an alternative to CNIs is associated with improves renal functions. However, there has been conflicting data about the risk of adverse outcomes such as infections and malignancies.

Methods: A systematic search for RCTs assessing the safety and efficacy of Bela in adult kidney transplant recipients was conducted in multiple online databases including Google Scholar and PubMed. RStudio was used for statistical analysis. Results are expressed as relative risk ratio (RR) and 95% confidence interval (CI).

Results: Five RCTs were included in our meta-analysis. The results showed no significant difference between the Bela and CNIs based-regimen in terms of renal allograft loss (RR= 0.77, 95% CI 0.52 – 1.09), cytomegalovirus (CMV) viremia (RR= 0.0.98, 95% CI 0.47 – 1.30), BK viremia (RR= 0.83, 95% CI 0.35 – 2.02), and malignancy (RR= 1.31, 95% CI 0.81 – 2.13). There was a significant increase in the risk of post-transplant lymphoproliferative disorder (PTLD) (RR= 3.87, 95% CI 1.08 – 13.82), but the majority of those patients were Epstein-Barr virus (EBV) seronegative.

Conclusions: Overall, the use of Bela as maintenance immunosuppressive therapy in kidney transplantation was generally safe and with no substantial increase in the risk of infection or malignancy. There was an increased risk of PTLD associated with this regimen in patients with EBV-negative serology. Avoiding Bela in EBV-negative patients may help lower this risk.

TH-PO833

Expanded One-Year Experience of Bimonthly Belatacept

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Background: Belatacept (bela) is a common immunosuppressive (IS) drug in kidney transplant (KT). We have over 300 KT patients on bela. Our initial cohort of expanded 2 monthly belatacept had favorable results so we expanded our cohort from 18 to 34 patients, and continued monitoring until year post conversion.

Methods: 34 patients at high risk of infection were included who were beyond one year from transplant and had no donor specific antibody (DSA) or prior episodes of rejection. They had stable allograft function and maintenance IS included bela 5mg/kg monthly, median mycophenolate mofetil dosing of 1g daily and prednisone 5mg daily. We monitored donor derived cell free DNA (ddcfDNA; Allosure), DSA, total IgG level, and CD4 counts at baseline and then at 2, 4, 6, and 12 months. Repeated measures ANOVA was used to assess statistical changes with multiple comparisons adjusted with Tukey-HSD.

Results: 20/34 (59%) patients were African American. The mean time on bela at initiation was 48.1± 30.0 months. The estimated glomerular filtration rate (eGFR; Mean± SE) did not change significantly between initiation and month 12 (43.5 ± 3.3 vs 46.3± 6.6 ml/min). There was no significant change in ddcfDNA between months 0 (0.23± 0.03%), 2, 4 and 6 (0.20±0.06%) months, though at month 12 there was an uptrend in mean ddcfDNA in 10 patients that have achieved this interval (0.43± 0.06%). There was no difference in absolute CD4 count; mean± SE between month 0 and 12 (326 ± 33.9 vs 368.7 ± 72.5; p= 0.94) and similar results were noted for IgG levels (939.5.2± 57.2 vs 861.0 ± 124.2; p=0.72). 1 patient developed low grade DSA at 6 months, which resolved spontaneously. 1 patient underwent biopsy for proteinuria which showed advanced diabetic nephropathy. One patient underwent biopsy for acute rise in ddcfDNA with DSA, which showed antibody mediated rejection, which resolved after intensive therapy and return to monthly bela infusions. There were no graft losses.

Conclusions: This report evaluating q2m bela, in a carefully selected and monitored cohort, demonstrates low risk of rejection with change in dose interval. There was no significant change in DSA or ddcfDNA or incidence of major opportunistic infections. Long term outcome monitoring is needed, and close interval assessment of ddcfDNA and DSA is critical for management of these patients in order to reduce the risk of acute rejection.

TH-PO834

Comparisons of Clinical Outcomes Between Hypertensive and Normotensive Living Kidney Donors: A Nationwide Prospective Cohort Study

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Background: Living kidney donors with hypertension is potential candidates to solve the imbalance between supply and demand for renal transplantation. However, the safety of hypertensive donor is not sufficiently ensured after donor nephrectomy and there are limited studies, which compare the clinical outcomes between hypertensive and normotensive donors.

Methods: All data from this study were obtained from the Korean Organ Transplantation Registry. A total 642 hypertensive donors and 4,848 normotensive living kidney donors were included from May 2014 to December 2020.

Results: Compared to normotensive donors, hypertensive donors had lower eGFR before nephrectomy and remained lower after kidney transplantation. However, the risk of eGFR below 60 ml/min/1.73 m²(adjusted HR, 0.87; 95% CI 0.70-1.09; P = 0.217) or below 45 ml/min/1.73 m²(adjusted HR, 1.52; 95% CI 0.79-2.94; P = 0.209) was not significantly increased in hypertensive donors after multiple adjustment. When comparing the rate of eGFR decline between the hypertensive and normotensive donors, there was no significant difference (adjusted unstandardized β, -0.19; -1.15 – 0.76, P = 0.691). The incidence of proteinuria occurrence in hypertensive donor was increased, and it tended to increase even after 4-5 years. Hypertensive donors were found to have significantly more proteinuria than normotensive donors (adjusted HR, 1.77; 95% CI 1.10-2.85; P =0.020).

Conclusions: Our study indicated that the risk of proteinuria after donation was increased in hypertensive donor, while it was not translated into significant decline in renal function. The careful monitoring for proteinuria should be required in hypertensive donor after nephrectomy.

Funding: Government Support - Non-U.S.

TH-PO835

Tegoprubart for the Prevention of Rejection in Kidney Transplant: Update of Emerging Data from an Ongoing Trial

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Background: Tegoprubart is a monoclonal antibody directed against the CD40 ligand (CD40L), a key mediator of co-stimulation. Inhibition of CD40L should result in a decrease in both cell and antibody mediated immunity and create a more tolerogenic immune environment. Tegoprubart has been shown to be effective in animal models and is currently being studied in kidney transplant recipients. It is being assessed to determine whether it can provide similar prevention of rejection as tacrolimus with superior graft function.

Methods: 12 adults receiving a kidney transplant from either a living or deceased donor will be enrolled. To be eligible, this must be their first transplant, they must be seropositive for EBV, free of donor specific antibodies, have low panel reactive antibodies, and the organ cannot be from an extended criteria donor or have a prolonged cold ischemia time. All participants will receive rATG and a regimen consisting of tegoprubart 20 mg/kg IV administered every 3 weeks after initial loading, mycophenolate and corticosteroids. The primary endpoint is safety at one year. Secondary endpoints include characterizing the pharmacokinetic profile of tegoprubart, the incidence of biopsy proven rejection (BPAR) and changes in estimated glomerular filtration rate (eGFR).

Results: As of the abstract submission deadline, May 2023, 5 participants have been transplanted, and 3 are ongoing. No participant has experienced rejection. One discontinued due to an SAE of BK viremia and another for mild alopecia and fatigue. BK viremia was the only SAE reported to date, and the drug appears safe and well tolerated. Participant information is summarized in Table 1, and mean eGFR is summarized in Figure 1.

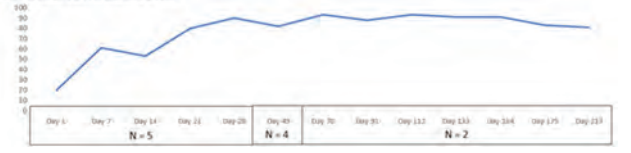
Conclusions: Improved graft function may improve long term outcomes in kidney transplantation. It is postulated that tegoprubart could be an alternative therapy for prevention of rejection in kidney transplant recipients. Data to date are encouraging, with no rejections, a good safety profile and excellent allograft function.

Funding: Commercial Support - Eledon Pharmaceuticals Inc

Table 1. Summary of Ongoing Participants

Participant	Demographics	LD vs DD	Status	Last eGFR
1	60 yo white ♀, PCKD, pre-dialysis	LD	EDC Day 232	77ml/min/1.73 m² Day 217
2	77 yo white ♀, DKD, hemodialysis	DD	Ongoing	85ml/min/1.73 m² Day 217
3	62 yo white ♂, PCKD, pre-dialysis	LD	EDC Day 56	54ml/min/1.73 m² Day 49
4	68 yo white ♂, DKD, peritoneal D	LD	Ongoing	93ml/min/1.73 m² Day 49
5	23 yo white ♀, IgAN, peritoneal D	LD	Ongoing	64ml/min/1.73 m² Day 28
6	44 yo Asian ♂, PCKD, hemodialysis	DD	Ongoing	Just transplanted
7	65 yo white ♂, DKD, hemodialysis	LD	Ongoing	Just transplanted

Figure 1. Mean eGFR in ML/min/1.73m²



TH-PO836

Anti-Thymocyte Globulin vs. Alemtuzumab Induction and Associated Complications in Kidney Transplantation: A 20-Year Multi-Center Experience

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Background: Antibody-depleting immunosuppression such as anti-thymocyte globulin (ATG) and alemtuzumab are commonly-used induction therapies after kidney transplantation, and may result in varying rates of associated complications including, but not limited to, acute or delayed allograft rejection, leukopenia, sepsis, allograft failure, CMV infection, BK virus nephropathy, or death.

Methods: We performed a retrospective multi-center cohort study using TriNetX, a global federated health research network, providing access to electronic medical records across large healthcare organizations [HCOs] grouped into Global Collaborative Network including 97 HCOs. We identified 4,920 propensity-matched kidney transplant recipients inducted with ATG (n=2460) or alemtuzumab (n=2460) between Jan 2003-2023 from 26 HCOs in 13 countries, compared for clinical outcomes with risk analysis and Kaplan-Meier survival analysis.

Results: Kidney allograft rejection occurred in 1,159(47.1%) patients with alemtuzumab induction as compared to 794(32.3%) patients in ATG cohort(RR=1.460;95%CI 1.36-1.57). Severe sepsis confirmed in 160(6.5%) patients with alemtuzumab vs 179(7.27%) in ATG group(RR=0.894;95%CI 0.73-1.09). With alemtuzumab, 908(36.9%) patients developed leukopenia vs 741(30.1%) patients in ATG cohort(RR=1.225;95%CI 1.13-1.33), and 135(5.48%) died in alemtuzumab group vs 176(7.15%) in ATG group(RR=0.77;95% CI 0.617-0.953). Kidney transplant failure (KTF) was confirmed in 1090(44.3%) patients in alemtuzumab group and 724(29.4%) patients in the ATG group (RR=1.506, 95% CI 1.396-1.624), with graft survival of 53.06% and 67.80% in alemtuzumab vs ATG cohorts, respectively(HR=1.68;95%CI 1.53-1.85; p=0.004). CMV disease confirmed in 860(34.9%) with alemtuzumab induction vs 693(28.8%) in ATG group(RR=1.241;95%CI 1.14-1.35). With alemtuzumab induction, BK virus nephropathy was diagnosed in 370(15.0%) vs 265(10.7%) in ATG group(RR=1.396;95%CI 1.21-1.74).

Conclusions: Kidney transplant patients with alemtuzumab induction had significantly increased risk of rejection, leukopenia, transplant failure, CMV infection, and BK virus nephropathy. Risk of death is significantly less in the alemtuzumab group as compared to ATG group. No significant difference in severe sepsis between alemtuzumab and ATG cohorts.

TH-PO837

Incidence and Outcomes of Post-Transplant Lymphoproliferative Disorder After Kidney Transplantation: A 20-Year Multi-Center Experience

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Background: Post-transplant lymphoproliferative disorder (PTLD) is a rare complication following solid-organ transplantation, involving a spectrum of lymphocytic and/or plasmacytic proliferations in immunosuppressed patients. While often associated with Epstein-Bar Virus (EBV) reactivation, the pathogenesis and risk factors of PTLD are not clearly understood; its clinical manifestations are diverse, and management is challenging with focus on immunosuppression reduction, chemoradiotherapy or surgical resection of localized lesions, while aiming to preserve graft function.

Methods: We performed a retrospective multi-center cohort study using TriNetX, a global federated health research network providing access to electronic medical records across large healthcare organizations (HCOs). We identified 163,826 post-kidney transplant patients from January 15 2003-2023 from 89 HCOs in 13 countries. Patients with confirmed diagnosis of PTLD (n=2181) and those without PTLD (n=161,645) post-renal transplantation were assessed for clinical outcomes including death and kidney transplant failure (KTF) with risk analysis and Kaplan-Meier survival analysis.

Results: Among 163,826 post-renal transplant recipients, 2,181 (1.3%) were identified with confirmed diagnosis of PTLD and 161,645 (98.6%) did not develop PTLD. At the time of transplant, the PTLD group was younger($p<0.0006$), more likely to have received a previous transplant($p<0.0001$), and on an immunosuppressive agent($p<0.0001$). Of those who developed PTLD, 534 (24.4%) died as compared to 23,824 (14.7%) in non-PTLD group; survival rate was 55.87% in PTLD vs. 44.79% in non-PTLD cohort [HR=0.434, 95% CI 0.398-0.473, p = 0.00). Risk difference for death in patients without PTLD vs. with PTLD was -0.097 [RR=0.602, 95% CI -0.116, -0.079; p=0.00]. KTF was confirmed in 34,643 (21.4%) in non-PTLD vs 600 (27.5%) in PTLD group. KTF risk in patients without PTLD and with PTLD was 0.214 and 0.275, respectively, with graft survival of 54.06% and 55.55% in non-PTLD vs. PTLD cohorts, respectively [HR=0.652, 95% CI 0.602-0.707, p=0.008].

Conclusions: Younger age, previous transplant and being on an immunosuppressive agent at time of kidney transplant is associated with occurrence of PTLD. Additionally, PTLD is associated with increased risk of graft failure and death.

TH-PO838

Histological Analysis of Protocol Biopsies and Outcomes in ABO-Incompatible Renal Transplants: A Single-Centre Prospective Study from West India

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Background: ABO Incompatible renal transplants(ABOiKtx) provide a viable option to increase donor pool for ever increasing need. Outcomes are comparable to ABO compatible counterparts. Limited data exist regarding role of Protocol Biopsies and the impact of histological changes on the outcomes of ABO incompatible renal transplants.

Methods: We Included all ABO incompatible renal transplant patients from April 2017 and have completed 6 months of follow up till march 2019. A Protocol biopsy was done when eligible at 3 and 12 months post transplant. All the patients were analyzed for outcomes. Mehtodology for Biopsy: Biopsy samples were processed at our hospital, 2 cores were taken for histology and IF, C4D done by IF. Protocol biopsies were assessed and deemed adequate for interpretation by pathologists and graded according to the revised Banff classification 2017.

Results: 34 patients who underwent ABOiKTX between April 2017 to March 2018 were included. 23/34 patients underwent biopsies at 3 months[17 protocol and 6 indication biopsy(5 didnot consent, 2 were on antiplatelets, and 4 grafts were lost)] and20/23 at 12 months[17 protocol and 3 indication biopsy(2 graft were lost and one was on antiplatelets)]. Protocol biopsies revealed no subclinical rejections. 3/17 and 8/17 had C4d positivity without rejection at 3 and 12 months respectively. Presence of C4d at 3 months did not significantly influence GFR or Chronicity on biopsy at 12 months. Analysis of indication biopsies 6/23 revealed 1 IFTA,1 ABMR 4 TCMR at 3 months. Overall 6 patients had TMA on biopsies(Indication biopsies) over 1 year follow up. At 1 year Patient survival was 94% and death censored graft survival of 87% (Causes- Graft artery thrombosis, HUS and Rejections). Subgroup analysis revealed no difference in graft outcomes with lower or higher doses of Rituximab for desesnitization (p= 0.6).

Conclusions: Presence of C4D positivity or Tubulo-interstitial inflammation at 3 months was not associated with reduced GFR or increased fibrosis at end of 1 year. Lack of subclinical rejections were encouraging. Those with normal biopsies at 3 months had good outcomes at 1 year. Graft Survival and patient survival were comparable with other centres.

TH-PO839

Clinical Outcomes and Health Care Resource Utilization Associated with Post-Transplant Neutropenia Among Kidney Transplant Recipients: A Real-World Evidence Study

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Background: Cytomegalovirus (CMV) remains one of the leading opportunistic infections after kidney transplantation (KT). Valganciclovir is the preferred drug for CMV prophylaxis, but neutropenia limits its use. The objective of this study was to examine the differences in clinical outcomes and HCRU among KT recipients (KTRs) with and without PTN.

Methods: This retrospective cohort study utilized the TriNetX Dataworks – USA Network, a federated network of de-identified electronic health record data for over 86 million patients in the US. Adult KTRs who received their first KT between 1/1/2012 and 9/30/2020 and valganciclovir/ganciclovir within 30 days post-KT were included. PTN was defined by laboratory ANC of <1000 cells/μl. We ran Chi-square tests for categorical variables and t-tests for continuous variables.

Results: Among 8,791 KTRs included in this study, 2,149 (24.4%) developed PTN. ***Table 1*** presents the comparison on clinical and HCRU outcomes. A higher proportion of KTRs with PTN had CMV infections/disease (12.1% vs. 4.4%), other opportunistic infections (e.g., bacterial septicemia (13.1 vs 8.4%)), graft rejection (30.5% vs. 25.8%), graft loss (7.6% vs. 5.2%), new-onset of diabetes mellitus (32.8% vs. 21.5%), and received dialysis (30.5% vs 25.8%) within 1 year post-KT. KTRs with PTN (vs. without) were more like to have hospitalizations (63.1% vs. 55.9%), ER visits (37.5% vs. 32.0%), outpatient visits (mean number of visits: 39.3 vs. 33.0), blood transfusions (23.5% vs. 20.1%), and G-CSF use (54.2% vs. 5.2%).

Conclusions: KTRs with PTN tended to experience more opportunistic infections, worse graft outcomes and higher HCRU. The findings suggest the need for treatment options to reduce the risk of PTN among KTRs to improve clinical outcomes and reduce HRCU post-KT.

Funding: Commercial Support - Merck & Co. Inc

Table 1: Clinical Outcomes and HCRU within 1 Year Post-KT

Clinical outcomes and HCRU	With PTN N (%) /Mean (SD)	Without PTN N (%) /Mean (SD)	P-value
	2,149 (24.4%)	6,642 (75.6%)	
Clinical outcomes			
Opportunistic infections			
CMV infection/disease	259 (12.1%)	292 (4.4%)	<0.01
Viral infections (non-CMV)	976 (45.4%)	2296 (34.6%)	<0.01
Bacterial infections	335 (15.6%)	679 (10.2%)	<0.01
Septicemia	281 (13.1%)	555 (8.4%)	<0.01
Fungal infections	356 (16.6%)	774 (11.7%)	<0.01
Graft Outcomes			
Graft rejection	656 (30.5%)	1,712 (25.8%)	<0.01
Graft loss	163 (7.6%)	348 (5.2%)	<0.01
Dialysis	600 (27.9%)	1,607 (24.2%)	<0.01
HCRU			
Hospitalization	1,357 (63.1%)	3,713 (55.9%)	<0.01
Emergency room visits	805 (37.5%)	2,126 (32.0%)	<0.01
Number of outpatient visits	39.3 (31.7)	33.0 (28.2)	<0.01
Blood transfusions	506 (23.5%)	1,332 (20.1%)	<0.01
G-CSF	1,165 (54.2%)	346 (5.2%)	<0.01

TH-PO840

Association of Metformin with Rejection and Graft Survival in Kidney Transplant Recipients Taking Tacrolimus with Post-Transplantation Diabetes Mellitus

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Background: Tacrolimus is a pivotal maintenance immunosuppressive drug in kidney transplantation (KT). Although diabetogenic property of tacrolimus is still an inevitable concern, it can reduce the risk of acute rejection and improve graft survival. Metformin, despite limited randomized controlled trial, has been found to be safe and effective in patients with post-transplantation diabetes mellitus. We aimed to investigate the effect of metformin on acute rejection and graft survival in kidney transplant recipients taking tacrolimus.

Methods: A number of 410 PTDM patients prescribed tacrolimus between 2000 and 2018 were collected. We conducted propensity score matching between the metformin and non-metformin group and evaluated the effects of metformin on the occurrence of T-cell mediated rejection and antibody-mediated rejection, and graft survival.

Results: Among 410 patients taking tacrolimus, 273 patients were treated with metformin for the average of 3.8 years. After 1:1 matching, cumulative incidences of TCMR (p=0.029) and graft failure (p=0.025) in the metformin group was lower than the non-metformin group, while no significant difference was observed in ABMR. Metformin use was associated with a reduced risk of TCMR (HR 0.40, 95% CI 0.18-0.90, p=0.026) and graft failure (HR 0.32, 95% CI 0.14-0.72, p=0.006). There was no significant difference in tubulitis, interstitial inflammation, and endarteritis scores of TCMR between the metformin and the non-metformin group.

Conclusions: Our study demonstrates that combination therapy with metformin and tacrolimus in KT recipients with PTDM is associated with a lower risk of acute rejection and graft failure.

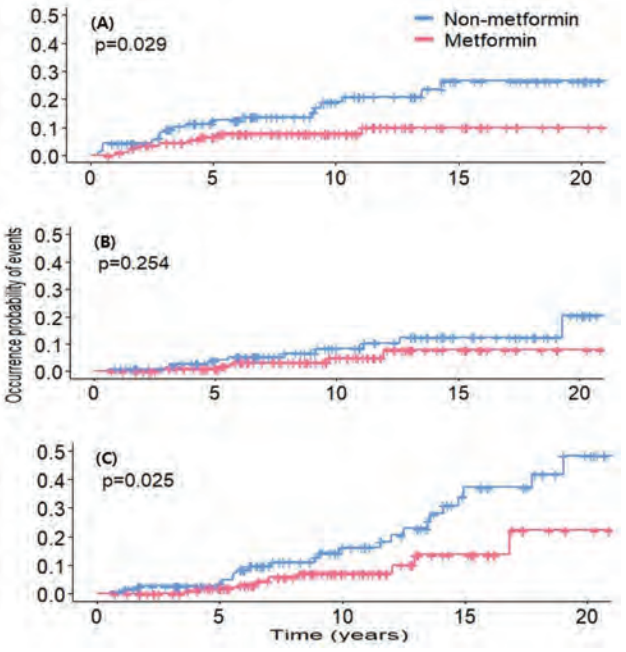

Figure1. The occurrence probability of TCMR (A), ABMR (B), and graft failure (C)

TH-PO841

Triple Jeopardy: Trialled Thrice in the Same Crime

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Introduction: Post-transplant lymphoproliferative disorder (PTLD) is a life threatening complication following solid organ transplantation. PTLD covers a wide range of lymphomas, however the most common is the B-cell type. While majority of the cases are associated with Epstein-Barr virus (EBV) infection, about 20 % of the PTLD can occur in EBV seronegative patients. Hemophagocytic lymphohistiocytosis (HLH) is a syndrome of excessive immune activation that can rapidly progress to multisystem organ failure and is mostly associated with infections and malignancies. Only two cases of HLH associated with EBV negative PTLD in a renal transplant patient have been reported in the literature. Hereby, we present an extremely rare (third) case of EBV-negative PTLD complicated by HLH in a kidney transplant recipient.

Case Description: 41 year old male with history of deceased donor kidney transplant for hypertensive nephrosclerosis about 10 years ago presented to the emergency department with complains of fever, fatigue and diarrhea for 3 weeks. His maintenance immunosuppression included tacrolimus, prednisone and mycophenolate. On presentation, he was hypotensive and febrile. Initial labs showed leukocytosis, anemia, thrombocytopenia, acute kidney injury, hypoglycemia, and severe lactic acidosis. The patient was started on broad spectrum antibiotics. Further work up revealed an undetected plasma EBV. His tremendously high serum ferritin, lactate dehydrogenase, triglycerides, soluble IL-2 receptor levels and abdominal imaging revealing splenomegaly did raise concern for HLH secondary to an underlying malignancy. He underwent bone marrow biopsy which showed findings consistent with diffuse large B cell lymphoma (DLBCL). He subsequently received 6 cycles of chemotherapy with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone) regimen resulting in complete remission of DLBCL.

Discussion: The incidence of PTLD in adult kidney transplant recipients ranges from 1-3%. The principal risk factors for PTLD include degree of immunosuppression and the EBV serologic status of the recipient. Clinical manifestations are non-specific and highly variable. B cell lymphoma with HLH in kidney transplant recipients is a rare entity and associated with a high mortality of >50%. Therefore, a high index of clinical suspicion and prompt initiation of chemotherapy is the key.

TH-PO842

CD8+ T Cells and Subpopulations as Potential Predictors for Cytomegalovirus (CMV) Viremia in Kidney Transplantation

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Background: CMV viremia is associated with reduced graft survival in kidney transplant recipients, despite potential prevention by antiviral prophylaxis. Identification of patients at risk remains a key challenge in transplant nephrology. Here, we examined the predictive value of pretransplant $CD8^+$ T cell subtype immunophenotyping on CMV viremia after transplantation.

Methods: Flow cytometric analysis of peripheral blood leukocytes and $CD8^+$ T cell subpopulations was performed shortly before transplantation (timepoint V1) in 65 kidney transplant recipients. CMV viremia was defined as above 100 CMV copies/ml in at least one PCR during the first year of transplantation.

Results: CMV viremia (CMV+) was frequent (n= 33, 50.8%) in our cohort. After one year, eGFR was worse in CMV+ compared to CMV- patients (1.66 vs. 1.25ml/min/1.73m^2, p<0.001), underlining its detrimental effect on graft function. Overall, pre-transplant frequencies of $CD3^+CD8^+$ in lymphocytes (19.7% vs. 15.4%, p=0.05) and $FoxP3^+CD25^+$ in $CD3^+CD8^+$ T cells (1.45% vs. 0.74%, p<0.01) were significantly higher in CMV+. Absolute numbers of leukocytes (4145/µl vs. 5249/µl, p=0.01), granulocytes (2576/µl vs. 3317/µl, p=0.01) and monocytes (222/µl vs. 315/µl, p=0.01) were lower in CMV+. Although not generally regarded as risk factor, women were disproportionally affected by CMV in our cohort (16 CMV+ in 25 women, 64% vs. 17 CMV+ in 40 men, 42.5%). Although we are limited by a small sample size, we sought to explore potential sex-specific risk factors for CMV within the peripheral blood at V1: For men, $CD3^+CD8^+$ T cells were increased in those who latter developed CMV viremia (21% vs. 15.2%, p=0.04). $FoxP3^+CD25^+$ in $CD3^+CD8^+$ T cells were elevated (1.19% vs. 0.71%, p=0.01), and monocytes (211/µl vs. 358/µl, p=0.02) were decreased in women, who became CMV+.

Conclusions: Pre-transplant predictors of CMV viremia within the peripheral leukocyte and $CD8^+$ T cell pool may aid in selecting patients for antiviral prophylaxis. While $CD8^+$ T cells are generally regarded as cytotoxic, expansion of regulatory subtypes like $FoxP3^+CD25^+CD8^+$ T cells may render individuals susceptible to infections. Our findings further hint towards sex-specific differences in immune cell abundance and function, which ought to be confirmed in a larger cohort.

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

TH-PO843

A National Retrospective Cohort Study of BK Viraemia in Renal Transplant Recipients

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Background: BK nephropathy is an important cause of graft dysfunction and graft loss. Treatment options are limited and involve immunosuppression reduction. In Ireland, post-transplant BK DNA is checked monthly between months 1-6 and thereafter at month 9 and 12. We examine incidence, risk factors and effect of BK viraemia on long-term graft survival.

Methods: A national retrospective cohort study of renal transplant recipients in the first 12 months post-transplant between 2011-2021 was performed using data from the National Renal Transplant Registry and the National Virus Reference Lab. Patients were followed up for a minimum of 3 months and BK viraemia was defined as >5000 DNA copies per ml (CPM). A cox proportional hazards model was used to assess risks associated with BK viraemia. Statistical analysis was performed using Stata 16 SE.

Results: Of 1319 transplanted patients, BK surveillance rates were high across all nephrology centres (96-99% of patients had results available as per monitoring protocol). 179,14% of recipients developed BK viraemia with peak levels occuring at two months and levels falling to 1000 CPM by six months. Rates of BK viraemia were higher in males than females, 145 per 1000 patients (95% CI 121-175) versus 103 per 1000 patients (95% CI 76- 141). Highest rates of BK viraemia were seen in ages 49-59 (190 per 1000 patients, 95% CI 146-247). Higher rates of biopsy-proven rejection at one year (HR 1.65 CI 1.01-1.77 p-value 0.044) was associated with BK viraemia. Neither pGEN >95% (HR 1.04 CI .61- 1.77 p value 0.896) or delayed graft function (HR1.01 CI 0.68-1.49 p-value 0.969) was associated with the development of BK viraemia. At one year the average serum creatinine was 115umol/L in recipients without BK-viraemia versus 126umol/L in those with BK-viraemia (p value 0.0017). Kaplan-Meier survival graphs demonstrated no difference in renal graft survival in those with BK viraemia than those without at 10 years. (p-value 0.37).

Conclusions: No significant difference in graft survival was observed in those who developed BK viraemia in the first 12 months post-transplant over a decade of transplantation in Ireland. The next step of this analysis is the examine the effect of immunosuppression changes on the development of donor specific antibodies.

TH-PO844

A Comparison of BK Polyomavirus Nephropathy Between Native and Allograft Kidneys

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Background: BK polyomavirus nephropathy (BKVN) has emerged as an important but uncommon cause of renal dysfunction and loss in allograft kidney and native kidneys from hematopoietic stem cell transplant recipients (HSCTRs). Yet it is unclear whether there is difference between these two populations on the clinicopathological features and renal outcomes.

Methods: Patients diagnosed as BKVN by renal biopsy from 2019 to 2022 were collected for a retrospective cohort study. The patients were divided into native kidney group (including 7 HSCTRs) and allograft kidney group (including 50 KTRs).

Results: By the time of diagnosis, the median age of native kidney group was younger than that of allograft kidney group (median 14.4 vs. 35.3y, *P*<0.001). There

was no difference of time interval from transplantation to diagnosis between the two groups (median 12.0 vs. 11.0 months, *P*=0.742). The native kidney group had higher i, ci, ct scores (Banff 2019) and percentage of SV40-T positive tubules (all *P*<0.05). More positive SV40-T glomerular parietal epithelial cells was found in native than in allograft kidney group (*P*<0.05). In a 1:1 propensity score matching by age, the native kidney group also showed higher i score, higher proportion of SV40-T positive tubules and advanced AST stage patients than allograft kidney group (all *P*<0.05). The rate of eGFR decline was greater in native than allograft kidney group (median -1.82 vs.0.44 ml/min per 1.73 m2/year, *P*=0.044; Fig A). One year cumulative renal failure rate after BKVN diagnosis was 57.1% in native and 4% in allograft kidney group (*P*<0.001; Fig B). The risk of progression to renal failure was significantly higher in BKVN of native than BKVN of allograft kidney (HR, 0.02; 95% CI, 0.00-0.59; *P*=0.025). Multivariate Cox regression analysis demonstrated that advanced AST stage was independently associated with worse renal outcome (HR, 2.36; 95% CI, 1.05-5.33; *P*=0.038).

Conclusions: BKVN of native kidneys in HSCTRs have a poorer renal survival than allograft kidney, which may correlate with more severe tubulointerstitial chronic lesions and higher tissue polyomavirus load at the time of renal biopsy.

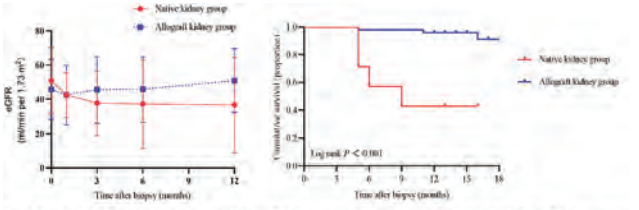

Fig A. Trend of eGFR over time in native and allograft kidney group. B. Renal survival in native and allograft kidney group.

TH-PO845

Increased Incidence of Kaposi Sarcoma Among African and Hispanic Kidney Transplant Recipients

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Background: Post-transplant Kaposi's sarcoma (PTKS) is a rare complication among transplant patients. However, the incidence of PTKS is 100-500 times higher than Kaposi's sarcoma (KS) in the general population. There have been no retrospective analyses characterizing increased incidence of PTKS among racial minorities in the U.S.

Methods: We performed an IRB-approved retrospective analysis of all adult patients greater than 18 years of age diagnosed with KS at Montefiore Medical Center. We reviewed electronic medical records based on ICD-9/10 code between the dates of 01/01/2014 – 09/01/2022 and identified 80 patients with KS, 10 of which were diagnosed with PTKS. Nine patients with PTKS after kidney transplant were included and 1 patient with PTKS after bone marrow transplant was excluded.

Results: Of the 9 patients that received kidney transplants and subsequently developed PTKS, 3 were female and 6 were male. All patients were minorities, with 6 African American and 3 Hispanic patients. Median age at transplantation was 60 years (range 44-70). Average time elapsed between transplant and PTKS development was 832.3±834.97 days (range 125-2630). Anatomic locations of PTKS lesions in patients included lower extremities (n=5), upper extremities (n=3), lymph nodes (n=3), kidney (n=1), and lung (n=1). Immunosuppression included tacrolimus (n=9), mycophenolate (n=7), cyclosporine (n=1), and steroids (n=10). After PTKS diagnosis, 7 patients had immunosuppression switched to sirolimus, 1 patient had tacrolimus and mycophenolate reduced, and 1 patient expired before treatment modification. All patients continued steroids. Four patients required additional treatment including radiotherapy (n=2), excision (n=1), and excision and imiquimod (n=1). One patient experienced PTKS recurrence approximately 18 months after initial resolution. Mortality was high (44%), and 4 patients died at a median of 95 days (range 19-1760) after diagnosis.

Conclusions: This study demonstrates high mortality rate in PTKS patients in minority kidney transplant recipients.

TH-PO846

Efficacy and Safety of Sodium-Glucose Cotransporter-2 Inhibitor in Diabetic Kidney Transplant Recipients: A Case-Control Study

Ashraf A. Ibrahim, Mohamed Y. Ali, Ali Mahgoub, Rasha Mohamed Abdul Rahman, Mohamed Abdelhalim, Ahmed F. Hamdi, Tarek A. Ghonimi, Tarek A. Fouda, Mohammed E. Hussain, Mostafa Elshirbeny, Fatima B. Eltayeb, Musab Elgaali, Shaimaa A. Arroub, Rania A. Ibrahim, Essa Abuhelaiqa, Abdullah I. Hamad, Hassan A. Al-Malki, Mohamad M. Alkadi. *Hamad Medical Corporation, Doha, Qatar.*

Background: KDIGO guidelines recommend initiating sodium-glucose cotransporter 2 inhibitors (SGLT2i) in diabetic chronic kidney disease (CKD) patients for its cardiovascular and renal protective effects. However, up till now, there are no recommendations regarding its use in diabetic kidney transplant recipients (KTR). The aim of this study was to determine the efficacy and safety of SGLT2i in diabetic KTR.

Methods: This was a retrospective case-control study. Cases (diabetic KTR using SGLT2i) and controls (diabetic KTR not using SGLT2i) were matched for recipient age, gender, year of transplant, and donor type. This study has been approved by Hamad general hospital research center. MRC-01-23-077

Results: There were 78 cases and 78 controls. The mean follow-up period in cases and controls was 23.9 and 24.1 months, respectively. Both groups had similar baseline graft function and HbA1c. Compared to controls, cases had a statistically significant reduction of BMI (-1.1 vs. +0.23; P<0.001). There was also a trend for better graft function and diabetes control, but it did not reach statistical significance. Both groups had similar adverse events such as AKI, UTI, cardiovascular and cerebrovascular complications (figure 1).

Conclusions: SGLT2i use in diabetic KTR was associated with a significant reduction in BMI and a trend for better kidney function and diabetes control. Longer prospective randomized controlled trials are needed to confirm their safety and efficacy outcomes in KTR.

Funding: Government Support - Non-U.S.

Figure 1: Efficacy and safety of SGLTi in diabetic KTR

Variables	Cases (n=78)	Controls (n=78)	P value
Change in BMI (Kg/m²)	-1.05±1.8	+0.23±1.3	**0.001**
Change in serum creatinine (µmol/l)	-0.38±13	+4.06±22	0.14
Change in urine Protein/Creatinine ratio(mg/mmol)	-0.25±16	+3.3±38	0.351
Change in HbA1C %	-0.32±1.6	+0.02±1	0.125
Acute kidney injury	11	12	0.743
Urinary tract infection	22	14	0.13
Congestive heart failure	0	2	0.144
Acute coronary syndrome	3	2	0.682
Cerebrovascular accident	1	0	0.325
Amputation	1	0	0.325

TH-PO847

Economic Impact of Dementia After Kidney Transplantation: A Matched Cohort Analysis

Krista L. Lentine,[1] David Axelrod,[3] Huiling Xiao,[1] Mara McAdams-DeMarco,[2] Yusi Chen,[2] Sunjae Bae,[2] Yasar Caliskan,[1] Dorry L. Segev,[2] Mark Schnitzler.[1] *[1]Saint Louis University, Saint Louis, MO; [2]New York University, New York, NY; [3]University of Iowa Hospitals and Clinics, Iowa City, IA.*

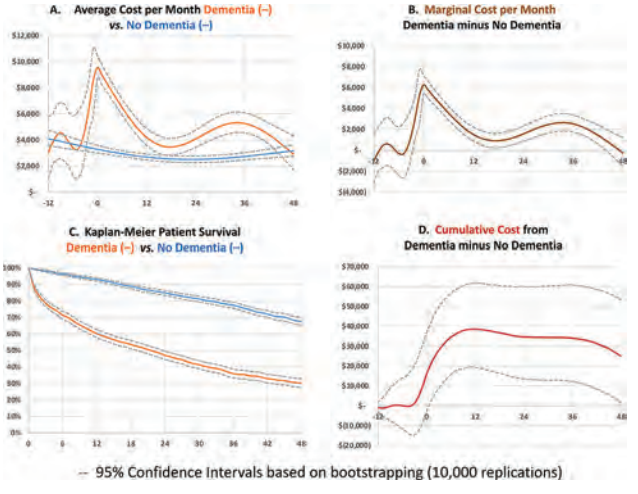
Background: Dementia risk is increased among patients with kidney disease, including kidney transplant (KTx) recipients, and is assocaited with adverse outcomes. To date, the cost implications of dementia after KTx are not well described.

Methods: We examined USRDS data (2006–2016) to compare costs incurred in the care of Medicare-insured KTx recipients with diagnosed dementia vs. matched controls, based on payments on Medicare claims. KTx recipients age 65+ years with post-KTx dementia were identified by diagnosis codes and matched to recipients without dementia, based on propensity score for dementia using recipient (demographic and clinical), donor, and transplant factors. Average costs per month, marginal costs per month, and cumulative costs were compared after the dementia diagnosis vs after equivalent time post-KTx in the controls.

Results: We identified 1,556 KTx recipients with dementia after KTx (mean time to diagnosis: 4.2±2.8) and 3,112 controls. Cases and controls were well balanced with regard to baseline factors, including mean age (70.3±4.2 vs 70.1±4.0 yrs.), sex (37.7% vs. 35.8% women), race (26.0% vs. 25.5% African American), and cause of ESKD (46.2% vs. 46.3% diabetes). Monthly costs approaching a dementia diagnosis rose to peak of ~$9,229, and exceeded that of cases over 36 mos. of follow-up (**Fig. A**). The marginal cost impact of dementia diagnosis ranged from $6,215 to $945 (**Fig. B**). At 36-mo. post dementia diagnosis, dementia patients incurred $34,034 (95% CI $12,192–$60,816) more costs than those without dementia. Higher spending occurred despite substantially lower survival in patients with dementia vs. matched controls.

Conclusions: KTx recipients with dementia incur higher costs of care and experience lower survival compared to matched controls. Further research is needed to develop care pathways to optimize clinical and economic outcomes of KTx recipients with dementia.

Funding: NIDDK Support, Private Foundation Support



TH-PO848

Transition of Care of Stable Kidney Transplant Patients to Referring Nephrologists: A National Survey of US Transplant Centers

Krista L. Lentine,[1] Neeraj Singh,[2] Kenneth J. Woodside,[3] Kennan R. Maher,[4] Tarek Alhamad,[5] Roy D. Bloom,[6] Darshana M. Dadhania,[7] Mona D. Doshi,[8] Ronald Parsons,[9] Gaurav Gupta,[10] Amy D. Waterman,[11] Bekir Tanriover,[12] Gary G. Singer,[13] Prince M. Anand.[14] *[1]Saint Louis University, Saint Louis, MO; [2]Willis-Knighton Health System, Shreveport, LA; [3]Gift of Life, Ann Arbor, MI; [4]Willis-Knighton, Shreveport, LA; [5]Washington University in St Louis, St Louis, MO; [6]University of Pennsylvania, Philadelphia, PA; [7]Cornell University, Ithaca, NY; [8]University of Michigan, Ann Arbor, MI; [9]Emory University, Atlanta, GA; [10]Virginia Commonwealth University, Richmond, VA; [11]Houston Methodist, Houston, TX; [12]Banner University Medical Center Tucson, Tucson, AZ; [13]Midwest Nephrology, St. Louis, MO; [14]Medical University of South Carolina, Charleston, SC.*

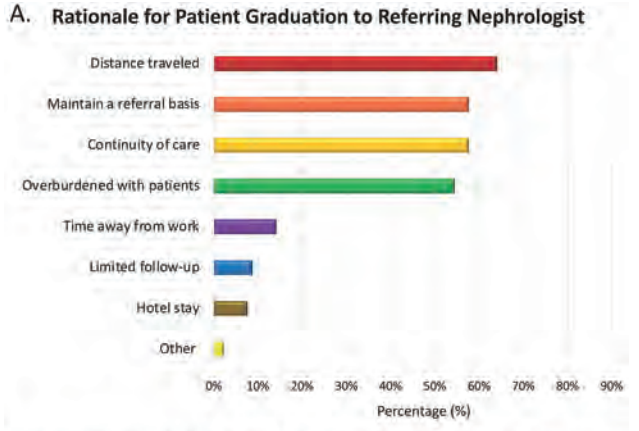
Background: Transition of care from transplant centers (TC) to referring nephrologists is critical for long-term care of kidney transplant (KTx) recipients. We conducted a national survey to assess opinions and experiences of TC staff related to care graduation processes.

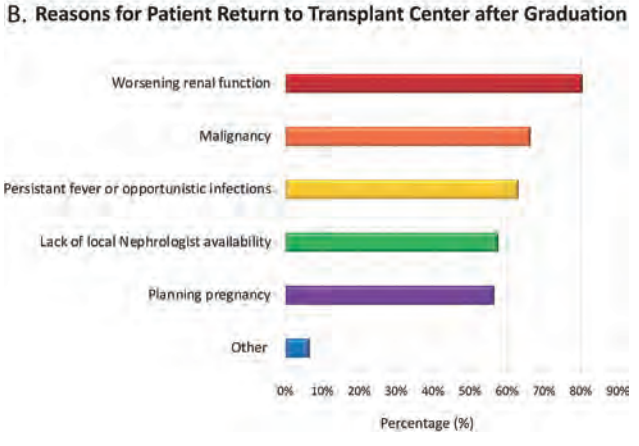
Methods: After IRB approval, staff at U.S. adult kidney TC were surveyed using the Qualtrics survey platform (4/5/22–10/31/22). Respondents were invited via email and professional society list-servs. If >1 survey was submitted for a TC, a selection hierarchy was utilized (e.g. prioritizing nephrologists).

Results: Respondents represented 55% of YC (n=108) and 67% of national KTx volume. The majority of respondents (78%) were nephrologists. Full graduation to referring nephrologists was reported by 37% of TC, while 48% reported partial graduation with ongoing co-management. Rationales for graduation included patient travel distance (64%), maintenance of referral base (58%), continuity of care (58%), and TC burden (54%) (**Fig. A**). Common reasons cited by TC for post-graduation return of care included worsening renal function (80%), malignancy (66%), opportunistic infection (63%), local nephrologist availability (58%), and pregnancy planning (57%) (**Fig. B**). Additional staff were cited by 78% of TC as needed to enable TC perpetual care, with 70% expressing need for more clinicians. Nearly 50% thought more physical space or telemedicine are required.

Conclusions: Graduation of KTx patients is common, with half of TC using joint-care. With continued growth of the KTx population, expanded opportunities related to transplant care for the general nephrology community are essential.

Funding: Private Foundation Support





TH-PO849

Transition of Care of Successful Kidney Transplant Patients from the Transplant Center: A National Survey of Referring Nephrologists

Krista L. Lentine,[1] Prince M. Anand,[2] Kenneth J. Woodside,[3] Roy D. Bloom,[4] Neeraj Singh,[5] Tarek Alhamad,[6] Matthew Cooper,[7] Darshana M. Dadhania,[8] Mona D. Doshi,[9] Gaurav Gupta,[10] Ronald Parsons,[11] Bekir Tanriover,[12] Amy D. Waterman,[13] Gary G. Singer.[14] *[1]Saint Louis University, Saint Louis, MO; [2]Medical University of South Carolina, Charleston, SC; [3]Gift of Life, Ann Arbor, MI; [4]University of Pennsylvania, Philadelphia, PA; [5]Willis-Knighton Health System, Shreveport, LA; [6]Washington University in St Louis, St Louis, MO; [7]Froedtert Hospital, Milwaukee, WI; [8]Cornell University, Ithaca, NY; [9]University of Michigan, Ann Arbor, MI; [10]Virginia Commonwealth University, Richmond, VA; [11]Emory University, Atlanta, GA; [12]Banner University Medical Center Tucson, Tucson, AZ; [13]Houston Methodist, Houston, TX; [14]Midwest Nephrology Associates, St. Louis, MO.*

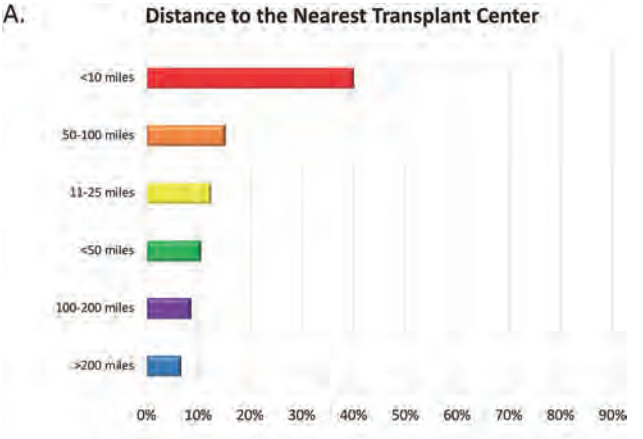
Background: We conducted a national survey of nephrologists to assess opinions and experiences related to the process of returning kidney transplant (KTx) patients from the transplant center ("graduating") to referring nephrologist care.

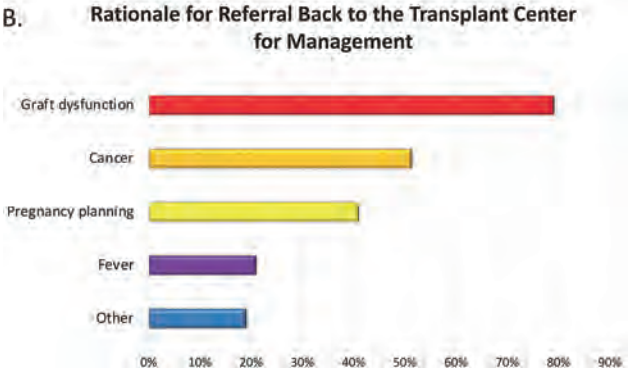
Methods: After IRB and Renal Physicians of America (RPA) approval, RPA members were surveyed using the Qualtrics electronic survey platform during October, 2022.

Results: The majority of the 105 respondents self-identified as private practice general nephrologists (78%). While 40% of respondent practices were within 10 miles of a transplant center (TC), >30% were more than 50 miles from a TC (**Fig. A**). Post-graduation visits were most frequently reported as every 3 mos. (51%) or every 6 mos. (29%), with lab draw intervals more frequent (monthly 32%, every 2 mos. 11%, and every 3 mos. 33%). Practices that did not accept patients back when ready for graduation (n=15) most typically cited the inability to work closely with the TC (67%) or inadequate staffing/resources for immunosuppression monitoring (53%); time commitment (40%) and patient complexity (33%) were less frequent concerns. Clinicians reported referring KTx recipients back to TC for management after graft dysfunction (79%), cancer (51%), pregnancy planning (41%), or fever (21%) (**Fig. B**).

Conclusions: Despite many general nephrologists being relatively close to a TC, most care for KTx patients. As expected, allograft dysfunction often leads to referral back to the TC after graduation. Nephrologists who do not accept KTx patients have concerns about communication with the TC or lack of office resources--both of which TC can actively help develop.

Funding: Private Foundation Support





TH-PO850

Outcomes of Living Related Kidney Donors in a Tertiary Care Kidney and Liver Transplant Facility of a Developing Country

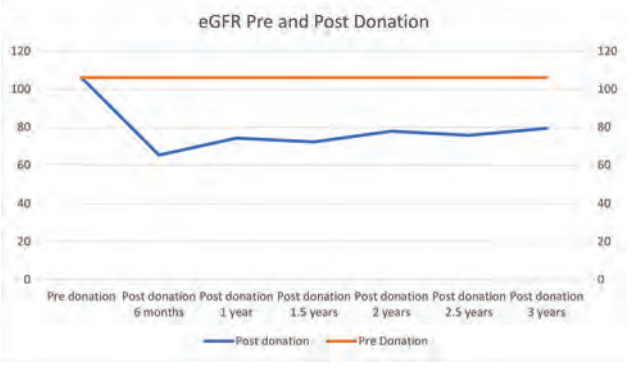
Maria Ijaz,[1] Tahreem Afroz,[1] Hafiz I. Ahmad,[1] Adil Manzoor,[1] Muhammad Awais,[3] Syed Rizwan A. Bokhari.[2] *[1]Pakistan Kidney and Liver Institute & Research Center, Lahore, Pakistan; [2]University of Rochester Medical Center, Rochester, NY; [3]University Hospital Kerry, Tralee, Ireland.*

Background: The long-term effects of unilateral nephrectomy for the live kidney donors are a neglected area of study in the developing countries. In Western countries like US, there is extensive data on living donor outcome through National Health and Nutrition Examination Survey (NHANES III), while no such resource is available in Pakistan. The purpose of this study is to evaluate the outcome of kidney donors at a large public sector Academic hospital, Pakistan Kidney and Liver Institute, Lahore.

Methods: One hundred and thirty-two successive donors with living donor nephrectomies (during March 2018 to Feb 2021) were enrolled in this prospective observational study. Off these, 100 donors were successfully followed up once every six months for total of six encounters in 3 years. Outcome included short and intermediate term effects of unilateral nephrectomy on donor physical parameters (blood pressure and BMI), kidney function (serum creatinine, eGFR) and glycaemic status (HbA1c) by comparing pre and post donation data. Estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation.

Results: Out of 100 living donors followed, 51 were male. All donors were in age range of 18-69 years with mean age 30-49 years. Left donor nephrectomy was performed in 89 (89%) patients. Mean diastolic blood pressure was slightly decreased and mean HbA1C pre and post donation were not statistically significant. Mean eGFR value before nephrectomy was 106.1ml/min and it dropped by 38% (65.2 ml/min) at 6 months. The eGFR then increased by 12% at 1year, 10% at 1.5 years, 16% at 2 years, 14% at 2.5 years and 18% (79.3ml/min) at 3 years post nephrectomy.

Conclusions: We hereby conclude that living kidney donation resulted in initial decline in the renal function because of loss of one kidney. Subsequently, taking post-donation value of eGFR at 6 months as baseline, it gradually increased by 18% at 3 years.



TH-PO851

Prevalence and Correlated Factors of Vascular Calcification and Vascular Stiffness in Kidney Transplant Patients

Peachaphol Chongvoranond, Monravee Tumkosit, Jeerath Phannajit, Natavudh Townamchai, Somchai Eiam-Ong, Kearkiat Praditpornsilpa, Yingyos Avihingsanon, Paweena Susantitaphong. *King Chulalongkorn Memorial Hospital, Bangkok, Thailand.*

Background: Mineral and bone disorders related with chronic kidney disease (CKD) increased risk of vascular health in both CKD and dialysis patients, leading causes of morbidity and mortality. Although, kidney transplantation (KT) is the best way to treat end stage kidney disease and some important risk factors might be improved after KT, the prevalence of vascular diseases seems to be persistently high in KT recipients. Early detection, prevention and optimal management is the key to attenuate vascular diseases in KT.

Methods: This cross-sectional study was conducted in 400 KT recipients who received KT for at least 1 year and followed up at King Chulalongkorn Memorial Hospital. Plain film of lateral abdomen was done to assess the presence of vascular calcification (Abdominal aortic calcification scores) while cardio-ankle vascular index was performed to evaluate vascular stiffness. Severe vascular calcification was defined by using abdominal aortic calcification scores ≥ 5.5. Baseline characteristics, laboratory data, and medications were collected for evaluation of important risk factors by multivariable logistic regression analysis.

Results: 400 KT recipients were enrolled in this study. The prevalence of severe vascular calcification and vascular stiffness were 35.94% and 27.75%, respectively. By multivariable logistic regression, diabetes mellitus and post parathyroidectomy were correlated with severe vascular calcification (OR 2.299; 95%CI 1.036-5.100, OR 7.668; 95%CI 2.928- 20.082, respectively). Systolic blood pressure, mean arterial pressure and severe vascular calcification were related with vascular stiffness (OR 0.960; 95%CI 0.928-0.992, OR 1.085; 95%CI 1.038-1.133, OR 2.256; 95%CI 1.223-4.162, respectively) while elderly was correlated both severe vascular calcification and vascular stiffness (OR 1.108; 95%CI 1.074-1.142, OR 1.094; 95%CI 1.057-1.133, respectively).

Conclusions: The prevalence of vascular calcification and vascular stiffness were still high in KT recipients. Optimal management of important risk factors including mineral bone disorders (CKD-MBD) before and after KT, diabetes and blood pressure control should be highlighted to attenuate cardiovascular diseases in KT recipients.

Funding: Private Foundation Support

TH-PO852

Calciphylaxis in Kidney Transplantation Recipients

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Background: Calciphylaxis, also called calcific uremic arteriolopathy (CUA), is a rare vascular disorder of subcutaneous microcirculation calcification and thrombosis. CUA results in painful non-healing necrotic ulcers and often portends poor outcomes. Minimal data exist describing post-kidney transplant calciphylaxis's incidence, management, and long-term outcomes. Herein we describe a series of calciphylaxis in kidney transplant recipients.

Methods: Single-center observational cohort study of patients who received kidney transplantation (KT) between 1/1/1994 and 1/1/2023 and who developed calciphylaxis at any time after transplant with a functional kidney allograft.

Results: During the 29-year study period, nine patients had biopsy-proven calciphylaxis (CUA). Six patients had kidney transplant (KT) alone, two had a simultaneous pancreas and KT, and one had simultaneous liver and KT. None of the patients had a preemptive KT; only one received a living donor transplant. The mean age at the time of KT was 41 ± 13.4 years, and the mean at the time of calciphylaxis diagnosis was 45 ± 16.5 years. All patients received lymphocyte-depleting induction (anti-thymocyte globulin) at the time of transplant. The mean duration on dialysis before KT was 3.4 ± 2. The mean time from transplant to the diagnosis of CUA was 4 ± 6.4 years); six patients developed CUA within twelve months of KT. Only one patient had a history of calciphylaxis before the transplant. At the time of CUA diagnosis, the mean eGFR was 57 ± 23 mL/min/1.73 m2; the mean for calcium was 10 ± 0.7, phosphorous was 3.6 ± 1, and iPTH was 212 ± 284 pg/ml. Location of CUA was distal lower extremity in seven patients. Eight patients required debridement, and four patients received sodium thiosulphate. Six patients were concurrently on anticoagulation at time of CUA diagnosis. Before 2001, three of four patients recieved parathyroidectomy. After 2001, one of five patients had parathyroidectomy. The mean follow up after the calciphylaxis diagnosis was 3 ± 3.2 years. At the last follow-up, three patients lost their kidney allograft, and four died.

Conclusions: Post-transplant calciphylaxis is rare and associated with high mortality and allograft loss. More extensive studies are needed to examine this condition's risk factors and management.

TH-PO853

Hypercalcemia of Humoral Malignancy After Kidney Transplant

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Introduction: Hypercalcemia of humoral malignancy (HHM) occurs due to a tumor-produced parathyroid hormone-related peptide (PTHrP) and is associated with increased morbidity and mortality. HHM typically presents with severe hypercalcemia (>13 mg/dl), decreased or normal parathyroid hormone (PTH), and elevated PTHrP with variable serum 25 hydroxy vitamin D levels. Although HHM has been associated with renal, bladder, breast, ovarian carcinomas and squamous cell carcinomas of the lung, head, and neck, it can very rarely can present with squamous cell carcinoma of the skin. We describe a case of HHM in a Kidney Transplant (KT) Recipient (KTR).

Case Description: A 41-year-old Black man with a history of KT in early 2019, ESRD from Hypertension and Dysplastic Kidneys with a baseline serum creatinine of 1.8-2.2 mg/dL was admitted for a groin mass. Relevant medical history included failed KT (2005), tertiary hyperparathyroidism s/p two lobe parathyroidectomy in 2018 (on sensipar), with baseline serum calcium 9.0-10.0mg/dL and baseline PTH of 200-400 pg/mL. The patient noted a perineal mass about two months prior to admission, that developed into a purulent and bleeding ulcer. Home medications included monthly Belatecept infusions, Mycophenolate 750 mg BID, and prednisone 5 mg daily. Laboratory data included serum creatinine 2.6 mg/dL, serum calcium 11 mg/dL, 25-OH vitamin D 18.71 ng/mL, and PTH of 133 pg/mL. Intravenous fluids were initiated, and a punch biopsy was performed by Dermatology. On post-admission day 7 with serum Calcium of 14.1 mg/dL, ionized calcium of 2.1 mmol/L, calcitonin was administered and sensipar was increased to 60 mg BID. Punch biopsy reported a well-differentiated squamous cell carcinoma, which was excised 10 days after admission. Serum Calcium dropped to 11.9 mg/dL, 4 days after surgery. PTHrP obtained before excision returned elevated at 60.2 pmol/L, while serum creatinine remained baseline. Serum Calcium had normalized to 9.2 mg/dL, about 4 weeks after surgery.

Discussion: HHM has been associated with solid organ cancers but can occur with dermatologic malignancies. Clinicians should be aware of the possibility of HHM as a rare complication of squamous cell skin cancer. In patients with tertiary hyperparathyroidism, it can present with severe hypercalcemia, non-suppressed PTH, and an elevated PTHrP.

TH-PO854

Hypercalcemia as a Rare Manifestation of Pneumocystis jirovecii Pneumonia

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Introduction: Pneumocystis Jirovecii pneumonia (PJP) is a fungal infection which disproportionally affects immunocompromised individuals. We present two cases of PJP associated with hypercalcemia and acute kidney injury (AKI) in renal transplant recipients (RTR).

Case Description: Case 1: A 40-year-old male RTR patient presented with one-week of fever, cough, and shortness of breath. CT Chest showed peripheral ground-glass opacities. Patient remained febrile, tachycardic, and hypoxic. Given the clinical presentation and Fungitell > 500 pg/mL, treatment for PJP was started with Atovaquone and steroids. Hypercalcemia (ionized calcium 1.62 mmol/L) was reported with routine workup insignificant for pharmacological or alternate underlying conditions. PTH was suppressed at 6 pg/mL and 1,25 DiHydroxyvitamin D was elevated above 200 pg/mL. 25-Hydroxy Vitamin D levels were within normal limits. Due to lack of improvement in hypercalcemia with IV hydration, Denosumab was prescribed with improvement in serum calcium levels. Bisphosphonates were contraindicated with renal dysfunction. Case 2: A 63-year-old male RTR patient presented with a three-week history of fatigue, cough, and chills. Workup similarly revealed PJP, hypercalcemia, and AKI with an elevated 1,25 DiHydroxyvitamin D. Due to failed treatment with IV Saline, Miacalcin, and Ketoconazole, Denosumab was used with improvement in Hypercalcemia. Clinical improvement of PJP reported with Primaquine and Clindamycin.

Discussion: Two renal transplant patients, on immunosuppressive medications, presented with AKI, hypercalcemia, and PJP. This hypercalcemia is believed to be due to an alveolar macrophage mediated process, increasing 1-a-hydroxylase activity and elevating 1,25-DiHydroxyvitamin D. Both patients responded favorably to denosumab, a RANK-L inhibitor which prevents osteoclast activation. PJP was suspected based on bilateral ground-glass opacities on imaging, elevated fungitell, and presence of dry cough in an immunocompromised patient. LDH was not elevated in Case 1, as sensitivity of LDH elevation in non-HIV patients with PJP is as low as 63%. Clinical improvement noted with treatment of PJP. Hypercalcemia is a unique presentation of PJP in renal transplant recipients. Early intervention is recommended given the potential for continued alveolar macrophage mediated Hypercalcemia and AKI.

TH-PO855

Greater Incidence of Severe Hyperparathyroidism Requiring Early Parathyroidectomy After Kidney Transplantation in Patients Previously Under Etelcalcetide than Cinacalcet

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Background: Etelcalcetide is a novel and highly effective intravenous calcimimetic agent used to reduce intact parathyroid hormone (iPTH) levels in patients on maintenance hemodialysis (HD). The clinical impact of discontinuing etelcalcetide at the time of kidney transplantation has not been investigated yet.

Methods: We retrospectively reviewed all patients who received a kidney transplant at our institution between January 01st, 2015 and December 31st, 2022. The incidence of parathyroidectomy and the evolution of calcium, phosphate, and intact PTH after transplantation was analyzed according to the history and type of calcimimetic treatment before transplantation (cinacalcet versus etelcalcetide versus none). Kaplan-Meier estimates and Cox regressions were applied to assess the time to post-transplant parathyroidectomy.

Results: Overall 372 patients (aged 53 [IQR 42-62] years) were included. At the time of transplantation, 35, 75, and 262 patients were treated with etelcalcetide, cinacalcet or no calcimimetic, respectively. After a median follow-up of 1064 (IQR 367-1658) days, the incidence of parathyroidectomy in the etelcalcetide *vs*. cinacalcet *vs*. no calcimimetic groups was 29% (n=10) vs 12% (n=9) vs 1% (n=2), respectively (p<0.001). Etelcalcetide was associated with an increased incidence of parathyroidectomy after transplantation, both in unadjusted analyses and after adjustment for age, sex and hemodialysis vintage (HR 91.0, 95% CI 19.1-493.9, p<0.001). The incidence of parathyroidectomy was related to etelcalcetide dosage (6/11 [54.6%] in patients with ≥10 mg vs 4/24 [16.7%] in patients with < 10 mg/dialysis session, p= 0.02). Moreover, calcium levels were higher (2.81 [IQR 2.60-2.99] mMol/L vs 2.63 [IQR 2.58-2.72] mMol/L, p<0.001) and parathyroidectomy was performed earlier (median 80 *vs.* 480 days, p<0.001) in the etelcalcetide compared with the cinacalcet group. Long-term graft function, graft loss and mortality were similar between groups.

Conclusions: Etelcalcetide use during maintenance HD is associated with an increased incidence of early parathyroidectomy after transplantation compared to cinacalcet or no calcimimetic.

TH-PO856

0-ABDR Mismatch Transplants Do Not Confer Additional Immunologic Protection in Non-White Recipients

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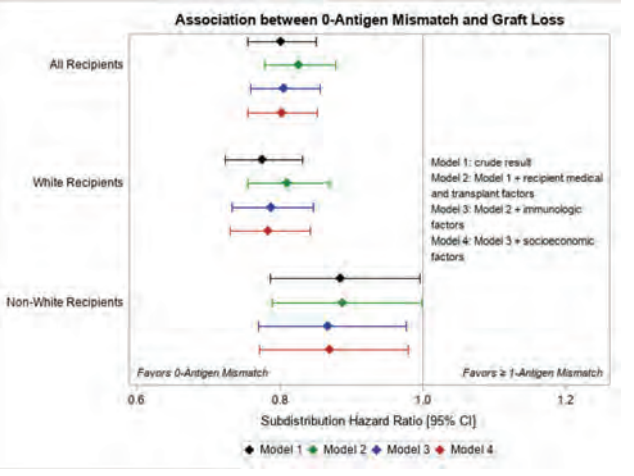
Background: In kidney transplants, matching donor and recipient human leukocyte antigen (HLA) alleles reduces allorecognition and eases reliance on immunosuppression. We hypothesize that 0-antigen mismatch transplants provide stronger protection against graft loss in racial minorities in whom systemic barriers to healthcare may explain higher rates of graft failure.

Methods: We included adult, single-organ, US deceased-donor kidney transplants from 2007-2016. We examined time-to-allograft failure (competing risk of death) using imputed Kaplan Meier and Weibull models. Degree of HLA mismatch (0- vs. ≥1-mismatch) was the main exposure. Models were adjusted for potential confounders and included an interaction term between mismatch and recipient race. Additional analyses were stratified by recipient race (white vs. non-white).

Results: We analyzed 102,114 transplants over a median of 5.6 years (16,862 graft loss events, 18,994 deaths). White recipients comprised 59,254 transplants (7628 0-mismatch) vs. 42,860 non-white recipients (1439 0-mismatch). In the cohort, 0-antigen mismatch was associated with improved graft survival (subdistribution hazard ratio [sHR] 0.80, 95% CI [0.75-0.85]) and was similar after adjusting for covariates. In crude models the effect of 0-antigen mismatch was more pronounced in white (sHR 0.78 [0.72-0.83]) vs. non-white recipients (sHR 0.88 [0.79-0.99], interaction p-value 0.03). This was attenuated after adjusting for covariates (sHR 0.78 [0.73-0.84]) vs sHR 0.87 [0.77-0.98], interaction p-value 0.09, Figure 1).

Conclusions: 0-antigen mismatch transplants were associated with a 20% risk reduction in graft loss. In non-white recipients the protective effect of 0-antigen mismatch transplants was not enhanced vs. white recipients. This may be due to the degree of mismatch at other HLA alleles and minor antigens, or due to systemic barriers to healthcare borne by minority recipients.

Funding: Private Foundation Support



TH-PO857

Effectiveness and Safety of Denosumab on Osteoporosis Treatment in Kidney Transplant Recipients

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Background: It is known that the use of immunosuppressive agents influences the bone status of kidney transplant recipients (KTRs). In particular, glucocorticoids, the main immunosuppressants, can induce osteoporosis in KTRs. Denosumab, a potent antiresorptive agent, has been reported to increase bone mineral density (BMD), but the clinical impact and safety of denosumab on osteoporosis in KTRs remain controversial.

Methods: We analyzed 98 KTRs who used denosumab from 2018 to 2023. We investigated the change of BMD, chemical parameters, allograft function, tacrolimus trough level (TTL), complications of denosumab, fracture risk assessment tool (FRAX) score, acute rejection within 1 year and graft failure and death.

Results: Mean T-scores at 1-year post-denosumab were significantly increased comparing to mean T-scores pre-denosumab at the femur neck and spine area, respectively (-2.68±0.68 vs. -2.81±0.68, P<0.001; -2.78±0.96 vs. -3.21±1.00, P<0.001). The levels of calcium and phosphorus were significantly decreased and those of vitamin D were significantly increased at 1-year post-denosumab, but there were no significant differences in PTH, allograft function and TTL. There were no recurrent fractures among the 12 KTRs with a history of fracture, but 3 de novo fractures happened. Cardiovascular event occurred in 3 patients. Denosumab-induced hypocalcemia developed in 8 patients, but severe hypocalcemia was observed in only 1 patient. Acute kidney injury did not happen.

Urinary tract infection (UTI) was in 17 patients. Arthralgia occurred in 4 patients. Median 10-year probability of a major osteoporotic fracture and hip fracture by FRAX tool was significantly decreased after denosumab. Acute rejection within 1 year after denosumab developed in 3 patients. There was no graft failure and no patient death.

Conclusions: The use of denosumab in KTRs is effective and safe for the treatment of osteoporosis and prevention of fracture, but it should be carefully monitored for complications, especially, UTI.

Funding: Government Support - Non-U.S.

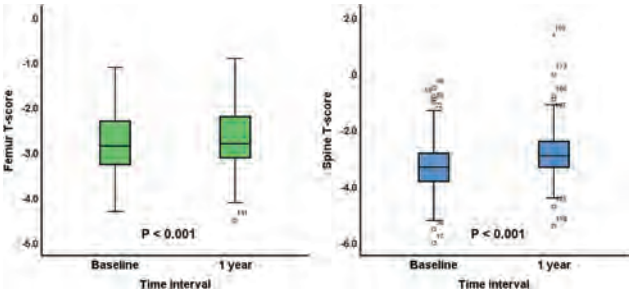

Figure 1. Mean T score of femur and spine at denosumab and 1 year after denosumab

TH-PO858

Correlates of Bone Mineral Density and Fractures in Kidney Transplant Recipients

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Background: Although kidney transplant recipient are known to be at high risk for bone disease, the optimal timing of testing for bone health and risk factors for osteodystrophy remain unclear.

Methods: We conducted a retrospective analysis of 65 patients from the Veterans Affairs at Loma Linda, California who underwent at least one DEXA scan after receipt of kidney transplantation.

Results: The mean age of our cohort was 64.0+/-12.2 and was predominantly male. Most patients received a combination of calcineurin inhibitor, antimetabolite and steroids for immunosuppression. Thirty patients had normal DEXA scans, while 25 patients were osteopenic and 10 were osteoporotic by DEXA; and 11 had documented fracture(s). Many patients received calcium and vitamin D prophylaxis but few received bisphosphonates or calcimimetics post transplant. (Table 1) In a multivariate model, after adjusting for age, dialysis vintage and other characteristics, we found that female gender was correlated with higher risk of fractures. In the same model, there was also a trend towards diabetes and high PTH (>300) predicting higher risk of fractures although this relationship did not reach statistical significance.

Conclusions: Despite the prevalence of bone disease among kidney transplant recipients, we found that a significant portion of such patients may not be receiving optimal therapy. Further studies are needed to establish effective treatments and determine the optimal monitoring frequency of bone parameters.

	All N=65	Normal N=30	Osteopenia N=25	Osteoporosis N=10	P-value
Age	64.0 ±12.2	61.8 ± 11.9	65.3 ± 12.8	65.6 ± 11.8	0.54
Sex (male)	62 (95.4%)	29 (96.7%)	23 (92.0%)	10 (100%)	0.20
Transplant type					0.003
DDKT	48 (73.9%)	25 (83.3%)	16 (64.0%)	7 (70.0%)	
LRKT	6 (9.2%)	3 (10.0%)	2 (8.0%)	1 (10.0%)	
LUKT	7 (10.7%)	1 (3.3%)	4 (16.0%)	2 (20.0%)	
Other	4 (6.2%)	1 (3.3%)	3 (12.0%)	0 (0%)	
Years transplanted	9.3 ±5.3	10.0 ±5.8	8.0 ± 4.7	9.6 ±3.5	<0.01
Years dialyzed till transplant	3.9 ± 2.9	4.5 ± 3.7	3.6 ± 1.7	2.5± 1.3	0.40
eGFR, ml/min	60.8 ± 21.0	58.6±21.9	67.7 ±22.5	52.3 ± 18.7	0.15
Calcium, mg/dL	9.4 ± 0.5	9.2 ±0.4	9.6 ±1.4	9.4 ± 1.0	0.30
Phosphorus, mg/dL	3.5 ±0.5	3.5 ±0.5	3.3 ±0.4	3.8 ±0.5	0.02
PTH, pg/mL	135 ±102.7	118.1 ± 81.8	136.0± 80.2	192.9 ± 179.5	0.14
Prednisone	60 (92.3%)	27 (90.0%)	25 (100%)	8 (80.0%)	0.03
Calcium + Vitamin D	57 (87.7%)	29 (96.7%)	20 (80.0%)	8(80.0%)	0.01
Bisphosphonate	5 (7.8%)	1 (3.3%)	3 (12.0%)	1 (10.0%)	0.46
Statin	31 (47.7%)	14 (46.7%)	15 (60.0%)	2 (20.0%)	0.006
Diabetes	37 (56.9%)	15 (50.0%)	15 (60.0%)	7 (70.0%)	0.03
Fractures present	11 (16.9%)	4 (13.3%)	6 (24.0%)	1 (10.0%)	0.05

Table 1: Cohort characteristicsLegend: DDKT: deceased donor kidney transplant; LRKT: living related kidney transplant; LUKT: living unrelated kidney transplant. Values are reported as mean ± SD or N (%), as appropriate.

TH-PO859

Association Between Hemoglobin Levels and Hypercalcemia due to Persistent Hyperparathyroidism in Kidney Transplant Recipients

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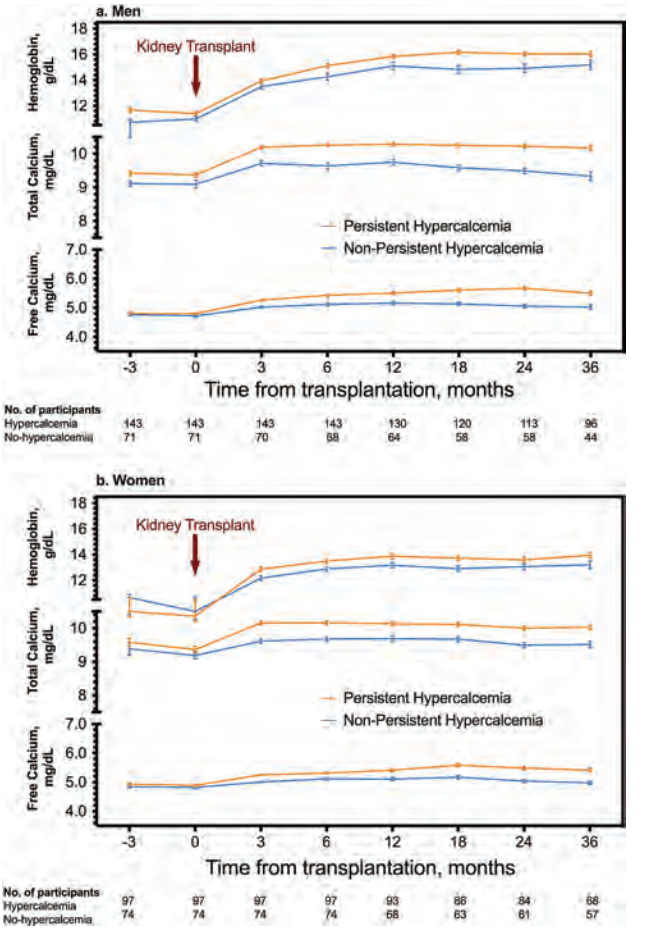
Background: Hypercalcemia has emerged as a potential non-traditional factor associated with erythrocytosis following transplantation. We hypothesized that hypercalcemia due to persistent hyperparathyroidism is positively correlated with hemoglobin levels in kidney transplant recipients (KTRs).

Methods: We conducted a prospective cohort study investigating the trajectory of hemoglobin in KTRs with and without persistent hypercalcemia (free calcium >5.2 mg/dL in ≥80% of measures). We performed mixed model analyses adjusting for potential confounders.

Results: We included 385 subjects. Persistent hypercalcemia was present in 66% (56% male, median age 36 [IQR 28-48] years, median follow-up 4.1 [IQR 1-8.2] years). KTRs with hypercalcemia due to persistent hyperparathyroidism had a mean increase in hemoglobin levels of 0.76 g/dL/year (95% CI 0.45-1.08) compared to KTRs without hypercalcemia, 0.80 (95% CI 0.32-1.27) g/dL/year for males and 0.36 (95% CI 0.16-1.08) g/dL/year for females. Hypercalcemia was significantly associated with post-transplant erythrocytosis according to the WHO (47% vs. 24%, OR 2.8, 95% CI 1.8-4.4) and altitude-adjusted criteria (22% vs. 10%, OR 2.5, 95% CI 1.2-4.5). The significance of the effect of hypercalcemia on hemoglobin levels was consistent after adjusting for potential confounders.

Conclusions: Hypercalcemia due to persistent hyperparathyroidism after kidney transplantation was significantly associated with higher hemoglobin levels and an increased likelihood of developing post-transplant erythrocytosis.



The trajectory of hemoglobin, total calcium, and free calcium in KTRs with and without persistent hypercalcemia.

TH-PO860

Incidence, Risk Factors, and Outcomes of Post-Transplant Erythrocytosis Among Simultaneous Pancreas and Kidney Transplant Recipients

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Background: Post-transplant erythrocytosis (PTE) is a common condition after kidney transplantation. In the current era of immunosuppressive medication and management, the incidence, risk factors and outcomes of PTE among simultaneous pancreas and kidney (SPK) transplant recipients is poorly defined.

Methods: We analyzed all SPK transplant recipients at our center between 1998 to 2021. PTE was defined as at least 2 consecutive hematocrit (Hct) levels of > 51% within the first 2 years of transplant. Controls were selected at a ratio of 3:1 at the time of PTE occurrence using event density sampling. Risk factors for PTE and graft survival were examined.

Results: Of 887 SPK recipients, 108 (12%) developed PTE a median of 273 days (IQR: 159.5-393) after transplantation. The incidence rate of PTE was 7.5 per 100 person-years. Multivariable analysis found increased incidence associated with being on dialysis before transplant (HR: 3.15, 95% CI: 1.67-5.92, p<0.001), nonwhite donor (HR: 2.14, 95% CI: 1.25-3.66, p=0.006), female donor (HR: 1.50, 95% CI: 1.0-2.26, p=0.05), and male recipient (HR: 2.33, 95% CI: 1.43-3.70, p=0.001). The 108 cases of PTE were compared to 324 control recipients without PTE. PTE was not associated with pancreas graft failure (HR: 1.36, 95% CI: 0.51-3.68, p=0.53) or kidney graft failure (HR: 1.16, 95% CI: 0.40-3.42, p=0.78).

Conclusions: In the modern era of immunosuppression, PTE is still a common complication among SPK recipients. Likely due to proper management, PTE among SPK recipients was not associated with adverse graft outcomes.

TH-PO861

Cytomegalovirus-Associated Pulmonary Embolism

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Introduction: Thromboembolism has been associated with acute CMV infection or reactivation in transplant recipients. Here, we present a case of a young man with no apparent risk of a hypercoagulable state who developed a PE in the setting of a significant CMV viral load.

Case Description: The patient is a 24-year-old male with a PMH of ESRD secondary FSGS, status post LDKT 7 months earlier. Induction was with anti-TG and basiliximab, follow by maintenance immunosuppression. He was CMV and EBV IgG antibody positive at the time of transplant and did receive 3 months of prophylaxis with oral valganciclovir. The patient presented to the hospital with complaints of gastrointestinal symptoms, dyspnea, and pleuritic chest pain. He reported having watery diarrhea for over 10 days, as well as nausea, vomiting, chills, fatigue and an episode of fever to 102F. A few days prior to his admission, he developed pleuritic chest pain and dyspnia. Physical examination was unremarkable except for dry mucous membranes and low BP, which improved with volume resuscitation. CT angiogram revealed a right middle, lower segmental and sub-segmental pulmonary emboli with partial occlusion. Stool studies were normal. CMV PCR of the blood was positive with more than 222,000 copies. EBV PCR blood was negative. He was started on a therapeutic heparin drip and was transitioned to Apixaban prior to discharge. Induction dosing of IV ganciclovir was started for CMV viremia which continued upon discharge.

Discussion: The etiology of acute PE in our patient is believed to be triggered by the CMV infection. It has been reported in the medical literature that CMV can cause endovascular injury that can lead to thrombus formation and embolization. CMV reactivation is mostly seen in CMV discordant recipients (D+/R-), however, CMV reactivation can occur, albeit less frequently and at a lower viral load in seropositive recipients, as in this case. Latent CMV has been found on the endothelial cells of both venous and arterial vascular walls. It has been postulated that CMV-infected endothelial cells increase the expression of tissue factor II, which is involved in hemostasis and thrombus formation. CMV and other enveloped viruses have phosphatidylserine-like procoagulant activity on their surfaces which predispose to thrombus formation. In conclusion, acute CMV infection is a risk factor for thrombosis in transplant recipients and immunocompromised patients.

TH-PO862

Trend in Utilization and Transplant Outcomes of COVID-19-Positive Deceased-Donor Kidneys

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Background: While the pandemic of coronavirus disease-19 (COVID-19) enters a new phase and the proportion of individuals with a prior COVID-19 diagnosis grows, the national trend in utilization and medium-term outcomes of kidney transplantation (KT) from COVID-19 positive donors remain unknown. This study evaluated the trend in utilization and KT outcomes of kidneys from donors with active or resolved COVID-19.

Methods: This retrospective cohort study used Standard Analysis and Research (STAR) data from 3/1/2020 to 3/30/2023. The exposure was donor SARS-CoV-2 NAT results, i.e., positive NAT within 7 days as active COVID-19, and positive NAT 7 days before procurement as resolved COVID-19. Kidney non-utilization, graft failure, all-cause death, acute rejection in six months, length of hospital stay (LOS), and delayed graft function (DGF). Multivariable logistic regression for kidney non-utilization, rejection, and DGF, multivariable linear regression for LOS, and Cox analyses for graft failure and all-cause death were performed. All models were adjusted for inverse probability treatment weighting.

Results: The likelihood of non-utilization of kidneys from active or resolved COVID-19+ donors declined over time. During 2020-2022, kidneys from COVID-19+ donors had a higher risk of non-utilization compared to kidneys from donors without COVID-19. In 2023, kidneys from active or resolved COVID-19+ donors were no longer associated with higher risk of non-utilization. No higher risk of graft failure was found in KT recipients receiving active COVID-19+ kidneys (adjusted hazard ratio [aHR], 1.03; 95% CI, 0.78-1.37) or resolved COVID-19+ kidneys (aHR, 1.10; 95% CI, 0.88-1.39). Donor COVID-19 positivity was not associated with all-cause death, longer LOS, higher risk of acute rejection, neither DGF.

Conclusions: This cohort study found that the non-utilization rate of kidneys from COVID-19+ donors declined over time and donor COVID-19 positivity was not associated with inferior KT outcome within 2 years post-transplantation.

Table: Non-utilization of active and resolved COVID-19 positive kidneys and transplant outcome, OPTN 2020-2023

	Kidney Discard[a] Odds Ratio (95%CI)					Transplant Outcomes[b] Hazard Ratio (95% CI)	
	Overall	2020 (Mar-Dec)	2021	2022	2023 (Jan-Mar)	Kidney graft failure	Patient death
COVID-negative	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Active COVID-19 positive	1.55 (1.38, 1.76)	11.26 (2.29, 55.38)	2.09 (1.58, 2.79)	1.47 (1.28, 1.70)	1.07 (0.75, 1.63)	1.03 (0.78, 1.37)	1.17 (0.84, 1.66)
Resolved COVID-19 positive	1.31 (1.16, 1.48)	3.87 (1.26, 11.90)	1.94 (1.54, 2.45)	1.09 (0.99, 1.28)	1.18 (0.80, 1.73)	1.10 (0.88, 1.39)	0.95 (0.70, 1.28)

[a]Adjusted for donor characteristics, including age, sex, race and ethnicity, body mass index, presence of diabetes, presence of hypertension, donation after cardiac death, cause of death, serum creatinine level, hepatitis C virus status, and kidney donor profile index score.

[b]Adjusted for donor characteristics (age, sex, race and ethnicity, body mass index, presence of diabetes, presence of hypertension, donation after cardiac death, and kidney donor profile index score), recipient characteristics (age, sex, race and ethnicity, education attainment, insurance status, body mass index, presence of diabetes, dialysis duration, peak panel reactive antibody level, organ share type, and days on waiting list before transplant), and transplant characteristics (blood type compatibility, human leukocyte antigen matching, cytomegalovirus concordance status with donors, cold ischemia time, center volume of COVID-19 positive KTs, and year of transplant).

TH-PO863

Sequelae of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Among Kidney Transplant Recipients: A Large Single-Center Experience

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Background: Kidney transplant recipients (KTR) are a vulnerable immunocompromised population at risk of severe disease and mortality from COVID-19. We characterized the sequelae of infection in KTRs at our center.

Methods: We studied all adult KTRs who had their first episode of COVID-19 between 04/2020 and 04/2022 and at least 12 months of follow-up (unless graft failure or death). Outcomes of interest included risk factors for hospitalization, all-cause mortality, and COVID-19-related mortality.

Results: Of 979 KTRs, 381 (39%) were hospitalized due to their first episode of COVID-19. There were some differences in baseline characteristics: those hospitalized had advanced age at COVID-19 diagnosis (59.8 (12.9) vs. 53.7 (12.6), p<0.001), were more likely to be male (63% vs. 55%, p=0.02), non-white (28% vs. 16%, p<0.001), have diabetes mellitus as a cause of ESKD (33% vs. 14%, p<0.001), and less likely to be living donor recipients (35% vs. 48%, p<0.001). In multivariate analysis, risk factors for hospitalization included advanced age at COVID diagnosis (HR: 1.03, 95%CI: 1.02-1.04), male recipient (HR: 1.29, 95%CI: 1.04-1.60), nonwhite recipient (HR: 1.48, 95%CI: 1.17-1.88), and diabetes as a cause of ESRD (HR: 1.77, 95%CI: 1.41-2.21). Vaccination against COVID-19 protected against risk of hospitalization (HR: 0.73, 95%CI: 0.59-0.90), risk for all-cause mortality (HR: 0.52, 95%CI: 0.37-0.74), and risk for COVID-related mortality (HR: 0.47, 95%CI: 0.31-0.71). Risk factors for both all-cause and COVID-related mortality in the multivariate analyses included advanced age (HR: 1.05, 95%CI: 1.03-1.07; HR: 1.04, 95%CI: 1.02-1.05), hospitalization (HR: 6.76, 95%CI: 3.43-13.28; HR: 24.3, 95%CI: 6.9-85.7), and respiratory symptoms for hospital admission (HR: 2.29, 95%CI: 1.42-3.68; HR: 2.73, 95%CI: 1.52-4.89). Furthermore, additional risk factors for all-cause mortality in multivariate analysis included being a nonwhite recipient (HR: 1.46, 95%CI: 1.01-2.12) and diabetes as a cause of ESKD (HR: 1.42, 95%CI: 1.0-2.01), with being a recipient of a living donor as protective (HR: 0.69, 95%CI: 0.48-1.0).

Conclusions: Hospitalization due to COVID-19 is associated with increased mortality. Vaccination against COVID-19 is a protective factor against hospitalization and mortality.

TH-PO864

A Rare Case of Malakoplakia in a Renal Transplant Patient

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Introduction: Malakoplakia is a rare condition that affects immunocompromised patients, typically resulting in chronic inflammation, infections, and increased risk of bleeding in the affected tissues due to impaired bacterial clearance. Here we present a case of malakoplakia in a renal transplant patient that was complicated by bleeding and ultimately resulted in renal graft loss.

Case Description: A 70 y/o man presented to the emergency room with abdominal pain, fullness, and an acute kidney injury. He had a medical history of end-stage renal disease due to obstructive uropathy, deceased-donor renal transplantation in 2022 with anti-thymoglobulin induction, and was currently on triple immunosuppression with tacrolimus, mycophenolate, and prednisone. Abdominal computed tomography showed a large irregular mass in the right pelvis involving the right ureter, bladder, and renal transplant. Biopsy showed malakoplakia with chronic and acute inflammation, and ultimately grew *Bacillus* species. A drain was placed, and the patient was discharged with four weeks of piperacillin/tazobactam. Four months later, the patient was admitted with hypotension and abdominal pain. Abdominal imaging showed a subcapsular hematoma in the native right kidney originating from the malakoplakia lesion and extending into the right ureter, which required interventional radiology embolization. Imaging showed malakoplakia was still present throughout the native urinary tract. Immunosuppression was further reduced on discharge and suppressive antibiotics were continued to allow for adequate clearance of the chronic infection. The patient was ultimately readmitted with worsening kidney disease and restarted on dialysis. Malakoplakia findings were still present and largely unchanged on imaging. Immunosuppression was completely stopped and antibiotics were continued. The patient is currently undergoing nutritional optimization and chronic suppressive antibiotic therapy with the aim of pursuing surgery to remove the native urogenital tract.

Discussion: Here we show a case of malakoplakia in a renal transplant patient that required reduction of immunosuppression and subsequently led to graft function loss. Malakoplakia must be considered when imaging findings consistent with post-transplant lymphoproliferative disorder are seen in the urogenital tract.

TH-PO865

Urothelial Tumor in Transplant Patient with BK Nephropathy

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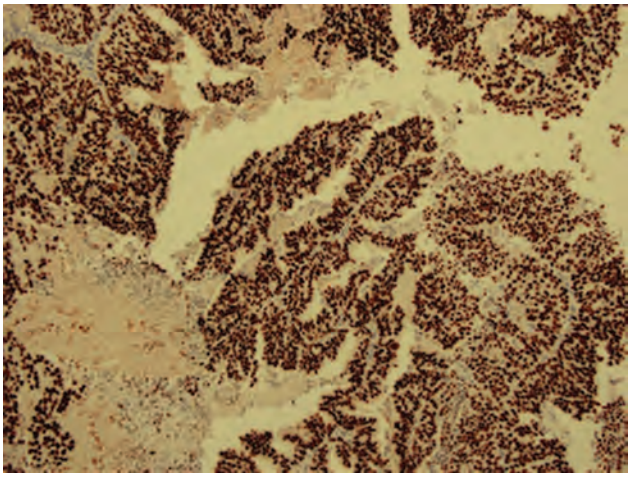
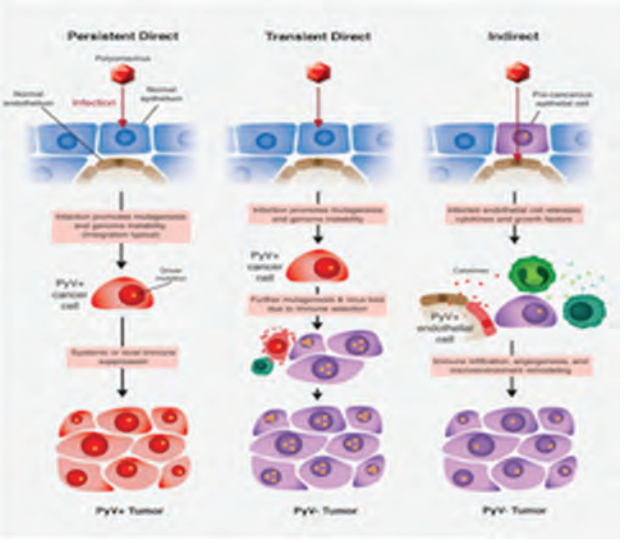
Introduction: BK is a dsDNA virus in polyomaviridae family. BK does not cause disease in immunocompetent hosts. However BK can get activated in immunocompromised & cause BK nephropathy, ureteric stenosis in renal Tx, hemorrhagic cystitis in HSCT and rarely associated with urothelial carcinoma. We present a case of urothelial cancer in patient with persistent BK viremia, presenting with new onset microscopic hematuria.

Case Description: A 62 y/o WM with a history of LDKT in 2016, on Prograf, MMF, steroid. He developed BK viremia & nephritis 2 years postTx. Appropriate reduction in IS was implemented, along with wkly IVIG. His allograft function remained stable with CKD3b. BK viremia remained stable in the range of 40K -100K. He was found to have Microscopic Hematuria in 2022, cystoscopy revealed 2 Invasive Papillary bladder cancer which stained positive for BK by SV40 stain.

Discussion: BK Nephropathy is known cause of allograft loss, BK virus related malignancy is rarely reported & discussed. It is unclear if higher risk of Urothelial cancer in these immunocompromised hosts is directly related to IS & BK merely is an innocent bystander but new reports suggest role of BK in tumorigenesis. BK surveillance is recommended for upto 3 yrs post Tx. Our patient did not have any risk factors for bladder tumors other than persistent BK & IS meds. Persistent BK viremia and microscopic hematuria in transplant patients warrant further workup for urothelial cancers.





TH-PO866

Mystery Lung Mass in a Kidney Transplant Recipient

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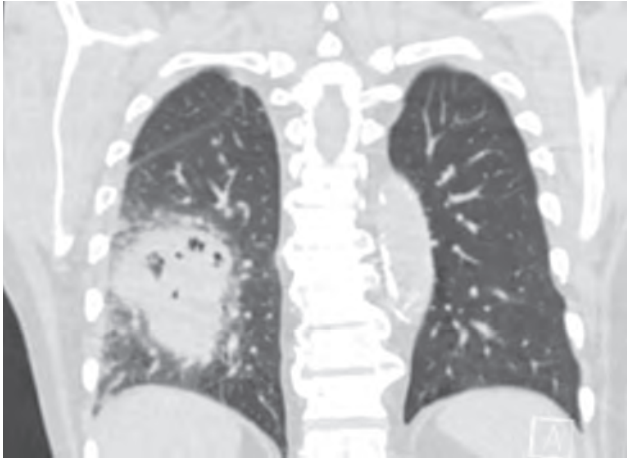
Introduction: The differential for lung masses in solid organ transplant recipients is broad. It includes infections particularly fungal and mycobacterial infections, malignancy, and recurrence of underlying systemic disease (e.g.GPA). The overlapping clinical and radiographic findings make diagnosis challenging.

Case Description: This is a 64-year-old female with ESKD due to hypertension who underwent a deceased donor kidney transplant with Alemtuzumab and methylprednisolone induction. She received sulfamethoxazole-trimethoprim for *Pneumocystis* prophylaxis. She was maintained on tacrolimus, mycophenolate mofetil, and prednisone. She had no prior episodes of rejection. She presented one-year post-transplant with 20-lb weight loss, fevers, generalized weakness, and productive cough. CT chest revealed a large right lung mass. Sputum and BAL cultures grew *Nocardia* nova. Transbronchial needle aspiration of the mass was negative for malignancy. She was treated with imipenem/cilastin and trimethoprim-sulfamethoxazole. Her mycophenolate mofetil was held. She subsequently improved clinically with marked improvement of radiographic findings.

Discussion: Nocardia is a low virulence organism found in soil and water. It is a rare life-threatening opportunistic infection that affects the lung, brain, and skin. It is more common in solid organ transplants recipients and usually presents 1-2 years post-transplant. Pulmonary nocardia presents with non-specific clinical symptoms. Imaging typically shows cavitary lesions. The risk of nocardiosis increases with net immunosuppression, rejection episodes, and time since transplantation. Prophylaxis with trimethoprim-sulfamethoxazole covers nocardia. This case demonstrates the importance of high index of suspicion for nocardia and a low threshold to send testing for sputum AFB/culture and to pursue early bronchoscopy/BAL. Timely diagnosis and initiation of treatment allow for a good clinical outcome such as what was achieved in this case.



TH-PO867

Complete Remission of Donor-Derived Metastatic Urothelial Carcinoma After Transplant Nephrectomy and Discontinuing Immunosuppression

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Introduction: De novo urothelial carcinoma is associated with kidney transplant and tends to present with advanced disease at diagnosis. We present a case of donor derived metastatic urothelial carcinoma with complete remission following transplant nephrectomy and withholding immunosuppression.

Case Description: A 55-year-old male with ESRD secondary to hypertensive nephropathy was on dialysis from 1992 -2005 and underwent deceased donor kidney transplant in 2005. Dual kidney transplant was performed due to donor's smoking history and donor finding of > 10% glomerulosclerosis. He did well post-transplant, baseline creatinine, 1.3 mg/dL. He developed allograft dysfunction with biopsy showing BK Polyoma Nephropathy in 2006. In 2021, he presented with bilateral flank pain and gross hematuria for 1 week. Urine cytology was positive for urothelial carcinoma. Bladder and prostatic urethra biopsies and right native renal pelvis washing were negative for carcinoma. Cytology from superior transplant kidney demonstrated high-grade urothelial carcinoma. PET CT in June 2021 showed abdominopelvic retroperitoneal nodal metastatic disease extending cephalad into the right retrocrural region with relative sparing of the pelvic nodal chains and focal hypermetabolism of the left adrenal gland, presumed to be metastatic. Both transplant kidneys were surgically removed in June 2021. Lymph node dissection and adrenalectomy were not performed due to position and proximity to the aorta. A 5 x 4 cm high grade urotheilial carcinoma with lymphovascular invasion was present in the pelvis of the superior allograft. BK virus DNA was undetectable in 2021. Immunosuppressive therapy included CNI, mycophenylate, and low dose prednisone. Immunosuppression was discontinued after resuming hemodialyis. Patient did not receive chemotherapy. Subsequent PET CT scans as recently as March 2023 demonstrated complete remission of metastatic disease. Cell-free DNA was < 0.12%, below the threshold for detection, supporting the absence of tumor.

Discussion: We report a case of complete remission of donor derived metastatic urothelial carcinoma following transplant nephrectomy and immunosuppression withdrawal. Future research should explore the balance between innate immunity as a protective factor against malignancy and immunosuppression to prevent rejection.

TH-PO868

When the Diagnosis Is Skin Deep: A Case of Cutaneous Chromoblastomycosis in a Patient with Kidney Transplant

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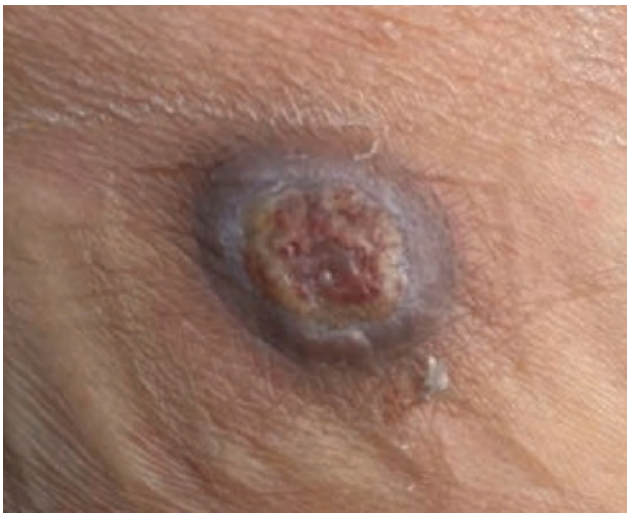
Introduction: Chromoblastomycosis, caused by fungi from the Herpotrichiellaceae family, primarily affects skin and soft tissues. Although it's prevalent in tropical and subtropical regions, U.S. cases have been reported. The disease presents various dermatologic lesions and can, in rare cases, affect lungs, bones, and brain. Treatment includes physical interventions, antifungal therapy, and is notoriously difficult due to frequent relapses and possible bacterial infections.

Case Description: A 67-year-old male kidney transplant recipient with a history of end-stage kidney disease from hypertension presented with a persistent, expanding skin lesion on his right anterior leg. Despite being non-pruritic, non-painful, and without any surrounding inflammation, his interest in gardening raised suspicion. A skin biopsy confirmed the diagnosis of chromoblastomycosis. The patient began itraconazole treatment, resulting in slow lesion improvement.

Discussion: Melanized fungal infections, such as chromoblastomycosis, are infrequent, particularly in temperate climates, making diagnosis challenging. This case illustrates the necessity of an early skin biopsy for accurate diagnosis. Immunocompromised patient, are at an elevated risk of disseminated disease. Thus, early diagnosis and treatment are critical to reduce potential morbidity and mortality.



Picture 1: Right Anterior Leg, Skin Lesion

TH-PO869

Case of Kidney Allograft Failure: A Pandora Box

Lakshna Sankar, Pooja Sanghi. *Geisinger Health, Danville, PA.*

Introduction: Post kidney transplant acute kidney injury could be due to drug toxicity, recurrence of primary disease, transplant rejection and vascular complications.

Case Description: 43 year old male with end stage kidney disease secondary to IgA nephropathy status post living related kidney transplant from an outside hospital in 2011, presented with shortness of breath of 1 week duration. He was on mycophenolate mofetil 500 twice daily and tacrolimus 3 mg twice daily. On clinical examination, he appeared hypervolemic. Review of labs showed elevated creatinine of 21.4 mg/dl (baseline 1.8 mg/dl) and was started on hemodialysis. Serology, infectious work up and echocardiogram were unremarkable. Tacrolimus level was supratherapeutic at 11 ng/ml. A doppler ultrasound showed large parenchymal arteriovenous fistula (AVF) in the midpole (Figure 1A). He underwent transplant arteriogram and was successfully embolized (Figure 1B). Subsequently, allograft biopsy showed recurrence of Ig A nephropathy, acute T-cell mediated rejection Banff criteria grade 1A, interstitial fibrosis and tubular atrophy of 70%, features suggestive of chronic thrombotic microangiopathy and glomerular sclerosis favoring chronic calcineurin inhibitor toxicity (Figure 2 A-C). Given the severity of scarring in the kidney, we did not treat him for rejection, as the adverse effects outweighed the benefits.

Discussion: Incidence of AVF in kidney allograft ranges from 0.5-16.9%; they can be traumatic (after biopsy), congenital or from the donor kidney. Our patient never had a biopsy since his transplant. Thus it is possible that this was donor derived. He was asymptomatic all these years till the AVF was diagnosed in his allograft and endovascularly ligated. Kidney biopsy revealed a myriad of other etiologies that ultimately lead to his graft failure. This case brings on a better insight to causes of allograft failure highlighting the gargantuan effort in evaluation and management of complications in a transplanted kidney.

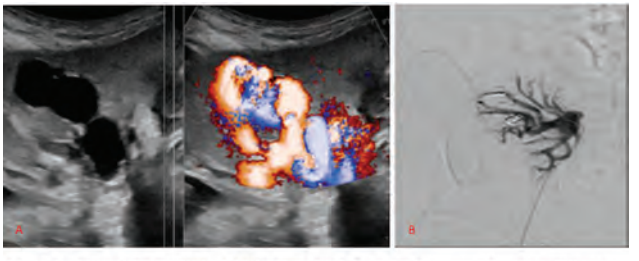


Figure 1: A - Ultrasound kidney transplant with doppler showing AVF; B - Post transplant arteriogram showing coil embolization

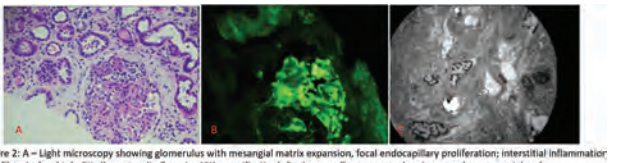


Figure 2: A – Light microscopy showing glomerulus with mesangial matrix expansion, focal endocapillary proliferation; interstitial inflammation and fibrosis, focal tubulitis (hematoxylin & eosin, 40X magnification); B – Immunofluorescence showing granular, mesangial and focal capillary loop fluorescence with IgA (3+); C - Electron microscopy showing subendothelial deposits.

TH-PO870

Impact of Area Deprivation Index on Early Stages in the Kidney Transplantation Process

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Background: Socioeconomic factors play major roles in kidney transplantation (KT) access and outcomes but are difficult to identify. Area Deprivation Index (ADI) is a measure of socioeconomic conditions at the census block group level. We hypothesized that ADI may be a useful tool to identify patients at risk for inequities in the KT process. We investigated whether ADI was associated with attendance at KT clinic and subsequent waitlisting (WL).

Methods: We performed a retrospective cohort study of adults referred for KT evaluation from 1/1/15 -12/31/21. We compared clinical and sociodemographic characteristics between patients who were 1) seen vs. not seen in KT clinic and 2) WL vs. not WL. Wilcoxon rank sum test for continuous variables and chi-square test for categorical variables were used. Multivariable logistic regression analysis was performed to examine the association between ADI and WL.

Results: 2,284 patients were referred for KT evaluation during the study period. Patients from the most vulnerable neighborhoods (ADI 44-100) were less likely to be seen following referral (31% vs 26%; p=0.008). 1,691 (74.0%) patients attended KT evaluation, of these patients, 643 (38%) were waitlisted for KT. Residents in the highest ADI quartile (44-100) had a 38% less odds of being WL relative to the residents in the lowest ADI quartile (1-18) (OR 0.62, 95% CI 0.45-0.87; p=0.005).

Conclusions: Patients residing in higher ADI neighborhoods are at increased risk of not being seen in KT clinic and not being WL after KT evaluation. These findings suggest that ADI may be a useful marker to proactively identify patients at risk for early inequities in advancement through the KT process and could help guide early intervention efforts to ensure a more equitable evaluation process.

Funding: NIDDK Support

Table 1: Multivariable Logistic Regression for Being Waitlisted for Kidney Transplantation if Seen in Clinic

Characteristic	OR	CI	P
ADI Quartiles			
1-18			
19-29	0.67	0.50-0.91	**0.010**
31-43	0.77	0.56-1.05	0.100
44-100	0.62	0.45-0.87	**0.005**
Age (per year)	0.97	0.96-0.98	**<0.001**
Gender Female	0.98	0.78-1.24	0.900
Marital Status			
Married or partnered			
Divorced, widowed, or separated	0.45	0.31-0.65	**<0.001**
Single	0.51	0.39-0.68	**<0.001**
Unknown	0.38	0.19-0.76	**0.006**
Preferred Language			
English			
Other	1.16	0.76-1.76	**0.490**
Spanish	0.91	0.53-1.57	0.750
Unknown	0.86	0.31-2.43	0.780
Insurance			
Private			
Medicaid	0.25	0.16-0.39	**<0.001**
Medicare	0.80	0.62-1.03	0.090
Other	0.85	0.42-1.71	0.650
Renal Disease			
Glomerulonephritis			
Congenital or hereditary	0.92	0.37-2.26	0.850
Diabetes mellitus	0.28	0.20-0.38	**<0.001**
Hypertensive	0.48	0.33-0.72	**<0.001**
Other	0.37	0.25-0.54	**<0.001**
PKD	1.26	0.73-2.18	0.410
Unknown	0.10	0.01-0.91	**0.040**
Dialysis			
None			
Hemodialysis	0.70	0.54-0.91	**0.010**
Peritoneal Dialysis	1.53	1.08-2.17	**0.020**
Unknown	0.86	0.47-1.58	0.630

TH-PO871

Unraveling the Hemodialysis Patient Network: Results from the Social Network and Renal Education (SNARE) Transplant Intervention

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Background: In-center Hemodialysis (HD) is a unique therapy occurring in a group setting, facilitating patient social network formation. Social networks are a key social determinant of health, amenable to intervention if influential members are identifiable. The goal of our study is to determine whether patients who are more clustered (a network member whose alters are interconnected) vs. more central (a network member who has multiple alters who are not interconnected) within HD networks are more likely to disseminate the COmmunicating About Choices in Transplant (COACH) intervention. This intervention has been shown to improve knowledge, communication skills, and behaviors regarding living/deceased-donor kidney transplantation (KT).

Methods: For this pilot network intervention clinical trial (NCT03536858), in a North Philadelphia HD clinic, the Monday, Wednesday, Friday patients were stratified to centrality spread and Tuesday, Thursday, Saturday to clustering spread. Outcomes including number of transplant evaluation steps completed, change in KT knowledge, self-reported KT conversation self-efficacy, and living donation requests were assessed using repeated questionnaire data and chart review prior to the intervention, at 3-months, and 9-months post-intervention. Data analysis was performed using *t*-tests, repeated measures ANOVA, and Fisher's exact test.

Results: Twenty-eight transplant-eligible patients completed the study. Groups (centrality N=11; clustering N=17) did not differ significantly in demographic or clinical variables. The clustering group completed more KT evaluation steps (+0.79 ± 1.72 vs -0.38 ± 1.3, p=0.02) and reported higher conversation self-efficacy scores than the centrality group (21± 2.6 vs.16 ± 1.4, p=0.03). The difference in living KT requests was not significant (3 vs 1, p=0.5). No differences were observed in knowledge outcomes.

Conclusions: Selection of patients with the highest clustering yielded more efficient dissemination of the COACH intervention. Notably, this network intervention improved transplant behaviors but not knowledge, indicating a peer-network imitation effect on behaviors without changing knowledge. Further research is indicated to assess these effects in a larger population and with expanded network targeting strategies.

Funding: NIDDK Support

TH-PO872

Disparities in Access to Kidney Transplantation for Asian, Hispanic, and Black Candidates

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Background: Disparities in access to kidney transplantation (KT) for minoritized end-stage kidney disease (ESKD) patients are persistent and pervasive. The distinct points along the KT continuum where disparities are most prominent are poorly understood, however their identification is crucial for developing targeted interventions. We quantified disparities from ESKD diagnosis to listing and first KT for Asian, Hispanic, and Black candidates, compared to White candidates.

Methods: Engaging USRDS data, we identified 2,200,356 adults with initial ESKD diagnosis between 1999-2019**.** We used Fine and Gray sub-distribution hazards models, adjusted for age, sex, race/ethnicity, comorbidities, primary health insurance, to determine adjusted sub-hazards ratio (aSHR) of listing after ESKD diagnosis, and KT after listing, with death as a competing risk. We tested the proportional hazards assumption using complementary log-log plots and Schoenfeld residuals.

Results: White candidates were more likely to be waitlisted and transplanted than candidates of other racial/ethnic groups. Waitlisted White candidates were also more likely to receive KT, especially LDKTs (Black aSHR (95% confidence interval (CI)): 0.33 (0.32-0.35); Hispanic aSHR (95%CI): 0.66 (0.64-0.69); Asian aSHR (95%CI): 0.45 (0.42-0.47)) and pre-emptive KTs (Black aSHR (95%CI): 0.53 (0.47-0.60); Hispanic aSHR (95%CI): 0.65 (0.56-0.75); Asian aSHR (95%CI): 0.47 (0.38-0.58).

Conclusions: The field of transplantation should engage communities to identify interpersonal, community, and societal barriers to access to KT among minoritized candidates.

Funding: Private Foundation Support

Table 1: Likelihood of access to key transplantation steps from 1999-2019, stratified by candidate race/ethnicity

Race/ Ethnicity		ESKD, N[a]	Informed[b]	Listed[c]	Transplanted[d]	Transplant Type: DDKT	Transplant Type: LDKT	Transplant Type: Preemptive
White[e]	Crude	1,169,196	55.3%	11.3%	57.6%	65.5%	31.9%	2.7%
	aSHR[f]		*Reference*	*Reference*	*Reference*	*Reference*	*Reference*	*Reference*
Black[e]	Crude	612,382	56.1%	10.9%	49.8%	63.4%	14.6%	2.1%
	aSHR[f]		1.02 (1.02-1.03)	0.73 (0.73-0.74)	0.68 (0.67-0.69)	0.89 (0.87-0.91)	0.33 (0.32-0.35)	0.53 (0.47-0.60)
Hispanic/ Latino	Crude	320,479	63.1%	19.9%	48.4%	73.1%	25.0%	1.9%
	aSHR[f]		1.03 (1.02-1.03)	0.74 (0.73-0.74)	0.71 (0.70-0.73)	0.75 (0.73-0.77)	0.66 (0.64-0.69)	0.65 (0.56-0.75)
Asian[e]	Crude	98,299	63.1%	22.1%	46.7%	76.5%	21.7%	1.8%
	aSHR[f]		1.01 (1.00-1.01)	0.77 (0.76-0.78)	0.62 (0.61-0.64)	0.73 (0.71-0.76)	0.45 (0.42-0.47)	0.47 (0.38-0.58)
Total	Crude	2,200,356	57.7%	14.6%	52.6%	73.0%	24.7%	2.3%

[a]Non-Hispanic; Asian includes Asian American, Native Hawaiian, and Pacific Islander
[b]Adjusted prevalence ratio for candidate being informed of transplant, adjusted for era of ESKD diagnosis, cause of ESKD, sex, age, comorbidities [hypertension, diabetes mellitus, alcohol use, cancer, CAD, COPD, CVD, PVD, heart failure, inability to transport, functional impairment, tobacco use], and primary health insurance.
[c]Adjusted sHR of being listed after ESKD diagnosis [adjusted for: candidate race, era of first service, cause of ESKD, sex, age at first service, hypertension, diabetes, heart failure, CAD, PVD, CVD, COPD, cancer, functional impairment, inability to transport, alcohol use, tobacco use, and health insurance], and adjusted sHR of being transplanted after listing [adjusted for: candidate race, era of listing, cause of ESKD, sex, age at listing, hypertension, diabetes, heart failure, CAD, PVD, CVD, COPD, cancer, functional impairment, inability to transport, alcohol use, tobacco use, health insurance, and blood type]
[d]N from ESKD to Listing: 2,199,657
[e]N from Listing to Transplantation: 320,611

TH-PO873

Effect of Kidney Allocation System (KAS) Policy on Renal Transplantation in Elderly Recipients

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SUNY Downstate Health Sciences University, New York City, NY.

Background: Prior to 2015 KAS policy creation and implementation, there were inordinate number of kidneys being allocated to recipients who were not matched appropriately to enhance the longevity of the transplanted organ. Our aim was to analyze the impact of KAS policy on patient mortality.

Methods: This study includes retrospective analysis of primary DDRT patients age ≥ 65 years reported to UNOS/OPTN and performed between 2010 and 2022. Patients were divided into preKAS and KAS group by dialysis status. Comprehensive univariate and multivariable analyses were performed.

Results: There were 34717 patients analyzed. Fig1 shows the changes in factors over time. The number of transplants increased significantly as well as the number of preemptive transplants. The wait time decreased significantly and the number of Black and Hispanic recipients increased significantly. Fig1 shows patient and graft survival at 3 years. During the KAS era outcomes declined. The analysis showed an increased Relative Risk for transplants during KAS (RR: 1.39,1.32-1.46) while the outcome for preemptive transplants is significantly lower (RR: 0.68,0.64-0.73).

Conclusions: The number of kidney transplants in this elderly transplant group increased over time which offers an increased life-expectancy. While overall the mortality risk could not be reduced, a shorter waitlist time was noted, which is important. This analysis also shows the importance of early transplantation in this age group to reduce mortality.

	Pre-KAS		Kas	
Dialysis	No	Yes	No	Yes
#Transplants (%)	2894 (28)	7364 (72)	4873 (20)	19586 (80)
Wait Time [Mos]	30.2 (0-220)	25.3 (0-158)	23.5 (0-190)	19.4 (0-252)
Male (%)	1689 (58)	4670 (63)	2643 (54)	12299 (63)
Age	69 (65-86)	69 (65-88)	69 (65-87)	69 (65-92)
Race (%)				
White	1992 (69)	3674 (50)	3377 (69)	8382 (43)
Black	443 (15)	1949 (26)	748 (15)	5959 (30)
Hispanic	213 (7)	1062 (14)	354 (7)	3091 (16)
Asian	212 (7)	568 (8)	343 (7)	1808 (9)
Diabetes (%)	866 (30)	3180 (43)	1483 (30)	9033 (46)
3-Year Patient survival	88.0%	83.6%	85.9%	78.7%
3-year kidney graft survival	84.8%	79.0%	83.3%	75.9%

Fig 1

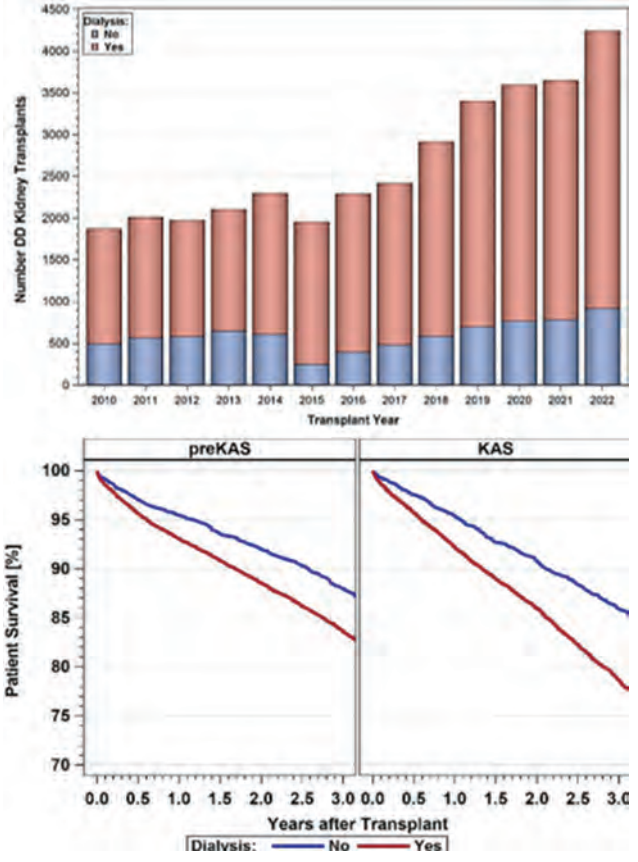


Fig 2

TH-PO874

Geographic Proximity to Donor Care Units Among Deceased Organ Donors After Brain Death

Emily A. Vail,[1,2] Vicky Tam,[3] Richard Hasz,[4] Peter Abt,[1,5] Peter P. Reese,[1,5] Niels D. Martin,[1] Kim M. Olthoff,[1,5] Vishnu S. Potluri.[1,2] *[1]University of Pennsylvania Perelman School of Medicine, Philadelphia, PA; [2]Leonard Davis Institute of Health Economics, Philadelphia, PA; [3]The Children's Hospital of Philadelphia, Philadelphia, PA; [4]Gift of Life Donor Program, Philadelphia, PA; [5]Penn Transplant Institute, Philadelphia, PA.*

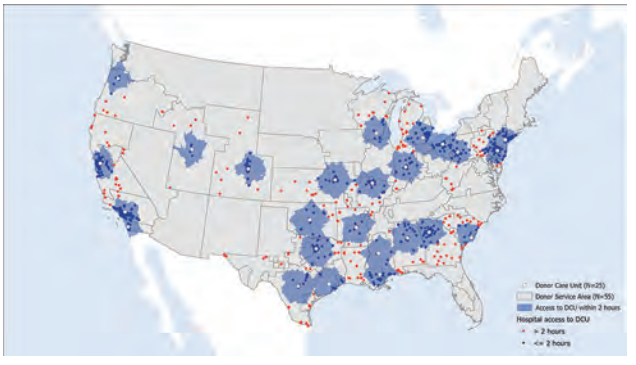
Background: The National Academies recommend that all United States (US) organ procurement organizations (OPOs) operate deceased donor care units (DCU) but adoption is incomplete. Donors in hospitals at greater distances from DCUs may be less likely to transfer. We sought to characterize the geographic proximity of donors in hospitals to operating DCUs as a proxy for nationwide DCU access.

Methods: Retrospective analysis of all adult deceased donors after brain death with recovery dates Jan 2010 - Jun 2022 in Organ Procurement and Transplantation Network data. Driving times and distances between donor hospitals and DCUs were measured using ArcGIS road network software. We defined geographic proximity to a DCU by estimated driving times; primary outcome was drive time <2 hours (feasible for ground transport). We estimated the number of donors who would gain access to DCUs if OPO donor service area boundaries were ignored.

Results: Among 92 085 donors in 2574 hospitals, 42 302 (42.0%) were managed in one of 25 OPOs with DCUs. Among donors in those areas, a majority (86.7%, 36 687 donors in 999 hospitals) were within 2 hours' driving distance of a DCU. Rates of DCU proximity varied by OPO (median 43.5% (IQR 0-67.8%) of donors per OPO). When OPO area boundaries were ignored, 8164 additional donors in 229 hospitals were within 2 hours' distance of at least one DCU (Fig 1). Donor characteristics were similar between groups.

Conclusions: Less than half of donors were within 2 hours drive of a DCU. Proximity rates rates varied across donor service areas. A substantial number of donors were in hospitals proximate to an existing DCU in a neighboring area. OPOs may consider collaborating to transfer donors from hospitals in nearby areas or opening additional DCUs. Future work is needed to understand whether, and how, optimally located DCUs may improve kidney donation and transplantation outcomes.

Funding: Private Foundation Support



Distribution of acute-care hospitals in US mainland donor service areas with operating DCUs.

TH-PO875

Using Machine Learning to Identify People Considering Living Kidney Donation on Reddit

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Background: Machine learning (ML) strategies may help to identify potential kidney recipients and living kidney donors on online digital platforms, who are considering living kidney donation (LKD), to target helpful information to them. Our study's aims were to: (1) Identify people sharing their personal LKD experiences on the digital platform Reddit, (2) Determine whether ML models could distinguish between simplified or more nuanced labels.

Methods: A multidisciplinary team of engineers and transplant experts created and piloted a user labeling system to code 3,292 posts created by Reddit users from 2010-2023 using 3 simplified labels and six nuanced labels (Table). To validate the system, four team members independently labeled the same 100 posts manually, and definitions were refined until reaching unity. The remaining 3,192 posts were manually labeled using refined definitions. We explored the ability to automate this classification process using an ML model known as Bidirectional Encoder Representations from Transformers (BERT). Two models were trained to predict simplified and nuanced labels, respectively. Exploratory work using ChatGPT was also included for automatic classification.

Results: The BERT model accurately classified the simplified labels with 87% accuracy, but when trained to classify all six nuanced labels, was only able to perform with 67.1% accuracy. Preliminary experiments using ChatGPT showed poorer alignment with automated user labeling than ML models (69% and 45.3% for simplified and nuanced labels, respectively).

Conclusions: Using expert defined classification criteria combined with ML methods, it is possible to identify those who may be interested in LKD on digital platforms. Current methods perform better on more simplified classifications, but improvements can be made and advances in ML may increase the predictive power of future models. Future work will explore ways to enhance the BERT method using integration with ChatGPT.

Type of Post	Simplified Type	Number (%)	Example Post
Current Direct – Personally involved with LKD at present	**Current**	363 (11.0%)	A friend of mine is in need of a kidney. My first instinct is to offer one of mine. I have Googled and read LOTS of info. What would you do? Have you donated a kidney? What am I missing?
Current Indirect – Secondhand experience with LKD at present	**Current**	177 (5.4%)	I need help finding a kidney for my dad.
Past Direct – Personally involved with LKD in the past	**Past**	164 (5.0%)	Eight years ago today, I donated a kidney to a friend. Ask me anything.
Past Indirect – Secondhand experience with LKD in the past	**Past**	58 (1.8%)	[Here's a] picture of my dad and the woman who donated a kidney to save his life.
General Commentary/Hypothetical	**Impersonal**	159 (4.8%)	If you donate a kidney, then later your only one starts to fail, would you be put on a higher priority?
News/Noise	**Impersonal**	2371 (72.0%)	Story: A man donated his kidney to his wife of 51 years after finding out he's her perfect match.

Table 1 – Distribution of comment categories with examples

TH-PO876

Sociodemographic Barriers to Interest and Pursuit of Living Donation Among ESKD Patients

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Background: Living donor kidney transplants result in better patient and graft survival compared to deceased donor kidney transplants. Despite these benefits, only 23% of all kidney transplants in 2022 were from a living donor. To provide insight of potential barriers to living donation, we quantified the associations of interest in, and pursuit of, living donor transplant with geographic, demographic, and socioeconomic factors among end-stage kidney disease (ESKD) patients.

Methods: This was a retrospective study of 151,656 adult ESKD patients on dialysis for whom preferences and potential pursuit of transplant status were documented. Publicly available data sources were used for classification of socioeconomic status. Outcomes considered were interest in living donation and separately, pursuit of a living donation. Associations between patient characteristics and outcomes were quantified with odds ratios and 95% confidence intervals derived from multivariate logistic regression models assuming a binomial distribution.

Results: For the 59,893 patients in whom interest was recorded, 11,675 (19.5%) were interested in living donor transplant. Among those interested, 7,376 (63.2%) reported having pursued a living donation. The following factors were associated with interest in living donation: age at dialysis start, race/ethnicity, sex, diabetes status, insurance type at dialysis start, kidney education attendance, and poverty level. The following factors were associated with pursuit of a living donation: age at dialysis start, race/ethnicity, and insurance type at dialysis start. Both interest and pursuit of living donation varied by state, but no obvious regional trends were observed.

Conclusions: Our results identify subgroups of patients who could potentially benefit from additional education regarding living donor transplant. This information may be useful in the design of interventions to increase living donor kidney transplantation rates.

Variable/Category	Interest in Living Donation Odds Ratio (95% CI)	Pursuit of Living Donation Odds Ratio (95% CI)
Age at dialysis start, years (ref: 18-49)		
50-64	0.77 (0.73-0.80)	0.87 (0.80-0.95)
65-75	0.81 (0.76-0.86)	0.99 (0.87-1.14)
Race (ref: white)		
Black	0.79 (0.74-0.83)	0.63 (0.57-0.70)
Hispanic	0.90 (0.85-0.96)	1.01 (0.90-1.13)
Asian	0.73 (0.66-0.81)	0.64 (0.53-0.78)
Other/Unknown	0.97 (0.90-1.04)	0.90 (0.79-1.04)
Female sex	1.09 (1.04-1.13)	1.12 (1.03-1.21)
Diabetic	0.85 (0.81-0.88)	0.93 (0.86-1.01)
Insurance at dialysis start (ref: commercial)		
Medicare	0.76 (0.72-0.80)	0.82 (0.74-0.92)
Medicaid	0.81 (0.76-0.85)	0.86 (0.78-0.96)
Other/Unknown	0.73 (0.66-0.80)	0.81 (0.67-0.97)
Attended kidney education	1.17 (1.11-1.22)	1.08 (0.99-1.18)
Poverty above national average (11.4%)	0.83 (0.79-0.87)	0.91 (0.83-0.99)
Rurality (ref: urban core)		
Suburban	1.02 (0.94-1.10)	1.15 (0.98-1.35)
Large town rural	1.04 (0.95-1.13)	1.00 (0.85-1.17)
Small town rural	1.12 (1.02-1.23)	1.25 (1.04-1.50)
State transplant rate 60 kidney transplants/yr	0.98 (0.93-1.03)	1.014 (0.95-1.15)

TH-PO877

Experiences of Ethnically Diverse Living Kidney Donors

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Background: Living kidney donors enter the donation process in good health but are often ill-prepared to face any negative outcomes following donation. Adverse post-donation outcomes are more prevalent among ethnic minorities. We aimed to provide an in-depth description of ethnically diverse donors' positive and negative outcomes to inform development of an online module of lived experiences.

Methods: We used the DIPEx (database of individual patient experiences) method to conduct in-depth individual interviews with a diverse sample of donors. This method combines in-depth patient interviews with rigorous systematic, purposeful sampling and qualitative analysis. All interviews were conducted by a primary and secondary interviewer and analyzed by a qualitative research team.

Results: Fourteen donors (9 women; 8 White, 5 Hispanic, 1 Native American) completed narrative interviews. Findings highlight the critical role of social support in validating the decision to donate and aiding post-donation recovery. Participants felt compelled to donate to prevent dialysis use or death for their recipient. Although familial duties seemed to motivate donation for Hispanic and Native American women, a call to action as a healthy individual was a greater motivator among the White donors. Most (n=13) felt well-supported by healthcare providers throughout the entire pre-donation period, though three participants reported erroneously being told they had developed kidney disease in primary care due to a lack of clarity regarding post-donation clinical care. Among directed donations (n=12), most reported either no change or improvement in the relationship to the recipient. Many donors (n=11) experienced unanticipated outcomes post-donation, including minor complications (e.g., constipation, fatigue, pain), moderate complications (e.g., hernia, gout), or emotional distress (e.g., depression, mourning loss of kidney). Despite these adverse outcomes, all participants were enthusiastic about donation and reported no regrets.

Conclusions: Adverse outcomes post-donation did not preclude living donors' enthusiasm and support of donation; therefore, greater transparency about post-donation outcomes is warranted. An online DIPEx module presenting these diverse experiences may enhance awareness and understanding of the donation process for future living kidney donors.

Funding: Other NIH Support - National Center for Advancing Translational Services - UL1TR001449

TH-PO878

Healthcare System Intervention Changed Negative Perceptions of Healthcare in Kidney Transplant Candidates

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Background: The kidney transplant (KT) evaluation process is lengthy for patients but even longer for Black patients. One potential reason for these longer times is past negative experiences with healthcare contributing to mistrust toward healthcare systems. We examined whether engaging in a streamlined evaluation process at a transplant center reduced negative perceptions of the healthcare system among Black patients.

Methods: We recruited patients undergoing KT evaluation, and the intervention occurred during the evaluation period. We collected survey responses at T1 (before evaluation initiation) and T2 (following KT evaluation completion). Surveys assessed experience of discrimination in healthcare, perceived racism in healthcare, medical mistrust, and trust in physician. Regression analyses adjusted for baseline characteristics. We examined whether negative perceptions of healthcare changed from T1 to T2 among White and Black participants.

Results: The final sample included 883 participants (658 White, 225 Black). White participants consistently had lower scores for discrimination, racism, and mistrust but higher scores for trust in physician, compared to Black participants, across both time points (all $p<.001$). Interaction effects indicate that White participants experienced a significant reduction in discrimination, racism, and mistrust scores at T2, and Black participants experienced a significant reduction in discrimination, mistrust, and trust in physician scores at T2 (all $p<.05$). The difference in change-in-perception scores between Whites and Blacks was statistically significant for trust in physician ($p = .012$).

Conclusions: A coordinated healthcare system intervention reduced perceptions of discrimination, racism, and mistrust in patients undergoing KT evaluation, but results varied by race. Future work will ascertain whether perceptions of discrimination, racism, and mistrust are associated with faster time to KT waitlisting, treatment adherence, and quality of life post-transplant.

Funding: NIDDK Support

TH-PO879

Disparities in Phase Progression in Kidney Transplant Evaluation

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Background: Inequity in access to kidney transplantation by race/ethnicity is a significant challenge. In this study, we evaluate the association between race and progression to subsequent phases of transplant in patients being evaluated for a kidney transplant.

Methods: We conducted a retrospective cohort study of patients undergoing kidney transplant evaluation at our center from 2020-2023. Using time-to-event analyses, we examined the time to reaching the next phase of transplant by self-identified patient racial group. Patients determined to be ineligible for listing were censored at committee review date while remaining patients were censored at the end of the study period. We then created a multivariate Cox proportional hazards model to assess the association between race and phase progression while controlling for age, gender, employment status, cause of end-stage renal disease, and insurance type.

Results: We identified 957 patients who were evaluated for kidney transplant with a documented race. Of these, 9% were Asian, 28% were Black/African American, 29% were Hispanic/Latino and 35% were White. Median progression time from evaluation to listing was 181 days and listing to transplant was 264 days. The unadjusted probability of progressing from evaluation to listing was significantly different between all four racial groups (p<0.0001), but there was no difference in progressing from listing to transplant (p=0.12) (Figure). In adjusted models, Black/African American patients had 37% lower rate of progressing from evaluation to listing (p=0.0001) and 35% lower rate of progressing from listing to transplant (p=0.01) compared to White patients, and Hispanic/Latino patients had 34% lower rate of progressing from evaluation to listing (p=0.0005) compared to White patients.

Conclusions: Disparities in progression from evaluation to waitlisting contribute to racial disparities in kidney transplant access.

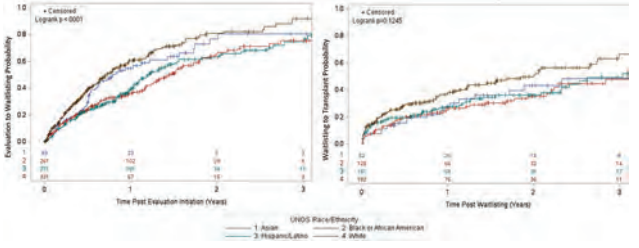

Figure: Kaplan-Meier failure curves displaying progression from evaluation to listing and listing to transplant, stratified by race

TH-PO880

Public Survey of Financial Incentives for Kidney Donation

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Background: With the increasing prevalence of end-stage kidney disease in Bahrain, kidney donation is of vital importance. In this study we want to assess how financial incentives will influence peoples' views and decisions regarding kidney donation. The aim is to establish strategies to increase the number of kidneys for transplantation in Bahrain.

Methods: We adapted a previously established questionnaire on financial incentives for living kidney donations. The questionnaire assessed the public opinion in Bahrain on how kidney donation can be influenced by two different financial incentives, namely 10,000 BHD and life-long health insurance. We collected a convenient sample of 446 participants by distributing an electronic version of the questionnaire. SPSS-23 software was used for data entry and analysis.

Results: Of the total participants 39% were male and 61% were female. Eighty-percent of the participants believed that their chances for kidney donation will not increase in turn of receiving a financial compensation, while 20% of them believed that it will increase. Our study found that generally married participants (70%) find it a preferable development for health insurance companies to offer financial compensation for kidney donation, while non-married participants (30%) found it not a preferable but also not an adverse development (P-value 0.038). Furthermore, there is a positive correlation between age and preferable views toward financial incentives to increase kidney donation (P-value <0.001).

Conclusions: Although financial incentives for kidney donation might encourage a minority of the population, the majority may not be influenced by implanting a financial incentives' system for kidney donation.

TH-PO881

Neighborhood Deprivation and Access to Living Donor Kidney Transplantation: Reducing Health Care Disparities

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Background: Living donor kidney transplantation (LDKT) offers better health outcomes for individuals with end-stage kidney disease (ESKD). Deprived neighborhoods have low socioeconomic status, limited social cohesion, and reduced access to health care. However, the role of neighborhood deprivation on access to LDKT is understudied.

Methods: We used SRTR data to identify 510,674 non-Hispanic (NH) White, NH Black, NH Asian, and Hispanic KT candidates (age≥18) who were listed for first KT from 1995-2021. The National Cancer Institute's Neighborhood Deprivation Index (NDI) was averaged at the ZIP code level using population weights from the American Community Survey. Proportional hazards models were used to determine the likelihood of LDKT across tertiles of NDI, adjusting for clinical and neighborhood-level factors.

Results: Candidates residing in high-deprivation (HD) neighborhoods had a lower access to LDKT than those in low-deprivation (LD) neighborhoods (adjusted hazard ratio (aHR)=0.80, 95% confidence interval (CI): 0.79-0.82); notably, Black candidates living in HD neighborhoods had 37% lower access to LDKT than those in LD neighborhoods (aHR=0.63, CI: 0.60-0.67). Similarly, Asian and Hispanic candidates living in HD neighborhoods had 22% (aHR: 0.78, CI: 0.70-0.88) and 21% (aHR: 0.79, CI: 0.75-0.83) lower access to LDKT, respectively, relative to White candidates.

Conclusions: Neighborhood deprivation is associated with decreased access to LDKT, particularly among Black candidates. Identification of structural factors impacting healthcare access in disadvantaged neighborhoods can be used by policymakers and healthcare providers to develop interventions to address barriers and disparities in LDKT access.

Funding: Other NIH Support - NIA

Table 1. Neighborhood Deprivation Levels and access to LDKT (N=510, 674)

	Neighborhood Deprivation Index[d] Adjusted Hazard Ratio (aHR) (95% Confidence Interval)					
	Minimally Adjusted Model[b]			Fully Adjusted Model[c]		
	Low Deprivation	Medium Deprivation	High Deprivation	Low Deprivation	Medium Deprivation	High Deprivation
LDKT[a] Overall	Reference	0.88 (0.86-0.90)	0.72 (0.71-0.74)	Reference	0.93 (0.91-0.95)	0.80 (0.79-0.82)
Race						
White	Reference	0.91 (0.89-0.93)	0.78 (0.76-0.81)	Reference	0.96 (0.94-0.98)	0.87 (0.85-0.90)
Black	Reference	0.78 (0.74-0.83)	0.58 (0.55-0.61)	Reference	0.82 (0.78-0.86)	0.63 (0.60-0.67)
Asian	Reference	0.84 (0.78-0.92)	0.70 (0.62-0.79)	Reference	0.91 (0.84-0.99)	0.78 (0.70-0.88)
Hispanic	Reference	0.86 (0.81-0.91)	0.72 (0.68-0.75)	Reference	0.89 (0.85-0.94)	0.79 (0.75-0.83)
P-value		<0.001	<0.001		<0.001	<0.001

[a]Adults aged ≥18 at the time of listing
[b]Adjusted for age, sex, and race
[c]Adjusted for age, sex, race, BMI, blood type, cause of ESKD, primary health insurance, neighborhood deprivation levels (NDI)
[d]Neighborhood deprivation index scores are provided by the National Cancer Institute

TH-PO882

Ongoing Sex Disparities in Living Kidney Transplantation: A UNOS Analysis

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Background: In the United States, the prevalence of chronic kidney disease (CKD) is higher in females (16.2%) than in males (13.4%). Studies in Asia and Mexico have shown that females comprised 62% to 69% donors and were LKDT recipients in only 20% of cases. Disparities are not fully explained by socio-cultural or biological factors. Outdated U.S. data showed a lower rate of LDKT in females. We aim to explore current trend of LDKT in the US.

Methods: We queried the UNOS database for all adult primary single organ LDKTs from 2011 to 2022. We excluded deceased donor recipients which has been previously described. Comprehensive univariate and multivariate analyses were performed to describe changes and risk factors.

Results: There were 60,865 LDKTs, 36% were female recipients and 63.5% were donors (Table 1). The likelihood to receive a LDKTA decreased with increasing age. Black females were more likely to be donorsreceive a LD KTA when compared to white females (OR 1.4 [1.3-1.5] <0.001). Female donors recipients were less likely to be biologically related to male recipients to receive a nonbiologically related KTA (OR 0.89 [0.86-0.93] <0.001). Furthermore, female recipients were longer on the transplant waiting list and were more likely to have a higher a cPRA (OR 6.2 [6.2-7.3] <0.001). Female to Male donors accounted for 40.6% of donors, this trend remained stable throughout the study period.

Conclusions: Females are more likely to be donors than LDKTA recipients and face longer times in the transplant waiting list. Black females were more likely to be donors and less likely to be recipients when compared to white females. The sex disparities in KT

listing and LKDT remains. However, socio-cultural factors, as well as biological factors influencing such disparities are yet to be elucidated. Data informed policy is warranted to bridge the sex disparities in LKDT.

Table 1. Donor and Recipient Characteristics.

Variables [a]	All recipients N=60,865	Female Recipients n=22,437	Male Recipients N=38,428	p-value[b]
Age, years	52 (18-88)	51 (18-52)	52 (18-88)	<0.001
Race/Ethnicity				<0.001
Black, non-Hispanic	13%	5.3 %	7.7 %	
White, non-Hispanic	64.1%	22.7 %	41.4 %	
Hispanic	15.7%	5.6 %	9.9 %	
Clinical Characteristics				
Time on waiting list, d	7.8 (0.0 – 62)	8.0 (0-61.9)	7.6 (0-62.)	<0.001
RRT before transplant	64.7%	22.6%	44.2%	<0.001
cPRA >60%	5.7%	4.3%	1.4%	<0.001
Variable	**All donors N=60,865**	**Female Donors n = 38,667**	**Male Donors n =22,198**	**p-value[b]**
Age, years	43.7±12.4	43.5 ± 12.4	43.8± 12.3	0.01
Race/Ethnicity				0.002
Black, non-Hispanic	9.5 %	5.8 %	3.7 %	
White, non-Hispanic	69.6 %	44 %	25 %	
Hispanic	15 %	9.6 %	5.4 %	
Relationship with recipient				<0.001
Biological	43.5 %	41.3 %	47.3 %	
Non-biological	56.5 %	58.7 %	52.7%	

[a] Data presented as % for categorical variables and median - range and mean – standard deviation for continuous variables depending data distribution.
[b] p-value for F vs. M comparisons

TH-PO883

Use of "Marginal Kidneys" to Improve Access to Care: No Adverse Impact on Short-Term Outcomes

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Background: In an effort to improve both equity and utility of organ allocation, the current kidney allocation system (KAS) assigns kidneys from donors with higher kidney donor profile index (KDPI) to recipients with a lower expected posttransplant survival (EPTS) score and vice versa. However, many kidneys with a high KDPI (especially >80%) are discarded for fear of poor outcomes. This study examines our experience with high KDPI kidneys.

Methods: We queried our transplant QI database for all adult primary deceased kidney donor transplants (DDKT) from 2022-2023. The cohort was dichotomized based on high vs lower KDPI (>80% vs.<80%). One-year mortality and allograft failure were compared across groups.

Results: Of 115 DDKT, 81.7% were African-American, 46% were females, median age was 60 years. The recipients with a KDPI < 80% represented 70%. Recipients with a KDPI >80 % were older (66 vs. 57), had longer ischemic times (26.6 hours vs. 23.8 hours) and had a slightly higher EPTS (64% vs. 68%) when compared to the lower KDPI group (table 1). Recipients in the high KDPI group had similar rates of mortality and marginally lower delayed graft function (DGF), these differences were not statistically significant when compared to recipients with a KDPI <80%.

Conclusions: -In keeping with the KAS, organs from donors with KDPI <80% were more likely to be allocated to younger highly sensitized recipients. -Mortality and graft failure at 1-year pos-transplant did not differ between recipients of KDPI >80% vs. <80% kidneys despite the older age of the high KDPI recipients. -The high DGF rate in our low KDPI group was likely to be due to our acceptance of allografts from donors with acute kidney injury in an effort to transplant recipients who were ranked lower. -Our results suggest that high KDPI kidneys should be utilized although the early transplant period requires a strong multidisciplinary transplant team to guarantee good outcomes in underserved communities with low rates of DDKT such as ours.

Variable	All Patients n = 115	KDPI <80% n =82	KDPI >80% n=33	P[b]
Age, years	60 (52 – 68)	57.5 (50 – 65)	66 (60 – 72)	0.001
Female %	46 %	36.6 %	48.5%	0.239
African American %	81.7 %	80.5 %	84.9%	0.584
Cold ischemic time, h	26 (20 – 29)	23.8 (19.0 –28.1)	26.6 (24.5–32.3)	0.014
EPTS %	65 % (40 - 85)	64 % (34 - 83)	68 % (53 - 92)	0.039
cPRA > 80%	17.4 %	20.7 %	9.1 %	0.136
Length of Stay, days	5 (4 – 8)	5 (4 – 7)	5 (4 – 8)	0.898
Outcomes at 1-year				
DGF (%)	58 %	53.6 %	42.4%	0.276
Creatinine at discharge	6.2 (2.9 – 8.9)	6.5 (3.3 – 9.2)	5.4 (2.8 - 7.9)	0.232
Graft failure at %	6.8 %	6.1%	9.1%	0.568
Mortality at 1 year %	4. 2 %	4.8 %	3.0 %	0.660

[a] Data presented as % for categorical variables and median - IQR –continuous variables
[b] p-value between KDPI <80% and >80%

TH-PO884

Living Kidney Donation in the United States from 2017 to 2022

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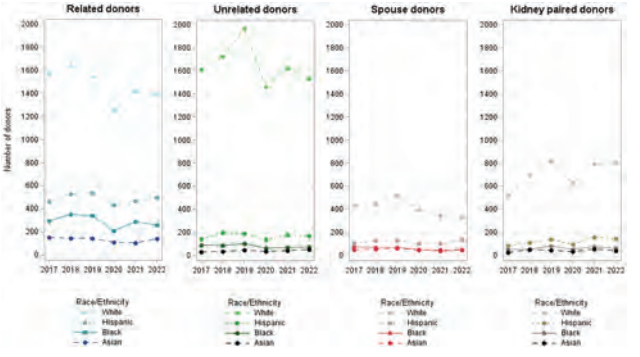
Background: Living kidney donation has not recovered to pre-pandemic rates. To inform the national efforts for increasing living kidney donation rates in the United States, we sought to characterize post-pandemic trends to guide future interventions.

Methods: We studied a US national registry (SRTR) of 35,511 living kidney donors from 2017 to 2022 (median age [IQR], 44 years [34-54], 64% female, 71.8% White, 15.2% Hispanic, 8.4% Black, 4.6% Asian donors). We used Poisson regression models to describe changes in the number of donors in 2020-2022 vs. 2017-2019 by donor-recipient relationship and race/ethnicity.

Results: Among biologically related donors aged <34, 35-4, ≥50 years the number of White donors aged <34, 35-49 and ≥50 decreased by 13%, 13%, and 18%, and Black donors aged <34, 35-49 years decreased by 27% and 22. Among unrelated donors <35, 35-49, ≥50 White donors decreased by 13% across age groups and Black donors <34 decreased by 49%. Among spousal donors aged 35-49 and ≥50 White donors decreased by 21% and 23% and Black donors decreased by 44% and 38% Among kidney-paired donors White donors ≥50 increased by 18%, and Hispanic donors aged <34 and ≥50 increased by 31% and 65%. No significant changes were observed for Asian donors across these described subgroups.

Conclusions: The decline in living kidney donation in the wake of the pandemic was driven by White and Black donor subgroups, warrantying targeted efforts to uncover what new barriers may be responsible for these observations.

Funding: NIDDK Support, Other NIH Support - NIA



Observed number of living kidney donors in the United States from 2017 to 2022, by donor-recipient relationship and race/ethnicity

TH-PO885

Living Kidney Donors' Perspectives of Telemedicine Video Visits for Donor Evaluation: A Qualitative Study

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Background: Living kidney donor evaluation is a complex multiphase process that takes approximately one year. It requires in-person visits where access to a transplant center becomes a barrier for willing candidates. Telemedicine via synchronous video enhances care coordination of donors. We conducted a qualitative study to understand donors/donor candidates' perceptions of telemedicine in donor evaluation.

Methods: We conducted in-depth, semi-structured interviews between 11/23/2021 and 03/17/2022. We interviewed 20 donors/donor candidates who completed their evaluation via telemedicine or in-person visits at a tertiary transplant center in Baltimore, Maryland. Interviews were analyzed using thematic analysis.

Results: Participants reported the following: 1) Telemedicine reduces travel time and travel-related expenses. 2) Telemedicine requires less time commitment compared to in-person, which allowed for more flexibility with scheduling their visit and made it easier to take less time off work. 3) Telemedicine reduced the burden of arranging for child and family care. 4) Interest in having introductory information provided prior to their visit. 5) Some concerns about telemedicine visit privacy and security. 6) Suggestions for using visual aids to facilitate the information shared during their visit. 7) Preferences in telemedicine versus in-person based on the providers' roles, specifically noting that they would prefer to meet the surgeon in-person. 8) Differences in levels of personal connectedness and communication. 9) Advantage of telemedicine allowing family and significant others to attend their visits.

Conclusions: Our findings provide information about donors/donor candidates' experiences and attitudes toward using telemedicine for donor evaluation. The reported views help inform a care coordination model in the donor evaluation process to enhance engagement of donor candidates and support completion of their evaluation.

Funding: NIDDK Support

Table 1. Participants' Characteristics by Donor Evaluation Type

Characteristic		Telemedicine (n=11)	In-Person (n=9)
Age, median (IQR), years		38 (37, 49)	46 (39, 52)
Gender, n (%)	Female	8 (73)	7 (78)
Race/Ethnicity, n (%)			
	White	7 (64)	4 (44)
	Black/African American	4 (36)	3 (33)
	Hispanic	0 (0)	1 (11)
	Other*	0 (0)	1 (11)
Education, n (%)			
	High School Grad or Equivalent	2 (18)	1 (11)
	Some College	3 (28)	3 (33)
	Bachelor's	1 (9)	4 (44)
	Post-Graduate	5 (45)	1 (11)
Marital Status, n (%)			
	Married	9 (82)	5 (56)
	Divorced/Separated	0 (0)	2 (22)
	Single	2 (18)	2 (22)
Insurance Type, n (%)			
	Private	10 (91)	6 (67)
	Public	0 (0)	1 (11)
	Uninsured	1 (9)	2 (22)
Inteded Recipient of Kidney Donation, n (%)	Biologically Related	4 (36)	6 (67)
	Biologically Unrelated	6 (55)	3 (33)
	Non-Directed	1 (9)	0 (0)

TH-PO886

Automated 3D Cortical Thickness Measurements from CT Images: A Novel Predictor of Low Kidney Function in Living Kidney Donors

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Background: The kidney cortex volume can be quantified on contrast-enhanced CT and is prognostic for chronic kidney disease (CKD) outcomes. Reduced cortical thickness is routinely reported from kidney ultrasound, however, cortical thickness is highly variable throughout the cortex and can be difficult to estimate from 2D images. Additionally, the relative contributions of cortical thickness and cortical volume to CKD risk are unclear.

Methods: This study examined a cohort of 1,132 living kidney donors with robust cortico-medullary differentiation on contrast-enhanced CT of the kidneys. AI techniques first separately segmented the cortex and medulla. Automated post-processing was employed to measure kidney length and volume of cortex. Then a distance map-based method was used to calculate average, maximal, and summed cortical thickness of the retained kidney. Cox proportional hazards models assessed the risk of measured glomerular filtration rate (mGFR)<60ml/min/1.73m^2 after donation with all five kidney cortex measures in analyses that were unadjusted and adjusted for cortex volume.

Results: Higher levels of all five AI-derived kidney cortex measures correlated with higher pre-donation mGFR (r_s=0.15-0.33, p<.0001). In unadjusted analyses, lower levels of all cortex measures associated with onset of a mGFR<60ml/min/1.73m^2 at a median 4 months post-donation. After adjusting for cortex volume, lower sum of cortex thickness and higher mean cortex thickness associated with onset of a mGFR<60ml/min/1.73m^2.

Conclusions: At the same level of cortex volume, a donor with lower total cortex thickness is at a higher risk for lower kidney function. Decreased total cortical thickness relative to total cortical volume may better detect loss of nephrons from nephrosclerosis than does cortical volume alone.

Funding: NIDDK Support

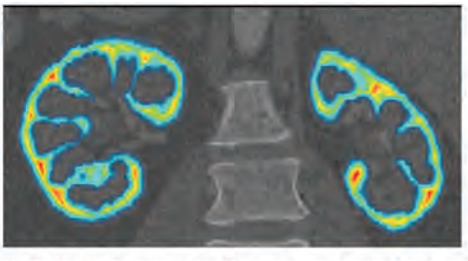

Figure. Example CT image with distance map of kidney cortex (displayed as a color overlay) used to derive cortical thickness.

Table. Imaging biomarkers as predictors of GFR<60ml/min/1.73m^2 in short-term donor follow up.

Median follow-up of 4.4 months by clinical care (n=1132)	Unadjusted		Adjusted for cortex volume	
	OR (95%CI)	P value	OR (95%CI)	P value
Cortex volume	0.43 (0.36-0.50)	<0.0001	---	---
Kidney length	0.65 (0.57-0.74)	<0.0001	0.98 (0.83-1.15)	0.82
Cortex thickness, sum	0.63 (0.55-0.72)	<0.0001	0.75 (0.65-0.87)	0.0002
Cortex thickness, average	0.84 (0.73-0.96)	0.01	1.41 (1.19-1.67)	<0.0001
Cortex thickness, maximum	0.73 (0.63-0.84)	<0.0001	1.17 (0.99-0.38)	0.07

TH-PO887

Beliefs and Intention to Organ Donation

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Background: Efforts to increase organ donation globally have not been successful, as seen in the low donor rates in Middle Eastern countries like Saudi Arabia, despite advanced healthcare systems and supportive government policies. Multiple factors, including psychosocial, cultural, religious, and structural elements, influence organ donation rates, some of which are unique to Saudi Arabia. The theory of planned behavior (TPB) is used to study how attitudes, beliefs, and norms affect organ donation intention and practice. This study explores normative, behavioral, and control beliefs among Saudi Arabian residents.

Methods: This was an online survey conducted from June to December 2021 using a Google form questionnaire among residents of Saudi Arabia. The survey covered demographic factors and explored normative, behavioral, and control beliefs related to organ donation.

Results: This study received 1245 valid responses. Among the study participants, only 19.6% were willing to register as an organ/tissue donor. The intention for organ donation showed a statistically significant positive association with beliefs that organ donation is a good thing (123.51, df: 4, p<0.001), could save somebody's life (81.38, df: 4, p<0.001), could have a positive impact on life after death (114, df: 4, p<0.001), and that the provision of better social support to the family of the deceased can increase organ donation (68.43, df: 4, p<0.001). Knowledge about family objections (190.76, df: 4, p<0.001), transplantation process (179.35, df: 4, p<0.001), religion's view (120.345, df: 4, p<0.001), and registration facilities (241.64, df: 4, p<0.001) increased willingness to donate organs. Worry about receiving less care (OR=4.25, 95% CI 1.57-11.51), belief in better social support increasing donation (OR=10.49, 95% CI 1.56-70.43), and concern for family emotions during donation (OR=4.37, CI 1.57-12.23) strongly predict intention to donate organs.

Conclusions: The study finds a positive correlation between normative/behavioral beliefs and definite intention for organ donation in the Saudi population. Control beliefs show a negative correlation. Promoting awareness about the organ donation process, including religious permissibility, is needed to increase donation rates.

TH-PO888

Procurement Retardation Improves Organ Recovery

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Background: The conditioning of the donor is crucial to avoid delayed graft function (DGF), which occurs in nearly 30% of cases and is associated with graft loss. A third of brain-dead donors have a recovered cardiac arrest (RCA), thus leading to a first episode of renal ischemia before procurement. Even if ischemia is known to be deleterious, studies conducted so far did not find an association between the donor's RCA and DGF. We hypothesize that the time interval (TRCA) between the RCA (1st ischemia) and the graft's procurement (2nd ischemia) could influence the function and survival of the graft. Using the French CRISTAL database, we found that a TRCA shorter than 3 days is associated with an increased risk of DGF. Several data suggest that proliferative cells are more sensitive to stress than non-proliferative ones. Given that an acute injury induces the proliferation of tubular cells, a procurement occurring during the proliferative phase of the tubular epithelium induced by the RCA-mediated ischemia could favor DGF. We used a mouse model to test this hypothesis and identify mechanisms responsible for the increased risk of DGF after an 'early' 2nd ischemia.

Methods: To mimic the situation of a donor with RCA, we performed two renal ischemias separated by either 2 or 5 days ('early' and 'late' 2nd ischemia), using a vascular occluder we recently developed. We evaluated the Glomerular Filtration rate (GFR) 24h after each ischemia by measuring the transcutaneous excretion kinetics of FITC-sinistrin (MediBeacon®). The histological analysis was carried out 24h after the 2nd ischemia by evaluating (i) the tubular injury and (ii) the cellular response using markers of proliferation (BrdU) and cell death (TUNEL).

Results: Comparably to the human data, the GFR following an early 2nd ischemia is lower than after a late 2nd ischemia. There was also a trend towards increased tubular lesions in the early group compared to the late one. Our future goal is to examine the effects of inhibiting proliferation after an early 2nd ischemia on the function and structure of the kidney (short & long-term after ischemias).

Conclusions: Our results suggest that delaying kidney procurement after RCA could ameliorate the function and survival of the graft. Given that it concerns a frequent situation, our study could improve the quality of grafts by recommending an optimal time interval for procurement after an RCA.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO889

Health-Related Quality of Life in Altruistic vs. Directed Kidney Donors

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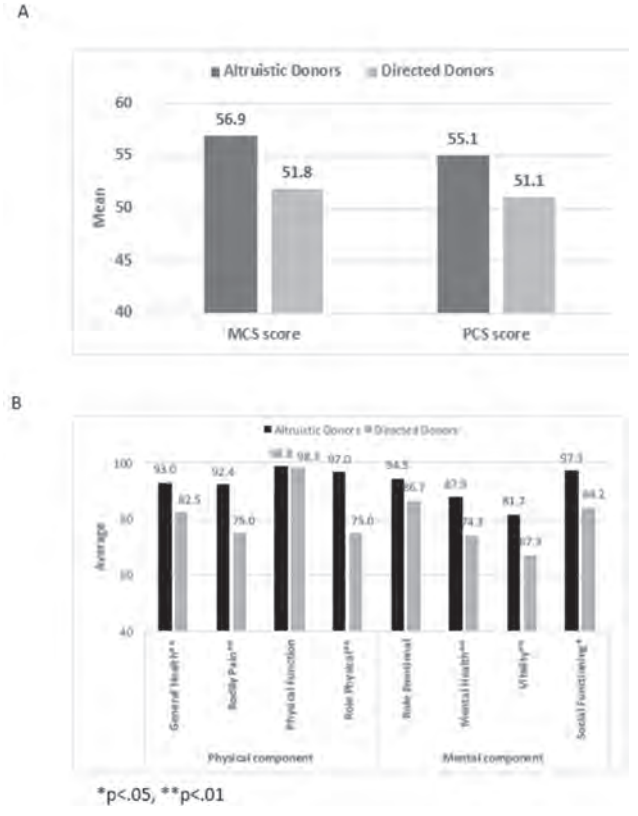
Background: Despite the significant increase in the rate of living kidney donation, there has been a lack of sufficient investigation into the post-donation health related quality of life (HRQoL) of altruistic donors (ADs) in comparison to directed donors (DDs).

Methods: We analyzed 112 living kidney donors (82 ADs and 30 DDs) who completed a SF-12 questionnaire and four supplementary questions. We compared the PCS and MCS scores between the two groups and examined secondary outcomes such as admission length of stay (LOS), time to return to normal activity and to physical activity, pre- and post-donation exercise rates, and physical activity continuation post-donation.

Results: Living kidney donors had higher mean PCS-12 and MCS-12 scores compared to the general population, with significantly higher scores in ADs than DDs ($p<0.001$). ADs returned to physical activity sooner than DDs (45 vs. 60 days), exercised more before and after donation, and continued post-donation. ADs had shorter admission LOS (3.4 vs. 4.4 days, $p<0.001$). Multivariable regression analyses revealed donation type and WBC count predicted PCS-12 score (altruistic vs. DDs: +2.69 (1.02), $p=0.01$) and donation type predicted MCS-12 score (altruistic vs. DDs: +4.43 (1.53), $p=0.005$). Altruistic donation type predicted a shorter LOS (by 0.78 days, $p<0.001$) and the odds of having PCS-12 and MCS-12 scores above 50 were almost 10 and 16 times higher in ADs, respectively ($p<0.05$).

Conclusions: ADs exhibit significantly higher physical and mental HRQoL compared to DDs post-donation, indicating the safety and potential benefits of promoting altruistic donation. However, it is essential to maintain a careful selection process to prevent any harm and ensure that donors' genuine desire to help others is not exploited.



SF-12 questionnaire results

TH-PO890

Comorbidity and Multimorbidity Burden in Living Kidney Donors

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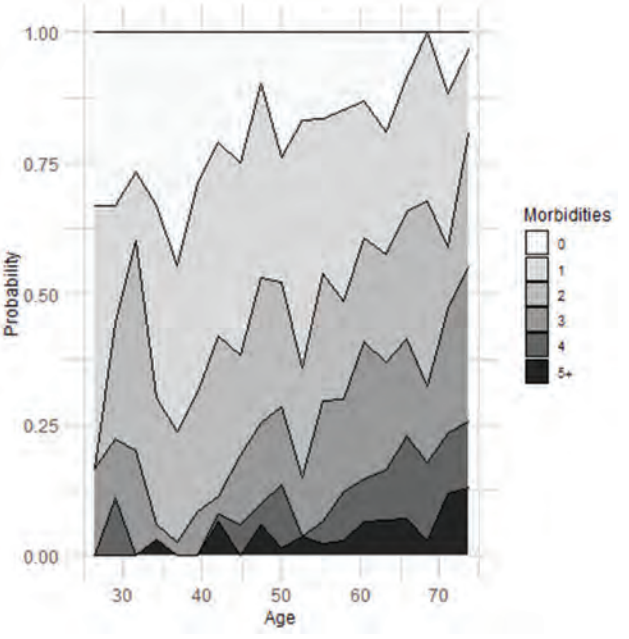
Background: After donation, living donors may develop one or more risk factors that increase the likelihood of subsequent cardiac and kidney adverse events.

Methods: We conducted a cross-sectional, population-based cohort study using linked healthcare databases to study 979 living kidney donors who had donated between 1994 and 2019 in Alberta, Canada. The primary outcome was the presence or history of cardiac and kidney comorbidities, as of March 31, 2020. Cardiac comorbidities included hypertension, diabetes, or major cardiovascular events (myocardial infarction, stroke, or transient ischemic attack). Kidney comorbidities included sustained low eGFR (<45 mL/min/1.73 m^2), moderate-severe proteinuria, or kidney stones. Secondary analyses included the presence of other comorbidities, such as cancer, depression, and chronic pain.

Results: The median time since donation was 13 years (IQR 7–19). Of the cardiac comorbidities, hypertension was the most common (31%), followed by diabetes (7%), then major cardiovascular events (5%). Both hypertension and diabetes were present in 5% of donors. For the kidney comorbidities, a history of kidney stones was the most common (12%), while low eGFR (5%) and proteinuria (4%) were uncommon. For the other comorbidities, chronic pain (40%) was most common, followed by depression (36%). Overall, approximately three-quarters of donors had at least 1 comorbidity with the proportion of donors with multimorbidity (≥2 comorbidities) rising with increasing age.

Conclusions: Comorbidity and multimorbidity in the living kidney donor population rises with increasing age. The results of this study may inform long-term follow-up care of donors by identifying those who may benefit most from periodic health reviews.



TH-PO891

Sex Disparity and Kidney Function in Living Kidney Donors

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Background: While a sex disparity in chronic kidney disease exists, it remains unclear if there is a disproportionate difference in kidney function following kidney donation.

Methods: A retrospective cohort study using OPTN/SRTR includes adult living kidney donors (LKD) undergoing donation between June 1972 and September 2022. The time-to-event of >35% rise in post-donation serum creatinine (SCr) from pre-donation SCr between female and male LKD was investigated by multiple Cox proportional hazard regression.

Results: In a cohort of 136,814 living kidney donors, mean±SD age was 42±12 years and 61% were female. Out of 103,938 LKD with post-donation SCr data at 6, 12, or 24 months, 75,343 (72%) experienced the event within a median time to follow-up of 6.3 months (IQR 4.1, 8.7). The incidence rate of the event was 0.09 person-months. The mean and median pre-donation SCr was 0.85±0.19 and 0.80 mg/dL, respectively with notably female and male mean pre-donation SCr were 0.77±0.14 and 0.99±0.17 mg/dL, respectively (mean difference of 22%; (95%CI 0.22, 0.22; P <0.001). Compared to female LKD, male LKD had a 12% significantly higher risk of experiencing an increased post-donation SCr >35% (HR 1.12; 95%CI 1.10, 1.13; P <0.001). After adjusting for age, race/ethnicity, U.S. citizenship, education level, history of pre-donation hypertension, pre-donation BMI, SBP, DBP, post-donation proteinuria, and the interaction term between sex and pre-donation SCr (≤0.8 or >0.8), male LKD remained at a significantly higher risk for the event (HR 1.42; 95%CI 1.36, 1.47; P <0.001). Furthermore, pre-donation SCr was identified as an effect modifier with an increased risk of rising SCr >35% observed in male LKD with pre-donation SCr >0.8 mg/dL ($P_{interaction}$ <0.001).

Conclusions: Male LKD with pre-donation SCr >0.8 mg/dL are at a higher risk of experiencing an increased post-donation SCr >35% compared to female LKD regardless of other pre- and post-donation factors. Despite women contributing as LKD more than men, addressing the underlying causes of sex disparity may provide the opportunity to increase donations while taking precaution for high-risk population.

TH-PO892

Changes in Sex Lives Pre- and Post-Kidney Transplantation

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Background: Sexual dysfunction among patients with kidney disease (KD) is common. Although studies have demonstrated improvements in sexual function after kidney transplantation (KT), the impact of KD on patients' sex lives pre- and post-KT is unknown.

Methods: We leveraged a prospective cohort of 497 adult KT recipients who responded to the Kidney Disease Quality of Life questionnaire from 2014 to 2022 at Johns Hopkins. Adjusted logistic regression models were used to estimate characteristics associated with self-reported sexual bother due to KD pre-KT, and sexual bother pre- and 3 years post-KT was compared using a Chi-squared test. We estimated unadjusted trajectories of the prevalence of sexual bother due to KD pre- and post-KT using mixed-effect logistic models. We also assessed the prevalence of sexual activity pre- and 3 years post-KT.

Results: The mean age was 52.2 ± 13.5 years, 37.0% were female, 43.1% were Black, 59.6% were partnered, and 41.6% were prior or current smokers. Overall, 43.5% (26.6% of females and 53.4% of males) had sexual bother due to KD pre-KT versus 22.8% (14.8% of females and 26.9% of males) 3 years post-KT (p=0.001). Pre-KT, participants who were male (adjusted odds ratio [aOR]=3.08 [95%CI:2.02-4.69]), non-Black (aOR=1.65 [95% CI:1.09-2.51]), partnered (aOR=1.93 [95% CI:1.27-2.93]), or prior or current smokers (aOR=1.65 [95% CI: 1.10-2.47]) had significantly more sexual bother. Estimated sexual bother due to KD improved significantly over time across all subgroups (Table 1). Overall self-reported sexual activity within the past month also increased significantly from 39.9% pre-KT to 44.0% 3 years post-KT (p=0.009). Both male and female participants had similar increases in sexual activity from pre- to 3 years post-KT (males: 39.6% to 44.0%, p=0.045; females: 40.3% to 44.0%, p=0.178), though the increase was only statistically significant among male participants.

Conclusions: Sexual bother due to KD is common and improves significantly after KT for patients across varying subgroups. The impact of KD on patients' sex lives can be mitigated by KT.

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Table 1: Estimates of sexual bother due to kidney disease pre-kidney transplantation (KT) and at various time points post-KT. Estimates of percent who report sexual bother and annual change in percent who report sexual bother were obtained using mixed-effect logistic models. Percentages are transformed from log odds.

	Estimated percent who report sexual bother due to kidney disease (95% CI)					Estimated annual change in percent who report sexual bother due to kidney disease (95% CI)	
	Pre-KT	6 months post-KT	1 year post-KT	2 years post-KT	3 years post-KT	Per year post-KT	p-value
Overall (%)	26.95 (9.28, 57.10)	18.32 (5.75, 44.98)	11.99 (3.44, 34.29)	4.79 (1.07, 19.00)	1.83 (0.30, 10.37)	0.37 (0.24, 0.58)	<0.001
Age (%)							
>60 year	26.89 (9.23, 57.09)	18.35 (5.80, 45.08)	12.08 (3.40, 34.91)	4.88 (0.99, 20.79)	1.88 (0.25, 12.63)	0.37 (0.22, 0.65)	<0.001
≤60 year	24.62 (8.15, 54.62)	16.59 (5.04, 42.41)	10.68 (2.93, 32.17)	4.19 (0.85, 18.20)	1.58 (0.22, 10.44)	0.37 (0.22, 0.62)	<0.001
Odds Ratio	0.89 (0.54,1.47)	0.88 (0.54, 1.44)	0.87 (0.46, 1.63)	0.85 (0.28, 2.56)	0.84 (0.16, 4.36)	0.98 (0.55, 1.75)	0.947
Sex (%)							
Male	26.64 (9.21, 56.51)	18.68 (5.98, 45.34)	12.69 (3.69, 35.53)	5.50 (1.34, 21.20)	2.28 (0.37, 12.63)	0.40 (0.25, 0.61)	<0.001
Female	9.45 (2.59, 29.06)	5.10 (1.38, 17.66)	2.69 (0.61, 11.01)	0.73 (0.11, 4.82)	0.19 (0.02, 2.36)	0.27 (0.13, 0.56)	0.001
Odds Ratio	0.29 (0.17, 0.48)	0.23 (0.14, 0.39)	0.19 (0.09, 0.39)	0.13 (0.03, 0.47)	0.08 (0.01, 0.59)	0.66 (0.33, 1.31)	0.236
Race (%)							
Non-Black	27.99 (9.66, 58.31)	17.66 (5.32, 44.05)	10.62 (2.95, 31.67)	3.52 (0.70, 15.82)	1.11 (0.15, 7.79)	0.31 (0.16, 0.59)	<0.001
Black	25.13 (8.55, 54.64)	18.65 (6.03, 45.67)	13.85 (4.02, 38.15)	7.14 (1.55, 27.31)	3.55 (0.53, 20.36)	0.48 (0.29, 0.80)	0.005
Odds Ratio	0.87 (0.54, 1.41)	1.08 (0.67, 1.76)	1.35 (0.72, 2.55)	2.11 (0.70, 6.34)	3.28 (0.84, 16.84)	1.56 (0.88, 2.75)	0.127
Marital Status (%)							
Partnered	27.75 (9.62, 58.08)	18.27 (5.78, 44.91)	11.51 (3.28, 33.33)	4.22 (0.92, 17.27)	1.47 (0.23, 8.77)	0.34 (0.21, 0.54)	<0.001
Non-partnered	15.40 (4.83, 40.56)	11.28 (3.25, 32.52)	8.16 (2.14, 26.47)	4.15 (0.81, 18.70)	2.07 (0.27, 14.19)	0.49 (0.28, 0.85)	0.011
Odds Ratio	0.47 (0.29, 0.77)	0.57 (0.36, 0.90)	0.68 (0.38, 1.21)	0.98 (0.37, 2.63)	1.41 (0.33, 6.10)	1.44 (0.86, 2.42)	0.168
Smoking Status (%)							
Prior/Current	26.31 (8.98, 56.39)	18.48 (5.85, 45.29)	12.39 (3.60, 35.72)	5.44 (1.18, 21.98)	2.28 (0.34, 14.71)	0.40 (0.24, 0.67)	<0.001
Never	14.19 (4.25, 38.65)	8.54 (2.37, 26.77)	4.95 (1.22, 17.99)	1.66 (0.27, 8.86)	0.50 (0.05, 4.69)	0.31 (0.16, 0.59)	<0.001
Odds Ratio	0.47 (0.30, 0.75)	0.43 (0.26, 0.65)	0.36 (0.19, 0.68)	0.28 (0.08, 0.92)	0.22 (0.04, 1.33)	0.77 (0.41, 1.44)	0.427

Candidates were enrolled at admission for KT. The percentages were estimated for a reference "standard population": Age >60 years, non-Black, male, partnered, prior or current smoker, less than high school education, Charlson Comorbidity Index>1.0 (pre-KT median), and time on dialysis>2.2 years (pre-KT median)

TH-PO893

Care Considerations and Management of Transgender Individuals After Kidney Transplantation: A Single Institution Experience and Literature Review

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Introduction: It is estimated that there are 0.04% to 0.06% transgender people in the United States. More than 4000 of them are affected by End Stage Kidney Disease (ESKD). There are limited studies on transgender patients undergoing kidney transplantation, and there is little awareness about the challenges faced by them. We describe 2 cases at our center highlighting this and review available literature.

Case Description: Case #1: 48-year-old Trans-female, with past medical history of ESKD secondary to IgA nephropathy and major depressive disorder(MDD), underwent Deceased Donor Kidney Transplant (DDKT) in 2018. Course was notable for recurrent Herpes labialis. Patient reported onset of gender dysphoria 6 months post-transplant. Patient sought gender-affirming care and started transdermal estradiol, finasteride and cosmetic hair removal. Counseling, screening for sexually transmitted infections, and age-appropriate cancer screening were done at each visit. MDD and medication adherence improved significantly. Renal function has remained stable. **Case #2:** 57-year-old Trans-male with ESKD secondary to polycystic kidney disease, underwent DDKT in 2016. Patient reported onset of gender dysphoria in early childhood and took depot medroxyprogesterone since puberty to suppress menstruation. 3 years post-transplant, patient sought gender-affirming care, started testosterone injections, and had bilateral mastectomy. Post this, patient developed polycyathemia, and most recently was diagnosed with osteoporosis. Renal function has remained stable and medication adherence has been good.

Discussion: Transitioning through gender-affirming care can be stressful for a Transgender person. In the early peri-transplant phase, estrogen may lead to venous thromboembolic events and allograft loss. When used with calcineurin inhibitors (CNI) or Bactrim, androgen-lowering agents like spironolactone can increase hyperkalemia risk. Erythropoiesis is stimulated by androgenic therapy and may increase polycythemia risk. Gender-affirming surgeries can cause urological complications. Regular screening for osteoporosis and sexually transmitted infections, as well as psychotherapeutic support, is necessary. As hormone therapy can affect muscle mass and body composition, it is recommended to use a non-sex-dependent estimation of GFR using cystatin C.

TH-PO894

Kidney Allograft Outcomes Are Similar in Recipients with Living Donors with Hematuria Compared with Recipients with Living Donors Without Hematuria

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Background: The impact of hematuria in living kidney donors on future donor outcomes has been previously described; but to the best of our knowledge, no previous studies have examined the impact of such hematuria on recipient outcomes. In this study, we study the allograft outcomes in recipients who received an allograft from living donors with persistent microscopic hematuria.

Methods: All adult kidney transplant recipients at our program between 1/1/2000-6/30/2022 who received allograft from living donor with urine microscopy showing >5 RBC's/HPF[DM1] in their pre-donor evaluation were included in this study. This cohort was compared to recipients with living donors without hematuria during the same time period. Primary outcomes were allograft failure (defined as re-transplant or return to dialysis) and death censored allograft failure.

Results: 112 recipients that received their allograft from a living donor with microscopic hematuria were identified and compared to 1967 recipients that received their allograft from a living donor without microscopic hematuria. Mean recipient age was 51.7 (±14.1) years compared to 50.3 (±13.9) years of donors with hematuria and without hematuria respectively. 40% of recipients were females and 9% were non-white in both groups. Mean age of donors with hematuria and without hematuria was 43.8 (±11.3) years and 44.9 (±11.6) years respectively. There were a total of 773 allograft losses which includes death and 411 death censored graft losses among 2079 kidney transplant recipients. The risk of graft loss (HR 1.06 95% C.I. 0.79, 1.44; p-value 0.67) and death censored graft loss (HR 0.91 95% C.I. 0.59, 1.41; p-value 0.67) was similar in recipients with living donors with hematuria compared to recipients with living donors without hematuria. The risk of graft loss was similar even after adjustment for donor age, donor race, donor sex, recipient age, recipient race, recipient sex and HLA mismatch between the two groups.

Conclusions: The risk of graft failure and death censored graft failure was similar among recipients who received their graft from living donors with hematuria compared to living donors without hematuria.

TH-PO895

Impact of Suspensions and Reactivations from Waitlist on Quality of Life in Canadian-Australasian Randomised Trial of Screening Kidney Transplant Candidates for Coronary Artery Disease (CARSK)

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Background: There is limited information on individuals' health-related quality of life (HRQoL) on the waiting list for a kidney transplant. Understanding the HRQoL among patients undergoing suspensions and reactivations could shed light on their experiences and the impact of illness burden.

Methods: The HRQoL among eligible participants (not transplanted or deceased within 12 months) was assessed using the EuroQoL 5 domains, five levels (EQ-5D-5L) questionnaire administered at baseline, 6 and 12-months. The HRQoL index ranged from 0 (dead) to 1 (full health). Within these 6-month intervals, the effect of waitlist suspensions and reactivations on HRQoL was examined using Generalized Estimating Equations models. Factors associated with HRQoL such as age, sex, ethnicity, dialysis modality, time on dialysis, diabetes status, cause of end-stage kidney disease, prior kidney transplant, baseline EQ-5D score, and waitlist status (never suspended, suspended but not reactivated, suspended and reactivated) were investigated.

Results: 1,457 patients from Australia (32%), New Zealand (17%), and Canada (51%) were recruited. From baseline to 12 months, 1,013 patients were suspended, 170 patients were suspended and not reactivated, and 187 were suspended and reactivated. Average age was 54 years (SD 12), 63% males, 35% diabetics. Of these, 671 (46%) were managed with facility-based hemodialysis, 247 (17%) with home hemodialysis, and 539 (37%) with peritoneal dialysis. On average, patients spent 1,039 days on dialysis. The mean EQ5D index at baseline, 6 months, and 12 months was 0.87 (SD 0.14), 0.89 (SD 0.13), and 0.89 (SD 0.14), respectively. Compared with patients not suspended, those who were suspended and not reactivated had a lower mean EQ5D index (0.042, 95% CI 0.014 to 0.070, p = 0.004).

Conclusions: Our findings indicate that patients' suspension from the waitlist due to health factors making them unfit for a deceased donor kidney transplant significantly impacts their self-reported HRQoL.

Adjusted Mean EQ5D index

Visits	Never suspended	Suspended and not reactivated	Suspended and reactivated
6 months	0.891 (95% CI 0.842 - 0.940)	0.849 (95% CI 0.798 - 0.900)	0.878 (95% CI 0.829 - 0.928)
12 months	0.887 (95% CI 0.838 - 0.935)	0.845 (95% CI 0.794 - 0.895)	0.874 (95% CI 0.825 - 0.923)

TH-PO896

Patient and Provider Discordant Perspectives on Patient Transplant Experiences

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Background: While transplant is the optimal treatment for end stage kidney disease (ESKD), there is a kidney shortage. In 2022, over 4000 people died waiting for a transplant. Both patients and providers have unique vantage points of patient transplant challenges. To gain insight from both perspectives, the American Kidney Fund (AKF) conducted qualitative research with each group.

Methods: AKF hosted 2, 90-minute focus groups (FG) of 6 transplant patients/donors and 6, 60-minute in-depth interviews (IDI) with 4 renal specialists and 2 patients unable to attend FG. Sixteen IDI and 10 FG open-ended questions were asked to reveal participants' unique perspectives on challenges accessing transplant, process awareness, helpful resources, and transplant information-sharing methods. IDI and FG were recorded, transcribed, and analyzed using a deductive approach via concept-driven coding in NVivo. Themes were indicated by frequency of mentions (FM).

Results: AKF identified 7 themes: challenges, empowerment, resources, post-transplant experiences, pre-transplant experiences, living donor, and educational material mechanics. Distinctions in patient and provider conversations were on patient challenges, living donor and post-transplant experiences. Provider discussions on patient challenges focused on "maintaining health" or difficulties maintaining waitlist eligibility, attending appointments, and taking medications (FM=24) while patient challenge discussions were on finding a donor (FM=11). For useful patient resources, providers (FM=8) and patients (FM=18) discussed "doctors, clinical team," yet patients also valued "mentors, peers" (FM=15) and "support groups" (FM=10). Conversations on post-transplant patient experiences were limited, but providers emphasized the patients' need to "maintain health" (FM=4) and prepare for post-transplant life (FM=4), while patients mentioned "recovery process" (FM=1).

Conclusions: Qualitative results reveal discordant focuses between patient and provider on patient transplant challenges, donor experiences, and post-transplant life. Given the limited sample, future research is needed to further understand what causes the differences in perspectives. This research would bring insight into patient barriers and ways to augment patient and provider education materials to bring a unified approach to transplant.

TH-PO897

Higher Dialysis Facility Patient-to-Nurse Staffing Ratio Is Associated with Lower Hazard of Kidney Transplantation Among Adolescents and Young Adults

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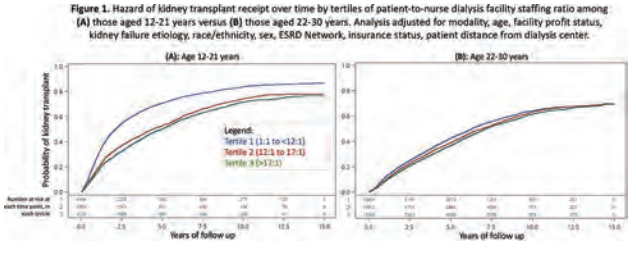
Background: Higher patient-to-nurse ratios at dialysis facilities have been associated with worse patient outcomes in older adults. We aimed to examine if this nurse staffing ratio is associated with access to kidney transplant in children and young adults.

Methods: This is a retrospective analysis of the US Renal Data System, of patients 12-30 years who initiated dialysis from 2005-2019 at US dialysis facilities. Cox models were used to relate the primary exposure (patient-to-nurse ratio at the dialysis facility) to receipt of kidney transplant (either living or deceased donor).

Results: 51,419 individuals were included (74% were ≥22 years, 84% initiated with hemodialysis). Median staffing ratio was 14 patients per 1 nurse (IQR 10:1 to 19:1). Over a median follow-up time of 2.4 years, 53% of those <22 years vs. 34% of those ≥22 years received a kidney transplant. In adjusted analysis, each doubling of the patient-to-nurse ratio at a facility resulted in 15% lower hazard of transplantation (HR 0.85; 95% CI: 0.84-0.87). There was an interaction ($p<0.001$) by age at dialysis initiation, such that the association between higher patient:nurse ratio and access to transplantation was more pronounced in those 12-21 years (HR 0.79, 95% CI: 0.77-0.82) vs. 22-30 years (HR 0.96, 95% CI: 0.94-0.99).

Conclusions: Adolescents and young adults receiving care from facilities with higher patient-to-nurse ratio had lower hazard of transplantation compared to those receiving care facilities with lower staffing ratios. Low dialysis nurse staffing ratios may represent a crucial facility characteristic that promotes successful kidney transplantation, particularly for adolescents.

Funding: NIDDK Support



TH-PO898

Understanding Barriers and Strategies to Increase Pancreas Transplantation: A Delphi Survey of US Transplant Professionals

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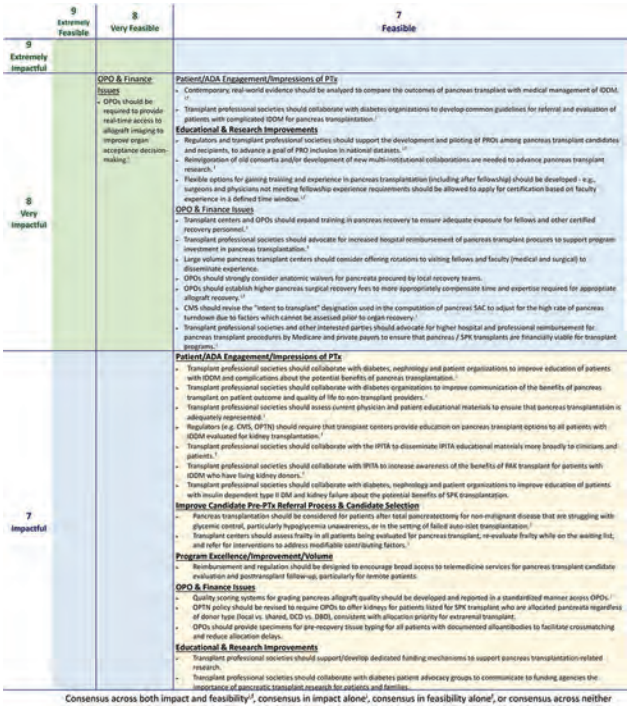
Background: To better understand barriers to expanding U.S. pancreas transplantation (PTx) practice, and the anticipated impact and feasibility of potential strategies to address, we conducted a modified Delphi survey of professional and patient stakeholders.

Methods: An electronic survey was distributed to 53 stakeholders, including surgeons, nephrologists, endocrinologists, OPO professionals, and patients, who participated in a national workshop in Boston, MA (distrubution: 6/25/22-8/14/22) Participants ranked the importance of 16 barriers to PTx, and the anticipated feasibility and impact of associated strategies, using 9-point Likert scales. Consensus was defined *a priori* as when ≤30% responded outside an item's Interquartile Range (IQR).

Results: Of 16 analyzed barriers, 8 met consensus as 'very important', incl.: candidate medical and psychosocial complexity, inadequacy of available tools to assess and transmit quality information, allocation delays, financial barriers, inadequate provider and patient education, and insufficient number of trained surgeons. While no strategy met consensus as 'very feasible', 15 strategies met consensus as 'very impactful' (**Table: Highest Impact X Feasibility subset**). 1 strategy was ranked as both 'very important' and 'very feasible': OPOs should provide real-time access to allograft imaging to improve acceptance decisions.

Conclusions: While stakeholders generally agree on barriers to PTx utilization, a diversity of strategies may be impactful and feasible, including focus on improving organ assessment, logistics of the organ recovery operation and allocation, and mitigation of financial disincentives for organ utilization.

Funding: Private Foundation Support



TH-PO899

Pre-Transplant Biomarkers of Cellular Senescence Are Associated with Death with Function After Kidney Transplantation

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Background: Cellular senescence has associated with aging and medical risk in non-transplant populations. The goal of this study was to examine the relationship between pre-transplant biomarkers of cellular senescence and death with function after kidney transplantation.

Methods: We conducted a prospective, observational cohort study involving consecutive adult patients who received a kidney transplant at Mayo Clinic in Minnesota between 1/2006 and 12/2018. We measured biomarkers of cellular senescence in pre-transplant serum. Cox analyses, Kaplan Meier survival analyses, and gradient boosting machine modeling were used to examine the relationship between biomarkers and death with function after kidney transplantation.

Results: Our cohort consisted of 1,595 kidney transplant recipients, of whom 62.9% were male and 83.2% were non-Hispanic white. Over a mean follow-up time of 7.4 ± 3.9 years, 19.7% of patients (n=315) experienced death with function. Higher levels of growth differentiation factor-15 (GDF-15), interleukin-6 (IL-6), monokine induced by gamma interferon (MIG), and soluble tumor necrosis factor receptor-1 (sTNF-R1) were associated with death with function. Adding these biomarkers to a clinical Cox model improved the C-statistic for death with function from 0.732 to 0.750, while using a gradient boosting machine modeling approach instead improved the C-statistic to 0.768.

Conclusions: Pre-transplant biomarkers of cellular senescence predict death with function after kidney transplantation. Measuring serum concentrations of GDF-15, IL-6, MIG, and sTNF-R1 may help risk stratify kidney transplant candidates.

Funding: NIDDK Support

TH-PO900

Graft Outcomes in Spousal Donor Kidney Transplantation: Impact of Donor-Recipient Sex Mismatch

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Background: Despite increasing demand for kidney transplantation (KT) due to the rising prevalence of end-stage kidney disease (ESKD), the shortage of kidney donors remains critical. Spousal donors have emerged as an essential source for living donor kidney transplantation (LDKT) in modern nuclear families. Given that patients' sex is a biological characteristic, the mismatch between the donor and recipient's sex can potentially affect the survival and function of the transplanted kidney. Moreover, female recipients are exposed to donor HLA antigens during pregnancy, increasing the immunological risk. We aim to investigate the impact of donor-recipient sex mismatch on the outcomes of spousal donor kidney transplantation.

Methods: We analyzed 456 spousal donor kidney transplantation (SDKT) recipients at Seoul St. Mary's Hospital from 1986 to 2022. Recipients were categorized based on immunological risk determined by Panel Reactive Antibody. Among the 367 standard-risk SDKT recipients, 75 were husband-to-wife (H2W) and 292 were wife-to-husband (W2H). In the high-risk group of 89 SDKT recipients, 55 were H2W and 34 were W2H. We assessed graft survival and allograft rejection based on donor-recipient sex mismatch.

Results: Long-term graft survival and the incidence of biopsy-proven acute rejection (BPAR) with 1 year after KT were comparable between H2W and W2H recipients in standard-risk group (10-year survival rate: 90.7% vs. 87.6%, p value = 0.428; incidence of BPAR: 3% vs. 7%, p value = 0.178). In the high-risk group, long-term graft survival was similar between H2W and W2H recipients (83.6% vs. 91.2%, p-value=0.593), while H2W recipients showed a higher incidence of BPAR within 1 year after KT compared to W2H recipients (3% vs. 17% p value = 0.044), mainly due to acute antibody-mediated rejection (AAMR).

Conclusions: Our findings indicate that donor-recipient sex mismatch does not have a significant impact on graft survival. However, among high-risk SDKT recipients, H2W SDKT recipients exhibited a higher risk of AAMR compared to W2H SDKT recipients, who face similar immunological risks. H2W SDKT recipients with a high immunological risk should receive careful management through personalized desensitization protocols and tailored immunosuppressant strategies to reduce the incidence of AAMR following KT.

TH-PO901

Risk of Symptomatic Kidney Stones After Kidney Donor Evaluation in Stone Formers

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Background: There are limited data on outcomes of kidney donor candidates with nephrolithiasis. We sought to identify risk factors for symptomatic kidney stone events after donor evaluation.

Methods: A survey was sent in 2022 to 446 adults with self-reported history or CT imaging evidence of nephrolithiasis at the time of kidney donor evaluation at Mayo Clinic (3 sites) between 2000 and 2016. The survey queried post-evaluation symptomatic (renal colic or gross hematuria) kidney stone events, complications, and management. Analyses assessed differences in stone burden between approved and denied donors and risk factors associated with symptomatic stone events.

Results: Survey was completed by 161 (36%) of 446 kidney donor candidates with kidney stones, of whom 113 were approved and 48 were denied for donation. 26 (16%) experienced a symptomatic stone event after donor evaluation and this occurred more frequently in denied vs approved donors (27% vs 12%, p=0.019), in the first 4 years after evaluation (19% vs 1%, p<0.001). Factors associated with denial for donation included presence of medullary sponge kidney, ≥2 stones on CT imaging, presence of bilateral kidney stones, and diameter of largest stone ≥3mm. [Table 1] There was no difference in medical management, surgical/procedural management, or reported development of chronic kidney disease between the two groups. Risk factors for symptomatic stone events after evaluation include bilateral kidney stones (p<0.001), kidney stone diameter≥3mm (p=0.019), younger age (p=0.008), and ≥2 stones on CT imaging (p=0.003).

Conclusions: Our findings identified kidney stone characteristics associated with denial for donation and risk for symptomatic stone event after donor evaluation that may better inform donor candidates of the risk for symptomatic stone events. The lack of significant differences in management and complications between approved and rejected donor candidates questions current approaches to denial based on stone risk.

Table 1. Baseline characteristics of donor candidates comparing those who were approved vs denied donation.

	Approved (N=113)	Denied (N=48)	P-value
Medullary sponge kidney	7%	19%	0.046
≥2 stones on CT imaging	27%	52%	0.004
Bilateral kidney stones	11%	40%	<0.001
Mean diameter of largest stone on CT ≥3mm	25%	42%	0.039
Symptomatic stone event before evaluation	20%	15%	0.787
Symptomatic stone event after evaluation	12%	27%	0.019

TH-PO902

Risk of Developing CKD Following Live Kidney Donation: A Prospective Observational Study

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Background: Chronic Kidney Disease (CKD) is a major concern among live kidney donors. Understanding the risk factors to development of CKD is crucial for optimizing donor selection and post-donation management. This study is aimed to identify the incidence and risk factors associated with development of CKD after one year kidney donation.

Methods: This prospective observational study was conducted using 57 live kidney donors at the National Hospital, Kandy, Sri Lanka. Pre-operative demographic, clinical and pre-implantation kidney biopsy (bx) findings of live donors were examined. We evaluated the estimated glomerular filtration rate (eGFR) using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Donors who had eGFR of less than 60 mL/min per 1.73 m2 at one-year post kidney donation considered as development of CKD among kidney donors.

Results: The mean age of the participants was 47.8 years, with males representing 50.9% (n=29) of the study cohort. 19.3% (n=11) of the donors developed CKD at the end of one year post donation. According to Kaplan-Meir analysis, there is a significant decrease in survival of donors with smoking (p=0.001), alcohol consumption (p=0.016), past medical history of hypertension (p=0.002), presence of donor/recipient relationship, (p=0.018), more than 50 years of age (p=0.005), presence of tubular atrophy (TA) (p=0.001), interstitial fibrosis (p=0.006), interstitial inflammation (p=0.007 and high activity index (p=0.04) in pre-implantation bx. Logistic regression analysis showed that, presence of TA (p=0.007) in histology and having a related donor (p=0.009) had 2.4 and 2.5 times higher risk of developing CKD at final follow-up respectively.

Conclusions: Incidence of development of CKD was high among live kidney donors in a cohort of Sri Lanka with highest risk of being presence with TA in pre-implantation bx and presence of being related kidney donor. These findings emphasize the requirement of a better biomarker to predict the risk of complications as the kidney biopsy is not applicable to do in routine practice. Indeed, the implementation of targeted interventions and follow-up protocols can potentially mitigate the risk of CKD progression among live kidney donors.

TH-PO903

Impact of Donor Warm Ischemia Time on Graft Survival for Donation After Circulatory Death Kidney Transplantation

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Background: To meet demands for kidney transplantation (KT), expanded donor criteria has increased utilization of donation after circulatory death (DCD) donors. Due to ischemic injury associated with DCD organ procurement, the impact of donor warm ischemia time (DWIT) on long-term graft survival has been a notable topic of interest; yet our understanding of this impact on KT outcomes remains limited. Herein, we seek to investigate the impact of DWIT on rates of graft failure after DCD KT.

Methods: Retrospective analysis was conducted on donors and recipients of DCD KT utilizing the Standard Transplant Analysis and Research (STAR) dataset. Demographic data were analyzed and probability of one-year graft failure was assessed based on increasing DWIT using mixed effects logistic regression, stratifying by Kidney Donor Profile Index (KDPI).

Results: From January 2010 to August 2020, 17,169 donors and 22,096 recipients of DCD KT were studied. KPDI decreased from 47% for patients with DWIT 0-45 minutes to 36.5% for DWIT >90 minutes (Table 1). When stratified by KDPI, the impact of increasing DWIT >90 minutes for low KDPI (<50%) recipients was minimal. High KDPI (>50%) recipients demonstrated higher probability of one-year graft failure with increasing DWIT up to 30 minutes compared with low KDPI recipients, but this effect plateaued (Figure 1). No increased probability of graft failure in DWIT >60 minutes was apparent, though confidence intervals widened.

Conclusions: For low KDPI (<50%) kidneys, impact of prolonged DWIT (>60 minutes) on graft survival is minimal, likely reflecting the resilience of higher quality renal allografts to ischemic insult over time. Caution should be taken in considering KT of high KDPI (>50%) kidneys with prolonged DWIT given overall lack of confidence in the existing dataset.

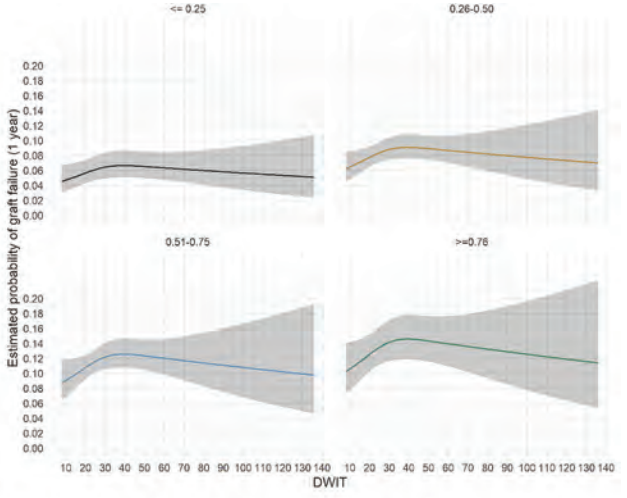

Figure 1. Death-censored probability of graft failure at one year following kidney transplantation with respect to increasing dWIT, stratified by very low (<=0.25), low (0.26-0.50), high (0.51-0.75) and very high (>=0.76) KDPI values

TH-PO904

Association of Pre-Donation Kidney Length with Estimated Glomerular Filtration Rate in Living Kidney Donors

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Background: The compensatory mechanism increases estimated glomerular filtration rate (eGFR) after unilateral native nephrectomy. Predicting post-living kidney donation eGFR may depend on pre-donation factors, including kidney length. We aimed to examine the association between kidney length and post-donation eGFR.

Methods: A single-center cross-sectional study included adult living kidney donors (LKD) between February 2015 and January 2023. The association between the pre-donation kidney length (by CT scan)/height ratio (LHR) of the remaining kidney and post-donation eGFR was examined by multiple linear regression analyses.

Results: Of 136 LKD, the mean±SD age was 47±12 years and 59% were female. The median (IQR) of LHR was 6.34 (6.07, 6.71) cm/m. Mean pre-donation creatinine clearance (CrCl) were 130.9±32.8 ml/min, followed-up (F/U) eGFR at 1 wk, 6-, 12-, and 24-mos post-donation were 67.8±15.1, 70.7±16.2, 71.3±15.4, and 73.6±16.3 ml/min/1.73 m^2, respectively. The eGFR increased from quartile 1 to 4 of LHR for all F/U periods (P_{trend} <0.001, 0.004, 0.004, and 0.003; Figure 1A). Each 0.1 cm/m increase in LHR was associated with 0.9 – 1.2 ml/min/1.73 m^2 greater eGFR of all post-donation F/U periods with the lowest and highest eGFR at 12 and 24 mos, respectively(β (95%CI) $_{1wk}$ 11.8 (6.1, 17.5); β_{6mo} 11.3 (4.7, 17.9); β_{12mo} 9.3 (3.2, 15.5); β_{24mo} 12.0 (4.8, 19.2); Figure 1B-1D). After adjusting for age, sex, race, pre-donation BMI, CrCl, urinary microalbumin:urinary creatinine ratio, systolic and diastolic blood pressures, the magnitude and direction of the LHR – eGFR association remains (β_{1wk} 11.2 (5.8, 16.7); β_{6mo} 12.1 (6.5, 17.8); β_{12mo} 10.5 (4.6, 16.3); β_{24mo} 15.1 (7.7, 22.5)). There was no effect modification observed in all major covariates for the LHR – eGFR association.

Conclusions: Pre-donation LHR is positively associated with post-donation eGFR during 24 mos F/U, suggesting its relevance in selecting potential LKD with low eGFR.

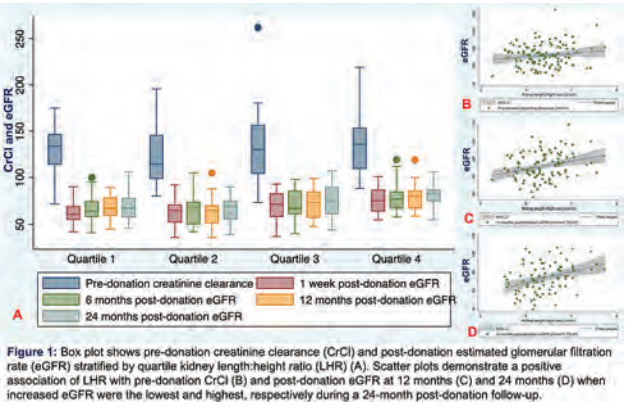

Figure 1: Box plot shows pre-donation creatinine clearance (CrCl) and post-donation estimated glomerular filtration rate (eGFR) stratified by quartile kidney length:height ratio (LHR) (A). Scatter plots demonstrate a positive association of LHR with pre-donation CrCl (B) and post-donation eGFR at 12 months (C) and 24 months (D) when increased eGFR were the lowest and highest, respectively during a 24-month post-donation follow-up.

TH-PO905

Males Show Greater eGFR Recovery than Females Following Kidney Donation

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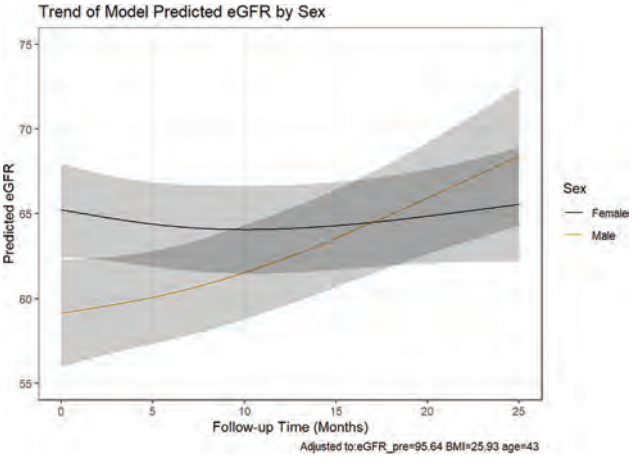
Background: Living donor kidney transplantation is the optimal treatment for end-stage kidney disease and requires donor risk assessment. More data is needed to understand kidney function recovery after donation. We aimed to assess the impact of BMI, age, and sex on post-donation estimated glomerular filtration rate (eGFR) in kidney donors over 2 years.

Methods: We analyzed data from 178 kidney donors who underwent living donor nephrectomy at a single medical center between Nov. 2017 and Jan. 2022. Follow-up visits occurred at approximate 1-month, 6-month, 12-month, and 24-month intervals. eGFR was calculated using the CKD-EPI equation (2021) at each timepoint. We utilized Friedman's test to identify variations in eGFR over the follow-up periods. Relationships between post-donation eGFR and BMI, age, and sex were explored using a generalized least squares model with AR1 error structure. The resulting relationships were plotted using model-estimated eGFR values.

Results: The study included 57 male and 121 female kidney donors. Median pre-donation eGFR was similar for males and females (98.85 vs 94.59, p=0.184). Pre-donation eGFR, BMI, and age did not significantly affect eGFR trajectories (p=0.89, p=0.37, and p=0.17, respectively). However, sex appears to significantly affect eGFR trajectories. As seen in Figure 1, despite the initially lower eGFR (59.13 vs. 65.21, p<0.001), males showed a significantly greater eGFR recovery than females through 24-month follow-up (p=0.003).

Conclusions: Our study suggests that male kidney donors recover kidney function to a greater degree than females after donation. These findings may have implications for donor evaluation, pre-operative patient counseling, and sex-specific monitoring. Further studies are needed to investigate underlying mechanisms and potential interventions to enhance eGFR recovery in both male and female kidney donors.



TH-PO906

Safety of Low-Dose ACE Inhibition in Living Kidney Donors

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Background: ACE inhibitor (ACEi) medications have positive effects on vascular function separate from their anti-hypertensive effects. We evaluated the safety of low dose ACEi, (Ramipril 1.25mg) in kidney donors and impact on flow mediated dilatation (FMD) at 6 months post donation.

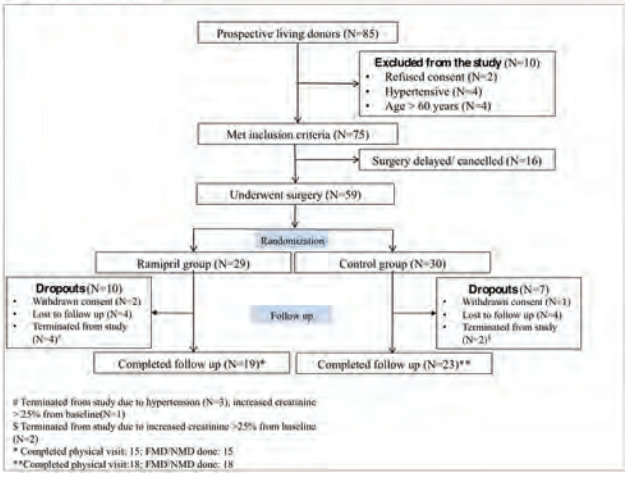
Methods: In an open label, randomized control trial, all prospective living renal donors, 18-60 years, with no hypertension or allergy to ACEi were enrolled. Baseline eGFR and FMD were recorded, and subjects were randomized (1:) at the time of discharge to receive either daily dose of 1.25 mg of Ramipril or no medication. Repeat measurement of FMD and eGFR was done at 6 months after kidney donation. Subjects were withdrawn from the study during follow up if serum creatinine increased by >25% as compared to baseline, or serum potassium rose to >5.5 mEq/L, or systolic blood pressure (SBP) fell to <90 mm Hg or fell by >25% as compared to baseline.

Results: Total 59 subjects were enrolled and randomized. 29 and 30 participants were allocated to the Ramipril and Control arm respectively. At 6 month, 19 subjects in the intervention arm and 23 subjects in the control arm completed follow up (Figure 1). One participant in intervention arm developed side effect (increase in serum creatinine >25% from baseline). In the control arm, 2 subjects had a rise in serum creatinine. Mean difference in eGFR was 25.4±16.3ml/min/1.73m2 in intervention arm while 26.0±17.1ml/min/1.73m2 in the control arm (p=0.909). The mean difference in FMD at 6 months vs baseline in intervention arm was 3.63±10.76% while in control arm was -2.62±10.28% (p=0.098).

Conclusions: Use of ramipril in dose of 1.25 mg once every day in living kidney donors was safe. A trend in improvement in vascular function (increase in FMD) was noted in intervention arm suggesting further study the effect of ACEi on vascular function in post kidney donation with adequate sample size.

Funding: Government Support - Non-U.S.

Figure 1: Patient flow



Patient flow

TH-PO907

Vertebral Fracture Risk Is Increased Among Living Kidney Donors 25 Years After Donation: Survey-Based Study

Hilal Maradit Kremers,[1] Brandon R. Grossardt,[1] Bertram L. Kasiske,[2] Arthur J. Matas,[3] Sundeep Khosla,[1] Walter K. Kremers,[1] Hatem Amer,[1] Rajiv Kumar.[1] *[1]Mayo Clinic Minnesota, Rochester, MN; [2]Hennepin Healthcare System Inc, Minneapolis, MN; [3]Regents of the University of Minnesota, Minneapolis, MN.*

Background: Living kidney donors may have an increased risk of fractures due to reductions in renal mass, lower concentration of 1,25-dihydroxyvitamin D, secondary increases in parathyroid hormone and bone turnover markers. We compared the long-term risk of fractures among living kidney donors with matched controls from the general population.

Methods: Surviving kidney donors from 3 transplant centers completed a survey about bone health and history of fractures. Age, sex, and race-matched non-donor controls without a history of comorbidities that would have precluded kidney donation were identified from population-based resources and completed the survey. The proportion of persons reporting fractures was compared using standardized incidence ratios (SIR).

Results: A total of 1,930 donors and 1,615 controls responded to the survey. Average time between donation/index date and survey date was 24.8 years for donors and 27.3 years for controls. At the time of the survey, donors were 1.1 years younger than the controls (67.4 vs 68.5 years). Although the overall rate of fractures in donors was significantly less than in controls (SIR 0.91; 95% CI 0.82-0.99), there were significantly more vertebral fractures in donors than in controls (SIR 1.43; 95% CI 1.06-1.86) and more hip fractures in women donors compared to controls (SIR 1.90; 95% CI 1.01-3.26).

Conclusions: Our findings suggest excess vertebral fractures in both men and women and excess hip fractures in women among living kidney donors compared to controls after 25 years of follow-up.

Funding: NIDDK Support

Age-, sex-, and time after index-standardized incidence ratios (SIRs) for fracture risk in donors vs. controls

	Overall			Women			Men		
Fracture site	Obs.*	Exp.†	SIR (95% CI)‡	Obs.*	Exp.†	SIR (95% CI)‡	Obs.*	Exp.†	SIR (95% CI)‡
Any fracture reported	420	462.2	0.91 (0.82 to 0.99)	282	295.0	0.96 (0.85 to 1.07)	138	167.2	0.83 (0.69 to 0.98)
Fragility fracture	153	140.3	1.09 (0.92 to 1.28)	105	93.9	1.12 (0.92 to 1.35)	48	46.4	1.03 (0.76 to 1.37)
Hip	21	14.7	1.43 (0.89 to 2.19)	13	6.8	1.90 (1.01 to 3.26)	8	7.9	1.02 (0.44 to 2.01)
Lower arm or wrist	91	99.7	0.91 (0.74 to 1.12)	68	70.9	0.96 (0.75 tp 1.22)	23	28.8	0.80 (0.51 to 1.20)
Spine or back (vertebrae)	50	35.0	1.43 (1.06 to 1.88)	30	21.2	1.41 (0.95 to 2.02)	20	13.8	1.45 (0.89 to 2.24)

*Observed fractures in kidney donors. †Expected # of fractures in kidney donors by applying age-, sex-, and time after index-specific fracture rates observed in controls.

‡Standardized incidence ratio (SIR) for risk of fractures in kidney donors compared to risk in controls. SIR > 1.0 means more fractures in kidney donors than in controls.

TH-PO908

Harnessing Synergies, Healthy Heart, Allograft Optimized: The Positive Impact of Arteriovenous Fistula (AVF) Closure After Kidney Transplant

Zeeshan Azeem, Prince M. Anand. *Medical University of South Carolina, Lancaster, SC.*

Introduction: The AVF remains the preferred vascular access for hemodialysis (HD) and after kidney transplant (KT) for future graft failure but consensus on ligation or preservation of AVF after KT is lacking. While AVF ligation offers established cardiovascular benefits, its impact on allograft function is uncertain with conflicting outcomes (improvement vs deterioration). We present a case of improved allograft function following AVF ligation prompted by symptomatic AVF aneurysm.

Case Description: A 60-year-old male underwent a deceased donor KT for end-stage renal disease secondary to type II diabetes mellitus on 10/03/2022. Prior to a KT patient had a left upper extremity AVF as HD access. Pre-transplant echocardiogram (ECHO) showed an ejection fraction of 60% and mild pulmonary hypertension (RVSP-36mmHg). The postoperative course was complicated by delayed graft function with rapid progressive weight gain despite optimal diuretics with limited salt intake, normal urine output, and elevated creatinine (1. 8-2.4mg/dl- nadir 1.6mg/dl). The immunosuppression regimen was changed from Tacrolimus-based therapy to IV Belatacept without any significant improvement in creatinine. Additionally, worsening swelling at the site of AVF three months post-transplant necessitated a surgical consult. Following AVF ligation due to a symptomatic aneurysm, weight and creatinine improved remarkably accompanied by symptomatic improvement. ECHO and renal allograft resistive indices post-AVF ligation are pending.

Discussion: Our case highlights that risk-benefit assessment of AVF closure after kidney transplantation requires contextual evaluation via a possible scoring system and/or a multi-disciplinary committee to ensure informed decision-making and to optimize primary cardiac and secondary outcomes.

TH-PO909

High Coronary Artery Calcium Score Is Associated with an Increased Risk of Death in Patients Evaluated for Kidney Transplant

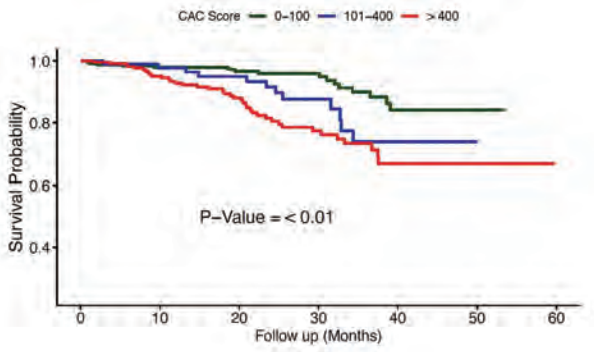
Nagaraju Sarabu, Yasolatha Chalicheemala, Himabindu Yerneni, Arksarapuk Jittirat, Sadeer Al-Kindi, Percy Adonteng-Boateng. *University Hospitals, Cleveland, OH.*

Background: Coronary artery calcification (CAC) is a marker of coronary artery disease which is related to increased risks of cardiovascular complication in kidney transplant recipients. Over the past 5 years, our transplant center has utilized CAC score for cardiac risk stratification in pre-evaluation of kidney transplant. This is a single center, retrospective observational study to evaluate the association between CAC score and death from any cause among kidney transplant (KT) evaluations.

Methods: Retrospective observational study including adults, > 40 years, evaluated for a KT between January 1, 2018, and December 31, 2022. All-cause mortality was ascertained through electronic medical records and the Ohio death index. CAC scores were grouped into low (0-100), medium (100-400), and high (>400). Cox proportional hazard models were used to explore the relationship between CAC score and the mortality.

Results: Of the 570 subjects included, 345 (60%) were male, 272 (48%) were of white race, and 245 (43%) were black. The mean age was 57.8 years. CAC scores were: 247 (43%) low, 91(16%) medium, and 232 (41%) high. The median follow-up for the entire cohort was 22.4 months (IQR 21.4 months). During the study period, 71(12.4%) received kidney transplants, and 67(11.7%) died. Multivariate Cox model showed high CAC score (> 400) was associated with a high hazard of death (HR 3.29, 95% CI: 1.71-6.32).

Conclusions: High CAC score is independently associated with death from any cause in patients evaluated for a kidney transplant. Transplant centers should consider closely monitoring patients with high CAC scores to ensure better performance in the Organ Procurement and Transplant Network metric of waitlist mortality.



Kaplan-Meier Curves of Death from Any Cause by Coronary Artery Calcium (CAC) Score Categories

TH-PO910

Impact of Recipient Hepatitis C Virus (HCV) Sero-Status on the Outcomes Following Kidney Transplantation from HCV Viremic Donors in the Era of Directly Acting Anti-HCV Agent Use

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Background: Kidneys from hepatitis C virus (HCV) infected donors were historically utilized for transplantation into HCV seropositive recipients and in recent years with the availability of highly effective directly acting anti-HCV (DAA) agents into HCV-naive recipients. We aimed to look at the trend in the use of kidneys from HCV infected donors stratified by recipient HCV sero-status and compared transplant outcomes with respect to recipient HCV sero-status.

Methods: OPTN/UNOS files were used to identify all HCV viremic donors for whom each kidney was transplanted into a first-time kidney-only recipient with a known HCV sero-status from 01/2015 to 12/2022. Length of stay (LOS), delayed graft function (DGF), time to death and graft failure were assessed. Marginal models with robust sandwich estimators were used to account for clustering by donor, allowing odds ratio (OR) for DGF and hazard ratios (HR) for graft failure, death-censored graft failure and death to be calculated within a mate-kidney frame work. Models were adjusted for multiple recipient and transplant related variables.

Results: Median study follow up was 22 (10-35) months. There were 3524 recipients of matched HCV+ donor kidneys and 80.5% of recipients were HCV-. There was an increase in HCV+ donor kidney availability over time from 116 in 2015 to 614 in 2022. HCV+ to HCV- transplantation increased from 6% of all kidneys in 2015 to 95% in 2022. LOS was similar for HCV+ [5 days (4-6)] vs. HCV- [4 days (3-6)] recipients (p=0.7). Transplant outcomes for HCV+ (n=688) vs. HCV- (n=2836) recipients are shown in the table.

Conclusions: Our analysis showed increasing utilization of HCV+ (viremic) kidneys over time with preferential use in HCV- recipients more recently. Similar graft and patient outcomes of HCV+ kidney transplantation into HCV+ vs. HCV- recipients likely reflect availability of DAA agent. Our study demonstrates reduced accessibility of HCV+ kidneys for HCV+ recipients in recent years despite equivalent outcomes.

Outcome	Univariate		Adjusted	
	OR (95% CI)	P	OR (95% CI)	P
Delayed graft function	1.32 (0.83-2.11)	0.2	1.25 (0.72-2.17)	0.4
	HR (95% CI)	P	HR (95% CI)	P
Graft failure	0.86 (0.68-1.56)	0.2	0.81 (0.62-1.04)	0.1
Death-censored graft failure	1.08 (0.70-1.66)	0.7	0.98 (0.62-1.54)	0.9
Death	0.82 (0.64-1.05)	0.1	0.81 (0.61-1.07)	0.1

TH-PO911

Phospholipase A2 Receptor Antibody (PLA2Rab) Epitope Spreading (ES) Associates with Recurrent Membranous Nephropathy (MN)

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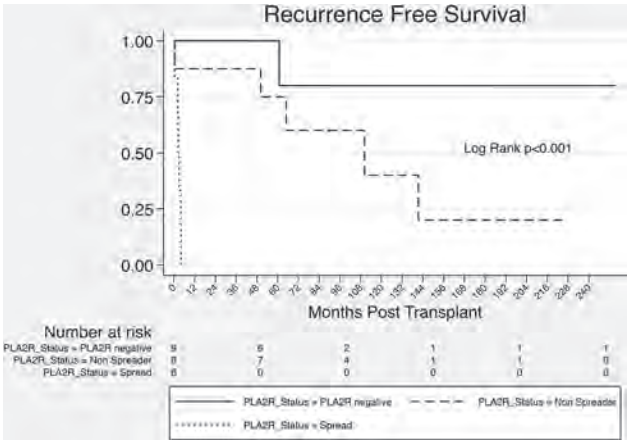
Background: Anti-PLA2Rab ES has been associated with higher anti-PLA2R ab titers, more severe disease, greater likelihood of progression to ESRD, and need for higher doses of Rituximab. The objective of this study was to determine if epitope spreading associates with recurrent MN post kidney transplant (KTx).

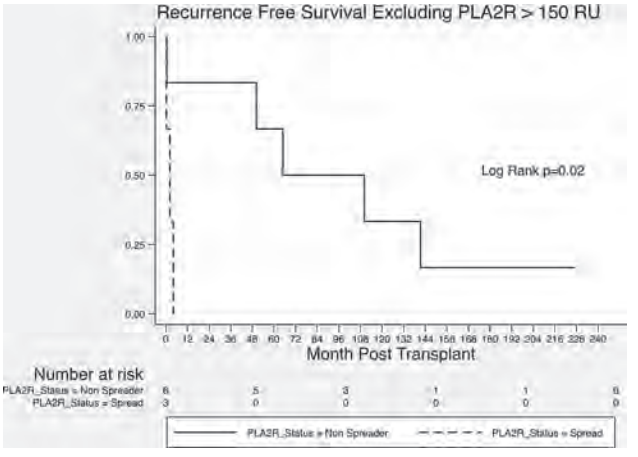
Methods: Pre-transplant serum from 23 KTx recipients with ESKD due to MN was analyzed by ELISA and Western blot for presence of anti-PLA2R abs and ES. Recurrence was diagnosed by protocol biopsies and proteinuria measurements.

Results: Age 50.9± 12.8 year, 65.2% males, 82.6% received a kidney from a living donor, 43.5% were preemptive transplants. There were no demographic differences between those with positive anti-PLA2Rab or not, nor those with ES vs. not. PLA2Rab was detected in 14 (60.9%) patients. Epitope spreading was present in 6/14 (42.9%) of those: 100% if PLA2Rab>150RU, 50% if >50 <150 RU, and 20% if < 50RU. One was positive for CTLD1-3 and one for CTLD4-8 with the remainder co-positive. PLA2Rab+ patients were more likely to recur HR 8.8 (1.13, 68.00). In PLA2Rab+, ES associated with increased risk of recurrence HR 15.2 (1.7, 133.3) unadjusted and 9.8 (1.03, 94.1) adjusted for PLA2Rab level. Seven patients required therapy with Rituximab for recurrent MN with no graft loses.

Conclusions: ES of PLA2Rab associates with a higher likelihood of post KTx recurrence of MN and may be useful to determine in those with PLA2Rab < 150 RU.

Funding: Clinical Revenue Support





TH-PO912

Social Support and Dietary Behaviors Among Adults with ESKD and Obesity

Bengucan Gunen,[1] Ann C. Klassen,[1] Brandy-Joe Milliron,[2] Jasmine M. Sweeting,[4] Joanna H. Lee,[3] Jennifer R. Haileselasse,[1] Sneha S. Hingorany,[3] Meera N. Harhay.[3] *[1]Drexel University Dornsife School of Public Health, Philadelphia, PA; [2]Drexel University College of Nursing and Health Professions, Philadelphia, PA; [3]Drexel University College of Medicine, Philadelphia, PA; [4]Jefferson Health, Wayne, PA.*

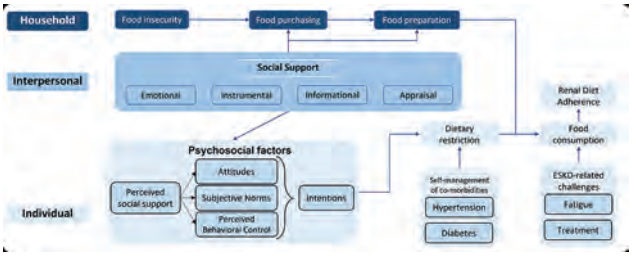
Background: End stage kidney disease (ESKD) patients with obesity (~40% of the dialysis population) have unique challenges with weight management and diet. Few studies have explored the role of different types of social support in achieving optimal dietary intake and renal dietary adherence.

Methods: We conducted semi-structured, 60-90-minute phone interviews in 2020-21 with 40 adults with ESKD and obesity (body mass index, BMI, ≥30 kg/m^2). Participants were recruited from dialysis centers and patient networks in 22 states, using purposive sampling for geographic and demographic diversity. Interviews were audio recorded and transcribed verbatim. A coding framework was developed by an interdisciplinary team including a nephrologist, a nutrition scientist, and a social scientist. By memoing patient narratives on the role of social support in dietary behaviors, codes were finalized to include sources of social support (family, friends, community members, fellow patients) and types of social support (emotional, appraisal, instrumental, informational). Patient typologies based on social support levels were identified to explain patterns of dietary behaviors.

Results: Mean age of participants was 55 years; average BMI was 39.5kg/m^2, 58% of patients were female, 35% were Black/African American, 60% had diabetes. Participants reported receiving the most varied types of social support from family members in their household, while also accessing emotional support from fellow patients, and informational and appraisal support from online communities. Qualitative data analyses identify patient typologies based on social support levels to explain patterns of dietary behaviors. Using behavior change theory and study data, the included figure illustrates how social support influences diet adherence.

Conclusions: Social support buffers the negative health consequences of adverse life events and helps patients with self-management, with implications for renal diet adherence and promoting healthy diets among patients with ESKD and obesity.

Funding: NIDDK Support



TH-PO913

Comparing the Value of Periodic Assessment of Three Objective Nutrition Scores on the Prognosis of Hemodialysis Patients: A Multicenter Longitudinal Study

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Background: The prognostic value of objective nutrition scoring tools for longitudinally assessing the relationship between nutritional status and prognosis in hemodialysis patients remains unclear. In this multicenter retrospective cohort study, the prognostic nutritional index (PNI), controlling nutritional states scores (CONUT), and geriatric nutritional risk index (GNRI) were used to longitudinally evaluate nutritional status, and their predictive values for all-cause and cardiovascular mortality were compared.

Methods: Hemodialysis patients from four hospitals were included in the study, and laboratory data and nutrition scores were collected at the start of dialysis, 6 months, 12 months, and 18 months of dialysis. A joint model was used to analyze the relationship between changes in the three nutritional scores and patient prognosis, and area under the curve (AUC) was used to compare their predictive values.

Results: Of the 863 patients included in the study with a median follow-up of 37 months, 23.8% died during follow-up, with 14% being cardiovascular deaths. Malnourished patients had a higher risk for all-cause and cardiovascular mortality. Dynamic changes in PNI and GNRI scores were significantly associated with a reduced risk of all-cause and cardiovascular mortality. Longitudinal increases in PNI and GNRI scores were associated with a 4% and 3% reduction in all-cause(PNI: hazard ratio [HR], 0.96; 95%confidence interval [CI], 0.95-0.98. GNRI: HR, 0.97; 95% CI, 0.96-0.98) and cardiovascular mortality risk(PNI: HR, 0.96; 95% CI, 0.94-0.98. GNRI: HR, 0.97; 95% CI, 0.95-0.98) respectively, with increasing dialysis duration. CONUT score changes were not significantly associated with all-cause death and cardiovascular mortality. The AUC of three joint models showed that GNRI (0.8925) score showed higher predictive accuracy for all-cause than PNI(0.8315) and CONUT(0,852). Similar results were found for the three scores regarding cardiovascular mortality.

Conclusions: Malnutrition strongly associates with increased all-cause and cardiovascular mortality in hemodialysis patients. Regular assessment of nutritional status using GNRI has higher predictive accuracy than CONUT score and PNI score for all-cause and cardiovascular mortality in patients with MHD.

TH-PO914

Effect of Geriatric Nutritional Risk Index (GNRI)-Based Stratified Diet Intervention on Nutritional Status and Self-Efficacy of Elderly Patients with Maintenance Hemodialysis

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Background: To explore the effect of stratified dietary intervention based on geriatric nutritional risk index (GNRI) on nutritional status and self-efficacy in elderly patients with continuous hemodialysis (MHD).

Methods: A total of 60 elderly patients with MHD from the Second Affiliated Hospital of Nanjing Medical University from January 2020 to January 2021 were randomly selected and divided into an intervention group and a control group by random number table method, with 30 cases in each group. The control group implemented conventional intervention measures, and the intervention group implemented GNRI stratified dietary intervention based on conventional intervention measures. The nutritional status of the two groups before and after 3 months of intervention, including the score of the subjective global assessment (scored patient-generated subjective global assessment, PG-SGA), body mass index (body mass index, BMI) and triceps skin triceps skin fold (TSF), self-efficacy [general self-efficacy scale (GSES) score, dietary treatment attitude [the attitude scale for the dietary therapy of hemodialysis] patients, ASDTH) score], quality of life [kidney disease quality of life short form (KDQ) score] changes.

Results: After 3 months of intervention, the intervention group PG-SGA score, BMI, TSF, Event coping, goal achievement and individual problem solving, ASDTH score and KDQ score were higher than those of the control group ($t = 5.450, -2.199, -3.510, -5.122, -5.142, -5.085, -4.280, -4.959$; respectively; $P < 0.001, 0.032, 0.001, P < 0.001, P < 0.001, 0.001, P < 0.001$ and $P < 0.001$.

Conclusions: GNRI stratified dietary intervention can improve the nutritional status of elderly MHD patients, help to enhance their self-efficacy, improve Diet therapy attitude, improve the quality of life, has high clinical application value.

Funding: Government Support - Non-U.S.

TH-PO915

Veteran Diet Quality and Associations of Unprocessed Plant Nutrients on Vascular Function

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Background: Over 500,000 Veterans have chronic kidney disease (CKD) with higher incidence (16-36%) than the general population. Most CKD is caused by diabetes and associated with hypertension and cardiovascular disease. Dietary changes may prevent, delay, or manage hypertension, diabetes, and CKD. Poor dietary quality and low adherence to recommended diets is common in CKD. The purpose of this study was to describe diet quality and cross-sectional associations of plant-based diet components with vascular function measures in Veterans with CKD.

Methods: We conducted a secondary analysis of baseline data from the Phosphate Lowering in CKD Trial (NCT02209636) that recruited 66 Veterans with CKD stage 3b-4. Primary study outcomes were vascular function measures, carotid-femoral pulse-wave velocity (PWV) and flow mediated dilation (FMD). We calculated plant-based diet components from 3-day dietary records by linking the Food and Nutrient Database for Dietary Studies with food composition data provided by the USDA Nutrient Database for Standard Reference. We classified food and nutrient degree of processing by the NOVA diet classification system. Analysis included basic descriptive statistics and paired T-tests to compare nutrient intake above/below the median with PWV and FMD.

Results: Mean±SD ultra-processed calories was 64.3±15.1% of total intake and animal protein was 52.3±19.6% of total protein intake. Mean ± SD combined processed/ultra-processed nutrients intake was: 72.4±17.8% of total sodium (2,358g), 56.2±14.9% of total potassium (1,191g), 64.1±16.5% of total phosphorus (743g). No participants were Dietary Approaches to Stop Hypertension (DASH) diet adherent (1.3±0.9 points of 9) and the Healthy Eating Index score was 48.9±11.7 (out of 100). Individuals with unprocessed plant protein above the median intake had lower PWV (996.5±237.1 m/s) than those below the median intake (1223.5± 09.1 m/s, p=0.04). Those with unprocessed plant phosphorus above the median intake also had lower PWV (979.2±233.8 m/s) than those below the median intake (1241.8±399.4 m/s, p=0.02).

Conclusions: Veterans in the Phosphate Lowering in CKD Trial had low dietary quality, however, those who consumed more unprocessed plant protein and phosphorus had better vascular function at baseline. These results indicate opportunities for nutritional intervention and future research.

Funding: Veterans Affairs Support

TH-PO916

Dietary Patterns and Kidney Function in West Africans with CKD

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Background: There is little known about the impact of dietary patterns on chronic kidney disease (CKD) in West Africa. Our study describes associations of dietary patterns with estimated glomerular filtration rate (eGFR) and is the first study to do so in a well-phenotyped West African CKD cohort.

Methods: We analyzed participants in the Diet, Apolipoprotein L1 and CKD (DCA) study from 7 centers in West Africa (Ghana and Nigeria). Data from 24-hour dietary recalls were categorized into 32 food groups and 3 dietary patterns were derived via principal component analysis (PCA). Using mixed effect linear regression models, we estimated the b coefficients and 95% confidence intervals for quartiles of the dietary patterns and eGFR (2009 CKD-EPI equation, not corrected for race).

Results: Among 583 people with a mean age of 49±17 years and 51% males, the mean eGFR and median 24-hour urine protein were 68±39 mL/min/1.73m^2 and 0.31(IQR=0.13-1.07) g respectively. We identified the **Dried Fish and Oil dietary pattern, Poultry and Cereal dietary pattern** and the **Fruit and Cereal dietary pattern**. Compared to Q1 (lowest consumption) of the Poultry and Cereal pattern, higher quartiles were associated with higher eGFR in the unadjusted model (p for trend<0.001, **Table 1**). Adjusting for covariates attenuated the association. Age was associated with the Poultry and Cereal dietary Pattern (-0.02, $p < 0.001$). No other dietary patterns were associated with eGFR.

Conclusions: In our cross-sectional analyses, there was no association of dietary patterns with eGFR. Future studies on diet quality and nutrient contents and CKD progression in Africans are needed. Our next steps are to investigate other factors associated with dietary patterns in our population (aside from age) and examine longitudinal associations of dietary patterns with CKD progression.

Funding: NIDDK Support

Table 1: Associations of Dietary Patterns with eGFR

	Q1	Q2	Q3	Q4	P for trend
Dried Fish and Oils					
Unadjusted	Ref	0.26 (-9.41 to 11.49)	-6.74 (-17.86 to 6.43)	-2.15 (-13.78 to 11.98)	0.47
Adjusted	Ref	2.62 (-5.05 to 10.87)	-2.96 (-11.76 to 6.59)	-1.25 (-10.52 to 8.67)	0.55
Poultry and Cereal					
Unadjusted	Ref	7.67 (-1.49 to 16.59)	**12.91 (3.82 to 21.94)**	**24.87 (15.91 to 33.79)**	**< 0.001**
Adjusted	Ref	7.65 (0.24 to 15.01)	6.94 (-0.48 to 14.43)	7.84 (0.26 to 15.54)	0.07
Fruit and Cereal					
Unadjusted	Ref	0.23 (-8.75 to 9.24)	-1.62 (-10.81 to 7.63)	-1.75 (-11.33 to 7.74)	0.65
Adjusted	Ref	1.37 (-5.85 to 8.64)	-1.39 (-8.70 to 6.04)	1.16 (-6.60 to 8.83)	0.96

* Adjusted for Age, Sex, Education, Income, Smoking, Alcohol, Diabetes, Hypertension, BMI, and Total eGKL. (clinical cancer in Random Effect)

TH-PO917

Dietary Sodium and Potassium Intake Estimations in Different Stages of CKD by Multiple 24-Hour Urine Collections

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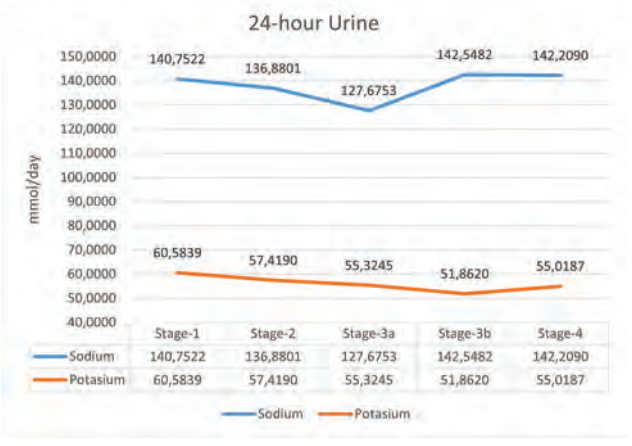
Background: Dietary sodium (Na) and potassium (K) intake in chronic kidney disease (CKD) patients can be calculated most accurately by multiple 24-hour urine (24hU) samples. While Na intake targets are known, optimal K intake according to different stages of CKD is not known. We aimed to examine how much Na intake met the guideline recommendations and the effect of K intake on serum K values in CKD patients.

Methods: This retrospective cohort study was based on 253 stable patients (who collected 5 or more 24hU between 2012-2022) at different stages of CKD. Clinical data was obtained through database of Hacettepe University Hospitals. 24hU sodium (24hUNa) and potassium (24hUK), serum Na, K and creatinine (Scre) values were analyzed. Generalized linear model for analysis of parametric variables was used.

Results: There was a total of 3493 urinary Na values from a mean of 13 collections in 253 patients. Mean 24hUNa was 134.3 +-70,5 mmol/d. Only 32.7% (n=1142) were below the recommended target of 100 mmol/d. There was a total of 1959 urinary K values from a mean of 14 collections in 135 patients. Mean 24hUK was 58,3 +-22 mmol/d. 24hUNa and 24hUK excretion according to the CKD stages was shown in Figure. There was no correlation between CKD stages and 24hUNa and 24hUK excretion. Scre values and 24hUNa values were inversely proportional, with beta:-0.001 and p:0.04. Scre values and 24hUK values showed an inverse correlation, with beta: -0.007 and p:0.00. When serum K values and 24hUK values were analyzed, beta is negligible, p:0.884. No statistically significant correlation was found between serum K values and 24hUK values.

Conclusions: 24hUNa levels with recommended Na targets is present only in one third of the samples. The lack of relation with serum K and 24hUK values needs further studies to define an optimal K intake in different stages of CKD.



TH-PO918

Effects of High Dietary Salt on Immunome and Microbiome Composition: Results from a Randomized Clinical Trial

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Background: Increased dietary salt intake ranks among the most prominent nutritional risk factors worldwide and has been tied to arterial hypertension and all-cause mortality. The mechanisms responsible are incompletely understood and have recently been extended to include inflammatory and microbiome-associated mechanisms. Building on our preliminary data, the present study investigates whether a moderate increase in salt intake in healthy subjects primes host physiology to a more transiently unstable state, potentially leading to changes in the microbiome-immune axis.

Methods: We conducted a prospective, randomized, double-blinded trial to evaluate the effect of high dietary salt in healthy participants (NCT03024567), where the intervention group (n = 19) was given 6g of salt (NaCl) in addition to their daily normal salt intake, essentially doubling the recommended salt intake against a placebo group (n=19) for 14 days. Clinical parameters, stool, and PBMC were collected at baseline and day 14. Shotgun metagenomic sequencing, metabolomics (stool and serum), and single-cell sequencing (Cellular Indexing of Transcriptomes and Epitopes by Sequencing (CITEseq)) of whole PBMC and CD4+ T cells (~150k single cells) was performed.

Results: Our results confirm previously established findings showing an increase in the dissimilarity of the microbiome composition (Jensen-Shannon Divergence) under a high salt diet. Differential abundance of the microbiome's functional space, as quantified by functional gut-specific modules, picked up a salt-specific module (M00494, NatK-NatR (sodium extrusion) two-component regulatory system) in the salt intervention group. A short-chain fatty acid-specific module (MF0128, Propionate conversion to succinate) was reduced in the salt arm. CITEseq revealed a significant amount of differently expressed genes (DEGs) solely in the salt group. We found 602 DEG in naïve conventional T cells (Tconv) and 202 DEGs in non-naïve Tconv, e.g. belonging to NF-kB and T cell receptor signaling pathways.

Conclusions: Our placebo-controlled study is the first to utilize different omics techniques to investigate and identify high-salt-induced changes in the microbiome and immunome in healthy individuals that may be relevant to the development of pathological conditions in the long term.

TH-PO919

High-Salt and Low-Salt Diets Can Modulate Kidney Immune Cells and Endothelial Cells

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Background: Kidney immune cells and endothelial cells mediate kidney ischemia-reperfusion injury and can affect kidney transplant outcomes. We aimed to study the effect of changes in dietary salt intake on kidney immune cells and endothelial cells in experimental models and kidney transplants.

Methods: We treated C57BL/6 mice with normal diet, low-salt diet, or high-salt diet and obtained kidneys after 6 weeks of allocated diets. Kidney sections were stained for CD45. To compare intrarenal sodium buffer, glycosaminoglycan (GAG) concentration was measured with kidney protein extracts. Lymphocytes isolated from kidneys were analyzed by flow cytometry. Human kidney transplant tissues obtained at 2 weeks after kidney transplantation by a protocol biopsy were stained with CD45 and CD31 and analyzed per donors' pre-donation 24h urine sodium levels. Induced pluripotent stem cell-derived endothelial cells (iPSC-ECs) from healthy individuals and end-stage kidney disease (ESKD) patients were treated with additional sodium, and proliferation was assessed.

Results: Mice kidneys from high-salt diet group had higher kidney leukocytes ($CD45^+$) than those from normal diet group (1.9±0.3% vs 0.9±0.1%, P=0.043). Kidney GAG level was lower in high-salt diet group than in low-salt group (41.0±3.1 vs 48.3±1.3 ng/mg, P=0.004). Both low-salt and high-salt diets increased effector-memory $CD4^+$ T cells (normal 44.2±2.6%; low-salt 57.1±3.5%, P=0.020; high-salt 62.1±2.5% of $CD4^+$ T cells, P=0.002) and mature B cells (70.0±1.5%; 79.1±1.4%, P=0.001; 76.7±1.6% of $CD19^+$ cells, P=0.015), whereas decreased naïve $CD4^+$ T cells (45.9±2.1%; 32.7±3.2%, P=0.016; 27.8±3.1% of $CD4^+$ T cells, P=0.001) in kidneys. Human kidney transplants from donors under low-salt diet exhibited lower leukocytes ($CD45^+$, 0.3±0.1% vs 0.9±0.3%, P=0.019) and higher capillary density ($CD31^+$, 29.0±2.2% vs 16.1±1.8%, P=0.009) than those from donors under high-salt diet. The proliferation of iPSC-ECs from healthy individuals and ESKD patients after hypoxia was reduced under higher sodium concentrations.

Conclusions: High-salt and low-salt diets seem to exert adverse effects on kidney immune cell numbers and phenotypes as well as endothelial cells. Modulation of kidney microenvironment by modifying dietary salt intake could be a potential strategy to improve kidney transplant outcomes.

TH-PO920

Dietary Potassium and Fiber Intake and Health-Related Quality of Life in a Multicenter Prospective Hemodialysis Cohort

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Background: Guidelines recommend dietary potassium (K) restriction in ESKD patients due to concerns about hyperkalemic CV events. However, K-rich foods tend to be from heart-healthy sources with high fiber content. We examined the relationship of dietary K and fiber intake with health-related quality of life (HRQOL) in a prospective HD cohort.

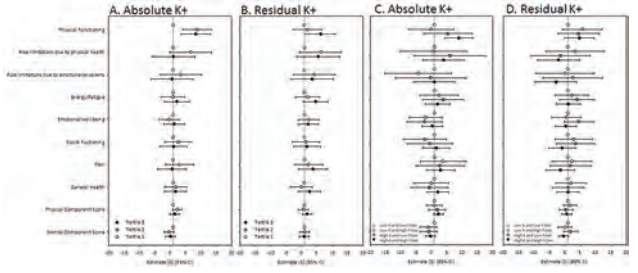
Methods: Among 583 HD patients from the multicenter NIH MADRAD cohort recruited across 16 outpatient dialysis clinics, information regarding dietary K intake was obtained using protocolized Food Frequency Questionnaires (FFQs) and HRQOL was assessed using Short Form 36 surveys administered over 10/2011-9/2022. We examined associations of dietary K intake categorized as tertiles with HRQOL using linear mixed

effect models. We also examined different pairings of dietary K and fiber intake across four exposure groups (low K/low fiber, low K/high fiber, high K/low fiber, high K/high fiber) with HRQOL.

Results: In expanded case-mix + laboratory analyses, the highest tertile of absolute dietary K intake was associated with better trajectory of physical functioning and physical component scores (PCS) over time (ref: lowest tertile): Estimates (β) (95%CI) +8.33 (+3.59, +13.08) and +1.48 (-0.13, +3.09) (Fig A). Similarly, the highest dietary K tertile in residual models were associated with better trajectory of PCS and energy/fatigue (Fig B). In adjusted analyses of pairings of dietary K/fiber intake in the absolute (Fig C) and residual models (Fig D), patients with high K/high fiber intake had better physical functioning and PCS vs. those with low K/low fiber intake.

Conclusions: In a prospective HD cohort, higher dietary K and fiber intake were associated with better HRQOL, particularly related to physical function domains. Further studies are needed to determine the causal mechanisms linking dietary intake and physical function in this population.

Funding: NIDDK Support



TH-PO921

Different Effects of Dietary Selenium on All-Cause Mortality According to the Baseline Characteristics Based on the Nationwide Population Study: Results from the NHANES, 1999-2016

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Background: As an antioxidant, selenium has a beneficial role in human health including metabolism and thyroid function. Based on the metabolism process, kidney function status has a potential role in the bioavailability of dietary selenium. Herein, we aimed to evaluate the impact of dietary selenium on all-cause mortality in different baseline characteristics including kidney function status.

Methods: We used data from the US National Health and Nutrition Examination Survey 1999-2016. Based on a 1-day 24-hr dietary recall, the intake of selenium was divided by quintile; the third quintile was regarded as a reference. Baseline characteristics included kidney function, body mass index, and alcohol consumption status. We used a multivariate Cox proportional hazard model to identify the impact of selenium on all-cause mortality.

Results: A total of 41,423 subjects were included in the study. The risk for all-cause mortality was significantly increased in subjects included in the 1st quintile (adjusted hazard ratio [aHR] 1.12, 95% confidence interval [CI] 1.03-1.21) after adjustment with age, gender, ethnicity, education, income, comorbidities (hypertension, diabetes), BMI, total calorie intake, laboratory results (hemoglobin, serum albumin, total cholesterol, serum glucose, and estimated glomerular filtration rate). In subgroup analysis, lower intake of selenium increased mortality in subjects with eGFR ≥60 mL/min/1.73 m2 (aHR 1.14, 95% CI 1.03-1.27), BMI 25-30 kg/m2 (aHR 1.24, 95% CI 1.08-1.43), and moderate to heavy drinker (aHR 1.27, 95% CI 1.11-1.44). Selenium intake and blood level of selenium showed a positive correlation, and it was prominent in subjects with eGFR <60, BMI 25-30, and non-drinkers. The impact of the blood level of selenium on all-cause mortality was the same as the results in selenium intake.

Conclusions: Deficiency in selenium intake and lower levels of blood selenium significantly increased all-cause mortality, especially in subjects with preserved kidney function, overweight, and moderate to heavy drinkers.

TH-PO922

Diet and the Discrepancy Between Cystatin C- and Creatinine-Based eGFR in Middle-Aged and Older Community-Dwelling Japanese Adults

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Background: Discrepancy between creatinine-based eGFR ($eGFR_{creat}$) and cystatin C-based eGFR ($eGFR_{cys}$) is associated with kidney health and frailty. Dietary factors may affect serum creatinine concentration, but little is known about the association between diet and eGFR discrepancy.

Methods: Baseline data from a Japanese community-based cohort (age 40–97 years) comprising 3,029 men and 3,115 women were analyzed. We cross-sectionally assessed nutrients and food groups derived from a food frequency questionnaire adjusted by energy intake, using the residual method. eGFR was calculated according to the equation developed for the Japanese population, using creatinine and cystatin C. Discrepancy between $eGFR_{creat}$ and $eGFR_{cys}$ was assessed as $eGFR_{cys}$ divided by $eGFR_{creat}$, with $eGFR_{cys}$ / $eGFR_{creat}$ > 1.4 used as an outcome variable in this study. The association between diet and eGFR discrepancy was analyzed using logistic regression analysis, with adjustment for potential confounders according to sex.

Results: eGFR discrepancy ($eGFR_{cys}$ / $eGFR_{creat}$ >1.4) was observed in 9.3% of men and 14.5% of women, with a median $eGFR_{creat}$ and $eGFR_{cys}$ of 73.9 (interquartile interval: 64.1, 84.7) and 84.7 (72.7, 97.0) in men, and 73.7 (64.8, 83.6) and 87.3 (76.4, 98.6) in women, respectively. In the multivariable logistic regression model, protein, phosphorus, vitamin D, and fish intakes were positively and carbohydrate and grain intakes were negatively associated with eGFR discrepancy in men, while energy, potassium, and phosphorus intakes were positively and carbohydrate and grain intakes were negatively associated with eGFR discrepancy in women (Table).

Conclusions: This study found that some dietary features were associated with the eGFR discrepancy in men and women. The results suggest that not only whole protein intake but also its sources and other dietary features should be taken into account when considering kidney health.

Funding: Government Support - Non-U.S.

Table: Multivariable logistic regression analysis of diet and eGFR discrepancy by sex.

eGFR discrepancy was defined as $eGFR_{cys}$ / $eGFR_{creat}$ > 1.4. The multivariable adjusted model included age, smoking status, drinking habits, exercise habits, body mass index, diabetes, hypertension, and $eGFR_{creat}$. Nutrients and food groups were adjusted by energy intake using the residual method and treated as quartiles in the logistic regression model.

Men	Adjusted odds ratio [95%CI]	Women	Adjusted odds ratio [95%CI]
Protein	1.16 [1.02, 1.33]	Energy	1.16 [1.04, 1.29]
Phosphorus	1.17 [1.02, 1.33]	Potassium	1.13 [1.01, 1.26]
Vitamin D	1.27 [1.12, 1.45]	Phosphorus	1.13 [1.01, 1.26]
Fish	1.26 [1.11, 1.44]	Carbohydrate	0.89 [0.80, 0.99]
Carbohydrate	0.83 [0.73, 0.94]	Grain	0.89 [0.80, 0.99]
Grain	0.82 [0.72, 0.93]		

TH-PO923

Association of Obesity, Metabolic Syndrome, and Diabetes with CKD in Men and Women: National Health and Nutrition Examination Survey (NHANES), 2003-2020

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Background: Associations between chronic kidney disease (CKD), obesity, and metabolic syndrome (MetS) have been documented previously, but how these associations vary across obesity/metabolic phenotypes in males and females has not been evaluated extensively.

Methods: Data were analyzed for 8,586 male and 8,420 non-pregnant female adults (≥20 years), from the 2003-2020 cycles of the NHANES. CKD (defined as albuminuria and/or eGFR<60ml/min), MetS (defined as ≥3 of the following: hypertension, prediabetes, hypertriglyceridemia, low HDL cholesterol, and/or central obesity), and obesity (BMI≥30) were identified by physical examination and/or results from fasting laboratory samples. Diabetes was identified by self-report, prior diagnosis, and/or high fasting glucose or hemoglobin A1C. Participants without diabetes were further categorized according to 4 obesity/metabolic phenotypes: metabolically healthy non-obese (MHNO), metabolically unhealthy non-obese (MUNO), metabolically healthy obese (MHO), and metabolically unhealthy obese (MUO). Multivariable-adjusted logistic regression models were used to examine the relationship of CKD with obesity/metabolic phenotypes using appropriate sampling weights.

Results: The prevalence (95% CI) of CKD for male and female diabetics was 36.7% (33.6-39.8) and 35.9% (32.2-39.9), respectively. The prevalence of CKD for male and female MUNO was 13.2% (10.6-16.5) and 21.0% (18.0-24.3), respectively; for MUO 10.9% (9.1-13.1) and 14.8% (12.9-16.9); for MHNO 5.6% (4.9-6.5) and 9.6% (8.5-10.9); and for MHO 4.6% (3.4-6.2) and 8.4% (6.6-10.7). CKD was associated with the metabolically unhealthy phenotypes in males [adjusted odds ratio: MUNO 1.94 (1.41-2.68) and MUO 1.83 (1.40-2.38)], but only with MUNO [1.50 (1.12-1.99)] among females.

Conclusions: These findings suggest different associations between MetS and CKD between males and females. Understanding how sex-specific differences, such as sex hormones, modulate the interaction between obesity/metabolic phenotypes and CKD may provide additional avenues for prevention and treatment.

Funding: NIDDK Support

TH-PO924

Ketogenic Diet Mitigates Renal Fibrosis and Partially Preserves Kidney Function in Nephrotoxic Serum Nephritis

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Background: Ketogenic diet (KD) has garnered medical interest due to its potential health benefits in various diseases including a significant regulatory impact on inflammatory processes. Our study examined the effects of a KD on an experimental mouse model of immune-complex-mediated glomerulonephritis (GN).

Methods: Male C57BL/6 mice were put on a KD or continued with standard chow (SC) three days after the induction of nephrotoxic serum nephritis (NTS). Mice were observed for 21 days post-induction. Key parameters like the albumin-to-creatinine ratio (ACR) in spot urine and kidney histology were evaluated. Further, we transitioned mice back to SC on day 21 and observed them for an additional 5 weeks. During this period, kidney function was monitored using transdermal glomerular filtration rate measurement devices. Kidney fibrosis was assessed using Sirius Red staining. To thoroughly examine the molecular mechanisms associated with a ketogenic diet, we employed a multifaceted approach incorporating comprehensive immunophenotyping of blood and lymphatic tissues via flow cytometry and immunohistochemistry, renal NMR spectroscopy (metabolomics), and renal bulk RNA-sequencing.

Results: KD significantly reduced levels of albuminuria. We noticed fewer crescents and lower PAS scores, indicating an improved glomerular phenotype in the KD group, but a trend toward increased tubular injury and tubular fat deposition. Mice switched back to SC after the initial KD phase demonstrated a reduction in kidney fibrosis and preserved kidney function with regression of the tubular fat deposits. KD mice showed major systemic immunological and metabolic adaptions like a reduction in blood leukocyte numbers and an increase in the concentration of renal ketone bodies. We further observed an increase of renal neutrophil infiltrates and changes in bulk inflammatory signatures including a decrease in *Mpo* expression. Notably, transcriptomics analysis revealed a decrease in extracellular matrix production.

Conclusions: A therapeutic KD was protective in a mouse model of GN, leading to a reduction in albuminuria, preserved kidney function, and reduced renal fibrosis. Further research is needed to fully understand these protective mechanisms.

Funding: Private Foundation Support, Government Support - Non-U.S.

TH-PO925

Dietary Acid Reduction with Either Fruits and Vegetables or Oral NaHCO3, Adjuvant to Angiotensin-Converting Enzyme Inhibition, Slows Progression of Macroalbuminuric Stage G1 CKD

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Background: Patients with macroalbuminuric (urine albumin-to-creatinine ratio > 200 mg/g creatinine) chronic kidney disease (CKD) are at increased progression risk despite angiotensin converting enzyme inhibition (ACEI). As high acid-producing diets are associated with risk for CKD progression, we tested the hypothesis that dietary acid reduction with either base-producing fruits and vegetables (F+V) or oral NaHCO3 (HCO3) slows progression in macroalbuminuric CKD with initially normal eGFR (> 90 ml/min/m2 or stage G1).

Methods: One hundred fifty-three macroalbuminuric, non-diabetic G1 participants on ACEI were randomized to F+V (n=51) in amounts to reduce dietary potential renal acid load 50%, oral NaHCO3 (HCO3, n=51) 0.4 meq/Kg bw/day, or no additional intervention (Usual Care, n=51). They were followed annually for 5 years, measuring eGFR and these urine parameters per g creatinine: albumin (Ualb), N-acetyl-D-glucosaminidase (UNAG, indicator of tubulointerstitial injury), angiotensinogen (UAGT, index of kidney angiotensin II), and isoprostane 8-isoprostaglandin F2α (U8-iso, index of systemic oxidative stress). Mixed linear regressions with random person intercepts tested differential group trajectories, p-values from the relevant interaction terms are included below.

Results: We highlight group differences at year-5 for brevity and provide p-values from the full model. For F+V and HCO3 relative to UC, 5-year eGFR was higher ([mean (SE)], F+V [96.5(0.79)], HCO3 [95.9 (0.96)] vs. UC [92.1 (1.23), ml/min/1.73 m2, ps<0.001]). 5-year Ualb and UNAG were lower in F+V and HCO3 than UC (Ualb, F+V [306 (8.5)], HCO3 [308 (8.4)], UC [416 (15)], mg/g, ps<0.001); UNAG, F+V [2.5 (0.05)], HCO3 [2.5 (0.05)], UC [2.8 (0.06)], U/g, ps<0.001). Additionaly, 5-year UAGT and U8-iso were lower in F+V and HCO3 than UC (UATG, F+V [20.9 (0.32)], HCO3 [20.6 (0.35)], UC, [23.1 (0.40), µg/g, ps<0.001]; 8-iso, F+V [1.08 (0.02)], HCO3 [1.06 (0.02)] vs. UC [1.27 (0.03)], µg/g, ps<0.001]).

Conclusions: Dietary acid reduction with either F+V or NaHCO3, adjunctive to ACEI, yielded better eGFR preservation than UC in macroalbuminuric G1 CKD, associated with reductions of indicators of kidney angiotensin II and systemic oxidative stress, each potential mediators of CKD progression.

TH-PO926

The Relevance of a Personalized Low-Normal Protein High-Calorie Diet in Nephrectomized Patients for Renal Cell Carcinoma (RCC): Myth or Reality?

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Background: Nutritional therapy (NT) based on a controlled protein intake represents a cornerstone in the management of CKD. However, if a CKD patient is at the same time affected by cancer, oncologists suggest a diet based on high protein intake to avoid malnutrition. International guidelines are not diriment in this asset of patients. In particular, no clear nutritional management is established in the radical nephrectomy (RN) patients for RCC. The aim of our study was to investigate the efficacy of a Low-Normal Protein High Calorie (LNPHC) diet in a consecutive RN cohort of RCC pts using an integrated nephrologist and nutritionist approach.

Methods: A consecutive cohort of 40 nephrectomized pts for RCC was enrolled in a tertiary institution between 2020-2022. Inclusion criteria: Age >18 years old, eGFR<60 ml/min/1.73,RN for RCC. An initial nephrological and nutritional evaluations were performed and then a conventional CKD LNPHC diet integrated with aproteic foods (0,7-1 g/Kg/die: calories: 30-35 kcal per kg body weight/die) for a period of 6 months (+/- 2 moths). MST, Body Mass Index (BMI), Phase Angle (PA), Fat Mass percentage (FM%), Fat-Free Mass Index (FFMI), body cell mass index (BCMI), extracellular/intracellular water ratio (ECW/ICW), waist/hip circumference ratio (WHC), lab test exams and clinical variables were examined at baseline and after 6 months. Statistical analysis: Kruskal-Wallis rank sum test; Data analysis: R programming language and RStudio integrated development environment.

Results: Descriptive analysis is showed in Table 1. Our results clearly highlighted that LNPHC was able to generate a significant improvement in several nutritional parameters (Tables 2 and 3). Moreover, LNPHC was responsible for a significant decrease of urea.

Conclusions: LNPHC represents a new important therapeutic strategy to apply in the onco-nephrological patients with solitary kidney due to renal cancer.

TH-PO927

Descriptive Analysis of Renal Function and Potential Renal Acid Load in Adult Patients with Long-term Home Parenteral Nutrition Support: A Retrospective Study

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Background: Home parenteral nutrition (HPN) is an established therapy for chronic intestinal failure (CIF). The relationship between CIF and HPN with renal function and kidney disease has yet to be well described in this population. Our study aims to describe chronic kidney disease (CKD) with renal function and potential acidosis load in patients who received long-term HPN.

Methods: We conducted a retrospective study in Edmonton, Alberta. Adult patients aged ≥18 who visited the HPN clinic between Jan 2022 and Mar 2023 were enrolled. The patient admitted to the program for less than six months was excluded. Electronic medical records were reviewed for five years to collect demographic data, the presence of CIF, HPN indications and prescription, the presence of CKD and renal functions. The primary outcome was the estimated glomerular filtration rate (eGFR) with its change after admission to the program and potential total acids load (PTAL). Secondary outcomes included predicted pH, amino acids, glucose, lipid, electrolytes, trace elements, acetate concentration and estimated osmolality load in TPN prescription.

Results: Sixty-one adult patients were included in the study. The mean age was 59.20 ± 11.51 years old, 27.9 % were male and short bowel syndrome was noted in 59%; the most common cause of short bowel syndrome was Crohn's disease. Diabetes mellitus was 16.4 %, Hypertension was 39.3%, and CKD was 47.5%. The most common cause of CKD was nephrolithiasis. The duration of HPN was 6.03 years. An average eGFR was 84.51 ± 27.09 ml/min/1.73 m^2 with a mean change of -2.69 ± 3.21 ml/min/1.73 m^2/year, and the incident rate of rapid GFR decline was 27.9% in five-year follow-up. The median amount

of amino acids was 1.19 (0.85, 1.55) g/kg/day. The average pH of the TPN solution was 5.33 ± 0.36. The median of PTAL was 71.43 (48.35, 95.05) mmol/bag without statistical correlation with CKD when normalised by body weight.

Conclusions: The prevalence of CKD in the HPN was higher than in the general population, with a high rate of eGFR decline. The study showed no statistical correlation between PTAL and CKD in those patients. A prospective study with different GFR measurements should be conducted for the accuracy of eGFR and to demonstrate risk factors for the deterioration of renal function.

Funding: Government Support - Non-U.S.

TH-PO928

Do Protein Intake, Serum Bicarbonate, and Inflammatory Markers Explain the Associations of Advanced CKD with Muscle Wasting?

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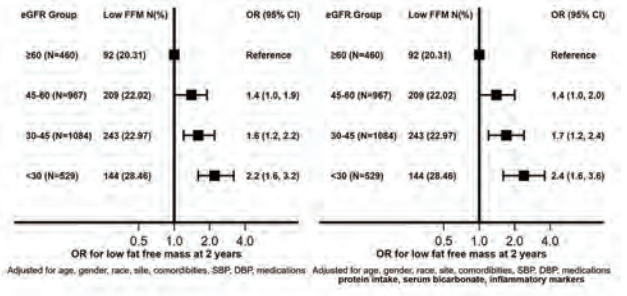
Background: Muscle wasting is a significant concern in individuals with chronic kidney disease (CKD) as it adversely affects their overall well-being and increases the risk of mortality. Low protein intake, metabolic acidosis and systemic inflammation are considered to be some of the main drivers of muscle wasting in CKD. Therefore, we examined in the Chronic Renal Insufficiency Cohort (CRIC), whether these factors explain muscle wasting in CKD.

Methods: We included 3040 eligible CRIC participants. Baseline protein intake was determined from dietary protein intake. Serum bicarbonate was used as marker of acid-base status. Serum hsCRP, IL6, fibrinogen, TNFa and IL1beta were used to derive a previously published CRIC inflammatory score. Muscle wasting was defined as gender specific lowest quartile of fat-free mass estimated from bioelectrical impedance analysis (BIA) at month 24 visit. We investigated the association between low fat-free mass (FFM) and eGFR groups using logistic regression, with covariate adjustment for age, gender, race, site, comorbidities, SBP, DBP, and medications. With additional adjustment for baseline protein intake, serum bicarbonate, and inflammatory score, we examined whether the associations of CKD stages with low FFM at month 24 were attenuated.

Results: Mean baseline age was 58 ± 11 years, 56% were male, 40% were black, and mean eGFR was 45 ± 15. Mean weight was 91 ± 23 kg and mean FFM was 61 ± 16 kg. n multivariate logistic regression model, more advanced CKD was associated with significantly higher risk of low FFM (Figure 1 Panel A). These associations persisted after adjusting for baseline protein intake, serum bicarbonate, and inflammatory score (Figure 1 Panel B).

Conclusions: More advanced CKD is strong predictor of muscle wasting. These associations are not fully explained by protein intake, serum bicarbonate and inflammatory markers. Further studies are needed to unravel the mechanisms of muscle wasting in CKD.

Funding: NIDDK Support



TH-PO929

Evaluation of Protein Malnutrition in CKD Patients on Low-Protein Diet

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Background: Low-protein diet is considered crucial to slow down kidney function deterioration in patients with chronic kidney disease and control metabolic variables such as serum phosphate, urea and bicarbonate. However, low-protein diet may result in malnutrition if patients do not respect nutritional prescription. Thus, the present study examined the risk of protein malnutrition in CKD patients who started a low-protein diet.

Methods: Anthropometric variables, blood variables, nutrient intake and body composition were measured in 40 patients with CKD stage 4-5 (M/F 23/17; age 70±15 years; body weight 70±17 kg) before and after 3-months of a low-protein diet (0.6 g/kg; energy intake 30 Kcal/kg). Nutrient intake was estimated with a food frequency questionnaire; body fat mass (FM), free-fat mass (FFM) and skeletal muscle mass normalized to height^2 (SMI) were assessed using bioimpedentiometry analysis.

Results: In the whole sample, after a 3-month diet protein intake decreased from 0.85±0.24 to 0.71±0.20 g/kg (p<0.001) without a decrease in calory intake (22.3±5.9 and 21.5±4.9 kcal/kg). The diet induced a decrease in body weight (70±17 to 69±16 kg; p<0.001), BMI (26.5±6.4 to 25.9±6.2 kg/m^2; p=0.001), FM (21±10 to 20±10 kg; p=0.003), serum urea (168±48 to 134±43 mg/dl; p<0.001). Eight patients (20%; 4 diabetics) had a protein intake lower than 0.6 g/kg after 3-months of diet. Compared with patients having a higher protein intake, these patients showed lower protein intake at baseline (0.71±0.21 vs 0.89±24 g/kg; p=0.05) and serum albumin (36.3±2.7 vs 40.5±3.2 g/l; p=0.012). Their protein intake after the diet was significantly lower than that at baseline (0.53±0.2 vs 0.71±0.21 g/kg; p=0.016). They also showed a significant decrease in SMI (9.5±1.9 to 8.5±1.8; p=0.003). Conversely, the other 32 patients did not change SMI (9.2±2 to 9,2±2 kg/m^2), but significantly decreased FM (23±11 to 21±11 kg; p=0.002) and increased phase angle (4.2±0.9 to 4.6±0.9; p=0.017).

Conclusions: Protein malnutrition may occur during a low-protein diet in CKD patients with a low consumption of proteins before starting this diet. Nutritional analysis is necessary to identify CKD patients at risk of protein malnutrition and to adequately follow up CKD patients on low protein diet.

TH-PO930

Phosphorous Balance Calculator, an Individualized Tool for Treatment of Hyperphosphatemia in Hemodialysis Patients: A Randomized Clinical Trial

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Background: Lack of evaluations of the dietary phosphorus and dialysis phosphorus removal in daily clinical practice are the common obstacle to assess phosphorus balance and control phosphorus in hemodialysis patients. We aimed to investigate whether the individualized therapy using phosphorus balance calculator improves phosphorus control.

Methods: A randomized, open-lable, multicenter, 4-week clinical trial was conducted. 119 patients aged 18 to 85 years old and with serum phosphorus level higher than 1.45mmol/l from 3 university teaching hospitals in Shanghai were enrolled and randomized in a 1:1 ratio to individualized (n=60) or conventional therapy (n=59). The primary outcome was the serum phosphorus concentration after 4-week treatment.

Results: Among 119 randomized participants (mean age, 62 years; 68 male[57%]), 116 completed the trial. By using the phosphorus balance calculator, the individualized group achieved a better phosphorus equilibrium state, significantly reduced the serum phosphorus (1.62±0.45mmol/l versus 1.85±0.45 mmol/l, *P*=0.006), increased the proportions of patients achieving target serum phosphorus range (41% versus 18%, *P*=0.006), and had greater adjusted mean difference in change in serum phosphorus over the 4 weeks (-0.47 versus -0.23mmol/l, *P*=0.010) when compared to conventional therapy.

Conclusions: Phosphorus balance calculator was proved to improve serum phosphorus control in patients undergoing maintenance hemodialysis, offering a new tool for managing refractory hyperphosphatemia.

Funding: Government Support - Non-U.S.

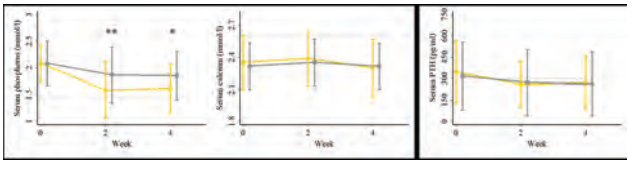

Figure 1. Changes in serum phosphorus, calcium and PTH over 4 weeks in response to individualized and conventional treatment in hemodialysis patients

	Observed concentrations		
	Baseline	Week 2	Week 4
Phosphorus in target			
conventional	-	16%	18%
individualized	-	46% **	41% *
Calcium in target			
conventional	68%	72%	79%
individualized	69%	68%	66%
PTH in target			
conventional	23%	32%	23%
individualized	29%	29%	32%

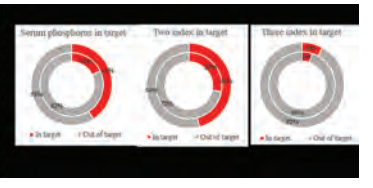

Figure 2. Percentage of in target of serum phosphorus, calcium and PTH during the study period in two groups

TH-PO931

Exposure Estimates of Both Inorganic and Organic Phosphate-Containing Food Additives in US Grocery Household Food Sales in 2022 Validates Need for Labeling Phosphorus Content

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Background: A new paradigm based on the degree of food processing to assess the health of dietary patterns has replaced the traditional approach based on the nutrient content of the foods consumed. Dietary patterns where ultraprocessed foods (UPF) dominate are linked to adverse health conditions including CKD, CVD and mortality. Industrial use of food additives is a hallmark of UPF with 60% of foods purchased by Americans containing food additives, a 10% increase in use since 2001. Use of phosphate (PO_4) additives in UPF is a possible mechanism underlying CKD and other conditions by contributing to the total excessive dietary PO_4 intake. Average underestimated intake of 1400 mg P/d by the general public was significantly linked to increased mortality.

Methods: Since no databases exist to estimate phosphate additive intake from processed foods, our objective was to use 2 proxy methods to estimate exposure to all commonly used PO_4-containing food additives, both inorganic salts and less studied organic PO_4 additives (e.g., lecithins, phosphated modified starches). We used household grocery product food label information from USDA's Branded Food Product Database (BFPD) to estimate the number of foods being sold to American consumers that contain inorganic and organic PO_4 additives in foods (Table). Sales data from Euromonitor International were then used to identify products sold by the top 25 food and beverage manufacturers in the US. The proportion of products from these top 25 manufacturers that contained both organic and inorganic phosphates was also determined.

Results: Only 3% of products in the BFPD displayed P content compared to 5% in foods from the top 25 manufacturers. Both proxy measures showed a much higher proportion of products contained inorganic and organic additives than what displayed P on the label.

Conclusions: These findings justify the need for P content labeling of foods to accurately link the health consequences of excessive P intakes in CKD and the general public.

No. of Grocery Foods	USDA BFPD N=396,062 (% total number)	Top 25 Grocery Producer Sales N=36,763 (% matched foods)
No. with Inorganic PO4 additives	77,659 (20%)	11,209 (30%)
No. with Inorganic & Organic PO4 additives	140,111 (35%)	20,741 (56%)
No. Total Data Set with P on Label	12,046 (3%)	1,888 (5%)

TH-PO932

Inorganic Phosphate Additives in US Household 2022 Product Sales from the Top 25 Grocery Store Food Manufacturers: An Existential, Pervasive Risk Factor for CKD

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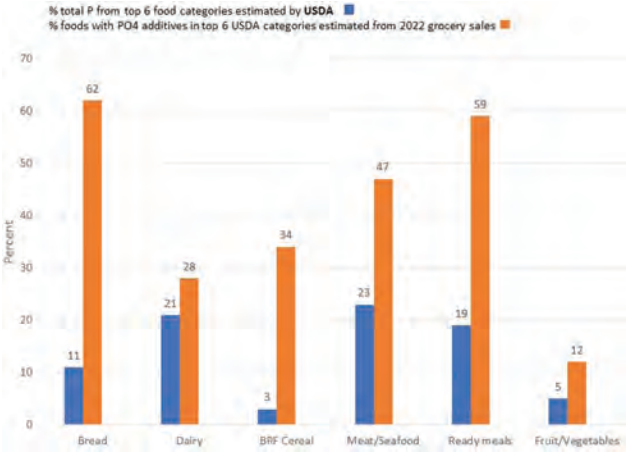
Background: Restricting dietary phosphorus (P) intake is critical to managing CKD and is an important therapeutic personal action CKD patients can take to slow the progression of kidney failure, hyperphosphatemia and cardiovascular disease. Limiting dietary P intake is not a simple task of consuming less natural food sources rich in P (red meats, dairy) since the use of inorganic phosphate (PO_4) additives to process a variety of foods can contribute significant P hidden in processed food. Additives present a unique problem different from natural organic protein and lipid bound P in foods. PO_4 additive salts are rapidly dissociated in stomach acidity, absorbed quickly and can acutely disrupt serum P homeostasis and hormonal dysregulation linked to cardiovascular disease and mortality. Control of P intake is further complicated by the unknown extent of exposure to these PO_4 additives from packaged food and beverage products.

Methods: To estimate exposure to PO_4 additives, we examined ingredient labels of US household packaged products from the top 25 food and beverage manufacturers to identify the total number of food products containing PO_4 additives across USDA's 23 food categories. USDA identifies 6 food categories contributing the majority of total P intake (81%); however, this is thought to be mostly natural P as additive contribution is rarely included.

Results: Using category-level sales data as a proxy for actual intake of foods with PO_4 additives, we show the % of foods that contained PO_4 additives in the 6 categories (Figure). More than 50% of bread, processed meats and ready meals contained PO_4 additives. USDA survey intakes of total P are thought to significantly underestimate total P when PO_4 additive use is not included.

Conclusions: Our findings support this claim of underestimated total P intake, showing evidence of the wide spread use of PO_4 additives in the foods contributing the most P to daily intake.



TH-PO933

Calcium- and Iron-Based Phosphate Binders Impact the Gut Microbiome in Rats with CKD

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Background: Limited studies suggest that phosphate binders may impact the gut microbiome. Our objective was to examine the effects of a calcium-based binder and an iron-based binder on the cecal microbiota and gut-derived uremic toxins in a rat model of progressive CKD.

Methods: Rats with normal kidney function (NL) were compared to rats with CKD (Cy/+ male rats): 1) control (CKD), 2) 2% ferric citrate (CKD + FC), 3) 2% calcium gluconate in water (CKD +Ca). Rats consumed the treatments for 10 weeks (18 to 28 weeks of age; mild to moderate/advanced CKD, respectively). The V4 region of the 16S rRNA gene was sequenced from cecal digesta and analyzed using QIIME2. Serum gut-derived uremic toxins were quantified using ultra-performance liquid chromatography-tandem mass spectrometry.

Results: Richness of the microbiota (alpha-diversity) was similar between groups, but overall microbial composition (beta-diversity) was different from each other. At the phylum-level, all CKD rats had lower relative abundance of Firmicutes, and CKD+Ca had higher Bacteroidetes. At the genus-level, CKD+FC had a higher relative abundance of *Akkermansia,* unclassified Desulfovibrionaceae, and *Clostridium,* and a lower relative abundance of *Allobaculum, Bifidobacterium,* and *Lactobacillus.* CKD+Ca had higher relative abundance of unclassified Lachnospiraceae and *Blautia.* Indoxyl sulfate and p-cresyl sulfate were elevated in CKD but were not affected by phosphate binders. However, phenyl sulfate and phenyl glucuronide were lower in CKD+Ca.

Conclusions: Calcium- and iron-based phosphate binders altered the gut microbiota, but only the calcium-based binder impacted phenyl-derived uremic toxins.

Funding: NIDDK Support, Other NIH Support - NIAMS T32, Commercial Support - Keryx pharmaceuticals for parent study.

TH-PO934

Effects of Curcuma longa L. and Green Propolis Extract-Loaded Microcapsules Supplementation on Inflammation in Hemodialysis Patients

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Background: Nutritional interventions with food that contains bioactive compounds such as *Curcuma longa L.* and propolis can mitigate inflammation in patients with CKD on hemodialysis (HD). Although broadly available, there are limitations in using these bioactive compounds when ingested in their traditional forms. In this way, the microencapsulation process of these natural compounds can be a good alternative. This longitudinal, double-blind, placebo-controlled study aims to evaluate the effects of *Curcuma longa L.* and green propolis extract-loaded microcapsules supplementation on inflammatory markers in HD patients.

Methods: Patients were randomized into two groups: Intervention (137mg/d of *Curcuma longa L.* and 500mg/d of concentrated and standardized green propolis extract EPP-AF®, Apis Flora, Brazil) as microcapsules administrated hard vegetable capsules or placebo for eight weeks. The levels of inflammatory biomarkers (IL-5, GM-CSF, TNF-α, IL-1B, IL-13, IL-4, MCP-1, IL-8, MIP-1, IL-10, G-CSF, IL-7, IL-12 and IL-17) were analyzed by multiplex assay (Bio-Plex Magpix®). C-reactive protein (CRP) was analyzed using a Bioclin device. All analyses were adjusted according to age, sex, BMI and time on HD.

Results: 38 patients completed the study; 18 patients in the intervention group (49 ± 18.6 yr.; BMI 21.6 ± 5.2Kg/m^2; 8 men) and 20 in the placebo group (49 ± 16.2 yr.; BMI 24.4 ± 3.4Kg/m^2; 10 men). After supplementation, MIP-1 and CRP plasma levels were significantly reduced (**Fig 1**).

Conclusions: Supplementation with 137 mg/d of *Curcuma longa L.* and 500mg of microencapsulated EPP-AF® green propolis extract in hemodialysis patients for eight weeks significantly reduced MIP-1 and CRP values, evidencing the potential anti-inflammatory effects of the supplement.

Funding: Government Support - Non-U.S.

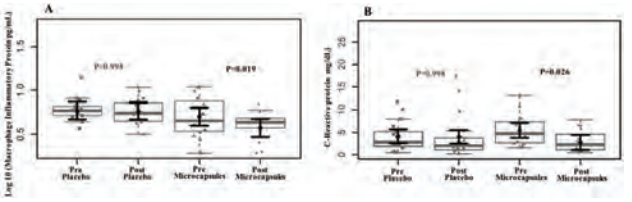

Fig 1. There was evidence of reduced plasma levels of MIP-1 (A) and CRP (B) after microcapsules with turmeric and propolis supplementation.

TH-PO935

Does Dark Chocolate Intake Influence Magnesium Status in Hemodialysis Patients?

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Background: Magnesium (Mg^{2+}) is a fundamental mineral that maintains cell function. Magnesium deficiency can be observed in patients with CKD and is associated with increased inflammation, disease progression, and mortality. Studies have shown that patients with high Mg^{2+} serum levels have shown better survival. Dark chocolate is an excellent source of magnesium and polyphenols. Thus, the study aimed to evaluate the effects of 70% cocoa chocolate on magnesium plasma levels in patients with CKD on hemodialysis (HD).

Methods: These are secondary analyses from a previous controlled pilot study that included 59 CKD patients undergoing HD. Patients were allocated into two groups; the chocolate group received 40 grams of 70% cocoa chocolate during HD sessions (3 times a week) for two months. The control group did not receive any intervention. Routine biochemical parameters, including potassium, phosphorus and Mg^{2+}, were evaluated by a colourimetric test using a commercial kit (Bioclin®).

Results: Thirty-five patients in the chocolate group (17 women, 53.4 ± 12.9 years) and 11 in the control group (4 women, 46.7 ± 10.9 years) completed the study. The median of Mg^{2+} serum levels was 2.4 (0.4) mg/dL, with no significant differences between the groups. After two months of supplementation, there was no change in potassium and phosphorus plasma levels, but the Mg^{2+} serum levels were significantly increased in the chocolate group **(Figure 1)**.

Conclusions: Dark chocolate intake increased the Mg^{2+} serum levels in patients with CKD on HD. Therefore, dark chocolate might be a promising nutritional strategy to improve Mg^{2+} levels in patients with CKD on HD. The offered dose was safe, not altering plasma phosphorus and potassium levels.

Funding: Government Support - Non-U.S.

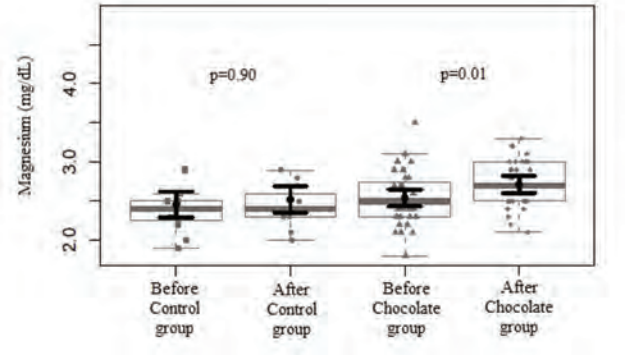

Figure 1. Comparison of plasma magnesium levels before and after two months in the control and chocolate groups.

TH-PO936

Febuxostat vs. Allopurinol in CKD Patients: Observational Study on Cardiovascular Events and Deaths

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Background: Recent trials have investigated the effects of urate-lowering agents, such as febuxostat and allopurinol. The CARES trial (2018) reported higher all-cause deaths with febuxostat compared to allopurinol. Then the FAST trial (2020) showed that febuxostat did not increase cardiovascular events nor deaths compared to allopurinol. However, these trials did not include severe chronic kidney disease patients, leaving uncertainty regarding febuxostat's efficacy in this population. Moreover, high prevalence of hyperuricemia in severe chronic kidney disease patients, we aimed to assess febuxostat's impact on cardiovascular events and deaths in this population.

Methods: We conducted an observational study using Japanese nationwide administrative data. Patients aged over 60 years with chronic kidney disease (eGFR<60ml/min/1.73 m^2), including severe CKD (eGFR <30), prescribed either febuxostat or allopurinol were identified. The outcomes were cardiovascular events (myocardial infarction, cerebral infarction, unstable angina requiring urgent revascularization) and all-cause deaths. We did intention-to-treat analysis, in which we ignored switching of drugs, using Cox proportional hazard regression models.

Results: A total of 4,793 patients were enrolled: febuxostat group (n = 3,783; median age 74 years; 2,479 [65.5%] men; 1,455 [38.5%] with diabetes; median eGFR 22.8ml/min/1.73m^2; median urate 8.3mg/dl) or allopurinol group (n = 596; median age 75 years; 426 [71.5%] men; 185 [31%] with diabetes; median eGFR 28.5ml/min/1.73m^2; median urate 7.3mg/dl). With respect to cardiovascular events and deaths, febuxostat (1032 patients [0.035 events per 100 patient-years]) was superior to allopurinol (227 patients [0.042 events per 100 patient-years]; adjusted HR 0.861 [95% CI 0.741 – 1.001]).

Conclusions: This analysis using Japanese nationwide data suggested that febuxostat seemed to decrease cardiovascular events and deaths compared to allopurinol in chronic kidney disease patients.

TH-PO937

Antioxidative Effects of Molybdenum and Its Association with Reduced Prevalence of Hyperuricemia in the Adult Population

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Background: The relationship between molybdenum and kidney-related disease outcomes, including hyperuricemia, is not well investigated. This study aims to determine whether molybdenum and its antioxidative property are associated with systemic inflammation and kidney-related disease parameters including hyperuricemia.

Methods: Urinary molybdenum's epidemiological relationship to hyperuricemia and kidney-disease related outcomes was evaluated in 15,370 adult participants in the National Health and Nutrition Examination Survey (NHANES) collected between 1999 and 2016. Individuals' urinary molybdenum levels were corrected to their urinary creatinine concentrations. The association between urinary molybdenum-to-creatinine ratio and kidney-disease related outcomes were assessed by multivariable linear and logistic regression analyses, adjusting for covariates including age, sex, ethnicity, diabetes mellitus, hypertension, body mass index, and estimated glomerular filtration rate. Antimony and tungsten were used as control trace metals. Experimentally, HK-2 cell was used to assess molybdenum's antioxidative properties. HK-2 cells were challenged with H2O2-induced oxidative stress. Oxidative stress was measured using a fluorescent microplate assay for reactive oxygen species (ROS) and antioxidation levels were assessed by measuring the expression of manganese superoxide dismutase.

Results: In the adult NHANES population, urinary molybdenum-to-creatinine ratio was significantly associated with decreased serum uric acid (β, -0.119; 95% CI, -0.148 to -0.090) concentrations, and decreased prevalence of hyperuricemia (OR, 0.73; 95% CI, 0.64-0.83) and gout (OR, 0.71; 95% CI, 0.52-0.94). Higher urinary molybdenum levels were associated with lower levels of systemic oxidative stress (gamma-glutamyltransferase levels; β, -0.052; 95% CI, -0.067 to -0.037) and inflammation (C-reactive protein levels; β, -0.184; 95% CI, -0.220 to -0.148). In HK-2 cells under H2O2-induced oxidative stress, molybdenum upregulated manganese superoxide dismutase expression and decreased oxidative stress.

Conclusions: Urinary molybdenum levels are associated with decreased prevalence of hyperuricemia and gout in adult population. Molybdenum's antioxidative properties might have acted as an important mechanism for the reduction of systemic inflammation, ROS, and uric acid levels.

TH-PO938

Characterizing the Metabolic Response of the Zebrafish Kidney to a High-Calorie Diet

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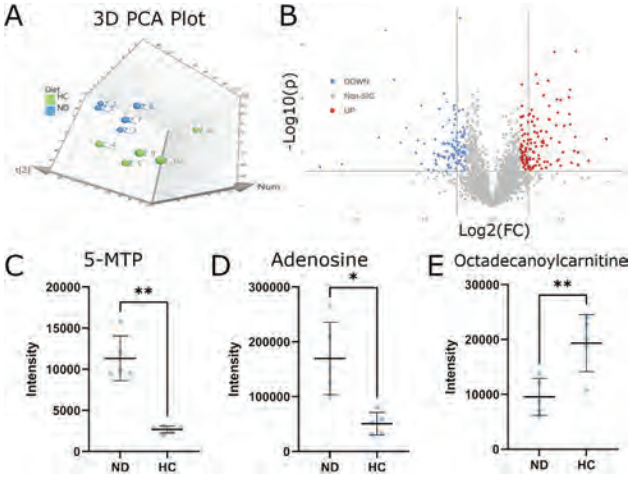
Background: Obesity is an epidemic risk factor for the development of chronic kidney disease. Obesity induces systemic changes in metabolism; its effect on kidney metabolism specifically is not known.

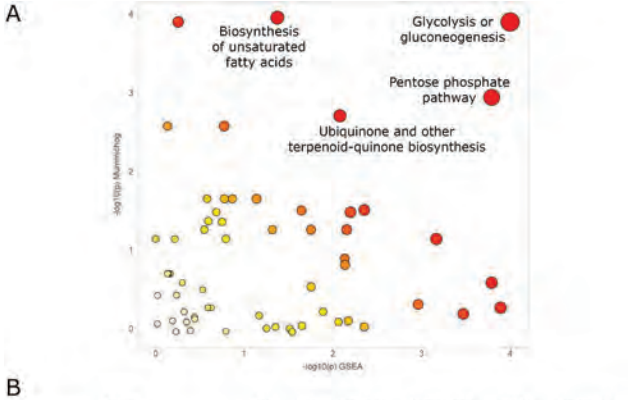
Methods: We treated zebrafish for 8 weeks with a control (ND) and a high calorie (HC) diet and performed an untargeted metabolomic analysis on the kidney tissue of fish using ultra-high performance liquid chromatography coupled mass spectrometry. We used mummichog and gene set enrichment analysis to uncover differentially affected metabolic pathways.

Results: Overfed zebrafish were heavier and had larger kidneys. Kidney metabolomes differed significantly **(Figure 1A)**, and 235 metabolites were significantly different between groups (125 upregulated in high calorie diet, 110 downregulated) **(Figure 1B)**. Analysis of specific metabolites suggested alterations in tryptophan

metabolism, purinergic signaling and fatty acid oxidation **(Figure 1C-E)**. Pathway analysis demonstrated alterations in metabolic pathways including glycolysis and fatty acid synthesis **(Figure 2A-B)**.

Conclusions: Our findings show that diet induced obesity leads to metabolic changes in the kidney tissue and implicate metabolic pathways including glycolysis and tryptophan metabolism in the pathogenesis of obesity related kidney disease, demonstrating the power of untargeted metabolomics to identify pathways of interest by directly interrogating kidney tissue.





B

Pathway	Total Size	Hits	Significant Hits	Mummichog p value	GSEA p value	Combined p value
Glycolysis or Gluconeogenesis	23	8	8	0.021	0.017	***0.0034***
Pentose phosphate pathway	22	8	6	0.055	0.021	***0.0091***
Biosynthesis of unsaturated fatty acids	33	6	6	0.021	0.24	***0.034***
Ubiquinone and other terpenoid-quinone biosynthesis	9	4	3	0.069	0.12	***0.048***
Glycerophospholipid metabolism	15	5	2	0.54	0.021	0.063
Galactose metabolism	27	18	11	0.32	0.04	0.068
Starch and sucrose metabolism	12	10	5	0.32	0.04	0.068
Glycerolipid metabolism	7	4	1	0.74	0.019	0.074
Folate biosynthesis	24	6	6	0.022	0.76	0.085
Vitamin B6 metabolism	9	3	2	0.22	0.092	0.093

TH-PO939

Diet Significantly Influences the Induction of Endoplasmic Reticulum Stress (ERS) in the Kidneys of Male C57Bl/6 Mice

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Background: Previous studies have associated ERS with different forms of kidney disease, but it is unclear whether ERS influences renal physiology in normal, non-diseased states. Previous work has suggested an interaction exists between diet and ERS in other organs. Therefore, this study aimed to determine if diet alters the severity of tunicamycin (TUN)-induced ERS in male C57Bl/6 mice.

Methods: Weanling male C57Bl/6 mice were randomly assigned to receive one of three diets: chow, commercially available Western Diet (WD), or a novel Americanized diet (AD) formulated to match 50th percentile nutrient intake in humans. After 6-weeks, mice were injected with TUN (1 mg/kg, IP), or saline, to induce ERS. 24-hours later, mice were euthanized, and plasma and kidneys were collected. Plasma BUN and creatinine were quantified using commercially available assays and mRNA expression of ERS-related genes was quantified using commercially available PCR arrays. All data were analyzed using GLM procedures and significance identified with $P<0.05$.

Results: Mice fed the WD had the greatest body weight and adiposity ($P\leq0.002$). TUN alone did not influence either measure, but a significant diet*TUN interaction was observed where only mice fed WD had a 20% reduction in body weight and adiposity ($P\leq0.01$) with TUN. TUN reduced ($P<0.001$) BUN (20.6±0.7 mg/dL) as compared to control mice (28.0±0.0.8), and a diet*TUN interaction was observed with mice fed AD having lower ($P<0.001$) BUN with TUN. Diet alone had no effect on BUN ($P=0.3$), but plasma creatinine was higher in mice fed AD regardless of TUN (0.65±0.04 mg/dL, $P=0.005$). Neither diet or TUN influenced renal inflammation by CD45$^+$ mRNA expression. Diet alone significantly ($P<0.05$) influenced the expression of 30% (26 of 84) of the quantified ERS-related genes, and a significant diet*TUN interaction was observed in 14 genes. Generally, mice fed the AD had greater change in ERS-related genes with TUN.

Conclusions: These data highlight an interaction between diet and ERS on renal function in a non-disease setting. Our data suggest that diet, formulated to model typical American intakes, modulates the expression of ERS-related genes. Further studies are needed to validate these findings and understand their physiologic significance.

TH-PO940

Alterations in Jejunal Transcriptome of Mice on High Fructose Diet Recapitulate Those of Jejunal Organoids in Obese Individuals

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Background: Metabolic syndrome (MetS) is manifested by visceral obesity, hypertension, and insulin resistance. The markedly increased incidence of MetS over the last 4 decades correlates with enhanced consumption of fructose and sucrose (a fructose/glucose disaccharide); yet, the pathogenesis of hypertension in MetS remains speculative. Increased consumption of fructose and sucrose activates molecules/pathways that enhance salt and carbohydrate absorption in the small intestine that are critical to the development of salt-overload and hypertension in MetS.

Methods: Jejunal transcriptomes of mice fed high fructose (HF) or high glucose (HG) at 60% vs. control for 2 weeks were compared to those of jejunal organoids from obese individuals (OI) (BMI>35) vs. lean subjects (BMI<25). Differentially expressed transcripts (DET) and activated pathways were identified. Northern/western blot analyses and immunofluorescence labeling were performed to verify the results.

Results: Expression of GLUT5 robustly increased in jejunum of OI and HF mice. The expression of PAT1 (SLC26A6), the Cl^-/HCO_3^- exchanger, which works with NHE-3 to absorb salt in the small intestine, was significantly increased along with ATP1B1 (the Na^+/K^+ ATPase B1 subunit) in OI and HF mice but not in HG mice. The expression levels of SGLT1, GLUT2, ATP1A1, INS2, and LEP significantly increased in OI, HF and HG groups. Mice on HG diet showed enhanced expression of MR (mineralocorticoid receptor) and SGK1 in jejunum, signifying NHE3 activation. KEGG enrichment analysis indicates that pathways critical to the development of obesity, diabetes, and hypertension are activated in OI, HF, and HG.

Conclusions: Robust expression of GLUT5, PAT1, and ATP1B1 in jejunum of OI and mice on HF diet strongly points to enhanced fructose and salt absorption in individuals with MetS. A similar activation of ATP1A1, GLUT2, and SGLT1 in OI, HF or HG points to additional pathways for salt and glucose/fructose absorption. Enhanced fructose or sucrose consumption in the setting of enhanced salt intake activates salt absorption in the small intestine, and can lead to a state of salt overload and hypertension in MetS/obesity.

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TH-PO941

Kynurenine 3-Monooxygenase Limits De Novo NAD+ Synthesis Through Dietary Tryptophan in Cultured Renal Proximal Tubule Epithelial Cells

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Background: Nicotinamide adenine dinucleotide (NAD^+) is an essential coenzyme involved in regulation of mitochondrial function. Depletion of kidney NAD^+ levels has been linked to acute kidney injury (AKI). The *de novo* NAD^+ can be synthesized through the tryptophan-kynurenine pathway. Renal proximal tubular epithelial cells (RPTECs) are susceptible to diverse injuries in AKI and maybe important for de novo NAD+ generation. However, despite feeding cultured RPTECs with isotope labeled tryptophan, we were unable to detect the synthesis of NAD^+. To address this, we aim to investigate whether the use of 3D culture of primary human RPTECs can enhance *de novo* NAD^+ synthesis.

Methods: Primary hRPTECs were cultured in ULA plates for 4 days to form spheroids. Gene expression levels were assessed by qPCR. Human Kynurenine 3-monooxygenase (hKMO) was overexpressed in hRPTEC spheroids through transduction of Adv-hKMO vector. Cells were treated with isotope-labeled Tryptophan (*Trp) or isotope-labeled 3-hydroxyanthranilic acid intermediate (*3HAA). The relative concentrations of intracellular *Trp, $*NAD^+$ and metabolite intermediates in the hRPTEC spheroids were analyzed by LC-MS/MS.

Results: 3D culture of primary human RPTECs led to a significant increase in the expression of tubular marker genes and enzyme genes involved in *de novo* NAD^+ synthesis. However, *de novo* NAD^+ synthesis was not detected. To investigate why 3D tubular cells were unable to metabolize Trp beyond kynurenine (KYN) metabolite, supplement of *3HAA to hRPTEC 3D spheroids was applied and resulted in its effective incorporation into $*NAD^+$. Furthermore, overexpressing KMO, the enzyme responsible for converting KYN to 3-hydroxykynurenine (3HK), achieved successful rescue of *de novo* NAD^+ synthesis through Trp in the hRPTEC 3D spheroids.

Conclusions: Our data demonstrate that 1) *in* cultured primary RPTECs, the tryptophan-kynurenine pathway loses its function for *de novo* NAD^+ synthesis, 2) the downregulation of a key enzyme gene *KMO* disrupts the conversion of KYN to 3HK in the pathway.

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TH-PO942

Glucocorticoid Treatment Induces Lymphatic Dysfunction via ATP-Sensitive Potassium Channel

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Background: Previously, we showed proteinuric disease impairs lymphatic vessel function. Glucocorticoid (GC) therapy is a cornerstone treatment of proteinuric diseases but commonly increases adiposity. Since lymphatics are the principal conduit for transport of lipoprotein particles and clearance of excess lipids, adiposity has been proposed as an indicator of impaired lymphatic function. We investigated whether glucocorticoids directly disrupt lymphatic integrity and function.

Methods: We exposed cultured lymphatic endothelial cells (LECs) to dexamethasone (DXMS) or control medium and assessed relevant parameters including proliferation, migration, and expression of tight junction protein-1 (*TJP1*), vascular endothelial growth factor receptor 3 (*VEGFR3* or *flt4*), and caspase 2/3/9 (*caps2/3/9*) genes. Ex vivo myography studies evaluated DXMS effects on dynamics by exposing isolated rat mesenteric lymphatic vessels to increasing concentrations of DXMS. We also studied mesenteric lymphatic dynamics in vessels harvested from rats receiving daily DXMS or vehicle x 2 weeks. Finally, we evaluated effects of chronic DXMS exposure on response to vasoactive agents: L-NAME, PGE_2, furosemide, and pinacidil, an ATP-sensitive potassium channel (K_{ATP}) agonist.

Results: Our findings revealed that DXMS significantly reduces proliferation, migration, and *TJP1* gene expression in LECs, while enhancing *Flt4* gene expression. DXMS did not alter apoptosis of LECs. In mesenteric lymphatic vessels isolated from normal rats, DXMS increased frequency and end-systolic diameter (ESD), along with decreased amplitude of contraction (AMP) and ejection fraction (EF) with little effects on end-diastolic diameter (EDD). Similarly, vessels from DXSM-treated rats had decreased AMP and EF vs vehicle-treated rats. Moreover, chronic exposure to DXMS dramatically diminished responsiveness to pinacidil when compared to vessels of control rats, suggesting that DXMS can alter lymphatic function via modulation of K_{ATP} channels.

Conclusions: Our data suggest the novel observations that glucocorticoids are powerful modulators of lymphatic vessel function, lymphatic endothelial cell integrity and growth. These alterations may contribute to impaired lipid clearance and visceral adiposity commonly associated with glucocorticoid therapy in the context of proteinuric kidney disease.

Funding: Other NIH Support - NHLBI

TH-PO943

Environmental Circadian Disruption Accelerates 5/6 Nephrectomy-Induced Chronic Kidney Injury in Mice

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Background: Circadian disruption such as shift work, jet lag, has gradually become a global health issue and is closely associated with many metabolic disorders. The effect and mechanism of circadian disruption on renal injury and chronic kidney disease (CKD) remains poorly understood. Here, we evaluated the effect of environmental light/dark shifting on the progression of chronic renal injury in CKD mice.

Methods: Mice were subjected to 5/6 nephrectomy and then exposed to either a standard 12h light/12h dark (12L/12D) cycle or weekly light-dark cycle reverse (LDDL) or weekly 6h phase advance (6h advance) for 3 months. Plasma and kidney tissues were harvested for renal function and histological examination. RNA-seq and untargeted metabolomics were performed for mechanistic investigation.

Results: The results showed that 3-month light interference by weekly LDDL significantly exacerbated renal dysfunction, accelerated renal injury, and promoted renal fibrosis in mice with 5/6 nephrectomy, while light interference by weekly 6h phase advance failed to worsen renal function and kidney injury. RNA-seq and untargeted metabolomics results revealed significant upregulation of genes related to inflammatory response and immune cell chemotaxis, while obvious downregulation of genes and metabolites related to energy metabolism was indicated in the LDDL-conditioned CKD kidneys. Consistently, the renal content of ATP was decreased and ROS production was increased in the residual kidney tissues of the LDDL-challenged CKD mice.

Conclusions: We concluded that circadian disruption by environmental light interference may aggravate chronic kidney injury by facilitating inflammatory response and suppressing energy metabolism in the CKD kidneys. Targeting the circadian machinery and keeping routine light-dark cycles may represent promising approaches for the prevention and treatment of CKD.

TH-PO944

Decreased TFH, GCB, PC, and Increased TFR Cell Frequencies in Spleen of Mice Fed with a Glutamine-Free Diet

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Background: We investigated the effects of a glutamine (Gln)-free diet (GFD) and the Gln analog 6-Diazo-5-oxo-L-norleucine (DON) on immune cell populations in mice. Specifically, T follicular helper cells (TFH), T follicular regulatory cells (TFR), germinal center B cells (GCB), and plasma cells (PC) in spleen. Additionally, we assessed the impact of CD4-specific GLS1 deficiency (KO) on TFH frequency and evaluated the therapeutic effects of GFD and DON in a lupus mouse model.

Methods: Animal and Groups: Eight-week-old WT B6 male mice were divided into four groups: chow+PBS or DON, GFD+PBS or DON. After 2-week treatment, mice immunized with LPS-OVA Alum and sacrificed 7.5 days later. **Cell Frequencies:** Flow cytometry was performed to determine the TFH, TFR, GCB, and PC frequencies. **CD4 T cell-GLS1 KO:** $GLS1^{f/f}CD4\text{-}cre^{0/0,\ Tg/0}$ mice were utilized. **Lupus Mouse Model and Therapeutic Interventions:** 1. Five- to six-month-old MRL/lpr mice were used and divided into two groups: GFD-fed mice and DON-treated mice. 2. Cell frequencies in spleen and kidney were determined. 3. Serum anti-ANA, anti-dsDNA, and IgG1 antibodies were measured. 4. Kidney sections were examined for anti-glomerulus IgG deposition.

Results: Effects of GFD and DON on T and B Cell Frequencies 1. Mice treated with chow+DON, GFD+PBS or DON exhibited decreased TFH, GCB, and PC frequencies compared to chow+PBS mice. 2. GFD+PBS treatment led to the highest frequency of TFR cells among all groups. **CD4 T Cell-GLS1 KO and TFH Frequency** CD4 T cells with GLS1 KO showed a primary reduction in TFH frequency. **Therapeutic Effects of GFD and DON in Lupus Mice** 1. Mice with GFD or DON exhibited amelioration of lupus symptoms. 2. TFH and PC frequencies in spleen were reduced in GFD-fed mice. 3. GFD and DON treatments resulted in lower level of serum anti-ANA, anti-dsDNA, and IgG1 antibodies. 4. DON treatment significantly reduced the total frequency of kidney infiltrated lymphocytes.

Conclusions: Our findings demonstrate that a GFD can decrease TFH, GCB, and PC cell frequencies, while increasing TFR cell frequency in spleen of mice. CD4 T cell-specific GLS1 KO primarily reduces TFH frequency. Furthermore, both GFD and DON show therapeutic effects in ameliorating lupus symptoms in the MRL/lpr mouse model. These results suggest the potential of manipulating Gln metabolism as a therapeutic strategy for autoimmune diseases like lupus.

Funding: Private Foundation Support

TH-PO945

Dietary Supplementation with Bacillus Superoxide Dismutase Protects Against Kidney Ischemia Reperfusion Injury in Mice

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Background: Superoxide dismutase (SOD) is a metalloenzyme that play an important role in antioxidant defense against oxidative stress. Bacillus strains are known to produce manganese containing SOD (Mn-SOD) and thus have been shown to have protective effect in inflammatory bowel disease animal model. Based on recent data showing the important role of gut dysbiosis, aberrant gut mucosal immunity as well as well-known oxidative stress in kidney injury, we investigated the renoprotective potential of orally administered enteric-coated SOD protein purified from *Bacillus amyloliquefaciens* (SOD-BA) in kidney ischemia/reperfusion injury (IRI) in mice.

Methods: Six week old C57BL/6 male mice were fed with SOD-BA 24 hours prior to IRI. Serum BUN, creatinine and histologic alterations as well as oxidative stress, inflammation in kidney tissue were determined. Gut microbiome analysis, permeability, epithelial damage as well as various antioxidant enzymes including catalase and SOD activity were also determined.

Results: Oral supplementation of SOD-BA conferred significant renoprotective effect in kidney IRI and this was associated with significantly increased level of SOD levels in kidneys. Gut microbiota structure in SOD-BA +IRI group was clearly distinguished from that of IRI group in principal coordinate analysis, showing that the relative frequency of family Porphyromonadaceae, Muribaculaceae and Bacteroidacea increased. SOD-BA administration also led to decreased colon epithelial apoptosis with partial restoration of gut permeability. Despite significant renoprotective effect, there was no difference in colon and kidney inflammation.

Conclusions: SOD-BA could be served as an orally available, potent antioxidant in the prevention and treatment of acute kidney injury. Our data showed a therapeutic potential of gut bacterial product in kidney IRI that can overcome the safety issue regarding the use of probiotics.

TH-PO946

Case Report on Successful Treatment of Life-Threatening Anemia in ESRD Patient on Maintenance Hemodialysis Who Is a Jehovah Witness and Refusing Blood Transfusion

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Introduction: Anemia is prevalent in patients with advanced chronic kidney disease (CKD) and end-stage renal disease (ESRD) who undergo regular hemodialysis. This is primarily attributed to reduced production of erythropoietin by the kidneys. Existing guidelines recommend managing anemia when the hemoglobin (Hgb) is below 11 g/dL by administering intravenous iron and erythropoietin injections. In cases who have severe anemia with hemoglobin levels below 7-8 g/dL and experience symptoms, blood transfusion is typically recommended. Blood transfusions help in correcting anemia, alleviating symptoms, and enhancing tissue oxygenation. However, providing appropriate treatment for anemia becomes challenging when patients refuse blood transfusion due to religious beliefs, such as our patient. In our case report, we present a successful treatment approach for severe anemia in an ESRD patient without utilizing blood transfusions.

Case Description: 60-year-old woman with history of Hypertension, ESRD on hemodialysis (HD) due to Systemic lupus erythematosus with failed kidney transplant presented with altered mentation. She was found hemodynamically unstable, in atrial-flutter requiring ablation and cardiac monitoring on admission. She had a long hospitalization with Hgb at presentation~9. It gradually went down to 4.8 over 3 weeks. Due to her religious beliefs as a Jehovah's witness, she declined blood transfusion. To treat her anemia, we initiated a daily treatment regimen consisting of short-acting erythropoietin alfa at a dose of 40,000 Units for seven days, along with daily intravenous iron sucrose at 100 mg. After one week of this treatment, the patient's hemoglobin level improved to 11.5 g/dL and felt markedly better.

Discussion: For Jehovah Witness patients undergoing HD, who have severe anemia and decline blood transfusions, we suggest initiating a daily, short-term treatment of erythropoietin alfa at a dosage of 40,000 U, alongside intravenous iron, for a duration of one week. If the patient is already receiving long-acting darbepoetin alfa, it is advised to transition to short-acting erythropoietin alfa. This approach may also be applied for preoperative management of significant anemia, regardless of whether the patients are receiving renal replacement therapy or not.

TH-PO947

SGLT2i-Induced Erythrocytosis Unveiling Heterozygous Hereditary Hemochromatosis (HH) Gene Mutation in an Individual with CKD

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Introduction: SGLT2i were shown to increase hemoglobin (Hb) levels in clinical trials. We report a case of symptomatic erythrocytosis in an individual treated with SGLT2i empagliflozin who was later found to have a HH gene mutation.

Case Description: This was a 72-yo male with CKD and baseline serum creatinine (SCr) of 2.1mg/dL (eGFR 33mL/min/1.73m^2), controlled type 2 diabetes (A1C 6.9%) and hypertension. Empagliflozin 12.5mg daily was initiated due to persistent grade A3 proteinuria (uACR ~1.5g/g) despite daily combination of losartan 100mg and spironolactone 25mg. Hb and hematocrit (Hct) were 16.8g/dL (normal 13.5-17) and 49.5% (normal 38-50) at the time of SGLT2i start. The patient had no history of obstructive sleep apnea. There was a remote history (>30 years ago) of smoking. Over the years, he had intermittent mild Hb elevation in 17-17.5g/dL range. At that time, erythropoietin level was normal and polycythemia vera was excluded. Within 6 months of empagliflozin initiation, Hb (Hct) gradually rose to 20g/dL (59.3%) despite advice to maintain adequate hydration. The patient reported worsening fatigue and diffuse myalgias. Physical examination and vital signs were normal. Transferrin saturation (Tsat) was 30%. Ferritin was 145ng/mL. SCr rose to 2.6mg/dL (eGFR 25 ml/min/1.73m^2). Screening for HH in the nephrology clinic revealed H63D heterozygosity in the HFE (Hemostatic Iron regulator) gene and negative C282Y gene mutation. Two serial phlebotomies were performed and lead to the normalization of Hb (Hct) to 16.5g/dL (48%), resolution of symptoms, and an improvement in SCr to 2.0mg/dL (eGFR 35 ml/min/1.73m^2). Tsat and ferritin remained stable. Empagliflozin was continued for renoprotection. Monthly phlebotomy was continued to maintain adequate Hb.

Discussion: SGLT2i reduce risk of anemia in patients with CKD. Their use may also be associated with erythrocytosis. The presence of underlying heterozygous HH gene mutation was likely predisposing risk factor of SGLT2i-induced erythrocytosis. This case suggests that periodic monitoring of Hb level should be considered. Additionally, screening for HH could be offered to patients with SGLT2i-induced erythrocytosis to implement phlebotomy if a HFE gene mutation is detected. Stopping SGLT2i will likely lower Hb to baseline, but it will also remove their cardiorenal benefits.

TH-PO948

Successful Treatment of Anemia with Roxadustat in a Hemodialysis Patient Following Erythropoietin-Induced Pure Red Cell Aplasia

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Introduction: Erythropoietin (EPO) antibody (Ab)-induced Pure Red Cell Aplasia (PRCA) is a rare condition. Treatment usually requires immediate withdrawal of EPO and treatment with immunosuppression or renal transplantation. Here, we present the successful treatment of a case of EPO Ab-induced PRCA with cyclosporin (CyA) and Roxadustat, a hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI).

Case Description: A 58-year-old man developed kidney failure as a result of diabetes mellitus. In July 2021, shortly before he began dialysis, he was commenced rHuEPO (Jimaixin, epoetin-α, KexingBio, Shandong, China) subcutaneously 5000 IU twice a week. He began hemodialysis (HD) in November 2021. He was switched to intravenous rHuEPO (6000 IU) (Yipuding, epoetin-α, NCPC GenetechBio, Hebei, China) once a week. His Hb increased to 116 g/L in the first 3 months but fell to 75 g/L 6 months into HD. 3½ weeks later, he presented with a pneumonia and a Hb of 48 g/L. He was treated with antibiotics and was transfused. His EPO was stopped. He was started on Roxadustat. 18 days later, his Hb fell to 38 g/L, his reticulocytes was 2900/uL. A bone marrow (BM) biopsy showed a proliferative active BM but reduced erythropoiesis and an erythroid precursor of 7%. A diagnosis of EPO Ab-induced PRCA was suspected. However, an anti-EPO Ab ELISA test later turned out negative. Some likely causes of PRCA such as lymphoproliferative disorder, parvovirus B19 infection, thymoma and systemic autoimmune disease were excluded. The Roxadustat was discontinued. A second BM biopsy showed a erythroid precursors of 5.2%. The suspicion of a EPO Ab-induced PRCA was maintained. The patient was commenced CyA 3mg/kg/day and was given 25 more units of blood over 2 months. The reticulocyte counts took 3 months to recover to normal. The patient was recommenced on Roxadustat 100 mg TIW and his Hb stabilized.

Discussion: Even though the anti-EPO Ab was negative by ELISA assay in our case, the clinical course, with markedly reduced reticulocyte count <10000/ul, a BM biopsy revealing reduced erythroblasts only, and its subsequent response to CyA, were in keeping with EPO Ab-induced PRCA. Anti EPO Ab assay is not always positive in EPO Ab-induced PRCA. Our case illustrates that treatment with Cyclosporin and a switch to Roxadustat are useful in treating EPO Ab-induced PRCA.

TH-PO949

Risk Factors Involved in Erythropoietin Resistance in Patients with CKD in a Hemodialysis Unit

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Background: Recombinant human erythropoietin is administered to patients with end-stage chronic kidney disease for the treatment of anemia. However, there are different factors that generate resistance to this treatment. This paper seeks to evaluate the impact of a structured team approach for the management of anemia in erythropoietin-resistant hemodialysis patients.

Methods: Prospective study of 18 months. A total of 27 patients in a hemodialysis unit of a reference center, where erythropoietin resistance was defined as those patients who had erythropoietin >300 units/kg/week. Hemoglobin, iron indices, parathyroid hormone, folate, vitamin B12, and reticulocyte counts were determined at baseline. Said previous parameters were followed every 6, 12 and 18 months. The target hemoglobin was 10-12 g/dl. All factors potentially contributing to erythropoietin resistance were evaluated and, if possible, treated every 4 weeks by a specialized nephrology team. Downward erythropoietin dose adjustments of 12.5 to 25% to the nearest 1000 units were considered if the underlying causes of resistance could not be identified or reversed, or if hemoglobin exceeded the target level.

Results: Parathormone levels and iron deficiency were the predominant treatable factors associated with erythropoietin resistance. At 4 months, mean erythropoietin dose decreased significantly from 469 to 319 units/kg/week ($p < 0.001$) and mean hemoglobin increased significantly from 10.6 to 11.6 g/dl ($p = 0.023$), a At 8 months, the patients had erythropoietin doses of less than 300 units/kg/week, reaching target hemoglobin levels.

Conclusions: A structured team approach of nephrologists and a monthly adaptation with an individualized management of the patient managed to significantly reduce the dose of erythropoietin with an improvement in serum hemoglobin reaching the objectives set in the international guidelines, identifying and solving the factors involved.

TH-PO950

3-Carboxy-4-Methyl-5-Propyl-2-Furanpropionate (CMPF), an Endogenous Protein-Bound Uremic Solute, Renders Erythrocyte Osmotically More Fragile, Possibly Through a Piezo1 Pathway

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Background: Shortened red blood cell (RBC) life span contributes to renal anemia and may be caused by uremia-induced premature RBC death (eryptosis). Recently, it was hypothesized that the uremic solute CMPF interacts with the Piezo1 mechanoreceptor on the RBC surface due to CMPF's structural similarity with Jedi1, a well-characterized synthetic Piezo1 agonist (Kotanko *et al*., 2022). In this study, we compared the effects of Jedi1 and CMPF on RBC osmotic fragility.

Methods: RBC from 5 healthy subjects were incubated for 30 min with CMPF or Jedi1 (both at concentrations of 87 μM) in phosphate-buffered saline with 4% human serum albumin. RBC incubated without CMPF or Jedi1 were negative controls. Subsequently, RBC suspensions were incubated in NaCl solutions of increasing osmolarity (NaCl 3 to 9 g/L). Free hemoglobin was measured in the supernatant by spectrophotometry at 540 nm. The data were fitted to a 4-parameter logistic regression curve to obtain the osmotic fragility index (IC50). IC50 is defined as the NaCl concentration that causes 50% hemolysis.

Results: RBC incubation with CMPF or Jedi1 increased IC50 (i.e., increased osmotic fragility) when compared to the negative control (Table 1). The IC50 increase was most pronounced in RBC incubated with CMPF.

Conclusions: Our findings suggest that CMPF - an endogenous metabolite and uremic solute - may increase RBC osmotic fragility, possibly through a Piezo1 pathway. Understanding the molecular mechanisms involved may aid the developing new therapeutic approaches to renal anemia.

Table 1 – RBC osmotic fragility index (IC50) under different experimental conditions

Experimental condition	IC50 mean±SD (95% CI)	Mean IC50 difference (95%CI) to controls	p-value
Negative control	4.57 ± 0.31 (4.18 – 4.97)	Not applicable	Not applicable
Jedi1 (87μM)	5.02 ± 0.28 (4.66 – 5.37)	0.45 (0.06 – 0.83)	0.031
CMPF (87μM)	5.57 ± 0.39 (5.09 – 6.06)	1.00 (0.61 – 1.38)	0.002

TH-PO951

A Retrospective View of the Relationship of Soluble Fas with Anemia and Outcomes in CKD

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Background: Anemia is common in chronic kidney disease (CKD) and is related to serum levels of soluble Fas (sFas), which are associated with resistance to erythropoietin (EPO). The study objeticves to compare clinical data and serum levels of sFas, EPO, and pro- inflammatory markers between non-dialytic CKD patients and healthy individuals. To assess the relationship of serum EPO and sFas between these patients with and without anemia.

Methods: Retrospective study of 58 CKD patients under conservative treatment and 20 healthy individuals. Complete blood count, renal function, serum EPO, sFas, and inflammatory markers (CRP, IL-6, and IFN-γ) were compared at baseline. We then analyzed these variables between patients who progressed to anemia and those without anemia. We evaluated the frequency of outcomes in these patients with elevated sFas levels. We performed a multivariate analysis of factors associated with anemia.

Results: CKD when compared to healthy individuals had lower eGFR (35.7 ±2.5 vs 89.7 ±3.32 ml/min; p<0.001), and Hb (12.8 ±0.27 vs 14.4 ± 0.25 g/dl; p=0.003), major inflammatory markers, sFas (2894 ±172 vs 1136 ±97pg/ml; p<0.001), and EPO/Hb (8.76 ±1.16 vs 4.90 ± 0.58 IU/mg/dl; p=0.003). CKD with anemia, when compared to non-anemic individuals, had lower eGFR (27.7 ±1.72 vs 54.9 ±5.26; p<0.001) and higher sFas/ eGFR (150.9 ±16.6 vs 45.2 ±9.95; p<0.001), EPO/Hb (10.3 ±1.56 vs 5.12 ±0.69; p=0.04) and sFas (3339 ±181 vs 1820 ±240; p=0.001). We found an independent association in the multivariate analysis of serum sFas levels with long-term renal anemia sFas (OR 4.322, 95% CI, 1464-12.753; p=0.008).

Conclusions: As an elective risk factor, serum sFas levels were independently associated with long-term renal anemia.

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TH-PO952

Depression and Anxiety Are Associated with Iron Deficiency Anemia for Patients with Stages 2-4 CKD

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Background: Neuropsychiatric disorders, mainly cognitive decline, depression, and anxiety, are more common in CKD patients. The association between iron deficiency anemia (IDA) and cognitive decline is well-known for this population. For patients without CKD, IDA is associated with depression and anxiety. However, the link between depression, anxiety, and IDA is not clear in subjects with non-dialysis-dependent CKD. In this work, we aimed to evaluate the association above.

Methods: We selected a cohort of patients with stable stage 2-4 CKD and assessed them with Beck's depression inventory (BDI) and Beck's anxiety inventory (BAI). We excluded patients with acute kidney injury or decompensation, hematological/ solid malignancies, and those suffering from psychological trauma. A diagnosis of schizophrenia, major depression, and bipolar disorder or using antidepressant/ antipsychotic drugs were reasons for exclusion. We also did not include those needing EPO or those with other causes of anemia.

Results: Two hundred patients were included in the final analysis. 76 of 200 (38%) patients were anemic. Patients with anemia were older and had worse GFR. BDI scores were worse for patients with anemia. Furthermore, with a cut-off of eleven for BDI, 31,7% of patients in non-anemic and 51,4% of patients in anemic groups deserved further evaluation for clinical depression. The difference was significant (p=0,007). Univariate analysis did not reveal a relationship between BDI and hemoglobin, transferrin saturation, and ferritin levels. A multivariate analysis was not undertaken due to the low number of patients. A subgroup analysis of anemic patients also showed that patients who had received iron, despite being still anemic, had lower BDI scores compared to those with untreated anemia (p<0,001) BAI scores were similar between groups. In addition, frequencies of minimal, mild, moderate, and severe anxiety were similar. However, in subgroup analysis, patients who had received iron despite being still anemic had lower BAI scores than those with untreated anemia.

Conclusions: Our work hints at a viable link between depression, anxiety, and IDA in subjects with Stage 2-4 CKD. However, this study is observational and thus only can generate a hypothesis. Prospectively designed studies on iron replacement may further elaborate our understanding of these associations.

TH-PO953

Red Blood Cell Transfusion Rates in the Early Dialysis Period: Comparing Hemodialysis (DOPPS) and Peritoneal Dialysis (PDOPPS) in an International Setting

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Background: The transition to dialysis is a period of clinical instability during which red blood cell transfusion (RBCT) use may be indicated. Given key differences in pre-dialysis nephrologist care and anemia management between patients who initiate hemodialysis (HD) and peritoneal dialysis (PD), patterns in RBCT rates in the early dialysis period should be investigated.

Methods: We used data from 22,643 in-center HD patients from 20 countries in the Dialysis Outcomes and Practice Patterns Study (DOPPS) phases 5–7 (2012–2022) and 3557 PD patients from 6 countries in the Peritoneal DOPPS (PDOPPS) phase 1 (2014-2018). In these prospective cohort studies, RBCT receipt (yes/no) was prospectively captured each month, with rates presented by time since dialysis initiation (vintage).

Results: Hemoglobin levels measured within 30 days after dialysis initiation were lower in HD (mean 9.5; 37% <9 g/dL) vs. PD (mean 10.8; 12% <9 g/dL) patients. The RBCT rate (per 100 patient-years) was 74.0 during the first 90 days of HD vs. 12.7 during the first 90 days of PD. After 90 days, RBCT rates were very similar in the HD (21.0) vs. PD (20.8) populations. These patterns – relatively lower RBCT rates during the early PD period but higher RBCT rates during the early HD period – were consistently observed across countries, with rates generally stabilizing after the first 9–12 months of dialysis (Figure 1).

Conclusions: Using uniform and standardized RBCT capture across countries and modalities, this study showed high RBCT rates in the first few months of HD, but not PD, therapy, likely reflecting differences in patient profiles. When considering the short-term and long-term risks of RBCT, awareness of this relationship may help inform anemia management before, during, and after this important transition period to reduce the need for RBCT intervention.

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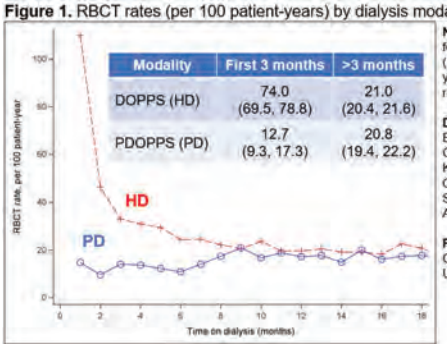
Figure 1. RBCT rates (per 100 patient-years) by dialysis modality and vintage



Notes: 95% confidence intervals for red blood cell transfusion (RBCT) rates (per 100 patient-years) estimated by Poisson regression.

DOPPS countries: Australia, Bahrain, Belgium, Canada, China, France, Germany, Italy, Kuwait, New Zealand, Oman, Qatar, Russia, Saudi Arabia, Spain, Sweden, Turkey, United Arab Emirates, UK, US.

PDOPPS countries: Australia, Canada, New Zealand, Thailand, UK, US.

TH-PO954

Hemoglobin Level Variability and Infectious Risk in Hemodialysis Patients in the Era of Long-Acting Injectable Erythropoiesis-Stimulating Agents

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Background: Target hemoglobin level is suggested in the management of chronic kidney disease. However, hemoglobin levels often fall below or exceed the target range. Past retrospective cohort studies of patients undergoing hemodialysis with conventional short-acting erythropoiesis stimulating agents found that hemoglobin level fluctuations predicted mortality and cardiovascular adverse events; thereafter long-acting agents have been widely available.

Methods: We adopted Cox regression models to evaluate associations between hemoglobin level variability and all-cause death, hospitalization, and cardiovascular, thrombotic, or infectious adverse event outcomes in 3,063 hemodialysis patients' data from the Japanese Dialysis Outcomes and Practice Patterns Study from 2012 to 2018.

Results: All-cause mortality was lowest in the first quartile and tended to be higher in the groups with greater hemoglobin variability (hazard ratio: 95% confidence interval for the fourth quartile of an absolute value of hemoglobin variability: 1.44 [0.99–2.08], p for trend = 0.056). Intriguingly, infectious event incidence was higher than the first quartile for the second through fourth quartiles (p for trend <0.01). The association was more pronounced in patients with lower serum ferritin levels or with iron supplementation. However, cardiovascular and thrombotic event incidence was not associated with hemoglobin variability.

Conclusions: Maintenance hemodialysis patients on erythropoiesis stimulating agent treatment with higher hemoglobin variability are at higher risk for all-cause mortality and particularly infectious events.

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TH-PO955

Hemoglobin Variability in Hemodialysis Patients Improves Under Individualized Anemia Therapy

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Background: Anemia is a common complication in patients receiving hemodialysis. Anemia treatment with erythropoiesis-stimulating agents (ESAs) is challenging and Hgb outcomes vary widely in clinical practice. In a randomized controlled clinical trial (RCT), we investigated the impact of an individualized anemia therapy tool on hemoglobin (Hgb) variability.

Methods: Patients were randomized 1:1 to be treated with an individualized ESA dose recommendation tool (intervention (INT) group) or an anemia management protocol (standard of care (SoC) group) for 26 weeks; 82 patients completed the study (INT: N=40, SoC: N=42). The recommendation tool utilized a previously validated physiology-based model of anemia to estimate key patient-specific physiological characteristics, such as red blood cell lifespan, to create a digital twin from recent routine clinical data (Fuertinger et al., PLOS ONE 13(4):e0195918, 2018). Based on the patient's digital twin, individual ESA dose recommendations for methoxy polyethylene glycol-epoetin beta were generated to target a Hgb window of 10-11 g/dL.

Results: Interpatient variation in mean Hb levels over the study period was smaller in the INT group than in the SoC group (Variance 0.15 vs 0.66 g^2/dL^2, F-test, p<0.001) while the mean shifted to the center of the target range (10.5 vs 10.8 g/dl). The distributions of mean monthly Hgb levels progressively narrowed in the INT group over time (see Fig. 1, left panel). Further, intrapatient Hgb variability, defined as the standard deviation around the mean Hgb levels, improved in the INT group compared to the SoC group (median [IQR]: 0.7 [0.3] vs 0.9 [0.6] g/dL, Wilcoxon-rank sum test, p=0.001) (see Fig 1, right panel).

Conclusions: The RCT results suggest that the individual ESA recommendations of the anemia therapy tool improves inter- and intrapatient Hgb variability, while also bringing mean Hgb levels into the desired target range.

Funding: Commercial Support - Fresenius Medical Care

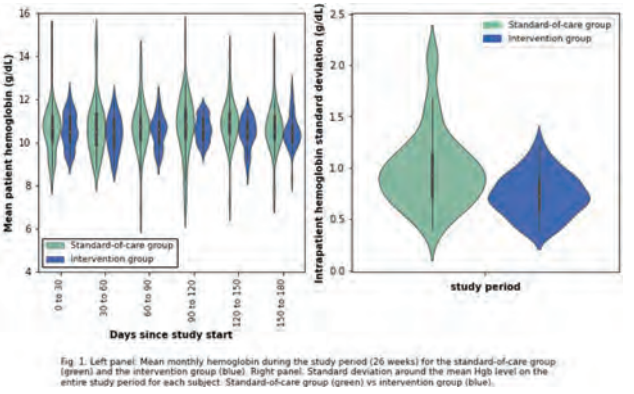

Fig. 1. Left panel: Mean monthly hemoglobin during the study period (26 weeks) for the standard-of-care group (green) and the intervention group (blue). Right panel. Standard deviation around the mean Hgb level on the entire study period for each subject. Standard-of-care group (green) vs intervention group (blue).

TH-PO956

Hemoglobin Variability Is Associated with Nutritional Status in Hemodialysis Patients Undergoing Darbepoetin-Alfa Treatment

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Background: Anemia is common in hemodialysis (HD) patients, and their response to erythropoietin (EPO) treatment is inconsistent. Fluctuations in hemoglobin levels, known as Hb variability, occur during EPO therapy. This study investigated the association between EPO responsiveness, Hb variability, and nutritional status in HD patients undergoing NESP® (darbepoetin-alfa; Kyowa Kirin Korea Co., Ltd.) treatment.

Methods: This prospective study enrolled 98 adult HD patients (age >20 years, HD vintage >6 months). The target Hb level followed Korean reimbursement guidelines (10-11 g/dL). NESP® dosage adjustments were based on monthly Hb measurements. EPO resistance index (ERI) was calculated as the average weekly NESP® dose divided by Hb level. Hb variability was assessed using Hb-Coefficient of Variation (Hb-CV) with over 24 monthly Hb data points. Nutritional parameters, including body mass index (BMI), fat tissue index (FTI), lean tissue index (LTI), body cell mass index (BCMI), and phase angle (PhA), were evaluated using BCM® (Fresenius Medical Care a Deutschland GmbH, Germany). Clinical and biochemical parameters were also considered.

Results: The study comprised patients with a mean age of 64.0±11.9 years, of which 55.0% were male. HD vintage averaged 54.9±46.8 months, and the follow-up duration was 79.3±47.9 months. Mean Hb level was 10.7±1.3 g/dL. Patients were divided into tertiles based on ERI and Hb-CV. The average ERI was 0.02±0.01, 0.04±0.01, and 0.07±0.03 in ERI-T1, ERI-T2, and ERI-T3, respectively. The ERI-T3 group exhibited lower Hb levels (p=0.038) and higher EPO doses (p=0.001). ERI-T3 correlated with lower PhA (p=0.044), BMI (p=0.001), and FTI (p=0.046). The Hb-CV-T3 group displayed lower BMI (p=0.002) and FTI (p=0.002). FTI was negatively correlated with ERI (r= -0.193, p=0.046) and Hb-CV (r= -0.268, p=0.005) and positively correlated with age (r=0.197, p=0.017) and female sex (r=0.386, p=0.001). Multiple linear regression analysis indicated a negative association between FTI and ERI (β= -0.218, p=0.014) as well as Hb-CV (β= -0.181, p=0.039). Age (β= 0.197, p=0.017) and female sex (β= 0.386, p=0.001) were positively associated with FTI.

Conclusions: Higher EPO resistance and Hb variability were associated with compromised nutritional status, particularly reduced fat tissue, in HD patients on darbepoetin-alfa.

TH-PO957

Red Blood Cell Distribution Width-Coefficient of Variation as an Indicator of the Requirement for and Efficacy of Daprodustat in Hemodialysis Patients Switching from Erythropoietin-Stimulating Agents

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Background: Red blood cell distribution width (RDW) is an index of red blood cell volume variability and is used as a marker of iron deficiency anemia. In both hemodialysis and chronic kidney disease patients, a high RDW is associated with a higher mortality risk. Indicators of the requirement for and efficacy of daprodustat have not been reported previously. Therefore, we investigated whether the RDW-coefficient of variation (CV) is an indicator of the requirement for and efficacy of daprodustat when switching from erythropoietin-stimulating agents (ESAs) to daprodustat in patients undergoing maintenance hemodialysis.

Methods: This historical cohort study included 37 patients undergoing maintenance hemodialysis and who switched from ESAs to daprodustat at our affiliated institutions.

The patients were divided into two groups by an RDW-CV cut-off of 14.2%. Propensity score matching was performed by sex, diabetes mellitus, iron sufficiency, albumin concentration, and C-reactive protein concentration. We examined whether there was a difference in the requirement for daprodustat and in the hypoxia-inducible factor prolyl hydroxylase inhibitor resistance index (HRI; defined as daprodustat dose / dry weight / hemoglobin) after 6 months between the two groups.

Results: In the two groups of patients matched for background factors by propensity scores (10 patients with an RDW-CV of ≤14.2%, 10 patients with an RDW-CV of >14.2%), significant differences were observed in both the requirement for daprodustat (4.4 mg at an RDW-CV of ≤14.2%, 8.0 mg at an RDW-CV of >14.2%; $P < 0.05$) and HRI (0.0068 at an RDW-CV of ≤14.2%, 0.0120 at an RDW-CV of >14.2%; $P < 0.05$) after 6 months.

Conclusions: RDW-CV is an indicator of the requirement for and efficacy of daprodustat in hemodialysis patients switching from ESAs.

TH-PO958

High Hemoglobin and High ESA Responsiveness Are Good Prognostic Factors in CKD Patients: An Attribute-Based Analysis Using a Cross-Classification Approach in the BRIGHTEN Study

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Background: The BRIGHTEN study, a multicenter, prospective, observational study for patients with non-dialysis-dependent chronic kidney disease with renal anemia, reported the initial erythropoiesis-stimulating agent (ESA) response index (iEResI) to be positively associated with male sex, low hemoglobin (Hb) and iron supplementation, and darbepoetin alfa (DA) administration frequency, suggesting that the iEResI could associated with 'adequacy of anemia treatment'.

Methods: We analyzed the data for the 1,480 patients registered in the BRIGHTEN study. The primary outcome was progression of renal dysfunction. The iEResI was calculated by dividing Hb changes resulting from 12-week DA administration by the weight-adjusted total dose of DA administered in that period. Cross-classification (4 groups) of sex × 65 years was used for analysis per attribute.

Results: The baseline Hb levels were similar in all groups, ranging between 9.7–9.9 g/dL, regardless of sex or age. The DA dose/kg was the lowest in men <65 years (0.80 μg/kg/12 weeks) and the highest in women >65 years (1.08 μg/kg/12 weeks), whereas iEResI was the highest in men <65 years (0.61) and the lowest in women >65 years (0.45). The Kaplan–Meier survival curves indicated that men <65 years and women >65 years had the worst and best renal prognoses, respectively, among the cross-classified sub-cohorts. Multivariate Cox analyses in the present study revealed that high levels of Hb (hazard ratio [HR] 0.75, P<0.001) and high levels of iEResI (HR 0.77, P=0.002) were associated with good renal prognosis. Notably, when divided into four subgroups for cross-classification, anemia was associated with renal prognosis in three subgroups: men <65 years, men >65 years, and women >65 years, whereas iEResI was associated with renal prognosis only in men <65 years. In men <65 years, iEResI (HR 0.63, P=0.030), Hb (HR 0.65, P<0.001), eGFR (HR 0.91, P<0.001), and urinary protein excretion (HR 1.12, P<0.001) were associated with renal prognosis.

Conclusions: Anemia and ESA response index (iEResI) were associated with renal prognosis, suggesting that anemia treatment may improve renal prognosis. Cross-classification clarified that men <65 years may benefit more from anemia treatment than other patients.

TH-PO959

Patient-Reported Outcomes in a Real-World Study of Anemia of CKD in the Middle East and Africa

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Background: Anemia is a common complication of chronic kidney disease (CKD) that can negatively impact quality of life. Treatment satisfaction of patients with anemia of CKD living in the Middle East or Africa was explored.

Methods: SATISFY was a real-world study in Egypt, Saudi Arabia, South Africa and Turkey (1 Jun–1 Sep 2022). Physicians and patients completed cross-sectional surveys of treatment perceptions; patients' clinical characteristics were recorded via retrospective review of medical records. Eligible physicians were nephrologists with ≥1 year of experience. Eligible patients were aged ≥18 years with CKD stage 3b–5 at anemia diagnosis and ≥2 years of follow-up data. Data were analyzed descriptively.

Results: In total, 217 physicians and 766 patients (457 [60%] non-dialysis dependent; 286 [37%] dialysis dependent; 23 missing [3%] at data extraction) completed surveys. Mean patient age (standard deviation) was 48 (14) years; 457 (60%) were male. Treatment satisfaction was high (89% of physicians and 84% of treated patients [n=478] were satisfied/very satisfied). Overall, 24% of treated patients had severe-to-very severe anemia symptoms, 15% reported worsening symptoms since initiating most recent treatment and 38% had quite-to-very bothersome side-effects (**Figure**). Over 80% of both patients and physicians reported that physicians made the final treatment decisions.

Conclusions: Despite high treatment satisfaction, patients with anemia of CKD in the Middle East and Africa reported high symptom burden, treatment side-effects and worsening of symptoms, suggesting a high unmet need.

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Figure 1. Patient global impressions of symptom severity, change in symptoms since initiating most recent treatment and treatment tolerability (proportion of patients)

Data shown are for patients who were receiving treatment or on treatment holiday at time of data extraction.

DD, dialysis dependent; NDD, non-dialysis dependent; Patient Global Impressions of Severity (PGI-S), severity of anemia symptoms within 7 days prior to data collection; PGI-C, Patient Global Impressions of Change (PGI-C), change in anemia symptoms since patients started their current treatment; Patient Global Impressions of Treatment Tolerability (PGI-TT), how bothersome side-effects of current treatment were within the 7 days prior to data collection.

TH-PO960

Physical Quality of Life, Anemia, and Iron Stores Among Incident Peritoneal Dialysis Patients: Preliminary Findings from a Multinational Observational Study

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Background: Adequate hemoglobin (Hb) and iron reserves are vital for tissue/organ functions, and impaired oxygen delivery and iron availability can lead to fatigue and reduced exercise tolerance, ultimately impacting a patient's quality of life (QoL). We aimed to describe biomarkers of anemia and iron stores across different thresholds of KDQOL Physical Component Summary (PCS) scores in patients starting peritoneal dialysis (PD).

Methods: We used data on incident PD patients from a cohort in Brazil (BR) and the United States (US) during Dec 2004-Jan 2011. Patient, lab, and medication data was compared by PCS categories representing an individual's physical well-being/ functioning. PCS scores were categorized as ≤35 (low PCS), >35 to ≤40 (moderate-low PCS), >40 to ≤50 (moderate-high PCS), >50 (high PCS).

Results: Demographics for patients who started PD (BR=2,022; US=1,657) were consistent between countries for mean age (BR=57.3 & US=55.6 years) and albumin (both 3.7 g/dL), yet there were more males (BR=45% vs US=54%) and patients of a white race (BR=62% vs US=72%) in the US. Mean PCS scores were slightly higher in BR (41.2) vs the US (38.4). Patients in BR had higher TSAT values (43%) vs the US (30.5%). Erythropoietic stimulating agents (ESA) use was higher in the US (90%) than in BR (35%), as was IV iron use (BR=35% vs. US=42%). Across both cohorts, patients with lower PCS tended to be older, with lower albumin and higher ferritin. While use of ESA tended to be a little higher among patients with lower PCS, Hb and TSAT were similarly distributed across groups in both cohorts (**Figure 1**).

Conclusions: Physical QOL among patients starting PD in BR and the US appeared to be related to age, nutrition, and ferritin levels. Patients with low PCS scores had relatively preserved iron stores compared to those with better PCS. Results may suggest inflammation could be a driver of lower quality of life in patients with adequate TSAT and Hgb levels.

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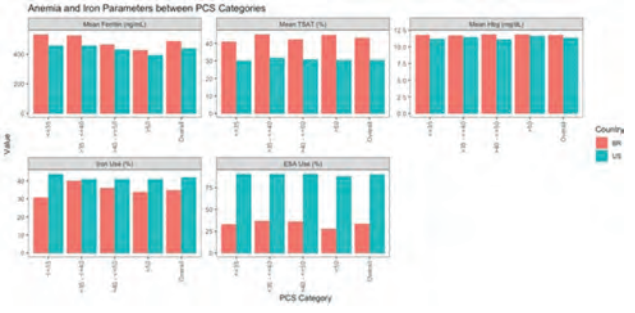

TH-PO961

Treatment Patterns and Clinical Events in Non-Dialysis-Dependent CKD Patients with Elevated C-Reactive Protein and Anemia: A Nationwide Hospital-Based Cohort Study in Japan

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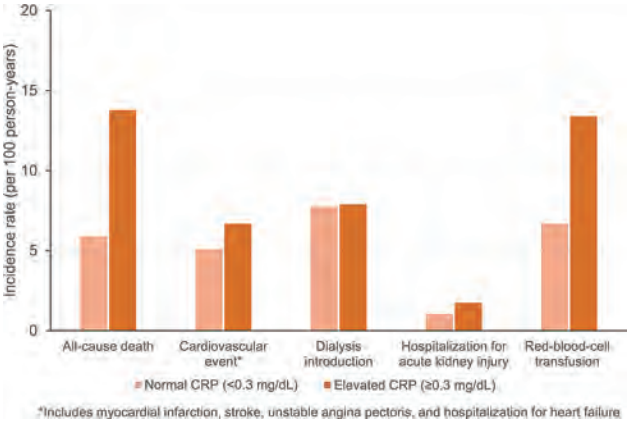
Background: Treating anemic CKD patients with inflammation (identified from increased CRP) is challenging due to associated ESA resistance. Contemporary evidence for anemia management and clinical event risk in NDD-CKD patients with elevated CRP are limited.

Methods: A retrospective cohort study was conducted using a Japanese nationwide EMR-based hospital database in adult patients with stage≥3a NDD-CKD and Hb<11g/dL (January 2013–November 2021; N=26,626). Serum CRP was collected during the baseline period. Anemia treatment patterns (initiation and discontinuation) and clinical events including all-cause mortality, CV events, dialysis introduction, hospitalization for AKI, and RBC transfusion were assessed.

Results: 9086 (34.1%) had normal CRP (<0.3mg/dl, mean 0.1mg/dL), 13,642 (51.2%) had elevated CRP (≥0.3mg/dl, mean 5.4mg/dL), and 3898 (14.6%) had no CRP measurements. Compared to normal CRP, patients with elevated CRP had lower Hb (9.8 vs 10.0g/dL), higher ferritin (212.4 vs 140.9ng/mL), and lower TSAT (23.7 vs 27.5%). The cumulative incidence of anemia treatment initiation within 12 months was lower in patients with elevated CRP (34.1 vs 39.0%), including ESA 23.0%, iron oral 16.5% iron iv 6.0%, and HIF-PHI 0.1%. Anemia treatment discontinuation within 12 months was higher in patients with elevated CRP (88.9 vs 86.9%) including ESA 95.4%, iron oral 81.1%, iron iv 99.3%, and HIF-PHI 60.0%. Incidence rates (per 100 person-years) for all clinical events were higher in patients with elevated CRP. (Fig)

Conclusions: The proportion of patients with elevated CRP was high in anemic NDD-CKD. Combination of anemia and elevated CRP was associated with adverse effects. Despite a significantly higher rate of RBC transfusion, many patients remain untreated and for those treated discontinuation was high in both groups.

Funding: Commercial Support - Bayer Yakuhin



TH-PO962

Contemporary Treatment Patterns of Clinically Meaningful Anemia Among Non-Dialysis-Dependent CKD Patients in the United States

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Background: Anemia is a common complication in non-dialysis dependent chronic kidney disease (NDD-CKD) patients, and the appropriate management of anemia is important. This study aimed to describe the treatment patterns of clinically meaningful anemia in line with the KDIGO guidelines [90-day average hemoglobin (Hb) level ≤ 10g/dL after the first date of Hb < 12 g/dL following CKD diagnosis] and the characteristics of NDD-CKD patients with clinically meaningful anemia using Optum Electronic Health Records (EHR) database in the United States (US).

Methods: The data source was Optum EHR which had 73 million patients with at least 1 year of data available from January 1, 2015 to December 31, 2021. NDD CKD patients with anemia (≥ 3 eGFR results <60 mL/min/1.73 m^2 on separate dates) were included in the analysis. Among those patients, the treatment patterns of anemia were described, including the use of erythropoiesis-stimulating agents (ESA), intravenous (IV) iron, and red blood cell (RBC) transfusion.

Results: The study included 14,922 NDD-CKD patients with clinically meaningful anemia. 46.3% were men, mean age was 73.8 ± 10.3 years. Comorbidities were common, with hypertension in 74.1%, peripheral vascular disease in 24.2%, and coronary artery disease in 27.2%. The average baseline eGFR was 44.3 ± 12.8 mL/min/1.73m^2. The average baseline Hb level was 9.2 ± 0.6 g/dL. 96.3% had average baseline Hb between 8.0g/dL to 9.9g/dL, 3.7% in the range of 6.5 g/dl to 7.9g/dl, and 0.1% below < 6.5 g/dL. In this study, IV iron was prescribed to 18.4%, RBC transfusion to 24.6%, and ESAs to 4.8% as first anemia treatment. Throughout the study period, 24.9%, 33.1% and 9.5% of NDD CKD patients received one or more prescriptions of IV iron, RBC transfusion, and ESAs. However, 52.2% did not receive any prescription of IV iron, RBC transfusion, or ESAs after anemia diagnosis.

Conclusions: A substantial proportion of contemporary NDD-CKD patients with clinically meaningful anemia in the US were not receiving treatment. Blood transfusions were prescribed in more than 20% of patients as the first anemia treatment which potentially may be avoidable.

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TH-PO963

Anemia Management in Non-Dialysis CKD Patients

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Background: Anemia is common in CKD and is closely associated with advanced stages of CKD. KDIGO recommends treating iron deficiency when TSAT is below 30% and administering ESA when Hb levels drop below 10 mg/dL. Current guidelines suggest maintaining Hb levels between 10-11.5 mg/dL. Despite this, anemia in CKD is often undertreated. This initiative aims to improve anemia management by addressing ESA hypo-responsiveness, administrative gaps, and missed treatments through quality improvements.

Methods: Our quality improvement project aimed to improve anemia management with two goals: 1) Increase Hb levels above 10 g/dL in at least 90% of patients on ESA for six months or more; 2) Decrease transfusion and hospitalization rates by 10%. To achieve these goals, we made minor changes in our clinic and utilized a new EMR system introduced in October 2022. The EMR system allowed for easy scheduling of follow-ups and labs, reducing administrative errors, and ensuring timely interventions. We upgraded the nursing ESA protocol by adding labs to screen for B12 and folate deficiencies. Nurses received re-education on ESA use and anemia management. Nurse Practitioner clinic was

utilized to provide frequent follow-up for patients on home ESA, with a specific Retacrit protocol created for them. We maintained an "ESA panel" list to monitor and review patients on both home and in-clinic ESA for follow-up and outcomes.

Results: The intervention phase started in February 2022, and we anticipate results in the coming months. Data extraction from the EMR system spanned its entire duration to measure changes over the last three quarters. Among the 4,000 clinic patients, 1,722 were diagnosed with anemia based on the ICD codes. Preliminary analysis shows a decrease in blood transfusions from 43 in the first quarter to 30 in the current quarter. Nephrology-ordered iron infusions decreased from 60 to 30, while the use of Retacrit increased from 8 to 17. These initial findings suggest the impact of our interventions on anemia management, but further analysis and evaluation are required to determine the full extent of improvements achieved.

Conclusions: Our study highlights the inadequate management of anemia in CKD patients, leading to avoidable healthcare utilization and compromising the chances of successful transplantation. Improved anemia management is urgently needed to address these concerns and optimize patient outcomes.

TH-PO964

Red Blood Cell Transfusion Use in Dialysis-Dependent Patients with Anemia of CKD in the United States: A Systematic Literature Review

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Background: Anemia of chronic kidney disease (aCKD) occurs frequently in dialysis-dependent (DD) patients (pts). Management includes iron supplementation, erythropoiesis-stimulating agents, and when clinically indicated, red blood cell transfusions (RBCT). There are limited collated data on RBCT use in the US; thus, a systematic literature review evaluating frequency, predictive factors, complications, healthcare resource use and costs was undertaken.

Methods: A comprehensive literature search for studies published between 1980 and June 2022 was conducted in Embase, MEDLINE and gray literature sources, to identify real-world (RW) studies and randomized controlled trials (RCTs) reporting RBCT use in US DD CKD pts. Titles and abstracts were reviewed against pre-defined criteria. Results were summarized descriptively.

Results: Of 182 relevant studies identified, 37 RW studies and 22 RCTs reported data in DD CKD US pts. In RW studies, overall frequency of RBCT use ranged from 0.0–66% (n=26); for hemodialysis (HD) pts 0.0–66% (n=19); peritoneal dialysis (PD) pts 5.5–7% (n=1); and HD and PD patients 1.4–35.5% (n=4). Rates of RBCT per 100 person-years (PY) in DD CKD pts ranged from 1.1–504 (n=12); for HD pts 1.1–148.4 (n=10); PD pts 28.8–504 (n=2); and HD and PD pts 19.2–49.7(n=1). RBCT use varied by population, pt factors and study design. For the 22 RCTs (single country [n=7], multi-country [n=15]), overall frequency of RBCT use ranged from 0.7–62%; for HD pts 1.2–62% (n=11); and HD and PD pts 0.7–21.1% (n=10), comparable to RW studies. Rates of RBCT per 100 PY ranged from 3.5–10.3 among HD and PD pts (n=3); no HD only/PD only studies were found. Predictors of RBCT based on quantitative multivariable analysis were identified in 6 RW studies; 5 reported RBCT complication data; 2 HCRU data and 2 direct costs associated with RBCT use and complications.

Conclusions: RBCTs form part of aCKD management in DD CKD US pts, with higher rates in RW studies than in RCTs, although frequencies were comparable. Factors accounting for the variations in frequency, and predictive factors for RBCT use were identified. There are limited data on complications, HCRU and costs of RBCT.

Funding: Commercial Support - Funded by GSK (Study 218929)

TH-PO965

Hemoglobin (Hgb) Targets in Hemodialysis (HD) Patients: What Is the Optimal Target Range?

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Background: Based on RCTs a hgb target range between 10 to 11 g/dL is mandated in the US. Retrospective analyses have shown lower hospitalization and death rates with higher values. We investigated the association between all-cause mortality hazard ratio (HR) and time spent outside the target range.

Methods: We studied incident HD patients (pts) initiated on a long-acting ESA (Mircera; Vifor) within the first 90 days. In pts with at least 12 hgb during the 6-months baseline (BL), we quantified the patient-individual area under the target excursion curve (AUC) 'above' and 'below' the target range (10 to 11 g/dL). We used these metrices as predictors in proportional hazard models predicting HR in the following 18 months. We fitted the HR as a spline function of mean BL hgb. We built an additional model, adjusted for race, sex, age, diabetes, serum albumin and phosphorus, as spline functions in a bivariate fashion as a function of AUC above and below as a contour plot. Sensitivity analyses considering cumulative ESA doses, iron status, vintage, excursion frequency, nutrition and inflammation were performed.

Results: We studied 64,042 pts out of 517,860 pts. We found a preferable target range to be between 10.3 and 12.2 g/dL (**Figure 1**). AUC 'below' in the presence of low AUC 'above' conferred a higher risk of death, whereas a higher AUC "above" only started to increase risk only at around 150 g/dLxdays (**Figure 2**). Sensitivity analyses did not change the interpretation.

Conclusions: A wider and higher target range associates with more favorable outcomes. Limitations of retrospective research apply. Adequately powered and designed experimental studies are needed. **Figure 1:** HR as a function of mean BL hgb levels. **Figure 2:** HR as a function of AUC above and below.

Funding: Commercial Support - Vifor Fresenius Medical Care Pharma Ltd

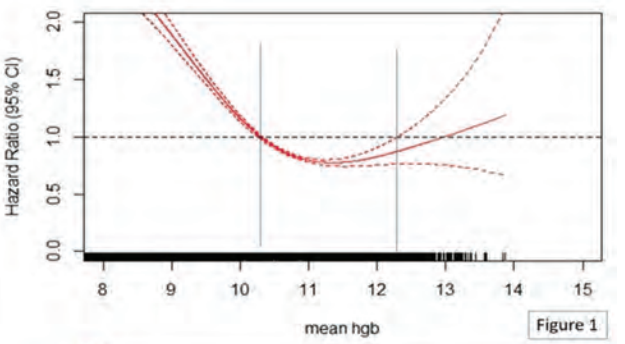

Figure 1

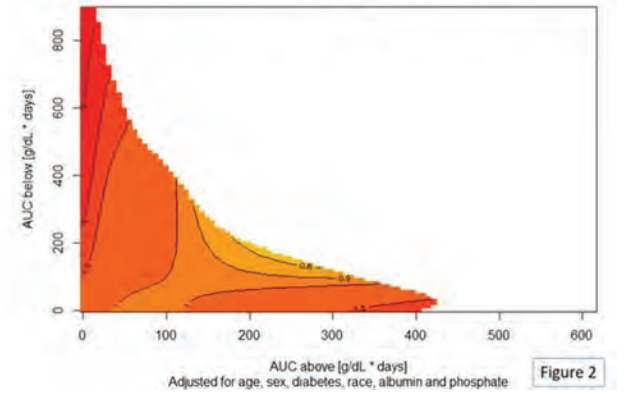

Figure 2

TH-PO966

The Setting of Administration of Erythropoiesis-Stimulating Agents Among Home Dialysis Patients in a Mid-Sized Dialysis Provider

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Background: For patients undergoing home hemodialysis (HHD) or peritoneal dialysis (PD), an erythropoiesis-stimulating agent (ESA) may be administered by healthcare professionals during clinic visits or self-administered at home. The latter option may be convenient for patients, including those with long travel time to the clinic, but may increase the risk of nonadherence. We assessed the incidence and predictors of self-administration of ESAs among home dialysis patients.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. In 2021 and 2022, we identified all administered doses of epoetin alfa and darbepoetin alfa among home dialysis patients. For each administered dose, we identified the prescribed frequency of administration, the home dialysis modality (HHD, PD), and months since home dialysis initiation, as well as the age, sex, and race/ethnicity of the patient. We fit a logistic regression of self-administration of the ESA, using generalized estimating equations to account for intra-patient correlation.

Results: The cohort comprised 1984 patients and 54,301 ESA dose administrations. Overall, 42.0% of ESA doses were self-administered. In HHD patients, 78.1% of doses were self-administered; in PD patients, the corresponding statistic was 25.0%. Use of darbepoetin alfa, relative to epoetin alfa, was not associated with self-administration (adjusted odds ratio, 0.88; 95% CI, 0.56-1.37). Relative to once-monthly dosing, adjusted odds ratios of self-administration were 2.04 (95% CI, 1.70-2.45) with every-other-week dosing, 3.27 (2.64-4.05) with once-weekly dosing, and 4.84 (3.49-6.73) with multiple doses per week. Neither age nor sex was associated with self-administration, but relative to non-Hispanic White patients, Asian patients were less likely to self-administer ESAs (adjusted odds ratio, 0.52; 95% CI, 0.32-0.86). Each one-month increment in home dialysis duration was associated with 3% higher adjusted odds of self-administration.

Conclusions: Among contemporary home dialysis patients, self-administration of ESAs is common with HHD and uncommon with PD. Increased frequency of ESA administration and longer duration of home dialysis were associated with higher odds of self-administration, whereas Asian race was associated with lower odds.

TH-PO967

Randomized Assessment of Auryxia® Therapy for In-Center and Home Dialysis Patients

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Background: Auryxia (ferric citrate) is an FDA approved iron-based phosphate binder for adults with dialysis-dependent chronic kidney disease. This study investigated the impact of Auryxia as primary phosphorus lowering therapy on utilization of erythropoiesis-stimulating agent (ESA) and intravenous (IV) iron.

Methods: In this randomized, open-label, active-controlled, multicenter study (NCT04922645), subjects receiving ESA and either in-center hemodialysis or home dialysis were randomized 1:1 to Auryxia (starting dose of 6 tablets per day) or remain on standard of care (SOC) phosphate lowering therapy for up to 6 months. Dose adjustments were at investigator discretion to achieve target serum phosphorus. The primary endpoint was difference in change from baseline (BL, Month -3 to Day 1) to efficacy evaluation period (EEP, Months 4-6) in mean monthly ESA and IV iron doses between groups. Secondary endpoints included difference in proportion with Hb ≥10.0g/dL and serum phosphate ≤5.5 mg/dL.

Results: 209 subjects were randomized to Auryxia (n=103) or SOC (n=106). The two groups had generally similar baseline characteristics, although atherosclerotic CV disease and congestive heart failure were more common in the SOC group. During the EEP, the mean treatment difference in ESA administration was -31 mcg/month (p=0.02). A non-statistically significant change in mean monthly IV iron administration of -37 mg/month (p=0.17) was observed. Mean Hb, TSAT, and ferritin all increased from BL to the EEP in the Auryxia vs. SOC group. The proportion of subjects with Hb ≥10.0 g/dL and serum phosphate ≤5.5 mg/dL did not differ between groups. Three subjects stopped Auryxia due to GI intolerance (n=2) or adverse events (n=1). Serious adverse events (SAEs) occurred in 39% of subjects receiving Auryxia vs. 59% in those receiving SOC. No related SAEs were reported. Fewer patients randomized to Auryxia experienced CV (8.7% vs. 13.2%) or infectious (8.7% vs. 17.9%) SAEs.

Conclusions: Treatment with Auryxia as compared to remaining on SOC phosphate binders resulted in increased Hb, increased iron stores, statistically significantly less average monthly ESA use and a non-statistically significant reduction in monthly IV iron use.

Funding: Commercial Support - Akebia

TH-PO968

Survey of Erythropoiesis-Stimulating Agent (ESA) Use in Non-Dialysis-Dependent CKD (NDD-CKD) in Civilian vs. Military Practice

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Background: There is a paucity of data on barriers to ESA use in the pre-dialysis chronic kidney disease (CKD) population. In the context of universal health care coverage within the Military Health System (MHS), we evaluated ESA use in patients with stage 3-5 NDD-CKD among nephrologists practicing in military facilities vs. former military nephrologists practicing in the civilian sector.

Methods: We conducted an anonymous online survey of nephrologists assigned to military facilities and graduates of the Walter Reed Nephrology fellowship program from 1988-2022 who have transitioned to civilian practice (n=104).

Results: The response rate was 63/104 (61%) with a 95% complete rate. Most of the respondents (97%) were in active clinical nephrology practice; 53% were in military facilities and 41% in civilian practice. Fifty-two percent of military and 29% of civilian nephrologists estimated that 5%-10% of their NDD-CKD patients were receiving ESA therapy (p=0.09). Sixty-eight percent of military nephrologists vs. 58% of civilian nephrologists would start an ESA if the hemoglobin (Hgb) ≤ 9 g/dL (p=0.46). Sixty-eight percent of military nephrologists vs. 62% civilian nephrologists targeted a Hgb between 10-11 g/dL on ESA (p=0.69). Patients had their ESA administered in the clinic, at home, or in both settings in 42%, 10%, and 45%, respectively, in military practice vs. 38%, 8% and 42%, respectively, in civilian practice (p=0.49). Compared to military nephrologists, civilian nephrologists were more likely to identify low reimbursement rate (29% vs. 0%, p=0.0013), drug cost and affordability (54% vs. 0%, p<0.001), and restriction on ESA formulations by health insurance (38% vs. 3%, p=0.001) as barriers to ESA therapy. Military nephrologists were more likely to report that there were no particular barriers to ESA therapy compared to their civilian counterparts (52% vs. 12%, p=0.002).

Conclusions: Although the practice patterns of ESA therapy in NDD-CKD are comparable between military and civilian nephrologists who had similar training/background, the former group experiences less barriers to implementing therapy in the MHS. *Disclaimer: The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

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TH-PO969

Conversion from Darbepoetin Alfa to Epoetin Alfa in a Multi-Center Cohort of In-Center Hemodialysis Patients

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Background: Over the past two decades of anemia treatment, many dialysis patients have been converted from a short-acting erythropoiesis-stimulating agent (ESA) to a long-acting ESA. However, there is little data about conversion of a population in the opposite manner, from a long-acting ESA to a short-acting ESA. We investigated the initial results of conversion of a population of in-center hemodialysis patients from darbepoetin alfa to epoetin alfa in early 2023.

Methods: During January and February 2023, 69 outpatient hemodialysis centers at Satellite Healthcare converted from first-line anemia treatment with darbepoetin alfa (*Aranesp*) to treatment with epoetin alfa (*Epogen*). Patients were converted according to a protocol-based dosing algorithm derived from the *Aranesp* package insert and published studies. To assess changes in anemia-related parameters before and after conversion, we analyzed hemoglobin, ESA dose, transferrin saturation, and ferritin in patients who completed ≥4 hemodialysis treatments during a 2-week period of each month from July 2022 to April 2023; the period comprised the prescheduled week of blood draws and the week thereafter.

Results: On average, monthly cohorts included 6633 patients, among whom 6193 (93.4%) completed ≥4 treatments during the 2-week observation period. In 2022, 5.0% of ESA-treated patients received epoetin alfa, 94.8% received darbepoetin alfa, and 0.2% received both agents. In February 2023, 99.3% of ESA-treated patients received epoetin alfa, 0.4% received darbepoetin alfa, and 0.3% received both agents; by April, 99.6% received epoetin alfa. The distribution of hemoglobin was stable during and after the conversion process (table). The ratio of mean weekly epoetin alfa dose (IU) in February 2023 to darbepoetin alfa dose (mcg) in 2022 was 309; from February to April, mean weekly epoetin alfa dose decreased 3%. From December 2022 to March 2023, distributions of transferrin saturation and ferritin shifted modestly downward.

Conclusions: A protocol-based ESA dosing algorithm can be used to convert in-center hemodialysis patients from darbepoetin alfa to epoetin alfa in a short timeframe, without disruption of the hemoglobin distribution.

	Jul-Dec 2022	Jan 2023	Feb 2023	Mar 2023	Apr 2023
Mean (SD) hemoglobin, g/dL	10.7 (1.2)	10.7 (1.2)	10.6 (1.2)	10.7 (1.2)	10.7 (1.2)
Hemoglobin <9 g/dL, %	7.5%	8.4%	8.3%	7.4%	7.4%
Hemoglobin ≥12 g/dL, %	12.7%	13.5%	11.9%	12.3%	13.7%
Any ESA treatment, %	86.8%	86.9%	89.1%	89.1%	89.1%
Mean (SD) ESA dose, in users					
Epoetin alfa, IU/wk	17,137 (20,921)	10,638 (16,415)	11,743 (15,703)	11,613 (15,272)	11,399 (14,783)
Darbepoetin alfa, mcg/wk	38 (45)	37 (44)	92 (132)	101 (117)	127 (120)

TH-PO970

Efficiency and Efficacy of Anemia Therapy with Epoetin Beta: Results from a Randomized Controlled Trial of Therapy Software vs. Standard of Care

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Background: Anemia is common in patients on hemodialysis (HD) and typically treated with erythropoiesis-stimulating agents (ESA). Recurrent ESA dose adjustments are challenging due to delayed effects on patient hemoglobin (Hb) levels and interpatient variability in ESA responsiveness. We developed a novel software providing personalized ESA-dose recommendations based on a mathematical model of anemia. Here, we report results from a randomized controlled trial, comparing the software versus standard-of-care (SOC) anemia treatment in using ESAs efficiently to bring patients' Hb levels into a given target range.

Methods: We enrolled 96 subjects on HD; 82 of them completed the study. Patients were randomized to be managed by our anemia therapy software (intervention group, "INT", 40 patients) or continued SOC treatment (42 patients). For 26 weeks, the software generated biweekly patient-specific ESA recommendations to target a Hb of 10–11 g/dL. Recommendations were passed on to clinicians.

Results: In the SOC group, mean Hb levels across the study period showed a negative dependence on the mean amount of ESA per month (Fig. 1A) and total number of ESA administrations during the study period (Fig. 1B). In the INT group, this effect was significantly reduced (Fig. 1). The mean amount of ESA per kg patient weight was also significantly reduced in the INT group (INT: 1.1 [0.6–1.5] mcg/30 days/kg, median [IQR]; SOC: 1.5 [0.9–2.1] mcg/30 days/kg; Wilcoxon rank-sum test, p=0.031) while the number of ESA administrations within the study period was comparable in both groups (INT: 9 [6-10]; SOC: 8 [6-10]; Wilcoxon rank-sum test, p=0.76).

Conclusions: Trial results suggest that our therapy software utilizes ESA more efficiently and controls Hb levels better at low and high ESA dose levels than SOC treatment, while requiring less ESA per kg patient weight and a comparable number of ESA administrations.

Funding: Commercial Support - Fresenius Medical Care

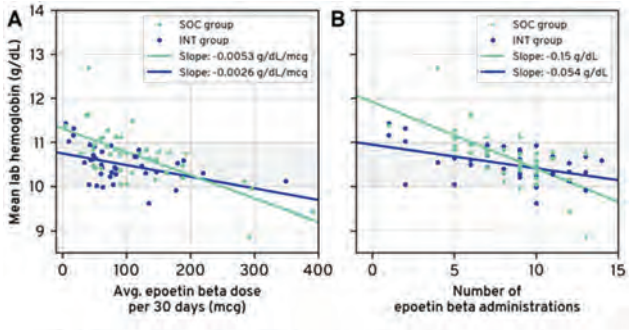

Fig. 1: Mean lab hemoglobin within the study period (26 weeks) vs. (A) avg. epoetin beta dose per 30 days and (B) number of epoetin beta administrations for the intervention (INT) group (blue) and the standard-of-care (SOC) group (green). Dots show patient-individual data points, lines show linear regressions. Data points of 3 patients who received zero administrations were excluded from the analysis (intervention group: 2; SoC group: 1).

TH-PO971

Medication Evaluation of Early Post-Transplant Anemia Management

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Background: Post-transplant anemia (PTA) is a common phenomenon in kidney transplant recipients (KTR). There are currently no consensus guidelines for PTA, however patients are commonly treated with erythropoiesis-stimulating agents and receive iron deficiency correction. Dosing and duration for these regimens remain unclear. The purpose of this study is to evaluate the efficacy of erythropoietin use and intravenous iron supplementation on hemoglobin in KTR with PTA.

Methods: This is a single center, retrospective cohort study from 10/1/2021 – 4/1/2022. Primary outcome was hemoglobin at 6 months in KTR who received ESA, iron sucrose or neither. Secondary outcomes included kidney function, iron studies, transfusions, dapsone use > 7 days post-transplant. All continuous data was analyzed using a student T-test. All categorical data was analyzed using a chi square test.

Results: Ninety-seven KTR were included in our final analysis. A total of 59 (60.8%) of KTR received either ESA alone or in combination with IV iron. Hemoglobin and renal function trends over time are represented on Figure 1 and 2. Of note, 16 (42.1%) of the patients who did not receive ESA or IV iron were living donor transplant recipients. There was no difference in hemoglobin outcomes at 6 months in patients who received IV iron repletion with ESA versus ESA alone (Figure 3). Patients who received IV iron < POD 30, had significantly higher Hgb outcomes than those who got IV iron >POD 30 (Figure 4). Dapsone use >7 days was associated with significantly reduced Hgb during the duration of use (Figure 5).

Conclusions: Patients with PTA did not show additional hemoglobin increases when given any ESA as compared to those who received no ESA. Differences in treatment groups including higher numbers of deceased donors and poor graft function may have contributed to the poor response to ESA. A prospective, randomized study is warranted for the best use of these interventions in a judicious manner.

TH-PO973

Hospitalizations and Red Blood Cell (RBC) Transfusions in Patients with Dialysis-Dependent-CKD (DD-CKD) on Auryxia® Compared with Other Phosphate Binders

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Background: Auryxia (ferric citrate) is an FDA approved iron-based phosphate binder for adults with dialysis-dependent chronic kidney disease (DD-CKD). Primary efficacy results of this study of Auryxia as phosphorus lowering therapy compared to standard of care (SOC) in patients with CKD undergoing dialysis showed a statistically significant reduction in erythropoiesis-stimulating agents (ESAs) and a reduction in intravenous (IV) iron. Here, we further explore hospitalizations and red blood cell (RBC) transfusions.

Methods: This open-label, active-controlled, multicenter study (NCT04922645), in subjects receiving ESA and either in-center or home dialysis, were randomized 1:1 to receive Auryxia or remain on SOC phosphorus-lowering therapy for up to 6 months. Dose adjustments were at investigator discretion to achieve target serum phosphorus. The primary endpoint was the difference in change from baseline (BL, Month -3 to Day 1) to efficacy evaluation period (EEP, Months 4-6) in mean monthly ESA and IV iron doses between groups. Safety and exploratory analyses estimated the rate of hospitalizations, hospital days, RBC transfusion, and units of packed red blood cells (PRBC) per person-month from day 1 through the end of study.

Results: 209 subjects were randomized to Auryxia (n=103) or SOC (n=106). The two groups had generally similar baseline characteristics, although atherosclerotic CV disease and congestive heart failure were more common in the SOC group. Hospitalization event rates per 100 person-months were 7.4 and 10.6 in the Auryxia (40 events) and SOC (63 events) treatment groups, respectively. Subjects in the Auryxia group had 60 hospitalization days per 100 person-months compared to 82.6 days in the SOC group. RBC transfusion rates per 100 person-months were 1.5 and 4.2 in the Auryxia (8 events) and SOC (25 events) treatment groups, respectively. The rates of PRBC transfusions, per 100 person-months were 2.4 and 7.1 with Auryxia (13 units) and SOC (42 units), respectively.

Conclusions: Treatment with Auryxia as compared to remaining on SOC phosphate binders resulted in lower hospitalization rates, fewer hospitalization days, fewer RBC transfusions and fewer PRBC units used.

Funding: Commercial Support - Akebia

TH-PO974

Validate Optimal Iron Management When Using Hypoxia-Inducible Factor-Prolyl Hydroxylase Domain Inhibitor (HIF-PHI) in Renal Anemia: Excessive Iron Administration Is Unnecessary

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Background: Hypoxia-inducible factor prolyl hydroxylase domain inhibitors (HIF-PHIs), new therapeutic agent for renal anemia, shows its effects through a mechanism not only by transcription factor-mediated erythropoietin production but also by iron metabolism. Therefore, although the importance of iron supplementation has been emphasized, it is presumed that iron utilization is also promoted endogenously and that a mischievous iron overdose is not necessary. In the present study, we examined optimal iron management under HIF-PHI administration.

Methods: The subjects were 30 maintenance hemodialysis patients who switched from darbepoetin alfa (DA) to Roxadustat (Rox). To examine iron kinetics during the switchover, reticulocyte hemoglobin content (CHr), which reflects recent Hb synthesis, was measured in addition to conventional iron-related parameters. The iron-regulated hormone hepcidin was also measured. Iron deficiency was defined as CHr<32.0 pg. ROC curves were used to determine cut off values for the point at which CHr sufficiency was met.

Results: After the switching to Rox, there was a significant increase in Hb and RBC and a decrease in ferritin and hepcidin (all, $p<0.01$), suggesting increased iron demand. In the results of the ROC curve with the endpoint CHr≥32pg on Day0, cutoff values for s-ft and TSAT were respectively 49.7 ng/mL and 21.6% on Day 0 and 35.5 ng/mL and 16.2% on Day 28. With the endpoint CHr ≥ 32.0 pg on Day 28, cutoff values for s-ft and TSAT on Day 0 were 81.6 ng/mL and 23.9%, respectively. In a patient with s-ft 184 ng/mL and TSAT 10.6%, there was a rapid increase in Hb from 8.0 to 10.0 g/dL after 2 weeks of switching.

Conclusions: The present study suggests that a serum ferritin of at least 81.6 ng/mL at the time of switching, and most recently 35.5 ng/mL, may avoid iron deficiency when switching from DA to Rox. Iron deficiency is pointed out to increase the risk of thrombosis due to hypercoagulability and increased platelet count. In our previous report (Acta Haematol 2022), the cutoff value of ferritin for platelet increase was 77.2 ng/ml (area under the curve 0.76, 95% CI 0.55 – 0.96) when ROX was administered. Moreover, it has also been shown that functional iron deficiency with ferritin sufficiency may result in a rapid rise in Hb. Thus, the amount of iron required at the time of switchover may be less than expected.

TH-PO975

A Regional Perspective of Hypoxia-Inducible Factor-Prolyl Hydroxylase (HIF-PH) Inhibitors in Dialysis

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Background: Hypoxia-inducible factor prolyl hydroxylase enzyme inhibitors (HIF-PHI) were developed as an alternative to erythropoiesis-stimulating agents (ESA) to treat anemia in chronic kidney disease (CKD) patients. As of fielding, daprodustat was the only approved HIF-PHI in the United States (US) and roxadustat and vadadustat were approved in the European Union (EU); all agents are indicated to treat dialysis patients, while only roxadustat is approved to treat CKD non-dialysis patients in the EU. This analysis of nephrologist attitudes provides insight into regional perceptions of HIF-PHIs as a treatment option for dialysis patients.

Methods: Responses were collected via online surveys with 207 US-based nephrologists (February 2023) and 208 EU-based nephrologists (March through April 2023). Additional insights were captured via an independent, retrospective chart audit of 1,282 CKD non-dialysis patient records collected from 263 EU-based nephrologists (December 2021 through February 2022). EU countries surveyed included the UK, Germany, Italy, France, and Spain.

Results: To date, roxadustat has experienced slow uptake among EU nephrologists, with physicians reporting that 6% of their HD patients and 8% of their PD patients are currently on therapy. In the CKD non-dialysis setting, audited patient records reveal that roxadustat treatment rates are even lower at 3.5%, with increased use as patients progress in their CKD. As of fielding in the US, daprodustat had not been officially launched; however, 52% of physicians report that they are likely to be more reserved and selective in their prescribing once it is available, relying heavily on peers and KOLs for guidance. US physicians also expect that availability and dialysis center protocols will be key drivers of adoption. Looking towards future use, 55% of EU nephrologists report that the advantages of roxadustat outweigh the potential risks in dialysis patients, compared

to 44% of US physicians believing the same for daprodustat. Most nephrologists across regions (70% EU, 55% US) indicate they are anxious to gain clinical experience with the drugs.

Conclusions: Despite recognition of the benefits of HIF-PHIs in dialysis patients, slow adoption of roxadustat in the EU and hesitancy among US-based nephrologists to prescribe daprodustat may stifle treatment evolution in the anemia space, with ESAs likely to remain the standard of care in the dialysis setting.

TH-PO976

Efficacy and Safety of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors (HIF-PHIs) in Patients with CKD: Metanalysis of Phase 3 Randomized Controlled Trials

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Background: HIF-PHIs are new therapeutic agents for anemia of CKD. We evaluated by metanalysis and meta-regression efficacy and safety of HIF-PHIs in patients with CKD-related anemia.

Methods: We selected phase-3 RCTs comparing HIF-PHIs and ESA in dialysis and non-dialysis CKD patients. Efficacy outcomes were the changes from baseline of hemoglobin (Hb), iron parameters and intravenous iron dose; safety outcomes included cancer, major adverse cardiovascular events (MACE), MACE+ (MACE plus hospitalization for HF, unstable angina or thromboembolism), thrombotic events (deep vein thrombosis, pulmonary embolism), artero-venous fistula (AVF) thrombosis, and death.

Results: In 26 RCTs (N=24,387 patients) included, comparators were long-acting ESA (darbepoetin or CERA) in 17 RCTS and short-acting ESA (epoetin-α or-β) in 9 trials. Summary of difference between HIF-PHI and ESA for efficacy and safety is depicted in Figure 1. Random effect meta-analysis of unstandardized mean difference between HIF-PHIs and ESAs showed a significant change from baseline in Hb levels. Meta-regression analysis showed significantly higher Hb change for HIF-PHIs in younger patients and in studies using short-acting ESA as comparator (+0.21 g/dL, 95%CI, 0.12-0.29 vs -0.01, 95%CI, -0.09-0.07 in studies using long-acting ESA, P<0.001). Heterogeneity was not affected by type of HIF-PHIs. In comparison with ESAs, HIF-PHIs induced a significant decline in hepcidin and ferritin and a significant increase in serum iron and TIBC; IV iron dose was lower with HIF-PHI. Rate ratio of cancer, MACE, MACE+, thrombotic events and death did not differ between HIF-PHIs and ESAs.

Conclusions: In comparison with ESA therapy, HIF-PHIs are effective in correcting anemia and improving with a significant impact on iron metabolism without notable difference among various agents. No safety signals emerge with use of HIF-PHIs.

	HIF-PHI versus ESA	P
EFFICACY [Mean changes from baseline (95%CI)]		
Hemoglobin (g/dL)	0.10 (0.02-0.17)	**0.012**
Hepcidin (ng/mL)	-19.2 (-28.5 to -9.9)	**<0.001**
Serum iron (µg/dL)	9.7 (5.7 to 13.8)	**<0.001**
Total Iron Binding Capacity (µmol/L)	36.3 (31.9 to 40.7)	**<0.001**
Transferrin Saturation (%)	-0.3 (-1.7 to 1.0)	0.636
Ferritin (ng/mL)	-16.8 (-32.4 to -1.3)	**0.034**
IV iron dose (mg/week)	-3.4 (-6.2 to -0.5)	**0.020**
SAFETY [rate ratio (95%CI)]		
Cancer	0.93 (0.76-1.13)	0.520
MACE	1.00 (0.94-1.07)	0.905
MACE+	1.01 (0.95-1.06)	0.875
Thrombotic/pulmonary embolism events	1.08 (0.84-1.38)	0.967
Artero-venous fistula thrombosis	1.02 (0.93-1.13)	0.227
All-cause death	1.02 (0.95-1.13)	0.670

Summary effects of HIF-PHIs compared with ESA on efficacy and safety measures

TH-PO977

Evaluating the Outcomes of Roxadustat Treatment for Anemia in Dialysis-Dependent CKD: A Systematic Review and Meta-Analysis

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Background: Chronic kidney disease (CKD) patients often grapple with anemia, a complication that severely impinges on their quality of life and overall prognosis. Roxadustat, an innovative oral hypoxia-inducible factor prolyl hydroxylase inhibitor, has emerged as a potential solution to this pervasive issue. However, its effectiveness and safety need to be comprehensively analyzed. This study aims to investigate the efficacy and safety of Roxadustat for anemia in CKD patients.

Methods: We systematically searched PubMed, Web of Science, and Cochrane Library databases until October 2022. We sought randomized controlled trials (RCTs) that compared Roxadustat with Epoetin Alfa or a placebo in dialysis-dependent CKD patients. The primary outcomes were changes from baseline in hemoglobin, hepcidin, ferritin, and transferrin saturation (TSAT) levels. Secondary outcomes were the incidence of adverse and major adverse events. The data were aggregated using a random-effects model and expressed as standardized mean differences (SMDs) for continuous outcomes or relative risks (RRs) for dichotomous outcomes. The meta-analysis was executed using R version 4.0.3, employing the metafor and meta packages.

Results: We included five studies comprising 3,478 participants (1,847 administered Roxadustat and 1,631 given Epoetin Alfa or a placebo). Roxadustat was found to significantly enhance hemoglobin (SMD: 0.32, 95% CI: 0.12-0.52, $p < 0.01$, I^2=39%) and lower hepcidin levels (SMD: -0.29, 95% CI: -0.45- -0.14, $p < 0.01$, I^2=23%) from baseline, as compared to the control group. However, changes in ferritin (SMD: 0.03, 95% CI: -0.17-0.24, $p = 0.76$, I^2=0%) and TSAT levels (SMD: 0.14, 95% CI: -0.07-0.34, $p = 0.19$, I^2=0%) were not statistically significant. Adverse events (RR: 1.02, 95% CI: .96-1.07, $p = 0.5$, I^2=33%) and major/critical adverse events (RR: 1.05, 95% CI: 0.96-1.16, $p = 0.3$, I^2=20%) were marginally more frequent in the Roxadustat group, but these differences lacked statistical significance.

Conclusions: Roxadustat may potentially elevate hemoglobin and decrease hepcidin levels in dialysis-dependent CKD patients. However, its effects on ferritin and TSAT levels are unclear. Future, more extensive studies are needed to validate these findings and determine Roxadustat's optimal use.

TH-PO978

Roxadustat vs. Erythropoiesis in the Nephroprotection Treatment of Patients with CKD and Anemia

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Background: Roxadustat has been approved for patients with chronic kidney disease(CKD) and renal anemia in China since 2019. It is now widely used around the world. Although studies have found that roxadustat may improve tissue fibrosis, inflammation, and oxidative stress, there have been few studies on its nephroprotection. We aim to elucidate the nephroprotection of roxadustat versus erythropoiesis-stimulating agent (ESA) in CKD patients with anemia.

Methods: We conducted a retrospective cohort study of CKD patients with anemia diagnosed in ruijin hospital between January 2010 and December 2022. CKD patients aged 14 years at diagnosis, coexisting with anemia, an estimated glomerular filtration rate(eGFR) greater than 15 ml/min/1.73m^2, 24-hour urine protein, follow-up data, and received roxadustat three times a week or ESA, were included. The patients were 1:1 assigned to two groups by propensity score matching based on indicators including sex, age, eGFR, 24-hour urine protein and follow-up time. The primary outcome was composite renal endpoint defined as a 50% decline in eGFR and end-stage kidney disease (ESKD).

Results: A total of 288 patients were included after PSM. The significantly lower incident of composite renal outcomes in the roxadustat group compared with the ESA group were observed (39.58% *vs.* 26.39%, p=0.017). By multivariate Cox regression analysis, roxadustat was associated with a lower risk for the composite kidney outcomes compared to ESA (HR=0.61, 95% CI: 0.40-0.94, p=0.023) after adjusting for age, gender, baseline eGFR, 24-hour urine protein, MAP, and hemoglobin. Moreover, subgroup analysis showed similar results in different subgroups defined by hyperlipidemia, high urine acid. Notably, in the roxadustat group, eGFR decreased at a slower rate than in the ESA group [median eGFR slope: -2.14 *vs.* -7.46 ml/min/1.73m^2/yrs, p=0.099]. We found that roxadustat group had a higher hemoglobin level than the ESA group (110.64±17.13 *vs.* 104.33±23.14 g/L, p=0.04). Compared to the ESA group, the roxadustat group had more 50% decline in proteinuria after 12 months (43.06% *vs.* 29.86%, p=0.02).

Conclusions: Roxadustat is superior than ESA in treating CKD patients combined with anemia, especially for nephroprotection. Our findings need to be validated in further.

TH-PO979

Efficacy and Safety of Desidustat for the Treatment of Anaemia in Patients with CKD: A Retrospective, Open-Label, Single-Centre Study

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Background: CKD is associated with an increased risk of anaemia, significantly impacting patients' quality of life. Current therapy includes injectable erythropoiesis-stimulating agents which have limitations and safety concerns. Desidustat has shown promise in stimulating endogenous erythropoiesis and addressing anaemia in CKD. This study assesses the real-world clinical efficacy & safety of the desidustat treatment in CKD patients with anaemia.

Methods: This is a retrospective, observational, open-label, single-centre, single-arm study of CKD anaemic patients. Patients were administered with desidustat 100mg orally thrice a week for a period of 24 weeks. 83.3% of patients received 300mg/ week dose of desidustat as starting dose. Dose adjustment was done every 4 weeks as per the Hb level of the patients. The primary outcome was to assess the change in the Hb from baseline to the end of 24 weeks and the secondary outcome was the evaluation of AEs if occur.

Results: Out of 84 patients, 51.2% were previously on ESA therapy, 48.8% were treatment naïve, 38.1% were on dialysis and 56% non-dialysis patients. The results show statistically significant improvement in mean Hb level at the end of 24 weeks (1.306g/dL; p<0.01). Within groups including - treatment naïve patients, patients previously on ESA, non-dialysis and on dialysis patients improvement in mean Hb from baseline to end of 24 weeks was statistically significant, with most significant improvement seen in treatment naïve patients (p<0.01) and non-dialysis patients (p<0.01), the improvement in mean Hb values being 9.5±0.91 to 11.3±0.87, 9.7±1.16 to 11.2±0.87 respectively. The serum potassium showed mild variation from a mean of 4.7±0.80 to 4.8±0.47. AEs were observed in 13.1% patients, including AV Fistula failures (4.8%), LVF (2.4%), Arterial thrombosis (1. 2%), DVT (1.2%), Acute Pancreatitis (1.2%), Haemorrhagic stroke (1.2%) and Transaminitis (1.2%).

Conclusions: The short-term desidustat treatment demonstrated statistically significant improvement in Hb levels in patients. Therefore, making it a viable alternative

to current treatment options. Since the present study was retrospective in nature the causality assessment was not assessed. Hence, further research is needed to gather long-term data and compare the cardiovascular safety of desidustat with the injectable ESAs.

TH-PO980

A National, Multi-Center, Prospective Study Evaluating the Long-Term Safety and Effectiveness of Roxadustat for Anemia Treatment in Patients with CKD (ROXSTAR Registry)

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Background: Anemia is associated with increased morbidity/mortality in chronic kidney disease (CKD) patients. Roxadustat (RXD) stimulates erythropoiesis & has demonstrated effectiveness for anemia treatment. We conducted a real-world clinical study on the safety/effectiveness of RXD for CKD-associated anemia (CKD-anemia) treatment & its effect on quality of life (QOL).

Methods: This phase 4, prospective, clinical study enrolled patients aged ≥18 years with CKD-anemia (with or without dialysis) in 61 centers in China. Patients received a starting dose of 70–120-mg RXD orally thrice a week for 52 weeks. Primary & secondary outcomes were long-term safety & effectiveness. Safety assessments included the number of patients with treatment-emergent adverse events (TEAEs). Effectiveness was assessed by hemoglobin (Hb) change from baseline & percentage of patients with mean Hb >100 g/L. QOL was assessed by changes from baseline at 24 weeks in the Short Form (SF)-36 Vitality (V) & Physical Functioning (PF) subscales & self-reported Rapid Assessment of Physical Activity (RAPA) scores.

Results: Of 2024 patients enrolled, 1830 were RXD-naïve, 193 were previously RXD-treated, & 1 was unknown. In total 2021 (99.9%) received ≥1 RXD dose (hemodialysis: n=851 [42.1%]; peritoneal dialysis: n=676 [33.4%]; non-dialysis-dependent: n=494 [22.4%]) & 1592 (78.8%) completed the study. The mean±standard deviation (SD) age was 50.2±13.5 years, the weekly RXD dose was 254.13±103.16 mg & 53.8% were male. In total 1643/2021 patients (81.3%) reported TEAEs (hyperkalemia, 15.4%; upper respiratory tract infection, 10.0%; peripheral oedema, 5.2%) & 219 (10.8%) patients had drug-related TEAEs (nausea, 1.3%; hypertension, 1.0%; insomnia, 0.9%). TEAEs led to death in 38 patients (1.9%), but none were deemed related to RXD. In RXD-naïve patients (n=1804), the mean±SD Hb increased by 14.28±0.38 g/L over weeks 36–52. From weeks 24–52 the mean percentage of patients with Hb >100 g/L was 86.3% in RXD-naïve patients & 85.9% in treated patients (baseline, 45.6% & 61.1%). There were no changes in QOL at 24 weeks.

Conclusions: RXD had tolerable safety & increased Hb to >100 g/L in >85% of patients over 24–52 weeks; these results support RXD treatment for CKD-anemia patients in a real-world setting.

TH-PO981

Low vs. Standard Starting Dose Oral Roxadustat for Treating Anemia in Chinese Patients with CKD on Dialysis: A Prospective, Randomized Clinical Trial

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Background: Part 1 of this phase 4 study (NCT04059913) descriptively evaluated the efficacy and safety of a one dose step lower roxadustat starting dose in Chinese chronic kidney disease patients receiving dialysis as compared to the approved standard starting dose.

Methods: ESA naïve and previously ESA-treated patients on dialysis were randomized to receive a standard or lower roxadustat starting dose TIW for 20 weeks, titrated to maintain hemoglobin (Hb) within 100–120 g/L. The primary endpoints were the proportion of ESA-naïve patients achieving Hb≥110 g/L in the first 20 weeks and the proportion of ESA-treated patients achieving mean Hb≥100 g/L averaged over week 17 - 21 visit. Other efficacy endpoints include change from baseline (CFB) in Hb over week 17-21 etc. Adverse events (AEs) were monitored and assessed.

Results: Among 318 patients randomized to the lower vs. standard starting dose (ESA-naïve: 57 vs. 56; ESA-treated: 103 vs. 102), baseline characteristics including overall Hb (ESA-naïve: 87.73 vs. 86.17 g/L; ESA-treated: 104.81 vs. 105.34 g/L) were generally comparable. Numerically comparable proportions of low and standard dose patients within the ESA naïve and ESA-treated groups achieved the pre-defined Hb target levels (ESA naïve: 77.2% vs. 73.2%; ESA-treated: 82.5% vs. 79.0%). The mean Hb CFB to the average over week 17-21 visits were also comparable (ESA-naïve:20.7 g/L vs. 21.6 g/L; ESA-treated:4.9 g/L vs. 6.0 g/L). Treatment-emergent AEs (TEAEs) were comparable between treatment arms.

Conclusions: One dose level lower roxadustat starting dose showed similar efficacy and safety profile as compared to the approved standard starting dose in Chinese CKD patients receiving dialysis.

Funding: Commercial Support - This study was sponsored by FibroGen and AstraZeneca.

TH-PO982

Real-World Clinical Use of Roxadustat in Patients with Anemia of CKD: Interim Results from a Post-Marketing Surveillance Study in Japan

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Background: Roxadustat is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI) approved in Japan to treat anemia of non-dialysis-dependent (NDD) or dialysis-dependent (DD) chronic kidney disease (CKD). A post-marketing surveillance study is underway in Japan to examine the safety and effectiveness of roxadustat in real-world clinical use. Here, we report the results of a planned interim analysis from this study.

Methods: This open-label, non-comparative, non-interventional observational study had an observation period of 104 weeks. Eligible patients had anemia of CKD and were naive to roxadustat. Enrollment began in June 2020 (DD CKD patients receiving hemodialysis [HD] or peritoneal dialysis [PD]) and January 2021 (NDD CKD), with a planned interim analysis as of December 16, 2022. Incidence of adverse drug reactions (ADRs), including specified safety outcomes, and change in mean hemoglobin (Hb) level were reported descriptively after 12 weeks of roxadustat treatment.

Results: In total, 1468 patients (safety analysis population: NDD: 768; HD: 608; PD: 90; 2 patients received both HD and PD) were analyzed. A total of 839 patients (57.2%) switched from erythropoiesis-stimulating agents (ESA) to roxadustat, 16 patients (1.1%) concomitantly used ESA and roxadustat, 586 patients (39.9%) were ESA-naive, 23 patients switched from a HIF-PHI (1.6%), and 4 (0.3%) were missing data for prior ESA use. ADRs and serious ADRs occurred in 17.03% and 6.54% (overall), 13.02% and 3.52% (NDD CKD), 20.39% and 9.70% (HD), and 25.56% and 10.00% (PD), respectively (**Table**). Mean Hb level (g/dL) changed from 9.82 at baseline to 11.79 (NDD CKD), 9.83 at baseline to 11.06 (HD), and 10.22 at baseline to 11.21 (PD) after 12 weeks of roxadustat treatment.

Conclusions: The results from this interim analysis of a post-marketing surveillance study in Japan found that the incidence of ADRs was similar to the known roxadustat safety profile and showed the effectiveness of roxadustat in patients with anemia of CKD in clinical practice for up to 12 weeks.

Funding: Commercial Support - This study was funded by Astellas Pharma, Inc.

Table. Incidence of ADRs and Serious ADRs

	Overall Population N=1468			NDD Patient Population N=768			HD Patient Population N=608			PD Patient Population N=90		
	Serious	Non-serious	Total	Serious	Non-serious	Total	Serious	Non-serious	Total	Serious	Non-serious	Total
Number of patients with ADRs*	96	181	250	27	77	100	59	84	124	9	17	23
Number of events of ADRs	130	300	430	33	112	145	86	161	247	10	24	34
Incidence of ADRs	6.54%	12.33%	17.03%	3.52%	10.03%	13.02%	9.70%	13.82%	20.39%	10.00%	18.89%	25.56%

ADR, adverse drug reaction; HD, hemodialysis; NDD, non-dialysis-dependent; PD, peritoneal dialysis.
*Patients may have experienced a serious ADR and a non-serious ADR.

Table. Incidence of ADRs and Serious ADRs

TH-PO983

Safety and Efficacy of Vadadustat Thrice Weekly in Patients with Anemia due to Dialysis-Dependent CKD

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Background: Vadadustat (VADA) is an oral hypoxia-inducible factor prolyl hydroxylase inhibitor (HIF-PHI). This study investigated the efficacy and safety of conversion from the long-acting IV erythropoiesis-stimulating agent methoxy polyethylene glycol-epoetin beta (CERA; MIRCERA®) to oral VADA thrice weekly (TIW) for the maintenance treatment of anemia in patients with dialysis-dependent chronic kidney disease (DD-CKD).

Methods: This randomized (1:1:1), open-label, active-controlled, sponsor-blinded trial compared VADA, at starting doses of 600 mg and 900 mg TIW, and CERA treatment in patients with DD-CKD for up to 52 weeks. Primary and secondary endpoints were mean change in hemoglobin (Hb) from baseline to the primary evaluation period (PEP; weeks 20–26) and secondary evaluation period (SEP; weeks 46–52), respectively (noninferiority margin, –0.75 g/dL). Other key endpoints included the proportion of patients requiring red blood cell (RBC) transfusions during the PEP and those with Hb levels >11g/dL and 12g/dL. Treatment-emergent adverse events (TEAEs) and serious TEAEs were reported as primary safety endpoints.

Results: VADA TIW (n=304) was noninferior to CERA (n=152) for mean change in Hb from baseline during the PEP (least-squares mean difference: –0.33 g/dL; 95% CI: –0.53, –0.13) and SEP (–0.33 g/dL; 95% CI: –0.56, –0.09). The percentage of patients receiving RBC transfusions during the PEP was 3% for both groups. The proportion of patients with Hb levels >11g/dL and 12g/dL were lower in the VADA group (61.6% and 20.5%, respectively) vs the CERA group (78.2% and 30.6%, respectively). VADA and

CERA had similar incidences of TEAEs and serious TEAEs. The proportion of patients with TEAEs resulting in death was 9% in the VADA group and 11% in the CERA group. The most common TEAEs were COVID-19 and diarrhea in both groups. Incidence of cardiac arrest was more common in the CERA group (7.3%) compared to the VADA group (1.7%). No differences in abnormal liver enzymes were observed between treatment groups.

Conclusions: VADA TIW was noninferior to CERA in Hb efficacy. VADA had a lower proportion of patients with Hb excursions compared to CERA. The incidence of TEAEs and serious TEAEs was similar between VADA and CERA.

Funding: Commercial Support - Akebia Therapeutics, Inc.

TH-PO984

Effects of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors on Copper Metabolism and Association with Organ Damage in CKD

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Background: Excess copper accumulates in visceral organs throughout the body producing reactive oxygen species which ultimately causes organ damage. In patients with chronic kidney disease (CKD), excess copper accumulation is known to be a risk factor for worsening renal function. HIF-PhD inhibitors are recently used to treat renal anemia worldwide. Several studies have demonstrated that HIF-PhD inhibitors affect iron kinetics. Meanwhile, there are few reports on copper metabolism. In the present study, we investigated whether HIF-PhD inhibition has an impact on copper metabolism in CKD rodents model and patients with CKD or patients with peritoneal dialysis (PD).

Methods: 7 patients with advanced CKD and 9 patients with PD were enrolled in the present study. Serum copper, iron, and zinc were evaluated before and 3 months after the initiation of HIF-PHD inhibitors. In vitro, CuSO4 was administered to cultured proximal tubules to explore whether excess cooper accumulation causes cellular damage. In vivo experiments, GSK360A, a HIF-PHD inhibitor, GSK360A plus HIF-1α inhibitor, or GSK360A plus HIF-2α inhibitor were injected into C57BL/6J mice after induction of CKD by repeated low dose cisplatin injections to examine which HIF compartment is involved in cooper metabolism.

Results: Serum copper was elevated after the treatment with HIF-PhD inhibitors in patients with advanced CKD (104±5→131±24 μg/dL) and PD (101±15→148±20 μg/dL). Meanwhile, serum iron and zinc concentration were not affected by HIF-PhD inhibitors. In vitro experiment, co-incubation with CuSO4 increased α-SMA and cleaved caspase3, suggesting that excess cooper causes fibrotic pathway and ultimately cell death. In vivo experiment, serum copper was elevated in CKD rodents when compared to control, which was further enhanced by treatment with GSK360A. Pharmacological inhibition of HIF-1α did not affect GSK360A-induced increase in copper accumulation, suggesting that HIF-2α might be involved in copper metabolism in response to HIF-PhD treatment.

Conclusions: Copper accumulation can be induced by HIF-PhD inhibitors which might be associated with renal fibrosis and cell death. HIF-2α might mediate copper metabolism in response to HIF-PhD inhibitors.

TH-PO985

Anemia Treatment Among Prevalent Hemodialysis and Peritoneal Dialysis Patients in the United States

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Background: This study aims to assess anemia treatment in chronic kidney disease (CKD) patients (pts) undergoing dialysis to understand the evolving landscape of CKD anemia management.

Methods: Using USRDS data, we conducted an observational, descriptive cohort study of adults (≥18 years) receiving dialysis on Jan 1, 2018 (index) and with 6 months of Medicare fee-for-service coverage pre-index. Pts with prior kidney transplant, cancer, and hospitalization for heart failure, myocardial infarction, or stroke in the previous month were excluded. Follow-up was from index until death, loss of Medicare coverage, kidney transplantation, or Dec 31, 2019. Use of erythropoiesis-stimulating agents (ESA), IV iron, and blood transfusions were assessed during follow-up. ESA, iron use, and transfusions were identified by a combination of HCPCS codes, ICD-10-PCS procedure codes, and/or revenue center codes. ESA use was calculated as days covered/week (total days covered by ESA divided by follow-up time in weeks; 3 epoetin alfa administrations covered 7 days; 1 darbepoetin for 14 days), IV iron calculated as number of administrations per week, and transfusions as number per 100 person-years. Overall rates were calculated as weighted mean of pt-level rates using follow-up as weight.

Results: Overall, 209,408 pts were on HD and 20,647 on PD; median follow-up was 24.0 months (HD, IQR: 14.6–24.0; PD, 13.0–24.0), PD pts were younger (median age 62.2 vs 64.7 yrs). More PD pts were White (53.5 vs 39.1%), higher income (34.0 vs 48.7% with Medicare/Medicaid dual enrollment), and with glomerulonephritis as the cause of end-stage kidney disease (15.2 vs 8.5%). PD pts had fewer comorbidities and shorter dialysis duration (median 2.7 vs 3.9 yrs). During follow-up (**Table**), PD pts had lower ESA and IV iron use (1.24 vs 2.64 days of ESA coverage/week; 0.15 vs 0.48 iron administrations/week) and a higher transfusion rate (38.3 vs 32.4 /100 person-years).

Conclusions: In this descriptive study, PD pts had lower ESA and iron use and a higher transfusion rate than HD pts during follow-up. Anemia management may need improvement among PD patients.

Funding: Commercial Support - Funded by GSK (Study 217316)

Table. Anemia treatment in prevalent dialysis patients, by modality

Modality	N	ESA* (95% CI)	Iron† (95% CI)	Transfusion‡ (95% CI)
HD	209,408	2.64 (2.63, 2.64)	0.48 (0.48, 0.48)	32.4 (32.2, 32.6)
PD	20,647	1.24 (1.24, 1.24)	0.15 (0.15, 0.15)	38.3 (37.6, 39.0)

*Days covered per week; †Administrations per week; ‡Transfusions per 100 person-years
CI, confidence interval; ESA, erythropoietin-stimulating agent; HD, hemodialysis; PD, peritoneal dialysis

TH-PO986

Effect of Multiple Doses per Day vs. Daily vs. Alternate Day Oral Iron Therapy in Iron Deficiency Anemia with CKD

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Background: We investigated the effect of 2-3 times a day (typical clinical practice) vs. once-a-day vs. alternate-day oral iron administration on the improvement of Hgb and iron indices in patients with Iron deficiency anemia (IDA) & CKD.

Methods: Retrospective observational study of the veterans with IDA [defined as Hgb < 12 g/dL and either 1.) iron saturation < 20% or 2.) ferritin < 50 micrograms/L] and CKD [defined by eGFR < 60 ml/min/1.73m²] who received the first index outpatient prescription of oral iron for 90 days with one additional refill within 120 days from 2009-2019. Patient were classified into three groups: daily (once-a-day), multi-doses per day (> = 2-3 times per day) and alternate-day dose based on their oral iron dosing schedule. Groups were analyzed with longitudinal mixed effects models to estimate mean improvement (change-from-baseline) in Hgb & iron indices over the course of the time.

Results: 25,882 veterans were included in final cohort. Table 1 shows baseline characteristics & change in Hgb & iron indices at 90 & 210 days. Figure 1 shows estimated Hgb improvement in different groups. Hgb & iron indices significantly improved in multi-dose iron group compared to the daily group. Alternate day group showed slower pace of improvement in Hgb & iron indices. After adjusting all covariates, it did not affect the final results.

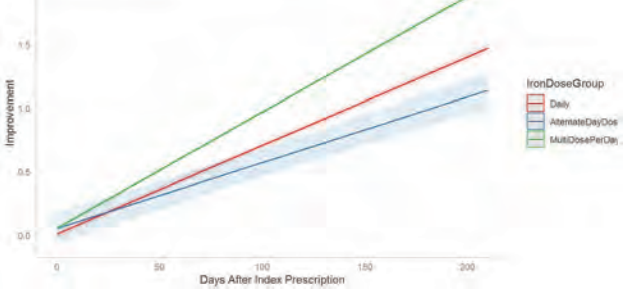
Conclusions: All different oral iron strategy improves Hgb & iron indices over time, although, multi-dose per day strategy improves at a much faster pace. The choice of oral iron therapy should depend on the rapidity of response desired, & patient preference due to adverse effects.

	Daily (n=10548)	Multi-Dose per Day (n=14888)	Alternate Day Dose (n=466)	p-value
Characteristics				
Male Sex	10043 (95.2%)	14182 (95.4%)	442 (94.8%)	0.67
Age > 80	5834 (55.2%)	13564 (91.4%)	408 (93.6%)	<0.001
Body Mass Index (BMI) > 35	7775 (73.7%)	11365 (76.4%)	340 (73.0%)	<0.001
DCI > 3	6259 (58.3%)	8388 (56.4%)	303 (65.0%)	<0.001
Mean eGFR (Std. Dev.)	43.80 (11.29)	45.96 (11.26)	42.41 (11.66)	0.01
ACE-I/ARB	5864 (52.7%)	8182 (55.1%)	244 (52.3%)	<0.001
Anticoagulant	3369 (31.9%)	4371 (29.4%)	154 (33.0%)	<0.001
Antiplatelet	3297 (31.3%)	4139 (27.8%)	155 (33.3%)	<0.001
Diabetes	6340 (60.1%)	8966 (60.2%)	277 (59.4%)	0.94
COPD	3603 (34.2%)	4862 (32.6%)	144 (30.9%)	0.04
Heart Failure	4883 (46.3%)	7002 (47.1%)	198 (42.5%)	0.05
Sleep Apnea	2081 (19.7%)	2598 (17.5%)	133 (28.5%)	<0.001
Current/Former Smoker	5122 (48.6%)	7355 (49.5%)	262 (56.2%)	0.003
Outcomes				
Median (IQR) Days 1 g/dL +Gdf Increase	92 (55-141)	89 (56-133)	92 (55-138)	<0.001
Timepoint*				
90 Days (Estimated improvement with 95% CI)	HGB: 0.62 [0.61, 0.64] Ferritin: 5.50 [1.35, 11.65] TIBC: -14.48 [-15.79, -13.13] ISAT: 4.32 [4.05, 4.59]	HGB: 0.82 [0.78, 0.85] Ferritin: 18.41 [13.48, 23.35] TIBC: -23.65 [-25.69, -20.60] ISAT: 5.46 [4.91, 6.01]	HGB: 0.46 [0.38, 0.55] Ferritin: 3.47 [-8.39, 15.33] TIBC: -8.44 [-15.32, -1.56] ISAT: 4.42 [3.20, 5.65]	Unadjusted
210 Days (Estimated improvement with 95% CI)	HGB: 1.46 [1.42, 1.49] Ferritin: 22.16 [17.14, 27.19] TIBC: -33.74 [-39.84, -30.65] ISAT: 10.07 [9.51, 10.63]	HGB: 1.91 [1.83, 1.99] Ferritin: 42.87 [31.44, 54.49] TIBC: -56.64 [-63.79, -49.84] ISAT: 12.74 [11.45, 14.03]	HGB: 1.09 [0.88, 1.29] Ferritin: 8.09 [-19.59, 35.77] TIBC: -19.70 [-36.76, -3.64] ISAT: 10.32 [7.47, 13.17]	Unadjusted

* Obtained using models without covariate adjustment. Adjusting for covariates did not affect conclusion

Table 1: Baseline Characteristics and Outcomes

Figure 1: Estimated Hgb improvement slopes from longitudinal mixed model. Obtained using unadjusted model (no covariates included).



TH-PO987

Long-Term Safety of Hypoxia-Inducible Factor Prolyl Hydroxylase Inhibitors in CKD: A Systematic Review and Meta-Analysis of Randomized Trials

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Background: Hypoxia-inducible factor (HIF) prolyl hydroxylase inhibitors are an oral treatment for anemia of chronic kidney disease (CKD). We assessed long-term safety of HIF prolyl hydroxylase inhibitors in CKD.

Methods: In this systematic review and meta-analysis, MEDLINE, Embase and Cochrane databases were searched to March 2023. Randomized trials comparing HIF prolyl hydroxylase inhibitors with an erythropoiesis-stimulating agent (ESA) or placebo with ≥48 weeks of follow-up were eligible. Major adverse cardiovascular events (MACE), individual components of composite cardiovascular endpoints, thrombotic events, and non-cardiovascular adverse events were evaluated. We conducted analyses separately in people with CKD treated with dialysis and those not treated with dialysis (PROSPERO registration CRD42021278011).

Results: Twenty-five trials involving 26,478 participants proved eligible. Of these, 13 trials were conducted in 13,230 participants with dialysis-dependent CKD, and 12 trials involved 13,248 participants with CKD not requiring dialysis. There was no evidence that HIF prolyl hydroxylase inhibitors and ESA had different effects on MACE in people with dialysis-dependent CKD (relative risk [RR] 0.99, 95% CI 0.92 to 1.08) and non-dialysis CKD (RR 1.08, 95% CI 0.95 to 1.22). Similarly, there was no evidence that HIF prolyl hydroxylase inhibitors and placebo had different effects on MACE (RR 1.10, 95% CI 0.96 to 1.27) in people with non-dialysis CKD. The lack of difference between HIF prolyl hydroxylase inhibitors and ESA or placebo was observed for individual components of MACE, and for cardiovascular death. The safety of HIF prolyl hydroxylase inhibitors for other outcomes was similar to ESA in dialysis-dependent CKD. In non-dialysis CKD, dialysis access thrombosis, infections, hyperkalemia and seizures occurred more frequently in the HIF prolyl hydroxylase inhibitor group than the placebo group. In non-dialysis CKD, esophageal or gastric erosion was more frequent with HIF prolyl hydroxylase inhibitors than ESA.

Conclusions: The long-term effects of HIF prolyl hydroxylase inhibitors were similar to ESA in dialysis-dependent CKD. However, HIF prolyl hydroxylase inhibitors increased the incidence of some adverse outcomes in non-dialysis CKD.

TH-PO988

The Effect of Sodium-Glucose Cotransporter 2 Inhibitors on Hemoglobin Levels in Patients with CKD

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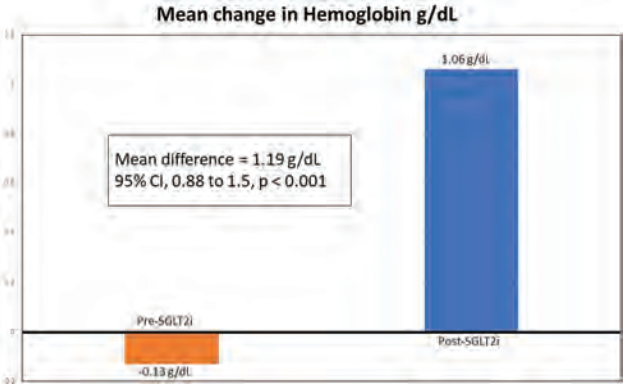
Background: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) confer kidney and cardiovascular protection in patients with chronic kidney disease (CKD). Some studies have analyzed the effects of SGLT2is on hemoglobin levels. Potential mechanisms for rising hemoglobin include hypoxia-induced activation of HIF2α, hepcidin inhibition resulting in iron metabolism modulation, and hemoconcentration. We aimed to assess the effect of SGLT2is on hemoglobin levels in CKD patients.

Methods: We conducted a retrospective study in patients seen in a community nephrology practice with eGFR 25-90 ml/min per 1.73 m^2 who received either dapagliflozin 10 mg daily or empagliflozin 10 mg daily between 1/2022 and 9/2023. The primary outcome was the mean difference in hemoglobin levels 8 months prior and 8 months post initiation of SGLT2i therapy.

Results: Among 402 patients screened from 1/2022 to 9/2023, 72 were prescribed either dapagliflozin 10 mg daily or empagliflozin 10 mg daily, with a mean eGFR of 51.2 ml/min/1.73 m^2. Of those 72 patients, 46 (63.88%) were male and 26 (36.11%) female. No one received any iron supplements or erythropoietin therapy. The mean hemoglobin level 8 months before initiating SGLT2i therapy was 12.8 g/dL, with a mean drop of 0.13 g/dL (95% CI, –0.32 to +0.06) in 8 months. Eight months following the addition of SGLT2is, patients experienced an increase in hemoglobin levels of 1.06 g/dL (95% CI, 0.88 to 1.25). Overall, we observed a mean hemoglobin difference of 1.19 g/dL (95% CI, 0.88 to 1.5, $p < 0.001$) before and after initiating SGLT2i therapy. (Figure 1)

Conclusions: The use of either dapagliflozin or empagliflozin for eight months resulted in a significant elevation in hemoglobin levels in patients with CKD. Larger prospective trials can help better understand the size of the effect and confirm the mechanisms that explain this finding. Elevation of hemoglobin with SGLT2is may be closely linked to the reduction of cardiovascular mortality and heart failure hospitalization risk.



TH-PO989

Utility of a Novel Point-of-Care Test for Albuminuria in Communities at High Risk for CKD

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Background: Albuminuria is a key prognostic marker in chronic kidney disease (CKD). Reliable testing tools for albuminuria and are scarce in many world settings due to limited availability and cost. We tested the utility of novel and low-cost point-of-care test (POCT) for albuminuria to asymptomatic individuals at high risk of CKD in Thailand.

Methods: A community-based cohort study of 2,307 adults with hypertension, diabetes, and/or over age 60 in Ban Phaeo District, Samut Sakhon Province, Thailand. We measured serum creatinine and urine albumin-creatinine ratio (UACR) using a POCT urine albumin strip test (Albii®, K. BioSciences, Bangkok, Thailand) and urine dipstick test for protein, and validated with standard laboratory measures. To confirm the chronicity of abnormalities, participants with albuminuria, regardless of eGFR or patients with eGFR <60 ml/min/1.73m^2 at the first screening (suspected CKD) received follow-up tests for CKD risk. CKD was defined based on standard criteria.

Results: At baseline, 468 participants had reduced eGFR and/or albuminuria. Follow ups were conducted with 260 participants 3 months later, and 140 were confirmed with CKD (Figure 1). Among those diagnosed with CKD, 68 had albuminuria (UACR ≥30mg/g) with normal eGFR, 49 had impaired eGFR without albuminuria, and 22 had both albuminuria and impaired eGFR (Figure 2). The median eGFR was 93.23 [87.82, 98.73] ml/min/m^2, and the median UACR was 9.15 [5.09, 20.96] mg/g for all participants. The POCT urine albumin strip showed a sensitivity of 0.86, specificity of 0.98, and accuracy of 0.96 compared to the standard UACR. Conversely, the POCT urine dipstick for protein had poor sensitivity, positive predictive value, and accuracy. The test results and interpretation were mailed to each participant in a sealed envelope. Participants identified with CKD were advised to attend the outpatient kidney clinic at the district hospital for appropriate management to slow CKD progression.

Conclusions: The urine albumin strip test is a highly effective tool for conducting point-of-care screening for early CKD among high-risk populations. Given the test's low cost- and ease of use, it can facilitate the implementation of large-scale and affordable early detection programs for CKD.

Funding: Government Support - Non-U.S.

TH-PO990

Micral-Test® Strip to Detect Albuminuria Among Patients with CKD Risk Factors

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Background: CKD is often asymptomatic and remains undiagnosed in its early stages. Screening and early identification of CKD allows implementation of treatment to delay progression and prevent adverse outcomes. To improve screening uptake and decrease screening cost in primary care, we piloted a 2 stage-screening strategy:pre-screening using microalbuminuria (Micral-Test®) strips, and confirmatory laboratory testing for positive results. In this study, we examined the testing characteristics of this screening strategy.

Methods: We provided Micral-Test® strips to 15 General Practitioners in Singapore. Individuals with these risk factors were offered screening:diabetes mellitus(DM), hypertension(HT), BMI>27.5kg/m^2, age>60 years, cardiovascular/cerebrovascular disease, family history of kidney disease or smoking history. Patients with positive test were offered a specialist review for confirmation of albuminuria. We calculated a minimum sample size of 97 is needed to achieve 10% margin error and 95% confidence interval.

Results: 209 patients were recruited between April 2022 to April 2023; 72% had HT and 23% had DM. 111(53%) were screen positive and 43% of screen-positive subjects

did not follow up with confirmatory testing. Of the 63 patients who proceeded with a confirmatory urine albumin-creatinine ratio test, 37(58.7%) had confirmed albuminuria; 29 moderately increased albuminuria and 8 severely increased albuminuria. The positive predictive value (PPV) of Micral-test was highest in patients with DM, with or without other comorbidities, and is relatively low in patients without any comorbidities(age>60 years only).

Conclusions: Majority of patients with risk factors for CKD have undiagnosed albuminuria. Our study suggests that Micral-test® strip can be used as an effective screening tool for albuminuria especially in patients with DM. There remains a large proportion of patients with screen positive results that declined further follow-up; further education and screening strategy should target this group for better CKD identification.

Funding: Commercial Support - AstraZeneca

Test characteristics in different subpopulations

Population	Screen positive(%)	PPV(%)
All	53.1	58.7
Diabetes Mellitus	77.6	80.8
Hypertension	53.0	58.8
Diabetes mellitus, hypertension and age>60 years old	74.1	77.8
Age>60 years old only	33.3	0

TH-PO991

Trace Proteinuria Is a High-Risk Marker for Developing ESRD and for Shortening the Lifespan: Findings from an 18-Year Follow-Up Cohort with Half a Million Asian Participants

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Background: Trace proteinuria, obtained by urine dipstick, has not received its due attention in clinic visits. It was particularly overlooked in the younger people, even though it had three times more trace proteinuria than the elderly. This study aims to investigate its role in kidney diseases such as End Stage Renal Disease and its association with mortality outcomes and life-shortening effects in a large Asian cohort.

Methods: A cohort of 646,987 adults, who have undergone health screening programs successively since 1994, were followed for a median of 18 years. Through encrypted identification numbers, 49,216 deaths and 4,101 ESRD cases were identified. Dipstick, in contrast to the old color-comparison method, is a semi-automated computer-assisted urinalysis system. Results reported as trace, 1+, 2+, and more. The association between proteinuria, ESRD, and mortality risks was evaluated using Cox proportional hazards models.

Results: Trace proteinuria existed around 5% among healthy adults, contributed to nearly half of all CKD (9.5%), with younger adults (age <60 years) having a threefold higher prevalence than the elderly (age ≥60 years). Trace proteinuria significantly increased the risk of ESRD independent of eGFR, with up to 4-5 folds in normal eGFR subjects. The HR was 3.54, 95% CI: 2.67, 4.69 when eGFR ≥ 90 ; HR: 3.86, 95% CI: 3.08, 4.84 when eGFR 60-89; HR: 12.26, 95% CI: 9.24, 16.28 when eGFR 45-59; HR: 44.60, 95% CI: 31.39, 60.55 when eGFR 30-44 ml/min/1.73m^2) when compared with negative proteinuria. Participants with trace proteinuria also had a significantly higher risk of all-cause mortality (HR: 1.48, 95% CI: 1.42, 1.54), and associated with a reduction in life expectancy of up to 4-5 years. Dipstick tests demonstrated relatively high sensitivity (84%) and specificity (96%) in detecting microalbuminuria.

Conclusions: Trace proteinuria, overlooked in the clinics, was associated with a 4-5 fold increase in developing ESRD later in life and a shortened lifespan of five years, with nearly 50% increase in all-cause mortality. Trace proteinuria can be screened easily in the clinic or among the public with a dipstick, an inexpensive test with instant results. More than 80% with microalbuminuria in an apparently healthy population could be identified.

TH-PO992

Cost-Effectiveness of Home-Based Screening for Albuminuria in the General Population in the Netherlands

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Background: Screening the general population for albuminuria may identify individuals at high risk of chronic kidney disease (CKD) events and cardiovascular disease (CVD) and allow early preventive interventions. Previous studies on the cost-effectiveness of albuminuria population screening were inconclusive, modelled screening by family physicians, and included only CKD events. We evaluated the cost-effectiveness of home-based general population screening for increased albuminuria to prevent CKD and also CVD events.

Methods: We developed an individual-level health-state transition model to assess cost-effectiveness from the Dutch healthcare perspective with a lifetime horizon. Inputs were based on the THOMAS study, a prospective study in which we screened the general population aged 45-80 years, published in Lancet 2023. THOMAS consisted of a home-based albuminuria screening and subsequent elaborate screening of individuals with elevated albuminuria for CKD and CVD risk factors, to be treated by their family physicians. Risks of CKD and CVD events were calculated by simulating albuminuria and eGFR progression and the SCORE2 algorithm. Treatment relative risk reduction, quality of life weights, resource use, and cost inputs were obtained from the literature. Outcomes included the number of events, total costs, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratio (ICER) of screening versus usual care (no screening), based on probabilistic analysis.

Results: The relative reduction in lifetime dialysis, kidney transplantation, non-fatal myocardial infarction, non-fatal stroke, and fatal CVD events of screening was respectively 11%, 12%, 6%, 5%, and 2%. The incremental costs and QALYs of screening were €1,584 and 0.18 QALYs. This resulted in an ICER of €8.689/QALY, which would be considered cost-effective at the Dutch willingness to pay threshold of €20.000/QALY. The probability of screening being cost-effective for this threshold was 96%. Screening was more cost-effective in subjects aged 65-80 years, compared to those aged 45-65, and if implementation of care after screening was improved.

Conclusions: Home-based screening for increased albuminuria to prevent cardiovascular and chronic kidney disease events is likely cost-effective.

Funding: Private Foundation Support

TH-PO993

Screening for Urine Protein as a Risk Factor for ESRD Using a Large Claims Database

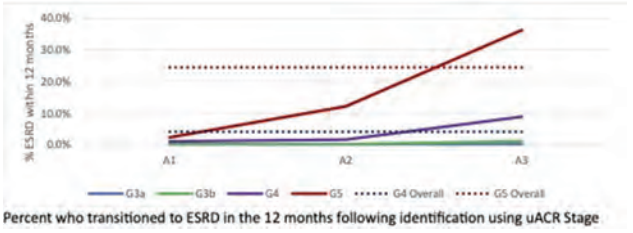
Rahul Dhawan, Ashley Crossman, Lisa M. Latts, Gregory Wysocky. Optum Kidney Solutions: Nurses, Product Team and the OHS Medical Office Team. *Optum Inc, Eden Prairie, MN.*

Background: Proteinuria screening serves as a crucial diagnostic tool in identifying chronic kidney disease (CKD) and mitigating the risk of progression to end-stage renal disease (ESRD). Timely detection and intervention can enhance patient outcomes and provide cost savings, as proteinuria serves as a predictor for ESRD and all-cause mortality rates.

Methods: A large health insurance claims database was used to analyze the relationship between estimated glomerular filtration rate (eGFR), urine albumin-creatinine ratio (uACR), and the progression to ESRD in a population of Medicare members with CKD stages 3a to ESRD during the index month of January 2021. The analysis included data from the 12 months prior to the index month to determine the presence or absence of proteinuria and data from the 12 months following the index month to determine ESRD transition. Data from 32,194 individuals was included. Sources included Medicare claims, labs, and demographics.

Results: Of the 32,194 members in this analysis, 47% were female and the average age was 57.3 years. Thirty-six percent of individuals who had eGFR stage G5 and A3 (severely increased) degree of proteinuria in the twelve months starting January 2021 progressed to ESRD. Twenty-three percent of individuals with eGFR stage G5 patients without proteinuria screening progressed to ESRD. Eighteen percent of the population had proteinuria screening and 22.9% of these patients were CKD 3B, 12.1% were stage 4, and 13.8% were stage 5. Of these patients, 26% were A3, 42% were A2 (Moderately increased) and 32% were A1 (Normal to mildly increased).

Conclusions: Proteinuria screening can provide an early warning of CKD that may progress to ESRD and potentially allow for risk mitigation. In this analysis, more than one-third of CKD G5A3 patients progressed to dialysis within a year. Prompt detection of patients with proteinuria and management, coupled with adherence to ACE and SGLT2 inhibitors, may curtail progression. Utilizing a health plan database is a useful tool to identify individuals who have proteinuria and are at risk of CKD progression and earlier diagnosis can lead to improved outcomes and delay in CKD progression.



Percent who transitioned to ESRD in the 12 months following identification using uACR Stage

TH-PO994

Development of a New Equation for Estimated 24-Hour Proteinuria: Modified Urine Protein-Creatinine Ratio Adjusted by Urinary Creatinine Excretion

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Nara Medical University, Kashihara, Japan.

Background: Instead of the 24h proteinuria, the urinary protein-to-creatinine ratio (Up/Ucr) in spot urine, based on the assumption of 24h urinary creatinine excretion (CER) of 1 g/day, is widely used in clinical practice. However, the actual CER is often deviated from 1g/day because it is affected by individual muscle mass and kidney function, and Up/Ucr is often not accurately estimated for 24h proteinuria.

Methods: Data from a prospective observational study in patients with chronic kidney disease or cardiovascular disease in our hospital were used. Patients with both 24h urine collection and spot urine the day after 24h urine collection were included. First, we examined the relationship between Up/Ucr in 24-hour urine collection and UP/Ucr in spot urine, and then created estimated CER using age, sex, and serum creatinine. Finally, a modified Up/Ucr equation was developed adjusting for estimated CER and the relationship between Up/Ucr in 24-hour urine and UP/Ucr in spot urine.

Results: Among 1031 patients, 813 patients for whom spot urine and 24h urine data were available were included in the analyses of this study. Up/Ucr in spot urine increased by 7% compared to Up/Ucr in 24h urine, and both were closely associated with each other (R2=0.90), suggesting an increase in proteinuria due to exercise in spot urine at hospital visit as compared with 24h urine. Mean CER for males and females was 1.04 and 0.69 g/day, respectively, meaning 4%-overestimation in males and 31% underestimation in females when using Up/Ucr compared with measured 24h proteinuria. CER was also negatively associated with older age especially >60 years and increased in serum creatinine. The mean difference from measured 24h proteinuria for Up/Ucr in spot urine was -45.4% and that for modified Up/Ucr was -21.2% (P <0.001). The numbers within 15% and 30% of measured 24h proteinuria was 17% and 34% for Up/Ucr in spot urine, respectively and 24% and 46% for modified Up/Ucr, respectively (P <0.001).

Conclusions: Using spot urine immediately after 24-hour urine collection and estimated CER, a modified Up/Ucr equation was newly developed, which could be more useful in clinical practice than classical Up/Ucr.

TH-PO995

Disparities in Etiologic Classification of CKD

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Background: Understanding the etiology of CKD is critical for targeted therapy. No prior study has evaluated disparities in assigning an etiology for CKD in practice. Due to widely described health disparities in CKD, we hypothesized that etiologic assignment would be lower for patients of Black race, Hispanic ethnicity, and female sex.

Methods: We identified adults in the Veterans Health Administration who had incident CKD stage G3 or higher (G3+) from 2005-2015. Incident CKD G3+ was defined as the first occurrence of two eGFRs <60 ml/min/1.73m^2 >90 days apart. Patients with ICD-9/ICD-10 codes for general CKD (i.e., 585.X; N18.X) before the index date were excluded. Using 290 specific ICD-9/ICD-10 codes (e.g., N03.3) classified in 6 etiologic domains (diabetic, hypertensive/vascular, obstructive/urologic, glomerular, cystic/congenital, tubulointerstitial), we identified specific etiologic diagnoses of CKD within 3 yrs before or after incident CKD G3+. Logistic regression was used to evaluate disparities in assignment of a specific etiologic code by race/ethnicity and sex, stratified by age. We adjusted for geographic region, year of incident CKD, and comorbidities.

Results: Out of 452,851 patients (438,414 male/14,437 female), 42.5% received an etiologic assignment. Contrary to our hypothesis, rates of etiologic assignment among patients of non-Hispanic Black race or Hispanic ethnicity were higher compared to non-Hispanic White race/ethnicity. We found consistently lower rates of etiologic assignment among females compared to males in all age groups (**Table**).

Conclusions: Efforts are needed to improve the assignment of etiology of CKD, particularly among female Veterans. More work is needed to evaluate rates of specific etiologies and their accuracy in CKD.

Funding: NIDDK Support

Table. Adjusted odds ratios (95% confidence intervals) of etiologic assignment within 3 years before or 3 years after incident CKD

	Overall	Age group 18-44	Age group 45-64	Age group 65-74	Age group 75 and above
Female vs Male	0.47 (0.45-0.48)	0.51 (0.40-0.64)	0.43 (0.41-0.45)	0.49 (0.45-0.53)	0.53 (0.48-0.58)
Asian, Native Hawaiian/Pacific Islander vs White	1.09 (1.03-1.15)	1.54 (0.72-3.27)	1.12 (1.01-1.25)	1.07 (0.96-1.18)	1.04 (0.94-1.15)
Black vs White	1.56 (1.53-1.59)	1.59 (1.27-1.99)	1.70 (1.65-1.76)	1.51 (1.46-1.56)	1.39 (1.34-1.44)
Hispanic vs White	1.17 (1.13-1.21)	1.76 (1.12-2.74)	1.33 (1.25-1.41)	1.15 (1.08-1.22)	1.02 (0.96-1.09)
American Indian/Alaska Native vs. White	1.11 (1.01-1.22)	1.68 (0.44-6.42)	1.09 (0.93-1.27)	1.14 (0.98-1.33)	1.10 (0.91-1.33)
Multiple or other races vs. White	1.04 (0.98-1.09)	0.85 (0.46-1.55)	1.09 (1.00-1.19)	1.05 (0.96-1.14)	0.97 (0.88-1.07)

TH-PO996

Incorporation of Cystatin C in Estimating Kidney Function: Real-World Experience in Sweden

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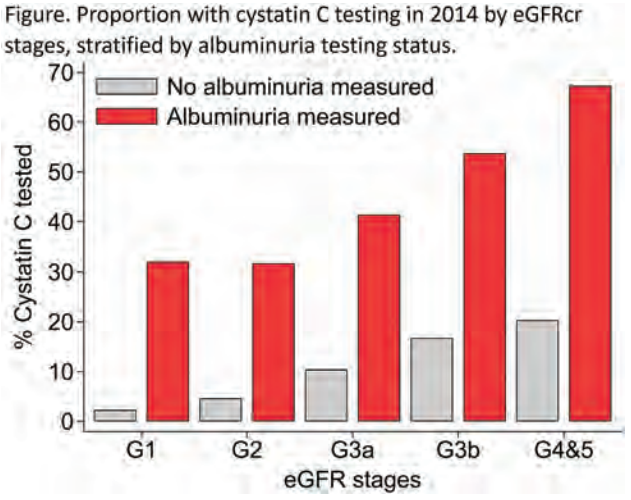
Background: Cystatin C is a filtration marker that, when used in combination with serum creatinine, provides a more precise estimate of GFR than using serum creatinine alone. However, many US physicians are unfamiliar with cystatin C and guidelines are vague on use of cystatin C as an adjunct test. Cystatin C has been routinely tested in Sweden for over a decade.

Methods: Using routine clinical data collected from 2010-2018 in the Stockholm Creatinine Measurements (SCREAM) project, we investigated rates of routine outpatient cystatin C testing over time as well as clinical care and patient characteristics associated with cystatin C testing. We used logistic and Cox proportional hazards regressions, stratified by ACR testing status, to further examine associations with cystatin C testing.

Results: Among the 1.37M adult individuals with serum creatinine tested, 11.2% also had serum cystatin C tested. The annual rate of cystatin C testing ranged between 4-7% each year. Those who had both markers tested were more likely to be older, male, have a lower eGFRcr, have more comorbidities, and more likely to have an ACR test. Among those with ACR testing, we found higher odds for a lower eGFRcr and, much higher risks of KFRT for the same level of eGFRcr in the population with cystatin C testing compared to those without. Among those without ACR testing, we found higher odds for older age and anemia, similar KFRT risk, but higher mortality risk among those with cystatin C testing compared to those without.

Conclusions: Cystatin C testing in Sweden followed two distinct patterns: for those at heightened risk of kidney failure (who were also receiving albuminuria testing) and for older adults who were more likely to have anemia and at higher risk of mortality. This study provides a real-world account of cystatin C testing and supports the utility of cystatin C for clinical practice.

Funding: NIDDK Support, Private Foundation Support



TH-PO997

Cystatin C as a Marker for GFR Estimation in Clinical Populations: A Systematic Review

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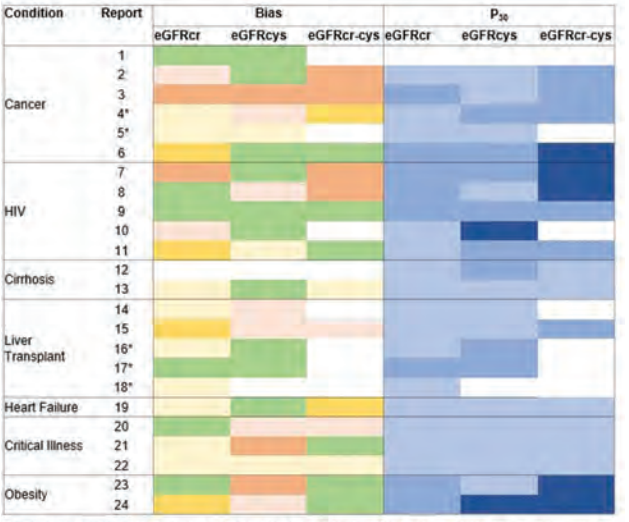
Background: GFR estimated using creatinine (eGFRcr) is often inaccurate in populations with acute and chronic illness. The accuracy of GFR equations that use cystatin C (eGFRcys) or creatinine-cystatin C (eGFRcr-cys) is not well studied in these populations.

Methods: Using a systematic review, we identified 21 studies of populations with comorbid illnesses that evaluated eGFRcr and eGFRcys compared to measured GFR (mGFR) using standardized assays for the markers: cancer (5); HIV (5); cirrhosis (2); liver transplant (3); heart failure (1); critical illness (3); and obesity (2). The performance of each equation was the unit of analyses ("report"). We assessed equation performance using bias as the median or mean difference between eGFR and mGFR, and accuracy as the percentage of eGFR within 30% of mGFR (P_{30}).

Results: eGFRcr had more reports of moderate-to-large bias than for eGFRcys and eGFRcr-cys, and of overestimation, than underestimatation, of mGFR. There were large inconsistencies in the relative performance of eGFRcr vs eGFRcys even for populations with the same illness. eGFRcr-cys was most accurate in populations with cancer, HIV and obesity, but did not perform consistently better in cirrhosis, liver transplant, heart failure and critical illness populations. Notable limitations are that participants were selected because of concern for inaccurate eGFRcr, and most studies had small sample sizes, limiting generalizability.

Conclusions: eGFRcr-cys improves GFR estimation in populations with a variety of acute and chronic illnesses, supporting current recommendations for more frequent use of cystatin C into more clinical practice. These data provide early evidence base for indications for cystatin C.

Funding: NIDDK Support



*Children only studies. Green indicates small bias, -5 to +5 mL/min/1.73m². Dark peach indicates medium underestimate, bias of -5 to -10 mL/min/1.73m². Light peach indicates large underestimate, bias > -10 mL/min/1.73m². Dark yellow indicates medium overestimate, bias of 5 to 10 mL/min/1.732m². Light yellow indicates large overestimate, bias >10 mL/min/1.73m². Dark blue indicate high accuracy, P_{30} > 90%. Medium blue indicates moderate accuracy, P_{30} of 80 to 90 %; light Medium blue indicates low accuracy, P_{30} < 80%.

TH-PO998

Estimating GFR from Cystatin C Without Including a Sex Variable: CKD-EPI 2023 Equation

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Background: Use of a binary sex variable in eGFR equations may limit their use in gender subgroups. There are smaller differences between sex groups in cystatin C than creatinine independent of GFR. Other research groups have developed equations to estimate GFR using cystatin without sex [Pottel et al, NEJM 2023; Grubb et al, Clin Chem 2014]. We developed a CKD-EPI cystatin C equation that does not include a variable for sex and evaluated its performance in an external validation population.

Methods: Using the same population (5,352 participants from 13 studies) used for development of the current equation that includes age and sex (CKD-EPI 2012 eGFRcys AS), we developed a new eGFR cystatin C equation without sex (CKD-EPI 2023 eGFRcys A). We used least squares linear regression of measured GFR (mGFR) vs serum cystatin C and age on the logarithmic scale, with separate slopes for cystatin C at low vs. high values using the same spline knot as the 2012 equation (0.8 mg/L), and assessed model performance using root-mean-square error (RMSE). We assessed performance in the CKD-EPI 2021 external validation population (4,050 participants from 12 studies) using bias (systematic error, mL/min/1.73m^2) as the median difference between mGFR and eGFR, and accuracy as the percentage of eGFR within 30% of mGFR (P_{30}).

Results: In the development and validation population, 2,245 (42%) and 1,557 (38%) were female, respectively. Removing the sex variable led to a minimal increase in RMSE overall and in both sex subgroups (Table). In the external validation population, removing the sex variable led to a small increase in bias in both subgroups, with greater decrease in accuracy for females vs males although at levels considered acceptable (P_{30} >80%).

Conclusions: The availability of acceptably accurate eGFRcys equations that do not include a sex variable provides an option to use in people whose gender identification differs from their sex assigned at birth. Further studies can explore the impact of using these equations in the general population.

Funding: NIDDK Support

Performance of CKD-EPI 2012 and 2023 cystatin C eGFR equations

Equations	Development (13 Studies) mean (SD) mGFR 68 (39) mL/min/1.73m² and age 47 (15) years.	External Validation (12 Studies) mean (SD) mGFR 76 (30) mL/min/1.73m² and age 57 (17) years.	
	RMSE (95%CI)	Bias (95%CI)	P30 (95%CI)
Overall	**N=5,352**	**N=4,050**	
CKD-EPI 2012 AS	0.224 (0.217, 0.231)	0.6 (0.1, 1.1)	88.2 (87.2, 89.2)
CKD-EPI 2023 A	0.226 (0.220, 0.233)	0.9 (0.3, 1.3)	86.3 (85.3, 87.4)
Female	**(n=2,245, 42%)**	**(n=1,597, 38%)**	
CKD-EPI 2012 AS	0.231 (0.219, 0.244)	-1.1 (-1.8, -0.5)	88.7 (87.1, 90.3)
CKD-EPI 2023 A	0.235 (0.223, 0.248)	**-3.7 (-4.5, -3.0)**	**84.8 (83.0, 86.6)**
Male	**(n=3,107, 58%)**	**(n=2,493, 62%)**	
CKD-EPI 2012 AS	0.219 (0.211, 0.226)	1.8 (1.2, 2.5)	88.0 (86.7, 89.2)
CKD-EPI 2023 A	0.220 (0.213, 0.228)	**3.6 (3.0, 4.3)**	87.3 (86.0, 88.6)

A positive and negative value for bias indicates underestimation and overestimation of mGFR, respectively. Bold font indicates non-overlapping 95% confidence intervals compared with the CKD-EPI 2012 AS (reference equation).
Confidence intervals were calculated using bootstrap resampling with 2000 replicating samples. Equations are below:
CKD-EPI 2023: For Scys ≤0.8 mg/L, eGFR = 129 x (Scys/0.8)$^{-0.523}$ x 0.9962^{Age}; and for Scys >0.8 mg/L, eGFR = 129 x (Scys/0.8)$^{-1.328}$ x 0.9962^{Age}
CKD-EPI 2012: For Scys ≤0.8 mg/L, eGFR = 133 x (Scys/0.8)$^{-0.499}$ x 0.9962^{Age} x 0.932[If female]; and for Scys >0.8 mg/L, eGFR = 133 x (Scys/0.8)$^{-1.328}$ x 0.9962^{Age} x 0.932[If female]

TH-PO999

Effect of Race-Free Estimated Glomerular Filtration (eGFR) Equation on CKD Prevalence in the US Military Health System (MHS)

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Background: The 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation removed race as a factor in the calculation of eGFR. We assessed the potential impact on CKD prevalence using the MHS Data Repository, a large network health care database covering a diverse population comparable to the US general population.

Methods: We extracted MHS data from 2016-2019 for adults age ≥18. We compared CKD prevalence using eGFR calculated from the 2009 race-adjusted vs. the 2021 race-free CKD-EPI equations. Race was classified as Black or non-Black and was imputed in 23.7% of the population. CKD stages 3-5 was defined as eGFR < 60 mL/min/1.73m² for ≥90 days. We evaluated addtional population changes at eGFR thresholds (<45, <30, <20 mL/min/1.73m2) important for clinical decision-making.

Results: The study included 1,970,433 adults with median (IQR) age 40 (29–55) yrs, 49.2% female, and 18.0% Black adults. With the 2021 equation, Black adults with CKD increased from 5828 to 8928, a change in crude prevalence from 1.6 to 2.5% (Table). Non-Black adults with CKD declined from 43,126 to 30,932, a crude prevalence change from 2.7 to 1.9%. The Black adult population with eGFR <60, <45, <30, and <20 mL/min/1.73m² increased by 53.2%, 29.0%, 18.6%, and 28.7%, respectively while that for non-Black adults declined by –28.3%, –26.6%, –26.0%, and –27.8%, respectively. Cumulatively, 44.4% of Black adults with CKD and 42.1% of non-Black adults with CKD were reclassified across eGFR strata.

Conclusions: The new eGFR equation in the MHS will reclassify many Black adults to new or more advanced CKD stages, with the opposite effect on non-Black adults. The impact on time to diagnosis, clinical management, and outcomes is unknown but there may be shifts in referral patterns to nephrology, dialysis, and transplant services. Ongoing surveillance of CKD is warranted. *The views expressed in this abstract are those of the authors and do not reflect the official position of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, the Department of Health and Human Services, or the US Government.*

Funding: Other U.S. Government Support

	ALL ADULTS	BLACK ADULTS	NON-BLACK ADULTS
No. (95% CI)	1,970,433	355,310 (354,064-356,563)	1,615,119 (1,613,870-1,616,368)
2009 CKD stages 3–5 (95% CI), n	48,954 (48,524–48,384)	5826 (5669–5926)	43,126 (42,718–43,574)
2009 CKD stage 3–5 (95% CI), %	2.5 (2.46–2.51)	1.6 (1.60–1.68)	2.7 (2.65–2.70)
2021 CKD stages 3–5 (95% CI), n	39,960	8928 (8735–9121)	30,932 (30,586–31,279)
2021 CKD stages 3–5 (95% CI), %	2.0	2.5 (2.46–2.57)	1.9 (1.85–1.94)
CKD stages 3-5, relative change, %	-18.6	+53.2	-28.3
Cumulative reclassification, (95%CI), n	22,137 (21,859–22,496)	3871 (3841–4102)	18,166 (17,859–18,439)
Cumulative reclassification, % of CKD population	45.2	44.4	42.1

TH-PO1000

Potential Implications of 2021 CKD-EPI Equation in Patients with CKD from British Columbia, Canada

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Background: One in 10 British Columbians has kidney disease. The implications of implementing 2021 CKD-EPI equation in British Columbia (BC) is unknown. This was investigated in a population-level cohort of CKD patients from BC, Canada.

Methods: CKD patients aged ≥19 years and registered in the "Provincial Renal Program" on March 31, 2023 (index date) were included. Patients needed to have ≥1 serum creatinine recorded within 1 year before index date. We excluded patients who received transplantation before index date. We calculated eGFR using CKD-EPI 2009 and 2021 equations, and estimated the mean difference in eGFRs and corresponding Kidney Failure Risk Equation (KFRE) 2-year risks by age and sex. We assessed the implications in two clinical aspects: (1) reclassification between eGFR categories (G1-G5) (2) reclassification between KDIGO risk categories (low, moderately increased, high and very high risk). Finally, we investigated patient characteristics among those who were reclassified in eGFR categories (switcher; yes/no).

Results: Study sample included 16,037 patients, median age 74 years, 54% male. Compared to 2009 equation, eGFR calculated using 2021 equation was on average 1.80-2.60 ml/min higher in women and 2.86-3.33 ml/min higher in men. The 2021 equation downgraded the CKD severity with highest % of patients downgraded in G5 category (Fig.1). In KDIGO risk categorization, ~4% of patients in the very high risk group were reclassified to a lower risk group. The switchers appeared to be older male, majority (~43%) were in eGFR category G4 followed by 27% in G3b. KFRE 2-year risk score calculated using eGFR from 2021 equation was lower compared to that of estimated using eGFR from 2009 equation, median (IQR) in difference was -0.854 (-2.516, -0.258). Difference was larger in males.

Conclusions: The eGFR calculated using CKD-EPI 2021 was higher compared to 2009 equation. A large number (~17%) of patients currently under the care of nephrologists in BC would have categorically less severe CKD. The implications of this on resource utilization, care plans and outcomes are unknown.

CKD patients registered in Provincial Renal Program								
# Pts		CKD-EPI 2021: eGFR category						
		G1	G2	G3a	G3b	G4	G5	Total
CKD-EPI 2009: eGFR category	G1	754	0	0	0	0	0	754
	G2	172 (14%)	1023	0	0	0	0	1195
	G3a	0	310 (17%)	1492	0	0	0	1802
	G3b	0	0	776 (16%)	3980	0	0	4756
	G4	0	0	0	1166 (19%)	5124	0	6290
	G5	0	0	0	0	278 (22%)	962	1240
	Total	926	1333	2268	5146	5402	962	16037

TH-PO1001

CKD EPI 2021 Equation for Estimation of Glomerular Filtration Rate (eGFR) Has Good Efficacy to Predict Clinical Outcomes in a Large Prospective Cohort of Adult Koreans

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Background: A new eGFR equation using serum creatinine (CKD-EPI 2021) without race were developed by Chronic Kidney Disease Epidemiology Collaboration in 2021. We projected the changes of eGFR, CKD prevalence, and incidence of end stage renal disease (ESRD) and mortality in a large prospective cohort of adult Koreans who had voluntary health check-ups, using current (CKD-EPI 2009) and new equation (CKD-EPI 2021).

Methods: We included 112,772 adult participants, aged 18 years or older, who had voluntary routine health check-ups at three medical centers in Korea from 2003 to 2009. We compared the difference of eGFR and predictability of mortality and ESRD between eGFR values calculated by CKD-EPI 2009 and 2021. The incidence of mortality data was extracted from Statistics Korea and the ESRD data from the ESRD registry of the Korean Society of Nephrology.

Results: At baseline study, there were 60,723 males (53.8 %). The value of IDMS-traceable serum creatinine was 0.86 ± 0.21 mg/dl. Levels of eGFR at baseline study were 93.5 ± 15.6 ml/min/1.73 m² by CKD-EPI2009, and 97.1 ± 15.0 ml/min/1.73 m² by CKD-EPI2021. CKD stage was improved in 11,828 (10.5%) participants using eGFR calculated by CKD-EPI 2021 instead of CKD-EPI 2009, however, only 0.63 % of participants with eGFR <60 ml/min/1.73 m² by CKD-EPI equation was reclassified into eGFR ≥60 ml/min/1.73 m² by CKD-EPI 2021. During 11.6 ± 2.0 years, 3354 (3.00 %) subjects were dead and 151 (0.13%) subjects had end stage renal disease (ESRD) before death. Any eGFR or stage of eGFR was an independent risk factors to ESRD or mortality estimated by Cox's hazard proportional model adjusted by related factors. AUC to estimate renal survival by eGFRs was not different between eGFRs by CKD-EPI2021 and CKD-EPI2009 [0.739 (0.687-0.790) vs 0.740(0.688-0.792), p=0.170]. p<0.001]. AUC to estimate survival by eGFRs calculated through CKD-EPI equation was slightly higher than that by CKD-EPI2021 equation [0.673(0.664-0.682) vs 0.667(0.658-0.676), p<0.001], however, the difference of AUC was negligible [standard error of AUC difference by two eGFRs; 0.96 (95% CI; 0.006-0.007)].

Conclusions: The eGFR calculated by CKD-EPI2021 was higher compared to eGFR calculated by CKD-EPI2009. The power to estimate renal survival was not different between eGFRs by CKD-EPI2021 and CKD-EPI2009.

TH-PO1003

Identifying CKD Stage 3 with Excess Disease Burden

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Background: Chronic kidney disease (CKD) is a widely prevalent disease with heterogeneous disease progression. Current practice guidelines recommend nephrology referral when patients are diagnosed with CKD stage 4. Prior studies suggest earlier referral to nephrologists can improve health outcomes for patients with chronic kidney disease (CKD), however claims-based methods to identify high-risk CKD stage 3 patients remain lacking. We assessed cost, utilization, and disease progression in patients with various stages of CKD, including an identified subset of patients with CKD stage 3 and common medical comorbidities.

Methods: This is a retrospective study of Medicare fee-for-service beneficiaries with CKD stages 3-5. We identified seven comorbidities with high prevalence in patients with progressive CKD and segmented beneficiaries with CKD stage 3 based on the presence of

these comorbidities. Outcomes including costs, utilization, and disease progression were then compared across beneficiaries with different stages of CKD.

Results: We identified that beneficiaries with CKD stage 3 and at least one of the selected comorbidities (CKD stage 3-plus), represented 35.4% of all beneficiaries with CKD stage 3. The CKD stage 3-plus cohort had cost and utilization patterns that were more similar to beneficiaries with CKD stages 4 and 5 compared to beneficiaries with CKD stage 3 without the selected comorbidities.

Conclusions: Our findings demonstrate the use of a claims-based algorithm to identify patients with CKD stage 3 that are high cost and at risk of disease progression, highlighting a potential subset of patients who might benefit from earlier nephrology intervention.

TH-PO1004

Undiagnosed Early CKD in Patients with Hypertension and Cardiovascular Disease in the United States

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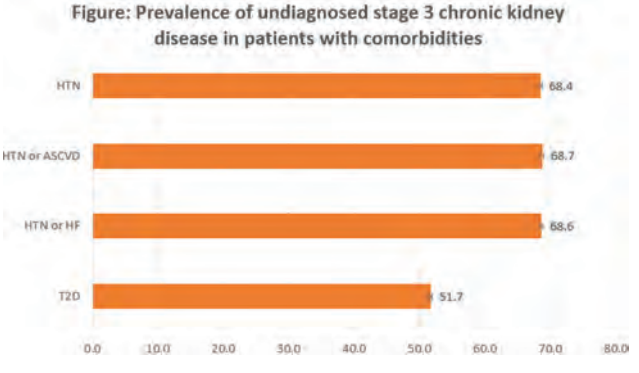
Background: Chronic kidney disease (CKD) is a growing public health issue and widely under-recognized in the United States. Hypertension (HTN) and cardiovascular diseases (CVD) are well-known risk factors for CKD; and KDIGO recommends screening in both high-risk groups. Early diagnosis of CKD and active management can slow disease progression and improve outcomes, but the prevalence of undiagnosed early-stage CKD in patients with comorbidities other than type 2 diabetes (T2D) has not been reported. This analysis assessed the prevalence of undiagnosed stage 3 CKD in patients with HTN and CVD in the absence of T2D.

Methods: Data were extracted from the US TriNetX database. Patients were aged ≥18 years with 2 consecutive estimated glomerular filtration rate (eGFR) results ≥30 and <60mL/min/1.73m^2 recorded 91-730 days apart between 2015 and 2020. Undiagnosed CKD was defined as the absence of a CKD diagnosis code any time before and up to 6 months after the second eGFR (index date). The analysis cohorts included patients with the following at or before index: 1) HTN ICD 9/10 diagnosis code but not for T2D; 2) HTN or atherosclerotic cardiovascular disease (ASCVD) ICD 9/10 diagnosis code but not for T2D; 3) HTN or heart failure (HF) ICD 9/10 diagnosis code but not for T2D; and 4) ICD 9/10 diagnosis code for T2D.

Results: In the absence of T2D, the proportion of undiagnosed stage 3 CKD in patients with HTN was 68.4% (95%CI: 68.2%, 68.7%). Similar proportions were observed in patients with either HTN or ASCVD (68.7%, 95%CI: 68.4%, 69.0%), and with HTN or HF (68.6%, 95%CI: 68.3%, 68.8%). These proportions were greater than those with undiagnosed stage 3 CKD and T2D (51.7%, 95%CI: 51.3%, 52.0%) (**Figure**).

Conclusions: A high prevalence of undiagnosed CKD in patients with existing HTN and CVD in the absence of T2D was observed in a large contemporary US database. These results highlight an opportunity to increase early identification of CKD in people with high-risk comorbidities other than T2D in order to implement targeted evidence-based therapies to slow progression of CKD and improve patient outcomes.

Funding: Commercial Support - AstraZeneca



TH-PO1005

Renal Protective Treatment Use for Non-Diabetic CKD in Japan, Sweden, and the United States

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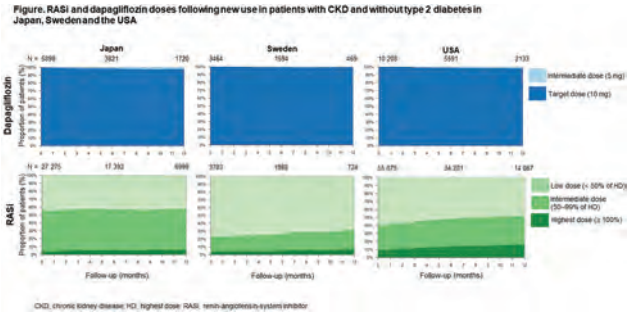
Background: Chronic kidney disease (CKD) is an underdiagnosed disease affecting 10% of people worldwide. Appropriate management of CKD delays progression and reduces its burden. Renin–angiotensin system inhibitors (RASis) have been the mainstay of CKD treatment until recently. Here we describe the use of RASis and the sodium–glucose co-transporter-2 inhibitor dapagliflozin in a contemporary population of patients with CKD.

Methods: This study used secondary data extracted from electronic health records or claims data sources. Adult patients with CKD (either two estimated glomerular filtration rate [eGFR] measurements ≥ 90 days apart of which both were ≤ 60 mL/min/1.73 m^2 or an eGFR ≤ 60 mL/min/1.73 m^2 followed by a CKD diagnosis) who were new RASi or dapagliflozin users during 2021–2023 were included. Patients with type 1 or gestational diabetes, stage 5 CKD or on dialysis were excluded. RASi and dapagliflozin doses and persistence were assessed in the year following initiation.

Results: Overall, 159 220 patients were included (Japan, 57 222; Sweden, 10 861; USA, 91 137). Median ages were 75, 72 and 72 years, and 63%, 66% and 52% were males in Japan, Sweden and the USA, respectively. Of patients without type 2 diabetes, a high proportion receiving dapagliflozin remained on the evidence-based 10 mg target dose (Figure). A large proportion of patients treated with RASis received low doses. At 12-month follow-up, dapagliflozin persistence was approximately 65%, 80% and 55% in Japan, Sweden and the USA, respectively, and was 34%, 75% and 64% for RASi, respectively.

Conclusions: CKD treatment with dapagliflozin was associated with a high likelihood of receiving and remaining on target dose compared with RASi treatment. Efforts to maintain patients on renal protective treatment are needed.

Funding: Commercial Support - AstraZeneca



TH-PO1006

Prevalence of Antihypertensive Use in CKD

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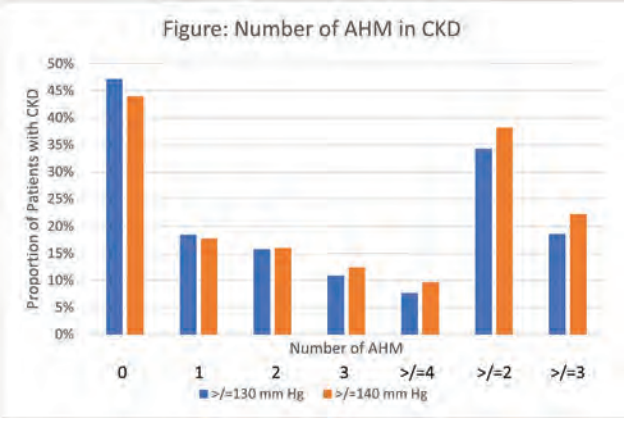
Background: Treatment-resistant hypertension (TRH) is a comorbidity of concern in patients with chronic kidney disease (CKD) and elevates the risk of cardiovascular events. The aim of this analysis was to identify the prevalence of antihypertensive medication (AHM) use in patients with persistent TRH concurrent with CKD, overall and stratified by CKD stage.

Methods: The study cohort was comprised of adults with CKD in the US TriNetX database between 2008 and 2020. CKD index was defined as the second of two consecutive eGFR measurements <75 ml/min/m^2 between 91-730 days apart or ICD-9/10 code of CKD or dialysis. Patients with ≥1 systolic blood pressure (SBP) ≥130 mm Hg within 6 months before or any time after index were included, and of these, TRH was defined as taking ≥3 AHM classes. The number of AHM prescribed 0 to ≥4 were described overall and by CKD stage. A sensitivity analysis using SBP ≥140 mm Hg was also performed.

Results: In the cohort with CKD and SBP ≥130 mm Hg (N = 109,385), mean (SD) age was 64 (13) years, 57% were female, and 77% were White and 20% were Black. Median (IQR) SBP measurements was 3 (1,5). Proportion of patients with TRH was 18.6% overall, and by CKD stage was 13.8% (S1 and 2), 21.5% (S3), 35.7% (S4), and 37.5% (S5). These proportions were modestly increased in the sensitivity analysis.

Conclusions: In a large real-world cohort, TRH was detected in nearly 1 in 5 individuals with CKD, and no AHM use was observed in nearly half of CKD patients with elevated SBP. An opportunity clearly exists for improved management of TRH in order to avoid adverse clinical outcomes in this high-risk population.

Funding: Commercial Support - AstraZeneca



TH-PO1007

The Prevalence of CKD in Australian Primary Care: Analysis of a National General Practice Dataset

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Background: CKD prevalence in Australia varies substantially across reports. Using a large, nationally-representative general practice data source in Australia, we determined the contemporary prevalence and staging of CKD in Australian primary care.

Methods: We performed a retrospective, community-based observational study using healthcare data from MedicineInsight, a national general practice data source in Australia. We included all adults with ≥1 visit to a general practice participating in MedicineInsight and ≥1 serum creatinine measurement (with or without a UACR measure) between 2011-2020; n=2,720,529 patients. CKD prevalence was estimated using 3 definitions: (1): an eGFR (mL/min/1.73m^2) <60 or an eGFR ≥60 with a UACR (mg/mmol) >2.5 for M and >3.5 for F, (2) 2 consecutive eGFR measures <60, ≥90 days apart or an eGFR ≥60 with a UACR >2.5 for M and >3.5 for F and (3) 2 consecutive eGFR measures <60, ≥90 days part and/or 2 consecutive UACR measures >2.5 for M and >3.5 for F ≥90 days apart. Patient characteristics were assessed across the 3 definitions.

Results: CKD prevalence progressively increased over the 10-year study period, irrespective of the method used to define CKD. The annual prevalence of CKD varied across the 3 CKD definitions, with definition 1 resulting in the highest estimates. In 2020, CKD prevalence in the study cohort was 8.4% (n=123,988), 4.7% (n=69,110) and 3.1% (n=45,360) using definitions 1, 2 and 3, respectively. The number of patients with UACR measurements was low such that, among those identified as having CKD in 2020, only 3.8%, 3.2% and 1.5% respectively, had both eGFR and UACR measures available in the corresponding year. Patients in whom both eGFR and UACR measurements were available mostly had moderate or high risk of CKD progression (83.6%, 80.6% and 76.2%, respectively). Comorbid burden in patients with CKD was also frequently observed.

Conclusions: In this large, nationally-representative study, we observed an increasing trend in CKD prevalence in primary care settings in Australia. Most patients with CKD were at moderate to high risk of CKD progression with a significant comorbid burden. These findings highlight the need for early detection and effective management to slow progression of CKD.

Funding: Commercial Support - This study was supported by an unrestricted research grant from Boehringer Ingelheim.

TH-PO1008

Predictors of Differences in Cystatin C- and Creatinine-Based eGFR

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Background: Large differences between eGFR based on cystatin C (eGFRcys) and creatinine (eGFRcr) are common. A comprehensive evaluation of factors that account for these differences is needed to guide the interpretation of discrepant eGFR values.

Methods: We randomly divided the study population of 468,969 UK Biobank participants into 2 nonoverlapping cohorts, 80% for model training and 20% for model testing. In the training set, we used Bayesian model averaging to identify a parsimonious set of predictors among 34 candidate variables, including sociodemographic, lifestyle, physical and clinical factors of large eGFRdiff. Large eGFRdiff was defined as eGFRcys minus eGFRcr <-15 (negative eGFRdiff) or ≥15 mL/min/1.73 m^2 (positive eGFRdiff). We incorporated the identified set of predictors into a multinomial logistic regression model to estimate the odds of negative or positive eGFRdiff. We assessed model performance in the test set.

Results: The mean age was 56y; 46% were male. The overall mean ± SD of eGFRcys was 88±16 and eGFRcr was 95±13 mL/min/1.73 m^2; 25% of participants had negative eGFRdiffs and 5% had positive eGFRdiff. Strong predictors of negative eGFRdiff included older age, male sex, South Asian ethnicity, current smoker (vs. never smoker); history of thyroid dysfunction, chronic inflammatory disease, steroid use, higher waist circumference and body fat, and UACR >300 mg/g (Table 1). Odds ratio estimates for these predictors were largely inverse of those for positive eGFRdiff. The model's AUC was 0.75 in the test set, with good calibration (1.00).

Conclusions: This study highlights the multitude of demographic, lifestyle, and health characteristics associated with wide eGFRdiff. These results may help clinicians to interpret discrepant eGFRcys and eGFRcr values.

Funding: NIDDK Support, Veterans Affairs Support

Predictor	Prevalence	Negative vs. Concordant eGFRdiff OR (95% CI)	Positive vs. Concordant eGFRdiff OR (95% CI)
Demographics			
Age, per SD		1.26 (1.25, 1.27)	0.73 (0.72, 0.75)
Sex			
Female	54.2%	Ref	Ref
Male	45.8%	1.75 (1.67, 1.84)	0.37 (0.34, 0.40)
Race/Ethnicity			
White	94.3%	Ref	Ref
Black	1.6%	0.24 (0.22, 0.26)	7.32 (6.80, 7.89)
East Asian/Southeast Asian	0.4%	0.70 (0.59, 0.83)	0.85 (0.67, 1.08)
South Asian	1.7%	1.59 (1.50, 1.68)	0.86 (0.72, 1.03)
Other	2.1%	0.81 (0.76, 0.85)	1.53 (1.39, 1.68)
Lifestyle/Socioeconomic			
Meat intake, per week			
<1 time	3.6%	Ref	Ref
1-4 time	88.9%	0.38 (0.36, 0.39)	2.69 (2.34, 3.09)
≥ 5 time	7.5%	0.35 (0.33, 0.37)	3.22 (2.78, 3.73)
Physical activity, MET-min/week			
Low (<600)	2.6%	1.13 (1.07, 1.19)	1.00 (0.88, 1.13)
Moderate (600-3000)	66.6%	0.96 (0.94, 0.98)	1.01 (0.98, 1.05)
High (≥3000)	30.8%	Ref	Ref
Smoking			
Never	54.5%	Ref	Ref
Previous	34.6%	0.97 (0.95, 0.99)	0.96 (0.93, 0.99)
Current	10.5%	2.79 (2.72, 2.87)	0.58 (0.54, 0.63)
Grip strength, per SD		0.74 (0.73, 0.75)	1.46 (1.42, 1.50)
Townsend deprivation index, per SD		1.10 (1.09, 1.11)	0.98 (0.97, 1.00)
Comorbidities/Medications			
Diabetes	6.0%	1.09 (1.05, 1.14)	0.76 (0.67, 0.85)
Hypertension	53.3%	1.08 (1.06, 1.11)	0.95 (0.91, 0.99)
Thyroid dysfunction	5.7%	1.22 (1.18, 1.26)	1.05 (0.98, 1.13)
Chronic inflammatory disease	1.5%	1.56 (1.47, 1.66)	0.60 (0.49, 0.73)
Steroid use	1.0%	1.93 (1.80, 2.08)	0.62 (0.50, 0.77)
Trimethoprim use	0.1%	0.43 (0.32, 0.59)	3.70 (2.72, 5.04)
Physical/Laboratory Measures			
Waist circumference, per SD		1.31 (1.29, 1.33)	0.97 (0.94, 1.00)
Body fat %, per SD		1.33 (1.31, 1.36)	0.77 (0.74, 0.79)
UACR, mg/g			
<30	95.4%	Ref	Ref
30-300	4.2%	1.13 (1.08, 1.17)	0.59 (0.53, 0.66)
>300	0.4%	1.20 (1.07, 1.35)	0.12 (0.07, 0.19)

Multinomial logistic regression model adjusted for all predictors listed, plus average household income, cancer, bone fracture in last 5 years, systolic BP, HbA1c, albumin, BUN and hemoglobin. The negative eGFRdiff category comprised individuals with eGFRdiff < -15, the concordant eGFRdiff category served as the reference and comprised individuals with eGFRdiff between -15 and 15, and the positive eGFRdiff category comprised individuals with eGFRdiff ≥ 15.

TH-PO1009

Mapping CKD Prevalence Burden in a Reportedly High Australian Health District Region

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Background: Chronic kidney disease (CKD) affects 10% of the worldwide population but varies globally and regionally. In Australia, it ranges from 3% to 20%, with reports indicating a high prevalence of almost 20% among Illawarra and Shoalhaven Local Health District (ISLHD) residents. We aimed to determine the true prevalence of CKD among ISLHD residents and to identify potential risk factors.

Methods: Retrospective cohort longitudinal analysis on data from adult patients (>18 years of age), who attended an ISLHD facility between January 2008 and December 2017. Data variables included baseline demographics, comorbidities (defined from international classification of disease [ICD 10AM]), and CKD status defined using ICD-10AM codes or two creatinine or urine protein measurements, within 3-12 months apart, confirming CKD as per Kidney Disease Improving Global Outcome (KDIGO) definitions. Proportion of CKD in each suburb was calculated to identify suburbs with low and high prevalence of CKD. We preformed multivariate Cox proportional hazard analysis to determine CKD risk among the ISLHD suburbs, using time to CKD as an endpoint. Variables known to influence CKD risk (such as age, diabetes, hypertension, history of acute kidney injury) were included in the analysis.

Results: In total 135,585 patients were followed up for 580,118 patient years. Mean age was 53 (standard deviation 21.2) years and the most common comorbidity was hypertension (26%), diabetes (14%) and coronary artery disease (10%). CKD affected 9% of the population with an incidence of 2 per 100 patient year. CKD patients were more likely

to have, compared to non-CKD patients, a history of hypertension (43% vs 25%) diabetes (18% vs 12%) and acute kidney injury (20% vs 9%), *P*<0.001. The CKD prevalence differed highly across the 80 suburbs within the region, ranging from 4% to 24%. However, multivariate cox regression analysis which included risk factors known for CKD, found none of the suburbs had a statistically significant CKD risk above the known average.

Conclusions: Despite reports to the contrary, ISLHD CKD prevalence is within the national average. The large variability among the ISLHD suburbs can be explained by known risk factors and older age.

TH-PO1010

Prevalence and Outcomes of CKD in England (CaReMe CKD UK)

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Background: The CaReMe CKD study indicates that one in ten adults in Europe and Canada likely have chronic kidney disease (CKD). In England, 6.5% of the population has been diagnosed with CKD, but rates of possible and undiagnosed cases remain unknown. To address this, we updated the analysis with more comprehensive electronic health records (EHR) to determine the prevalence of diagnosed and potentially undiagnosed CKD and associated clinical adverse outcomes in England.

Methods: Patients were identified using linked national EHR (Clinical Practice Research Datalink, Hospital Episode Statistics and Office for National Statistics) by either having a CKD diagnosis or a single pathological value of eGFR <60 ml/min/1.73 m2 or urine albumin-creatinine ratio (UACR) ≥30 mg/g before 1st November 2020. CKD stages were defined in accordance with Kidney Disease: Improving Global Outcomes (KDIGO) criteria. CKD was categorized into three groups based on laboratory values or diagnosis codes (Figure). One year cardiovascular and renal event rates were determined using the first recorded in-hospital diagnosis at the main position.

Results: In a background population of 10,363,493, the prevalence of possible CKD was 9.2% (mean age 71, 55% women, 32% diabetes, 46% using renin-angiotensin-aldosterone system inhibitors); while one out of three did not have a corresponding CKD-specific diagnostic code, half could not be confirmed with KDIGO criteria. Prevalence of CKD was consistently higher in females across definitions. Among CKD patients confirmed by KDIGO criteria, the majority (64%) were in KDIGO stage 3A, 3% were stages one or two. Adverse events were common and 6.7%-8.7% died annually (Figure).

Conclusions: One in ten adults in England is affected by CKD, which leads to significant adverse outcomes. Diagnosis rates underestimates the actual prevalence of CKD. There is significant public health potential to identify and treat those who currently remain undiagnosed.

Funding: Commercial Support - AstraZeneca

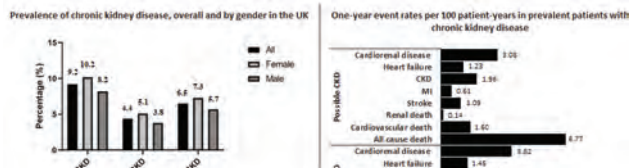

Figure. CKD: chronic kidney disease. Possible CKD: patients with a CKD diagnosis or one pathological UACR or eGFR measurement. Measured CKD: patients with KDIGO confirmed CKD using UACR and eGFR. Diagnosed CKD: patients who have a registered CKD diagnosis. UK: United Kingdom.

Event rates: the first event registered between index and the end of follow-up or death were defined by the first recorded in-hospital diagnosis of CKD (including diabetic kidney disease, acute kidney failure, CKD, unspecified kidney disease, hypertensive kidney failure and dialysis), HF (including hypertensive HF), stroke (including ischaemic and haemorrhagic stroke), myocardial infarction and peripheral artery disease, as the main diagnosis. Cardiorenal disease reflected as a diagnosis of HF or CKD as first diagnosis.

Prevalence, outcomes and definitions.

TH-PO1011

Prevalence and Progression of Kidney Diseases Among Ethiopian Immigrants Compared with Other Immigrant and Native Populations in Israel

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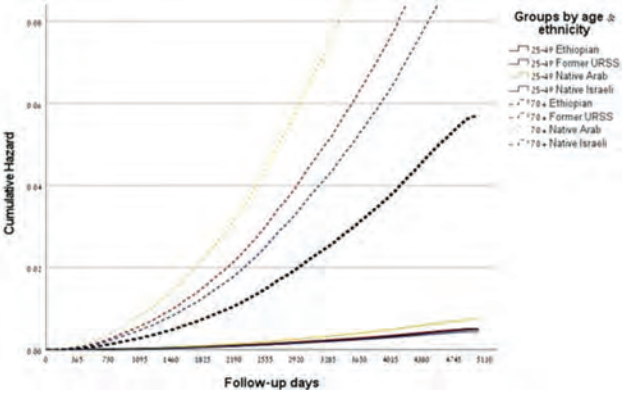
Background: The worldwide prevalence of kidney disease in the Ethiopian population is unknown. This study assessed the prevalence of CKD and risk-factors for progression among Ethiopian immigrants compared to Soviet Union immigrants, as well as Israeli-born Jewish and Arab population.

Methods: The study included all people above 25 years old who were insured by Clalit Health Services from 01/01/2007 until 31/12/2017, and had more than two plasma creatinine measurements at least 28 days apart, which demonstrated similar CKD stage. Follow-up was until 31/12/2020. Primary outcome was at least 50% decrease in estimated glomerular filtration rate (eGFR) calculated with CKD-epi equation. Cox regression model was used to analyze risk-factors for CKD progression.

Results: The study included 1,734,501 people, of whom 41,260 (2.4%) were Ethiopian immigrants, mean age 44.8±16.6 years, baseline eGFR 111.1±16.5 ml/min/1.73m^2; 273,476 (15.8%) former Soviet Union immigrants, mean age 56.3±18.1 years, baseline eGFR 88.2±22.5 ml/min/1.73m^2; 366,789 (21.1%) native Israeli Arabs, mean age 42.5±14.5 years, baseline eGFR 107.9±18.8 ml/min/1.73m^2, and 1,052,976 (60.7%) native Israeli Jews, mean age 43.1±14.3 years, baseline eGFR 102.6±18.7 ml/min/1.73m^2. (p<0.001 for age and eGFR). Decrease in eGFR ≥50% was documented in 38,913 (2.2%) people: 573 (1.4%) were Ethiopian immigrants. Cox regression model was performed in three age groups: Ethiopian ethnicity was associated with higher risk for CKD progression in the young group (<50 years), HR 1.70 (95% CI: 1.54-1.90, p <0.001), but had no effect in the 50 to 70 years age group, HR 1.14 (95% CI: 1.05-1.24, p =0.098) and had a protective effect in the older, ≥70 years group, HR 0.62 (95% CI: 0.57-0.68, p <0.001).

Conclusions: Young Ethiopian immigrants had higher risk for CKD progression which was absent among older Ethiopian immigrants, suggesting a genetic/familial etiology or adaptive factors. Further research is desirable.



TH-PO1012

National Trends in the Prevalence of CKD Among Korean Adults, 2007-2020, Including the COVID-19 Pandemic: A Korean Representative Serial Study

Kyunghwan Jeong,[1] Soo-Young Yoon,[1] Dae Kyu Kim,[1] Hyo Jin Lee,[1] Yang Gyun Kim,[2] Jin sug Kim,[1] Ju young Moon,[2] Hyeon Seok Hwang.[1] *[1]Kyung Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.*

Background: Little is known about the prevalence of chronic kidney disease (CKD) during the coronavirus disease 2019 (COVID-19) pandemic, as well as the pandemics' impact on CKD diagnosis. We aimed to investigate the long-term trends in CKD prevalence throughout the pre- and early pandemic periods in adults using a nationwide serial survey from South Korea.

Methods: We used data from 108,152 Korean adults from 2007 to 2020 obtained from a representative longitudinal serial study. We defined CKD as a condition when the participant's estimated glomerular filtration rate was <60 mL/min/1.73 m^2, one-time spot proteinuria was ≥1+ on a urinary dipstick test according to recent guidelines, or previous diagnosis of CKD. We examined the overall trends in the prevalence of CKD during the study period and the impact of the early pandemic on the prevalence of CKD.

Results: Among the included adults (n=80,010), the overall national prevalence of CKD was 6.2%. The trend slope gradually increased from 2007 to 2019, however, there was a sudden decrease in 2020 (2007–2010, 5.1% [95% confidence interval (CI), 4.7–5.5]; 2017–2019, 7.1% [95% CI, 6.6–7.6]; pandemic period, 6.5% [95% CI, 5.7–7.3]; and β_{diff}, -0.19; 95% CI, -0.24–-0.13). The prevalence of CKD among younger adults and those with poor medical utilization significantly decreased during the early pandemic.

Conclusions: This study was the first large-scale study to investigate the longitudinal prevalence of CKD from 2007 to 2020. Further research is needed to fully understand the exact causes for this decline and to identify healthcare policy strategies for preventing and managing CKD.

TH-PO1013

Prevalence and Risk Factors for CKD and CKDu in León, Nicaragua

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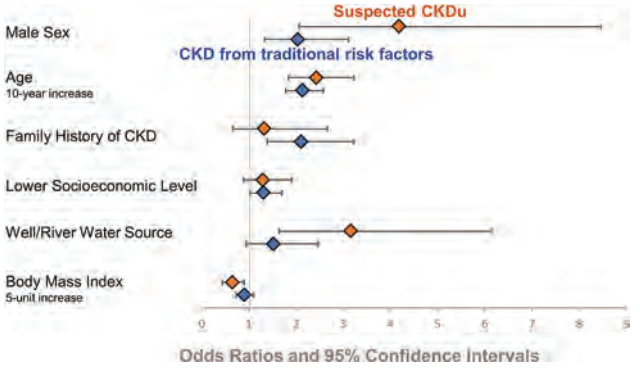
Background: CKD of unknown etiology (CKDu) disproportionately affects young people in Central America who lack traditional CKD risk factors (diabetes and hypertension) and is instead linked to heat stress, occupational and environmental exposures, nephrotoxic medications, and/or genetic conditions. This study aimed to estimate the prevalence of CKD and to identify risk factors for traditional CKD and CKDu in Nicaragua.

Methods: Surveys and assessment for CKD markers in urine and serum were performed in 15-59 year olds in households of the León municipality of Nicaragua. The survey included questions on demographics, health behaviors, occupation, and medical history. Participants with CKD were subdivided into traditional CKD and suspected CKDu based on history of diabetes, hypertension, or other specified conditions. A multinomial logistic regression model was used to identify factors associated with traditional CKD and CKDu, compared to the non-CKD reference group.

Results: In 1795 study participants, CKD prevalence was 8.6%. Prevalence in males was 2-fold higher than females (12% vs 6%). Of those with CKD, 30% had suspected CKDu. Both traditional CKD and CKDu were associated with male sex and increasing age. Traditional CKD was associated with a family history of CKD and lower socioeconomic status, while CKDu was associated with non-treated water sources and a lower body mass index.

Conclusions: Both traditional CKD and CKDu are significant burdens in this region. Our study supports previous hypotheses of CKDu etiology and emphasizes the importance of CKD screening.



Odds ratios and 95% confidence intervals from a multinomial logistic regression model for CKD from traditional risk factors and suspected CKDu compared to the non-CKD reference group.

TH-PO1014

CKD of Unknown Origin (CKDu) Is Associated with Subclinical Rhabdomyolysis

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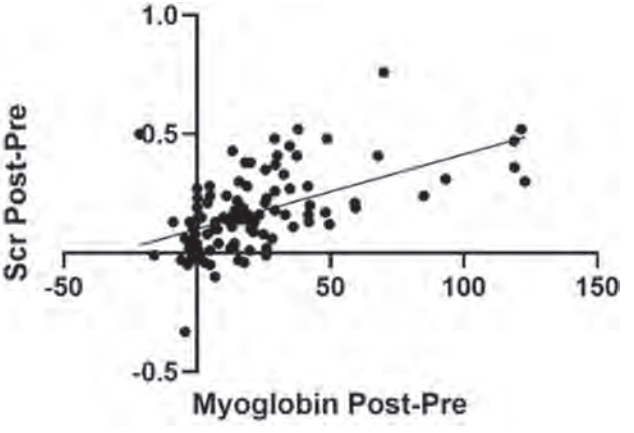
Background: CKDu is a type of chronic kidney disease, unrelated to diabetes and hypertension, mostly described in young sugar cane workers in El Salvador, Nicaragua and Mexico (Mesoamerican Nephropathy). Many etiologies have been assessed, including pesticides, heavy metals, silica, fructose-rich soft drinks, tobacco use, nutritional factors, and strenuous work in hot climate. Occupational heat stress is now an accepted key etiologic factor, but pathophysiologic pathways need further clarification. The role of rhabdomyolysis has been considered but myoglobin levels are unknown and serum creatine kinase (CK) levels during the harvest season are only mildly elevated.

Methods: We determined serum myoglobin (ng/ml, electrochemiluminescence immunoassay), CK (units/L) and creatinine (Scr, mg/dl) before (Pre) and after (Post) a 5 to 12 hour working shift in 109 sugar cane cutters (1 female), 19-78 years old from Tierra Blanca, Veracruz, a previously identified hot spot region for CKDu.

Results: Levels (mean±sem) of myoglobin (Pre=33.2±1.42; Post=60.0±5.02; p<0.0001), CK (Pre=164.8±9.24; Post=218.9±12.10; p<0.0001) and Scr (Pre=0.98±0.053; Post=1.17±0.058, p<0.0001) increased significantly (paired T test) during the working shift. There was a direct linear correlation between the increment in Scr and both the increments in CK (n=104, r2=0.161; p<0.0001) and myoglobin levels (n=104; r2=0.284; p<0.0001 (Figure).

Conclusions: The serum levels of myoglobin and CK are below the levels usually reported in rhabdomyolysis-related acute kidney injury. Nevertheless, subclinical rhabdomyolysis occurs daily during the harvest season in sugar cane workers and the role of repeated mild episodes of rhabdomyolysis in CKDu deserves to be investigated.

Funding: Private Foundation Support



TH-PO1015

Long-Term Exposure to High Perceived Temperature and Risk for Mortality Among CKD Patients

Ara Ko,[1] Jeonghwan Lee,[2] Jung Pyo Lee.[2] *[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea.*

Background: Risks for climate change is emerging and interest in health risks from high temperature exposure is growing. The perceived temperature (PT) is an equivalent temperature based on a complete heat budget model of the human body. We aimed to analyze the effect of PT on the overall mortality among chronic kidney disease (CKD) patients.

Methods: A total of 32,870 patients with CKD in Seoul participated in a retrospective cohort (2001-2018) at three medical centers. PT during summer season was calculated using meteorological factors including air temperature nearby automated weather station, dew point temperature, wind velocity, and total cloud amount. We assessed the association of PT using Kriging spatial interpolation on mortality in CKD patients in the time-varying Cox proportional hazard model that was adjusted for sex, age, body mass index, hypertension, diabetes mellitus, estimated glomerular filtration rate, smoking, alcohol consumption, and education level.

Results: During the 6.14 ± 3.96 years of follow-up, 3,863 deaths (13%) were observed. In multivariable analysis, average level of PT (hazard ratio (HR) 1.292, 95% confidenc interval (CI) 1.255-1.331) and maximum level of PT (HR 1.356, 95% CI 1.309-1.404) showed increased risk for overall mortality among CKD patients. The c-index for mortality was high in the order of PT, temperature, discomfort index, and heat index (average level, 0.790, 0.785, 0.785, and 0.784; maximal level, 0.790, 0.784, 0.782, and 0.781). When stratified by age, diabetes mellitus, and estimated glomerular filtration rate, CKD patient with old age (age above 65 years old), without diabetes mellitus, and estimated glomerular filtration rate above 60 ml/min/1.73 m2 showed higher c-index levels. In addition, the risk for death in winter and spring seasons was also proved as significant with HR of 1.152 (95% CI 1.088-1.220) and 1.067 (95% CI 1.014-1.123) compared with the summer and autumn season mortality with according to HR of 1.401 (95% confidence interval 1.313-1.496).

Conclusions: Long-term exposure to high perceived temperature during summer season increase the risk of mortality among CKD patients.

TH-PO1016

Long-Term Exposure to Low Perceived Temperature in Winter Increases the Risk of Death in CKD Patients

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Background: Because of the rapid climate change, global interest about its impact on human health has been heightened. Perceived temperature (PT) is defined as a temperature that reflects the actual effect of temperature on the human body by considering the wind speed, amount of clouds, and humidity information. Due to the insufficiency of data on the health effects of long-term exposure to low temperature in chronic kidney disease (CKD) patients, we aimed to analyze the effect of PT in winter on the overall mortality among CKD patients.

Methods: 32,870 CKD patients in Seoul participated in a retrospective cohort at three medical centers. PT was calculated by the Staiger's equation, using the temperature of a nearby automated weather station, dew point temperature, wind velocity, and cloud amount. PT is interpolated using Kriging method and mortality was assessed by using the time-varying Cox proportional hazard model. The Cox regression model was used to assess the PT corresponding to the temperature for cold wave watch or warning.

Results: During the 6.14 ± 3.96 years of follow-up, 6,147 (18.7%) deaths were observed Since 2000, maximal and average PT had not significantly been changed. In multivariable analysis, the hazard ratio (HR) of maximum PT was 1.091 (95% confidence interval (CI) 1.073-1.109, p-value 0.<0001), and HR of average, minimal PT were 1.042 (CI 1.018-1.065, p-value 0.0004), 1.036 (CI 1.022-1.049, p-value <0.0001) respectively. The maximum PT had the highest C-index for mortality (0.783), followed by the risk of average and minimum PT (0.780). In addition, each PT for cold wave watch and warning were -21.86°C, -25.63°C. The cold wave warning at a PT of -25.63°C indicated the risk of death as HR 1.874 (CI 1.806-1.944, p-value<0.0001) and c-index 0.807.

Conclusions: Exposure to lower PT during winter season could increase the risk of mortality among CKD patients.

TH-PO1017

Particulate Matter and Risk of CKD: A Global Exposure-Response Analysis

Feifei Zhang. *Peking University Health Science Center, Beijing, China.*

Background: Associations between particulate matter (PM) air pollution and chronic kidney disease (CKD) have been increasingly reported, yet the exposure-response association is insufficiently estimated. This study aimed to combine all available associations between PM of two different sizes ($PM_{2.5}$ and PM_{10}) and CKD to generate exposure-response functions over concentrations experienced by populations in the globe.

Methods: Based on data from two prospective, population-based cohorts in the United Kingdom and China (UK biobank and China Health and Retirement Longitudinal Study), we used the shape constrained health impact function to generate exposure-response functions between both $PM_{2.5}$ and PM_{10} and CKD within each country. We then collected additional data on $PM_{2.5}$-CKD and PM_{10}-CKD associations from published literature and used the global exposure mortality model to construct exposure-response functions for CKD over a full range of global $PM_{2.5}$ and PM_{10} concentrations.

Results: In the United Kingdom, the exposure-response functions for both $PM_{2.5}$ and PM_{10} and CKD showed a linear association at lower concentrations and then a sublinear association at higher concentrations. In China, the risk of CKD also increased linearly with the increasing $PM_{2.5}$ and PM_{10} at lower concentrations, but the associations for both air pollutants did not reach the statistical significance. After combining with all other published associations, the exposure-response function revealed a near linear association of the natural log relative risk of CKD with $PM_{2.5}$ (**Figure 1a**) and a sublinear association with PM_{10} (**Figure 1b**), respectively.

Conclusions: Both $PM_{2.5}$ and PM_{10} exposure increased the risk of CKD, particularly at higher concentrations. Our findings highlight the urgency for air pollution management in areas with severe PM pollution to protect kidney health.

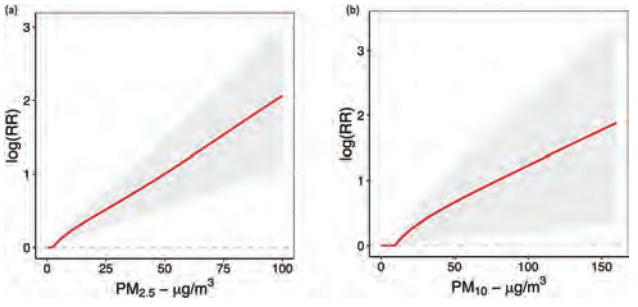

Figure 1 Exposure-response relationships between particulate matter and chronic kidney disease. (a) $PM_{2.5}$, (b)PM_{10}. Red line represents the log (relative risk) and grey shaded area represents its 95% confidence intervals.

TH-PO1018

Exposure to Organic Pollutants in Adults with CKD: A Pilot Study

Howard Trachtman,[1] Wenbo Wu,[2] Kurunthachalam Kannan,[3] Zhongmin Li,[3] Vineet Kumar Pal,[3] Sunmi Lee,[2] David M. Charytan.[2] *[1]University of Michigan, Ann Arbor, MI; [2]New York University, New York, NY; [3]Wadsworth Center, Albany, NY.*

Background: In pediatric patients with chronic kidney disease (CKD), exposure to organic pollutants is associated with intra-renal oxidant stress and tubular injury; however, the impact on longitudinal estimated glomerular filtration rate (eGFR) or proteinuria is minimal. Less is known about the adverse effects of exposure to these chemicals in adults with CKD.

Methods: In this pilot study, we utilized HPLC-MS/MS to measure urinary concentrations of bisphenols, phthalates, organophosphate pesticides, polycyclic aromatic hydrocarbons, melamine, and cyanuric acid at years 1, 3 and 5 after enrollment in 40 adults with CKD from the Chronic Renal Insufficiency Cohort (CRIC) study. We assessed associations with clinical kidney and cardiovascular outcomes, cardiovascular function markers, markers of mineral and bone metabolism, and baseline and longitudinal trajectory of eGFR and proteinuria.

Results: Mean baseline eGFR and urinary protein:creatinine ratio were 33 ml/min/1.73 m^2 and 0.58 mg:mg, respectively. Of 52 compounds assayed, 30 were detectable in ≥50% of participants. Urinary chemical concentrations were comparable in CKD patients to healthy subjects from contemporaneous National Health and Nutrition Examination Survey (NHANES) cohorts. Phthalates were the only class with a trend towards higher exposure in CKD patients. In a univariate analysis of time updated exposure to the individual compounds, there was a wide range of association with changes in kidney function. There was an inverse relationship between the level of exposure and eGFR slope for select compounds in the chemical classes including bisphenol F, mono-(3-carboxypropyl) phthalate, mono-benzyl phthalate, mono-[2-(carboxymethyl) hexyl] phthalate, and melamine. There were no significant associations between organic pollutant exposure and cardiovascular outcomes.

Conclusions: Simultaneous measurement of multiple organic pollutants in adults with CKD is feasible. Exposure levels are comparable to that in the healthy population. A subset of contaminants may be associated with more rapid deterioration in kidney function especially in the phthalate class. Our findings provide a useful reference for future studies of the impact of organic pollutant exposure in the CKD population.

Funding: NIDDK Support

TH-PO1019

The Increased Burden of CKD in Young Adults with Questionable Levels of Education and Health Literacy

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Introduction: This case highlights the harmful effects of unsatisfactory healthcare education that may contribute to poor patient insight in certain communities across the United States.

Case Description: This patient is a 29-year-old G4P2113 black female with a past medical history of uncontrolled hypertension(HTN), chronic kidney disease(CKD), and morbid obesity. Her health insurance is managed by Medicaid. At age 17, she had her 1st spontaneous vaginal delivery(SVD) in the emergency department(ED) with no prenatal care(PNC). Urinalysis(UA) during her 3rd trimester was significant for 3+ proteinuria. She was discharged with normal blood pressure(BP). The patient was noncompliant with post-partum follow-up. Her 2nd term SVD was at age 18 with limited PNC(2 ED visits were for severe HTN and proteinuria was noted). BP at discharge was normal but she had proteinuria. In the next 5 years, she lost her 3rd pregnancy. At age 25, she presented for an annual GYN exam where she was diagnosed with HTN and given NifedipineCC. ED visits documented that she had no primary care provider(PCP) and showed CKD stage 3A. A year later, she returned to the ED with uncontrolled HTN to confirm her 4th pregnancy. She had CKD stage 3B with 2+ proteinuria and a GFR of 43mL/min. She was admitted to labor and delivery and had a preterm SVD. When seen post-partum, the patient was in denial about her diagnosis of CKD. She did not comply with a renal diet and refused anti-hypertensives. To date, she does not have a PCP or nephrologist although she was referred and told about the gravity of the diagnosis.

Discussion: Many factors contributed to the progression of this patient's illness: individual, interpersonal, societal and institutional factors. This patient lacked insight into the consequences of proteinuria and HTN that progressed to CKD. She had 3 children without family support. Her early pregnancies interfered with her high school education. We believe that her low socioeconomic status(SES) and domicile negatively impacted her access to a healthy diet. Her race, gender and SES predispose her to poorer health outcomes(HO). The effect of her education and health literacy highlights the impact of healthcare on young adults: It must be further studied to provide focused upstream interventions. An education program incorporating health literacy in high school may help prevent adverse HO.

TH-PO1020

First Detection of Microplastics Fragments in Human Urine and Kidney Tissues

Sara Massardo,[1] Edoardo La Porta,[2] Enrico E. Verrina,[2] Francesca Lugani,[2] Stefano Alberti,[1] Claudia Caboni,[1] Matteo Santostefano,[3] Daniela Verzola,[4] Pasquale Esposito,[4,5] Gianluigi Zaza,[6] Cristina Artini.[1,7] *[1]Chemistry and Industrial Chemistry Department, University of Genoa, Genova, Italy; [2]UOC Nephrology, IRCCS Istituto Giannina Gaslini, Genova, Italy; [3]PM_TEN Srl, Genova, Italy; [4]Department of Internal Medicine, University of Genoa, Genova, Italy; [5]IRCCS Ospedale Policlinico San Martino, Genova, Italy; [6]Nephrology and Dialysis Unit, Department of Medical and Surgical Sciences, University of Foggia, Foggia, Italy; [7]CNR-ICMATE, Genova, Italy.*

Background: Microplastics (MPs) are small plastic particles (< 5 mm) continuously released into the environment, contaminating natural habitats. Humans are constantly exposed to this kind of pollution: studies proved the presence of MPs in their lungs, liver, placenta, blood, and breast milk. To date, risks related to the uptake of plastic fragments are not well clarified, but their correlation with emerging diseases of unknown etiology cannot be *a priori* excluded. Due to an epidemic of Chronic Kidney Disease (CKD) that steadily increases over the decades and emerging new diseases worldwide as CKD of uncertain etiology (CKDu), the presence of MPs in human urines and kidney was investigated, to clarify their contribute to kidney damage.

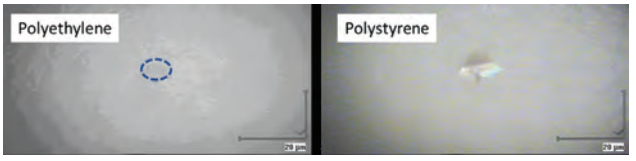
Methods: MicroRaman spectroscopy is a technique of election for MPs detection in different matrices, thanks to its high sensitivity towards different polymers and its

high spatial resolution. Urine samples from healthy individuals and kidney tissues from nephrectomies were collected, digested in a KOH 10% solution, and filtered. Particles retained on the surface of the filters were analysed with a Renishaw System 2000 Raman imaging microscope (633 nm laser source). The collected spectra were investigated, to determine the nature of the detected particles.

Results: This study revealed the presence of different polymer fragments in both urines and kidneys (polyethylene, polystyrene, and styrene-isoprene gum, Figure 1), as well as pigments residuals (*e.g.*, hematite, Cu-phthalocyanine (blue), and cerulean blue).

Conclusions: This study revealed for the first time the presence of microfragments of materials of anthropogenic origin (polymers, pigments, and inorganic particles) in human kidney and urine. The current investigation laid the foundations for further studies on the mechanisms of renal clearance and deposition of these particles, and on their possible role in promoting kidney damage.

Sample;total n	Positive samples;total particles	Particle Material				
		Cu-phthalocyanine blue	Hematite	Polyethylene	Polystyrene	Other
Urine;10	7;9	1	4	2	1	1
Kidney;10	7;17	4	7	1	1	4



Polymer fragments detected in the samples.

TH-PO1021

Association of Co-Exposure to Cadmium and Lead with CKD and Cardiovascular Disease (CVD) Comorbidity in US Adults: NHANES 2003-2018

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Background: Environmental exposure to cadmium (Cd) and lead (Pb) have been implicated in both CKD and CVD. The two metals can be detected together at or above the respective population medians in 45% of the US population 6 years and older. Although both metals exhibit similar renal pathology and toxic mechanisms, the relationship between the metal mixture and the CKD and CVD comorbidity is not clear. The objective of this cross-sectional study was to examine the associations of Cd and Pb exposure with CKD and CVD outcomes and to see if the two metals are independently associated with the outcomes.

Methods: We included data from the National Health and Examination Survey (NHANES) 2003-2018 participants 20 years and older with urine Cd, blood Pb, serum creatinine, and urine albumin/creatinine measurements (n=12,851). Pregnant women and participants with CKD stage 5 were excluded. We used generalized logistic regression to calculate adjusted odds ratios for CVD, CKD, or both CKD and CVD relative to none of these co-morbidities. We tested for interactions, both on multiplicative and additive scales, between the two metals with and without other covariates (gender, race/ethnicity, attained education, smoking, alcohol use, body mass index (BMI), and quadratic age).

Results: Both multiplicative and additive interaction effects were not statistically significant at the p-value of 0.05 level. It is possible that our sample size was too small to detect the effect. The final model included urine Cd, blood Pb, gender, race/ethnicity, education, smoking, alcohol use, BMI, and quadratic age. The Cd effect was statistically significantly associated with CKD+CVD (OR=1.19, 95%CI=1.03-1.38, p=0.02) after adjusting for the effect of Pb and other covariates, whereas Pb was significantly associated with CKD (OR=1.22, 95%CI=1.07-1.39, p=0.003) and CVD+CKD (OR=1.39, 95%CI=1.16-1.65, p=0.0004) after adjusting for the effect of Cd and other covariates.

Conclusions: These results suggest that the effects of Cd and Pb are independent each other, and more pronounced in participants who had both CKD and CVD, supporting their role as risk factors even at exposures below the levels typically associated with occupational hazards. However, reverse causation because of underlying kidney damage cannot be ruled out.

Funding: Other U.S. Government Support

TH-PO1022

Association Between Blood Cadmium Level and Kidney Function: Analysis of NHANES 2017-2020

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Background: Recent studies have highlighted the significant impact of cadmium toxicity on various organs, including kidneys and the cardiovascular system, whether the association between a wide range of cadmium levels from normal to high toxic levels and kidney function remains unclear.

Methods: A cross-sectional study involving participants (≥ 18 years old) in the 2017 - 2020 NHANES was examined by using multiple linear regression analysis for the association between blood cadmium levels (Cd) and kidney function measured by serum creatinine level (SCr).

Results: Of 12,102 participants with Cd results, the mean ± SD age was 37+/-24 years old, and 50.6% were female. White accounts for 33%, followed by Black (25%), Mexican American (13%), and Asian (10%). The Median (IQR) SCr was 0.82 (0.68 - 0.98) mg/dL. We stratified the participants into four quartiles based on their Cd results; the average Cd for each quartile was 0.08, 0.16, 0.29, and 0.93 ug/L, respectively (Figure 1). We found that Q2, Q3, and Q4 participants had significantly higher SCr values of 0.06, 0.08, and 0.14 mg/dL, respectively than those in Q1. (β SCr Q2: 0.06, 95%CI 0.02, 0.09; Q3: 0.08, 95%CI 0.05, 0.12; Q4: 0.14, 95%CI 0.11, 0.17). After adjusting for age, gender, race, BMI, smoking status, high systolic blood pressure (<130 vs.>130 mmHg), diabetic status, and urine albumin creatinine ratio, individuals in the Q3 and Q4 still had significantly higher SCr levels of 0.04 mg/dL. (β SCr Q3: 0.04, 95%CI 0.01,0.07; Q4: 0.04, 95%CI 0.01, 0.07).

Conclusions: Our study found a positive correlation between blood cadmium levels and the risk of declining kidney function, even within the normal range that is not considered toxic. However, future longitudinal studies are required to elucidate this relationship.

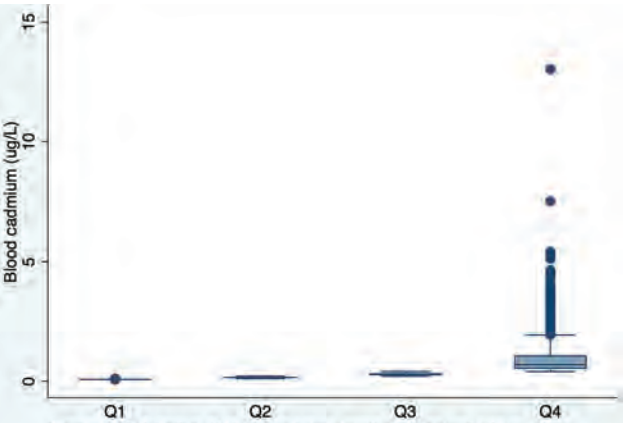

Figure 1: Distribution of blood cadmium levels categorized into quartiles.

TH-PO1023

Nonlinear Associations Between Serum Manganese with CKD: Results from Two Nationwide Studies in the United States and China

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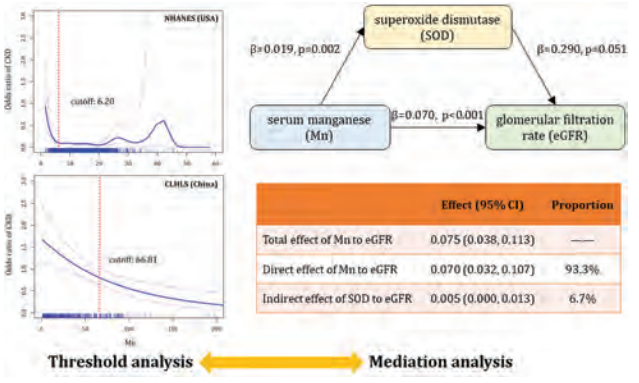
Background: This study aimed to better evaluate the association between serum manganese (Mn) and chronic kidney disease (CKD) by using data from the US National Health and Nutrition Examination Survey (NHANES) and the Chinese Longitudinal Healthy Longevity Study (CLHLS).

Methods: A total of 15411 and 451 participants were selected from NHANES and CLHLS, respectively. The primary diagnosis of CKD was defined as eGFR <60 mL/min/1.73m^2 and urinary albumin-creatinine-ratio (ACR) ≥30 mg/g. Multivariable regression and threshold analyses were used to assess the associations between Mn level and CKD.

Results: The prevalence of CKD was estimated to be 8.1% in NHANES and 47.7% in CLHLS. After adjusting for covariates, participants with the highest quartile (Q4) of Mn had an increased likelihood of CKD than those with Q1 (OR=0.67, 95% CI 0.55-0.82 in NHANES, and OR=0.31, 95% CI 0.16-0.58 in CLHLS). The non-linear associations revealed that the OR values of CKD were decreased with Mn before reaching the threshold (OR=0.64 per 1 μg/L increase of Mn in NHANES and 0.98 in CLHLS). The trends of protective effects then became flat with no longer significance. This association remained robust by using the continuity of eGFR and ACR as the outcome. Exploration analysis showed that superoxide dismutase (SOD) mediated 6.7% of the effect of Mn levels on CKD.

Conclusions: The higher Mn concentration was significantly associated with a lower prevalence of CKD through different non-linear patterns.

Funding: Government Support - Non-U.S.



TH-PO1024

Comparison of National and Global Utilization Trends of Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) and Glucagon-Like Peptide 1 Receptor Agonists (GLP-1RA) in CKD

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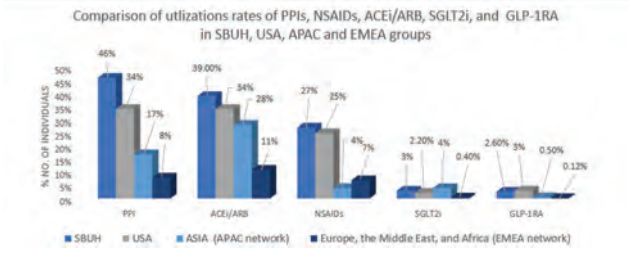
Background: Despite the mounting evidence demonstrating the reno and cardiovascular benefits of SGLT2i and GLP-1RA in diabetic and non-diabetic CKD, there appears to be a degree of therapeutic inertia in using these agents in routine clinical practice. The assessment of the utilization rates and practice patterns of these drugs in patients with CKD remains scarce.

Methods: We used TriNetX Analytics, including Stony Brook Healthcare, US-network, AMA (Asia), and EMEA (Middle east, Europe, Africa) collaborative networks. The estimated glomerular filtration rate (eGFR) mL/min/1.73 m2 (CKD-EPI equation) lab values and the KDIGO eGFR classification were used to define the CKD stages. Individuals with age > 18 years with ambulatory visits (CPT 1013626) from 2000 to 2022 were included. Patients with end-stage renal disease (CPT 1019051), acute kidney injury (ICD-10-CM N17), and kidney transplant recipients (CPT 50380) were excluded.

Results: SGLT2i and GLP-1RA use were highest among non-Hispanic white males (55% vs 55%) with Type 2 DM (86% vs 79%) and Hypertension (87% and 82%). The use rates of ACEi/ARB were noticeably low among all cohorts; 34% (280,0219) in the US, 28% (77,011), and 11% (38,599) in the AMA and EMEA groups. In the AMA group, the SGLT2i use rate was 4% (11,786), and the lowest prescription rate was noticed in the EMEA group at 0.40% (1681). The prevalence of GLP-1RA use was relatively higher in Stony Brook and US cohorts, 2.60% (4370) and 3% (230,925), as compared to AMA and EMEA groups at 0.50% (1763) and 0.12% (431), respectively.

Conclusions: Despite the high national and global burden of CKD, the prescription rates of ACEi/ARBs are alarmingly low. In contrast, a relatively high prevalence of potential nephrotoxins (i.e., NSAIDs and PPIs) use has been noticed. Overall national and global SGLT2i and GLP-1 RA utilization rates have increased over the last few years. However, the use rates of these agents are still significantly suboptimal among CKD patients.



TH-PO1025

Predictors and Outcomes of Discontinuation of Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT2is) in CKD

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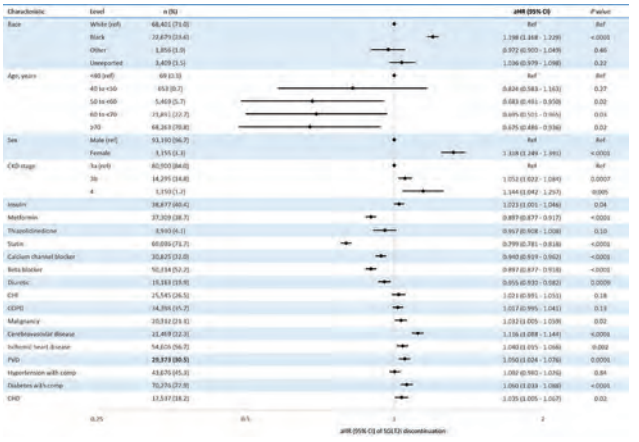
Background: SGLT2is decrease the progression of CKD and improve cardiovascular outcomes. However, their utilization remains low. Little is known about treatment discontinuation and its associations with patient characteristics and outcomes.

Methods: We identified adults with CKD stages 3-4 receiving care at Veterans Affairs (VA) facilities from 2005-2022 from the VA Corporate Data Warehouse. Individuals who had an incident prescription for an SGLT2i were included, with the date of prescription considered the index date. The primary outcome was treatment discontinuation, defined as an interruption in SGLT2i prescription for at least 90 days. Cox proportional hazards regression identified factors associated with time to treatment discontinuation. Cox proportional hazards regression treating SGLT2i discontinuation as a time-varying covariate assessed the association of treatment discontinuation with time to all-cause death.

Results: Of 96,345 individuals who received an SGLT2i, 97% were male, 71% were White, 24% were Black, 71% were age ≥70, and 84% had CKD stage 3a. Discontinuation (at least once) occurred in 35,953 (37%) SGLT2i users over a median (IQR) of 1.01 (0.58, 1.74) years of follow up. Black race, female sex, younger age, and more advanced stage of CKD were associated with SGLT2i discontinuation (**Figure**). There were 8698 deaths. SGLT2i discontinuation, included as a time-varying covariate, was associated with all-cause death (HR 1.57 [95% CI 1.49, 1.66], P<0.0001) independent of age, sex, race, CKD stage, medical comorbidities, and concomitant medication use.

Conclusions: Discontinuation of SGLT2is is common and is associated with an increased risk of mortality. Further studies to understand the reasons for SGLT2i discontinuation (both temporary and permanent), and additional efforts to improve adherence are warranted.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support



TH-PO1026

ACEi/Angiotensin Receptor Blocker (ARB) Prescribing Practices and Patient Experiences in CKD: A Qualitative Study of Clinicians and Patients

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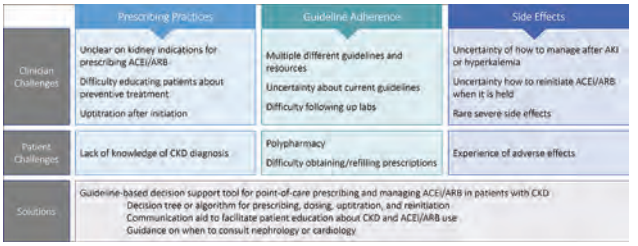
Background: Angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARB) improve clinical outcomes but are underutilized in chronic kidney disease (CKD). Little is known about reasons for discontinuation and lack of reinitiating these medications, which contributes to underutilization.

Methods: We conducted in-depth interviews with a multi-profession sample of clinicians and patients with documented ACEi/ARB side effects in the past 6 months. Participants were recruited from 2 Veterans Affairs (VA) healthcare systems. We used inductive and deductive qualitative data analysis approaches to identify themes related to experiences with ACEi/ARB. Thematic analysis focused on prescribing decisions and practices, clinical guidelines, and perception of side effects. Data were analyzed as they amassed. Recruitment was stopped at the point of thematic saturation.

Results: Participants included 15 clinicians (primary care, geriatrics, cardiology, and endocrinology; 8 physicians, 3 NPs/PAs, 4 clinical pharmacists) and 10 patients (mean age 69 years, 40% men). Clinicians prescribe ACEi/ARB for blood pressure control and kidney protection, and many emphasized the role these agents play in diabetes management. Clinicians described providing comprehensive patient education about CKD and ACEi/ARB. However, patient interviews revealed knowledge gaps about CKD and the need for ACEi/ARB, with many patients unaware of their CKD diagnosis or why they had been prescribed ACEi/ARB. Clinicians' drug management strategies and understanding of prescribing guidelines varied widely. They identified structural and patient-level barriers to prescribing, and many endorsed the development of a decision support tool to facilitate ACEi/ARB prescribing and management (Figure).

Conclusions: Our qualitative exploration of clinicians' and patients' experiences with ACEi/ARB will inform the development of a decision support tool to improve prescription rates of these agents for patients with CKD.

Funding: Veterans Affairs Support



TH-PO1027

Patient- and Provider-Related Factors Associated with Changes in Antihypertensive Treatment in CKD

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Background: Despite the existence of effective antihypertensive drugs, blood pressure (BP) remains off-target in a large number of CKD patients. We aimed to assess patient- and provider-related factors associated with changes in antihypertensive drug prescription in CKD.

Methods: We included 2,755 patients with CKD stages 3–4 and hypertension, under nephrology care, from the French CKD-REIN cohort study. We collected all drug prescriptions over 5 years and classified antihypertensive drugs in 14 mutually exclusive classes. We estimated cause-specific hazard ratios (HR) of add-on and withdrawal of antihypertensive drugs associated with patient- and provider-related factors by using hierarchical shared-frailty models, and accounting for clustering at the nephrologist level.

Results: At baseline, 81% of the patients (median age, 69; 66% men; mean eGFR 33 mL/min/1.73 m2) had BP ≥ 130/80 mmHg. Over a median 5-year follow-up (IQR 4.6-5.2), the rates of any antihypertensive drug class change, add-on, withdrawal, and switch were 50, 23, 25, and 4 per 100 person-years, respectively. In multivariable models, drug add-on hazard was higher for older patients (HR, 1.11; 95% confidence interval [CI], 1.04-1.18), for those with higher BMI (HR, 1.04 95% CI, 1.01-1.07), and poor medication adherence (HR, 1.39; 95% CI, 1.10-1.68). Drug withdrawal hazard was higher for patients with cardiovascular history (HR, 1.19 95% CI, 1.04-1.35), and those with shorter formal education (HR, 1.23; 95% CI, 1.02-1.45 for 9-11 years versus ≥12). The higher the number of nephrologist visits, the higher the add-on and withdrawal hazards (HR for ≥4 versus none, 1.50; 95% CI 1.14-1.86 and 1.57; 1.24-1.90, respectively). Associations with withdrawals and add-ons of antihypertensive drug prescriptions and the number of other physicians' visits differed according to their specialty.

Conclusions: Our findings highlight the dynamics of antihypertensive drug prescriptions in the search for BP control, with heterogeneity in practices among the multiple physicians involved in the care of CKD patients.

Funding: Commercial Support - Fresenius Medical Care; GlaxoSmithKline; Vifor France; Sanofi-Genzyme; Baxter and Merck Sharp & Dohme-Chibret; Amgen; Lilly France; Otsuka Pharmaceutical; AstraZeneca; and Boehringer Ingelheim France, Government Support - Non-U.S.

TH-PO1028

Association Between Reduced RAASi Therapy and Progression to ESKD in Hyperkalemic CKD Patients

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Background: Renin-angiotensin-aldosterone system inhibitor (RAASi) therapy is renoprotective in patients (pts) with chronic kidney disease (CKD) but increases hyperkalemia (HK) risk. Despite recommendations to maintain RAASi using novel anti-HK treatment, RAASi therapy is often limited/withdrawn in pts with HK. This observational study investigates risk of progression to end-stage kidney disease (ESKD) associated with HK-related RAASi reduction in CKD.

Methods: Data from hospital records/claims from the US (Optum's de-identified Market Clarity Data) and Japan (Medical Data Vision) were analyzed. Pts with CKD Stage 3/4 and baseline RAASi use with an HK episode (ICD-10 code E87.5) during July 2019–Sept 2021 (US)/May 2020–Sept 2021 (Japan) were included. Based on RAASi prescriptions 3 months (mo) before vs after the HK episode, pts were categorized as down-titrated, discontinued, or maintained treatment. Risk of progression to ESKD (diagnosed CKD Stage 5/ESKD or dialysis initiation) within 6 mo in pts who down-titrated/discontinued vs maintained RAASi was assessed.

Results: In total, 11,873 (US) and 1427 (Japan) pts were included. Mean age was 71 (US) and 76 (Japan) years; 52% and 66%, respectively, were male. In the US, 7506 pts filled a RAASi prescription within 3 mo prior to index event and had ≥3 mo follow-up; of these, 33% discontinued and 6% down-titrated. Of the corresponding 1179 pts in Japan, 27% discontinued and 5% down-titrated. Risk of progression to ESKD was 70–74% higher in all pts who discontinued, and 60% higher in US pts who down-titrated vs maintained RAASi (**Table**).

Conclusions: HK-prompted RAASi therapy reduction is associated with increased risk of progression to ESKD, indicating a need for improved guideline adherence in managing HK to maintain RAASi therapy.

Funding: Commercial Support - AstraZeneca

Risk of progression to ESKD in patients with CKD Stage 3/4 who discontinued or down-titrated vs maintained RAASi therapy following an HK episode

Country	RAASi status	N	Events	Adjusted HR (95% CI) †	*P*-value
US	Maintained	4586	138	(ref)	
	Discontinued	2460	138	1.74 (1.37–2.21)	<0.001
	Down-titrated	460	23	1.60 (1.02–2.49)	0.039
Japan	Maintained	793	41	(ref)	
	Discontinued	323	26	1.70 (1.01–2.86)	0.045
	Down-titrated ‡	63	n/a	n/a	n/a

† Cox proportional hazards regression adjusted for age, sex, history of HK, diabetes, heart failure, CKD including stage, and baseline use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors, and mineralocorticoid receptor antagonists.
‡ This category was not included in the Cox regression analysis due to the low patient numbers.
CI, confidence interval; CKD, chronic kidney disease; ESKD end-stage kidney disease; HK, hyperkalemia; HR, hazard ratio; RAASi, renin-angiotensin-aldosterone system inhibitor; ref, reference group.

TH-PO1029

Association Between Hyperkalemia, CKD Progression, and All-Cause Mortality: The REVOLUTIONIZE II Study

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Background: The association of hyperkalemia (HK) with progression of chronic kidney disease (CKD) has not been well studied. This real-world study described and compared CKD progression and mortality among patients with HK and matched patients without HK.

Methods: Adults with stage 3b or 4 CKD with HK (defined as serum K>5.0 mmol/L and a HK diagnosis) and matched patients without HK were identified from the Optum de-identified Market Clarity database (1/2016-8/2022). Index date was the first eligible CKD diagnosis. Time to CKD progression (defined as stage 4 or 5 CKD, provision of dialysis, or kidney transplantation) and time to death were compared between cohorts using cause-specific Cox proportional hazard models reported as hazard ratios (HR) and 95% confidence intervals (CI). Subgroup analyses were conducted by CKD stage and renin-angiotensin-aldosterone system inhibitor (RAASi) use.

Results: 6,619 matched pairs were included in the overall sample. Mean age was 74.5 years, 47% male, 76% white, and 71% had stage 3b CKD at index date. Among all groups, patients with HK had statistically significantly higher rates of CKD progression (overall: HR 1.60 [95% CI 1.50, 1.71], p<0.001) (**Figure 1**). Patients with HK also had higher rates of all-cause mortality than patients without HK in the overall cohort (1.09 [1.02, 1.16]), RAASi subgroup (1.14 [1.05. 1.23]) and CKD stage 3b subgroup (1.11 [1.03, 1.20]) (all p<0.01).

Conclusions: Patients with HK experienced significantly higher rates of CKD progression and all-cause mortality compared to patients without HK, with consistent findings irrespective of use/non-use of RAASi.

Funding: Commercial Support - AstraZeneca

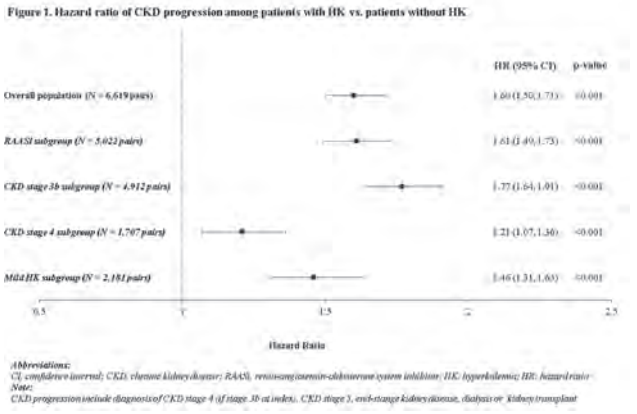

Figure 1. Hazard ratio of CKD progression among patients with HK vs. patients without HK

TH-PO1030

Prevalence of Elevated Serum Potassium in CKD Population by KDIGO Risk and eGFR Categories in a Representative US Population: NHANES 1999-2018

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Background: Among patients with CKD, hyperkalemia has been independently associated with poorer outcomes. However, the prevalence, risk factors, and severity of hyperkalemia in the US by demographic groups, KDIGO risk categories, eGFR categories and levels of albuminuria have not been reported.

Methods: We used data of 101,316 participants from the National Health and Nutrition Examination Survey (NHANES) between 1999 to 2018. We calculated 20-year weights to account for the complex survey design and the oversampling of certain age and minority groups. We defined and examined hyperkalemia by different levels of elevated serum potassium > 5.0, >5.5, and >6 mmol/L. Univariate and multivariate regression analysis was performed to identify independent predictors for hyperkalemia. Each model was adjusted for age, gender, race/ethnicity, diastolic blood pressure, hypertension, diabetes, HbA1c, hemoglobin, triglyceride, and CVD history. In the model of eGFR as exposure, UACR was additionally adjusted and in the model of UACR as exposure, eGFR was additionally adjusted.

Results: In a nationally representative sample of US adults with CKD, the prevalence of mild hyperkalemia (K>5.0 mmol/L) was 2.46%, moderate hyperkalemia (K>5.5 mmol/L) was 0.43%, and severe hyperkalemia (K>6 mmol/L) was rare at 0.06% (Table). While mild hyperkalemia was common in patients with KDIGO very high-risk category (9.72%) and in eGFR <15 to 29 ml/min/1.73m^2 (15.67%), severe hyperkalemia was rare at 0.54% and 1.45%, respectively. Both KDIGO risk and eGFR categories independently predicted mild and moderate hyperkalemia.

Conclusions: Mild hyperkalemia is relatively common in patients with advanced CKD, although not as high as previously reported in unweighted samples of CKD patients. Severe hyperkalemia is rare. The most important predictors of hyperkalemia are high and very high KDIGO risk categories as well as eGFR of <15-29 ml/min/1.73m^2.

Prevalence (95% CI)	Serum K >5 mmol/L	Serum K >5.5 mmol/L	Serum K >6 mmol/L
Overall	2.46 (2.01, 3.01)	0.43 (0.29, 0.64)	0.06 (0.02, 0.17)
Age group			
Age <65	1.21 (0.81, 1.80)	0.25 (0.12, 0.53)	0.09 (0.02, 0.36)
Age ≥65	3.75 (3.07, 4.57)	0.62 (0.40, 0.95)	0.04 (0.02, 0.09)
By Gender			
Male	2.93 (2.29, 3.75)	0.45 (0.30, 0.67)	0.03 (0.02, 0.06)
Female	2.11 (1.68, 2.66)	0.42 (0.22, 0.79)	0.08 (0.02, 0.31)
By Race/Ethnicity			
Non-Hispanic White	2.82 (2.22, 3.57)	0.42 (0.25, 0.73)	0.06 (0.01, 0.25)
Non-Hispanic Black	2.03 (1.48, 2.78)	0.67 (0.37, 1.22)	0.13 (0.03, 0.55)
Hispanic	1.53 (1.05, 2.21)	0.25 (0.12, 0.52)	0.03 (0.00, 0.22)
Other	1.47 (0.75, 2.83)	0.32 (0.10, 1.06)	0 ¶(0, 0)
KDIGO risk categories			
Moderately increased risk	1.07 (0.76, 1.51)	0.06 (0.02, 0.14)	0 ¶(0, 0)
High risk	3.86 (2.91, 5.10)	1.00 (0.49, 2.04)	0 ¶(0, 0)
Very high risk	9.72 (7.16, 13.06)	2.05 (1.23, 3.40)	0.54 (0.15, 1.85)
eGFR categories			
eGFR >=60	0.70 (0.41, 1.20)	0.02 (0.00, 0.09)	0 ¶(0, 0)
eGFR 30-59	3.66 (2.98, 4.47)	0.63 (0.37, 1.08)	0.01 (0.00, 0.07)
eGFR <15 to 29	15.67 (11.69, 20.68)	4.28 (2.45, 7.39)	1.45 (0.48, 4.31)
UACR categories			
UACR <30	3.26 (2.48, 4.27)	0.70 (0.35, 1.39)	0.02 (0.00, 0.17)
UACR 30-300	1.53 (1.17, 1.99)	0.17 (0.10, 0.31)	0.01 (0.00, 0.10)
UACR >300	4.66 (3.05, 7.05)	0.93 (0.42, 2.05)	0.32 (0.06, 1.81)

¶ Rare event, no observation.

TH-PO1031

Instantaneous and Persistent Elevation of Serum Potassium and Progression of CKD

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Background: The adverse effect of hyperkalemia on chronic kidney disease (CKD) progression has not been well studied.

Methods: The study population was recruited from outpatients of Peking University First Hospital for patients with CKD G1-4 between 2010 and 2020. Those with ≥2 measurements of serum potassium during the first year after recruitment (baseline period) were included in the analysis. Instantaneous hyperkalemia was defined as occurrence of serum potassium≥5.0 mmol/L for once or lasting for < 3 months, while persistent hyperkalemia as repeated occurrence lasting for ≥ 3 months. The initiation of kidney replacement therapy (KRT) was followed after baseline period until death, loss of follow-up or Dec. 31 of 2020. Cox proportional hazards regression model was used to estimate the association between exposure and outcome, while linear mixed effects model to estimate the slope of estimated glomerular filtration rate (eGFR) with interactions between time and hyperkalemia status indicating difference of slope. Two-sided P<0.05 was statistically significant.

Results: A total of 527 patients were included in the analysis, with mean age of 56±16 years and 54.7% of male. CKD stage 1, 2, 3 and 4 accounted for 3.6%, 12.0%, 55.4% and 29.0% of the patients. There were 331, 85 and 111 patients with no, instantaneous and persistent hyperkalemia, respectively. During a mean follow-up of 4.45±3.27 years, 61 events of KRT occurred. Hyperkalemia was associated with higher risk of KRT (Figure 1). After multivariable adjustment, both instantaneous hyperkalemia and persistent hyperkalemia were associated with increased risk of KRT (hazard ratio: 2.43 [95%CI: 1.14-5.18] and 2.86 [95%CI: 1.48-5.54], respectively) and higher rate of eGFR decline (-2.23 and -3.92 versus -1.97 ml/min/1.73m^2/year).

Conclusions: Hyperkalemia, especially persistent status, was associated with higher risk of CKD progression among patients with CKD.

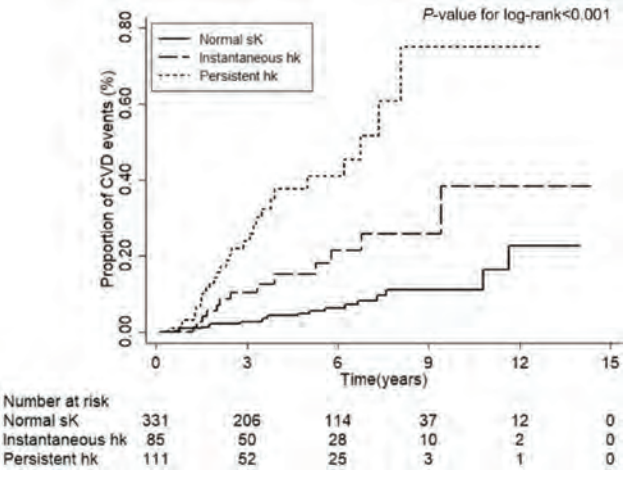

Figure 1

TH-PO1032

Performance of the European Kidney Function Consortium (EKFC) Creatinine-Based Equation in American Cohorts

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Background: The new creatinine-based European Kidney Function Consortium (EKFC) equation has been developed and validated in datasets of European subjects. This equation is based on rescaled creatinine, with the rescaling factor (Q-value) which is the median normal value of serum creatinine in a given population. The EKFC equation performed well across the whole age spectrum. However, the validation was limited in Black and non-Black Americans.

Methods: Cross-sectional analysis with separate pooled datasets for validation from 9 US research and clinical studies with measured GFR, age, sex, and self-reported race available. Two strategies were considered with population specific Q-values in Black and non-Black men and women ($EKFC_{PS}$) or a race-free Q value ($EKFC_{RF}$) which is the mean of the Q values obtained in Black and non-black populations. Performance (bias, precision and accuracy within 30% (P30) was compared with the CKD-EPI_{2021} equation.

Results: In the whole adult population (n=12,854), the $EKFC_{PS}$ equation showed no statistical bias (0.14 95%CI [-0.07;0.35] mL/min/1.73m2), and the statistical bias of the $EKFC_{RF}$ (0.74 [0.51;0.94] mL/min/1.73m2) was closer to zero than the CKD-EPI_{2021} equation (1.22 [0.99;1.47]) mL/min/1.73m2]. The percentage of estimated GFR within

30% of measured GFR was similar for CKD-EPI$_{2021}$ (79.2% [78.5%-79.9%]) and EKFC$_{RF}$ (80.1% [79.4%-80.7%]) but improved with the EKFC$_{PS}$ equation (81.1% [80.5%-81.8%]).

Conclusions: The EKFC-equation can be used in the USA to estimate GFR incorporating either self-reported race or unknown race at the patient's discretion per hospital registration records. The performance of the EKFC equation is as at least good as the CKD-EPI$_{2021}$ equation.

Table: Performance of the CKD-EPI$_{2021}$ and EKFC equations to estimate glomerular filtration rate

	CKD-EPI$_{2021}$	EKFC$_{RF}$	EKFC$_{PS}$
Whole population, n=12,854			
Median bias (95% CI)	1.22 [0.99; 1.47]	0.74 [0.51; 0.94]	0.14 [-0.07; 0.35]
IQR (Q1; Q3)	16.0 [-6.6; 9.4]	15.7 [-7.6; 8.0]	15.4 [-8.1; 7.3]
P30 (95% CI)	79.2 [78.5; 79.9]	80.1 [79.4; 80.7]	81.1 [80.5; 81.8]
P20 (95% CI)	61.6 [60.7; 62.4]	62.4 [61.6; 63.3]	63.7 [62.9; 64.5]
Non-Black population, n=10,064			
Median bias (95% CI)	2.78 [2.55; 3.04]	1.93 [1.67; 2.18]	0.85 [0.62; 1.09]
IQR (Q1; Q3)	16.1 [-4.8; 11.3]	15.6 [-6.4; 9.3]	15.6 [-7.6; 8.0]
P30 (95% CI)	78.3 [77.5; 79.1]	79.0 [78.2; 79.8]	80.4 [79.6; 81.2]
P20 (95% CI)	61.4 [60.5; 62.4]	61.9 [61.0; 62.9]	63.3 [62.4; 64.3]
Black population, n=2,790			
Median bias (95% CI)	-4.01 [-4.44; -3.56]	-3.12 [-3.70; -2.62]	-2.22 [-2.72; -1.83]
IQR (Q1; Q3)	13.9 [-11.6; 2.3]	14.3 [-11.1; 3.2]	14.1 [-10.0; 4.2]
P30 (95% CI)	82.5 [81.1; 83.9]	83.8 [82.4; 85.2]	85.7 [82.4; 85.1]
P20 (95% CI)	62.1 [60.3; 63.9]	64.3 [62.5; 66.0]	64.9 [63.1; 66.7]
Non-Black women, n=4,605			
Median bias (95% CI)	2.54 [2.20; 2.92]	0.45 [0.08; 0.86]	0.45 [0.08; 0.86]
IQR (Q1; Q3)	16.3[-5.2; 11.1]	15.7 [-7.9; 7.8]	15.7 [-7.9; 7.8]
P30 (95% CI)	78.9 [77.7; 80.1]	80.9 [79.8; 82.0]	80.9 [79.8; 82.0]
P20 (95% CI)	62.0 [60.6; 63.4]	63.7 [62.3; 65.1]	63.7 [62.3; 65.1]
Non-Black men, n=5,459			
Median bias (95% CI)	3.01 [2.66; 3.43]	3.09 [2.76; 3.41]	1.14 [0.85; 1.43]
IQR (Q1; Q3)	15.9 [-4.5; 11.3]	15.7 [-5.0; 10.7]	15.6 [-7.3; 8.3]
P30 (95% CI)	77.7 [76.6; 78.8]	77.4 [76.3; 78.5]	80.0 [79.0; 81.1]
P20 (95% CI)	60.9 [59.7; 62.2]	60.4 [59.1; 61.7]	63.1 [61.8; 64.4]
Black women, n=1,087			
Median bias (95% CI)	-2.98 [-3.75; -2.30]	-3.39 [-4.12; -2.67]	-3.39 [-4.12; -2.67]
IQR (Q1; Q3)	13.6 [-10.7; 2.9]	14.0 [-11.6; 2.4]	14.0 [-11.6; 2.4]
P30 (95% CI)	79.8 [77.4; 82.2]	80.3 [78.0; 82.7]	80.3 [78.0; 82.7]
P20 (95% CI)	60.5 [57.6; 63.4]	60.8 [57.9; 63.7]	60.8 [57.9; 63.7]
Black men, n=1,703			
Median bias (95% CI)	-4.64 [-5.15; -4.10]	-2.91 [-3.69; -2.30]	-1.35 [-1.97; -0.75]
IQR (Q1; Q3)	14.4 [-12.3; 2.1]	14.4 [-10.7; 3.7]	14.2 [-8.8; 5.4]
P30 (95% CI)	84.3 [82.5; 86.0]	86.0 [84.4; 87.7]	85.9 [84.3; 87.6]
P20 (95% CI)	63.1 [60.8; 65.4]	66.5 [64.2; 68.7]	67.5 [65.2; 69.7]

CKD-EPI$_{2021}$: race-free Chronic Kidney Disease Epidemiology; EKFC$_{RF}$: European Kidney Function Consortium with race-free Q-values. EKFC$_{PS}$: European Kidney Function Consortium with population specific Q-values. IQR: interquartile range. P30: accuracy within 30%, P20: accuracy within 20%. Q1: quartile 1, Q3: quartile 3.
Bias and IQR are expressed in mL/min/1.73m^2, P30 and P20 are expressed in %

TH-PO1033

New Argentine Equation to Estimate the Glomerular Filtration Rate

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Background: Latin Americans are poorly represented in the current glomerular filtration rate equations (eGFR), so their predictions are difficult to extrapolate in our population. Objetive: to develop a new equation to estimate GFR based on data from Argentina and compare its performance with those currently available.

Methods: Cross-sectional study. We included all adults whose GFR was measured with urinary clearance of iothalamate (mGFR) between 2007 and 2017 (development sample–DS-, n=583). The chosen equation was based on a quasi-likelihood model with identity variance function and logarithmic link to predict mGFR from the square root of creatinine, age, sex, monoren, albumin and the logarithm of urea. Later, an independent sample was added between 2018 and 2019 (temporary validation sample -TVS-, n=78). The performance of the new equation was compared with the previous ones (MCQ, MDRD 4 and 6, CKD-EPI 2009 and 2021) in the DS (by 10-fold cross-validation) and in the TVS.

Results: There were no differences in the baseline characteristics in both samples and they presented a wide range in the mGFR (1.9-186.6 ml/min/1.73 m^2). Within the previous equations, CKD-EPI (2009 and 2021) obtained the best performance (comparator). In the DS, Argentine Equation (AE) presented a lower RMSE, higher P15, bias median closer to zero, and a higher %CC compared to CKD-EPI 2009. In addition, from Q1, M, and Q3 of the bias, a greater shift to the left of CKD-EPI 2009. Compared with CKD-EPI 2021, AE obtained a median bias closer to 0, and in the rest of the metrics it was slightly lower, although very similar (table 1). In the TVS, AE presented a lower RMSE, higher r, P30 and %CC compared to CKD-EPI in its two versions. In addition, it presented a median bias closer to 0 and a higher P15 compared to CKD-EPI 2009.

Conclusions: AE presented a better global performance to estimate GFR in residents of Argentina compared to the currently equations.

Table 1. Performance of the equations in the development sample (by 10-fold cross validation) and in the temporary validation sample.

	RMSE	Bias (Q1 / Q3)	P15	P30	r	%CC
Development Sample by 10-fold cross validation (n=583)						
CKD-EPI 2009	18.3	-4.3 (-13.8 / 6)	58	84.4	0.868	73.6
CKD-EPI 2021	17.9	-0.6 (-10.1 / 9.5)	61.2	83.7	0.869	73.9
AE	18	-0.3 (-10.1 / 9)	60.7	83.2	0.867	73.8
Temporary Validation Sample (n=78)						
CKD-EPI 2009	16.8	-4.6 (-16.2 / 2.4)	57.7	88.5	0.882	70.5
CKD-EPI 2021	15.4	-1.1 (-12.4 / 6.4)	61.5	85.9	0.887	74.4
AE	15	-1.1 (-12.1 / 6.9)	60.2	89.7	0.894	79.5

RMSE= Root mean squared error, Bias= Median difference between the estimated and measured GFR; Q1 and Q3= 1th and 3th quartile; P15 and P30= % of the eGFR within ±15 or 30% of the mGFR; r= Pearson's correlation coefficient; %CC= Percentage of patients correctly classified in CKD stages; AE= Argentine Equation

TH-PO1034

Performance Evaluation of CKD-EPI Equations for Estimated Glomerular Filtration Rate Compared with Inulin Clearance in Koreans

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Background: A race-free glomerular filtration rate (GFR) estimation equation has recently been developed. However, the performance of the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations needs to be evaluated in Asian populations.

Methods: We performed a cross-sectional study at a single center in South Korea. The measured GFR (mGFR) was determined based on systemic inulin clearance. The GFR was estimated using the following five CKD-EPI equations incorporating creatinine (cr), cystatin C (cys), and cystatin C and creatinine (cr-cys): 2009 CKD-EPIcr, 2012 CKD-EPIcr-cys, 2012 CKD-EPIcys, 2021 CKD-EPIcr, and 2021 CKD-EPIcr-cys.

Results: The bias of 2009 CKD-EPIcr (2.24) and 2012 CKD-EPIcr-cys (6.74) were lower than those of 2021 CKD-EPI equations (5.40 and 10.54 mL/min/1.73 m^2). The accuracy of the five eGFR equations measured as the percentage of study participants with eGFR values within 30% of the mGFR of original CKD-EPIcr and CKD-EPIcr-cys were higher than those of 2021 equations (85.4 vs. 83.3% and 84.1 vs. 80.8%). The overall concordance rate between mGFR and estimated GFR was higher in the 2009 CKD-EPIcr (0.393) and 2012 CKD-EPIcr-cys (0.473) than in the 2021 CKD-EPIcr-cys (0.372 and 0.456). The CKD prevalence in 2009 CKD-EPIcr, 2021 CKD-EPIcr, 2012 CKD-EPIcr-cys, and 2021 CKD-EPIcr-cys was 54.8%, 51.0%, 47.7%, and 44.8%, respectively.

Conclusions: Our study demonstrated better performance of the original CKD-EPIcr and CKD-EPIcr-cys equations than the 2021 new CKD-EPI equations. We do not recommend the adoption of the new CKD-EPI equations in Korea.

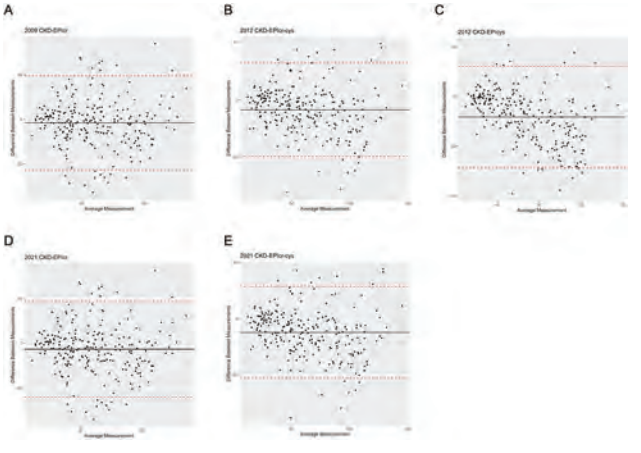

Figure 1. Bland-Altman plots for the concordance rate between mGFR and eGFR.

Equations	Intercept (95% CIs)	Slope (95% CIs)	[a]Median bias (95% CIs)	[b]Accuracy, %		
				15%	30%	50%
2009 CKD-EPIcr	20.01 (13.37–26.65)	0.61 (0.51–0.71)	2.24 (-8.83–17.39)	79.5	85.4	91.2
2012 CKD-EPIcr-cys	9.98 (4.89–15.07)	0.71 (0.64–0.78)	6.74 (-2.81–20.80)	75.3	84.1	91.6
2012 CKD-EPIcys	12.75 (7.80–17.70)	0.57 (0.52–0.63)	16.07 (2.23–38.91)	57.7	64.9	73.6
2021 CKD-EPIcr	19.40 (12.6–26.21)	0.59 (0.5–0.69)	5.40 (-6.04–20.40)	76.2	83.3	89.1
2021 CKD-EPIcr-cys	8.44 (3.29–13.58)	0.70 (0.64–0.77)	10.54 (0.30–24.37)	69.0	80.8	87.4

Figure 2. Performance comparison between five glomerular filtration rate-estimating equations

TH-PO1035

The Impact of Muscle Mass on eGFR Accuracy with Creatinine and Cystatin C

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Background: The use of creatinine (Cr) for estimating glomerular filtration rate (eGFR) is limited by non-GFR factors such as muscle mass, diet and drugs. Calculating lean tissue mass (LTM), a surrogate for muscle mass, or cystatin-c (Cys-c) – an alternative filtration marker unaffected by muscle mass or diet - may improve GFR estimation. We explored the relationship between LTM and eGFR accuracy using Cr and/or Cys-c, compared to measured GFR (mGFR) at multiple timepoints.

Methods: Participants with CKD were recruited. Demographics (age, sex, ethnicity) and 0, 6- and 12-month weight (kg), LTM (kg), mGFR, Cr and Cys-c were recorded. eGFR was calculated using the Modification of Diet for Renal Disease (MDRD), European Kidney Function Consortium (EKFC), CKD Epidemiology Collaboration (CKD-EPI) 2009, 2012 and 2021 equations for Cr, Cys-c and combined Cr-Cys-c. The relationship between LTM, mGFR and eGFR equations were assessed using beta coefficient. Association at baseline and over 12 months with LTM was assessed using regression analysis and multilevel mixed-effects linear regression respectively.

Results: Of 41 participants, 28 (68.3%) were male and mean age was 53.2 ± 14.1 yrs. Baseline median (IQR) weight, LTM and mGFR were 85.5kg (71.2, 104.4), 44.3kg (36.5, 53.6) and 35 mL/min/1.73m^2 (23.0, 46.0) respectively. Baseline LTM (kg) was associated with higher values of mGFR-eGFR beta-coefficients for all Cr based equations ($p<0.05$). LTM as percentage of weight was weakly associated with CKD-EPI 2021 Cr equation (0.66; 95% CI 0.01-1.31;$p<0.05$). Cys-c eGFR equations compared with mGFR showed no significant associations with LTM. At 12 months, there was also a significant relationship between mGFR-eGFR Cr-based beta-coefficients (figure 1).

Conclusions: LTM was associated with Cr-based eGFR's relationship with mGFR. There was no significant association involving Cys-c based equations, providing further evidence of independence of muscle mass, making its use more appealing in specific cohorts (e.g. liver cirrhosis, malignancy). Analysis of a larger cohort may allow a factor for LTM to further improve eGFR equation accuracy.

Figure 1. Relationship between Lean mass and kidney function at 12months (n=41)

	Beta-coefficient (95% CI)
m-GFR	0.05 (-0.16, 0.25)
M- GFR - egfr_cysc_2012	-0.10 (-0.26, 0.07)
M- GFR - egfr_crcysc_2012	0.03 (-0.09, 0.14)
M- GFR - egfr_crcysc_2021	0.03 (-0.09, 0.14)
M- GFR - egfr_cr_ckdepi_2009	0.19 (0.06, 0.32) **
M- GFR - egfr_cr_ckdepi_2021	0.18 (0.05, 0.31) **
M- GFR - egfr_mdrd	0.19 (0.06, 0.32) **
M- GFR - egfr_ekfc	0.17 (0.05, 0.30) **

* p<0.05, ** p<0.01, *** p<0.001

TH-PO1036

Impact of Obesity on the Associations of Cystatin C-Based eGFR with Clinical Outcomes

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Background: Cystatin C-based eGFR (eGFRcys) has stronger associations with adverse clinical outcomes than creatinine-based eGFR (eGFRcr). Obesity may be associated with higher cystatin C levels, independent of kidney function, but whether obesity affects the prognostic utility of eGFRcys is unknown.

Methods: This prospective cohort study included 27,249 US adults enrolled in the Reasons for Geographic and Racial Differences in Stroke study between 2003 and 2007. We constructed multivariable Cox and Fine-Gray models with multiplicative interaction terms to investigate whether waist circumference (WC) quartiles modified associations of eGFR with risks of all-cause mortality, ESKD, incident atherosclerotic cardiovascular disease (ASCVD), and incident heart failure (HF).

Results: Participants had a mean age of 65 y; 54% were women, and 41% were Black. Baseline prevalence of abdominal obesity (WC ≥88 cm for women or ≥102 cm for men) was 48% and obesity (BMI ≥30 kg/m^2) was 38%. During a median follow-up time of 12.1 years, 9350 (34%) participants died, 511 (2%) developed ESKD, 2271 (11%) had an incident ASCVD event, and 1053 (4%) had an incident HF hospitalization. In adjusted analyses (Table 1), each 15-mL/min/1.73 m^2 lower eGFRcys was associated with higher risk of mortality in each WC quartile (Q1: HR 1.10 [1.15, 1.24]; Q2: HR 1.22 [1.18, 1.26]; Q3: HR 1.20 [1.16, 1.24]; Q4: 1.19 [1.15, 1.23]). WC did not modify associations of eGFRcys with mortality (p-interaction >0.05). Similarly, WC did not modify associations of eGFRcys with the other outcomes (all p-interactions >0.05). Compared with eGFRcr, eGFRcys had stronger associations with mortality in all WC quartiles ($p<0.001$ in all quartiles).

Conclusions: The association of eGFRcys with adverse outcomes did not differ by WC. Among individuals with obesity, cystatin C may be used to examine associations of eGFR with important clinical adverse outcomes related to kidney disease.

Funding: Other NIH Support - NINDS, Veterans Affairs Support

	Hazard and Subhazard ratios (95% CI) per 15 mL/min/1.73 m^2 lower eGFR and by quartile of waist circumference				
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P interaction *
All-cause mortality					
Proportion w/event (%)	1,999/ 6,263 (32)	2,305/ 7,005 (33)	2,474/ 7,257 (34)	2,572/ 6,664 (39)	-
eGFRcys	1.19 (1.15, 1.24)	1.22 (1.18, 1.26)	1.20 (1.16, 1.24)	1.19 (1.15, 1.23)	p=0.74
eGFRcr	1.07 (1.02, 1.12)	1.13 (1.08, 1.17)	1.10 (1.06, 1.14)	1.08 (1.04, 1.11)	p=0.21
ESKD					
Proportion w/event (%)	49/ 6,263 (0.8)	107/ 7,005 (1.5)	135/ 7,257 (1.9)	220/ 6,664 (3.3)	-
eGFRcys	2.34 (1.84, 2.99)	2.21 (1.84, 2.65)	2.53 (2.15, 2.99)	2.08 (1.82, 2.37)	p=0.27
eGFRcr	2.53 (1.88, 3.39)	2.22 (1.83, 2.69)	2.23 (1.92, 2.59)	1.86 (1.65, 2.10)	p=0.093
Incident ASCVD					
Proportion w/event (%)	425/ 5,137 (8)	528/ 5,415 (10)	580/ 5,392 (11)	739/ 5,385 (14)	-
eGFRcys	1.13 (1.05, 1.22)	1.06 (0.99, 1.13)	1.10 (1.03, 1.17)	1.07 (1.01, 1.13)	P=0.44
eGFRcr	1.09 (1.00, 1.19)	0.98 (0.90, 1.06)	1.07 (0.99, 1.15)	1.04 (0.98, 1.10)	p=0.21
Incident HF					
Proportion w/event (%)	150/ 5,912 (2.5)	217/ 6,232 (3.5)	282/ 5,863 (4.8)	369/ 6,341 (5.8)	
eGFRcys	1.08 (0.96, 1.23)	1.11 (1.00, 1.23)	1.14 (1.04, 1.24)	1.05 (0.97, 1.14)	p=0.55
eGFRcr	1.01 (0.88, 1.16)	1.06 (0.95, 1.17)	1.07 (0.97, 1.18)	0.99 (0.91, 1.07)	p=0.54

* p for interaction of waist circumference with eGFR. Models for mortality and ESKD adjusted for age, sex, race, income, diabetes, hypertension, hyperlipidemia, coronary artery disease, peripheral artery disease, history of stroke, smoking, aspirin use, LDL, HDL, CRP and UACR. Models for incident ASCVD and HF adjusted for age, sex, race, income, diabetes, hypertension, hyperlipidemia, peripheral artery disease, smoking, aspirin use, LDL, HDL, CRP and UACR.

TH-PO1037

Indexing to Body Surface Area Diminishes GFR Estimation and Increases CKD Staging in Overweight and Obese Population

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Background: Estimated glomerular filtration rate (eGFR) is usually indexed to a standard body surface area (BSA) of 1.73m^2. This allows comparing values of individuals of different sizes but can potentially affect eGFR in individuals with extreme BSA. We aimed to evaluate the differences in eGFR with and without indexing for BSA in a cohort of ambulatory patients with different body mass index (BMI) and how indexing affects CKD classification.

Methods: 390 patients of a nephrological clinic were evaluated with ambulatory 24-hour creatinine clearance (CrCl) and their demographic and anthropometric data was registered in an anonymous database. Patients were divided in 3 groups according to BMI (18-24.9; 25-29.9; ≥30 kg/m^2). GFR was estimated with MDRD-4, CKD-EPI 2009 and 2021 equations, with and without indexing to 1.73m^2. CKD classification was also performed with and without indexing eGFR.

Results: 224 of 390 patients were men (57.4%).103 (26.4%) had normal BMI (group 1), 193 (49.5%) were overweight (group 2) and 94 (24.1%) were obese (group 3). The difference between non-indexed and indexed CrCl was +2.2 ml/min, - 2.9 ml/min y – 9.3 ml/min in groups 1, 2 and 3, respectively. Using MDRD-4, CKD-EPI 2009 and 2021 equations, the differences were -2.0, -2,1 and -2,2 in group 1; +2.2, +2,3 and +2,5 in group 2; and +7.3, 7,6 and +8.0 ml/min in group 3. Non-indexed eGFR was significantly higher in obese patients ($p<0.001$). Classification of CKD was significantly affected by removing indexing using CKD-EPI 2021 equation, with almost 20% of the patients switching stage of CKD (17.5% group 1, 18.7% group 2 and 12.8% group 3). Diagnosis of GFR <60 mL/min was more frequent when GFR estimation was indexed in overweight and obese patients (15% and 13.3% more, respectively). Converserly, removing indexing reclassifies 11.7% of patients with normal BMI into GFR <60 mL/min.

Conclusions: Indexing to standard BSA lowers eGFR in overweight and obese patients, leading to a higher prevalence of < 60 ml/min CKD diagnosis.

TH-PO1038

Potential Value of Near Real-Time Transdermal GFR Measurement: Estimated GFR Results by CKD-EPI Serum Creatinine Misclassifies CKD Stage in One of Three Adults

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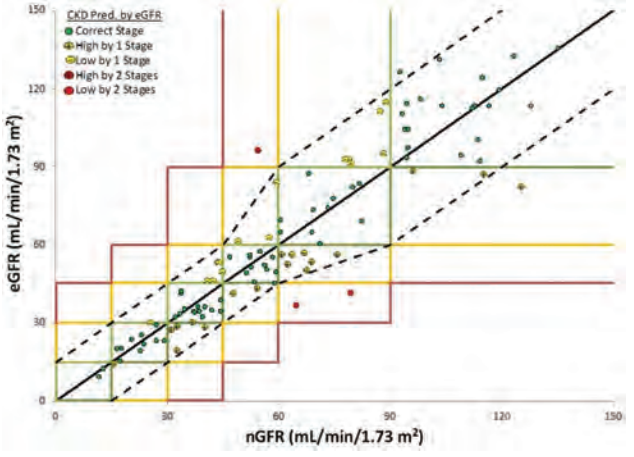
Background: Currently, chronic kidney disease is most often staged using the serum creatinine-based CKD-EPI equation to estimate GFR (eGFR). Serum creatinine is confounded by several well-known factors including chronic inflammation, muscle mass, medications, tubular SCr secretion and hydration status. Available measured GFR methods are challenged by need for multiple blood draws, radiological equipment and time or prolonged urine collections which are unreliable. We have previously shown our plasma GFR assessment (nGFR) with novel fluorescent tracer agent, relmapirazin (also known as MB-102 in the literature), demonstrates outstanding correlation with iohexol measured GFR in Phase I and II studies (n=120 patients, r^2=0.99). We have also previously shown transdermal MB-102 GFR assessment (tGFR) shows outstanding correlation with MB102 nGFR (r^2=0.95), and can report GFR within 90-120 minutes at the bedside. We assessed the agreement between nGFR and eGFR in the 120 Phase I and II subjects.

Methods: This prospective study evaluated nGFR with the MediBeacon Inc system in 120 adult patients with CKD Stages 1-4. MB-102 distributes in body tissues over 90-

120 minutes and starts to be cleared solely by glomerular filtration. We compared the CKD Stage by CKD-EPI and nGFR using plasma measurements MB-102 over 8-12 hours.

Results: Data from all 120 subjects (64 female, median age 55.5 years, median BMI 29 kg/m^2) were available for analysis. Reported patient race was White (69), Black (48), American Indian/Alaskan Native (2), Asian (1) and all 6 of the Fitzpatrick Skin Scales were represented. **Figure 1** shows that nGFR and CKD-EPI eGFR differed by at leas one CKD Stage in 32% and at least CKD Stages 4% of the time. Over- and underestimation of CKD was evenly divided.

Conclusions: CKD-EPI eGFR misclassifies true GFR based CKD stage in more than 1/3 of patients. We have completed a Phase II study comparing nGFR to tGFR to demonstrate accurate near real-time GFR assessment at the bedside.



TH-PO1039

Machine Learning and Multiparametric MRI for Noninvasive Diagnosis of the Etiology of CKD

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Background: Multiparametric magnetic resonance imaging (MRI) has the potential to provide various types of biological information about the kidney. In this study, we aimed to diagnose the underlying etiology of chronic kidney disease (CKD) non-invasively by combining MRI images and machine learning.

Methods: T1-weighted images (water-weighted images using the Dixon method), T1 value maps, T2* value maps of blood oxygen level-dependent MRI, perfusion maps of arterial spin-labeling, fractional anisotropy value maps from diffusion tensor imaging, and apparent diffusion coefficient value maps from diffusion-weighted imaging were used. We calculated the cortical values and cortical-medullary gradients using a 12-layer concentric object method. We created a multiclass classifier using a support vector machine and features such as MRI measurement values, age, estimated glomerular filtration rate (eGFR) at the time of imaging, and hemoglobin value. K-fold cross-validation was used to evaluate classifier accuracy.

Results: A total of 197 patients [60.9 ± 14.9 years old, 65.0% male, 15.2% with diabetic kidney disease (DKD), 34.0% with chronic glomerulonephritis (CGN), 50.8% with nephrosclerosis (NS), and a mean eGFR of 42.3 ± 22.2 ml/min/1.73 m^2] were included. After model optimization, we obtained a relatively good overall accuracy of 0.65, and area under the curve values of 0.72 for DKD, 0.76 for CGN, and 0.73 for NS on the receiver operating characteristic curve. There were some estimation errors, particularly in cases diagnosed with DKD by physicians, and accuracy of the estimation tended to be low. Among cases of DKD, there were also cases that showed imaging characteristics similar to those of NS or CGN, suggesting an overlap of pathologies.

Conclusions: Conventional and functional kidney MRI and machine learning/augmented intelligence diagnosis have the potential to be useful noninvasive diagnostic tools, and further improvements in accuracy can be achieved by refining the features. We observed some cases diagnosed with DKD by nephrologists based on the clinical course and results of blood/urine test that showed MR imaging characteristics resembling those of NS or CGN. Kidney biopsy or renal MRI may be effective for accurate diagnosis and determination of an appropriate treatment plan.

TH-PO1040

Feasibility and Safety of Percutaneous Kidney Biopsy in Small Kidneys: Breaking the Paradigm

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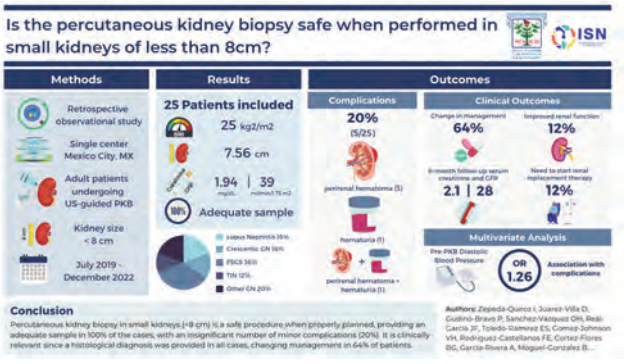
Background: Percutaneous kidney biopsy (PKB) is a vital diagnostic tool, there are absolute and relative contraindications. Kidney size considered a relative contraindication due to poor accessibility and risk of complications, therefore, there is no consensus regarding the best approach in this setting.

Methods: Retrospective cross sectional at the Interventional Nephrology Department of the Instituto Nacional de Cardiologia Ignacio Chavez. Patients older than 16 years old who had kidney length of ≤ 8 cm and underwent a PKB of native kidneys from July 2019 to December 2022 were included. Sampling was performed in real time guided by ultrasound. For the comparative analysis, the Chi-square or Fisher's exact test were used for qualitative variables, and the T-student or Mann-Witney U test for quantitative variables, according to their distribution.

Results: 25 patients were included, 19 women and 6 men. The mean age was 42.3 ± 18.04. The mean kidney length was 7.56 ±0.33 and the mean width was 4.2 cm. All patients received only one puncture, with an average of 12 glomeruli. The mean serum creatinine was 1.94 mg/dL. Minor complications occurred in 5 patients, perirenal hematoma 3, hematuria in 1, and hematoma plus hematuria in 1 patient. Histological examination showed FSGS in 36% of cases, lupus nephritis in 20%, other glomerular diseases in 16%, crescentic glomerulonephritis in 16%, and tubulointerstitial nephritis in 12%. Management was modified in 64% of cases. A bivariate analysis was performed for complications versus without complications based on clinical and ultrasound characteristics, where statistical significance was found for complications with pre-biopsy DBP of 89 ± 5.80 mmHg (p>0.001).

Conclusions: PKB in small kidneys is a feasible and safe procedure when properly planned, providing an adequate sample in all cases, with an insignificant number of minor complications, and that is clinically relevant.

Funding: Government Support - Non-U.S.



TH-PO1041

Quantifying the Delay from Laboratory-Based Detection to Diagnosis of CKD in the United States

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Background: While delays from chronic kidney disease (CKD) onset to diagnosis are common, these delays have yet to be quantified. The study objective was to quantify the delay from laboratory-based physiologic detection (using eGFR) to diagnosis of CKD (using ICD 9/10 code).

Methods: A retrospective cohort study was conducted using 2009 -2020 Optum® Market Clarity data. Individuals aged 18 years and older, who had two laboratory records showing eGFR < 60 mL/min/1.73 m^2, 3-12 months apart, were included. The second eGFR < 60 was defined as the index date. Patients with pre-existing ICD code of CKD during the 12-month pre-index period (baseline), or before the first eGFR <60 were excluded. Individuals were followed from the index date until a diagnosis of CKD or censoring (date of death, end of follow-up, or disenrollment). Cohorts were stratified by the presence or absence of comorbid diabetes and heart failure (HF) at baseline. Survival analysis was performed to evaluate the factors associated with delays in diagnosis, for overall and stratified cohorts.

Results: A total of 1.39 million adults with laboratory evidence of CKD (mean (±SD) age 71 (±10); 63% women; 87% Caucasian) were included. Over 90% of them were in KDIGO stage 3, 5% in stage 4 and 1% in stage 5. Overall, 62% of individuals had neither diabetes nor HF, 24% had diabetes, 8% had HF, and 6% had both. The mean follow-up was 2.7 (SD 2.4) years. Overall, the median time to CKD diagnosis was 469 days (interquartile range [IQR]: 120-1062); time to CKD diagnosis was 537 days (IQR: 152-1163) among those without diabetes or HF, 449 days (IQR: 114-1007) among those only with diabetes, 319 days (IQR: 62-793) among those with only HF, and 270 days (IQR: 54-694) among those with both diabetes and HF. Factors associated with longer time to CKD diagnosis included: absence of diabetes or HF; less severe CKD; younger age; female sex; and Caucasian race.

Conclusions: In a large cohort of individuals with laboratory-based evidence of CKD, the time to diagnosis was delayed, on average, by over a year. In light of newer therapies that can slow kidney disease progression and reduce cardiovascular complications, these findings reinforce the need for early recognition of CKD that would inform optimal guideline-based treatment and improve outcomes in these patients.

Funding: Commercial Support - Boehringer Ingelheim

TH-PO1042

Exploring the Spectrum of Retroperitoneal Fibrosis

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Background: Retroperitoneal fibrosis (RPF) is a rare disease characterized by fibroinflammatory tissue surrounding the abdominal aorta and iliac arteries. Due to the nonspecific nature of its clinical presentation, diagnosis is challenging and often delayed. This study aims to comprehensively analyze the clinical characteristics, treatment approaches, and renal outcomes in a diverse cohort of RPF patients.

Methods: Electronic Health Records of patients who underwent evaluation for RPF between 01/2015 to 09/2022 at Johns Hopkins Hospital were reviewed to collect data on baseline demographics, clinical information, laboratory findings, imaging results, histopathology, and outcomes. Follow-up was from the first nephrology visit until end of study or last follow-up.

Results: 43 patients underwent evaluation for RPF. The most common lesion was idiopathic RPF which was present in 23 (54%) patients (mean age: 62 years, 48% Male; 35% Black, mean eGFR: 58 ml/min/1.73m^3), followed by Erdheim Chester Disease (ECD) in 4 (9%) patients (mean age: 68 years, 75% Male, 0% Black, mean eGFR: 81 ml/min/1.73m^3), and IgG4 disease in 4 (9%) patients (mean age: 58 years, 100% Male, 75% Black, mean eGFR: 58 ml/min/1.73m^3). The remaining 7 (16%) patients (mean age: 62 years, 57% Male, 43% Asian, mean eGFR: 74 ml/min/1.73m^3) had diverse diagnoses, including Follicular Lymphoma, Secondary RPF (from asbestos and Renal Cell Carcinoma), Non-Langerhans Cell Histiocytosis, Thrombosed Aneurysm, and Adnexal Cyst. 5 (12%) patients are currently under evaluation. Common symptoms included pain (flank, abdominal, or back), emesis, and ≥ 5lb weight loss. Imaging showed hydronephrosis in most patients and periaortic findings in those with IgG4 disease and idiopathic RPF. 19 (44%) patients had acute kidney injury at diagnosis. In the first year, 17 (74 %) idiopathic RPF patients received medical therapy (Mycophenolate, Rituximab, Tamoxifen, or Steroids), and patients who tolerated medical therapy had stable or improved disease outcomes. IgG4 disease and ECD patients received immunosuppressants and ECD-specific treatment after biopsy confirmation resulting in improved or stable disease during follow-up.

Conclusions: This study offers valuable insights on diagnosing, managing, and evaluating patients with RPF and related conditions. Our diverse cohort enhances understanding of this rare disease and informs clinical decision-making in RPF cases.

TH-PO1043

Bilateral Multiple Renal Arteries as a Cause for Renal Infarction

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Introduction: Atrial fibrillation is the most common cause of renal infarction followed by valvular or ischemic heart disease, and coagulopathy. However, when all tests are unremarkable, renovascular abnormalities must be kept in the differential. We present one such case of bilateral double renal artery as a likely cause of renal infarction.

Case Description: Forty-six-year-old male with no known past medical history presents to the emergency department for sudden onset left lower quadrant pain radiating to left flank and thigh, severe, 10/10, constant and progressively worsening. Patient denies any dysuria, hematuria, or change in urine output. Patient is hemodynamically stable. The physical exam elicited left sided flank tenderness, left testicular tenderness without swelling or evidence of varicose veins. Lab results showed elevated white blood cell count of 16.5, normal BUN and creatinine. The erythrocyte sedimentation rate was normal. ECG showed normal sinus rhythm with early repolarization pattern. CT abdomen pelvis with IV contrast showed multiple medium sized wedge-shaped parenchymal hypodensities in the left kidney. Complete renal ultrasound denoted occult findings of renal infarction. MRI angiogram of the abdomen with contrast showed two renal arteries bilaterally and reaffirmed renal infarctions in the left upper, middle, and lower kidney. Transthoracic and transesophageal echocardiograms were unremarkable for cardiac thrombosis. Pharmacological nuclear stress test was normal. The patient was started on therapeutic anticoagulation, initially on heparin drip and subsequently discharged on Rivaroxaban. C3 complement was 232 and C4 Complement was 54. Anti-nuclear antibody, lupus anticoagulant, Protein C & S, beta-2 glycoprotein antibodies, Anticardiolipin antibody, and rheumatoid factor were unremarkable.

Discussion: This case is unique because this patient has double bilateral renal arteries which is anatomically rare. Predominantly, there are two renal arteries, originating from the aorta. Few are seen to have double renal arteries and rarely bilaterally. To the best of our knowledge, multiple renal arteries have not been reported as a cause of renal infarction. Therefore, we emphasize renal anatomical abnormalities as an etiology of renal infarction, given all other hypercoagulable work up and cardiac work up is unremarkable.

TH-PO1044

Clinical Course and Recurrence in TAFRO Syndrome: A Case Series Analysis

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Background: TAFRO syndrome is a rare systemic inflammatory disease characterized by five manifestations: thrombocytopenia, anasarca, fever/inflammation, renal insufficiency/reticulin fibrosis of the bone marrow, and organomegaly. It is considered a severe subtype of idiopathic multicentric Castleman disease (iMCD), with the potential for dire outcomes such as hemodialysis or death. Despite prior reporting on TAFRO syndrome's clinicopathological features, its long-term clinical course remains unknown. This study presents a case-series analysis of ten patients with TAFRO syndrome, exploring the long-term prognosis and recurrence of TAFRO syndrome.

Methods: We conducted a retrospective case-series study of patients with TAFRO syndrome at Toranomon Hospital or Toranomon Hospital Kajigaya from January 2012 to June 2021. Diagnosis was based on the criteria proposed by Nishimura *et al*. We collected clinicopathological data from medical records. Clinical course analysis was performed, with the diagnosis day defined as Day 1.

Results: A total of 10 patients were enrolled. All patients were Japanese, with a median follow-up period of 1,636 days (185 – 3,566). All patients underwent corticosteroid treatment, with 9 out of 10 receiving tocilizumab (TCZ) therapy. Rituximab and cyclosporin A were added in 4 and 1 patients, respectively. Recurrence occurred in 2 cases after reducing the TCZ dosage. By contrast, 2 patients maintained long-term remission after terminating all medications. One patient died due to severe pneumonia during immunosuppressive therapy.

Conclusions: The study revealed the potential for disease recurrence in TAFRO syndrome, particularly following TCZ dosage reduction. These findings suggest that the diathesis of TAFRO syndrome may persist long after the initial onset of the disease, and insufficient maintenance therapy could trigger a relapse. On the other hand, some patients maintained long-term remission even after stopping TCZ, indicating the possible varying degrees of IL-6 contribution to the etiology of TAFRO syndrome. Further studies are needed to enhance our understanding of this rare disease's pathogenesis and to optimize its stratified management.

TH-PO1045

The Crash-Lander Advanced Renal Disease Study (CLARD) Study

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Background: Advanced renal disease (ARD) patients can present very late which carries a high risk of morbidity and mortality. Patients with ARD need dialysis support and treatment to be planned ahead. The aim of this study is to review the characters, presentation, renal replacement therapy requirement and outcome of advanced renal diseases cases who required unplanned dialysis in our institution.

Methods: All adult patients who presented acutely to our secondary care Al Wakra Hospital, Hamad Medical Corporation Qatar with serum creatinine >1000mmol/L between 1/1/2016 to 31/12/2022 reviewed. Their initial presentation and need for urgent dialysis, comorbidities, clinical and biochemical parameters, duration of hospital stay have been studied. We intend to assess their outcome with regards to dialysis need, morbidity and mortality during admission and 90 days after presentation. Data collected from the hospital electronic health records.

Results: Out of initially screened 340 patients, 172 fulfilled the inclusion criteria.149 (86%) were males. The mean age was 47 years. 144 (83%) required dialysis during their admission. 12 (6.9%) patients improved without the need for dialysis and 16 (9.3%) patients refused dialysis. 64 (37.2%) patients were sick enough to require ICU/HDU admission. Most patients (93%) managed with hemodialysis. 94 (65%) required temporary vascular access, 38 (26%) Permcath, 9 (6%) peritoneal catheter and only 3 (2%) AVF. The main renal disease was Diabetes in 47 (27.3%) patients, unknown in 49 (28.5%) patients and Hypertension in 26 (15%) patients. 66 (38%) patients were diabetic. 68 (39%) patients had previous encounter with nephrologist sometime in the past. Out of the dialyzed patients, 122 (85%) required to be on long term dialysis. Length of hospital stay was 2 weeks, 1 week and 3 weeks for 60 (34%), 57 (33%) and 26 (15%) patients, respectively. Out of the172 patients, on day 90 from admission, 94 (55%) patients were alive, 3 (2%) expired and 75 (43%) lost follow up.

Conclusions: - Crash- lander ARD is not uncommon in day to day practice and carries high morbidity and represent a heavy burden on health system. - 85% of patients with presenting creatinine > 1000mmol/L will need long term renal replacement therapy. - Despite the severity of the presenting illness, there was low mortality rate for the patients on 90 days follow up.

TH-PO1046

Clinical Characteristics, Comorbidities, and Management of Patients with CKD: Insights from iCaReMe Global Registry

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Background: CKD is recognized as a global health concern with an increased prevalence, and attributable morbidity and mortality particularly in low- and middle-income countries where there is a need to better understand clinical characteristics, and risk factors for CKD within the Cardiovascular Renal Metabolic Continuum. iCaReMe

registry is an opportunity to fill this knowledge gap by providing a comprehensive global real-world data source on patients' characteristics, disease management and outcomes. The objective of our analysis is to describe clinical features, major risk factors, and management of CKD patients based on data from the iCaReMe Registry.

Methods: iCaReMe Global Registry (NCT03549754) is a multinational, prospective, observational study to assess the management and quality of care of patients with CKD, T2D, HTN, and/or HF. We present baseline cross-sectional descriptive analysis of the CKD cohort enrolled from February 2018 to December 2022.

Results: Overall, 2977 adults with CKD (mean age 60.6 years, 54.6% male) were enrolled in 21 countries* across the six WHO regions**. DKD and HKD were the most common etiologies. HTN, T2D, dyslipidemia, HF were present in 80.2%, 72.1%, 44.1% and 35.3% of patients respectively. Mean UACR was 556.7 mg/g available in 891 (30%) patients and mean eGFR was 46.1ml/min/1.73m^2 reported in 2492 (83.7%) patients. ACEi or ARB were prescribed to 37.8% of patients, and 20.6% received an SGLT2i.

Conclusions: Our results highlight opportunities to improve CKD management particularly in patients with CVD multimorbidity and advanced CKD by enhancing the use of albuminuria monitoring and the adoption of evidence-based treatments.

Funding: Commercial Support - AstraZeneca

Table: Clinicodemographic Characteristics and treatment

Characteristics	Overall (N=2977)	CKD+T2D (N=2052)	CKD+HTN (N=2018)
Age (years) Mean ± SD	60.6 ± 13.5 (N=2970)	62.8 ± 11.4 (N=2045)	61.9 ± 12.4 (N=2011)
Male n (%)	1624 (54.6)	1081 (52.7)	1105 (54.8)
BMI (kg/m^2) Mean ± SD	28.3 ± 5.7 (N=2262)	28.9 ± 5.8 (N=1636)	28.6 ± 5.6 (N=1545)
Systolic BP (mmHg) Mean ± SD	133.0 ± 20.5 (N=2693)	133.0 ± 20.2 (N=1930)	135.8 ± 20.6 (N=1865)
Diastolic BP (mmHg) Mean ± SD	77.9 ± 12.1 (N=2690)	76.7 ± 11.6 (N=1926)	78.7 ± 12.5 (N=1864)
HbA1c (%) Mean ± SD	7.5 ± 1.8 (N=1830)	7.8 ± 1.8 (N=1581)	7.4 ± 1.8 (N=1272)
Potassium (mEq/L) Mean ± SD	4.5 ± 0.6 (N=2184)	4.5 ± 0.6 (N=1462)	4.6 ± 0.6 (N=1600)
Sr Creatinine (mg/dL) Mean ± SD	2.1 ± 1.6 (N=2492)	1.8 ± 1.4 (N=1820)	2.2 ± 1.7 (N=1723)
eGFR (mL/min/1.73m^2) Mean ± SD	46.1 ± 26.2 (N=2492)	48.6 ± 25.3 (N=1820)	42.7 ± 24.5 (N=1723)
UACR (mg/g) Mean ± SD	556.7 ± 1169.9 (N=891)	406.3± 847.6 (N=669)	609.3 ± 121.1 (N=625)
Comorbidities			
Stroke n(%)	98/2043 (4.8)	77/1261 (6.1)	82/1530 (5.4)
CAD n(%)	538/2037 (26.4)	417/1255 (33.2)	421/1503 (28)
HF n(%)	729/2066(35.3)	523/1271(41.1)	510/1513(33.7)
Dyslipidemia n(%)	966/2189 (44.1)	823/1402(58.7)	820/1643 (50)
T2D n(%)	2052/2846(72.1)	2052(100)	1425/1942(73.4)
HTN n(%)	2018/2515(80.2)	1425/1663(85.7)	2018(100)
Etiology of CKD			
DKD n(%)	876/1963 (44.6)	858/1234 (69.5)	713/1506 (47.4)
HKD n(%)	676/1965 (34.4)	310/1234 (25.1)	597/1506 (39.6)
eGFR KDIGO Categories			
G1 (≥ 90) n(%)	159 (6.3)	116 (6.4)	79 (4.6)
G2 (60-<90) n(%)	545 (21.4)	447 (24.6)	311 (18)
G3a (45-<60) n(%)	471 (18.5)	374 (20.5)	320 (18.6)
G3b (30-<45) n(%)	565 (22.2)	427 (23.5)	415 (24.1)
G4 (15-<30) n(%)	458 (18)	305 (16.8)	370 (21.5)
G5 (<15) n(%)	345 (13.6)	151 (8.3)	228 (13.2)
UACR KDIGO Categories			
A1 (<30 mg/g) n(%)	218 (24.5)	159 (23.8)	149 (23.8)
A2 (30-300 mg/g) n(%)	380 (42.6)	312 (46.6)	251 (40.2)
A3 (>300 mg/g) n(%)	293 (32.9)	198 (29.6)	225 (36)
Treatment	**Monotherapy N=2977**	**Combination N=2977**	**Total N=2977**
ACEi/ARB n(%)	194 (6.5)	932 (31.3)	1126 (37.8)
SGLT2i n(%)	142 (4.8)	473 (15.9)	615 (20.7)

*List of countries: Argentina, Cuba, Egypt, Ethiopia, Georgia, Greece, Hong Kong, Indonesia, India, Jordan, Kenya, Lebanon, Malaysia, Morocco, Poland, South Africa, Thailand, The Philippines, Turkey, Ukraine, United Arab Emirates.
**WHO regions: Africa, Americas, South-East Asia, Eastern Mediterranean, Europe, Western Pacific.

ACEi: Angiotensin converting enzyme inhibitors; ARB: Angiotensin II receptor blockers; BMI: Body mass index; BP: Blood pressure; CAD: Coronary artery disease; CKD: Chronic kidney disease; CVD: Cardiovascular disease; DKD: diabetic kidney disease; eGFR = estimated glomerular filtration rate; HbA1c = Glycated hemoglobin; HF = Heart failure; HKD= Hypertensive kidney disease; HTN= Hypertension; KDIGO= Kidney disease: improving global outcomes; SD= Standard deviation; SGLT2i= Sodium glucose cotransporter-2 inhibitors; Sr= Serum; T2D= Type 2 diabetes; UACR= Urine Albumin-to-Creatinine Ratio; WHO= World health organization.

TH-PO1047

Clinical Characteristics and Treatment Pattern in Patients with CKD: Real-World Insights from iCaReMe Registry-Middle East and Africa (MEA) Cohort

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Background: The global burden of CKD has witnessed a nearly 30% rise in past 30 years with increasing prevalence of hypertension (HTN) and type 2 diabetes (T2D). The MEA region shares disproportionate burden of CKD with paucity of data on patients' characteristics and management. The iCaReMe Global Registry (NCT03549754 multinational, prospective, observational study) aims to generate real world data on characteristics, management patterns, and outcomes in patients with CKD, T2D, HTN, or HF.

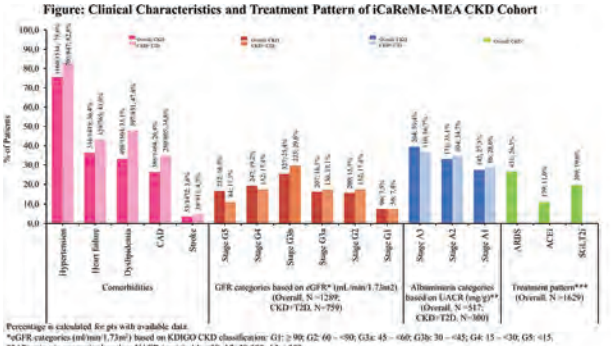
Methods: Baseline cross sectional descriptive analysis of clinicodemographic characteristics and treatment patterns in CKD patients enrolled from MEA region in the iCaReMe registry between February 2018 and December 2022.

Results: 1629 adults with CKD (mean±SD age; 59.7±14.5years, 56.1% male) were enrolled from 8 MEA countries (Egypt, Ethiopia, Jordan, Kenya, Lebanon, South Africa, Turkey, and United Arab Emirates). HTN (75.6%), T2D (54.4%) and HF (36.4%) were the most common comorbidities. UACR and eGFR were available in 31.7% and 79.1% of patients, respectively while 10.9% had both. The prevalence of KDIGO GFR G3-5 was 77.0% and albuminuria A2/A3 was 72.5%. The medications included ARB (26.5%) and ACEi (11.0%); about 19.6% were on SGLT2i. (Figure)

Conclusions: Most of the enrolled patients were at high/very high risk of CKD progression. Only one third had UACR testing. Less than one third received optimal guideline-directed medical therapy (GDMT). Our results highlight underutilization of UACR screening and suboptimal adherence to GDMT in patients with CKD in the MEA region.

Funding: Commercial Support - AstraZeneca

Figure: Clinical Characteristics and Treatment Pattern of iCaReMe-MEA CKD Cohort



Percentage is calculated for pts with available data.
*eGFR categories (ml/min/1.73m^2) based on KDIGO CKD classification: G1: ≥ 90; G2: 60 – <90; G3a: 45 – <60; G3b: 30 – <45; G4: 15 – <30; G5: <15.
**Albuminuria categories based on UACR (mg/g): A1: <30; A2: 30-300; A3: >300.
*** Drugs were given as monotherapy or in combination.
ACEi: angiotensin converting enzyme inhibitors; ARB: angiotensin II receptor blockers; CAD: coronary artery disease; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure, SGLT2i: sodium/glucose cotransporter-2 inhibitors; T2D: type 2 diabetes; UACR: urine albumin-to-creatinine ratio.

TH-PO1048

Impact of CKD on Patients' Health-Related Quality of Life: Results from PaCE-CKD, a Multinational Survey

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Background: Chronic kidney disease (CKD) has a substantial burden on patients' health-related quality of life (HRQoL). The aim of this study was to quantitatively determine the effect of CKD on patient HRQoL from early disease to kidney failure in a multinational setting.

Methods: A cross-sectional survey enrolled individuals with CKD in the US, UK, Germany and Mexico. HRQoL was assessed using the EQ-5D-5L instrument, scoring problems in five domains – anxiety/depression, mobility, pain, self-care, and usual activities. EQ-5D index scores were estimated by the inclusion of local tariffs. Scores were compared against a general population cohort, matched in sample size and key demographic characteristics (e.g. sex, age).

Results: Patients were enrolled from the US (n=199), UK (n=212), Germany (n=201) and Mexico (n=204). Inclusion criteria included patients with CKD stages 1-5 and those receiving dialysis. Of patients enrolled, a proportion were dialysis dependent (DD) in the US (32.2%), UK (54.8%), Germany (42.3%) and Mexico (56.9%). Across all countries, patients received haemodialysis more commonly than peritoneal dialysis and the majority were on treatment for less than five years. Patients with CKD had a 28% reduction in mean EQ-5D-5L scores than the general population in all settings. Patients in the UK experienced the lowest EQ-5D scores with a 32% reduction and mean index scores of 0.64 [0.27] versus 0.95 [0.08]. Patients in Mexico and the UK receiving dialysis had lower mean [SD] EQ-5D-5L scores than non-dialysis dependent (NDD) patients (0.66 [0.21] vs 0.74 [0.18]; 0.60 [0.25] vs 0.68 [0.27] respectively). There was no difference in HRQoL between DD and NDD patients in the US and Germany. Patients with CKD had problems in all five EQ-5D domains, with an 88% increase in reporting related to usual activities. Results for other countries will also be presented at Kidney Week.

Conclusions: This survey provides evidence across multiple countries on the HRQoL decrement associated with CKD. Evidence based policy interventions should be aimed towards slowing CKD progression to improve patient quality of life.

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TH-PO1049

PaCE-CKD: Health-Related Quality of Life of Caregivers of Individuals with CKD: Results from a Multinational Survey

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Background: Patients with chronic kidney disease (CKD) often rely on informal caregivers such as friends and relatives for support with their condition. The study aim was to measure the multinational impact of CKD on caregiver health-related quality of life (HRQoL) versus the general population.

Methods: A non-interventional survey enrolled unpaid caregivers from the UK, US, Mexico and Germany. A cohort representing the general population was also enrolled, matched for key demographics. HRQoL was measured by the EQ-5D-5L instrument which scored health across five domains: mobility, self-care, pain, usual activities, and anxiety/depression. Local tariffs were used to estimate ED-5D index scores. The CarerQol-7D instrument measured the impact of caregiving for patients with CKD and were compared against published estimates in other disease contexts.

Results: Surveys enrolled caregivers from the UK (n=116), US (n=113), Mexico (n=138) and Germany (n=99). Caregivers typically cared for a parent (36.5%) or spouse/partner (30.2%). Most caregivers cared for dialysis dependent patients (UK: 67.2%; US: 81.4%; Mexico: 65.2%; Germany: 64.6%). Support for patients typically comprised of taking medications (86.9%) and transport to/from hospital appointments (85.6%). In all countries, caregivers experienced worse health states and lower mean [SD] EQ-5D-5L scores, with caregivers in Mexico scoring 15% lower than the general population (0.79 [0.18] versus 0.94 [0.07]). Caregivers reported more problems across all EQ-5D-5L domains, most commonly in carrying out usual activities, and experiencing pain, anxiety, and depression. Caregivers in CKD had worse weighted average CarerQoL-7D scores (69.2) across all countries versus caregivers for patients with breast cancer (92.4) and hip fractures (83.7). Results for other countries will be also presented at Kidney Week.

Conclusions: The study explores an aspect of the broader societal burden of CKD, demonstrating a significant impact to caregivers' HRQoL. Strategies to address the growing burden of CKD should take its indirect effect on caregivers into consideration.

Funding: Commercial Support - AstraZeneca

TH-PO1050

Aversive Response Against High Salt Taste Is Disturbed in CKD Patients

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Background: Reducing salt intake is a vital lifestyle modification in the management of hypertension. Initiatives aimed at reducing salt intake are based on the premise that we prefer salt, but we exhibit an aversive response against high salt taste. It is postulated that salt intake behavior is influenced by the balance between attraction to low salt taste and aversion to high salt taste. However, aversion to high salt has not been quantitively investigated in both healthy individuals and CKD patients.

Methods: As a pilot study, we performed a salt taste test on 125 healthy volunteers, wherein we devised nine different concentrations of NaCl (ranging from 0.3% to 20%). The participants placed a filter paper containing each solution on their tongues, and we assessed the recognition threshold as a parameter of taste accuracy, and "minimum aversion level" for the concentration at which the initial dislike sensation emerged. Based on the results of the pilot study, a definition of "lack of salt taste aversion" was determined, and the same test was conducted on 70 CKD patients.

Results: In the pilot taste test conducted on 125 healthy subjects, the number of subjects exhibiting an aversive reaction increased with higher salt concentrations. The threshold for normal taste perception was arbitrarily defined as 10% NaCl, with approximately half (47.2%) of the healthy subjects displaying an aversive reaction. Among the 70 CKD patients, only 30% could recognize salt taste at 0.6% NaCl, which is considered normal, and 10% of CKD patients could not recognize salt taste even at the highest concentration of 20% NaCl, suggesting that taste perception is significantly impaired in CKD patients. Age and the use of dentures were factors associated with lower taste perception thresholds in patients. A high proportion (84%) of CKD patients exhibited decreased aversive reactions to high salt taste, with gender and denture usage being associated factors.

Conclusions: This study confirmed the anticipated aversive response to high salt taste in humans and demonstrated its attenuation in CKD patients, implying that CKD patients have reduced resistance to high salt intake. When implementing salt reduction strategies in clinical practice, it is crucial to pay attention to the decrease in aversive response to high salt taste as well as the increase in salt preference.

Funding: Commercial Support - House Foods Group Inc.

TH-PO1051

Concordance Between Patient-Reported Symptoms and Provider Documentation During Ambulatory Nephrology Encounters

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Background: Accurate assessment is the first step toward management of the symptom burden faced by many patients with CKD, but whether symptoms are being routinely discussed during ambulatory nephrology encounters is uncertain. We compared patient self-reporting of 3 common CKD symptoms with providers' documentation from the concomitant encounter note.

Methods: From 2016 to 2020, adult patients treated at a single, ambulatory, academic nephrology practice were asked to complete the Kidney Disease Quality of Life (KDQOL) instrument prior to visits. The KDQOL queries symptom severity over the prior 4 weeks, with Likert-scale response options ranging from 1 to 5. We restricted the present analysis to the symptoms of fatigue, pruritus, and dyspnea and defined a patient-reported symptom as a response of "moderately bothered (3)" or greater. Provider documented symptoms were determined by manual search of the visit note associated with each KDQOL response for the terms fatigue, pruritus, and dyspnea and their synonyms.

Results: Over 4 years, a total of 441 adult patients completed 556 KDQOL surveys. The average eGFR was 36 ± 18 mL/min/1.73 m^2, and the median time between KDQOL completion and the clinic visit was 4.2 hrs (IQR 0.1 – 125 hrs). Rates of patient-reported, moderate or greater fatigue, pruritus, and dyspnea were 28%, 18%, and 20%, respectively. Agreement between patient-reported and provider-documented symptoms was low (Figure 1). Cohen's kappa, a coefficient of agreement corrected for random chance, was 0.17 (standard error [SE] 0.04) for fatigue, 0.07 for pruritus (SE 0.03), and 0.29 (SE 0.04) for dyspnea, suggesting fair agreement at best.

Conclusions: Rates of physician documentation of fatigue, pruritus, and dyspnea are considerably lower than rates of patient-reporting of the same symptoms. Tools for standardizing symptom assessment in routine nephrology care are needed to help close this gap.

Funding: NIDDK Support

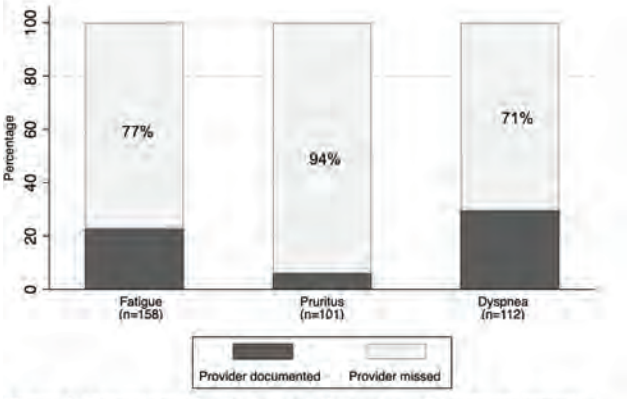

Figure 1. Percentage of patient-reported symptoms (≥moderate severity using the KDQOL) missed (in light grey) and identified (in dark grey) by physicians during the associated clinical encounter. This figure is restricted to instances in which the patient positively reported a symptom (numbers shown beneath each symptom)

TH-PO1052

Implications of the Acute and Chronic GFR Slopes for Time-to-Event End Points in Clinical Trials of CKD

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Background: In a companion abstract, we apply a multivariable model to relate treatment effects on the established clinical endpoint (CE) based primarily on serum creatinine (SCR) doubling to treatment effects on the acute (evaluated prior to 3 months) and chronic (evaluated after 3 months) GFR slopes across 66 randomized treatment comparisons (RTCs). Here, we apply the same model to alternative time-to-event (TTE) endpoints defined by progressively larger GFR declines, including the established CE as a special case.

Methods: For each RTC, we used mixed effects models and Cox regression, respectively, to estimate treatment effects on the acute and chronic GFR slopes, and on four TTE endpoints (Table heading, expressed as log hazard ratios). We then used multivariable Bayesian meta-regressions to relate the treatment effects on each TTE endpoint jointly to the treatment effects on the acute and chronic slopes.

Results: Treatment effects on the acute and chronic slopes jointly predicted treatment effects on each TTE endpoint with high accuracy (all trial-level R^2s ≥ 0.91). After accounting for the treatment effect on the chronic slope, a 1 ml/min/1.73m^2 greater negative acute effect led to a positive shift in the HR (against the treatment) by 15.4%, 11.4%, and 5.7%, respectively, for TTE endpoints based on 30% GFR decline, SCR doubling, and KFRT and GFR ≤ 15 ml/min/1.73m^2, showing that the role of the acute slope substantially attenuated for TTE endpoints based on larger GFR decline.

Conclusions: Acute effects have a small but measurable impact on KFRT or GFR decline to less than 15 ml/min/1.73m^2 after accounting for the chronic slope. However, relative to their small impact on progression to kidney failure, the role of the acute effect is moderately overstated by the established CE based on SCR doubling, and more severely by TTE endpoints based on 30% or 40% GFR decline.

Funding: Private Foundation Support

Meta-Regressions Relating Treatment Effects on Time-to-Event Endpoints to Treatment Effects on the Acute and Chronic Slopes

Variable	30% GFR decline, GFR≤15, KFRT	40% GFR decline, GFR≤15, KFRT	SCR Doubling, GFR≤15, KFRT	KFRT, GFR ≤15
Summary Measure	Median (95% Bayesian CI)	Median (95% Bayesian CI)	Median (95% Bayesian CI)	Median (95% Bayesian CI)
Intercept	-0.03 (-0.08, 0.01)	-0.04 (-0.09, 0.01)	-0.03 (-0.10, 0.03)	-0.09 (-0.18, -0.02)
(% change in HR for 1 ml/min per 1.73m2 greater negative acute effect)	15.3% (12.9%, 17.9%)	13.4% (10.8%, 16.1)	11.3% (8.0%, 14.9%)	5.6% (1.2%, 10.2%)
% change in HR for 0.75 ml/min per 1.73m2 per year greater treatment effect on chronic slope	-19.5% (-23.1%, -15.9%)	-22.6% (-26.6%, -18.8)	-22.8% (-27.6%,-18.0%)	-14.2% (-20.0%, -7.1%)
Trial-level R2	0.93 (0.84, 0.98)	0.94 (0.85, 0.99)	0.95 (0.78, 1.00)	0.91 (0.49, 0.99)

KFRT: Kidney Failure with Renal Replacement Therapy

TH-PO1053

The Clinical Implications of Acute and Chronic GFR Slope in Clinical Trials of CKD

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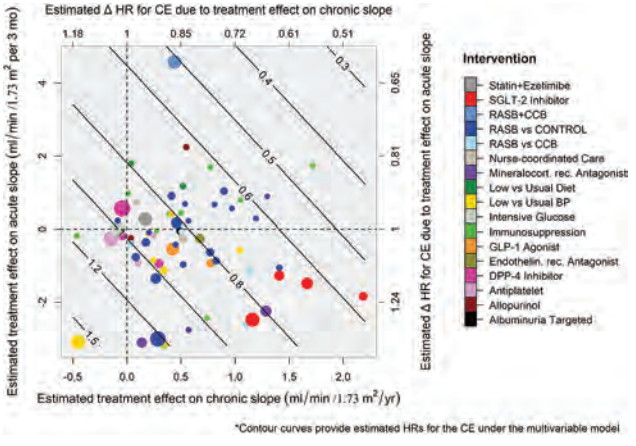
Background: Randomized trials for CKD traditionally use the established clinical endpoint (CE) of kidney failure or doubling of serum creatinine as the primary outcome. These are late events in CKD, thus requiring trials with long follow-up or restriction to patients with rapidly progressive or advanced disease. GFR slope has been proposed to circumvent these limitations, but acute effects often complicate interpretation. We use a multivariable model to resolve ambiguities from acute effects.

Methods: Using individual patient data from 66 randomized treatment comparisons (RTCs), we used mixed effects models to estimate treatment effects on the acute (baseline to 3 months) and chronic GFR slopes (after 3 months), and Cox regression to estimate treatment effects on the CE (hazard ratios (HRs)). We used a multivariable Bayesian meta-regression to relate the treatment effects on the CE jointly to the treatment effects on the acute and chronic slopes.

Results: Across the 66 RTCs, the multivariable model showed that optimally weighting the acute and chronic slopes accurately predicted the treatment effects on the CE, with a trial-level R^2 (95% Bayesian credible interval) of 0.95 (0.78,1.00). For a fixed treatment effect on the chronic slope, each 1 ml/min/1.73m^2 greater acute GFR decline for the treatment vs. the control *increased* the HR for the CE by 11.3%, in the direction against the treatment. For a fixed acute effect, each 0.75 ml/min/1.73m^2/year greater treatment effect on the chronic slope *reduced* the HR for the CE by 22.8%, in favor of the treatment. The Figure shows the model's decomposition of the estimated treatment effects on the CE into separate components due to the acute and chronic slopes for each RTC.

Conclusions: Treatment effects on both the acute and chronic slopes are strong, independent determinants of the treatment effect on the CE. Optimal weighting of the acute and chronic slopes accurately predicts treatment effects on the CE.

Funding: Private Foundation Support



TH-PO1054

Association Between Initial Dip and Long-Term Prognosis After Dapagliflozin Administration in Patients with CKD

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Background: Renoprotective effects of dapagliflozin (sodium glucose transporter 2 inhibitor) have been reported in several randomized controlled trials. The main mechanism considered is correction of hyperfiltration, which can be observed as an acute decline in eGFR referred to as "initial dip". While association between initial dip and long-term renal prognosis have been reported, no consistent conclusions have been reached. We aimed to investigate this relationship in real-world clinical practice.

Methods: We performed a retrospective observational cohort study of patients at Yokohama City University Medical Center in Japan. Patients administered to dapagliflozin between May 2014 thru December 2022 were included. Excluding those with eGFR over 90 or less than 15mL/min/1.73m^2 at baseline, history of kidney transplant, dialysis, or cancer, and those with dosage changes of dapagliflozin, 146 patients had complete data at baseline, 4 weeks, and 12 months, and were applicable for this study. We defined initial dip as eGFR decline from baseline to 4 weeks. Chronic change, which reflect long-term renal prognosis, was defined as eGFR decline from 4 weeks to 12 months. The association between initial dip and chronic change was examined using linear regression models. Also, eGFR changes between a year before and after starting dapagliflozin were compared for those whose data were available. (n=74)

Results: Absolute eGFR changes before and after starting dapagliflozin were -4.8±9.6 and -1.5±8.3mL min/1.73m^2 per year, respectively. ($p<0.05$) Long term renoprotective effect of dapagliflozin was observed regardless of initial dip. Furthermore, Pearson's correlation coefficient revealed that the degree of initial dip and chronic change were inversely correlated ($r=-0.37$, $p<0.001$). Multivariate regression analysis demonstrated initial dip was an independent determinant factor for chronic change. ($p<0.001$)

Conclusions: The real-world clinical data showed that the greater the initial dip, significantly smaller the subsequent decline in eGFR. Renoprotective effect of dapagliflozin was observed regardless of initial dip.

TH-PO1055

Caffeine Effects on eGFR Dip in Patients Who Started SGLT2 Inhibitors

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i) have widespread effects including antihyperglycemia, renoprotection, and cardioprotection. Renoprotection is thought to be mainly mediated by a reduction in glomerular filtration rate (GFR) via tubuloglomerular feedback (TGF), which is referred to as the GFR "dip". Adenosine plays an important role in signal transmission in the TGF mechanism and caffeine is a nonselective adenosine receptor antagonist. We hypothesized that patients with high caffeine intake have reduced eGFR dip after starting SGLT2i compared to patients with no or small caffeine intake.

Methods: This is a retrospective cohort study conducted at Saint Louis University. Caffeine consumption was collected via survey. Retrospective chart review was performed to trend creatinine before and 1-2 months after the initiation of SGLT2i. Inclusion criteria included adult patients receiving SGLT2i regardless of indication (diabetes mellitus, heart failure, or chronic kidney disease) and eGFR ≥30 ml/min/1.73 m^2 at the time of initiation. Student's t test was used to analyze differences of eGFR change (% change from the baseline) between patients with high caffeine intake and low caffeine intake. Pearson's correlation coefficient was used to analyze correlation between caffeine intake and eGFR change.

Results: The survey was collected from 36 patients (N=13 on Dapagliflozin, N=22 on Empagliflozin, and N=1 on Ertugliflozin). The mean age of the study cohort was 62.9±11.1 years old and 58.3% were female. The median eGFR at SGLT2i initiation was 50 ml/min/1.73 m^2. Top quartile caffeine takers (≥400 mg/day, N=9) had significantly lower % eGFR dip compared to the low caffeine takers (<400mg/day, N=27); 0.46±12.51 % vs 11.83±14.45%, respectively ($p<0.05$). In a subgroup analysis of those who were not on loop diuretics, which could affect TGF, % eGFR dip was inversely correlated with the caffeine intake (N=24, $r=-0.55$, $p<0.01$).

Conclusions: Our study shows that caffeine consumed at high levels (above 400mg daily) can mitigate the eGFR dip after SGLT2i initiation. Further study is needed to assess its long-term effects on SGLT2i's renoprotective property.

Funding: Private Foundation Support

TH-PO1056

Clinical Characteristics and Predictors of Glomerular Filtration Rate Decline in Patients with CKD of Unknown Etiology (CKDu) in Agricultural Communities of Odisha, a CKDu Hotspot

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Background: Chronic Kidney Disease of Unknown Etiology (CKDu) is characterized by the absence of traditional risk factors for CKD such as diabetes mellitus hypertension, and glomerulonephritis. Odisha in India has been identified as a potential 'hotspot' for CKDu.

Methods: Patients aged 18–60 years who met clinical criteria for CKDu from 1st April 2021 to 31st April 2023 were enrolled in the study. A kidney biopsy was performed according to the feasibility. The study's primary objective is to describe the clinical characteristics and predictors for glomerular filtration rate (eGFR) decline.

Results: A total of 120 patients were enrolled in the study. The mean age of participants was 39.78 ± 8.85 years, with 85 % males. About 96.3% of cases belonged to rural areas, 90 % belonged to lower socioeconomic classes, and only 3 % had a family history of diseases. 75.4 % were farmers, exposure to agrochemicals was reported in 20.4% of cases; and 25.7 % of patients had no formal education. 40% and 25% of the participants were of CKD stage 3 and stage 4 respectively. The mean hemoglobulin level and uric acid levels were 10.3/ dl and 5.9 mg/ dl respectively. A kidney biopsy was performed on 20 patients. Histopathology was predominantly interstitial fibrosis with mononuclear infiltration, tubular atrophy, and global glomerulosclerosis. After adjustments for confounding factors, predictors of GFR decline were found to be baseline GFR, baseline serum albumin, low haemoglobin, and male sex.

Conclusions: There is a need for a multipronged approach to address the CKDu epidemic, particularly in CKDu hotspots. The need to take steps to increase awareness, prevention, appropriate screening, and surveillance is imperative.

TH-PO1057

Associations Between Albuminuria and Clinical Outcomes in Patients with CKD with and Without Diabetes: New Insights from DAPA-CKD

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Background: Albuminuria is a strong determinant of kidney and cardiovascular (CV) risk in patients with chronic kidney disease (CKD) with and without type 2 diabetes (T2D). Early albuminuria reduction may be an indicator of decreased risk. In the DAPA-CKD trial, dapagliflozin reduced the risk of kidney and CV events in patients with CKD with similar effects in those with and without T2D. We examined risk associations between baseline and early changes in albuminuria and kidney outcomes in patients with CKD with and without T2D.

Methods: In DAPA-CKD, 4304 patients with and without T2D with urinary albumin-to-creatinine ratio (UACR) 200-5000 mg/g and eGFR of 25–75 mL/min/1.73m² were randomized to receive dapagliflozin 10 mg or placebo daily, on top of standard of care, and followed for a median 2.4 years. We assessed associations among baseline UACR, early change in UACR (baseline to Month 4), and the primary outcome (≥50% eGFR decline, end-stage kidney disease, death from a kidney or CV cause) using multivariable adjusted Cox regression analyses.

Results: Every doubling of baseline UACR was associated with a near doubling of risk: hazard ratio (HR) 1.89 (95% confidence interval [CI] 1.71–2.08) in patients with T2D and 1.84 (95% CI 1.54–2.20) in those without T2D. Dapagliflozin reduced UACR (placebo-adjusted) from baseline to Month 4 by 35.7% (95% CI 29.0–42.5) in participants with T2D and 19.7% (95% CI 10.6–28.8) in those without T2D, with a large between-individual variation in both treatment groups. The HR for every 50% decline in UACR from baseline to Month 4 was 0.86 (95% CI 0.79–0.93) and 0.70 (95% CI: 0.59–0.83) in participants with and without T2D, respectively.

Conclusions: In patients with CKD with and without T2D, higher baseline albuminuria was associated with a higher risk of progressive kidney disease or cardiovascular death, and early albuminuria reduction was associated with a decreased risk. Because dapagliflozin reduced clinical outcomes in patients with and without T2D but reduced albuminuria to a larger degree in those with T2D, these findings suggest that the clinical benefits gained via dapagliflozin's albuminuria-reducing effects are more potent among patients with T2D.

Funding: Commercial Support - AstraZeneca

TH-PO1058

Mediators of the Kidney Protective Effects of Dapagliflozin in Patients with CKD with or Without Type 2 Diabetes

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Background: The DAPA-CKD trial demonstrated that dapagliflozin attenuates progression of chronic kidney disease (CKD) in patients with and without type 2 diabetes. This post-hoc analysis assessed possible mediators of the observed kidney protective effect.

Methods: In DAPA-CKD, 4304 patients with an estimated glomerular filtration rate (eGFR) 25–75 mL/min/1.73m² and urine albumin-to-creatinine ratio (UACR) 200–5000 mg/g were randomized to receive dapagliflozin 10 mg or placebo. The primary outcome was a composite of sustained ≥50% eGFR decline, end-stage kidney disease, or kidney or cardiovascular death. We considered biomarkers that were significantly affected by dapagliflozin versus placebo over time, as assessed using mixed effect model for repeated measures: UACR, hematocrit, HbA1c, blood pressure (systolic [SBP] and diastolic [DBP]), serum sodium and potassium, and body weight. We calculated the proportion of the effect of dapagliflozin explained by the change in each biomarker by fitting a multivariable-adjusted, time-dependent, Cox model, adjusted for baseline sex, age, body mass index, eGFR, SBP, and UACR. We estimated confidence intervals using 1000-iterations bootstrap. Analyses were repeated by type 2 diabetes status.

Results: Compared with placebo, dapagliflozin reduced UACR (29.3% [95%CI: 25.2–33.1]), SBP (2.9mmHg [2.3–3.6]), DBP (1.0mmHg [0.6–1.4]), HbA1c (0.08% [0.03–0.14]), serum potassium (0.035mEq/L [0.012–0.057]) and body weight (0.85kg [0.61–1.08]), and increased hematocrit (2.3% [2.1–2.5]) and serum sodium (0.14mEq/L [0.02–0.26]). The effect of dapagliflozin on the primary outcome was explained by changes in hematocrit (35.5% [95%CI 24.3–69.0]), UACR (35.4% [23.0–52.8]), and SBP (4.9% [1.3–9.1]), but not through the other tested biomarkers. The proportion of dapagliflozin's effect explained by change in hematocrit was 31.2% (20.0–70.3) in participants with type 2 diabetes, and 32.4% (14.3–76.5) in those without type 2 diabetes. The respective proportions explained by the change in UACR were 41.7% (26.1–75.9) and 16.6% (3.2–34.4).

Conclusions: The kidney protective effect of dapagliflozin in patients with CKD is associated with its effects on albuminuria and hematocrit.

Funding: Commercial Support - AstraZeneca

TH-PO1059

Inflammatory Cytokines and Adipokines in Obese Patients with and Without CKD

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Background: Global epidemic of obesity & metabolic disorders are fuelling increasing cases of CKD worldwide. Besides having higher incidence of DM & hypertension, obesity is independent risk factor for CKD. Mechanisms involved are poorly studied, though obesity related inflammation mediated by shift in adipokine and cytokine production towards pro-inflammatory state is implicated. We in this case control study looked at important pro-inflammatory mediators (leptin, IL-6, TNF-α) and anti-inflammatory mediators (adiponectin, IL-10) in obese with & without CKD, non-obese CKD & healthy controls.

Methods: 50 consenting subjects in each group were studied. Besides detailed history, co-morbidity charting, BMI calculation; serum levels of HsCRP, adipokines (leptin & adiponectin) & cytokines (IL-6, TNF-α & IL-10) were assessed using commercially available ELISA kits.

Results: Table shows demographic, clinical & study parameters of each group. Patient groups had similar representation of DM & were slightly older than controls. Obese subjects with & without CKD had higher HsCRP, leptin & IL6 than controls & CKD patients, with obese patients with CKD showing maximum aberrations. Adiponectin concentration was higher in patients with obesity alone but suppressed in patients with obesity & CKD.

Conclusions: Inflammation & pro-inflammatory *milieu* as evidenced by high levels of Hs-CRP, IL-6 & leptin and low levels of adiponectin might be important drivers for obesity related complications like CKD. Larger, prospective studies are required to confirm the same.

Funding: Government Support - Non-U.S.

Demographic, clinical & study parameters of each group

Parameter	Control	Obese without CKD	Obese with CKD	Non-obese CKD
Age (yr)	45.7±13.7	51.1±12.7*	50.4±10.8*	49.7±12.2*
Male (%)	68	70	68	72
DM (%)	0	30*	32*	28*
BMI	22.4±2.1	33.4±5.7*$	32.8±6.2*$	21.8±1.8*#
eGFR (ml/min)	81.5±26.4	84.2±20.8	41.2±18.2*^	38.9±20.2*^
HsCRP (mg/L)	1.5±1.4	4.2±0.4*#$	8.7±2.1*^$	2.5±1.1*^#
Leptin (ng/ml)	2.2±0.6	4.4±2.7*#$	8.8±2.9*^$	1.9±0.8*#
Adiponectin (pg/ml)	5.1±1.1	35.3±29.1*#$	3.4±0.7*^	3.9±0.6*^
IL-6 (pg/ml)	44.9±16.3	503.4±153.8*#$	894.9±370.1*^$	254.3±78.2*^#
TNF-α (pg/ml)	99.1±12.6	113.4±16.1#	136.7±21.2*^$	101.3±19.1#
IL-10 (pg/ml)	82.3±35.9	128.9±36.9*#	316.3±126.2*^#	115.1±18.6*#

*p<0.05 vs group 1, ^ p<0.05 vs group 2, # p<0.05 vs group 3, $ p<0.05 vs group 4

TH-PO1060

Association of N-Terminal Pro-Brain Natriuretic Peptide (NT-proBNP) with the Progression of CKD in Indian CKD Cohort

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Background: It has been shown that elevated NT-proBNP levels are associated with the progression of kidney disease and may serve as a prognostic marker. This study aims to determine the association between baseline levels of NT-proBNP with renal and cardiovascular outcomes in CKD patients in the Indian Chronic Kidney Disease (ICKD) Study.

Methods: The study encompassed 783 individuals diagnosed with mild to moderate CKD, enrolled in ICKD study, followed up for mean duration of 4.89 years. Unadjusted and adjusted Cox proportional hazard models were used to study the association of time to occurrence of events: Major adverse kidney events (MAKE), end stage kidney disease (ESRD), ≥50% decline in eGFR, all-cause mortality, and cardiovascular (CVD) mortality. In assessing CVD mortality as a primary focus, deaths resulting from renal causes were considered as competing events. Similarly, when examining 50% eGFR decline, ESRD, and MAKE as key outcomes, non-renal deaths were treated as competing events.

Results: In the study cohort, mean age of patients was 48 years, 35% were women and the mean eGFR at baseline was 46 mL/min/1.73m^2. 249 (32%) developed MAKE and 197 (25%) progressed to ESKD. Median (IQR) level of NT-proBNP at the baseline was 4.65 (1.63, 16.36) ng/ml. Similar association was found for unadjusted and adjusted Cox proportional hazard models suggesting that increase in the levels of NT-proBNP is associated with higher risk of MAKE (1.16; 1.01-1.34) and ESKD (1.19; 1.01-1.41) (Table 1). However, no significant association was found between the levels of NT-proBNP with respect to death and 50% eGFR decline.

Conclusions: This study establishes the evidence that higher levels of NT-proBNP at baseline is a risk factor for CKD progression.

Funding: Government Support - Non-U.S.

Association of NT-proBNP with Outcomes CKD subjects

	Model 1 Sub-hazard ratio (95%CI)	Model 2 Sub-hazard ratio (95%CI)	Model 3 Sub-hazard ratio (95%CI)
Major adverse kidney events (MAKE)	1.16 (1.02, 1.32) P = 0.02	1.17 (1.03, 1.33) P = 0.02	1.16 (1.01, 1.34) P = 0.04
50% eGFR decline	1.15 (0.99, 1.35) P = 0.07	1.16 (0.99, 1.35) P = 0.06	1.14 (0.97, 1.35) P = 0.11
End stage kidney disease (ESKD)	1.18 (1.02, 1.37) P = 0.03	1.19 (1.03, 1.38) P = 0.02	1.19 (1.01, 1.41) P = 0.04
All-cause mortality*	1.11 (0.89, 1.38) P = 0.37	1.09 (0.88, 1.36) P = 0.43	1.09 (0.86, 1.38) P = 0.47
CVD mortality	1.20 (0.84, 1.73) P = 0.32	1.19 (0.83, 1.73) P = 0.35	1.15 (0.77, 1.72) P = 0.48

Model 1 was unadjusted. Model 2 was adjusted for age and gender. Model 3 was adjusted for variables in model 2 + systolic BP, tobacco consumption status, estimated glomerular filtration and urine albumin-to-creatinine ratio.

*Hazard ratio is reported.

TH-PO1061

Intact Fibroblast Growth Factor 23 and Progression of CKD

Ashok K. Yadav,[1] Monica Kundu,[2] Arpita Ghosh,[2] Vivek Kumar,[1] Vivekanand Jha.[2] Indian Chronic Kidney Disease Study Group. *[1]Post Graduate Institute of Medical Education and Research, Chandigarh, India; [2]The George Institute for Global Health India, New Delhi, India.*

Background: Elevated levels of fibroblast growth factor 23 (FGF23) are associated with mortality in patients with end-stage kidney disease. Still, its relationship with adverse kidney outcomes in the early stages of chronic kidney disease is unknown. We investigated the association of intact FGF23 with the progression of CKD in the Indian Chronic Kidney Disease (ICKD) Study.

Methods: The study includes a subset of adult participants with mild to moderate CKD enrolled in ICKD study. Linear regression model was used to study the association between baselines levels of intact FGF23 and estimated glomerular filtration (eGFR) decline in the study period, adjusting for other covariates including age, gender, baseline eGFR, blood pressure, tobacco consumption and urine albumin-to-creatinine ratio. Further, to assess the association between FGF23 levels with respect to time-to-event adverse outcomes of interest, namely, major adverse kidney events (MAKE), end stage kidney disease (ESRD), ≥50% decline in eGFR, all-cause mortality, and cardiovascular (CVD) mortality, Cox proportional hazard models were used. Competing risk analysis was taken into account while fitting Cox models.

Results: A total of 605 individuals with mild to moderate CKD were included in this analysis. Mean age of the CKD patients of age was 48 years, and baseline mean eGFR was 45.8 mL/min/1.73m^2. Mean (SD) follow up duration of the study was 5.33 (2.37) years with median (IQR) baseline level of intact FGF23 as 111 (78, 163) pg/ml. Baseline levels of intact FGF23 were significantly and positively associated with eGFR decline in the study period (p=0.02). Unadjusted and adjusted Cox regression models indicated that higher levels of FGF 23 were significantly associated with greater risk of MAKE (1.34; 1.15-1.56), 50% eGFR decline (1.25; 1.06 - 1.49) and ESKD (1.35; 1.13-1.62) (table 1).

Conclusions: Among individuals with mild to moderate CKD, baseline levels of intact FGF-23 are independently associated with the adverse kidney outcomes of CKD.

Funding: Government Support - Non-U.S.

Table 1: Association of intact FGF23 with Outcomes in CKD patients

	Model 1 Sub-hazard ratio (95%CI)	Model 2 Sub-hazard ratio (95%CI)	Model 3 Sub-hazard ratio (95%CI)
Major adverse kidney events (MAKE)	1.39 (1.19, 1.61) P<0.01	1.40 (1.20, 1.63) P <0.01	1.34 (1.15, 1.56) P <0.01
50% eGFR decline	1.24 (1.05, 1.45) P = 0.01	1.25 (1.06, 1.47) P 0.01	1.25 (1.06, 1.49) P = 0.01
End stage kidney disease (ESKD)	1.41 (1.19, 1.68) P<0.01	1.43 (1.20, 1.70) P<0.01	1.35 (1.13, 1.62) P<0.01
All-cause mortality*	1.28 (0.99, 1.65) P = 0.06	1.25 (0.96, 1.62) P = 0.10	1.15 (0.88, 1.48) P = 0.30
CVD mortality	0.82 (0.65, 1.04) P = 0.11	0.83 (0.65, 1.05) P = 0.11	0.85 (0.69, 1.04) P = 0.11
Model 1 was unadjusted. Model 2 was adjusted for age and gender. Model 3 was adjusted for variables in model 2 + systolic BP, tobacco consumption status, estimated glomerular filtration rate and urine albumin-to-creatinine ratio. *Hazard ratio is reported			

TH-PO1062

Association Between Plasma Uric Acid Levels and Mortality and Cardiovascular Outcomes According to Kidney Function

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Background: Plasma uric acid levels rise with worsening renal function, but it is not known whether uric acid levels affect the risk of death and cardiovascular disease according to renal function.

Methods: We conducted a multicenter retrospective observational cohort study based on data from the Observational Medical Outcomes Partnership Common Data Model. Adult non-dialysis patients with at least one measurement of serum uric acid levels during study period were screened, and the participants were classified according to their estimated glomerular filtration rate (eGFR); eGFR >= 60 ml/min/1.73m2 (high eGFR) and eGFR < 60 ml/min/1.73m2 (low eGFR). Primary outcome of this study was all-cause mortality. And secondary outcomes were the development of myocardial infarction requiring coronary intervention and heart failure.

Results: We included 240197, 84858, and 59044 participants from three centers. In multivariable Cox regression analysis, uric acid level showed J-shaped association with all-cause mortality risk in both high and low eGFR groups. In pooled analysis for three centers, pooled hazard ratios for mortality in uric acid levels > 10 mg/dL compared to uric acid levels 6-7mg/dL were 1.8 (1.36-2.39) and 2.0 (1.51-2.65) in low and high eGFR groups, respectively. The risk for myocardial infarction was neither associated with uric acid levels in low and high eGFR groups from all three centers. The risk for heart failure showed linear association with uric acids levels, especially in high eGFR groups, and this finding was consistent in three centers.

Conclusions: Plasma uric acid levels showed J-shaped association with mortality regardless of eGFR status, while it showed linear association with heart failure in high eGFR participants

TH-PO1063

Elevated Serum and Urinary Secreted Protein Acidic and Rich in Cysteine (SPARC) Levels Are Novel Biomarkers of Kidney Fibrosis Severity

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Background: Interstitial fibrosis is the main determinant of the progression of chronic kidney disease (CKD), and noninvasive identification of interstitial fibrosis is a major challenge. We aimed to explore the diagnostic value of serum and urinary secreted protein acidic and rich in cysteine (SPARC) in kidney fibrosis.

Methods: 674 renal biopsy CKD patients in 1 clinical center serving as the training cohort (n = 322) and in 3 clinical centers serving as the validation cohort (n = 352). The serum and urinary SPARC levels were measured at the time of kidney biopsy. *In vivo* and *in vitro* kidney fibrosis models were also applied to confirm the role of SPARC.

Results: Increased SPARC expression was found in kidney fibrosis tissues. Higher serum and urinary SPARC levels were detected in the kidney fibrosis group than nonkidney fibrosis group. The higher levels of serum SPARC were associated with increasing severity of kidney fibrosis. Moreover, the serum SPARC level had a higher area under the receiver operating characteristic curve (AUC-ROC) (AUC 0.86) than urinary SPARC and the estimated glomerular filtration rate (eGFR). The combination of serum

SPARC, urinary SPARC and eGFR could increase the AUC-ROC for kidney fibrosis from 0.86 to 0.90. The diagnostic performance of serum or urinary SPARC were consistent in the validation cohort. *In vivo* and *in vitro* kidney fibrosis models also confirmed the upregulation of SPARC expression.

Conclusions: Serum and urinary SPARC levels may be potential biomarkers for kidney fibrosis, which may be helpful for the noninvasive diagnosis of kidney fibrosis.

Funding: Private Foundation Support

TH-PO1064

Serum Myostatin Is Independently Associated with Endothelial Dysfunction in Non-Dialysis CKD Stages 3 to 5

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Background: Myostatin expressed by skeletal muscle cells where it limits muscle growth and promotes protein breakdown and may have a role in obesity, insulin resistance, cardiovascular disease. However, its relationship with endothelial function in patients with chronic kidney disease (CKD) remains inconclusive. This study aimed to investigate the association between serum myostatin levels and endothelial function in patients with stages 3–5 CKD.

Methods: Fasting blood samples were obtained from 136 CKD patients. Serum myostatin levels were determined using the enzyme-linked immunosorbent assay. The endothelial function, demonstrated as a vascular reactivity index (VRI), was measured noninvasively through digital thermal monitoring test. The serum myostatin levels were determined using commercially available enzyme-linked immunosorbent assays. In this study, VRI < 1.0 was used as the poor vascular reactivity, 1.0 ≤ VRI < 2.0 was used as the intermediate vascular reactivity, and VRI ≥ 2.0 was used as the good vascular reactivity.

Results: 25 CKD patients (18.4%) were categorized as poor vascular reactivity (VRI < 1.0), 63 CKD patients (46.3%) were categorized as intermediate vascular reactivity (1.0 ≤ VRI < 2.0), and 48 CKD patients (35.3%) had good vascular reactivity. Older age (p = 0.026), higher serum blood urea nitrogen (p = 0.020), creatinine (p = 0.021), urinary protein-to-creatinine ratio (UPCR, p = 0.015), and higher serum myostatin level was associated, while lower estimated glomerular filtration rate (eGFR) was associated with poor vascular reactivity. After multivariable forward stepwise linear regression analysis noted that older age (β = –0.331, adjusted R^2 change = 0.081, p < 0.001), serum creatinine (β = –0.273, adjusted R^2 change = 0.070, p = 0.001) and log-transformed myostatin level (β = –0.256, adjusted R^2 change = 0.057, p = 0.002) were significantly and independently negatively associated with VRI values in patients with CKD.

Conclusions: Myostatin together with old age and serum creatinine is negatively associated with VRI values and is a potential endothelial function modulator and a valuable biomarker of endothelial dysfunction in patients with CKD.

TH-PO1065

Lower Estimated Glomerular Filtration Rate Is Associated with Cognitive Decline and Longitudinal Structural Brain Changes over Six Years

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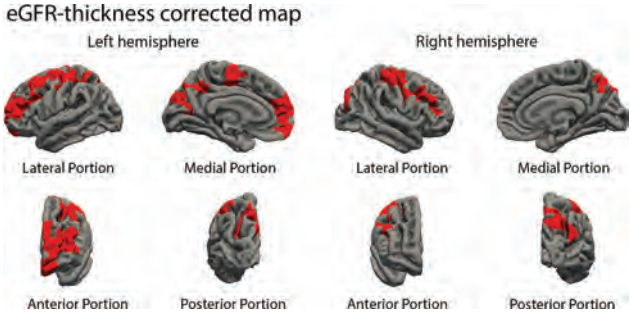
Background: Chronic kidney disease (CKD) is characterized by albuminuria and/or reduced estimated glomerular filtration rate (eGFR). CKD is linked to cognitive deficits and structural alterations, such as brain atrophy. The mechanisms connecting decreased kidney function, cognitive impairment, and brain function are not yet fully understood. Here, we examined the correlation between eGFR, cognition, and longitudinal brain structure.

Methods: We analyzed a population-based sample of 15,897 participants (53.9 ± 7.5 years old, 49% women) from the CARTaGene cohort in Quebec, Canada. We conducted multivariate linear regressions to explore the relationship between baseline eGFR and cognitive performance. Vertex-based cortical surface analysis was done on the T1-weighted brain MRI scans acquired in 1367 participants six years after baseline to examine whether cortical thickness associated with baseline eGFR adjusting for age, sex, body mass index, vascular risk factors, and white matter lesion volume. Gene set enrichment analysis was done to identify the genetic features of regions where eGFR associated with thickness.

Results: Cognitive performance declined with decreasing eGFR after adjusting for age, sex, income, education, smoking, alcohol intake, vascular risk factors, body mass index, and psychoactive medication use (P<0.001). Lower eGFR associated with cortical thinning in frontal and posterior regions and with increases in the temporal and cingulate areas (Figure 1). Brain regions exhibiting lower eGFR-associated thinning were enriched for mitochondrial gene expression, whereas regions with increased thickness were enriched for genes involved in protein-containing complex remodeling, with apolipoprotein E and angiotensinogen being key elements.

Conclusions: Baseline eGFR is associated with cognition and longitudinal brain structural changes in regions with specific gene expression characteristics.

Funding: Government Support - Non-U.S.



Brain maps showing the regions where lower eGFR was significantly associated with cortical thinning.

TH-PO1066

Kynurenine Metabolism and Neurocognition in CKD: CRIC Study

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Background: Kynurenine metabolites and chronic kidney disease (CKD) are independently linked with neurocognitive dysfunction. We examined the associations between the Tryptophan (TRP) and Kynurenine (KYN) metabolites with neuro-cognitive function in CKD patient in the Chronic Renal Insufficiency Cohort (CRIC).

Methods: CRIC participants with data on TRP and KYN metabolites and cognitive tests were included in the analysis. TRP and KYN and its metabolites (kynurenic acid (KYNA) and Quinolinic acid (QYN)) were measured at baseline using mass-spectrometry. The neurocognitive tests included Modified Mini Mental State Examination (MMSE), Trail Tests A and B, Buschke Selective Reminding, Category fluency and Boston Naming. Cognitive tests were measured at baseline and then every 2 years thereafter for 10 years. Linear regression and linear mixed models were used for analysis. Model was adjusted for demographics, co-morbidities and eGFR.

Results: Among 240 participants, mean age was 62±8 yrs and 66% had CKD stage 3. TRP levels were lower (p<0.001) whereas KYN, KYNA and QYN levels were greater (p <0.001) for more advanced CKD stage. In fully adjusted regression model, lower TRP levels were associated with poor performance on the Boston, verbal, MMSE, recall and Trail-A and B tests. In contrast, higher QYN levels were associated with lower MMSE, recall and higher trail-A and trail-B score (Figure). These findings were similar in longitudinal analysis over mean follow-up of 10 years.

Conclusions: Our study indicates disturbed metabolism of the KYN pathway in CKD. Low levels of TRP and high QYN levels were related with worse neuro-cognitive function, independent of eGFR. Interventions to modulate the KYN pathway may improve cognition in CKD.

Table. Cross-sectional analysis of Tryptophan and Kynurenine metabolites with neuro-cognition and depression in CRIC

	Beta coefficient	95% CI	P value
	BOSTON		
Tryptophan	0.76	0.27, 1.23	0.003
Kynurenine	0.29	0.03, 0.56	0.03
Kynurenine acid	-0.11	-0.37, 0.16	0.42
Quinolinic acid	-0.07	-0.23, 0.09	0.37
	Verbal		
Tryptophan	3.30	1.71, 4.90	0.001
Kynurenine	0.36	-0.52, 1.24	0.42
Kynurenine acid	0.37	-0.50, 1.23	0.42
Quinolinic acid	-0.50	-1.03, 0.02	0.06
	Mini-Mental State Exam		
Tryptophan	4.48	2.85, 6.69	0.001
Kynurenine	0.33	-0.75, 1.41	0.55
Kynurenine acid	-0.49	-1.55, 0.56	0.36
Quinolinic acid	-1.07	-1.70, -0.44	0.001
	Recall		
Tryptophan	1.25	0.37, 2.12	0.006
Kynurenine	-0.28	-0.75, 0.20	0.23
Kynurenine acid	-0.34	-0.81, 0.12	0.15
Quinolinic acid	-0.29	-0.58, -0.01	0.04
	Trail-A		
Tryptophan	-19.90	-30.33, -9.46	0.001
Kynurenine	-4.26	-9.98, 1.47	0.15
Kynurenine acid	5.89	0.30, 11.48	0.05
Quinolinic acid	5.64	2.29, 8.99	0.001
	Trail-B		
Tryptophan	-59.38	-82.44, -36.33	0.001
Kynurenine	-9.89	-22.82, 3.05	0.13
Kynurenine acid	6.34	-6.38, 19.06	0.34
Quinolinic acid	14.36	6.83, 21.89	0.001
	Beck Depression		
Tryptophan	-3.87	-6.35, -1.40	0.002
Kynurenine	-0.64	-1.98, 0.69	0.34
Kynurenine acid	-0.71	-2.02, 0.61	0.29
Quinolinic acid	0.75	-0.05, 1.54	0.07

Model adjusted for demographics, comorbidities and eGFR.

TH-PO1067

Impaired Incretin Homeostasis in Non-Diabetic Moderate-Severe CKD

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Background: Incretin hormones are critical regulators of insulin secretion and glucose homeostasis. Little is known about the incretin response in CKD. We hypothesized that CKD is associated with impaired incretin secretion during oral glucose tolerance testing (OGTT).

Methods: We performed a cross-sectional study of 59 people with non-diabetic CKD (eGFR<60 ml/min per 1.73 m^2) and 39 healthy control participants (eGFR>60 ml/min per 1.73 m^2). We measured total area under the curve (tAUC) of plasma glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) during a 2-hour OGTT. We used linear regression adjusting for demographic, body composition, and lifestyle factors.

Results: Mean age of CKD patients was 64±14 yrs with 51% females versus 61±12 yrs with 44% females among controls. The mean eGFR in CKD participants was 38 ± 13 compared to 89 ± 17 ml/min per 1.73 m^2 in controls (**Table 1**). GLP-1 tAUC and GIP tAUC were higher in CKD than controls with a mean of 3420 ± 1948 versus 2384 ± 1546 pM*120min (*P*=0.03), and 79400 ± 38670 versus 53994 ± 28191 pg/ml*120min (*P*=0.01), respectively (**Figure 1**). After adjustment, CKD was associated with estimated 1032 pM*120min greater GLP-1 (95% CI 74, 1989) and 19103 pm/ml*120min greater GIP (95% CI 4116, 34090) compared to control. There were no differences in insulin secretion and glucose tolerance between CKD and controls.

Conclusions: CKD is associated with increased incretin hormone levels during OGTT but no difference in insulin secretory response. Further studies are needed to investigate pancreatic response to incretin hormones in CKD.

Funding: NIDDK Support

Table 1. Participant characteristics.

Characteristics	Controls (n=39)	CKD (n=59)
Age	61.0 (12.4)	63.6 (13.9)
Female (%)	17 (44)	30 (51)
Race (%)		
White	33 (87)	31 (69)
Black	4 (10)	13 (22)
Asian/Pacific Islander	1 (3)	5 (8)
Body weight (kg)	82.6 (20.6)	88.1 (19.8)
eGFR (mL/min/1.73 m2)	88.8 (17.1)	37.6 (12.5)

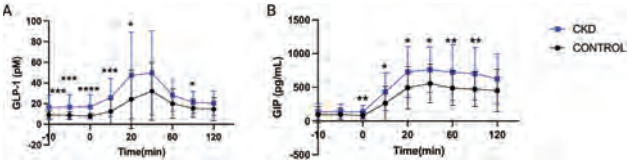

Figure 1. Changes in plasma GLP-1 and GIP in response to OGTT comparing CKD and controls.

TH-PO1068

Choroidal and Retinal Thinning in CKD Are Modifiable with Treatment and Independently Associate with eGFR Decline

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Background: Cardiovascular disease is the commonest complication of chronic kidney disease (CKD). As estimated glomerular filtration rate (eGFR) declines, cardiovascular risk increases. There is an unmet need for novel biomarkers that reliably track kidney injury, demonstrate treatment-response, and predict patient outcomes. We investigated the ability of retinal optical coherence tomography (OCT) to achieve these ends.

Methods: Patients with stable, pre-dialysis CKD (including those with a kidney transplant), patients with kidney failure undergoing kidney transplantation, living kidney donors, and healthy volunteers were recruited into a series of prospective, cross-sectional, and longitudinal studies. We used the SPECTRALIS OCT machine to examine retinal thickness, macular volume, and choroidal vascular layer thickness.

Results: Compared to healthy volunteers, macular volume was reduced in CKD patients (health *vs.* CKD: 8.73±0.36 mm^3 *vs.* 8.44±0.44 mm^3, p <0.001). Kidney transplant recipients also had a reduced macular volume compared to health of a similar magnitude to that seen in CKD patients. The choroid was thinner in CKD patients (health *vs.* CKD, macular locations I, II and III: 234±80mm *vs.* 197±85mm, 319±93mm *vs.* 274±93mm, 292±83mm *vs.* 262±84mm, p <0.01 for each). Conversely, patients with a kidney transplant had choroidal thicknesses similar to healthy levels, suggesting reversal of thinning. In those with CKD, the degree of choroidal thinning related to increasing age (r= -0.25, p =0.008), falling eGFR (r=0.30, p =0.001) and severity of kidney scarring (r= -0.60, p <0.001). Patients undergoing kidney transplantation (n=25) demonstrated rapid choroidal thickening (~10%) that was maintained at 1-year post-transplant. These patients also demonstrated increases in both retinal thickness and macular volume over this period. Conversely, kidney donors (n=22) demonstrated gradual choroidal thinning over 1-year but there were no changes in retinal thickness or macular volume. In patients with CKD (n=289), both retinal and choroidal thickness independently associated with eGFR decline over 2 years.

Conclusions: These observations highlight the potential for retinal OCT to act as a non-invasive monitoring and prognostic biomarker of kidney injury. Larger, longer-term clinical trials are now warranted.

Funding: Government Support - Non-U.S.

TH-PO1069

Disease Progression in Patients with Two APOL1 Variants and Proteinuric CKD from the AASK, CRIC, and FSGS-CT Datasets

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Background: Two variants in *Apolipoprotein L1* (*APOL1*) lead to proteinuric chronic kidney disease (CKD) referred to as APOL1-mediated kidney disease (AMKD). Disease progression in persons with two *APOL1* variants and proteinuric CKD is not well-understood.

Methods: We analyzed data from non-diabetic patients with two *APOL1* variants and proteinuric CKD enrolled in the African American Study of Kidney Disease and Hypertension (AASK), Chronic Renal Insufficiency Cohort (CRIC) study, and Focal Segmental Glomerulosclerosis Clinical Trial (FSGS-CT). The analysis included participants in AASK and CRIC with urine protein to creatinine ratio (UPCR) ≥0.7 g/g and participants in FSGS-CT with UPCR ≥1.0 g/g. Baseline age, sex, UPCR, and estimated glomerular filtration rate (eGFR) were determined at enrollment. For each data

set, we derived an annual eGFR slope estimate as related to persistent proteinuria, median time to end-stage kidney disease (ESKD), and median time to composite clinical outcome based on a decline of ≥30% from baseline in eGFR, the onset of ESKD, or death.

Results: A total of 38 patients from AASK, 47 patients from CRIC, and 27 patients from FSGS-CT were found to have two *APOL1* variants, CKD, and proteinuria. The estimated annual eGFR slope in AASK, CRIC, and FSGS-CT was -5.80, -8.55, and -19.08 mL/min/1.73m²/year, respectively. Across all studies, patients had a median time to ESKD of <4 years and a median time to composite clinical outcome of ≤2.14 years.

Conclusions: These results highlight the rapid rate of decline in kidney function in patients with AMKD relative to other glomerular diseases and may inform the design of clinical trials testing the safety and efficacy of APOL1-targeted therapies.

Funding: NIDDK Support, Commercial Support - Vertex Pharmaceuticals Incorporated

Demographics, Baseline Disease Characteristics, and Disease Progression in Patients with Two *APOL1* Variants and Proteinuric CKD

	AASK N=38	CRIC N=47	FSGS-CT N=27
Demographics, Baseline Characteristics			
Age (years), mean (SD)	45.8 (11.7)	44.0 (13.7)	21.2 (9.3)
Female, n (%)	16 (42.1)	20 (42.6)	6 (22.2)
Baseline eGFR[a] (mL/min/1.73m²) Mean (SD)	35.0 (11.7)	39.2 (15.0)	88.6 (30.5)
Baseline UPCR[b] (g/g) Mean (SD)	1.5 (0.6)	1.8 (1.3)	5.5 (3.9)
Disease Progression			
Estimated annual eGFR slope[a,c] (mL/min/1.73m²/year) Estimate (95% CI)	-5.80 (-7.51, -4.08)	-8.55 (-9.83, -7.27)	-19.08 (-26.65, -11.50)
Time to ESKD[d] (years) Median (95% CI)	3.14 (2.39, 4.35)	3.84 (2.85, 5.27)	1.41 (0.37, 2.15)
Time to composite clinical outcome[e] (years) Median (95% CI)	2.12 (1.60, 3.49)	2.14 (1.91, 2.77)	1.40 (0.37, NE)

AASK: African American Study of Kidney Disease and Hypertension; *APOL1: Apolipoprotein L1*; CI: confidence interval; CKD: chronic kidney disease; CRIC: Chronic Renal Insufficiency Cohort; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; FSGS-CT: Focal Segmental Glomerulosclerosis Clinical Trial; NE: not estimable; NIDDK CR: National Institute of Diabetes and Digestive and Kidney Diseases Central Repository; SD: standard deviation; UPCR: urine protein to creatinine ratio

Note: Data provided by NIDDK CR, a program of the National Institute of Diabetes and Digestive and Kidney Diseases

[a]eGFR values over 120 mL/min/1.73m² were set to 120 mL/min/1.73m²

[b]Patients in the AASK and CRIC studies with baseline UPCR ≥0.7 g/g and patients in the FSGS-CT study with UPCR ≥1.0 g/g were included in the analyses

[c]eGFR slope estimates were calculated based on a regression model with covariate of change from baseline in log-transformed UPCR

[d]ESKD was defined as dialysis, kidney transplantation, or eGFR of <15 mL/min/1.73m²

[e]Time to composite clinical outcome was based on a decline of ≥30% from baseline in eGFR, the onset of ESKD, or death

TH-PO1070

Rapidly Increased Pattern of Erythropoiesis–Stimulating Agent (ESA) Resistance Is a Predictor of Poor Renal Prognosis in Predialysis CKD Patients: BRIGHTEN Study Subanalysis

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Background: As CKD progresses, Hb level becomes sluggish in pre-dialysis CKD patients even though the dosage of ESA increases. We investigated whether renal prognosis can be predicted from transition pattern in ESA resistance as a sub-analysis of the BRIGHTEN study.

Methods: The ESA Resistance Index (ERI) was defined as Darbepoietin (DA) dosage/Hb. After the start of DA administration, ERI measured over time and renal events (dialysis initiation/ kidney transplantation) were investigated. The onset relationships were analyzed with Joint latent class models for longitudinal and time-to event data. The Kaplan-Meier method was used to estimate renal survival curves for each ERI transitional pattern. The patient background was compared.

Results: During an average observation period of 3.5 years in 1625 patients, renal events in 517 dialysis initiation and 18 kidney transplantation were analyzed. ERI transition pattern were divide into 3 classes: ERI unchanged Class A (1237 patients, Hb 9.9g/dL, Cr 2.6mg/dL), moderately increased ClassB (274 patients, Hb 9.6g/dL, Cr 3.6mg/dL), and rapidly increased Class C (114 patients, Hb 9.4g/dL, Cr 3.8mg/dL). Class C showed significant poor renal survival curve in 3 groups, and Class B showed intermediate(P<0.0001). The median renal survival time was 1.09 years in Class B, and 0.61 years in Class C. Between Class B and C, though there was no significant difference in Cr levels at the start of DA, Class C showed significant higher ERI throughout all observation period, higher rate of hypertension and ischemic heart disease.

Conclusions: (Discussion) In HD patients, several studies showed that the ESA resistance is an independent predictor of mortality. On the other hand, in pre dialysis CKD patients, a few reports showed the relationship between ESA resistance and mortality, cardio-renal outcome. The BRIGHTEN study of 1724 Japanese was the largest study and found that reduced initial responsiveness to DA was a risk factor for cardio-renal outcomes. In this sub-analysis, even if the initial response is good, rapidly increased ESA resistance during the course of CKD indicates poor renal prognosis. (Conclusion) Rapidly increased pattern of ESA resistance is a predictor of poor renal prognosis in pre-dialysis CKD.

Funding: Clinical Revenue Support

TH-PO1071

Baloxavir Marboxil (BXM) Treatment of Influenza in Renally Impaired Patients: Post Hoc Analysis of CAPSTONE-2

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Background: Renally impaired patients (pts) have a higher mortality rate from influenza vs pts without renal impairment. In the US, oseltamivir (OSL) is used for influenza but requires dose adjustment for pts with creatinine clearance (CrCl) <60 mL/min. CAPSTONE-2 (NCT02949011), a global phase 3 study of BXM vs OSL vs placebo (PBO) in high-risk pts ≥12 years with influenza, demonstrated the efficacy and safety of prompt single dose BXM treatment: median time to improvement of influenza symptoms (TTIIS) was (BXM vs OSL vs PBO) 73.2 vs 81.0 vs 102.3 h; no new safety signals were identified. This post hoc analysis examined BXM efficacy and safety in renally impaired pts with influenza.

Methods: In CAPSTONE-2, pts received a single oral dose of BXM (40 mg: <80 kg, 80 mg: ≥80 kg), OSL 75 mg twice daily for 5 days or PBO and were to be excluded if CrCl was <60 mL/min (<30 mL/min for Japan). At the time of enrolment, a small cohort of renally impaired pts was deemed eligible for inclusion as judged by the PI and were included in the intention to treat infected (ITTI) population. For this study, renal impairment was CrCl <55 mL/min. Endpoints were TTIIS, time to alleviation of symptoms (TTAS), time to cessation of viral shedding (TCVS) and safety.

Results: Overall, 89/1153 (7.7%) renally impaired pts were in the ITTI population; 33/384 (8.6%), 23/386 (6.0%), and 33/383 (8.6%) received BXM, OSL or PBO, respectively. For renally impaired pts, median TTIIS was numerically shorter for BXM (62.4 h [95% CI 29.2–86.2]) vs PBO (92.2 h [44.0–115.9]; p=0.1602) and similar vs OSL (69.4 h [45.5–123.2]; p=0.2061) with similar results for median TTAS (BXM: 62.4 h [29.2–86.2] vs PBO: 92.2 h [44.0–115.9]; p=0.1602; OSL: 78.2 h [48.8–123.2]; p=0.0729). Median TCVS was significantly shorter for BXM (48 h [24–72]) vs PBO (120 h [96–168]; p=0.0016) and OSL (96 h [96–144]; p=0.0029). Overall, 54 (34.2%) pts had ≥1 adverse event.

Conclusions: In this analysis of renally impaired pts (CrCl 21.7 to 54.9 mL/min), there was clinical benefit of single dose BXM with a similar median TTIIS and TTAS as well as significantly better median TCVS vs OSL; analysis of the safety data from this small cohort did not identify any new safety concerns.

Funding: Commercial Support - Genentech, Inc.

TH-PO1072

Real-World Effectiveness and Tolerability of Bictegravir/Emtricitabine/Tenofovir Alafenamide (B/F/TAF) in Treatment-Experienced (TE) People with HIV with a History of CKD

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Background: TAF-containing regimens, eg B/F/TAF, are approved in the US in people with an estimated CrCl ≥30 mL/min and have demonstrated comparable long-term renal safety vs non–tenofovir-based regimens. No proximal renal tubulopathies have been reported in 26 TAF trials or in a trial rechallenging those with history of tubulopathy on tenofovir disoproxil fumarate.

Methods: We investigated the renal safety profile and efficacy of B/F/TAF in the BICSTaR study, in which 963 TE participants with HIV switched from current antiretroviral therapy (ART) to B/F/TAF.

Results: Of 843 participants with baseline (BL) eGFR data available, 90 had CKD (MDRD eGFR <60 mL/min/1.73 m²), 83% were male and 85% were non-Black. More participants with vs without BL CKD were >50 yrs old (79% vs 43%; P<0.001), had ≥1 cardiovascular condition (54% vs 20%; P<0.001), diabetes mellitus (12% vs 6%; P=0.029) and hypertension (44% vs 16%; P<0.001). Those with vs without BL CKD had longer prior exposure to ART and time from diagnosis to B/F/TAF initiation (Table). Drug-related (DR) AEs were reported in 16% of people with BL CKD vs 15% in those without. A single DR renal AE (RAE) was reported in 1 person with BL CKD (proteinuria, drug continued); there were no DR RAE discontinuations or serious DR RAEs. Median eGFR was stable through 24 months for people with BL CKD (Fig.).

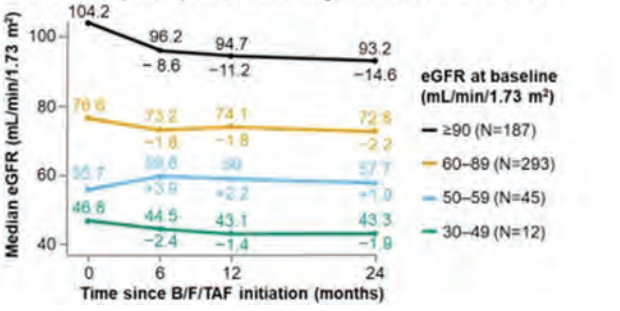
Conclusions: B/F/TAF was effective and safe with respect to renal outcomes in this real-world study in TE people with HIV and CKD switching to B/F/TAF, supporting use of TAF-based regimens in people with eGFR <60 mL/min/1.73 m^2.

Table: Baseline Characteristics and 24-Month Effectiveness and Safety Outcomes

	eGFR <60 mL/min/1.73m^2 (N=90)	eGFR ≥60 mL/min/1.73m^2 (N=753)	P-value*
Baseline Characteristics			
HIV-1 RNA, n (%)†: <50 c/mL / ≥50 c/mL	80 (93) / 6 (7)	676 (92) / 60 (8)	0.704
No. of previous antiretroviral therapy regimens, median (IQR)	3.0 (2.0, 5.5)	2.0 (1.0, 4.0)	0.027
MDRD eGFR (numeric formula), median (IQR), mL/min/1.73 m^2	55.2 (51.2, 57.3)	85.5 (74.4, 99.6)	<0.001
Time from HIV diagnosis to B/F/TAF, median (IQR), years	14.5 (7.2, 21.8)	10.0 (4.0, 17.0)	<0.001
24-Month Effectiveness and Safety Outcomes			
HIV-1 RNA viral load at 24 months, n (%)‡: <50 c/mL / ≥50 c/mL	67 (100) / 0 (0)	556 (95) / 30 (5)	0.058
Change in MDRD eGFR at 24 months from baseline, median (IQR), mL/min/1.73 m^2	1.3 (−3.6, 6.7)	−6.0 (−15.0, 1.6)	<0.001
Drug-related AE within 24 months, n (%)	14 (16)	111 (15)	0.978
Drug-related renal AE within 24 months, n (%)	1 (1)§	0 (0)	0.062

*Chi squared test for categorical data / Kruskal–Wallis tests for numeric data; †Missing = Excluded analysis; ‡Proteinuria (did not result in dosage change/study withdrawal); AE, adverse event; B/F/TAF, bictegravir/emtricitabine/tenofovir alafenamide; c, copies

Figure: Median MDRD eGFR over time for people with results at all timepoints
Values below data points represent median change from baseline in MDRD eGFR



TH-PO1073

Comparative Effectiveness of Opioids vs. Non-Opioid Analgesics on the Risk of ESRD and Mortality Among US Veterans with CKD and Chronic Pain

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Background: Pain is common among individuals with CKD, in whom commonly used analgesics such as NSAIDs are often contraindicated. Opioids can be an alternative, but they are associated with unwanted adverse effects, leaving patients with few choices for analgesia. Non-opioid non-NSAID analgesics (e.g., gabapentin, acetaminophen, antipyrine) represent potential alternative choices, but their long-term outcomes in CKD. We compared the association of chronic opioid vs. non-opioid analgesics with end-stage kidney disease (ESKD) and all-cause mortality among patients with CKD and chronic pain.

Methods: We examined patients with CKD (defined as two or more eGFR <60 or UACR >30) and chronic pain (defined as 2 or more pain scores ≥7, 90 to 365 days apart). Chronic opioid and non-opioid analgesic use was defined as at least one 30-day supply in the one-year period following the second pain score. The association of opioid vs. non-opioid use with ESKD and mortality was examined using Kaplan-Meier estimates and multivariable adjusted Cox proportional hazards models.

Results: The total sample included 16,494 patients, of which 13,631 (82.6%) used non-opioid and 2,863 (17.4%) used opioid analgesics. Overall, patients were 69.1±11.7 years old, 96% were men, and 19% were African American, with a mean baseline eGFR of 66±22 and with 38% with UACR of >30. Opioid use (vs. non-opioid use) was associated with significantly higher risk of mortality, but not with the incidence of ESKD (Table).

Conclusions: The use of opioid analgesics was associated with higher risk of mortality among patients with CKD and chronic pain. Additional studies are needed to examine whether non-opioid analgesics could be considered as safer agents for chronic pain management among patients with CKD.

Funding: Veterans Affairs Support

Multivariable Adjusted Cox Proportional Hazards Models to Compare the Association of Chronic Opioid vs. Non-Opioid Analgesics with ESKD and All-Cause Mortality among Patients with CKD and Chronic Pain

	Mortality Adjusted HR [95% CI]	ESKD Adjusted HR [95% CI]
Model 1: Unadjusted	1.42 (1.34,1.50)	1.23 (0.98,1.53)
Model 2: Model 1+Demographic factors	1.34 (1.27,1.42)	1.32 (1.05,1.66)
Model 3: Model 2+Smoking+BMI+comorbidities	1.21 (1.14,1.29)	1.08 (0.83,1.40)
Model 4: Model 3+income+insurance	1.19 (1.12,1.28)	1.08 (0.81,1.43)
Model 5: Model 4+egfr+uacr	1.22 (1.13,1.31)	1.00 (0.67,1.50)

TH-PO1074

A Multi-Omics Approach to Renal Epithelial Senescence Urinary Biomarker Discovery

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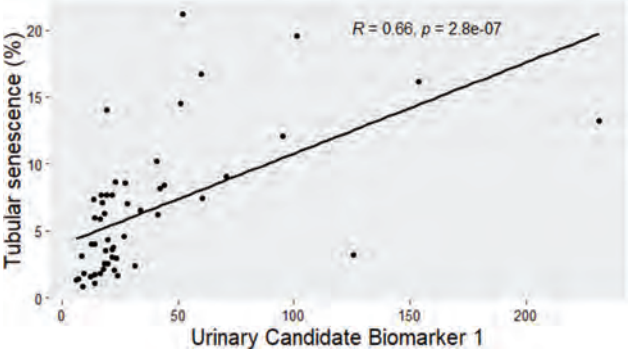
Background: Epithelial senescence is proposed as a driver of kidney fibrosis with senescent cell (SC) depletion improving outcomes. There are no non-invasive biomarkers for quantifying renal SCs. We used samples from patients with kidney disease and cultured human renal proximal tubular epithelial cells (hRPTECs) to identify urinary biomarkers of renal tubular senescence (rtSCs).

Methods: hRPTEC senescence was induced *in vitro* using 10Gy irradiation. Bulk RNAseq was performed comparing SCs with proliferating controls (n=5/group). Immunofluorescence staining for p21CIP1, Ki67 and tubular markers CD10/CKPAN was performed in human kidney tissue from 131 CKD patients. P21CIP1 (+) / Ki67 (neg) tubular cells were classified as senescent (expressed as % of all tubular cells). In subgroup 1 (collected in Edinburgh, n=51), LC-MS studies were performed on matched urine samples. Proteins qualified as candidate biomarkers if they predicted the level of histological senescence in multivariate linear regression models alongside baseline eGFR, age and ACR and were upregulated in senescence transcriptomically. Candidate biomarkers were validated in subgroup 2 (collected in Glasgow, matching baseline characteristics to subgroup 1, n=53) that had both urine and kidney tissue available.

Results: *In vitro:* Irradiation increased mRNA levels of *CDKN1A* and reduced *LMNB1* and *MKI67* in keeping with senescence induction. *In vivo*: rtSCs increased with age (rho = 0.58, p<0.001) and inversely with baseline eGFR (rho = -0.48, p<0.001). 331 proteins were detected by LC-MS. 5 candidate biomarkers were identified; 3 of which remained highly correlated with and predictive of histological senescence in the validation subgroup (fig. 1) [not named pending patent applications].

Conclusions: We have identified and validated 3 urinary biomarkers of senescence. These could aid patient selection for clinical trials of senolytic treatments in kidney disease.

Funding: Government Support - Non-U.S.



Spearman rank correlation used.

TH-PO1075

Prognostic Comparisons of Carbamylated Albumin and Homocitrulline-Two Circulating Markers of Protein Carbamylation in CKD

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Background: Protein carbamylation, a urea driven post-translational protein modification, associates with adverse outcomes in CKD. Circulating markers of carbamylation include carbamylated albumin (C-Alb) and homocitrulline (HCit, carbamylated lysine), but prognostic comparisons between the 2 have never been made. Demonstrating comparability of the 2 markers could facilitate study comparisons and support HCit use from existing databases (HCit is a common analyte on metabolomic platforms). We thus compared the prognostic performance of C-Alb and HCit in a prospective CKD cohort.

Methods: Baseline C-Alb and HCit levels were assayed using mass spectrometry (Broad Institute Metabolomics Platform for HCit) in 1659 patients with CKD stages

2-4 enrolled in the Chronic Renal Insufficiency Cohort (CRIC) study. We compared associations to the endpoints of death and end stage kidney disease (ESKD). Adjusted Cox proportional hazard models (including eGFR and proteinuria) and C-statistics were used to compare the prognostic performance of each marker.

Results: Participant demographics included mean (SD) age 57 (10.7) years; 712 (42.9%) females; 704 (42.4%) White. Participants in the highest quartile across the two-biomarkers had similar baseline characteristics (e.g., serum urea nitrogen for HCit was 45 [35-58] mg/dL, for C-Alb 44 [34-58] mg/dL). The 2 markers showed a correlation coefficient of 0.64, P<.001, (HCit was the strongest correlate to C-Alb amongst >400 analytes from the Broad platform). In multivariable adjusted Cox models, on a continuous scale or in quartiles, HCit and C-Alb showed similar increase in the risk of either death or ESKD with increasing risk observed at higher levels (HR for death in 4th quartile compared to the 1st was1.86 (95% confidence interval [CI]:1.26-2.77) for HCit, and 1.90 (1.36-2.65) for C-Alb. The top quartile of both biomarkers had a similar but distinct HRs for ESKD with overlapping CIs. Measures of model performance showed significant and identical improvements when each carbamylation biomarker was added to fully adjusted models.

Conclusions: HCit was similar to C-Alb across multiple prognostic assessments, thus may have potential to be utilized like C-Alb in CKD clinical outcomes studies.

Funding: NIDDK Support

TH-PO1076

CKD Progression with Remote Pulmonary Artery Pressure (PAP) Monitoring in Heart Failure (HF)

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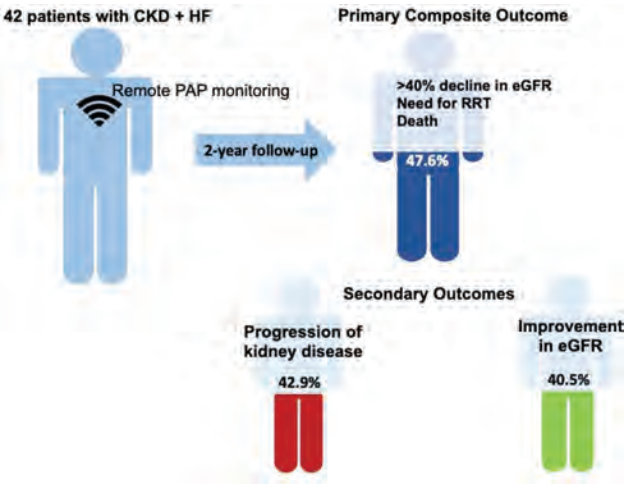
Background: CardioMEMS HF system is FDA approved for remote monitoring of PAP in patients with NYHA class III HF to reduce HF hospitalizations. Subgroup analysis of the CHAMPION trial with CKD patients reported a mean estimated glomerular filtration rate (eGFR) change of 1.0±14.48 ml/min/1.73m^2 in 6 months in the CardioMEMs group and was similar in controls. Limited data is available on the role of remote PAP monitoring on kidney function in a real-world population that includes patients with advanced CKD over longer follow up.

Methods: This is a retrospective observational study where we included patients with CKD (eGFR <60 ml/min/m^2 for atleast 90 days as screened by a nephrologist) and HF who were managed with the CardioMEMs HF system. Patients on dialysis, kidney and heart transplant recipients were excluded. Baseline characteristics were collected at the time of CardioMEMs implant. Outcome characteristics were collected after 2 years. Primary outcome was a composite of >40% decline in GFR, need for dialysis or transplant, and death.

Results: Baseline characteristics are summarized in table 1. Of 42 patients, 73.8% had NYHA Class III HF, 71.4% were diabetic and 90.5% were hypertensive. 20 (47.6%) reached the primary composite outcome. 9 (21.4%) had >40% decline in eGFR, 4 (9.5%) required chronic dialysis and 10 (23.8%) died. While 18 (42.9%) patients developed progression of kidney disease, 17 (40.5%) patients had an improvement in their eGFR. Of those, 10 (23.8%) improved by more than 20%. The median change in eGFR at 2-yrs was +11.81% (16.88, 34.7). Median number of hospitalizations was 5.0 (3.0,7.0).

Conclusions: In this cohort of adults at high risk for renal progression at the time of cardioMEMs insertion, we observed an improvement in eGFR despite the expected renal progression. A larger study with a control group is warranted to better understand the impact of remote PAP monitoring on CKD progression.

Baseline Characteristics	Values
Age, median (IQR)	71 (63.25,77.00)
Male, n (%)	24 (57.1)
Race/Ethnicity, n (%)	22 (52.4)
-Caucasian	16 (38.1)
-African American	30 (71.4)
Diabetes, n (%)	30 (71.4)
Hypertension, n (%)	9 (21.4)
CKD Stage	16 (38.1)
-stage IIIA	14 (33.3)
-stage IIIB	3 (7.1)
-stage IV	14 (33.3)
-stage V	19 (45.2)
Etiology of CKD	3 (7.1)
-Presumed/proven DKD+/- CRS	6 (14.3)
-Hypertensive +/- CRS	50.50 (35.00,60.00)
-Other	17 (40.47)
-Not specified	2 (4.76)
LV EF, median (IQR)	21 (50.00)
<40%- n (%)	11 (26.2)
41-49%- n (%)	22 (52.4)
>50%- n (%)	8 (19.0)
Etiology of HF	1 (2.4)
-ICM	17 (40.5)
-NICM	33 (78.6)
-Other	17 (40.5)
-Not specified	14 (33.3)
Medications, n (%)	21 (50.0)
-RAASi	
-Beta-blockers	
-MRA	
-SGLT2i	
ICD/CRT-D	



TH-PO1077

Cytomegalovirus Exposure in Nontransplant, Critically Ill CKD Patients

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Background: This study aimed to provide a comprehensive understanding of the incidence, and prevalence and to determine whether CMV infection had any significant impact on the clinical course and prognosis of non-transplant CKD patients in the intensive care unit setting.

Methods: A prospective study involved 94 patients with known cases of CKD stage 3 and above admitted to ICU due to acute illness or comorbidities. CKD Patients who had received corticosteroids, cytotoxic therapy, immunosuppressive medications, or had undergone solid organ or bone marrow transplantation were excluded. In our case, at the end of 3 weeks, the prevalence of CMV infection was defined as the percentage of patients who had the infection at that time, and incidence was defined as the percentage of patients who developed the infection at any point between the time of admission and 3 weeks. At 0, 1, and 3 weeks, a quantitative RT PCR analysis for CMV DNA was conducted. The primary outcome was to evaluate the incidence and prevalence of CMV infection. The secondary outcome was to assess the effect of CMV infection on patient outcomes, hospital stay, and 30-day mortality.

Results: The prevalence of CMV infection was 9.57% with an incidence of 10.63 per 1000 patients. The mean age of CMV-infected patients was slightly higher (58.22± 8.829 vs 56.9 ± 7.638, p 0.148) compared to CMV non-infected. There was no significant difference in gender or the number of comorbidities between the two groups. The most common admitting diagnosis in both groups was sepsis (88.8% and 72.9%). The severity of the disease was higher in CMV-infected patients (p 0.044). CMV infection was associated with longer lengths of ICU stay but did not significantly impact hospital stay or 30-day mortality.

Conclusions: CMV infection is not uncommon among critically ill patients, irrespective of their immune status. It can occur in CKD patients even in the absence of overt immunodeficiency. The acquisition of CMV infection appears to be associated with the severity of illness in the ICU and is linked to higher morbidity. Such studies would provide valuable insights into the relationship between CKD and CMV, shedding light on associated risks and potential interventions.

TH-PO1078

Clinical Utility of Tenascin-C Levels in Patients with CKD

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Background: Tenascin-C (TNC), an extracellular matrix protein, is a novel biomarker associated with kidney fibrosis. Within the kidney, it activates fibroblasts and induces epithelial-mesenchymal transition. Increased levels of TNC have been seen in kidney biopsies of patients with chronic kidney disease (CKD). Current literature lacks studies evaluating TNC and associations with clinical parameters and clinical outcomes.

Methods: We retrieved prospectively collected 24-hour urinary and plasma samples from 126 CKD patients and 99 healthy participants. TNC levels were assayed using IBL Tenascin-C Large (FNIII-B) assay kit. TNC concentration was assessed for associations with serum creatinine, cystatin-C, eGFR albuminuria, and rate of eGFR decline. Other factors evaluated include age, gender and body mass index. Differences in TNC concentration between groups were compared using analysis of variance, chi-squared tests. Univariate analysis was performed to assess correlation between TNC and variables of interest. Multiple regression analysis was performed to identify predictors of eGFR decline/year. Significance was taken at $P < 0.05$.

Results: CKD patients versus healthy participants: age (59 vs. 42), gender (44% female vs. 51%), non-smokers (78% vs. 81%), BMI (27.7 vs. 24.8), eGFR (45 vs. 100mL/min/1.73m2), serum creatinine (171 vs. 69 μmol/L). 24-hour urinary concentration of TNC is elevated in CKD patients (1.45 vs. 0.32ng/ml, p<0.001). It is associated with

serum creatinine levels (p<0.001), serum cystatin-C levels (p<0.001), eGFR (p<0.001) and albuminuria (<0.001). Urinary TNC concentration is highest in patients with diabetes mellitus (DM, n=52), followed by non-DM (n=43) and healthy controls (n=92). (1.86, 0.95, 0.32ng/ml, p<0.001). In CKD patients, urinary TNC concentration is associated with rate of eGFR decline/year (p<0.001). Plasma TNC concentration was not associated with eGFR, albuminuria and GFR decline.

Conclusions: 24-hour urinary tenascin C level offers novel clinical utility in management of patients with CKD. Early detection of high risk CKD patients will allow for earlier intervention and may serve to delay ESKD onset.

Funding: Other NIH Support - Pitch For Fund - NUHS Research

TH-PO1079

The Effect of Fibrates on Kidney Function: A Systematic Review and Meta-Analysis

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Background: Randomized controlled trials (RCTs) have investigated the effects of fibrates on cardiovascular events. Fibrates are known to cause an acute decline in estimated glomerular filtration rate (eGFR) but their long-term effect on kidney function is unclear. Some trials have indicated that following the acute decline fibrates improve the long-term rate of eGFR decline. We conducted a systematic review and meta-analysis to elucidate the impact of fibrates on kidney function.

Methods: This review was prospectively registered on PROSPERO (CRD42023377211) and conducted according to the PRISMA 2020 guidelines. Literature searches were conducted in MEDLINE, EMBASE, CINAHL and Scopus. Inclusion criteria were RCTs in adults comparing fibrates to placebo or active comparator that reported eGFR at at least two timepoints. Screening, data extraction and risk of bias assessments were conducted in-duplicate. Random-effects, restricted maximum likelihood, inverse variance meta-analyses were used to pool treatment effects. Primary outcomes included the effect on acute change in eGFR (defined as within the first 4 months), chronic eGFR slope (defined as the eGFR slope following the acute period) and post-washout eGFR. Additional outcomes were change in albuminuria and the incidence of ESRD.

Results: Fifteen (N=16,957) eligible RCTs were included. When compared to control, fibrates led to an acute decline in eGFR (MD -9.53 ml/min/1.73 m2; 95% CI -12.12 to -6.94) that was present at the end of the study period as well (MD -6.29 ml/min/1.73 m2; 95% CI -14.64 to -2.06). Based on the data available, we were unable to meta-analyze the effect of fibrates on chronic slope. However, two RCTs reported a beneficial effect of fibrates on chronic eGFR slope (-1.19 vs -2.03 ml/min/1.73 m2 per year and -0.27 vs -1.26 ml/min/1.73 m2 per year, p<0.001). Following washout, fibrates improved eGFR as compared to control (MD 3.60 ml/min/1.73 m2; 95% CI 0.02 to 7.17). Fibrates reduced albuminuria (MD -0.17 mg/g; 95% CI -0.25 to -0.10). There was no statistically significant effect on ESRD (RR 0.93; 95% CI 0.71 to 1.22).

Conclusions: Fibrates cause an acute decline in eGFR and an improvement in the rate of eGFR decline thereafter. Further studies are needed to determine the long-term impact of fibrates on renal function.

TH-PO1080

Non-Skeletal, as Opposed to Skeletal, Alkaline Phosphatase Associates with Mortality in Patients with CKD Not Yet on Dialysis

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Background: High total alkaline phosphatase (ALP) levels associate with increased mortality in patients with chronic kidney disease (CKD). The underlying mechanisms remain poorly understood. Emphasis has been on the skeletal fraction and its link with accelerated vascular calcification, but intestinal and liver ALP may be implicated given their role in the detoxification of bacterial endotoxins. This study aimed to identify the ALP fraction driving the association with mortality in CKD.

Methods: Demographics, Framingham risk factors, total and bone-specific ALP, and parameters of inflammation (CRP) and metabolic endotoxemia (lipopolysaccharide binding protein (LBP)) were assessed in 432 patients with CKD grade 1-5. Non-skeletal ALP levels were estimated as residuals of linear regression (according to Filipowicz et al. CJASN 2013). Mortality data were censored at time of renal replacement therapy or loss of follow up.

Results: Median age was 63 years, 54% were men, 19% had diabetes, and 31% had cardiovascular disease. During a median follow-up of 8.0 years, 131 patients died. High total and non-skeletal ALP were significant and independent predictors of increased all-cause mortality risk, while bone ALP was not predictive (Table). Total and non-skeletal ALP were independent determinants of elevated CRP (>10 mg/L) after adjusting for demographics and eGFR. Non-skeletal ALP was also independently associated with high LBP (Figure).

Conclusions: Non-skeletal ALP drives the association of total ALP with all-cause mortality in patients with CKD not yet on dialysis. We speculate that inflammation and metabolic endotoxemia are implicated in the poor outcomes seen with elevated total ALP.

Funding: Government Support - Non-U.S.

Table. Cox proportional hazard model showing association of serum ALP and mortality

Model	Total ALP HR Per SD	95% CI	P value	Bone-specific ALP HR Per SD	95% CI	P value	Non-skeletal ALP HR Per SD	95% CI	P value
Unadjusted	1.40	1.23, 1.59	**<0.001**	1.09	0.97, 1.23	0.2	1.53	1.28, 1.82	**<0.001**
Model 1	1.46	1.23, 1.73	**<0.001**	1.09	0.93, 1.28	0.3	1.33	1.11, 1.59	**0.002**
Model 2	1.31	1.10, 1.56	**0.003**	1.01	0.86, 1.20	0.9	1.31	1.09, 1.57	**0.004**
Model 3	1.31	1.10, 1.55	**0.002**	1.02	0.88, 1.20	0.8	1.28	1.06, 1.54	**0.009**

Model 1: Adjusted for age and gender
Model 2: Adjusted for the above and eGFR
Model 3: Adjusted for the above and Framingham risk factors (diabetes mellitus, body mass index, systolic blood pressure, LDL and current smoke status)

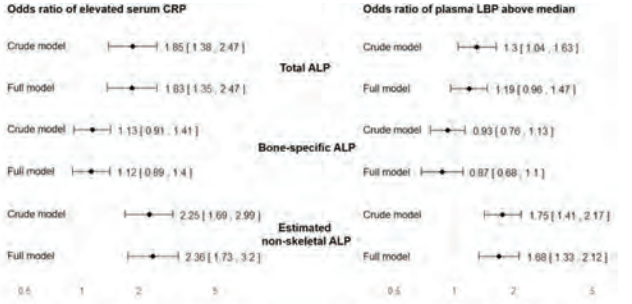

Figure. Association of serum total, skeletal and estimated non-skeletal alkaline phosphatase levels with elevated serum CRP (>10 mg/L) and plasma LBP above median.
Full model is adjusted for age, gender, eGFR, diabetes mellitus and body mass index

TH-PO1081

Kidney Clearances of Protein-Bound Uremic Toxins in Various Stages of CKD and Their Predictive Role for Clinical Prognosis

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Background: Studies on the characteristics of 24-hour kidney clearances of protein bound uremic toxins (cPBUTs) in patients with CKD are limited.

Methods: Patients with non-dialyzed CKD from 2018 to 2020 were enrolled. The concentrations and 24-hour kidney clearances of indole sulfate (IS), p-cresol sulfate (pCS), and indole-3-acetic acid (IAA) among different CKD stages and levels of proteinuria were analyzed. 186 patients were followed up until September 2022. The primary and secondary outcomes were renal and hospitalization events, respectively.

Results: This was a single-center prospective cohort. The 24-hour kidney clearances of IS, IAA and pCS (cIS, cIAA and cPCS) decreased with eGFR (CKD5 VS CKD1: IS, 2.2 ml/min VS 26.7 ml/min; pCS, 1.8 ml/min VS 18.4 ml/min; IAA, 2.1 ml/min VS 12.1 ml/min). Only cIAA was positively correlated with level of proteinuria in CKD1 and CKD5 (p= 0.003; p= 0.007). The cPBUTs could effectively predict renal events (cIS: area under the curves [AUC]=0.764, p<0.001; cIAA: AUC=0.624, p=0.026; cPCS: AUC=0.657, p=0.006). Higher kidney clearance of PBUTs were associated with increased cumulative renal event free survival rates (Figure 1). Increased cIS and cIAA were associated with reduced renal events' risk ratio respectively in adjusted Cox regression models (cIS, hazard ratio [HR], 0.957, p=0.029; cIAA, HR 0.925, p=0.014). The cIAA was also associated with hospitalization risk ratio (HR, 2.55; p = 0.024) (Table 1).

Conclusions: The clearances of IS and IAA decreased with eGFR decline. They were independent predictors of worse prognosis.

Funding: Government Support - Non-U.S.

Table 1. Multivariate Cox regression analysis of renal and hospitalization events related to PBUTs

Characteristics		Renal Events HR (95% CI)	p Value	Hospitalization Events HR (95% CI)	p Value
cIS (ml/min)					
	Unadjusted	0.927(0.887,0.969)	0.001	0.970(0.952,0.989)	0.002
	Adjusted	0.957(0.920,0.995)	0.029	0.982(0.961,1.00)	0.106
cIAA (ml/min)					
	Unadjusted	0.906(0.854,0.961)	0.001	0.938(0.904,0.974)	0.001
	Adjusted	0.925(0.869,0.984)	0.014	0.953(0.914,0.994)	0.024

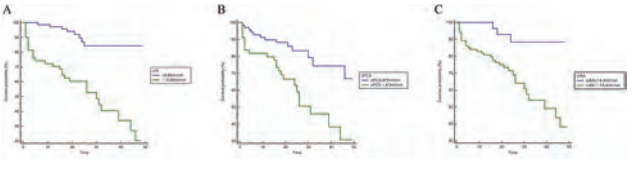

Figure 1. Kaplan-Meier proportion of surviving patients of renal events.

TH-PO1082

Association Between Declining Kidney Function and Abdominal Aortic Calcification: Insights from NHANES Study

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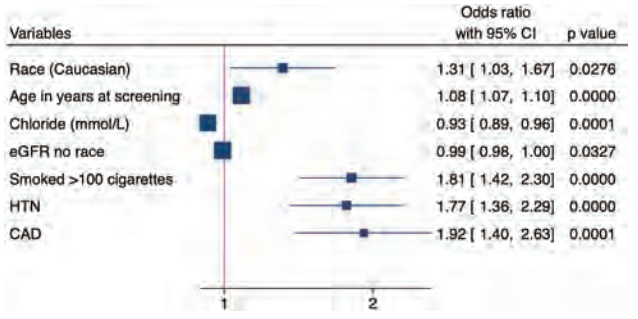
Background: Abdominal Aortic Calcification (AAC) is a strong predictor of cardiovascular disease (CVD), which is affected by age. Gender, comorbidities, inflammation, smoking, phosphate and chloride levels, and the presence of chronic kidney disease (CKD). The exact mechanism of increased risk of AAC in CKD remains unclear, but bone and mineral metabolism and endothelial dysfunction are stipulated causes. With this in mind, we analyzed the NHANES database, which provided measurements of AAC.

Methods: 3140 subjects from the NHANES 2013-2014 dataset were included in the analysis of 40 demographic, clinical, and laboratory variables that were evaluated using univariate and multivariate analysis. Variables found to be significantly associated with AAC were included in a stepwise forward logistic regression analysis. Additionally, K means cluster analysis was performed in 2,943 subjects.

Results: Severe AAC was present in 423 subjects (13%). Stepwise forward logistic regression analysis demonstrated that Caucasian race, older age, smoking, coronary artery disease, and hypertension were associated with increased risk of AAC. In contrast, higher eGFR and higher serum chloride were associated with decreased risk. K means cluster analysis identified 3 clusters, C1, C2, and C3, representing 61%, 1%, and 38% of subjects, respectively. Compared to C2 and C3, subjects in C1 had lower AAC, higher eGFR, a lower degree of proteinuria, lower neutrophile lymphocyte ratio (NLR), higher klotho levels, and younger age.

Conclusions: A higher eGFR is independently associated with reduced risk of AAC in individuals, even in the presence of traditional risk factors. In addition, several phenotypes can be classified mainly on renal function parameters, inflammation (lower NLR), higher Klotho levels, and glomerular injury. Early interventions to maintain eGFR in individuals with traditional risk factors may improve CVD outcomes.



Logistic Regression

TH-PO1083

Impact of CKD on Complications of Hypertensive Emergency

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Background: Hypertension in chronic kidney disease (CKD) is primarily volume-dependent. We sought to examine the impact of CKD on the development of complications in hospitalizations with hypertensive emergency.

Methods: We conducted a retrospective cohort study using the National Inpatient Sample from 2016-2019. We used the International Classification of disease-10 to identify hospitalizations with hypertensive emergency and then stratified them based on whether they had CKD. We used Chi-square and t-test to compare categorical and continuous outcomes, respectively. Multivariate regression analysis was used to adjust for confounders. Adjusted odds ratios (aOR) were reported with 95% confidence intervals (CI) and results were considered statistically significant if P values <0.05.

Results: Among the 750,595 total hospitalizations with hypertensive emergency 335,805 had CKD. The mean age was 63 (without CKD) VS 61 (with CKD). Of those with CKD, 45% were African Americans and 35% were Caucasians. After adjusting for patient demographics, comorbidities, and hospital characteristics those with CKD had higher odds of developing acute kidney injury (aOR: 2.85, p<0.001, CI: 2.77 - 2.94), acute pulmonary edema (aOR: 1.94, p<0.001, CI: 1.79 - 2.09), and retinal hemorrhage (aOR: 1.96, p<0.001, CI: 1.36 - 2.81). CKD was associated with lower odds of developing aortic dissection (aOR: 0.44, p<0.001, CI: 0.4 - 0.5), subarachnoid hemorrhage (aOR: 0.34, p<0.001, CI: 0.32 - 0.35), and acute ischemic stroke (aOR: 0.42, p<0.001, CI: 0.4 – 0.44). There was no statically significant difference in the odds of developing acute coronary syndrome (aOR: 1.03, p=0.395, CI: 0.96 - 1.1) and posterior reversible encephalopathy syndrome (aOR: 1.06, p=0.226, CI: 0.96 - 1.18).

Conclusions: Among hospitalizations with hypertensive emergency, CKD was associated with higher odds of acute kidney injury, acute pulmonary edema, and retinal hemorrhage.

TH-PO1084

Influence of Impaired Renal Function on the Efficacy and Safety of Intravenous Thrombolytic Therapy with Tenecteplase vs. Alteplase in Patients with Acute Ischaemic Stroke

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Background: Data about intravenous thrombolysis (IVT) therapy among stroke patients with chronic kidney disease (CKD) are limited, especially for tenecteplase. We aimed to investigate the impact of renal dysfunction on efficacy and safety of tenecteplase versus alteplase in patients with acute ischemic stroke (AIS) based on the TRACE-2 trial.

Methods: A total of 1,412 thrombolysis-eligible patients with AIS were randomly assigned to intravenous tenecteplase or alteplase within 4.5 hours of symptom onset. Patients were categorized by their eGFR ≥90 (normal), 60-89 (mild CKD), and <60mL/min/1.73 m^2 (moderate CKD). The primary efficacy outcome was the proportion of participants who had a mRS score of 0–1 at 90 days. The primary safety outcome was symptomatic intracranial haemorrhage (ICH) within 36 h.

Results: Patients across the renal function strata did not have a statistically significant difference in primary efficacy outcomes with tenecteplase therapy versus alteplase (normal: RR 1.07, 95% CI, 0.97-1.18; mild: RR 1.14, 95% CI, 0.95-1.37, moderate: RR 0.86, 95% CI, 0.59-1.27) with no significant interaction between renal dysfunction and treatment assignment ($P_{interaction}$ = 0.55). The safety outcomes including proportions of symptomatic ICH ($P_{interaction}$ = 0.55) or rates of mortality ($P_{interaction}$ = 0.65) were also not different between the two treatments based on renal function.

Conclusions: CKD did not modify the treatment effect of tenecteplase versus alteplase. IVT with tenecteplase for AIS had the same efficacy outcomes compared with alteplase without increasing ICH, mortality and other bleeding events in reduced renal function, thus these patients should not be excluded from tenecteplase treatment.

Funding: Government Support - Non-U.S.

Efficacy outcomes at 3 months according to 3 eGFR category

	eGFR(mL/min/1.73m2)	Tenecteplase,%	Alteplase,%	Effect size	P value	Interaction P value
mRS score 0-1 at 3 months	≥90	302(65.51)	293(61.17)	1.07(0.97-1.18)	0.53	0.55
	60-89	114(58.76)	86(51.5)	1.14(0.95-1.37)	0.13	
	<60	21(46.67)	26(52.0)	0.86(0.59-1.27)	0.74	
mRS score 0-2 at 3 months	60-89	355(77.01)	363(75.78)	1.01(0.94-1.09)	079	0.79
	≥90	132(68.04)	108(64.67)	1.04(0.90-1.21)	0.60	
	<60	26(57.78)	31(62)	0.94(0.69-1.30)	0.73	
mRS at 3 months	≥90	1(0 to 2)	1(0 to 2)	1.12(0.89-1.41)	0.34	0.63
	60-89	1(0 to 3)	1(0 to 3)	1.16(0.81-1.68)	0.42	
	<60	2(1 to 4)	1(0 to 4)	0.82(0.40-1.68)	0.59	

TH-PO1085

Rapid Serologic Response of Patients with Advanced CKD to HepB-CpG Vaccination

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Background: Vaccination against Hepatitis B virus (HBV) is recommended in patients with CKD who are at risk for progressive kidney disease due to risk from sporadic outbreaks in hemodialysis units. There are 3 recommended HBV vaccines available in the US: Recombivax-HB, Engerix-B and Heplisav-B (HepB-CpG). HepB-CpG has been reported to have improved immunogenicity, especially in groups known to have low responses historically e.g. patients with CKD and ESKD.

Methods: The following retrospective cohort study is an analysis of sero-response rates to HepB-CpG in the outpatient CKD clinic at the University of Colorado hospital. All patients with documented administration of at least one dose of HepB-CpG between January 1, 2021 to December 31, 2022 were included in this study.

Results: 96 patients at our clinic received at least one dose of the HepB-CpG vaccine. Of these 96 patients, 67 patients had a follow-up hepatitis B surface antibody (HepBsAb) titer measured. Common reasons for non-measurement of follow up titers included death, start of kidney replacement therapy and loss to follow up. Of the 67 patients with measured follow up titers, there was an 80% (53/67) serologic response (HepBsAb > 10mIU/ml) after 1-3 doses of the vaccine (scheduled to be given at 0, 1 and 6 months). There was similar serologic response between CKD stages [CKD5: 22/27 (81%), CKD4: 22/27 (81%), CKD3b: 7/9 (77%), CKD1-CKD3a: 1/2 (50%)]. Only 2 of these patients required more than one series for a serologic response. Of the 14 non-responders who received at least two doses of the HepB-CpG vaccine, 6 patients were solid organ transplant recipients on immunosuppression (5 liver, 1 kidney), 2 patients had active multiple myeloma, and 2 patients had solid organ malignancies.

Conclusions: In our real world clinical experience, HepB-CpG produces a rapid serologic response in advanced CKD patients requiring less doses compared to the high dose of the traditional HBV vaccines (Engerix or Recombivax-HB). Ongoing immunosuppression and active malignancy were the common causes of response failure.

TH-PO1086

Prevalence and Factors Associated with Hyperkalemia in Outpatients with CKD

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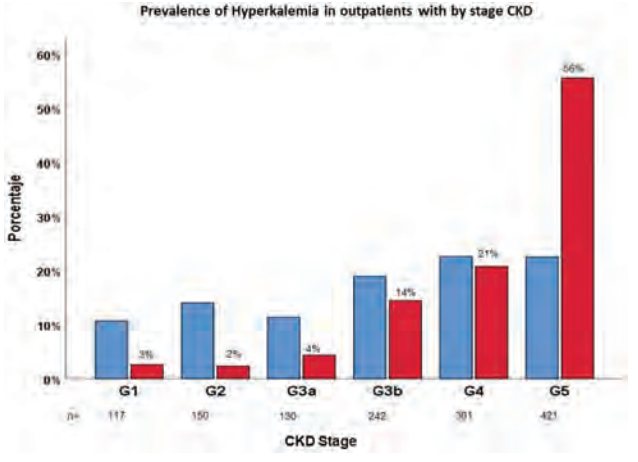
Background: Hyperkalemia (HK) is a frequent complication of chronic kidney disease (CKD), with a prevalence of between 14-20%, which is associated with different factors, such as the use of some antihypertensives (ARA's, IECAS), age, gender, Diabetes Mellitus (DM), cancer. Our aim was to determine the prevalence and factors associated with HK in patients with CKD.

Methods: Transversal study. Patients with CKD who attended the nephrology service of the Hospital General de México during the period Feb 2019 to August 2022 were included. The prevalence and factors associated with HK (K>5) by CKD stage were estimated using regression logistics (95% CI).

Results: 1368 patients were included, with an average age of 55.2±18.8 years; 51% of the population female. The time of suffering from CKD was 1 year (RIQ 2); 16% (223) are in renal replace therapy (93% HD). 74% were overweight or obese, with a mean BMI of 27.1±5.4. The main comorbidities were anemia (55%), hyperuricemia (52%), hypertriglyceridemia (50%), DM (46%), Hypertension (26%). The prevalence of HK was 25% (347), Figure 1. The factors associated with HK by CKD stage were stage 3a, DM (OR 7.5, 1.6-34.7), the use of IECAS (OR 3.7, 12-11.2) and hypertension (OR3.5, 1.1-10.9); in stage 3b, DM (OR 2.06, 1.1-3.8), AINES (OR 2.5, 1.04-6.2, 0.04), Glucose >100 ml/DL (OR 2.01, 1.04-3.8); stage 4 used ARAS (OR 3.9, 1.3-11.3); and in Stage 5 was identified the male gender (OR 1.6, 1.13-2.45) and being on HD (OR 1.8, 1.2-2.7).

Conclusions: HK presented a high prevalence in our population, which increases the risk of death, cardiovascular disease, and hospitalization. An intentional search is necessary from the early stages of CKD, as well as the different associated factors according to the CKD stage.



TH-PO1087

Proximal Tubular Secretory Clearance Is Preserved in Cirrhosis

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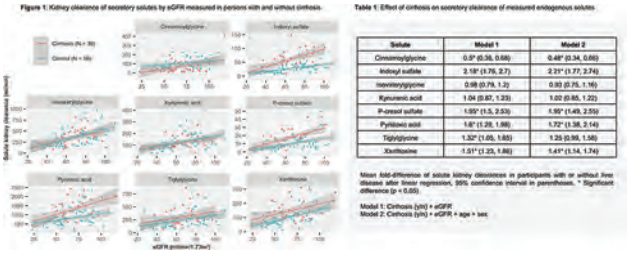
Background: Cirrhosis promotes substantial changes in the metabolic and circulatory milieu, leading to vasoconstriction of the kidney arterioles and a consequent reduction in the glomerular filtration rate (GFR). Liver disease further leads to the retention of toxic metabolites that may impair proximal tubular functions. We tested whether cirrhosis is associated with alterations in tubular secretory clearance in patients referred for liver transplantation.

Methods: We recruited 39 outpatients with end stage liver disease undergoing workup for transplantation. We selected 58 control subjects without liver disease, matched to patients with cirrhosis by their estimated GFR (±10 ml/min/1.73m^2). We estimated tubular secretory solute clearance based on 24-hour urine and plasma concentrations of endogenous solutes measured by LC/MS. We determined the mean fold-difference of secretory clearance using regression of log-transformed clearances and adjusted for eGFR, age, and sex.

Results: Cirrhosis patients were characterized by a mean Child-Pugh 7.9±1.8 or moderate (B) liver disease, 72% male, age 57 ±9 years, and eGFR 65.6 ±19.7 ml/min/1.73m^2. Tubular secretory clearances of most endogenous solutes was equal to or higher in patients with cirrhosis compared to control persons (Fig. 1), which persisted after adjustment for eGFR, age, and sex (Tab. 1). The plasma concentrations of many solutes were substantially lower in cirrhosis (Fig. 2).

Conclusions: In contrast to our hypothesis, proximal tubular secretory clearance is largely preserved or increased in outpatients with cirrhosis. Cirrhosis patients had substantially lower plasma levels of many solutes despite similar kidney function.

Funding: NIDDK Support

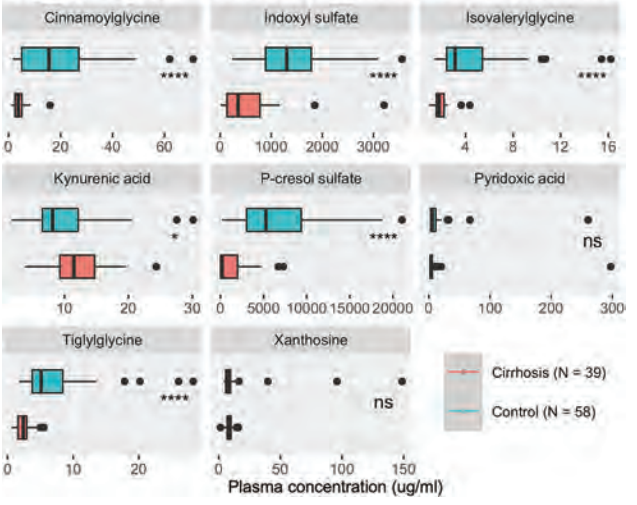


Solute	Model 1	Model 2
Cinnamoylglycine	0.9* (0.56, 0.69)	0.48* (0.34, 0.66)
Indoxyl sulfate	2.18* (1.76, 2.7)	2.21* (1.77, 2.74)
Isovalerylglycine	0.98 (0.79, 1.2)	0.93 (0.75, 1.16)
Kynurenic acid	1.04 (0.87, 1.23)	1.02 (0.85, 1.22)
P-cresol sulfate	1.95* (1.5, 2.53)	1.95* (1.49, 2.55)
Pyridoxic acid	1.6* (1.29, 1.99)	1.72* (1.38, 2.14)
Tiglylglycine	1.32* (1.05, 1.65)	1.25 (0.99, 1.58)
Xanthosine	1.51* (1.23, 1.86)	1.41* (1.14, 1.74)

Mean fold-difference of solute kidney clearances in participants with or without liver disease after linear regression, 95% confidence interval in parentheses. * Significant difference (p < 0.05).

Model 1: Cirrhosis (y/n) + eGFR
Model 2: Cirrhosis (y/n) + eGFR + age + sex

Figure 2: Solute plasma concentration in persons with and without cirrhosis



TH-PO1088

Perceptions About Influenza and COVID-19 Vaccines Among People with CKD: CRIC Study

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Background: Vaccine uptake in people with CKD is suboptimal. Understanding reasons for not getting vaccinated ("non-vaccination") could inform programs seeking to address these concerns.

Methods: In a subset of Chronic Renal Insufficiency Cohort (CRIC) Study participants, we administered a survey on perceptions about influenza and COVID-19 vaccines. Survey development followed the Health Belief Model, including themes of perceived risk, perceived benefits and harms, and cues to action. Response was based on a 5-level Likert scale (strongly agree, agree, neutral, disagree, strongly disagree). The odds of agreeing to each statement in the questionnaire (strongly agree/agree vs. others) were compared between those who did and did not have non-vaccination status, defined as never having received either an influenza vaccine in the last 5 years or a COVID-19 vaccine at any point preceding the survey.

Results: Between July 2022 and March 2023, 199 participants completed the survey (age 71 years, 42% female, 45% Black race, mean eGFR 50 ml/min/1.73m^2); 24 (12%) and 35 (18%) had influenza and COVID-19 non-vaccination status. For both vaccines, agreeing that benefits are exaggerated, that people are lied to about the risks of vaccines, and that vaccines cause side effects were associated with higher odds of non-vaccination; whereas agreeing that vaccines prevent people from becoming seriously ill was associated with lower odds of non-vaccination (Figure). Agreeing that the vaccine causes people to get COVID-19, and that people who had influenza do not need the influenza vaccine, were associated with their non-vaccination status.

Conclusions: Among people with CKD, negative perceptions about vaccine safety and benefits were associated with non-vaccination status. Effectively communicating accurate information tailored by vaccine type may be essential to improve vaccination uptake in people with CKD.

Funding: NIDDK Support

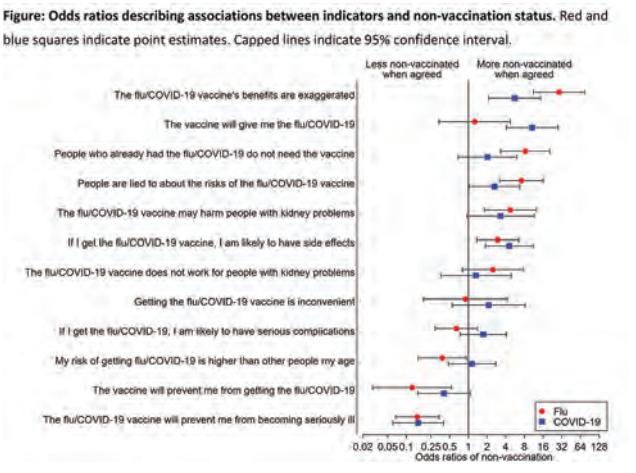

Figure: Odds ratios describing associations between indicators and non-vaccination status. Red and blue squares indicate point estimates. Capped lines indicate 95% confidence interval.

TH-PO1089

Evaluating the Effect of COVID-19 Pandemic on Anxiety in Solid Organ Transplant Recipients

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Background: The impact of the SARS-CoV-2 on mental health, specifically on anxiety symptoms may be pronounced among solid organ transplant recipients (SOTRs), who are immunocompromised and at a higher risk of infection. This study aims to assess the impact of the pandemic on anxiety symptoms in SOTRs.

Methods: Cross-sectional convenience sample of adult kidney, kidney-pancreas, liver and kidney-liver transplant recipients, recruited in studies validating PROMIS tools between 1997-2023. Demographic data are self-reported, clinical data is from health records. Patients completed the PROMIS-29 anxiety v2.0 using 4-item SF or CAT, scored on a T-score metric, where higher score indicates more anxiety symptoms. In our primary analysis, we compare anxiety between patients who completed the questionnaires prior to the pandemic (PRE) vs after the onset of the pandemic (POST). In our secondary analysis, we further divide our POST group into those who were transplanted before (POST-B) and those who were transplanted after the pandemic (POST-A), to further delineate the potential association between the pandemic and anxiety symptoms. Scores were compared using two-sample t-test and linear regression adjusted for organ type, age, sex, ethnicity, education, marital status, economic disadvantage, comorbidity, time since transplant, serum albumin and hemoglobin.

Results: Of 682 participants, 422 (62%) were male, mean(SD) age was 53(15) years. In our primary analysis, mean(SD) PROMIS-29 anxiety scores were higher in POST vs PRE (54[9] vs 52[9], p=0.004). POST anxiety scores were significantly higher in the fully adjusted regression model (coefficient[95% CI]: 2.9[0.9,4.9], p=0.007). In our secondary analysis, the fully adjusted regression model showed that the timing of transplant (prior to or after COVID onset) status was associated with anxiety scores (reference: PRE): POST-A (coefficient[95%CI]: 4.2[0.8,7.6], p=0.019), POST-B (2.4[0.6,5.4]).

Conclusions: Anxiety scores collected in this sample of SOTRs were higher after the onset of the pandemic. These findings suggest that mental health support for SOTRs is relevant and important in the context of the pandemic. Longitudinal studies can assess the development of anxiety symptoms in the future.

TH-PO1090

Psychological Impact After the COVID-19 Epidemic on Hemodialysis Patients in China: A Multi-Center Cross-Sectional Study

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Background: Patients on hemodialysis often suffer from anxiety, depression and sleep disturbances. The questionnaire was used to assess the anxiety, depression,insomnia and social support of Chinese hemodialysis patients after the novel coronavirus disease (COVID-19) epidemic period.

Methods: Sent self-questionnaire to hemodialysis patients to record demographic and clinical information and use Generalized Anxiety disorder 7(GAD-7), Insomnia Severity Index(ISI), Patient Health Questionnaire 9(PHQ-9), Perceived social support scale(PSSS) to investigate the anxiety, sleep, depression and social support. We used logistic regression to analyses independent factor of anxiety, sleep, depression and social support**.**

Results: A total of 1044 questionnaires were collected. 480 cases (46.0%) had mild or higher anxiety, 480 cases (46.0%) had mild or higher insomnia, 927 cases (88.8%) had mild or higher depression, and among which 85.1% had suicidal tendency. 1044 cases (100%) had various degrees of social support. Work status, comorbid underlying diseases, COVID-19 vaccination, social support, depression, and insomnia are independent risk factors for anxiety. Marriage, residence, anxiety, and insomnia are independent risk factors for depressive. Comorbid underlying diseases, COVID-19 infection, anxiety, depression and social support are independent risk factors for insomnia. Comorbid underlying diseases, COVID-19 infection, COVID-19 vaccination, anxiety, depression and insomnia are independent risk factors for social support in hemodialysis patients. (P<0.05).

Conclusions: After the COVID-19 epidemic period, there is a high incidence of anxiety, depression, and sleep disorders in hemodialysis patients, and what needs to be concerned is 85.1% of depressed patients expressed suicidal tendencies. Although hemodialysis patients all have varying degrees of social support, which need more attention.

TH-PO1091

Dynamic Changes of Cycle Threshold Values and Chest CT Quantification in a Prospective Cohort of Hemodialysis Patients with SARS-CoV-2 Omicron Variant

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Background: Hemodialysis patients are at high risk of severe forms of SARS-CoV-2 infection due to their impaired immunity. Earlier warning and intervention may help to avoid adverse outcome. We aim to study the clinical characteristics, dynamic changes of cycle threshold (Ct) values and chest CT quantification in hemodialysis patients with SARS-CoV-2 Omicron variant and to explore the risk factors affecting the outcome in these patients.

Methods: We performed a single center, prospective study in Shanghai sixth People's hospital, a designated hemodialysis center. Clinical information, laboratory results, dynamic Ct values and AI based chest CT quantitative parameters were collected. Primary endpoint was defined as death or ICU admission. Patients were prospectively followed up from the first day of admission until they reached the endpoint or were discharged from hospital. Patients were divided into mild group and severe group according to the exposure to outcome or not. All aforementioned data were compared and analyzed and generalized estimating equation (GEE) was used to identify risk factors from the cohort.

Results: A total of 161 hemodialysis patients with SARS-CoV-2 Omicron variant were included and followed up (median 62 days), among which 31 patients reached the endpoint. Compared to mild group, severe group had a lower Ct value in Day 4. Ct values of the two groups tended to be equal after Day 4. In CT quantitative parameters, severe group had higher thin-section CT scores (TSS), higher percentage of ground glass opacity (GGO) volume (PGV) and higher percentage of consolidation volume (PCV). Both PGV and PCV values got faster growth from Day 0 to Day 4 in severe group than those in mild group, which kept continuously increasing at Day 7 in patients with poor outcome. Multivariate GEE showed age, PCV and phosphorus were independent risk factors for death or ICU admission in hemodialysis patients with Omicron variant, while albumin and lymphocyte count were protecting factors.

Conclusions: Our new findings suggest early and dynamic monitoring of Ct values and AI based chest CT quantitative parameters could be helpful to assess the survival and outcome in hemodialysis patients with SARS-CoV 2 Omicron variant. Optimizing dialysis strategies and improving nutritional status are important in these patients.

Funding: Government Support - Non-U.S.

TH-PO1092

Incorporation of Chest Computed Tomography Quantification to Predict Outcomes in Hemodialysis Patients with COVID-19

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Background: Patients undergoing maintenance hemodialysis are vulnerable to coronavirus disease 2019 (Covid-19) with a higher risk of hospitalizations and mortality. Early identification and intervention is important to prevent the disease progression in these dialysis patients with Covid-19.

Methods: A total of 186 Covid-19 patients from a hemodialysis center in Shanghai 6th People's hospital, China were enrolled between March 2021 and June 2021. 70% of patients (n = 130) were randomly selected in the training set for the establishment of a prognostic nomogram. 30% (n = 56) were included for the validation of the predictive model. Artificial intelligence (AI) based parameters of chest computed tomography (CT) were quantitated; demographic features, comorbidities and laboratory examination items were screened using univariate and multivariate Cox regression analyses to construct a nomogram predicting the risk of death or transferring to ICU within 28 days in hemodialysis patients with COVID-19. The concordance statistics (C- statistics) and calibration curves were used to assess model performance.

Results: The recruited patients had a median age of 65 years (IQR 56-73 years) and 58.6% of participants were male. Median time on dialysis was 4 years (IQR 2-8 years). 81.2% dialyzed through arteriovenous fistula. Age, diabetes mellitus, serum phosphorus, lymphocyte count and thin-section CT scores were identified as independent prognostic factors ($p < 0.05$) which were further incorporated into the nomogram. The C-statistics were 0.865 and 0.748 in the training and validation sets, respectively. Calibration plots show good agreement between expected and actual outcomes.

Conclusions: This is the first study to develop a reliable nomogram using clinical indicators and AI based CT image parameters to predict outcome and survival probabilities in hemodialysis patients with COVID-19. This model could be helpful to clinicians in treating SARS-CoV-2 infection, managing serum phosphorus and adjusting the dialysis strategies in these patients to against severe-critical disease progression.

Funding: Government Support - Non-U.S.

TH-PO1093

Safety and Efficacy of Pre-Exposure Prophylaxis with Tixagevimab/ Cilgavimab (Evusheld) in Patients with Glomerular Diseases Who Received Rituximab

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Background: Patients on B-cell depleting agents may have a suboptimal response to vaccination, placing them at a higher risk of contracting SARS-CoV-2 or suffering from a more severe prognosis. Indeed, available data on pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld) in subjects with glomerular diseases (GD) who received rituximab is limited.

Methods: We conducted a prospective study analyzing the safety and efficacy of tixagevimab/cilgavimab for pre-exposure prophylaxis in patients with GD who received rituximab in the previous 12 months. Rate of symptomatic infections and hospitalizations were compared to patients with GD treated with rituximab who refused to receive tixagevimab/cilgavimab.

Results: Tixagevimab/cilgavimab was administered to 22 patients (12 females, mean age 58,4±19, 6 years) with GD diagnoses including membranous nephropathy, lupus nephritis, ANCA-associated vasculitis and focal segmental glomerulosclerosis. No patient treated with tixagevimab/cilgavimab experienced symptomatic infection with SARS-CoV-2 during the follow-up (mean observation time follow-up was 112 ± 23 days), while 11 out 28 controls (39,3%) reported a symptomatic infection (p=0,001), requiring hospitalization in 2 cases. Reported adverse events were mild, namely self-limiting headache (4), discomfort at the injection site (3), flu-like symptoms/myalgia (3), and fever (1). No serious adverse event, (e.g., cardiac events, anaphylaxis) was reported.

Conclusions: Pre-exposure prophylaxis with tixagevimab/cilgavimab (Evusheld) seems safe and lowering of about 40% the risk of symptomatic SARS-CoV-2 infection in vaccinated subjects with GD who received anti-CD20 therapy. Possible applications in the subset of patients who need immunosuppressive therapy, especially with Rituximab, in a pandemic setting might be envisaged.

TH-PO1094

Effect of Remdesivir on Long-Term Adverse Cardiac and Kidney Outcomes in Patients with COVID-19 and Impaired Kidney Function

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Background: Patients (pts) who survive COVID-19 are at increased risk for cardiac and kidney sequelae. We sought to determine if the use of remdesivir in pts with underlying kidney impairment who were hospitalized for COVID-19 is associated with differences in long-term cardiac and kidney adverse outcomes.

Methods: We performed a propensity-score matched cohort study to compare the risk of major adverse cardiovascular events (MACE), major adverse kidney event (MAKE), slope of eGFR decline among pts hospitalized for COVID-19 with admission eGFR<60mL/min who received remdesivir versus historical comparators admitted prior to EUA for remdesivir (Figure 1). Among pts surviving 30 days and followed up to 18 months, we used Cox proportional hazards model to predict risk of hospitalization/death from MACE and MAKE; we used mixed effect linear model to estimate the eGFR decline slope.

Results: Among the 412 pts who survived >30 days (N=162 for remdesivir-treated cohort, N=250 for historical comparators, variable matching used, Figure1), mean age was 71(SD13), 55% were male, 18% were black, 11% required mechanical ventilation and mean admission creatinine was 1.5mg/dL (1.3 – 2.0). By 18 months, there was no significant difference in MACE or MAKE between the two groups. However, remdesivir use was associated with a significant attenuation of eGFR decline between 30 days to 18 months (-0.77 vs. -2.81 mL/min/year) (Table1).

Conclusions: Among pts with underlying kidney impairment hospitalized for COVID-19 who survived >30 days, remdesivir use was not associated with reduction of MACE or MAKE. However, there was attenuation of eGFR decline in pts treated with remdesivir.

Funding: Commercial Support - Gilead Science

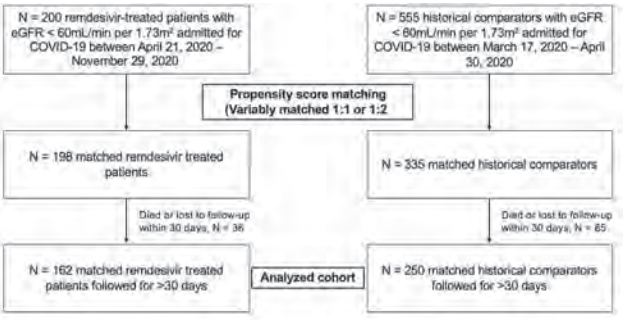

Figure 1: Patient flow: We matched patients across independent variables associated with remdesivir administration, including age, sex, race/ethnicity, sequential organ failure assessment (SOFA) score at admission, presenting creatinine, history of diabetes, hypertension, cardiovascular disease, chronic kidney disease and ESKD status, prior solid organ transplantation, and number of inpatient and outpatients encounters within MGB within 1 year prior to COVID-19. We performed variable 1:1 or 1:2 nearest-neighbor matching without replacement with a caliper of 0.1 standard deviation of the propensity score.

Unadjusted Model	eGFR slope	95% CI		p value
All patients survived ≥30 days (n=384)				
Controls	-2.90	-3.93	-1.86	<0.01
Remdesivir	-0.74	-2.01	0.53	
Multivariable Model*	**eGFR slope**	**95% CI**		**p value**
All patients survived ≥30 days (n=384)				
Controls	-2.81	-3.85	-1.78	0.01
Remdesivir	-0.77	-2.03	0.50	

Table 1. Slope of eGFR (mL/min/1.73m²/year) of the 384 patients without ESKD at baseline. Sensitivity analysis of only paired patients (N=336) revealed similar findings. The multivariable model is adjusted for age, sex, black race, diabetes, hypertension, coronary artery disease, congestive heart failure, solid organ transplant, requiring mechanical ventilation within 72 hours, SOFA score, admission serum creatinine, frequency of overall and inpatient encounters in the year prior to admission for COVID-19.

TH-PO1095

Safety and Efficacy of Nirmatrelvir/Ritonavir in Patients with Moderate-Severe CKD with COVID-19: A Real-World Data Study

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Background: Chronic kidney disease (CKD) is a mortality risk factor for COVID-19, predisposing patients to poor clinical outcomes. Nirmatrelvir/ritonavir (Nm/r) is currently the most effective oral antiviral agent for COVID-19, with 89% reduction in hospitalization and mortality. The U.S. Food and Drug Administration advised against Nm/r in severe CKD patients due to lack of study. In this propensity-matched retrospective study, we assess side effects, efficacy, and severity of clinical outcomes in Nm/r-treated moderate-severe CKD patients with COVID-19.

Methods: Patient data was accessed from TriNetX, a platform that aggregates health record data of over 123 million patients. The experimental group consisted of Stage 3-5 CKD patients, with 2 separate eGFR measurements of <60 mL/min/1.73m², prescribed Nm/r after COVID-19 infection. The control cohort was any non-CKD patient with COVID-19 prescribed Nm/r. Cohorts were 1:1 propensity matched for age, sex, race, and comorbidities: diabetes mellitus, hypertension, ischemic heart disease, heart failure, cerebrovascular disease, respiratory disease, smoking, and alcohol use. Outcomes assessed were COVID-19 rebound within 5-14 days, side effects within 5-35 days, and clinical outcomes (hospitalization, emergency department (ED) visit, intensive care unit (ICU) admit, and mortality) within 35 days. Odds ratio (OR) and hazard ratio (HR) with 95% confidence intervals (95%CI) and Kaplan-Meier analysis were calculated.

Results: After matching, 2,491 patients were included in the analysis. Moderate-severe CKD patients were at greater risk of developing nausea/vomiting (OR 4.32, 95%CI 2.35-7.93), diarrhea (OR 2.78, 95%CI 1.64-4.72), and fatigue (OR 1.78, 95%CI 1.23-2.55). These side effects were associated with lower survival probability within 35 days, by 2.1%, 1.6%, and 1.5%, respectively. CKD patients were also at greater risk of COVID-19 rebound (OR 1.33, 95%CI 1.08-1.65), hospitalization (HR 5.75, 95%CI 4.06-8.15), and ED visit (HR 1.68 95%CI 1.29-2.17).

Conclusions: Our findings show that moderate-severe CKD patients fare greater risk of side effects, COVID-19 rebound, and severe outcomes compared to non-CKD high-risk groups even after Nm/r. Providers should counsel patients and monitor the side effect profile and risk of COVID-19 rebound in Nm/r treated CKD patients.

Funding: Other NIH Support - This project was supported in part by the Clinical and Translational Science Collaborative of Cleveland which is funded by the National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Science Award grant, UL1TR002548. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

TH-PO1096

Outcomes of Nitrelmivir-Ritonavir in Patients with Advanced CKD and COVID-19

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Background: Patients with chronic kidney disease (CKD) are vulnerable to severe novel coronavirus-2019 infection (COVID-19). Nirmatrelvir-ritonavir is an effective oral antiviral therapy, but it is not recommended in patients with eGFR < 30 ml/min/1.73m².

Methods: This is a prospective interventional trial that included COVID-19 patients with eGFR < 60 ml/min/1.73m² including dialysis. A 5-day course of nirmatrelvir-ritonavir was prescribed at a modified dosage. The adverse event, viral response and disease rebound were compared between high (> 30 ml/min/1.73m²) and low eGFR (< 30 ml/min/1.73m²). We further compare the treatment failure rate with a cohort treated with molnupiravir.

Results: 59 of the 85 participants had stage 5 CKD and were on dialysis. 9.4% had adverse events, which were comparable between eGFR groups. The viral load significantly reduced on day 5, 15 & 30 (p < 0.001 for all), including the low eGFR group (Fig 1). 10 patients had virological rebound, though was transient and asymptomatic. The rate of adverse clinical outcome was significantly lower compared to molnupiravir users (6.8% vs 21.7%, p = 0.01, Fig 2), and the significance persisted in the multivariate model (odds ratio 0.16, 95% confidence interval 0.04 – 0.71, p = 0.016).

Conclusions: Modified dose of nirmatrelvir-ritonavir is well-tolerated and effective in patients with COVID-19 and CKD including dialysis.

Funding: Private Foundation Support

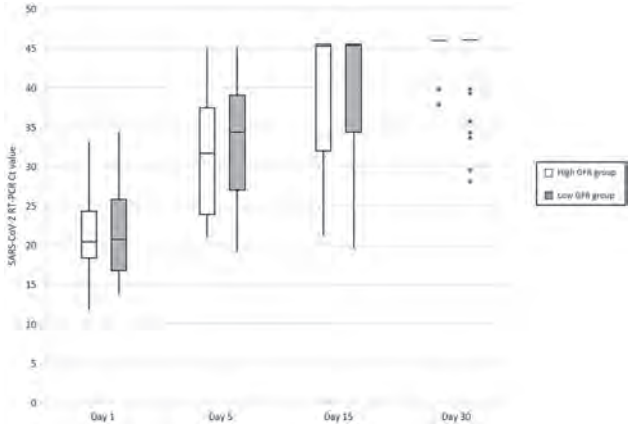


Figure 1

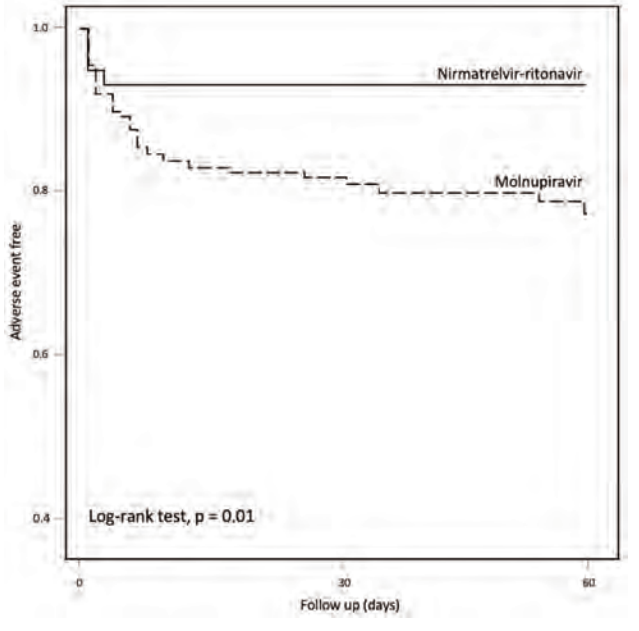


Figure 2

TH-PO1097

A Meta-Analysis to Evaluate the Safety of Remdesivir in Patients with Reduced Renal Function

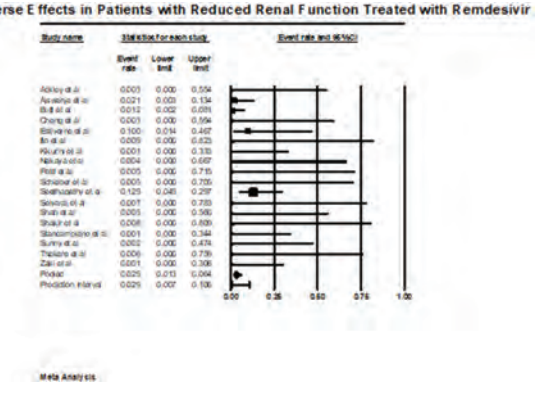
Deepak Chandramohan,[1] Divya Chandramohan,[2] Apoorv Deotare,[1] Ashwini S. Pujari,[1] Sreekant Avula.[3] *[1]The University of Alabama at Birmingham, Birmingham, AL; [2]The University of Texas at San Antonio, San Antonio, TX; [3]University of Minnesota Twin Cities School of Medicine, Minneapolis, MN.*

Background: Remdesivir is approved by the U.S. FDA for treating coronavirus disease-2019 (COVID-19). However, the clinical trials assessing remdesivir's efficacy did not include patients on dialysis and those with an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m2. Sulfobutylether-β-cyclodextrin (SCEBD), the solubilizing excipient used in intravenous formulations could accumulate in renal tubules causing further renal dysfunction. We performed a meta-analysis to find the safety profile of this therapeutic agent.

Methods: We systematically searched PubMed, Google Scholar, EMBASE, Cochrane, Web of Science and Clinical trials.gov from inception to January 2023 to identify studies with CKD and ESRD patients over 18 years of age with COVID-19 who received Remdesivir therapy. Using a random effects model, proportional effect sizes were calculated. The heterogeneity between study-specific estimates was assessed by the I^2 statistics. The primary outcome were the pooled rates of liver failure, renal failure and serious adverse effects. Secondary outcomes assessed were requirements of oxygen, mechanical ventilation, and mortality rate.

Results: Eighteen studies (764 patients) met the inclusion criteria. 58.3% (95% CI: 49.5-66.6; I^2= 76.9%) were males. 82.6% (95% CI: 65.3-92.3; I^2= 87.7%) were ESRD on dialysis. Severe liver failure occurred in 1.6% (95% CI:0.6-3.9; I^2= 0%). The rate of renal failure in eGFR of <30 mL/min/1.73 m2 was 8.9% (95% CI:4.6-16.5; I^2= 0%). The pooled proportion of all serious adverse effects due to remdesivir was 2.9% (95% CI:1.3-6.4; I^2= 7.8%). 17.7% (95% CI: 13.0-23.7; I^2= 62.5%) were on mechanical ventilation. The mortality rate in CKD and ESRD patients treated with remdesivir was 26.8% (95% CI: 21.1- 33.5; I^2= 65.4%).

Conclusions: The use of remdesivir in CKD and ESRD is relatively safe from our meta-analysis. Randomized clinical trials are needed to further evaluate the safety and other adverse effects of remdesivir in this population.



TH-PO1098

Remdesivir in COVID-19 Patients with Kidney Disease: A Study on the Renal Function and Outcomes

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Background: The COVID-19 pandemic has high mortality rates in patients with kidney disease. Remdesivir, an antiviral nucleotide prodrug, showed to shorten time to recovery in adults hospitalized with COVID 19. However, individuals with kidney disease were not included in clinical trials, thus when emergency use authorization was granted, it was recommended to avoid use in patients with eGFR <30mL/min "unless benefit outweighs the risk". In this study, we aim to determine the effect of Remdesivir on renal function and outcomes among COVID19 patients with kidney disease.

Methods: This retrospective study included the following: >18 years old, RT-PCR confirmed COVID19 infection treated with Remdesivir and who were confirmed to have kidney disease.

Results: There were 106 patients included; the mean age was 62.25±13.96 years old, more than half of the population were males (53%). The majority of the population had acute kidney injury (70.7%) while the rest had chronic kidney disease and 25% underwent renal replacement therapy. Most of them were classified as severe (66%) and critical (25%) COVID infection. To determine effects on renal function laboratory parameters were determined at baseline and after completion of treatment. There was an overall significant improvement in eGFR (<0.01), albuminuria (0.013) and in acid-base balance (0.003) and odds ratio showed that none of the demographic, clinical and laboratory profile significantly increased the chance of death in terms of overall clinical outcome. In terms of overall clinical outcome, this study had a mortality rate of 4.9% as 5 out of 106 patients expired.

Conclusions: Use of Remdesivir in patients with kidney disease was not associated with renal function deterioration. Contrary to concerns there was rather an overall significant improvement in eGFR, degree of albuminuria and acid-base balance after treatment regardless of their disease severity and its use in patients on hemodialysis have not shown any detrimental impact on mortality.

TH-PO1099

COVID-19-Associated C-ANCA Vasculitis

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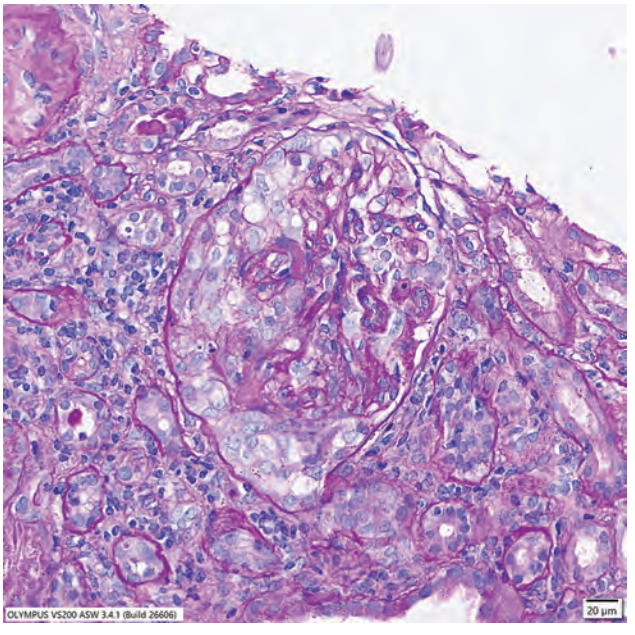
Introduction: Anti-neutrophil cytoplasmic antibody (ANCA) associated vasculitis is a group of systemic vasculitis that causes inflammation and destruction of the small and medium-sized blood vessels and can cause acute renal failure. SARS-CoV-2 (COVID-19) has been shown to increase the risk for autoimmune diseases. We present a case of C-ANCA vasculitis a few weeks after COVID-19 infection which was successfully treated with steroids and Rituximab.

Case Description: 87-year-old female with hypertension presented with generalized weakness, malaise, and myalgias. She had COVID-19 infection with bronchitis symptoms a few weeks before the presentation. She has no history of kidney disease; labs showed creatinine of 2.99 mg/dl, BUN of 36 mg/dl with eGFR of 14. Urine dipstick showed 3+ proteinuria and 3+ hematuria. Labs showed serum Anti-proteinase-3 antibody titers of 1:946, C-ANCA titers of 1:1280, and myeloperoxidase, P-ANCA were negative. Renal biopsy showed necrotizing and crescentic glomerulonephritis. Immunofluorescence: granular mesangial and capillary loop staining with 3+ staining for IgG, IgM, C3, kappa, and lambda. Infection-related crescentic vasculitis was considered and ruled out with negative blood and urine cultures. She was given pulse dose steroids and four weekly doses of Rituximab. Prednisone was tapered to 10 mg daily over 8 weeks. She had significant improvement with her generalized weakness, anemia, and myalgias. Even though her eGFR recovery (17) was marginal, proteinuria and hematuria resolved completely and ANCA titers improved which indicates improving vasculitis activity.

Discussion: A few cases of COVID-19-associated ANCA vasculitis have been reported but data regarding management is scarce. Our case highlights the safety and efficacy of prompt Rituximab and steroid therapy in patients with COVID-associated ANCA vasculitis.



TH-PO1100

A Case of Newly Diagnosed Systemic Lupus Erythematosus and Lupus Nephritis After COVID-19 Infection

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Introduction: Systemic Lupus Erythematosus (SLE), the most common form of lupus, is a chronic autoimmune inflammatory disease with clinical manifestations affecting any organ. Kidney involvement is seen in about 50% of patients, leading to CKD or ESKD. The year 2019 brought on a pandemic caused by the virus Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Here we illustrate a case of SLE and lupus nephritis with clinical manifestations discovered after COVID-19 infection.

Case Description: A 39-year-old Hispanic male presented to our institution with abdominal pain associated with nausea and vomiting, recurrent skin rash, hematuria, weight loss of 40 pounds over the past several months and joint pains. Prior to this admission, he had multiple visits to the hospital for abdominal pain, general malaise, and joint pain that started about 9 months after a 5-day course of COVID-19 infection; and subsequently diagnosed with urticarial vasculitis with colitis during one of his hospital admissions. Physical examination was notable for tenderness to the epigastric and periumbilical region, and multiple umbilicated papules of the elbows and palms and tense bulla of the left third digit. His laboratory findings revealed elevated creatinine, anemia and urinalysis showed hematuria. Previous autoimmune workup was positive for ANA, ds-DNA, Sjogren's antibodies and low C3 and C4 complements. His CT abdomen without contrast showed a thickened terminal ileum with inflammatory changes consistent with colitis. Skin biopsy findings were consistent with small vessel vasculitis. Subsequent renal biopsy confirmed immune complex – mediated glomerular nephritis with full house tubular inclusions and subepithelial deposits consistent with membranous lupus nephritis. He was treated with IV methylprednisolone, PO prednisone, with plans for starting Cyclophosphamide.

Discussion: The link between lupus and colitis is rare in the literature. Similarly, the link between lupus and COVID-19 is also rare with only case reports of both scenarios currently existing. This and other case reports in the literature hopes to spark the discussion and later the investigation as to the possible reasons for both occurrences.

TH-PO1101

COVID-19 Vaccination (VAX) and Infection (INF)-Related Glomerular Diseases (GNs)

Phuong-Chi T. Pham,[1] Vinod K. Valluri,[1] Golriz Jafari,[1] Anita Kamarzarian,[1] Kulwant S. Bath,[1] Masoud Haghi,[1] Phuong-Thu T. Pham.[2] *[1]UCLA Medical Center Olive View, Sylmar, CA; [2]University of California Los Angeles, Los Angeles, CA.*

Background: There have been numerous reports of GNs associated with both COVID-19 VAX and INF. We performed a systematic review per PRISMA involving reported COVID-19 VAX and INF-associated GN cases to explore for supportive evidence of a cause-and-effect rather than a fortuitous relationship.

Methods: We searched NLM, EMBASE, and the World Health Organization COVID-19 database for case reports and series, and observational studies for reported VAX or INF-associated GNs.

Results: Of 1261 articles identified, 117 articles were included. Fifty-eight articles pertained to infection- and 59 to vaccine-related GNs. Among vaccine-related GNs, the top 3 diagnoses were IgA nephropathy (IgAN, 35 out of 111 cases, 31.5%), anti-neutrophil cytoplasmic antibody-associated GN (ANCA, 23 out of 111, 18.9%), and minimal change disease (MCD, 23 out of 111, 18.9%). Among infected patients, the top 3 were focal segmental glomerulosclerosis (FSGS, 90 out of 162, 55.6%), ANCA-associated GN (34 out of 162, 21.0%), and IgAN (12 out of 162, 7.4%). The distributive patterns of reported GNs associated with the VAX and INF differ significantly compared with that in the pre-COVID era, where excluding diabetic glomerulosclerosis, the top 3 GNs globally were FSGS 17.4%, IgAN 16.5%, and MN 12.1%.

Conclusions: Based on the pathogenesis of GNs and systemic immune response to COVID-19 VAX and INF and the observed differences in GN patterns among pre-COVID era, VAX, and INF-reported GN cases, we suspect that the relationship betweent VAX and INF-reported GNs were directly causal rather than coincidental.

GN	Pre-COVID global distribution (%)	COVID-19 vaccine n (%)	COVID-19 infection n (%)
Focal segmental glomerulosclerosis	17.4	3 (2.7)	90 (55.6)
IgA nephropathy/Henoch Schonlein purpura	16.5	35 (31.5)	12 (7.4)
Diabetic kidney disease	13.9	0 (0)	0 (0)
Membranous nephropathy	12.1	10 (9)	6 (3.7)
Lupus nephritis	12.2	4 (3.6)	1 (0.6)
ANCA	6.2	21 (18.9)	34 (21)
Minimal change disease	5.2	21 (18.9)	2 (1.2)
MPGN/C3GN	3	3 (2.7)	0 (0)
Renal amyloid	2.9	1 (0.9)	1 (0.6)
TTP/HUS	2.5	4 (3.6)	12 (7.4)
Others	8.1	9 (8.1)	4 (2.5)
Total	100	111 (99.9)	162 (100)

Glomerular diseases reported following COVID-19 vaccination and infection in non-transplant patients.

TH-PO1102

Impact of COVID-19 Infection in a Glomerular Disease Unit

Miguel Uriol Rivera, Felipe I. Ojeda, Estela M. Ródenas, Aina Obrador, Sonia Jimenez. *Hospital Universitario Son Espases, Palma, Spain.*

Background: COVID-19 infection poses a significant global health challenge, yet its impact on glomerular disease patients (GDP) remains understudied. This research aims to investigate the mortality and chronic renal replacement therapy (CRRT) rates among GDP, identify predictive factors, and explore the influence of proteinuria on the evolution of estimated glomerular filtration rate (eGFR).

Methods: This retrospective study compares the annual eGFR changes in GDP before and after COVID-19 infection. The study period spans from January 10, 2020, to July 28, 2022. Proteinuria was defined as a urine protein/creatinine ratio exceeding 0.2 mg/mg.

Results: Among the 302 GDP included, 64 (21%) contracted COVID-19. The mean age was 47 years. Sex: Females 31 (48%) patients. Infection rates were 9% in 2020, 28% in 2021, and 63% in 2022. Of the infected patients, 12 (19%) either died

(9) or initiated CRRT (3). Age, eGFR, and proteinuria at admission were identified as independent predictive factors for death or the need for chronic renal replacement therapy. Hospitalization was required for 21 (33%) patients, with 6 necessitating intensive care unit admission. Excluding those who died or initiated CRRT, 52 patients were followed up for an average duration of 17 months (ranging from 9 to 40 months). During this period, the annual mean change in eGFR between the pre- and post-COVID-19 infection periods was -10.3 mL/min/1.73m2 (95% confidence interval: -17.9 to -2.8, P=0.008). At the time of infection, eGFR decreased by 6.8 mL/min/1.73m2 (3.9 to 9.8). Patients without proteinuria experienced eGFR recovery, while those with proteinuria exhibited a progressive decline in eGFR (Figure 1).

Conclusions: Twelve (19%) GDP patients either died or initiated CRRT, with age, eGFR, and proteinuria serving as significant predictor factors. The trajectory of eGFR shifted following COVID-19 infection in GDP, with proteinuria notably contributing to a progressive and accelerated decline in eGFR.

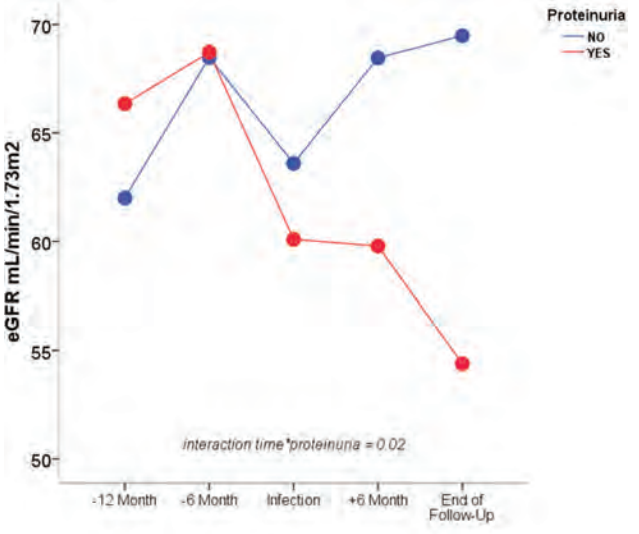


Figure 1

TH-PO1103

Risk Factors for the Relapse and Aggravation of Patients with Primary Membranous Nephropathy After COVID-19 Infection

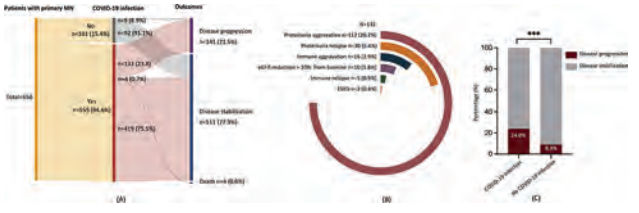
Yue Shu, Zhao Cui. *Peking University First Hospital Department of Nephrology, Beijing, China.*

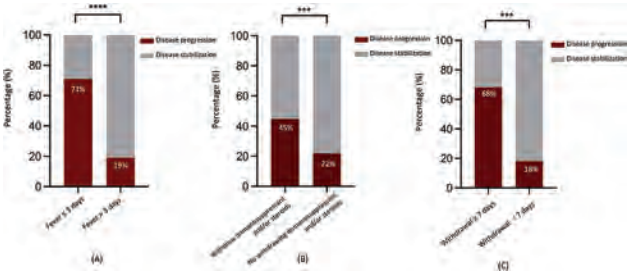
Background: Relapse cases of membranous nephropathy (MN) and other glomerular diseases have been reported after the infection of COVID-19. The risk factors for MN disease progression after COVID-19 infection need to be clarified.

Methods: A retrospective study were conducted from November 11th, 2022 to February 22nd, 2023 on 656 consecutive patients with biopsy-proven primary MN who had been treated and followed up for more than 6 months. Logistic regression analyses were performed to identify the risk factors.

Results: 555 (84.6%) patients underwent COVID-19 infection. Among them, 112 (20.2%) patients experienced urinary protein aggravation > 50% from the baseline, including 30 (5.4%) patients with relapse of nephrotic syndrome. 16 (2.9%) patients got immune aggravation with the increase of anti-PLA2R levels and five (0.9%) patients got immune relapse with antibody reoccurrence. Ten (1.8%) patients got kidney dysfunction with eGFR reduction > 30% from the baseline, among them two (0.4%) patients progressed into ESKD. Four (0.7%) patients died of respiratory failure. Taken together, 132 (24%) patients experienced disease progression after COVID-19 infection. Multivariate logistic analysis showed that the longer duration of fever (OR 1.118, 95% CI 1.029-1.356, *P*=0.018), the withdrawal of immunosuppressants and/or steroids (OR 2.571, 95% CI 1.377-4.799, *P*=0.003) and the longer time of withdrawal (OR 1.113, 95% CI 1.045-1.186, *P*=0.001) were independent risk factors for MN progression.

Conclusions: The findings proposed an active anti-virus treatment and no or shorter time of immunosuppressants withdrawal for a better prognosis of kidneys on the clinical practice of MN patients with COVID-19 infection.





TH-PO1104

A Case of Membranous Nephropathy and Collapsing Focal Segmental Glomerulosclerosis After COVID-19 mRNA Vaccination

Mark Rudy, B. Peter E. Sawaya, Sadiq Ahmed. *University of Kentucky College of Medicine, Lexington, KY.*

Introduction: The mRNA COVID-19 vaccines have been an effective method for combating the deadly COVID-19 virus. In the literature, there are case reports of glomerulopathies developing after vaccination. It is important to be aware of this potential association to allow for prompt investigation and treatment. We highlight a case of combined membranous nephropathy and collapsing focal segmental glomerulosclerosis in a 36-year-old male after mRNA COVID-19 vaccination.

Case Description: A 36-year-old white male was referred to our clinic for nephrotic syndrome. He developed symptoms of lower extremity edema and fatigue two months after receiving the second dose of an mRNA COVID-19 vaccination. He did not seek medical care at that time. After 11 months he had laboratory studies that showed a serum creatinine of 0.78 mg/dL, serum albumin of 1.6 g/dL, PLA2R antibody titer of 108 Ru/mL, and 24-hour urine with > 15 grams of protein. A kidney biopsy showed membranous glomerulopathy Stage II-III with frequent segmental sclerosis with collapsing features as well as severe interstitial inflammation. He was treated with ACE-I, statin, and two infusions of 1-gram Rituximab given two weeks apart. 6 months after his treatment, his serum albumin was 3.1 g/dL, PLA2R antibody titer was 10 RU/mL, and urine protein to creatinine ratio was 6.1 g/g and his lower extremity edema and fatigue markedly improved.

Discussion: This case illustrates an unusual combination of membranous nephropathy, collapsing FSGS and interstitial inflammation after receiving COVID-19 mRNA vaccination with partial response to Rituximab at 6 months. Membranous nephropathy and FSGS have been reported after COVID-19 vaccines or infection, but the combination is rarely seen in the literature. This case emphasizes the need for awareness of the diversity of glomerulopathies associated with the COVID-19 mRNA vaccination.

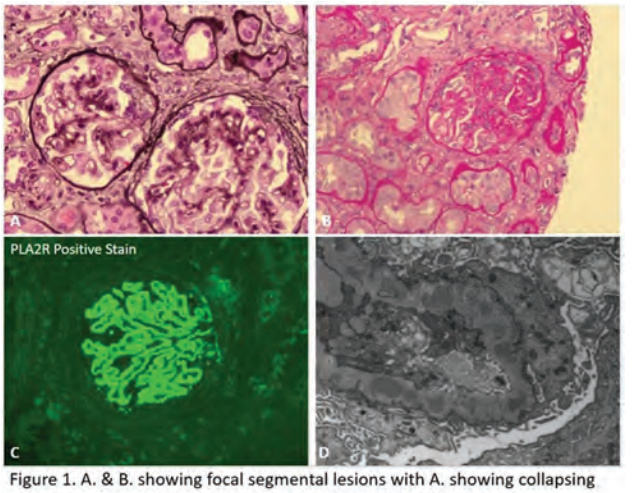


Figure 1. A. & B. showing focal segmental lesions with A. showing collapsing features C. PLA2R Positive Stain D. Subepithelial deposits

TH-PO1105

Case of Membranous Nephropathy (MN) After COVID-19 Vaccine

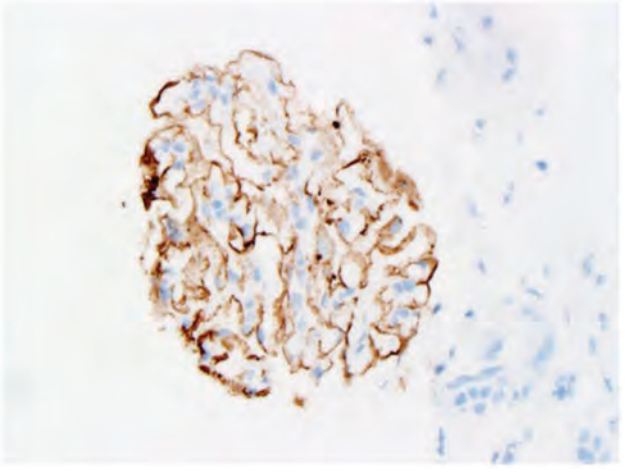
Tahir A. Jatoi, Sandeep R. Sasidharan, Omar N. Elhawary, Mohammad W. Abushawer, Sonalika Agarwal, Mary C. Mallappallil, Isha Puri. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Covid vaccines are considered the best approach to prevent SARS-CoV-2 infection. There are few biopsy proven cases reported of glomerular pathology associated with COVID-19 vaccines. Here we present a case of primary membranous nephropathy (anti-PLA2R positive) that developed after Pfizer-BioNTech COVID-19 vaccine.

Case Description: 56 y-o M with history of HTN and recent PE with negative hypercoagulability work up, on Eliquis presented with complaints of leg and orbital

edema for 6 weeks. He had similar complaints few months ago and presented to an outside hospital when he was diagnosed with PE. He reported that he first noted swelling in his lower extremities after the first dose of covid vaccine which worsened after he received the second dose. Labs showed a Serum Creatinine of 1.3 mg/dl, urine protein>300, Serum albumin 1.7 mg/dl, HbA1c of 5.8, Spot UPCR was 6.8 g/g and anti-PLA2R titers were 539. Renal biopsy was done which showed positive granular capillary wall staining for PLA2R1 (2+) and mild interstitial fibrosis with tubular atrophy. Immunofluorescence was positive for IgG, C3, Kappa and Lambda light chains. Electron Microscopy showed glomerular subepithelial dense deposits, with slight mesangial expansion and epithelial foot process effacement diagnostic for stage 1 MN and ATN. He was treated with supportive measures initially and later switched to Rituximab infusion for two doses after biopsy confirmed MN. He had poor response and his UPCR remained >10g/d. Tacrolimus was subsequently added for persistent proteinuria but without sufficient response. He was then started on a cyclical corticosteroids and Cyclophosphamide with successful achievement of remission.

Discussion: MN accounts for 20-30% of Nephrotic syndrome cases. Anti-PLA2R antibodies are identified in 70-80% of primary MN cases. Given recent reports of de-novo glomerular diseases after receiving COVID-19 vaccines in depth studies of vaccinated patients are needed to establish a causal relationship.



Biopsy

TH-PO1106

New Onset of Membranous Nephropathy and Renal Vein Thrombosis After SARS-CoV-2 Infection

Areebah Qadir,[1] Aamna F. Hameed,[2] Mohammad R. Khan,[1] Aemen S. Khakwani,[3] Nabiha Mustafa,[1] Sadaf Munir,[4] Usman A. Khan.[5] *[1]Bakhtawar Amin Medical and Dental College, Multan, Pakistan; [2]Shifa College of Medicine, Islamabad, Pakistan; [3]Suburban Community Hospital, Norristown, PA; [4]CMH Multan Institute of Medical Sciences, Multan, Pakistan; [5]University of Oklahoma and VA Medical Centre, Oklahoma City, OK.*

Introduction: COVID-19 was identified as a cause of a cluster of pneumonia cases in the province of Wuhan in China in 2019 and soon was declared a pandemic by WHO in February 2020. Though COVID-19 is mainly a pulmonary disease, there have also been reports of extrapulmonary manifestations of the disease affecting the renal system, among other systems. We present a unique case of a patient diagnosed with membranous nephropathy post-COVID-19 infection.

Case Description: A 37-year-old man presented to the Emergency department with primary complaints of hematuria, fever, and right lower quadrant abdominal pain. Recent past medical history revealed mild Covid-19 infection with resolution in 2 weeks. Laboratory analysis showed creatinine at 1.8mg/dL, protein to creatinine ratio of 9.5g/g, and albuminuria of 12g/L. Doppler of both kidneys showed right renal vein thrombosis. Biopsy on day 4 showed thickening of the basement membrane with PLA2R staining positive. The patient was started on ACE inhibitors and rituximab for 14 days. After following the prescribed regimen, the patient showed complete resolution of proteinuria, with normal creatinine function.

Discussion: Membranous nephropathy can be primary PLA2R+ or secondary, and COVID-19 infection and immunization have recently been linked to its increased incidence. Podocytes, neutrophils, airway epithelial cells, and macrophages all express PLA2R-Antigen, and upon getting triggered by a foreign antigen such as COVID-19 these cells release extracellular vesicles containing PLA2R or cause the longitudinal release of PLA2R by engendering extracellular traps, subsequently exciting B lymphocytes to produce PLA2R-Antibody. Additionally, the oxidative environment induced by inflammatory cytokines may result in longstanding expression of PLA2R pathogenic epitopes and increase their ability to bind to circulating antibodies. We believe a recent COVID-19 infection, triggered this cascade in our young 37-year-old patient and resulted in nephrotic syndrome, albuminuria, membranous nephropathy, and renal vein thrombosis.

TH-PO1107

Series of Glomerular Diseases Developed After COVID-19 mRNA Vaccination

Kenichiro Abe,[1] Hitoshi Suzuki,[1,2] Yukako Umezawa,[1] Hitomi Hirose,[1] Takeo Koshida,[1] Tomomi Hirasawa,[1] Arisa Kato,[1] Hiromitsu Fukuda,[1] Hisatsugu Takahara,[1] Yusuke Suzuki.[2] *[1]Juntendo Daigaku Igakubu Fuzoku Urayasu Byoin, Urayasu, Japan; [2]Juntendo Daigaku Igakubu Daigakuin Igaku Kenkyuka, Bunkyo-ku, Japan.*

Introduction: The coronavirus disease 2019 (COVID-19) vaccine has been proven effective in preventing severe COVID-19 infection. Meanwhile, many vaccine-related adverse events have been reported with the increasing use of messenger RNA (mRNA)-based COVID-19 vaccines. In fact, cases of vaccine-related new-onset and relapsing glomerular diseases, including minimal change disease (MCD), anti-neutrophil cytoplasmic autoantibody-associated vasculitis, immunoglobulin (Ig)G4-related disease, and IgA nephropathy (IgAN), have been reported. Here, we report 40 patients who developed glomerular diseases after COVID-19 mRNA vaccination.

Case Description: We evaluated the clinical characteristics, vaccine types, and clinical outcomes of 40 patients whose urinalysis indicated proteinuria and/or occult blood after COVID-19 mRNA vaccination. For a definitive diagnosis, we performed a renal biopsy and evaluated their histological findings. Out of 40 patients, 27 (67.5%) were female, and 13 (32.5%) were male. The median patient age was 41 years (range, 15–78). Seventy-five percent of patients received BioNTech Pfizer vaccines, and 25% received Moderna vaccines. Gross hematuria was observed in 85% of patients, and 15% presented with nephrotic syndrome. Twenty-seven patients (67.5%) were diagnosed as IgAN by renal biopsy, while the remaining were diagnosed with MCD, TAFRO syndrome, membranous nephropathy, proliferative glomerulonephritis with monoclonal Ig deposits, thrombotic microangiopathy, and anti-glomerular basement membrane disease. Four patients with IgAN who previously diagnosed and underwent treatment showed exacerbation of urinary abnormalities.

Discussion: Various glomerular diseases developed after COVID-19 mRNA vaccination. However, the mechanisms underlying mRNA vaccine induced kidney disease remain unclear. Several hypotheses have been proposed regarding the mechanism by which an mRNA vaccine triggers an adaptive immune response to display its protective effect, which may stimulate a hyperinflammatory condition. Further studies are necessary to elucidate the underlying biological mechanisms and identify the exact causal relationship.

TH-PO1108

The Severity of Microscopic Hematuria in IgA Nephropathy Correlates with the Incidence of Gross Hematuria Following SARS-CoV-2 mRNA Vaccination

Shinya Yokote, Nobuo Tsuboi, Akihiro Shimizu, Masahiro Okabe, Kotaro Haruhara, Takaya Sasaki, Hiroyuki Ueda, Takashi Yokoo. *Tokyo Jikeikai Ika Daigaku, Minato-ku, Japan.*

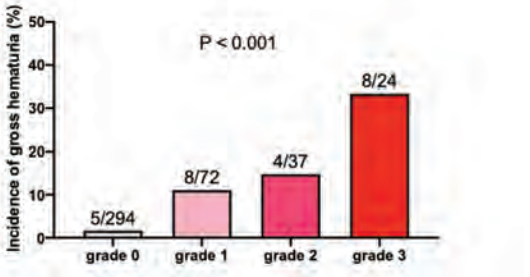
Background: Since the initiation of a global vaccination program against the COVID-19 pandemic, numerous cases of newly diagnosed or worsening immunoglobulin A nephropathy (IgAN) with gross hematuria have been reported following SARS-CoV-2 mRNA vaccination. Recent case studies have indicated a possible link between baseline urinary findings and the appearance of gross hematuria following SARS-CoV-2 mRNA vaccination.

Methods: Outpatients with biopsy-proven IgAN aged 18 years or older were included in this study. The association between pre-vaccination microscopic hematuria (urine sediment < 5 /HPF) or proteinuria (< 0.3 g/gCr) and post-vaccination gross hematuria was retrospectively analyzed.

Results: A total of 417 IgAN patients (mean age, 51 years; 56 % female; eGFR, 58 mL/min/1.73 m^2) were included. The frequency of post-vaccination gross hematuria was higher in patients (20/123; 16.3%) with pre-vaccination microscopic hematuria than in patients (5/294; 1.7%) without pre-vaccination microscopic hematuria ($p < 0.001$). There was no association between pre-vaccination proteinuria and post-vaccination gross hematuria. After adjustment for potential confounders such as gender (female), age group (< 50 years), eGFR category (≥ 60 mL/min/1.73m^2), and prior tonsillectomy or corticosteroid therapy, microscopic hematuria was still associated with post-vaccination gross hematuria (OR 8.98, $p < 0.001$). Notably, as the severity of pre-vaccination microscopic hematuria increased, the incidence of post-vaccination gross hematuria increased (**Figure 1**).

Conclusions: These results suggest that baseline microscopic hematuria predicts gross hematuria after SARS-CoV-2 mRNA vaccination in patients already diagnosed with IgAN. The correlation between the severity of pre-vaccination microscopic hematuria and the incidence of post-vaccination gross hematuria suggests that IgAN disease activity is involved in this association.

Figure 1



The red blood cell (RBC) count in the urinary sediment was graded as follows: 0, <5 RBC/high-power field (HPF); 1, 5–19 RBC/HPF; 2, 20–49 RBC/HPF; and 3, ≥50 RBC/HPF.

TH-PO1109

Elucidating the Mechanism of Gross Hematuria in IgA Nephropathy: Analysis of the Biomarkers in Patients with Gross Hematuria After COVID-19 Vaccination

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Background: Gross hematuria (GH) is observed shortly after an upper respiratory tract infection in 30–40% of the patients with immunoglobulin A nephropathy (IgAN), however, its mechanism is unclear. Recently, several reports showed the cases with GH after vaccination against coronavirus disease 2019 (COVID-19) in patients with IgAN. Here, we sought to clarify the mechanism of GH in IgAN by detailing the clinical characteristics and measuring serum and urinary galactose-deficient IgA1 (Gd-IgA1), which are known to be associated with development of IgAN, in patients with GH after COVID-19 vaccination. We conducted a prospective cohort study of 82 patients who presented with GH after COVID-19 vaccination.

Methods: All the patients visited either Juntendo University Hospital or Juntendo University Urayasu Hospital between May 11, 2021, and July 31, 2022. We collected the serum and urine samples at the time of the first presentation to the hospital with GH (GH 0) and six months after GH (GH 6). IgA1 were measured by enzyme-linked immunosorbent assays.

Results: We found that majority of patients who developed GH after COVID-19 vaccination were females (58 patients, 71%). GH was observed after the second or subsequent vaccinations in most patients (75 patients, 92%). Among the 82 patients, 22 had been already diagnosed with IgAN or IgA vasculitis (IgAV) prior to vaccination. In the remaining 60 patients, 42 performed kidney biopsies, who were all diagnosed with IgAN or IgAV. Although serum Gd-IgA1 were comparable throughout the observation period (GH 0: 5135.7 ng/mL; interquartile range [IQR] 3930.3-6914.4 ng/mL vs. GH 6: 5354.8 ng/mL; IQR, 4288.5-7937.9 ng/mL; p=0.319), urinary Gd-IgA1 was increased at the time of GH (GH 0: 42.7ng/mL; IQR, 21.6-110.1 ng/mL vs. GH 6: 31.7ng/mL; IQR, 12.8-93.9 ng/mL; p=0.030). These data suggests that deposition of Gd-IgA1 in the glomeruli was enhanced by COVID-19 vaccination by a mechanism other than increasing serum Gd-IgA1.

Conclusions: Our cohort study suggests that GH in IgAN is triggered by some alternations in glomerulus itself that facilitate the deposition of Gd-IgA1. Increased incidence of GH after COVID-19 vaccination in females and after the second or subsequent vaccinations may help to clarify the mechanism of GH in detail.

TH-PO1110

COVID-19 Vaccination Implications for Individuals Receiving Anti-Complement Therapy During the SARS-CoV-2 Pandemic

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Introduction: Treatment of complement mediated thrombotic microangiopathy (CM-TMA) with anti-complement agents such as Eculizumab during the COVID-19 Pandemic posed unique clinical decision making challenges in the area for COVID vaccination.

Case Description: A 36 year old African American lady, presented to the obstetric ER for hypertension and underwent emergency C-section due to fetal distress. Postoperative course was complicated by blood loss and oliguric acute renal failure. Based on lab data and clinical findings, diagnosis of CM-TMA was made. Genetic testing revealed heterozygosity for c.989-78G>A (rs1962149) variant of MCP/CD46 haplotype. Patient received transient hemodialysis for uremia and definitive treatment with anti-complement therapy- Eculizumab which resulted in complete renal recovery and remission for a 15 month follow up period. Due to ongoing COVID-19 pandemic, patient expressed interest in obtaining COVID vaccine for protection of herself and her newborn infant. After review of literature and observing her clinical progression, patient received 2 doses of mRNA vaccines: first dose administered 15 days after the final eculizumab infusion; and the second dose, three weeks after 1st dose. Her renal function and CM-TMA parameters were closely monitored post vaccination without event. The antibody response to vaccination could not be tested.

Discussion: Concurrent administration of COVID-19 vaccine with anti complement therapy poses special clinical challenges due to lack of conclusive data and guidance. SARS-CoV-2 virus, mRNA and adenovirus vaccines have shown to trigger Microangiopathic Hemolytic anemia (MAHA) and CM-TMA. Additionally, inconclusive data exists regarding the use of Eculizumab in the treatment of COVID-19. Data regarding strength of immune response after vaccination while on therapy is also limited. Due to increasing use of anti-complement therapies, we call for further research to aid development of guidelines for timing of covid vaccination. Such data will not only be useful in timely administration of preventive vaccination but also guide further management of complement mediated disorders.

TH-PO1111

Collapsing FSGS in a Patient with Post-COVID-19 Infection

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Introduction: Focal segmental glomerulosclerosis accounted for about one sixth of cases of nephrotic syndrome prior to the COVID pandemic. This disease is focal, involving some glomeruli, and segmental, involving part of the glomerulus. Patients may present with either nephrotic or nephritic syndrome. This abstract describes a 40-year-old Caucasian female who presented post-COVID pandemic with nephrotic range proteinuria after being asymptomatic for the past 14-years. Renal biopsy revealed collapsing glomerulopathy. This case demonstrates CKD patient post-COVID that presented with nephrotic range proteinuria, however non-uremic and not on dialysis despite worsening laboratory findings. Kidney failure in the form of COVID associated nephropathy (COVAN) is associated with increased morbidity and mortality. Few large cohort studies of kidney biopsies from patients with COVID-19 have been completed-to-date.

Case Description: A 40-year-old Caucasian female with a history of Hypertension, Vitamin-D deficiency, CKD stage 5 and nephrotic range proteinuria with a baseline creatinine around 2 mg/dL for the last 14-years presented asymptomatically with a serum creatinine of 4.5-4.9 mg/dL after approximately 1-year hiatus due to the COVID pandemic. Renal biopsy was performed and revealed collapsing glomerulopathy with focal segmental glomerulosclerosis. A biopsy approximately 15 years ago showed unremarkable pathological findings. She started treatment with repository corticotropin injection with subsequent development of anasarca and interval elevation in creatinine to 6 mg/dL. Treatment was stopped. She remained non-oliguric with close monitoring and supportive management of her co-morbidities.

Discussion: The progress of our patient's sub-nephrotic range proteinuria and CKD before and after COVAN with transition into nephrotic range proteinuria and without ATN findings shows the unique presentation of individuals with COVID associated FSGS. There is still yet to be understood regarding the mechanism in which patient present with worsening prognosis depsite remaining Non-oliguric and non-uremic. Few studies have shown an endpoint in the understanding and management of COVID FSGS and despite different treatment therapies available, COVID-FSGS remains yet to be fully understood. Patients infected with COVID-19 may present with mimicking features of commonly presenting renal pathology.

TH-PO1112

Risk Factors for Post-COVID-19 Incident CKD in the National COVID Cohort Collaborative

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Background: COVID-19 has been associated with accelerated GFR decline in hospitalized patients (pts), but prior studies are limited by cohort sizes, duration of follow-up and geo-specificity. Moreover, characterization of incident CKD in non-hospitalized patients with COVID is lacking.

Methods: Electronic health record data were obtained from 77 health systems in the United States in the National COVID Cohort Collaborative. Adults diagnosed with COVID between Mar 1, 2020, and Oc 1, 2022, and without pre-COVID CKD, were evaluated for incident post-COVID CKD until Dec 31, 2022. CKD was identified via outpatient eGFR measurements or diagnosis (dx) codes. Multivariable (MV) models were applied to analyze risk factors like demographics (age, sex, race/ethnicity), geographical regions (Midwest, Northeast, South, West), hospitalization, AKI, and a reported diagnosis (U09.9) of long-COVID (PASC).

Results: Among 3.7m pts, 76k (2%) had incident post-COVID CKD. Of these pts, 55k (73%) were not assigned a CKD dx code but met requirements for eGFR-based CKD. In MV models, incident CKD was associated with older age, male sex, and Black and Native Hawaiian or Pacific Islander race (compared to White). Compared to pts never hospitalized during follow-up, event rates for incident CKD for pts hospitalized during the COVID dx were significantly higher (11.4 vs 28.7 /1000 patient-years [pt-yrs]). Among hospitalized pts, those with AKI (vs no AKI) had an even higher rate of incident CKD (98.3 vs 21.2 /1000 pt-yr). In MV analyses, when compared to pts never hospitalized, those hospitalized during COVID with AKI had much higher incidence of

CKD (hazard ratio [HR] 3.82, p <0.001). The adjusted odds ratios for incident CKD were higher in the West (1.32, p<0.001) and South (1.03, p<0.001) and lower in the Northeast regions (0.94, p<0.001) compared to the Midwest. In a sub-cohort of 1.5mpts evaluated at U09.9-reporting sites, PASC was associated with a moderately higher HR for incident CKD (1.41, p<0.001).

Conclusions: In one of the largest studies on this topic, we observe that incident CKD in pts with COVID was underdiagnosed and influenced by geographical region, hospitalization and AKI. Pts with PASC had higher rates of CKD compared to those without.

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FR-PO001

A Network-Based View of AKI and CKD at Cell Subtype and Spatial Niche Resolution

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Background: Understanding functional relationships between genes and their regulators and how they are altered in acute kidney injury (AKI) and chronic kidney disease (CKD) is a crucial challenge. New computational methods are necessary to elucidate disease-specific gene regulation and function in spatial context.

Methods: We develop a computational framework to integrate spatial transcriptomics with single cell multiomics data (Table 1) and infer disease-associated gene networks at spatial niche and cell type resolution. We identify spatial niches using a biological-knowledge-informed matrix decomposition method, align single-cell multiome data with spatial transcriptome data, and infer functional regulatory relationships between genes using an integrated Bayesian framework.

Results: Using glomerular identification as an example, the spatial transcriptome-based niche pattern is concordant with image-based digital pathology. We build functional regulatory gene networks for ~50 kidney cell subtypes for each disease state. Focusing on the adaptive proximal tubule (aPT) networks, we rank >13000 gene ontology terms based on their differential network connectivity between disease states. The terms with highest differential connectivity include regulation of nephron tubule epithelial cell differentiation (CKD vs AKI), phospholipase A2 inhibitor activity (reference vs. AKI), and regulation of kidney size (CKD vs. reference). The regulatory networks mediated by HNF4A and NFKB1 in aPT cells are further validated on independent single cell data (Lake et al 2023). These disease-associated cell type networks are aligned to spatial niches, enabling a spatially-resolved, cell-type specific characterization of molecular pathways in kidney disease.

Conclusions: Our framework provides a network-based view of molecular differences between kidney disease states, cell subtypes, and spatial niche patterns.

Funding: NIDDK Support, Private Foundation Support

Table 1. Number of biopsies for each disease state.

Data types	AKI	CKD	Reference
Spatial transcriptome	6	10	10
sc/sn-RNA-seq	14/21	36/42	20/54
sc-multiome	In process		9

FR-PO002

Integrative Metagenomic, Metabolomic, and Deep Immune Profiling Reveal Coordinate Effects on Host-Microbe Interactions in CKD

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Background: Perturbation of gut dysbiosis is present in chronic kidney disease (CKD) and associated with a sophisticated milieu of metabolic and immune dysregulation. However, the underlying host-microbe interaction is unclear.

Methods: We performed multi-omics measurements, including systems-level gut microbiome, targeted serum metabolome, and high-dimensional immunotyping, in a cohort of 72 CKD patients and 20 controls.

Results: Our analyses on functional profiles of gut microbiome showed that loss of renal function decreased the diversity and abundance of carbohydrate-active enzyme (CAZyme) genes, but increased the abundance of antibiotic resistance, nitrogen cycling enzyme, and virulence factor genes. Models generated using measurements of circulating metabolites (amino acids, bile acids, and short-chain fatty acids) or immunotypes were predictive of renal impairment but less so than many of the taxonomic or functional profiles derived from gut microbiota, with the CAZyme genes being the top performing model to accurately predict early stage of diseases. Correlation analyses among different omics parameters revealed coordinated host-microbe relationships in CKD. Specifically, significant correlations were identified with circulating metabolites by several taxonomic and functional profiles of gut microbiome, while immunotype features were only moderately associated with the abundance of microbiome-encoded metabolic pathways and serum levels of amino acids.

Conclusions: Our multi-omics integration revealed signatures of the systems-level gut microbiome in robust associations with host-microbe co-metabolites and renal function, highlighting potential etiological and diagnostic implications in CKD.

Funding: Private Foundation Support, Government Support - Non-U.S.

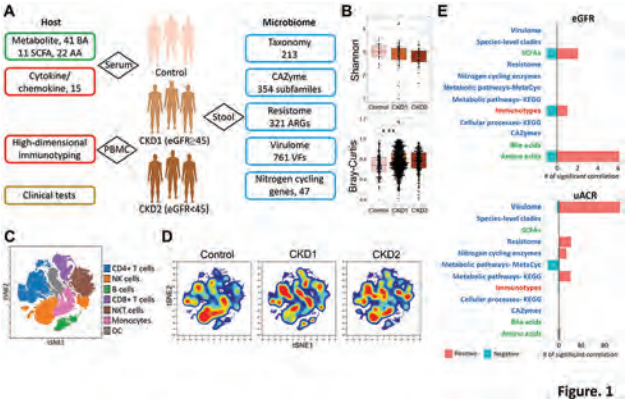

Figure. 1

Integration of the multi-omic experiment **(A)** The types and sample sources of omics analyses. **(B)** α- and β-diversity among the groups. **(C)** t-SNE plot detected by the flow cytometer. **(D)** PBMCs abundance densities from the groups. **(E)** Correlations between multi-omic data types and renal function.

FR-PO003

Developing a Kidney Genetics Registry Within an Electronic Medical Record

Asheeta A. Gupta,[1,2] Ciara Mcdonnell,[1] Josiah Shanks,[1] Grainne H. Butler,[1,2] Kushani C. Jayasinghe,[3] Catherine Quinlan.[1,2] *[1]The Royal Children's Hospital Melbourne, Parkville, VIC, Australia; [2]Murdoch Children's Research Institute, Parkville, VIC, Australia; [3]Monash Health, Clayton, VIC, Australia.*

Background: Dynamic patient registries within the electronic medical record (EMR) can provide security in a clinical setting by using existing tools to automate database compilation, reducing the time burden required to populate information whilst maintaining the accuracy of patient lists and data entry. A kidney genetics registry within the EMR facilitates decision-making that directly affects clinical care whilst concurrently contributing to a better understanding of disease processes and therapeutic approaches. We present our approach to the development of an EMR-embedded kidney registry in a tertiary pediatric setting highlighting the implementation challenges of amalgamating clinical data from multiple platforms.

Methods: An encounter-based EPIC registry was designed and created in collaboration with the Centre of Health Analytics for all patients referred to the Kidney Genetics clinic at the Royal Children's Hospital, Melbourne from February 2016 to present. Metrics for data capture included demographic information, growth parameters, clinical diagnoses, non-genetic diagnostic test results (including imaging and histopathology), and surveillance (including clinical parameters, hematological and biochemical test results). Triggers to warrant genetic re-evaluation or clinical intervention were included. A subsequent validation study was performed with a manually collated cohort of patients.

Results: The complete registry consisted of 516 patients (median age at presentation of 24 months). Challenges included the identification of appropriate patients, inclusion of genetic results from external laboratories, manual validation of non-machine-readable genetic reports, and the concurrent use of paper-based family genetic files. Sequencing was undertaken in the form of a clinical exome or whole exome sequencing with or without microarray depending on clinical indication. A genetic diagnosis was found in 88/212 (41.5%), variants of uncertain significance in 16/212 (7.5%), and incidental findings in 2/212 (0.94%).

Conclusions: Obtaining a genetic diagnosis can instigate a precision medicine approach, aiding risk stratification, tailored surveillance, initiation of disease-modifying therapies, and transplant planning. Combining genetic results with real-time monitoring of patients has the potential to streamline and automate this process.

FR-PO004

ADPKD Predictor: A Cloud-Based Prognostic Tool for Autosomal Dominant Polycystic Kidney Disease

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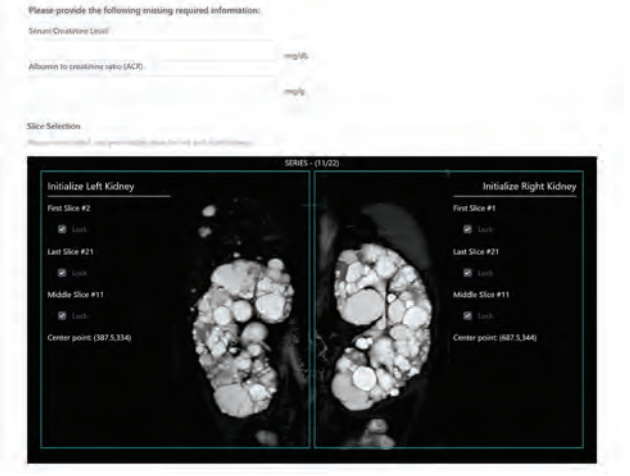
Background: Total Kidney Volume is accepted by FDA and EMA as a prognostic biomarker for ADPKD and is currently used to select patients eligible for drug treatment. We developed ADPKD Predictor, a user-friendly cloud-based tool for fast and accurate estimation of disease classification and progression, based on advanced image processing techniques.

Methods: The tool was designed on Microsoft Azure Cloud to facilitate the use of a MATLAB algorithm to automatically detect kidneys and cysts contours from MRI data (Figure 1). TKV is automatically calculated and ADPKD Imaging Classification, eGFR, GFR Category, eligibility for drug treatment and estimated effect are obtained (Figure 2).

Results: The proposed solution is extremely fast and precise compared to manual segmentation (absolute mean error 2.4% ± 2.7%), and more accurate than ellipsoid-based method, resulting in a manifold reduction of misclassification error (2.5%). No numerical expertise, software or hardware is required since computations run remotely in the cloud.

Conclusions: ADPKD Predictor provides a fast and reproducible assessment of risk classification and disease progression. It is extremely useful to researchers and clinicians for effective stratification of patients, hence supporting correct therapy administration.



ADPKD Predictor - Input page

ADPKD Predictor - Results page

FR-PO005

Abstract Withdrawn

FR-PO006

Abstract Withdrawn

FR-PO007

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FR-PO008

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FR-PO009

Using Deep Learning to Determine Kidney Function Decline in Patients with ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with progressive kidney cyst growth, eventually leading to kidney failure in many patients. The current risk stratification tool uses height-adjusted total kidney volume (TKV) by age. However, it does not include clinical or other imaging features that may contribute to kidney function decline. In this study, we developed a deep learning classifier that integrates clinical and imaging features to predict rapid estimated GFR (eGFR) decline in patients with ADPKD.

Methods: We included 120 patients with confirmed ADPKD with at least one MRI scan and at least 3 serial eGFR measures. An eGFR decline of 4 mL/min/1.73 m² per year or greater was defined as rapid progression. We tripled the sample size by extracting the largest manually segmented 2D MRI slice and its two neighbouring slices for each patient and assigning the corresponding clinical features. Pixel-level and spatial-level transformations were applied to the images to enhance our deep model's generalizability and robustness. The model consisted of three components: 1) EfficientNet-b2, 2) FuseNet, and 3) Classifier with the train:validation:test split of 63:17:20. The EfficientNet-b2 extracted 1000 features from each MRI slice. The FuseNet performed feature fusion on 15 clinically relevant features associated with ADPKD. The feature maps obtained from both models were concatenated and fed into the Classifier. Weighted-average F1 and AUC scores and the confusion matrix were used to assess the model's performance.

Results: The mean age of the study cohort was 46 years (SD 14), 54% were male, 95% were non-Black, hypertension prevalence was 79%, the median eGFR was 67 ml/min/1.73 m² (IQR 45-99), height-adjusted TKV was 940 mL/m (IQR 542-1373), tolvaptan use was 53%, and the Mayo Imaging Class was 8%, 17%, 40%, 23%, 10%, and 2% for 1A, 1B, 1C, 1D, 1E and class 2, respectively. The weighted-average F1 and AUC scores and the true positive and true negative values were 0.88, 0.88, 0.88, and 0.88 on the validation set, respectively and 0.83, 0.83, 0.86, and 0.80 on the test set.

Conclusions: Our study demonstrates that a deep learning approach which integrates clinical information with MRI features can successfully classify patients at risk for rapid eGFR decline. Further validation in an external cohort is required.

FR-PO010

In Silico Drug Repurposing of Aquaporin 1

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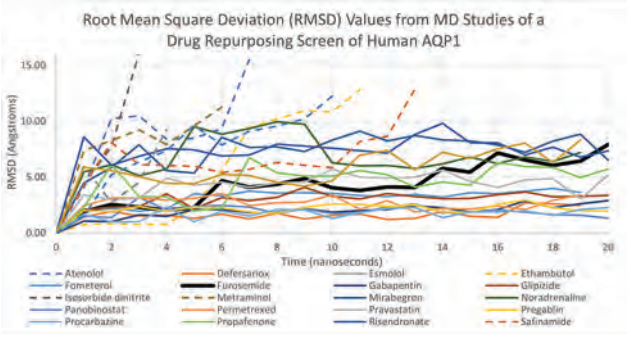
Background: Drug repurposing is the identification of new therapeutic targets for existing licensed medicinal compounds. We have developed protocols and programs for an *in silico* high-throughput repurposing screen using structural modelling, docking, and molecular dynamics (MD). Uniquely our approach uses a bespoke interface on Google Colab for graphic processing units (GPU's) to run the MD simulations. We describe its application to human aquaporin 1 (AQP1).

Methods: The library of British National Formulary listed compounds was obtained from NCBI PubChem. I-TASSER was used to generate monomeric structural models and Modeller for assembling oligomers. PLANTS was used for docking simulations. CHARM-GUI and bespoke software were used to prepare membrane-bound systems to run in GROMACS using GPU's in Google Colab. 20 nanosecond simulations were undertaken (300 Kelvin and 1 bar) to discriminate between binding and non-binding events.

Results: Complete monomeric and tetrameric structural models of human AQP1 were obtained incorporating chains of water molecules traversing the pores. Docking studies of 1002 drug compounds at the cytoplasmic opening of AQP1 identified 200 compounds binding in the pore. 45 compounds exhibited a higher calculated binding energy higher than the known binder furosemide and underwent further testing using

MD. The 20 nanosecond MD simulations distinguished the compounds which were not binding and elucidated the dynamics of the binders. A noteworthy finding was that furosemide induced a conformational change in the cytoplasmic chain.

Conclusions: We have developed a robust docking-MD protocol for high throughput repurposing screening. We have demonstrated that shorter simulations than previously published can reliably detect active binding conformations and identify compounds that could interact with human AQP1. Several commonly used medications exhibited stable interactions including furosemide, gabapentin, pregabalin, pravastatin and esmolol.



FR-PO011

Histopathological Prediction of CT-Based Radiomic Imaging Biomarkers in Native Kidney Biopsies

Ji Eun Kim, Kipyo Kim. *Inha University Hospital, Incheon, Republic of Korea.*

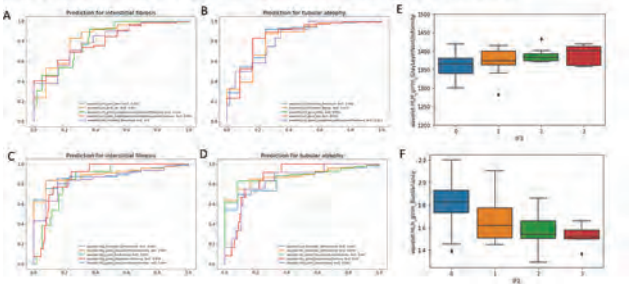
Background: In recent years, there has been a growing interest in radiomics as a quantitative approach for image analysis. This study aims to explore the relationship between radiomic features extracted from CT scans and histological findings obtained from kidney biopsies.

Methods: We retrospectively enrolled participants who underwent abdomen CT scan within 7 days before native kidney biopsy. Three-dimensional kidney segmentation was performed in two different methods; the entire kidney parenchyma and isovolumumic cortical area. We extracted various radiomics features such as shape, first-order, and texture features from the CT images. The histological findings were assessed using a semiquantitative scoring system, which assigned severity grades to various parameters including interstitial fibrosis (IF), tubular atrophy (TA), glomerulosclerosis (GS), interstitial inflammation (II), and arterial intimal thickening (IT).

Results: Total of 124 patients were included in the main analysis. The ROC curve analysis of the extracted radiomic features revealed higher AUC values for moderate IF, TA, and II in both the total kidney parenchyma and cortex. However, the ability to distinguish GS and IT was relatively lower. The most discriminatory features extracted from total kidney for IF and TA were GLCM IDMN (LLH-wavelet) and GLCM IDN (LLH-wavelet), with the AUCs approximately 0.83. For the kidney cortex, GLRLM GLNU (HLL-wavelet), GLDM DE (HLL-wavelet), and GLRLM RV (HLH-wavelet) had the texture features with the highest AUCs for IF and TA, with the AUCs of 0.84-0.88. Texture features extracted from kidney cortex showed higher correlation with histologic features. We found that CT-based texture features consist of volume-dependent and independent components. Volume-independent texture features extracted from kidney cortex showed more a higher degree of correlation with chronic histologic scores.

Conclusions: In conclusion, our findings suggested the potential of CT-based radiomics in predicting chronic histological findings in kidney biopsies.

Figure 1. The associations between interstitial fibrosis scores and representative texture features with high ROC-AUC values. (A) and (B) from the entire kidney parenchyme. (C) and (D) from cortical area. The associations between IF scores and (E) wavelet-HLL_glrlm_GrayLevelNonUniformity (F) wavelet-HLH_glrlm_RunVariance.



FR-PO012

Assessment of Hemodialysis Arteriovenous Shunt (AV Shunt) Sounds by Using a Novel Electronic Stethoscope and Machine Learning Techniques

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Background: Hemodialysis AV shunt management is performed by screening for auscultated shunt sounds. However, determining stenosis with a stethoscope requires skill, and it is difficult to make assessment objectively and quantitatively. We linked the echo findings of AV shunt to audio data obtained from a novel electronic stethoscope (Togo Medikit Co., Ltd., Japan) and used these data to train AI, and then developed software that estimated two labels with AI. In this study, the usefulness of this software in clinical settings was examined by comparing the rating of trained staffs and AI for auscultatory sounds.

Methods: The quality and intensity of the shunt sounds were evaluated in six levels each by trained staff just before and after dialysis by auscultation mainly just above the shunt creation site. At the same time, 20 seconds of shunt sound data were electromagnetically recorded from each patient by a novel auscultation device. The sound quality rating by the staffs was 0~3 as bad, 4-5 as good, while the electromagnetically recorded sound data was rated as normal or abnormal using the developed software. Match rate, sensitivity, and specificity by both evaluation methods were calculated.

Results: We compared the ratings of trained nurses and AI for 191 auscultatory sounds. The matching rate between the two was 66.0%. 83.3% of the subjects were calculated as abnormal by AI, when trained staff judged as “bad”. 94.1% of the subjects were judged “good” by trained staff, when AI calculated as normal. Contrary to expectations, the rate of AI judging as normal was higher after dialysis than before, even though the intensity of the shunt sound was weaker after dialysis. When echo examination showed shunt blood flow reduction, it was more likely to be judged as abnormal by AI compared to the judgment by the staff.

Conclusions: In this study, AI rating for AV shunt sounds was considered to be at an acceptable level for clinical use. However, there are differences between trained staff and AI results for “normal” results. This reason for this may be that the AI label is based on the echo. This evaluation method using a new device is expected to become more useful with additional AI learning.

FR-PO013

eGFR Trajectories Among Children with CKD Using a Multi-Institutional Electronic Health Record Database

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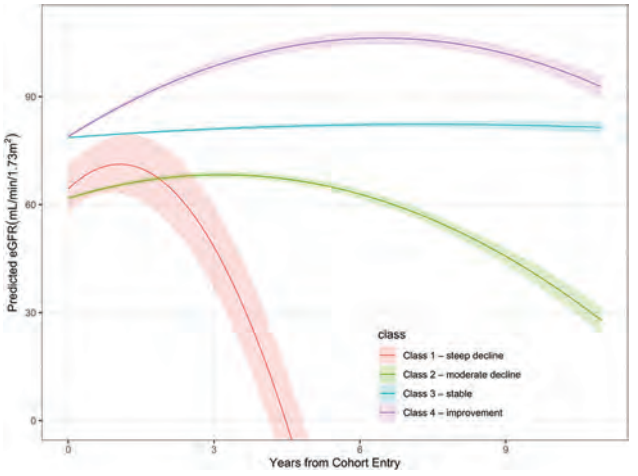
Background: Progression of pediatric chronic kidney disease (CKD) is highly variable across patients and may be nonlinear over time. This study’s objective was to describe eGFR trajectories among a large, unselected cohort of children with CKD.

Methods: Using electronic health records from 16 healthcare institutions within PCORnet, a computable phenotype was implemented to identify children ages 1-18 with mild to moderate CKD (two eGFRs between 30-90 mL/min/1.73m^2 at least 90 days apart). Latent class mixture models were used to identify classes of eGFR trajectories from cohort entry until dialysis, transplant, or last follow-up.

Results: N=17,168 children with CKD were grouped into four eGFR trajectory classes [Figure]. Class 1 (“steep decline”) contained N=499 (2.9%) patients with mean eGFR at cohort entry of 66.4 and a steep, nonlinear decline in eGFR. Class 2 (“moderate decline”) had N=6,661 (38.8%) patients with mean entry eGFR of 59.2 and a moderate, nonlinear decline. Class 3 (“stable”) had N=7,999 (46.6%) patients with mean entry eGFR of 78.1 and little change in eGFR over time. Class 4 (“improvement”) had N=2,009 (11.7%) patients with mean entry eGFR of 79.5 and an increase in eGFR. Class 1 (steep decline) patients had more clinic visits and hospitalizations and a larger proportion on anti-hypertension medications, whereas those in Class 4 (improvement) were slightly younger.

Conclusions: Four distinct classes of eGFR trajectories were identified among children meeting criteria for CKD stage 2-3. Over half were in stable or improving eGFR subgroups, and only a small proportion exhibited steep decline. These subgroups provide a real-world, multi-institutional characterization of eGFR trajectories among children with mild-moderate CKD.

Funding: Other U.S. Government Support



FR-PO014

Regulation of the Adaptive Proximal Tubule Cell State by ELF3, KLF6, and KLF10

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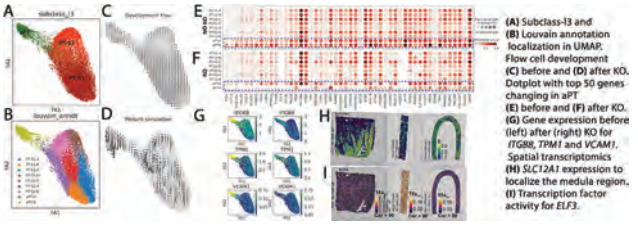
Background: Gene regulatory regions modulate gene expression and maintain cell function. In response to injury, the proximal tubule (PT) undergoes adaptation, including differentiation or epithelial to mesenchymal transition, resulting in successful or failed repair. Single-cell multiome, whole genome bisulfite sequencing (WGBS), and CUT&RUN were used to study the regulatory control of the PT as it undergoes this adaptation.

Methods: Single-cell multiome with ATAC-seq data was generated and analyzed for 12 kidney tissue samples. TRIPOD and scMEGA were used for analysis. Celloracle *in silico* perturbation tested DEG changes after the knockout of transcription factors (TFs). scMEGA was used to map TF activity in spatial transcriptomics samples (N=3). Regulatory relationships were characterized by WGBS and CUT&RUN.

Results: Between the PT-S12 and aPT, we observed 25,356 DARs and 4194 DEGs at adj-P<0.05. aPT marker genes like *TPM1* were targeted by the TFs *ELF3, KLF6,* and *KLF10* which also cross-regulated each other, suggesting a regulatory network of adaptation in the PT. The TF *ELF3* targeted 316 DARs of the aPT, including 248 in positively regulated genes. *In silico* perturbation resulted in the downregulation of *TPM1* and other aPT genes such as *VCAM1* and *ITGB8*. The correlation matrix estimated by scMEGA for *ELF3* transcription factor activity predicted that 495 genes are bound by *ELF3* with a correlation >90%. By transferring these labels to spatial transcriptomics samples, colocalization of TF activity was identified in injured cortical regions with PT. By WGBS and CUT&RUN, the *TPM1* peak 106234, targeted by *ELF3* was an active promoter with reduced DNA methylation.

Conclusions: *ELF3, KLF6,* and *KLF10* contribute to the PT's adaptative response to injury as a regulatory network, specifically localized to the PT.

Funding: NIDDK Support



FR-PO015

Evaluating the Impact of a Tailored Electronic Medication Management System on Anemia Management in Outpatient Hemodialysis Patients

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Background: The prevalence of Medication-related problems (MRPs) in outpatient hemodialysis patients, especially in anemia management, is high. We developed a tailored electronic medication management system for outpatient hemodialysis (the New System) and evaluated its impact on anemia management.

Methods: The New System was collectively developed by our hospital and Spectrum Healthcare, building on the existing electronic information system. We compared the percentage of patients with hemoglobin, ferritin, transferrin saturation within the KDIGO recommended range, and cardiovascular events six months before (control period) and after (study period) the implementation of the New System.

Results: Using the New System, physicians perform evaluations and prescribe medications based on patients' lab reports. After patient payment and pharmacist review, medications are auto-allocated to a virtual pharmacy in the Hemodialysis Center. The New System then generates a medication form before each dialysis session for nursing staff. On dialysis days, the system displays the predetermined prescriptions. After administration by nurses, the system auto-deducts the used medication. The control period included 285 patients (190 males and 95 females, aged 62.4±13.2 years), and the study period included 278 patients (193 males and 85 females, aged 62.8±13.2 years). Compared with the control period, the percentage of patients at the study period with hemoglobin (40.2% [687/1710] vs 47.8% [797/1668], P<0.001), ferritin (31.2% [178/570] vs 39.0% [217/556], P=0.006), transferrin saturation (58.6% [334/570] vs 64.7% [360/556], P=0.034) within the KDIGO recommended range was higher. The occurrence of cardiovascular events during the study period was 11.2% (31/278), which was lower (P=0.043) compared to the control period where it was 16.5% (47/285).

Conclusions: The implementation of the New System in the Hemodialysis Center improves anemia management in outpatient hemodialysis patients. The study hints that an electronic medication management system tailored for outpatient hemodialysis holds potential in addressing partial MRPs.

Funding: Government Support - Non-U.S.

FR-PO016

Deep Learning Model for Evaluating Histopathology of Acute Renal Tubular Injury

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Background: Acute tubular injury is the most common cause of acute kidney injury (AKI). Histopathological diagnosis may help distinguish between the different types of acute kidney injury and aid in treatment. Currently, no studies have utilized deep learning models to assist in the histopathological diagnosis of acute kidney injury. The aim of this study is to perform histopathological segmentation to identify the four structures of acute renal tubular injury using deep learning models.

Methods: We use a segmentation model (glomerulus, healthy tubules, tubules with cast, and necrotic tubules) to classify tubule-specific injuries after cisplatin treatment. A total of 45 whole slide images with 400 generated patches are used in the segmentation model and 27,478 annotations are created for four classes, namely glomerulus, healthy tubules, necrotic tubules and tubules with cast. A segmentation model was developed utilizing the DeepLabV3 architecture with the MobileNetv3-Large backbone to accurately identify four histopathological structures associated with acute renal tubular injury in mouse PAS-stained samples. In the segmentation model for four structures, the highest Intersection over Union and the Dice coefficient are obtained for the segmentation of the "glomerulus" class, followed by "necrotic tubules," "healthy tubules," and "tubules with cast" classes.

Results: The overall performance of the segmentation algorithm for all classes in the test set includes an Intersection over Union of 0.7968 and Dice coefficient of 0.8772. The Dice scores for the glomerulus, healthy tubules, necrotic tubules, and tubules with cast are 91.78 ± 11.09%, 87.37 ± 4.02%, 88.08 ± 6.83%, and 83.64 ± 20.39%, respectively.

Conclusions: The utilization of deep learning in a predictive model has demonstrated promising performance in accurately identifying the histopathological structures of injured renal tubules. These results may provide new opportunities for applying the proposed methods to more effectively evaluate renal pathology in the future.

FR-PO017

Proximal Tubule Neighborhood in AKI, CKD, and Healthy Control Kidney Tissue Using Spatial Transcriptomics

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Background: The interaction of proximal tubules (PTs) with neighboring immune, stromal, and endothelial cells may impact their physiological functions. Using spatial transcriptomics (ST), we sought to establish the spatially anchored microenvironments of the PT across kidney samples in chronic kidney disease (CKD), acute kidney injury (AKI) and healthy human kidney biopsy samples.

Methods: We interrogated 23 samples from the HuBMAP, Kidney Precision Medicine Project (KPMP) and Biopsy Biobank Cohort of Indiana with Visium ST. Cell labeling was performed using a transfer score methodology of the publicly available snRNAseq atlas. Label score vectors were utilized to cluster and identify niches in R. Pathway analysis was performed in PathfindR.

Results: Clustering revealed 33 distinct PT neighborhood clusters with colocalization of injured PTs, stromal cell and immune cell dominant PT neighborhoods. The adjusted p-value of 0.05 was considered as the significance threshold. Adaptive PT (aPT) enriched clusters in AKI revealed increases in injury, repair, and immune responses compared to normal PTs. Pathway enrichment displayed activation of ERK1/2 cascade, TOR signaling, neutrophil chemotaxis, positive regulation of interleukin−2 production and T cell receptor signaling pathways. CKD samples were enriched for B and plasma cell niches. Upregulation of immunoglobulin genes and pathways contributing to activation of complement cascade were observed in CKD.

Conclusions: Distinct cell type compositions were identified within normal and disease cell clusters. ST facilitated spatial anchoring of cells within the kidney. The neighborhood analyses of PTs in disease and health provide insights into alteration of cell networks in kidney disease.

Funding: NIDDK Support

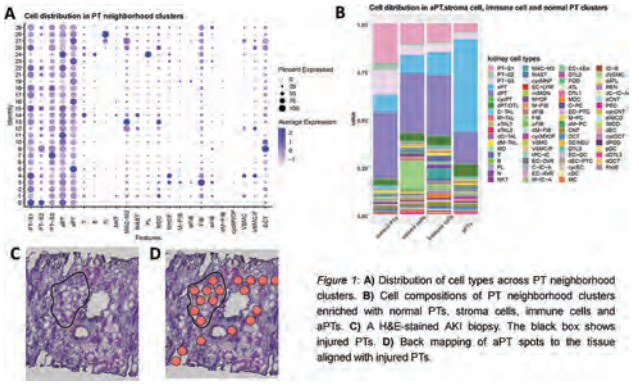

Figure 1: **A)** Distribution of cell types across PT neighborhood clusters. **B)** Cell compositions of PT neighborhood clusters enriched with normal PTs, stroma cells, immune cells and aPTs. **C)** A H&E-stained AKI biopsy. The black box shows injured PTs. **D)** Back mapping of aPT spots to the tissue aligned with injured PTs.

FR-PO018

Capturing Spatial Transcriptomics Around Cysts with Deep Learning and Image Processing Is a Novel Method to Reveal Therapeutic Targets in ADPKD

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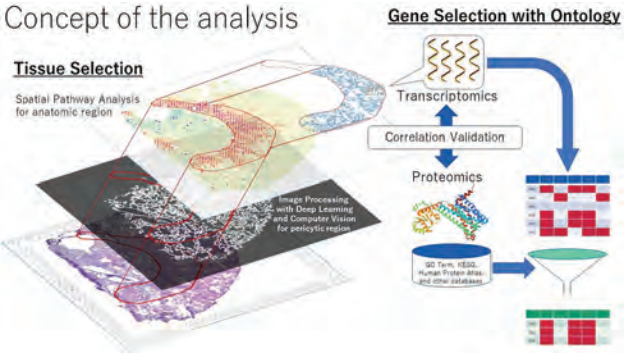
Background: There are still many unknowns in ADPKD. Current therapies are not sufficiently effective. To search for new therapeutic targets, we examined the mechanism of PKD progression in pericystic areas using a new method that integrates histology, proteomics, spatial transcriptomics, GO (gene ontology) analysis, analysis of DEG (differentially expressed genes), deep learning, and image processing.

Methods: DBA/2J as a normal control mouse and DBA/2FG-pcy as a PKD model mouse were used for the analysis. Frozen kidneys of mice were subjected to proteomic measurement by LC-MS. Spatial transcriptomic measurement (Visium, 10X Genomics) and H&E staining were performed using formalin-fixed, paraffin-embedded samples. Image regions of tissues and cysts were obtained with a deep learning program. The pericystic tissue area was further clarified with image processing. Barcoded spots of Visium in this area were fixed by superimposing the spot locations over the images of the pericystic areas and genetically classifying them with GO analysis or cluster analysis. Barcoded spots were also obtained in the corresponding area in normal control mice to obtain DEG in pericystic areas. GO terms were organized for new criteria to exclude inflammatory or fibrosis genes which are usually upregulated in PKD tissues and include membrane protein genes.

Results: In a mouse model of PKD, proteomics and spatial transcriptomics suggested that genes and proteins were generally present in a constant ratio. We identified the pericystic tissue areas with methods described above. A group of genes was identified by DEG analysis of Barcoded spots in these areas. A list of histopathology-related genes was created by filtering these genes through pre-designed selection criteria.

Conclusions: We created a new list of genes associated with pericystic regions but unrelated to all-kidney tissue that could be involved in PKD progression. We will conduct more detailed investigations on the genes in this list to identify therapeutic targets.



FR-PO019

Interactive Visualization of Kidney Structural Segmentations and Associated Pathomic Features on Whole Slide Images

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Background: The Kidney Precision Medicine Project (KPMP) is a collaborative study generating histology images and spatial molecular data from patient biopsies. To enable seamless study of whole slide images (WSI) and derived data, it is important to integrate solutions for navigation and visualization into computational pipelines.

Methods: We built a pipeline to (a) apply previously developed segmentation models of kidney structures on KPMP PAS-stained WSIs, including for globally/non-sclerotic glomeruli, arteries/arterioles, tubules, peritubular capillaries (PTC), interstitial fibrosis and tubular atrophy (IFTA), and the cortical interstitial fractional space (Ginley et al., bioRxiv 2023); (b) extract quantitative features from these structures; and (c) load these data in Vitessce (http://vitessce.io), a web-based framework for visualization and analysis of bioimaging data.

Results: Segmented KPMP WSIs linked to corresponding extracted features are visualized using quantitative colormaps and statistical plots such as histograms, violin plots, and bar charts. As a use case, we explore the spatial relationship between different structures and associated features (i.e., aspect ratio of PTCs in IFTA and non-IFTA regions).

Conclusions: Image analysis methodologies paired with web-based visualization tools allow for the interactive examination of renal morphometry. These tools enable KPMP investigators and a broader public to exploit WSI-extracted data for integration with other omics data and hypothesis generation and testing.

Funding: NIDDK Support

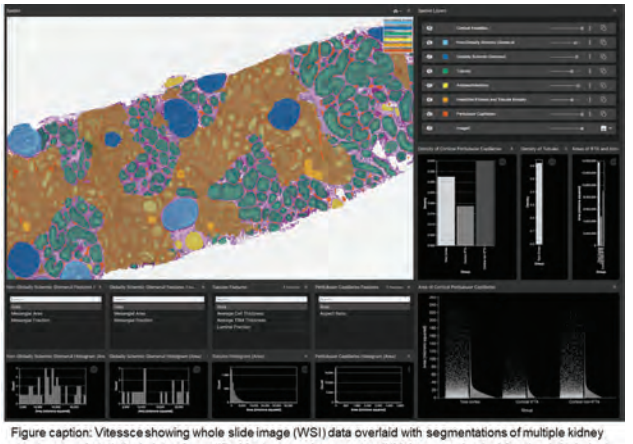

Figure caption: Vitessce showing whole slide image (WSI) data overlaid with segmentations of multiple kidney structures and statistical plots of quantified features such as area, cell thickness, or luminal fraction (of tubules) associated with those structures.

Vitessce showing WSI data overlaid with segmentations of multiple kidney structures and statistical plots of quantified features such as area, cell thickness, or luminal fraction (of tubules) associated with those structures.

FR-PO020

Self-Supervised Learning Applied to Kidney Histomorphology in Whole Slide Images

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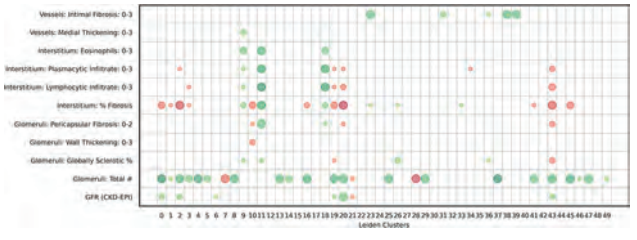
Background: Current approaches to characterize medical imaging data typically use some degree of supervision, relying heavily on expert annotation. Pathologist reads can have high inter-observer variability. A supervised model built on these reads will mimic the idiosyncrasies of the expert and may perpetuate inter-observer inconsistencies. Supervised approaches also require time-consuming and meticulous labeling on the input images. Given the limitations, supervised learning may not be optimal for unbiased and generalizable characterization of histologic patterns in the kidneys, which are complex.

Methods: Histomorphological Phenotype Learning leverages the latest advances in self-supervised learning (SSL), the Barlow-Twins method, to learn representations of image tiles that are later clustered by the Leiden method, a state-of-the-art community detection algorithm. This strategy was used to discover de novo clusters of morphologically similar tissue from 254 whole slide images (WSIs) of the kidney without any prior diagnostic information from pathologists. These clusters were then projected onto validation (N = 254), test (N = 255), and external validation (N = 113) sets, visually inspected across sets, and correlated with expert-provided histology scores. Additionally, elastic net models were trained to predict histology scores using proportion of patients' tiles in each cluster.

Results: Visual inspection of representative tiles from clusters revealed comparable histologic patterns across sets. Clusters that were visually indicative of disease were positively correlated with fibrosis; clusters representing healthy tissue were negatively correlated with fibrosis (Figure 1). The best-performing elastic net model used 17 clusters to predict percent fibrosis (R^2 in test set = 0.81).

Conclusions: In this study, we demonstrated the application of SSL to characterize WSIs of the kidney. Features extracted from this approach were associated with and demonstrated good prediction of expert-provided histology scores. Subsequent work will link clusters to gene expression and metabolic processes.

Funding: NIDDK Support



FR-PO021

Diverse Immune, Stromal, and Vascular Niches Along the Cortico-Medullary Axis of the Human Kidneys by Integrating 10 Different Modalities Performed on the Same Tissue Block

Seth Winfree,[1] Blue Lake,[2] Ricardo Melo Ferreira,[3] Anthony A. Fung,[4] Angela R. Sabo,[3] Madhurima Kaushal,[5] Daria Barwinska,[3] Bo Zhang,[4] Joseph Gaut,[5] Kun Zhang,[2,4] Lingyan Shi,[4] Michael T. Eadon,[3] Tarek M. El-Achkar,[3] Sanjay Jain.[5] HuBMAP. *[1]University of Nebraska Medical Center, Omaha, NE; [2]Altos Labs Inc, Redwood City, CA; [3]Indiana University School of Medicine, Indianapolis, IN; [4]University of California San Diego, La Jolla, CA; [5]Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Methods to delineate cell types and microenvironment using multiple modalities (DNA, RNA, protein and metabolites) across cortico-medullary axis and that are applicable in a clinical setting are needed to understand cellular basis of kidney disease.

Methods: Multimodal assays were performed on same or sequential sections using an innovative freezing and processing method on prechilled metal blocks: 1) 10X multiome (snRNAseq and snATACseq on same cell, 280μm), 2) Light microscopy (5μmH&E, 5μmPAS), 3) 10X VISIUM and H&E (spatial transcriptomics, 10μm), 4) CODEX (40plex antibody panel for nephron, immune, endothelial, stromal and kidney injury, 10μm) and H&E, 5) Label free imaging with Stimulated Raman Scattering (SRS) microscopy on the same section as CODEX to generate lipids, extracellular matrix and pseudo-H&E data. Integration of modalities used molecular, cellular, and morphological bridges across kidney functional tissue units (FTUs).

Results: The tissue processing pipeline was feasible with multiple omic and spatial technologies from the same block at multiple institutions with passing QC for each assay. 10X multiome data from ~200K nuclei (12 donors) identified more than 25 immune, 20 stromal and 20 endothelial cell identities with clear zonation along the cortico-medullary axis. Novel niches of several fibroblast and immune cells were identified using VISIUM integrated with CODEX where 3.9 million cells (5 donors, 30 cell types based) on protein markers showed distinct zonation and higher protein-to-lipid ratio and increased lipid saturation in podocytes and mesangial cells versus distal tubules were seen in CODEX-SRS mapping.

Conclusions: This work outlines the collection and construction of a multimodal atlas of the human kidney from same tissue by 1) Integrating multimodal single cell and FTU spatial map using less than half depth of a kidney biopsy is feasible and compatible in a clinical setting, 2) Identifying zonation of interstitium and vascular cell diversity along the cortico-medullary axis by multiple modalities, 3) RNA-protein-lipid-ECM-histology mapping in millions of cells, neighborhoods and FTUs.

Funding: NIDDK Support

FR-PO022

Accuracy of Bayesian Improved First Name Surname Geocoding (BIFSG) for Race and Ethnicity Imputation in a Kidney Care Management Program to Assess Racial Disparities

Liana D. Bruce, Christopher S. Krasniak, Cliff S. Eddings, Brandon Phan, Bassem Mikhael, Joe Kimura. *Somatus, McLean, VA.*

Background: Self-reported race and ethnicity data are ideal for classifying race and ethnicity to improve equity and close health outcome disparities, but these data have low response rates, typically <20%. Our goal was to validate race and ethnicity imputed using the BIFSG algorithm against self-reported data in a kidney care management population.

Methods: Patients are assessed at baseline and responses classified into six Office of Management and Budget standardized combined categories. We applied RAND's indirect estimation method to generate estimates based on first names, surnames, and ZIP Codes. Accuracy, specificity, sensitivity, and positive predictive value (PPV) were then calculated to compare BIFSG-imputed values with self-reported values in a validation subsample.

Results: 53,695 (16%) of 326,679 patients self-reported race/ethnicity. BIFSG predicted 269,354 (82%) of the overall population, including 44,964 of the self-report cohort. After imputation, 278,085 (85%) of patients had non-missing race/ethnicity. Overall imputed value accuracy compared to self-report was 99%. PPV was highest for Hispanic and lowest for American Indian or Alaskan Native, while accuracy was highest for Native and lowest for White.

Conclusions: Imputation of race/ethnicity can improve analyses of health disparities in kidney disease. The BIFSG imputation model obtained highly accurate (99%) predictions of race and ethnicity in a large chronic kidney disease population, increasing coverage of racial identity from 16% to 85%. The BIFSG algorithm could be supplemented with additional sources eg, historical records to impute residual missing values. Incorporating additional data and advanced machine learning models will improve predictions to better track health disparities.

Funding: Commercial Support - Somatus

Metric	Calculation	Overall	White	Black or African American	Hispanic	Asian or Pacific Islander	American Indian or Alaskan Native
Precision (PPV)	TP/(TP+FP)	80.53%	75.10%	89.14%	92.23%	69.20%	51.35%
Recall (Sensitivity)	TP/(TP+FN)	80.48%	93.96%	64.66%	82.79%	60.49%	6.55%
Specificity	TN/(TN+FP)	99.31%	88.71%	99.45%	99.90%	99.98%	99.99%
Accuracy	(TN+TP)/(TN+TP+FP+FN)	98.67%	90.11%	97.17%	99.67%	99.94%	99.91%

TP: True Positives, FP: False Positives, FN: False Negatives, TN: True Negatives

FR-PO023

Prediction of Individual Educational Attainment in ESKD Patients Using Zip Code-Derived Measures

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Background: Social determinants of health (SDOH) are associated with various health outcomes. Area-level SDOHs based on patients' zip codes or census tracts have been commonly used in research instead of individual SDOH. Previous work showed that zip code-derived SDOH measures were inaccurate in highly heterogeneous urban neighborhoods. Therefore, we aimed to predict individual SDOH by using machine learning.

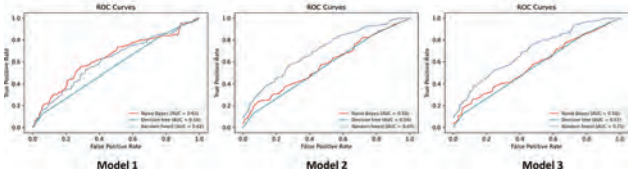
Methods: We used data from ESKD patients ≥ 25 years old enrolled in two studies at Mount Sinai in NY. All patients completed a questionnaire regarding the highest level of education, age, gender, and race/ethnicity. We used data from the American Community Survey to achieve the zip code-derived education based on the patient's zip code, gender, and race/ethnicity. We tested several machine-learning algorithms, including Naïve Bayes, decision tree, and random forest (RF). We then developed three multi-class prediction models to predict individual educational attainment. Model 1 used only zip code-derived education. Model 2 included model 1 + demographic variables and comorbidity. Model 3 included model 2 + neighborhood SDOHs (GINI and dissimilarity indices). The cohort was divided into 75/25 training and test sets, and 5-fold cross-validation was employed.

Results: A total of 603 ESKD patients were identified. The mean age was 58±12 years, 55% of patients attained less than high school, 32% completed high school, and 13% had a bachelor's degree or higher. Only 31% of zip code-derived education accurately matched actual education. The RF model has the best overall performance. Using RF, model 1 enhanced accuracy to 51% with an AUROC of 0.62 (95%CI 0.53 to 0.67). Model 3 demonstrated the highest accuracy (59%) and AUROC (0.71, 95%CI 0.63 to 0.77) (Figure 1).

Conclusions: Combining zip code-derived educational attainment with demographic data and neighborhood SDOH measures can improve the prediction of individual education in ESKD patients. This may improve the performance of models that incorporate SDOH as a feature.

Funding: NIDDK Support

Figure 1



FR-PO024

Uncovering Subgroups of Diabetic Deceased Donor Kidney Transplant Recipients with Differing Outcomes Using Consensus Cluster Analysis

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Background: Diabetic donor kidney transplants have inconsistent clinical outcomes, possibly due to population heterogeneity. This study aimed to use an unsupervised machine learning approach to cluster recipients of diabetic deceased donor kidney transplants and identify subgroups with higher risk of inferior outcomes and associated variables.

Methods: The study analyzed recipient-, donor-, and transplant-related characteristics of 7,876 recipients of diabetic deceased donor kidney transplants from 2010 to 2019 in the OPTN/UNOS database. Consensus cluster analysis was performed to identify important characteristics of each assigned cluster and compare posttransplant outcomes between the clusters.

Results: The analysis identified three clinically distinct clusters. Cluster 1 (N=2,903) recipients were characterized by the oldest age (64±8 years) and highest rate of comorbid diabetes mellitus (55%). They were more likely to receive kidney allografts from older donors (58±6.3 years) with hypertension (89%), meeting ECD status (78%), having a high rate of cerebrovascular death (63%) and carrying a high-KDPI (KDPI ≥85%) (77%). Cluster 2 (N=687) recipients were younger (49±13 years) and all were re-transplant patients with higher PRA (88 [IQR 46, 98]), receiving kidneys from younger (44±11 years), non-ECD deceased donors (88%) with low number of HLA mismatch (4 [IQR 2, 5]). The cluster 3 cohort was characterized by first-time kidney transplant recipients (100%) who received kidney allografts from younger (42±11 years), non-ECD deceased donors (98%). Compared to cluster 3, cluster 1 had a higher incidence of primary non-function, delayed graft function, patient death, and death-censored graft failure, while cluster 2 had a higher incidence of delayed graft function and death-censored graft failure but comparable primary non-function and patient death.

Conclusions: An unsupervised machine learning approach identified three clinically distinct clusters of diabetic donor kidney transplant patients with differing outcomes. The study suggests opportunities to improve utilization of high KDPI kidneys coming from diabetic donors in recipients with survival-limiting comorbidities, such as those observed in cluster 1.

FR-PO025

Exploring the Diversity of Clinical Profiles and Outcomes in Kidney Transplant Recipients with Limited Education Using Clustering Analysis

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Background: Education level has been identified as a potential predictor of post-transplant outcomes for kidney transplant recipients. However, there is a lack of research focusing on recipients with lower education levels and their unique clinical characteristics. Therefore, the objective of our study was to utilize unsupervised machine learning techniques to cluster kidney transplant recipients with lower education levels.

Methods: We performed consensus clustering analysis on 20,474 kidney transplant recipients with education levels below college/university using recipient, donor, and transplant data from the OPTN/UNOS database (2017-2019). We identified significant characteristics for each cluster and compared posttransplant outcomes.

Results: Most recipients had completed high school (86%) and were non-white (64%). We identified four clusters: Cluster 1 comprised young, non-diabetic patients receiving kidneys from young, non-hypertensive, non-ECD deceased donors with lower KDPI. Cluster 2 included preemptive or early dialysis initiators, predominantly white, receiving kidneys from living donors. They showed better outcomes. Cluster 3 consisted of young kidney re-transplant recipients with higher PRA and fewer HLA mismatches. Cluster 4 involved older, diabetic patients receiving kidneys from lower-quality donors. Cluster 2 exhibited the best outcomes, while clusters 1, 3, and 4 had higher risks of graft failure and patient mortality.

Conclusions: Unsupervised machine learning successfully clustered kidney transplant recipients with lower education levels into four distinct groups, each with unique clinical profiles and varying posttransplant outcomes. Cluster 2 demonstrated the best outcomes, while clusters 1, 3, and 4 had higher risks of graft failure and patient mortality. These findings have implications for personalized care and risk stratification in kidney transplant recipients with lower education levels.

FR-PO026

Interpretable Machine Learning-Based Individual Analysis of AKI in Immune Checkpoint Inhibitor Therapy

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Background: Acute kidney injury (AKI) is a critical complication in immune checkpoint inhibitor (ICI) therapy. Since the etiologies of AKI in cancer therapy vary among patients, clarifying AKI causes in individuals is critical for optimal cancer treatment. Although it is essential to individually analyze ICI-treated patients for underlying pathologies existing behind each AKI onset occurring at different times, these analyses have not been realized with conventional clinical research methods.

Methods: We created a dataset from the electronic medical records (EMR) of 616 patients who received ICI therapy at the Kyoto University Hospital from July 2014 to September 2019. AKI was defined by serum creatinine changes based on the KDIGO guideline. We developed a gradient-boosting decision tree-based machine learning (ML) model continuously predicting AKI within 7 days from each time point, using 287 clinical variables obtained from EMR as input features. We noted that the temporal changes in individual predictive reasoning in AKI prediction models represented the key features contributing to each AKI prediction, and clustered AKI patients based on the pattern of features with high predictive contribution quantified in time-series by SHapley Additive exPlanations (SHAP), a model interpretation framework. We searched for common clinical backgrounds of AKI patients in each cluster, compared with annotation by three nephrologists.

Results: One hundred and twelve patients (18.2%) had at least one AKI episode. They were clustered per key features and their SHAP value patterns, and the nephrologists assessed the clusters' clinical relevance. Receiver operating characteristic analysis revealed that the area under the curve was 0.880. Patients with AKI were categorized into four clusters with significant prognostic differences (p=0.010). The leading causes of AKI for each cluster, such as hypovolemia, drug-related, and cancer cachexia, were all clinically interpretable, which conventional approaches cannot obtain.

Conclusions: Our results enabled us to clarify the background of AKI development in ICI-treated patients with complicated AKI risks and suggested the potential for applying ML prediction models as interpretable artificial intelligence to medical care, which had been a challenge to explainability.

FR-PO027

Development, Implementation, and Outcome of Telemedicine to Improve Access to Renal Health During the COVID-19 Pandemic at the National Kidney and Transplant Institute (NKTI)

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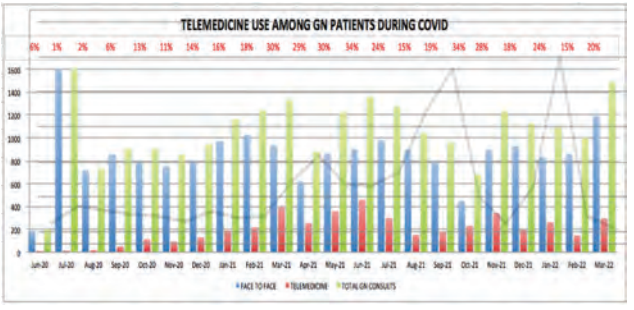
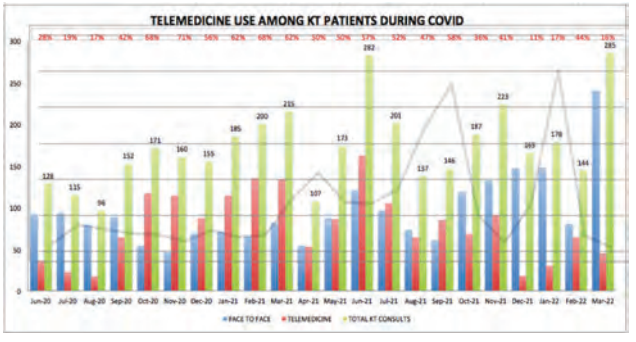
Background: With health care facilities becoming high risk places during the COVID pandemic, NKTI has developed adjustments in the provision of healthcare for out-patient consultation during the pandemic. This study aims to describe the development, implementation and outcome of telemedicine among service renal patients of Adult Nephrology Department in NKTI Out-Patient Service (OPS).

Methods: A hybrid model of telemedicine and ambulatory visits was utilizing synchronous video consults integrated with electronic medical records (EMR). Data were collected from the NKTI-OPS and Adult Nephro System including e-survey forms to assess patient satisfaction.

Results: Comparing with pre-pandemic, a 29% decrease in the mean service renal patient consultation/month was noted, with 28% and 50% reduction in GN and KT respectively. During the 4-month dry run of the program, the GN telemedicine utilization was only 4% while 27% for KT. With the full operation by October 2020, an increase of telemedicine usage was observed for both GN and KT consults with a high percentage among KT 68% vs 34% in GN patients. Majority of patients who utilized telemedicine were within 30-40 age group with comparable demographics between sex. Telemedicine was used by patients in almost all regions in the Philippines. Over-all patient satisfaction rate was 95.2%.

Conclusions: Delivering telehealth consultation to renal patients in our Institute during the COVID-19 pandemic demonstrated that it is feasible and well accepted alternative in augmenting patient care.





FR-PO028

Using Telemedicine Compared with Face-to-Face Visits for Outpatient Management in CKD Patients

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Background: In the recent past, Coronavirus disease 2019 (COVID-19) was a pandemic. Telemedicine is thought to be used for outpatient management in chronic kidney disease (CKD) patients because we want to reduce hospital visits and congestion in CKD clinic to decrease the risk of COVID-19 infection in CKD patients. This study aimed to compare the effectiveness of telemedicine with face-to-face visits for outpatient management in CKD patients.

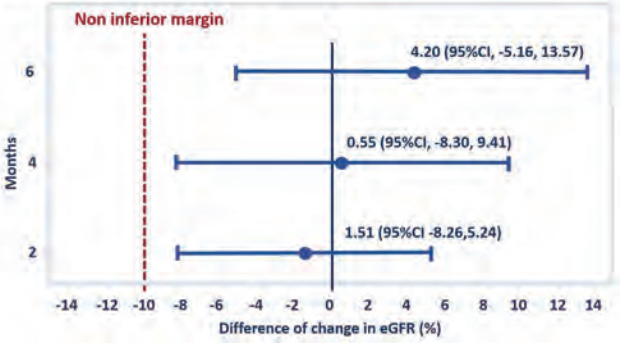
Methods: A non-inferiority, non – randomized open-label controlled trial in a CKD clinic at Bhumibol Adulyadej Hospital, Bangkok, Thailand from January 2022 to January 2023. The patients were divided into 2 groups, using telemedicine and face-to-face visits. The primary outcome was to compare the percentage change of eGFR-EPI between the two groups.

Results: There were 32 patients in both the telemedicine and face-to-face visit groups. The majority were male 60.9%. The mean age was 72.2 ± 11.2 (SD) years. CKD KDIGO stage 4 was the majority by 56.2% and mean eGFR-EPI was 24.6 ± 9.9 (SD) ml/min/1.73 m^2. The eGFR increased by 2.1% in the telemedicine group and decreased by 2.1% in the face-to-face visits group (p 0.374). There was no difference between the two groups in all-cause mortality, hospitalization, emergency department visits, renal replacement therapy initiation rate, co-morbidities and CKD complications controlled, adherence, and satisfaction with the service. Telemedicine had higher quality of life, measured from the EQ-5D scales (69.5 vs 58.4 scores, $p = 0.009$), and used shorter timing in the visit (52.5 vs 189.5 minutes, $p < 0.001$) than the face-to-face visits group.

Conclusions: Compared to face-to-face visits, telemedicine for outpatient management in CKD patients is not inferior in the percentage change of eGFR, co-morbidities, and CKD complications. Telemedicine tends to have a better quality of life, shorten the timing of the visit, and lower travel costs to the hospital.

Funding: Government Support - Non-U.S.

The difference in change of eGFR between the telemedicine group and face-to-face visits groups at 2, 4, and 6 months in follow-up times.



FR-PO029

Integration of CODEX and Brightfield Histology for Cell Type Segmentation and Classification Using Deep Learning

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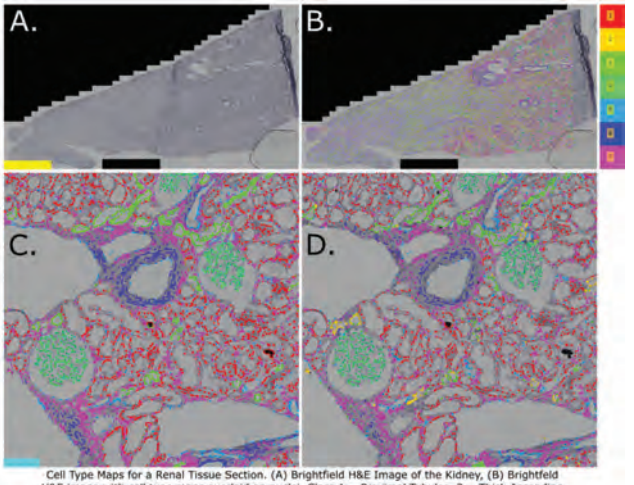
Background: Cell types in a biopsy provide information on disease processes or organ health. Multiplex imaging technologies like CODEX provide spatial context to protein expression and detect cell types in a tissue sample. New CODEX workflows allow for hematoxylin and eosin (H&E) staining on the same sections. Deep learning can automate the process of image analysis, saving time. We seek to segment and classify cell nuclei from renal tissue sections using deep learning with CODEX generated cell labels as a ground truth.

Methods: Images consisted of brightfield H&E whole slide images (WSIs) from two institutions, collected from human reference kidneys. Nuclei were segmented using deep learning, and CODEX markers were measured for each nucleus. Cells and their markers were clustered in an unsupervised manner and assigned labels according to upregulated markers and biological priors. Cell types included: proximal tubules, distal tubules connecting tubules and collecting ducts, thick ascending limb, podocytes, endothelium, vessels, and immune cells. Cell maps were used to train a Deeplab V3+ semantic segmentation model. Classification was assessed in hold-out slides from CODEX generated sections.

Results: Two segmentation models were trained on WSIs from each institution. For the model trained on 3 sections containing ~3.9M cells, we achieved a balanced accuracy of 0.68, and for the model trained on ~350k cells from 11 sections, we achieved 0.75.

Conclusions: We were able to automatically segment and classify nuclei from various cell types directly from H&E stained WSIs. In future work, we seek to extend these segmentations to typical WSIs in renal pathology, with no prior molecular interrogation.

Funding: NIDDK Support, Other NIH Support - R21DK128668, OT2 OD033753, R01 DK114485



Cell Type Maps for a Renal Tissue Section. (A) Brightfield H&E Image of the Kidney, (B) Brightfeld H&E image with cell type maps overlaid on nuclei. Class 1 = Proximal Tubules, 2 = Thick Ascending Limb, 3 = Distal Convoluted tubule, connecting tubule, and collecting duct, 4 = Podocytes, 5 = Endothelium, 6 = Vessels, 7 = Immune Cells. Yellow scale bar = 2mm, Cyan scale bar = 100μm

FR-PO030

Comparison of a Deep Learning Model with Human Expert Annotations for Segmentation of Kidneys, Tumors, and Cysts in Routine CT Imaging Exams

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Background: This study explores if a deep learning model for automatic kidney, tumor, and cyst segmentation from abdominal CT images can match interrater agreement.

Methods: A deep learning model was developed to segment the kidneys, tumors, and cysts from abdominal CTs. The training/validation set consisted of 1003 images from 479 unique subjects. A urologic oncologist with expertise in renal tumor evaluation and treatment (reference standard) and two radiology residents with experience in general abdominal CT imaging manually segmented 30 images, a held-out test set subset. Segmentation overlap between the reference standard and residents, or AI segmentations was assessed via the Dice coefficient. Confidence intervals (CI) for the probability the Dice coefficient between the reference standard and AI segmentation was larger than the with the residents based on a Mann Whitney U equivalence test were generated for left kidney, right kidney, tumor, and cyst.

Results: The mean and standard deviation of the Dice coefficients between reference standard and residents (AI) were 0.91±0.03 (0.93±0.03) for left kidney, 0.92±0.02 (0.94±0.02) for right kidney, 0.80±0.23 (0.86±0.18) for tumor mask, and 0.24±0.35 (0.42±0.37) for cyst mask, 0.81±0.24 (0.83±0.23) (see Figure 1). The 90% CIs tended to be greater than 0.5 in all cases but the tumor masks (see Table), suggesting the AI is often performing within expected interrater agreement.

Conclusions: A fully automated kidney, tumor, and cyst segmentation algorithm was trained and evaluated against three independent readers. The AI algorithm was found to compare similarly to interrater agreement.

Table 1: The estimated probability (point estimate) and corresponding 90% confidence interval for the probability a given Dice coefficient between the reference standard (urologic oncologist) and the AI segmentation is greater than or equal to the Dice coefficient between the reference standard and the two residents for each mask type (whole mask or individual connected component/lesion) and mask label (left kidney, right kidney, tumor, and cyst). Note 90% CIs were constructed based on a Mann Whitney U equivalence test with a level of significance of 0.05. If the 90% CI exceeds 0.5, the AI is performing within interrater agreement. This is the case for all but the tumor lesion masks, which are likely close to interrater agreement.

Mask Type	Mask Label	Point Estimate	90% CI
Whole	Left Kidney	0.746	[0.650, 0.841]
	Right Kidney	0.804	[0.716, 0.892]
	Tumor	0.581	[0.477, 0.685]
	Cyst	0.874	[0.812, 0.936]
Individual Lesion	Tumor	0.556	[0.450, 0.661]
	Cyst	0.839	[0.790, 0.888]

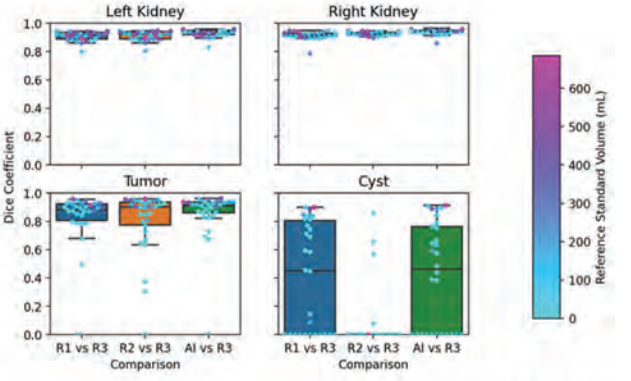

Figure 1: Box plots of the Dice coefficients based on the comparison (reader 3 is the reference standard) for the whole mask. Note the individual points are color coded based on the reference standard volume for the whole mask.

FR-PO031

Development and Evaluation of a Vision Transformer-Based Machine Learning Model for Improved Nephron Segmentation in Kidney Disease Analysis

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Background: Impacting over 20 million globally, kidney diseases mostly stem from nephron lesions. Nephrons' complex tubular structure complicates 3D pathology assessment. We've created a workflow merging optical clearing and AI to automate and improve this process. Optical clearing transfer samples transparent for accurate nephron mapping. Light-sheet microscopy visualizes these structures, but precise segmentation is required for measurements like tubule volume. Our proposed vision transformer-based machine learning model automates these measurements, assisting diagnosis and offering gene expression insights. This adaptable method extends to other tubular tissues, promising wider benefits.

Methods: We collected 36 quarter-mouse-kidney light-sheet microscopy images, each 2048x2048 pixels, with a depth range of 700-1200 pixels. Images are splitted into blocks and individually segmented. Each block is treated as a 2D image series. Adjacent images' local features and segmentation results are encoded using a convolutional neural network. The transformer encoder/decoder processes high-level contextual representations, while the convolutional decoder recovers spatial dimensions and generates a tubule probability map. The final segmentation mask is derived from a normalized output probability map, and blocks are reassembled into an original-size image. Segmentation results can be visualized and validated using VR.

Results: Amid ongoing data annotation, preliminary tests of our model on a synthetic dataset of 6000 images showed promising results. After ten epochs of training on 4800 images, it demonstrated an IoU score (Intersection over Union, a measure of the overlap between the predicted segmentation and the ground truth) of 93%, Binary Accuracy (percentage of correctly predicted data points out of all predictions) of 98%, and F1 Score (100% indicates a more robust prediction) of 96% on a validation set of 1200 images.

Conclusions: Despite synthetic data's simplicity, our model's promising performance implies its potential with real-world data. We'll keep refining the model and, once enough real-world data is annotated, we'll test and compare it with baseline models like the Classical 3D Convolutional Neural Network. At that point, we'll release the model's structure, code, annotated data, and performance results.

FR-PO032

Automated Pipeline for Peritubular Capillary Inflammation Scoring

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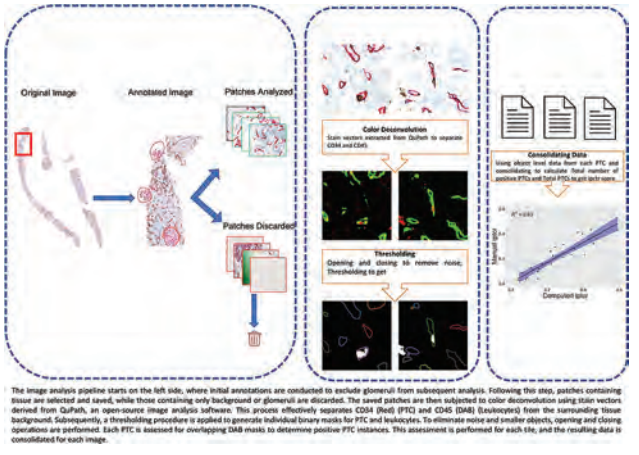
Background: Antibody-mediated rejection (AMR) can occur after kidney transplantation and is characterized by immune cell-mediated microvascular injury in response to donor-specific antibodies (DSA) and results in progressive graft survival and function. Using dual immunostaining for endothelium (anti-CD34)/leukocytes (anti-CD45), we identified peritubular capillaries (PTCs) and intracapillary leukocytes to determine the inflamed peritubular capillary ratio (*iptcr*), a quantitative Microvascular Inflammation (MVI) score that in a previous study correlated with renal graft failure and DSA strength.

Methods: Initially, we selected our stain vectors through QuPath. Used them to implement color deconvolution to separate CD34 (Red) (PTCs) and CD45 (DAB) (leukocytes). Thresholding and noise removal techniques were applied to each WSI to segment PTCs and leukocytes. The *iptcr* was determined by the ratio of total leukocyte (>1 cell) containing PTCs to total PTCs. Automated iptcr scores were compared to ground truth iptcr from manual scoring.

Results: There was a high correlation between pathologist and automated *iptcr* score (R-square: **0.83**). Perhaps even more important automated iptcr was **4X** faster versus manual pathologist scoring for each WSI.

Conclusions: Our automated approach based on using a relatively simple analytical pipeline (intensity transformation/enhancement, texture analysis, binarization, and morphological processing) makes iptcr scoring feasible. Our early results demonstrate the potential of the *iptcr* score pipeline as an efficient supplementary tool for improved AMR evaluation to replace the current discontinuous scoring system in place. Further validation and exploration of larger cohort are warranted.

Funding: NIDDK Support



The image analysis pipeline starts on the left side, where initial annotations are conducted to exclude glomeruli from subsequent analysis. Following this step, patches containing tissue are selected and saved, while those containing only background or glomeruli are discarded. The saved patches are then subjected to color deconvolution using stain vectors derived from QuPath, an open-source image analysis software. This process effectively separates CD34 (Red) (PTC) and CD45 (DAB) (Leukocytes) from the surrounding tissue background. Subsequently, a thresholding procedure is applied to generate individual binary masks for PTC and leukocytes. To eliminate noise and smaller objects, opening and closing operations are performed. Each PTC is assessed for overlapping DAB masks to determine positive PTC instances. This assessment is performed for each tile, and the resulting data is consolidated for each image.

FR-PO033

Multimodal Data Analysis with Spatial Transcriptomics

Samuel Border,[1] Nicholas Lucarelli,[1] Ahmed Naglah,[2] Sayat Mimar,[2] Tarek M. El-Achkar,[3] Sanjay Jain,[4] Ricardo Melo Ferreira,[3] Michael T. Eadon,[3] Pinaki Sarder.[2] *[1]University of Florida Department of Biomedical Engineering, Gainesville, FL; [2]University of Florida Department of Medicine - Quantitative Health Section, Gainesville, FL; [3]Indiana University School of Medicine Department of Medicine Division of Nephrology, Gainesville, FL; [4]University of Washington St Louis Department of Medicine Division of Nephrology, St. Louis, MO.*

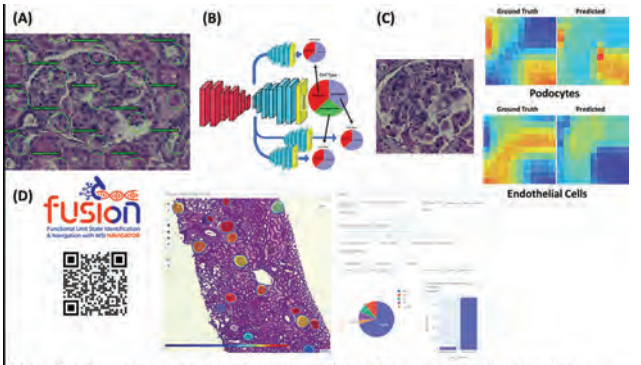
Background: Spatial transcriptomics (ST) methods have provided researchers the ability to link morphological observations in histology with molecular mechanisms. This expanded view has great potential in a clinical setting towards improving patient stratification and treatment design. However, it is difficult for a human to handle all of these data. Machine Learning (ML) methods are specially equipped to handle dense datasets, exhibiting high performance on image-related tasks. ML can be used to provide details about cell populations and their cell states in non-specially prepared tissues.

Methods: We first built a visualization tool, *FUSION*, that allows users to examine the distribution of cell types and their states across functional tissue units. Users can also select regions of interest over which to aggregate ST data. We then made a prediction model (*SpotNet*) to characterize cellular information from histology tissues. Our model uses a ResNet50 encoder and a set of branched layers to predict cell types and states. Two models were trained using glomerulus and tubule-specific cells. There were more tubules than glomeruli. A dynamic patching approach greatly increased the diversity of our training data without substantial augmentation. Predictions made on a patch-level were converted into heatmaps for visualization of cell type localization.

Results: *FUSION* is deployed on the web for public access. *SpotNet* achieved a Mean Absolute Error (MAE) of 6.4±3.2%, 10.1±1.8%, 1.2±1.16%, 11.9±4.2% on prediction of 6 cell types and 4 cell states for glomeruli and 12 cell types and 4 cell states for tubules respectively. Predicted cell localizations overlapped well with ground truth.

Conclusions: We present a method for interactive viewing of ST data and a novel ML model for prediction and interpretation from images. Integration of this model into our visualization platform will enable highly granular analysis of histology.

Funding: Other NIH Support - OT2 OD033753



Multimodal data analysis using Spatial Transcriptomics: (A) Input Visium Spatial Transcriptomics data example. (B) *SpotNet* prediction model architecture. (C) Example cell localization for two glomerular cell types. (D) *Functional Unit State Identification & Navigation with WSI (FUSION)* interactive visualization tool for analysis of spatial –omics data on an functional tissue unit level.

FR-PO034

The Acceptability and Usability of My Kidneys & Me, a Digital Self-Management Health Intervention for CKD

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Background: The use of digital health interventions (DHIs) to provide education and support has rapidly increased, especially in the post-COVID era, due to potential cost-effectiveness and ease of equitable delivery. We co-developed My Kidneys & Me (MK&M), an educational self-management DHI for CKD. Here we report the usage metrics of MK&M during a 20-week evaluation.

Methods: As part of a randomized trial, participants at 26 UK sites were given access to MK&M for 20-weeks. MK&M provided online education sessions (underpinned by behaviour change theory), and digital applications to track goals, symptoms, physical activity, and clinical measures. Access to and usage data of MK&M were collected, alongside perceived usefulness (scored from 0 (not useful at all) to 10 (very useful)). Frequency analysis identified the frequency and length of time spent on MK&M sessions.

Results: 281 patients received MK&M (age 60.8±12.8 years, 58% male, eGFR 38.9±18.5 ml/min/1.73m^2). 205 (73%) used MK&M at least once. The median number of logins per person was 10.0 (IQR 4.0-28.0). The median time per login was 12 mins (IQR 7-25 mins). 'The kidneys' was the most accessed session (n=152 participants). Table 1 displays top three sessions by total number times accessed and total duration spent on session. All sessions scored ≥7/10, with 'Kidney disease and general health' considered the most useful session (8.7/10). Goal setting was considered the most useful tracker (8.5/10) and symptoms the least (6.7/10).

Conclusions: MK&M was well received and utilised by participants. Our findings show that people with CKD are capable and willing to use DHIs for kidney health. Identification of real-life usage and usability issues will help refine MK&M, improving the content and delivery before clinical implementation.

Top three sessions by the total number of times session accessed and total duration of time spent on the session per participant

	Total number of times session accessed per participant		
	Session title	Median (n)	IQR
1	Managing my symptoms	15	15-17
2	How to move more and be active	13	13-18
3	Treatment options available	13	13-15
	Total duration of time spent on session per participant		
	Session title	Median (mins)	IQR
1	Kidney disease and general health	11	6-22
2	Kidney disease	11	6-17
3	Treatment options available	9	5-16

NB. IQR: interquartile range

FR-PO035

Tracking the 3D Architecture of Hundreds of Nephrons and Peritubular Capillaries in Health and Disease Using Light Sheet Microscopy and Deep Learning

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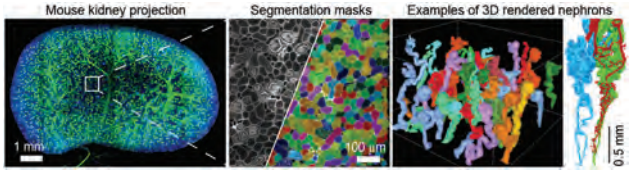
Background: Until recently, it has been practically impossible to study whole kidney nephrons and peritubular capillaries throughout the many millimeters of tissue necessary to examine them in their entirety. This technical limitation has obscured correlations and causal relationships between different parts of the same nephron, and between nearby nephrons and vasculature in cases of injury. Our study will use recent technical breakthroughs in 3D imaging, tissue clearing, and artificial intelligence to study thick specimens and process large datasets. We aim to establish a 3D connectivity map of hundreds to thousands of nephrons and study the coupling of injuries between glomeruli, tubules, adjacent nephrons, and peritubular capillaries at different stages of chronic kidney disease.

Methods: We used in vivo antibody labeling and solvent-based clearing to uniformly stain and clear whole mouse kidneys, which were then imaged on a custom-built lightsheet microscope with sub-cellular spatial resolution. We processed the 3D fluorescence data using a human-in-the-loop AI method, a deep-learning-based supervised image segmentation that allows for scaling up to large volumes and segmenting many nephrons at a time.

Results: From a single fluorescence label, our deep learning segmentation model traced hundreds of whole nephrons in 3D. We also used vasculature labeling to visualize and quantify the characteristics of the peritubular capillary network around the nephrons. So far, we have generated 3D renderings of nephrons and connectivity maps, and performed associated morphometrics (length, volume, tortuosity) for nephrons in healthy kidneys.

Conclusions: We have developed a pipeline using 3D imaging and artificial intelligence to extract relevant 3D features in hundreds of whole nephrons and capillaries in the same tissue. We will apply this framework to study the spatial correlations of injuries at various timepoints in models of chronic kidney diseases, such as focal segmental glomerulosclerosis and ischemia-reperfusion injury.

Funding: Private Foundation Support



FR-PO036

Data-Driven Disease Detection: A Learning Health System

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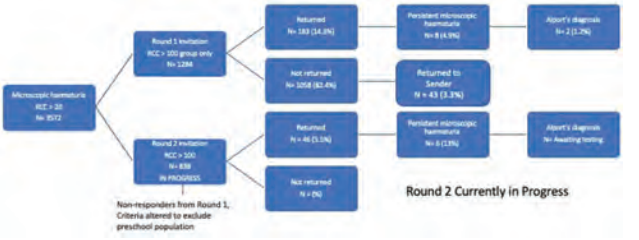
Background: Achieving pre-clinical diagnosis in time to change the course of disease is the promise of data analytics and genomic medicine. Our Kidney Genomics Clinic(KGC) showed a high diagnostic yield for Alport syndrome(AS) in a pediatric cohort with persistent microscopic haematuria. Early diagnosis of AS in childhood offers an opportunity to start treatment and delay progression. Large studies of variant databases have shown heterozygous pathogenic variants in COL4A3/COL4A4 are present in 1 in 106 and pathogenic variants in COL4A5 in 1 in 2320. Despite guidelines and education, referral rates remained static and follow up rates were low. We created a digital health solution using data analytics of the electronic medical record(EMR) to identify children with an incidental finding of microscopic haematuria and offer early genomic diagnosis to those at risk of AS.

Methods: EMR databases were interrogated using Microsoft SQL to identify patients with incidental findings of microscopic haematuria and no prior or subsequent results below the threshold(20 RCC). Patients were stratified according to levels of haematuria and those with pyuria excluded. Patients were contacted with a letter outlining the need for repeat testing utilising bulk communication and ordering functions within the EMR. All those with persistent microscopic haematuria were offered genomic sequencing through the KGC. We developed a suite of web-based resources to enhance recruitment and webpage analytics were monitored for views and engagement. As a learning health system, we sought to integrate feedback and lessons learned to iteratively improve each round of patient contact.

Results: Figure 1

Conclusions: Direct patient contact through the EMR is feasible and acceptable demonstrating how digital health strategies can be employed to solve problems in healthcare. Response rates using postal contact are poor; alternate modes of communication may improve uptake. Lessons learned from this will be utilized to develop a prospective strategy automating the process for recall of future findings of microscopic haematuria.



FR-PO037

ToxiPedia: A Website Research and Education Tool on Uremic Toxins

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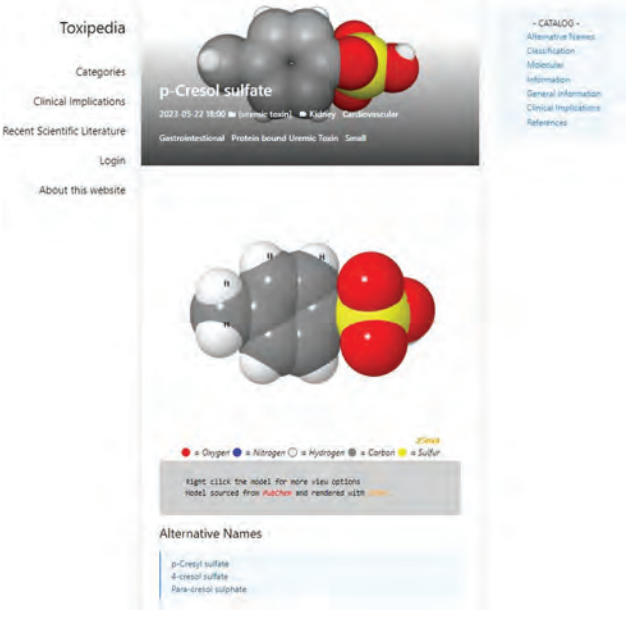
Background: Mounting evidence suggests that current understanding of uremic toxicity is limited. As many different uremic toxins are being identified there is a need for research tools to better study, classify and analyze the different molecules implicated in uremic toxicity, their origin, chemical structure, metabolism, and ill effects. ToxiPedia, is an encyclopedic free access website, to be used as a tool to store all information on each toxin, its effects, chemical structure, metabolomic, proteomic, and toxicological classifications, and other pertinent information. It may also provide a continuously updated resource for researchers to study and analyze uremia. The clinical impact of uremic toxins will also be retrievable. The website aims to serve as an educational and research tool to improve renal replacement therapies that eliminate these toxins, improve the quality of life, and reduce morbidity and mortality.

Methods: The website is designed with a website generator to allow physicians and researchers to easily contribute to it. An advisory committee will validate the project to provide independent guidance and expert advice to improve the project before it is completed, along with a peer review process for every page. As new data on uremic molecules develops researchers can update and revise relevant pages to keep the website up to date.

Results: Online free acccess catalogue of Uremic Toxins allows retreiving all relevant information on Uremic Toxins.

Conclusions: This website may close current knowledge gaps and improve the accessibility of information on uremic toxins. It will also provide a much-needed resource to organize the large mass of emerging data on the uremic syndrome, causes, mechanisms, and complications. It is hoped that Toxipedia will contribute to more knowledge and better treatment of uremic toxicity.



FR-PO038

Perceived Value of Advance Care Planning Documents in the Electronic Health Record: A Qualitative Study of Chief Medical Information Officers, Clinicians, and Patients with CKD

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Background: Older adults with advanced chronic kidney disease (CKD) are at high risk for hospitalization, serious complications, cognitive decline, and death. Despite this, advance care planning (ACP) remains low among this population. Barriers to ACP completion and the impact of ACP availability in the electronic health record (EHR) are not well understood.

Methods: Qualitative study using semi-structured interviews (March 2022-March 2023) with purposively sampled patients (CKD stage 4-5 patients, age ≥50), chief medical information officers (CMIOs), and clinicians. Participants discussed EHR-related barriers and facilitators to ACP completion and accessibility. Audio recordings were transcribed verbatim and a thematic analysis was conducted.

Results: 72 participants (29 clinicians, 11 CMIOs, 33 patients) completed interviews. Among clinician and CMIO participants, 33% were women and 43% were from the Northeast. Among patients, 36% were women, 39% identified as Black, and mean age was 70 ± 9 years. Four themes with subthemes emerged: 1) Challenges to ensuring patient autonomy (document ownership, evolving patient preferences, ensuring preferences are actionable); 2) Valuable ACP requires interoperability (lack of standardized ACP protocols, variable access across settings, limited infrastructure and incentives, policies for improving interoperability); 3) Complexity of timing (in-the-moment decision-making, clinical triggers for ACP, opportunities for automation and improved workflow); and 4) Consequences of inconsistent ACP protocols (discordant care, overconfidence that patient wishes are known).

Conclusions: The perceived value of ACP is negatively impacted by inconsistent accessibility of ACPs across settings. Recommendations for increasing the reliability of ACP at the time of need include encouraging patient ownership of ACP documents; ensuring revisions occur regularly and are reconciled in the EHR; institution-level training on storage and documentation of ACP in the EHR; employing available EHR tools such as trigger messages; and introducing financial incentives for sharing across institutions.

Funding: Private Foundation Support

FR-PO039

Implementing a Supportive Information System for the Vaccination Program of CKD Patients: Project from the Regional Nephrology Program, Military Hospitals, Taif Region, Saudi Arabia

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Background: Vaccination rates remain particularly low in chronic kidney disease (CKD) patients, with diminished immune responsiveness due to delayed vaccination. Based on an in-depth review of vaccination-related processes, this project aimed at ensuring CKD patients timely receive all recommended vaccines, while boosting vaccination culture among healthcare providers, and implementing information system support for smoothly shared documentation through the continuum of care.

Methods: An in-depth review of national and international guidelines related to the vaccination of CKD patients was undertaken. Existing local policies were reviewed in comparison. Additionally, real-life practices were scrutinized to understand the level of adherence to policies, physicians' vaccination culture, prescription and administration of vaccine processes, and the information systems that underlay them.

Results: Standardizing and centralizing electronic vaccine prescription and documentation was one of the specific objectives of the project. Different, non-linked supports -electronic and paper- were used in the different nephrology units, which resulted in siloed in-unit data, that was impossible to be shared instantly or consulted remotely. The absence of a defined process in the clinics hindered vaccine prescribing for outpatients. Prescribing was standardized by adding vaccines to the regular medication form on the electronic medical record (EMR). To standardize documentation, the EMR native pediatric vaccination form was upgraded to hold adult vaccines. A reminder -that would pop up whenever the EMR is opened- was added to the system to help staff carry out planned vaccination. The preventive medicine (PM) vaccination clinic was linked to the information system to support the vaccination of nephrology outpatients. The clinic was mapped with an individual code, allowing for referral and booking, and for full access of the PM nurses to the prescription information and to the newly created vaccination form for documentation.

Conclusions: A coherent information system, that allows for readily available and smoothly shared information, is an essential component to support the development of a comprehensive vaccination program for chronic kidney disease patients through their continuum of care.

FR-PO040

Have You Googled Your Kidney? Interpretation of Google Trends Data During World Kidney Day

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Background: World Kidney Day (WKD) is a global campaign conducted yearly in March to raise awareness of the importance of kidney disease. Analysis of the public's online interest may provide insight into the effectiveness of such awareness efforts. Our objective is to evaluate the impact of WKD by examining the temporal correlation between online searches related to kidney disease and the WKD campaign.

Methods: Using Google Trend (Gtr), we performed a retrospective study looking at relative search volumes (RSVs) of terms related to kidney disease from January 2006 to April 2023 in the USA. The search terms' RSVs during March of each year were compared to the other months. Pearson correlation coefficient was used to determine the statistical significance of the change in the RSV of WKD and its related search terms such as "Kidney Disease", "Chronic Kidney Disease", "Kidney damage", "Acute Kidney Injury", and "Dialysis".

Results: Throughout the years, an upward trend was observed in the RSVs of WKD and its associated terms. However, no consistent statistically significant correlation was found between the RSVs of WKD and related terms during March compared to the other months of the year. There were isolated statistically positive correlations found in March 2023 between RSVs for WKD, "dialysis," and "kidney disease" ($p=0.04$ and $p=0.019$, respectively), as well as an isolated positive correlation in March 2019 with the term "kidney disease" ($p=0.006$). Surprisingly, the data showed a significant negative correlation ($p=0.039$) between WKD and "Kidney Failure" for all the years analyzed.

Conclusions: Studies with similar designs have shown solid statistical correlations between the public's online queries and the Pink October campaign for breast cancer and the GoRedW campaign for heart disease. The interpretation of these findings suggests that these campaigns have successfully raised public awareness. Our study found an inconsistent positive correlation between WKD and specific terms over the years within our study period. Moreover, a negative correlation was noted with "Kidney Failure" for all years. Our research emphasizes the need for more studies on creating and executing awareness campaigns for kidney disease that can achieve the same success as those for other similarly burdensome illnesses.

FR-PO041

Characterizing the Genetic Architecture of Rare Glomerulonephropathy Disease: The Landscape of RNA Binding Protein Dysregulation

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Background: The majority of primary glomerular nephropathy (GN) cases present with either immunoglobulin A nephropathy, focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease. Despite overlapping presentations, each diagnosis may represent many distinct disease subtypes with unique etiologies. Even as most disease risk is concentrated in a small number of genes, most patients do not carry syndromic mutations in GN-associated genes. Regulatory mutations that alter the magnitude or spatiotemporal aspect of expression may contribute to the genetic architecture of disease. RNA binding proteins (RBPs) regulate the life cycle of the RNA molecule (e.g. alternative splicing). Here we employ a genome-wide analysis of >67 million mutations in WGS of GN patients from the Cure Glomerulonephropathy (CureGN) cohort using a set of RBPs and their target sites to characterize the role RBPs play in the GN disease.

Methods: To assess the pathogenic contribution of RBP dysregulation to GN, we identified the functional impact of GN patient variants on RBP binding profiles using Seqweaver, a deep learning framework for predicting variant dysregulation for over 200 RNA-binding protein models with single nucleotide sensitivity. To determine if there are global signals of RBP dysregulation across the CureGN cohort, we identified trends in RBP disease impact scores across the patient variants. A pipeline was designed to select high-impact variants that are disease specific to identify mechanisms of disease. Beyond looking at individual genes and variants in isolation, we utilized a network-based approach to nominate active disease processes at a pathway level.

Results: We observed genes enriched for predicted high-impact variants from different patients (e.g. *VAV3*), and together, the rare variants associated with GN GWAS genes had significantly higher average disease impact than control variants associated with all other genes. Importantly, we also observed significant enrichment of RBP impact in kidney cell types. Seqweaver variant predictions provide hypotheses for biochemical mechanisms that explain GWAS association signals.

Conclusions: These findings suggest that RBP regulatory mutations of known kidney disease genes may harbor substantial disease risk.

Funding: NIDDK Support

FR-PO042

Vascular Calcification Heterogeneity Evaluated by Deep Radiomics Based on Chest Radiography

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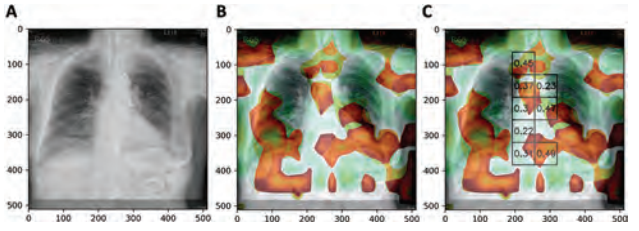
Background: Vascular calcification (VC) is regarded a systemic pathology involving most arterial segments. Recent studies suggest that calcification heterogeneity exists, meaning that VC involves different wall components and locations, indicating diverse calcification patterns. We previously established a chest radiography-based radiomic approach for identifying VC. In this study, we aimed to evaluate whether radiographic calcification heterogeneity existed, in the form of different VC distributions between those with and without chronic kidney disease (CKD).

Methods: We devised a classification method using the attention mechanism of a deep learning neural network, whose architecture was first trained in a large chest radiography dataset, and then used as an initialization for the target domain with fine-tuning. We divided substrate images into subdivisions with grids and numeric values showing the radiomics features guided by deep learning attention mechanism. Boxes were used to indicate regions more significantly attentioned in patients with at least stage 3b CKD comparing to those in non-CKD populations. We visualized the attention of the network and extracted attentional areas.

Results: We analyzed chest radiography images from 11,106 general population (3.3% with VC) and 59 stage 3b or higher CKD patients (61% with VC). We examined the differentially attentioned areas between CKD and non-CKD patients after deep learning (Figure 1A, overlapping images). Activated areas, or differentially calcified areas in CKD patients included the ascending aorta, carotid vessels, and inter-diaphragmatic areas of thoracoabdominal aortas (Figure 1B). Quantitative analysis revealed inter-diaphragmatic areas exhibited the highest radiomic feature values, followed by carotid vessels and ascending aorta region (Figure 1C).

Conclusions: Using deep radiomics, we demonstrated specific aortic segments and branch arteries to be more significantly affected by VC among CKD patients than those without. Calcification heterogeneity can be detected using deep radiomics.



FR-PO043

Automated Detection of Renal Contrast Phases

Seyed Moein Rassoulinejad Mousavi, Bardia Khosravi, Alexander Weston, Hillary Garner, Naoki Takahashi, Timothy L. Kline, Bradley J. Erickson. Mayo AI Lab. *Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Renal contrast phases are vital for evaluating renal function, assessing pathology, detecting abnormalities, and formulating treatment plans. In this study, we utilized a combination of deep learning (DL) and regression techniques to identify contrast agents in CT scans and determine the specific stages of contrast-enhanced (CE) renal imaging. Initially, DL was employed to differentiate between CE and non-CE scans. For scans with administered contrast agents, a random forest regression model was trained to predict the complete range of values associated with the contrast phases. This approach allows for a more precise analysis of the continuous chronological sequence of contrast phases, rather than relying on predefined categories like classification.

Methods: The DL model is trained using a ConvNeXt-Femto architecture to classify CE and non-CE renal imaging. We used 3033 CT scans from 1017 patients with renal cell cancer. Using a segmentation model the left and right kidney were segmented. We selected five 2D slices of renals for classification: the middle slice based on the right kidney, two slices above, and two slices below. This simplified the input data while leveraging renal image characteristics. Features extracted from DL were used as input for a regression task using random forest to associate a value with each contrast phase based on chronological sequence aspects of renal enhancement. We employed five-fold cross-validation for training, using a sixth fold as the test set.

Results: The models performed well both in contrast detection and phase association tasks. The DL achieved an accuracy of 98% in classifying CE versus non-CE. For predicting other contrast phases, the model had a mean absolute error (MAE) of 0.34 on the test set. The model effectively associates numerical values with the eight contrast phases from “early corticomedullary” to “late pyelographic”, enabling characterization of renal contrast enhancement patterns.

Conclusions: Coupling DL and regression, proved to be highly effective in automating the detection of contrast agents in CT scans and accurately determining the specific stages of CE in renal imaging. This approach enables comprehensive analysis of the continuous chronological sequence of contrast phases, surpassing the limitations of predefined categories typically used in classification.

Funding: Other NIH Support - NIH T32 training grant 5T32DK007013-44

FR-PO044

Characterizing Urinary Tract Infections and Their Treatment Pathways EHR

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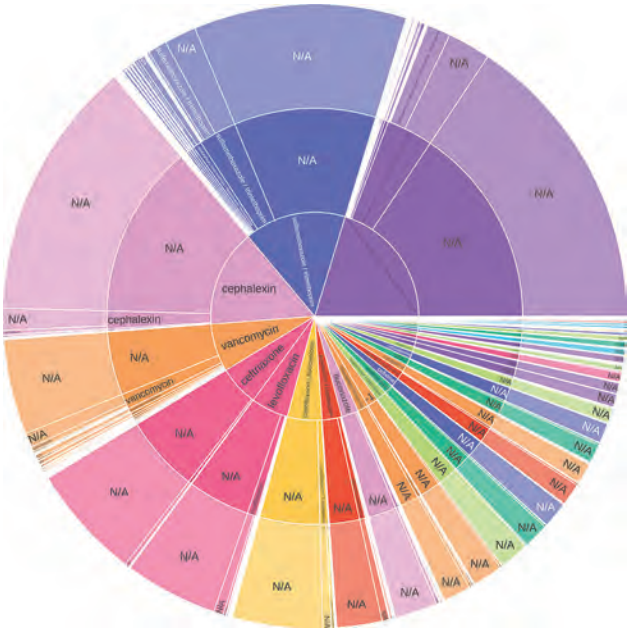
Background: UTIs are one of the most common infections worldwide. UTI epidemiology studies show a 27% recurrent rate in women within 6 months after the first UTI. Hence UTI early diagnosis and systematic treatment are very important. This project studies antibiotics treatment pathways (medication usage sequence) using big data.

Methods: We developed an electronic UTI phenotype identifying UTI by having at least 1 diagnosis/positive urine culture. It can further subgroup UTI as having a single episode of UTI or recurrent UTIs using 1-week time window to define each episode. UTI treatment pathways were analyzed for those who had at least one antibiotic in EHR. The patient had to have at least a 1-year of data in the database before the first UTI occurrence to be included. The medications were defined by ingredients using RxNorm and were grouped to drug class using ATC. The medications were extracted, and then ordered by first exposure. The sunburst plots were generated to visualize the pathways.

Results: Analyzing ~5M CUIMC EHR spanning back to 1980s, we identified 176,533 UTI patients (71% single vs 29% recurrent), consistent with prior reports. Among them, 112,126 patients qualified for this analysis. Recurrent UTIs patients were younger than single UTI patients (48 vs 53 years). The prevalence of female UTI was significantly higher than male UTI (female in overall 83%, in single UTI 82%, in recurrent UTI 87%). The five most commonly used antibiotics were nitrofurantoin monohydrate (24%), cephalexin (23%), nitrofurantoin/tetracaine (22%), ceftriaxone (18%), sulfamethoxazole/trimethoprim (17%) (Fig 1).

Conclusions: We designed a new electronic phenotype to detect single and recurrent UTI events. This algorithm can be useful for big data approaches to studies of UTI epidemiology and treatment patterns.

Funding: Other NIH Support - National Human Genome Research Institute (NHGRI)



4 level treatment pathways for UTI. The inner circle shows the first relevant medication that the patient took, and so forth. N/A means no drug.

FR-PO045

A Machine Learning Approach to Differentiating Between Typical Diabetic Nephropathy (DN) and Atypical DN with Podocytopathy in Periodic Acid-Schiff (PAS)-Stained Whole Slide Images of the Kidneys

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Background: Diabetic nephropathy (DN) is a leading cause of end-stage kidney disease. Other podocytopathies may occur in the setting of diabetes, leading to atypical presentations and potential responsiveness to immunosuppressants. Differentiation between typical and atypical cases is infeasible with light microscopy alone. We show that atypical DN with other podocytopathy can be differentiated from typical cases by uncovering clusters in a 2D projection of quantitative morphological features of glomeruli.

Methods: 99 PAS-stained whole slide images of DN kidney biopsies (91 typical; 8 atypical) were fed into a deep learning model to segment glomeruli, from which

315 morphological features were quantified. Features were categorized according to compartment: global, PAS-positive (P), luminal (L), nuclear (N), both P & L, both P & N, and both L & N. They were further categorized according to type: morphological, size, color, radial, relative distance, textural. Points representing cases in a 315-dimensional hyperplane (1 dimension per feature) were projected onto 2D while preserving high-dimensional clusters using uniform manifold approximation and projection.

Results: Points representing typical DN cases clustered separately from atypical cases (top of projection). See Fig. 1.

Conclusions: Since some podocytopathies in the setting of DN respond to immunosuppressants, our approach could inform treatment in DN cases with suspicion of co-occurring podocytopathy. Given the infrequency of atypical cases and the overwhelming background diabetes, data are scarce. Future research may identify features that contribute to the clustering and to understand how morphology can inform diagnosis.

Funding: NIDDK Support

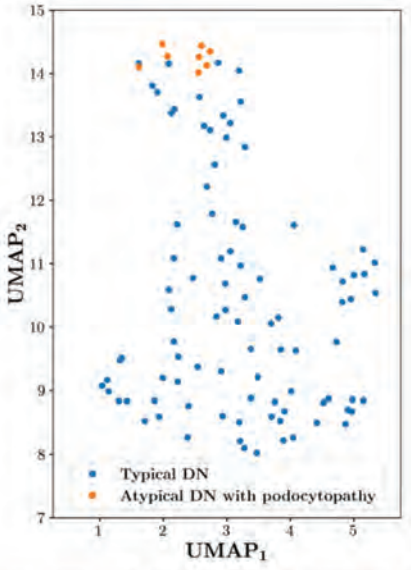

Fig. 1: Two-dimensional uniform manifold approximation and projection (UMAP) of 315 morphological image features of glomeruli from 99 cases of diabetic nephropathy [DN; (91 typical, 8 atypical)]. Points representing typical DN cases (blue points) occupied the greater part of the projection and clustered separately from atypical cases (orange points; top of projection). This illustrates that atypical DN cases with other podocytopathies could be differentiated using quantitative morphological features of glomeruli extracted from PAS-stained whole slide images of DN kidney biopsies.

FR-PO046

Symptom Trajectories in the Electronic Health Record During the Transition to Dialysis

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Background: How symptoms recorded in the electronic health record (EHR) change during the transition to dialysis has not been fully explored.

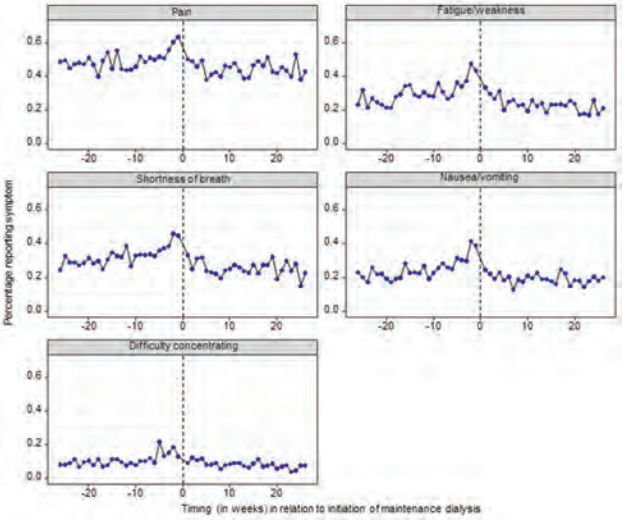
Methods: Using Optum's de-identified Integrated Claims-Clinical Dataset, we identified individuals with CKD stages 4-5 who transitioned to dialysis. We searched clinical notes for symptoms, identified by natural language processing, recorded across weekly intervals in the 6 months before and after dialysis initiation. We estimated changes in the odds of a symptom being recorded with an interrupted time series analysis using segmented logistic regression.

Results: The cohort comprised 728 individuals (mean age 67.7 ± 13.1 years, 44.0% women, 55.9% White and 29.9% Black). During the 6 months prior to dialysis initiation, 83.3% were recorded as having pain, 68.4% had fatigue/weakness, 66.3% had shortness of breath, 60.6% had nausea/vomiting, and 37.1% had difficulty concentrating. Before initiation, odds of an individual being recorded as having pain increased (slope: OR 1.02 per week, 95% CI 1.01 – 1.03); dialysis initiation was associated with a decrease (intercept change: OR 0.70, 95% CI 0.60 – 0.83). After initiation, odds of pain were unchanged (post-dialysis slope: OR 1.00 per week, 95% CI 0.99 – 1.01), although this represented a trajectory change relative to the pre-dialysis period (change in slope: OR 0.98 per week, 95% CI 0.96 – 0.99). For fatigue/weakness, odds increased before initiation (OR 1.03 per week, 95% CI 1.02, 1.04), but decreased upon initiation (OR 0.62, 95% CI 0.52 – 0.76) and thereafter over time (OR 0.98 per week, 95% 0.97 – 0.99), representing a reduction in slope relative to the pre-dialysis period (OR 0.95 per week, 95% CI 0.94 – 0.97). Patterns for shortness of breath, nausea/vomiting, and difficulty concentrating were similar to those of fatigue/weakness.

Conclusions: Natural language processing can be used to study symptom changes recorded in individuals with advanced CKD.

Funding: NIDDK Support

Figure



FR-PO047

Performance of Large Language Models in Self-Assessment Questions for Nephrology Board Renewal: Comparative Study of ChatGPT (GPT-3.5, GPT-4) and Bard

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Background: The GPT series, Large Language Models (LLMs) pre-trained on vast data, have highly influenced recent Natural Language Processing advances. While GPT-4 demonstrated high accuracy in US law and medical exams, its performance in specialized areas like nephrology is unclear. This study aimed to compare ChatGPT (GPT-3.5, GPT-4), Bard, and their potential clinical applications in area of nephrology.

Methods: In this study, 99 questions from the "Self-Assessment Questions for Nephrology Board Renewal" from the years 2018-2022 were presented to two versions of ChatGPT plus (GPT-3.5, GPT-4), and Bard. The prompts were presented in Japanese, beginning with "I will now present a problem related to kidneys. Please answer in the form of 'answer', 'explanation'." Questions that included images only used the text of the question as input. We calculated the overall correct answer rates for the five years and each year, and checked whether they exceeded the pass criterion of a correct answer rate of ≥ 60%. We also conducted a comparative study of the correct answer rates by category and image presence. Statistical analysis was performed using Chi-square tests and Fisher's exact tests.

Results: The overall correct answer rates for GPT-3.5, GPT-4, and Bard were 31.3% (31/99), 54.5% (54/99), and 32.3% (32/99), respectively, thus GPT-4 showed significantly higher accuracy than GPT-3.5 ($p < 0.01$) and Bard ($p < 0.01$). While GPT-3.5 and Bard did not meet the pass criteria in any year, GPT-4 met the pass criteria in three years. GPT-4 showed significantly higher accuracy in clinical questions and non-image questions compared to GPT-3.5 ($p = 0.01$, $p < 0.01$) and Bard ($p = 0.02$, $p < 0.01$). No significant differences were observed between GPT-3.5 and Bard in any analysis.

Conclusions: GPT-4 significantly outperformed GPT-3.5 and Bard in overall accuracy, clinical, and non-image queries. It met Japanese Nephrology Board renewal standards in three of five years, with future improvement expected in image input and nephrology-specific fine-tuning. These findings underline the potential application of LLMs in nephrology and their pros and cons. As LLMs advance, nephrologists should understand their performance and reliability for future applications.

FR-PO048

External Validation of a Machine Learning Model for Progression of CKD in the CREDENCE and CANVAS Trials

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2i) are indicated for slowing progression of chronic kidney disease (CKD). A previously validated machine learning model (Klinrisk model) accurately predicts 40% decline in eGFR or kidney

failure using routinely collected laboratory data. We sought to validate this model in the pooled CANVAS/CREDENCE trials.

Methods: The CANVAS/CREDENCE trials evaluated the effects of the SGLT2i canagliflozin on cardiorenal outcomes in patients with type 2 diabetes at high cardiovascular risk or with CKD. We validated the Klinrisk model for prediction of CKD progression, defined as greater than 40% decline in eGFR or kidney failure. The model applies results from complete blood cell counts, chemistry panels, comprehensive metabolic panels, and urinalysis. Model performance was assessed up to 3 years (median follow up 2.4 years) with the area under the receiver characteristic operating curve (AUC), Brier scores, and calibration plots of observed and predicted risks. We compared performance of the model to standard of care using eGFR (G1-G4) and urine ACR (A1-A3) KDIGO heatmap categories.

Results: Among 14,464 patients in CANVAS/CREDENCE, we found the Klinrisk model provided excellent discrimination for CKD progression (696 events at 2 years), with an AUC of 0.81 (95% confidence interval 0.78 – 0.83) for prediction of the outcome at 1 year, increasing to 0.88 (0.86 – 0.89) at 3 years. Brier scores were 0.020 (0.018 – 0.022) at 1 year, increasing to 0.056 (0.052 – 0.059) at 3 years. Calibration was satisfactory, with minor overprediction in patients randomized to canagliflozin. Compared to the KDIGO heatmap, the Klinrisk model had improved performance at every interval (Table 1).

Conclusions: The Klinrisk machine learning model using routinely collected laboratory features was highly accurate in its prediction of CKD progression in the CANVAS and CREDENCE trials.

Table 1. Results of model performance

	Klinrisk model	Klinrisk model	eGFR and ACR categories (KDIGO heatmap)	eGFR and ACR categories (KDIGO heatmap)
Time frame, years	AUC (95% CI)	Brier score (95% CI)	AUC (95% CI)	Brier score (95% CI)
1	0.81 (0.78 - 0.83)	0.020 (0.018 - 0.022)	0.74 (0.71 – 0.76)	0.021 (0.018 – 0.023)
2	0.85 (0.84 - 0.87)	0.042 (0.039 - 0.046)	0.79 (0.78 – 0.81)	0.046 (0.042 – 0.050)
3	0.88 (0.86 - 0.89)	0.056 (0.052 - 0.059)	0.83 (0.81 – 0.84)	0.063 (0.059 – 0.067)

Brier scores range from 0 to 1, with lower values representing higher accuracy.

FR-PO049

The KIDNEE Club: An Acceptability and Feasibility Study of a Preclinical Medical Student Experience in a Pediatric Dialysis Unit Pilot Program

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Background: Recently, concerns have developed over the sustainability of the pediatric nephrology workforce. Studies indicate that preclinical exposure may impact medical students' interest in field specialization. Seeking to provide early pediatric nephrology exposure to medical students, we implemented an educational intervention to pair preclinical students with pediatric dialysis patients, called the KIDNEE (Kids In Dialysis, Nephrology Exposure and Education) club. We aimed to study the acceptability and feasibility of this pilot intervention for the students, patients, and unit staff.

Methods: For the 2022-23 academic year, seven first year medical students were paired with pediatric dialysis patients. Students met with their "match" once weekly during dialysis sessions. We distributed surveys to participants six months after program implementation to assess feasibility and acceptability of this pilot program. Surveys, based on a previously published Likert scale tool assessing student and parent impression of a preclinical exposure program, were iteratively revised after review by medical education experts. Surveys were distributed via REDCap to the medical students, staff, and patients/families who participated in the program.

Results: From October 2022-April 2023, the 7 medical students spent ~173 hours in the dialysis unit. All (100%) students, 8 of 24 (33%) dialysis staff, and 2 of 7 (28%) patients/families responded to the survey. Students reported increased interest in caring for children with kidney disease after participation in the KIDNEE Club. Staff and parents unanimously reported students were helpful to patients and played an important role in patient's overall happiness. They all reported that they would recommend the KIDNEE club to other families. One parent reported that the program "improved my child's mood and maybe made it easier for the necessary care to take place because he was more cooperative/motivated."

Conclusions: Preliminary data suggests the KIDNEE club pilot was both feasible and acceptable for students, staff, and patients/families. As our results are limited by small sample size given the pilot nature of the program, future study is needed with program expansion and longitudinal assessment of the impact on students' career trajectories.

FR-PO050

Overview and Outcomes of the Kidney STARS Program

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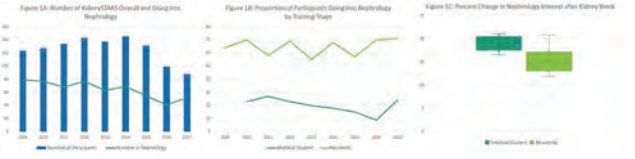
Background: The ASN Kidney Students and Residents (STARS) program was founded to increase interest in Nephrology careers. In addition to tailored events and networking opportunities, this program provides travel support and complimentary registration to attend the Annual Meeting during ASN Kidney Week. Understanding the impact of Kidney STARS participation on recruitment of trainees into the nephrology workforce is critical.

Methods: We tracked medical students (MS) and residents (PGY) STARS participants from 2009-2017 using Doximity, ABIM, and ABP by searching for the participants' first and last names. Two reviewers validated the search results. MS began to be accepted into the program in 2010. Those that participated multiple times were logged in their first year of participation only. Participants who were still in training at the time of tracking (e.g., MS or PGY), were international participants, or were unable to be validated by the reviewers were excluded from final analysis. Starting in 2010, assessment of participant interest in nephrology pre- and post- participation was obtained via a post-Kidney Week survey.

Results: There have been 1,624 STARS participants over those nine years, of which 1,128 were included in our tracking metrics. MS made up 26% of the participants while PGY constituted 74%. 52% of participants completed a fellowship in nephrology (Figure 1A). A larger proportion of PGY participants chose a career in nephrology compared to MS participants (64% vs. 18%, P<0.001) (Figure 1B) with significantly higher odds (OR 8, 95% CI 5.8-11.2). While MS had lower pre- and post- interest than residents (Pre 6.2 vs. 7.7, P<0.001 and Post 7.4 vs. 8.9, P<0.001), relative change in interest was higher in MS (19 vs. 15.3, P=0.007) (Figure 1C).

Conclusions: The ASN Kidney STARS program has been adapted to include diverse levels of learners, has built programs in mentorship, and has refined its approaches. The program has been successful with more than half of participants in the STARS program completing a fellowship in nephrology. Continued investment into the Kidney STARS program is critical to attracting trainees into nephrology.

Funding: NIDDK Support



FR-PO051

Reimagining Safety in the Learning Environment: A Grounded Theory Exploration of Identity Safety in Clinical Medical Students

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Background: Trainees in nephrology who identify as underrepresented in medicine and/or international medical graduates are at high risk for identity threats such as stereotype threat and microaggressions. Identity threats impair learning and erode well-being. In contrast to identity threat, less is known about how learners experience feelings of safety regarding their identity. This exploratory study aims to develop a theory of identity safety in the clinical learning environment.

Methods: This multi-institutional, qualitative interview study was informed by constructivist grounded theory and critical pedagogy. Participants were clinical students at three US medical schools. Investigators purposively sampled interviewees based on their responses to an 11-item survey with an open-ended question soliciting students' personal identities and their scores on the racial/ethnic and gender Stereotype Vulnerability Scales. The investigators interviewed, coded, constantly compared, and continued sampling in alignment with grounded theory. The team engaged in critical reflexivity throughout the analytic process to enrich data interpretations.

Results: Sixteen diverse students were interviewed. We organized their identity salient experiences into identity safety, identity threat, and threat mitigation. Identity safety occurred when learners existed as their authentic selves without feeling the need to monitor others' perception of their identities. This arose when: 1) learners demonstrated agency to leverage their identities for patient care, 2) others upheld their personhood and saw them as unique individuals, and 3) learners felt they belonged. Participants experienced identity threat when they experienced stereotype threat or interpersonal threat. Threat mitigation occurred when someone intervened against an identity threat, dampening but not eliminating the impact of the identity threat.

Conclusions: Identity safety may foster learning by liberating learners from self-monitoring, insulating them from identity threats, and enabling them to leverage their identities to contribute to patient care.

FR-PO052

Building Diagnostic Schemas Improves Resident Confidence in Managing AKI

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Background: The complexity of nephrology has been identified as a major contributing factor as to why fewer resident physicians are pursuing it as a career. Improving resident comfort and knowledge about nephrology topics, particularly acute kidney injury (AKI), is imperative to decreasing resident perception of their difficulty. There is a paucity of data on effective teaching methods for AKI for resident physicians. Therefore, we designed and tested a workshop where interns build an AKI diagnostic schema to see if that improved their comfort with the topic.

Methods: The workshop took place during dedicated didactic time for interns at an academic hospital's internal medicine residency. They received a pre-workshop survey that explored their perceived knowledge of AKI etiology, diagnosis, and management as well as their comfort level with explaining AKIs to patients and medical students. Interns were briefed on how to use diagnostic schemas and together constructed one for AKI (pre-renal, intrinsic, and post-renal causes). They then underwent didactics on pathophysiology, clinical manifestations, diagnostic work up, and management of AKI using this schema. Finally, the group used the schema to map out a general approach for a patient presenting with an AKI and answered practice questions. Finally, they took a post-workshop survey with the same questions as the pre-survey.

Results: 12 interns completed the pre-workshop survey and 15 completed the post-workshop survey. In the pre-survey, only 25% of the interns "agreed" or "strongly agreed" they felt comfortable working up and managing a patient with an AKI and only 16% had an organized approach compared to 80% of interns in the post-survey for both responses. 8% and 16% of interns felt comfortable explaining AKIs to patients and medical students, respectively, which improved to 73% and 57% after the workshop.

Conclusions: Internal medicine interns felt more confident diagnosing and managing AKI as well as discussing it with their patients and medical students after building and practicing with a diagnostic schema. Though this study was limited by study size and lack of control group, it serves as a first step in collecting data and exploring effective teaching methods for common nephrology topics, with the crucial goal to increase resident comfort level with kidney disorders and bolster interest in nephrology.

FR-PO053

Handout on Over-the-Counter Medication Safety in CKD Improves Internal Medicine Resident Confidence and Knowledge

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Background: Drug-related nephrotoxicity can lead to acute kidney injury, chronic kidney disease (CKD) progression, or even end stage kidney disease. There are limited electronic medical record (EMR)-based educational materials with information on over-the-counter (OTC) medication safety for patients with CKD. The goal of our study was to introduce an EMR-based educational handout to internal medicine resident physicians and evaluate whether their knowledge and confidence in OTC medication safety counseling for CKD changed following.

Methods: Internal medicine and internal medicine-pediatric (med-peds) residents at the University of Michigan were recruited to participate in the introduction and training for the EMR-based handout. The handout was previously developed by experts in nephrology for use during patient-provider encounters. Pre-tests and post-tests were administered prior to and immediately after review of the handout. Resident confidence was gauged using survey questions with item responses consisting of a 7-point Likert scale. Differences in proportions were assessed using chi-squared tests. This project was IRB approved.

Results: 35 residents completed training for the EMR-based handout: mean (SD) age was 28.3 years (1.8) and 46% were female. Ninety-four percent were general internal medicine and 6% were med-peds residents. Comparing pre-test and post-test scores, a higher proportion of residents correctly identified medication safety profiles for patients with CKD following training: low dose aspirin (pre-test = 57.1% vs post-test = 94.3%, $p < 0.01$), antihistamines (71.4% vs 97.1%, $p < 0.01$), guaifenesin (74.3% vs 97.1%, $p = 0.01$), dextromethorphan (40.0% vs 88.6%, $p < 0.01$), and Pepto-Bismol (68.6% vs 91.4%, $p = 0.03$). A higher proportion noted concerns with pseudoephedrine (68.6% vs 94.3%, $p = 0.03$) and Kaopectate (42.9% vs 100.0%, $p < 0.01$) for routine use in patients with CKD. Following training, residents felt more confident in their knowledge (4.2 vs 6.3, $p < 0.01$) and in counseling patients with CKD on OTC medication safety (4.0 vs 6.2, $p < 0.01$).

Conclusions: One-time didactic training using an EMR-based handout about OTC medication safety enhanced resident knowledge and confidence in counseling patients with CKD.

FR-PO054

Career Development in Nephrology: A Pilot Fellowship Mentorship Program

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Background: Mentorship programs can improve career enhancement for trainees and mutually benefit the mentor. Structured mentorship programs in graduate medical education have been shown to enhance the training experience and are met with high satisfaction. We implemented a structured 2-year mentorship program in the nephrology fellowship at the University of Pennsylvania from 2021-2023.

Methods: Between 2021 and 2023, nephrology faculty volunteered as mentors. Faculty created career and special interest profiles. Fellows reviewed faculty profiles and ranked mentor preferences, which program leadership used to create mentor-mentee pairs. Pairs met quarterly throughout the academic year and participated in professional development sessions (Figure). End of year feedback was obtained using anonymous surveys to assess satisfaction and effectiveness of the program using Likert scales (1-6, extremely dissatisfied to extremely satisfied, extremely ineffective to extremely effective). This program was deemed exempt by the University of Pennsylvania IRB.

Results: 34 mentor-mentee pairs were created between 2021-2023. 22 fellows (65%) and 22 faculty (65%) responded to anonymous surveys. Average overall program satisfaction score among fellows was 5.0/6.0 (SD 1.1), and among faculty was 3.9 (1.2). Fellows were satisfied with support of their professional aspirations (avg 5.3, SD 1.1). Faculty were satisfied with mentor resources (avg 4.3, SD 1.1). Perceived effectiveness of mentorship among fellows was satisfactory across all domains (Table).

Conclusions: The nephrology fellowship mentorship program at the University of Pennsylvania was met with active participation and high overall satisfaction. Limitations include survey response rates and assessment of attitudes rather than professional outcomes. Based on the pilot program, we will continue to evolve the professional development sessions and faculty resources to meet the needs of the fellows.

Table: Perceived effectiveness of mentorship domains among fellows, 2021-2023 (22 Respondents)

	Clinical Skills Advancement No. (%)	Career Planning No. (%)	Networking No. (%)	Sponsorship & Advocacy No. (%)	Research Productivity No. (%)	Professionalism* No. (%)
Effective (Likert 4-6)	21 (95)	20 (91)	20 (91)	20 (91)	18 (82)	20 (91)
Ineffective (Likert 1-3)	1 (5)	2 (9)	2 (9)	2 (9)	4 (18)	2 (9)

*Professionalism domain explored mentoring on handling sensitive or challenging issues

Figure: Mentorship Program Schedule

	Session #1	Session #2	Session #3	Session #4
Year 1	Introduction	Strength Assessment	Career Panel	CV Workshop
Year 2	Getting/Giving Advice	Goal Setting	Nephrology Boards Planning	Concluding Session

FR-PO055

Creation and Validation of a Formative Assessment Tool for Nephrology Fellows' Clinical Reasoning in a National Cohort

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Background: Deficits in clinical reasoning are common among graduate medical learners. We created and validated an instrument to assess clinical reasoning in a national cohort of first-year nephrology fellows and established performance thresholds for remedial coaching.

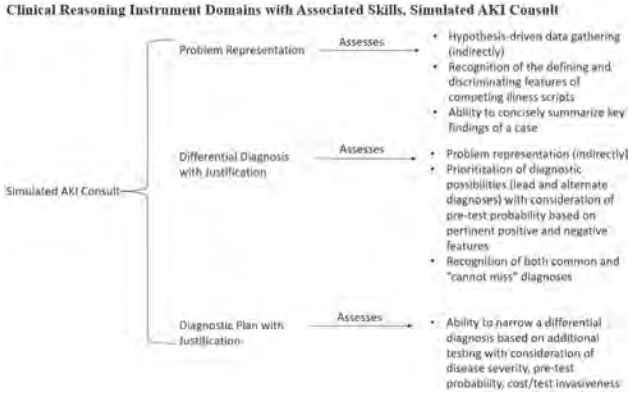
Methods: Experts in nephrology education and clinical reasoning remediation designed an instrument to measure clinical reasoning through a written patient-encounter note from a web-based, simulated AKI consult (https://sites.temple.edu/rene/case-2/). The instrument measured clinical reasoning in three domains (Problem Representation, Differential Diagnosis with Justification, Diagnostic Plan with Justification). Inter-rater reliability was established in a pilot cohort of first-year fellows using a two-way random effects agreement intraclass correlation coefficient (ICC) model. The instrument was then administered to a larger cohort of first-year fellows to establish performance standards for coaching using the Hofstee method.

Results: Both the pilot cohort (n=15 fellows; 4 training programs) and study cohort (n=61 fellows; 20 training programs) were representative of first-year nephrology fellows nationwide. The ICCs for Problem Representation, Differential Diagnosis, and Diagnostic Plan were 0.90, 0.70, and 0.50. Passing thresholds (% total points) in Problem

Representation, Differential Diagnosis, and Diagnostic Plan were 59%, 57%, and 62%. Fifty-nine percent (n=36) met the threshold for coaching in at least one domain.

Conclusions: We provide validity evidence for a simulated AKI consult for formative assessment of clinical reasoning in nephrology fellows. The majority met criteria for coaching in at least one of three reasoning domains, demonstrating a need for assessment and instruction in clinical reasoning.

Funding: Private Foundation Support



The simulated consult measures three domains, which map to a part of the linear clinical reasoning pathway.

FR-PO056

A Qualitative Analysis of Advanced Training in Glomerular Diseases: Results from a Program Directors' Survey

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Background: Several centers around the world offer either an extra year of training in glomerular disease (GD) or focus on specialized GD training during nephrology fellowship. Data on the successes and limitations of advanced fellowship programs or focused training in GD is scant.

Methods: As part of the education committee of the International Society of Glomerular Disease (ISGD), we conducted a 10-question survey of all program directors that offer an advanced year in GD training. Open-ended questions were used to evaluate measures of success and challenges of each program and data were analyzed using thematic content analysis.

Results: 15 programs responded to the survey (>90% response rate). 6/15 programs have had GD specific training for over 15 years; and the remaining ranged from 5-15 years. The majority of the programs were in USA (10/15) and 5/15 programs were located in Europe. 11/15 program graduates entered academia. All had a renal pathologists. The majority (9/15) of programs did not have a formal fellowship curriculum. Fig 1 and Fig 2 discuss success and challenges programs faced with GD fellowships. Success was noted as having departmental resources, multidisciplinary teams and local expertise in GD and protected time for research. Challenges included funding, interest in nephrology, visa issues, lack of resources for patient education in GD.

Conclusions: There is a lack of GD focused training programs in nephrology. Data from this study can help to inform the development of new guidelines and educational curricula for trainees and highlight the need to foster international collaborations that can provide peer support, aid with funding, and promote GD research.

FACTORS CONTRIBUTING TO GD PROGRAM SUCCESS	
Multidisciplinarity	"[We have a] close collaboration with rheumatology and immunology." "We have an interdisciplinary (Nephrology, Rheumatology, Dermatology and OB/GYN) lupus clinic." "We do offer a combined pediatric adult GN clinic [and] training in kidney biopsy." "[We have] nephropathology [as part of the program]." "Integration of our clinics with rheumatology and pulmonary as there is significant overlap in the systemic diseases that result in GD."
Institutional support for research	"Protected time for Clinician Scientists to study GNs and more." "Clinical research opportunities for interested fellows."
Local expertise	"Program directors completed GN fellowships at other institutions." "Multiple faculty members devoted to GN." "Our success is due to massive expertise locally in GN."
Educational curricula	"Dedicated GN clinics that GN fellow attends with 2 attendings allowing for different perspectives on management." "A 2-year fellowship for more longitudinal exposure, and it is tied to doing a Master's degree in clinical epidemiology with a large focus on research." "There is lots of flexibility for fellows to be able to attend on service or join the nephropathology department."
Patient-related factors	"Clinically we have a lot of patients coming to our institution and that provides a wealth of knowledge and experience for our GN fellows." "Wide variety of referral cases." "Large and diverse patient population"

Fig 1

CHALLENGES FOR GD PROGRAMS	
Financial resources/funding	"Finding money to pay fellow salaries." "[Get] funding for an additional year of training in glomerular disease." "Funding - we don't have specific funding for fellowships; hence our "fellows" have to do a lot of ordinary renal residency work. [There's] great demand for properly funded GN fellowships."
Political factors/ US immigration	"Inability to recruit fellows with visas." "Inability to hire J-visa candidates." "Interested people are often from overseas and as there is clinical work, state board licensure becomes an issue."
Declining interest in nephrology and nephrology research	"The number of young doctors interested in nephrology is gradually decreasing." "Appointment of young physicians due to the burden of this specialty [is difficult]." "Finding fellows who want to do basic, translational, and clinical research..." "Identifying nephrology fellows interested and dedicated to doing 2 years of extra training."
Healthcare and patient-related factors	"Many of our patients are non-English speaking with limited health literacy, which complicates understanding of diagnosis and potential treatment options." "Reimbursement of biologicals [is an issue]."

Fig 2

FR-PO057

Results and Economic Benefits of the Implementation of an Interventional Nephrology Program in a Third-Level Center in Mexico City

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Background: Diagnostic and Interventional Nephrology (DIN) is an area of great interest and growth, it has shown great operational utility in the departments. Since 2015, a DIN program has been started in our center, with an area of ultrasound equipment and procedures. It has shown significant benefits for patients and in the training of nephrology residentss, mainly in renal graft biopsies (RGB), vascular access (VAs) and kidney biopsies (KB).

Methods: A retrospective, observational and descriptive study. RGB procedures (January/2015-May/2023) and VAs (July/2017-May/2023) were included; RGBs are performed on an outpatient basis; VAs with USG guidance, without fluoroscopy, with local anesthesia.

Results: A total of 4,092 procedures were performed, 2,167 RGBs (52.9%); 931 (22.7%) VAs for HD and KB 994 (24.2%). The most frequent indication for RGB was by protocol 699 (32.2%) and the presence of DSAs 586, (27%); 2115 (97.6%) were successful, and there were 52 complications (2.3%), 8 (0.3%) serious. Of the VAs, 601 (64.5%) were non-tunneled catheters (NTC) and 327 (35.1%) tunneled catheters (TC); the most frequent indications were chronic HD 438 (47%) and uremic syndrome 161 (17%); there were 57 complications (6.1%), 1 death. The economic burden reduction (EBR) was US $318.83 for each RGB and a total of US $690,904 (in 8 years). The EBR of the NTC VAs was US $140.59 per procedure, and a total of US $84,494 and for each TC the savings were US $179 with a total of US $58,533 (in 7 years). The EBR of the KB was US $214.25 per procedure, and a total US $212,964. The EBR of all procedures was US $1,046,895.

Conclusions: The implementation of the NDI program has yielded significant cost reductions of at least US $1,046,895 while ensuring the safety and well-being of patients. Beyond its financial impact, the program has also had broader benefits, including the advancement of resident training and the establishment of a specialized diploma in interventional nephrology of comprehensive 6-month training program and university validity, equips aspiring interventional nephrologists with essential skills and knowledge, solidifying its value in the field of nephrology education and practice.

FR-PO058

Nephrology Associate Program Director and Core Faculty Survey: Protected Time for Training Program Administration

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Background: In 2024-25, the Accreditation Council for Graduate Medical Education (ACGME) will require core faculty to have 4 hrs/week of protected time for program administration. Associate program directors (APDs) must receive 4 hrs/week (more if >6 fellows). Program directors (PDs) surveyed in April 2022 reported protected time for core faculty was a median 1.5 hrs/week (39% had none) and a median 4 hrs/week for APDs.

Methods: In a follow-up survey of all US adult nephrology PDs (March 2023), we asked PDs to forward an anonymous survey link to APDs/core faculty, and to indicate how many were sent. We asked APDs and core faculty how much protected time they had, to indicate their program-related tasks, and estimate time needed to perform them.

Results: 57/149 (38%) of PDs forwarded the link to 454 faculty. Response was 27% (121/454); 87% completion. 52/57 PDs who forwarded the link had an APD; 94% (49/52) responded. 50% of PDs reported their APD had <4 hrs/week protected time. 37% had none. APDs had a median 2 hrs/week (IQR 0,4), and estimated needing 5 hrs/week (IQR 4.25,8) to effectively fulfill their role, regardless of program size. 67/402 (17%) core faculty responded. PDs reported faculty protected time was 2 hrs/week (IQR 0,4). 41% had none. Core faculty had a median 0.5 hours/week (IQR 0-2.75), and estimated needing

4 hrs/week (IQR 2.25, 5.75) to effectively fulfill their role, regardless of program size. 90-100% taught fellows during clinical rotations. >95% gave lectures; >85% attended conferences; >95% did fellow evaluations. 73% of APDs and 56% of faculty assisted in fellow remediation. 90% participated in recruitment; >85% mentored scholarly work; >60% mentored quality/safety training. APDs commonly managed rotations (62%) and wellness events (55%). 27% of APDs and 20% of faculty were at high risk for emotional exhaustion, reporting feeling "burned out from my work" daily or a few times a week.

Conclusions: APDs and core faculty have little protected time for program administration/didactic teaching, despite contributing substantially in these areas. About 40% have none. They estimate needing 4-5 hrs/week to effectively do their work, regardless of program size. *The views expressed in this abstract are those of the authors and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

FR-PO059

A Comparative View of Early Career and Established Nephrologist Perspectives

Stephen Regan. *Spherix Global Insights, Exton, PA.*

Background: As nephrologists transition from fellowship to an established clinical practice, their perspectives change regarding areas of interest, perceived unmet needs, and approaches to treatment. This analysis of nephrology fellows, early career, and established nephrologists reveals differences in viewpoints based on tenure.

Methods: Responses were collected from established nephrologists with over 10 years in practice (n=50), new nephrologists with 2 to 5 years in practice (n=37), and current nephrology fellows (n=44) via an online survey in August 2022. Respondents were required to spend at least 70% of their professional time in a clinical setting seeing patients.

Results: Glomerular diseases are a top area of interest for nephrologists, regardless of their tenure. Nuances exist in other areas, as established and new nephrologists show a greater interest in critical care nephrology (60% new, 50% established) and hypertension (38% new, 50% established) compared to fellows (41% and 25%, respectively). While 45% of current fellows rank dialysis/modalities within their top three areas of interest, nearly half feel unprepared to manage peritoneal dialysis patients, and this only increases to 79% for home hemodialysis patients. Interestingly, despite encouragement within the industry to transition more dialysis patients to home modalities, new and established physicians show greater interest in other topics. Perspectives on unmet needs for new therapeutic agents to treat specific conditions also differ by tenure. AKI is perceived as having a high unmet need by 64% of established nephrologists, compared to 27% of new nephrologists and 41% of fellows. Within glomerular diseases, newer practitioners perceive a greater unmet need for IgA nephropathy (39% fellows, 41% new), while only 16% of established nephrologists share the same sentiment. KDIGO guidelines are followed more closely by fellows, 91% of whom report that they always reference them when making treatment decisions. Established and new nephrologists instead rely more heavily on their own clinical experience.

Conclusions: As a nephrologist's career progresses, their interests become narrower and more specialized based on clinical experience. Nephrology fellows often express more innovative views but many report feeling ill-prepared for the movement of dialysis patients to home modalities.

FR-PO060

Institute of Nephrology

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Background: Home dialysis has shown to have potentially positive clinical and lifestyle impacts for many patients such as preserving residual kidney function or flexibility with schedules when compared to in-center hemodialysis (ICHD). However, peer-reviewed research suggests that nephrologists receive inadequate exposure to home dialysis during their fellowships, creating a barrier to increasing the use of home dialysis. Moreover, use of home dialysis in the US is lower than in many other developed countries. It is therefore crucial to improve nephrologists' competence in home dialysis as a way to improve patient care and access. We are addressing these challenges with a new virtual educational platform for nephrologists, advanced practice providers and nephrology fellows: the Institute of Nephrology (IoN).

Methods: IoN offers online courses on a variety of home dialysis topics, selected based on numerous interviews and surveys of practicing nephrologists. Content is self-paced to accommodate physicians' busy schedules and aligns with nephrologists' preference for interactive, case-based content. Nationally-recognized home dialysis experts developed the content on subjects such as mitigating peritoneal dialysis (PD) transfer to ICHD, peritonitis, Home dialysis prescription optimization, embedded PD catheters, and urgent start PD. Additionally, the courses are accredited for Continuing Medical Education and Maintenance of Certification credit, allowing nephrologists to satisfy licensure requirements while building knowledge in home dialysis.

Results: In the first three months after the launch, 600 of nephrologists have accessed IoN. The most popular topic has been Urgent Start PD, an important area for increasing the number of patients starting on PD and helping patients be successful on that modality. IoN users have varied widely in their familiarity with home dialysis: while 2/3 of users have > 20% of their patients on home dialysis, 25% of users have no patients treating on home dialysis.

Conclusions: The early results of IoN suggest that there is appetite in the nephrologist community for more education on home dialysis. Nephrologists play a vital role in supporting their patients' modality selection and treatment; resources such as IoN empower nephrologists to address gaps in nephrology fellowships in a single platform dedicated to home dialysis education and may improve the utilization of home dialysis in the US.

FR-PO061

AKI Education of Internists: A Needs Assessment

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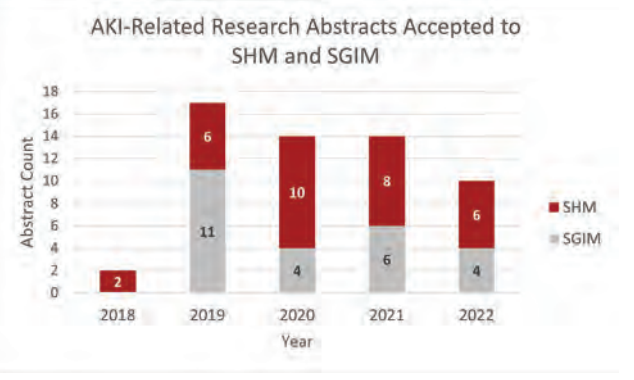
Background: Acute kidney injury (AKI) is one of the most common complications of hospitalized patients. The pooled incidence in North America is estimated to be 22.3%, and the rate of AKI has been increasing. Many patients with AKI are managed by internists during and after hospitalization. As the Society of General Internal Medicine (SGIM) and the Society of Hospital Medicine (SHM) are major internal medicine meetings focusing on high-yield education for internists, we examined the prevalence of AKI-related education at their annual meetings.

Methods: This is a retrospective review of SGIM Annual Meeting session titles, session agendas, and accepted abstracts, and SHM Converge accepted abstracts from 2018-2022. SHM session titles and agendas are not publicly available. Any session title or description, or abstract containing keywords "kidney," "renal," or "nephrology" was manually reviewed by authors for relevance to: A) prevention of AKI, B) treatment of AKI, C) post-AKI care. Descriptive analysis was performed.

Results: Among 5203 research abstracts presented at SGIM and SHM national meetings from 2018-2022, a total of 259 (5.0%) abstracts contained one or more keywords. Of the keyword positive abstracts, 57 (1.1% of the total abstracts) were related to AKI (Figure). Of those, 38 abstracts (67%) were related to prevention of AKI, 7 abstracts (12%) were related to treatment of AKI, and 12 abstracts (21%) explored post-AKI care. Among the 1022 sessions at SGIM and their descriptions in that timeframe, only 2 contained the keywords, neither of which were directly related to prevention, treatment, or management of AKI.

Conclusions: Despite the clinical importance of AKI and the fact that patients with AKI are frequently managed by internists, we identified no SGIM Annual Meeting sessions dedicated to AKI education over a 5-year period. Between SGIM and SHM, only 1% of accepted abstracts over the last 5 years were related to AKI, with a nominal decline in number since 2019. These findings suggest a substantial need to increase AKI education opportunities for internists.

Funding: Clinical Revenue Support



FR-PO062

Insights from the ASN Kidney Week 2022 Point-of-Care Ultrasound Precourse

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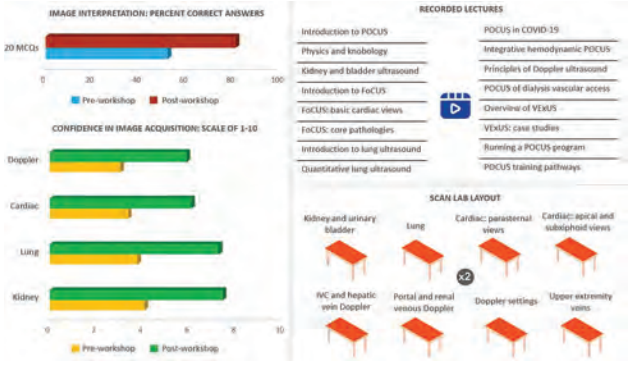
Background: A multi-organ point of care ultrasound (POCUS) precourse was offered at the ASN Kidney Week in November 2022 with the objective of introducing core theoretical concepts and image acquisition techniques to practicing nephrologists and trainees, co-chaired by the authors. We share some insights from the course.

Methods: The course was limited to 80 registrants and had full attendance. It was conducted in hybrid format consisting of on-demand virtual content and an in-person hands-on workshop. The virtual content comprised of video lectures listed in the Figure, which were provided to the registrants prior to workshop. The in-person workshop consisted of a refresher lecture and hands-on practice on healthy subjects. 2 identical scanning rooms (40 attendees per room) were set up with 8 stations each teaching a predefined sonographic application (see Figure). We conducted anonymous pre- and post-course surveys to assess the impact of the training on participants' knowledge, confidence, and satisfaction.

Results: The pre- and post-course surveys were answered by 60 and 46 registrants respectively (response rate of 75% and 57.5%). The mean % of correct answers on the pre-course survey (image interpretation) was 51.9 ± 20.4, which significantly increased to 81 ± 13.1 on the post-test ($p<.001$). Similarly, the self-reported confidence in image acquisition improved from 3.56 ± 0.4 to 6.66 ± 0.7 on a scale of 1-10 ($p<0.001$) after

the workshop. 41.9% of the post-course survey respondents felt that the course met their expectations whereas 51.2% reported it exceeded their expectations. Most attendees reported lack of protected time, inadequate expert supervision and limited availability of ultrasound mahines as barriers to continued POCUS practice at their institutions.

Conclusions: The POCUS course led to significant improvement in the knowledge and confidence of the participants. Nonetheless, as we cannot expect anyone to master physical examination by attending a one- or two-day workshop, same applies to POCUS and continued hands-on practice is the key to achieving mastery.



FR-PO063

Nephrologist-Led Cardiac Point-of-Care-Ultrasound (POCUS) Workshop Using High-Fidelity Simulation: Insights and Observations

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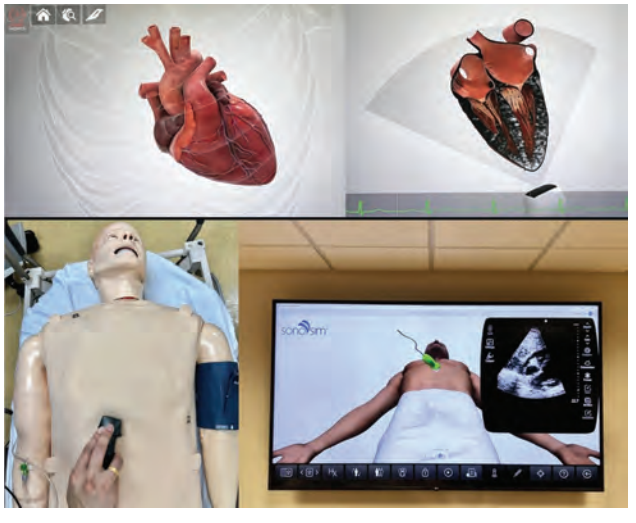
Background: Cardiac point of-care-ultrasonography (POCUS) is an integral component of bedside volume status assessment. We sought to explore the effectiveness of a short simulation-based POCUS workshop for medical students taught by a nephrologist.

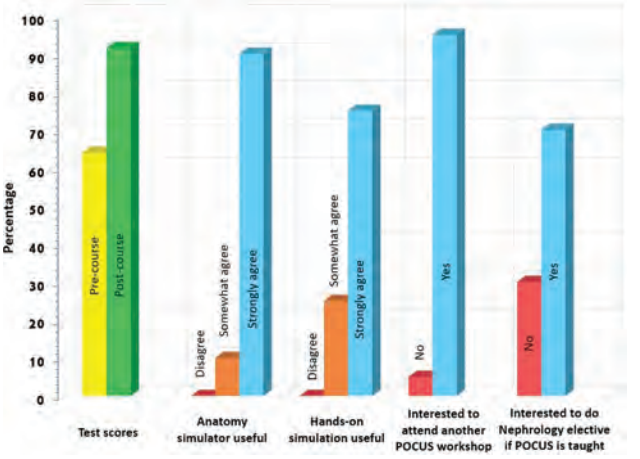
Methods: Workshops were conducted for two different groups of 4th year medical students with a total of 25 attendees. The workshop consisted of a 1-hour lecture followed by 15 minutes of cardiac anatomy simulation and a 2-2.5-hour hands-on session in the simulation laboratory [Fig 1]. An anonymous pre-course survey comprising of 10 questions assessing the interpretation of common greyscale POCUS findings encountered in patients with undifferentiated hypotension was performed. A post-course exam and feedback survey were also administered.

Results: 23 and 20 students answered the pre- and post-course surveys, respectively. The mean total score on the pre-test was 63.8% ± 13.6%, which significantly increased to 91.5% ± 10.5% on the post-test (P<.001). 90% of the respondents strongly agreed that the cardiac anatomy simulation improved their understanding of the cardiac sonographic anatomy. 75% strongly agreed that the hands-on simulation enhanced their confidence in image acquisition and interpretation. 70% said they would choose nephrology elective if POCUS training was integrated with it [Fig 2].

Conclusions: A Nephrologist-led diagnostic POCUS workshop using simulation techniques is effective may increase medical student interest in Nephrology elective rotations

Funding: Private Foundation Support





FR-PO064

Simulation of Ultrasound-Guided Renal Biopsy Using a Novel Custom-Made Training Model

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Background: Kidney biopsy is a critical procedure in nephrology fellowship training, necessitating extensive simulation to prevent biopsy-related complications. There's a need to practice optimizing ultrasound imaging and guiding the biopsy needle to target points in real-time images. We introduce a novel, cost-effective renal biopsy training model.

Methods: We developed a model using Konjac jelly and soft-boiled chicken or duck eggs to simulate ultrasound-guided renal biopsy. The soft-boiled eggs' yolk and egg white were distinctly depicted in grayscale images due to their differences in echogenicity, resembling the renal sinus and corticomedullary area of the kidney's lower pole (Figure 1A). Trainees were instructed to sample the egg white selectively. The biopsied yolk and egg white samples were easily distinguishable with the naked eye (Figure 1B), allowing trainees to verify if the sample was successfully obtained from the target with immediate feedback. The materials were readily available, and the model was easy to construct and reproduce. Trainees were able to simulate the operation of biopsy devices, optimize ultrasound imaging, and guide the biopsy needle in real time.

Results: Nephrology fellows underwent the simulation training using the model before performing kidney biopsies on patients. After implementing this curriculum, a total of 186 kidney biopsies were performed from March 3, 2022, to May 20, 2023. Biopsies were conducted with a 16-gauge needle under ultrasound guidance. There were no failed procedures. Complications included three minor hematomas that resolved with bed rest and one arteriovenous fistula that was treated with coil embolization. In pre- and post-training surveys, trainees' confidence levels in performing renal biopsies significantly improved.

Conclusions: This novel model may assist nephrology fellows in familiarizing themselves with biopsy procedures and enhancing their skills before commencing renal biopsies in a clinical setting.

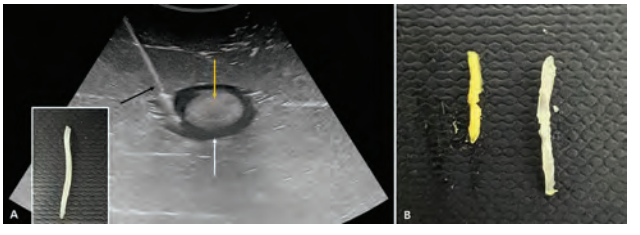

Figure 1.A. A duck egg embedded in Konjac jelly (white arrow: the egg white, yellow arrow: the yolk, black arrow: biopsy needle). B. the yolk (left) and egg white (right)

FR-PO065

Virtual Nephron: Assessment of a Virtual Reality (VR) Educational Tool

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Background: Recent technological advancements within the VR sphere have allowed for the development of innovative technological tools. Using funding from ASN's Bennett Clinical Scholars Program, we developed a 3D VR physiology course and assessed its efficacy on learners' knowledge gains.

Methods: Internal medicine PGY1 residents were randomized into 2 groups: a VR group (exposed to the VR session) and a traditional group (received a printed script of the VR learning course). The VR session consisted of a 3D review of water and electrolyte transport across the nephron and of the mechanism of action of diuretics. Within a week of the intervention, both groups underwent a 2-hour seminar on physiology of solute/water transport and diuretics. Knowledge acquisition and retention were assessed with a test administered immediately after the conclusion of the 2-hour seminar and repeated within 6-12 weeks. The 40-question test was issued using the secure platform RedCAP. Tests were anonymous, thereby preventing paired test comparisons. We used independent t-tests to compare the number of correct answers and the percent correct between the VR and traditional groups. Initial and follow up tests were evaluated separately.

Results: Of the 188 PGY1 residents who were scheduled and randomized to participate, 117 completed the initial testing. Sixty-four were randomized to the VR group and 53 were randomized to the traditional group. 51.3% of participants were males and average age was 27.3±2.0 years old. Initial test results showed higher scores among VR compared to the traditional group (76.5% correct vs. 68.8%, Table 1). Seventy-eight PGY1s participated in the follow up testing (46 VR group vs. 32 traditional group). Results of the follow up test showed no significant difference in test results. Test score results are summarized in Table 1.

Conclusions: The 3D VR platform appeared to have improved short-term learning but without improving long-term retention. A larger student cohort with longer term follow up will help assess the long-term impact of VR technology and its effect on transfer of learning.

Table 1. Test results by group participation

Initial Test Score Results	Overall (N=117)	VR (N=64)	Traditional (N=53)	p-value
Score out of 40 questions, Mean ± SD	29.2±5.0	30.6±4.4	27.5±5.3	<0.001
Percent correct, Mean ± SD	73.0±12.6	76.5±11.1	68.8±13.2	<0.001
Follow up Test Score Results	**Overall (N=78)**	**VR (N=46)**	**Traditional (N=32)**	**p-value**
Score out of 40 questions, Mean ± SD	26.2±5.0	26.6±5.2	25.6±4.7	0.40
Percent correct, Mean ± SD	65.5±12.5	66.5±13.0	64.1±11.7	0.40

FR-PO066

Success of Virtual Patient Simulation at Improving Management of CKD-Associated Pruritus

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Background: We sought to determine if online, virtual patient simulation (VPS)-based continuing medical education (CME) can improve performance of nephrologists and primary care physicians (PCPs) related to comprehensive management of chronic kidney disease sssociated pruritus (CKD-aP).

Methods: The intervention comprised two different patients presenting at a given time points in a VPS platform that allows learners to order lab tests, make diagnoses, and prescribe treatments similar to actual practice. Tailored clinical guidance (CG), based on current evidence, was provided after each decision, followed by the opportunity to modify the decision. Decisions were collected post-CG and compared with each user's baseline (pre-CG) using a McNemar's test to determine *P* values. The activity posted September 2022; initial data were collected through December 2022.

Results: 281 nephrologists and 234 PCPs completed the activity (all decisions within at least 1 case) and were included. Case 1: 13% increase of nephrologists (67% pre-CG vs 80% post-CG; P<.001) and 11% increase of PCPs (76% pre-CG vs 87% post-CG; P<.01) who ordered a patient health questionare-9 (PHQ-9) assessment 28% increase of nephrologists (56% pre-CG vs 84% post-CG; P<.001) and 29% increase of PCPs (45% pre-CG vs 74% post-CG; P<.01) who diagnosed CKD-aP 46% increase of nephrologists (6% pre-CG vs 52% post-CG; P<.001) and 45% increase of PCPs (0% pre-CG vs 45% post-CG; P<.001) who ordered difelikefalin for a patient with CKD-aP 37% increase of nephrologists (11% pre-CG vs 48% post-CG; P<.001) and 38% increase of PCPs (10% pre-CG vs 48% post-CG; P<.001) who ordered an antileptic agent for a patient with CKD-aP Case 2: 24% increase of nephrologists (51% pre-CG vs 75% post-CG; P<.001) and 30% increase of PCPs (47% pre-CG vs 77% post-CG; P<.001) who diagnosed CKD-aP 38% increase of nephrologists (16% pre-CG vs 54% post-CG; P<.001) and 35% increase of PCPs (13% pre-CG vs 48% post-CG; P<.001) who treated CKD-aP.

Conclusions: VPS that immerses and engages specialists in an authentic and practical learning experience can improve evidence-based clinical decisions related to comprehensive management of CKD-aP.

Funding: Commercial Support - Developed through an independent educational grant from CSL Vifor

FR-PO067

Providing Patient-Centric Education in Type 2 Diabetes and CKD: The "YOU" Project™

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Background: Recently, we have seen many new and impactful therapeutic options to treat Type 2 Diabetes (T2D) and Chronic Kidney Disease (CKD). Clinicians are challenged to educate patients with TD2 and CKD during a limited appointment time. To address this, we created a simple patient-centric education tool to help them understand the factors impacting their disease, treatment guidelines, and medication options to positively impact disease progression. We assessed how the tool impacted patient knowledge.

Methods: As of this submission, 43 patients with CKD completed a questionnaire PRE (5 questions) and POST (7 questions) clinic visit to assess knowledge.

Results: See Table.

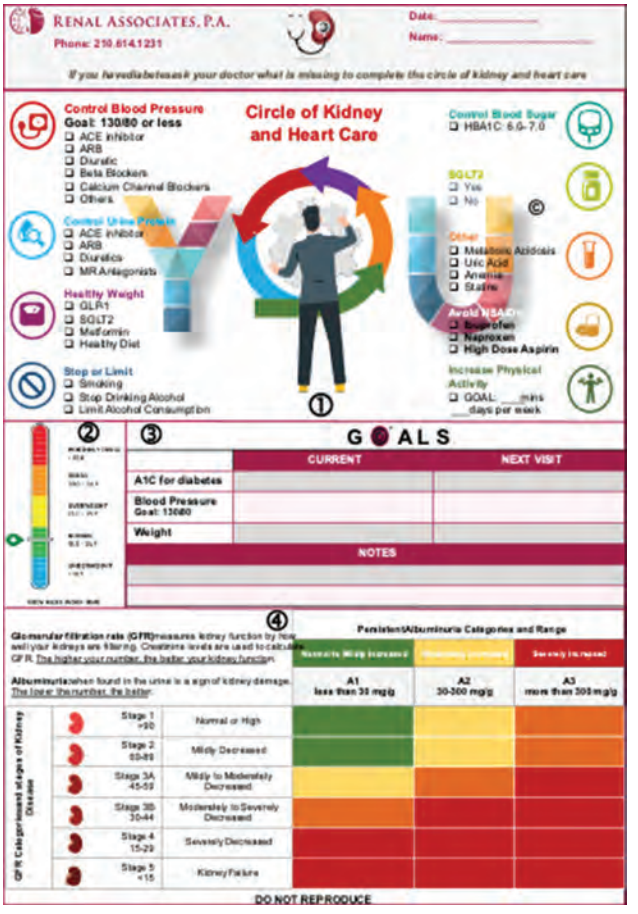
Conclusions: The "YOU" patient education tool was well received by patients and allowed clinicians to cover a broad range of information efficiently. All patients showed consistent improvement in their knowledge of disease state, laboratory values, factors that can delay progression, and various medications used, while having a guide to take home and track progress. Patients will be followed, and long-term benefits described in a future publication.

Funding: Clinical Revenue Support

RESULTS

QUESTION	PRE-TEST	POST-TEST	% CHANGE
I am very clear in my understanding of the stage of my kidney function	3.8	4.8	+20%
I am very clear in my understanding of how to protect my kidneys	3.9	4.7	+16%
I am very clear in my understanding of my blood pressure, labs and which medications manage it	4.1	4.7	+12%
I am very clear in my understanding of how to manage excess protein in the urine	2.8	4.0	+24%
I am very clear in my understanding of how to control diabetes (blood sugar)	3.4	3.9	+10%
(POST ONLY) The tool that the Doctor provided helped me to better understand my medical conditions and how to better manage it	Very Helpful: 31 Patients Helpful: 12 Patients		
(POST ONLY) What section of the tool did you find most useful?	The YOU Circle: 28 Patients GFR: 12 Patients Goals: 2 Patients BMI: 1 Patient		

5 = Strongly Agree, 4 = Agree, 3 = Neither or N/A, 2 = Disagree, 1 = Strongly Disagree. Note: It is very likely that patients overestimated their knowledge base when being asked pre-test questions. 43 patients agreed that the "YOU" educational tool improved their comprehension and understanding of kidney disease.



FR-PO068

EMR-Based CKD Patient Education and Decision Support in Primary Care Improves Patient Satisfaction

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Background: We pilot-tested an EMR-based CKD patient education and decision support tool in primary care. Systems engineering optimized seamless integration into clinical workflow.

Methods: With input from patients and providers we developed an EMR-based patient education and decision support tool called an Encounter Decision Intervention (EDI). The EDI was designed to be used during primary care encounters when patients and providers discussed a CKD diagnosis and decided on management steps. Patients were enrolled into an intervention (received EDI) or control group (did not receive the EDI) using a prospective, cross-sectional design. Measurement of outcomes occurred after patient visits via validated surveys of patient perceived and objective kidney disease knowledge, CKD-specific stress, and satisfaction. Chi-square tests, t-tests, and Kruskal-Wallis were used to detect associations between outcomes and measured characteristics, as appropriate.

Results: Seventy-four patients completed the pilot study (37 per group). There were no statistically significant differences in patient characteristics between groups, nor were there statistically significant differences in overall kidney objective knowledge (mean (SD) of 67 % correct (15)), perceived knowledge (mean (SD) out of 4 total, 3.0 (2.1)) or CKD-specific stress (1.9 (0.7)). Satisfaction scores with provider communication, care, and providers themselves were all significantly higher in the intervention group: The proportion of participants rating satisfaction with provider communication as all 5's (scale 1-5), showed n= 16 (43%) in usual care and 30 (81%) in the EDI group, p=0.0016. For satisfaction with care, 26 (70%) in usual care and 35 (95%) in the intervention group rated all 5's, p=0.012. The proportion of patients rating all 5's for satisfaction of providers themselves were 29 (78%) in the usual care group and 36 (97%) in the EDI group, p = 0.028. All three satisfaction scores remained statistically significant in multivariate analysis. Patients rated use of the EDI high (4.1 (out of 5) CI 3.8-4.4).

Conclusions: The EDI was seamless to care delivery and associated with more patients who were very satisfied with provider communication, overall care, and the primary care providers themselves.

Funding: NIDDK Support

FR-PO069

A Pilot Plant-Based Cooking Class to Improve CKD Patient Education

Linda-Marie U. Lavenburg, Alayna L. Letteri, Manisha Jhamb. *University of Pittsburgh, Pittsburgh, PA.*

Background: Diet has a crucial role in chronic kidney disease (CKD) management, but patients experience barriers such as limited knowledge, cooking skills, and conflicting dietary restrictions with other comorbidities. We previously designed and implemented a plant-based cooking class for nephrology providers to unify counseling to the updated Kidney Disease Outcomes Quality Initiative dietary guidelines. We adapted feedback from the provider classes to design and pilot a CKD plant-based cooking class for patients aimed at making CKD education more actionable compared to the conventional lecture-based format.

Methods: A renal dietitian and chef created a menu of plant-based meals and modified recipes to minimize sodium and ensure low to moderate phosphorus, potassium, and protein content. We recruited adult (age ≥ 18 years) patients and their support persons from a university-affiliated nephrology clinic and a local dialysis unit. We administered a pre-class phone survey to determine baseline cooking skills, meal planning, and understanding of a CKD diet. The 3-hour hands-on CKD cooking class was led by a chef and included a knife skills component. During the class, two nephrologists and a renal dietitian provided practical education on a plant-based kidney friendly diet. Recipe cards with nutrient content and estimated price per meal were provided. Participants completed a satisfaction survey at the cooking class. We present descriptive statistics of the baseline and satisfaction surveys.

Results: Of 11 participants who completed two surveys and attended the pilot CKD plant-based cooking class, 9 were female, 6 were black, and 7 had CKD stage ≥ 3, which included 3 who are dialysis-dependent. At baseline, 73% of respondents reported intermediate to advanced cooking skills, but 45% were not confident in their ability to describe a diet good for kidney health. All 11 class attendees reported high satisfaction and 91% reported improved understanding of a CKD diet, a high likelihood of changing eating patterns and attending another class.

Conclusions: A hands-on plant-based cooking class is an accepted and effective method to improve understanding of a healthful CKD diet and provide actionable steps to adopt plant-based eating. A follow-up survey will assess if participants actually changed their diet, and future classes will provide opportunity to collect additional participant feedback.

Funding: Other NIH Support - Vascular Medicine Institute NIH T32 Translational Research Training, 2T32HL110849-11A1

FR-PO070

Patient Questions Related to Peritoneal Dialysis: An Analysis of Online Search Data

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Background: End-stage renal disease patients must often decide whether to receive peritoneal dialysis (PD) or hemodialysis (HD), and much of the academic literature has focused on comparing quality of life differences between PD and HD. However, the type of information that patients themselves seek when considering PD is relatively unknown. As more patients utilize the Internet to access health information, understanding PD search trends can help identify areas for targeted improvement in patient education. Here, we address this knowledge gap by characterizing online search data related to PD.

Methods: In May 2023, Google search data based on the term "Peritoneal Dialysis" were analyzed using "Search Response" (https://searchresponse.io/), a search engine optimization tool. Searches were performed for the most common People Also Ask (PAA) questions against a dataset of over 150 million queries, and the top 100 PAA questions relevant to the "Peritoneal Dialysis" keyword were ranked based on popularity. Two reviewers (AZ and MT) independently grouped the questions into categories adapted from standards in the literature, and a third reviewer (KMS) resolved any discrepancies.

Results: The Search Response tool generated 1,747 PAA questions for "Peritoneal Dialysis." Coding of the top 100 questions revealed that the greatest number of questions related to Procedure (41) (e.g., "What are the steps in peritoneal dialysis?"), Complications (14) (e.g., "What are the side effects of peritoneal dialysis?"), Definition (10) (e.g., "What are the types of peritoneal dialysis?"), Prognosis (8) (e.g., "How long can you live on peritoneal dialysis?"), Quality of Life (8) (e.g., "Can you swim with a peritoneal dialysis catheter?"), and then Comparison to Other Forms of Dialysis (6) (e.g., "Which is better hemodialysis or peritoneal dialysis?"). Thirteen questions were uncategorized (e.g., "How long is training for peritoneal dialysis?").

Conclusions: The most common theme for questions related to PD was Procedure, which reveals a knowledge gap in the procedural aspects of PD. While it is important to compare different treatment options from a quality of life standpoint, providers should take steps to thoroughly educate patients about the procedural details surrounding PD (e.g., the equipment used or the steps involved in PD) to address patients' most common questions and informational needs.

FR-PO071

Investigating Online Search Trends to Improve Patient Education in Nephrolithiasis

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Background: Nephrolithiasis can cause severe pain and affects one in ten individuals globally. Successful treatment requires patient cooperation, and managing the condition can be complex. While a variety of interventions ranging from citrate supplements to hydrochlorothiazide to shock wave lithotripsy exist, patients' informational needs for nephrolithiasis are not well understood within the literature. As an increasing number of patients turn to the Internet for health information, analyzing search trends offers an opportunity to identify knowledge gaps and improve health literacy. Here, we characterize online search data related to nephrolithiasis to inform efforts to improve targeted patient education.

Methods: In May 2023, Google search data based on the term "Kidney Stones" were analyzed using "Search Response" (https://searchresponse.io/), a search engine optimization tool. Searches were performed for the most common People Also Ask (PAA) questions against a dataset of over 150 million queries, and the top 100 PAA questions relevant to the "Kidney Stones" keyword were ranked based on popularity. Two reviewers (AZ and MT) independently grouped the questions into categories adapted from standards in the literature, and a third reviewer (KMS) resolved any discrepancies.

Results: The Search Response tool generated 19,376 PAA questions for "Kidney Stones." Coding of the top 100 questions revealed that the greatest number of questions related to Management and Nutrition (31) (e.g., "What is the best food to eat when you have kidney stones?"), Treatment and Medication (25) (e.g., "What is the best treatment for kidney stones?"), Definition, Diagnosis, and Symptoms (20) (e.g., "What are the 4 types of kidney stones?"), and then Causes, Risk Factors, and Prevention (15) (e.g., "What are the main causes of kidney stones?"). Nine questions were uncategorized (e.g., "How painful is a stent for kidney stones?").

Conclusions: The most common themes for questions regarding nephrolithiasis were Management and Nutrition, followed by Treatment and Medication; Definition, Diagnosis, and Symptoms; and Causes, Risk Factors, and Prevention. Therefore, targeted provider information about nutrition and other lifestyle interventions should be prioritized to address patients' most common concerns regarding nephrolithiasis, and may help improve health literacy for this widespread condition.

FR-PO072

Enhancing Patient Education: ChatGPT's Potential in Addressing Dialysis FAQs

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Background: Patient education empowers those with ESKD to understand and navigate their treatment options. FAQs websites are valuable resources for information on dialysis, but AI's effectiveness in addressing patient queries about dialysis remains unexplored. ChatGPT, an AI model powered by natural language processing, has shown promise in providing accurate information across varied domains. This study evaluates ChatGPT's performance in delivering accurate patient education on dialysis.

Methods: A total of 57 patient questions related to dialysis were collected from the official Mayo Clinic website for the purpose of patient education. These questions were categorized into five steps: original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with incomplete sentences, paraphrased questions with misspelled words, and paraphrased questions with verbs and prepositions removed. ChatGPT (March 23 Version) generated responses to each question; the accuracy of its answers was evaluated by nephrologists and compared with the FAQs website.

Results: ChatGPT consistently demonstrated high accuracy by providing correct responses to all 57 questions across various complexity levels and paraphrasing variations. ChatGPT's answers to patient FAQs for 1) original questions, 2) paraphrased questions with different interrogative adverbs, 3) paraphrased questions with incomplete sentences, 4) paraphrased questions with misspelled words, and 5) paraphrased questions with verbs and prepositions removed were all consistently accurate. However, there was one inconsistent response to "what are the requirements for a patient undergoing hemodialysis?"; ChatGPT initially provided the expected requirements related to patient behavior but later included technical requirements for patient dialysis candidacy.

Conclusions: These results highlight the ChatGPT's accuracy in providing education on dialysis across different complexity levels and variations in question paraphrasing, indicating that it has the potential to serve as a valuable resource for patient information on dialysis, supplementing FAQs websites. However, one inconsistency calls for refinement to ensure accurate information. With improvements, AI models potentially can significantly contribute to patient education, further empowering those with ESKD.

FR-PO073

Abstract Withdrawn

FR-PO074

The Cautionary Tale of Co-Administrating Piperacillin-Tazobactam and Vancomycin

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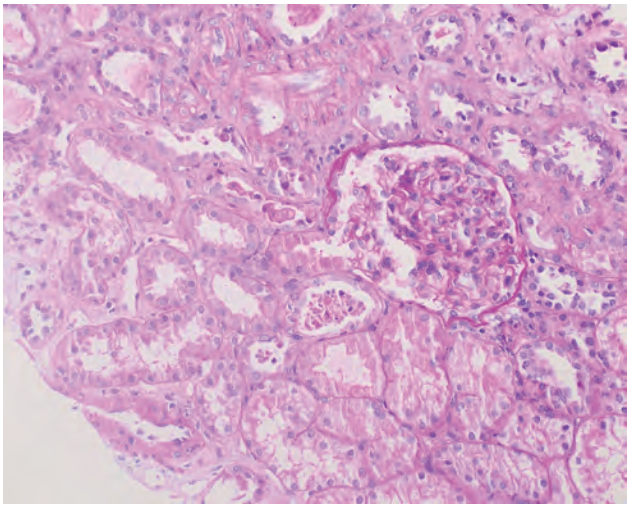
Introduction: Vancomycin and piperacillin-tazobactam (Zosyn) are commonly used antibiotics for their broad spectrum of antimicrobial coverage. However, their combined use has been associated with an increased risk of acute renal injury. Despite the widespread use of these antibiotics, there are only a few reported cases where a kidney biopsy was performed to investigate the cause of renal injury.

Case Description: This report presents a unique case of a 40-year-old man with acute refractory diverticulitis who developed acute kidney injury after being treated with vancomycin and piperacillin-tazobactam. The patient had failed outpatient therapy of ciprofloxacin and metronidazole, had a high white blood cell count, and was clinically septic. The infectious disease consultant started the patient on a combination of antibiotics to provide broad coverage of anaerobes and VSE gram positives. Over several days, the patient's creatinine levels increased, leading to the diagnosis of acute kidney injury. Interestingly, the patient had no prior history of renal conditions, and a kidney biopsy was performed to investigate the cause of kidney failure. The biopsy showed acute tubular necrosis (ATN) and mild acute tubulointerstitial nephritis (ATIN). The patient progressed to end-stage renal disease (ESRD) and required hemodialysis but recovered after three months and is now dialysis-free.

Discussion: The findings from this case highlight the importance of carefully weighing the risks and benefits of using antibiotics that have a higher incidence of causing acute kidney injury. In this case, the ability to perform a kidney biopsy allowed for a more accurate diagnosis of kidney failure and highlighted the importance of continued research into the mechanisms behind vancomycin-induced renal injury.



Diffuse ATN and ATIN

FR-PO075

Utility of Urinary Microscopy Score to Identify Patients with Subclinical AKI and Subsequent Clinical AKI

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Background: ADQI group has proposed a new AKI classification to recognize early stage of AKI termed subclinical (1S) using functional and structural biomarkers. However, these novel structural biomarkers are not available in resource-limited settings. We propose that urinary sediment score (USS), which reflects kidney structural damage could detect subclinical AKI and subsequent development of clinical AKI.

Methods: We included 103 consecutive hospitalized patients who were at moderate to high-risk of AKI using AKI Risk Assessment algorithm (Rizo-Topete et al. Blood Purif. 2017;43(1-3):82-88). Fresh urine was obtained and examined and urine sediment was assigned a score (Perazella et al. score Clin J Am Soc Nephrol 2010 Mar;5(3):402-8.) from 1 to 3 at admission, at 48 hours and at day 7. Renal function was followed up daily up to 7 days. We defined subclinical AKI (ADQI stage 1S) as a urinary sediment score (USS) ≥2 in the absence of rise in serum creatinine (sCr). Clinical AKI was defined by KDIGO sCr criteria and classified using the new propossed ADQI classification (1A, 1B, 2A, 2B, 3A or 3B) depending on the presence or absence of elevated damage (USS) or functional (sCr) biomarkers. We analyzed the predictive value of this scoring system for the subsequent development of clinical AKI, need of kidney replacement therapy (KRT) and mortality.

Results: Among 103 patients, 38% (39/103) have a USS ≥ 2 and were classified as AKI-1S. At 48 hours, 80% (31/39) patients of the AKI-1S group developed clinical AKI. At 7 days, only 9 % of patients with a USS ≤ 1 developed clinical AKI vs. 75% of AKI-1S patients; $p < 0.0001$. A USS ≥ 2 at admission have a good performance in predicting clinical AKI with a ROC-AUC 0.84 (95% CI 0.75-0.92); $p < 0.0001$. Need of KRT (10.3% vs. 1.6%; $p = 0.05$) was higher in patients with AKI-1S vs. patients with normal kidney function who later developed clinical AKI. Mortality was also higher in patients who developed AKI-1S versus patients with normal kidney function at admission (43.6% vs. 14.6%; $p = 0.008$).

Conclusions: Urine sediment score can identify early phase of AKI and will be useful tool to refine the diagnostic and staging criteria for AKI especially in resource-limited settings.

FR-PO076

A Case of Semaglutide-Associated Severe AKI in an Immunocompromised Patient

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Introduction: Glucagon-like peptide 1 receptor agonists (GLP-1RAs) have been FDA approved for weight loss and are increasingly prescribed for patients with diabetes or obesity. So far, only 3 cases of semaglutide associated acute kidney injury (AKI) were reported. Herein, we report a unique case of a patient with heart transplant who developed rapid worsening of renal function after an increased dose of semaglutide.

Case Description: A 61-year-old woman presented to the hospital with 4 weeks of decreased appetite, 2 weeks of nausea, vomiting and diarrhea. Five months prior to the index hospitalization, semaglutide 0.25 mg was prescribed and the dose was eventually up titrated to 1 mg, 5 weeks prior to the presentation. Symptoms began 1 week after the dose

of semaglutide was increased to 1 mg. Medical history pertinent for heart transplantation, type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD) 3b. Laboratory data at the time of admission revealed elevated serum creatinine (Scr) of 12.5 mg/dL (baseline 1.5 mg/dL), blood urea nitrogen of 83 mg/dL, tacrolimus level of 2.4 ng/mL, urine protein to creatinine ratio (UPCR) of 1.83 g/g. Urinalysis positive of 1+ protein, 2+ blood and 4 red blood cells per high-power field. Urine microscopy revealed hyaline, granular and a few muddy brown casts. Serological evaluation for acute glomerulonephritis, CMV, EBV, BK PCR resulted negative. Kidney ultrasound was normal. Semaglutide was held on admission and IV fluids were started without improvement in Scr. Kidney biopsy was perfomed and revealed acute tubular injury (ATI) with diffuse flattening of tubular epithelium and brush border attenuation, chronic striped fibrosis secondary to long term exposure to calcineurin inhibitors (CNI) and mild diabetic nephropathy. No immune complex or paraprotein deposits identified by IF or EM. Patient had gradual recovery of renal function with a Scr down to 1.6 mg/dL on last follow up.

Discussion: GLP-1RAs agonists can be associated with severe volume depletion from suppressed appetite and intractable vomiting, predisposing to ischemic ATI. Patients with solid organ transplant and on CNI could be particularly vulnerable. Clinicians should ensure adequate oral intake before escalating the doses and plan a close follow-up.

FR-PO077

GLP-1 Agonists-Associated Kidney Toxicities

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Background: Data on kidney related side effects of GLP-1 agonists have not been well defined. Sparse case reports of AKI have been reported.

Methods: We reviewed the FDA adverse event reporting system (FAERS) and queried for kidney adverse events associated with GLP-1 agonists (semaglutide, exenatide, tirzepatide, liraglutide, albiglutide, dulaglutide, Ozempic, Bydureon, Mounjaro, Victoza, Tanzeum, Trulicity, Saxenda, Byetta) between 2010 and 2022 using search terms all related to AKI, electrolyte disorders and hypertension. SAS enterprise guide v7.12 was used to pull data and analysis.

Results: In the last 12 years, a total of 2375 total kidney related adverse events were reported to the FAERS in reference to GLP-1 agonists. AKI was the most common with 58.65% with equal distribution for male's vs females. HTN(22.02 %) was the next most common event followed by hyperkalemia as the most common electrolyte disorder. Most of the other electrolyte disorders and capillary leak syndrome were uncommon. (Figure). Limitations: The events are reported by providers and/or patients and therefore could have a reporting bias. It is not possible to determine whether an event is truly caused by the drug as opposed to the underlying disease or concomitant medications or by prior drugs administered to these patients. In addition, we cannot get an accurate assessment of incidence rate.

Conclusions: As GLP-1 agonists are being used for DMII and weight loss, as nephrologists we need to be aware of AKI as a potential adverse event associated with this class of agents. The mechanism of injury needs to be determined.

Name of Medication Class	Reaction	Male (N=1023) n (%)	Female (N=1160) n (%)	Missing (N=192) n (%)	Overall (N=2375) n (%)
GLP1 agonists	*Acute Kidney Injury*	*586 (57.28)*	*681 (58.71)*	*126 (65.63)*	*1393 (58.65)*
	Hypertension	212 (20.72)	279 (24.05)	32 (16.67)	523 (22.02)
	Hyperkalemia	64 (6.26)	22 (1.90)	9 (4.69)	95 (4.00)
	Hypokalemia	35 (3.42)	45 (3.88)	9 (4.69)	89 (3.75)
	Thrombocytopenia	34 (3.32)	37 (3.19)	0 (0.00)	71 (2.99)
	Hyponatremia	22 (2.15)	24 (2.07)	3 (1.56)	49 (2.06)
	Proteinuria	17 (1.66)	11 (0.95)	2 (1.04)	30 (1.26)
	Acidosis	14 (1.37)	16 (1.38)	2 (1.04)	32 (1.35)
	Hypercalcemia	13 (1.27)	12 (1.03)	1 (0.52)	26 (1.09)
	Hypomagnesemia	11 (1.08)	17 (1.47)	2 (1.04)	30 (1.26)
	Hypocalcemia	5 (0.49)	5 (0.43)	1 (0.52)	11 (0.46)
	Hypophosphataemia	4 (0.39)	7 (0.60)	2 (1.04)	13 (0.55)
	Hypernatremia	2 (0.20)	2 (0.17)	2 (1.04)	6 (0.25)
	Renal Tubular Acidosis	2 (0.20)	0 (0.00)	0 (0.00)	2 (0.08)
	Tumor Lysis Syndrome	1 (0.10)	1 (0.09)	0 (0.00)	2 (0.08)
	Hypertensive Urgency	1 (0.10)	0 (0.00)	0 (0.00)	1 (0.04)
	Hyperphosphatemia	0 (0.00)	1 (0.09)	0 (0.00)	1 (0.04)
	Capillary Leak Syndrome	0 (0.00)	0 (0.00)	1 (0.52)	1 (0.04)

Adverse events reported as (Renal Failure, Renal Impairment, Renal Failure Acute, Renal Injury, Nephritis) presented as one group (RENAL INJURY) - Percentage (%) =n/N*100.

FR-PO078

In Search of Declining Weight, a Significant Decline in Kidney Function: A Rare Case of Liraglutide-Induced Interstitial Nephritis

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Introduction: Liraglutide is a glucagon-like peptide-1 (GLP-1) agonist known to improve glycemic control in diabetics and result in weight loss. There are reports of GLP-1 agonists causing acute interstitial nephritis (AIN) primarily in the setting of preceding gastrointestinal symptoms or pre-existing chronic kidney disease (CKD). We present a case of rapid decline in renal function one month after starting liraglutide with concomitant use of an angiotensin-receptor blocker (ARB).

Case Description: A 50 year-old Caucasian male with history of hypertension, dyslipidemia, obesity presented to the hospital for acute renal failure noted as an outpatient from a baseline creatinine of 1.15 mg/dL and GFR 78 mL/min/1.73m^2. Patient was asymptomatic without any hematuria, dysuria, decreased urinary output, rashes, or respiratory complaints. Home medications included olmesartan-HCTZ 40/25 mg, pravastatin 80 mg, and the recent addition of Liraglutide (Saxenda) one month ago to aid with weight loss. Labs on presentation were notable for significant renal dysfunction with BUN/Creatinine of 53/4.71 mg/dL and eGFR 14 mL/min/1.73m2. Urinalysis showed a protein of 100 mg/dL (1-2+) and protein-creatinine ratio of 9.04 mg/mg. Further work-up including ANA, anti-GBM Ab, HIV, ANCA, Ds-DNA Ab, C3/C4 was normal. A renal biopsy showed interstitial inflammatory infiltration, focal interstitial edema, and mild tubular injury. No evidence of acute glomerulonephritis, immune complex glomerulopathy, or paraprotein related nephropathy was identified. Patient was extensively counseled to discontinue use of both ARB and liraglutide, however he declined to stop liraglutide since he had been achieving excellent weight loss results.

Discussion: Drug-induced AIN is often considered when unexplained renal insufficiency is detected or when an abnormal urinalysis is noted in someone who has been exposed to medications known to cause AIN, with renal biopsy being the gold standard investigation to make a definitive diagnosis. Our case highlights a patient with no CKD and GI symptoms with rapid elevation of creatinine following initiation of liraglutide for weight loss. This effect seems to have been compounded by existing use of ARB, which highlights importance of closer and more frequent monitoring of patients on GLP-1 agonists to prevent unwarranted adverse effects.

FR-PO079

Nonsteroidal Anti-Inflammatory Drug (NSAID)-Induced Acute Tubular Injury with Eosinophiluria

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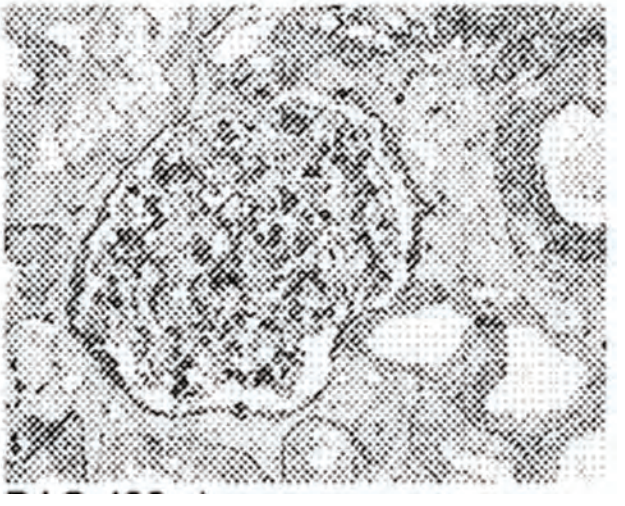
Introduction: Age, Diabetes and Hypertension are major risk factors of AKI resulting in hospitalizations. Age adjusted acute kidney injury hospitalizations increased by 230% between 2000-2014 and are mostly related to drugs. We share an interesting/atypical presentation of drug induced Acute Tubular Injury causing Eosinophiluria.

Case Description: 74 year old male with history of hypertension presented with chest pain, lower extremities edema, shortness of breath and a diffuse rash which started one day ago following Ketorolac injection for back pain. Vital signs on presentation showed blood pressure of 95/65 and tachycardia. Physical exam revealed a diffuse erythematous rash, mild wheezes in bilateral lungs and anasarca. Laboratory studies were only remarkable for serum creatinine 1.8 (baseline 1.0), blood urea nitrogen 41, white blood cells 21.9, eosinophils 32.3%. Echocardiogram, electrocardiogram, renal parenchyma ultrasound, venous doppler ultrasound of lower extremities and chest X-Ray were unremarkable. Further evaluation showed random urine creatinine 274.8, urine protein 19, spot UPCR 500 and urinalysis showed eosinophiluria. Skin biopsy revealed spongiotic dermatitis with eosinophils. Kidney biopsy showed acute tubular injury, mild interstitial fibrosis, tubular atrophy and was negative for AIN. Patient was started on steroids and responded well to the treatment.

Discussion: NSAIDs cause renal complications including AKI & AIN due to a reduction in renal blood flow, tubular obstruction through crystal deposition, direct cytotoxicity and cell-mediated immune injury. AIN usually necessitates renal biopsy and may require high-dose steroids and/or immunosuppressants. Patients manifest allergic features such as fever, rash and eosinophilia after initiating NSAIDs. Although eosinophiluria is often present in cases of AIN, its sensitivity is 60% as it also occurs in other renal diseases associated with AKI.



Biopsy shows tubular atrophy & interstitial fibrosis

FR-PO080

Renal Tubular Injury Biomarkers in the Early Detection and Diagnosis of Drug-Induced AKI: IMI/SAFE-T/TransBioLine

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Background: Drug induced kidney injury (DIKI) is a common adverse outcome in clinical practice and clinical trials. Serum creatinine (Scr) and urine output are "gold" standard biomarkers used to diagnose and stage acute kidney injury (AKI), limited by their sensitivity and delayed detection of measurable change from time of injury. Novel AKI biomarkers with more proximal times to onset are increasingly recognized as clinically useful for earlier detection of AKI.

Methods: IMI/SAFE-T analyzed data from 2 different clinical trial cohorts — (i)105 oncology patients (normal baseline eGFR) receiving their 1st dose of IV cisplatin (≥65 mg/ m2/ cycle); (ii) 20 patients with similar cancers treated with non-nephrotoxic agents. Blood and urine samples were collected for all participants. 3 blinded expert nephrologists adjudicated presence or absence of AKI. Biomarkers (adjusted for Ucreat for urine biomarkers) maximum change from baseline accuracy — area under the ROC (AUROC), sensitivity, specificity, and 95% confidence intervals — for Cisplatin treated and AKI cases versus non-treated patients were then estimated for 3 standard biomarkers or 8 novel biomarkers.

Results: Individual novel biomarkers exceeded performance in treated vs non-treated control patients and in AKI-adjudicated vs non-treated control patients. Well performing novel biomarker median time-to-peak value was 1-3 days vs. standard biomarkers (7 days). Combination of biomarkers has also the potential to increase sensitivity and specificity of detecting AKI (exploratory result not shown in abstract).

Conclusions: Multiple individual novel urine biomarkers (uαGST, uKIM1, uOPN) exceeded performance and/or signalled AKI onset prior to individual standard biomarkers (Screat, eGFR, uALB).

Individual and Combined Biomarkers Performance in Cisplatin Treated and AKI adjudicated Patients vs. Non-Treated Patients

		Treated vs non-treated		AKI vs non-treated	
Biomarker	Number of non-treated subject	Number of treated subjects	AUROC and 95% CIs	Number of AKI subjects	AUROC and 95% CIs
uOPN	17	88	0.95 [0.90;0.98]	58	0.96 [0.92;0.99]
uKIM1	17	88	0.95 [0.87;0.99]	58	0.96 [0.89;1.00]
uTPROT	17	95	0.93 [0.84;0.99]	63	0.95 [0.88;1.00]
uα-GST	17	88	0.84 [0.71;0.93]	58	0.84 [0.71;0.94]
uCYSC	17	88	0.79 [0.64;0.90]	58	0.82 [0.68;0.93]
uCLU	17	88	0.78 [0.60;0.90]	58	0.81 [0.66;0.92]
uNGAL	17	88	0.71 [0.52;0.85]	58	0.73 [0.52;0.89]
uALB	17	92	0.95 [0.90;0.98]	62	0.97 [0.93;1.00]
Screat	17	103	0.84 [0.74;0.92]	69	0.88 [0.79;0.95]
SCys	17	103	0.92 [0.85;0.97]	70	0.92 [0.85;0.97]
eGFR	17	103	0.84 [0.73;0.92]	69	0.87 [0.78;0.95]

FR-PO081

Severe AKI due to Antibiotic Loaded Cement Spacer of Knee

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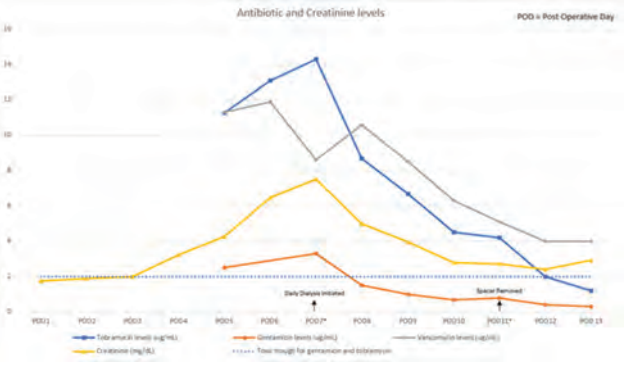
Introduction: Periprosthetic joint infection after total knee arthroplasty is frequently treated with a two-stage revision involving an antibiotic-loaded acrylic bone cement spacer (ALCS) placed in the joint space for infection control weeks before placement of a new prosthesis. The antibiotics within the spacer are expected to remain localized, but studies have found that systemic absorption can occur and can be associated with acute kidney injury (AKI). However, many cases are associated with confounding factors such as the concomitant use of nephrotoxic intravenous antibiotics or associated sepsis, and only rarely have patients required dialysis treatment. We present a case of a 71 year old male who developed AKI on chronic kidney disease (CKD) requiring hemodialysis due to toxic antibiotic exposure from ALCS placement.

Case Description: Our patient had a history of hypertension and CKD 3, who had developed a joint infection with methicillin sensitive staph aureus. An ALCS containing vancomycin, tobramycin and gentamicin using standard doses was placed. Five days post operatively creatinine was 4.1 mg/dl, from 1.75 mg/dl the day of the surgery. Antibiotics levels were sent, tobramycin and gentamicin levels were elevated at 13 mcg/ml and 2.5 mcg/ml respectively (Figure). Despite daily hemodialysis (HD), tobramycin levels remained in toxic range, prompting spacer exchange with a spacer containing 3 grams of cefazolin. He required 8 weeks of HD before recovering.

Discussion: Previous studies have shown a risk for developing new AKI after exposure to antibiotics in bone cement spacers of 14-27% with increased risk in those patients with underlying CKD. Tobramycin appears to be strongly linked but concomitant gentamicin in the ALCS may increase the risk. Clinicians should be cognizant of the potential of serious nephrotoxicity from the antibiotics in the ALCS, especially when they are at high doses in patients with underlying CKD. Combined aminoglycoside antibiotics may exacerbate the risk.



FR-PO082

Validation of Urine Clusterin and MCP1 in Predicting Drug-Induced AKI

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Background: We have published that elevated urine clusterin, MCP1, β2MG, KIM1 and cystatin-C predict drug-induced AKI in patients receiving nephrotoxic drugs(vancomycin, aminoglycosides and calcineurin inhibitors) with a 1–3 day lead-time. We aim to validate the best-performing biomarkers for drug-induced AKI prediction in susceptible patients.

Methods: The reproducibility of the five proposed urine biomarkers to predict AKI in 13 drug-induced AKI patients and 13 controls was determined, to curate the best-performing three biomarkers using a multiplex assay. A prospective single-centre study of 137 patients receiving nephrotoxic drugs was subsequently conducted. Urine samples were collected 2–5 days before AKI onset by KDIGO criteria or before the end of nephrotoxic therapy in non-AKI patients. The primary analysis was the ability of the selected biomarkers to predict AKI with a 2-day lead time using individual ELISA.

Results: Urine clusterin, MCP1, β2MG yielded consistent AKI prediction with respective AUCs of 86%, 75%, 74%, and were superior to that of KIM1 and cystatin-C in the initial 26 patients. Of the validation cohort of 137 patients, 28% developed AKI. AKI and non-AKI patients had a similar mean age of 55 years, with AKI patients having a higher baseline eGFR than non-AKI patients (104 vs 98 mL/min/1.73m^2 respectively, p=0.01). Median levels of biomarkers were higher in eventual AKI cases vs non-AKI patients (p<0.0001 for clusterin and MCP1, p=0.03 for β2MG). Their AUC for AKI prediction was 73(64-82)% with clusterin, 77(68-86)% with MCP1, and 62(51-72)% with β2MG. We determined threshold levels of clusterin and/or MCP1 for optimal AKI prediction.

Conclusions: Urinary clusterin >150 ng/mL or MCP1 >200 pg/mL predicts drug-induced AKI, with best precision achieved by further elevations of both biomarkers.

Funding: Government Support - Non-U.S.

n=26 (13 AKIs vs 13 non-AKIs matched for age, baseline eGFR, and culprit drug)				
Biomarker cut-offs*	Precision	Sensitivity	Specificity	Accuracy
Clusterin > 40 ng/mL	71%	92%	62%	77%
MCP1 > 300 pg/mL	69%	85%	62%	73%
β2MG > 900 ng/mL	71%	77%	69%	73%
*using multiplex immunoassay platform				
Performance metric of biomarkers for AKI prediction (single timepoint, n=137)				
Biomarker cut-offs**	Precision	Sensitivity	Specificity	Accuracy
Clusterin > 150 ng/mL	39%	82%	48%	58%
Clusterin > 500 ng/mL	59%	51%	86%	76%
MCP1 > 200 pg/mL	38%	85%	45%	56%
MCP1 > 600 pg/mL	59%	69%	81%	77%
β2MG > 900 ng/mL	34%	38%	70%	61%
Clusterin > 150 ng/mL OR MCP1 > 200 pg/mL	37%	87%	41%	54%
Clusterin > 500 ng/mL AND MCP1 > 600 pg/mL	61%	49%	88%	77%
Performance metric of serial biomarkers for AKI prediction (2 timepoints, n=80)				
Biomarker cut-offs**	Precision	Sensitivity	Specificity	Accuracy
FIRST Clusterin > 150 ng/mL OR MCP1 > 200 pg/mL	34%	91%	34%	50%
SUBSEQUENT Clusterin > 500 ng/mL AND MCP1 > 600 pg/mL	81%	59%	95%	85%
**using specific ELISA assay for each biomarker				

FR-PO083

Apixaban in CKD, a Life-Threatening Cause of Pericardial Bleed with Resultant Acute Tubular Necrosis (ATN) and Dialysis Dependency

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Introduction: Bleeding is a common complication associated with oral anticoagulants. It can be revealed or concealed, including upper and lower gastrointestinal hemorrhage, central nervous system macro and microbleeds, and bleeding in the genitourinary system. After a thorough literature search, we found no reported case of a large pericardial bleed causing cardiac tamponade. Therefore, we report a case of a large pericardial bleed that caused tamponade, which resulted in ATN in a patient with chronic kidney disease (CKD) who then required dialysis.

Case Description: A 77-year-old Chinese woman with a history of diabetes mellitus type-2, hypertension, atrial fibrillation, left middle cerebral artery stroke status post thrombectomy, and CKD with a baseline creatinine of 1.8 mg/dl (two months prior) was brought to the emergency department (ED) due to elevated blood urea nitrogen (BUN) and creatinine. On arrival at the ED, her creatinine was elevated at 8.3 mg/dl, BUN at 76 mg/dl, and hemoglobin at 7.0 g/dl, with normal platelet and white cell count. She was alert but not oriented and had jugular venous distension, with a blood pressure of 100/60 mmHg. EKG showed no acute changes, a chest x-ray revealed a globular heart, and the septic workup was negative. Echocardiogram demonstrated severe pericardial effusion with right ventricular collapse. She was taking Apixaban 5 mg twice daily. Renal failure workup was all negative or normal, including autoimmune and hepatitis profile, infection, and myeloma screening. Pericardial bleed was suspected in light of an acute drop in hemoglobin, so a pericardial window was made, and a 2-liter bloody effusion was drained on day-1 with a total of 4 liters over a week. Pericardial fluid was negative for atypical cells, gram stain, AFB stain, QuantiFERON, and viral PCRs, and cultures were negative for bacteria and fungi.

Discussion: Oral anticoagulants can cause a potentially life-threatening pericardial bleed and resultant cardiac tamponade. Though apixaban and other non-vitamin K analogs require less monitoring than warfarin and may be associated with lesser chances of bleeding, however, it can cause a large pericardial bleed and can lead to shock and ATN. Care should be exercised in prescribing apixaban to patients who have an increased risk of bleeding, especially those with CKD.

FR-PO084

Validation of a Six-Point Bedside Risk Score for Prediction of AKI After Transcatheter Aortic Valve Replacement

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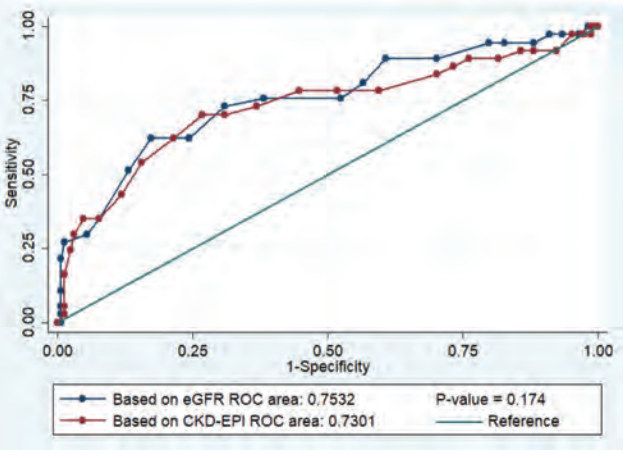
Background: Post-transcatheter aortic valve replacement (TAVR) acute kidney injury (AKI) is a significant complication linked to increased mortality, dialysis rates and myocardial infarction underscoring the need for a reliable prediction tool. Zivkovic et al. (2018) developed a bedside risk score with six pre-procedural variables (NYHA class, non-femoral access, valve-in-valve procedure, hemoglobin level, creatinine clearance, weight) to predict post-TAVR AKI. Validation of this score improve evidence for wider adoption in patient care.

Methods: A retrospective analysis of 205 patients who had TAVR was done. Patient characteristics were compared between AKI and non-AKI groups. Diagnostic accuracy was assessed using the receiver operating characteristics curve.

Results: AKI incidence was 18%. Significant AKI predictors were NYHA class (OR: 2.1170; p=0.001), non-femoral access site (OR: 2.6672; p=0.021), elevated baseline creatinine (OR: 4.1459; p<0.001), decreased hemoglobin levels (OR: 0.6319; p<0.001), eGFR<30 (OR: 0.9634; p<0.001). Age, gender and contrast volume showed no differences. AKI group had higher 10-year follow-up mortality (54.05% vs 31.55%, p=0.010), with 40% of AKI group mortalities occurring in the first year post-TAVR compared to 20% in non-AKI. Post-TAVR dialysis was higher in the AKI group (immediately after: 18.9%, 1 year post-TAVR: 16.2% vs. 0.0% respectively, p<0.001). The bedside risk score demonstrated promising discrimination (AUROC 0.75, accuracy of 69.76%), with a 23.43% increased odds of AKI per score increase.

Conclusions: Zivkovic et al.'s risk score shows promise in predicting post-TAVR AKI and can improve patient care through targeted monitoring and intervention. Guideline development for timely nephrology referral based on the risk score will optimize outcomes for high-risk patients.



Area under the ROC curve of Bedside Risk Score

FR-PO085

From Mega Men to Mega Kidney Failure

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Introduction: Acute interstitial nephritis (AIN) is a type of acute kidney injury associated with the presence of inflammatory infiltrates and interstitial edema. It accounts for 15-27% of biopsies in the category of acute kidney injuries and 1-3% of all renal biopsies. AIN can be caused by infections, systemic disease, idiopathic causes, but drug-induced AIN accounts for over 75% of the cases. Common offending agents are antibiotics, NSAIDs, allopurinol, furosemide, and omeprazole. Here, we describe a case of AIN caused by an over-the-counter (OTC) supplement requiring emergent dialysis.

Case Description: A 50-year-old male without known medical history nor supplement intake, presented with generalized abdominal pain. Upon evaluation, he was afebrile and hemodynamically stable. Serum creatinine was noted to be 17.8 with a GFR of 3 on admission. A right femoral temporary catheter was placed for emergent dialysis. Serological markers were obtained and resulted as negative. He underwent multiple dialysis sessions and his creatinine improved from 17.8 to 7.18. He had lower back pain during his hospitalization with negative findings on lumbosacral spine x-ray. His kidney biopsy showed severe acute tubulointerstitial nephritis with acute tubular injury. During an outpatient visit, he admitted to taking a dietary supplement called Mega Men. The supplement was discontinued and a prednisone taper was started. The last dialysis session was 1 month after his admission, and the patient's creatinine stabilized to a new baseline of 1.38.

Discussion: The case above highlighted a drug induced AIN caused by a non-FDA-approved OTC supplement. With an abundance of easily accessible supplements, it is critical to consider AIN as a diagnosis in those with an acute worsening of renal function as 40% of AIN cases require dialysis. Drug induced AIN presents with a multitude of non-specific symptoms such as fever, rash, arthralgia and in this case abdominal pain and lower back pain. Although duration of use and severity of renal failure are not strongly correlated, the first step after suspecting AIN is removal of the offending agent. A few days after the onset of interstitial inflammation, irreversible fibrosis follows. Early treatment with steroids is recommended to minimize the irreversible renal damage.

FR-PO086

Evaluation of Risk Stratification for AKI: A Comparative Analysis of EKFC, 2009, and 2021 CKD-EPI Glomerular Filtration Estimating Equations

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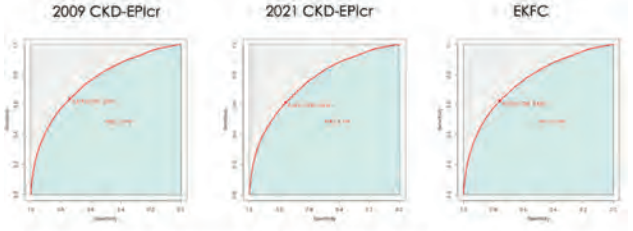
Background: The adoption of the 2021 CKD-EPIcr equation for glomerular filtration rate (GFR) estimation provided race-free eGFR calculation. We aimed to evaluate the differences in acute kidney injury (AKI) risk discrimination power according to 2009 and 2021 CKD-EPIcr, and EKFC equations.

Methods: We performed a retrospective observational study within a tertiary hospital from 2011 to 2021. AKI was defined according to KDIGO serum creatinine criteria. GFR estimates were calculated by three GFR estimating equations: 2009 and 2021 CKD-EPIcr, and EKFC. AKI risk discriminative performances were evaluated with area under receiver operator curves (AUROC) and net reclassification improvement.

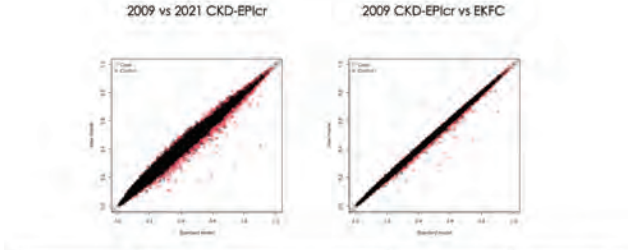
Results: A total of 187,139 individuals, including 27,447 (14.7%) of AKI and 159,692 (85.3%) of control, were enrolled. In multivariable regression prediction model, 2009 CKD-EPIcr model (0.7583 [0.755 – 0.7617]) showed superior performance in AKI prediction than 2021 CKD-EPIcr (0.7564 [0.7531 – 0.7597], <0.001) or EKFC model in AUROC (0.7577 [0.7543 – 0.761], <0.001). In reclassification of AKI, 2021 CKD-EPIcr and EKFC models showed a worse classification performance than 2009 CKD-EPIcr model. (-7.24 [-8.21 – -6.21], -2.38 [-2.72 – -1.97] %).

Conclusions: Regarding AKI risk stratification, the 2009 CKD-EPIcr equation showed better discriminative performances compared to 2021 CKD-EPIcr equation.



	AUC	*Comparison of AUC		
		A vs. B	A vs. C	B vs. C
2009 CKD-EPIcr	0.7583 (0.755 – 0.7617)			
2021 CKD-EPIcr	0.7564 (0.7531 – 0.7597)	<0.001	<0.001	<0.001
EKFC	0.7577 (0.7543 – 0.761)			

Figure 1. Performance of GFR estimating equations in classifying AKI using Multivariable ROC-AUC



	Proportion of participants correctly reclassified		NRI, % (95% CI)	AKI reclassified (N)
	AKI reclassified, % (95% CI)	Non-AKI reclassified, % (95% CI)		
2009 CKD-EPIcr vs.				
2021 CKD-EPIcr	-4.43 (-5.54 – -3.46)	-2.8 (-2.94 – -2.64)	-7.24 (-8.21 – -6.21)	1,136 (887 – 1,421)
EKFC	-2.40 (-2.75 – -1.99)	0.02 (0.00 – 0.04)	-2.38 (-2.72 – -1.97)	615 (510 – 705)

Figure 2. Net reclassification improvement for AKI (multivariable-model 2)

FR-PO087

Influence of Acute Kidney Disease on the Incidence of AKI and Patient Outcomes in Critically Ill Patients Admitted to the Intensive Care Unit

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Background: The Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for acute kidney injury (AKI) proposed the concept of acute kidney disease (AKD), however, its impact on critically ill patients is rarely studied. The aim of this study is to investigate the influence of baseline AKD on the incidence of AKI and patient outcomes in critically ill patients admitted to intensive care unit (ICU).

Methods: This is a retrospective study based on the electronic medical record-extracted ICU cohorts in two 3rd affiliated hospitals in South Korea. We retrospectively categorized baseline kidney function status as no kidney disease (NKD), AKD, and chronic kidney disease (CKD) based on the eGFR levels. AKI was defined based on the KDIGO serum creatinine criteria. The outcome measurements were the incidence of AKI in the ICU and in-hospital mortality.

Results: A total of 7,153 patients were included. The median age was 67 (18-110) years, and 57.6% were male. In all, baseline NKD, AKD, and CKD were seen in 4,792 (66.6%), 926(12.9%), and 1,465(20.5%) patients, respectively. During the ICU stay, AKI was observed in 2,461(34.4%) patients, which was more frequent in AKD [OR 2.354(1.996-2.776)] and CKD [OR 2.347(2.028-2.716)] compared to NKD (Fig 1A). During the median 16(9, 23) days of hospital stay, 819(11.4%) were dead. The in-hospital mortality rate was 1.546(1.328-1.800) folds higher in patients with AKI regardless of the baseline kidney function status, whereas, in patients without AKI, the risk of mortality was 2.176(1.625-2.915) folds higher in AKD compared to NKD (Fig 1B).

Conclusions: AKD was observed in 12.9% of ICU-admitted patients, and it was associated with a higher risk for incident AKI and in-hospital mortality. This study implies the significance of recognizing AKD in the management of ICU patients.

Funding: Government Support - Non-U.S.

Fig 1(A)

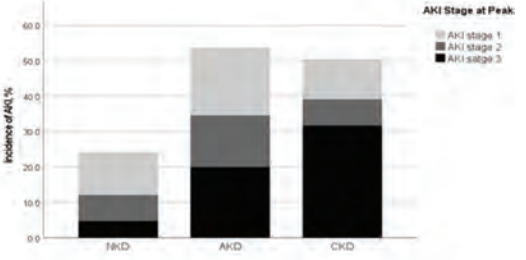
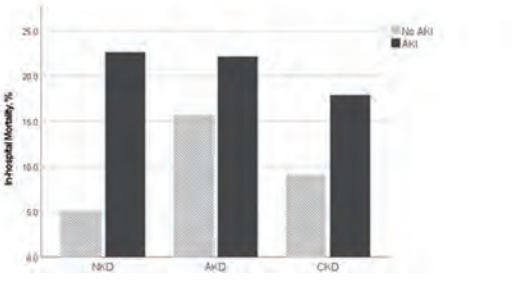


Fig 1(B)



FR-PO088

Community-Acquired AKI: A Prospective Case-Control Study

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Background: Acute kidney injury (AKI) is a common clinical entity in the hospital setting but data on community-acquired AKI is lacking. The aim of this study was to examine the causes and risk factors for community acquired AKI.

Methods: This was a prospective case-control study in which serum creatinine (SCr) of all individuals admitted to the emergency department (ED) of Landspitali–The National University Hospital of Iceland were examined for the presence of AKI. We present data from January 1 until March 3, 2020, May 19 until September 21, 2020, and February 1 until June 15, 2021. The study was paused between these periods due to the COVID-19 pandemic. Patients who met the SCr component of the KDIGO criteria for AKI were invited to participate. Randomly selected control cases (1:2) were paired according to age, sex, and date of ED visit. Participants answered questions about their medical history and use of medications, including over the counter (OTC) drugs. Past medical history was obtained from electronic medical records. Conditional logistic regression was used to identify factors associated with AKI.

Results: A total of 602 AKI cases were identified in 574 persons during the study period, 488 of whom participated (512 cases). The mean (±SD) age of AKI cases and controls was 67.1±16.6 years and 67.2 ±16.2 years, respectively; 48% of cases and controls were female. AKI cases were significantly more likely than controls to have used non-steroidal anti-inflammatory drugs (NSAID) (26.0% vs 18.0%, p=0,001) in the week preceding the ED visit, particularly OTC NSAID (23.3% vs 15.9%, p<0.001). In adjusted analysis, AKI was associated with vomiting (odds ratio [OR] 2.62, 95% confidence interval [CI] 1.95-3.53), diarrhea (OR 1.35, 95% CI 1.04-1.75), urinary retention (OR 1.86, 95% CI 1.32-2.62) and use of NSAID (OR 1.60, 95% CI 1.18-2.23), diuretics (OR 1.48, 95% CI 1.12-1.99) or ACEi/ARB (OR 1.49, 95% CI 1.12-1.99). A statistically significant relationship was not observed for diabetes, hypertension, vascular- or chronic kidney disease.

Conclusions: Volume depletion and the use of NSAID and ACEi/ARB seem to play a major role in the development of AKI in the community setting. Use of OTC NSAID is surprisingly frequent and should be addressed considering serious adverse effects.

Funding: Government Support - Non-U.S.

FR-PO089

The Association Between Skeletal Muscle Mass and Survival/Renal Recovery from Dialysis in Patients with Sepsis-Associated AKI Receiving Continuous Renal Replacement Therapy

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Background: Lower skeletal muscle mass at intensive care unit (ICU) admission has been associated with poor outcomes. In this study, we investigate the independent association between computed tomography (CT)-measured skeletal muscle mass and survival, as well as renal recovery from dialysis, in patients with sepsis-induced acute kidney injury (SIAKI) who are undergoing continuous renal replacement therapy (CRRT).

Methods: In this retrospective study, a total of 618 patients with SIAKI who CRRT in our ICU were included. Within three days prior to ICU admission, all patients underwent abdominal CT scans. The cross-sectional area of skeletal muscle at the 3rd lumbar vertebra was measured, and the skeletal muscle index (SMI), a normalized measure of skeletal muscle mass, was calculated. Patients were categorized into sarcopenia and non-sarcopenia groups using Korean-specific cutoffs of SMI.

Results: Out of the 618 patients included in the study, 301 expired within 28 days of ICU admission. Non-survivors exhibited a higher prevalence of sarcopenia and SMI compared to survivors. The results of multivariable Cox regression analysis revealed that sarcopenia independently predicted 28-day mortality (hazard ratio [HR]: 2.66; 95% confidence interval [CI]: 1.42–2.38; P < 0.001). Among the survivors, sarcopenia was independently associated with a lower likelihood of renal recovery from dialysis within 28 days of ICU admission (HR: 0.42, 95% CI: 0.26–0.68; P < 0.001). Kaplan-Meier analysis demonstrated that sarcopenic patients had lower rates of survival and renal recovery from dialysis within 28 days of ICU admission compared to non-sarcopenic patients.

Conclusions: This study demonstrated that sarcopenia assessed by CT-derived skeletal muscle mass was independently associated with both survival and renal recovery from dialysis in patients with SIAKI receiving CRRT. These findings highlight the potential value of sarcopenia as a prognostic tool in this patient population.

FR-PO090

The Significance of Initial Emergency Room Six-Hour Urine Volume for Survival in Critically Ill Patients Receiving Continuous Renal Replacement Therapy

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Background: The impact of initial emergency room(ER) factors on survival and renal function in critically ill patients receiving continuous renal replacement therapy(CRRT) has been poorly understood. This study aimed to investigate whether initial factors in ER have an influence on the survival and renal recovery of critically ill patients undergoing CRRT.

Methods: This retrospective single-center study included 332 critically ill patients who were admitted to intensive care units and received CRRT via the ER between March 1, 2018, and May 31, 2021. Various clinical parameters, such as urine output, estimated glomerular filtration rate (eGFR), and serum neutrophil gelatinase-associated lipocalin (NGAL), were assessed. The primary outcomes measured were the mortality rates at 30 days and 90 days, while the secondary outcomes focused on the duration of dialysis-free periods at 30 days and 90 days.

Results: The group with low urine output (LUO), defined as < 0.5 mL/kg/hr x 6 hours, displayed a significant association with both 30-day and 90-day mortality rates. The results of multivariable Cox regression analysis indicated that the LUO group had a significantly higher risk of 30-day mortality and 90-day mortality (hazard ratio, 1.935 and 2.141, respectively) compared to the high urine output (HUO) group, defined as ≥ 0.5 mL/kg/hr x 6 hours. There was no significant correlation between 30-day or 90-day mortality rates and initial eGFR or plasma NGAL levels. In critically ill patients undergoing CRRT, the HUO group and the group with initial eGFR ≥ 30 ml/min/1.73m2 were associated with a decreased 30-day and 90-day dialysis-free duration. However, serum NGAL levels did not show a significant association with 30-day and 90-day renal replacement therapy free duration.

Conclusions: The initial urine volume in ER emerges as a crucial factor for both 30-day and 90-day mortality rates in critically ill patients receiving CRRT.

FR-PO091

Impact of Fluid Balance After Sepsis-Associated AKI on Development of Persistent AKI

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Background: Persistent AKI (pAKI), defined as AKI lasting ≥48h is seen in over half the patients with sepsis associated AKI (SA-AKI). Fluid overload is common in patients with SA-AKI and is associated with worse outcomes. It is however unclear if net fluid balance within 48h after onset of SA-AKI (NFB-48) is associated with development of SA-pAKI.

Methods: We conducted a retrospective study using MIMIC IV database. We identified adult patients (≥18y) with sepsis who developed AKI within 48 hours of ICU admission. We defined AKI using both creatinine and urine output based KDIGO criteria. We then identified association between NFB-48 (used as tertiles) with development of SA-pAKI using logistic regression adjusted for demographics, comorbidities, SOFA score, vital signs, laboratory measurements, vasopressors and mechanical ventilation use.

Results: Of 10,739 SA-AKI patients, 62.2% developed SA-pAKI. In comparison with patients whose SA-AKI resolved within 48h, those with SA-pAKI had higher max creatinine level (1.1 vs 1.7 mg/dL; p<0.001), higher SOFA score (4.3 vs 6.3; p<0.001), more use of vasopressors (28% vs 47%; p<0.001) and mechanical ventilation (38% vs 56%;p<0.001). They also had a higher NFB-48 (0.4 vs 1.7L; p<0.001). On adjusted analysis positive NFB-48 was significantly associated with increased odds of developing SA-AKI in a stepladder pattern (Table 1).

Conclusions: We have shown that positive NFB within 48 hours after onset of SA-pAKI is significantly associated with development of SA-pAKI. The study underscores the need for optimal fluid balance in patients with SA-AKI.

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Impact of NFB-48 on Development of SA-pAKI

Net Fluid Balance within 48h after S-AKI onset (NFB-48)	Adjusted OR	95% CI
Less than -0.3L	1	
-0.3 to 1.9L	1.41	1.26 – 1.58
More than 1.9L	2.45	2.14 – 2.81

FR-PO092

The Impact of C-Reactive Protein-to-Albumin Ratio on Mortality in Patients with AKI Requiring Continuous Kidney Replacement Therapy: A Multicenter Retrospective Study

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Background: The C-reactive protein-to-albumin ratio (CAR) is a prognostic marker in various diseases that represents patients' inflammation and nutritional status. Here, we aimed to investigate the prognostic value of CAR in critically ill patients with severe acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT).

Methods: We retrospectively collected data from eight tertiary hospitals in Korea from 2006–2021. The patients were divided into quartiles according to CAR levels at the time of CKRT initiation. Cox regression analyses were performed to investigate the effect of CAR on in-hospital mortality. The mortality prediction performance of CAR was evaluated using the area under the curve (AUC), net reclassification improvement (NRI), and integrated discrimination improvement (IDI).

Results: In total, 3995 patients who underwent CKRT were included, and the in-hospital mortality rate was 67.3% during the follow-up period. The 7-day, 30-day, and in-hospital mortality rates increased toward higher CAR quartiles (all *P*<0.001). After adjusting for confounding variables, the higher quartile groups had an increased risk of in-hospital mortality (quartile 3: adjusted hazard ratio [aHR], 1.15, 95% confidence interval [CI], 1.02–1.30, *P*=0.023; quartile 4: aHR, 1.33; 95% CI, 1.18–1.50, *P*<0.001). CAR combined with APACHE II or SOFA scores significantly increased the predictive power compared to each severity score alone for the AUC, NRI, and IDI (all *P*<0.05).

Conclusions: A high CAR is associated with increased in-hospital mortality in critically ill patients requiring CKRT. The combined use of CAR and severity scores provides better predictive performance for mortality than the severity score alone.

Table 1. Cox regression analyses for in-hospital mortality in CAR quartile groups.

	Model 1		Model 2		Model 3		Model 4	
	HR (95% CI)	P	aHR (95% CI)	P	aHR (95% CI)	P	aHR (95% CI)	P
Quartile 1	Reference		Reference		Reference		Reference	
Quartile 2	1.08 (0.96–1.20)	0.193	1.07 (0.96–1.20)	0.239	1.07 (0.95–1.19)	0.257	1.11 (0.98–1.26)	0.099
Quartile 3	1.19 (1.07–1.33)	0.002	1.18 (1.06–1.32)	0.003	1.20 (1.07–1.34)	0.001	1.15 (1.02–1.30)	0.023
Quartile 4	1.45 (1.28–1.60)	<0.001	1.41 (1.27–1.58)	<0.001	1.40 (1.26–1.57)	<0.001	1.33 (1.18–1.50)	<0.001

Model 1: unadjusted.

Model 2: adjusted for age and sex.

Model 3: adjusted for age, sex, hypertension, and CCI.

Model 4: adjusted for age, sex, hypertension, CCI, APACHE II score, and mechanical ventilator use.

Table 2. Comparison of the AUC and predictive power of prognosis for in-hospital mortality

Variables	AUC (95% CI)	P	NRI (95% CI)	P	IDI (95% CI)	P
CAR	0.580 (0.564–0.595)	Reference				
CRP	0.555 (0.540–0.571)	<0.001				
APACHE II	0.665 (0.646–0.684)	Reference	Reference		Reference	
APACHE II + CAR	0.674 (0.656–0.693)	0.016	0.151 (0.084–0.223)	<0.001	0.007 (0.004–0.010)	<0.001
SOFA	0.669 (0.650–0.687)	Reference	Reference		Reference	
SOFA + CAR	0.677 (0.658–0.695)	0.004	0.134 (0.065–0.204)	<0.001	0.007 (0.004–0.010)	<0.001
APACHE II + SOFA	0.697 (0.679–0.715)	Reference	Reference		Reference	
APACHE II + SOFA + CAR	0.703 (0.684–0.720)	0.036	0.130 (0.060–0.200)	<0.001	0.005 (0.003–0.007)	<0.001

FR-PO093

Clonal Hematopoiesis of Indeterminate Potential Is Associated with AKI

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is a recently recognized risk factor for several chronic diseases of aging including cardiovascular disease and chronic kidney disease. In these contexts, clonal populations of mutated myeloid cells contribute to end-organ damage through inflammatory dysregulation. We recently identified CHIP as a novel risk factor for AKI: it was associated with an increased risk of incident AKI in ICD code-based prospective clinical data from three large cohorts totalling nearly half a million individuals (adjusted hazard ratio: 1.26, 95% CI: 1.19–1.34).

Methods: In the current work, we sought to investigate determine whether CHIP was associated with impaired functional recovery from AKI. We first examined the association between CHIP and AKI recovery in the ASSESS-AKI cohort. We then assessed long-term post-AKI outcomes in a mouse model of CHIP (partial *Tet2*$^{-/-}$ bone marrow transplant) subjected to ischemia reperfusion injury.

Results: We identified that certain subtypes of CHIP exhibited a non-resolving pattern of injury and had poorer long-term outcomes after AKI. At 28 days post-ischemic injury, we observed higher levels of kidney injury markers KIM-1 and NGAL as well as more kidney fibrosis in the CHIP mice compared to wild type mice. Kidney macrophage infiltration was markedly increased in CHIP mice at this timepoint, and concomitant upregulation of pro-inflammatory and fibrotic signaling pathways was noted.

Conclusions: This work identifies CHIP as a novel and potentially targetable risk factor for impaired recovery from AKI.

Funding: NIDDK Support, Other NIH Support - Canadian Institutes of Health Research Project Grant (application # 427810), R01DK132155, Government Support - Non-U.S.

FR-PO094

Genome-Wide Association Study (GWAS) in Critically Ill Sepsis Patients Identifies Single Nucleotide Polymorphisms (SNPs) Associated with AKI by Multiple Definitions

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Background: Identifying replicable genetic variants associated with AKI has been challenging, potentially related to differences in AKI definition across studies. We conducted GWAS of AKI, defined multiple ways, in critically ill sepsis patients.

Methods: We included 1955 critically ill patients without ESKD enrolled in a sepsis cohort from 2011-2020. We extracted genomic DNA from whole blood and genotyped with the Affymetrix Axiom TxArray. We defined AKI using 1) Kidney Disease Improving Global Outcomes (KDIGO) creatinine (Cr) criteria which include both worsening and rapidly resolving AKI, and 2) Acute Kidney Injury Network (AKIN) Cr criteria which require Cr increase from admission. We used PLINK to conduct additive multivariable logistic regression, adjusting for age, sex, and principal components, stratified by European (n=1312) or African (n=643) ancestry (EA, AA). We assessed SNPs associated with AKI at $p<5x10^{-5}$ by one definition for significance at $p<5x10^{-3}$ by the other.

Results: AKIN-AKI occured in 43% of EA patients and 45% of AA patients, while KDIGO-AKI occured in 58% of EA patients and 63% of AA patients. In AAs, 21 had $p<5x10^{-5}$ for AKIN-AKI and 18 for KDIGO-AKI; 4 SNPs were associated with the other AKI definition at $p<5x10^{-3}$ (Table). *NOD1* encodes a bacterial pattern-recognition receptor that initiates inflammation. *ERO1B* encodes an oxidoreductase in the endoplasmic reticulum that regulates reactive oxygen species production. In EAs, 14 SNPs had $p<5x10^{-5}$ for AKIN-AKI and 11 for KDIGO-AKI; none were associated with the other AKI definition at $p<5x10^{-3}$. However, NKAIN2 is extensively expressed in the kidney and is associated with glomerular filtration rate in children, while rs10031539 (*KCNIP*) is associated with CKD.

Conclusions: We identified SNPs associated with both KDIGO and AKIN defined AKI that may be pathophysiologically relevant.

Funding: NIDDK Support, Other NIH Support - NHLBI

SNPs of interest

SNP	Function	Gene	Ancestry	AKIN OR (95%CI)	p	KDIGO OR (95%CI)	p
rs1104940	Intronic	NKAIN2	EA	0.71 (0.61-0.83)	2.02 x 10-5	0.81 (0.70-0.95)	7.68 x 10-3
rs10031539	Intronic	KCNIP	EA	1.42 (1.21-1.67)	2.01 x 10-5	1.25 (1.07-1.47)	6.52 x 10-3
rs113286694	Intronic	NOD1	AA	0.54 (0.38-0.75)	2.58 x 10-4	0.51 (0.37-0.71)	4.72 x 10-5
rs1749557	Intronic	ERO1B	AA	1.64 (1.31-2.10)	1.99 x 10-5	1.46 (1.16-1.84)	1.44 x 10-3
rs2463188	Intronic	ERO1B	AA	1.63 (1.29-2.04)	2.59 x 10-5	1.39 (1.11-1.75)	4.73 x 10-3

FR-PO095

Association of Angiotensin-Converting Enzyme Inhibitor/Angiotensin Receptor Blocker Use with Kidney Diseases Among Long-COVID and Non-Long-COVID Adults: Retrospective Cohort Study of Real-World Data

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Background: Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin II receptor blockers (ARBs) are widely prescribed for hypertension. In vitro studies have suggested that ACEIs/ARBs upregulate ACE-2 expression, the receptor for SARS-CoV-2 entry, particularly in kidneys. It was hypothesized that the risk of kidney diseases may be elevated in individuals with Long COVID receiving ACEI/ARB therapy. The objective of this research is to examine the relationship between ACEI/ARB usage and the occurrence of acute kidney injury (AKI) in both Long COVID and non-Long COVID populations.

Methods: A retrospective cohort study using TriNetX datasets was conducted, with diagnoses of long COVID and kidney outcomes identified via International Classification of Diseases 10th revision (ICD-10) codes. Four cohorts were built: long COVID ACEI/ARB users (LCAU), long COVID non-users (LCAN), non-long COVID ACEI/ARB users (NLCAU), and non-long COVID ACEI/ARB non-users (NLCAN). Multivariable stratified Cox proportional hazards regression models were used to analyze the relationships. Meanwhile, we also compared the hazard ratio of AKI, CKD, and MAKE between ACEI/ARB and an active comparator, calcium channel blockers (CCB).

Results: A total of 164,070 qualified participants were included from 10/01/2021 to 02/14/2023, with 10,627 long COVID patients and 12,574 ACEI/ARB users. After controlling for demographics, drug histories, and comorbidities, ACEI/ARB use did not significantly impact the risk of AKI, CKD, and MAKE, when comparing LCAU to LCAN, and NLCAU to NLCAN. However, an increased AKI risk was associated with long COVID when comparing LCAN to NLCAN (aHR, 1.61; 95% CI, 1.27 – 2.06). No significant difference in HR of each kidney outcome between ACEI/ARB and CCB was found in both long COVID and non-long COVID cohorts.

Conclusions: ACEI/ARB use does not appear to elevate the incidence of AKI in comparison to non-users and active comparators for both Long COVID and non-Long COVID participants. Instead, it is Long COVID that has been associated with an increased risk of AKI.

FR-PO096

Prevention of Renal Damage Caused by Activation of Rhabdomyolysis-Induced Inflammasome

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Background: Rhabdomyolysis (RM) is a clinical and biochemical syndrome characterized by skeletal muscle rupture and massive release of cellular components including myoglobin (MG), which causes one of the most serious complications, acute renal failure (ARF) by direct cytotoxicity and tubular obstruction due to precipitation of MG itself. The heme group induces an inflammatory response by activation of the NLRP3 inflammasome, release of different cytokines and the phenotype changes of proinflammatory (M1) to antiinflammatory (M2) macrophages. Cilastatin, a renal dehydropeptidase-I inhibitor, has demonstrated its usefulness in the protection of ARF induced by nephrotoxic drugs due to interference with lipid rafts. We evaluate if cilastatin is able to block inflammasome activation and protect from RM-induced renal damage.

Methods: RM was induced in Wistar rats by administering in the hind legs with 50% glycerol (or vehicle to the control group). Cilastatin (150 mg/kg) or its vehicle, was administered immediately and every 24h after RM induction. Renal damage was assessed 48h after glycerol/vehicle administration by measuring serum levels of creatinine, potassium, LDH, blood urea nitrogen (BUN) and glomerular filtration rate (GFR), as well as morphology in renal tissue and ferric iron, specific biomarkers of inflammasome activation, also phenotype change in macrophages.

Results: RM worsened renal function compared to the control group, which was confirmed by the presence of severe morphological changes and iron accumulation in tubular cells, as well as a statistically significant increase of the biomarkers of inflammasome and cytokines levels, along with a change in phenotype M1 to M2. Cilastatin treatment completely prevented renal dysfunction, restored significantly all other parameters to levels found in the control groups, and reduced many of the histological symptoms of renal damage.

Conclusions: Our results support the theory of a possible use of cilastatin in the prevention and treatment of ARF-induced by RM. Therefore, cilastatin may be a very beneficial therapeutic strategy in clinical practice for patients with some type of trauma or susceptible to renal damage due to RM.

Funding: Government Support - Non-U.S.

FR-PO097

Effects of Sodium Bicarbonate on Clinical Outcomes in CKD Patients with Contrast-Associated AKI (CA-AKI): A Meta-Analysis on Randomized Controlled Trials (RCTs)

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Background: Contrast Associated Acute kidney Injury (CA-AKI) has been linked to the causal effect in a small increase of creatinine without serious adverse outcomes. However, this transient decrement in kidney function may associate with serious adverse outcomes such as dialysis or mortality. Intravenous fluid volume expansion with sodium bicarbonate (NaBiC) were highly recommended for prevention of CA-AKI in KDIGO guidelines. However, the independent role of NaBiC in CA-AKI is not fully explored especially on patients with chronic kidney disease (CKD).

Methods: The randomized controlled trials with NaBiC supplement were compared to that of hydration in CKD patient with CA-AKI were surveyed. Electronic databases: Pubmed, Embase, Web of science, and Cochrane library were searched with predefined key words/MeSH terms to identified relevant studies. In addition, reference lists of included studies were screened manually. We conducted meta-analysis by using random effects model. The results were expressed as risk ratio for categorical outcomes with 95% confidence interval and mean difference with 95% confidence interval for continuous outcomes.

Results: A total 25 studies were included in our final analysis after screened with predefined criteria, including 4396 patient with CKD. The risk ratio of CA-AKI when comparing NaBiC to hydration is 0.74 [95% CI: 0.56, 0.97] in subgroup of early CKD (eGFR between 45-60ml/min). However, the Risk ratio of dialysis and mortality are 0.97 [95% CI: 0.46, 2.03] and 0.90 [95% CI: 0.67, 1.20] in all population, respectively. Mean difference of creatinine between NaBiC group and hydration group within 24 hours, 48 hours and 72 hours are -0.04 [95% CI: -0.17, 0.10] mg/dl, -0.02 [95% CI: -0.12, 0.08] and -0.44 [95% CI: -0.72, -0.16] mg/dl, respectively. Mean difference of eGFR within 24 hours, 48 hours and 72 hours between NaBiC and hydration group is 0.06 [95% CI: -0.23, 0.35], 0.12 [95% CI: -0.06, 0.30] and 0.67 [95%CI: 0.34, 1.01] ml/min/1.73m². Mean difference of hospital stay length is -0.55 [95% CI: -1.56, 0.47] days between NaBiC and hydration group. The funnel plot showed no bias.

Conclusions: In compared to intravenous fluid volume expansion, sodium bicarbonate may benefit in eGFR in early CKD patients, however, in regards to mortality, dialysis or hospital stay, NaBiC supplement showed no additional advantages in patients with CKD.

FR-PO098

The Use of Anti-Adrenergic Agents as a Predictor of AKI and Delayed Recovery of Kidney Function: The NARA-AKI Cohort Study

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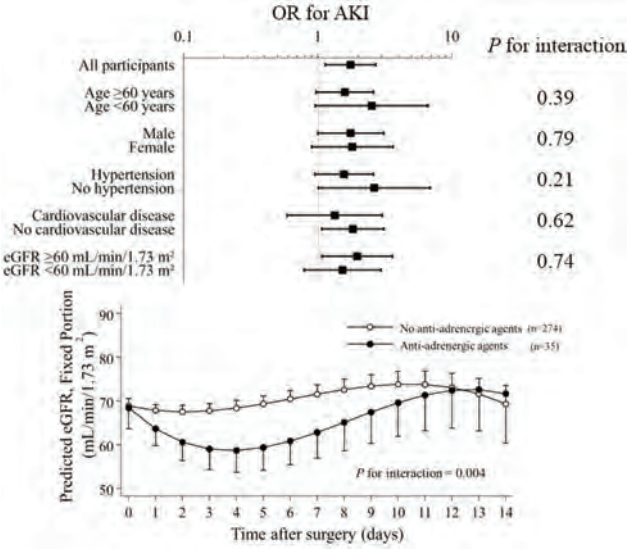
Background: Association of anti-adrenergic agents with postoperative acute kidney injury (AKI) and with trajectory of kidney function after AKI is still unknown.

Methods: In a retrospective cohort study, adults undergoing non-cardiac surgery under general anesthesia were included. Obstetric or urological surgery, missing data, or preoperative dialysis was excluded. The exposure of interest was preoperative regular use of anti-adrenergic agents. The outcomes were AKI within 1 week postoperatively and trajectories of kidney function within 2 weeks postoperatively among patients with AKI. Multivariable logistic regression models were used to examine the association of anti-adrenergic agents with AKI. Linear mixed-effects models were used to compare the trajectories of postoperative kidney function after AKI between patients with and without anti-adrenergic agents.

Results: Among 5168 patients, 245 had used anti-adrenergic agents. A total of 309 (6.0%) developed AKI, and the use of anti-adrenergic agents was independently associated with postoperative AKI even after adjustment for preoperative and intraoperative potential confounders [OR (95% CI): 1.76 (1.14–2.71)]. As a sensitivity analysis, propensity score matched analysis yielded the similar result [OR (95% CI): 1.78 (1.003–3.15)]. The association was similar across preexisting hypertension or cardiovascular disease. Analyses restricted to patients with AKI suggested that the timing and stage of AKI were similar among those with and without anti-adrenergic agents; however, the recovery of kidney function was delayed among those with anti-adrenergic agents (*P* for interaction = 0.004).

Conclusions: The use of anti-adrenergic agents was associated with postoperative AKI, and delayed recovery of kidney function after AKI. Temporary withdrawal of anti-adrenergic agents during perioperative periods may contribute to prevent AKI and shorten the duration of AKI.



FR-PO099

Metabolic Acidosis Increases the Risk of AKI in Critically Ill Patients: A Multicenter Cohort Study

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Background: Acute kidney injury (AKI) is a common complication in critically ill patients admitted to the intensive care units (ICU), as well as metabolic acidosis, characterized by low levels of serum bicarbonate. However, the possible association between both is not clear yet. The aim of the present study was to evaluate metabolic acidosis as a risk factor for the development of AKI.

Methods: A prospective cohort study was conducted by collecting data from three ICUs in the Federal District, Brazil. The serum bicarbonate level in the first 24 hours after ICU admission was used to define the acid-base disorders; acidosis (<22 mEq/L) and alkalosis (>26 mEq/L). The KDIGO guideline for AKI was used to define it based on serum creatinine levels. The mortality outcome was followed up to 28 days during the ICU stay. Odds ratio and Cox regression were performed with corrections for age, male sex, serum creatinine, and the presence of any comorbidity.

Results: A total of 2,732 patients (66±19 years and 55% men) were analyzed, with metabolic acidosis found in 26% (n=705) and metabolic alkalosis in 32% (n=865). Compared with the patients without acid-base disorders, those with acidosis were 81% more likely to develop AKI (OR=1.81; 95%CI:1.10–2.99), while those with alkalosis were 44% less likely (OR=0.56; 95%CI:0, 32–0.98). Both acidosis and alkalosis were not associated with increased risk of mortality (HR=1.03; 95% CI: 0.68–1.56 and 0.99; 95% CI: 0.68–1.42, respectively).

Conclusions: In critically ill ICU patients, metabolic acidosis, but not alkalosis, was associated with the development of AKI compared to the patients without acid-base disorders. On the other hand, metabolic alkalosis was a protective factor to the development of AKI. For the mortality outcome, none of the acid-base disorders was significantly associated with it.

FR-PO100

AKI in Patients with Acute Decompensated Heart Failure Undergoing Aggressive Diuresis and Its Effect on Short-Term Outcome

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Background: Acute heart failure (AHF) patients treated with diuretics often develop worsening of renal functions with resultant acute kidney injury (AKI) during hospitalization. AKI could be a result of renal tubular injury or simply indicate a hemodynamic / functional change in glomerular filtration.

Methods: 100 AHF patients who underwent aggressive diuresis were included (excluding patients requiring inotropic support or haemodialysis). Urine NGAL was measured on the day of admission and after 72 hours. Serum creatinine was measured on day of admission, at 48 hours and at 72 hours post admission. AKI was defined as per KDIGO guideline as increase in creatinine by 0.3mg/dL or more in 48 hours or urine output < 0.5 mL/kg/h for 6 hours. All patients were contacted at 30 days and reviewed regarding requirement of readmission/mortality. Patients who developed AKI got their creatinine checked again at day 30 from the day of admission.

Results: Mean eGFR of patients was 48.1 ml/min/m2. Mean NT-proBNP was 11000 pg/ml. Mean LVEF was 43%, with 38% patients having HFrEF and 62% patients had HFpEF. Of total 100 patients, 37 developed AKI. Rise in NGAL from day 0 to day 3 was noted in 34 cases. There was no correlation found between rising creatinine levels and rising NGAL levels (including patients with AKI). Mean NT-proBNP was higher in patients with AKI as compared to those without AKI (p-value=0.048). Of 37 AKI patients,

10 (27%) patients had creatinine value at day 30 higher than at day 3, while 27 (73%) patients had creatinine value at day 30 lower than at day 3. 30 patients needed readmission within 30 days after discharge; 5 patients expired by day 30. Occurrence of AKI did not show association with readmission within 30 days or with mortality at 30 days.

Conclusions: AKI occurred in 37% patients with AHF undergoing aggressive diuresis. This AKI had no correlation with serial NGAL levels (tubular injury biomarker) but was associated with elevated baseline NT-proBNP levels. 73% AKI patients showed improvement in creatinine levels by day 30 post discharge & occurrence of AKI did not affect short term morbidity (readmission at 30 days) and mortality at 30 days. This implies that AKI in the setting of AHF & aggressive diuresis is mild, mainly functional/ hemodynamic and should not affect decisions with decongestive therapy.

FR-PO101

Analysis of Influencing Factors of Poor Prognosis in Patients with Acute Respiratory Distress Syndrome Complicated with AKI

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Background: To study the influencing factors of poor prognosis in patients with acute respiratory distress syndrome (ARDS) complicated with acute kidney injury (AKI) in ICU.

Methods: Retrospective analysis was performed on patients with ARDS complicated with AKI admitted to the ICU. The stage of AKI was determined according to the change of blood creatinine value within 7 days after the diagnosis of AKI. They were divided into 28-day survival group (28-S) and 28-day death group (28-D) according to their survivalist 28 days. Multivariate COX regression analysis was used to analysis of influencing factors of 28-day death in patients with ARDS complicated with AKI.

Results: 265 patients with ARDS complicated with AKI has a median age of 68 (54,75) years old. 154 patients died within 28 days(58.1%). Compared to the 28-S group, age, proportion of renal function early unrecovered, proportion of combined coronary heart disease, proportion of combined malignant tumor, acute physiology and chronic health evaluation scoring system II, proportion of pulmonary ARDS, proportion of positive fluid balance accumulated on day 2 of ICU admission, proportion of severe AKI, blood lactic acid of the 28-D group were higher (P<0.05). The arterial partial pressure of oxygen, arterial oxygen saturation, oxygenation idex of the 28-D group were lower (P<0.05). Multivariate COX regression analysis showed that renal function early unrecovered (HR=1.936, 95%CI 1.238~3.027, P=0.004), combined malignant tumor (HR=1.983, 95%CI 1.301~3.023, P=0.001), positive fluid balance accumulated on day 2 of ICU admission (HR=1.428, 95%CI 1.013~2.015, P=0.042), oxygenation index(HR=0.647, 95%CI 0.447~0.937, P=0.021) were independent influencing factors for the 28-day death in patients with ARDS complicated with AKI.

Conclusions: Renal function early unrecovered, combined malignant tumor, positive fluid balance accumulated on day 2 of ICU admission, oxygenation index decreased are associated with poor prognosis in patients with ARDS complicated with AKI.

Funding: Government Support - Non-U.S.

Influencing factors of 28-day death in ARDS patients complicated with AKI

Factors	Multivariate COX regression analysis		
	P-value	HR	95%CI
Renal Function Early Unrecovered(Yes/No)	0.004	1.936	1.238~3.027
Combined Malignant Tumor(Yes/No)	0.001	1.983	1.301~3.023
Positive Fluid Balance Accumulated on Day 2 of Icu Admission(Yes/No)	0.042	1.428	1.013~2.015
Oxygenation Index(Every 1mmHg increase)	0.021	0.647	0.447~0.937

FR-PO102

Building a Prediction Model for Postoperative AKI Using Machine Learning: The CMC-AKIX Model

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Background: Postoperative acute kidney injury (AKI) is associated with increased mortality and morbidity in patients undergoing surgeries performed under general anesthesia. There are several models that predict postoperative AKI risk, but most are single-center studies that need external validation.

Methods: In this retrospective cohort analysis, we included noncardiac surgeries performed between 2009 and 2019 at 7 university hospitals in South Korea. Postoperative AKI was defined as an increase of serum creatinine at least 1.5 times the baseline value or initiation of renal replacement therapy within 30 days of the postoperative period. We tested 6 machine learning prediction models: deep neural networks (DNN), logistic regression, decision tree, random forest, light gradient boosting machine (GBM), and naïve Bayes, and compared model performance using the area under the curve (AUC) of the receiver-operating characteristic.

Results: A total of 239,267 surgeries were included, and 7,935 postoperative AKI events (3.3%) occurred. The 6 different statistical analysis methods were run on various combinations of 40 independent preoperative predictors that we had selected. Model 1 included all variables, Model 2 included variables that had been significantly associated with postoperative AKI in previous studies, and Model 3 included variables that were found significant on multivariate analysis. Among them, Model 1 run on DNN (AUC = 0.821) and light GBM (AUC = 0.823) and Model 3 run on DNN (AUC = 0.807) demonstrated the best prediction performance.

Conclusions: We have developed a high-performance risk prediction system for postoperative AKI that can be easily applied using preoperative patient characteristics and laboratory data.

FR-PO103

Acute Kidney Disease in Outpatient Setting: Epidemiological Insights from National Digitalized Big Data Practice

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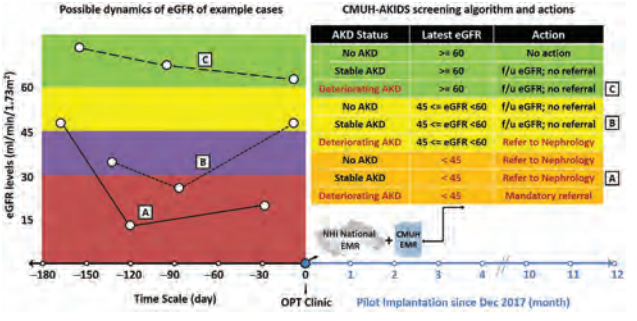
Background: The burden of acute kidney disease in outpatients (AKD_{OPT}) is largely unknown due to health data silos and its asymptomatic nature. We established an Acute Kidney Injury Detection System (AKIDS) that integrates local electronic medical records and National Health Insurance Cloud to screen for AKD_{OPT}, and enable risk-based referrals in real-time.

Methods: AKIDS was integrated into the backend of outpatient HIS during 2017.12-2020.05. AKD_{OPT} within 180 days prior to a clinic visit is defined as the percent change between the max and min of (1) serum creatinine (SCr) >50%, or (2) eGFR >35%. AKD_{OPT} is considered deteriorating if the last two SCr decreased by >0.3 mg/dL; otherwise, it's termed stable. We ensured a 1-year follow-up by including adult patients with the first AKD_{OPT} occurring during 2017.12-2019.06 and without ESRD or cancer. One-year composite kidney outcome (CKO) was defined as having ESRD or ≥40% drop of outpatient eGFR during follow-up. All-cause mortality was determined by National Death Registry. Multivariable Cox proportional modeling was used to estimate the risk of outcomes associated with AKD_{OPT}.

Results: The monthly cumulative incidence density of AKD_{OPT} was 6.9 to 8.1% (**Figure**). AKD_{OPT} patients had significantly higher 1-year CKO (1.8 vs 0.2%) and mortality (8.2 vs 1.4%), compared with those without. Of 79838 outpatients, 15.7% had AKD_{OPT} (12.7% stable; 3.0% deteriorating). Multivariable analysis found that AKD_{OPT} was significantly associated with increased 1-year risk of CKO by 5-fold (adjusted HR [aHR]=5.2; 95% CI=4.0-6.8) and mortality by 3-fold (2.6 [2.4-2.9]). The risk of 1-year CKO for deteriorating AKD_{OPT} (7.6 [5.5-10.5]) was higher than that for stable AKD_{OPT} (4.4 [3.3-5.8]).

Conclusions: By integrating national–local data and creating a kidney data ecosystem, we conducted the first study to fully characterize the epidemiologic profile of AKD_{OPT}—a obscured AKI phenotype. This study illustrates the potential of healthcare big data in transforming global approaches to AKD patterns and prevention.

Funding: Government Support - Non-U.S.



FR-PO104

Novel Data-Driven Phenotyping to Support Genome-Wide Association Study (GWAS) Exploration in AKI

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Background: Traditional phenotyping may have limited sensitivity for detecting meaningful phenotypes. Machine learning may detect patterns of variables for novel phenotype identification. We applied this approach to identify phenotypes of acute kidney injury (AKI).

Methods: A cohort of VA patients hospitalized from 2002-2019 was aggregated. AKI was defined as KDIGO Stage 1 or greater during hospitalization. 5,515 data features including individual demographics, laboratory tests, medications, and billing codes were used to calculate longitudinal curves anchored on each patient hospitalization, and endophenotypes inferred with Independent Component Analysis (ICA). Ten iterations from

200,000 randomly selected hospitalizations with AKI were analyzed, resulting in 11,985,029 learning instances. GWAS was performed on 167,051 MVP patient hospitalizations with and without AKI were scored for each phenotype. Each patient was represented only once with that patient's hospitalization being randomly selected. Single variant linear regression analyses were performed using imputed data, adjusting for sex, age, the top 10 principal components, stratified by HARE race/ethnicity, followed by meta-analysis. Phenotypes were retained if they had at least 1 significant SNPs and inflation between 0.98-1.1.

Results: 2,137 distinct phenotypes were identified. 50 phenotypes with data patterns potentially relevant to AKI were selected by expert adjudication. Nine of 50 phenotypes were retained. We selected two phenotypes, one clinically consistent with patterns of acute glomerulonephritis (AG) and one with cardiorenal syndrome (CS). The former was associated with serum complement and albumin levels, hyperlipidemia, and acute/chronic hepatitis C. The latter was characterized by acute on chronic heart failure, elevated BNP, and acute renal failure (ARF) codes. The presence of ARF in both phenotypes enriched for intrinsic/more severe injury. Two loci with AG (HLA and COL4A2), and one locus (FANCL) with CS reached genome-wide significance.

Conclusions: An entirely data-driven process can identify both well-established and potentially novel endophenotypes of AKI that can be explored for clinically provocative features. These findings show promise for novel phenotype discovery and significant genetic association detection.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO105

Time to Blood Pressure Control and Blood Pressure Targets Significantly Impact Mortality Among Veterans Following AKI

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Background: Acute kidney injury (AKI) complicates 20-25% of hospital admissions, and is associated with increased long-term mortality. Effective blood pressure (BP) control following AKI may improve outcomes, but appropriate BP targets and optimal timing of BP medication initiation are unclear.

Methods: This retrospective cohort analysis included adult Veterans admitted from 2013 to 2018 with in-hospital AKI and ≥1 blood pressure measurement within 30 days of discharge. Systolic BP control was treated as time dependent and categorized as <120, 120-129, and 130-139, relative to >140 mm HG. The primary outcome was time to death. Cox Proportional Hazards regression was adjusted for demographics, chronic lung disease, unexplained weight loss, dementia, congestive heart failure (CHF), hematocrit, blood urea nitrogen, bilirubin, and albumin. [YM1] To evaluate the impact of BP control over time, we calculated hazard ratios (HR) at 7 different timepoints (30, 60, 90, 120, 180, 270, and 365 days after discharge).

Results: A total of 97,376 Veterans were included and 14,819 (15%) died within 1 year of discharge. The cohort had high rates of hypertension (85%), CHF (28%), and diabetes mellitus (19%). All BP categories <140 mmHg had significantly reduced HRs for mortality relative to uncontrolled BP, but the 130-139 mmHg group had the lowest HRs (Table). For all BP categories, hazard ratios relative to uncontrolled BP were lowest at the 30-day mark and increased over time (Table).

Conclusions: Among post-AKI Veterans, BP control within 30 days of discharge was associated with reduced mortality, but this benefit was attenuated over time. All BP targets were superior to blood pressure >140 mmHg, but the 130-139 mmHg group had the lowest risk of death at each timepoint. These findings highlight the importance of achieving BP control promptly post-AKI and suggest that targeting a systolic BP of 130-139 is ideal.

Table. Hazard Ratios and 95% confidence intervals for mortality over time, by blood pressure category

		Systolic Blood Pressure (mmHg)			
		<120	120-129	130-139	>=140
Days From Hospital Discharge	30	0.66 (0.66-0.67)	0.56 (0.56-0.57)	0.47 (0.46-0.48)	Reference
	60	0.69 (0.68-0.69)	0.59 (0.59-0.60)	0.50 (0.49-0.50)	Reference
	90	0.71 (0.71-0.71)	0.62 (0.61-0.62)	0.52 (0.52-0.53)	Reference
	120	0.74 (0.73-0.74)	0.65 (0.64-0.65)	0.55 (0.55-0.56)	Reference
	180	0.80 (0.79-0.80)	0.71 (0.71-0.72)	0.62 (0.61-0.62)	Reference
	270	0.89 (0.89-0.89)	0.82 (0.81-0.82)	0.72 (0.72-0.73)	Reference
	365	1.00 (0.99-1.01)	0.95 (0.94-0.96)	0.86 (0.85-0.87)	Reference

FR-PO106

AKI Increase the Risk of Fractures: A Retrospective Cohort Study of an Australian Health District

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Background: Kidneys play an important role in maintaining bone mineral balance and bone health. However, this may be disrupted following an acute kidney injury (AKI), affecting bone health. We hypothesized that AKI increases the risk of fractures and investigated this association.

Methods: Retrospective cohort study utilising adult (>18 years of age) patient-data (January 2008-December 2017), from an Australian Local Health District. AKI was based on serum creatinine measurements consistent with Kidney Disease Improving Global Outcome (KDIGO) AKI definition or international classification of disease (ICD) 10AM AKI code. Demographics, comorbidities and fractures were also extracted from ICD codes. Adjusted time-varying (time to AKI) Cox proportional hazards was used to determine the risk for future fractures (hazard ratio [HR], 95% confidence intervals [CI]) after AKI uring no AKI history as a reference. Variables in multivariable analysis included those associated with fractures such as age, gender, history of chronic kidney disease, hypertension, diabetes, cardiac history, cancer and osteoprosis. Sensitivity analysis using only biochemistry confirmed AKI was also undertaken.

Results: Of 139,080 patients; 19,188 (13.8%) had AKI; 14,914 (10.7%) experienced a fracture. Median time to fracture following AKI was 4.2 [Interquartile range 2.3,6.6] years. Crude fracture incidence for the cohort was 27.9/1,000 patient-years (95% CI 27.5-28.3). Fracture incidence was higher in the AKI group (44.5, 95% CI 42.6-46.5) compared to the non-AKI group (26.6, 95% CI 26.2-27.1) (P<0.001). In unadjusted analysis AKI was significantly associated with a risk of fracture (HR 2.1, 95% CI 2.0-2.2,P<0.001), which persisted in multivariate analysis (HR 1.2, 95%CI 1.1-1.3,P<0.001). Sensitivity analysis showed similar estimates (univariate analysis HR 1.4, 95% CI 1.4-1.5, P<0.001 and multivariate analysis HR 1.1, 95%CI 1.0-1.2, P=0.007).

Conclusions: In a large cohort of patients representing an Australian local health district, AKI was found to be associated with an increased risk of fractures. This association should be further examined and verified in other patient cohorts.

FR-PO107

Assessment of Individualized Mean Perfusion Pressure Target for Cardiac Surgery-Associated AKI: PrevHemAKI Trial

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Background: Retrospective studies support that mean perfusion pressure (MPP) deficit in cardiac surgery patients is associated with a higher incidence of post-operative acute kidney injury. The aim of our study was to apply an algorithm based on MPP = mean arterial pressure (MAP)-central venous pressure (CVP) in the postoperative period of cardiac surgery patients to determine whether management with an individualized target compared to standard treatment reduces the incidence of acute kidney injury (CC-AKI).

Methods: Randomized controlled trial of patients undergoing cardiac surgery with extracorporeal circulation between October 2019 and September 2022. Inclusion criteria were: adults with valve replacement and/or bypass surgery intervention with Leicester score >30. Patients were randomized to follow target of MPP >75% baseline vs standard follow-up during the first 24h.

Results: 98 patients were recruited, 82.7% male with mean age 72.96 +- 7.25 years and eGFR of 55.3 +/-16.6 ml/min. 49 were randomized to the intervention arm and 49 to the standard treatment arm. Mean MAP during the intervention was higher in the intervention group (73.6/75.9 p=0.008), with no differences in mean MAP and MPP of the first 24h (75.5 vs 76.7, p=0.32 and 66.5 vs 67.5, p= 0.375 respectively) although a higher use of noradrenaline was found in the intervention arm (38.78 vs 63.27, p= 0.026). The percentage of time with MPP<75% baseline was similar in both groups (21.5/21.4%, p=0.811). Mean 24h fluid balance was similar (331 [-384-1206] vs 26 [-984-999], p=0.154). The incidence of CC-AKI was 36.7% (72.2% of them stage 1), with no differences between both groups but with a tendency to a higher incidence of AKI in the presence of PPM deficit of >20% (p=0.064).

Conclusions: There was a tendency to a higher incidence of AKI if MPP deficit >20% but individualized hemodynamic management based on MPP compared to standard treatment did not reduce the incidence of AKI associated to cardiac surgery in our study. Larger cohorts are needed in order to confirm these findings.

Funding: Private Foundation Support

FR-PO108

Real-World Evidence on the Impact of Incident AKI on Mortality, Healthcare Resource Utilization, and Costs Among Patients Undergoing Cardiac Surgery with Cardiopulmonary Bypass (CPB) from US Hospitals

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Background: AKI is among the most common complications in hospitalized patients, including 100,000 US cases per year in patients undergoing CPB. AKI is underdiagnosed and its severity is not routinely captured by ICD-10 codes. Therefore, we used serum creatinine (SCr) values (i.e., KDIGO criteria) to evaluate the true impact of AKI on mortality, healthcare resource utilization (HCRU), and costs among inpatients undergoing CPB.

Methods: Using an all-payer US hospital-based database, this retrospective cohort study included adult patients undergoing CPB with an index visit between January 2018 and December 2020. All-cause death, HCRU, and index hospitalization costs were described by AKI stage. Incident AKI and staging were defined by KDIGO criteria and/or an ICD-10 (or dialysis procedure) code at index. Propensity score matching was used to create matched cohorts to address differences in demographic and clinical characteristics between patients with severe AKI (stage 2/3) and no or mild AKI (stage 1). A comparison by presence vs absence of AKI by ICD-10 code was done as a reference.

Results: More severe AKI was associated with higher risk of death and greater HCRU (Table). Adjusted analysis indicated independent associations of severe AKI with 34.1x and 2.5x higher odds of death and 30-day readmission, mean LOS increase of 9.8 days, and mean increased costs of $58.4k compared to confirmed non-AKI or AKI stage 1. The impact of severe AKI was underestimated for ICD-10 AKI diagnosis vs. absent: 9.3x and 1.9x higher odds of death and 30-day readmission, mean LOS increase of 5.4 days, and mean increased costs of $25.5k.

Conclusions: Severe AKI in patients undergoing CPB is associated with significantly high mortality, HCRU, and cost compared to no or mild AKI. ICD-code based definition can underestimate the impact of AKI.

Funding: Commercial Support - Janssen Research & Development

Mortality, HCRU, and Costs by AKI stage

AKI Stage	Mortality at Index (%)	30-Day Readmission (%)	Index LOS (Mean Days)	Index Hospitalization Costs (Mean)
Confirmed non-AKI	0.4	8.9	8.9	$43,960
Stage 1	2.6	15.0	13.1	$63,486
Stage 2	13.3	22.0	20.8	$101,569
Stage 3 w/o dialysis	17.8	22.2	21.9	$104,465
Stage 3 w/ new dialysis	39.2	26.2	26.1	$166,222

FR-PO109

Renal Functional Reserve After AKI Predicts Adverse Outcomes at 180 Days

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Background: There is a lack of evidence to guide optimal post-acute kidney injury (AKI) care. Renal functional reserve (RFR) measures the capacity of the kidney to increase glomerular filtration rate (GFR) under various physiologic stresses and is potentially a marker to predict the susceptibility to injury and refine the recovery of kidney function. We aim to examine the association between post-AKI RFR and major adverse kidney events at 180 days after hospital discharge ($MAKE_{180}$) including death, new kidney replacement therapy, and persistent renal dysfunction.

Methods: We enrolled patients with baseline eGFR of >60 mL/min/1.73 m^2 who survived from moderate to severe AKI with eGFR of >30 mL/min/1.73 m^2 at hospital discharge between November 2021 to March 2023. RFR was measured by using intravenous amino acid infusion at 1 and 3 months after discharge. Primary end point is the predictive performance of post-AKI RFR for $MAKE_{180}$. Secondary end points include the performance of RFR to predict recurrent AKI and incident chronic kidney disease (CKD) within 6 months.

Results: Among 56 AKI survivors enrolled, median RFR at 1 and 3 months after AKI are significant lower in those who developed $MAKE_{180}$ compared with those who did not (0.86 (4.6-10.6) vs 13.48 (8.6-21.8) mL/min/1.73 m^2, p=0.002 and -0.69 (-4.67-3.5) vs 17.57 (10.83-38.1) mL/min/1.73 m^2, p=<0.001, respectively). Patients with $MAKE_{180}$ had RFR declination (negative difference RFR), in contrast, those without $MAKE_{180}$ had RFR improvement over 3 months (-4.39 (-7.42-0.64) vs 14.34 (9.7-22.14) mL/min/1.73 m^2, p=<0.001). The RFR at 1 and 3 months could predict $MAKE_{180}$ with an AUC of 0.77 (95% CI, 0.62-0.93) with the cut-off value of 8.3 mL/min/1.73 m^2 (sensitivity 76%, specificity 74%) and AUC of 0.91 (95% CI, 0.81-1) with the cut-off value of 8.6 mL/min/1.73 m^2 (sensitivity 93%, specificity 83%), respectively. Those who developed incident CKD and recurrent AKI had a significantly lower post-AKI RFR at 1 and 3 months and predicted incident CKD and recurrent AKI with good AUC.

Conclusions: Post-AKI RFR is highly predictive of poor kidney outcomes at 6 months. Larger prospective studies are warranted to explore the association between a reduced RFR and poor outcomes in post-AKI survivors.

Funding: Government Support - Non-U.S.

FR-PO110

The Incidence, Aetiology, and Short-Term Outcomes of AKI in Adults

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Background: Acute Kidney Injury (AKI) is a common clinical syndrome in hospitalized patients associated with an increased risk of poor prognosis and mortality. We aimed to identify the incidence, aetiology, and short-term outcomes of adults with AKI on presentation to the hospital.

Methods: Data were prospectively collected over a two-month period. The patients were followed till the time of discharge from the hospital. Patients admitted over two months were investigated, and those with AKI as defined by the Kidney Disease: Improving Global Outcomes (KDIGO) criteria) were identified at the time of admission. Patients with known End Stage Renal Disease (ESRD) on dialysis, renal transplant, Paediatric, and Gynaecology admissions were excluded. Data was collected from the admission records in the emergency department, medical notes, laboratory system and discharge summaries.

Results: There were a total of 2847 patients admitted over the study period, and 2397 were reviewed. The incidence of AKI was 5.92% (n=142). In the AKI population, 54.22% were males and 45.77% were females. The mean±standard deviation(SD) age was 74.6±14.7 years. Chronic kidney disease was present in 53.52%. The mean±SD creatinine at baseline (pre-admission) was 106±47.1umol/L(1.2±0.53mg/dL), at presentation 190±91.1umol/L (2.15±1.44mg/dL), and 127±67.2umol/L(1.44±0.76mg/dL) on discharge. The most common aetiology of AKI was a decrease in effective circulating volume (prerenal)(78.17%) secondary to primarily sepsis (44.36%), decompensated heart failure(4.96%), acute coronary syndrome(6.34%), stroke or seizure(7.4%), gastrointestinal bleed(4.22%) and diabetic ketoacidosis (3.52%). Obstructive nephropathy was present in 9.15%. Polypharmacy contributing to AKI was present in 61.97%. The median length of stay was 8 days (inter-quartile range 5 to 13 days). Renal replacement was required in 13.38%, and 11.27% were admitted to the intensive care unit. On discharge from the hospital, complete renal recovery was seen in 57.75%, residual renal impairment in 22.54% and dialysis dependence in 5.63%. The all-cause mortality was 6.34%.

Conclusions: The incidence of AKI was 5.92% in the study population. Sepsis was a common aetiology. A large proportion of patients had residual renal impairment on discharge, indicating high morbidity with AKI.

FR-PO111

Clinical Characteristics and Outcomes in AKI in Non-Critically Ill Patients

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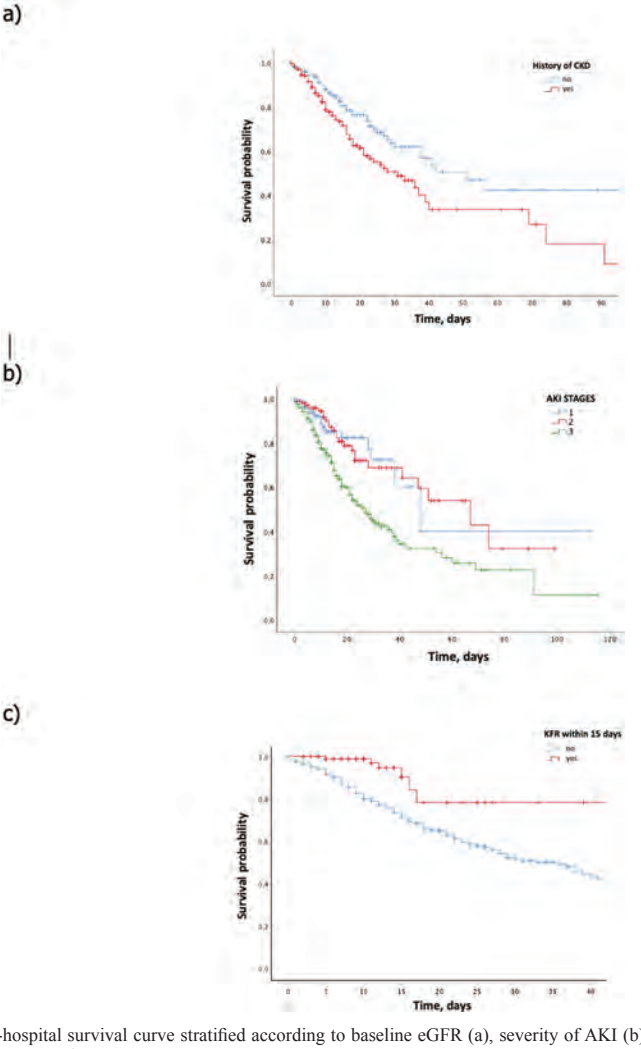
Background: Although many studies have been focused on critically ill patients in ICUs, AKI occurs even in non-critical care settings. Epidemiological data of AKI outside the ICU are not well investigated. We aim to describe main features and outcomes of AKI in non-critically ill patients in our teaching hospital.

Methods: We performed a retrospective analysis including AKI patients referred to nephrology consultation in a 6-month period at AOU Policlinico, Bari, Italy. We analyzed the main features of AKI episodes, including AKI stages, the need for dialysis, mortality rate and factors associated to kidney function recovery (KFR).

Results: Among 899 patients referred for nephrologists, 415 (46%) were evaluated for AKI. 52.5% of AKI episodes were classified as KDIGO Stage 3, and 54 patients (13%) required RRT. In-hospital mortality was 36.9%, higher in patients with pre-existing CKD, in patients with stage 3 AKI and among those who did not present KRF. Cox analysis showed a higher mortality risk for older age (HR 1.032, 95%CI 1.012–1.053, p=0.002) and pre-renal AKI (HR 2.823, 95%CI 1.219-6.536, p=0.015), while KFR was associated to lower mortality (HR 0.246, 95%CI 0.098-0.615, p=0.003). KFR was observed in 197 patients (47.5%) mainly in patients with mild AKI (stage 1 62.6% vs stage 2 57.6% vs stage 3 36.8%, p<0.001). Higher baseline eGFR (OR 1.025, 95%CI 1.014-1.036, p<0.001) was associated with KFR. Severe AKI was independently associated with lower probability of KFR (OR 0.420, 95%CI 0.248-0.711, p=0.001).

Conclusions: AKI episodes outside the ICU are severe and associated with a high mortality rate even outside the ICU. A timely nephrologist consultation is important to limit AKI severity.



In-hospital survival curve stratified according to baseline eGFR (a), severity of AKI (b) and kidney function recovery (c)

FR-PO112

Development and Feasibility of a Remote Patient Monitoring Program for AKI Survivors

Mariam Charkviani, Andrea G. Kattah, Jennifer A. Ferguson, Kianoush Kashani, Kristin C. Mara, Heather P. May, Lindsey M. Philpot, Swetha Reddy, Jordan K. Rosedahl, Andrew D. Rule, Erin F. Barreto. *Mayo Clinic Minnesota, Rochester, MN.*

Background: One-third of acute kidney injury (AKI) survivors lack appropriate follow-up after hospital discharge. Remote patient monitoring (RPM) may improve post-discharge care quality. We report an AKI RPM program's development and preliminary feasibility.

Methods: Mayo Clinic launched an AKI RPM program in October 2021 for individuals who experienced AKI with a nephrology consultation during a hospitalization. Once enrolled, patients were discharged with RPM technology (e.g., blood pressure cuff, scale), and vital signs and symptoms were monitored daily. In-center laboratory assessments were scheduled weekly. RPM nurses evaluated the data daily and adhered to prespecified protocols for alerts and care escalation management. Patients were followed for up to three months. Individuals graduated from the AKI RPM program if they remained dialysis independent, with a stable creatinine for 2 consecutive weeks, and no urgent or emergent results in the prior week. Feasibility was defined as the proportion of enrolled patients who submitted at least one set of vitals or symptom data after program initiation.

Results: Of the 50 people approached, 41 (82.0%) were enrolled in RPM. The median (IQR) baseline eGFR was 37 (28, 60) mL/min/1.73m^{2,} and 83% experienced stage 3 AKI. The length of time in the program was 31 (28, 38) days. Eight (20%) patients were lost to follow-up or withdrew. Thirty (73%) individuals had at least 1 RPM alert, most for weight gain or edema. Six emergency department referrals were made for AKI RPM patients. Among the 33 patients who graduated from the AKI RPM program, 25 (76.0%) were referred to nephrology for evidence of chronic kidney disease. 17 (68%) of those individuals completed a nephrology visit within 90 days of program graduation.

Conclusions: The AKI RPM workflow was feasible and addressed a vital gap for AKI care after discharge. Digital health solutions such as RPM offer a unique opportunity to bridge the care transition from hospital to home, increase access to quality care for the most vulnerable AKI survivors, and direct the attention of nephrologists to patients most likely to benefit from specialty consultation.

FR-PO113

A Self-Funded, Value-Based, Post-AKI Care Program: Predicted vs. Observed Outcomes

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Background: Readmissions occur in 20% patients with Acute Kidney Injury (AKI), adding $20000 in healthcare costs. While post-AKI care improves outcomes, studies are limited to non-dialysis referred patients. As one of the earliest post-AKI clinics, we set up a self-sustaining multi-disciplinary post-AKI care program.

Methods: Target population/interventions were finalized by interviewing nephrologists, patients and AKI!Now Workgroup. Since May 2022, hospitalized adults with high-risk stage 2/3 AKI at Geisinger Medical Center were identified in real-time. Those eligible were provided inpatient AKI education, nurse coordinator services, flexible scheduling, non-face-to-face care and expedited nephrology visits. Follow-up was up to 90 days post-discharge. Observed vs Predicted (Grampian-Aberdeen model) 90-day rehospitalization/mortality risk were compared.

Results: On screening 1198 patients, 303 were eligible; 195 (64.4%, 5% on dialysis) were enrolled (Fig 1) and 154 have completed 90 days. More than 95% received direct or non-face-to-face nephrology care. Fig 2 shows predicted vs observed outcomes: 90-day rehospitalization/mortality was 30.2% vs a mean risk of 45.8%. Graphical pattern suggests steady benefit lending itself to a Difference-in-Difference estimation.

Conclusions: We developed a value-based comprehensive post-AKI care model showing improvement over predicted outcomes. Our approach allows quasi-experimental analysis and could be widely applicable.

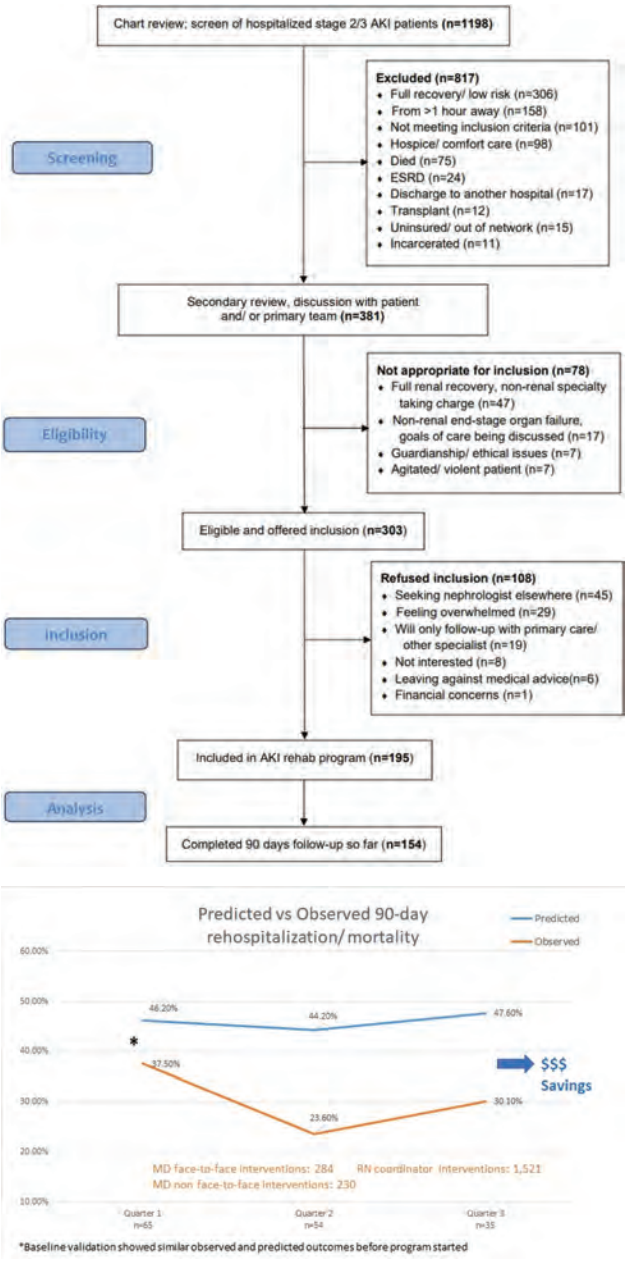

Figure 2

FR-PO114

An Exploratory Needs Assessment for AKI Patient Education: Results from a Focus Group

Daniel P. Murphy,[1] Patricia F. Kao,[2] Rajit K. Basu,[3] Andrew J. Lewington,[4] Marla Levy,[5] Linda Awdishu,[6] Jorge Cerda,[7] Kathleen D. Liu,[8] Marlies Ostermann,[9] Ashita J. Tolwani,[10] Bonnie L. Freshly,[5] Michael Heung.[11] ASN AKINow Education Workgroup. *[1]University of Minnesota Twin Cities, Minneapolis, MN; [2]Washington University in St Louis, St Louis, MO; [3]Ann and Robert H Lurie Children's Hospital of Chicago, Chicago, IL; [4]Leeds Teaching Hospitals NHS Trust, Leeds, United Kingdom; [5]American Society of Nephrology, Washington, DC; [6]University of California San Diego Skaggs School of Pharmacy and Pharmaceutical Sciences, La Jolla, CA; [7]Albany Medical College, Albany, NY; [8]University of California San Francisco School of Medicine, San Francisco, CA; [9]Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom; [10]The University of Alabama at Birmingham Department of Medicine, Birmingham, AL; [11]University of Michigan, Ann Arbor, MI.*

Background: Literature on the type, content, and effectiveness of patient education regarding acute kidney injury (AKI) is scarce. The American Society of Nephrology AKINow Education Workgroup conducted a focus group of relevant stakeholders with

AKI experience to discern major themes in the educational needs, level of resources, and opportunities in the realm of AKI-education.

Methods: The focus group was held virtually in May 2023 with participants recruited from the United States and United Kingdom. Participants included patients, physicians, nurses, pharmacists, and social workers and were divided into four breakout sessions to discuss for 40 minutes one topic each: (1) AKI-related education in the hospital and at discharge; (2) long-term education needs based on degree of AKI-recovery; (3) education in the outpatient dialysis unit regarding dialysis-requiring AKI; or (4) counseling patients at risk for AKI.

Results: Focus group participants included 7 patients, 15 nephrologists, 2 primary care physicians, 1 intensivist, 3 nurses, 6 pharmacists, and 2 social workers. Several common themes emerged, including: general lack of knowledge among the public regarding "what kidneys do;" uncertainty of what questions patients would be well-served by asking; and a desire for improved and/or more frequent communication to patients and amongst their medical team regarding updated, germane AKI-related information. Additional major themes from session 1 included: key signs/symptoms to monitor for, and clear directions to navigate clinical changes in a patient's AKI course. Major themes from session 2 included: recommended steps to improve or protect health after AKI, including medications and diet. Major themes from session 3 included: inconsistency in provider messaging around the evolving assessment of AKI-recovery vs. end-stage kidney disease. Major themes from session 4 included: the need for multimodal patient education (e.g., written and multimedia resources) in addition to education from trusted providers.

Conclusions: There is an urgent need to improve education for patients with AKI through all phases of the AKI experience and to co-produce these resources with patients.

FR-PO115

Feasibility of a Randomized Pilot Trial of a Multidisciplinary AKI Survivor Program in Primary Care

Heather P. May, Joan M. Griffin, Joseph Herges, Kianoush Kashani, Andrea G. Kattah, Rozalina G. McCoy, Andrew D. Rule, Angeliki G. Tinaglia, Erin F. Barreto. For the ACT Study Group. *Mayo Clinic Minnesota, Rochester, MN.*

Background: AKI survivor care delivery in nephrology specialty clinics has been limited by poor recruitment. The AKI in Care Transitions (ACT) Program was designed to address this barrier by facilitating kidney health follow-up within primary care. This study aimed to describe the recruitment and retention of patients in a clinical trial on the feasibility of ACT compared to usual care.

Methods: The study included adults with stage 3 AKI during hospitalization from 2022-2023 at Mayo Clinic in Rochester, MN, who were expected to discharge to home in the local area, not on dialysis. Consenting individuals were randomized 1:1 to ACT or usual care. Patients in the ACT group received education before discharge and coordination of post-discharge laboratory and clinician (primary care physician [PCP], pharmacist) follow-up in primary care within 14 days. The Usual Care group received no study-specific intervention. The percentage of AKI survivors screened, approached, and who provided consent was reported. Reasons for declining participation were recorded if volunteered. We described the proportion of patients in the ACT group in which pre-discharge education was completed and post-hospital laboratory and clinician follow-up orders were placed.

Results: An electronic health record alert identified 549 potential candidates. There were 429 exclusions based on pre-specified study criteria and 106 individuals were approached for participation. Forty-five (42%) consented to participate and were enrolled. Among 14 patients who declined with a reason, concerns about time commitment and feeling overwhelmed predominated. Of 23 ACT patients, 22 completed education, and 21 had orders placed for post-discharge follow-up. One patient withdrew from the ACT group due to feeling overwhelmed.

Conclusions: These data demonstrate the ability to recruit AKI survivors into a care transitions program within primary care. While ACT recruitment appeared more successful than in other controlled trials of nephrologist follow-up, feeling overwhelmed remained an important barrier to participation. AKI survivor interventions should be simplified where possible to limit treatment burden.

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FR-PO116

Revolutionizing AKI and Critical Care Nephrology Education: Evaluating ChatGPT's Accuracy on Core Questions

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Background: ChatGPT is a state-of-the-art language model with exceptional proficiency in various natural language processing tasks, including generating responses that closely mimic human-generated ones. While there is growing speculation about ChatGPT's potential to serve as a substitute for physicians in clinical settings, its proficiency in nephrology, including acute kidney injury and critical care nephrology, remains uncertain. This study aims to evaluate the performance of ChatGPT in answering core questions related to acute kidney injury and critical care nephrology.

Methods: The accuracy of ChatGPT was evaluated in answering questions related to acute kidney injury and critical care nephrology using the Nephrology Self-Assessment Program (NephSAP) and Kidney Self-Assessment Program of the American Society of Nephrology (KSAP). Questions containing images were excluded from the assessment due to current limitations in ChatGPT's image processing capabilities. One hundred ten questions were included in the evaluation, 45 from NephSAP and 55 from KSAP. Each question bank was executed twice using ChatGPT. The level of concordance between the initial and subsequent runs, which were conducted two weeks apart, was also examined.

Results: In the case of NephSAP questions, ChatGPT achieved accuracies of 55% and 69% on the initial and subsequent runs, respectively. For KSAP questions, it achieved accuracies of 46% and 40%, respectively. ChatGPT's accuracy on all 110 questions combined was 52% and 51% for the initial and subsequent runs. The overall concordance between the initial and subsequent runs was 78%, with 86 questions (78%) receiving the same response and 24 (22%) receiving different responses. Correct concordance was 57%, and incorrect concordance was 43%. Among the 24 questions with divergent responses, ChatGPT rectified 11 incorrect responses to become correct. Conversely, it changed its response from correct to incorrect in 5 out of 24 questions.

Conclusions: Our study shows that ChatGPT only responded correctly to half of the questions related to acute kidney injury and critical care nephrology with low reliability. Therefore, ChatGPT as an educational tool may not be precise or reliable, and further development may be necessary to improve its performance.

FR-PO117

Epidemiology and Outcome of Community- and Hospital-Acquired AKI in a Developing Country

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Background: Acute Kidney Injury (AKI) is associated with adverse short-term and long-term outcomes in hospitalized patients. In developing countries, including India, Community acquired AKI (CAAKI) is more common than hospital acquired AKI (HAAKI) and the pattern varies with different geographical areas. This single-centre study aimed to assess the clinical spectrum, risk factors for in-patient mortality and renal outcome of patients with CAAKI compared to HAAKI.

Methods: In this prospective observational cohort study conducted in a tertiary care hospital in India, hospitalized patients with AKI were enrolled and followed-up for upto 12 months after discharge. Patients with renal dysfunction at admission or worsening renal dysfunction in the first 48 hrs of hospitalization were classified as having CAAKI while patients with renal dysfunction after 48 hours of hospitalization were classified as HAAKI. Outcome variables were in-hospital all-cause mortality, renal function (by creatinine) at discharge and on long-term.

Results: A total of 476 AKI patients were enrolled in this study; 395 (83%) were CAAKI. The mean age was 44.8±18.7 years. Sepsis (176/476; 36.9%) was the most common cause of AKI. The in-hospital mortality was 38%. The peak serum urea and creatinine was higher in patients with CAAKI than HAAKI. The need for ventilator (34.9% vs 67.9%), inotropic support (38% vs 73%) and in-hospital mortality (31% vs 73%) was more in HAAKI. Patients with HAAKI had significantly higher mortality (72% vs 31%). Age >60 yrs (HR=1.51; 95% CI,1.11–2.07), oliguria (HR=1.48; 1.05–2.10), need for ventilator (HR=2.45; 1.36–4.41) and/or inotropes (HR = 14.4; 6.28–33.05) were predictors of in-hospital mortality. Of the 295 patients discharged, 146 (30.7%) had complete renal recovery, while 149 (31.3%) had partial renal recovery. Of the 295 patients on follow-up, 211 (71.5%) patients had normal renal function, 4 (1.4%) died and 41(14%) developed CKD while 6 (2%) were dialysis dependent. All patients having CKD on follow-up were patients of CAAKI group.

Conclusions: Present cohort study with long follow-up showed that there is a definite risk of CKD in recovered patients and they should be monitored periodically. AKI in hspitalized patients still has high mortality especially in patients with HAAKI.

FR-PO118

AKI in the Surgical Ward: A Single-Center Study

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Background: Acute Kidney Injury (AKI) is a non-uncommon condition with unknown incidence, mostly it take place in hospitalized patients and it is often under recognized. AKI significantly affects short and long-term morbidity and mortality.

Methods: A retrospective single center cohort study was performed, using the electronic medical records (EMR) of the hospital. AKI was defined as an increase of serum creatinine level of at least of 0.5 mg/dl from the previous test. We identified patients with AKI during the period January 1st –December 31, 2019, hospitalized in our hospital in the non-cardiac surgical clinics during this period. Chronic dialysis patients were excluded from the analysis.

Results: The final analysis included 203 patients hospitalized in Surgical Wards. Median age of patients was 75 (20-97), while 62% were men, almost 50% were diabetics, showing a mean Charlson score of 6. Almost 50% had CKD before the hospitalization with a median eGFR 61 ml/min. Seventy seven percent of patients were operated during the hospitalization. Most (66%) of operations were non elective. In 9% cases renal replacement therapy (RRT) was performed. All of them underwent non-elective operations. Patients needing RRT were younger, with lower hemoglobin, more frequent use of nephrotoxic antibiotics, received intravascular contrast, were mechanically ventilated and hypotensive, with sepsis. All-cause 90-day mortality was 33%. All-cause 90-day mortality was higher in cases of non-elective operations, in patients with hemoglobin level less than 8 mg/dl, higher American Society of Anaesthesiologists score, and hypotension during the hospitalization. Mortality rate was lower in diabetic patients (p=0.009). Management of AKI: only 47% of patients had urinalysis, renal imaging was done in 15%, monitoring of urine output was performed in 76%. Only in one third of cases there was any addressing to AKI in the EMR, and only in 43% of AKI was a main diagnosis at discharge.

Conclusions: It seems that non-diabetic, severely anemic (hemoglobin less than 8 mg/dl) patients with high ASA Score are at higher risk to AKI. More efforts should be done to recognize high risk patients with aim to prevent AKI, and improve renal failure management in the surgical departments.

FR-PO119

Intensive Care Unit Improves Dialysis Care Quality While Reducing Costs

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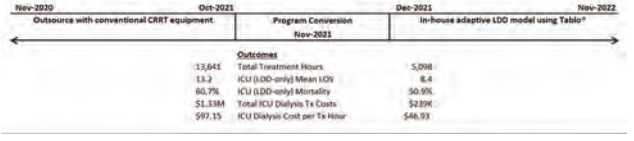
Background: In November 2021, a medium-size hospital ICU in Michigan initiated a quality improvement dialysis program, converting their outsourced continuous renal replacement therapy (CRRT-only) to an in-house adaptive long-duration dialysis (LDD) model, using the Tablo® Hemodialysis System (Tablo) to provide treatments >6 hours, as medically necessary. This conversion was done with the goals of (1) improving quality of care for ICU patients requiring LDD, and (2) reducing both dialysis-related nursing staff burden and dialysis treatment costs. We compared patient characteristics and treatments performed in the one year before and one year after the in-house LDD program launch.

Methods: We evaluated ICU stays requiring LDD in the one year before and after the month of the dialysis quality improvement program launch. EHR data were reviewed. compiled and analyzed by ICU staff, using MS Excel. Data include, demographics, select clinical diagnoses including kidney disease, heart failure, sepsis, and COVID. The results are presented as descriptively only. No cohort adjustments or statistical significance tests were performed.

Results: There were 145 ICU stays with 13,641 hours of CRRT among 145 pts before, and 116 ICU stays with 5,098 hours of LDD among 116 pts in the year after program launch. Mean dialysis treatment hours per patient were reduced from 93.7 to 43.1, increasing ICU nurse productivity by 50.6 hours per patient. Similar dialysis treatment time savings occurred in both COVID and no-COVID subsets. Concurrently, mean ICU length of stay for these patients declined by 4.8 days between the pre and post periods, from 13.2 to 8.4 days, respectively. Mortality declined between the periods, from 60.7% to 50.9% overall, and declining in both COVID and no-COVID subsets. Total dialysis treatment costs were reduced from $1.33M to $239k, and costs per treatment hour declined 52% from $97.15 to $46.93, in the pre and post periods, respectively.

Conclusions: Converting from an outsourced CRRT-only program to an in-house adaptive long-duration dialysis program, a medium-size hospital ICU in Michigan improved dialysis care quality and patient outcomes, while reducing costs and increasing nurse productivity.



FR-PO120

Initial Outpatient Dialysis Orders in AKI-D vs. ESKD

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Background: Many hospitalized patients with dialysis-requiring acute kidney (AKI-D) do not fully recover renal function and are discharged to continue hemodialysis at dialysis centers oriented toward treating patients with end-stage kidney disease (ESKD). Little is known about dialysis practice patterns in this population.

Methods: We examined initial outpatient dialysis orders for 1,754 AKI-D patients initiating in-center hemodialysis between 7/1/2017 and 6/30/2022 across 67 dialysis centers operated by a medium-sized, not-for-profit dialysis provider. For comparison, 6,197 contemporary patients initiating in-center hemodialysis for ESKD were identified.

Results: Patients initiating outpatient dialysis for AKI-D and ESKD had similar demographics (mean age, 63 in AKI-D vs 64 in ESKD; 60% male in both groups) and body mass indices (mean, 29 kg/m^2 in both groups). However, mean pre-dialysis serum creatinine, interdialytic weight gain and pre-dialysis systolic blood pressure, were lower in the AKI-D group (5.3 versus 5.9 mg/dL, 0.9 versus 1.1 kg, and 135 versus 144 mmHg, respectively). Despite these differences, initial dialysis orders were similar. The initially prescribed hemodialysis frequency was 3x/week dialysis for 94% of AKI-D patients and 95% of ESKD patients. Hemodialysis session duration, dialysate sodium, and dialysate temperature were also similar.

Conclusions: Despite dissimilar medical profiles at hemodialysis initiation in the outpatient setting, initial hemodialysis orders for AKI-D and ESKD are largely the same. Greater individualization of dialysis orders may improve patient care.

Funding: NIDDK Support, Commercial Support - Satellite Healthcare, Inc, not-for-profit dialysis provider

Initial outpatient dialysis prescriptions in AKI-D and ESKD

	Incident AKI-D	Incident ESKD
Sample size (N)	1,754	6,197
Treatment frequency 3 treatments/week	94%	95%
Session duration ≥4.0 hours	20%	23%
3.5-3.9 hours	35%	37%
<3.5 hours	45%	40%
Dialysate sodium ≥140 mEq/L	9%	8%
138-139 mEq/L	52%	49%
136-137 mEq/L	30%	30%
<136 mEq/L	9%	13%
Dialysate potassium 3 mEq/L	70%	63%
2 mEq/L	29%	37%
Other	<1%	<1%
Dialysate temperature Celsius, mean (SD)	36.8 (0.5)	36.8 (0.4)

FR-PO121

Impact of Using Blood Warmer During Continuous Kidney Replacement Therapy on Hemodynamic Instability

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Background: Continuous kidney replacement therapy (CKRT) can lead to heat loss in the extracorporeal circulation. Hypothermia may have detrimental effects; however, rewarming of blood may alter vascular reactivity and induce hypotension.

Methods: We screened patients with acute kidney injury (AKI) who required CKRT between 1/1/2012 and 1/1/2021 and were admitted at a tertiary academic hospital. Intradialytic hypotension (IDH) was defined as mean arterial pressure (MAP) ≤ 60 millimetermercury (mmHg) or a decrease in MAP by ≧ 10 mmHg, systolic blood pressure (SBP) less than or equal to 90 mmHg or a decrease in SBP by ≧ 20 mmHg, or increased vasopressor requirement. These were measured in 15-minute increments and the number of episodes in each hour was recorded. The number of events was analyzed by Poisson regression with repeated-measures analysis of variance using the generalized estimation equation.

Results: There were 669 patients with AKI who required CKRT during the study period. Use of blood warmer on first day of CKRT was in 324 (48%) patients. Patients where a blood warmer was used were more likely to have required vasopressor or inotropes (56% vs 45%, p =0.003), be diagnosed with sepsis/septic shock (81% vs 74%, p=0.04), and were in a less positive fluid balance at the time of CKRT initiation (1.0 vs 1.3 L, p=0.03) compared to patients where a blood warmer was not used. The incident rate ratio for IDH during the first 24 hours of CKRT in patients where a blood warmer was used was 1.06 (95%CI 0.98; 1.13) compared to those where blood warmer was not used. After adjusting for variables that were different between the two groups and clinically relevant ones (norepinephrine equivalents, mechanical ventilation and MAP at time of CRRT initiation and ultrafiltration on CRRT day1), using a blood warmer did not increase IDH episodes. Overall, the within-subject effect of temperature on IDH on first day of CRRT was negative, meaning that higher temperature was associated with fewer IDH (relative risk of 0.94, 95% CI 0.9; 0.99 for each 10 degrees increase, p 0.007).

Conclusions: Blood warming techniques during CKRT were not associated with worsening hemodynamic instability during first day of CKRT.

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FR-PO122

Impact of Ultrafiltration Rate Among Adults with AKI Treated with Continuous Renal Replacement Therapy (CRRT)

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Background: Observational data supports the view that fluid removal with dialysis in critical illness confers survival benefit. The optimal fluid removal rate is unknown with some suggesting that ultrafiltration rate (UFR) greater than 1.75 mL/kg/hr may be harmful.

Methods: We conducted a single-center retrospective cohort study among adult AKI patients admitted to the intensive care unit (ICU) at University of Chicago treated with CRRT from April 1, 2016 to March 31, 2020. We collected information regarding patient demographics, severity of illness, daily fluid balance (all intakes minus outputs, inclusive of RRT), RRT ultrafiltration, and outcomes (length of stay, dialysis dependence, and mortality). We calculated UFR restricted to the first 72 hours of dialysis treatment as net ultrafiltrate (mL) per hour treatment duration adjusted for patient's baseline body weight.

Results: 742 patients had low UFR (≤1.01 mL/kg/hr), 269 had moderate UFR (between 1.01 and 1.75 mL/kg/hr), and 167 had high UFR (≥1.75 mL/kg/hr). Those with low UFR were older, had higher baseline body weight, and had less positive fluid balance in the 72 hours prior to starting dialysis. Severity of illness (SOFA) and burden of co-morbidities were not significantly different across UFR groups. Those with low UFR had a median cumulative fluid balance of 2.38 L over 72 hours, lower likelihood to remain dependent on dialysis at 90-days, and highest 90-day mortality (Table 1).

In an adjusted Cox proportional hazards model, low UFR was associated with an increased risk of 90-day mortality (HR 1.88, 95% CI 1.10-3.21 p=0.02) whereas high UFR was not significantly associated with 90-day mortality (HR 0.66, 95% CI 0.31-1.42, p=0.29).

Conclusions: Low UFR is associated with increased 90-day mortality while high UFR was not associated with 90-day mortality. Future studies should investigate the ideal UFR to improve patient outcomes.

Funding: Commercial Support - Fresenius Medical Care

Outcomes By 72 Hour Net Ultrafiltration Rate

	Low NUF <1.01 ml/kg/hr	Moderate NUF 1.01-1.75 ml/kg/hr	High NUF >1.75 ml/kg/hr	p-value
N	742	269	167	
72H Fluid Balance (L), med (IQR)	2.38 (-0.02, 5.97)	-0.62 (-3.33, 2.37)	-3.25 (-5.38, -0.35)	<0.001
72H UFR (mL/kg/hr), med (IQR)	0.39 (0.07, 0.71)	1.29 (1.14, 1.47)	2.27 (1.93, 2.76)	<0.001
ICU Days, med (IQR)	8 (3, 19)	12 (6, 24)	13 (5, 25)	<0.001
Hospital Days, med (IQR)	14 (5, 27)	19 (9, 33)	19 (9, 31)	<0.001
RRT at Day 90 (%) Survivors, N=403	31 (14.3)	13 (12.1)	16 (20.3)	0.016
90-Day Mortality (%)	525 (70.8)	162 (60.2)	88 (52.7)	<0.001

FR-PO123

Impact of Positive Fluid Balance and Timing of Renal Replacement Therapy in AKI in a Real-Life Scenario

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Background: Objective: To determine if a fluid overload of less than 10% of body weight and early initiation (<12 hours) of RRT behave as an independent prognostic factor for mortality in patients with AKI KDIGO 3 in the ICU.

Methods: Retrospective cohort study that included patients hospitalized in the ICU of a hospital in Medellín-Colombia with a diagnosis of AKI KDIGO 3 and need for RRT.

Results: 278 patients with a median age of 63 years, 58.6% (163) men and 60.4% (168) diagnosed with sepsis were included. 166 (59.7%) were classified as early RRT and 112 (40.3%) as late RRT. The cumulative fluid balance was 9565 ml and 7496 ml, respectively. Mortality was 69% (192), with no significant differences according to the time of RRT (67 vs. 71%). There were no statistically significant differences between the early and late therapy group (OR adjusted 1.34, 0.65-2.75); nor in those with a percentage of accumulated fluid balance greater than 10% of body weight (OR adjusted 1.27; CI 0.73-2.23).

Conclusions: Early initiation of RRT, less than 12 hours from diagnosis, and with an accumulated fluid balance of less than 10% of body weight, did not have a lower risk of in-hospital mortality in patients with AKI KDIGO 3 in the ICU.

Variable	OR crude	OR adjusted
Early RRT	1.07 (0.56-2.06)	1.34 (0.65-2.75)
Fluid Balance >10% of body weight at RRT	1.49 (0.88-2.52)	1.27 (0.73-2.23)
Age	1.01 (0.99-1.03)	1.03 (1.01-1.05)
Charlson Index	0.90 (0.81-1.00)	0.82 (0.71-0.95)
Modality of RRT: HDFVVC	1.28 (0.92-1.79)	1.21 (0.81-1.79)
Sepsis	1.19 (0.72-1.99)	1.02 (0.56-1.85)
SOFA	1.07 (1.00-1.14)	1.02 (0.95-1.11)
APACHE II	1.01 (0.98-1.04)	1.01 (0.98-1.05)

Table 1. Baseline characteristics of the patients in the Cohort

	Total (*n*=278)	Early RRT (n=166)	Late RRT (*n*=112)
Age (Median, IQR)	63 (54-72)	62 (53-71)	64 (57-74)
Sex, %			
Male	163 (58.63)	99 (60)	64 (57)
Female	115 (41.37)	67 (40)	48 (43)
Baseline Creatinine[a] (mg/dl)	1.02 (0.78-1.54)	1.09 (0.79-1.58)	0.96 (0.74-1.52)
Baseline eGFR[a,b] (ml/min)	72.7 (43-97)	70 (38-98)	82 (43-94)
Comorbidities, %			
Hypertension	161 (57.91)	99 (60)	48 (43)
Diabetes	83 (29.86)	46 (27)	37 (33)
CKD	47 (16.91)	21 (13)	26 (23)
Heart Failure	45 (16.19)	27 (16)	18 (16)
Ischemic disease	32 (11.51)	17 (10)	15 (13)
COPD	53 (19.06)	29 (17)	24 (21)
Charlson Index [a]	3 (1-5)	2 (1-4)	3 (2-5)
Sepsis Diagnosis [c], %	168 (60.43)	109 (65)	60 (54)
Severity on admission to the ICU[a]			
SOFA	12 (9-14)	13 (10-14)	11 (7-14)
APACHE II	16.5 (10-24)	15 (7-23)	20 (12-25)
Cause of admission to ICU, %			
Medical	193 (69.42)	119 (72)	74 (66)
surgical	63 (22.66)	37 (22)	26 (23)
Post cardiac surgery	18 (6.47)	7 (4)	11 (10)
Trauma	4 (1.44)	3 (2)	1 (0.9)
Vasopressor requirement, %	240 (86.33)	152 (92)	88 (79)
Mechanical ventilation (days)[a]	10 (3-15)	10 (4-18)	7 (2-15)
Creatinine at diagnosis [a] (mg/dl)	3.55 (2.42-4.78)	3.3 (2.3-4.6)	3.9 (2.8-4.9)
Urinary output at diagnosis [a] (ml/kg/hour)	0.19 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.3)
Cause of AKI, %			
Pre-renal	229 (82.37)	143 (86)	86 (77)
Intrinsic	49 (17.63)	23 (14)	26 (23)
Modality of RRT, %			
IHD (Intermittent hemodialysis)	59 (21.22)	41 (25)	18 (16)
SLED or PIKRT	110 (39.57)	36 (22)	74 (66)
HDFVVC	109 (39.21)	89 (54)	20 (18)
Time since KDIGO 3[a] (hours)	6.6 (3.8-10.8)	8.4 (6.6-9.9)	15.7 (13.9-23.2)
Fluid balance at RRT (ml)	8620 (4600-17000)	9565 (5000-17900)	7496 (4061-15462)
Hospital mortality, %	192 (69.06)	112 (67)	80 (71)

FR-PO124

Volume Control Strategy and Patient and Kidney Survival in Sepsis-Associated AKI Receiving Continuous Kidney Replacement Therapy: A Randomized Controlled Trial

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Background: Volume overload in patients with sepsis-associated acute kidney injury (AKI) requiring continuous kidney replacement therapy (CKRT) is associated with an increased risk of mortality. However, the optimal strategy for volume control and the clinical implication of achieved volume control in these patients is uncertain.

Methods: We randomly assigned patients with sepsis-associated AKI receiving CKRT accompanying volume overload with either conventional volume control strategy or bioelectrical impedance analysis (BIA)-guided volume control strategy for 3 days. The outcomes of interest were patient survival at 28 and 90 days. A *post-hoc* analysis was performed to compare patient survival according to achieved volume accumulation rate ([cumulative fluid balance during 3 days×100]/fluid overload) using multivariate Cox regression model.

Results: Of the 73 patients, 39 were randomly assigned to conventional volume control strategy, and 34 to BIA-guided volume control strategy. At 28 days after randomization, 20 (51.3%) deaths had occurred in the conventional volume control group and 19 (55.9%) deaths in the BIA-guided volume control group (*P*=0.69). There were no differences in 28-day mortality (HR, 1.19; 95% CI, 0.63–2.23) or 90-day mortality (HR, 0.99; 95% CI 0.57–1.75) between conventional volume control group and BIA-guided volume control group. In the secondary analysis, achieved volume accumulation rate was significantly associated with patient survival. Compared with the achieved volume accumulation rate of ≤-50%, the HRs (95% CIs) for the risk of 28-day mortality were 0.90 (0.16-5.02), 0.21 (0.03-1.61), and 8.08 (1.18-55.50) in that of -50–0%, 1–50%, and >50%, respectively. In addition, the HRs (95% CIs) for the risk of 90-day mortality were 1.21 (0.29-5.01), 0.55 (0.12-2.48), and 7.18 (1.58-32.51) in that of -50–0%, 1–50%, and >50%, respectively.

Conclusions: BIA-guided volume control in patients receiving CKRT due to sepsis-associated AKI with volume overload did not improve patient outcomes. In the secondary analysis, achieved volume accumulation rate was associated with patient survival.

FR-PO125

Hypotensive Episodes During Continuous Kidney Replacement Therapy and Mortality

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Background: Continuous kidney replacement therapy (CKRT) is often the preferred modality in hemodynamically unstable patients who develop acute kidney injury (AKI) and require kidney replacement therapy.

Methods: Patients with acute kidney injury (AKI) who required CKRT between 1/1/2012 and 1/1/2021 and were admitted to a tertiary academic hospital were included. We assessed the impact of hypotensive episodes on in-hospital mortality and major adverse kidney events (MAKE) at 90 days. MAKE is a composite outcome of need of kidney replacement therapy, doubling of the serum creatinine from baseline or death. Hemodynamic instability episodes were defined as mean arterial pressure (MAP) < 60 mmHg or a decrease in MAP by ≥ 10 mmHg, systolic blood pressure <90 mmHg or a decrease in SBP by ≧ 20 mHg, or increased vasopressor requirement. These were measured in 15-minute increments and the number of episodes in each hour was recorded.

Results: There were 669 patients with AKI that required CKRT during the study period. The median number of hypotensive episodes during the first 24 hours of CKRT was 51 (Interquartile range: 46-55). There were 320 (48%) who suffered in-hospital mortality. Patients who had in-hospital mortality were older (62 vs 58), and had higher SOFA score (11 vs 9), higher norepinephrine equivalent (NEE) requirement (0.16 vs 0.07 mcg/kg/min), more frequent hypotensive episodes (medians: 52 vs 49), higher lactate (6.2 vs 3.2 mmol/L), lower mean arterial pressure (MAP) (74 vs 79 mmHg) and were more likely to be requiring mechanical ventilation (81% vs 61%) at CKRT initiation compared to patients who did not suffer in-hospital mortality, p<0.001. After adjusting for age, baseline serum creatinine and SOFA score, lactate, MAP, mechanical ventilation and NEE at CKRT initiation, the number of hypotensive episodes during the first 24 hours was independently associated with in-hospital mortality (OR: 1.2, 95% CI: 1.11-1.35, p<0.001) and MAKE-90 (OR: 1.1, 95% CI 1.01-1.2, p-value=0.04) per 10 increase in hypotensive episodes.

Conclusions: Hypotension is a significant independent risk factor for in-hospital mortality and occurs frequently in patients receiving CKRT.

Funding: Other NIH Support - National Institute of General Medical Sciences of the NIH under Award Number 2U54GM104942-07. Dr. Ankit Sakhuja disclosed funding from NIH/NIDDK 1K08DK131286.

FR-PO126

Association of Dynamic Hemoglobin Change and Renal Recovery in Patients with Severe AKI Requiring Continuous Renal Replacement Therapy

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Background: Anemia in patients with severe acute kidney injury (AKI) requiring continuous renal replacement therapy (CRRT) is associated with increased mortality and morbidity. However, the relevance of dynamic hemoglobin level variability (HbV) to renal recovery after AKI is still largely unknown. This study investigated the correlations between HbV and renal recovery at the time of discharge in patients with severe AKI who requiring CRRT.

Methods: We collected 1,897 AKI patients who underwent CRRT from two university hospitals between 2006 and 2021. The HbV was defined as the standard deviation (SD) and coefficient of variation (CV) during CRRT. To investigate the effects of HbV on RRT-dependence at discharge, we estimated the sub-distribution hazard ratio (HR) considering the mortality, adjusted by sex, age, charlson-comorbidity index, hypertension, SOFA, APACHE, and serum chemistry data.

Results: Of 1,897 AKI patients, 38 % were male, and the mean (standardized deviation) age was 66.1 (16.1) years. The proportion of outcome at discharge was 8% for RRT dependence, 29% for RRT independence, and 63% for mortality. The Cox regression analysis showed that HbV was positively correlated with RRT-dependence (SD, HR 0.77, 95% confidence interval [CI], 0.66 to 0.89; CV, HR 0.97; 95% CI 0.96 to 0.99).

Conclusions: This study showed that HbV during dialysis was associated with short-term renal recovery after severe AKI requiring CRRT.

FR-PO127

Association of Changes in Platelet and White Blood Cell Counts with Hospital Mortality in Patients with AKI requiring CRRT: A Multicenter Cohort Study

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Background: The relationship of platelet and white blood cell counts and adverse outcomes has been extensively studied in diverse critically ill populations. These parameters have seldom been studied in patients with AKI requiring CRRT. Given that the delivery of CRRT may directly impact these parameters, we aim to examine the association of changes in platelet and white blood cell (WBC) counts from pre-CRRT to during CRRT with hospital mortality.

Methods: Multicenter retrospective cohort study of 1,413 critically ill adult patients with AKI that required CRRT at two academic medical centers between 2011 and 2021. Platelet and WBC count change from pre- to during CRRT was assessed as a percentage and categorized by SD groups (<1 SD, within 1 SD, and >1 SD of the mean). Multivariable LASSO regression and interaction analyses were utilized to investigate associations with hospital mortality.

Results: Hospital mortality occurred in 53.2% of patients. In models adjusting for demographics, comorbidity, baseline kidney function, and SOFA scores, >1 SD platelet count drop during CRRT (>62% from pre-CRRT) was independently associated with hospital mortality (aOR: 1.82, 95% CI: 1.06, 3.13), while >1 SD WBC count increase during CRRT (>136% from pre-CRRT) exhibited non-significant increased mortality (aOR 1.41, 95% CI: 0.88, 2.29). Four high-risk patient phenotypes were identified from interaction analyses: 1. Pre-CRRT low platelet count that remained low, 2. Pre-CRRT normal platelet count with a drop of >1 SD, 3. Pre-CRRT elevated WBC count that remained high and 4. Normal or elevated pre-CRRT WBC count that increased to >1 SD.

Conclusions: In critically ill adult patients with AKI requiring CRRT, a drop in platelets and an increase in WBC from pre-CRRT to during CRRT can assist in patient phenotyping and mortality risk-classification. Further discovery and validation of relevant CRRT patient phenotypes is needed to better guide CRRT delivery.

Funding: NIDDK Support

Clinically Relevant Phenotypes

Phenotype	Pre-CRRT mean platelet count ($x10^3$)	Drop in platelets during CRRT	Pre-CRRT mean WBC count ($x10^3$)	Rise in WBC during CRRT	Observed odds of hospital mortality	Model adjusted odds (25, 75p) of hospital mortality
1 (n=71)	<55	34 to 62%	2.1 to 27	-59 to 136%	1.22	1.42 (1.07, 1.85)
2 (n=63)	55 to 263	>62%	2.1 to 27	-59 to 136%	1.74	1.61 (1.14, 2.17)
3 (n=37)	55 to 263	34 to 62%	>27	-59 to 136%	2.08	1.88 (1.13, 3.35)
4 (n=41)	55 to 263	34 to 62%	2.1 to 27	>136%	2.15	1.73 (1.22, 2.15)

FR-PO128

Hypomagnesemia in Critically Ill Patients Undergoing Continuous and Prolonged Intermittent Kidney Replacement Therapies: Still a Matter of Debate?

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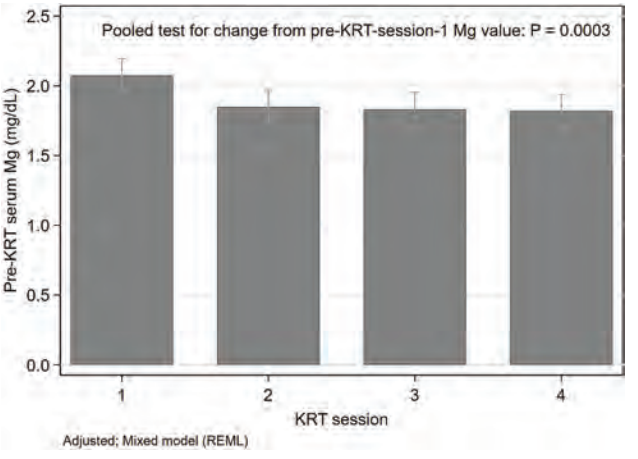
Background: Hypomagnesemia may represent a fearsome complication in critically ill patients undergoing Continuous and Prolonged Intermittent Kidney Replacement Therapy (CKRT, PIKRT). Given its negative impact on morbidity and mortality, strategies aimed at reducing its incidence should be timely implemented. We carried out a prospective observational study aimed at assessing the incidence and outcome of hypomagnesemia in ICU patients undergoing CKRT and PIKRT with Regional Citrate Anticoagulation.

Methods: KRT was performed by the Prismax system and AN69 filters (Baxter), combining a trisodium citrate solution (Regiocit 18/0, Baxter) with a Mg-containing solution used as dialysis and/or post-dilution replacement fluid (Mg^{2+} 0.75 mmol/L; Biphozyl, Baxter). Each patient underwent 72-h CKRT or 3 consecutive 8-h SLED sessions. Mg losses were replaced, when needed, with Mg sulphate. We used linear mixed-effects and time-varying Cox multiple regression models to assess s-Mg level and its association with mortality.

Results: We enrolled 47 patients on CVVH, CVVHDF and SLED (mean APACHE II 25±7.0); s-Mg was 2.07±0.48 mg/dL at baseline and decreased by -0.25 mg/dL during KRT (P=0.0003, **Figure 1**), with the nadir being reached since the first KRT session. Hypomagnesemia (s-Mg<1.6 mg/dL) was observed, at least once, in 46.8% of patients, despite an average supplementation of 1.18 g/day. There was a trend, albeit not statistically significant, of lowest s-Mg values to be associated with increased mortality, after adjusting for potential confounders.

Conclusions: Hypomagnesemia is an incident complication of CKRT and PIKRT, mainly depending on baseline s-Mg. It seems associated with ICU mortality. Among preventive strategies, the evaluation of ionized s-Mg levels may represent a useful tool to better clarify Mg mass transfer during KRT.



FR-PO129

Magnesium Supplementation Is Associated with Reduced Mortality in AKI Requiring Continuous Kidney Replacement Therapy (CKRT)

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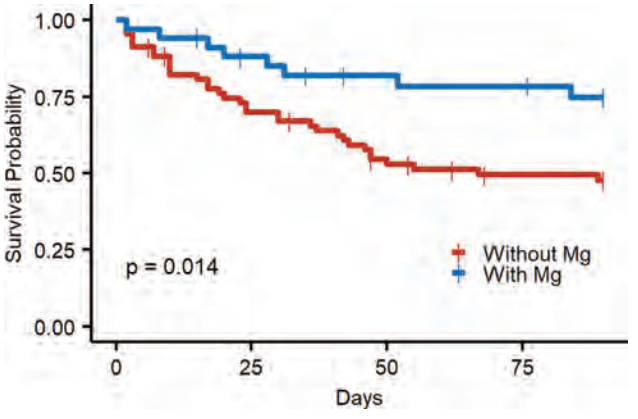
Background: Hypomagnesemia is a common electrolytic disorder and associated with mortality and delayed renal recovery in AKI patients. Although prevention and treatment of hypomagnesemia are suggested, evidence that magnesium (Mg) supplementation could improve survival is still lacking.

Methods: We retrospectively collected the data on AKI patients requiring CKRT with the support of vasopressors and/or ventilators. After excluding patients without measurement of serum magnesium at the day of CKRT start and those who died within 48 hours from CKRT start, patients were divided in two groups according to presence or absence of Mg supplementation within 48 hours of CKRT. Propensity score matching was performed using a 2:1 nearest neighbor matching algorithm. The primary and secondary outcomes were mortality and KRT free at 90 days. The association with Mg supplementation and outcomes was evaluated using a multivariable Cox regression model and a Fine and Gray model.

Results: After excluding 296 patients who died within 48 hours or did not have measurement of serum Mg, 296 patients without and 37 with Mg supplementation were eligible. After propensity score matching, 68 patients without and 34 patients with Mg supplementation were analyzed. There is no difference in age, sex, presence of sepsis, baseline kidney function, illness severity and serum magnesium. Patients with Mg supplementation received 24.4±10.6mEq of Mg during 48 hours. The mortality rate was lower in patients with Mg supplementation than in those without (Figure). Mg supplementation is inversely associated with 90-day mortality with adjusted hazard ratio of 0.38 (95%CI, 0.18 – 0.83). Mg supplementation was associated with KRT free at 90 days with hazard ratio of 2.07 (95%CI, 1.23–3.49).

Conclusions: The study using propensity score matching revealed the association of Mg supplementation with improving survival rate and renal recovery.



Kaplan-Meier Survival Curve

FR-PO130

Calcium Balance in Slow Extended Dialysis: Effect of Regional Citrate vs. Other Anticoagulation Strategies in a Randomized Trial

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Background: Regional citrate anticoagulation (RCA) has been used as an alternative to heparin during slow extended dialysis (SLED) in patients with acute kidney injury (AKI). However, there is scanty data on the impact of different anticoagulation strategies on calcium balance during these procedures. This study aimed to determine calcium balance in SLED using RCA compared to saline or heparin in a crossover randomized clinical trial (RCT).

Methods: We included 20 critically ill adults with AKI who were eligible to SLED (6 to 8 hours) in a tertiary center in Brazil. They were randomized to either RCA or standard of care (heparin as the first choice or continuous saline flush, in case of heparin contraindication) in a crossover manner. Dialysis was carried out using single-pass batch equipment, until the maximum of six therapies per subject. RCA used ACD 2.2% at 3mmol/L (320mL/h), post filter calcium target 0.6 - 0.7mmol/L, and pre-filter calcium target 1.10 - 1.32mmol/L. Dialysate calcium was 1.25 mmol/L in all therapies. The primary outcome was calcium balance.

Results: In 48 procedures, 24 used citrate, and 24 used heparin or continuous saline. Each participant performed 2 (1 - 3) sessions in the protocol. Patients age was 66 (40 - 71) years, 55% men, 15% on mechanical ventilation, and 20% using vasoactive agents. All groups had a negative calcium balance, markedly in dialysis using RCA.

Conclusions: In this RCT, SLED was associated with negative calcium balance independently of the anticoagulation strategy, although calcium loss was more prominent in the RCA group. Further studies are needed to corroborate our results and investigate the determinants of calcium loss during SLED.

Funding: Government Support - Non-U.S.

Dialysis parameters (n = 48)

	CITRATE (24)	HEPARIN (14)	SALINE (10)
Blood / dialysate flow (mL/min)	180 (180 - 180)	180 (180 - 180)	180 (180 - 180)
Time (min)	420 (397 - 470)	390 (360 - 480)	420 (366 - 420)
UF (L)	2.0 (1.9 - 2.4)	2.1 (1.9 - 2.5)	2.0 (1.3 - 2.1)
Total volume removed (L)	4.9 (4.5 - 5.3)	2.5 (2.3 - 2.9)	3.4 (2.8 - 3.7)
Calcium balance (mg) **	-625 (-373 to -740)	-527 (-253 to -678)	-422 (-168 to -609)

*Calcium balance, difference between given calcium in infusion pump and dialysate and the estimated calcium lost in effluent and ultrafiltration (UF)

FR-PO131

Association Between Body Mass Index and Clinical Outcomes in Patients with AKI Requiring Continuous Renal Replacement Therapy

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Background: Obesity is associated with higher mortality in general population. However, there has been controversy over the effect of obesity in critically ill patients. In this study, we retrospectively reviewed medical records to investigate the association between body mass index (BMI) and mortality or ESRD incidence in critically ill patients who admitted to intensive care unit (ICU) and receiving continuous renal replacement therapy (CRRT).

Methods: A total of 891 adult patients were admitted to the ICU and received CRRT at three institutions of the Catholic Medical Center from July 2012 to December 2020. Of these patients, 845 subjects were eligible for the study, excluding patients without BMI data or patients with extracorporeal membrane oxygenation (ECMO) treatment. Patients were categorized into 4 groups according to the BMI criteria of the Korean Society for The Study of Obesity (BMI less than 18.5, 18.5-22.9, 23.0-24.9, 25.0kg/m^2 or greater). The association between BMI and 1-year overall mortality and 1-year ESRD incidence were investigated.

Results: The 1-year mortality was 43.3%, 47.9%, 36.2% and 39.0% in the underweight, normal, overweight, and obese groups respectively. The mortality rate of obese patients was significantly lower than that of normal patients in Kaplan-Meier analysis (p=0.002). Multivariable logistic regression analysis showed that obese patients had a lower risk of mortality than normal group (hazard ratio [HR], 0.60; 95% confidence interval [CI], 0.42-0.85; P=0.005). The 1-year ESRD incidence was 43.6%, 37.9%, 32.4% and 25.0% in the underweight, normal, overweight, and obese groups respectively. In a multivariable logistic regression analysis adjusted for confounding factors, obesity was associated with a decreased risk of ESRD (HR, 0.56; 95% CI, 0.34-0.92; P=0.023). In subgroup analysis according to age, 1-year mortality consistently showed an inverse correlation between BMI and mortality, but ESRD incidence was inversely related with obesity only in patients with age > 65.

Conclusions: In critically ill patients admitted to ICU with AKI requiring CRRT, obesity (BMI>25.0kg/m^2) was associated with lower 1-year mortality and 1-year ESRD incidence, suggesting obesity paradox in patient survival and renal survival.

FR-PO132

Effect of Urinary Output on Withdrawal from Continuous Renal Replacement Therapy in a Tertiary Referral Center in Western Mexico

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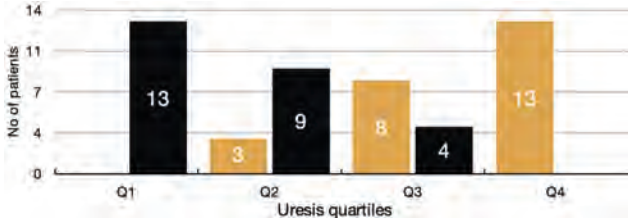
Background: The withdrawal of Continuous Renal Replacement Therapy (CRRT) in patients with severe AKI has not been standardized. New evidence suggests that releasing CRRT too soon, as well as unneeded and extended CRRT, might negatively affect the clinical course and economic cost of AKI.

Methods: A retrospective cohort of critically ill adult patients hospitalized in four intensive care units of a tertiary care center in western Mexico, who presented with acute kidney injury requiring CRRT, in which renal replacement therapy (RRT) was interrupted without the intention of migrating to another form of RRT, from January 2016 to March 2021. We defined CRRT withdrawal success as 72 h without the need for a TRR reset after CRRT discontinuation.

Results: Fifty-two patients who met the inclusion criteria were evaluated. Due to the abnormal distribution of the uresis values in both groups, it was decided to carry out the analysis by quartiles, finding the distribution regarding the success or failure of CRRT withdrawal. We found that uresis below the first quartile (<1,200 ml) was a risk factor for failure to withdraw CRRT (OR 2.85, 95% CI 1.84-4.41, p<0.001). Other variables that showed a risk of CRRT withdrawal failure in the multivariate analysis were lower systolic and diastolic blood pressure, the presence of comorbidities, more total hours of CRRT, and absence of diuretic use at the time of CRRT withdrawal.

Conclusions: A urine output of less than 1 liter was associated with almost three times the risk of failure to withdraw CRRT in our population. In turn, diuretics use

facilitated withdrawal. Urinary volumes were greater in our CRRT-withdrawing study compared to those reported in other places.



FR-PO133

Proenkephalin May Improve Strategies for Successful Weaning from RRT

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Background: Acute kidney injury (AKI) is associated with fatal outcomes, particularly in patients requiring renal replacement therapy (RRT). Conventional kidney biomarkers such as serum creatinine (SCr) are incapable of indicating kidney recovery in patients receiving RRT. Proenkephalin A (penKid) is a novel kidney biomarker with unique characteristics. We hypothesized that penKid could provide a more accurate prediction of successful weaning from RRT than established standards of care.

Methods: Measurement of penKid plasma levels were implemented in the daily blood routine at our center. In this preliminary analysis, data of 1473 patients were gathered. The start of a weaning trial was defined as 48h without RRT, and weaning was considered successful if a patient did not require RRT for five consecutive days.

Results: RRT procedures were performed in 234 patients of whom 54 patients were chronically dependent on hemodialysis prior ICU admission. Baseline and maximum penKid levels showed a stepwise increase with rising AKI stage (KDIGO criteria). Median penKid levels at RRT start were 128.2 pmol/L and increased further under RRT. In contrast, SCr levels decreased in association with RRT procedures. In patients with pre-existing chronic RRT-dependency, penKid levels were significantly higher than in patients with acute RRT requirements at any time after RRT initiation (Day 3 after RRT Start: 134.7 vs. 403.9 pmol/L), while SCr was already indifferent on day 3 (1.60 vs. 1.49 mg/dL). Differing RRT modalities had no effect on penKid levels, whereas continuous RRT forms were more effective than intermittent RRT in clearing SCr. On the day of last RRT, the area under the curve (AUC) for predicting successful RRT weaning was higher for penKid compared to UO with 0.76 (95% CI 0.58-0.94, p=0.014) and 0.74 (95% CI 0.55-0.94, p=0.039), respectively. One day earlier, predictive performance was even more favorable for penKid compared to UO (AUC 0.72 [95% CI 0.54-0.91, p=0.036] vs. 0.58 [95% CI 0.36-0.80, p=0.879]).

Conclusions: Our data suggest that penKid may provide additional information to standard of care rgarding kidney integrity under RRT, making it a valuable biomarker to predict liberation from RRT. This has large clinical implications given the importance of avoiding unnecessary RRT-procedures.

FR-PO134

Predictors of Early Peritoneal Dialysis Start in Newborns and Young Infants Following Cardiac Surgery

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Background: This single center, retrospective cohort study was conducted to investigate the predictors of early peritoneal dialysis (PD) start initiation in newborns and young infants undergoing cardiac surgery.

Methods: There were fifty-seven newborns and young infants. All subjects received PD catheter after completion of the cardiopulmonary bypass (CPB). Worsening postoperative (post-op) positive fluid balance and oliguria (<1 ml/kg/hour) despite furosemide were the clinical indications to start early PD (PD +). Demographic, clinical and laboratory data were collected from the pre-operative, intra-operative and immediately post-operative periods.

Results: Baseline demographic data were indifferent except that PD + group had more newborns. Preoperative serum creatinine was higher for PD + group (p= 0.025). PD + group had longer CPB time (p=0.044), longer aorta cross-clamp time (p=0.044) and less urine output during early post-op 24 hours (p= 0.008). In the univariate logistic regression model, pre-op serum creatinine was significantly associated with higher odds of being in PD+ (p= 0.021) and post-op systolic BP (p=0.018) and post-op MAP (p=0.001) were significantly associated with reduced odds of being in PD + (p= 0.018 and p= 0.001, respectively). Post-op MAP showed a statistically significant association (aOR= 0.89, 95% CI [0.81, 0.96], p=0.004) with PD + in multivariate analysis after adjusting for age at surgery.

Conclusions: : In our single center cohort, pre-op serum creatinine, post-op systolic BP and MAP were demonstrated statistically significant association with PD +. This finding may help to better risk stratify newborns and young infants for early PD start following cardiac surgery.

FR-PO135

Role of Immunomodulation Therapy with Selective Cytopheretic Device (SCD) in Reversing Acute on Chronic Liver Failure (ACLF) with Hepatorenal Syndrome (HRS) and Multi-Organ Failure

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Introduction: ACLF is a clinical disorder characterized by acute clinical deterioration in patients with pre-existing chronic liver disease. ACLF develops from systemic inflammation, often due to bacterial infections or alcoholic hepatitis, and progresses to multi-organ failure. Severe ACLF with ≥ 4 organ failure has a grave prognosis with a mortality rate at 28 days of 100%. Early liver transplant is the treatment of choice for those who are refractory to medical treatment. Intervention to modulate and lessen this systemic inflammatory state may alter the progression of multi-organ dysfunction and allow time for liver transplantation.

Case Description: Case 1. A male patient in his 30s presented with acute alcohol associated hepatitis, ACLF, HRS, and ≥4 organ failure. He required vasopressors, mechanical ventilation, and CKRT. MELD score was 38. **Case 2.** A male patient in his 60s with non-alcoholic steatohepatitis (NASH) was admitted for hypotension and decompensated cirrhosis. He required vasopressors and developed HRS. MELD score was 37. Both patients were enrolled into a clinical trial (NCT 04898010) to evaluate an extracorporeal immunomodulating device, SCD. Both patients showed rapid clinical improvement associated with a decline in elevated blood cytokine concentrations and diminution of activation levels of circulating leukocytes. On follow up Case 1 was alive at day 90 after treatment and undergoing liver transplantation evaluation and Case 2 had a successful liver transplantation 6 days after SCD therapy ended.

Discussion: The final common pathway of systemic hyper-inflammation resulting in multi-organ failure is the effector cells of the innate immunologic system. The activation of neutrophils and monocytes is the key driver of the developing hypoxic and toxic tissue damage of solid organs. The immunomodulation of these cellular elements rather than removal or inhibition of soluble cytokines or chemokines of inflammation is the critical target for effective therapy, as demonstrated with SCD treatment. These cases represent the first in human treatment of ACLF with SCD. These results suggest a role for SCD treatment in the management of HRS-AKI and ACLF as a bridge to liver transplantation.

FR-PO136

Safety Summary of the Selective Cytopheretic Device (SCD): A Review of Safety Data Across Multiple Clinical Trials in ICU Patients with AKI and Multi-Organ Failure

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Background: AKI is a frequent and serious complication in critically ill patients, occurring at a rate of 1 in 5 adults and 1 in 3 children hospitalized with acute illness. AKI requiring CKRT is a significant complication in ICU patients with mortality rates exceeding 50%. A dysregulated immune response can lead to systemic inflammation caused by a hyperactivity of pro-inflammatory neutrophils & monocytes leading to tissue damage. Damage resulting from hyperinflammation associated with AKI frequently progresses to other organs, such as the heart, lung, or liver. The SCD is an investigational medical device in a new class of cell-directed extracorporeal therapies distinct from cytokine adsorbers or filters, as it targets activated leukocytes, the key cellular sources driving the hyperinflammatory process. This report summarizes safety data from the major clinical studies of the SCD across a variety of patient types with AKI and multi-organ failure.

Methods: Safety was assessed in each study through the collection of AEs & SAEs. All-cause mortality was also assessed. As all-cause mortality can help in interpreting safety, this report will also summarize survival rates in each study.

Results: Results from each of the 5 studies will be described herein, including that 5 of 6 studies had no device-related SAEs and AEs from each study were consistent with those expected in a critically-ill ICU population. Although studies were not powered to detect differences in mortality, there were trends toward higher survival rates in SCD patients vs. controls.

Conclusions: These studies support that the SCD can be added as a therapeutic intervention in critically ill AKI patient populations with additional multi-organ failure without adding additional safety risks. Any intervention with the potential to improve survival in such a critical patient population would be welcome.

Funding: Commercial Support - SeaStar Medical

Summary of Adverse Events from Studies

Study (Descriptor)	# AEs	# SAEs
Study 1 (China Pilot Study)	14	0
Study 2 (ARF-002)	199	28
Study 3 (SCD-003)	354	80
Study 4 (SCD-PED-01)	47	12
Study 5 (SCD-005)	70	50
Totals	684	170

FR-PO137

Sepsis-Associated AKI (SA-AKI) Requiring Kidney Replacement Therapy (KRT): Role of Hemofiltrate Reinfusion (HFR)-Supra on Inflammation and Outcome

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Background: Sepsis is life-threatening organ dysfunction caused by dysregulated body response to an infection. Mortality rate ranging over 60% for septic shock. AKI is final common pathway of this immune dysregulation leading to systemic inflammation (SI) due to uncontrolled circulating levels of pro-inflammatory mediators and cytokine induced direct organ damage. KRT is often required in SA-AKI and could improve SI removing pathogens and inflammatory factors. Various blood purification techniques have been used: HCO/MCO membranes, hemoperfusion, plasma filtration/adsorption and, anecdotal, Hemo Filtrate Reinfusion Supra (HFR): endogenous reinfusion HDF based on adsorbing resin cartridge that remove pro-inflammatory cytokines but whose full spectrum is not yet know. Aim of this study is to test HFR on outcome of SA-AKI in critically ill pts.

Methods: Retrospective observational study evaluated 8 SA-AKI pts requiring RRT. All were treated with daily HFR(Bellco-Medtronic, Italy), mean of 8.3 ±5.4 treatments. We daily assessed (as mean ±SD): urea, sCr, CRP, procalcitonin (PCT), WBC, myoglobin(Myo), albumin; in addition need for vasopressor and outcome. AKI was defined according to KDIGO.

Results: The mean age was 74.1±9.4 years, 6 pts were male (75%). Over 30% obese, 20% with nephropathies, some hypertensive, with diabetes or COPD. HFR: Qb= 250 ±18.8 ml/m, TT 238.7 ±27.7m. HFR confirm valid URR, highly significant abatement of CRP (271.7 ± 68.4 *85.7 ± 61.1 p< 0.0003*), meaningful cut of PCT (65.7 ±65.9 *10.5 ±20.2 p< 0.03*) and Myoglobin (3648.5 ± 1709.2 *511.7 ± 435.9 p < 0.01*), stable Albumin. Lower need of vasopressor (13.5± 3.8 *7.5± 3.1 p < 0.002*) highlights improved hemodynamic instability with no poor intradialytic compliance. 3 pts not survived (2 for surgical, 1 for pulmonary complications) everyone else had renal recovery.

Conclusions: HFR decrease SI and support renal recovery in SA-AKI pts, even in the not survived. The sorbent cartridge remove many proinflammatory cytokines, that lead to improved MAPs and lower critical illness scores, and allow to eliminate myoglobin too. Finally HFR-Supra is the cheapest technique for SA-AKI in comparison to the other (eg CRRT, HCO, Cytosorb). There is no study on HFR in SA-AKI and very few experience on his use to hypermyoglobinemia. Larger studies need to confirm our evidence but, in the meantime, we could help to build a new scientific evidence.

FR-PO138

Plasma Cystatin C Predicts Kidney Function Recovery in Patients Requiring Continuous Kidney Replacement Therapy (CKRT) for AKI

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Background: AKI requiring KRT is a common complication in hospitalized patients that confers increased mortality. Tools to predict timing of kidney function recovery and mortality are needed. Cystatin C (CysC) is a marker of kidney function that may reflect residual kidney function while on KRT. Herein, we tested the hypothesis that lower plasma cysC concentrations would predict early kidney function recovery in patients with AKI requiring CKRT.

Methods: 51 patients without chronic kidney disease requiring CKRT for AKI were studied. Plasma was collected prior to CKRT initiation, and plasma and effluent were collected on days 1, 2, and 3 of CKRT. Two groups were studied: early kidney function recovery (EKFR, liberated from dialysis within 7 days of CKRT initiation, N = 15) and delayed kidney function recovery or death (DKFR/D, on dialysis 21 days after CKRT initiation or death prior to renal recovery, N = 36). CysC, creatinine, and blood urea nitrogen (BUN) were measured in plasma and effluent, and CKRT dose and urine output were recorded.

Results: Mean plasma cysC (mg/L) was significantly lower on days 1 (1.79 vs 2.41, p = 0.03) and 2 (1.91 vs 2.41, p = 0.03) of CKRT in patients with EKFR versus DKFR/D. There was no difference in serum creatinine or BUN between the two groups. CysC on days 1 and 2 of CKRT predicted early kidney function recovery (day 1 ROC AUC 0.765, p = 0.003; day 2 ROC AUC 0.751, p = 0.010). CKRT clearance of cysC and cysC sieving coefficient were similar between the two groups. The average cysC sieving coefficient in all patients was 0.59, 0.61, and 0.61 on days 1, 2, and 3 of CKRT respectively.

Conclusions: CysC on days 1 and 2 of CKRT predicts early kidney function recovery. The lower concentration of plasma cysC in patients with EKFR was not due to differences in CKRT cysC clearance. Since cysC is moderately cleared by CKRT, it is only predictive at early timepoints after CKRT initiation. CysC is available in clinical practice, thus measuring cysC in patients on CKRT for AKI is feasible and would fill a void in data that is needed to support discussions between clinical providers and patients regarding outcomes and prognosis.

Funding: Commercial Support - Baxter Investigator Initiative Grant, Private Foundation Support

FR-PO139

Impact of Early Renal Replacement Therapy in Leptospirosis on Mortality and Long-Term Renal Function: A Retrospective Analysis over 11 Years in Reunion Island

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Background: Leptospirosis is a widespread zoonosis that can cause severe acute kidney injury (AKI-L) and remote chronic renal disease (CKD-L). Anecdotal evidence suggests that early renal replacement therapy (RRT) may improve mortality associated with AKI-L. Conversely, intensive care unit (ICU)-based trials, including the landmark AKIKI carried have disproved a positive impact of early RRT on patient mortality. We aimed to determine i) whether the timing of RRT positively impacts mortality ii) provide an estimation of the incidence of post-leptospirosis CKD.

Methods: We conducted a retrospective study over 11 years in Reunion Island, including adult patients with confirmed leptospirosis complicated by KDIGO 2 or 3 AKI. The primary endpoint was a composite endpoint including death and CKD-L up to 3 years after hospital discharge. Factors associated with CKD-L and death were determined using logistic regression models with different adjustment variables.

Results: Three hundred eighty patients were included, 39% of whom required RRT with a median time to initiation of 1 day (0-2 days). According to the composite criterion, the mortality rate was 4% in the study population and the incidence of CKD-L was 8%. On univariate analysis, factors associated with the composite criterion included ICU severity scores, age, baseline kidney function, oligo-anuria and the need for RRT. Using bivariate models adjusting on age or SAPS2 or prior renal function, we showed that when compared to patients who did not require dialysis, no significant difference was found between early or late dialysis initiation on the composite endpoint. Odds ratio (OR) for RRT before 24h was 5.7 (1.9-17.9) and OR for RRT after 24h was 5.7 (2.1-16.3).

Conclusions: In conclusion, leptospirosis accounts for significant CKD. Early RRT does not seem to improve the composite mortality-CKD endpoint. Further investigations are needed to substantiate the potentially protective effects of early RRT on CKD-L.

Bivariate analysis of factors associated with death or CKD at last follow-up, according to time to initiation of RRT and patients' SAPS2 score

Variable	OR	CI 95%	p
RRT < 24 hours	5.7	1.9 - 17.9	< 0.01
RRT > 24 hours	5.7	2.1 - 16.3	< 0.001
SAPS2, per unit	1.1	1 - 1.1	< 0.001

FR-PO140

A Roadmap to Recovery: Managing AKI in a Case of Hemophilia B

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Introduction: Hemophilia, a rare inherited bleeding disorder, poses unique challenges in the management of patients requiring renal replacement therapy. Acute Kidney Injury is a serious complication that can occur in hemophilic patients following prolonged hospitalization secondary to trauma. There is limited data on the appropriate dialysis modality selection, and prescription of dialysis treatments in these patients.

Case Description: We present a case report highlighting the innovative approach adopted for the management of acute kidney injury (AKI) in a 31-year-old male hemophiliac patient with a history of abdominal trauma following a road traffic accident. The diagnostic workup revealed intra-abdominal bleeding and sepsis, leading to the development of AKI. Given the patient's complex clinical profile, a tailored approach was necessary to balance the need for renal replacement therapy while minimizing the bleeding risks associated with hemophilia. Sustained low-efficiency daily dialysis (SLEDD) was utilized for renal support, with modifications made to minimize bleeding risks. The modifications included the use of normal saline and cryoprecipitate to maintain adequate clotting factor levels, to minimize bleeding during catheter insertion and removal and to prevent coagulation of the circuit, and close monitoring of coagulation parameters throughout the dialysis sessions. 6 such dialysis sessions were done following which the acute kidney injury was resolved.

Discussion: In this case, the key challenge to overcome was concerning the use of heparin to prevent coagulation in the extracorporeal circuit, but at the same time it carried the risk of prolonging the already prolonged Actiavted Partial Thromboplastin Time (APTT). The solution was to use saline and cryoprecipitate in the process to maintain the dialysis circuit and the hemodynamic stability of the patient. The modality of choice was SLEDD, because of its capacity to offer continuous renal support while retaining a low risk of bleeding. SLEDD with modifications proved to be a safe and effective method for managing AKI in our patient. Further research is needed to establish optimal management strategies for AKI in patients with Hemophilia B.

FR-PO141

Suspected Scleroderma Renal Crisis in Patient with Severe Hypertension and AKI

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Introduction: Although rare, scleroderma renal crisis is a potentially fatal complication that affects up to 10% of patients with systemic sclerosis. The etiology of scleroderma renal crisis is poorly understood, however it is thought that vascular

endothelial injury, vascular thrombosis and arterial narrowing leads to decreased perfusion of the kidneys. This in turn activates the renin-angiotensin-aldosterone system causing severe hypertension.

Case Description: A 67 year old male with history of scleroderma, pulmonary hypertension, pulmonary fibrosis and hyperlipidemia presented with worsening shortness of breath. Initial systolic blood pressure noted to be in the 180s on occasion reaching 220s with diastolic blood pressures in the 100s. Labs significant for BUN 47, creatinine 1.6 (baseline 0.7), GFR 47 (baseline 100s), CRP 1.17, troponin 0.248, platelets 80, LDH 405, haptoglobin < 20 and urinalysis showing protein > 500 mg. Renal ultrasound showed echogenic kidneys consistent with chronic parenchymal disease. Scleroderma renal crisis was suspected and plan was to initiate captopril 6.25 mg q 4 hrs, however medication was non-formulary. Therefore, Enalapril 2.5 mg IV q 4 hrs was ordered and after 1 dose, systolic blood pressures noted to be in the 130s-150s and diastolic blood pressures in the 70s-90s. He was then started on lisinopril 5 mg po qHS and amlodipine 5 mg po daily to control his blood pressure.

Discussion: The diagnosis of scleroderma renal crisis must be considered in all patients with systemic sclerosis presenting with AKI and accelerated hypertension. Several risk factors for development of scleroderma renal crisis include renal impairment within first 5 years of disease course, scleroderma skin involvement, glucocorticoid therapy within 6 months and autoantibodies to RNA polymerase III. Scleroderma renal crisis is a diagnosis of exclusion and treatment is more likely to be effective when initiated early, therefore prompt recognition significantly improves outcomes and mortality. While the patient initially presented with typical features of scleroderma renal crisis, his hemodynamic stability and rapid response to ACEi makes it unlikely. Once the patients blood pressure was controlled, renal function significantly improved. The patients symptoms more representative of hypertensive emergency in setting of poorly managed hypertension.

FR-PO142

Ichthyosiform Sarcoidosis with Renal Involvement

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Introduction: The ichthyoses, also called disorders of keratinization, are a heterogeneous group of disorders characterized by generalized skin scaling. The great majority of ichthyoses are inherited, but acquired forms can develop in the setting of malignancy, autoimmune or infectious diseases.

Case Description: A 51-year-old man presented to the hospital for evaluation of acute kidney injury. The skin exam showed xerosis with hyperpigmented scales lesions on his arms, legs, abdomen, and back (Figure 1-A). Initial workup revealed the following: creatinine 6.27 mg/dL (baseline 0.8 mg/dL), calcium 15.1 mg/dL, PTH 9.1 pg/mL (10-55 pg/mL), vitamin D 1,25 dihydroxy 97.3 pg/mL (20-76 pg/mL), and angiotensin-converting enzyme 120 u/L (14-82 u/L). Urinalysis was positive for proteinuria with a urine protein/creatinine ratio of 900 mg/g Cr. Renal biopsy demonstrated diffuse granulomatous interstitial nephritis (Figure 2-A). Immunofluorescence showed granular capillary wall IgG. Electron microscopy showed podocyte foot process effacement and subepithelial electron-dense deposits (Figure 2-B). Skin biopsy revealed hyperkeratosis with non-necrotizing granulomas. The patient was diagnosed with ichthyosiform sarcoidosis, granulomatous interstitial nephritis, and secondary membranous nephropathy. He was started on prednisone 60 mg daily. His serum creatinine and serum calcium returned to normal with significant improvement in his ichthyosis (Figure 1-B).

Discussion: Ichthyosiform lesions are one of the extremely rare cutaneous manifestations of sarcoidosis that may precede or coincide with the diagnosis of systemic sarcoidosis. Renal manifestations include abnormal calcium metabolism, nephrolithiasis and nephrocalcinosis, acute interstitial nephritis, and membranous glomerulonephritis.

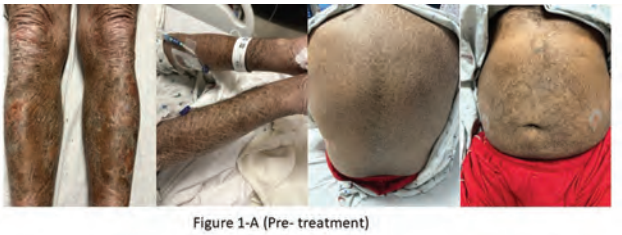

Figure 1-A (Pre- treatment)

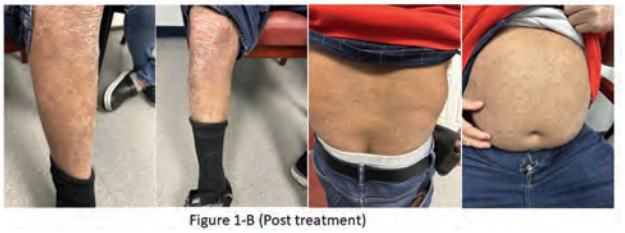

Figure 1-B (Post treatment)

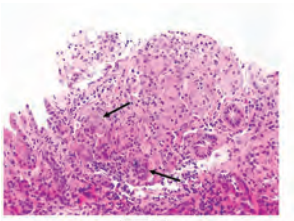

Figure 2-A

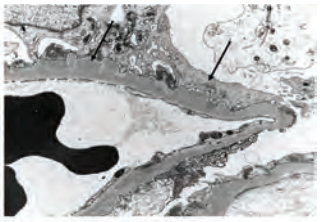

Figure 2-B

FR-PO143

Successful Management of TAFRO Syndrome-Related Renal Thrombotic Microangiopathy with Interleukin-6 Inhibitor

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Introduction: TAFRO [**T**hrombocytopenia, **A**nasarca (edema, pleural effusions, ascites), **F**ever, **R**eticulin myelofibrosisis (or Renal insufficiency), and **O**rganomegaly (lymphadenopathy and hepatosplenomegaly)] that represents a severe subtype of idiopathic multicentric Castleman's disease (iMCD). Kidney involvement in TAFRO syndrome can be severe and may require hemodialysis (HD). However, detailed descriptions of this syndrome's aspect remain limited.

Case Description: A 20-year-old male presented as transfer from another hospital with anasarca, malaise, diffuse lymphadenopathy, and non-oliguric acute kidney injury. He has no past medical history. Initial concern for lymphoma; however, bone marrow biopsy, ascites, pleural fluid examination and flow cytometry were negative for malignancy. The lymph node biopsy showed diagnostic findings of Castleman disease-TAFRO variant. HHV-8, HHV-6, CMV, EBV and HIV were negative. Kidney functions continued to deteriorate driving hyperkalemia necessitated HD. Kidney biopsy was done showing thrombotic microangiopathy (TMA) with mesangiolysis. Serum Interleukin-6 (IL-6) and VEGF were high. Prednisolone was started and Siltuximab, an IL-6 monoclonal antibody, was initiated and continued at 3 weeks intervals. Patient started to improve within days after the first dose of IL-6 inhibitor and HD was discontinued along with full improvement of clinical symptoms and kidney functions.

Discussion: Rates of renal failure are much higher in TAFRO syndrome variant than typical iMCD. Histopathology of renal involvement in TAFRO syndrome has been reported in few publications. The majority have demonstrated a pattern consistent with membranoproliferative glomerulonephritis and few showed TMA. iMCD is known as hyper-IL-6 syndrome with polyclonal lymphadenopathy. Early recognition of disease and early initiation of IL-6 inhibition and glucocorticoids are of paramount importance in attaining complete.

FR-PO144

Investigating Vasopressin-Dependent Renal Medullary Osmolarity as a New Target for Renoprotection

Karen I. López-Cayuqueo, Felix Boivin, Janna Leiz, Shuang Cao, Christian Hinze, Kai M. Schmidt-Ott. Molecular Mechanisms of Kidney and Kidney Transplant Diseases. *Medizinische Hochschule Hannover, Hannover, Germany*.

Background: The renal medulla is characterized by a hyperosmolarity that depends on Avpr2 signaling. High osmolarity in the kidney medulla is required for urine concentration mechanisms. However, the role of the hyperosmolar medulla beyond electrolyte-free water reabsorption is not well understood. Here, we investigate the role of high osmolality in regulating kidney injury responses at molecular and cellular levels.

Methods: We analyzed kidneys from C57Bl/6N mice treated with tolvaptan (Avpr2 antagonist) and compared them to kidneys from control mice. Our analysis included single-nuclei and bulk RNA sequencing, in situ hybridization, and renal ischemia-reperfusion injury.

Results: Tolvaptan treatment reduced renal medullary osmolality and caused significant changes in the gene expression of tubular cells in the renal medulla. These changes included decreased expression of stress response and immune activation-related genes (such as Atf4, Ddit3, Hmgb1) and genes influenced by high tissue osmolality (such as Cryab, and Nupr1). The results were confirmed through bulk RNA sequencing and in situ hybridizations. Avpr2 antagonist treatment protected the renal medulla from fibrosis following unilateral renal ischemia-reperfusion injury.

Conclusions: Applying unbiased single-cell transcriptomics and orthogonal validation, we discovered that inhibiting Avpr2 in mice reduced the expression of osmolarity-regulated genes in tubular cells of the renal medulla, including those associated with stress and immune responses. Avpr2 inhibition protected the renal medulla from fibrosis development following ischemia-reperfusion injury. These findings suggest that targeting Avpr2-dependent medullary osmolality could be a potential strategy for renoprotection.

Funding: Government Support - Non-U.S.

FR-PO145

Caspase-3 Activation Increases with Age and Aggravates Kidney Injury After Ischemia-Reperfusion

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Background: Rarefaction of peritubular capillaries (PTC) after ischemia-reperfusion injury (IRI) predicts progressive renal failure, especially in older kidneys. We previously demonstrated the importance of caspase-3-dependent microvascular damage in progressive kidney dysfunction after IRI. We also showed that renal IRI increases circulating levels of ApoExo; an immunogenic type of exosome-like vesicles produced by apoptotic endothelial cells downstream of caspase-3 activation, and characterized by the presence of LG3/perlecan autoantigen and active 20S proteasome. Here, we hypothesize that age modulates caspase-3 activation after renal IRI leading to increased release of ApoExo, enhanced PTC rarefaction, fibrosis and renal dysfunction.

Methods: Unilateral renal pedicle clamping (30 minutes) and contralateral nephrectomy were performed in young (8 weeks-old) and old (27 and 53 weeks-old) mice. ApoExo were purified from serum-free medium conditioned by apoptotic murine endothelial cells *in vitro* and injected to mice via tail vein every other day. Endpoints were assessed 21 days post-IRI. ApoExo circulating levels were measured by proteasome activity and anti-LG3 titers by ELISA. Complement deposition, caspase-3 activation, PTC rarefaction and fibrosis were assessed by immunohistochemistry. Renal function was monitored by BUN level.

Results: At baseline, old mice showed higher levels of caspase-3 activation within PTC, lower PTC density and higher anti-LG3 titers. Renal IRI led to significant increase in PTC caspase-3 activation, ApoExo and anti-LG3 circulating levels with age. PTC C4d deposition, interstitial fibrosis and renal function were worsened by age. To test the role of ApoExo in fueling maladaptive responses to IRI, young mice were injected with ApoExo to reach circulating levels observed in old mice. ApoExo injection increased anti-LG3 formation, PTC C4d deposition, caspase-3 activation, PTC rarefaction and interstitial fibrosis, and aggravated renal dysfunction.

Conclusions: Our results suggest that caspase-3 activation within PTC increases with older age leading to more ApoExo production post-IRI. The latter enhances microvascular damage and fibrosis, favoring progressive kidney dysfunction.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO146

Hypoxia-Inducible Factor-1Alpha Induces Apoptosis of Tubular Cells in Renal Ischemia-Reperfusion Injury via Regulating Glutathione-Specific Gamma-Glutamylcyclotransferase 1

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Background: Renal ischemia-reperfusion (I/R) is the major cause of acute renal failure in the native and transplanted kidneys. Hypoxia-inducible factor (HIF)-1α is a transcription factor for cellular adaption to hypoxia. It is shown that HIF-1α expressed in renal tubules is up-regulated during renal ischemia and contributes to recovery of the I/R induced renal injury (IRI). However, precise mechanisms for the renal protective effect of HIF-1α in the IRI remain unclear. In the present study, we aimed to clarify the role of HIF-1α on renal IRI by employing a heterozygous HIF-1α knockout (hKO) mouse model.

Methods: Male hKO and wild type (WT) littermate mice were used for IRI model. Mice were anesthetized and the right kidney was resected. Then the left kidney was occluded with a vascular clamp at the hilus for 45 min. The clamp was removed to allow blood reperfusion. For hypoxia-reoxygenation (H/R) treatment, human renal epithelial cell line HK2 were grown to approximately 80% confluence. The culture medium was changed to DMEM without either glucose or FBS and the cells were incubated for 24 h under 1% O_2 conditions. Then, the cells were incubated in DMEM containing 10% FBS under normoxia.

Results: Serum creatinine and blood urea nitrogen in hKO mice with IRI were higher than those in WT mice, confirming that HIF-1α contributes to repair of IRI. Apoptosis is induced in early phase of IRI in WT, while it is induced in late phase in the hKO. In hKO mice, Bcl-2/Bax ratio was increased compared with that of WT mice, indicating that Bcl-2 is a cause for the temporal difference of the apoptosis induction. We found that the pro-apoptotic factor glutathione-specific gamma-glutamylcyclotransferase 1 (CHAC1) was upregulated in tubules of WT after I/R but not in those of hKO. CHAC1 knockdown in HK2 cells induced Bcl-2 upregulation after H/R treatment. These results indicate that CHAC1 regulates apoptosis induction in tubules during IRI via Bcl-2 regulation. HIF-1α knockdown with RNA interference in HK2 cells reduced CHAC1 expression after H/R treatment, indicating direct regulation of CHAC1 by HIF-1α.

Conclusions: Induction of apoptosis in the early phase of IRI is regulated by HIF-1α-CHAC1 axis, contributing to the repair of IRI.

FR-PO147

Mitochondrial Infusion Attenuates Cisplatin-Induced AKI by Inducing Mitochondrial Dynamics

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Background: Acute kidney injury (AKI) is a critical clinical condition of hospitalization with high mortality. Approximate 30% of patients treated with cisplatin (CP) develop AKI. CP affects mainly proximal tubular cells as well as tubular mitochondria and several mechanisms have been involved such as oxidative stress, apoptosis, and mitochondrial damage which leads to AKI. Mitochondrial function and homeostasis is crucial for the maintenance of renal function. In the current study, we evaluated the use of mitochondrial infusion, which could be a promising strategy to prevent CP-induced AKI. Currently it is unknown whether mitochondrial infusion will reduce alterations in mitochondria bioenergetics and dynamics in CP-induced AKI.

Methods: 10-12 wks old male mice were divided into four groups. Group I = saline, group II = 20 mpk CP, group III and IV received 20 mg/kg or 50 μg/mouse isolated healthy liver mitochondria via I.V. injection 24 hrs after CP injection (Fig 1A).

Results: Mice receiving either low dose 50 μg/mouse or high dose 20 mg/kg mitochondria had significantly reduced plasma BUN (Fig 1B) and creatinine including renal injury markers (*Kim1* and *Ngal*). The inflammatory genes such as *Tnfa* (Fig 1C), *Il6, Il1b*, *Mcp1* induced by CP were significantly reduced in both groups III and IV. Treatment with mitochondria significantly increased mitochondrial biogenesis genes *Pgc1alpha,* mitochondrial transcription factor A (*Tfam*) and antioxidant marker *Nrf2* compared to CP group.

Conclusions: Our results demonstrate that mitotherapy protects from renal injury in CP induced model of AKI. This study indicating that mitochondrial infusion could be promising therapy to protect kidneys from CP induced AKI.

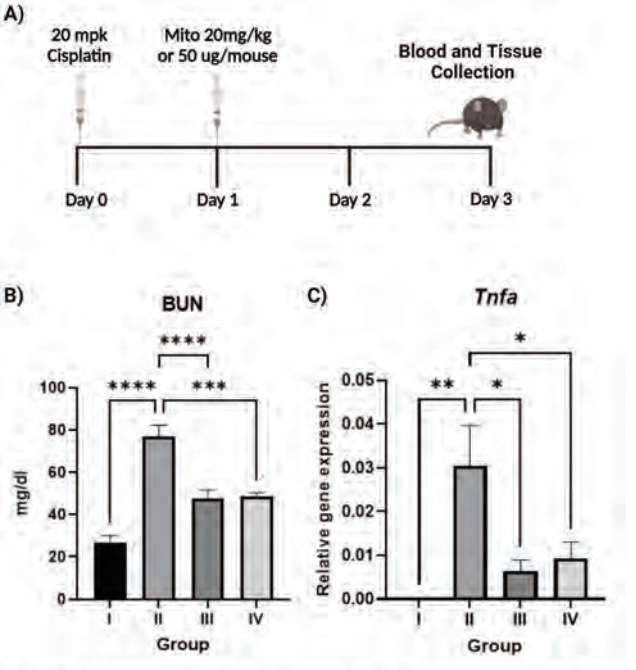

Figure 1. A) Experimental Schematic. B) BUN and C) gene level of *Tnfa. (*p ≤ 0.05; **p≤0.01; ***p≤0.001).* Group I: Saline; Group II: Cisplatin (20 mpk); Group III: CP+Mito (20 mg/kg); Group IV: CP +Mito (50 μg/mouse).

FR-PO148

Nrf2/Keap1 Pathway Activation Improves Kidney Injury in Nephrotoxic AKI in Mice

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Background: Acute kidney injury (AKI) is highly prevalent and increases the risk of chronic kidney disease without treatment options. Preclinical evidence shows that regulating nuclear factor erythroid 2–related factor (Nrf2/Keap1) pathways attenuate AKI by increasing expression of anti-oxidant and anti-inflammatory genes including peroxisome proliferator-activated receptor-γ, and heme oxygenase1. To establish an

AKI model to investigate the Nrf2/Keap1 pathway, we used the Nrf2 activator CDDO-Imidazolide (CDDO-IM) to benchmark its effects in cisplatin (Sic) nephrotoxicity, cecal slurry (CS) sepsis, and ischemia reperfusion (IRI) induced AKI models in mice.

Methods: The Cis-AKI model was induced by 20 mg/kg cis in C57 mice. **The CS sepsis-AKI** was caused by a single dose of 450 ul of CS. **The IRI-AKI** was induced by bi-clamping of mouse renal pedicles for 26 min. The mice were treated with CDDO-IM (10 mg/kg, PO) prior to AKI induction. Renal function was evaluated by plasma creatinine (pCr) and expression of Nrf2 target genes (Nqo1/Txnrd1), tubular injury markers (KIM1/NGAL). Acute tubular necrosis was evaluated and scored.

Results: In the cisplatin model pCr levels increased from d1 through d4 indicating acute kidney injury. Pre-treatment of mice with CDDO-IM significantly reduced the pCr levels through d4 (pCr 0.32±0.047 in CDDO-IM vs. Vehicle 0.98±0.23 mg/dl; p<0.001). Txnrd1 was upregulated while kidney injury markers KIM1 and NGAL were downregulated. Furthermore, tubular necrosis was reduced indicating CDDO-IM prevented tubular injury and improved recovery from AKI. Unexpectedly, pre-treatment with CDDO-IM did not attenuate kidney injury in the CS or IRI model despite clear enhancement of NRF2 target expression. In contrast, Dexamethasone significantly improved renal function in sepsis and IRI mouse models of AKI.

Conclusions: The protective effect of Nrf2 activator CDDO-IM was evaluated in commonly used AKI models. CDDO-IM pretreatment significantly attenuated plasma biomarkers and tubular necrosis in cis, but not in sepsis or IRI related AKI in mice. The reasons for the model differences are unclear but could be related to the timing of Nrf2 activation in relation to the induction and disease progression, the severity of injury and potentially altered kidney exposures due to AKI.

Funding: Commercial Support - J & J Janssen parmaceutical

FR-PO149

Recombinant Sestrin2 Ameliorates Oxidative Stress, Mitochondrial Damage, and Renal Dysfunction in Contrast-Induced AKI

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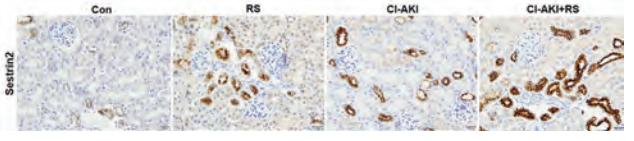
Background: Although the use of iodinated contrast agents is at times essential for accurate disease diagnosis, contrast-induced acute kidney injury (CI-AKI) is a possible complication. The pathogenesis of CI-AKI has not yet been fully elucidated, but increased oxidative stress is thought to be one important cause and mitochondrial damage is thought to accompany the consequences of oxidative stress. Sestrin2 is activated by many stress factors that have been associated with oxidative stress and mitochondrial damage.

Methods: In vivo experiments, C57BL/6 mice were divided into; control, recombinant sestrin2 (RS), CI-AKI and CI-AKI with RS groups. We examined the blood analysis, oxidative stress, mitochondrial damage and CT scans.

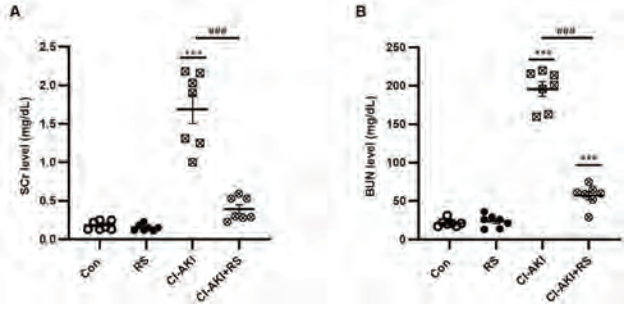
Results: Our results showed that RS decreases oxidative stress in the CI-AKI model. Mitochondrial damage presenting as morphological changes were alleviated and ATP synthesis was restored after administration of RS. Also, the decreases in relative blood volume significantly increased compared to the CI-AKI group after RS administration in the CT scan. Finally, renal injury markers also decreased and kidney function was preserved with RS. These results suggested that RS can mitigate the deterioration of renal function in CI-AKI model.

Conclusions: Sestrin2 could mitigate mitochondrial damage and apoptosis by regulating oxidative stress in a contrast-induced acute kidney injury model.

Funding: Government Support - Non-U.S.



Sestrin2 expression in the CI-AKI model



Recombinant sestrin2 attenuating renal function in the CI-AKI model

FR-PO150

Dissecting the Role of Tubular Manganese Superoxide Dismutase (MnSOD): Mitochondrial Oxidative Metabolism Disruption as an Adaptive Mechanism

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Background: Manganese superoxide dismutase (MnSOD) is an antioxidant enzyme that catalyzes the conversion of superoxide ($O_2^{\cdot-}$) to hydrogen peroxide (H_2O_2) in the mitochondrial matrix. Tubular MnSOD deletion results on renal histolgical abnormalities including tubular dilation, epithelial cell enlargement, and casts formation within the tubular lumen. However, there is no significant difference in serum creatinine or survival compared to WT mice suggesting that tubular MnSOD deletion leads to an adaptive response in mitochondrial metabolism that prevents renal dysfunction.

Methods: We developed a doxycycline-inducible pan-tubular MnSOD knock-out (Pax8rtTA-TetOcre-MnSODfl/fl, tMnSOD-KO). Mice were induced with doxycycline at 6 weeks of age, and seven months later we measued serum electrolytes and blood urea nitrogen (BUN). Transdermic glomerular filtration rate (tGFR) (WT=5 *vs.* KO=7) was evaluated prior to euthanasia. Whole kidney homogenates were used to measure mitochondrial electron transport chain (ETC) and tricarboxylic acid cycle (TCA) activities by spectrophotometric analysis and western blots (WT=11 *vs.* KO=5).

Results: No significant difference in serum electrolytes, tGFR, and BUN were noted between tMnSOD-KO and WT littermates. tMnSOD-KO and WT had no significant difference in citrate synthase activity, a surrogate marker of mitochondrial content. tMnSOD-KO kidneys demonstrated a decrease in ETC-Complex I and ETC-Complex II protein expression and activities. In contrast, ETC-Complex III and Aconitase activities were increased in the KO kidneys.

Conclusions: Tubular MnSOD deletion results in disruption of mitochondrial oxidative metabolism as well as TCA cycle enzymes 7 months post induction with preserved renal function. Future studies will provide insight into the implications of an adaptive response of mitochondrial oxidative metabolism in response to kidney injury.

Activity assay (umol/min/mg protein)	WT	KO	p
Citrate Synthase	0.004399 ± 0.0008	0.003961 ± 0.0009	ns
Aconitase	0.002190 ± 0.0004	0.002641±0.0003	*
Complex I	0.02073 ± 0.0031	0.01453 ± 0.0062	*
Complex II	0.04576 ± 0.0127	0.02585 ± 0.0085	**
Complex III	0.1256 ± 0.0175	0.1730 ± 0.0271	***
tGFR (ml/min/100g b.w.)	1.145 ± 0.1868	1.242 ± 0.3099	ns
Serum BUN (mg/dL)	33.48 ± 6.354	30.69 ± 5.535	ns

tGFR: Transdermic glomerular filtration rate; BUN: Blood urea nitrogen. Mean ± standard deviation. Mann Whitney test. * p>0.05, **p>0.01; ***p> 0.001.

FR-PO151

TRPA1 Promotes Cisplatin-Induced AKI by Regulating the Endoplasmic Reticulum Stress-Mitochondrial Damage

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Background: Cisplatin (DDP) is a widely used and effective chemotherapeutic agent against cancer. However, nephrotoxicity is one of the most common side effects of DDP, and it can proceed to acute kidney injury (AKI). The aim of this study was to investigate the mechanism of TRPA1 in promoting DDP-induced AKI through modulation of the endoplasmic reticulum stress (ERS)-mitochondrial damage.

Methods: A DDP-induced HK-2 cell model in vitro and mouse model in vivo were established and treated with the TRPA1 antagonist (HC-030031). We also used TRPA1 agonists, and treated with ERS inhibitors or GRP75 inhibitors. Renal function, histopathological changes, apoptosis, ERS and mitochondria-related proteins expression, mitochondrial changes, calcium ion concentration, cell proliferative activity, mitochondrial membrane potential (MMP), ATP, and ROS levels were also evaluated.

Results: DDP increased Scr and BUN levels, caused renal tissue injury and cell apoptosis, decreased ERS-related proteins GRP78, CHOP, and GRP75. The mitochondrial fusion-related proteins OPA1, MFN1, and MFN2, and mitochondrial division-related proteins p-DRP1 and MFF were elevated, DDP lead to mitochondrial dysfunction, and increased calcium ion concentration. In addition, DDP inhibited cell proliferation activity, decreased MMP and ATP levels, and increased ROS levels. In contrast, HC-030031 had protective effects against DDP-induced ERS and mitochondrial dysfunction

in vivo and *in vitro*. Futhermore, TRPA1 agonists promoted mitochondrial dysfunction via mitochondria-associated endoplasmic reticulum membrane. ERS inhibitors and GRP75 inhibitors increased cell proliferation activity, reduced cell apoptosis, and modulated ERS-mitochondrial damage and calcium overload to improve cell injury.

Conclusions: TRPA1 promotes DDP-induced AKI by regulating the ERS-mitochondrial damage.

FR-PO152

Long Noncoding RNA GSTM3P1 Induces mir-668 Degradation to Promote Ischemic AKI

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Background: Long non-coding RNAs (lncRNAs) play pivotal roles in ischemic acute kidney injury (AKI). Our study has identified a lncRNA, GSTM3P1, to be induced by hypoxia and to significantly enhance renal proximal tubular cell apoptosis post ATP depletion. Its mouse homologue, gstm2-ps1, exhibited a similar injurious role and induced in C57BL/6 mouse proximal tubules after 30-minute ischemia and 3-hour reperfusion. Proximal tubular specific depletion of gstm2-ps1 significantly protected mice from ischemic AKI. Our research also suggests a potential mechanism of GSTM3P1 to target a renal protective microRNA mir-668 by co-precipipation in the RNA-induced silencing complex.

Methods: A binding site of mir-668 in GSTM3P1 was confirmed through luciferase assay. However, unlike the routine lncRNA/microRNA sponge and neutralization, GSTM3P1 overexpression resulted in the degradation of mature mir-668 without affecting its primary transcript or precursor. Mutation of the mir-668 binding site in GSTM3P1 counteracted the mir-668 degradation. Thus, we hypothesized that GSTM3P1 induces mir-668 degradation through target-directed microRNA degradation (TDMD), a new regulation pathway for lncRNAs to suppress microRNAs.

Results: Accordingly, an HEK cell line with ZSWIM8 (a key TDMD complex component) knockout was established. In comparison to the wild type HEK cells, ZSWIM8 knockout hindered the mature form mir-668 degradation by GSTM3P1. Furthermore, to protect kidneys from ischemic AKI, we tested the effect of gstm2-ps1 knockdown. In vitro in cultured mouse proximal tubular cells (BUMPT), gstm2-ps1 siRNAs significantly suppressed ATP depletion-induced apoptosis. In vivo, C57BL/6 male mice were treated with negative control or gstm2-ps1 siRNAs and subjected to 25-minute bilateral kidney ischemia and 48-hour reperfusion injury. Compared to the negative control group, gstm2-ps1 knockdown exhibited significantly protection by reducing BUN and serum creatine levels. The histological examination indicated profound suppression of renal tubular necrosis and apoptosis, and a substantial decrease in renal tubular NGAL induction post injury.

Conclusions: In conclusion, lncRNA GSTM3P1/gstm2-ps1 contributes to renal proximal tubular cell death and ischemic AKI by binding to and inducing mir-668 degradation via TDMD. GSTM3P1/gstm2-ps1 can be a potential therapeutic target for mitigating ischemic AKI.

Funding: NIDDK Support

FR-PO153

Activation of Branched Chain Amino Acid (BCAA) Catabolism Protect Against AKI

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Background: BCAA (Valine, Leucine and Isoleucine) catabolic defects are implicated to be determinates of multiple diseases, however it is poorly studied in kidney injuries. Acute kidney injury (AKI) is a major risk factor for development of renal fibrosis and chronic kidney disease (CKD) but there are currently no therapies available to slow or reverse this process. AKI particularly affects proximal tubule cells (PT) and results in fundamental alterations in cellular metabolism. We previously showed that BCAA catabolic enzymes are downregulated in mice treated with the PT-specific toxin aristolochic acid I (AAI) to induce AKI, as well as human CKD. Our aim was to determine whether pharmacological activation of BCAA catabolism using the compound BT2 attenuates AAI-induced AKI.

Methods: C57Bl/6 mice were injected with 3 mg/kg AAI to induce AKI. After evaluating the frequency and dosage of AAI to induce AKI, mice were treated with two injections of AAI three days apart plus 20 mg/kg/day BT2 or DMSO. Serum was collected for urea nitrogen and creatinine measurements, and kidneys for histology, immunofluorescence, gene expression analysis, Western blotting and measurement of BCAA concentrations.

Results: There were no functional or histological differences between controls groups treated with DMSO or BT2 at baseline. Kidney function as assessed by creatinine and BUN was significantly reduced in mice treated with AAI but improved significantly in AAI+BT2 mice. Lotus lectin staining for mature PT showed extensive loss of PT in AAI-treated mice which was significantly rescued in AAI+BT2 mice. Moreover, PT injury markers such as kidney injury molecule1 (Kim-1), vimentin (Vim) and cytokeratin 20 (KRT-20) which were induced by AAI, were also attenuated in AAI+BT2 mice. We also identified an increased BCAA accumulation in kidney cortex of mice treated with AAI compared with controls, which was attenuated in AAI+BT2 mice. Interestingly, m-TORC1 pathway showed significant increase in AAI treated mice compared to controls which may be due to leucine accumulation in PT cells, whereas phospho-mTOR was reduced in AAI+BT2 mice.

Conclusions: Pharmacological activation of BCAA catabolism attenuated AKI features in mice by improving metabolism and reducing BCAA accumulation in cells which may be toxic for PT cells.

FR-PO154

TEAD1 Regulates Cisplatin-Induced AKI

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Background: Cisplatin is an inorganic platinum-based chemotherapeutic agent that is widely used for the treatment of solid tumors. However, a known complication of cisplatin administration is acute kidney injury (AKI). Despite recent advances in examining the molecular mechanisms, no potential strategy exists to prevent kidney injury. In this study, we examined the role of TEA domain family member 1 (TEAD1) in the pathogenesis of cisplatin-induced AKI.

Methods: We generated proximal tubule-specific TEAD1 knockout ($TEAD1^{PKO}$) mice by crossing TEAD1 floxed mice with PEPCK-Cre mice. Ten-week-old male $TEAD1^{PKO}$ mice and $TEAD1^{f/f}$ ($TEAD1^{CON}$) mice were administered a single intraperitoneal dose of cisplatin (20mg/kg body weight), or vehicle (saline) to induce AKI. Blood and kidneys were collected at 72h for assessment of kidney function, tubular cell injury, cell death and inflammation. Lentivirus transfection was utilized to knock down the expression of TEAD1 in mouse tubular epithelial cells *in vitro*. Cells were treated with cisplatin (20μM, 24h) for determination of intracellular ROS and mitochondrial function.

Results: TEAD1 expression was upregulated in tubular epithelial cells of kidneys with cisplatin-induced AKI. $TEAD1^{PKO}$ mice treated with cisplatin had increased tubular cell damage and enhanced kidney dysfunction compared with $TEAD1^{CON}$ mice. Additionally, $TEAD1^{PKO}$ mice had augmented necroptotic cell death and inflammatory response compared with $TEAD1^{CON}$ mice treated with cisplatin. Knockdown of TEAD1 in mouse tubular epithelial cells promoted intracellular ROS levels, which was associated with reduced ATP production and impaired oxygen consumption rate.

Conclusions: Taken together, our results indicate that TEAD1 plays an important role in the pathogenesis of cisplatin–induced AKI through regulation of necroptosis and inflammation which may be associated with impaired mitochondrial function. TEAD1 may represent a novel therapeutic target for cisplatin-induced AKI.

Funding: NIDDK Support

FR-PO155

AMPK Activation Protects Kidney Function After Renal Ischemia Reperfusion Injury in Rats

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Background: The kidney has a high energy demand to carry out its function, and with Acute Kidney Injury (AKI) such as ischemia reperfusion, there is profound mitochondrial damage. Adenosine Monophosphate Kinase (AMPK) is a key regulator of mitochondrial function and biogenesis. Here, we used a rat model of ischemia-reperfusion inducing AKI to explore the effect of pharmacological activation of AMPK.

Methods: Male Spraque Dawley rats were treated with a direct AMPK activator (n=12) or vehicle (n=12) one hour prior to ischemia reperfusion induced by bilateral clamping the renal pedicles for 35 minutes. Kidney functions was assessed by transcutaneous glomerular filtration rate (tGFR) measured at 5-7 hours using the Medibeacon technology, and kidney, plasma and urine were collected for analysis of plasma creatinine, urinary NephroCheck and kidney histology 7 hours post injury.

Results: Plasma creatinine and tGFR were significantly improved in the animals treated with AMPK activator compound compared to vehicle control with a 28% reduction of creatinine (1.53±0.257 versus 1.10±0.184 mg/dl, $p<0.001$) and 69% improvement in tGFR (0.0792± 0.0452 versus 0.135±0.0738 ml/min/100g bodyweight, $p<0.05$). AMPK activation improved urinary NephroCheck score (0.0764±0.0564 versus 0.00899±0.00356 $(ng/ml)^2/1000$ of IGFBP7 and TIMP2, $p<0.001$) and acute tubular necrosis in the cortex.

Conclusions: Pharmacological activation of AMPK alleviated kidney function and preserved tubular structure. These data support AMPK activation as a novel therapeutic approach for AKI.

Funding: Commercial Support - Janssen R&D

FR-PO156

Notch Signaling Pathway Mediates Anti-Inflammatory Effects of Vagus Nerve Stimulation

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Background: A novel strategy for the prevention and treatment of AKI is activating the cholinergic anti-inflammatory pathway (CAP), a neuroimmune circuit. The CAP can be initiated by vagus nerve stimulation (VNS) and subsequent activation of splenic and peritoneal macrophages (MΦ), leading to suppression of pro-inflammatory cytokine production. We previously showed that an increase in hairy and enhancer of split 1 (Hes1) in peritoneal MΦ contributes to renoprotective effects of CAP. Hes1 is a transcriptional factor, and its expression is regulated by the Notch signaling pathway. However, a direct

relationship between the CAP and Notch signaling has been unclear. In the current study, we focused on Notch signaling in MΦ to unravel the detailed molecular mechanism of CAP and to determine the utility of Notch signaling in ameliorating AKI.

Methods: To test if VNS activates Notch signaling in MΦ, we performed VNS before lipopolysaccharide (LPS)-induced AKI. After LPS administration, gene expression of Notch components, cytokines, and *Kim-1* was assessed by qPCR. MΦ-specific *Notch2* KO mice (*Cx3cr1Cre; Notch2$^{fl/fl}$*) and controls (*Notch2$^{fl/fl}$*) were subjected to VNS to evaluate whether Notch2 mediates anti-inflammatory responses in MΦ. Flow cytometry analysis was performed to examine the influence of MΦ-specific Notch2 expression on immune cell subpopulations.

Results: VNS suppressed an LPS-induced upregulation of pro-inflammatory cytokines (*Tnfa, Il1b*, and *Ccl2*) in MΦ and *Kim-1* in kidneys. This event was accompanied by an increase in Notch components including *Hes1* in MΦ. After VNS and LPS treatments, BUN levels were increased in *Notch2* KO mice, compared to WT controls. Consistently, these *Notch2* KO mice showed higher levels of *Ccl2* (but not *Tnfa* and *Il1b*) and *Kim-1* expression in the MΦ and kidneys, respectively. Flow cytometry analysis revealed that under physiological conditions, Notch2 deficiency in MΦ induced a decrease in MΦ and monocyte numbers in the spleen and circulation.

Conclusions: Our findings suggest that: 1) during LPS-induced AKI, Notch2 mediates anti-inflammatory effects of VNS by suppressing *Ccl2* expression in MΦ, and 2) Notch2 in MΦ positively regulates cell subpopulations of MΦ and monocytes, which might inhibit neutrophil infiltration into the kidneys and attenuate subsequent injury.

Funding: Private Foundation Support

FR-PO157

Transient Nucleus-to-Cilium Microtubule Assemblies Initiate Senescence in Stressed Renal Epithelial Cells

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Background: Cellular senescence plays a critical role in diminishing regenerative capacity and exacerbating kidney injury. In previous research, we demonstrated that the translocation of a ciliary protein, FBF1, to promyelocytic leukaemia nuclear bodies (PML-NBs) is crucial for inducing senescence in stressed human cells. However, how FBF1 translocates into the nucleus upon exposure to stressors remain elusive.

Methods: Human renal cortical tubular epithelial cells (RCTE) were exposed with irradiation, inflammatory cytokines, or oxidative stress to induce cellular senescence. Senescent level was determined using Senescent Associated (SA)-b-Gal staining, and protein and RNA levels of senescence and SASP markers. Immunofluorescence was employed to detect sinc-MTs. Microtubule assembly was disrupted in RCTE cells using Colchicine or knockdown CDK5RAP2. Knockdown of the tubulin glutamylases were performed to investigate the role of polyglutamylation in sinc-MT-mediated senescence induction. Western blotting, confocal imaging, and super-resolution Structure Illumination Microscopy (SIM) were used to determine the expression and subcellular localization of key components. Protein-protein interaction were analyzed through APEX2 based BioID analysis and confirmed by exogenous and endogenous immunoprecipitation assays.

Results: Here, we discovered a novel phenomenon that, in renal epithelial cells, irreparable stressors induce a transient assembly of nucleus-to-cilium microtubule assays (sinc-MTs), which are highly polyglutamylated, unconventionally polarized with minus-ends nucleating near the nuclear envelope and plus-ends anchored below the ciliary base. KIFC3, a minus-end-directed kinesin, is recruited to cilia base in stressed cells and use centrosomal protein CENEXIN1 as an adaptor to translocate FBF1 towards the nucleus along sinc-MTs. Deficiency of KIFC3 or CENEXIN1 abolishes both FBF1 translocation and senescence initiation in stressed cells.

Conclusions: Collectively, we elucidate the mechanistic insights into the essential role of a stress-induced sinc-MTs in transducing stress-induced ciliary signals into the nucleus to initiate senescence program in damaged renal epithelial cells. Our findings highlight the potential of targeting cilia as a therapeutic strategy for senescence-related kidney diseases.

FR-PO158

The Effects and Mechanism of Circadian Rhythm on Contrast-Induced Renal Injury

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Background: The circadian clock of mammals regulates various life activities. As an important metabolic organ in the body, the kidney exhibits a certain diurnal pattern in glomerular filtration function and ion transport of renal tubules. In view of the huge basic population of using contrast agents for diagnosis and treatment, as well as the potential long-term risks of renal diseases, contrast-induced acute kidney injury (CI-AKI) is a clinical problem that cannot be ignored. Although the pathogenesis of CI-AKI has been partially understood, the role and mechanism of circadian rhythm in contrast agent renal injury is still unknown.

Methods: The study retrospectively analyzed 33 patients undegoing percutaneous coronary angiography and coronary angioplasty in the cardiovascular center of our hospital from October 2020 to June 2022. In addition, all the mice were injected with 10 g/kg Iohexol through the tail vein at ZT0 or ZT12, respectively and sacrificed 24 hours later.

Results: The change of serum neutrophil gelatinase-associated lipocalin (NGAL) in the morning group (7:00~13:00) was higher than that of the afternoon group (13:00~20:00). The injection of Iohexol at ZT0 had almost no significant effects on the renal tissue of mice. While the injection of Iohexol at ZT12 increased the expression of kidney injury molecule 1 (KIM1), NGAL and lipid peroxidation products and reduced the expression of glutathione peroxidase 4. Knockdown of *Clock* in primary proximal renal tubular cells decreased the expression of *Nrf2* and its downstream antioxidant target genes, while over-expression of *Clock* restored the expression of *Nrf2*. Finally, 4-octyl itaconate was intraperitoneal injected to upregulate the expression of NRF2 at ZT12, which alleviated the renal tubular injury caused by Iohexol.

Conclusions: The study shows the circadian clock regulates NRF2 mediated antioxidant response, which in turn leads to diurnal differences in contrast-induced renal injury.

Funding: Government Support - Non-U.S.

FR-PO159

Autophagy-Associated FIP200 Protects Renal Tubules Against Apoptosis Following Renal Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI) easily progresses to chronic kidney diseases. Renal ischemia-reperfusion injury (IRI) is an important cause of AKI. The pathogenesis of renal IRI is complex, and its pathological characteristics mainly include renal tubular epithelial cell injury. Apoptosis is one of the main mechanisms of hypoxia-induced renal tubular epithelial cell death. Autophagy regulates apoptosis and plays a key role in the development of renal IRI. FAK family-interacting protein of 200 kDa (FIP200) is a crucial component of the ULK-1-Atg13-FIP200 complex formed in mammalian cells upon autophagy induction. However, the precise mechanisms of FIP200 in renal IRI-mediated AKI remains elusive.

Methods: The Billups hypoxic modular systemwas used to establish the hypoxia/reoxygenation (H/R) cell model in HK2 cells. Cells were maintained under hypoxia for 5 min, 30 min, 45 min, 1 h, 2 h, 4 h, 6 h, and 24 h, and then reoxygenated for 24 h. Cells in the control group were not subjected to hypoxia then reoxygenation. All animal studies were approved by the Ethics Committee of Sichuan Provincial People's Hospital (approval No. L201735). Twenty-four wild-type mice were divided into 8 groups, and the renal pedicles of their left kidney were clamped with microvascular forceps. Then, 12 FIP200 conditional knockout (FIP200loxp-/loxp--Ggt cre/mice) mice in the renal tubular epithelial cell, in parallel to 12 wild-type mice, were randomly divided into renal IRI group and sham operation group.

Results: The expression of the autophagy-related protein FIP200 was up-regulated in vivo and in vitro after renal IRI or hypoxia/reoxygenation (H/R). Mice with conditional FIP200 knockout in renal tubules showed severe renal tissue damage after IRI. Overexpression and knockdown of FIP200 in HK2 cells revealed its protective effects on H/R injury of renal tubular epithelial cells. FIP200 could interact with HMGB1 by immunoprecipitation assays and biolayer interferometry. FIP200 could induce autophagy by regulating the competitive binding of HMGB1 and autophagy-related factors.

Conclusions: Our data indicate that FIP200 has an important role in preventing renal tubular cell damage and death following renal IRI, and might be a novel potential target for prevention and treatment of AKI caused by IRI.

FR-PO160

JMJD3 Activation Contributes to Renal Protection and Regeneration Following AKI in Mice

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Background: We have recently demonstrated that Jumonji domain-containing protein D3 (JMJD3), a histone demethylase of histone H3 on lysine 27 (H3K27me3), is protective against renal fibrosis, but its role in acute kidney injury (AKI) remains unexplored.

Methods: Murine renal tubular epithelial cells (mRTECs) were treated with GSK or siRNA specific for JMJD3. A folic acid (FA)-induced AKI murine model was created by peritoneal injection of FA at 250 mg/kg and a biliteral I/R murine models were established by occluding with a non- traumatic vascular clamp for 35 minutes in mice.

Results: Injury to the kidney upregulated JMJD3 and induced expression of H3K27me3, which was coincident with renal dysfunction, renal tubular cell injury/apoptosis and proliferation. Blocking JMJD3 activity by GSKJ4 led to worsening renal dysfunction and pathological changes by aggravating tubular epithelial cell injury and apoptosis in both murine models of AKI. JMJD3 inhibition by GSKJ4 also reduced renal tubular cell proliferation and suppressed expression of cyclin E, phosphorylation of CDK2, but increased p21 expression in the injured kidney. Furthermore, inactivation of JMJD3 enhanced I/R- or FA-induced expression of TGF-b1, vimentin and Snail, phosphorylation of Smad3, STAT3 and NF-kB and increased renal infiltration by F4/80 (+) macrophages. Finally, GSKJ4 treatment caused a further downregulation of Klotho, BMP-7, Smad7 and E-cadherin, all of which are associated with renal protection and anti-fibrotic effects.

Conclusions: These data provide strong evidence that JMJD3 activation contributes to renal epithelial tubular cell survival and regeneration after AKI.

Funding: Government Support - Non-U.S.

FR-PO161

MLL1 Activation Contributes to Renal Protection and Regeneration Following AKI Induced by Folic Acid and Ischemia/Reperfusion

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Background: Mixed lineage leukemia 1 (MLL1) is a methyltransferase that induces histone H3 lysine 4 trimethylation (H3K4me3) and exerts its functional roles by interacting with multiple subunits including WD repeat-containing protein 5 (WDR5) and Menin. In this study, we investigated the role and mechanisms of MLL1 in murine models of acute kidney injury (AKI) induced by folic acid (FA) and ischemia/reperfusion (I/R).

Methods: A folic acid (FA)-induced AKI murine model was created by peritoneal injection of FA at 250 mg/kg and a biliteral I/R murine models were established by occluding with a non- traumatic vascular clamp for 35 minutes in mice.

Results: Injury to the kidney elevated expression of MLL1, Menin, WDR5 and H3K4Me3, which was accompanied by increased serum creatine (Scr) and blood urea nitrogen (BUN), renal tubular injury and apoptosis. Pharmacological inhibition of MLL1 activity with MI503 to disrupt the interaction between MLL1 with Menin further increased Scr and BUN levels, enhanced expression of neutrophil gelatinase associated lipocalin and kidney injury molecule-1, and induced more apoptosis in the kidney following FA and I/R injury. In contrast, MI503 decreased the expression of vimentin and proliferating cell nuclear antigen. Similarly, treatment with MM102 to disrupt the interaction between MLL1 and WDR5 also worsened renal dysfunction, aggravated tubular cell injury and apoptosis, and inhibited cellular dedifferentiation and proliferation in mice following FA injection. Moreover, MI503 inhibited FA-induced phosphorylation of epidermal growth factor receptor (EGFR), signal transducer and activator of transcription 3 and extracellular signal-regulated kinase-1/2 in injured kidneys.

Conclusions: Collectively, these data suggest that MLL1 contributes to renal protection and functional recovery and promotes renal regeneration through a mechanism associated with activation of the EGFR signaling pathway.

Funding: Government Support - Non-U.S.

FR-PO162

Histone Methyltransferase SMYD2 Promotes AKI and Renal Regeneration by Activating Epidermal Growth Factor Receptors

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Background: Protein methyltransferase SET and MYND domain containing protein 2 (SMYD2) is one of the most widely studied lysine methyltransferases. It is involved in the development of numerous tumors and renal fibrosis by inducing methylation of H3K36 and H3K4 as well as multiple non-histone protiens, but its role in acute kidney injury (AKI) remains unclear.

Methods: In this study, we investigated the role and mechanism of SMYD2 in murine models of AKI induced by folic acid (FA), ischemia/reperfusion (I/R), as well as cecal ligation and puncture (CLP) using highly selective inhibitor AZ505 and renal tubular conditional knockout mice of SMYD2.

Results: Following AKI, the expression levels of SMYD2 and H3K36Me3 were significantly increased, along with the increase of serum creatinine (Scr) and urea nitrogen (BUN) levels, renal tubule cell injury and apoptosis. Administration ofAZ505 further increased levels of Scr and BUN, enhanced the expression of neutrophil gelatinase- associated lipocalin (NGAL), kidney damage molecule-1 (Kim1), and the apoptosis-related proteins such as cysteine-aspartate protease 3 (Caspase3), polyadp ribose transferase (PARP) and BAX. Conversely, pharmacological inhibition of SMYD2 reduced the expression of proliferating cell nuclear antigen and Vimentin. Similarly, conditional knockout of renal tubule SMYD2 aggravated renal impairment, tubular cell injury and apoptosis and inhibited the dedifferentiation and proliferation of renal tubular cells in mice following acute injury. Moreover, AZ505 and tubule conditional SMYD2 knockouts significantly inhibited phosphorylation of renal epidermal growth factor receptor (EGFR), Akt and extracellular signal-regulated kinase 1/2 (ERK1/2). In cultured renal tubular cells, selective inhibition of SMYD2 by AZ05 or silencing of EGFR by siRNA also resulted in decreased phosphorylation of EGFR, Akt and Erk1/2.

Conclusions: These findings suggest that the expression and activation of endogenous SMYD2 contributes to renal protection and tubular cell regeneration through a mechanism involved in the activation of EGFR signaling pathway.

Funding: Government Support - Non-U.S.

FR-PO163

Upregulating NRF2 Is a Critical Regulatory Mechanism for the Protective Effect of Ultrasound to Mitigate Sepsis-Associated AKI

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Background: Sepsis-induced oxidative stress and dysfunction of innate immune response have emerged as key players in the pathogenesis of sepsis-associated acute kidney injury (S-AKI). Nuclear factor-erythroid-derived 2-related factor 2 (NRF2), a key oxidative stress regulator, has been implicated to play an important role in T cell–specific augmentation of Nrf2 to mitigate oxidative stress. Our previous studies indicated that pulsed ultrasound (pUS) can reduce inflammation and acute kidney injury in mice. We hypothesis that pUS mediated protection is associated with enhanced the expression of Nrf2 and reduced immune system dysfunction. In this study, we utilized LPS-induced S-AKI in normal and Nrf2–/– mice, and we used RAW264.7 cells to investigate the effects of pUS on LPS-induced kidney injury, macrophage filtration and NRF2. In addition, we also investigated whether pUS protection occurs through enhanced NRF2 expression and disturbed CD4+ T cells immune function in human Jurkat T cells.

Methods: C57/BL/6 mice received pUS 24 hours before LPS (5 mg/kg, ip) treatment. The parameters of pUS therapy followed the protocol we previously published. In vitro studies were performed using RAW cells and Jurkat T-cell lines, which were cultured and stimulated with LPS (100ng/ml) for 6h. NRF2 protein and mRNA expression was measured by immunofluorescence and RT-PCR respectively. Kidney injury was assessed by Kim1, cleaved-caspase-3 and plasma creatinine assay. Iba1, F4/80 and CD4+ T cells were used to evaluate immune cells/macrophage infiltration.

Results: LPS produced AKI and macrophage/lymphocyte filtration in WT mice with a dramatic decline of NRF2. Furthermore, pUS-treated mice with high Nrf2 expression had fewer Iba1+ and F4/80+ macrophage infiltration in the kidney and CD4+ T cells in Jurkat T cells and attenuated sepsis-induced AKI. In contrast, LPS stimulus induced greater infiltration of microphages, as well as more early time and more severe renal injury in Nrf2–/– mice compared with litter mate control mice. pUS attenuated S-AKI.

Conclusions: These results suggest that upregulating Nrf2 antioxidant defenses in kidney and in T cells are essential for ultrasound to attenuate oxidative stress-induced AKI. Our results reveal a novel mechanism for pUS protection from kidney injury during S-AKI.

Funding: NIDDK Support

FR-PO164

AKI-Induced Senescence as a Key Player in CKD Progression: Insights from an Aristolochic Acid Mouse Model

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Background: Senescence is a persistent cell cycle arrest accompanied by a senescence-associated secretory phenotype (SASP). The role of tubular senescence in driving chronic kidney disease (CKD) following acute kidney injury (AKI) remains controversial due to the multiple animal models used and different timepoints of senescent cell depletion. To accurately represent a direct injury induction of tubular senescence, we utilized a mouse model of Aristolochic acid (AA), a nephrotoxicant known in the clinical setting to promote DNA damage specifically in tubular epithelial cells (TECs). Our model of persistent injury following AA-induction of AKI leads to tubular senescence and allows to study diverse timepoints of CKD progression.

Methods: An AKI to CKD model was created by a single intraperitoneal injection of 5 mg/kg of AA into male C57BL/6 mice. *In vitro* studies utilized 1-10ug/ml AA, and HK-2 (human proximal tubule cell line), mTECs (primary mouse TECs), and NRK-49F (kidney fibroblast cell line). Senolytics (ABT-263) were used to eradicate senescent cells, while senomorphics (Metformin) inhibited SASP.

Results: *In vivo*: Compared to the control, AA-induced tubular senescence as early as 7 days post-injury, as shown by increased p53, p21, p16, γH2AX expression, and β-Gal activity in tubules. AA-treated mice displayed CKD signs of tubular damage and tubulointerstitial fibrosis. Timing of senolytic treatment affected therapeutic outcomes, with early clearance of senescent cells post AA injection protecting against fibrosis. Clearance of SASP factors using Metformin from day 3 post AA injection mitigated renal fibrosis and senescent burden. *In vitro*: AA-induced senescence in HK-2 and mTECs. Senescent HK-2 cell-derived conditioned medium promoted epithelial-to-mesenchymal transition in HK-2 cells and fibroblast-to-myofibroblast transition in NRK-49F cells, which was reversed by Metformin treatment.

Conclusions: Using a model of specific tubular DNA damage, our data reveal that: i) TEC senescence is a key link in the AKI to CKD transition; ii) Precise timing of senescent cell removal by senolytic treatment is critical to achieving therapeutic benefits; iii) Therapeutic inhibition of SASP by senomorphics reduces renal fibrosis and senescence, offering a potential alternative to senolytics.

Funding: Government Support - Non-U.S.

FR-PO165

Spns2 Deficiency Protects the Mouse Kidneys During Ischemia-Reperfusion Injury

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Background: Spns2 (Spinster homolog 2) is transmembrane protein that transports sphingosine 1-phosphate, a bioactive lipid that acts as an extracellular ligand and intracellular second messenger in a variety of biological functions. In the present study, we investigated the effect of inducible global *Spns2* deletion or pharmacological inhibition of Spns2 in mouse kidneys after bilateral ischemia-reperfusion injury (IRI).

Methods: *Ubiquitin-CreERT2*;*Spns2*$^{fl/fl}$ mice (*iSpns2*^{UBCKO}) and *iSpns2*$^{fl/fl}$ littermates were injected with tamoxifen (1 mg, i.p.) daily for 5 days and rested for 2 weeks before 28 min ischemia followed by 24 h reperfusion. C57BL/6 mice were pre-treated 24 h before IRI with Spns2 inhibitor (SLF1081851, 10 mg/kg, i.p.) or vehicle. Relative kidney *Spns2, Ngal, Kim1, Cxcl1, and Cxcl10* mRNA expression were estimated by qPCR and neutrophil infiltration by immunofluorescence labeling using Ly6G clone1A8 antibody.

Kidney injury was evaluated by measuring plasma creatinine (PCr) and BUN and by scoring acute tubular necrosis (ATN) in H&E stained sections.

Results: Relative kidney mRNA of *Spns2* in *iSpns2^{UBCKO}* mice after tamoxifen treatment was significantly reduced compared to *iSpns2$^{fl/fl}$* mice: 0.5±0.1 vs. 1.0±0.1, P=0.006. After IRI, the increase in mRNA of kidney injury markers *Ngal* and *Kim1* and PCr and BUN in *iSpns2$^{fl/fl}$* mice were significantly reduced in *iSpns2^{UBCKO}* mice (4.2±0.7 vs. 1.40±0.2, P=0.0023; 38.8±8.3 vs. 2.4±1.0, P=0.0042; 9±0.1 vs. 0.4±0.1, P=0.0017; and 186.7±13.3 vs. 56.6±11.4, P<0.0001). *Cxcl1* and *Cxcl10* mRNA and kidney neutrophil infiltration were similar in *iSpns2^{UBCKO}* and *iSpns2$^{fl/fl}$* mice after IRI. ATN scores for *iSpns2$^{fl/fl}$* vs. *iSpns2^{UBCKO}* were 57.6±3.6 vs.10.1±1.6 (P<0.0001). The increase in PCr and BUN in C57BL/6 mice was reduced significantly by SLF1081851 (1.4±0.3 vs. 0.4± 0.1, P=0.007; 159.7±15.0 vs. 79.9±18.9, P=0.006). SLF1081851 decreased ATN score compared to vehicle (42.8±9.4 vs.14.9±4.3, P=0.027).

Conclusions: Our results demonstrate that genetic global deletion or pharmacological inhibition with a selective Spns2 inhibitor protects kidneys from IRI, suggesting that SPNS2 can serve as a potential target to prevent AKI.

Funding: NIDDK Support

FR-PO166

Targeted IRAK4 Degradation Impairs Kidney Stromal Cell Myddosome Signaling and Reduces Tubulointerstitial Fibrosis in AKI

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Background: Renal fibrosis is a process of pervasive interstitial scarring driven by kidney stromal fibrogenic cells. Previous data have indicated that inflammatory signaling via the fibrogenic cell myddosome complex is critical for kidney fibrosis development. Within the myddosome, modulation of interleukin-1 receptor associated kinase 4 (IRAK4) by small molecule kinase inhibitors reduces fibrosis, but has limited anti-inflammatory effect, indicating that the IRAK4 scaffold function is sufficient for canonical activation of NF- kB.

Methods: Here we used a novel strategy to abrogate IRAK4 by means of targeted ubiquitination followed by proteasomal degradation. We tested the antifibrotic and anti-inflammatory activity of an IRAK4 degrader molecule in vitro and in vivo in a model of acute kidney injury in mice.

Results: Incubation with degrader resulted in abrogation of IRAK4 protein levels, and reduced formation of myddosome complex in primary kidney fibrogenic cells. In human kidney organoids, IRAK4 degradation reduced both extracellular matrix deposition, as well as fibrosis gene expression caused by nephron tubule damage. Further, the treatment resulted in inhibition of NF-kB activation and downstream inflammatory cytokine expression. In vivo, the IRAK4 degrader showed increased efficacy compared to the small molecule kinase inhibitor CA-4948 in ameliorating fibrosis and inflammation following ischemia/reperfusion injury.

Conclusions: Collectively, our results indicate that targeted degradation of IRAK4 is a superior therapeutic approach to kinase inhibitors for the treatment of renal fibrosing disorders.

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FR-PO167

mRNA Editing via the Apobec1 Gene Promotes Recovery from AKI

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Background: Cisplatin (CP) and Ischemia/reperfusion Injury (IRI) induces AKI whereby proximal tubules (PT) undergo necrosis. We now examine the role of Apobec1, which regulates mitochondrial metabolism and cell fate, in the recovery from these forms of AKI.

Methods: Wild type (WT) and Apobec1 knockout (KO) mice received CP 15 mg/kg or were subjected to 20min IRI. Renal function, histology, mRNA, protein, lipids, and RNA sequencing were analyzed and compared. Bone marrow-derived macrophages (BMDM) were isolated from mice treated with or without CP, and their morphology, polarization, and cytokines secretion were analyzed.

Results: Apobec1 KO resulted in more severe CP-AKI as compared to WT (plasma creatinine (pCr): 2.07 mg/dL ± 0.59 vs 0.23 ± 0.09, p < 0.01 in WT) and IRI-AKI (pCr: 1.34 ± 0.22 vs 0.75 ± 0.06, p<0.05 in WT). Inflammatory cytokines were markedly increased in the Apobec1 KO animals after CP. The kidneys of Apobec1 KO showed greater necrosis, neutrophil invasion, activated T cells, elevated markers of injury, as macrophages were unexpectedly reduced. Apobec1 KO BMDM failed to polarize to M1 phenotype in vitro and to home to the kidney in vivo. High resolution microscopy of BMDM isolated from KO AKI animals revealed reduced mitochondria numbers and altered mitochondrial structure as compared to WT AKI animal. Activation of both AMPK α and β was observed in Apobec1 KO AKI, suggesting increased mitochondrial fatty acid oxidation. Mutational and pathway analysis of apobec1 derived mRNA editing differences in WT AKI and Apobec1 KO AKI showed Apobec1 potentially edits genes involved in oxidative stress, inflammation, sterol regulatory element-binding protein signaling, apoptosis and ferroptosis. Overexpression of Apobec1 in PTs in vitro reduced the ferroptosis regulator Acsl4 expression. The Apobec1 KO phenotype in CP-AKI could be rescued by intravenous injection of either BMDMs isolated from WT animals, or of the mitochondrial uncoupler BAM15.

Conclusions: We have identified Apobec1 as a crucial gene regulating the stress response to AKI. The absence of Apobec1 provoked greater oxidant stress and prevented the homing of macrophages to the injured kidney, thus preventing repair and regeneration. Increasing Apobec1 activity could be an effective strategy to reduce or prevent AKI.

FR-PO168

Meprin β Activity Modulates Cellular Proliferation via Trans-Signaling IL-6-Mediated AKT/ERK Pathway in Ischemia/Reperfusion (IR)-Induced Kidney Injury

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Background: Inflammation plays a central role in the progression of kidney injury induced by ischemia/reperfusion (IR). Meprin metalloproteinases have been implicated in the pathophysiology of IR-induced kidney injury. We previously showed that meprin β modulates cellular survival (BCL-2) through IL-6/JAK/STAT signaling pathway in IR-induced kidney injury. However, it's not known how meprin β modulation of the IL-6 signaling pathway impacts the cellular proliferation in IR-induced AKI. IL-6 trans-signaling induces proliferation through either MAPK/ERK or PI3K/AKT pathway or in crosstalk with AKT/ERK. PCNA is a cellular proliferation marker that is induced through activation of the IL-6 signaling pathway. The goal of the current study was to determine how meprin β modulation of the IL-6 signaling pathway impacts downstream cellular proliferation in IR-induced kidney injury.

Methods: We used the unilateral IR as a model of renal inflammation in wild-type (WT) and meprin β knockout (βKO) male mice, with the contralateral kidneys serving as controls. The mice were sacrificed at 96 h post-IR, and kidney tissue processed for evaluation by RT-PCR and immunohistochemistry. Statistical analysis of data utilized two-way ANOVA.

Results: Our PCR data showed significant increase in mRNA levels for IL-6 and PCNA in WT and βKO mice at 96 h-post IR when compared to WT control kidneys. Immunohistochemical data showed significant increases in IL-6, PCNA, p-AKT and p-ERK in select tubules in both genotypes at 96 h post-IR compared to control kidneys. Data from immunofluorescence of kidney tissues showed that the levels of IL-6, PCNA, p-AKT and p-ERK were higher in meprin β-expressing proximal tubules (PTs), at 96 h post-IR when compared to the distal kidney tubules (DTs), which lack meprins. High levels of IL-6 were also present in the lumen of PTs and DTs from WT and βKO kidneys at 96 h post-IR, suggesting increased release into filtrate and subsequently into urine. However, high levels of PCNA, p-AKT and p-ERK were present in the lumen of PTs only from both genotypes at 96 h post-IR.

Conclusions: In conclusion, our data shows that meprin β activity modulates cellular proliferation via trans-signaling IL-6-mediated AKT/ERK pathway in IR-induced kidney injury.

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FR-PO169

Kidney Metabolomics of NHERF1 Deficiency

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Background: Mice lacking NHERF1 (Na^+-hydrogen exchanger regulatory factor isoform 1) show increased susceptibility to toxin-induced acute kidney injury (AKI) associated with increased activity of enzymes of the pentose phosphate pathway. We hypothesize that NHERF1 deficiency results in altered kidney cell metabolism associated with enhanced injury response. To test this hypothesis, we performed targeted metabolomic analysis of kidney cortex of wild type (WT) and NHERF1 knockout littermates (KO) in response to saline (vehicle; V) or cisplatin (C).

Methods: 5 WT and 5 KO littermate mice underwent IP injection with either saline or 20 mg/kg body weight of cisplatin (n=20). Kidneys were harvested after 72 h for metabolite extraction with HPLC-grade methanol. Ultrahigh-performance liquid chromatography tandem mass spectrometry performed by the UTSW Metabolomics Core within the Dept of Biochemistry identified over 140 metabolites in the four experimental groups: WTV; WTC; KOV; and KOC.

Results: Principal component analysis demonstrated significant variance between all four experimental groups implicating both NHERF1 absence and cisplatin-induced AKI in metabolic shift. A clear separation was seen between WTV and KOV. Enrichment and Pathway Analysis comparing WTV/KOV demonstrated enrichment of metabolites associated with methylhistidine and glycerophospholipid metabolism, phosphatidylcholine biosynthesis, and the pentose phosphate pathway. After cisplatin, major differences were noted between WTC and KOC in metabolites associated with lipid and phospholipid biosynthesis, nucleotide sugar metabolism, and mitochondrial electron transport chain.

Conclusions: NHERF1 deficiency alters carbohydrate and lipid metabolism similar to what is seen in response to kidney disease such as diabetes and uninephrectomy and alters metabolic response to injury. Whether these metabolic changes are due to deficient nutrient uptake or altered intracellular pathway integrity and how these changes predispose to acute injury are unknown.

Funding: Veterans Affairs Support

KOV vs. WTV	Fold change	KOC vs. WTC	Fold change
N-acetyl-glutamate	↑	UDP-N-acetyl-glucosamine	↑
SN-glycerol-3-phosphate	↑	Adenylosuccinate-1	↑
NADP+	↑	UDP-D-glucose	↑
Choline	↓	CDP-ethanolaamine	↑
Gamma-aminobutyric acid	↓	UDP-D-glucoronate	↑
N-acetyl-putrescine	↓	UMP	↑
Carnitine	↓	Cystine	↑
S-adenosyl-L-methionine	↓	GMP	↑
Uracil	↓	Glutathione	↑
Allantoin	↓	N-acetyl-glutamine	↑
D-gluconate	↓	7_8-dihydrofolate	↑
6-phospho-D-gluconate	↓	4-Pyridoxic acid	↑
		Creatine	↑
		Allantoin	↑
		Dihydroxy-acetone-phosphate	↑
		Citrulline	↑
		Valine	↓
		Ethanolamine	↓
		Nicotinate	↓
		Serine	↓
		Phenylalanine	↓
		Threonine	↓
		Homocysteic acid	↓
		NAD+	↓
		Methionine sulfoxide	↓

FR-PO170

Altered Lipid Metabolism Exacerbates Endotoxin-Associated Kidney Injury in Diabetes

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Background: Diabetes is a risk factor for endotoxin-associated acute kidney injury (sAKI). In a non-comorbid murine model of sAKI, we previously identified that renal tissue plays a role in the mediation of innate immune responses and cell-specific temporal changes in the lipid metabolism transcriptome, culminating in organ failure (16 hr) followed by recovery (24 hr). Bioactive lipids (bL) are spatially and functionally dysregulated in both diabetes and sepsis and play diverse roles in immunity, inflammation, and kidney injury, with ceramide at the nexus of sphingolipid metabolism. We hypothesized that metabolic dysregulation of bL mediates sAKI in the diabetic milieu.

Methods: Lipopolysaccharide (LPS) was given intravenously (iv) to diabetic (BKS.Cg-Dock7m+/+ Leprdb/J) mice (db) and littermates (db+) sacrificed at 0 (baseline), 16 (injury), 24 hr (recovery) after LPS iv, serum, kidneys collected. Serum creatinine (Scr) quantified (MS). ScRNAseq: dissociated kidneys sequenced (10x Chromium) and clustered (Seurat). Cryogel mounted tissue (15 uM) imaged and untargeted DESI-MSI and analysis performed (positive and negative ion modes, m/z range: 100-1,200, Cardinal MSI), attributions assigned (Lipid Maps Structural Database and Human Metabolome Database).

Results: Db at 24 hr (vs. 0 hr) had persistent renal injury (Kim1 Log_2FC 8.32±1.01, Scr 0.38±0.34) vs. db+ (Kim1 Log_2FC 3.51± 0.58, Scr (0.10 ± 0.01). In db (vs db+), putative C16 ceramide remained elevated in the renal medulla (16, 24 hr), reduced levels of protective C24 ceramide in the cortex (0 hr). In db (0-24 hrs) there was significantly altered metabolism of glycerophospholipids (i.e., phosphoinositols), fatty acyls, sterols, compared to db+. Db scRNAseq at 16,24 hrs had decreased expression in glycosphingolipid-metabolic enzymes (Glb1) in proximal tubule and similar changes in ceramide synthases (e.g., Cers 1-6), sphingosine 1-phosphate receptors involved in sAKI inflammatory and immune responses.

Conclusions: We identified several classes of deregulated lipids and altered transcriptomic expression of associated enzymes in db mice which exhibited persistent renal injury. This may lead to the deregulation of cellular function and thus, maladaptive recovery from sAKI in db. Additional work to identify ions/genes of interest and their similarities with the human metabolome will be necessary to determine causality.

Funding: Private Foundation Support

FR-PO171

Proteomics and Metabolomics Conjoint Analysis Revealed Mitochondrial Function and Metabolic Disorders in Sepsis-Induced AKI

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Background: Sepsis-induced acute kidney injury (S-AKI) is a severe and life-threatening condition with high morbidity and mortality and poses a significant risk of chronic kidney disease. However, the early diagnosis and precaution of S-AKI remain challenged due to lacking effective diagnostic biomarkers and treatment targets.

Methods: We established an S-AKI mouse model using intraperitoneal injection of lipopolysaccharide (LPS) and control mice with 0.9% saline (both n=5). After 24 hours, the mice were euthanized to collect blood and kidney samples. The kidney proteins and dissolved metabolites were analyzed using liquid chromatography-tandem mass spectrometry. We integrated proteomics and metabolomics analysis approaches through various bioinformatic analyses, including Gene Set Enrichment Analysis (GSEA), protein and protein interactions (PPI), and MetaboAnalyst analysis.

Results: A total of 5185 proteins were identified in the kidney, including 353 upregulated and 166 downregulated proteins in S-AKI mice compared with the control group. The GO and KEGG analysis of the differentially expressed proteins (DEPs) indicated that downregulated proteins in S-AKI kidneys were primarily involved in mitochondrial functions such as mitochondrial translation and mitochondrial respiratory chain complex assembly. The hub proteins in PPI networks were mainly involved in the mitochondrial electron transport chain. The GSEA also indicated that mitochondrial dysfunction was an incredibly crucial facilitator for S-AKI development. S-AKI kidneys had 111 increased and 66 decreased metabolites compared to the control group. MetaboAnalyst enrichment analysis suggested that S-AKI mainly caused disorders of central carbon metabolism (such as transfer of acetyl groups into mitochondria, Warburg effect, and citric acid cycle), amino acid metabolism, and nicotinate and nicotinamide metabolism.

Conclusions: Proteomics and Metabolomics conjoint analysis provides new insights and a more comprehensive understanding of the pathophysiology of S-AKI with mitochondrial function and metabolic disorders, contributing to new diagnostic biomarkers and therapeutic targets.

FR-PO172

USP13 Targets MCL-1 to Protect Mitochondria-Attenuating AKI

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Background: Acute kidney injury (AKI)is a severe clinical syndrome with high mortality. Thus, investigation on its mechanism and drugable targets is of importance. Here we investigated the novel role and mechanism of ubiquitin specific proteases 13 (USP13) in AKI.

Methods: Eight weeks old WT and $USP13^{+/-}$ mice were subjected to cisplatin and folic acid (FA) to induce AKI. Rapid injection of USP13 plasmids via tail vein was applied to overexpress USP13 in kidney. The serum and kidney tissues were collected for analysis. In vitro cells were used for the mechanistic study.

Results: Immunofluorescence showed that USP13 was expressed in the kidney tubular epithelial cell of human and mouse. In WT mice, cisplatin or FA strikingly enhanced serum BUN, Cys C and Cr, which were further enhanced in $USP13^{+/-}$ mice by around 15% to 30%, respectively. Meanwhile, $USP13^{+/-}$ mice with AKI showed aggravated mitochondrial injury in kidney. In contrast, overexpression of USP13 in kidney significantly protected against AKI and mitochondrial damage. Furthermore, the mechanistic study suggested that USP13 deubiquitinated and stabilized myeloid cell leukelia-l (MCL-1) to protect mitochondria under AKI, thus resulting in a protection against AKI. Finally, pharmacological inhibition of USP13 by spautin-1 (10mg/kg, I.P., daily) also worsened AKI.

Conclusions: USP13 could deubiquitinate and stabilize MCL-1 to protect against mitochondrial injury and AKI. Targeting USP13 could be a potential strategy in treating AKI.

FR-PO173

Ultrastructural Analysis of AKI due to Rhabdomyolysis

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Background: Rhabdomyolysis (RM) develops due to being caused by skeletal muscle damage. The breakdown products are released into the bloodstream and filtered by glomeruli, causing tubular obstruction and inflammation due to protein precipitation. These injured the renal tubular and endothelial cells of the kidney and lead to acute kidney injury (AKI). However, the mechanism is still unclear. In this study, we analyzed the ultrastructure of the renal tubular and the endothelial glycocalyx in RM with scanning electron microscopy (SEM).

Methods: Ten-week-old male C57BLB6 mice were injected intramuscularly into the left thigh of the mice at a dose of 5 mL/kg of 50% glycerol after 24 hours of fasting to create an RM model mouse. The mice that survived were euthanized 96 hours after injection, and then kidney specimens and blood samples were obtained. To investigate the ultrastructure of the kidney, the glycocalyx fixation method, and the conventional fixation method were performed. Mice were perfused with a solution composed of glutaraldehyde with/without lanthanum nitrate at a steady flow rate.

Results: Serum blood urea nitrogen and creatinine were significantly elevated in the RM group. SEM analysis revealed that renal tubules are nourished by capillaries flowing through their interstices, and in normal kidneys, tubules and capillaries exist in close contact. However, in AKI induced by RM, a gap with fibrosis is created around the capillaries, creating a distance between the capillaries and the tubules. The surface of the proximal tubular cells in normal kidneys is densely packed with microvilli of unequal length and thickness, forming a brush border. In RM, microvilli on the surface of the proximal tubules had disappeared and their density was sparse. Under the RM condition, the endothelial glycocalyx was disrupted compared to the control group.

Conclusions: In conclusion, our data have shown the renal tubular and the vascular endothelial glycocalyx were injured and the newly formed gap creates a distance between them.

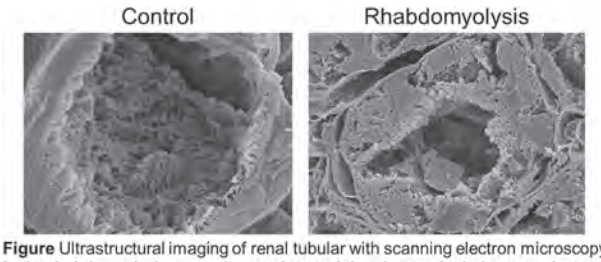

Figure Ultrastructural imaging of renal tubular with scanning electron microscopy. In the rhabdomyolysis group, it was observed that the renal tubular were destroyed, and the nucleus prolapsed.

FR-PO174

Following AKI, Transcriptional Expression of Repair Genes Are Differentially Regulated By 5-HT1F Receptor Agonism

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Background: Acute kidney injury (AKI) is often accompanied by a persistent reduction in mitochondrial function, fatty acid oxidation and vascular injury. We have shown that the FDA-approved 5-HT_{1F} receptor agonist lasmiditan stimulates mitochondrial biogenesis (MB), decreases vascular injury, and accelerates renal recovery in a mouse model of AKI. Given recent studies reporting conserved cellular responses and profiling successful and failed repair genes following AKI, we sought to explore the role of lasmiditan on these repair genes.

Methods: Male 8-week-old C57B/6J mice were administered 0.3 mg/kg lasmiditan or vehicle daily beginning 24h after ischemia/reperfusion-induced AKI (I/R-AKI) and continuing for 144h (n=6/group). The kidneys were collected and gene and protein expression of select repair genes analyzed in renal cortices.

Results: Serum creatinine and kidney injury marker 1 (KIM1) were maximally elevated 24h after IR-AKI. Lasmiditan treatment decreased serum creatinine and KIM1 compared to vehicle by 144h after I/R-AKI. qRT-PCR analysis 24h following I/R-AKI revealed decreased expression of successful repair genes *ACSM2a, LRP2, SLC5A12* and *HNF4A,* and increased expression of failed repair genes *VCAM1, LCN2, RELB* and *KCNIP4* in the renal cortex of injured mice. Lasmiditan treatment increased successful repair gene expression compared to vehicle treatment by 144h after I/R-AKI; but had no effect on failed repair genes. These findings were confirmed using immunoblot analysis.

Conclusions: While these data support lasmiditan-induced regulation of successful repair genes following I/R-AKI, contributing to increased fatty acid metabolism, reabsorption of lactate, and decreased inflammation, the mechanism remains unclear. Continued use of this approach will allow us to identify and assess key genes responsible for pathophysiological changes during AKI, other renal pathologies, and the effects of drugs stimulating repair/recovery.

Funding: Veterans Affairs Support

FR-PO175

Protective Effect of Piperazine Ferulate on AKI in Septic Rats

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Background: Ferulic acid piperazine is widely used in chronic nephritis and nephrotic syndrome in clinical practice. The aim of this study was to investigate the role of ferulic piperazine (PF) in sepsis-induced acute kidney injury (AKI) rats and its mechanism.

Methods: The sepsis-induced AKI model in male SD rats was prepared by cecum ligation puncture (CLP) method. The animals were randomly divided into five groups: normal group, sham-operated group, CLP group and two PF-treated groups, and PF was administered by gavage at a dose of 50 and 100 mg / kg, respectively. Renal index, serum creatinine, blood urea nitrogen and NGAL were measured to evaluate renal function. PAS staining was used to observe renal histopathological changes. Serum inflammatory mediators (PCT, IL-6) levels were measured to assess serum inflammation levels; oxidative stress indicators (T-SOD, CAT, MDA, GSH-PX) were measured to assess body redox activity and oxidative stress levels. western blot was used to detect the expression levels of nuclear factor E2-related factor 2 (Nrf2) protein and au-rich element (ARE) binding factor 1 (AUF1) protein expression levels.

Results: PF treatment significantly reduced renal index and serum creatinine, urea nitrogen, and NGAL levels in rats. PF was also effective in ameliorating renal pathological damage. PF treatment was observed to suppress renal inflammation by reducing PCT and IL-6 levels. PF treatment restored the decrease in serum GSH-PX (glutathione peroxidase), CAT (catalase) and T-SOD (total superoxide dismutase), while also modulating the elevation of MDA (malondialdehyde). In addition, PF treatment significantly enhanced the expression of Nrf2 and AUF1 proteins in the kidney.

Conclusions: PF has a potential therapeutic effect on AKI in septic rats, and its activity may be related to the activation of anti-inflammatory and antioxidant effects of Nrf2 and AUF1 proteins.

Funding: Clinical Revenue Support

FR-PO176

The Novel Dual-Effect Disintegrin, ARGD-RR, Attenuates AKI to CKD in Ischemic-Reperfusion Injury Models

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Background: Acute kidney injury (AKI) can lead to the development of renal fibrosis, ultimately resulting in chronic kidney disease (CKD) and end-stage renal disease (ESRD). Platelet activation has been identified as a key factor in the pathophysiology of AKI, triggering the formation of neutrophil extracellular traps (NETs), which exacerbate tubular necrosis and renal inflammation. Previous studies have demonstrated that antagonists or inhibitors of platelet activation hold promise as therapeutic interventions in AKI models induced by ischemia/reperfusion (I/R). Here, we tested whether the novel dual-effect disintegrin, ARGD-RR attenuated AKI to CKD in Ischemic-Reperfusion Injury.

Methods: In this study, we evaluated the therapeutic efficacy of a novel anti-platelet activation peptide called ARGDRR in a unilateral ischemic-reperfusion injury (uIRI) model. ARGDRR is a snake venom-derived dual-effect disintegrin-ARGDRR peptide that exhibits high affinity for binding to αIIbβ3 and αvβ3. Following ischemic-induced kidney injury, ARGDRR was administered, and we assessed renal dysfunction, renal fibrosis, and cell senescence after a 15-day period. Additionally, we examined the extent of platelet activation and NET formation in AKI.

Results: The mRNA levels of platelet glycoprotein IIb-GPIIIa (Itga2b and Itgb3) progressively increased in the uIRI kidney from day 1 to day 15, accompanied by platelet aggregation and neutrophil infiltration. Administration of ARGDRR ameliorated renal dysfunction, fibrosis, and cell senescence in the transition from AKI to CKD. Moreover, ARGDRR modulated platelet-neutrophil interaction and inhibited NET formation in AKI.

Conclusions: Our findings provide compelling evidence that the disintegrin-ARGDRR peptide holds significant potential for renal protection in the transition from AKI to CKD by inhibiting platelet activation and NET formation. These results contribute to the advancement of therapeutic strategies for AKI and CKD treatment.

Funding: Government Support - Non-U.S.

FR-PO177

Renal Tubular Epithelial Cells RIPK3 Promote AKI Progressing to CKD

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Background: Acute kidney injury (AKI) could increase the risk of long-term chronic kidney diseases (CKD) but its exact mechanism is still unclear. The purpose of this study was to clarify the role and mechanism of renal tubular epithelial cells RIPK3 in the AKI to CKD progression.

Methods: We evaluate the role of renal tubular epithelial cells RIPK3 through detecting its expression in renal puncture tissue and AKI to CKD progression animal model. The role of RIPK3 in promoting AKI-to-CKD transition and G2/M cell cycle arrest was evaluated using transgenic mice with specific knockout of proximal renal tubular epithelial cells RIPK3 or intervention of RIPK3 inhibitor GSK'872. Co-Immunoprecipitation and pull-down experiments were used to explore the interaction between the phosphorylated RIPK3 and CDK1. The mechanism that RIPK3 promote AKI to CKD transition through regulating G2/M cell cycle arrest were explored in vitro rescue experiments.

Results: Renal tubular epithelial cells RIPK3 was up-regulated in renal puncture tissues of CKD patients after cardiac surgery-associated AKI and AKI to CKD progression animal models. GSK'872 intervention or specific knockout of proximal renal tubular epithelial cells RIPK3 could attenuate renal interstitial fibrosis and G2/M phase cell cycle arrest. Co-Immunoprecipitation and pull-down experiments confirmed that phosphorylated RIPK3 and CDK1 could bind directly. siRNA inhibiting the expression of CDK1 could attenuate the reno-protective effect of GSK'872 intervention or RIPK3 silence after intervention of TGF-β.

Conclusions: Renal tubular epithelial cells RIPK3 is up-regulated and activated during the AKI to CKD progression and drive the AKI progressing to CKD. The possible mechanism may be that RIPK3 can inhibit the activity of CDK1, and mediate the G2/M cell cycle arrest of renal tubular epithelial cell, which could provide a new theoretical and therapeutic target for delaying the AKI to CKD progression.

FR-PO178

Decoy Receptor 2 Promotes Tubular Maladaptive Repair by Inhibiting Hmgcs2-Induced β-Hydroxybutyrate Production Following AKI

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Background: Tubular maladaptive repair after acute kidney injury (AKI) leads to chronic kidney disease or end-stage renal disease. However, the underlying mechanism remains unclear. The expression of DcR2 was abnormally increased in renal tubules in patients of AKI, and associated with renal prognosis. Similar results were found in moderate and severe ischemia-reperfusion injury and cisplatin-induced AKI mouse models.

Methods: Similar results were found in moderate and severe ischemia-reperfusion injury and cisplatin-induced AKI mouse models. Proteomics analysis and validation study showed that DcR2 mediated maladaptive repair by regulating the expression of Hmgcs2 (a rate-limiting enzyme of endogenous ketogenesis) and the levels of renal beta-hydroxybutyrate (β-OHB). Hmgcs2 inhibition or deletion aggravated kidney damage and

repressed renal repair. Nonetheless, β-OHB administration ameliorated these phenomena. Moreover, PTEC-specific DcR2/Hmgcs2 double deletion decreased β-OHB levels, which inhibited FOXO3 by regulating histone acetylation, thereby boosting tubular maladaptive repair.

Results: DcR2-GFP transgenic mice showed that DcR2 was specifically expressed in proximal tubular epithelial cells (PTECs) following AKI, and PTEC-specific deletion of DcR2 improved renal repair and prognosis by alleviating kidney damage, inhibiting cell senescence, promoting cell proliferation and regeneration, and repressing renal fibrosis.

Conclusions: These findings suggest that DcR2/Hmgcs2/β-OHB/FOXO3 signaling mediates tubular maladaptive repair and targeting DcR2 may enhance renal repair and improve AKI prognosis.

Funding: Private Foundation Support

FR-PO179

Irisin Modulates Renal Ischemia-Reperfusion Injury by Upregulating Mitochondrial Autophagy Marker Protein LC3

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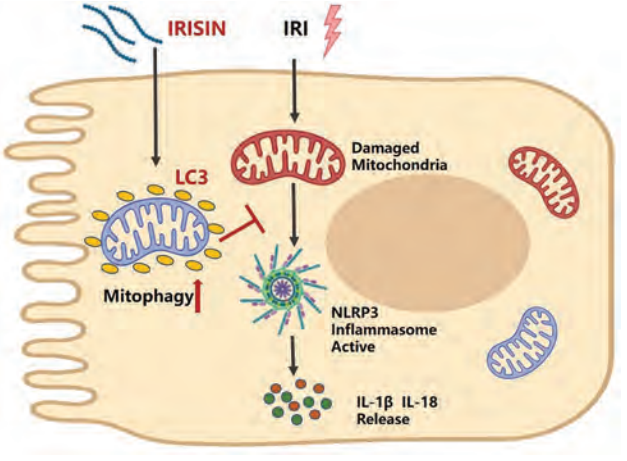
Background: Acute kidney injury (AKI) is a clinical syndrome with a high incidence and increased cost and mortality for hospitalized patients, and are still lacking of effective therapeutic drugs. Irisin has been reported to have inhibitory effects on cellular inflammation, reduced cell apoptosis, and antioxidant stress in various diseases. But it is still unknown whether Irisin has therapeutic effects after ischemic AKI.

Methods: We evaluated the serum Irisin levels and their correlation with renal function in AKI patients and healthy control groups. We constructed a mice model of ischemia-reperfusion(I/R) kidney injury and administered exogenous Irisin toinvestigated the potential therapeutic effects and mechanisms through a series of experimental techniques such as renal tubular microperfusion.

Results: We found that the Scr level in the AKI patient was significantly higher thanthat in the healthy control group (256.8 ± 30.5 vs 61.9 ± 10.5 umol/L, P<0.0001), the BUN level was significantly higher (17.1 ± 6.5 vs 5.1 ± 1.0 mmol/L, P<0.0001), and the Irisin level was significantly reduced (39.9 ± 8.2 vs 76.7 ± 13.8 ng/ml, P<0.0001). We found that exogenous Irisin reduced the renal damage indicators in mice model. The stability of mitochondrial JC-1 membrane potential increased and the ROS decreased after H/R in the Irisin treatment group. Irisin up-regulated the expression of renal mitochondrial autophagy related proteins PINK1 and PARK2 and marker protein LC3, enhanced mitochondrial autophagy, and down regulated the activation of NLRP3 inflammasome.

Conclusions: This study suggests that Irisin may serve as a potential biomarker of ischemic AKI. Irisin has therapeutic effects on renal IRI, and its protective effect may be related to enhancing mitochondrial autophagy by upregulating mitochondrial autophagy marker protein LC3. This study provides theoretical support for Irisin as a therapeutic drug for ischemic AKI.

Funding: Government Support - Non-U.S.



Hypothesis of the mechanism by which Irisin alleviates renal ischemia-reperfusion injury

FR-PO180

HNF4α Links PGC1α to Quinolinate Phosphoribosyl Transferase (QPRT) and De Novo NAD+ Biosynthesis

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Background: De novo NAD+ biosynthesis is suppressed in acute kidney injury (AKI), particularly the bottleneck enzyme Quinolinate Phosphoribosyl Transferase (QPRT), leading to NAD+ reduction and accumulation of upstream metabolites. We previously showed that QPRT is regulated by PPARgamma coactivator 1 alpha (PGC1a), a transcriptional co-activator that regulates many genes involved in metabolism and mitochondrial biogenesis. A transcription factor (TF) linking PGC1a and QPRT has not been identified.

Methods: The ENCODE TF Database was compared with Biogrid and the Human Reference Protein Interactome to identify TFs that interact with PGC1α and bind *QPRT*. Expression of PGC1α, HNF4α, and QPRT was assessed with qPCR. Compartment-specific NAD+ was measured using transfected biosensors. ATP and ChIP qPCR was measured via commercial assay.

Results: Analysis of public datasets identified HNF4α and RXRA as candidate TFs modulating QPRT via PGC1α. We focused on HNF4α as no RXRA mutations associate with kidney disease. HNF4α was suppressed in AKI proportionally to QPRT (R^2=0.5, P<0.01). HNF4α overexpression increased QPRT expression (1.27 fold change [FC], p<0.01), and HNF4α mirrored both QPRT and PGC1α with increased cellular NAD+ and ATP with HNF4α overexpression (NAD+ in cytoplasm 1.08FC, p<0.001; mitochondria 1.06FC, p<0.05; nucleus 1.09FC, p<0.05) (ATP 1.08FC, p<0.001) and decreased NAD+ and ATP with siHNF4α (NAD+ in cytoplasm 0.86FC, p<0.001; mitochondria 0.89FC, p<0.05; nucleus 0.86FC, p<0.05) (ATP 0.91FC, p<0.01). ChIP qPCR showed that HNF4α binds the *QPRT* locus in kidney (12.7FC over IgG) proportionally with PGC1α expression (R^2=0.58, p<0.05). Finally, siHNF4a co-transfected with PGC1α plasmids prevented PGC1α-induced increase in QPRT expression (PGC1α overexpression = 1.34FC increase in QPRT, p<0.001; PGC1α overexpression with siHNF4α = 1.1 FC in QPRT, p=0.19).

Conclusions: HNF4α is a known regulator of metabolic pathways in the liver and a critical component of kidney cell differentiation, but few studies have examined the role of HNF4α in adult kidney. This is relevant as recent multi-omics investigations have identified HNF4α recovery after injury as a critical feature of "recovered" tubular cells. In summary, the present results identify a transcriptional mechanism for HNF4α in regulating de novo NAD+ biosynthesis suppression in AKI.

Funding: NIDDK Support, Private Foundation Support

FR-PO181

Tryptophan Metabolism in AKI: A New Target in Kidney-Brain Axis

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Background: Partial recovery following AKI could lead to long-term consequences that predispose to chronic dysfunction and may also accelerate neurocognitive decline. Kidney-brain axis seems to play a pivotal role leading to detrimental outcome for AKI patients. Many studies suggest a high relationship between kidney damage and brain dysfunction even after AKI resolution. Patients who suffered AKI may afterward show a disturbance of arousal called brain-fog. Although advances in understanding the pathophysiology of AKI and brain dysfunction, there are no available preventive and therapeutic strategies. Recent findings have revealed link existing between dyslipidemia/low HDL levels and Kynurenine pathway (KP) alterations that lead to the production of neuroactive metabolites: kynurenine (KYN) and quinolinic acid (QA).

Methods: Sepsis-induced AKI (SI-AKI) was induced in a porcine model by intravenous infusion of a saline solution containing 300 µg/kg of LPS. After injection, 12 animals were treated with different doses of recombinant HDL (rHDL) (20-40mg/kg), while 6 animals did not receive treatment (LPS group). Animals were sacrificed after 24h from the start of experimental procedure.

Results: Endotoxemic pigs developed oliguric AKI with increased tubular and glomerular damage and interstitial inflammatory infiltrate. rHDL treatment decreased the inflammatory process and tubular damage, preventing AKI, especially in 40mg/kg rHDL group. The rate-limiting step of KP, the Indolamine-2,3-dioxygenase 1 (IDO1) enzyme is upregulated during inflammation in sera and brain tissue, and has been linked to cognitive dysfunction. In our model, LPS induced an increased activation of IDO-1 gene expression at brain level in endotoxemic animals, meanwhile it appears to be reduced in both treated arms (p<0.005). Sera from the rHDL group showed a significant reduction in IDO1 activity (KYN/Trp ratio) (p<0.05) and QA levels (p<0.005) compared with the LPS group. Moreover, a significant decrease of both systemic and brain IL-6 levels was observed after rHDL treatments.

Conclusions: Our data indicated that HDL-enhancing therapies may decrease the inflammatory response, the retention of waste products and neuroactive compounds, improving renal and cognitive function in SI-AKI.

FR-PO182

Metabolomics Screen in Cilia-Deficient Cells Identifies Tryptophan Metabolism as a Possible Mechanism for Cilia-Dependent Cyst Growth

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Background: Primary cilia and mitochondria are involved in polycystic kidney disease (PKD). We showed that knockdown (KD) or ciliary targeting sequence mutation (cts-mut) of Exoc5, a central exocyst complex component, resulted in cilia loss while Exoc5 overexpression (OE) resulted in longer cilia. Ift88 knockout (KO) also resulted in cilia loss which was reversed by Ift88 rescue.

Methods: Seahorse assays and metabolic profiling were performed on canine (MDCK control, Exoc5 cts-mut, KD, OE) and murine (Ift88 KO, rescue) kidney cells.

Results: Seahorse assays showed lower basal respiration (BR), maximal respiration (MR), and spare respiratory capacity (SRC) in Exoc5 KD and Exoc5 cts-mut compared

to control MDCK cells. Conversely, Exoc5 OE cells had higher BR, MR, and SRC. MR and SRC were also lower in Ift88 KO than rescue cells. A metabolomics screen showed tryptophan increased in Exoc5 KD and Exoc5 cts-mut cells by 58- and 113-fold compared to control. In Exoc5 OE cells, tryptophan decreased 59%. Similarly, tryptophan increased by 21% in Ift88 KO cells. Kynurenine is directly downstream of tryptophan and decreased by 83% and 20% in Exoc5 KD and cts-mut cells, and increased by 25% in Exoc5 OE cells. In Ift88 KO cells kynurenine decreased by 49%.

Conclusions: Kynurenine drives oxidative stress and mitochondrial dysfunction and was higher in MDRD Study participants with ADPKD compared to other CKD, and patients with ADPKD had higher plasma levels compared to healthy individuals which increased with disease progression. Nguyen et al (2022, *JCI Insight*) found decreased tryptophan and increased kynurenine in Pkd1 RC/RC mice. This is the opposite of what we found following cilia loss. IDO1 converts tryptophan to kynurenine. When Nguyen et al pharmacologically inhibited or genetically knocked out IDO1, cystogenesis decreased. In 2013 Ma et al (2013, *Nature Genet*) showed that cilia loss suppresses cyst growth in ADPKD mouse models. Shao et al (2020, *Kidney Int*) showed that Ift88 KO slowed cyst growth in a PKD1 mouse model. Therefore, we hypothesize that cilia loss inhibits cystogenesis by increasing tryptophan and decreasing kynurenine. These findings highlight a link between cilia and mitochondrial function and suggest that tryptophan metabolism via IDO1 could be a novel target for ADPKD treatment.

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FR-PO183

Loss of Pax2 and Pax8 Induces Resistance to Ischemia in S3 Proximal Tubule

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Background: Pax2 and Pax8 are two highly homologous transcription factors regulating kidney development and are re-expressed during acute kidney injury (AKI) and repair. Our aim was to determine whether Pax2 and Pax8 are necessary to regenerate new proximal tubule cells after ischemic AKI.

Methods: Pax mutations were targeted to the proximal tubule, the primary site of injury in ischemic AKI, using floxed Pax2 and Pax8 conditional alleles and a phosphoenolpyruvate carboxykinase (PEPCK) Cre driver. Control mice included PEPCK-Cre but wild type Pax2 and Pax8 loci. All animals expressed a GFP-Cre reporter to track Cre activity. No gross differences in kidney function or histology were observed at baseline. Mutant and control mice were subjected to unilateral ischemia-reperfusion injury (uIRI) with simultaneous contralateral nephrectomy. Samples were analyzed at various post-injury time points. Nuclei from whole kidneys of uninjured mutant and control mice were analyzed using single nucleus RNA sequencing (snRNA seq).

Results: Mice with proximal tubule Pax2 and Pax8 deletion were protected from both acute and chronic injury as measured by serum BUN, histological injury score, and expression of injury markers. Differences manifested as early as 6 h after injury, suggesting an inherent resistance to ischemia. Pre-injury snRNA seq revealed that mutant mice developed a unique population of S3 proximal tubule cells which was confirmed by immunostaining for cluster specific markers and invariably stained for GFP, marking Cre-mediated Pax2 and Pax8 deletion. The transcriptional profile of mutant S3 cells were strongly enriched in genes associated with a range of conditions that protect against ischemic injury including hypoxic preconditioning, caloric restriction, and female sex.

Conclusions: Our data indicate that neither Pax2 nor Pax8 is necessary for repair after ischemic AKI. On the contrary, Pax protein loss induced protection against ischemic injury by promoting a transcriptional program that strongly overlaps with other conditions that confer protection. These findings highlight critical genes and pathways that determine sensitivity to ischemic AKI and suggest a novel role for Pax proteins in the proximal tubule.

Funding: NIDDK Support

FR-PO184

Alternative Splicing Generates an Intracellular Uromodulin Isoform that Mediates Mitochondrial Function and Is Up-Regulated in AKI

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Background: Uromodulin (UMOD), a glycoprotein exclusively produced by renal tubular cells, is known to protect against acute kidney injury. Previous research has mainly focused on the secreted UMOD; however, the significance of intracellular UMOD has not been described.

Methods: We performed long-read RNA sequencing on human and mouse kidneys to explore alternative splicing variants of UMOD. RT-PCR and Sanger sequencing were conducted to validate the expression of the identified variant. The expression of the variant in mice after renal ischemia-reperfusion injury was quantified using RT-qPCR. To assess the localization and function, cDNA of the variant was overexpressed in kidney epithelial cells, and Western blotting, immunofluorescence, LDH assay, and Mito Stress Test were performed.

Results: Long-read RNA sequencing revealed a novel alternative splicing variant of UMOD, referred to as UMOD-AS, both in humans and mice. The existence of UMOD-AS mRNA was confirmed by RT-PCR and Sanger sequencing. UMOD-AS mRNA was up-regulated after renal ischemia-reperfusion injury, whereas canonical UMOD was down-regulated. In the cellular model, UMOD-AS localized in the cytoplasm, whereas canonical UMOD localized at the membrane and was secreted extracellularly. Interestingly, UMOD-AS-expressing cells showed better cell viability than canonical UMOD-expressing cells. Mito Stress Test suggested UMOD-AS up-regulates mitochondrial function compared to canonical UMOD.

Conclusions: UMOD-AS is an intracellularly-localized and cellular-protective isoform of UMOD. Notably, the localization and regulatory mechanisms of UMOD-AS are contrasted with canonical UMOD. Alternative splicing of UMOD may be a novel protective mechanism in acute kidney injury.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO185

Kidney Mitochondrial DNA Contributes to Circulating IL-6 in Sepsis-Associated AKI

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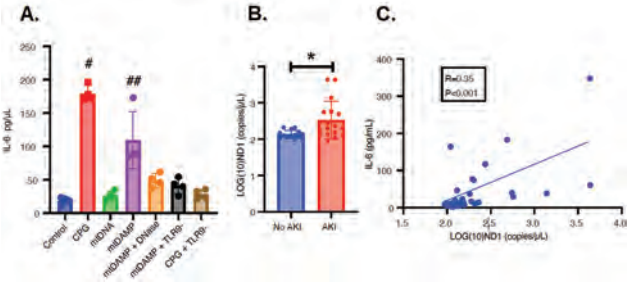
Background: Increased circulating cell-free mitochondrial DNA (CCF-mtDNA) and acute kidney injury (AKI) are associated with mortality in sepsis, but the role of CCF-mtDNA in the pathogenesis of sepsis-associated AKI (S-AKI) remains unclear. We hypothesized that CCF-mtDNA released from the injured kidney contributes to the systemic inflammatory response via IL-6 in S-AKI.

Methods: CCF-mtDNA isolated from the plasma of mice exposed to sepsis by cecal ligation and puncture (CLP) vs sham control (N=5-6/group) were sequenced and quantified by droplet digital PCR. Single nucleotide polymorphisms (SNPs) identified in the isolated mtDNA were compared to those found in the heart, kidney, liver, and lung of individual mice to infer tissue origin. In in-vitro studies, mouse bone marrow cells were treated with CpG (positive control), kidney mtDNA, or mitochondrial damage-associated molecular patterns (mtDAMPs) with and without DNase or toll-like receptor-9 inhibitor. IL-6 concentrations were compared across groups. In in-vivo studies, mice were injected with saline vs kidney mtDAMPs with and without DNase, and IL-6 concentrations were compared. Finally, CCF-mtDNA levels were quantified in the plasma of septic human subjects with and without AKI.

Results: CCF-mtDNA was significantly increased in the plasma of CLP mice compared to controls. Three out of five mice analyzed had unique SNPs in mtDNA fragments indicating kidney origin of release. In both in-vitro and in-vivo studies, exposure to kidney mtDAMPs led to increased IL-6 release, which was attenuated by treatment with TLR-9 inhibitor or DNase (Figure A). In human studies, plasma CCF-mtDNA levels were significantly increased in patients with S-AKI compared to those with sepsis without AKI, and increased CCF-mtDNA significantly correlated with plasma IL-6 (Figure B/C).

Conclusions: CCF-mtDNA released from the kidney contributes to increased plasma IL-6 in sepsis. Preserving kidney mitochondrial integrity, preventing mtDNA release, or clearing circulating mtDNA are translational avenues to pursue to decrease mortality from S-AKI.

Funding: NIDDK Support, Veterans Affairs Support



FR-PO186

Renal Congestion Exacerbates Sepsis-Induced AKI in Mice

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Background: Recent epidemiological studies demonstrated that renal congestion is a major factor in the development of renal dysfunction associated with heart failure. We previously established a novel unilateral renal congestion mouse model wherein the inferior vena cava was constricted between both renal veins, and reported its impact on the exacerbation of renal ischemia-reperfusion injury. However, the impact of renal congestion on septic AKI, the most common cause of AKI, is unclear.

Methods: We instigated sepsis via cecal ligation and puncture (CLP) in a unilateral renal congestion model. We comprehensively analyzed the pathophysiology of exacerbation of septic AKI by renal congestion, especially focused on the toll-like receptor (TLR) 2, a receptor of the innate immune system.

Results: After the induction of CLP in the unilateral renal congestion model, the transient decline in blood pressure was observed at 3 and 6 hours after CLP. Ultrasonography revealed the persistent dilation of renal veins in the congested kidney for a duration extending up to 7 days post-CLP. Histological analysis at day 7 exhibited marked fibrosis in the group subjected to congestive heart failure + CLP, while qPCR assays indicated upregulation of fibrosis markers including Col1a1, Acta2, Tgfb1, and Fn1.

At acute phase after procedures, extensive tubular damage with macrophage infiltration was noted in congestion + CLP group. qPCR demonstrated the upregulation of tlr2, in addition to inflammatory cytokines (Tnf, Ccl2). To further investigate the mechanistic insights focusing on the TLR2, we conducted CLP and renal congestion in TLR2-KO mice. Blood pressure transiently decreased at 3 and 6 hours after CLP, mirroring the response observed in WT mice. At 1 day post-CLP, tubular injury was exacerbated in the TLR2-KO group in comparison to the WT group, and qPCR analysis revealed an increase in Havcr1 expression and a decrease in Lrp2 expression, indicating that TLR2 might exert the inhibitive role on the exacerbation of sepsis-induced AKI by renal congestion.

Conclusions: This study using the combination of CLP and novel renal congestion model demonstrated the increased renal venous pressure may have contributed to the exacerbation of the AKI by inducing a reduction in renal perfusion following CLP, thereby implicating the involvement of TLR2 in this process.

FR-PO187

Anti-Inflammatory and Renal Protective Mechanisms by Controlling Parasympathetic and Sympathetic Balance

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Background: Acute kidney injury (AKI) lacks effective treatment. To understand renal homeostasis and develop therapeutic strategies, we investigate renal protection and anti-inflammatory effects mediated by the autonomic nervous and immune systems. Vagus and sympathetic nerve activation provide kidney protection, and stimulating both nerves yields synergistic anti-inflammatory effects in macrophages. However, achieving this synergy through autonomic nerve stimulation in vivo remains uncertain. This study aims to determine the optimal autonomic balance for kidney protection and explore in vivo autonomic nerve stimulation as a novel renal disease treatment.

Methods: *In vitro* experiments treated RAW 264 cells and HK-2 cells with autonomic nerve stimulants, assessing changes in renal injury markers, cytokines, and cellular properties. GTS-21 (α7nicotinic acetylcholine receptor: α7nAChR agonist) and salbutamol (β2 adrenergic receptor: β2AR agonist) were used. *In vivo* experiments used LPS-induced septic mice or renal ischemia-reperfusion injury as AKI models. Macrophage-specific α7nAChR and/or β2AR knockout mice were used to examine parasympathetic and sympathetic nerve stimulation effects on the kidney.

Results: *In vitro*, combining GTS-21 and salbutamol with LPS showed concentration-dependent, synergistic anti-inflammatory effects in RAW 264 cells. LPS and salbutamol treatment of HK-2 cells resulted in a concentration-dependent decrease in NGAL. Simultaneous administration of both agonists tended to further decrease NGAL expression. However, *in vivo* experiments with septic mice did not demonstrate synergistic anti-inflammatory effects when GTS-21 and salbutamol were administered together. Additionally, LysM-Cre: α7nAChR/β2AR flox mice showed attenuated renal injury compared to controls in bilateral ischemia-reperfusion injury.

Conclusions: Simultaneous parasympathetic and sympathetic stimulation synergistically reduced inflammation in macrophages and tubular cell damages. However, *in vivo* experiments did not support this synergistic effect. Autonomic nerve stimulation appears to have indirect anti-inflammatory and renal protective effects mediated by the immune system, as well as direct protective effects on the kidney. Maintaining a precise balance of these effects is crucial for biological homeostasis.

FR-PO188

miR-486-5p Protects Against Ischemic AKI and Prevents Transition to CKD

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Background: Recovery from acute kidney injury (AKI) is associated with increased risk for progressive chronic kidney disease (CKD). We previously showed that microRNA (miR)-486-5p protects against kidney ischemia-reperfusion (IR) injury in mice, with targeting of *phosphatase and tensin homolog* (*PTEN*) and downregulation of proximal tubular genes involved in apoptosis and tumor necrosis factor signaling. In cultured human endothelial cells however, miR-486-5p inhibits endothelial nitric oxide synthase (eNOS) expression. Here, we studied the effects of miR-486-5p on IR AKI and CKD development in rats with a focus on vasculature.

Methods: Kidney IR injury was induced in male rats by bilateral renal pedicle clamping followed by reperfusion. Lipid-encapsulated miR-486-5p (0.5mg/kg) was injected i.v. at the start of reperfusion. Outcomes were assessed after 24hr and 10 weeks. Kidney blood flow was measured by laser doppler flowmetry. Endothelium-dependent mesenteric artery reactivity was evaluated by myography.

Results: In rats with IR AKI, miR-486-5p preserved regional kidney blood flow at 24hr ($p<0.01$,n=7) and prevented increases in plasma Cr ($p<0.001$,n=10), neutrophil and macrophage infiltration, and apoptosis. miR-486-5p had no effect on kidney *PTEN* expression, but inhibited IR-induced expression of eNOS and intercellular adhesion molecule (ICAM)-1. At 10 weeks, while rats with IR alone had normal plasma Cr, kidneys displayed decreased peritubular capillary density with increased interstitial collagen, α-smooth muscle actin$^+$ myofibroblasts, and F4/80$^+$ macrophages. These changes were inhibited by miR-486-5p (CD31, collagen $p<0.0001$, n=6-8). Although blood pressure was similar across rat groups, IR inhibited endothelium-dependent vasorelaxation in mesenteric arteries at 10 weeks, which was prevented by miR-486-5p. Delayed administration of 2 doses of miR-486-5p (96hr, 3 weeks after IR) had no effect on capillary density, kidney fibrosis, blood pressure, or endothelial function.

Conclusions: In rats, early administration of miR-486-5p prevents kidney IR injury and preserves regional blood flow despite reduction in eNOS expression. miR-486-5p also protects against CKD development and associated endothelial dysfunction. The results suggest that miR-486-5p is a promising therapy for the prevention of ischemic AKI and its complications.

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FR-PO189

Reno-Protective Effect of Haptoglobin and Hemopexin by Inhibiting Ferroptosis in Ischemic Reperfusion AKI

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Background: Recent studies showed that cell free hemoglobin (CFH) increases in patients with sepsis and after heart surgery, which may cause acute kidney injury (AKI). Since CFH contains catalytically active iron, iron-dependent cell death, CFH related iron-dependent cell death, ferroptosis may induce AKI. This study investigates the reno-protective effect of haptoglobin (Hp) and hemopexin (Hx), which scavenge CFH, in an experimental AKI model.

Methods: Ischemic reperfusion injury (IRI) animal models were used as AKI animal models. After 2, 4, 6, 8, and 24 hours, CFH and hemin levels were evaluated in both the control and IRI groups. In addition, the IRI models were treated with different doses (25, 50, 100, and 200 mg/kg) of Hp or Hx via intravenous injection 30 minutes prior to IRI surgery. CFH, hemin, and kidney injury markers, as well as an oxidative stress marker, and ferroptosis markers were evaluated 24 hours later. Furthermore, kidney injury score was evaluated from kidney tissues based on the percentage of cell necrosis, loss of brush border, cast formation, and tubule dilatation.

Results: CFH and hemin levels increased in the IRI group at each hour compared to the control. Injection of Hp decreased CFH levels regardless of the dosage, while injection of Hx decreased hemin levels compared to the IRI group. Creatinine, BUN, NGAL, and MDA levels showed increases in the IRI group compared to the control. Treatment with Hp or Hx resulted in decreases in creatinine, BUN, MDA, and kidney injury score across all dosage compared to the IRI group. NGAL levels showed a decrease in all drug injection groups except for the Hp 25mg/kg group compared to the IRI group. In the IRI group, the mRNA expression of cystine/glutamate antiporter system Xc− decreased compared to the control, while ferritin heavy chain 1 increased. However, treatment with Hp or Hx resulted in an increase in cystine/glutamate antiporter system Xc− mRNA expression and a decrease in ferritin heavy chain 1 compared to the IRI group.

Conclusions: Hp and Hx, scavenger proteins, may aid as preventive agents for ischemic reperfusion AKI by inhibiting ferroptosis.

FR-PO190

Reduced Perivascular Cell Dynamin-Related Protein 1 (Drp1) Protects Against AKI and CKD in Mice

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Background: Mitochondrial dysfunction has been implicated in the pathogenesis of AKI and CKD. We have previously demonstrated that proximal tubule deletion of *Drp1* attenuated progressive kidney injury and fibrosis after ischemia-reperfusion injury (IRI). The role of *Drp1* and mitochondrial dysfunction in kidney perivascular cells (PVCs) during AKI and CKD has not been explored.

Methods: PVC specific germline (*Foxd1-Cre;Drp1$^{+/-}$*, *Foxd1-Cre;Drp1$^{-/-}$*) or inducible (*Pdgfrβ-CreERT2;Drp1$^{+/-}$*, *Pdgfrβ-CreERT2;Drp1$^{-/-}$*) *Drp1* heterozygote and knockout mice and respective littermate controls (WT) were generated. *Foxd1-Cre;Drp1$^{+/-}$*, *Foxd1-Cre;Drp1$^{-/-}$* and WT male and female mice were injected with folic acid (FA, 250 mg/kg i.p.). 24 and 48 hours later, mice were evaluated for kidney injury by plasma creatinine (PCr) and BUN and *Kim-1* and *Ngal mRNA*. In another model of AKI, *Pdgfrβ-CreERT2;Drp1$^{+/-}$*, *Pdgfrβ-CreERT2;Drp1$^{-/-}$* and WT male mice underwent bilateral kidney IRI (bIRI, 26 min). In a model of the AKI to CKD progression, *Foxd1-Cre;Drp1$^{+/-}$*, *Foxd1-Cre;Drp1$^{-/-}$* and WT male and female mice were injected with FA and followed for 14 days. Mice were evaluated for kidney fibrosis by mRNA levels of fibrosis genes (*Col1α1, Fn1)* and Masson's trichrome staining.

Results: 24 hours after FA, both male and female WT mice displayed a rise in plasma creatinine and BUN which was significantly attenuated in mice with partial deletion of PVC *Drp1* (*Foxd1-Cre;Drp1$^{+/-}$*). In contrast, mice with a full deletion of *Drp1* in PVCs (*Foxd1-Cre;Drp1$^{-/-}$*) displayed an increased susceptibility to injury in male mice and increased mortality in females. 14 days after FA, *Foxd1-Cre;Drp1$^{+/-}$* mice had reduced kidney fibrosis histologically and by mRNA levels of *Col1α1* and *Fn1* compared with WT and *Foxd1-Cre;Drp1$^{-/-}$* mice. After bIRI, both *Pdgfrβ-CreERT2;Drp1$^{-/-}$* and *Pdgfrβ-CreERT2;Drp1$^{+/-}$* mice had a decrease in plasma creatinine compared with WT controls.

Conclusions: Reduced expression of *Drp1* in PVCs had a protective effect during AKI and CKD, suggesting that PVC *Drp1* could serve as a therapeutic target. Although *Pdgfrβ-CreERT2;Drp1*$^{-/-}$ mice were protected from injury, *Foxd1-Cre;Drp1*$^{-/-}$ mice displayed increased susceptibility to injury. Studies to understand the effect of timing, cellular expression and level of *Drp1* reduction on AKI and CKD outcomes are ongoing.

FR-PO191

ATF3 Ameliorates Ischemic Kidney Damage by Controlling the Cross-Talk Between Immune and Kidney Cells

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Background: Acute kidney injury (AKI) is a leading cause of death. The molecular pathophysiological mechanisms of AKI remain only partially understood, and targeted therapies to facilitate recovery from renal failure are still elusive.

Methods: To find central signaling pathways that drive kidney regeneration, we performed single-cell RNA sequencing (scRNA-seq) after laser-induced injury of zebrafish pronephric tubules, and explored the function of *Atf3* in three different *Atf3*-deletion models, subjecting *Atf3*$^{f/f}$*Pax8-rtTA*TetO-Cre*, *Atf3*$^{f/f}$**Cx3cr1-Cre*, and *Atf3*$^{f/f}$**Ksp-Cre* mice to unilateral nephrectomy followed by ischemia-reperfusion injury (IRI). To determine the role of ATF3 in IRI, kidney cells were subsequently analyzed by histology, flow cytometry, bulk-/scRNA-seq, and CUT&RUN experiments.

Results: Depletion of zebrafish *atf3* by morpholino oligonucleotides compromised the repair process after pronephros injuries. While *Pax8*- or *Cx3cr1*-mediated deletion of *Atf3* did not affect renal function, *Ksp-Cre*-mediated *Atf3* loss intensified the renal failure after IRI in mice. The absence of *Atf3* in distal nephron segments reduced the expression of crucial chemokines including *Cxcl10*, resulting in decreased numbers of infiltrating F4/80^{+} macrophages and deficient macrophage "M2" polarization. Using RNA sequencing and CUT&RUN techniques, we found that ATF3 directly regulates *Umod* (Uromodulin), and promotes its secretion via increased *Kcnj1* (ROMK) expression after IRI. Gene Ontology enrichment analysis of the immune cell populations confirmed the downregulation of leukocyte migration, cytokine production, and cell-cell adhesion. CellChat analysis identified a weakened interaction between immune cells and the tubular epithelial cells of the thick ascending limb (TAL).

Conclusions: *Ksp-Cre*-mediated excision of *Atf3*, primarily affecting ATF3 production in the TAL, worsens renal failure after IRI. Loss of ATF3 affects the expression of several immune regulatory factors including Uromodulin, which is known to promote an anti-inflammatory macrophage phenotype. Our analyses reveal that ATF3 protects the kidney against ischemia by controlling the cross-talk between immune and kidney cells.

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FR-PO192

Pathomics Reveals Histomorphological Recovery During Nephrectomy-Induced Kidney Repair

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Background: Acute kidney injury (AKI) is a common disease, that can progress to chronic kidney disease (CKD). Nephrectomy (Nx)-induced repair describes the phenomenon of a remarkable functional and structural recovery of unilateral AKI upon removal of the contralateral healthy kidney. The underlying mechanisms remain largely unknown and a thorough analysis of structural recovery remains challenging. Therefore, we applied next generation morphometry and pathomics to comprehensively quantitate structural alterations in a validated model of Nx-induced repair after left unilateral ischemia reperfusion injury (UIRI).

Methods: C57BL/6J mice were divided into 3 groups: UIRI+Sham (n=54), UIRI+Nx (n=36), or healthy controls (n=6). Kidneys of all mice were acquired at days 1 to 7 and days 21, and 42 after UIRI (n=6/timepoint). Sham-surgery or Nx of the right kidney were performed 3 days after UIRI. Digitized PAS-stained tissue sections (whole slide images) were analysed using our pathomics pipeline.

Results: Quantitative pathomics on over 706090 tubules revealed a progressive decay of overall tubular area after UIRI with a loss of 22% by day 42 compared to controls. In accordance with tubular atrophy, tubular cross-sectional diameters (μm) and sizes (μm^2) became smaller after UIRI by 15% (diameter) and 32% (size) of control values from day 3 onwards. Nx prevented these changes, minimizing loss of tubular area to 5%. The mean tubular diameters and areas were comparable to control values, although their overall distribution changed from a bimodal (healthy control) to a unimodal distribution appearance, originating from the dimensional differences of cortical and medullary tubules. After UIRI, interstitial area steadily increased to 20% above controls by day 21. Nx abrogated this progression, with an interstitial area remaining stable at an average of 6.5% above controls.

Conclusions: Large-scale, automated quantification of structural alterations revealed the distinct histopathological fates of an acute injured kidney in comparison to its rescue by nephrectomy. These data show the utility of pathomics to investigate spatiotemporal histological shifts during kidney injury and repair.

FR-PO193

Inhibition of Histone Methyltransferase SET8 Attenuates Renal Tubular Cell Apoptosis by Restoring PTEN in Cisplatin-Induced AKI

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Background: SET8 is a histone H4K20 monomethyltransferase that regulates transcriptional and posttranslational modifications, heterochromatin formation, genomic stability, and cell cycle progression. Numerous studies have shown that SET8 is involved in various pathophysiological events, including cancer, inflammatory responses and metabolic disorders. However, its role in acute kidney injury (AKI) remains unexplored.

Methods: In this study, we aimed to investigate the role and mechanism of SET8 in cisplatin-induced AKI using a murine model and cultured renal epithelial cells.

Results: SET8 and its downstream histone H4 lysine 20 methylation (H4K20me1) expression were highly increased in cultured murine proximal tubule epithelial (TKPT) cells and kidneys from mice treated with cisplatin, along with decreased expression of phosphatase and tensin homolog (PTEN) and increased phosphorylation of p53 (p-p53). Pharmacologic inhibition of SET8 with UNC0379, a specific inhibitor, or siRNA-mediated silencing of SET8 suppressed apoptosis, p-p53 and preserved PTEN expression in TKPT cells exposed to cisplatin. Similarly, administration of UNC0379 in cisplatin-injected mice also improved renal function, attenuated tubular injury and inhibited apoptosis, which was coincident with repressing expression of SET8, H4K20me1 and p-p53, and restoring PTEN. Moreover, inhibition of PTEN with bpv (HOpic) or silence of PTEN aggravated cisplatin-induced apoptosis without affecting expression of SET8, H4K20me1. In contrast, inhibition of p53 with pifithrin-alpha (PFA) or silence of p53 lowered cisplatin-induced apoptosis without affecting expression of SET8, H4K20me1 and PTEN.

Conclusions: These findings indicate that SET8 relieved renal apoptosis induced by cisplatin by upregulating PTEN, which in turn repressed p53, and suggest that SET8 may serve as a novel therapeutic target for cisplatin-induced AKI by attenuating apoptosis and restoring PTEN expression.

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FR-PO194

Lats2 Ablation Exacerbates Severe Ischemia/Reperfusion-Induced Renal Maladaptive Repair Through the Upregulation of p53

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Background: Incomplete recovery of AKI can lead to long-term functional deficits and CKD. The Hippo pathway plays a regulatory role in the pathogenesis and repair of AKI and CKD progression. LATS2, a negative regulator of YAP in the Hippo pathway, has been proved to have a strong association with cell apoptosis independent of YAP. p53 has been known to mediate the progression of cell apoptosis and maladaptive kidney repair after AKI. Nevertheless, the relationship between LATS2 and p53 in post-AKI renal maladaptive repair remains far from clear.

Methods: We established proximal tubule *Lats2* conditional knockout (*Lats2*-CKO) mouse models. Then we constructed a mouse model of maladaptive kidney repair after severe kidney injury (unilateral I/R-induced AKI) on both *Lats2*-CKO and WT mice, and assessed the fibrotic state, inflammatory cellular infiltration, apoptosis and p53 expression in post-AKI kidney tissue. Next, we used the pharmacological p53 inhibitor Pifithrin-α (PFT-α) to treat post-IRI mice for 14 days. Hypoxia and reoxygenation (H/R) was used to mimic I/R in vitro.

Results: At 14 days after I/R, *Lats2*-CKO mice represented more severe tubulointerstitial damage than WT mice. Masson trichrome, Sirius red staining, and α-SMA staining suggested that fibrosis is exacerbated in renal maladaptation in response to *Lats2* knockout. F4/80 and CD3 renal positive staining indicated more severe I/R-induced macrophage and T cell infiltration in *Lats2*-CKO mice. Moreover, we found that proximal tubule-specific Lats2 knockout upregulates p53 expression, and also induces upregulation of p21 and Bax and downregulation of Bcl-2 and Bcl-xL, accompanied by higher rate of cellular apoptosis. *In vivo* administration of PFT-α in post-IRI mice reduced renal fibrosis, immune cell infiltration and apoptosis in both *Lats2*-CKO and WT group. Interestingly, *in vitro* experiments showed that *Lats2* overexpression elevated p53 expression under vehicle condition, whereas suppressed p53 expression with H/R treatment, which indicated that H/R stress could revert the role of *Lats2* on modulating p53 expression.

Conclusions: This study indicates that specific *Lats2* knockout on renal proximal tubular epithelial cells exacerbates tubulointerstitial fibrosis, immune cell infiltration, apoptosis in ischemic AKI-induced tubular maladaptive repair through the upregulation of p53.

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FR-PO195

Renal Protection Driven by Peroxisome Activity, Proximal Tubule Park7, and Protein Succinylation

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Background: Acute Kidney injury (AKI) is an unfortunately frequent disease acquired during hospitalization with nearly 1 in 5 patients exhibiting some form of AKI. With the recent COVID-19 epidemic increasing instances of hospitalization, the burden that AKI and ensuing Chronic Kidney Disease (CKD) has on healthcare underlines the critical need for early detection, protection, and treatment for AKI. To attenuate AKI occurrence therapeutically we need a better understanding of the physiological and cellular mechanisms underlying damage. The most pronounced effect of AKI is on the Proximal Tubule Epithelial Cells (PTECs) which have the highest metabolic activity and are therefore most susceptible to damage after ischemia, sepsis, or transplant stress. This damage causes an increase in radical oxygen species, oxidative protein stress, and decreased functionality of mitochondrial Fatty Acid Oxidation (FAO) enzymes.

Methods: Our approach to protect from long-lasting tissue damage is by modulating the metabolic regimen and activating FAO in peroxisomes, a normally underused metabolic organelle. Large classes of proteins can be modulated rapidly and reversibly through the activity of enzymes that ligate Posttranslational Modifications (PTMs). We have previously shown that succinylation of lysine residues on metabolic proteins can be protective during AKI, specifically when the activity of the desuccinylase Sirtuin 5 is inhibited.

Results: Maintenance of the succinylome in Sirtuin 5 knockout tissue requires the activity of a second PTM ligating enzyme, the deglycase Park7. Park 7 is activated by oxidative stress and has been linked to apoptotic protection and minimizing CKD through reduction of Advanced Glycation Endproducts. Mass spectrometry analysis of kidney lysates point towards a protective combination of activated Park7 and deactivated Sirtuin 5 increasing peroxisomal FAO. This relationship is confirmed by the use of a diet-induced peroxisome upregulation using dicarboxylic acid (DCA) supplementation. The protection seen with DCA after AKI is significantly dependent on functioning Park7.

Conclusions: We conclude that a rapid and effective target for AKI treatment can be found by analyzing and maintaining the succinylome of PTECs and we hope to harness this mechanism to develop novel therapies for AKI.

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FR-PO196

Scleroderma Renal Crisis: A Nephrologist's Enigmatic Therapeutic Dilemma

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Introduction: Scleroderma Renal Crisis (SRC), occuring in 5-20% of patients with systemic scleroderma, typically presents with hypertensive urgency, acute kidney injury (AKI), microangiopathic hemolytic anemia and renal thrombotic microangiopathy. SRC is one of the very few times when AKI treatment calls for aggressive ACE inhibition, especially with Captopril. We describe fatal SRC, more than 20 years after initial diagnosis, AKI requiring hemodialysis despite escalated oral Captopril therapy for hypertension. She died 10 days after starting hemodialysis.

Case Description: A 71-year-old female with scleroderma since 2000 and treated intracranial oligodendroglioma since 2010 was admitted in late December 2022, with abdominal pain and decreased appetite. Blood pressure was 186/109 mm Hg, pulse 108/min and pulse ox 94% on room air. She was diagnosed with SRC – hypertension, microangiopathic hemolytic anemia, elevated LDH, +1 schistocytes, AKI with more than doubled creatinine to 2.21 mg/dL, UACR 935 ug/mg, >50 RBC/HPF and >50 WBC/HPF. Escalated oral Captopril was initiated. PLASMIC score was 4 points, low probability for TTP. ADAMTS13 was 53%, nondiagnostic. Hypertension was controlled on 137.5 mg Captopril TID + Nifedipine 60 mg BID. She was discharged, after 3 weeks, with stabilized blood pressure, stable creatinine at 4 mg/dL, and urine output of 1 L/day. Six days later, she was readmitted with worsening hypoxia, hyperkalemia 5.9 mmol/L, and creatinine of 5.12 mg/dL, which improved with fluid resuscitation. Potassium improved with oral sodium zirconium cyclosilicate. Kidney biopsy demonstrated thrombotic microangiopathy. She was treated for hypotension. Intermittent hemodialysis was started for worsening AKI and uremic encephalopathy. The patient passed away nine days after starting hemodialysis.

Discussion: SRC is an early complication of systemic sclerosis (SS), usually within one year of diagnosis. This case corroborates the difficulty in treating SRC-induced hypertension and resultant kidney damage. Our patient was atypical, with SRC occurring more than 20 years after diagnosis, hence the need for heightened vigilance. SRC was previously the leading cause of death in SS; the prognosis improved significantly with the introduction of ACE inhibitors. Despite adequate management of hypertension, our patient ultimately succumbed to her disease.

FR-PO197

Ascites and Bilateral Hydronephrosis

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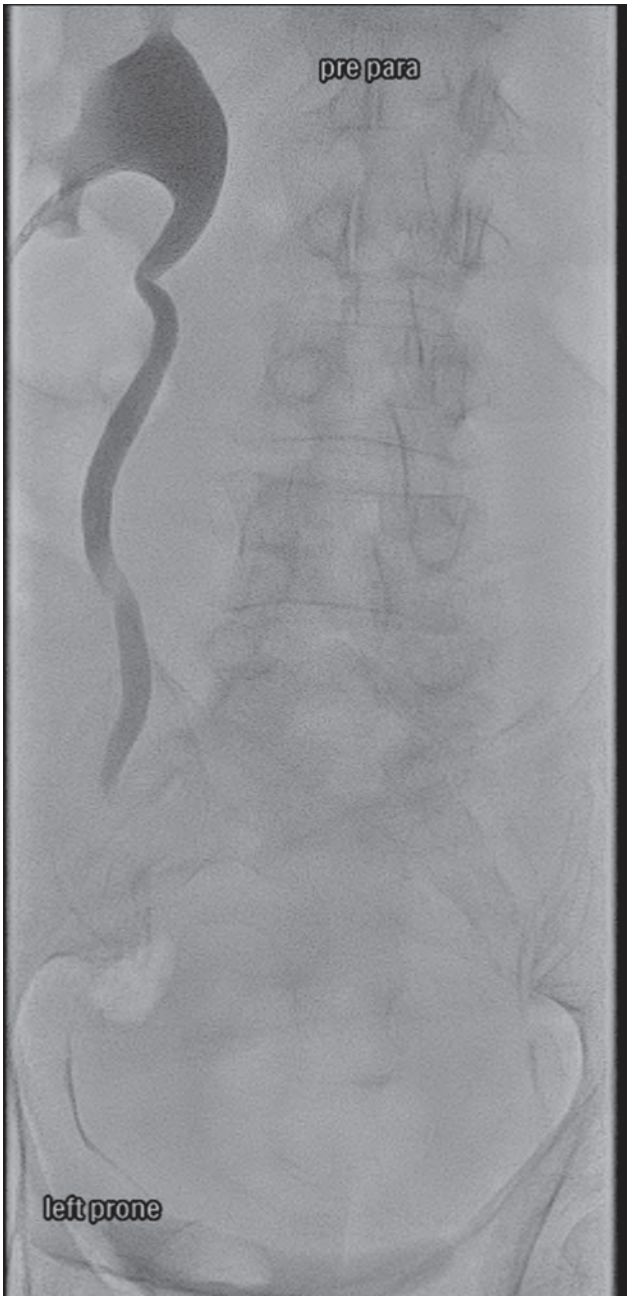
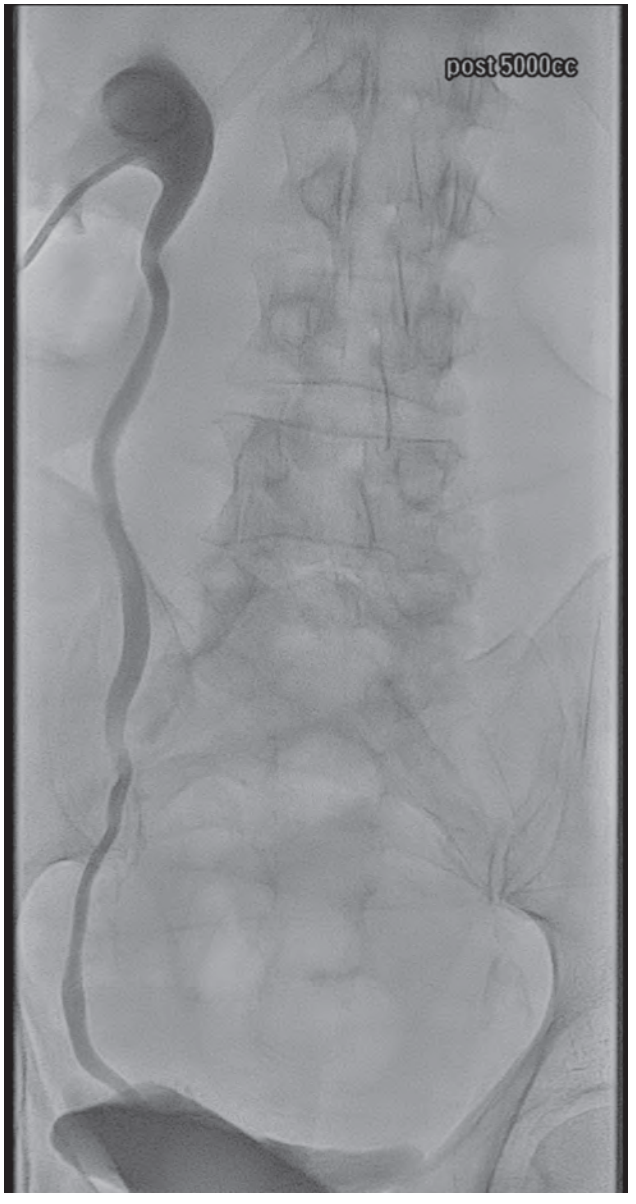
Introduction: Tense ascites resulting in bilateral hydronephrosis documented by antegrade nephrostograms before and after large-volume paracentesis (LVP).

Case Description: A 63-year-old man presented with cirrhosis presented with ascites, confusion and oliguria. Initial laboratory evaluation revealed elevated blood urea nitrogen 91 mg/dL and creatinine 5.97 mg/dL. Three months earlier, these were 7 mg/dL and 0.97 mg/dL, respectively. Ultrasound showed massive ascites and bilateral grade 2 hydronephrosis. A urinary catheter yielded 100 mL of urine. Computed Tomography confirmed bilateral hydronephrosis. It was hypothesized that massive ascites was the cause of the hydronephrosis. Antegrade nephrostogram found absent flow and fixed narrowing at the pelvic brim. The initial left renal pelvis pressure measured 15 mmHg. After LVP of 5 liter, renal pelvis pressure was 0 mmHg and fluoroscopy demonstrated ureteral peristalsis with antegrade flow into the bladder with resolution of the narrowed segment. Retroperitoneal ultrasound four days later confirmed resolution of hydronephrosis.

Discussion: Resolution of the elevated collecting system pressure and outflow obstruction after paracentesis supported tense ascites as the etiology for the acute kidney injury.



Pre-paracentesis



Post-paracentesis

FR-PO198

Plasma Cell-Rich Acute Interstitial Nephritis in VEXAS: An Under-Recognized Disease Feature

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Introduction: VEXAS syndrome (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) is a recently identified autoinflammatory disease with a large variety of disease manifestations. While recurrent fever, auricular chondritis, recurrent venous thromboembolism/thrombophlebitis, inflammatory skin lesions, ocular inflammation and cytopenias have been well-described, understanding of kidney manifestations is limited.

Case Description: Methods: Medical records of all patients with genetically confirmed VEXAS syndrome were reviewed for evidence of AKI or abnormal urinalysis. Patients who met the KDIGO criteria for AKI for at least two consecutive measurements of serum creatinine or cystatin C were considered as having AKI. Biopsy specimens (n = 4) were reviewed by four experienced nephropathologists. Clinical and laboratory features at disease onset and at time of AKI diagnosis were abstracted from direct chart review. **Results:** Among a cohort of 69 patients (all men, mean age 71 ± 9) with VEXAS syndrome, 16 (23%) developed AKI (mean age 75 ± 9) at some point during their follow up. A review of urinary findings revealed microscopic hematuria, mild proteinuria, and pyuria in 100%, 100% and in 82% of cases, respectively. Four patients had undergone renal biopsy for AKI. One patient had features of peri-tubular capillaritis and has been previously described. Three patients were found to have biopsy confirmation of interstitial nephritis (IN). All three patients had IN (acute in 2 and active chronic in 1) with plasma cell-rich infiltrate and tubulitis. Immunofluorescence was negative and electron microscopy did not show glomerular or extraglomerular immune deposits. Prednisone was initiated in all patients with biochemical improvement in renal function and resolution of urinary findings, however, AKI recurred following reduction in prednisone dose below 10-15 mg/day.

Discussion: AKI from Plasma cell-rich IN is an under-recognized feature in patients with VEXAS. AKI in VEXAS responds well to treatment with corticosteroids. Recurrence is common with lowering corticosteroids dose. Further investigations to Identify targeted, effective therapies is necessary.

FR-PO199

Renal Cortical Necrosis in Sickle Cell Trait

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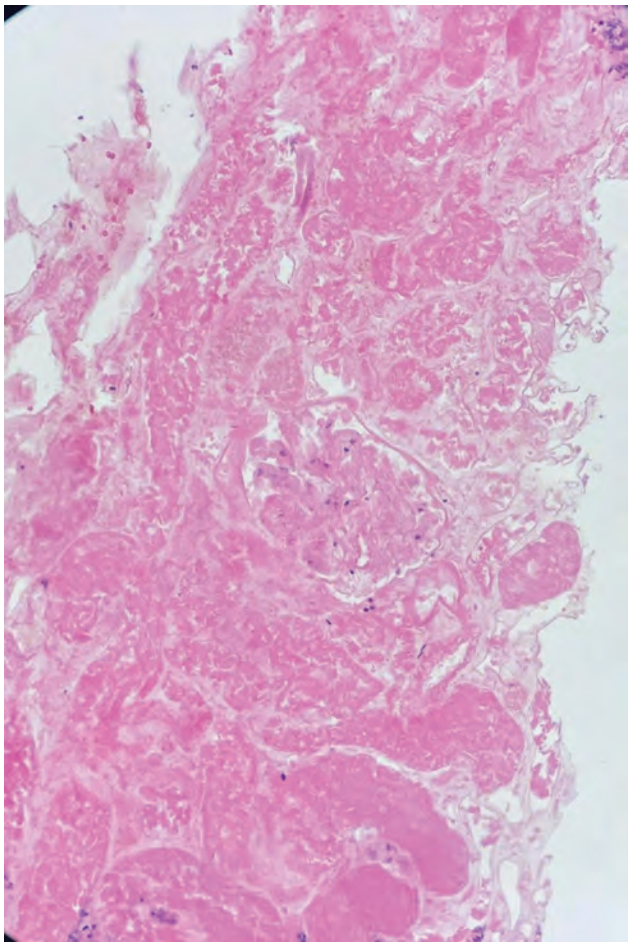
Introduction: Sickle cell disease (SCD) is a monogenic disorder characterized by an abnormal hemoglobin molecule due to a single nucleotide substitution in the β-globin gene. A homozygous inheritance causes sickling and hemolysis of erythrocytes and, subsequently, ischemia and end-organ damage. The heterozygous inheritance results in sickle cell trait (SCT) with a milder phenotypic presentation. We report a rare biopsy-proven renal cortical necrosis (RCN) in a patient with SCT.

Case Description: A 40-year-old male presented with severe, non-radiating lower abdominal pain and had lower abdominal tenderness on examination. His creatinine was 530 mmol/L. The urinalysis showed moderate pyuria and hematuria with negative urine culture. The urine protein:creatinine ratio was 1040 mg/g and his lactate dehydrogenase was 1209 units/L. The vasculitic and viral screens were negative, with normal complement levels. His hemoglobin electrophoresis showed a hemoglobin S of 31%. A kidney ultrasound showed normal size and morphology of both kidneys. A kidney biopsy showed diffuse extensive coagulative necrosis in the cortex, where the tubules and glomeruli were lined by pale ghost cells with pyknotic nuclei, there was marked interstitial inflammatory infiltrate composed predominantly of neutrophil ghosts. The immunofluorescence stains were negative. The patient's creatinine gradually improved over a 6-month period down to 176 mmol/L.

Discussion: Recurrent vaso-occlusive crises in SCD lead to many kidney manifestations, including RCN. Due to the relatively low levels of hemoglobin S, individuals with SCT rarely experience clinical manifestations. To the best of our knowledge, RCN has not been reported before in SCT.



H&E Stain showing necrotic areas with ghost outlines of glomeruli and tubules, and loss of cellular details

FR-PO200

Amoxicillin-Induced Crystalline Nephropathy

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Introduction: Amoxicillin-induced crystalline nephropathy (AICN) is characterized by the sudden onset of acute kidney injury (AKI) and microscopic examination of the urine revealing characteristic birefringent needles under polarized light. Surprisingly, the presence of intratubular amoxicillin crystals is not reported. We report here the first case of intrarenal deposits of amoxicillin crystals.

Case Description: A 55-year-old woman was referred for AKI within one week of the initiation of amoxicillin antibiotic therapy for mitral endocarditis. She was euvolemic and had no fever, tachycardia, or rash. Urine analysis revealed no signs of leukocyturia or hematuria. The initial serum creatinine level was 5.42 mg/dL and the urine protein/creatinine ratio was 1 g/g. Complement and serum electrophoresis results were within normal range. Renal ultrasound was unremarkable. Urine microscopy after amoxicillin withdrawal did not reveal any crystals. Renal biopsy detected elongated optically empty formations within the tubular lumen, suggesting the presence of material dissolved during sample preparation. Further examination of the frozen fragment of the kidney biopsy specimen under polarized light revealed numerous intratubular birefringent structures. Scanning electron microscopy confirmed the presence of crystals within the tubular lumen, suggesting amoxicillin crystallization. The definitive proof that these crystals were composed of amoxicillin was obtained through attenuated total reflectance (ATR)Fourier-transform infrared spectroscopic analysis of frozen kidney biopsy sections.

Discussion: Despite being one of the most frequent crystalline nephropathies, the presence of intratubular crystals of amoxicillin in situ has yet to be documented. This case highlights several important messages. First, the processing of kidney biopsies can cause dissolution of crystals, emphasizing the need for systematic analysis of frozen tissue under polarized light in suspected cases of crystalline nephropathy. Second, infrared spectroscopic analysis plays a crucial role in identifying the causative substance. Finally, the presence of crystals in urine is transient and crystalluria analyses may be negative if not performed during exposure to amoxicillin.

FR-PO201

Dual Autoimmune Processes, One IgG4 Stain

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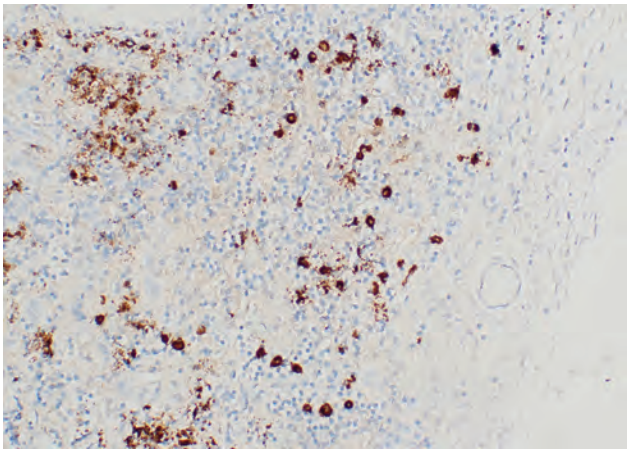
Introduction: IgG4-related disease (IgG4-RD) is an idiopathic immune-mediated fibroinflammatory disease often targeting the pancreas, kidney, retroperitoneum, and salivary glands. Pathology shows lymphoplasmacytic infiltrate with IgG4 plasma cells, storiform fibrosis, and obliterative phlebitis. We present an atypical presentation of a disease still being elucidated.

Case Description: A 30-year-old female with cirrhosis due to autoimmune hepatitis with primary sclerosing cholangitis overlap (AIH-PSC) and CKD stage III due to previous acute kidney injury (AKI) presented with new AKI (creatinine 3.3 mg/dl) during liver transplant evaluation. Serologic studies (table 1) showed elevated IgG with IgG4 predominance. Radiologic findings included retroperitoneal lymphadenopathy and groundglass pulmonary nodules. Although liver biopsy had not shown IgG4 plasma cell predominance, kidney biopsy revealed global glomerulosclerosis, interstitial fibrosis without storiform pattern, IgG4/IgG ratio of at least 30%, and >10 IgG4-plasma cells per high powered field (fig 1). She was treated for IgG4-RD with steroids and rituximab. Kidney function and pulmonary imaging improved dramatically within 6 months.

Discussion: This is a rare case of IgG4-RD in a young female with AIH-PSC without all characteristic pathologic findings. Diagnosis should be based on clinical, serological, radiological, and pathologic evidence. Underlying autoimmune disease may correlate with development of IgG4-RD.

Serologic Tests	Results	Normal range
Anti-neutrophil antibody (ANA) titer	>1:640	negative
Perinuclear anti-neutrophil cytoplasmic antibody (p-ANCA) titer	>1:640	negative
Myeloperoxidase (MPO) IgG	69 units	<20.0 units
Proteinase-3 (PR3) IgG	139.6 units	<20.0 units
Anti-double stranded DNA (Anti-dsDNA) titer	1:80	negative
Total IgG	6249 mg/dl	610-1616 mg/dL
IgG4	436.9 mg/dl	3.9-86.4 mg/dL



FR-PO202

Oxalate Nephropathy: An Insidious Cause of Renal Insufficiency

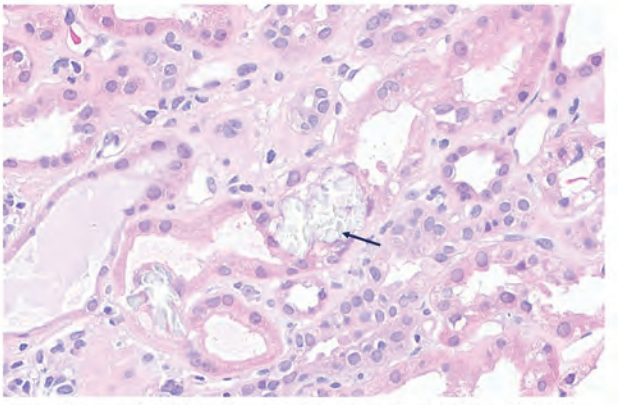
Alex D. Tarabochia, Jason R. Pettus, Roy Rajan. *Dartmouth Health, Lebanon, NH.*

Introduction: Oxalate nephropathy is caused by urinary super saturation of calcium oxalate, crystal formation with obstruction of tubules and deposition into the renal parenchyma.

Case Description: Patient is a 73-year-old male with Crohn's disease, distant history of oxalate renal stones 5 years ago, and hypertension referred for chronic kidney disease (CKD) with baseline serum creatinine (Cr) of 1.6 with stable Cr for more than a year, which increased to 2 over the period of six months. Blood pressure (BP) was at goal and he had not had a Crohn's flare in four years. Renal ultrasound (US) was negative for obstruction but did show small, non-obstructing (8mm on the left, 7mm on the right) renal stones in the bilateral lower renal poles. Specific gravity was 1.015, calcium was 8.5, protein: creatine (UPC) ratio was 0.1, and urine sediment was unremarkable with light microscopy. Routine labs were obtained one month later and serum Cr was 6.5. His symptoms were remarkable for fatigue and confusion. Pertinent medical history and repeat renal imaging were unremarkable. Specific gravity was 1.014 on urinalysis; calcium, UPC and light microscopy were unremarkable. The lack of obvious findings and lack of improvement with IV hydration prompted renal biopsy which showed tubular atrophy (15%) with diffuse calcium oxalate deposition and minimal acute tubular injury. Twenty-four-hour urine collection showed low urine citrate (113mg/day) and high urine oxalate (92 mg/day). He was started on potassium citrate and was instructed to increase fluid intake after which Cr improved to 2.5 over a period of two months.

Discussion: This case illustrates the insidious nature of oxalate nephropathy where the ongoing, mild super saturation leads to CKD and an acute super saturation leads to AKI. Risk factors include dehydration, high oxalate diet, and disorders with malabsorption

of fat including Crohn's disease which leads to saponification and increased oxalate absorption. The case highlights the importance of biopsy to distinguish this from other forms of AKI and 24-hour urine studies to manage stone formation.



Arrow pointing towards oxalate crystals in renal tubule with necrotic renal tubular epithelial cells.

FR-PO203

Allopurinol-Associated Renal Necrotizing Vasculitis

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Introduction: Allopurinol is a xanthine oxidase inhibitor frequently used in the treatment of gout, a common comorbidity in patients with chronic kidney disease (CKD). Post-marketing studies of allopurinol reported a higher incidence of acute kidney injury (AKI) with acute interstitial nephritis representing the most reported histologic finding. We report a case of allopurinol-associated renal vasculitis in a patient with diabetic kidney disease (DKD).

Case Description: A 68-year-old African American female with a history of DKD, hypertension, and gout was referred to the Emergency Room for nausea and AKI. Her baseline serum creatinine (sCr) was approximately 2.6 mg/dL and increased to 4.02 mg/dL on presentation. Two months prior to presentation, the patient was initiated on allopurinol therapy for gouty arthritis. Other notable findings were elevated liver enzymes and a diffuse purpuric rash. Serologic work-up revealed negative for ANCA, normal complement levels, and negative viral serologies. Because the AKI did not improve with hydration and cessation of allopurinol, a kidney biopsy was performed. The biopsy showed focal vasculitis with fibrinoid necrosis superimposed on a background of diabetic nephropathy with severe interstitial fibrosis and hypertension related arterial sclerosis. Review of the immunofluorescence did not reveal any staining for immunoglobulins, complement, or light chains. This biopsy was most consistent with necrotizing vasculitis. A prednisone taper was initiated for presumed allopurinol induced necrotizing vasculitis. The patient had improvement of kidney function and was subsequently discharged without requiring kidney replacement therapy.

Discussion: Rash is a known adverse effect of allopurinol therapy, and the majority of these cutaneous reactions improve with discontinuation of allopurinol therapy. The risk of severe adverse reactions is increased in patient of African, Korean, Chinese or Thai ancestry due to the high incidence of individuals who carry the HLA-B*5801 variant allele. Allopurinol-associated renal necrotizing vasculitis is likely a presentation of this type of severe hypersensitivity reaction. Upon initiation of allopurinol, especially the patients at high risk of cutaneous reactions should be counseled regarding this risk and instructed to promptly discontinue the medication and inform the treating provider if a rash is present.

FR-PO204

Tubulointerstitial Nephritis and Uveitis Syndrome (TINU)

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Introduction: Tubulointerstitial Nephritis and Uveitis Syndrome (TINU) is a rare, self-limiting interstitial nephritis and bilateral anterior uveitis.[1] Here, we describe an interesting case of TINU.

Case Description: A 42-year-old woman with no significant medical history presented to the hospital with acute kidney injury (AKI). She was noted to have elevated creatinine (Cr) of 2.2mg/dL with a baseline of 0.7-0.9mg/dL. Urinalysis was positive for blood (3+) and protein (30 mg). She reported using naproxen for menstrual cramps. Physical exam was negative for skin rash or lower extremity edema. Family history was significant for sarcoidosis. During inpatient stay, labs revealed urine protein to creatinine ratio (Pr:Cr) was 0.97 g/g. Serological work up was negative for ANA, ANCA, anti GBM, MPO, PR-3 and PLA2R. Complement levels were normal. Serum protein electrophoresis (SPEP) was negative for monoclonal protein. Free light chain ratio was elevated but acceptable for renal function. Urine eosinophils were negative. Kidney ultrasound (US) showed normal sized kidneys with normal echotexture and no evidence of hydronephrosis. Kidney biopsy showed acute interstitial nephritis. She received prednisone 60 mg daily which was tapered over 4 weeks. Cr improved to 1mg/dl on outpatient labs. She developed anterior uveitis after tapering the steroids and was prescribed methyl prednisone by ophthalmology. Repeat urinalysis showed significant pyuria with no nitrites nor proteinuria and Pr:Cr at 0.19 g/g. Repeat SPEP was negative. IgG4 subclasses were normal. Sjrogen antibodies, HLA B27 screening, Lyme's serology, quantiferon TB were all negative. ACE levels and 1,25 vit D levels were normal. Previous chest x-ray was negative for any hilar lymphadenopathy. Repeat renal biopsy showed resolving tubulointerstitial nephritis, however increased chronicity with moderate interstital fibrosis compared to mild previously.

Discussion: TINU is a diagnosis of exclusion[2,3] confirmed with renal biopsy. Management includes steroids with some severe cases requiring steroid sparing immunomodulators. Recurrence is common in the 1st few months to 2 years of stopping therapy.[3] **Conclusion:** An unexplained AKI that has been thoroughly worked up, in the presence uveitis, should prompt consideration for TINU, especially if it's been steroid responsive and recurring after its discontinuation.

FR-PO205

Use of Anti-C5 Inhibitor Leading to Renal Recovery in Combined Typical and Atypical Hemolytic Uremic Syndrome (HUS)

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Introduction: Hemolytic uremic syndrome (HUS) is classified as typical vs atypical with very different approaches to management. Only around 10% of cases are atypical HUS, a rare disease with poor outcome caused by uncontrolled activation of the alternative complement pathway. Here we present a case of a patient admitted for AKI requiring initiation of dialysis with clinical features suggestive of both typical and atypical HUS manifestation. Use of anti-C5 inhibitor, Eculizumab, ultimately provided full renal recovery.

Case Description: Patient is a 43 female, with no significant past medical history, and presented with nausea, vomiting, and bloody diarrhea. On admission, found to be in oliguric acute kidney injury (AKI), with hospital course complicated by worsening renal function and mental status requiring initiation of dialysis for clearance and volume optimization. Additional work up was significant for thrombocytopenia, elevated LDH, undetectable haptoglobin, with rare schistocyte concerning thrombotic microangiopathy (TMA). ADAMSTS13 29, given >10, not suggestive of TTP. O157:H7 grew on chromogenic agar with testing positive for Shiga toxin. As such, etiology of AKI initially thought secondary to typical HUS. However, given hemolytic anemia, thrombocytopenia, and kidney dysfunction, atypical HUS is still within the differential. Case discussed among transfusion medicine and nephrology team and patient was managed as atypical HUS with monoclonal anti-C5 inhibitor, Eculizumab 900mg weekly. Subsequent TMA complete genetic panel equivocal, but did show heterozygous missense for C5 polymorphism. Pt saw significant renal recovery after 4 doses of Eculizumab and was no longer dialysis dependent.

Discussion: Eculizumab is recommended as first-line treatment for atypical HUS; but its use in typical HUS has been controversial. However, our case illustrates the difficult but importance of early consideration of aHUS in patients presenting with TMA. More importantly, we highlight that near-normal renal recovery may be attained with eculizumab in adults even after a dependence on dialysis.

FR-PO206

Heuristic Is a Good Clinical Servant but a Bad Master: A Case of Delayed Diagnosis of Granulomatosis with Polyangiitis

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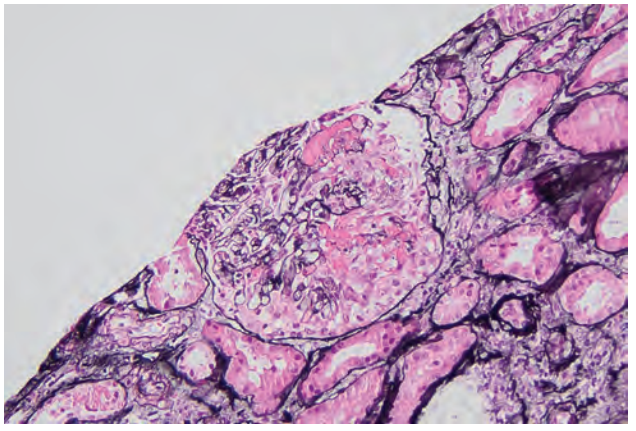
Introduction: Failure to connect the different and sometimes scattered symptoms of systemic vasculitis may result in delayed diagnosis of severe illnesses like Granulomatosis with Polyangiitis (GPA).

Case Description: 51-year-old male treated for CAP/sinusitis at an outside hospital 3 weeks prior and readmitted with diarrhea, hemoptysis, nausea, vomiting, dark stools, joint pains, epistaxis, and purpuric skin rash on extremities. Infectious work up, ANA with reflex, C3, C4, and hepatitis panel were unremarkable, but cANCA was positive at 1:160. Lactoferrin and calprotectin were elevated. CT abdomen was suggestive of colitis. Patient started on IV solumedrol for presumed inflammatory bowel disease (IBD) versus vasculitis, and transferred to our facility for GI evaluation. Serum creatinine rose from 1.0 to 1.8 mg/dl. UA showed hematuria, pyuria but no proteinuria. Colonoscopy with biopsy showed ulcerated mucosa without viral inclusions or features of IBD. Skin biopsy showed leukocytoclastic vasculitis. Working diagnosis was Henoch Schonlein Purpura, patient changed to oral steroids with plans for outpatient dermatology follow up. Kidney function however worsened so nephrology was consulted and a kidney biopsy pursued. This showed pauci-immune necrotizing crescentic GN. Therefore, patient was diagnosed with GPA and IV solumedrol and Rituximab were started. His clinical manifestations improved, but kidney function did not. He underwent PLEX. Creatinine plateaued at 5 mg/dl. At outpatient follow up visit, it decreased from 5.0 to 3.2 mg/dl. Patient reported feeling overall well with no symptoms recurrence.

Discussion: Recognizing the clinical presentations of rare diseases like ANCA associated vasculitis may help clinicians diagnose and promptly initiate of immunosuppressive therapy while awaiting kidney biopsy. This may yield better kidney prognosis.



Jones' silver stain 200x: Glomerulus demonstrating breaks in the GBM with associated fibrinoid necrosis.

FR-PO207

Weil Disease as a Cause of Electrolyte Wasting and AKI

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Introduction: Leptospirosis is a spirochetal illness that can manifest as a severe syndrome of Weil's disease, characterized by oliguric AKI, liver injury, jaundice, anemia, thrombocytopenia, rhabdomyolysis and pulmonary edema. AKI in Weil's disease is multifactorial, resulting from direct action of spirochetes on renal tissue, rhabdomyolysis, ATN and AIN.

Case Description: A 67-year-old woman from Haiti residing in the Boston area presented with lower extremity myalgias and weakness. Physical exam revealed scleral icterus and 4/5 muscle strength in the proximal lower extremities. She was found to have oliguric AKI with creatinine of 5.9 mg/dL, potassium of 4.3 mEq/L, phosphorus of 1.3 mg/dL and calcium of 8.2 mg/dL. LFT abnormalities included ALT 187 IU/L, AST 278 IU/L, total bilirubin 10.6 mg/dL and direct bilirubin 9.5 mg/dL. CPK was elevated at 3439 IU/L. CBC was remarkable for white blood cell count 19.8 K/uL, hemoglobin 8.9 g/dL and platelet count 23 K/uL. Reticulocyte count was low at 0.3% with haptoglobin 364 mg/dL and LDH 313 IU/L. INR and PTT were normal. ANA was negative. U/A revealed 1+ glucose, 3+ blood and 3+ protein (quantified at 4.7 g/g) with 10-15 isomorphic RBC/hpf, few granular casts and several renal tubular epithelial cells on microscopy. Infectious Diseases was consulted, and initially had low pre-test probability for infection given that the patient was afebrile and had been living in Massachusetts for 6 months, however recommended testing for leptospirosis, Dengue, chikungunya and tickborne diseases. Leptospira IgM returned positive with high titer of 12,800 for L. interrogans on MAT confirmatory testing. The patient was diagnosed with Weil's disease and was treated with ceftriaxone with normalization of laboratory parameters and symptoms.

Discussion: This patient's presentation of oliguric AKI with relatively preserved potassium and hypophosphatemia is characteristic of leptospirosis-associated renal injury, which is often preceded by electrolyte wasting that is thought to result from leptospire-induced changes in expression of tubular transport proteins along the nephron. It is important to maintain a high index of suspicion for leptospirosis in patients who present with AKI and evidence of electrolyte wasting, and in patients who present with direct hyperbilirubinemia out of proportion to other LFT abnormalities, even in the absence of exposure and recent travel history.

FR-PO208

Putting the Pieces Together: A Multifaceted Elevation in Creatinine

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Introduction: Goody Powder is OTC medicine containing aspirin, caffeine, and acetaminophen. When taken in excess and combined with alcohol it can induce undesirable elevations in blood pressure that can exacerbate renal dysfunction in an already compromised kidney. It can also cause severe gastric irritation with the risk for gastrointestinal bleeding. GI bleed could lead to blood loss, uremia, and dehydration. Furthermore, caffeine and alcohol exhibit diuretic properties intensifing dehydration and exacerbate AKI through the reduction of blood volume. Although aspirin and alcohol have been linked to kidney damage, there are few case reports demonstrating the rapid progression to ESRD.

Case Description: 33 y/o African American male BMI 37 and no reported PMH presented with complaints of fatigue, generalized weakness, nausea, vomiting, and diarrhea x 1 month. Reported daily episodes of vomiting with intermittent hematemesis. He also complains of dizziness, abdominal pain, decreased urine output. He denies fever, chills, chest pain, or dyspnea. The patient also reports prior heavy drinking with multiple alcoholic beverages/day till recently, and combining it with Goody powders for his abdominal pain. BP 175/88, HR 96. Lab Na 131, K 6.0, bicarb 6, BUN 238, creatinine 50, and eGFR 1, Hb 6.6. The patient was admitted for further workup where electrolytes were replenished, his hypertensive emergency was appropriately controlled, and he underwent dialysis. A renal biopsy demonstrated accelerated hypertension as one of the prime causes for his renal failure.

Discussion: Even though Goody Powders' controlled use is generally safe, its combined use with alcohol possibly accelerated the progression to ESRD in our patient. This patient possibly had baseline CKD due to uncontrolled hypertension that was never controlled but in the setting of above, he progressed to ESRD rather quickly. Also, he had concurrent hemolysis secondary to severe hypertension on top of potential GI bleed. It is important to note that combining caffeine with alcohol can have contradictory CNS manifestations especially when uremia sets in. Therefore, timely identification of metabolic abnormalities along with prompt management is crucial. Patient education should be emphasized to avoid prior behaviors and to avoid further damage.

FR-PO209

An Uncommon Presentation of Cocaine-Induced Acute Interstitial Nephritis

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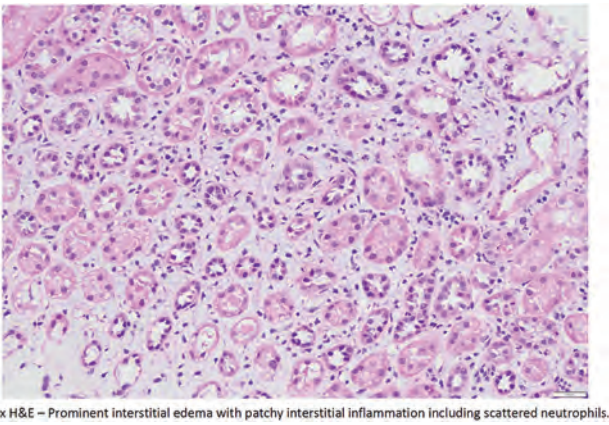
Introduction: Cocaine induced kidney injury may occur through multiple mechanisms including rhabdomyolysis, thrombotic microangiopathy, glomerulonephritis, vasculitis, and renal infarction. Acute interstitial nephritis (AIN) is characterized by inflammatory infiltrates in the kidney interstitium sparing the glomeruli, that may occur from systemic autoimmune disorders, infection or drug-related mechanisms. Cocaine-induced AIN is a rare entity that has been poorly studied.

Case Description: A 45-year-old male was brought to the ER after being found unresponsive. He had acute kidney injury with a creatinine of 4, lactic acidosis, creatine kinase greater than 40,000 IU/L and urine toxicology positive for cocaine. Manual urine microscopy showed occasional non-dysmorphic RBCs and no WBCs. The patient was treated with IV fluids without renal replacement therapy. After regaining consciousness, he communicated a prolonged history of cocaine use but no kidney injury. He was treated for myoglobin-related toxic kidney injury from rhabdomyolysis. Over the next few days, his creatinine plateaued around 4 despite volume resuscitation. On hospital day 15, a kidney biopsy revealed acute tubular injury with myoglobin casts, and prominent interstitial edema with inflammation suggestive of interstitial nephritits. This was presumed to be cocaine-induced AIN.

Discussion: The most common presentation of AIN is rash and fever (25-40%), with laboratory findings of acute kidney injury, eosinophilia (35-60%) and sterile pyuria (75-85%). The classical triad of fever, eosinophilia and AKI are present in <10% of all cases. A definitive diagnosis is made by a kidney biopsy which shows interstitial infiltrates and edema. In our patient, while diagnosis was confirmed with a classical picture on biopsy, the patient did not have any evidence of pyuria or eosinophils. This suggests that in a patient with cocaine overdose who shows non-improvement in creatinine, interstitial nephritis may be considered despite absence of classical clinical findings.



20x H&E – Prominent interstitial edema with patchy interstitial inflammation including scattered neutrophils.

FR-PO210

Acute Hyperoxaluria in Setting of Hereditary Spherocytosis Presenting as a Rapidly Progressive Glomerulonephritis (RPGN)

Barbara C. Mcmullan, Anna M. Burgner. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Hereditary spherocytosis (HS) is the most common inherited hemolytic anemia. Characteristic symptoms include anemia, jaundice, and splenomegaly. Clinical severity is variable with most remaining well compensated. Common complications include cholelithiasis, hemolytic episodes, and aplastic crisis. Despite causing hemolytic anemia, kidney injury is rarely associated with this disease.

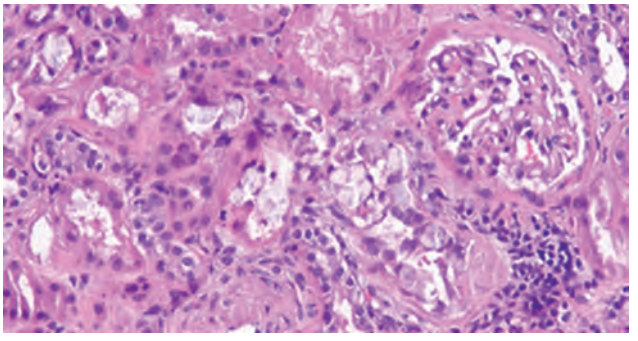
Case Description: A 32-year-old female with HS developed hemolytic crisis and AKI and was aggressively resuscitated. She had evidence of a rapidly progressive glomerulonephritis (RPGN) by labs, see Table 1. She was treated empirically with steroids and underwent kidney biopsy on hospital day 5. Biopsy results showed diffuse calcium oxalate crystals with minimal glomerular injury, see figure 1. Day 1 post biopsy

she required dialysis for metabolic derangements. With normalization of electrolytes and clearance of oxalate, she was able to cease dialysis with excellent kidney recovery.

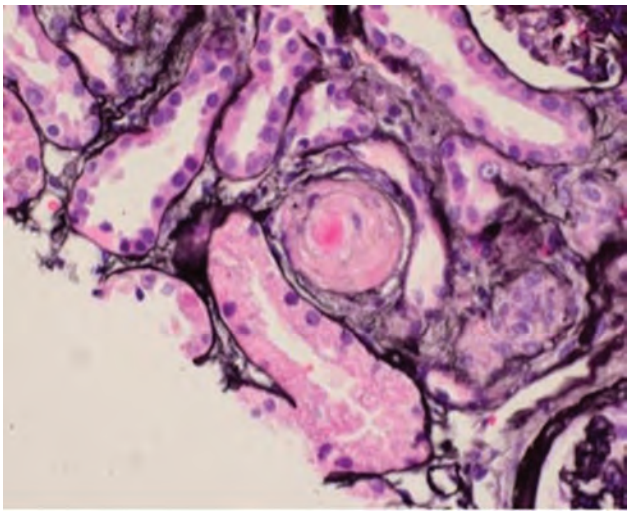
Discussion: The source of acute oxalosis was unknown. Erythrocytes carry oxalate but intact red blood cells do not increase risk of crystal formation. Red cell membrane fragments have been shown to promote oxalate crystal growth and aggregation up to 2.5 fold. However, she had a history of prior hemolytic episodes without AKIs or nephrolithiasis. We ruled out causes of oxalate including history of bariatric surgery and ethylene glycol poisoning. We learned that 2 days prior to admission she had received an infusion containing 2500mg vitamin C (Myers cocktail). We postulate that hypervitaminosis C in setting of hemolytic anemia caused acute oxalate crystal deposition with subsequent kidney failure. Various infusions have become readily available with minimal medical oversight, thus history taking remains paramount to patient care.

	A -2 days	Admission Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11	Day 12	Discharge D +8 days
Creatinine (mg/dl)	0.85	2.22	2.87	4.99	6.67	7.75	7.36	9.56	5.62	2.77	3.8	4.68	2.91	3.56	2.75	0.88
Calcium (mg/dl)		8.4	8.1	7.6	7.1	7.1	6.6	6.3	7.2	8.8	8.4	7.4	7.7	8.2	8.3	8.5
Hgb (gm/dl)	5.5	5	6.8	7.6	8	6.8	6.7	9.3	7.7	6	7.5	7	6.5	8.4	7.1	6.7
TbiR (mg/dl)	6.4	5.6	4.9	6	4.7	3.8	3.6	3.1	2.7	3.1	2.9	2.4	2.4	2.2	1.8	3.8
UPCR (mg/mg)		3.71		4.91												0.23
RBC (Urine/HPF)		317		417												1

Red = RRT day



Diffuse tubular injury with oxalate crystal deposition and focal hemosiderin tubulopathy



Renal Biopsy Showing Fibrin Deposition

FR-PO211

Atypical Hemolytic Uremic Syndrome from Recent HIV Diagnosis

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Introduction: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare thrombotic microangiopathic disorder characterized by reduced platelet counts, thrombocytopenia, and hemolytic anemia, often leading to kidney failure. It is associated with dysfunction of the Complement Alternative Pathway, and unlike Typical TMA, ADAMTS 13 activity levels are not low. While HIV-induced TMA has been documented, information on HIV-induced aHUS is limited. In this case, we present a rare instance of a patient with aHUS who was recently diagnosed with HIV.

Case Description: A 50-year-old male African American patient was recently diagnosed with HIV, with a CD4 count of 4 and a CD8 count of 158. He arrived at the hospital with complaints of abdominal pain, nausea, vomiting, generalized fatigue, and confusion. His Initial Lab results showed thrombocytopenia (plt:53k), anemia (Hgb:8), acute kidney injury (Cr:20, BUN:156), and accelerated hypertension. Tests for viral hepatitis, ANA, ANCA, and Syphilis were negative. The patient's renal biopsy revealed possible TMA with interstitial fibrosis and fibrin deposition. Plasmapheresis was initiated based on suspected TTP. Hemodialysis was started due to worsening renal failure and anuria. His ADAMTS13 levels were not low, suggesting atypical HUS. The patient's management was changed to Eculizumab therapy where his clinical condition and renal function improved after two doses. His dialysis was eventually discontinued.

Discussion: Existing literature links HIV with typical TMA, but no reports mention HIV-induced Atypical HUS. This case reveals a rare presentation of aHUS following a recent HIV diagnosis. HAART therapy is typically recommended but may take time to show clinical benefit, potentially leading to long-term dialysis due to irreversible scarring. This report demonstrates Eculizumab as an effective rapid therapy for acute TMA, allowing patients to improve without requiring long-term dialysis.

FR-PO212

Intraperitoneal Urinary Leak Presenting as Severe AKI After Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP)

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Introduction: About one in five hospitalizations is complicated by AKI, and patients with urological diseases are at higher risk of developing AKI, but severe AKI is a rare event after prostate surgery. We present a unique case of AKI following RALRP.

Case Description: A 60-year-old male with hypertension, type 2 diabetes, prostate cancer and normal kidney function at baseline, presented with severe lower abdominal pain six days after RALRP. His surgical drains were removed a day prior to presentation, but his urinary catheter was maintained. Abdominal exam revealed a tender right lower abdomen and clean surgical sites. He was afebrile, blood pressure was 149/86 mmHg, and pulse was 94 beats/minute. A non-contrast abdominopelvic computed tomography (CT) showed a pelvic hematoma to the right of the urinary bladder with small locules of gas. There was also a lower density fluid collection in the surgical bed. His serum creatinine was 1.72 mg/dL, potassium was 4.2 mEq/L, and blood urea nitrogen was 22 mg/dL. Hemoglobin was 10 g/dL. WBC, platelet count, creatinine kinase and coagulation profile were all within normal limits. Urinalysis was positive for blood, but negative for infection. The patient had worsening abdominal distension and pain and an abdominal ultrasound showed a new development of moderate ascites. At that time, patient also had doubling of his serum creatinine to 4.21 mg/dL while maintaining adequate urine output. Abdominal paracentesis performed in the left lower quadrant aspirated 2 liters of bloody fluid. Analysis of the peritoneal fluid showed creatinine of 10.4 mg/dL. A CT cystography confirmed a vesicourethral urinary leak with expansion into the peritoneal cavity. A pelvic drain was placed, resulting in normalization of serum creatinine and resolution of abdominal ascites.

Discussion: RALRP has become the dominant surgical approach for radical prostatectomy in the United States. Vesicourethral urinary leak is a common complication following RALRP, but the reported incidence of expansion of those leaks into the peritoneum was 1% and <0.5% required CT-guided drainage. Our case is unique given the acute presentation of severe non-oliguric AKI after RALRP with development of ascites after removal of the surgical drain resulting in pseudo-AKI from increased creatinine absorption through the peritoneal membranes.

FR-PO213

A Case of AKI due to Letermovir and Tacrolimus Interaction

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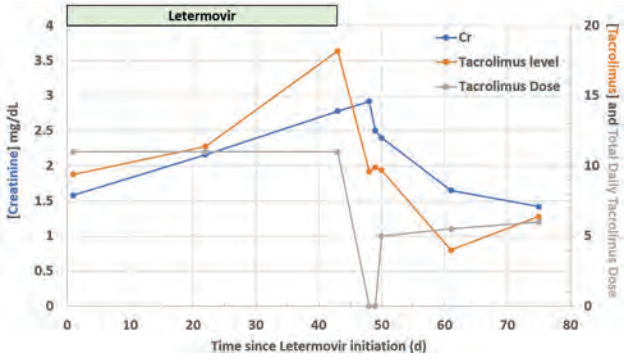
Introduction: Cytomegalovirus (CMV) is a significant pathogen causing morbidity and mortality among solid organ transplant recipients. Valganciclovir (VGC) and ganciclovir are first line for prophylaxis and treatment. Their use is limited by bone marrow toxicity, particularly leukopenia, and by viral resistance. Letermovir (LET) is a terminase complex inhibitor approved for CMV prophylaxis in hematopoietic stem cell transplant patients. Unlike VGC and ganciclovir, it doesn't have myelosuppressive properties. It is also a moderate inhibitor of cytochrome P450 3A4, which metabolizes commonly used immunosuppressive (IS) tacrolimus (TAC). One study suggests a TAC dose reduction of about 30% may be needed after starting LET.

Case Description: Our patient is a 68-year-old male with non-ischemic cardiomyopathy status post orthotopic heart transplant (CMV+/-) now with CKD (serum creatinine (SCr) 1.4-1.6 mg/dL) complicated by recurrent CMV viremia treated with VGC. His IS regimen included TAC with stable levels for several months. At 2.5 years after transplant, he developed leukopenia prompting a switch from VGC to LET. At visits

0, 3, and 6 weeks after LET initiation, SCr was 1.6, 2.2, and 2.8 mg/dL, respectively (see figure 1) with gradually increasing TAC levels (peak 18 ng/mL at week 6). He did not have any other new medications, diarrhea, abnormal liver tests or other explanation for the change in TAC level. He was admitted for AKI evaluation and workup was unrevealing. AKI was felt to be due to TAC nephrotoxicity secondary to drug-drug interaction with LET. LET was discontinued, TAC was reduced, and SCr improved. In subsequent outpatient visits, SCr returned to baseline and TAC dose had to be increased, confirming that LET was likely the etiology.

Discussion: To our knowledge, this is the first reported case of AKI following the initiation of LET with concurrent TAC use. Transplant physicians should be aware of this interaction and consider more frequent TAC level monitoring in the first month of starting or stopping LET.



FR-PO214

AKI and Hypercalcemia: A Complicated HIV Story

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Introduction: HIV causes kidney injury through direct viral effects, antiviral therapies, immune reconstitution, and superimposed infections. We report a case of kidney dysfunction in the setting of HIV/AIDS and disseminated mycobacterial avium complex (MAC) infection.

Case Description: A 23-year-old male with history of HIV/AIDS was admitted with acute kidney injury (AKI) and hypercalcemia (hyperCa) after outpatient evalutation for failure to thrive and lymphadenopathy. Creatinine peaked at 2.48mg/dL from a baseline of 1. HyperCa and hyperphosphatemia were noted at 13.5 and 5.2mg/dL respectively. Urinalysis showed 2+ protein with a UPCR of 0.6. Sediment analysis revealed muddy brown casts. Kidney US showed non-obstructing renal calculi without hydronephrosis. Workup showed low PTH levels, 25-OH Vitamin D of 26.8ng/mL (nl: 31-80) and 1,25-Dihydroxyvitamin D of 58.4pg/mL (nl 19.9-79.3). PTHrP was elevated at 4.1pmol/L (nl: 0-2.3). Per chart review, patient had a diagnosis of disseminated MAC and a recent kidney biopsy that showed acute on chronic interstitial nephritis. At that time, his AKI was attributed to MAC and antibiotics were started. Subsequently, patient had worsening adenopathy concerning for lymphoma, but a follow up biopsy could not be obtained. His symptoms were suggestive of uncontrolled MAC so the antibiotics and HIV therapy were adjusted. His AKI was thought to be related to the hyperCa which in turn was hypothesized to be related to the granulomatous infection due to activated vitamin D. The elevated PTHrP remained of concern. The hyperCa was managed with IV fluids and pamidronate. Patient was discharged on optimized HIV and MAC therapy with improvement of calcium level and kidney function. 9 months after admission, creatinine was down to 1.23 with a calcium of 9.7.

Discussion: HyperCa is a rare but potentially serious complication of disseminated MAC infection, with incidence ranging from 5 to 20%. The mechanism is thought to be due to increased 1-alpha hydroxylase expression in activated macrophages. A similar mechanism explains hyperCa seen with lymphomas. In the setting of HIV in general, and AIDS particularly, hyperCa should trigger an in-depth evaluation for an underlying granulomatous or lymphomatous disorder. Improvement generally follows treatment of the underlying pathology.

FR-PO215

Nivolumab-Induced Acute Interstitial Nephritis

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Introduction: Nivolumab, an anti-programmed death – 1 (PD-1) monoclonal antibody, is an immune checkpoint inhibitor that has recently been approved for use as treatment for various cancers including melanoma, renal cell carcinoma, non-small cell lung cancer and squamous cell carcinoma. However, immune checkpoint inhibitors have been linked to a different array of immune related side effects affecting dermatological, gastrointestinal, endocrinological, hepatic, and renal systems. There have been a few documented occurrences of nephrotoxic side effects.

Case Description: We present a case of a 73-year-old male patient who was diagnosed with clear cell renal cell carcinoma with extensive necrosis, lung metastasis and renal vein thrombosis in 08/2021. The patient was started on Cabozatinib chemotherapy with initial good response. The patient was started on Nivolumab in 01/2023 in combination with lower dose of Cabozatinib as the response to cabozatinib was suboptimal. Two months after starting Nivolumab the patient was admitted with c/o right flank pain. He was found to have evidence of acute kidney injury (AKI). BMP showed a creatinine of 7.21 mg/dl, BUN 57, Na 134 mg/dl, K 5.7 mg/dl. Urinalysis showed 30 mg / dl proteinuria, 4 rbc / hpf, +1 blood, and urine spot protein to creatinine ratio was 1 gm / gm. CBC revealed a normal white blood cell count and no eosinophilia. Soon after admission the patient developed uremic symptomatology and had to be initiated on Hemodialysis and a renal biopsy was planned. Renal biopsy report was consistent with signs of acute interstitial nephritis with associated tubulitis, normal appearing glomeruli, negative immunofluorescence, and minimal intimal fibrosis. The patient was started on intravenous methylprednisolone 2 mg / kg for a total of 3 days followed by oral prednisone 1 mg / kg. Kidney function slowly improved and stabilized after 2 weeks with a creatinine of 4.4 mg / dl with no need for further hemodialysis sessions.

Discussion: It is challenging to differentiate between cases of AIN versus acute tubular necrosis (ATN), which occur commonly in patients with cancer. The following case report highlights AIN as a cause of AKI in patients receiving Nivolumab and how good clinical judgement along with timely intervention can lead to reversal of dialysis dependent AKI

FR-PO216

Giant Abdominal Aortic Aneurysm (AAA): A Rare Cause of Obstructive Nephropathy

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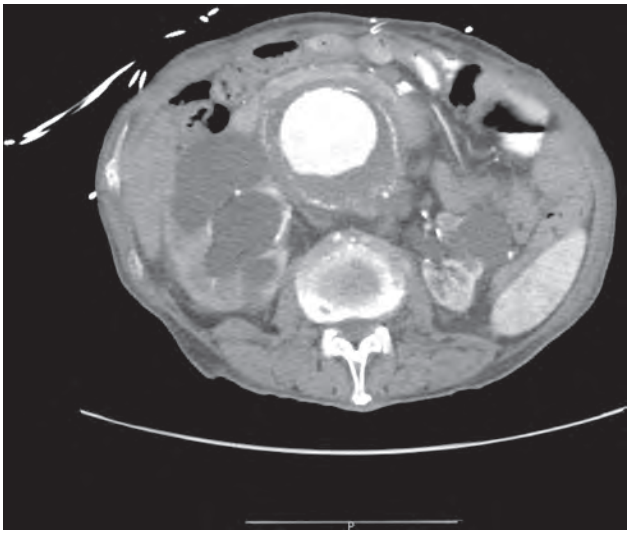
Introduction: Obstructive nephropathy (ON) accounts for 5-10% of all cases of AKI. The most common causes include benign prostatic hyperplasia, kidney stones or malignancy. Only few cases have been reported of ON caused by a large abdominal aortic aneurysm (AAA) producing ureteral compression. We present the case of a patient whose severe renal failure only became evident after presenting to the hospital with impending AAA rupture.

Case Description: A 72-year-old male with long-term tobacco use and no medical care for >15 years presented with abdominal pain and dyspnea. He denied any fever, chills, nausea, vomiting, diarrhea, or poor oral intake. In ED, blood pressure was 163/93, but otherwise stable. Blood work showed a creatinine 14.0 mg/dl, BUN 149 mg/dl, K 5.3 mmol/L, CO2 6 mmol/L, anion gap 29, and normal LFTs. CT without contrast revealed an impending aortic rupture with aneurysmal dilation measuring 8.6 x 10.6 cm in axial diameter causing severe right-sided hydronephrosis and mildly atrophic left kidney. Dialysis was initiated for optimization of acid-base status for emergent endovascular repair. The next day he underwent percutaneous stent graft repair and had a right nephrostomy tube placed resulting in complete resolution of right hydronephrosis. Urine output improved; however, clearance was still impaired so dialysis was restarted and continued without adequate renal recovery.

Discussion: AAA is a rare and potentially fatal cause of ON. AAAs larger than 8 cm carry an annual rupture risk of 30-50%. Once this occurs mortality risk is extremely high, making emergency surgery the only alternative. Our patient's case posed an added level of complexity as he was found to have acute renal failure requiring emergent dialysis for pre-op optimization. Although exceedingly rare, it is important to keep in mind aortic aneurysms as a cause of ON with the major difference from most other causes being the critical role prompt treatment plays in patients' survival.



AAA causing severe hydronephrosis

FR-PO217

Renal Limited IgG4-Related Disease: A Unique Clinical Entity

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Introduction: IgG4 related disease (IgG4-RD) is an immune mediated fibroinflammatory conditions that can affect many organs including kidneys, where involved organs share core pathologic, clinical and serological similarities. IgG4-related

kidney disease (IgG4-RKD) is a part of spectrum of IgG4-RD and more than 90% of patients with IgG4-RKD have manifestations of extrarenal involvement. Here, we describe a rare case where kidney is the sole organ involved in IgG4-RD.

Case Description: A 74-year-old man with history of long standing hypertension was admitted after a routine blood test showed acute kidney injury, serum creatinine 5.4 mg/dl, was 1.3 mg/dl two years prior. Work up is shown in Table 1. BP was uncontrolled on admission and patient was asymptomatic. CT abdomen/pelvis did not show any abnormalities. Kidney biopsy revealed diffuse interstitial fibrosis and tubular atrophy involving 90% of the cortical parenchyma, and immuno-labeling showed diffuse IgG4-positive plasma cells in the interstitium with 17-31 cells/HPF in most concentrated areas (Image 1).

Discussion: Tubulointerstitial nephritis (IgG4-TIN) is the most common renal manifestation of IgG4-RKD, it may present as acute or chronic renal insufficiency. Diagnosis of IgG-4 TIN is challenging without the presence of other extra-renal manifestations of IgG4-RD. IgG4 staining should be considered in TIN with presence of plasma cell infiltrates. To the best of our knowledge, our case is first to be reported in literature for isolated IgG4-TIN. Greater clinical awareness of this entity will lead to early diagnosis and early intervention.

Lab (reference range)	Patient values	Lab (reference range)	Patient values
Na (136-144 mmol/l)	141 mmol/l	Calcium (mg/dl)	8.4 mg/dl
K (3.3-5.1 mmol/l)	3.8 mmol/l	WBC (4.0-11.0 k/ul)	6.8 k/ul
Urea (7-22 mg/dl)	36 mg/dl	Hemoglobin (13-17 g/dl)	10.3 g/dl
Creatinine (0.6-1.4 mg/dl)	5.4 mg/dl	Platelet (130-400 k/ul)	217 k/ul
C3 (90-180 mg/dl)	107 mg/dl	C4 (10-40 mg/dl)	41 mg/dl
Urine studies			
Urine analysis: colorless, Ph 7.5, specific gravity 1.007, 20+ protein, -ve glucose, RBC 3-5 /HPF, WBC 11-25 /HPF			
Albumin/creatinine (0-30 mg/g)	144 mg/g	Protein/creatinine (0-200 mg/g)	860 mg/g
Serology			
ANA +ve 1:320	SSA/SSB -ve	HIV,HBV,HCV non-reactive	IgG 1712 (600-1600 mg/dl)
dsDNA -ve	ANCA -ve	SPEP –ve for monoclonal gammopathy	IgG4 64 (4-86 mg/dl)

Table 1.

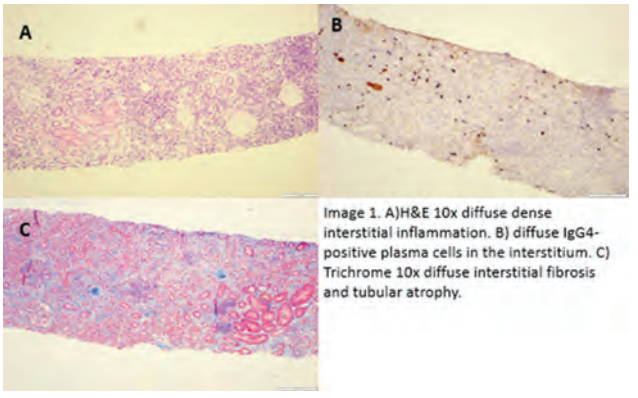

Image 1. A)H&E 10x diffuse dense interstitial inflammation. B) diffuse IgG4-positive plasma cells in the interstitium. C) Trichrome 10x diffuse interstitial fibrosis and tubular atrophy.

Image 1.

FR-PO218

Point-of-Care Ultrasound (POCUS) in Metastatic Ovarian Carcinoma: Kidney Injury and Inferior Vena Cava (IVC) Compression

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Introduction: Acute renal failure in metastatic cancer is common, with various causes. Point-of-care ultrasound (POCUS) aids in identifying complications like pleural effusions, edema, and thrombosis. Its utilization is validated both inpatient and outpatient, enhancing diagnostic capabilities at the bedside.

Case Description: A 65-year-old female with active metastatic serous ovarian carcinoma of Müllerian origin presented with progressive dyspnea on exertion and lower extremity edema over one month. Her treatment history included Doxil/Bevacizumab with partial response, followed by Carboplatin/Taxol/Avastin and Niraparib with disease progression. Surgical intervention was not an option. Vital signs were significant for tachycardia. Physical examination findings included diminished lung sounds in the left base, distended abdomen, and 3+ pitting edema up to the knees bilaterally. Laboratory workup showed acute kidney injury with creatinine 2.11 mg/dL (baseline 0.9-1.0 mg/dL) that had been gradually increasing over 6 months. Urinalysis revealed >300 mg/dL protein with a urine protein-to-creatinine ratio of 1.44 g/g. CT chest ruled out pulmonary embolism but revealed a moderate to large left pleural effusion. Intravenous diuretic therapy initially improved symptoms, but renal function subsequently worsened. POCUS demonstrated a patent but collapsible inferior vena cava (IVC) and an abdominal mass compressing the IVC. MRI confirmed flattening of the IVC throughout the abdomen with slit-like narrowing at the level of renal veins, attributed to mass effect from a large left hemiabdominal mass displacing bowel loops. Creatinine stabilized at 1.9 mg/dL, and the patient was discharged with daily furosemide for symptom management and volume status optimization.

Discussion: Acute kidney injury due to metastatic mass compression of the IVC is an uncommon but important complication to consider. Compression of the IVC by an abdominal mass can contribute to renal impairment and venous congestion. POCUS is a valuable tool for assessing the IVC and identifying IVC compression, CT or MRI can provide further confirmation. In such cases, diuretic therapy should be used judiciously, with careful consideration of the patient's renal function and overall clinical status. Management of edema and venous congestion in such cases should focus on optimizing volume status and providing symptomatic relief.

FR-PO219

Severe Hypothyroidism May Contribute to AKI but Not Hyponatremia: A Case Report

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Introduction: Hypothyroidism is commonly encountered in patients with chronic kidney disease but rarely contributes to acute kidney injury. Majority of the published cases of acute kidney injury (AKI) have associated rhabdomyolysis secondary to severe hypothyroidism. In addition, hypothyroidism work up is typically included as a standard practice in the etiology of hyponatremia. Herein, we report a severe case of hypothyroidism resulting in AKI without associated rhabdomyolysis or hyponatremia.

Case Description: An 89-year-old woman presented to emergency department with a chief complaint of left-sided hip pain following mechanical fall. Review of systems positive for fatigue and constipation. Medical history was pertinent for CKD IIIb, hypothyroidism and hypertension. Physical examination revealed persistent bradycardia (HR;30-50 bpm) and 2+ bilateral lower extremity edema. Telemetry additionally demonstrated intermittent sinuses pauses. Laboratory data at the time of admission revealed serum creatinine (Scr) of 1.8 mg/dL (baseline 1.3 mg/dL), thyroid stimulating hormone (TSH) of 298 uIU/mL, free T_4 < 0.40 ng/dL and total T_3 < 40 ng/dL, creatinine phosphokinase (CPK) was 404 U/L and serum sodium was 136 mmol/L. Urine analysis consistent with 1+protein, no blood and urine sediment notable for waxy and granular casts. Urine protein: creatinine ratio (UPCR) was 0.28 mg/dL and a kidney ultrasound was negative. Other serologies including AST, ALT, cortisol resulted negative. Upon further inquiry patient mentioned of missing several doses of levothyroxine as she ran out of several medications. Patient was started on intravenous (IV) fluid supplementation and high doses of IV levothyroxine. Meanwhile, with persistent bradycardia, a pacemaker was implanted. She had gradual resolution of her symptoms and thyroid function tests with thyroid hormone supplementation. Her Scr returned closed to baseline and she was eventually discharge on levothyroxine dose of 88 mcg daily with close follow up.

Discussion: Severe hypothyroidism can cause AKI secondary to associated cardiac conduction abnormalities and hemodynamic alteration, even in the absence of rhabdomyolysis. In addition, the traditional teaching of hypothyroidism as a cause of hyponatremia is a very rare entity.

FR-PO220

An Atypical Case of Typical Hemolytic Uremic Syndrome (HUS)

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Introduction: Typical hemolytic uremic syndrome (HUS) is a rare cause of thrombotic microangiopathy in adults. Predominantly a pediatric disease, typical HUS is caused by Shiga toxin producing Escherichia Coli. We present the case of an adult with typical HUS.

Case Description: A 60 years old woman with history of type 2 Diabetes Mellitus and no kidney disease was admitted to the ICU with a 5 day history of nausea, vomiting and bloody diarrhea. Her workup revealed colitis with sepsis, AKI, and thrombocytopenia. Platelet count was 61,000/mL and plummeted to 33,000/mL during the course. Serum creatinine on admission was 2.8 mg/dL and peaked to 6.0 mg/dL with progression to anuric renal failure over 3 days. Hemoglobin dropped from 16.9 g/dL on admission to a nadir of 6.6 mg/dL over 6 days requiring RBC transfusion. Features of non immune hemolytic anemia were detected including very low haptoglobin level (<1 mg/dL), elevated LDH level of 2301 IU/L and negative Coomb's test. Peripheral smear was notable for schistocytes. DIC panel with coagulation studies and fibrinogen levels were normal. The patient received IVF resuscitation and was started on antibiotics with IV ceftriaxone and metronidazole. Shortly after admission she developed seizure and required intubation. She received hemodialysis for renal failure. The combination of MAHA, thrombocytopenia and AKI warranted consideration for TTP. ADAMTS 13 level was ordered and the patient was started empirically on plasma exchange pending ADAMTS13 level. Urine microscopy showed extensive granular casts. ADAMTS 13 came back normal (45%) and plasma exchange was discontinued. Shiga toxin-producing E Coli PCR was positive in the stools. Renal function improved and dialysis discontinued after 3 sessions. Thrombocytopenia completely resolved with improvement in anemia and a creatinine at discharge of 3.42 mg/dL.

Discussion: Typical HUS caused by shiga-like toxin producing enteric organisms is most commonly encountered in children but can affect all ages and should be suspected when a patient presents with bloody diarrhea, MAHA, thrombocytopenia, AKI and neurological symptoms. The differential should always include TTP and empiric plasma exchange should be pursued while awaiting ADAMTS 13 levels as delaying treatment for TTP could be devastating. It is important to note that AKI, especially severe, is not a prominent feature of TTP and should warrant consideration of alternative diagnosis.

FR-PO221

Oliguric AKI Developed After Toxic Ingestion of Tribulus/Drug-Induced Liver Injury (DILI)

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Introduction: Liver disease is associated with multiple mechanisms of acute kidney injury (AKI). Bile cast nephropathy is a relatively rare (but potentially underdiagnosed) cause without great treatment options. Also, many non-tested supplements are available and widely used - some which may have a toxic effect on the kidneys and lead to AKI.

Case Description: A 46 year old male with AFib, bipolar disorder, and normal baseline kidney and liver function was admitted with severe cholestatic liver injury and developed an oliguric AKI. He had 5 weeks of progressive jaundice, fatigue, weight loss, and poor oral intake. Total bilirubin peaked at 48.5 mg/dl. Liver biopsy was consistent with drug induced liver injury suspected to be from a supplement obtained on Amazon called Tribulus used a "testosterone booster". Kidney function consistently worsened after admission as the patient became nearly anuric. Urine Na 62 meq/L and multiple reviews of the urine sediment showed bile casts without other granular casts. Kidney biopsy was deferred due to patient preference. Patient's mental status worsened and hemodialysis was initiated for potential uremic symptoms. Workup was initiated for potential liver transplantation. In an attempt to decrease inflammatory mediators contributing to liver disease, plasmapheresis was started which also had the effect of significantly reducing the serum bilirubin levels. Urine output drastically improved after plasmapheresis and no further hemodialysis sessions were needed as renal function recovered. Liver function also improved with supportive care.

Discussion: This case demonstrates a severe oliguric AKI in the setting of Tribulus injection and DILI with eventual recovery that was caused most likely by one of two mechanisms: 1. Direct tubular damage due to toxic drug effects or 2. Bile cast nephropathy that interesting may have resolved after plasmapheresis significantly decreased the serum bilirubin level. Further investigation into the toxic effects on renal tissue from over the counter supplements is warranted. It is unclear if the improvement in renal function was the direct results of plasmapheresis – though if the clinical findings are highly concerning for bile cast nephropathy in a severe AKI, plasmapheresis may be considered to lower serum bilirubin and potentially improve renal function when AKI is caused by bile cast nephropathy.

FR-PO222

Bartonella Endocarditis-Associated Glomerulonephritis Presenting as Acute Renal Failure

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Introduction: Acute kidney injury (AKI) in the setting of mitral valve endocarditis is often due to cardiorenal syndrome secondary to valvular dysfunction. We report a case of acute renal failure caused by Bartonella endocarditis-associated glomerulonephritis.

Case Description: A 28-year-old man from Nicaragua with a history of mitral valve replacement presented with left arm weakness. Brain MRI revealed a subacute right parietal lobe infarct. TTE and TEE showed thickened mitral valve leaflets and a high transvalvular pressure gradient, consistent with prosthetic valve endocarditis. Empiric antibiotics were initiated. Cultures remained negative throughout admission. On hospital day (HD)13, Bartonella henselae IgG was >1:2560, and antibiotics were changed to rifampin and doxycycline. Creatinine on admission was 1.3 (baseline 0.8), and stabilized at 1.1. On HD13, the patient's Cr uptrended to 1.5. Concurrently, he developed acute hypoxemic respiratory failure with evidence of volume overload, initially thought to be cardiorenal syndrome and the patient was diuresed. Despite reaching euvolemia, his Cr continued to uptrend to 6.4. UA with moderate hematuria and proteinuria. 24-hour protein was 1.3g. FeUrea was 47%, which was less consistent with pre-renal AKI and prompted an intrinsic AKI workup. Results notable for positive ANA, low C3 and C4, and positive PR3, which led to the clinical diagnosis of infectious glomerulonephritis. Renal biopsy to confirm the diagnosis was deferred in favor of definitive treatment with mitral valve replacement. The patient's creatinine improved to 2.9 after surgery, and he was discharged with a presumed diagnosis of C3-mediated Bartonella glomerulonephritis. He continued 3 months of doxycycline and 6 weeks of rifampin and his creatinine normalized within 2 weeks of discharge.

Discussion: Acute renal failure in the setting of endocarditis can be multifactorial, and it can be challenging to determine the etiology. The concomitant development of respiratory failure, valvular dysfunction, and acute renal failure was initially compelling for cardiorenal syndrome. However, worsening renal function after achieving euvolemia, along with positive PR3, hypocomplementemia, proteinuria, and hematuria in the setting of Bartonella endocarditis was later more consistent with infectious glomerulonephritis that resolved upon definitive treatment.

FR-PO223

Ciprofloxacin-Induced Crystal Nephropathy Is a Rare Cause of Reversible AKI

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Introduction: Ciprofloxacin is a commonly used antibiotic that is generally well tolerated. Acute kidney injury (AKI) related to ciprofloxacin is most commonly due to allergic interstitial nephritis or acute tubular injury (ATI). Additionally, ciprofloxacin-induced crystal nephropathy has been described as a rare cause of AKI. We present two patient cases of AKI due to crystal nephropathy after exposure to ciprofloxacin.

Case Description: Case 1. A 71-year-old female with a history of hypertension, diabetes, and metastatic endometrial cancer presented with a sudden elevation in serum creatinine (Cr) to 9.26 mg/dL from her baseline of 0.9 mg/dL. She had recently received treatment for a urinary tract infection, first with nitrofurantoin and then with ciprofloxacin 500mg twice daily for 7 days for persistent dysuria. On presentation, the patient was non-oliguric, normotensive, and well appearing without symptoms. Urine pH was 5.8 on urinalysis with minimal proteinuria. Urine microscopy at the time showed white blood cells and no evidence of ATI. Kidney biopsy demonstrated ATI, with birefringent crystalline material in several tubules. The cause of AKI was determined to be ciprofloxacin-induced crystal nephropathy. The patient remained non-oliguric and AKI resolved with supportive care over the next 3 weeks. Case 2. A 77-year-old female with a history of hypertension and chronic hypokalemia initially presented with diarrhea, abdominal pain, and new ascites. After one oral dose of metronidazole and ciprofloxacin 500mg for possible diverticulitis, the patient re-presented with decreased urine output and foamy urine. During the hospitalization, Cr increased from a baseline of 0.8 mg/dL four days prior to admission to peak at 8.07 mg/dL. Kidney biopsy demonstrated widespread ATI with interspersed pigmented and polarizable crystalline material within the tubules, likely ciprofloxacin-induced crystal nephropathy. Cr improved without intervention and was 2.06 mg/dL two weeks later at hospital discharge.

Discussion: We present two cases of elderly female patients with abrupt onset AKI due to ATI with crystal nephropathy after treatment with ciprofloxacin. In both cases, the patients recovered with supportive care and dialysis was not needed. Providers should be aware of ciprofloxacin-induced crystal nephropathy as a rare cause of AKI.

FR-PO224

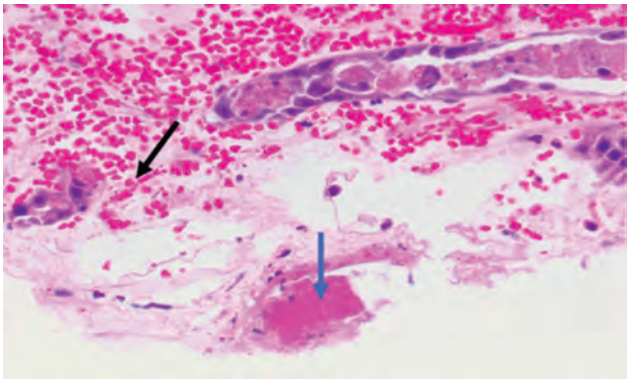
Thrombotic Microangiopathy from Chafing Fuel Intoxication

Nazanin Vaghari Mehr, Grace L. Malvar, Deepthi Gunasekaran, Shuta Ishibe, Gilbert W. Moeckel. *Yale School of Medicine, New Haven, CT.*

Introduction: Diethylene glycol (DEG) is widely used as an industrial diluent in chafing fuel, brake fluids, wallpaper strippers etc. Mass poisonings with high fatalities have been reported. Here we report a rare and unusual case of Thrombotic Microangiopathy (TMA) in a patient who ingested chafing fuel.

Case Description: A 58-year-old male with alcohol use disorder presented with five days of vomiting, diarrhea and altered mental status. His wife reported severe alcohol cravings and ingestion of hand sanitizer (isopropyl alcohol) and chafing fuel (DEG). He was anuric with creatinine of 8.2, a pH of 6.87, bicarb of 2 mmol/L, anion gap of 44 and osmolal gap of 45. Toxicology screen was negative. He was admitted to the intensive care unit for emergent hemodialysis. Hemodialysis was continued as there was no evidence of renal recovery. He then developed hypertension and thrombocytopenia. Peripheral smear was without schistocytes, LDH was elevated and haptoglobin was low. C3 was mildly decreased. C4, CH50, HIT antibody panel and ADAMTS13 activity were within normal limits. A kidney biopsy was performed on day 5 *(see figure)* which showed thrombotic microangiopathy and diffuse acute tubular injury. On day 6, he developed severe neurological defects including slurred speech, facial droop and progressive cranial neuropathies. He required mechanical ventilation for airway protection. He failed an empiric trial of steroids and expired on day 19.

Discussion: AKI in DEG toxicity is linked to high mortality rates and dialysis dependency. Typical Kidney biopsy lesions are extensive necrosis of the proximal tubule, severe interstitial hemorrhage and hyaline casts. In our case, TMA can be attributed to DEG in the absence of other causes. Vascular injury from necrotic glomeruli or direct endothelial injury from DEG are possible mechanisms. In DEG poisoning, TMA should be considered as a potential life-threatening complication.



Fibrinoid necrosis of arteriole (blue arrow). RBC fragments (black arrow).

FR-PO225

Pseudo-Renal Failure After Laparoscopic Hernia Repair

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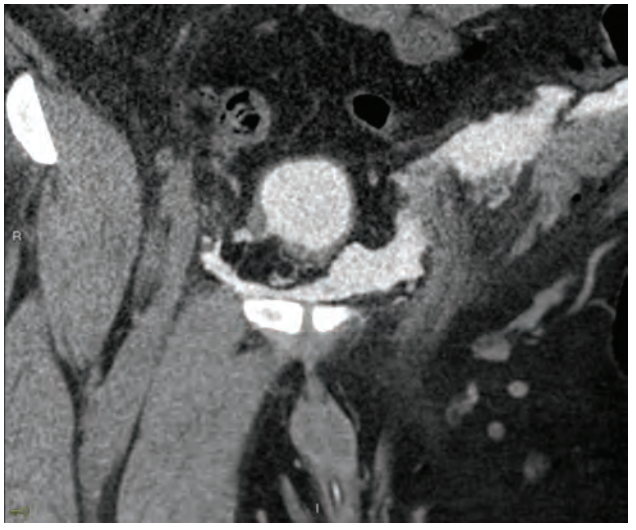
Introduction: Bladder wall rupture cause high mortality if not diagnosed urgently. It can lead to extravasation of urine in peritoneum followed by anuria, abdominal pain, rise in serum Creatinine and be misdiagnosed as acute renal failure. We report a rare case of pseudo-renal failure in the setting of bladder wall rupture following laparoscopic repair of umbilical and bilateral inguinal hernia.

Case Description: 50 year old man with seizure disorder presented for laparoscopic repair of bilateral inguinal hernia and umbilical hernia. He was admitted for observation due to self limited seizure. Labs showed rise in creatinine of 2.4 mg/ dL. Patient developed urinary retention and required straight catheterization. Serosanguis drainage from lower surgical port site developed. His abdominal pain increased significantly and Creatinine continued to rise to 3.4 mg/dL. Nephrology was consulted for presumed acute renal failure. Patient had continued urinary retention with minimal improvement with foley placement on POD 3. Surgical port site drainage Urea and Cr were 81 and 14.2 mg/dL respectively. A CT cystogram showed bladder wall rupture and fluid extravasation to pre-peritoneal space. Serum Creatinine returned to baseline (0.9 mg/dL) immediately post bladder wall repair.

Discussion: Bladder rupture and urinary ascites can cause pseudo-renal failure in presence of normal renal function. Urinary ascites alters concentration gradient of peritoneal fluid and serum resulting in rapid increase of serum urea and creatinine while maintaining normal GFR. We suggest pseudo-renal failure consideration when suspecting urinary ascites as well as using peritoneal urea and creatinine to help diagnosis. Urgent Cystoureterogaphy is key for bladder rupture diagnosis and urgent bladder repair along with foley placement to relieve obstruction is essential to avoid further complications and rapid return of labs to baseline.



FR-PO226

Lysozyme Nephropathy: A Rare Cause of Progressive Kidney Disease

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Introduction: A progressive decline in renal function with sub-nephrotic proteinuria in a diabetic is usually attributed to DKD. Lysozyme nephropathy is a rare cause of progressive decline in renal function with only a few underreported cases in the literature mostly in patients with hematological malignancy. AKI is seen in one-third of patients with hematological malignancy and has a negative impact.

Case Description: An 84-year-old male with stage 4 chronic kidney disease, type 2 diabetes mellitus, and chronic anemia on ESA was admitted with an upper GI bleed. He had hemorrhagic shock leading to acute tubular injury. Urinalysis showed trace protein with no RBCs on the microscopic sediment exam. A serologic workup was negative except for positive ANA and hepatitis B surface antibody, which had been previously negative. He had anemia and severe leukocytosis (WBC > 65 K/mm^3). His kidney function gradually improved over 2 weeks. Following hospital discharge, the patient was readmitted with worsening kidney function and a high anion gap metabolic acidosis. The urine sediment showed granular casts. A kidney biopsy was performed, which showed moderate (30-40%) tubulointerstitial scarring and patchy proximal tubular degenerative changes, consistent with acute and chronic tubulointerstitial nephropathy. Refractile, hypereosinophilic intracytoplasmic protein droplets were noted in the proximal tubular cells, which showed immunohistochemical reactivity for lysozyme. Immunofluorescent staining for kappa and lambda was negative.

Discussion: Lysozyme, also called muramidase, is a basic, cationic protein, primarily produced by monocytes/macrophages, salivary gland acinar cells, Paneth cells, and other cell types. Lysozyme is filtered by the glomerulus and reabsorbed by the proximal convoluted tubule where tubular injury occurs. Lysozyme nephropathy is seen with myeloid leukemias, myeloproliferative, myelodysplastic disorders, granulomatous disease, inflammatory bowel disease, and malignancy. This patient had leukocytosis with myelocytes on the smear which might have reflected underlying hematologic malignancy. A diagnostic evaluation was deferred as he was not a candidate for therapy based on age and comorbidities. Subsequently, his kidney function continued to decline. He opted for conservative management of end-stage kidney disease and hospice care.

FR-PO227

Thrombotic Microangiopathy from Metastatic Signet Ring Cell Carcinoma

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Introduction: Thrombotic microangiopathy (TMA) as a paraneoplastic syndrome is rare and outcomes can be devastating. We present a case of TMA as an initial presentation of metastatic signet ring cell carcinoma (SRCC).

Case Description: Our patient is a 36-year-old female with a history of type 2 diabetes mellitus who presented with 3 weeks of dyspnea, cough and hemoptysis, then respiratory failure requiring intubation. Chest CT scan showed bilateral parenchymal mosaic attenuation. Her hemoglobin and platelets decreased to 7.8 g/dL and 68,000/μL, from 10.3 g/dL and 111,000/μL, respectively. Other work up include: MCV 82 fL, WBC 13,100/μL, LDH 18, 238 U/L, haptoglobin <10 mg/dL, Coomb's negative, schistocytes on peripheral smear, fibrinogen 80 mg/dL, protime 14.7 seconds, INR 1.52, aPTT 40 seconds, potassium 8.4 mmol/L, creatinine 2.61 mg/dL, bicarbonate 9 mmol/L and lactate 19.1 mmol/L. She received FFP, PRBC and platelets. ADAMST13 was sent but plasmapheresis was initiated immediately. She was anuric and required CRRT. Despite the transfusions, her hemoglobin and platelets worsened at 5.3 mg/dL and 19,000//μL. She developed diffuse mottling and critical limb ischemia. After the 3rd hospital day, she was made comfort measures only. The autopsy showed metastatic poorly differentiated colon adenocarcinoma with signet-ring cell component, with diffuse bone marrow involvement.

Discussion: The management of secondary TMA, such as DIC, pre-eclampsia, severe hypertension, are focused on the underlying cause. Metastatic carcinoma with bone marrow involvement can be an obscure differential and can prove fatal if undetected. The mechanism of how TMA occurs is not clear but there may be a role in mucin production from the signet ring cell subtype which causes endothelial cell dysfunction and thus causing thrombus formation. Bone marrow involvement generates abnormal angiogenesis that damages blood vessels and causes release of Ultra Large Von Willebrand Factor multimers, which has been implicated in the pathogenesis of MAHA. Metastatic malignancies have been misdiagnosed as TTP does not respond to plasmapheresis, had more respiratory symptoms and higher LDH. TMA as a paraneoplastic syndrome ultimately requires prompt chemotherapy and/or resection. Mucin producing tumors have been reported to present initially as TMA but by the time the diagnosis is made, it has widely metastasized and prognosis is notably poor.

FR-PO228

Metformin-Associated Lactic Acidosis: A Mimicker of Acute Mesenteric Ischemia

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Introduction: Metformin-associated lactic acidosis (MALA) is a rare life-threatening complication of metformin. Metformin is renally excreted with a major precipitating factor for MALA being acute kidney injury (AKI). The clinical presentation of MALA is similar to that of acute mesenteric ischemia though imaging is usually negative. Here we present a case of MALA masquerading as acute mesenteric ischemia and intra-abdominal sepsis.

Case Description: A 52-year-old female with a history of HTN, Type 2 DM on metformin, CKD of unclear baseline presented with vomiting, poor oral intake, and abdominal pain for 2 days with finger-stick glucose of 35 mg/dL. She denied fever, chills, urinary symptoms, diarrhea, or overdose of metformin. Her initial vitals were T 95.6 degree Fahrenheit, BP 171/96, HR 91, RR 16, and SpO2 100% on room air. The physical examination showed only dry oral mucosa. Laboratory values were significant for potassium 6.8 mEq/L, serum creatinine 7.9 mg/dL, blood urea nitrogen 61 mEq/L, glucose 49 mg/dL, bicarbonate 5.0 mEq/L, anion gap 45.9 mEq/L, venous blood gas with pH 7.0, PCO2 21 mmHg, lactate >17 mmol/L, white blood cell 17.7/nL. CT of the abdomen showed thickened small bowel loops and a questionable single loop of small bowel with pneumatosis. The patient was admitted for sepsis in the setting of presumed ischemic bowel. However, the surgery service discounted this diagnosis as they felt that there was no pneumatosis upon their review and that the thickened loops of bowel can be due to enteritis. She was empirically treated with intravenous piperacillin/tazobactam. Given AKI and severe lactic acidosis, a metformin level was sent. The patient was treated with 2 sessions of hemodialysis. When blood and urine cultures returned negative, antibiotics were discontinued. Her renal function improved to a serum creatinine of 1.6 mg/dL 2 weeks later, at which time the metformin level returned to be elevated at 27 mcg/ml (therapeutic level 1-2 mcg/ml).

Discussion: Our case highlights that MALA can be confused with ischemic bowel on clinical presentation with abdominal pain, lactic acidemia and suggestive CT findings of pneumatosis intestinalis. Thus, high clinical suspicion and prompt treatment with renal replacement therapy is needed to avoid unnecessary surgery even without resulted metformin levels.

FR-PO229

Severe Hypothyroidism Presenting as Rhabdomyolysis and Acute Tubular Necrosis

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Introduction: Hypothyroidism often manifests with a broad range of muscular symptoms: cramping, generalized weakness, and diffuse myalgias. Rhabdomyolysis is a rare manifestation of severe hypothyroidism resulting in profound acute tubular necrosis

via myoglobin induced renal vasoconstriction, proximal tubule necrosis, and distal tubular obstruction. We present a case of acute tubular necrosis caused by rhabdomyolysis secondary to severe hypothyroidism.

Case Description: A 62-year-old female with past medical history of coronary artery disease, type II diabetes mellitus and hypothyroidism presented with fatigue, shortness of breath, fifteen pound weight gain and decreased appetite for a month. She reported myalgias and non-compliance with oral synthroid for seven months. Vital signs revealed normothermia without bradycardia. Physical exam was unremarkable. Laboratory work revealed elevated creatinine kinase (CK) 59,952 U/L, creatinine 6.37 mg/dL (baseline 0.8-1), very low free T4 <0.1 and very high TSH >1000. Urinalysis was positive for blood with minimal red blood cells, and urine sediment revealed granular casts. Treatment with intravenous fluids and synthroid significantly improved the TSH (75.9 mIU/L) and CK (10,791 U/L) on admission day ten. Renal function slowly improved over the hospitalization course with serum creatinine trend 6.37 mg/dL to 3.8 mg/dL on discharge with concurrent non-oliguric urine output. She was discharged home with oral thyroid hormone replacement therapy. She demonstrated complete renal recovery on outpatient follow up with serum creatinine 0.72 mg/dL, normal CK levels 31 U/L and thyroid function panel (TSH 0.97, free T4 1.5).

Discussion: The precise mechanism of hypothyroidism-induced rhabdomyolysis is unclear, however, it is thought to be related to impaired glycogenolysis or mitochondrial oxidation. This case is unique as there are no previously reported instances of patient sustaining such severe hypothyroidism-induced rhabdomyolysis (serum CK 400x upper limit of normal), and ATN in the absence of underlying chronic kidney disease. Therefore, prompt diagnosis, identification of causative factor, and timely treatment are crucial to prevent long-lasting renal injury in this disease. It also emphasizes medication compliance, patient education, and considering hypothyroidism in the differential diagnosis of rhabdomyolysis for improved patient outcomes.

FR-PO230

Oxalate Nephropathy: A Studded Case of AKI

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Introduction: Oxalate nephropathy (ON) is a rare manifestation of hyperoxaluria which can present as acute kidney injury (AKI) with the possibility of rapid progression to end stage kidney disease. We present a case of AKI with ON on biopsy.

Case Description: A 64-year-old male with obesity, type 2 diabetes mellitus and hypertension presented with nausea and unsteady gait. He has AKI with a serum creatinine (Cr) of 9.4 mg/dL on admission with a baseline Cr of 0.8 mg/dL 3 months prior. Clinical history did not reveal a cause for AKI. Urine studies showed the occasional granular cast but no dysmorphic RBCs, proteinuria or pyuria. Serological workup including antinuclear antibody, anti-neutrophilic cytoplasmic antibody, and serum monoclonal testing were unremarkable. He underwent kidney biopsy due to inadequate improvement of renal function with intravenous fluids. Kidney biopsy (Figure 1) showed widespread calcium oxalate deposition in the tubules (renal oxalosis) with associated mild acute tubular injury and mild interstitial nephritis. Genetic testing did not show a known mutation associated with Primary Hyperoxaluria.

Discussion: Primary Hyperoxaluria is due to a genetic defect leading to abnormal oxalate handling. Secondary Hyperoxaluria (SH) occurs due to excessive dietary oxalate intake and/or gastrointestinal disorders that increase absorption of oxalate or oxalate precursors, such as inflammatory bowel disease. Both diabetes mellitus (DM) and obesity have also been associated with increased urinary oxalate excretion. We assume that our patient suffered from SH with both obesity and DM playing a role. Although significantly less common than other causes of acute kidney injury, ON should be included in the differential for AKI of unclear etiology, especially in patients with concurrent DM and obesity.

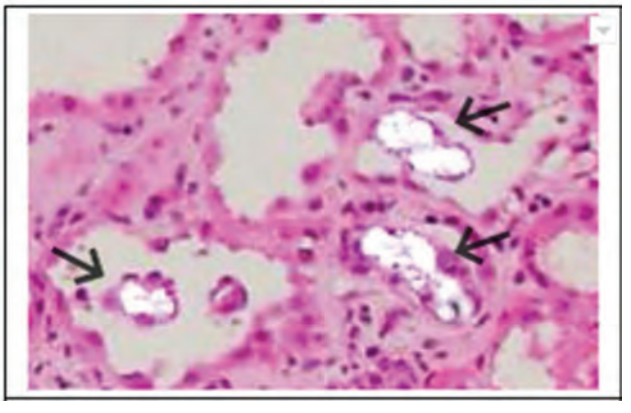


Figure 1: Widespread calcium oxalate deposition within the renal tubules under polarized light (arrows).

FR-PO231

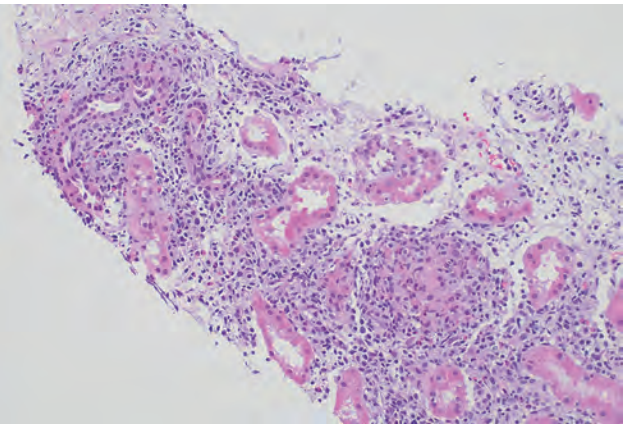
Say "No" to the DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms)

Hannah R. Miller, Tyler Sims, Sam Beavin. *University of Kentucky College of Medicine, Lexington, KY.*

Introduction: Healthy 25-year-old with rash due to DRESS and acute kidney failure due to granulomatous acute interstitial nephritis in the setting of EBV and RSMF infection.

Case Description: A 25-year-old woman with history of paroxysmal SVT and migraines was seen outpatient and treated with amoxicillin/clavulanic acid for suspected bacterial pharyngitis with lymphadenopathy. Four days later, she developed a pruritic rash on hands and shins that spread diffusely. Hospital workup showed positive IgM titers for Rocky Mountain Spotted Fever and IgG titers for Ebstein-Barr Virus. Patient started on topical steroids and doxycycline for suspected RMSF. She then developed flu-like symptoms and oliguria with severe kidney failure. Kidney function worsened to a peak creatinine of 11.71 mg/dL. Kidney US demonstrated increased parenchymal echogenicity, and UA was unremarkable. Hospital day 4 kidney biopsy showed severe tubular interstitial nephritis with substantial eosinophils in interstitium and formulation of granulomas. She was treated with IV methylprednisolone for 3 days and then switched to oral prednisone with significant improvement in kidney function.

Discussion: This case revealed the rare pathological finding of granulomatous tubulointerstial nephritis on kidney biopsy and rapid improvement of kidney function with high dose steroids. The presentation was mostly likely due to DRESS from the amoxicillin with associated AIN. Cases of AIN with granulomatous inflammation are not common and account for < 1% of all kidney biopsy findings (1). Most often this pattern is associated with antibiotics, NSAIDS and diseases such as sarcoidosis, TB, fungal infections and GPA (Shah S. 2015). Glucocorticoids were the treatment of choice as patient achieved resolution of both her DRESS and acute kidney failure with avoidance of dialysis.



Kidney Biopsy at 20X Magnification

FR-PO232

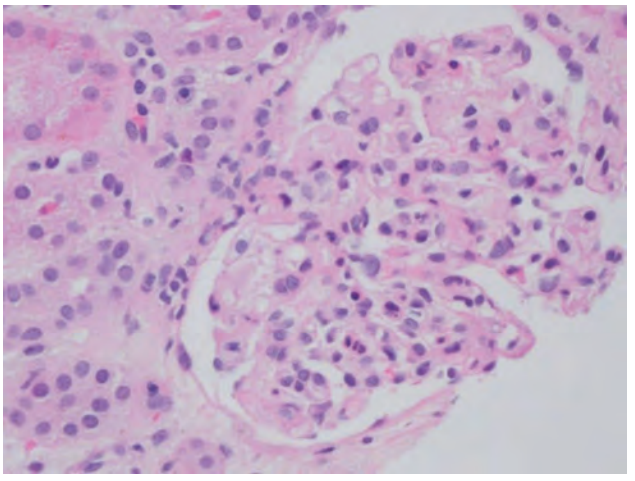
Infection-Related Glomerulonephritis

Dominik Thomas, Monica P. Revelo Penafiel, Josephine Abraham. *University of Utah Health, Salt Lake City, UT.*

Introduction: Infection-related (IE) glomerulonephritis (GN) can be associated with viral or bacterial infections and vary from asymptomatic microscopic hematuria to rapidly progressive GN with acute kidney injury requiring emergent dialysis. This patient presents with months of nonspecific symptoms and developed rapidly worsening renal function. He was ultimately found to have bacterial endocarditis.

Case Description: 50 year old male presented with progressive functional decline, cough, and unintentional weight loss in the setting of pancytopenia for 6 months and worsening creatinine (Cr) and hematuria over the preceding two weeks. He saw hematology and underwent imaging and bone biopsy with negative results. Serum Cr on admission was 2.75mg/dl but two weeks prior was 0.73 md/dl. UA showed 50-100 RBCs and urine microscopy revealed numerous dysmorphic RBCs. Urine protein to creatine ratio was 2974 mg/g (15-68mg/g). Renal biopsy showed endocapillary proliferative GN with dominant C3 deposits, a fibro-cellular crescent and patchy mixed interstitial inflammatory infiltrate with focal acute tubular injury. Infectious workup resulted in positive blood cultures for streptococcus mutans. He was started on Ceftriaxone. Transesophageal echocardiogram showed mobile mass on the posterior leaflet measuring 1.2 x 0.3 cm. He underwent mitral valve replacement. Cr trended down to 0.75 mg/dl along with improving proteinuria and hematuria.

Discussion: Sub acute bacterial endocarditis can present with non specific symptoms delaying diangosis. Treatment of IE-associated GN includes antibiotics and sometimes valve replacement. Control of the infection may not always be associated with a favorable outcome. One case series shows 21 percent of patients died; of the surviving patients, 10 percent progressed to end-stage kidney disease, 37 percent had persistent kidney function impairment, and only 32 percent had complete kidney recovery. Early recognition and prompt treatment is crucial for recovery.



H&E stain

FR-PO233

Pneumocystis jirovecii Pneumonia-Induced Hypercalcemia

Dominik Thomas, Josephine Abraham. *University of Utah Health, Salt Lake City, UT.*

Introduction: A growing number of case reports demonstrate the relationship between non-parathyroid mediated hypercalcemia preceding or occurring in conjunction with a diagnosis of Pneumocystis jirovecii pneumonia (PJP). Most cases described in literature occur in kidney transplant patients. We present a patient with heart transplant with nonspecific symptoms, acute kidney injury and hypercalcemia.

Case Description: 63 year old female with history of breast cancer status post chemoradiation with anthracycline induced cardiomyopathy requiring orthotopic heart transplant two years earlier presented with fever, chills, weight loss and fatigue for two months. She reported in addition a dry cough with increasing shortness of breath. She presented with a serum creatinine (SCr) of 5.23mg/dl, up from a baseline of 2.2 mg/dl. Creatinine improved to 4.1mg/dl after intravenous hydration. Admission urinalysis unremarkable. Renal US was with increased bilateral echogenicity. Serum Calcium was 12.9 mg/dl on admission with PTH of 7 pmg/ML (15-65 pmg/mL) and 1,25 Vitamin D of 87pg/mL. (19.9-79.3 pg/mL). CT chest demonstrated patchy ground glass opacities throughout the lungs. Infectious work up revealed Beta-D-Glucan >500. A bronchoscopy with BAL was performed and returned positive for PJP on PCR. She was started on atovaquone with improvement in symptoms. Cr trended down to baseline with resolution of hypercalcemia.

Discussion: Hypercalcemia related to PJP is thought to be associated via 1α-hydroxylase enzyme-dependent mechanism causing extra-renal production of 1α-hydroxylase. Some reports of PJP revealed the presence of inflammatory granulomas rich in macrophages and monocytes that are capable of vitamin D activation and thereby inducing hypercalcemia. The majority of cases are described in kidney transplant recipients possibly suggesting a susceptibility in these patients for developing PJP-related hypercalcemia but PJP can occur with any solid organ transplant.

FR-PO234

Unresolving AKI Diagnosed as a Case of Tubulo-Interstitial Nephritis with Uveitis Syndrome

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Introduction: Tubulo-interstitial nephritis and uveitis (TINU) is a very rare condition and till now around 250 cases have been reported so far. The pathogenesis of TINU syndrome remains unclear. Patients usually present with non-specific symptoms like nausea, vomiting and the ocular symptoms of uveitis might not always coincide with the diagnosis of acute kidney injury (AKI). The diagnosis can be easily missed with the clinical picture overlapping with prerenal etiology of AKI.

Case Description: We report a case of a 67-year-old female with a past medical history of diabetes mellitus, hyperlipidemia, hypertension, Grave's disease status post ablation presenting with nausea and vomiting for a few days. She was found to have acute kidney injury (AKI) with creatinine level of 2.06 mg/dl and was initially treated with intravenous fluids (IVF) as it was presumed to be prerenal with vomiting. However, the AKI did not improve with IVF and. Initial laboratory work ups were unremarkable to determine the etiology of AKI. Complete blood count showed a slightly raised eosinophil percentage of 5.7% (reference range less than 5%). Urinalysis demonstrated red blood cells (RBCs) of 6-10/ high power field (hpf) and glycosuria. On the third day of hospitalization, the patient had bilateral eye pain, redness and blurring of vision which was diagnosed as bilateral uveitis with posterior vitreous detachment. On further investigation, the patient had elevated urine Beta 2 Microglobulin of 3,704 ug/L (reference range 0-300 ug/L) and subsequent renal biopsy revealed tubulo-interstitial nephritis and diabetic glomerulopathy Class 2A thus confirming the diagnosis. Ocular symptoms improved with topical steroids and renal function continued to platue for few weeks. Patient did not require systemic steroids. On regular oupatient follow up renal fuction continued to improve but did not reach the baseline.

Discussion: TINU syndrome is a diagnosis of exclusion and can not be diagnosed by a single test. All the patients with suspected TINU syndrome do not undergo renal biopsy as kidney function usually improves with supportive treatment. Elevated urinary beta-2 microglobulin level is associated with TINU syndrome. Some severe cases might need systemic steroid therapy. It requires very high index of suspicion for timely diagnosis and management to prevent long term complications.

FR-PO235

Olaparib Associated AKI: Real or Fake?

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Introduction: Olaparib is a chemotherapy drug used in the treatment of metastatic ovarian and breast cancer. Olaparib, an inhibitor of human Poly-(ADP-ribose)-polymerase (PARP), is the first PARPi approved for the treatment of metastatic ovarian cancer. Olaparib has been associated with increases in serum creatinine thought to be due to a non-pathologic mechanism. As the renal function of oncology patients can affect their course of care, distinguishing pathologic kidney injury from non-pathologic laboratory changes is important.

Case Description: A 61-year-old woman with non-insulin dependent type II diabetes and hypertension was receiving chemotherapy for metastatic ovarian cancer with carcinomatosis. Baseline creatinine was 0.8 mg/dl with eGFR 67 ml/min. She received paclitaxel and then was started on Olaparib. Her creatinine rose over the course of several months to a peak of 2.0 mg/dl and eGFR of 28 ml/min. Urinalysis was negative. Urine protein-creatinine ratio was 55 mg/gm. Renal imaging was negative. Subsequent serum cystatin C was normal at 1.11 mg/l and eGFR of 63ml/min. This suggested Olaparib caused a non-pathologic increase in serum creatinine. Patient continued therapy and future kidney function evaluation used cystatin C.

Discussion: This case showcases the importance of distinguishing between pathologic and non-pathologic increases in serum creatinine in cancer patients. As kidney damage can alter the pharmacodynamics of chemotherapy drugs and alter the available pharmacologic options for individuals undergoing cancer treatment, determining the cause of alterations in serum creatinine is critical. Olaparib's effect on serum creatinine is thought to be due to interactions with creatinine secreting transporter proteins on the apical membrane of the proximal tubule. Interactions with these transporters can falsely increase the serum creatinine without intrinsically altering renal function. Cystatin C is freely filtered by the glomerulus without utilizing transporter proteins, therefore it is not affected by the use of Olaparib. A recent case series showed a 14% increase in creatinine in 66 patients receiving Olaparib without significant changes in cystatin-C measurements. In this patient with sustained elevation in creatinine but normal cystatin C following Olaparib treatment, the likely mechanism of an elevated creatinine was non-pathologic effects of Olaparib.

FR-PO236

Kidney Replacement Therapy and Death in Patients with Hyperuricemic AKI Treated with Rasburicase

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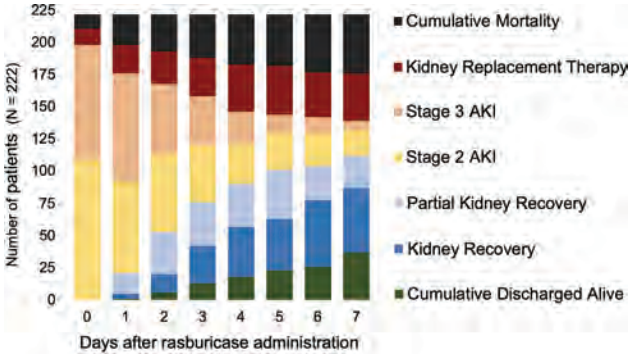
Background: Rasburicase is highly effective at rapidly lowering plasma uric acid levels in patients with cancer who develop tumor lysis syndrome and is the standard-of-care for preventing hyperuricemic AKI in this setting. However, few studies have examined the clinical outcomes of rasburicase-treated patients who already had AKI at the time of rasburicase receipt.

Methods: In this multicenter cohort study involving seven hospitals within the Mass General Brigham health care system (Boston, MA), we identified 222 adult inpatients from 2015-2020 with hyperuricemia (uric acid ≥8.0 mg/dL), active malignancy, and moderate-to-severe AKI (KDIGO stage 2 or 3) at the time of rasburicase administration. The primary outcome was kidney replacement therapy or death (KRT/death) within 7 days following rasburicase receipt. We used multivariable logistic regression to identify independent risk factors for KRT/death.

Results: A total of 83 of 222 patients (37%) progressed to KRT/death, 27 (12%) had persistent stage 2 or 3 AKI, 75 (34%) had partial or full kidney recovery, and 37 (17%) were discharged alive by day 7 (**Figure**). Independent risk factors for KRT/death were AKI stage 3 (odds ratio [OR] 2.11 [95% CI, 1.13-3.93]), admission to an ICU (OR 4.12 [95% CI, 1.94-8.74]), and elevated blood lactate (OR 5.10 [95% CI, 2.0-12.98] and 2.07 [95% CI, 1.05-4.10]) for lactate >5.0 and 1.3-5.0 mmol/L, respectively. The incidence of KRT/death ranged from 11% among patients with no risk factors to 81% among those with multiple risk factors.

Conclusions: Short-term clinical outcomes are poor among patients with cancer and hyperuricemic AKI treated with rasburicase, particularly among those with severe AKI, elevated blood lactate, and in the ICU. Additional data are needed to assess the efficacy of rasburicase in improving clinical outcomes in patients who already have AKI at the time of its administration.



Outcomes

FR-PO237

Incidence of AKI with Immune Checkpoint Inhibitors: A Five-Year Retrospective Review

Blathnaid O'Connell, Catherine M. Brown. *University Hospital Waterford, Waterford, Ireland.*

Background: Immune checkpoint inhibitors (ICPIs) are one of the most commonly prescribed cancer treatments. ICPIs prolong overall & progression-free survival in patients with a wide range of malignancies, but also cause AKIs. This can lead to dose delays, discontinuation of therapy, and prolonged courses of immunosuppression. The reported rate of ICPI-AKI is variable, ranging from 3%-7%. Use of ICPIs has increased significantly in recent years. The aim of this study was to describe the incidence & stages AKI associated with ICPIs, over a 5 year period.

Methods: Patients receiving ICPIs between 2016-2021 in University Hospital Waterford (UHW), were identified using the UHW oncology database. Data were then linked to our institutional electronic patient record to obtain laboratory data and kidney biopsy results. Medical charts were reviewed to obtain data on concurrent medications and treatment received for ICPI-AKIs. AKI was defined as per the KDIGO criteria.

Results: 202 patients commenced ICPIs, with a mean age of 69 & a male preponderance (1.6:1). 20.3% of patients experienced an AKI, & of those, 19.5% had eosinophilia. The incidence of AKI & eosinophilia differed by agent. AKI rates differed by agent; Pembrolizumab 21.2%, Nivolumab 20.9%, atezolizumab 10.8%, durvalumab 33.3% & ipilimumab 33.3%. Anti-CTL4 ICPIs had a higher rate of AKI compared to PD-1 ICPIs at 25% & 21%. 83% had a stage 1 AKI, 7% had a stage 2 AKI & 10% had a stage 3 AKI. Stages differed by agent. 71.4% with a stage 2 or 3 AKI received steroids, & 1 patient received infliximab. Only 1 patient had a renal biopsy, reporting ATN. The average time to develop an AKI was 85.7 days (ranging 7 to 314 days).

Conclusions: This demonstrates a considerable burden of AKI in patients on ICPIs. Incidence of AKI in our cohort is higher than previously reported, at 20.3%, but the majority were stage 1. Only 1 patient underwent a biopsy. Previously, biopsies were the standard of care, however current ASCO guidelines recommend empiric treatment. A high index of suspicion should be maintained throughout duration of treatment, even in patients established on ICPIs, due to the variation in time to develop an AKI after treatment initiation. The use of ICPIs is increasing & it is important to monitor for renal toxicity. Close monitoring of renal function, early recognition & management of AKI can prevent long-term renal damage and improve outcomes.

FR-PO238

AKI and Acute Kidney Disease After Radical Cystectomy for Muscle-Invasive Bladder Cancer: Two Underestimated but Dangerous Threats

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Background: Radical cystectomy (RC) represents the first line surgical treatment for muscle-invasive bladder cancer (MIBC), a worldwide increasing malignant neoplasm. However, RC represents the most complex and invasive surgery in urology, characterized by significant morbidity and mortality. Among RC patients, the incidence of post-operative acute kidney injury (AKI) and Acute kidney disease (AKD) is still not clear, due to the paucity of data. Aim of the study was to evaluate the incidence of AKI and AKD after RC.

Methods: A consecutive cohort of 839 patients who underwent RC for MIBC in a tertiary institution between 2010 and 2022 was collected. All clinical variables, comorbidities, surgeries techniques and oncological regimen were reported pre and after surgery. Serum creatinine and eGFR using CKD-EPI formula were collected at baseline pre-operative and in the acute setting at 24h, 48, 72h, 6 days for the AKI onset, and after 9,12,15,18,21,24,27,30,45, 60, 75, 90 days for the AKD establishment. Fisher's exact test; Wilcoxon rank sum test; Pearson's Chi-squared test were used for the statistical analysis.

Results: General characteristics of patients included in the study are summarized in Table 1. Surprisingly, a very high rate of both AKI (30%) and AKD (50%) was reported in the total cohort of patients, with an augmented incidence in the elder pts, low pre-operative eGFR, pre-existing CKD, BMI > 24, robotic surgery and hypertensive pts in the multivariate analysis (table 2). Moreover, stage II and III of both AKI and AKD affected a non-negligible percentage of patients, requiring advanced nephrological medical treatments and prolonged hospitalization.

Conclusions: AKI and AKD are very common but hidden side effects in the RC for MIBC. Therefore, a personalized nephrological counseling both in the pre and post -surgery asset is necessary to reduce morbidity and mortality.

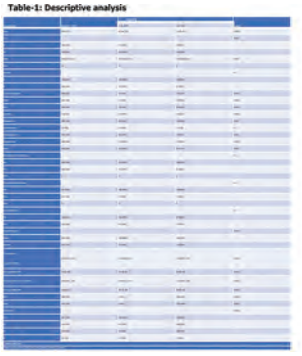


Table-1: Descriptive analysis

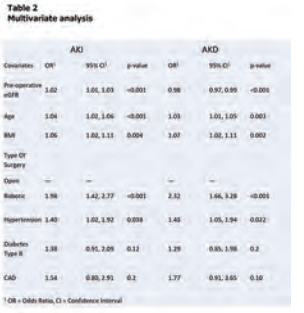


Table 2
Multivariate analysis

	AKI			AKD		
Covariates	OR[1]	95% CI[1]	p-value	OR[1]	95% CI[1]	p-value
Pre-operative eGFR	1.02	1.01, 1.03	<0.001	0.98	0.97, 0.99	<0.001
Age	1.04	1.02, 1.06	<0.001	1.03	1.01, 1.05	0.003
BMI	1.06	1.02, 1.11	0.004	1.07	1.02, 1.11	0.002
Type Of Surgery						
Open	—	—	—	—	—	—
Robotic	1.98	1.42, 2.77	<0.001	2.32	1.66, 3.28	<0.001
Hypertension	1.40	1.02, 1.92	0.038	1.48	1.05, 1.94	0.022
Diabetes Type II	1.38	0.91, 2.09	0.12	1.29	0.85, 1.98	0.2
CAD	1.54	0.83, 2.91	0.2	1.77	0.91, 3.65	0.10

[1] OR = Odds Ratio, CI = Confidence Interval

FR-PO239

GFR in the Era of Precision Medicine: A Face to Face Between Measured GFR (mGFR) and Estimated GFR (eGFR) in Onconephrology

Francesco Trevisani,[1] Giulia Quattrini,[1] Alessandra Cinque,[2] Umberto Capitanio,[1] Fabiana Laurenti,[3] Andrea Salonia,[1] Arianna Bettiga,[1] Giorgio Pizzagalli,[1] Francesco Montorsi,[1] Federico Di Marco.[1] *[1]IRCCS Ospedale San Raffaele, Milano, Italy; [2]Biorek srl, Milan, Italy; [3]Universita degli Studi dell'Aquila - Polo Coppito, L'Aquila, Italy.*

Background: Onco-nephrological patients deserve the highest attention in term of personalized medicine. Acute and chronic renal damages represent common major side effects, often as a results of drugs renal toxicities due to false dosage based on GFR. Therefore, a reliable assessment of renal function is mandatory. Aim of this study was to determine the extent of the error of eGFR common formulas compared to mGFR in onco-nephrology.

Methods: A consecutive cohort of 701 onco-nephrological patients (pts) was collected to compare the most used eGFR formulas (MDRD, CKD-EPI SCr 2012, CKD-EPI 2021 SCr, CKD-EPI Cys 2012, CKD-EPI Cys 2021, CKD-EPI Cys/SCr, Cockroft-Gault) with mGFR method (Iohexol Plasma Clearance). True positives and False positives were classified in CKD stages based on eGFR and mGFR. Comparisons between groups were performed using Wilcoxon ranks sum test for numerical variables and Pearson's Chi square test for categorical ones.

Results: Clinical data: overall median age was 66 years, median BMI 25, Male: 536, F: 165, Diabetes: 10.9%, Hypertension: 53.8%, CKD stage I: 3.7%, II: 25.5%, IIIA: 28%, IIIB: 27.5%, IV: 13.4%, V: 1.74%, mean Creatinine: 1,44 mg/dl, cystatin: 1,24. We reported a huge discrepancy between the eGFR formulas and mGFR values, suggesting the essential role of mGFR in the clinical decision making algorithm (Figures 1 and 2).

Conclusions: eGFR formulas showed a non-negligible error in all CKD stages classification in comparison to mGFR. In the onconephrological asset, the use of mGFR should be mandatory to obtain a tailored management.

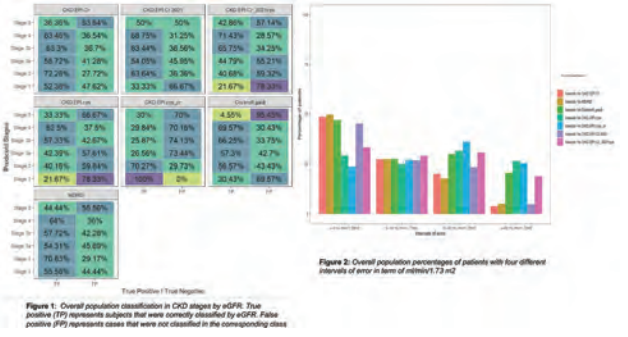


Figure 1: Overall population classification in CKD stages by eGFR. True positive (TP) represents subjects that were correctly classified by eGFR. False positive (FP) represents cases that were not classified in the corresponding class

Figure 2: Overall population percentages of patients with four different intervals of error in term of ml/min/1.73 m2

FR-PO240

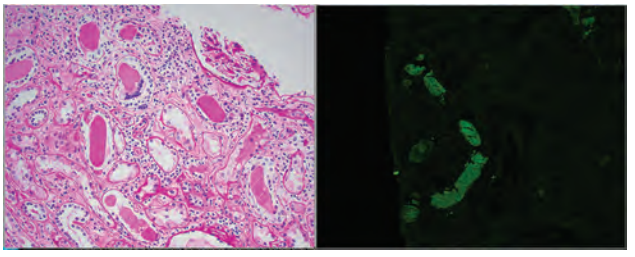
Myeloma Cast Nephropathy in an HIV Patient with AKI

Christian Nehme, Mrinalini Sarkar. *University of California Los Angeles, Los Angeles, CA.*

Introduction: HIV is associated with a multitude of renal pathologies that can involve the glomeruli, tubule, and interstitium. HIV is rarely associated with monoclonal gammopathy. We present a case of myeloma cast nephropathy in an HIV patient presenting with an AKI.

Case Description: 58-year-old male patient with a past medical history of well controlled HIV and CKD with a baseline creatinine of 1.3 mg/dL presented to the hospital with abnormal labs. His creatinine was 7.1 mg/dL. Hemoglobin was 7.1 g/dL. Patient reported generalized weakness of 2 weeks duration. On presentation, patient's vital signs and physical exam were unremarkable. Repeat labs revealed a BUN of 61 mg/dL, creatinine of 6.9 mg/dL, and hemoglobin of 6.7 g/dL. Patient received IV hydration in the ER with no significant improvement in creatinine and was admitted for further workup. Workup included SPEP which showed a monoclonal band in the gamma region; 9.2 g/dL. IgG was 10703 mg/dL and serum free kappa/lambda was 733.43. Renal biopsy showed light chain cast nephropathy, kappa light chain type in addition to minimal global glomerulosclerosis, mild interstitial fibrosis and mild to moderate arteriosclerosis. Multiple myeloma was suspected and was confirmed on bone biopsy which showed myeloma with kappa-restricted plasma cells, involving 80-90% of cellularity. Patient was started on daratumumab/bortezomib/dexamethasone for treatment of multiple myeloma. Over a month, his creatinine has steadily decreased down to 2.6 mg/dL.

Discussion: HIV can commonly cause focal segmental glomerulosclerosis, collapsing variant. It is also known to cause pan-nephropathy including glomerular, interstitial, and tubular pathology. HIV can also be associated with polyclonal hypergammaglobulinemia though monoclonal gammopathy and myeloma cast nephropathy are rare. Treating the underlying multiple myeloma can help improve kidney disease. Clinicians should have a broad differential for AKI, including multiple myeloma, in HIV patients especially if they present with anemia as treating the underlying etiology is essential in treating the kidney disease.



Atypical casts on light microscopy and Kappa light chain on immunofluorescence

FR-PO241

Onconephrology and AKI: A University Hospital Experience

Andrea C. Valenca, Alline Oliveira, Joseph L. Nascimento, Thiago M. Lacerda, Klebson F. Feijo de Melo, Italo R. Alves, Ana Paula Gueiros. *Hospital das Clinicas, Recife, Brazil.*

Background: Acute kidney injury (AKI) is prevalent in cancer patients and associated with poor outcomes. The aim of this study was to assess the clinical profile and outcomes of patients with cancer and AKI followed up in our onconephrology department.

Methods: This was a cross-sectional, retrospective study. The medical records of AKI patients were reviewed from January 2018-December 2022. AKI was diagnosed according to KDIGO. COVID-19 patients were excluded.

Results: We assessed 340 patients, 50% were male, with a median age of 62 years. The mean follow-up was 15 days. Seventy-eight percent of the patients presented with a solid tumor. The main associated cancers were: digestive tract (27.6%), cervix (15.3%) and lymphoma (12.4%). Comorbidities: hypertension (50%), diabetes mellitus (25%), and chronic kidney disease (24%). Around a third of patients were in ICU and 34% had sepsis. The AKI types were: intrinsic renal (38%), prerenal (31%) and obstructive (27%). Most patients (72%) were non-oliguric. Laboratory tests: creatinine (Cr mg/dL) on admission (CrA) 1.6 and Cr at the first nephrology visit (CrN) 2.7. Hyponatremia (sodium <135 mg/dL) was observed in 53% of patients. The median level of hemoglobin was 8.9 g/dL and albumin 2.9 g/dL. Renal replacement therapy (RRT) was required for 37% of patients. Patients on RRT differed from those who did not, by age (59 x 64; p=0.006), being in ICU (64 x 40; p<0.001), CrA (2.25 x 1.57; p=0.002), CrN (3.7 x 2.5 ; p<0.001), sepsis (50% x 24%; p<0.001), urine output (mL) (405 x 1300; p <0.001), sodium (133 x 135; p=0.034), potassium (mg/dL) (4.8 x 4.5; p= 0.008) and phosphorus (mg/dL) (4.6 x 3.9; p<0.001). In the multivariate analysis, CrN was the only independent risk for RRT (OR 12.6, CI 2.77 – 113; p=0.005). Thirty-five percent of patients died, and mortality was higher in those who underwent RRT (56% vs. 22%, p<0.001). Only 26% of patients fully recovered and 4% remained on RRT.

Conclusions: AKI in cancer patients is associated with high mortality. The clinical profile of cancer patients is unfavorable, with a high prevalence of hyponatremia, anemia and malnutrition. A late referral to a nephrologist is associated with higher rate of RTT and a poor prognosis.

FR-PO242

Impact of Race on Renal Recovery in Patients with New Diagnosis of Multiple Myeloma and AKI Requiring Dialysis

Swetha Rani Kanduri, Devang B. Patel, Prarthana Somaiah, Natalia R. Nombera, Ambuga Badari, Juan Carlos Q. Velez. *Ochsner Medical Center, New Orleans, LA.*

Background: Renal involvement is reported in about 20-50% of the patients with multiple myeloma. Although renal recovery is associated with improved survival, it is unclear whether a disparity exists among Black and White races with new diagnosis multiple myeloma (NDMM) and renal recovery. Additionally, factors associated with the probability of renal recovery are not clearly understood.

Methods: A retrospective review of medical records was conducted searching for cases of NDMM with acute kidney injury (AKI) needing renal replacement therapy (RRT) at Ochsner Medical Center over a 10-year period. Patients with relapses were excluded. We aimed to identify number of patients achieving RRT independence by race, mean time to renal recovery by race, and factors associated with RRT independence for the entire cohort.

Results: A total of 54 patients (27 Black and 27 White) were included. The mean age was 63 years, 63% males. Six (11%) had overt albuminuria. RRT independence was achieved in 9/27 (33%) Blacks and 6/27 (22%) Whites. Among those who recovered, 3/9 (33%) Blacks were alive at last follow-up compared to 5/6 (83%) Whites *(p=0.06)*. The mean time to renal recovery was 33 vs. 22 days in Blacks and Whites respectively (*p=0.48*). The mean *kappa* value before RRT initiation was 310 mg/dL for those who recovered vs 1024 mg/dL for those who did not (*p=0.015*), whereas the mean *lambda* value was 383 mg/dL in those who recovered vs 755 mg/dL in those who did not *(p=0.09*). Other variables, serum creatinine (*p=0.90*), urine protein/creatinine (*p=0.42*), LDH (*p=0.45*) B_2-microglobulin (*p=0.48*) were not different between groups. High risk cytogenetics {t(4:14), t(4:16), t(14,20), gain (1q21), del (1p), del (17p)} were reported in 3/15 (20%) in recovered vs 11/39 (28%) non-recovered (*p=0.55*)

Conclusions: A trend for better survival off RRT was observed in White patients with NDMM. However, limited number of patients with RRT recovery limited the analysis. Otherwise, no difference in renal recovery was observed between Black and White patients. In addition, high *kappa* light chain burden was associated with lower probability of renal recovery. Further studies are needed to expand upon these observations.

FR-PO243

Immobilization-Associated Hypercalcemia in Patients with Malignancy in the Hospital Setting: A Cohort Study

Swetha Rani Kanduri, Ana I. Stark, Alexander M. Smith, Walter Lam, Juan Carlos Q. Velez. *Ochsner Medical Center, New Orleans, LA.*

Background: Malignancy-associated hypercalcemia (MAH) is not uncommon in patients with cancer. Direct bone invasion (primary bone cancer, bone metastasis, multiple myeloma) and humoral hypercalcemia (elevated PTH, PTH-related peptide (PTHrP) and calcitriol) are the predominant etiologies. Although a significant proportion of patients with malignancy have poor functional status, immobilization-associated hypercalcemia (Immob-HCa) is not well recognized in this population. We examined the relative contribution of Immob-HCa to all causes of MAH in the hospital setting.

Methods: A retrospective review of medical records was conducted searching for cases of MAH over a 3-year period. Hypercalcemia was defined as serum calcium >11.0 mg/dL. *Definite* Immob-HCa was defined as presence of immobility >1 week prior to admission or ECOG score >4, needing complete assistance, combined with absence of disqualifying laboratory data (PTH >60 ng/dL, 1,25 vitamin D >70 pg/mL, 25 vitamin D >80 ng/mL, PTHrP >2.5 pmol/L) monoclonal gammopathy, lytic lesion by imaging or alternative etiology (sarcoidosis, exposure to thiazide, or calcium or vitamin D supplementation). *Probable* Immob-HCa was defined as documented immobility and absence of alternative etiology, but incomplete laboratory data.

Results: A total of 145 patients with in-hospital MAH were identified. The median age was 68 (33-92), 45% women, 64% white, 31% self-identified black; median peak serum calcium was 12.1 (11.2-17.8) mg/dL. High ionized calcium was verified in 41 (28%) cases. 74 (51%) had evidence of bone metastasis (including primary bone cancer), multiple myeloma accounted for 7 (5%) cases, elevated PTH for 10 (7%) cases, PTHrP for 11 (7%) and elevated calcitriol for 3 (2%) cases. One case was categorized as *Definite* Immob-HCa and 4 cases as *Probable* Immob-HCa. The etiology of MAH was undetermined in 35 (24%) cases. Thus, Immob-HCa accounted for up to 4% (5/145) of in-hospital MAH. Concomitant acute kidney injury (AKI) was present in 3 out of 5 (60%) cases of Immob-HCa.

Conclusions: Immob-HCa accounted for approximately 1 in 29 of cases of in-hospital MAH and is accompanied by AKI in about half of the cases. Notably, incomplete diagnostic work up for MAH was common and may underestimate the incidence of Immob-HCa.

FR-PO244

AKI and Anemia Are Common in Patients with Sarcopenia and CKD Receiving Carboplatin, Pemetrexed, and Pembrolizumab for Advanced Non-Small-Cell Lung Cancer

Nurit S. Katz, Lea Mantz, Paul Hanna, Tianqi Ouyang, Florian J. Fintelmann, Meghan E. Sise. *Mass General Brigham Inc, Boston, MA.*

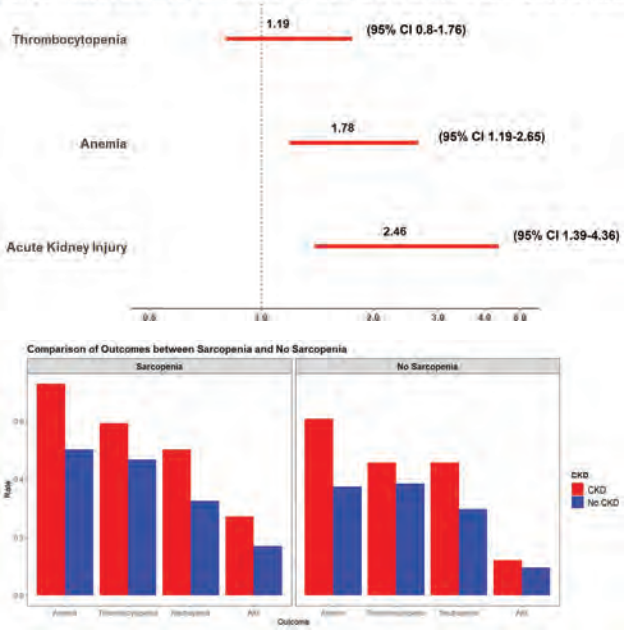
Background: Carboplatin, pemetrexed, and pembrolizumab (triplet therapy), which are first line treatment in advanced non-small cell lung cancer (aNSCLC) may cause acute kidney injury (AKI) and cytopenias. Carboplatin and pemetrexed are renally cleared and require dose adjustments in patients with reduced estimated glomerular filtration rate (eGFR), which may be overestimated in patients with sarcopenia. We hypothesized that patients with sarcopenia treated with triplet therapy have increased risk for AEs.

Methods: In this retrospective cohort study for adults with aNSCLC who received triplet therapy (2016-2022), we performed body composition analysis of T10 or L3 vertebral level on routine CT scan obtained within 90 days of treatment using a validated deep learning pipeline. Sarcopenia was defined using sex-specific cutoffs for skeletal muscle index (SMI). AEs included AKI, anemia, thrombocytopenia or neutropenia. We fit multivariable logistic regression to determine the association between sarcopenia and each AE, adjusting confounders. We assessed the rates of AE in patients with sarcopenia and without sarcopenia with or without CKD.

Results: 595 patients were included, mean age 65.9 ± 9.7, 51.4% female. 28.6% met CT-criteria for sarcopenia. 66.9% had one or more AEs. Patients with sarcopenia had increased odds of AKI and anemia (**Figure 1**), adjusted for confounders. Patients with concomitant sarcopenia and CKD had the highest rates of AEs (**Figure 2**).

Conclusions: Patients with aNSCLC and sarcopenia are at increased risk for AEs from triplet therapy, possibly due to eGFR overestimation and failure to appropriately dose-reduce chemotherapy.

Figure 1: Adjusted odds ratio for adverse outcomes in patients with sarcopenia receiving triplet therapy.



FR-PO245

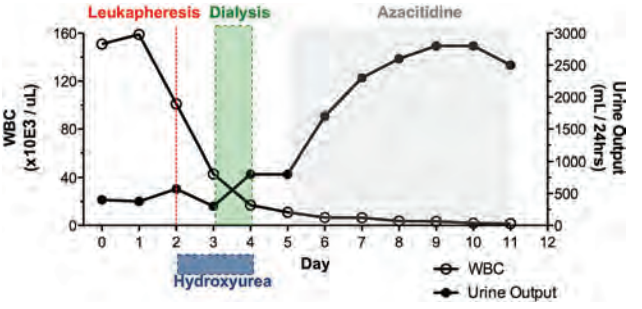
Role of Leukapheresis in the Management of AKI Associated with Hyperleukocytosis of Acute Myeloid Leukemia (AML)

Sherif Badra, Jusong Choi, Chintan V. Shah. *University of Florida, Gainesville, FL.*

Introduction: The rates of AML patients with hyperleukocytosis range from 8–12%. Due to very high early mortality rates, as high as 50% during 30 days after presentation, hyperleukocytosis—especially if complicated by leukostasis—is a hematologic emergency that requires prompt treatment. The role of leukapheresis remains controversial due to the lack of strong data. Hereby, we report a case of acute kidney injury (AKI) that resolved after one session of leukapheresis.

Case Description: A 73-year-old male presented to the hospital with abdominal pain, nausea, vomiting, and generalized fatigue of 2 weeks duration. He was found to have a WBC count of 159,000/μL with 98% peripheral blasts concerning for acute leukemia. On admission, nephrology was consulted for oliguric AKI without evidence of sepsis or hypotension. Urine microscopy revealed a few granular casts suggestive of ATN. The patient did not meet Cairo-bishop criteria for tumor lysis syndrome (TLS). The patient was initiated on hydroxyurea. Due to a lack of improvement in oliguric AKI after four days of presentation and without any other identifiable cause than cytostasis, he underwent one session of leukapheresis (Figure 1). This was followed by two consecutive sessions of dialysis for uremic encephalopathy. Two days later, his urine output increased to about 1.8 L with remarkable kidney function improvement, and he didn't require further dialysis. Unfortunately, the patient passed away after six weeks of a complicated hospital course and withdrawal of care with comfort measures.

Discussion: Renal failure can occur due to leukostasis from hyperleukocytosis in acute leukemia as a result of tubular and glomerular dysfunction. The exact mechanism is unknown but possibly due to mechanical obstruction from less deformable leukemic blasts, the release of proinflammatory cytokines, and matrix metalloproteinases that damage endothelial cells. No current guidelines exist for the treatment of renal injury in this setting. Our case suggests leukapheresis should be considered a therapeutic option for such patients.



FR-PO246

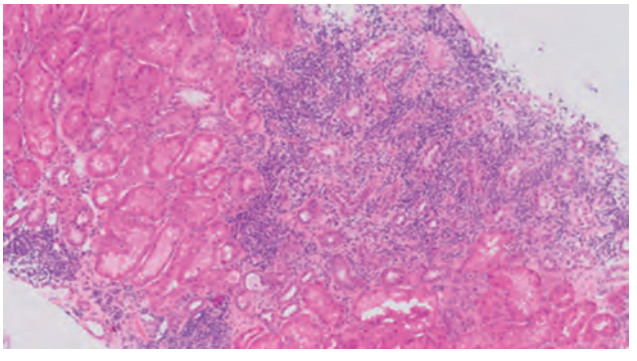
AKI due to Chronic Lymphocytic Leukemia Infiltration with Necrotizing Granulomas

Erika D. Critell, Amy Yau, Laura Biederman. *The Ohio State University, Columbus, OH.*

Introduction: Chronic lymphocytic leukemia (CLL) can commonly affect the kidneys. In autopsy findings, leukemic infiltration can be seen in up to 64-90% of cases, but direct involvement to the renal parenchyma causing acute kidney injury (AKI) is rare. In addition to leukemic inflammation, non-necrotizing granulomatous interstitial nephritis has been described.

Case Description: A 61 year old male with a past medical history of type 2 diabetes mellitus, ulcerative colitis, and immunoglobulin heavy chain variable region gene (IgHV) mutated CLL (not previously requiring therapy) presented in the outpatient setting with creatinine elevation from 1.0 mg/dL to 1.9 mg/dL. Work up revealed normal kidney size and new proteinuria of 493mg/24 hours. The creatinine rise was seen alongside a rise in his white blood cell (WBC) count from baseline 13-19 K/uL to 24-39 K/uL. Renal biopsy revealed leukemic infiltration with cells staining positive for CD20 and CD5 indicating direct involvement of the renal parenchyma along with necrotizing granulomas. The granulomas were found to be non-infectious, indicating a severe form of inflammation. He was started on acalabrutinib and obinutuzumab with hopes for AKI resolution.

Discussion: Other case reports note the appearance of necrotizing granulomatous inflammation seem to affect younger men; additionally, there is no correlation with WBC. Most cases have complete to partial renal recovery after initiation of chemotherapy, however case reports suggest patients with granulomatous inflammation may have a poorer response. The mechanism of renal injury is not clear. Some suggest leukemic cells secrete monoclonal immunoglobulins whereas others suggest renal damage from a hypersensitivity reaction to leukemic cells. Of note, previous case reports did not classify IgHV mutation status, which is now routinely evaluated for. Renal biopsy remains critical to diagnose this potentially reversible, specific, and rare cause of acute renal failure and dictate initiation and guidance of chemotherapy.



PAS stain showing leukemic infiltration

FR-PO247

Association Between Cancer and AKI Among Medicare Fee-for-Service Beneficiaries, 2006-2014

Yoshihisa Miyamoto, Linda J. Andes, Alain K. Koyama, Fang Xu, Meda E. Pavkov. *National Center for Chronic Disease Prevention and Health Promotion Division of Diabetes Translation, Atlanta, GA.*

Background: Acute kidney injury (AKI) is a heterogeneous syndrome characterized by an abrupt decline in kidney function. Although patients with cancer are likely to be susceptible to AKI, population-based incidence of AKI in patients with cancer is not well understood in the US.

Methods: We conducted a population-based retrospective cohort study among Medicare fee-for-service beneficiaries who were continuously enrolled for six-years, including an initial one year cancer-free window before the index year. The index year was defined by a new cancer diagnosis. Follow-up started with the index year and ended at the time of AKI, death, or censoring at the end of five years. We defined incident cancer

by the presence of two ICD-9 CM diagnosis codes in an outpatient setting or one ICD-9 CM inpatient code. A control group without cancer represented patients without any cancer diagnoses over the same time period, matched on age, sex, and race and ethnicity. The main outcome was time to AKI or death. All-cause death date was ascertained using the National Death Index. Association between cancer and AKI was assessed by cause-specific hazard and Fine-Gray competing risk models.

Results: We identified 5,613,285 Medicare fee-for-service beneficiaries with incident cancer and the same number of matched controls. Beneficiaries with cancer were at greater risk of AKI (unadjusted hazard ratio [HR]=1.66) and death (HR=2.83). The associations were significant after adjustment for covariates (HR=1.38 and HR=2.53, respectively). When death was modeled as a competing risk, unadjusted subdistribution hazard ratio (SHR) of AKI in patients with vs. without cancer was 1.20, and the adjusted SHR was 0.98. All outcomes were significant due to the large sample size.

Conclusions: Medicare fee-for-service beneficiaries with cancer were at greater risk of AKI, compared with those without cancer. However, because the cause-specific association of cancer with death was stronger than that with AKI, impact of cancer on cumulative incidence of AKI indicated by SHR was not notable.

Funding: Other U.S. Government Support

FR-PO248

Mortality of Patients with Cancer and AKI: What Are the Lessons?

Alline Oliveira, Andrea C. Valenca, Joseph L. Nascimento, Thiago M. Lacerda, Klebson F. Feijo de Melo, Italo R. Alves, Ana Paula Gueiros. *Hospital das Clinicas, Recife, Brazil.*

Background: Acute kidney injury (AKI) is a prevalent complication in cancer patients, contributing to mortality. This study aimed to assess factors associated with the mortality of patients with cancer and AKI monitored in the onconephrology clinic of a university hospital.

Methods: This was a cross-sectional, retrospective study. Medical records were reviewed of patients monitored from January 2018 to December 2022. Patients with COVID-19 were excluded. AKI was defined according to KDIGO criteria. The final creatinine (CrF mg/dL): last value measured before discharge or death; oliguria: diuresis <400 mL/24h. A comparative analysis was performed of patients who died and survivors. Univariate and multivariate analyzes were used in the search for risk factors for death. The impact was assessed of hyperphosphatemia (phosphorus>4.5mg/dL) and hyponatremia (sodium<135mEq/L) on mortality.

Results: A total of 340 patients (50% male), with a median age of 62 years, were studied. The mean follow-up time was 15 days. Most patients (78%) presented solid tumors. Types of AKI were: intrinsic renal (38%), prerenal (30%), and obstructive (27%). Outcome data were available on 336 patients. One hundred and eighteen patients (35%) died. Patients who died differed from survivors by being in ICU (55% x 17%; p<0.001), intrinsic renal AKI (57% x 27%; p<0.001), sepsis (58% x 19%; p<0.001), urine output (mL) (500 x 1050; p<0.001), need for renal replacement therapy (RRT) (60% x 25%; p<0.001), CrF (3.2 x 1.5; p<0.001), phosphorus (4.6 x 4.0; p=0.018) and albumin (g/dL) (2.8 X 3.0; p=0.046). In the univariate analysis, the following were associated with mortality: not being in ICU (OR 0.17; p<0.001), CrF (OR 2.26; p<0.001), intrinsic renal AKI (OR 3.47; p<0.001), no sepsis (OR 0.17; p<0.001), non- oliguric (OR 0.31; p<0.001), phosphorus (OR 1.2; p=0.023) and no need for RRT (OR 0.22; p<0.001). In the multivariate analysis, only CrF was an independent risk factor for death (OR 7.51; p=0.009). Hyperphosphatemia was associated with mortality (p=0.006), but hyponatremia was not (p=0.8).

Conclusions: We confirmed the high mortality rate of patients with cancer and AKI. The severity and persistence of AKI are determinants of mortality. Hyperphosphatemia seems to be a predictor of mortality in cancer patients with AKI.

FR-PO249

Lymphocytic Infiltrates on Kidney Biopsy of a Patient with AKI and Chronic Lymphocytic Leukemia: Interstitial Nephritis or Infiltration by Leukemia?

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Introduction: Chronic lymphocytic leukemia (CLL) is the most common adult leukemia. AKI has been reported in patients with CLL due to hypercalcemia, tumor lysis syndrome, or obstructive nephropathy. Infiltration of organs by CLL can occur, however, kidney involvement is unusual.

Case Description: A 60-year-old female with history of hypertension on treatment with lisinopril and HCTZ, gastroesophageal reflux recently on esomeprazole, and CLL with trisomy 12 and 14:19 translocation, on treatment with Ibrutinib for 5 years, was found to have worsening kidney function. In the ER, she reported abdominal discomfort and bloating for one month. On physical exam she had bilateral lower extremity edema. Three months earlier, she had a creatinine of 0.98 mg/dL. On current presentation, her creatinine was 5.27 mg/dL and potassium was 2.9 mmol/L. UA revealed proteinuria and pyuria. Spot UPCR was 400 mg/g. A kidney ultrasound showed normal size kidneys. A kidney biopsy was performed which showed acute granulomatous tubulointerstitial nephritis (TIN) with extensive interstitial lymphocytic infiltrate and scattered interstitial eosinophils. Evaluation by a hematopathologist confirmed involvement of renal parenchyma by CLL. By immunohistochemistry, lymphoma cells were positive for PAX5, CD20, and CD5. Treatment was initiated with prednisone. Ibrutinib was discontinued and she was started on Obinutuzumab and Venetoclax. 4 weeks later, her creatinine improved to 1.26 mg/dL and urinalysis was negative for proteinuria or pyuria.

Discussion: This case illustrates the importance of a multidisciplinary collaboration and high degree of suspicion when lymphocytic infiltrates are seen in a kidney biopsy of patients with CLL. The presence of TIN with eosinophils may indicate allergic TIN in this case due to either HCTZ or esomeprazole, but the presence of malignant cells due to CLL is the most likely contributor to the AKI. Mechanistically, AKI secondary to infiltrative disease secondary to CLL is poorly understood with one report hypothesizing tubular microvascular compression and infiltration-associated inflammatory response. Recognition of this phenotype of infiltrative disease in patients with CLL is vital for timely treatment.

FR-PO250

Clonal Hematopoiesis of Indeterminate Potential Is Associated with Kidney Disease Progression in a Multi-Cohort Meta-Analysis of Individuals with CKD

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is a common inflammatory condition of aging caused by acquired mutations in blood stem cells. CHIP causes myriad end-organ damage, including a doubling of the risk of cardiovascular disease independent of traditional risk factors. We have recently shown associations for CHIP with acute kidney injury and with kidney function decline in the general population, with a greater effect for CHIP driven by mutations in genes other than *DNMT3A* (non-*DNMT3A* CHIP). Longitudinal kidney function endpoints in individuals with pre-existing chronic kidney disease (CKD) and CHIP have been examined in two previous studies, which reported conflicting findings and were limited by small sample sizes.

Methods: In this study, we examine the prospective associations between CHIP and CKD progression events in four cohorts of CKD patients: the Chronic Renal Insufficiency Cohort (CRIC), the African American Study of Kidney Disease (AASK), the Canadian study of prediction of death, dialysis and interim cardiovascular events (CanPREDDICT), and BioVU (total N = 4853). The primary outcome was CKD progression (composite of 50% kidney function decline or end-stage kidney disease). Analyses were adjusted for age, age^2, sex, self-reported race, and the following baseline parameters: eGFR, proteinuria, smoking status, BMI, diabetes status, hypertension, and cardiovascular disease history.

Results: Across all cohorts, the average age was 67.4 years, the average baseline eGFR was 41.2 ml/min/1.73m^2, and 25% had CHIP. In a random-effects meta-analysis, non-*DNMT3A* CHIP was associated with a 59% increased risk of incident CKD progression (HR 1.59, 95% CI: 1.01-2.51). This effect was slightly more pronounced in the subgroup with baseline eGFR ≥ 30 ml/min/1.73m^2 (HR 1.77, 95% CI: 1.06-2.98).

Conclusions: Non-*DNMT3A* CHIP is a potentially targetable novel risk factor for CKD progression in a multi-cohort meta-analysis.

Funding: NIDDK Support, Other NIH Support - Canadian Institutes of Health Research Project Grant (application # 427810), R01DK132155, R01DK125782, Government Support - Non-U.S.

FR-PO251

5HT-1F Agonist-Mediated Protection Against Cisplatin-Induced Nephrotoxicity Is Abolished in a Murine Model of Lung Cancer

Andrew Orwick, Leah J. Siskind. *University of Louisville, Louisville, KY.*

Background: Anti-cancer drug-induced acute kidney injury (AKI) is a persistent problem. Cisplatin is a prominent example of this, 30% of patients develop AKI after a single dose and have an increased risk of chronic kidney disease (CKD). The mechanism driving the AKI to CKD transition in the repeated low-dose cisplatin (RLDC) model is not fully understood. Mitochondrial dysfunction plays a critical role in the transition from AKI to CKD. The role of kidney mitochondrial dynamics/quality control in the RLDC model is currently unknown. Preclinical cisplatin toxicity studies have been completed mostly in mice without cancer. The lack of appropriate preclinical models has led previous research down doomed pathways.

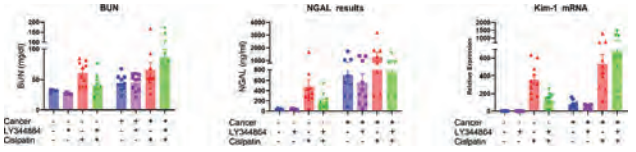
Methods: The objective of this study was to determine if nephroprotective strategies in mice without lung cancer will still protect mice with lung cancer. Eight-week-old B6129 mice with and without lung cancer were administered Cisplatin (7mg/kg) or saline via intraperitoneal (i.p.) injection once a week for four weeks. Following the first dose of cisplatin, mice were administered LY344864 (2mg/kg) or saline 6 days a week via i.p. injection. We pharmacologically induced mitochondrial biogenesis to increase kidney mitochondrial content to determine if this pathway will protect from cisplatin-induced nephrotoxicity.

Results: Stimulating mitochondrial biogenesis increased kidney mitochondrial content and reduced loss of kidney function, kidney injury, inflammation, and

development of fibrosis from RLDC in mice without cancer. However, these effects are nullified when the experiment was repeated in mice with subcutaneous lung cancer.

Conclusions: Previous clinical trials on nephroprotective agents have failed, and we propose that poorly representative mouse models may be responsible for misleading preclinical research. Our development of clinically relevant models of cisplatin-induced nephrotoxicity provides a foundation for developing nephroprotective agents that can be used as adjunctive therapy for cancer patients receiving cisplatin.

Funding: NIDDK Support



FR-PO252

Gut Microbiota and Kidney Injury After Allogeneic Hematopoietic Cell Transplantation (allo-HCT)

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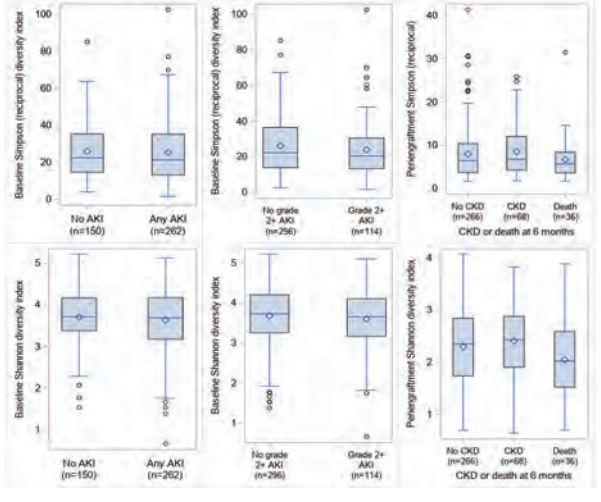
Background: Acute kidney injury (AKI) is a common complication of allo-HCT associated with an increase in non-relapse mortality. In contrast, higher diversity of gut microbiota at neutrophil engraftment is associated with lower mortality. We aimed to study the association of changes in gut microbiome diversity in an allo-HCT cohort who developed post-transplant AKI or CKD.

Methods: We performed a single-center study of 419 allo-HCT recipients from 2014-2017 at Memorial Sloan Kettering Cancer Center with analysis of gut microbiome diversity. We defined AKI and CKD based on KDIGO criteria and eGFR using the CKD-EPI equation. We defined gut microbiome diversity using Shannon and Simpson reciprocal diversity indices (DI), with higher levels indicating more diverse microbiota. We used Wilcoxon rank-sum test to compare baseline DI (within 7 days of HCT conditioning) between patients who did and did not develop AKI by 100 days post-HCT, and peri-engraftment DI (median DI in days 7-21 post-HCT) between those who did and did not develop CKD at 6 months.

Results: Simpson reciprocal and Shannon DI were 21.8 (IQR: 13.7, 35.2) and 3.7 (IQR: 3.2, 4.2) at baseline, and 6.3 (IQR: 3.7, 10.4) and 2.3 (IQR: 1.7, 2.8) at peri-engraftment, respectively. Of the 419 patients, 263 (63%) developed AKI; 114 (27%) was Stage 2+. CKD occurred in 68 patients (18%) at 6 months. There were no significant differences in microbiome DI at baseline or peri-engraftment in patients who developed AKI or CKD, compared to those who did not (all p>0.05, Figure 1).

Conclusions: Our findings do not support the existence of a link between baseline or peri-engraftment gut diversity and the risk for development of AKI or CKD in patients undergoing allo-HCT. This study highlights the complex and multifactorial etiology of AKI in allo-HCT recipients and the need for additional prospective and mechanistic studies.

Figure 1. Baseline and peri-engraftment Simpson reciprocal and Shannon diversity indices by any AKI in 100 days post-HCT and CKD at 6 months.



FR-PO253

Multiple Cancers Alters Renal Physiology and Induces Kidney Injury and Inflammation

Dana Hammouri, Leah J. Siskind. *University of Louisville, Louisville, KY.*

Background: The altered physiology of cancer patients and their unique susceptibility to kidney disease has led to the rapidly growing specialty of Onconephrology. Cancer patients often have decreased kidney function, and drug-induced acute kidney injury (AKI) is common and remains a hurdle. Drug-induced AKI can interrupt therapy and reduce overall survival. Our lab has recently shown that lung-cancer enhances the nephrotoxicity of cisplatin. Additionally, we were able to show that lung-cancer alone alters kidney physiology. However, we are unaware if this phenomenon is exclusive to the model we tested. In this study we used multiple cancer types to determine if kidney function, injury, and inflammation are being altered by subcutaneous cancer alone.

Methods: Eight- to ten-week-old B6;129 mice were randomly assigned into six group of non-cancer and various other cancer types. In the cancer groups, cancer cells were injected subcutaneously and followed for tumor size. Animals were euthanized once tumor size met necessary endpoint per IACUC protocol.

Results: Different cancer types have varying effects on altering kidney function, injury and inflammation. Metastatic lung cancer induces the largest changes, compared to non-metastatic lung cancer. Additionally, melanoma increased urinary NGAL, but did not increase KIM-1 expression.

Conclusions: The presence of subcutaneous tumors is sufficient to alter kidney biology, induces renal injury and inflammation and reduce renal function. Further studies will need to be conducted to elucidate the mechanism behind these changes. Understanding the tumor-kidney crosstalk may provide mechanistic insights and uncover novel therapeutic targets for onconephrology patients.

Funding: NIDDK Support

FR-PO254

Urine EGF and TNFR2: A Pilot Study of Novel Biomarkers to Predict Long-Term Renal Outcomes in Pre-Clinical Model of Cisplatin-Induced Chronic Kidney Injury

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Background: Cisplatin is associated with development of chronic kidney disease (CKD) and hypertension affecting around 45% of pediatric oncology patients. Novel urine biomarkers may allow early identification of patients at risk of CKD progression. Urine EGF (uEGF) has been shown to be an independent predictor of CKD progression in humans with an inverse correlation between uEGF and estimated glomerular filtration rate (GFR) decline. Tumor Necrosis Factors Receptor 2 (TNFR2) is a promising biomarker of inflammation with higher levels associated with increased risk of CKD progression. Murine cisplatin pre-clinical models result in long-term renal function decline and could facilitate identification of biomarkers to predict CKD progression.

Methods: Ten-week-old C57Bl6J male mice received 3 weekly intraperitoneal (IP) injections of cisplatin 8 mg/kg/dose vs 0.9% NaCl control (n = 18/group). Urine was collected at 14 days and 3 months after initial cisplatin dose, and transdermal GFR (tGFR) measurements were performed at 3 and 6 months after initial cisplatin dose. uEGF (ELISA, MEG00, R&D Systems) and uTNFR2 (R-PLEX assay, MESO QuickPlex SQ instrument) were measured according to manufacturer's instructions. tGFR analysis was performed calculating FITC-sinistrin clearance after retroorbital injection. Veterinarian Pathologist quantified tubular injury, inflammation and fibrosis in kidney sections (score 0-4).

Results: Survival was 89% (control 94% vs 83% cisplatin). At 6 months, cisplatin treated mice had lower tGFR, and higher tubular injury, interstitial fibrosis, and inflammation on histological analysis. Cisplatin treated mice had significant reduction in uEGF at 14 days, and 3 months and a significant increase in uTNFR2 at 14 days compared to control group (p<0.05 2way ANOVA). There is a significant negative correlation between uEGF at 3 months and tubular injury, inflammation, and fibrosis at 6 months and a positive correlation with tGFR at 6 months. There is a significant positive correlation between uTNFR2 at 14 days and tubular injury, glomerular changes, and fibrosis at 6 months (Pearson, p<0.05).

Conclusions: uEGF and uTNFR2 could be promising early biomarkers to predict CKD in pre-clinical models of cisplatin-induced CKD.

FR-PO255

Atypical Presentation of Renal Amyloidosis in a Patient with Plasma Cell Dyscrasia (PCD)

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Introduction: Amyloidosis (AD) is deposition of abnormal proteins that can lead to organ dysfunction. Light chain AD (AL amyloidosis) is the most common systemic form. This is commonly associated with PCDs such as multiple myeloma (MM). This case focuses on a patient with IgA PCD who develops an atypical presentation of renal AD.

Case Description: 76-year-old male with hypertension, diabetes, hyperlipidemia, coronary artery disease, heart failure, atrial fibrillation, urinary bladder AD and chronic kidney disease (CKD) was seen at CKD clinic. Cr was 1.8-2.0 mg/dl. Urinalysis with no hematuria, urine protein to creatinine ratio (UPCR) was 621 mg/g. SPEP signified M-spike and immunofixation with IgA-kappa monoclonal protein bands. Patient was referred to

hematology. Serum IgA was 952 mg/dL (103-591) with elevated kappa/lambda ratio 4.48 (0.53-1.51). Bone marrow biopsy showed 15-20% plasma cells and was negative for AD. PET CT with no lytic lesions. He was diagnosed with IgA PCD. MM labs remained stable with no treatment planned. Renal biopsy was indicated to rule out monoclonal gammopathy of renal significance. Urine immunofixation showed monoclonal IgA band and repeat UPCR was 132 mg/g. Biopsy revealed amyloid deposition limited to few glomeruli and arterioles with greater kappa than lambda light chains. Given IgA-kappa paraproteinemia, AL-type amyloidosis was the favored diagnosis.

Discussion: AD has a strong association with PCD. This case highlights an atypical presentation of renal AD which often presents with significant amounts of proteinuria and primarily affect the glomeruli. About 65% of patients with renal AD are afflicted with nephrotic syndrome. When amyloid deposition is found in the tubulointerstitial (TI) compartments, proteinuria is not a common feature. Additionally, lambda light chains are seen more often than kappa light chains as they are more amyloidogenic. Our case is atypical due to the absence of massive proteinuria and predominance of kappa light chains. Insignificant proteinuria can often be due to deposits confined to the TI or vascular compartments, however our patient had deposits in the glomeruli. Thus, it is important to note that even in the absence of significant proteinuria, a patient with known PCD with renal dysfunction, may still undergo renal biopsy. The histological findings can also vary despite the degree of proteinuria.

FR-PO256

Use of Radioactive Iodine in the Management of Thyroid Cancer in Those with Low-Clearance CKD/ESKD

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Background: Radioactive iodine (RAI) is a key adjuvant treatment of differentiated thyroid cancers. Iodide is cleared by the kidney which leads to complexities in the treatment of patients with end-stage kidney disease (ESKD) due to prolonged circulation of RAI.

Methods: A structured multidisciplinary care pathway was created for those receiving RAI with ESKD, involving Nephrology, Radiation Oncology, Medical Physics, and Biomedical Engineering. A shielded room is used for RAI with the addition of mobile shielding for staff to reduce staff exposure during dialysis. Alterations for water treatment were made to deliver ultrapure water suitable for HD. Patients were dialysed in isolation until levels <30MBq (1.5µSv/hr). Safety protocols for radiation protection for staff and dialysis waste management were implemented.

Results: **Case One** 47 year old man with invasive follicular thyroid carcinoma in the setting of CKD stage 4 (eGFR of 17ml/min/1.73m2). Following thyroidectomy, an avid focus present in left thyroid bed requiring treatment with RAI. He underwent radioactive iodine ablation therapy with a reduced dose protocol of 1.1 GBq. Levels were closely monitored and graphed compared to a normalised dose rate for those without renal impairment. His clearance was in line with the expected rate. **Case 2** 50 year old man with recurrent papillary thyroid carcinoma on a background of ESKD on HD. Initial treatment with surgery and RAI in 2017. He represented with recurrent nodal disease and underwent a neck dissection. RAI treatment was planned. Dialysis was arranged prior to treatment to familiarise staff with the new unit. He received a 50% reduction in RAI with a dose of 1.850 GBq. Following treatment, he underwent dialysis at 14 hours post treament then every 48 hours. His levels were reduced by >50% with each dialysis session (Figure).

Conclusions: RAI can be safely administered to patients with low clearance CKD/ESKD with the implementation of a structured care pathway utilising a multidisciplinary approach.

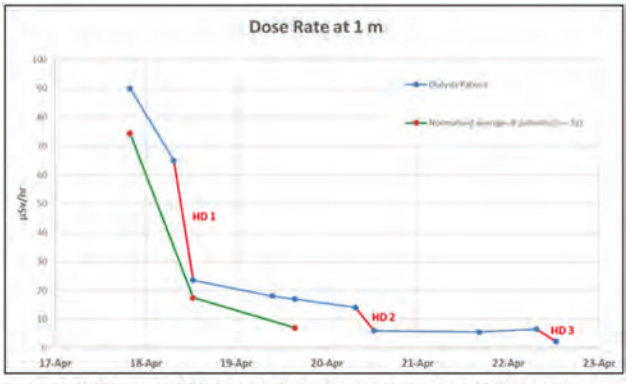

Figure 2. Clearance of RAI for Case 2 as compared to clearance of other cases

FR-PO257

Non-Proteinuric CKD: An Atypical Presentation of Multiple Myeloma

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Introduction: Light chain deposition disease (LCDD) is characterized by overproduction and deposition of monoclonal light chain immunoglobulins. LCDD usually has prominent kidney involvement; including proteinuria and kidney failure characterized by nodular glomerulosclerosis and tubular basement membrane thickening. Here we highlight an atypical presentation of biopsy proven kappa type LCDD without significant glomerular proteinuria in a patient found to have Kappa restricted Multiple myeloma (MM).

Case Description: Our patient is a 64-year-old male with medical history of asthma, hyperlipidemia, and tobacco use disorder (remission for 9 yr). He presented to nephrology clinic for evaluation of confirmed isolated elevation in creatinine of 2.1 (BUN 21) with normal CBC, electrolytes, total protein and albumin. History was negative for NSAID use, OTC supplements, frequent UTI or nephrolithiasis. There was no family history of CKD or ESKD. His only medication was Fluticasone-Vilanterol. His vital signs and physical exam were unremarkable. Urinalysis was negative for protein, but trace blood was noted. ANA, ANCA, C3/C4, RF, and viral hepatitis serologies were negative. UACR 10mcg/mg and UPCR 0.2mg/mg. SPEP was normal. Kappa FLC 273 mg/L, Lambda FLC 26.1 mg/L, Ratio 10.46. Renal imaging was notable for multiple bilateral cysts without evidence of enhancing lesion, stones or hydronephrosis. Renal biopsy was ultimately performed, and it revealed LCDD Kappa type, interstitial fibrosis/tubular atrophy of 70-80% with moderate arterio- and arteriolosclerosis. Bone marrow biopsy revealed normal cellular marrow with trilineage hematopoiesis and increased plasma cell (20% by CD 138 immunostaining). Flow cytometry revealed monoclonal kappa restricted plasma cell population. PET/CT was normal, implying that the kidneys were the sole site of the disease. He was started on cyclophosphamide, bortezomib and dexamethasone (CyBorD) and creatinine eventually improved. UACR increased slightly to 25mcg/mg.

Discussion: Kidney biopsy is almost always essential when the origin of CKD is unknown. Among patients newly diagnosed with MM, 20-50% have either AKI or CKD at the time of diagnosis. Early recognition and treatment of an underlying plasma cell disorder is important in preserving kidney function. This case highlights the importance of thorough workup for monoclonal gammopathy despite absence of typical presenting features.

FR-PO258

Chimeric Antigen Receptor T-Cell Therapy in a Dialysis Patient with Lymphoma

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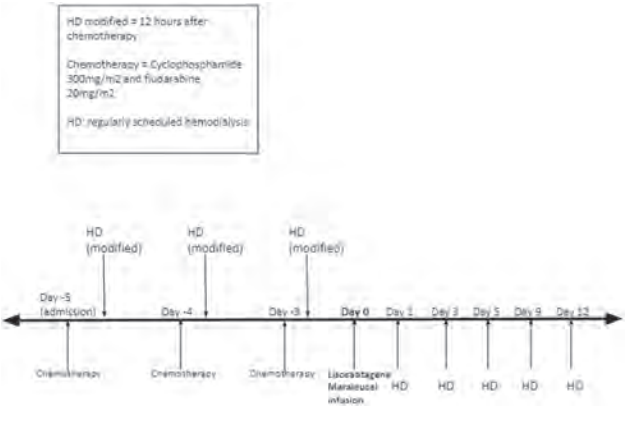
Introduction: Chimeric antigen receptor T-cell (CAR-T) therapy has become a revolutionary cancer therapy for multiple subtypes of hematologic malignancies. Despite this, CAR-T use in End Stage Kidney Disease (ESKD) patients is limited. We describe the successful administration of CAR-T therapy in a patient with ESKD.

Case Description: A 60-year-old female with a history of hypertension, heart failure, ESKD on hemodialysis (HD), and diffuse large B cell lymphoma (DLBCL) from an underlying chronic lymphocytic leukemia (CLL) was admitted for CAR-T therapy. Prior to the receipt of CAR-T, she received three days of lymphodepleting chemotherapy consisting of Cyclophosphamide (660 mg/24 hours) and dose-reduced fludarabine(20 mg/m2). During this regimen, she underwent HD on 3 consecutive days, approximately 12 hours after her fludarabine infusions. Following CAR-T infusion, the patient resumed her traditional 3 times per week HD schedule. The patient's course was complicated by pancytopenia, lasting for 13 days. The patient experienced Grade 2 cytokine release syndrome (CRS), and was treated with one dose of tocilizumab on Day 11 post CAR-T. At the time of the last follow-up, the patient remains with ESKD on HD, and is still in remission 12 months after CAR-T.

Discussion: When performing HD, timing is essential to limit toxicity and minimize drug removal prior to CAR-T infusion, while also not eliminating the drug prior to its distribution and onset of action. Given the uncertainties of HD timing, drug removal, and the apparent increased risk of complications, further investigations are needed to determine the ideal treatment strategies in patients with ESKD. Future efforts to elucidate the impact of lymphodepleting chemotherapy on cytokine profiles and other factors in patients with ESKD will help inform management strategies. Collaborative efforts and standardized protocols are needed to better define the optimal HD timing in CAR-T recipients.



FR-PO259

Daratumumab Monotherapy in Severe Patients with AL Amyloidosis and Biopsy-Proven Renal Involvement

Roberta Fenoglio, Savino Sciascia, Dario Roccatello. *University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases, Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, University of Turin, Turin, Italy.*

Background: Daratumumab is an anti-CD38 monoclonal antibody recently approved as a first-line therapy on top of standard therapy for the treatment of multiple myeloma and AL amyloidosis. The following data describe the good results reported by our group and the long-term experience achieved in recent years on the efficacy of daratumumab used in monotherapy.

Methods: We described 17 patients (pts) treated with Daratumumab alone, 24 iv administration at a dose of 16 mg/kg. All of them had an histological confirmation and staging of renal involvement and were ineligible for ASCT. Pts could either be naïve or refractory. When feasible, the patient who underwent the whole cycle of therapy underwent a second kidney biopsy at the end of the treatment.

Results: The mean age at diagnosis was 73 years. 16/17 pts had proteinuria that was associated with renal function impairment in 11. 2 pts were on dialysis at the time of therapy initiation. 9 pts completed the treatment; 13 over 17 underwent at least 12 infusions. At the 12th administrations 84,6% of pts had an overall hematological response. 46,5% of pts achieved a complete hematological response, 38% had a very good partial response, and 15.5% were non responders. 5/13 had already achieved an organ response.; the 2 pts who were in dialysis at the time of therapy initiation, remained on dialysis. 7/9 achieved a renal response. Proteinuria decreased rom 6,02 to 1,28 g/die ($p < 0.005$) with stabilization/improvement of sCr. 8/9 pts with cardiac involvement obtained at least amelioration. At the end of follow-up 5 pts have persistent hematological and renal response. 1 pt with initial partial response had a relapse. The last pt is still alive and is currently being treated with a second line of therapy, because no hematologic or organ response was achieved with Daratumumab. 7 pts underwent a second kidney biopsy at the end of the treatment. Histological findings showed stable deposits in 6 over 7 cases, while the last one showed a reduction in the extention and amount of amyloid deposits.

Conclusions: Our data, based on the real life experience of our center, suggest that daratumumab monotherapy may represent an effective therapeutic option, capable not only of inducing a substantial improvement in the renal status in pretreated or naïve pts, but also of limiting progression of amyloid deposition.

FR-PO260

Onconephrology: The Role of Kidney Biopsy in the Management of Side Effects of Targeted Therapies

Roberta Fenoglio, Savino Sciascia, Dario Roccatello. *CMID-Nephrology and Dialysis - San Giovanni Bosco - Turin, Torino, Italy.*

Background: The introduction of innovative therapies, resulting from revisiting cancer as a disease of the immune system, has changed the scenario of complications. These new classes of drugs, such as targeted therapies and immune checkpoint inhibitors, assure substantial advantages in cancer therapy, despite some side affecting various organs, including the kidney. Histological evaluations of kidney disorders induced by targeted/immunotherapy are limited.

Methods: In this study we examined the histological features of patients treated with new cancer agents who underwent kidney biopsy for new onset kidney failure and/or urinary abnormalities.

Results: The cohort included 30 adult patients. The most frequently administered therapies were immunotherapy (30%), targeted therapy (26.7%), immunotherapy plus targeted therapy (13.3%), immunotherapy plus chemotherapy (13.3%), targeted therapy plus chemotherapy (16.7%). The most common histological finding was tubular interstitial nephritis (30%) that was associated with acute tubular necrosis in 4 cases, and thrombotic microangiopathy (23.3%). After kidney biopsy, 16 of the 30 patients were treated according to the histological diagnosis. Fourteen patients were treated with steroids. One patient with membranous nephropathy was treated with a single dose of rituximab. A patient with severe thrombotic microangiopathy requiring dialysis received a treatment with eculizumab for 3 months. Overall some renal response was obtained in all patients treated with glucocorticoids, while complete kidney response was achieved in the patient treated with rituximab. Cancer treatment was resumed without change in 21 out of 30 patients.

Conclusions: Kidney biopsy is critical for the management of kidney toxicities and should be strongly encouraged for patients showing adverse kidney effects of novel cancer agents.

FR-PO261

Cancer Status and Mortality in Older Hemodialysis Patients: Data from a Korean Society of Geriatric Nephrology Retrospective Cohort

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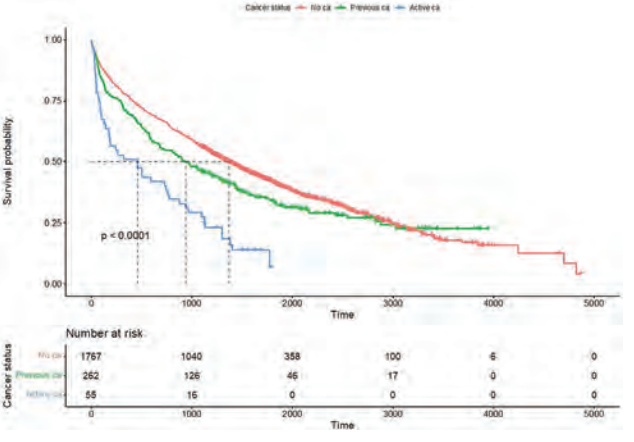
Background: Our study probed the correlation between cancer presence and mortality rates in elderly patients on hemodialysis, a link that is currently underexplored despite established associations between cancer, age, and chronic kidney disease (CKD).

Methods: We conducted a retrospective, multicenter cohort study through the Korean Society of Geriatric Nephrology. This study encompassed 2,085 patients aged 70 or above who commenced hemodialysis from 2010 to 2017. We employed the Kaplan-Meier survival estimator and Cox proportional hazards regression analysis to assess all-cause mortality.

Results: Among our cohort, 262 patients (12.6%) had a cancer history, while 55 patients (2.6%) were managing active cancer. Over a median follow-up period of 3.2 years, 1,357 deaths (65.1%) occurred. The active cancer group revealed significantly higher all-cause mortality in comparison to those with a cancer history or no cancer (85.5% vs 68.3% vs 64.0%; p<0.002). Kaplan-Meier analysis underscored this mortality disparity among the groups ($p < 0.001$, log-rank test). Further, the multivariate Cox regression analysis, post-adjustment for clinical variables, evidenced a strong correlation between active cancer and all-cause mortality (HR:1.89; 95%CI: 1.36–2.64; $p < 0.001$). However, a history of cancer did not significantly raise overall mortality (HR:1.07; 95%CI: 0.90–1.28; $p = 0.448$).

Conclusions: Elderly patients on hemodialysis with active cancer demonstrated a higher mortality rate compared to those with a history of cancer or no cancer. Interestingly, cancer survivors exhibited a mortality risk akin to those never diagnosed with cancer. Thus, elderly cancer survivors may be viable candidates for dialysis.



Pairwise log rank test showed all between-group comparisons significant.

FR-PO262

Cancer Screening for Dialysis Patients

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Background: Routine cancer screening is not recommended for end stage renal disease (ESRD) patients due to their high mortality rate. The current status of cancer screening in this population remains uncertain, and routine screening is deemed cost-ineffective. False-positive test outcomes may lead to unwarranted medical interventions, overtreatment, and psychological distress, highlighting the need for careful consideration in implementing such screening measures.

Methods: Among 340 ESRD patients at UPMC Harrisburg, 136 were ineligible, resulting in a cohort of 204 patients. Descriptive analysis reported categorical variables as number (percent). Group differences were assessed using chi-square tests, employing Fisher exact test for frequencies ≤5. A p-value <0.05 indicated statistical significance. SAS 9.4 (SAS Institute, Cary NC) was used for all analyses.

Results: Among the cancer screening rates examined, including breast cancer, colon cancer, prostate cancer, and cervical cancer, there was no statistically significant difference observed between patients who died from cancer-related causes and those who

died from non-cancer related causes. However, it is worth noting that the screening rate for lung cancer displayed a statistically significant difference between these two groups.

Conclusions: Cancer screening in ESRD patients should be tailored on anticipated survival, transplant eligibility, and cancer risk. However, this study is limited by small sample sizes. Larger patient cohorts are needed to provide more representative results. A personalized approach to cancer screening, considering specific risk factors and projected lifespan, is crucial in ESRD patients. Further retrospective studies are necessary.

	cancer related death		Non-cancer related death		p-Value
Total number of patients	13		188		
Male	9	69.23%	114	60.64%	
Female	4	30.77%	74	39.36%	
Breast Cancer (female only)					
Had mammogram - no.%	4	100.00%	46	63.89%	0.2925
Diagnosed of breast cancer - no.%	1	25.00%	4	5.56%	0.2427
Colon Cancer					
Had colonoscopy - no.%	5	38.46%	101	54.01%	0.2774
Diagnosed of colon cancer - no.%	1	7.69%	3	1.60%	0.2363
Prostate Cancer (male only)					
Had PSA - no.%	4	44.44%	86	75.44%	0.0574
Diagnosed of prostate cancer - no.%	2	22.22%	7	6.19%	0.1329
Cervical Cancer (female only)					
Had PAP smear - no.%	2	50.00%	23	31.08%	0.5894
Diagnosed of cervical cancer - no.%	0	0.00%	2	2.74%	1.0000
Lung Cancer					
Had CT scan - no.%	8	61.54%	45	23.94%	0.0062
Diagnosed of lung cancer - no.%	7	53.85%	2	1.07%	<0.0001

FR-PO263

Futility of Dialysis in Patients with Tumor Lysis Syndrome in Advanced Hematological Malignancy: A Case Series

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Background: Acute kidney injury (AKI) can occur as result of tumor lysis syndrome (TLS) in patients with an underlying hematological malignancy. In TLS, hyperuricemia and hyperphosphatemia can cause crystal nephropathies. In patients with advanced malignancies, excess lactic acid production occurs as neoplastic cells preferentially undergo anaerobic glycolysis, known as the Warburg effect, resulting in type B lactic acidosis. These patients typically are hemodynamically stable. While dialysis is frequently used in the management of TLS, data on outcomes of these patients with advanced hematological malignancy would aid in deciding utility of dialysis. The purpose of our study is to assess mortality outcomes in patients with an advanced hematological malignancy with TLS, type B lactic acidosis, and AKI to better determine the utility and outcomes of dialysis in this cohort.

Methods: For this case series we used the TriNetX search, then refined our cohort to only include patients with type B lactic acidosis and excluded patients with AKI also due to hypotension/hypoperfusion. We identified 10 patients admitted to the Medical University of South Carolina between 2014 and 2022 with an underlying hematological malignancy with type B lactic acidosis, TLS, and AKI. Renal outcomes were assessed based on death, dialysis, and transfer to hospice through 6 months.

Results: Death occurred in 100% of patients with an underlying hematological malignancy presenting with TLS, type B lactic acidosis and AKI, with median time from onset of TLS to death of 4.5 days (SD 55). 70% of patients began dialysis with median time to initiation following TLS diagnosis of 1 day (SD 1.3), and median time to death following dialysis initiation of 2 days (SD 25.4). Median pH was 7.29 (SD 0.08), median lactate 8.6 (SD 5.6), LDH 5817 (SD 7558), uric acid 15.45 (SD 7.34), peak SCr 3.7 (SD 1.53), phosphorous 8.6 (SD 3.5).

Conclusions: Patients in our cohort had very poor rates of survival and dialysis did not appear to change outcomes. Given poor outcomes in these patients we suggest dialysis may have limited utility in our cohort and the focus of care should be comfort.

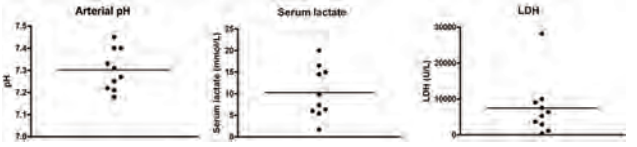


Figure 1. Median peak arterial pH, serum lactate, and LDH of each patient.

FR-PO264

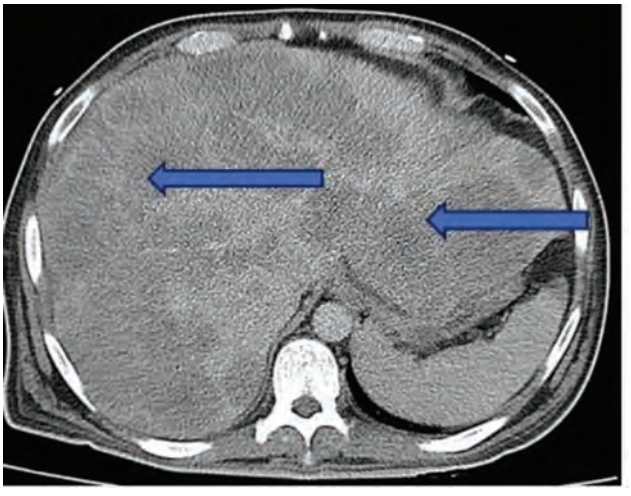
Type B Lactic Acidosis Secondary to Metastatic Liver Cancer in the Setting of Normal Renal Function: A Case Report

Tracy-Ann Poyser, Chidinma P. Amakiri, Steven Pham. *Unity Health White County Medical Center, Searcy, AR.*

Introduction: Lactic acidosis occurs when lactate levels are greater than 4 mmol/L. It is due to an overproduction of lactate or decreased metabolism. There are two types, Type A and Type B. Type B is more common in hematological conditions, such as multiple myeloma, leukemia, and lymphoma.

Case Description: We present a case of a 43-year-old male with Type B lactic acidosis secondary to stage IV colon cancer with metastasis to the liver. Computed Tomography scan of the abdomen and pelvis showed extensive hepatic metastasis with marked hepatosplenomegaly and mild ascites. He had a lactic acid of 16.5 mmol/L, glucose of 52 mg/dl, and bicarbonate of 8 mEq. He received aggressive fluid resuscitation, IV antibiotics, and bicarbonate supplementation. However, his lactic acid worsened, requiring urgent dialysis. Despite dialysis, he showed no significant improvement, and was placed on hospice.

Discussion: Type B lactic acidosis can arise as a complication of solid and, more commonly, hematological malignancies, such as multiple myeloma, lymphoma, and leukemia. It is a rare complication that requires prompt diagnosis and treatment of the underlying condition. Treatment modalities, such as hemodialysis and chemotherapy, have been studied, but the prognosis remains poor. Our patient with type B lactic acidosis received hemodialysis, sodium bicarbonate, and glucose supplementation with marginal initial improvement, followed by worsening lactic acidosis. Due to the late stage of his cancer, chemotherapy was not beneficial. There is a paucity of information due to the rarity of studies on severe lactic acidosis. More studies are needed to better understand the pathogenesis of type B lactic acidosis secondary to hematological malignancies to improve patient outcomes.



Imaging showing extensive liver metastasis with significant hepatosplenomegaly and ascites.

FR-PO265

Beyond Tumor Regression: Exploring the Fatal Consequences of Immune Checkpoint Inhibitor (ICI)-Induced Triple M Syndrome and Myoglobin Nephropathy

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Introduction: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy. Despite showing remarkable tumor regressions and anti-tumor efficacy, these agents can also lead to life-threatening immune-related adverse events (irAEs). One exceedingly rare irAE is ICI-induced myocarditis with myositis/myasthenia overlap, also known as Triple M Syndrome. We present a case of Triple M Syndrome with acute kidney injury and provide a review of the clinical course.

Case Description: A 76-year-old male with melanoma was treated with a single dose of adjuvant Nivolumab. Two weeks later, he was admitted with sudden-onset angina, respiratory failure requiring emergent intubation, and neurological symptoms.

Physical exam revealed bilateral ptosis, diplopia, and proximal muscle flaccid paralysis. Laboratory workup was notable for increasing troponins to 4783ng/L, markedly elevated liver enzymes, and elevated creatinine kinase (CK) of 6806 U/L. Serum myoglobin was elevated to 3799 mcg/L, aldolase was 100 U/L, and acetylcholine receptor antibodies were detected. EKG did not show ischemic features. Electromyography demonstrated significant abnormalities. The patient was diagnosed with ICI-induced myocarditis, myositis, and myasthenia gravis. Pulse dose steroid therapy was administered followed by plasma exchange. Persistent elevation of serum and urine myoglobin, even after CK normalization, resulted in pigment nephropathy requiring continuous renal replacement therapy (CRRT). Anti-thymoglobulin was administered for refractory irAE- but no benefit was observed. He ultimately expired. Autopsy revealed severe tubular injury with myoglobin casts, no ICI related interstitial findings, and focal lymphocytic myocarditis.

Discussion: This case presents Triple M Syndrome, an irAE characterized by myocarditis, myositis, and myasthenia overlap. The patient exhibited profound elevation in troponin and myoglobin levels, while CK levels were less remarkable. This suggests a predominant myocardial injury with a lesser extent of skeletal muscle involvement. Important to note is that the diagnosis of myositis relied on troponin and CK, while CK and myoglobin were necessary for diagnosing myoglobin pigment nephropathy. In summary, recognizing Triple M Syndrome as an irAE causing renal injury from myoglobin, and not necessarily only interstitial disease, is crucial.

FR-PO266

Ifosfamide-Induced Fanconi Syndrome: A Complication that Cannot Be Overlooked

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Introduction: Fanconi syndrome (FS) is a severe dysfunction of the proximal tubule, which causes urinary loss of glucose, amino acids, phosphorus, bicarbonate and potassium. Ifosfamide (IFO)-induced FS is reported in 1.4-5% of children being treated for solid tumors, but few cases have been reported in adults. We describe a case of FS in an adult who was taking IFO for sarcoma treatment.

Case Description: A male, aged 29, diagnosed with cervical fibrosarcoma at the age of 13. In September 2021, with the third recurrence of the disease, he initiated chemotherapy (CT) with IFO, vincristine and actinomycin D. On the 24th week of CT, after 48g/m^2 of IFO, the patient presented muscle weakness and renal dysfunction (Cr mg/dL 1.3), and CT was suspended. In September 2022, six months after interrupting CT, he was admitted with disabling muscle weakness (unable to walk) and polyuria (8.0 L/day). Laboratory: Cr 4.2; potassium (mEq/L) 2.6, phosphorus (mg/dL) 1.7, pH 7.19, bicarbonate (mEq/L) 13, chlorine 113 mEq/L, sodium 135 mEq/L, anion gap 12; urine: density 1007, glucose 4+ (normal blood glucose), no hematuria, 24h proteinuria 1.3 g/day, potassium in isolated sample 59 mEq/L and phosphorus excretion fraction 94%. After correcting electrolytes and metabolic acidosis, the patient's weakness improved significantly, urine output normalized and Cr was 3.2. He is currently undergoing outpatient follow-up, using chelated phosphorus, potassium citrate, sodium bicarbonate and potassium chloride. January 2023 exams: Cr 3.3, phosphorus 3.2, potassium 4.6, bicarbonate 18.

Discussion: IFO toxicity appears to be dose dependent and occurs mainly with cumulative doses greater than 45 g/m^2. It is believed that IFO nephrotoxicity is due to the action of metabolites, acrolein and chloroacetaldehyde in the renal tubules. It is important that oncologists and nephrologists are aware of the possibility of FS and nephrogenic diabetes insipidus with the use of IFO, so as to avoid serious and fatal complications. Our patient presented muscle weakness and altered renal function, IFO was suspended, but FS was not diagnosed at the time. We emphasize the importance of monitoring renal function and electrolytes in cancer patients undergoing CT, mainly because a wide range of old and new drugs is available.

FR-PO267

Prevalence of Cisplatin-Induced Nephrotoxicity in an Inner-City Population in the Bronx, New York

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Background: Cisplatin is a commonly used chemotherapeutic agent with known nephrotoxicity. Studies evaluating its nephrotoxicity in minorities are limited. We assessed the incidence of kidney injury among our adult patients receiving cisplatin.

Methods: Retrospective review of records for adult patients receiving cisplatin from Jan 2021 to Jan 2023 was conducted. Serum Creatinine (SCr) and estimated glomerular filtration rate (eGFR) were obtained at baseline and within 30 days after cycles 1, 2, and 3 of Cisplatin. KDIGO definition was used to diagnose AKI.

Results: Of the 47 patients included in the analysis, 51.1% were male (n=24), median (range) age was 58 years (19-78). 42.6% were Black (n=20), 21.3% White (n=10) and others consisting of Pacific Islanders, American Indians, and Asians represented 36.2% (n=17). 80% of whites were Hispanic. The median number of cisplatin cycles was 4 (range: 1-11). Median baseline eGFR and SCr was 99.7ml/min and 0.80 g/dl, respectively. Blacks had a mean baseline GFR of 86.1ml/min, while non-Blacks had a mean of 100.86 ml/min (t=2.223, p=0.031). The median eGFR and SCr at the last follow-up after cisplatin was 77.80 ml/min and 0.99 g/dl, respectively. 10.6% of the patients developed AKI after the first dose of Cisplatin. There was no statistically significant correlation between race, sex, BMI or the use of immune checkpoint inhibitors and development of AKI. Repeated measures ANOVA test was conducted to evaluate the change in patients' creatinine when measured before cisplatin, after 1st, 2nd and 3rd cycle. The results indicated a statistically significant rise in creatinine level following cisplatin therapy [Wilks' Lambda = 0.003, F (1, 26) = 13.7, $\eta^2 = 0.44$].

Conclusions: Our retrospective study in a minority based, low socioeconomic status adult population highlights the progressive risk of kidney injury following each cycle of cisplatin therapy, indicating risk for chronic dose-dependent cisplatin-induced nephrotoxicity. Patients from low socioeconomic backgrounds and minority populations may be at higher risk for renal dysfunction and progression to CKD. Further prospective studies targeting this specific population are warranted to validate these findings and develop tailored interventions to reduce cisplatin-induced nephrotoxicity.

FR-PO268

FGFR Inhibitors in Cholangiocarcinoma and Urothelial Bladder Cancer Resulting in Hyperphosphatemia, Low Parathormone, and High Calcitriol: The Side Effects of FGF23 Blockade

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Introduction: Hyperphosphatemia is the most frequent adverse event in patients treated with FGFR (fibroblast growth factor receptor) inhibitors. FGF23 and FGFR1 play key roles in phosphate homeostasis and hyperphosphatemia results from FGFR1 inhibition.

Case Description: Case series of patients with urothelial bladder cancer and cholangiocarcinoma (CCA) taking FGFR inhibitors (erdafitinib or futibatinib) at AC Camargo from July 2021 - February 2023. Creatinine, serum phosphate, parathyroid hormone (PTH), 1,25-dihydroxyvitamin D (1,25 vitD), 24h urinary phosphate level were measured after 4 weeks of therapy. As described in the table below, we included 4 patients with cholangiocarcinoma and 2 with urothelial bladder cancer. Hyperphosphatemia occurred in 100% of the patients, with serum phosphate ranging from 6 to 7.5 mg/dl, accompanied by decreased urinary phosphate. PTH was suppressed in 2 of the patients, whereas high 1,25 vitD was seen in half of them. Hyperphosphatemia caused a temporary interruption of treatment, to control serum phosphate. Also, phosphate binders were administered to all patients. Acetozolamide was admistered to patients 3 and 4, but had no effect on serum phosphate and caused worsening of dry mouth and metabolic acidosis. Ungual lesions were present in all cases and eye toxicities, such as serous retinal detachment, were seen in 4.

Discussion: FGFR1 blockade caused by FGFR inhibitors is associated with hyperphosphatemia, hypophosphaturia, high 1,25 vitD and PTH suppression, as described in animal models of FGF23 blockade. The metabolic changes caused by these drugs are a undesirable, but important side effects that might limit their use in many patients affected by cancer with genetic alterations in FGFRs.

Age/Sex	Cancer	Genetic alteration	Creat (mg/dl)	iCalcium (mmol/L)	P (mg/dl)	1,25 vitD (pg/ml)	PTH (pg/ml)	Urinary P (mg/24h)
62; M	Urothelial	FGFR3-TACC3	1,6	1.40	6.1	n/a	56	n/a
61; F	CCA	FGFR2	0.9	1.41	7.0	47	20	30
52; F	CCA	FGFR2-BICC1	0.7	1.35	6.9	123	67	365
73; M	CCA	FGFR2	1.6	1.31	6.0	93	107	155
67; M	Urothelial	FGFR3	1.3	1.28	7.5	n/a	17	103
75; F	CCA	FGFR2	0.8	1.20	6.1	17	40	36

CCA = cholangiocarcinoma; P = Phosphate; iCa = Ionized Calcium; Creat = creatinine; 1,25 vitD = 1,25-dihydroxyvitamin D; n/a = not available

FR-PO269

Abiraterone-Associated Syndrome of Mineralocorticoid Excess (SAME)

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Introduction: We present a patient with abiraterone-associated SAME and discuss its pathophysiology and treatment.

Case Description: A 77-year-old man with metastatic prostate adenocarcinoma was treated with abiraterone 1 gram daily. Prednisone 5 mg daily was added 3 months later. Soon after chemotherapy initiation, his plasma potassium declined (Figure 1), and did not improve despite potassium replacement requiring hospitalization. He was volume overloaded with signs of urinary potassium wasting (Table 1). Further investigations revealed an ACTH (adrenocorticotropic hormone) mediated SAME. Discontinuation of abiraterone with amiloride use improved serum potassium and decreased kaliuresis.

Discussion: Abiraterone acetate is a drug that irreversibly inhibits Cytochrome P450c17 with the suppression of 17 α-hydroxylase (17α-OH) and C17,20-lyase and is used for the treatment of prostate cancer. The inhibition of 17α-OH in the Zona Fasciculata causes an ACTH-mediated SAME due to accumulation of corticosterone and deoxycorticosterone. Therefore, it is co-administered with prednisone to inhibit ACTH. However, low-dose prednisone may not effectively suppress ACTH in all the patients on abiraterone. High dose steroids or spironolactone use is discouraged as they may be associated with worse outcomes. Potassium wasting can be managed effectively with

amiloride and low-dose steroids. Despite prednisone use, the possibility of abiraterone inducing SAME should be entertained in patients with hypertension, volume-overload, and/or hypokalemia.

Laboratory values

ACTH (pg/dl) (Ref 6-50) 220, Plasma Aldosterone Concentration (ng/dl) <1, Plasma Renin Activity (ng/ml/hr) 0.13, Plasma Corticosterone (ng/dl) (Ref AM 59-1293) >10,000, Deoxycorticosterone (ng/dl) 100, Plasma Total CO2 (mEq/L) 32 Arterial pH 7.46, Spot urine K/cr (mEq/gm): on day of admission - 206 and 4 days later while on amiloride- 59

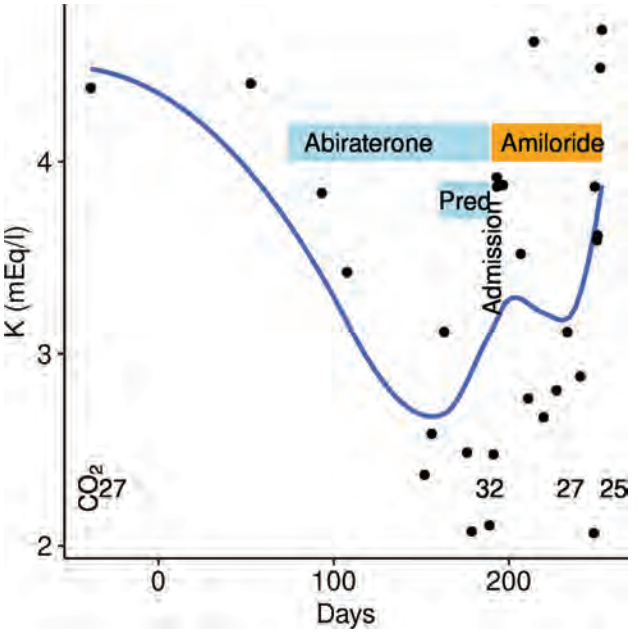

Figure 1: A graph showing plasma K (LOESS smoothed) and total CO_2 (mEq/L) since prostate-cancer diagnosis.

FR-PO270

Lysozyme Toxicity Causing Proximal Tubulopathy in Patient with Acute Monocytic Leukemia

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Introduction: Acute leukemia is a common malignancy that is often associated with acute kidney injury. While rare, lysozyme-induced nephropathy can occur in patients with monocytic leukemia. This condition is caused by overproduction of lysozyme, which is released into blood circulation, filtered by the glomerulus, and reabsorbed by the proximal tubule. The resulting tubular injury can lead to renal insufficiency and electrolyte imbalances.

Case Description: 22 years old male was admitted to the hospital with fever. Upon admission, labs revealed marked leukocytosis, white blood cell count of 114.94 k/uL. Bone marrow biopsy confirmed a diagnosis of acute monoblastic/monocytic leukemia. The patient was noted to have acute kidney injury with serum creatinine of 1.48 mg/dL. Urine microscopy was with numerous granular casts and few eumorphic red blood cells. Kidney ultrasound showed normal-sized kidneys, increased parenchymal echogenicity and no hydronephrosis. After rapid resolution of AKI to a baseline creatinine of 0.6mg/dL patient was noted to have hypokalemia with serum potassium of 3.2 mmol/L, hypophosphatemia with phosphorus of 1.4 mg/dL (normal range 2.2-4.5mg/dL) and uric acid levels of 1.3 mg/dL (normal range of 3.5-8.5mg/dL). Given the high percentage of blasts and monocytes, lysozyme-induced nephropathy with Fanconi syndrome was considered. Fractional excretion of potassium was > 10%, indicating increased renal loss of potassium. Additional testing revealed elevated serum lysozyme levels (>10.00 ug/mL; normal range 0 – 2.75 ug/mL), supporting a diagnosis of lysozyme-induced nephropathy. Patient was started on aggressive fluid hydration; electrolytes were replaced. The patient was eventually started chemotherapy with normalization of white blood cell count and renal function.

Discussion: Lysozyme-induced nephropathy is a rare complication of acute or chronic monocytic neoplasms associated with overproduction of lysozyme resulting in elevated serum and urine levels. Lysozyme is freely filtered by the glomerulus and reabsorbed in the proximal tubule. Lysozyme can be toxic to proximal tubule cells leading to acute tubular injury, renal insufficiency, hypokalemia due to renal potassium wasting and Fanconi syndrome. Kidney biopsy can be helpful to establish a diagnosis. Recognition of this rare etiology for AKI is important and may guide management of acute and chronic leukemias.

FR-PO271

Imatinib-Associated Fluid Retention

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Background: Imatinib is one of the first tyrosine kinase inhibitors and is used in several conditions based on effects on receptors like BCR-ABL, the platelet-derived growth factor receptor (PDGFR), and stem cell factor (SCF)/c-kit tyrosine kinases. It has been associated with fluid retention (FR) and the mechanism behind this is largely unknown. Here we provide laboratory data that suggests imatinib affects aquaporin 2 (AQP2) expression proposing a theory behind imatinib associated FR.

Methods: Mouse kidney inner medullary collecting duct cell line (IMCD-3) cells are grown on coverslips in 24-well plate with DMEM containing 10% fetal bovine serum to 95% confluency. The cells are starved in 1 ml/well plain DMEM F12 medium for 2 hours prior to treatment. They are then treated with DMSO as control or with either 5 μM imatinib for 1 hour or 100 nM AVP for 30 min. After treatment, cells are washed, fixed, permeablized, and incubated with anti-aquaporin 2 antibody and Alexa Flor Goat anti-rabbit IgG 488. The cells are counter-stained by DAPI to visualize nuclei and stained coverslips then are mounted to slides and visualized under fluorescence microscope.

Results: IMCD-3 cells express AQP2 with an even distribution in cytosol and membrane in untreated control cells. Stimulation of IMCD-3 with vasopressin promotes a dramatic membrane distribution of AQP2. Similar to vasopressin, treatment of IMCD-3 cells with imatinib also induced a profound membrane distribution.

Conclusions: To our knowledge, this is the first evidence that treatment of IMCD-3 with imatinib enhances AQP2 membrane distribution. The bidirectional control of AQP2 trafficking from cytoplasm to the apical plasma membrane is regulated by vasopressin/vasopressin receptor (VP/VPR) pathway and filamentous actin (F-actin) polymerization/depolymerization. The signaling pathways can be activated by growth factor receptors such as EGFR and PDGFR which also cross-talk to VP/VPR. Abl tyrosine kinases likely play important roles as downstream receptors in regulating actin cytoskeleton remodeling and intracellular trafficking. Activation of Abl tyrosine kinases increases cell surface expression of EGFR. Therefore, inhibition of Abl tyrosine kinases by imatinib may lead to blockade of the EGF/EGFR signaling that regulates AQP2 distribution and FR. Further study of Abl signaling as a potential regulator in AQP2 trafficking is warranted.

Funding: Private Foundation Support

FR-PO272

The Conundrum of Normal Kidney Endothelial HLA-DR Clarified by Checkpoint Inhibitor Toxicity: A Role for Microvascular Endothelium in Peripheral Tolerance

Kimberly A. Muczynski. *University of Washington, Seattle, WA.*

Background: Years ago we reported high constitutive expression of HLA-DR on microvascular endothelial cells of normal human kidney in the absence of inflammation. This surprised us and seemed incongruent with what is known about HLA class II antigen processing. Peptides bound to class II molecules are derived from the uptake of extracellular proteins which get processed intracellularly and then exported to the cell surface bound to HLA-DR where they can be recognized by specific T cell receptors. Would it, therefore, not be dangerous to have kidney endothelial cells constitutively express HLA-DR on their surface where they might encounter and activate circulating T cells?

Methods: We used flow cytometry and and T cell activity assays to investigate the role of HLA-DR on human kidney microvascular endothelial cells (KMEC).

Results: First, we show T cell proliferation and gamma interferon secretion of sensitized T cell when influenza hemagglutinin peptide is presented by KMEC of the appropriate HLA-DR specificity. Blockade of CD58 or HLA-DR reduces T cell activation while blockade of CD274 (PD-L1) enhances activation. **Second**, T cell co-stimulatory and inhibitory molecules on normal native and transplanted kidneys are identified by flow cytometry. CD274 expression is high on all KMECs and T cells within the kidney express CD279 (PD-1). **Third,** biopsies of acute kidney injury associated with checkpoint inhibitors that block the PD-1, PDL-1 axis show an intense perivascular lymphocytic infiltrate. **Finally,** human fetal kidneys express endothelial HLA-DR and CD274 at a similar time in development suggesting a fundamental property of the endothelial cells rather than resulting from an immune response.

Conclusions: Taken together, we propose a mechanism of peripheral tolerance whereby KMEC HLA-DR limits activation of sensitized T cells, even if a bound peptide is recognized, because of the constitutive high-co-expression of CD274 (PDL-1).

Funding: Private Foundation Support

FR-PO273

Acute Interstitial Nephritis and Its Recurrence due to BRAF-MEK Inhibitors for Melanoma

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Introduction: The efficacy of BRAF – MEK inhibitor therapy on survival in advanced melanoma has resulted in its widespread use. We describe two cases of biopsy proven Acute Interstitial Nephritis from BRAF-MEK inhibitors.

Case Description: *Case One* 51 year-old with melanoma, on binimetinib and encorafenib for two years developed acute kidney injury with creatinine of 2 mg/dL from

baseline of 0.76 mg/dL two weeks ago. Labs revealed leukocytosis to 17,000, urinalysis with 41 WBC, 3 RBC, urine protein-creatinine 1.5 g/g, urine albumin-creatinine 44 mg/g and a negative urine culture. Encorafenib and binimetinib were held. Other work up revealed total protein 7 g/dL, elevated globulin 4.9 mg/dL 1, ANA 1:640, anti-dsDNA 1:80, anti-RF 23 IU/mL. Kidney biopsy revealed AIN. Prednisone was initiated at 1mg/kg/day, with return of baseline kidney function in four weeks, at which time prednisone was tapered off. She is undergoing surveillance monitoring for melanoma off BRAF-MEK inhibitors, with plan to switch to alternative drug within the class should there be recurrence of disease. *Case Two* 64-year-old with metastatic melanoma on vemurafenib and cobimetinib for six months developed AKI with creatinine of 4 mg/dL from baseline of 1.2 mg/dL. Kidney biopsy revealed AIN. She was treated with prednisone 1 mg/kg/day and switched to encorafenib and binimetinib. Two months later, she developed another AKI, presumably AIN and steroids were prescribed. She was switched to immunotherapy, however due to progression of melanoma dabrafenib and trametinib was initiated, this time with prophylactic low dose prednisone at 10 mg daily. Her kidney function is improved with creatinine of 2 mg/dL and CKD stage 4.

Discussion: We report the first case series of AIN after BRAF-MEK inhibitors for advanced melanoma. We describe our approach to therapy which includes initial treatment with steroids to suppress the immune response, followed by switch to alternative drug, possibly within the same class. However, as described in case two, our patient developed an immune reaction to the second agent as well suggesting that the reaction is likely a class effect. This was offset by prophylactic low dose of steroids given at the time of re-initiating treatment with a BRAF-MEK inhibitor.

FR-PO274

An Unusual Case of Acute Tubulointerstitial Nephritis (ATIN) with CD8-Positive Cytotoxic T Cell Infiltrate

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Introduction: ATIN is a cause of acute kidney injury (AKI) characterized by tubulointerstitial inflammatory infiltrate, primarily lymphocytic and eosinophilic. We present a case of ATIN with an almost exclusive CD8+ cytotoxic T-cell infiltrate.

Case Description: A 65-year-old man with history of hypertension, nephrolithiasis, prostate cancer treated with brachytherapy, smoldering myeloma, thymoma s/p thymectomy, CD8+ granulomatous lymphadenitis on lymph node biopsy 2 years earlier and family history of autoimmunity presented with AKI amid NSAID use. Exam was normal. Patient discontinued NSAIDs. Work-up revealed proteinuria 378mg/d, serum creatinine 2.6(baseline 1.3)mg/dl, free lambda light chains on UPEP, serum lambda15mg/dl, K/L ratio 0.03 (stable). Urinalysis depicted protein 100mg/dL without abnormal cells or casts. HIV, hepatitis B/C, HTLV-I/II serologies, Parvo, CMV, AAV and EBV PCR were negative. c-ANCA was positive, ANA, dsDNA, PR-3, MPO antibodies negative, complements were normal. Kidney biopsy showed severe ATIN with CD8+ dominant T cell infiltrate, moderate interstitial fibrosis, no immune complex or amyloid deposition or glomerular crescents. Suspicion for a T-cell lymphoproliferative disorder was entertained. Hematologic workup was negative for thymoma recurrence or myeloma progression including flow cytometry. T-cell receptor studies were polyclonal. Patient was started on prednisone, creatinine improved to 2mg/dl after 2 weeks.

Discussion: This is a case of ATIN with an almost exclusively, atypical CD8+ cytotoxic T-cell infiltrate. Based on prior history, we suspect the underlying cause may be autoimmune dysregulation or T cell disorder. A careful workup to rule out active viral infections and underlying hematologic disorder was performed before starting immunosuppression with close follow up.

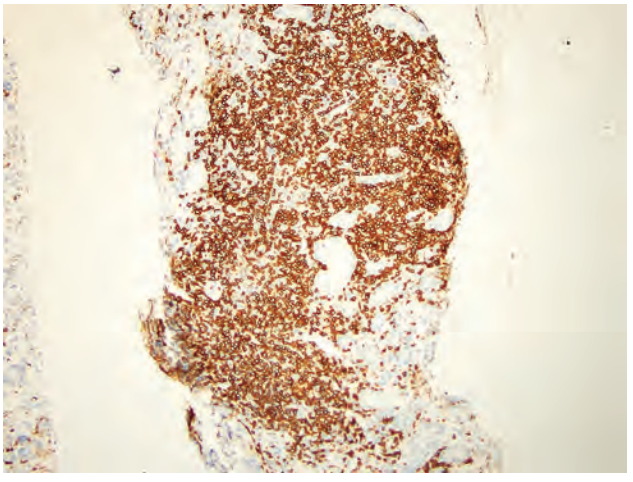

Figure 1. Renal biopsy illustrating tubulointerstitial nephritis with CD8 cytotoxic T cell infiltrate, CD8 IHC x20

FR-PO275

Pauci-Immune Necrotizing and Crescentic Glomerulonephritis due to Pembrolizumab

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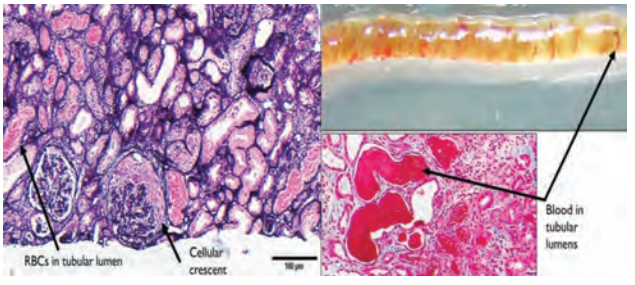
Introduction: Immune checkpoint inhibitors (ICI) have trailblazed the treatment of cancer in the past decade. However, these drugs are marred with occurrence of Immune-related Adverse Effects (irAEs). Most commonly reported renal irAE is acute tubulointerstitial nephritis(AIN). Lately, cases of acute kidney injury(AKI) from podocytopathy and glomerulonephritis with ICI are noted but true incidence is likely underestimated from missed diagnosis and under-reporting. We present an illustrative case of an elderly female with a rare manifestation of AKI during treatment with pembrolizumab(Keytruda) with complete recovery due to prompt diagnosis and effective therapy.

Case Description: 74-year-old female undergoing treatment for metastatic squamous cell carcinoma of head and neck presented to Nephrology clinic for evaluation of AKI, hematuria and new-onset proteinuria. 15 days ago, she received a third dose of Keytruda. Creatinine had rapidly risen to 2.8mg/dL from baseline 0.5mg/dL. Urine protein-creatinine ratio of 1.6g/g, urine sediment with numerous acanthocytes and RBC casts. Renal biopsy showed acute pauci-immune focal necrotizing glomerulonephritis with 30% cellular crescents, granular mesangial staining for IgM and C3 on immunofluorescence and foot process effacement by electron microscopy. Keytruda was discontinued;she was treated with methylprednisolone, cyclophosphamide and rituximab. Kidney function normalized within 8 weeks.

Discussion: The case highlights importance of clinical suspicion and knowledge of the heterogeneity of pathological findings with renal irAEs on ICI therapy. Emerging data suggest incidence of AKI from 2-20% with Keytruda, a highly selective monoclonal IGg4-kappa antibody against PD – 1 receptor. Renal irAEs can occur during and upto 2 months after therapy cessation. Many times, AKI is presumptively treated with steroids for AIN. The presence of glomerular hematuria, proteinuria or persistent AKI despite steroids warrants a renal biopsy as most patients can recover completely with early diagnosis and prompt treatment and possibly tolerate rechallenge of ICI.



Clockwise:LM Silver stain, Hand lens-biopsy core, LM H&E

FR-PO276

Membranoproliferative Glomerulonephritis (MPGN) Associated with Atezolizumab

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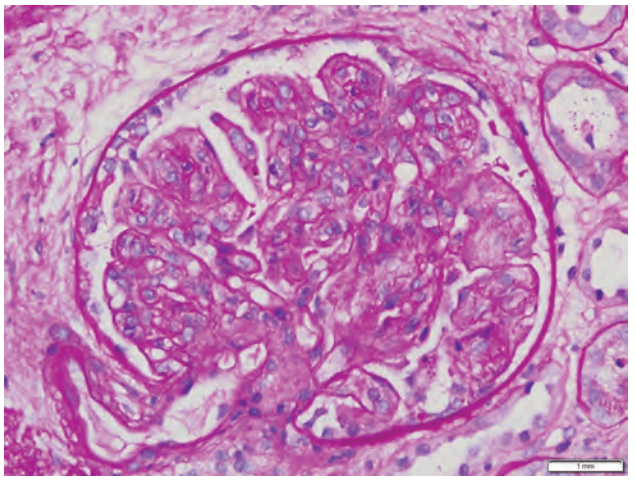
Introduction: Immunotherapy is a revolutionary approach to cancer management, particularly in advanced malignancies that have progressed despite traditional chemotherapy. Atezolizumab is a humanized monoclonal antibody immune checkpoint inhibitor that binds to programmed death ligand 1 (PD-L1) to selectively prevent the interaction between the PD-1 and B7.1 receptors. We present a unique case of a patient with acute kidney injury associated with nephrotic syndrome after starting atezolizumab for metastatic pancreatic carcinoma.

Case Description: 64 year old female with a past medical history significant for stage 1A endometrial cancer status post (s/p) total abdominal hysterectomy, biliary obstruction s/p stent for locally advanced unresectable pancreatic duct adenocarcinoma FOLFIRINOX completed chemoradiation. She was enrolled in i LOKON - 001 immunotherapy trial with oncolytic virus + atezolizumab + abraxane + gemcitabine and received 9 cycles. She was admitted for her complaints of shortness of breath and bilateral pedal edema. Her had hypertensive urgency with anasarca on clinical exam. Labs showed acute kidney injury with urinalysis positive for protein and blood. Further work up revealed nephrotic range proteinuria with UPCR 8 g/g. ANA, complements, Urine electrophoresis were negative. Serum electrophoresis showed IgG kappa monoclonal band. Anti-PLA2R receptor normal. Renal vein doppler was negative for renal vein thrombosis. Renal biopsy showed MPGN with full house pattern, immune complex deposit in subendothelium thought to be from atezolizumab. She was taken off the immunotherapy trial and started on diuretics and steroids with significant improvement in her proteinuria and anasarca.

Discussion: Nephrotic syndrome (NS) in this patient was thought to be related to atezolizumab as secondary work up for MPGN was all negative. NS resolved after stopping atezolizumab and starting steroids which is suggestive of atezolizumab related nephrotoxicity.



FR-PO277

Acute Tubulointerstitial Nephritis and Minimal Change Disease After Administration of Lenalidomide

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Introduction: Several case reports have raised concern regarding association between lenalidomide and acute tubulointerstitial nephritis (ATIN) or minimal change disease (MCD), mostly described in patients with plasma cell dyscrasia. Here we report a case of concomitant ATIN with MCD after lenalidomide initiation for a patient with myelodysplastic syndrome (MDS).

Case Description: A 68-year-old male with a history of MDS, hypertension, and coronary artery disease presented with a 2-week history of right flank pain, anasarca, and dark urine. He reported a 40-pound weight gain since the symptoms began. He had been taking lenalidomide for 7 months and was awaiting allogeneic hematopoietic stem cell transplantation. He was taking ibuprofen 2-3 tabs (200mg) per week over the last few years and denied other medication changes or contrast exposure. On admission, serum creatinine was 6.9 mg/dl (baseline 0.6-0.8 mg/dl) with albumin of 1.5 g/dL (baseline 3.5 g/dL). A urinalysis showed a specific gravity of 1.045, 51-100 WBC/hpf, 51-100 RBC/hpf, and many granular casts. Urine protein quantification was > 2000 mg/dl. Renal ultrasound showed medical renal disease. Hospital course was complicated by continued renal deterioration requiring initiation of hemodialysis. His renal biopsy showed mild acute tubulointerstitial nephritis with scattered eosinophils and some chronic ischemic changes. Ultrastructural studies revealed diffuse podocyte injury and extensive foot process effacement consistent with minimal change disease. The patient was started on prednisone 60mg daily with an ensuing taper initiated at discharge. At 13 weeks the patient reported near total renal recovery with cessation of hemodialysis needs.

Discussion: Lenalidomide has been reported to induce ATIN. To the best of our knowledge, there is only one case report of MCD associated with lenalidomide administration in a patient with Waldenström macroglobulinemia. NSAIDs can cause acute renal failure, ATIN and nephrotic syndrome, including MCD. NSAID-associated MCD may be present with or without ATIN, usually after long-term use. The elements of the history in our case suggests that consistent use of lenalidomide might have triggered the development of MCD with concurrent ATIN on a background of minimal NSAID use. Furthermore, rarely has MCD been reported in the setting of both MDS and lenalidomide exposure.

FR-PO278

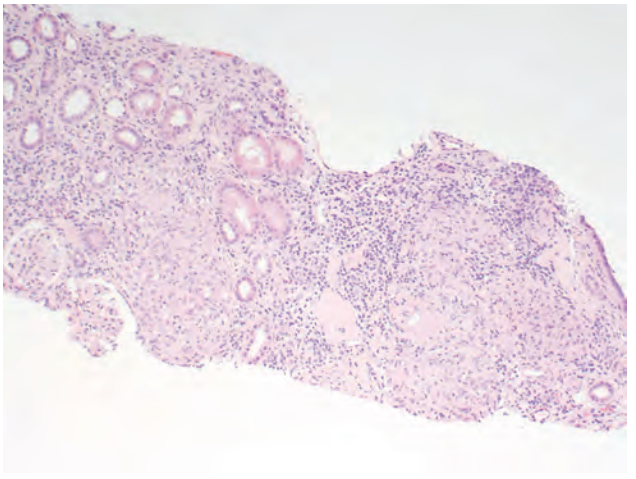
Immunotherapy-Related Renal Sarcoidosis in a Patient with Metastatic Melanoma

Avinash Rao Ullur, Rohan John, Abhijat Kitchlu. *University of Toronto, Toronto, ON, Canada.*

Introduction: Immune checkpoint inhibitors (ICIs) are widely used as standard of care therapy in management of metastatic melanoma. There have been various reported kidney complications associated with these treatments, though immunotherapy-related sarcoid-like reactions (SLRs) with kidney involvement are rare.

Case Description: A 57-year-old lady was diagnosed with metastatic melanoma stage IV and received first line Ipilimumab/Nivolumab followed by Nivolumab monotherapy q3 weekly. Her therapy was interrupted by an asymptomatic rise in serum creatinine (sCr) from a baseline of 0.9 mg/dL to 2.14 mg/dL with an incidentally detected serum calcium (sCa) of 13.23 mg/dL. She was managed with hydration & bisphosphonates. As sCr and sCa remained elevated with further ICI challenges, her treatment was changed to targeted therapy with oral Dabrafenib/Trametinib. Her melanoma remained in remission, but she persisted to have high sCr and sCa. Metabolic work-up revealed presence of hypercalciuria and elevated serum 1,25-(OH)2 vitamin D. A CT chest was suspicious for granulomatous disease, but bronchoalveolar lavage result was equivocal. The patient underwent a kidney biopsy which revealed findings consistent with sarcoidosis. She initially responded to oral steroids. As her disease remained steroid dependent, therapy was switched to oral mycophenolate mofetil. Patients' sCr has remained stable at 1.5 mg/dL after 4 months of follow up.

Discussion: In the presented case, it appears that renal SLR was related to immunotherapy as kidney dysfunction and hypercalcemia occurred after the patient was initiated on treatment. Renal SLR may also have been perpetuated with continuation of the treatment with targeted therapy, as Dabrafenib/Trametinib treatment has also been associated with SLR. In such situations, treating SLRs with steroids or immunosuppressive agents may be a reasonable option to allow continuation of therapy.



Interstitial nephritis with non-necrotizing granulomas.

FR-PO279

Acute and Chronic Kidney Dysfunction Associated with Anaplastic Lymphoma Kinase (ALK) Inhibitors

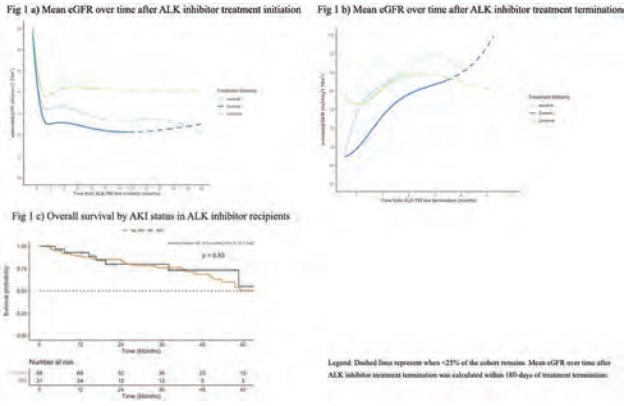
Avinash Rao Ullur,[1,2] Louis Pinard,[3] Louis C. Everest,[2] Khaleeq Khan,[2,4] Luna J. Zhan,[2,4] Geoffrey Liu,[2,4] Abhijat Kitchlu.[1,2] *[1]University of Toronto, Toronto, ON, Canada; [2]University Health Network, Toronto, ON, Canada; [3]Universite de Montreal, Montreal, QC, Canada; [4]Princess Margaret Hospital Cancer Centre, Toronto, ON, Canada.*

Background: Anaplastic Lymphoma Kinase (ALK) inhibitors have marked activity against ALK-positive non-small cell lung cancers (NSCLC). Kidney adverse effects of ALK inhibitors have been increasingly reported, though some may relate to impairment of creatinine secretion.

Methods: We performed a retrospective observational study of patients who received ALK inhibitors for NSCLC between 2010-2022. The primary outcome was incidence of acute kidney injury (AKI) within 90 days of ALK start, and chronic kidney disease (CKD) during treatment. AKI and CKD were defined via KDIGO criteria, using the creatinine-based CKD-EPI equation. We performed logistic regression for AKI risk factors and used Kaplan-Meier analysis to assess overall survival (OS) by AKI status. Spline curves were generated to estimate eGFR means over time.

Results: Among 149 Stage IIIB/IV NSCLC patients, median age was 60 years; 56% were female; 269 different TKIs were initiated: Alectinib (n=118), Ceritinib (n=30), Brigatinib (n=27), Crizotinib (n=68) and Lorlatinib (n=26). There were a total of 22 (15%) AKI events in the 90 days after initiating ALK inhibitors with 5 patients requiring treatment change due to kidney function. Figure 1 shows eGFR changes after ALK inhibitor initiation and termination. A total of 25(17%) patients developed CKD, 9 leading to treatment change. The mean eGFR for patients on Alectinib and Ceritinib was generally lower than Crizotinib. Age, hypertension, and diabetes were associated with AKI [adjusted OR (95%CI): 1.04 (1.00,1.08), 3.74 (1.50,9.54), 4.20 (1.55,11.2)]. OS did not differ by AKI status (Figure 1c).

Conclusions: There was a substantial number of AKI/CKD events observed, with a minority resulting in treatment change. Mean creatinine-based eGFR declined in the first 3 months post-ALK inhibitor start, but most patients had mild CKD during treatment, with eGFR recovering post-drug cessation. AKI did not impact OS. Our findings suggest that most patients may continue ALK TKI therapy despite kidney function changes.



FR-PO280

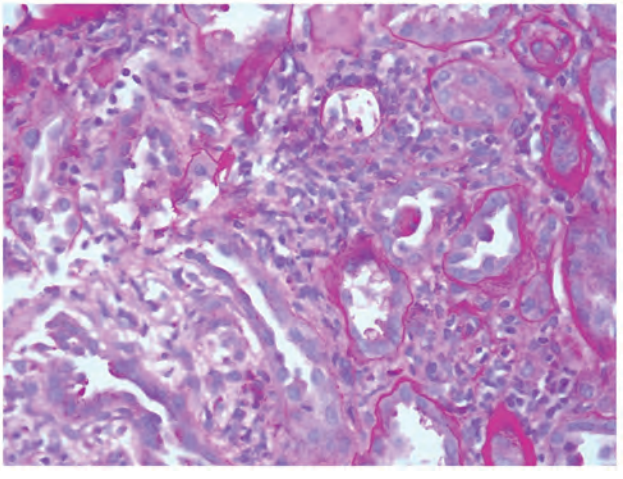
A Case of Acute Interstitial Nephritis Associated with Belvarafenib, a Novel pan-RAF Kinase Inhibitor for Metastatic NRAS Mutant Melanoma

Nabil Abu Amer, Carmen Avila-Casado, Abhijat Kitchlu. *University Health Network, Toronto, ON, Canada.*

Introduction: Belvarafenib is a potent oral type II pan-RAF kinase inhibitor that inhibits B-Raf V600E- and C-Raf-mediated signal transduction pathways and mutated Ras proteins, thereby demonstrating growth suppression of cancer with RAF or RAS mutation. This novel therapy has limited known adverse effects, with no reported kidney-related adverse events. Here, we present a case of interstitial nephritis associated with Belvarafenib treatment.

Case Description: A 79-year-old woman was diagnosed with stage IV melanoma (wild-type BRAF) with NRAS mutation on the pan-RAF agent (Belvarafenib). Eight months into the treatment, she presented to the melanoma clinic with nausea, fatigue, and severe weakness. The patient was pale on physical examination, and her vital signs were normal. Laboratory investigations revealed a serum creatinine of 260 μmol/L (from baseline 90 μmol/L) and protein trace in urinalysis with no leukocyturia or hematuria. Urine microscopy showed granular casts consistent with acute tubular necrosis. The kidney function was not improved despite hydration and discontinuing Belvarafanib. A kidney core biopsy revealed acute interstitial nephritis drug-related and acute tubular injury. She was treated with prednisolone1 mg/kg with improved renal function.

Discussion: Acute renal injury, particularly acute interstitial nephritis, is not a recognized side effect of Belvarafenib. This is the first reported case of a pan-RAF agent kidney adverse effects manifested by AIN and ATI. A literature review reported no renal adverse effects associated with pan-RAF agents. Belvarafenib is a novel agent; further research and time are required to determine its adverse effects incidence. However, clinicians must remain vigilant about the potential kidney adverse effects of this agent and consider a kidney biopsy to assess AIN in patients whose AKI does not respond promptly to discontinuing Belvarafenib and supportive care.



FR-PO281

Gemcitabine Hemolytic Uremic Syndrome (HUS) Associated with a New Complement Factor B (CFB) Mutation Successfully Treated with Eculizumab

Stephanie Lawanto, Spencer Hodgins, Daniel L. Landry, Jeffrey Mulhern, Gregory L. Braden. *UMass Chan Med School-Baystate, Springfield, MA.*

Introduction: Gemcitabine(G) HUS often causes chronic kidney disease or ESRD. We describe a patient(pt) who received a large cumulative dose of G who had a CFB mutation which caused dialysis dependency treated with eculizumab(E) successfully allowing cessation of dialysis.

Case Description: A 46 yr old woman with ER/PR positive & HER/2 negative breast cancer metastatic to her spine, liver and thoracic nodes was given G, 1500 mg on days 1 & 8 of ever 3 week cycle. After receiving 28040 mg/m2 of G she developed a BP of 160/100mmHg, dyspnea, an increase in serum creatinine from 1.3 to 3.7 mg/dl and MAHA with a Hg of 5.4 gm/dl, platelets 100,000, haptoglobin < 10 mg/dl, and LDH of 1046 IU/L & schistocytes on blood smear. C3 & C4 and ADAMTS13 were normal. Hepatitis A B&C, ANA, anti-DNA, cryos, ANCA, Shiga toxin, cardiolipin ab, rheumatoid factor, immunofioxation, INR, PTT, platelet antibodies, DAT, & direct coombs were all normal. After 2 plamaphareses a renal biopsy showed: Light: endothelial swelling, thickening of glomerular basement membranes, with double contours & intraluminal thrombi. IF :no tissue. EM: corrugated basememnt membranes with total foot process fusion and no immune deposits. She rapidly progressed to hemodialysis. Complement gene sequencing (Invitae, San Francisco, CA) showed a CFB mutation c.1937A>C (p.Tyr646Ser). She then received E 900 mg iv weekly x 4 & 1200 mg every other week for 4 months. MAHA quickly abated & after 3 months dialysis was stopped with a creatinine of 1.8 mg/dl. She died 4 months later from her cancer.

Discussion: We believe G-HUS occurs from a 2 hit hypothesis. G induces apoptosis & cell death in cultured bovine endothelial cells (AJ van Hall Cell Signal 34:86, 2017). This in the renal vessels coupled with a gain of function mutation in CFB could be enough to induce HUS. Several studies suggest E can treat G-HUS but they did not study complement mutations. Any pt with G-HUS should have complement gene testing performed & if positive E can induce MAHA remission & reverse dialysis dependency.

FR-PO282

Hyperacute Immune Checkpoint Inhibitor-Associated Acute Tubulointerstitial Nephritis (ICI-ATIN) Followed by ICI-Renal Tubular Acidosis (RTA): A Case Report

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Introduction: Hyperacute renal immune-related adverse events (irAEs) are rare. Immune-checkpoint inhibitor related renal tubular acidosis (ICI-RTA) has been described, but its true incidence is unknown. We report a case of biopsy proven hyperacute ICI-related acute tubulo-interstitial nephritis (ICI-ATIN) with probable ICI-RTA developing after completion of steroid therapy.

Case Description: A 67-year-old Skih male was referred for non-oliguric KDIGO 3 AKI (sCr 219μmol/L; baseline sCr 62μmol/L) and fever occurring 9 days after his first cycle of ipilimumab and nivolumab for treatment of metastatic clear cell renal cell carcinoma. Investigations showed pyuria (urinary leukocytes 168/μL) and subnephrotic range proteinuria (uPCR 2.42g/g). C-reactive protein was raised at 205mg/L. Renal obstruction was excluded. There was no exposure to nephrotoxic drugs. Empirical broad-spectrum antibiotics was commenced. Progression of AKI (peak sCr 351μmol/L) prompted the initiation of prednisolone (60mg/day) for treatment of presumptive ICI-ATIN, once infection screen returned negative. ATIN was subsequently confirmed on kidney biopsy. Favourable response was observed, and prednisolone was tapered over 6 weeks. ICI was not resumed. Tyrosine kinase inhibitor was commenced. Gradually worsening hypokalemia, normal-gap metabolic acidosis, hypophosphatemia were observed shortly after completion of steroid therapy. RTA was clinically suspected. However, concurrent pulmonary infection contraindicated further steroid therapy. Electrolyte/alkali replacement was commenced. Gradual dose de-escalation, but not cessation, of replacement was successful during 8 months of follow-up.

Discussion: ICI-ATIN should be suspected in all patients on ICI with AKI, regardless of timing of presentation. Differentials of AKI with fever in this context include sepsis-associated AKI, cytokine release syndrome and ICI-ATIN. Diagnosis may be challenging without kidney biopsy. An early, empiric trial of steroids may be considered as soon as infection is excluded. Limited evidence suggests that patients with hyperacute irAE(s) may develop further toxicities despite steroid therapy and cessation of ICI. ICI-RTA was a probable differential in our case. Steroid therapy remains the mainstay of treatment of ICI-RTA. It is uncertain if ICI-RTA can be transient or will persist as a chronic toxicity in patients managed without steroids.

FR-PO283

Colony-Stimulating Factor 1 Receptor Inhibitor (PLX3397) Attenuates Kidney Injury and Fibrosis Caused by Repeated Low-Dose Cisplatin

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Background: Cisplatin is a standard drug to treat many solid organ cancers. However, cisplatin can cause significant side effects including irreversible hearing loss and short-term (AKI) and long-term (fibrosis) renal impairment. Fernandez *et al* found that a mouse model of repeated low dose cisplatin (RLDC) treatment exhibited significant hearing loss and loss of cochlear mechanosensory hair cells. The colony-stimulating factor 1 receptor inhibitor PLX3397 ablated cochlear macrophages (>95% of immune cells in cochlea) and prevented hearing loss and hair cell loss. A recent report suggested that depletion of resident macrophages may mitigate renal fibrosis in the RLDC model. Therefore, we hypothesized that PLX3397 also would protect against cisplatin-induced nephrotoxicity.

Methods: CBAJ/CX3CR1GFP/+ (het) mice were used to label macrophages with GFP. Mice underwent three cycles of cisplatin treatment (3 mg/kg/day I.P. cisplatin for 4 days followed by a 10-day recovery). We fed mice with vehicle- or PLX3397-formulated chow one week prior, and then via daily oral gavage during the cisplatin cycles. We harvested kidneys, blood, and inner ears at 20 days after the last cisplatin injection for histological and biochemical analyses. Tissue platinum (cisplatin) was measured by inductively coupled plasma mass spectrometry.

Results: Mice that received cisplatin had increased plasma BUN and NGAL levels. In addition, cisplatin-treated mice had significant tubular injury and fibrosis, while administering PLX3397 significantly improved all parameters. We found that cisplatin increased CX3CR1+ cells in the kidney (without vs. with cisplatin, 8.6 ± 1.3 vs. 20.2 ± 2.6 cells/high-power field (HPF), n = 4-5/group, p = 0.001). We confirmed that PLX3397 treatment ablated CX3CR1+ cells in the kidney (Cisplatin without vs. with PLX3397, 20.2 ± 2.6 vs.1.5 ± 0.6 cells/HPF, n = 4-5/group, p < 0.001). Moreover, PLX3397 markedly prevented the accumulation of platinum in the kidney.

Conclusions: PLX3397 treatment mitigated cisplatin-induced kidney injury and renal fibrosis via ablation of renal CX3CR1+ cells. Additionally, PLX3397 treatment also decreased accumulation of cisplatin in the kidney. The pathogenetic roles of CX3CR1+ cells in cisplatin-induced nephrotoxicity of the RLDC model need to be elucidated in future studies.

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

FR-PO284

IgA Glomerulonephritis in the Setting of Immune Checkpoint Inhibitor Use Successfully Treated with Rituximab

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Introduction: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide, and occurs as either a primary autoimmune response or secondary to other pathology. Immune checkpoint inhibitor (ICI) therapy has improved the prognosis for many patients with advanced cancers, but despite the benefits, immune-related adverse effects remain common. We report a case of ICI-associated IgAN successfully treated with rituximab.

Case Description: A 73-year-old White man with hepatocellular carcinoma on nivolumab was initially referred for acute kidney injury (AKI). History and physical, serology, urine, and imaging was unrevealing. Steroids were deferred, serum creatinine (sCr) partially recovered, and nivolumab was resumed. Four months later, he developed recurrent, now dialysis-dependent AKI along with gross hematuria and nephrotic range proteinuria. Kidney biopsy demonstrated a proliferative, crescentic glomerulonephritis with both IgA and C3 deposition (**Figure 1**). Nivolumab was discontinued, glucocorticoids were administered without improvement, and rituximab was initiated. Five months later, he discontinued dialysis with recovery of sCr and proteinuria to baseline levels.

Discussion: Rituximab has been shown to be effective for IgA vasculitis affecting the kidney, but has yet to demonstrate consistent benefit in primary IgAN. Case reports of IgAN affecting kidney transplant recipients report positive outcomes, possibly due to a B-cell depleting effect within the enhanced post-transplant immunologic milieu. Our case illustrates a potential role for rituximab in salvage therapy for ICI-related IgAN, where it may act similarly to provide a "check" to the amplified immune response caused by immune checkpoint disruption. Nephrologists and oncologists must remain aware of ICI-associated glomerular disease and maintain a low threshold to obtain a kidney biopsy when the presentation is atypical for AIN.

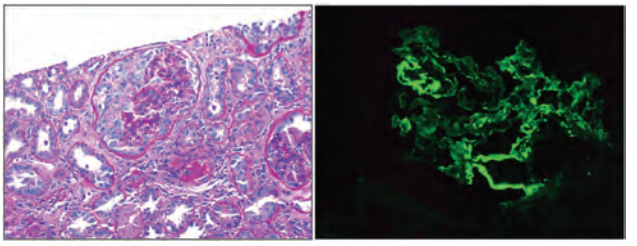

Figure 1. Native kidney biopsy demonstrating crescentic glomerulonephritis in the setting of active ICI use (left, light microscopy) with strong IgA staining (right, immunofluorescence).

FR-PO285

Allograft Rejection Following Immune Checkpoint Inhibition After Renal Transplantation: An In-Depth Analysis of PD-1, PDL-1, and CTLA-4 Checkpoint Inhibitors

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Background: Immune checkpoint inhibitors (ICIs) have emerged as one of the most pivotal therapeutic agents in tumor immunotherapy, and now used in solid-organ transplant recipients as salvage therapy post-tumor recurrence or for management of secondary tumors. However, ICI-associated allograft rejection has surfaced as a particular concern in solid-organ transplant recipients.

Methods: We performed a retrospective multi-center cohort study using TriNetX, a global federated health research network providing access to electronic medical records across large healthcare organizations (HCOs) grouped into a network called Global Collaborative Network of 105 HCOs from 14 countries. We identified 164,034 post-renal transplant recipients without ICI use and 247 patients receiving ICI after transplant until May 11 2023 from 37 HCOs. Post-kidney transplant recipients in propensity-matched groups receiving either ICI or non-ICI regimen (n=247 each) were assessed for allograft rejection within first year of ICI exposure as compared to first-year allograft rejection in non-ICI group, with risk analysis and Kaplan-Meier survival analysis as relevant, with further analysis of renal allograft rejection in propensity-matched cohort comparisons with PD-1, PDL-1 and CTLA-4 inhibition.

Results: Kidney allograft rejection within 1 year occurred in 14.9% of patients in the non-ICI cohort as compared to 11.33% in the ICI exposure group (RR=1.32; 95%CI 0.83-2.09). In renal transplant recipients on PD-1 versus CTLA-4 checkpoint inhibition, allograft rejection was confirmed in 30.3% of patients in each cohort (RR=1; 95%CI 0.48-2.08). Allograft rejection noted in 71% patients in CTLA-4 vs. PDL-1 cohorts(RR=1; 95%CI 0.63-1.59), and 50% of patients in PD-1 vs. PDL-1 cohort (RR=1; 95%CI 0.54-1.86). Our study demonstrates there was no significant difference in renal allograft rejection between ICI and non-ICI cohort.

Conclusions: After propensity matching, ICI exposure post-renal transplant was not associated with acute allograft rejection within one year of ICI exposure. Our analysis of allograft rejection with one-year exposure of either of three ICI classes did not reveal superior (or inferior) association as compared to first-year allograft rejection post-renal transplant in non-ICI cohort.

FR-PO286

Focal Segmental Glomerulosclerosis (FSGS) Associated with Chimeric Antigen Receptor T-Cell (CAR-T) Therapy

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Introduction: CAR-T therapy was first used to treat pediatric leukemia, and has since expanded to other hematologic malignancies. The most common adverse reactions include cytokine release syndrome (CRS) and neurotoxicity. Acute kidney injury (AKI) has been reported in up to 30% of adult patients post CAR-T. Treatment for CRS is non-standardized but may include tocilizumab or steroids. The mechanism behind CAR-T associated AKI is not well elucidated, given small retrospective studies lacking biopsy data. With increasing popularity of CAR-T therapy, better understanding the etiology and character of CAR-T associated kidney injury may improve kidney outcomes.

Case Description: We present a case of a 47-year-old man with IgA Kappa multiple myeloma, hypertension, and diabetes, with normal proteinuria at baseline. As part of a clinical trial, he received CAR-T therapy (ciltacabtagene autoleucel). He developed CRS on day 6, and was treated with tocilizumab and anakinra. Four days after infusion there was a gradual increase in serum creatinine (SCr) from baseline 0.9 to 1.35mg/dL, downtrending to 0.99mg/dL after one month. The patient also developed hypoalbuminemia, hyponatremia, and hypophosphatemia during his course, which improved by discharge. 24-hour urine protein one month post CAR-T was 2.6 grams, and subsequent UPCR peaked at 2.56 g/g three months post CAR-T. Kidney biopsy performed at that time showed FSGS, not otherwise specified (NOS) variant, without immune deposits or substantial interstitial scarring, and with preserved podocyte foot processes. The patient was treated conservatively with losartan, and subsequent UPCR improved to 0.17 g/g by 7 months post CAR-T.

Discussion: This is the second case report of biopsy-proven FSGS after CAR-T in the literature. In contrast to the other case, our patient did not have interstitial inflammation or complete podocyte foot-process effacement, suggesting against primary FSGS, nor did he develop oliguria or edema. The presentation of new-onset proteinuria was temporally related to the CAR-T infusion, possibly representing either a CRS-related global or an off-target local inflammatory response. This case highlights the importance of understanding of CAR-T's effects on the kidney. A limitation of our case is the lack of APOL-1 testing to investigate as a second-hit phenomenon.

FR-PO287

Preliminary Open-Labeled Study to Examine the Effect of Cilastatin on the Pharmacokinetics of Cisplatin in Patients with Lung Cancer Undergoing Cisplatin-Based Chemotherapy

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Background: In animal studies, the nephrotoxicity of cisplatin (CDDP) is reduced by cilastatin (CS), which is thought to be related to the function of the endocytosis receptor megalin in proximal tubular cells, and CS may antagonize megalin and reduce the nephrotoxicity of CDDP. CS is approved as a combination drug (Thienam®, imipenem–cilastatin sodium), not as a single agent, and its effects on the pharmacokinetics of CDDP in humans have not been examined. To evaluate the pharmacokinetics and safety of CDDP when Thienam® is administered during chemotherapy including CDDP in patients with non-small cell lung cancer (NSCLC).

Methods: Patients, aged >20 years but not >70 years with advanced stage NSCLC not amenable to surgery or radical irradiation, who had not previously received chemotherapy and had an eGFR of 60 mL/min/1.73 m^2 or higher, were included. Patients were administered pembrolizumab (200 mg/body) and pemetrexed (500 mg/m^2) followed by intravenous Thienam® and then CDDP (75 mg/m^2). The primary endpoint was the pharmacokinetics of CDDP in combination with CS, which was evaluated with serum platinum concentrations.

Results: Patients were sequentially administered 0, 0.5, and 1.0 g of Thienam®, and a total of nine patients, three in each group, were enrolled in the study. The median age was 65 (range, 47–70) years and eight (89%) patients were men. The stages were unresectable stage III in one, stage IVA in four, and stage IVB in four patients. The Cmax was 2.44±0.09, 2.61±0.34, and 2.43±0.26 μg/mL, T1/2 was 114.9±14.5, 114.6±31.7, 76.8±3.4 h, and area under the curve (AUC) was 8574±1418, 8184±2480, and 7764±1217 μg/mL min in the 0, 0.5, and 1 g thienam groups, respectively. No serious adverse events occurred; only one case of grade 3 or higher adverse event (leukopenia) occurred, which was thought to be due to chemotherapy.

Conclusions: In chemotherapy, including CDDP administered to chemotherapy-naive patients with advanced NSCLC, the T1/2 and AUC of serum platinum concentration were decreased, particularly in the high-dose thienam group. It might be due to the suppression of megalin-mediated renal uptake and retrieval of CDDP by CS (Trial registration: jRCTs031180329).

Funding: Clinical Revenue Support

FR-PO288

Refractory Hypokalemia due to a Rare Paraneoplastic Syndrome

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Introduction: Renal potassium wasting can occur due to a variety of etiologies. Understanding the pathway resulting in potassium wasting is critical to treating and ultimately correcting the acid/base and electrolyte derangements seen in these cases.

Case Description: We present a case of a 54 year old female with newly diagnosed high grade metastatic neuroendocrine tumor (NET) admitted for intractable diarrhea improving after octreotide administration. Her labs, however, showed persistence of severe hypokalemia and metabolic alkalosis despite aggressive repletion. Urine electrolytes suggested renal potassium wasting with undetectable renin and aldosterone levels. Further workup showed elevated urine and serum cortisol levels with elevated adrenocorticotropin hormone (ACTH) which failed to be suppressed with dexamethasone suppression testing (DST), suggesting a paraneoplastic etiology for ACTH release. Due diligence was taken to ensure that ACTH release was not from a primary pituitary tumor by obtaining imaging and appropriate hormonal workup. It was determined that elevated cortisol exerts aldosterone-like effects on the mineralocorticoid (MRA) receptor resulting in renal potassium and hydrogen loss. The patient was started on spironolactone and ketoconazole in addition to oral potassium repletion with gradual improvements in serum potassium levels.

Discussion: As this case highlights, it is critical to understand the relationship between cortisol and the MRA receptor in addition to determining the cause for hypercortisolism which can be ACTH dependent or independent. Once it's determined to be ACTH dependent, DST is performed. Failure to suppress cortisol with dexamethasone administration suggests paraneoplastic, autonomous ACTH release which can then stimulate cortisol synthesis in the adrenals via the steroid synthesis pathway. Cortisol, at high levels, acts upon the MRA receptor resulting in hypokalemic metabolic alkalosis. Targeting therapy by blocking the MRA receptor with spironolactone and inhibiting cortisol synthesis in the steroid synthesis pathway with ketoconazole ultimately lead to improvement in serum potassium levels in addition to oral repletion.

FR-PO289

One-Year Experiences of an Onconephrology Outpatient Clinic in New York

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Background: Onconephrology is an emerging field within nephrology, as novel treatments in oncology have unique implications for kidney disease and care. Consequently, dedicated onconephrology clinics have been established to facilitate interdisciplinary care. However, there are no descriptions of actual onconephrology clinic experiences in the US. We report our patient characteristics during the first year of our onconephrology clinic.

Methods: The onconephrology clinic operates one half-day per week since December 2021 and is staffed by two nephrologists. We performed retrospective chart reviews of all patients seen in the first 12 months of operation, collecting patient characteristics, referral indications, primary malignancy, and referral information.

Results: 88 patients were seen with a mean age of 65.4 years, and 52% were male. The average GFR at initial visit was 44 mL/min. CKD stage at the time of initial visit was 3% CKD I, 20% CKD II, 15% CKD IIIa, 30% CKD IIIb, 26% CKD IV, and 6% CKD V (albuminuria data not reliably available at initial visit). Patients had 25 distinct primary malignancies; the most common were 35% multiple myeloma, 13% MGUS, and 13% lung cancer. 74% of referred patients had CKD. Other reasons for referral included 28% AKI, 15% proteinuria, 7% hyperkalemia, 6% TMA, 5% hyponatremia, 2% hypomagnesemia, and 1% hypertension, referred by 45 distinct providers. Median time from referral to consult for non-CKD referrals was 19 days (IQR 11-43). 40% of patients had Medicaid insurance. 15% of patients seen underwent a kidney biopsy.

Conclusions: Our experiences with an onconephrology outpatient clinic in New York highlight the diverse patient population and range of kidney-related issues encountered in this setting. The majority of referrals were for CKD, with multiple myeloma as the most common malignancy. These findings underscore the importance of collaboration between oncology and nephrology specialists to provide optimal care for patients with cancer-related kidney diseases. Further studies may provide insight into the long-term outcomes and best practices for managing these complex patients.

Current and future areas of inquiry for onconephrology clinics

FR-PO290

Association of Proton-Pump Inhibitor Use and Immune Checkpoint Inhibitor-Associated AKI: Evidence from a Meta-Analysis

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Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer treatment but their use is associated with immune-related adverse events (irAEs), including kidney injury. Proton pump inhibitors (PPI) are commonly prescribed medications independently associated with kidney injury. Understanding the relationship between ICI-associated acute kidney injury (ICI-AKI) and PPI use is crucial for optimizing patient management and minimizing complications.

Methods: To explore the association between ICI-AKI and PPI use, a comprehensive literature review was conducted. Databases including MEDLINE and EMBASE were systematically searched for articles published until January 2023. Studies reporting the incidence and risk of ICI-AKI in patients receiving ICIs, with or without concomitant PPIs, were identified and included in our analysis. Pooled odds ratios (ORs) and 95% confidence interval (CI) were calculated using a random-effect, generic inverse variance method of DerSimonian and Laird.

Results: A total of 13 studies, involving 9371 patients, were included. The overall incidence of AKI from all-cause was 51.0% (95%CI, 32.9-68.9%) among patients on PPIs and 49.0% (95%CI, 31.1-67.1%) among those not on PPIs. Focusing specifically on ICI-AKI, the incidence was 59.0% (95%CI, 49.9-67.4%) among patients on PPIs, compared to 38.7% (95%CI, 30.7-47.4%) in those not on PPIs. Importantly, our analysis revealed a significant association between PPI use and the risk of ICI-AKI, with a pooled OR of 2.51 (95% CI 1.24-5.11). These findings indicate a higher likelihood of developing ICI-AKI when using PPIs.

Conclusions: In conclusion, our meta-analysis provides further evidence of an increased risk of ICI-AKI associated with the use of PPIs. Clinicians should exercise

caution and try to avoid prescribing PPIs in patients undergoing ICI therapy, as these medications may potentially incite renal irAEs.

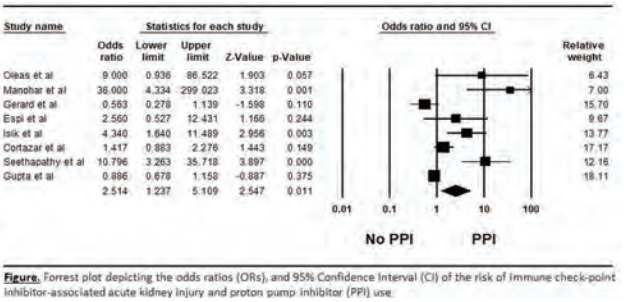

Figure. Forrest plot depicting the odds ratios (ORs), and 95% Confidence Interval (CI) of the risk of immune check-point inhibitor-associated acute kidney injury and proton pump inhibitor (PPI) use.

FR-PO291

Exploring the Biology of Non-Cleavable Klotho

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Background: Klotho is a type-I transmembrane protein that is a cell maintenance and cytoprotective factor. Klotho protein is primarily expressed in the kidney, but it is also found in the brain, parathyroid gland, and reproductive organs. Klotho protein exists in membrane-bound and soluble forms. Membrane- Klotho acts as a co-receptor for fibroblast growth factor (FGF)23, while the soluble form of Klotho circulates and acts systemically on distant organs. Known secretases cleave the membrane klotho to produce the soluble forms of circulating Klotho. The relative contribution of the two forms of Klotho to biology and pathobiology is not known as experimental genetic manipulation of Klotho affects both forms. Low circulating levels of Klotho is associated with numerous disorders, including chronic kidney disease, cardiovascular disease, and cognitive impairment. To dissociate the function of two forms of Klotho, we aim to generate a non-cleavable form of the Klotho protein (NCK), which will provide us with the means the creation to create of a murine model to study physiology and pathophysiology.

Methods: Using previously published data and our own mutational analysis of the putative cleavage sites, we finalized on one mutant called non-cleavable Klotho (NCK) mKLd^{L9}-956-S958L, with the replacement of 9 aa at 956LGSGTLGFR-to GGLGGGSGG and expressed it in HEK293 cells.

Results: We proceeded to test that NCK is: 1. Expressed normally and trafficked to cell surface, 2. Functionally intact. 3. Indeed, NCK expression in cells and cell surface is comparable to WT Klotho (immunoblot, immunocytochemistry, and surface biotinylation), and. NCK is functionally intact as evident by its ability to sustain FGF23 signaling (FGF23-induced phospho-ERK/total ERK. There is no detectable NCK in the supernatant despite abundant cell surface expression. The data supports a NCK that is trafficked to the cell membrane, functionally intact, but not released from the cell surface.

Conclusions: A mouse model of NCK replacing WT Klotho is being generated which will provide a valuable tool for studying the physiological and pathological roles of membrane vs. soluble Klotho protein.

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FR-PO292

Partial Klotho Deletion in the Renal Distal Segment Does Not Affect Ca2+ Handling

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Background: Klotho is a protein important in health and disease, as decrease of circulating Klotho levels is correlated with age increase and chronic kidney disease (CKD) progression. This highlights Klotho as a potential early biomarker for CKD, as well as a potential therapeutic strategy to improve health and lifespan of patients. Klotho influences renal electrolyte handling by modulating renal reabsorption of phosphate (PO_4^{3-}) and calcium (Ca^{2+}) through Ca^{2+} channel TRPV5 and Na^+/Pi co-transporter NPT2a, and by interacting with renal phosphaturic hormone fibroblast growth factor-23 (FGF23).

Methods: The mouse model with a partial deletion of Klotho (*Ksp-KL*$^{-/-}$) in the distal convoluted tubule (DCT) was generated using the Cre-Lox recombination system, and was characterized with a disrupted mineral metabolism, with hyperphosphatemia, elevated FGF23 levels and decreased parathyroid hormone levels. An interventional study was performed on *Ksp-KL*$^{-/-}$ mice by subjecting the mice to a 0.02% Ca^{2+} diet for 3 weeks immediately after weaning. 24-hour urine and blood samples were collected using metabolic cages, and kidney and intestines were processed and relevant gene expression levels were analysed (qPCR). This study aimed to assess Ca^{2+} handling in Ca^{2+}-deficient *Ksp-KL*$^{-/-}$ mice to increase our understanding of electrolyte disturbance.

Results: Urinary, serum and fecal Ca^{2+} levels were not influenced by the Ca^{2+} deficient diet or the genotype of the animals. Renal expression of *Klotho*, *Trpv5* and *Npt2a* was not significantly changed in *Ksp-KL*$^{-/-}$ mice compared to *Ksp-KL*$^{+/+}$ mice. Intestinal expression of *Trpv6* and *Npt2b* did not indicate a compensation towards intestinal electrolyte handling.

Conclusions: Partial deletion of Klotho (21%) in the DCT does not affect renal or intestinal Ca^{2+} handling, contrary to the global deletion of Klotho. We speculate that this may be due to insufficient challenge on the Ca^{2+} metabolism of the mice, as well as residual Klotho amounts that are sufficient to maintain normocalcemia and normocalciuria.

FR-PO293

Molecular Characterisation of Novel Klotho Variants Identified in Patients with Ca2+ Disturbances

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Background: CKD is the long-term loss of kidney function, which exerts multiple repercussions on other numerous organs, including the cardiovascular system. The progression of CKD is significantly associated with decreased serum levels of Klotho and elevated serum levels of FGF23, however the precise underlying molecular mechanisms are yet unsolved. Although CKD has a high heterogeneity in molecular changes, the disruption of the Klotho-FGF23 axis is a common feature, considering that the decline in serum levels of Klotho as the disease progresses is constant in all stages of CKD. Klotho is a protein with a large ectodomain that can get cleaved and released into circulation. Expressed in the proximal and distal tubules, Klotho is demonstrated to affect renal PO_4^{3-} excretion by interacting with NPT2a and reabsorption of Ca^{2+} by anchoring TRPV5.

Methods: The Klotho variants (c.1151T>C, c.1489T>C, c.1819A>G, c.2069C>T, c.2590G>A, c.2620G>A, c.3008A>G) were identified in a cohort by whole-exome sequencing. The variants were transiently transfected in HEK293 cells. The variants were characterized by investigating the shedding pattern, conditional cleavage, presence on the cell surface, cellular localization and co-localisation with TRPV5.

Results: Full-length shed Klotho (±130 kDa) and Klotho domains (±60 kDa) can be cleaved and identified by Western blotting. All results are compared to the wild-type Klotho condition. c.1151T>C, c.2590G>A and c.2620G>A do not show full-length shed Klotho nor shed Klotho domains, whereas c.1819A>G seems to have a lower molecular weight of the shed Klotho domain. In accordance with previous results, c.1151T>C, c.2590G>A and c.2620G>A show no surface expression on the cellular membrane. The variants c.1151T>C and c.2620G>A appear to have a diffused cytoplasmic localization, in contrast to wild-type Klotho, which has a membranous localization.

Conclusions: Our study indicates that the novel identified Klotho variants have an effect on the expression and shedding of Klotho, which directly affect the serum levels of circulating Klotho, leading to a potential decrease in circulating Klotho levels. These recent findings should allow for novel investigations on the effect of Klotho shedding in CKD.

FR-PO294

Bone-Specific Overexpression of Membrane Klotho Induces FGF23

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Background: Klotho, either membrane-bound or soluble (or cleaved) form, acts as a coreceptor that enhances the binding affinity of FGF23 to FGF receptors (FGFRs). Soluble Klotho has been shown to potently stimulate FGF23 production in osteocytes through a yet unknown mechanism, but little is known about the role of membrane Klotho in the regulation of FGF23 production.

Methods: We generated and characterized a novel mouse strain with targeted overexpression of membrane Klotho in the osteoblast lineage, driven by the 2.3-kb Col1a1 promoter.

Results: The transgenic mice are born alive and initially indistinguishable from their control littermates, but they show growth delay and die within a few days. Overexpression of membrane Klotho in osteoblasts/osteocytes resulted in a tremendous increase in serum intact FGF23 (>1500 fold) and bone Fgf23 mRNA (>400 fold), accompanied by reduced levels of 1,25-dihydroxyvitamin D and PTH, reduced Napi2a, and elevated Cyp24a1. Treatment of these mice with an FGF-receptor blocker markedly and dose-dependently suppressed the increased bone Fgf23 expression. Using primary osteoblasts isolated from the transgenic mice, we also show that the increased Fgf23 expression during osteogenic differentiation is primarily mediated by FGFR-dependent activation of the MAPK pathway.

Conclusions: These results suggest that membrane Klotho stimulates FGF23 production in osteoblasts/osteocytes, presumably by forming a positive feedback loop mediated by the FGF23-Klotho-FGFR signaling complex. Thus, membrane Klotho expressed in bone cells functions as an amplifier of FGF23 production.

FR-PO295

Merged In Vitro/In Vivo RNAseq/ATACseq Pinpointed FGF23 Target Genes Dysregulated with Klotho Deletion in Kidney Single-Cell Subpopulations

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Background: FGF23 controls phosphate and vitamin D synthesis in the kidney via its co-receptor αKlotho (KL), however, the cellular responses to FGF23 during normal and disease states are not fully understood. We hypothesize that FGF23 induces unique and generalized changes in transcription and genomic accessibility within specific nephron cell populations.

Methods: HEK293 cell line stably expressing membrane Klotho (HEK-mKL cells) was treated with FGF23 (50 ng/mL) for 4 and 16 hours, then processed for ATACseq and

RNAseq libraries. Differentially expressed genes were validated by qPCR as well as in an independent single-cell 10X Multiomics dataset from KL-KO mice. Dimensionality reduction via Uniform Manifold Approximation and Projection (UMAP) was used to identify distinct nephron cell types.

Results: HEK-mKL cell groups treated with FGF23 displayed clear segregation for both RNAseq and ATACseq following principal component analysis (PCA), with 9 and 7-fold increases in MAPK target genes *EGR1* and *FOS*. Vitamin D 24-hydroxylase *CYP24A1* (2-fold) and *VDR* (1.5-fold) increased at 4 and 16 hours, supporting this model. ATACseq showed FGF23 rapidly influenced genomic regions to control MAPK signaling as demonstrated by opening chromatin accessibility of an *EGR1* distal enhancer by 4h. In confirmation, HOMER motif discovery predicted enrichment in transcription factor binding for MAPK targets *FOS*, *JUN*, *AP1*, and *EGR1* across the genome (P<0.05). At both 4 and 16h, FGF23 bioactivity was associated with novel induction of ETV transcription factor family mRNAs (*ETV1* (3.7-fold), *ETV4* (8-fold), and *ETV5* (7.5-fold). Furthermore, FGF23 bioactivity increased the expression of *ETV1/4/5* target genes *MMP1*, *PTGS2*, and *VEGF*. Conversely, *in vivo*, 10X Multiome analysis of KL-KO mouse kidney proximal tubule-S1/S2 cells showed a 27% decrease in *Etv5* mRNA. Further, *Etv1* expression and chromatin accessibility decreased by 70% and 92%, respectively, contrary to the increase of these key factors with FGF23 treatment.

Conclusions: A unique combination of unbiased *in vitro* ATACseq/RNAseq pinpointed novel FGF23-induced transcriptional and genomic reprogramming. Translation to *in vivo* kidney cell subpopulations demonstrated these changes may influence cell-specific outcomes in FGF23-related diseases.

Funding: NIDDK Support, Other NIH Support - R01-HL145528

FR-PO296

Skeletal Muscle Is a Novel Source of FGF23 in Mouse Models of CKD

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Background: Fibroblast growth factor 23 (FGF23) increases renal phosphate (Pi) excretion, & beginning in early stages of CKD, FGF23 levels rise progressively in an attempt to maintain normal Pi levels. Pi is a potent inducer of FGF23 in bone. Previous studies suggested that bone might not be the sole source for systemic FGF23 elevations in CKD. Here we study whether mouse models of hyperphosphatemia express FGF23 in skeletal muscle (SM) & whether Pi treatments of cultured myotubes (MT) induce FGF23 expression.

Methods: C2C12 MT & primary mouse MT were treated with 1-12 mM Pi for 24 hours, followed by qPCR expression analysis of FGF23. MT were grown in chamber-slides, treated with Pi, & immunostained with anti-FGF23. We analyzed four models of hyperphosphatemia: two CKD models, i.e. mice with global deletion of collagen 4a3 (Col4a3-/-) & wildtype mice receiving an adenine-rich (0.2%) diet for 14 weeks, & two non-CKD models--a klotho deficient mouse & wildtype mouse receiving a high Pi (3%) diet for 3 & 6 months. We also studied Col4a3-/- mice receiving a low Pi (0.2%) diet for 7 weeks. Furthermore, we generated mice with SM-specific deletion of FGF23 (FGF23fl/fl;HSA-Cre+) & administered an adenine-rich or a high Pi diet for 14 weeks or 6 months, respectively. We studied FGF23 expression in SM by qPCR, ELISA & immunofluorescence microscopy, as well as serum levels of FGF23 & Pi.

Results: Pi treatments increased FGF23 expression in C2C12 MT & primary mouse MT in a dose-dependent manner. In all four mouse models we detected FGF23 in SM tissue on mRNA & protein level. When Col4a3-/- mice received a low Pi diet, FGF23 expression was reduced. FGF23fl/fl;HSA-Cre+ mice on an adenine or a high Pi diet had significantly lower FGF23 mRNA & protein levels in SM & reduced serum FGF23 levels, when compared to control mice on the same diet.

Conclusions: Mouse models with hyperphosphatemia produce FGF23 in SM tissue in the presence & absence of CKD. SM-derived FGF23 significantly contributes to the hyperphosphatemia-associated elevations in serum FGF23 levels. Our ongoing studies aim to determine whether SM-derived FGF23 has paracrine effects, & for example contributes to SM atrophy that we have detected in these mouse models. Furthermore, we will determine if SM-derived FGF23 has endocrine effects & increases renal Pi excretion.

Funding: NIDDK Support

FR-PO297

Glycerol-3-Phosphate Is an Independent Predictor of FGF23 Levels in Hemodialysis Patients

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Background: FGF23 levels are markedly elevated in kidney failure, but the mechanisms for the increased FGF23 production is incompletely understood. Emerging evidence shows that kidney-derived glycerol-3-phosphate (G-3-P), a byproduct of glycolysis, serves as a key mediator of FGF23 production in response to dietary phosphate loading. However, little is known about the role of G-3-P in kidney failure.

Methods: We measured serum G-3-P levels by LC/MS in 35 healthy individuals and 650 hemodialysis (HD) patients enrolled in the Tokai Dialysis Prospective Cohort Study. We employed multivariable linear regression to explore whether hyperphosphatemia is associated with increased G-3-P levels in HD patients. We next examined whether serum G-3-P is a determinant of FGF23 levels, independent of known regulators of FGF23 such as serum phosphorus, calcium, PTH, iron metabolism, and inflammation.

Results: The median serum G-3-P level in HD patients was 220 ng/mL (interquartile range [IQR], 118-325 ng/mL), which was 2.2-fold higher than that in healthy individuals (98 ng/mL; IQR, 80-129 ng/mL; $P < 0.001$). Patients with higher G-3-P were younger; were more likely to be male; were less likely to have diabetes; had higher body mass index and higher serum albumin, creatinine, phosphorus, and total cholesterol; and were more often prescribed calcium carbonate and cinacalcet. Higher serum phosphorus was strongly associated with higher G-3-P; this association was unchanged after multivariate adjustment and was significant even when the analysis was restricted to patients undergoing dialysis for more than 10 years. In univariate analyses, higher serum phosphorus, calcium, intact PTH, and G-3-P, and active vitamin D use were each significantly associated with higher FGF23. In multivariate analyses, G-3-P was identified as one of the independent predictors of FGF23. Further adjustment fortransferrin saturation, ferritin, and C-reactive protein did not qualitatively change these findings.

Conclusions: These findings suggest that even in patients with kidney failure, G-3-P is increased by phosphate retention and serve as a regulator of FGF23 production. Additional studies are needed to test these hypotheses and to explore whether the apparently non-functioning kidney still has the capacity to produce G-3-P.

FR-PO298

Multi-Trait Analysis of Mineral Metabolism Markers Identifies Novel Genetic Associations for FGF23

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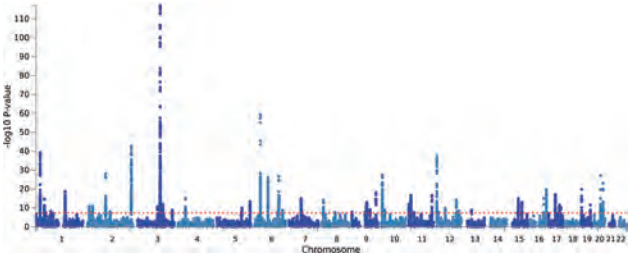
Background: Genome-wide association studies (GWAS) have identified numerous genetic loci associated with mineral metabolism markers but have exclusively focused on single-trait analysis. In this study, we performed a multi-trait analysis of GWAS data of mineral metabolism markers, exploring overlapping genetic architecture between the traits, to identify novel genetic associations for fibroblast growth factor 23.

Methods: We applied multi-trait analysis of GWAS (MTAG) to genetic variants common to GWAS of 5 genetically correlated mineral metabolism markers (phosphorus, FGF23, calcium and PTH) in European-ancestry subjects. We integrated information from the UKBioBank GWAS for phosphate and calcium (n=366,484), and two GWAS from the CHARGE consortium for PTH (n=29,155) and FGF23 (n=16,624).

Results: MTAG increased the effective sample size for all mineral metabolism markers, to n=50,325 for FGF23. After clumping, MTAG identified independent genome-wide significant SNPs for all traits, including 47 loci for FGF23. Many of these loci have not been previously reported in single-trait analyses, including loci involved in inflammation, lipid metabolism, glucose metabolism, and bone health.

Conclusions: MTAG boosted the number of genome-wide significant loci FGF23. Our findings highlight the importance of performing multi-trait analysis in GWAS studies of mineral metabolism markers to identify novel genetic associations. These genetic loci may provide insight into the biological mechanisms underlying mineral metabolism and may have implications for the development of therapies for mineral-related disorders.

Funding: NIDDK Support



Manhattan plot of the strength of association of genetic variants with circulating FGF23 after MTAG

FR-PO299

Activation of Fatty Acid β-Oxidation in Proximal Tubular Epithelial Cells Is an Intrinsic Mechanism for Suppressing Phosphorus-Induced Kidney Injury

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Background: Excess phosphorus is known to induce kidney injury. The kidneys are the primary organ that excretes phosphorus and are exposed to a phosphorus burden. Thus, it may be difficult for the kidneys to maintain their function over a lifetime unless they have some counteracting mechanisms against the phosphorus burden. This study aimed to clarify how the kidneys counteract the phosphorus burden.

Methods: Six-week-old male C57BL/6 mice were randomly divided into Ctrl and Phos groups. Mice in the Ctrl and Phos groups were fed with a 0.85% phosphorus diet and a 3.0% phosphorus diet, respectively. Since renal fibrosis was not observed in both groups 3 weeks after the start of dietary intervention, we assumed that the kidney was in

the stress compensation period and performed single-cell RNA seq (scRNA-seq) analysis at this point. The results obtained from scRNA-seq analysis were validated in vivo and vitro experiments.

Results: Kidney component cells were classified into 12 clusters and analyzed differentially expressed genes (DEGs) between the Ctrl and Phos groups in each cluster. Since the highest number of DEGs were detected in the S1/S2 segments of the proximal tubules (Prox_S1/S2), we focused on the Prox_S1/S2. Kyoto Encyclopedia of Genes and Genomes pathway analyses demonstrated that genes related to fatty acid β-oxidation (FAO) were the top activated pathway in the Prox_S1/S2 cluster of the Phos group. Single-cell regulatory network inference and clustering analyses identified peroxisome proliferator-activated receptor α (PPARα) as one of the most activated transcription factors that regulate the gene network in the Prox_S1/S2 cluster of the Phos group. Immunohistochemistry and western blot of the kidney showed up-regulated PPARα and carnitine palmitoyltransferase 1A (CPT1A), a rate-limiting enzyme of FAO, in the Phos group. In vitro experiments using cultured proximal tubular epithelial cells (PTECs) revealed that phosphorus directly increases CPT1A expression. Etomoxir, a CPT1 inhibitor, significantly reduced cell viability of PTECs only under high phosphorus conditions.

Conclusions: The activation of FAO is an intrinsic defensive reaction against phosphorus-induced cytotoxicity in PTECs.

FR-PO300

Calcimimetic Treatment Reduces Progression of High Phosphate-Induced Tubular Injury in Mice

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Background: High phosphate stimulates fibroblast growth factor 23 (FGF23) and both factors are discussed to promote chronic kidney disease progression. Recently, we demonstrated that a high phosphate diet (HPD) in mice leads to increased serum phosphate and Fgf23 levels and a Stat3/Kim-1-mediated proximal tubule injury and tubulointerstitial fibrosis. In parallel, inflammatory processes in the renal parenchyma with induction of MCP-1 (monocyte chemoattractant protein-1; *Ccl2*) and accumulation of macrophages as well as the development of perivascular tertiary lymphoid structures (TLS) in the medullary-cortical junction could be demonstrated in HPD mice. Calcimimetics show both cardio- and nephroprotective effects. Administration of etelcalcetide in hemodialysis patients results in a reduction of FGF23 and slower progression of left ventricular hypertrophy. Cinacalcet stabilizes podocyte function in mice. We therefore postulated that calcimimetics also have a beneficial effect on the progression of HPD-induced renal damage and the maturation of TLS in mice.

Methods: To investigate whether calcimimetic treatment positively affects kidney health, we induced kidney disease in male C57BL/6 mice by the use of a 2% HPD in comparison to a 0.8% phosphate control diet (Ctrl). After four months of dietary intervention, one HPD-fed group was concomitantly treated with 1 mg/kg body weight/day etelcalcetide (Etl) for further two months. At the end, blood and urine were taken and kidneys were harvested for histological and transcriptional analysis.

Results: Therapy with Etl reduced HPD-induced Fgf23 levels but had no effect on elevated serum phosphate levels. Etl reduced activation of the renal Stat3/Kim-1 signaling cascade and decreased HPD-mediated tubule damage. Furthermore, Etl significantly suppressed mRNA expression of *Ccl2* and the macrophage-specific marker *Adgre1* compared with the HPD group without therapy. Etl had no effect on the development and maturation of renal TLS in the HPD group, which were characterized by $CD3^+$ T cells, $CD45R^+$ B cell clusters, IgD-secreting cells, $CD138^+$ plasma cells, and podoplanin$^+$ cell networks.

Conclusions: Etl therapy reduces FGF23 levels and slows progression of tubule injury in mice on HPD. Maturation of renal TLS remains unaffected by Etl, which may be attributed to persistent hyperphosphatemia.

Funding: Commercial Support - Amgen

FR-PO301

Activation of the IKK2-NFkB Pathway in Vascular Smooth Muscle Cells (VSMCs) Inhibits Vascular Calcification and Stiffness in CKD by Reducing the Secretion of Apoptosis-Mediating Calcifying Extracellular Vesicles

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Background: Medial calcification is a major risk factor of cardiovascular mortality, particularly for patients with chronic kidney disease (CKD). IKK2-NFkB pathway mediated-inflammation in vascular smooth muscle cells (VSMCs) has been proposed to be an etiologic factor in vascular calcification. However, the VSMC-specific role of the IKK2-NFkB pathway in vascular calcification remains to be elucidated.

Methods: To study the role of the IKK2-NFkB pathway in vascular calcification, we used Cas9-CRISPR and Cre-loxP techniques to delete several key genes in the IKK2-NFkB pathway from cultured VSMCs and mice, respectively.

Results: CKD significantly induced inflammatory factors in VSMCs through activation of the IKK2-NFkB pathway. Unexpectedly, however, CRISPR-mediated knockouts of IKK2, RelA and NFKB1 in VSMCs all exacerbated osteogenic differentiation and mineralization of cultured VSMCs. In vivo studies showed that Cre-mediated VSMC-IKK2 deficiency aggravated vascular calcification and aortic stiffness in CKD mice, whereas the activation of NFkB by VSMC-IkB deficiency attenuated CKD-dependent medial calcification and vascular stiffness. Inhibition of the IKK2-NFkB pathway induced apoptosis of VSMCs in vitro and in vivo by reducing anti-apoptotic gene expression. In addition, increased calcifying extracellular vesicles through the inhibition of the IKK2-NFkB pathway induced mineralization of VSMCs.

Conclusions: Taken together, this study unexpectedly reveals that activation of the IKK2-NFkB pathway in VSMCs plays a protective role in CKD-dependent vascular calcification by reducing the release of apoptotic calcifying extracellular vesicles.

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FR-PO302

Hypo-Osmotic Condition Accelerates Calcification of Extracellular Matrix in Cultured Vascular Smooth Muscle Cells

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Background: Hyponatremia, one of the most frequently observed electrolyte disorders in patients with chronic kidney disease (CKD), is associated with increased mortality. Basic studies have shown that lower sodium levels or osmolar conditions in the culture media induce cell damages, oxidative stress, and apoptosis: the latter two are also shown to accelerate vascular calcification (VC), a critical complication in CKD patients. It is unknown whether hyponatremia or low osmolar condition plays roles in the pathogenesis of VC.

Methods: Human vascular smooth muscle cells (VSMCs) and dissected mouse aortic rings were cultured with calcifying medium, which was supplemented high calcium and phosphate. Sodium and other osmotic substances were further added to confirm their impact on VC and phenotypic changes of VSMCs. To determine the main signaling pathway of VC in relation to osmotic stress, we performed microarray analyses. Rac1-Akt pathway and sodium-calcium co-transporter (NCX1) were investigated. The effect of osmolarity on calciprotein particles formation (CPP) was also confirmed.

Results: The lower osmolarity in the culture media exacerbated calcification of the extracellular matrix in cultured VSMCs as well as cultured mouse aortic rings. Conversely, the higher osmotic condition induced less calcification. Activation of Rac1-Akt signaling pathway, oxidative stress, CPP generation, and osteochondrogenic differentiation of VSMCs were identified as underlying mechanisms of VC acceleration mediated by low osmotic medium. Furthermore, sodium-dependent transcellular calcium efflux through NCX1 induced by high osmotic condition was proposed as mechanisms to prevent VC.

Conclusions: Our data suggest that a lower osmolarity including hyponatremic condition accelerates high-phosphate-induced VC by activating multiple cell-mediated processes and approach to avoid hypoosmotic condition would be important to prevent VC in CKD.

FR-PO303

Role and Mechanism of Interaction Between Autophagy and Ferroptosis in Regulating Osteogenic Transformation of Vascular Smooth Muscle Cells in Vascular Calcification

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Background: Vascular calcification could cause death in chronic kidney diseases (CKD) patients, however, its pathogenesis is not clear. Osteogenic transformation of vascular smooth muscle cells (VSMCs) is key to vascular calcification in CKD, but its mechanism has not been fully elucidated. Our previous study has found an interaction between autophagy and ferroptosis involving osteogenic transformation of VSMCs in vascular calcification. This study aimed to elucidate the role of interaction between autophagy and ferroptosis in regulating osteogenic transformation of VSMCs.

Methods: We used the 5/6 nephrectomy rat model with a diet of 1.2 % phosphate at 16 weeks. Rat VSMCs were treated with supplemented medium β-glycerophosphate and CaCl2 for 7 days. All experiments were approved by the ethics committee of Sichuan Provincial People's Hospital (No. 2017. 36). And we measured autophagy and ferroptosis in CKD vascular calcification. Full-length transcriptome sequencing was performed upon rattus abdominal aortic tissues. After bioinformatics analysis with the results of sequencing, we verified the role of interaction between autophagy and ferroptosis in regulating osteogenic transformation of VSMCs in vascular calcification by molecular biology methods.

Results: The oxidative stress effect was enhanced with vascular calcification in CKD, accompanied by ferroptosis and autophagy in VSMCs. Full-length transcriptome sequencing results indicated differential expression that were related to ferroptosis and autophagy pathways significantly enriched, including significantly upregulated expression of Runx2, Atg7 and ATG5, RAB7A, ARNTL, HSP90, LAMP2A and Beclin-1 in VSMC. Protein-protein interaction analysis showed there were interactions among the differentially expressed genes that were related to autophagy and ferroptosis. Multispectral fluorescence imaging showed that the expressions of GPX4 and Sm22α decreased and the expressions of NCOA4, Smarca4 and Runx2 increased in calcified vessels of CKD.

Conclusions: These findings shed light on the role of interaction between autophagy and ferroptosis in regulating CKD-associated vascular calcification. Further studies are needed to explore the precise mechanism of interaction between autophagy and ferroptosis in CKD vascular calcification.

FR-PO304

Reversibility of Vascular Calcifications

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Background: Mechanisms of vascular calcification have been extensively studied but little is known about resorption of existing calcifications, which has important therapeutic implications. Current data suggest that vascular calcification is largely irreversible but potential mechanisms for resorption that could be exploited have not been explored. To this end, resorption of calcifications was examined in human arteries implanted subcutaneously in mice or cultured with macrophages, and compared to bone particles and hydroxyapatite (HA).

Methods: Calcified human arteries were obtained from amputation specimens and calcification was quantified by μCT before and after implantation. Devitalized bone particles were obtained by pulverizing mouse femurs in liquid N_2 after removal of marrow, and HA was obtained commercially. Calcium content was measured after acid extraction. Standard histology protocols were used and activity of tartrate-resistant acid phosphatase (TRAP), a marker of osteoclasts, was measured in Triton extracts. Arteries or bone particles were cultured with macrophages from mouse spleens in the presence of M-CSF and TNFα +/- receptor activator of nuclear factor κ-B ligand (RANKL) to induce osteoclast formation.

Results: There was no decrease in arterial calcifications up to 6 weeks after implantation (+2.8 ± 0.6%) and only slight, insignificant resorption of bone particles after 7 weeks (-10 ± 8%). By contrast, only 24 ± 7% of hydroxyapatite remained after 7 weeks. Osteoclasts were not observed in any implant although TRAP-negative multinucleated giant cells were observed in HA implants. Calcified arteries cultured with macrophages for 9 days showed a 34 ± 4% increase in medium calcium (p=0.01) consistent with resorption, without enhancement by RANKL. Findings were similar with bone particles.

Conclusions: Hydroxyapatite is resorbed in vivo by macrophages in an osteoclast-independent manner. This does not occur with vascular calcifications in vivo but can occur in vitro with added macrophages, suggesting that vascular calcification is not reversible in vivo due to the failure to form functional osteoclasts or recruit macrophages. Similar findings in bone particles suggest that this extends to other forms of biomineralization. Further studies are needed to determine the properties of vascular calcifications that prevent recruitment of resorptive cells and identify strategies to overcome this.

Funding: Private Foundation Support

FR-PO305

In the CKD-MBD Absent Vascular Disease, CKD Decreases Cardiac Mitochondrial Function and Activin A Is an Activator of Skeletal Activin Receptor Signaling

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Background: The CKD-MBD is an important factor in the cardiovascular mortality associated with CKD. The cardiac component of the CKD-MBD has not been studied in the absence of vascular disease.

Methods: We developed an animal model of the CKD-MBD without associated vascular disease. We randomized CKD Alport mice into two groups – treatment with a monoclonal Ab to activin A (CKD-AB) or an isotype matched IgG (CKD-IgG).

Results: The Alport- AB and IgG mice had CKD equivalent to human stage 4-5 CKD. PTH and FGF23 levels were one log order elevated, and circulating sclerostin was elevated. Activin A was strongly induced in the kidneys. Aortic Ca levels were not increased in the CKD mice. The CKD mice were not hypertensive, and there was no cardiac hypertrophy. Freshly excised cardiac tissue respirometry (Oroboros) revealed that ADP minus Palmitoyl Carnitine stimulated O2 flux was diminished from 52 to 22 pmol/mg ($p<0.05$) (Figure 1). RNA seq of cardiac tissue from CKD-IgG mice showed significantly decreased levels of cardiac mitochondrial oxidative phosphorylation genes. In the skeleton, the Activin A antibody decreased the effect of CKD to stimulate osteoclast number and eroded surfaces along with a decrease in the stimulation of osteoclast driven remodeling. Immunohistochemical detection of osteocytic sclerostin was increased in the CKD-IgG mice, and the antibody treatment had no effect.

Conclusions: Two important advances in the pathophysiology of the CKD-MBD are reported here. The first, that cardiac mitochondrial respiration is impaired in CKD of Alport mice in the absence of vascular disease. This is the first report of the direct effect of CKD on cardiac respiration. Secondly, we demonstrate the role of activin A in renal osteodystrophy pathogenesis. Activin A becomes the third renal produced factor after the Wnt inhibitors and klotho to contribute to the CKD-MBD.

Funding: NIDDK Support

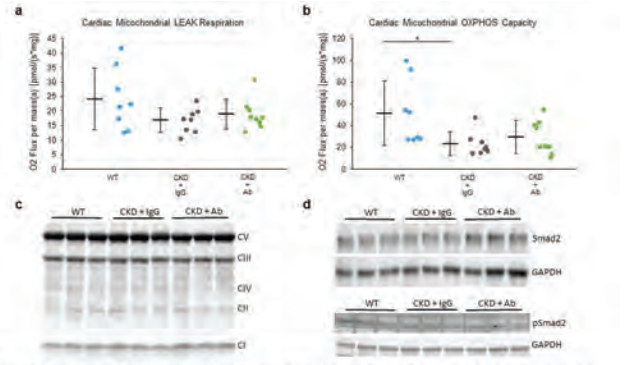

Figure 1. Cardiac mitochondrial function and oxidative phosphorylation by high resolution respirometry. a) Addition of palmitoyl carnitine and malate to permeabilized cardiac fibers to measure LEAK respiration. (**b**) Sequential addition of ADP to cardiac muscle fibers to measure fatty acid oxidative phosphorylation (OXPHOS) capacity. Cardiac fibers from 225 do Alport mice (CKD IgG) had significantly reduced rates of fatty acid oxidative phosphorylation compared to cardiac muscle fibers from WT mice. Inclusion criteria for the respirometry cohort were WT mice with BUN (mg/dL) <35 and CKD and CKD + antibody treatment mice with BUN >60. Data was limited to cardiac fibers with cytochrome c stimulated oxygen flux increase <35%. * $p<0.05$. Significance determined using the Kruskal-Wallis Test followed by pairwise comparisons with Bonferroni correction. Data represented as mean ± SD. (**c**) Cardiac mitochondrial complex I-V levels. (**d**) cardiac smad2 and psmad2 levels.

FR-PO306

4-[(Methylthio)-Phenylthio]-Methan Bisphosphonate Improves Bone Elastic Mechanical Properties in Uremic Rats

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Background: Recent clinical studies no longer reveal a strong relationship between parathyroid function and fracture risk in patients on maintenance hemodialysis therapy. However, fracture risks in this patient population remains high. We have previously reported that oxidative stress-derived deterioration in bone elastic material properties could induce bone fragility in uremic conditions. The compound 4-[(methylthio)-phenylthio]-methan bisphosphonate(MPMBP)is a non-nitrogen-containing bisphosphonate, exhibiting little anti-osteoclastic activity, with an antioxidant methylthio phenylthiol group on its side chain.

Methods: An adenine-containing chew was fed to 9-week-old Sprague-Dawley male rats for 7weeks, and the treatment groups were administered 0.6 or 1.2 mg/kgBW of MPMBP subcutaneously once per week.

Results: The serum creatine levels were elevated by 2-3 folds in the adenine-fed rat groups more than those in the non-adenine-fed groups. Subsequently, the bone turnover rate was significantly elevated in the adenine-fed rat groups, while the mineral densities of femoral bone decreased regardless of MPMBP administration. Furthermore, the amount of malondialdehyde content in the tibia increased to 3-fold more in the adenine-fed groups than that in the non-adenine-fed groups. Additionally, MPMBP decreased the malondialdehyde content in a dose-dependent manner. In the adenine-fed rats, the pentosidine/amino ratio, monitored by Raman spectroscopy, significantly increased; however, MPMBP administration decreased it in a dose-dependent manner. Finally, the femoral bone storage module that was reduced to approximately half its value in the non-adenine-fed rats was almost completely recovered by MPMBP administration.

Conclusions: According to the nature of bisphosphonates, most of the MPMBP molecules administered were immediately delivered to the calcified tissue. The accumulated MPMBP molecules could scavenge reactive oxygen species, forming an antioxidant barrier around the bone. The barrier aided in oxidative stress-derived non-physiological collagen crosslink formation and reduced osteocyte apoptosis-dependent apatite disorientation, thus improving the bone elastic material properties. MPMBP exhibits the potential to serve as a new therapeutic device for uremic bone owing to a novel pharmacological mechanism.

FR-PO307

Parathyroid Hormone (PTH) Promotes the Release of H+ by Osteoclasts via the ATF3/V-ATPase Signaling Pathway

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Background: Persistently high levels of parathyroid hormone (PTH) promote osteolysis in patients with end-stage renal disease (ESRD). It is an important part that release of hydrogen ions (H^+) by osteoclasts leads to hydroxyapatite crystal dissolution in osteolysis, which is closely related to the proton pump (V-ATPase) on the osteoclast membrane. Activating Transcription Factor 3 (ATF3) initiates the differentiation and activation of osteoclasts. This experiment aimed to investigate that PTH promotes the release of H^+ by osteoclasts via the ATF3/V-ATPase a3 signaling pathway.

Methods: Chromatin immunoprecipitation(ChIP) assay was used to examine the binding of ATF3 and V-ATPase a3 in mouse osteoclasts. With the stimulation of PTH, we used RT-qPCR and western blot to detect the expression of ATF3, V-ATPase a3 and the expression of V-ATPase a3 which treated with silencing and overexpression of ATF3. After PTH treatment in osteoclasts, we used BCECF-AM probe to detect the pH with silencing and overexpression of ATF3, and the stronger the green fluorescence, the lower the pH, which indirectly reflected the release of H^+ by osteoclasts.

Results: ChIP assay proved that ATF3 binds to the V-ATPase a3(Figure1 A-B). PTH promoted the expression of ATF3 and V-ATPase a3(Figure1 C-F), and weakened green fluorescence of the cell, increasing the release of H^+ by osteoclasts. After PTH treatment in osteoclasts, silencing ATF3 can decrease the expression of V-ATPase a3 and the release of H^+ by cells but enhance green fluorescence in osteoclasts (Figure2), while overexpression of ATF3 can increase the expression of V-ATPase a3.

Conclusions: ATF3 is a transcription factor of V-ATPase a3. PTH promotes the expression of ATF3 and V-ATPase a3, which then facilitates the release of H^+ by osteoclasts.

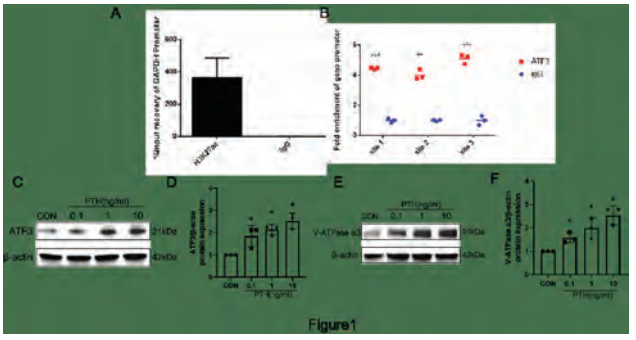

Figure1

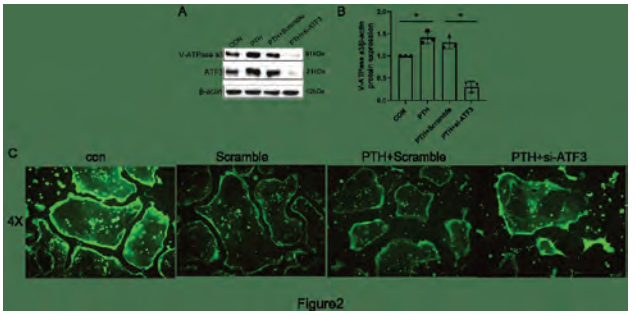

Figure2

FR-PO308

The Influence of MUC1 on Mg2+ Handling

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Background: Numerous genomic studies find an association between the common *MUC1* polymorphism rs4072037 (minor allele frequency 21-47%) and circulating Mg^{2+} levels. This polymorphism in exon 1 of *MUC1* alters mRNA splicing, elongating the N-terminus of mature MUC1. It is referred to as the long-signal peptide variant (LSP), as compared to the short-signal peptide variant (SSP). Although human genome association studies have found an association between the LSP variant and hypomagnesemia, no studies have demonstrated an effect of MUC1 on Mg^{2+} balance. MUC1 is known to enhance cell surface localization of Ca^{2+}-selective TRP channels (TRPV5 and TRPV6). MUC1 is co-expressed with the Mg^{2+}-selective channel, TRPM6 in the kidney's distal convoluted tubule (DCT). TRPM6 is a key mediator of renal Mg^{2+} handling. Reduced TRPM6 cell surface expression in response to blockage of the epidermal growth factor receptor (EGFR), leads to urinary Mg^{2+} wasting and hypomagnesemia. We hypothesized that MUC1 influences TRPM6 cell surface expression, contributing to renal tubular reabsorption of Mg^{2+}, and that LSP-MUC1 does this less effectively than SSP-MUC1.

Methods: We examined plasma Mg^{2+} levels in *Muc1*$^{-/-}$ mice and studied MUC1 and TRPM6 expression in polarized MDCK cells and in human kidney tissue samples.

Results: We find that *Muc1*$^{-/-}$ mice are hypomagnesemic. In polarized MDCK cells in culture, MUC1 co-immunoprecipitates with TRPM6 and its binding partner, TRPM7. MUC1 enhances cell surface expression of TRPM6 and TRPM7. Although the majority of MUC1 is expressed at the apical surface of polarized epithelial cells, a small fraction is expressed basolaterally, where EGFR is located. Both in MDCK cells and in human kidney tissue, that fraction of MUC1 is reduced in the LSP variant as compared to the SSP variant. EGFR is more heavily phosphorylated in response to basolateral EGF in MDCK cells expressing SSP-MUC1 compared with LSP-MUC1, suggesting that SSP-MUC1 enhances activation of the EGFR receptor, promoting activation of TRPM6.

Conclusions: These studies provide a mechanistic explanation for the influence of MUC1 upon Mg^{2+} homeostasis. On-going studies are exploring the specific importance of kidney tubule MUC1 for TRPM6 activity and Mg^{2+} balance and EGFR-dependence of differences in TRPM6 cell surface expression associated with the LSP vs SSP MUC1 variants.

Funding: NIDDK Support, Private Foundation Support

FR-PO309

Lactating Kidneys Upregulate Expression of Cell Proliferation Genes and TRPM6 in the Distal Convoluted Tubule (DCT), Suggesting DCT Hyperplasia

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Background: Lactating females provide large quantities of minerals to nursing offspring, including Ca^{2+}, but also Mg^{2+}. Lactation-associated Ca^{2+} conservation is stimulated when parathyroid hormone (PTH)-related peptide from the mammary gland activates renal tubular PTH receptors, promoting Ca^{2+} channel expression. However, mechanisms responsible for Mg^{2+} conservation are not described.

Methods: Female C57Bl/6 mice were mated and monitored for parturition. To normalize milk-demand, litters were culled to 4 pups at post-partum day 2 (P2). Urine was collected from P12 or nulliparous females. Mice were euthanized, and blood and kidneys harvested. Bulk RNA-Seq was performed in whole kidneys.

Results: Lactation reduced urinary Ca^{2+} and Mg^{2+}, even though circulating Ca^{2+} and Mg^{2+} were similar or higher, consistent with increased tubular reabsorption. We asked whether acute PTH receptor (PTHR) stimulation reduced urinary Mg^{2+} excretion. Acute treatment of animals with 1-34 PTH accelerated phosphorus excretion and delayed Ca^{2+} excretion, as expected, but had no net effect on Mg^{2+} excretion. Transcriptomic analysis in kidneys from lactating dams revealed increased mRNA encoding the Mg^{2+}-selective ion channel, TRPM6, exclusively expressed in the distal convoluted tubule (DCT). Transcript levels of proteins involved in paracellular transport (claudins 10, 16, and 19) were not significantly different. Kidneys from lactating dams were heavier, suggesting tissue hypertrophy. Segment-specific transcripts from the proximal convoluted tubule (PCT) and DCT were up-regulated, consistent with an increase in cell number in these tubule segments. Transcripts encoding numerous cell cycle-associated proteins also increased, including CDC20, cyclin-dependent kinase 1, cyclin D1, and cyclin D3. Cyclin D1 protein abundance also increased. In the early DCT, where TRPM6 is expressed, more cells from lactating than nulliparous females stained positive for cyclin D1.

Conclusions: These suggest that DCT hyperplasia may contribute to lactation-associated conservation of essential minerals.

Funding: NIDDK Support, Private Foundation Support

FR-PO310

Magnesium Decreases Urine Supersaturation but Not Calcium Oxalate Stone Formation in Genetic Hypercalciuric Stone-Forming Rats

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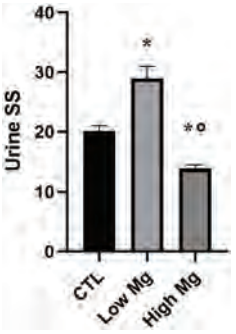
Background: This study assessed the effect of oral magnesium on urine parameters and stone formation in a genetic hypercalciuric stone-forming (GHS) rat model of human idiopathic hypercalciuria.

Methods: When fed the oxalate precursor, hydroxyproline, every GHS rat develops calcium oxalate stones. These rats, fed a normal calcium (Ca) and phosphorus (P) diet with hydroxyproline, were divided into three groups of ten rats per group: control diet with 4.0 g/kg MgO, low MgO diet (0.5 g/kg), and high MgO diet (8.0 g/kg). At baseline and at 6 weeks, twenty-four-hour urines were collected, and urine chemistry and supersaturation were determined. Stone formation was quantified.

Results: After six weeks those fed the low Mg diet had a significant reduction in urinary Mg and those fed the high Mg diet had a significant increase in urinary Mg compared to those fed the control diet. Dietary Mg did not alter urine Ca excretion while the low Mg diet led to a significant fall in urinary Ox. The low Mg diet increased urinary NH_4 and decreased urinary citrate while the high Mg diet reduced urinary NH_4 and increased urinary citrate. Urine supersaturation with respect to calcium oxalate was significantly increased with low Mg, whereas urine supersaturation was significantly decreased with high Mg. Neither a low nor high Mg diet altered kidney stone formation.

Conclusions: In genetic hypercalciuric stone-forming rats, dietary Mg significantly altered urinary CaOx supersaturation; a low Mg diet increased and a high Mg diet decreased CaOx supersaturation. There was no effect of dietary Mg on stone formation within 6 weeks of treatment.

Funding: NIDDK Support



Urine supersaturation (SS) of CaOx was differentially regulated by Mg. Results are mean ± SEM. $^{*}P < 0.05$ versus CTL; $^{o}P < 0.05$ versus low Mg.

FR-PO311

Subdued Limits E. coli Infection and Ca-Oxalate Crystallization in Drosophila Renal Tubules

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Background: Anoctamins (ANO) are Ca^{2+}-activated phospholipid scramblases, Ca^{2+}-activated Cl^{-} channels or both. Pathogenic ANO4 changes have been identified in dogs with calcium oxalate (CaOx) stones, and ANO4 protein expression is decreased in urinary extracellular vesicles of human CaOx stone formers. In *Drosophila* Malpighian tubules (MTs), *subdued* (ANO4-homolog) has these functions and participates in host defense against gram-negative bacteria. Urinary inoculation of mice with uropathogenic *E. coli* (UPEC) increases intrarenal CaOx crystallization. Thus, we investigated the interaction of *subdued* and UPEC for promoting *Drosophila* MT CaOx crystallization.

Methods: C724:Gal4, Uro:Gal4, and CG10116:Gal4 flies were crossed with UAS:subdued-RNAi flies to knockdown (KD) MT *subdued* in MT-stellate cells (SC), MT-principal cells (PC), or midgut cells (MG), respectively, with or without UPEC:eGFP. *Ex vivo*, dissected MTs were submerged for 90 min in a 10mM NaOx+UPEC:eGFP solution. *In vivo*, flies were fed a diet supplemented with 20mM NaOx+UPEC:eGFP for 4 days.

Results: SC *subdued*-KD slightly increased UPEC infection but did not change *ex vivo* or *in vivo* crystallization. PC *subdued*-KD facilitated UPEC invasion and increased crystal formation during short-term *ex vivo* assays. Neither crystal formation nor aggregation were changed by PC *subdued*-KD alone despite prolonged NaOx feeding *in vivo*. However, when UPEC was introduced with the NaOx diet, larger CaOx crystals were developed in MT of *subdued*-KD compared to wild-type flies. MG *subdued*-KD substantially increased UPEC presence in the MT lumen, nonetheless, this did not change CaOx crystallization in feeding experiments.

Conclusions: *Drosophila* are a useful genetic tool to study bacterial infection and CaOx crystallization. *subdued* KD in PCs or SCs, or UPEC infection alone did not change MT CaOx crystallization. However, the combination of PC *subdued*-KD and UPEC feeding *in vivo* increased bacterial infection and MT crystal formation with aggregation. These data suggest a role for ANO4 in bacterial-related human lithiases. U54-DK100227, R01-DK092408, F32-DK128987, FAPESP (2022/01226-1), ULTR002494, Mayo Foundation.

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

FR-PO312

SLC26A6 Plays a Major Role in Release of Soluble Oxalate from Macrophages Following Internalization of Calcium Oxalate Crystals

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Background: Accumulating evidence indicates that macrophages play an important role in recovery from oxalate-induced nephropathy. *In vitro* studies showed that macrophages can engulf and dissolve calcium oxalate crystals. *In vivo* models demonstrated that decreased renal macrophage infiltration is accompanied by increased crystal deposition, suggesting involvement of macrophages in removing oxalate crystals. Despite these findings, the mechanisms mediating crystal clearance by macrophages remain unknown. We previously showed that macrophages express transporter SLC26A6. SLC26A6 functions as a Cl-oxalate exchanger in macrophages. Our studies indicated that under steady-state conditions, SLC26A6 mediates net oxalate efflux and prevents intracellular oxalate accumulation in macrophages. In the present work, we analyzed the role of SLC26A6 in mediating the release of soluble oxalate from macrophages following internalization of calcium oxalate crystals.

Methods: Primary murine wild-type (WT) and Slc26a6-deficient ($Slc26a6^{-/-}$) macrophages were exposed to calcium oxalate crystals for up to 48 hours. Internalization of oxalate crystals by macrophages was analyzed by transmission electron microscopy (TEM). After crystal uptake, macrophages were washed and re-incubated in an oxalate-free medium. Release of soluble oxalate after crystal internalization was measured as appearance of oxalate in the supernatant by use of an enzymatic assay.

Results: We found that WT and $Slc26a6^{-/-}$ macrophages are equally capable of oxalate crystal internalization. The presence of soluble oxalate increases with time in the supernatant of both WT and $Slc26a6^{-/-}$ macrophages after preloading with oxalate crystals. When compared with WT macrophages, macrophages from $Slc26a6^{-/-}$ mice showed greatly reduced release of soluble oxalate after 48 hours.

Conclusions: Our findings indicated that soluble oxalate is released from macrophages following internalization of calcium oxalate crystals. $Slc26a6^{-/-}$ macrophages demonstrated greatly reduced soluble oxalate release compared to WT macrophages. We therefore concluded that Slc26a6 plays a major role in the release of soluble oxalate from macrophages following internalization of calcium oxalate crystals.

Funding: Government Support - Non-U.S.

FR-PO313

Gender Difference in Plasma and Urinary Oxalate Levels in a Mouse Model for Primary Hyperoxaluria Type 1

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Background: Mutations in the alanine–glyoxylate amino transferase gene (Agxt) cause primary hyperoxaluria type I (PH1). A mouse model for PH1 was previously reported, with males having ~17.6% higher urine oxalate compared to females.

Methods: mRNA and protein expression levels were assessed by qPCR and immunoblotting.

Results: We now observed that males have significantly higher (~1.7-fold) urine oxalate compared to females (24-h urine oxalate in μg/g body weight: wild-type = 1.60±0.18; males = 6.69±0.32; females = 3.89±0.14). Males also have significantly higher (2.1-fold) plasma oxalate (μM: males = 4.86±0.86; females = 2.35±0.39). We first confirmed that the observed gender difference in oxalate levels is not due to differences in genotyping by showing that both males and females are homozygous for $Agxt^{-/-}$. Anion transporters SLC26A1 (A1) and SLC26A6 (A6) play important roles in oxalate homeostasis. Proximal tubular oxalate secretion involves oxalate entry into the cell from blood via A1, and then its secretion into the urine via A6. A gender difference in liver and kidney A1 protein expression exists (with no change in mRNA), where higher A1 expression is observed in male compared to female rats and is associated with significantly higher plasma (~1.8-fold) and urine (~2-fold) oxalate levels in males (including high renal oxalate secretion). Male rats also have higher liver sulfate-oxalate exchange, which could lead to elevated plasma oxalate. We therefore examined whether gender differences in A1 and/or A6 expression contribute to the observed differences in urine and plasma oxalate levels in PH1 mice. Compared to males, females have significantly reduced kidney A6 mRNA (44.6%, using qPCR) and total glycosylated A6 protein (>40%) expression. There were no significant differences in liver and kidney (~19% reduction) A1 mRNA expression levels. We could not assess A1 protein expression due to lack of working antibodies, with reduced expression expected based on data from rats.

Conclusions: We conclude that male PH1 mice have significantly higher urine and plasma oxalate levels compared to females, and that differences in kidney A6 and/or A1 (liver and/or kidney) expression potentially contribute to the observed gender difference.

FR-PO314

Uremic Toxin Indoxyl Sulfate (IS) and Parathyroid Hormone (PTH) Interact and Affect Osteocyte Signaling and Function

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Background: Osteocytes are the master regulator of bone remodeling, and studies in CKD patients and animals show defective osteocyte function and maturation regardless of the PTH level suggesting other CKD specific factors may affect osteocytes. Indoxyl sulfate (IS) has been shown to have an effect on osteoclasts and osteoblasts, but the IS effect on osteocytes has not been evaluated. IS is a potent endogenous ligand for aryl hydrocarbon receptor (AhR) which is critical in the removal of toxins and can lead to inflammation, changes in steroid hormones and altered MAP kinase signaling.

Methods: We therefore evaluated the effect of IS with and without PTH on differentiation, signaling, and mineralization in mature osteocytes (day 35) and in early osteocytes when mineralization is occurring (day 14) using IDG-SW3 cell line.

Results: The results demonstrated that in mature osteocytes, the addition of IS for 24 hrs dose dependently increased the expression of bone forming genes SOST and Dkk1, bone resorbing genes RANKL/OPG ratio and oxidative stress genes NOX1 & NOX4 (all $P<0.01$) but no effect on FGF23. In contrast, PTH treatment for 24 hrs decreased SOST by 135 fold, Dkk1 by 155 fold ($p<0.01$) and increased RANKL/OPG ration by 1080 fold ($p<0.001$) with no effect on NOX. IS, but not PTH, inhibited MAP kinase activity (ERK1/2; $p <0.002$) and induced AhR activity assessed by downstream CYP1A1 (increased by10 fold) & CYP1B1 (increased by 4.5-fold) ($p<0.001$). Thus, in mature osteocytes, PTH and IS have opposing effects on osteocyte genes, oxidative stress, mediated by different mechanisms. To assess the impact of IS and PTH on mineralization, osteocytes were treated with IS or PTH alone or together for 14 days. IS and PTH both decreased alkaline phosphatase activity and together reduced further. IS also reduced mineralization but PTH had no effect. PTH increased cAMP secretion by 90%, whereas IS decreased cAMP secretion by 60% alone and significantly reduced PTH induced cAMP secretion in osteocytes ($p<0.002$).

Conclusions: In conclusion, IS and PTH have additive effects to inhibit early osteocyte mineralization, and opposing effects on mature osteocyte signaling and the gene expression involved in regulation of bone remodeling and differentiation. These results indicate IS is a major uremic toxin affecting osteocytes.

Funding: Private Foundation Support

FR-PO315

Evaluation of Mineral and Bone Metabolism in Living Kidney Donors: A 10-Year Follow-Up

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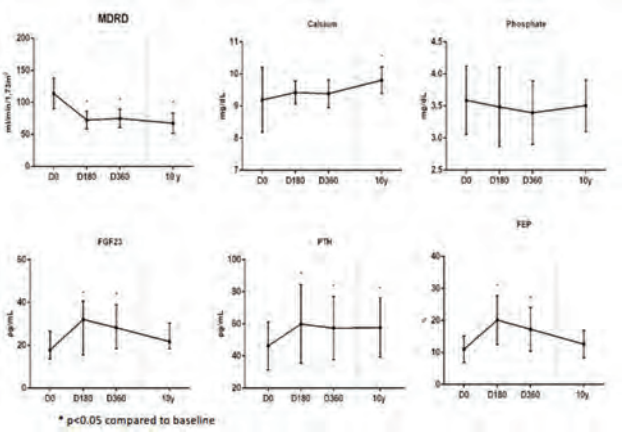
Background: Living kidney donors (LKD) experience an abrupt decline in glomerular filtration rate (GFR) resulting in abnormalities of mineral and bone metabolism (MBD), and this may have implications for the skeletal health. We prospectively studied acute and long term MBD adaptation of LKD from two kidney transplant centers (Brazil and USA).

Methods: We have measured renal function and MBD parameters longitudinally after live kidney donation (KD, baseline – D0, day 1, 14, 180 and 360 post-operatively) in 74 live donors (40ys, 73% female, 54% Brazilian). A subset of 20 brazilian LKD were reassessed after 10 years of KD.

Results: At baseline, Brazilian LKD presented lower FGF23 (20.8 vs 80.1 pg/mL*) and higher PTH (47.4 vs 40.1*) than their US counterparts. GFR decreased 41% just after KD, but improved 11% during the first year. PTH increased on D1 (65±30 vs D0 44±14 pg/mL*), as well as FGF23, which remained significantly higher at D360 (60 vs D0 44.4 pg/mL*). There was a reduction in serum phosphate (3.3±0.6 vs D0 3.7±0.5 mg/dL*) and calcium (7.9±0.5 vs D0 9.4±0.4 mg/dL*) on D1, which returned to baseline levels at D180 (3.5±0.6 and 9.4±0.5mg/dL, respectively). A higher fractional excretion of phosphate (FEP) was noted since D14. After 10 years of KD, Brazilian LKD presented a significant reduction in GFR [65 (55-69)ml/min] and in FGF23 [21.7 (18-30)pg/mL], as well as an increase in PTH [57 (42-66)pg/mL] and calcium levels. Despite that, FEP reduced and phosphate levels remained stable (figure 1). *$p<0.05$

Conclusions: The abrupt decline in kidney mass is associated with an increase in PTH and FGF23, which could not be explained by phosphate retention. In a long term evaluation, LKD showed a sustained drop in GFR, accompanied by an increase in PTH and calcium levels, while the reduction in FGF23 and FEP maintained phosphate stable.



FR-PO316

Mineral and Bone Biomarkers Associate with Adverse Cardiovascular Outcomes and Mortality Within the German Chronic Kidney Disease (GCKD) Cohort

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Background: Mineral and bone disorders (MBD) in chronic kidney disease (CKD) are tightly linked to cardiovascular disease. This study aimed to compare prognostic information of nine MBD biomarkers to determine those associating best with adverse cardiovascular (CV) outcomes and mortality in pre-dialysis CKD.

Methods: In 5217 participants of the German CKD (GCKD) study, enrolled for glomerular filtration rate (GFR) between 30-60 ml/min/1.73m² or overt proteinuria, serum osteoprotegerin (OPG), fibroblast growth factor 23 (FGF23), intact parathyroid hormone (iPTH), bone alkaline phosphatase (BAP), cross-linked C-telopeptide of type 1 collagen (CTX1), procollagen 1 intact N-terminal protein (P1NP), phosphate, calcium, and 25-OH vitamin D were measured at baseline. Participants with missing values among these parameters (N = 971) were excluded. Hazard ratios (HRs) for associations of OPG, FGF23, iPTH, BAP, CTX1, P1NP, phosphate, calcium, and 25-OH vitamin D each alone and in combination, with 1) CV death, 2) non-CV death, 3) combined major adverse CV events (non-fatal MACE), and 4) hospitalization for congestive heart failure (CHF) were estimated using Cox regression analyses adjusted for major clinical risk factors for CKD.

Results: During a median follow-up of 6.5 years, 385 non-CV deaths, 173 CV deaths, 643 non-fatal major adverse CV events (MACE) and 367 hospitalizations for congestive heart failure (CHF) were observed among 4246 participants. OPG and FGF23 were associated with all outcomes, with the highest hazard ratios (HRs) for OPG. In the final Cox regression model, adjusted for CV risk factors and all other investigated biomarkers, every standard deviation increase of OPG was associated with non-CV death (HR 1.84, 95%CI 1.41-2.40), CV death (HR 2.33, 95%CI 1.61-3.38), MACE (HR 1.42, 95%CI 1.15-1.76) and hospitalization for CHF (HR 2.13, 95%CI 1.62-2.79).

Conclusions: Out of the nine biomarkers examined, stratification based on serum OPG identified CKD patients best who were at highest risk for any adverse CV outcome and mortality.

FR-PO317

Targeting Probiotics in Hyperphosphatemia for Patients with CKD

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Background: Hyperphosphatemia and secondary hyperparathyroidism are critical consequences in chronic kidney disease (CKD) patients. Current therapeutic strategies to lower serum phosphate are dietary phosphate restriction and phosphate lowering drugs.

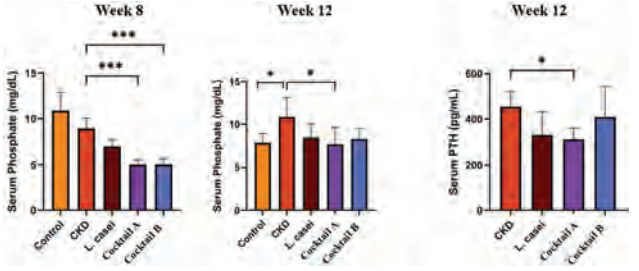
Since increased paracellular intestinal phosphate absorption is considered a main factor for hyperphosphatemia, we designed a probiotic cocktail to promote gut barrier, which could subsequently reduce phosphate absorption.

Methods: *B. longum* TCU1 and *L. salivarius* TCUA were tested in HK2 cell model to be able to promote zonula occluding-1 (ZO-1) expression and had anti-inflammatory effects. The Cocktail A including 10^9 CFU of *B. longum* TCU1 and *L. salivarius* TCUA, inulin and chitosan oligosaccharide (COS), and Cocktail B which was Cocktail 1 added with maltodextrin were used. Cisplatin-induced CKD rats were divided into (a) Control, (b) CKD, (c) CKD with *L.* casei (commercial probiotic) (d) CKD with Cocktail A and (e) CKD with Cocktail B (n=8 each) were experimented for 12 weeks. Blood was collected to measure calcium (Ca), phosphate (P) and parathyroid hormone (PTH). Immunohistochemistry of intestinal ZO-1 was measured.

Results: All rats with CKD had higher serum creatinine than Control throughout the experiment. AT Week 4 & 8, CKD rats treated with probiotics had lower serum P than CKD rats, while week 12, only CKD rats with Cocktail A had significantly lower serum P than CKD, without serum Ca change. In addition, CLD rats with Cocktail A had lower serum PTH level than CKD rats at week 12. Intestinal ZO-1 expression in Cocktail A rats had non-significantly increased compared to the CKD rats as well.

Conclusions: Our study demonstrated the potential therapeutic effects of targeting probiotic cocktail A, which included *B. longum*, *L. salivarius*, inulin and COS, to ameliorate hyperphosphatemia and hyperparathyroidism in rats with CKD. Further study in clinical trial of targeting probiotic had been funded.

Funding: Government Support - Non-U.S.



FR-PO318

Tenapanor in Combination with Phosphate Binders Improves Short- and Long-Term Control of Serum Phosphate (sP) in Patients on Dialysis with Hyperphosphatemia

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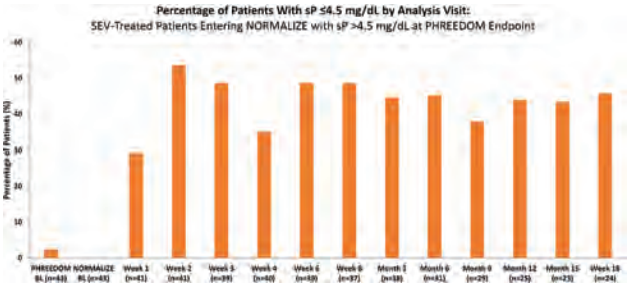
Background: Tenapanor (TEN) is a phosphate absorption inhibitor that blocks paracellular phosphate absorption by local inhibition of the intestinal sodium hydrogen exchanger isoform 3 (NHE3). In the 4-week AMPLIFY (NCT03824587) study, TEN in combination with the phosphate binder (PB) sevelamer (SEV) allowed more patients (pts) to achieve target sP. The NORMALIZE (NCT03988920) extension study was designed to help pts achieve sP ≤4.5 mg/dL (relaxed to ≤5.5 mg/dL with protocol amendment). Pts who completed the 1-year safety comparator arm (SEV) of PHREEDOM added TEN to control sP for up to 18 months. We report early and long-term control of sP in the subset of PHREEDOM pts who were inadequately controlled (sP >4.5 mg/dL) on SEV monotherapy.

Methods: 61 pts from the SEV arm of PHREEDOM (NCT03427125) entered NORMALIZE. Of these 61 pts, 43 (70.5%) had sP >4.5 mg/dL at NORMALIZE baseline when TEN 30 mg bid was added to the SEV dose. After starting TEN, SEV was decreased as long as sP was controlled, with the intention to decrease/eliminate SEV if possible. TEN could be up- or down-titrated in 10 mg increments, with a maximum dose of 30 mg bid, based on sP level and/or tolerability.

Results: Of the 43 pts entering NORMALIZE with sP >4.5 mg/dL, median baseline SEV use was 9 pills/day, dropping to 6 pills/day at the end of NORMALIZE. Percentage of pts achieving sP ≤4.5 mg/dL at each study visit is shown in the **Figure**. Adverse events reported were similar to those seen in other TEN studies; no new safety issues were identified.

Conclusions: The NORMALIZE study confirms the findings from AMPLIFY that TEN in combination with SEV enables a greater percentage of pts to achieve sP ≤4.5 mg/dL with no new safety issues. These data also demonstrate that TEN in combination with SEV can achieve long-term sP control in patients when SEV monotherapy fails to normalize sP.

Funding: Commercial Support - Ardelyx, Inc.



FR-PO319

Extended-Release Calcifediol Overcomes Impact of Low eGFR on Vitamin D Metabolism

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Background: Serum 25-hydroxyvitamin D (25D) falls below 30 ng/mL and serum 1,25-dihydroxyvitamin D (1,25D) becomes undetectable as chronic kidney disease (CKD) progresses. Cholecalciferol or ergocalciferol are widely prescribed but cannot reliably raise 25D and lower elevated parathyroid hormone (PTH). They are replaced/combined with calcitriol (or 1α-OH analog) when PTH inevitably rises, contrary to the current KDIGO guideline, with justification that too much renal CYP27B1 has been lost, limiting hormone production. Randomized clinical trials (RCTs) prove that extended-release calcifediol (ERC) safely and sufficiently raises serum 25D and 1,25D, and effectively treats elevated PTH despite declining eGFR, but the mechanism is not fully elucidated and requires further investigation.

Methods: Changes in serum $25D_3$, $24{,}25D_3$ and $1{,}25D_{(3)}$ during ERC treatment in four RCTs were compared as a function of eGFR. In one study, 80 non-CKD patients were treated for 4 weeks (wks) with 300 mcg/day (d) for three ds and 60 mg/d thereafter. In two studies (pooled), 285 non-dialysis patients with eGFR of 30.6±0.6 (mean±SE) mL/min/1.73m^2 were treated for 26 wks with 210 mcg/wk increasing, as needed, to 420. In another, 33 hemodialysis (HD) patients were treated for 26 wks with 900 mcg/wk.

Results: In these RCTs, baseline 25D was 37.7±12.1, 19.9±0.3 and 23.6±2.2 ng/mL, respectively. Mean 1,25D at baseline was inversely proportional to eGFR, ranging from 72.3±3.3 pg/mL in non-CKD patients to 9.4±1.0 pg/mL in HD patients. During treatment, mean $25D_3$ rose to >70 ng/mL with peak levels proportional to dose. Mean $1{,}25D_{(3)}$ rose linearly with $25D_3$ at similar rates in all eGFR groups but mean $24{,}25D_3$ (<2.9 ng/mL at baseline) increased at rates proportional to eGFR.

Conclusions: ERC reliably raised both serum $25D_3$ and $1{,}25D_{(3)}$, irrespective of eGFR, making it an attractive alternative to hormones for treating persistently rising PTH in CKD stages 3-4. Declining eGFR did not affect ERC's ability to increase the rate of $1{,}25D_{(3)}$ production, indicating that hormone generation occurred in extra-renal tissue. Increases in serum $24{,}25D_3$ were dependent on $25D_3$ elevation and limited by declining eGFR, suggesting that this metabolite derives solely from the kidney and is not disproportionately increased by ERC.

Funding: Commercial Support - OPKO Health, CSL Vifor

FR-PO320

Comparative Effectiveness of Cinacalcet Delivered Daily at Home vs. Three Times Weekly In-Center

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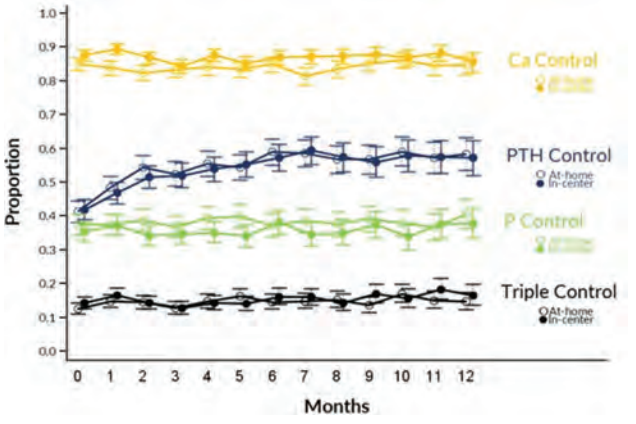
Background: Chronic kidney disease-mineral and bone disorder (CKD-MBD) is a common syndrome found in end stage kidney disease (ESKD) patients and marked by dysregulation of three chemicals in the blood: calcium, phosphorus and parathyroid hormone (PTH). A recent review of the evidence showcases that treatment of CKD-MBD should be based on better control of all 3 elements. Cinacalcet, an oral calcimemetic (a PTH-lowering therapy), is one of many daily treatments that ESKD patients are often prescribed, contributing to a high total pill burden. Recent clinical trials have provided evidence that in-center administration of cinacalcet might be a safe and effective treatment option. In this study we sought to evaluate the comparative effectiveness of cinacalcet delivered daily at home versus three times weekly in-center.

Methods: This was a retrospective matched cohort study of 2,894 matched adult in-center hemodialysis patients at a dialysis provider between January 01, 2008 and September 30, 2022 who initiated their first ever calcimemetic therapy (non-exposed group: at home use or exposed group: in-center administration at the end of dialysis). Patients were matched (1:1) on: age at index date, body mass index, cinacalcet dose, and baseline phosphorous, calcium, and PTH. Patients were followed until censoring (i.e., lost to follow up) or 12 months after baseline, whichever occurred first. The primary outcome was achieving triple control of PTH, phosphorous and calcium.

Results: Fitted proportion model results show no statistical difference in achieving triple control between in-center or at home cinacalcet administration groups (Figure 1). In addition, there was no meaningful difference in control of any component.

Conclusions: In an observational, well-matched cohort administering cinacalcet in-center at the end of dialysis is non-inferior as prescribing cinacalcet for use at home.



FR-PO321

Denosumab and Fracture Events in Patients on Hemodialysis

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Background: It is known that the risk of fracture is much higher in patients with dialysis than general population. In recent years, osteoporosis treatment has become more widespread including hemodialysis patients. However, there are few studies that analyzed the efficacy of denosumab for fracture events in hemodialysis patients.

Methods: We conducted a retrospective observational study of inpatients and outpatients at a maintenance hemodialysis facility to clarify the association between denosumab use and fracture events. The study term was from December 2013 to December 2022 and compared the incidence of fractures in the denosumab-treated and non-treated groups. The analysis was performed using the Cox proportional hazards model with the presence or absence of fracture occurrence as the objective variables and the presence or absence of denosumab use, various patient backgrounds, and laboratory values as explanatory variables.

Results: A total of 263 patients were enrolled in the study, with a mean age of 71.7 ± 12.1 years. Among them, 35.4% were female, and the median duration of hemodialysis was 48 [IQR 4-114] months. The number of patients who developed fractures was 52 in the non-treated group and 8 in the denosumab-treated group. After adjustment for factors such as age, gender, prior fracture, serum intact parathyroid hormone, serum TRACP5b and bone specific alkaline phosphatase, analysis using the Cox proportional hazards model showed that patients treated with denosumab were significantly less likely to develop fractures (HR 0.42 [95% CI: 0.18-0.98]). There were no significant differences in the incidence of hypocalcemia (OR 2.05[95%CI:0.79-5.29]. Our study has several limitations, such as single center study in Japan and small sample size, but our results have the potential to widespread fracture treatment by using denosumab for hemodialysis patients.

Conclusions: Our results suggest that denosumab may be effective in preventing fractures in hemodialysis patients. Further studies with larger sample sizes are warranted to validate and enhance the outcomes of this study.

FR-PO322

Histone Acetyltransferase p300 Inhibition Attenuates Kidney Fibrosis Under Diabetic Conditions

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Background: Diabetic nephropathy, the major cause of chronic kidney disease, is associated with progressive renal fibrosis. Transforming growth factor (TGF)-β1 plays important roles in extracellular matrix accumulation in diabetic nephropathy. Recently, acetyltransferase p300 has been shown to mediate intracellular TGF-β1 activity through facilitating Smad function. Therefore, in this study, the effect of p300 inhibition on kidney fibrosis under diabetic conditions was investigated to assess the therapeutic potential of p300 modulation.

Methods: Primary tubular epithelial cells (TECs) from C57BL/6 mice were treated with TGF-β1 with or without histone acetyltransferase p300 siRNA transfection of A485, a selective inhibitor for p300. For in vivo experiments, kidney samples were obtained from streptozotocin induced diabetic mice were administered with A485 (1mg/kg) oral gavage for 6 weeks.

Results: In vitro, TGF-β1 (5ng/ml) treatment significantly upregulated p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen mRNA and protein expressions in TECs. These increases were attenuated significantly when TECs were transfected with p300 siRNA. Similar findings were found when the cells were treated with p300 specific inhibitor A485 (100nM). In vivo, the mRNA and protein expression of p300, PAI-1, connective tissue growth factor (CTGF), fibronectin, and type I collagen were significantly increased in kidney samples form DM mice compared to non-diabetic control mice. Oral A485 administration abrogated these increases significantly. In addition, the increased blood urea nitrogen and albuminuria levels were significantly attenuated with oral A485 treatment in the diabetic mice. Immunohistochemistry and Sirius Red staining also revealed that fibronectin expression was significantly higher and tubulointersititial fibrosis was significantly worse in diabetic mice kidneys compared with control mice. These changes were ameliorated by A485 treatment.

Conclusions: These findings suggest that inhibition of histone acetyltransferase p300 could improve diabetic-induced tubular fibrosis and may be a potential therapeutic strategy for diabetic nephropathy.

FR-PO323

Pharmacologic Pyruvate Kinase M2 Activation Maintains Mitochondrial Metabolism by Regulating the Interaction Between HIF-1α and PGC-1α in Diabetic Kidney Disease

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Background: Previous findings have indicated that pyruvate kinase isoform M2 (PKM2) activation may protect kidney injury by improving mitochondrial dysfunction and anerobic glycolysis. However, the underlying molecular mechanisms are incompletely understood. Here, we aimed to clarify mechanistic link between PKM2 and HIF-1α-mediated PGC-1α suppression in animal model of diabetic kidney disease (DKD).

Methods: In an animal DKD study, *db/db* mice were intraperitoneally injected with TEPP-46, a PKM2 activator. *In vitro*, primary cultured renal tubular epithelial cells (RTECs) from C57BL/6 mice were treated with high glucose (HG) alone and HG+TEPP-46. The interactions between HIF-1α and PGC1α were further investigated using HIF-1α overexpression and HIF-1α knockdown. PKM2 activity, energy metabolism, mitochondrial mass, dynamics, and morphology, and cell injury markers were examined.

Results: In the kidney of *db/db* mice, diabetes resulted in decreased PKM2 activation, aberrant glycolysis, impaired fatty acid oxidation, and decreased mitochondrial mass, integrity, and function. These changes were accompanied by increased HIF-1α and decreased PGC-1α levels. Increased fibrosis and apoptosis markers were observed in diabetic mice. In addition, periodic acid–Schiff (PAS) staining revealed significant tubular injury in *db/db* mice. The direct PKM2 activation by TEPP-46 treatment attenuated the dysregulated energy metabolism, mitochondrial dysfunction, and cell death. Similar alterations were also observed in HG-treated RTECs, which were restored by TEPP-46. Notably, a chromatin immunoprecipitation assay revealed that HIF-1α directly binds to the regulatory region of the *Ppargc1a* promoter and that this interaction is inversely dependent on PKM2 activation. A luciferase reporter assay showed that HIF-1α regulates the transcriptional activity of PGC-1α in a PKM2-dependent manner. Moreover, *Hif1a* overexpression suppressed PGC-1α and induced aberrant energy metabolism, mitochondrial dysfunction, and apoptosis. Conversely, these changes were reversed by HIF-1α knockdown.

Conclusions: PKM2 activation improves impaired mitochondrial metabolism and function by modulating HIF-1α and PGC-1α interactions in DKD.

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FR-PO324

The Role of FRAS1 Loss of Function in Rapid Renal Decline: Insights into the Downregulation of NPR1

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Background: Progressive renal decline, leading to end-stage kidney disease (ESKD), is a hallmark of diabetic nephropathy. Recently, we identified a rare missense variant (p.R2516C) in the FRAS1 gene, which plays a crucial role in maintaining glomerular integrity as an extracellular matrix protein, in a family affected by both diabetes and ESKD. This study aims to investigate the impact of the p.R2516C variant on FRAS1 function and its potential involvement in the progression of ESKD.

Methods: To examine the functional consequences of the variant, we employed CRISPR-Cas9 gene editing technology to generate three distinct HEK293 cell lines. These included two FRAS1 knock-in cell lines, one harboring the p.H2520H synonymous mutation as a control and the other carrying the missense p.R2516C variant. Additionally, a FRAS1 knock-out cell line was generated. RNA sequencing was conducted on these cell lines to identify genes with differential expression patterns.

Results: Through comprehensive analysis of the RNA sequencing data, we identified 119 significantly differentially expressed genes following FRAS1 perturbation, consisting of 57 upregulated and 62 downregulated genes. Further investigation focused on the top 10 upregulated and 10 downregulated genes, which revealed NPR1 (Natriuretic Peptide Receptor A/Guanylate Cyclase A) as an intriguing downregulated candidate gene whose downregulation in diabetic nephropathy and other forms of kidney disease is further supported by publicly available transcriptomic datasets.

Conclusions: The findings of this study highlight the positive regulatory relationship between FRAS1 and NPR1, while emphasizing the contribution of FRAS1 LOF to rapid

renal decline. This study provides compelling evidence that the LOF of FRAS1 leads to the downregulation of NPR1, ultimately resulting in rapid renal decline. Given the crucial role of NPR1 in maintaining normal renal function, it represents a promising therapeutic target for individuals affected by FRAS1 LOF, diabetic kidney disease (DKD), or chronic kidney disease (CKD). Further investigations are warranted to explore the therapeutic implications of targeting NPR1 in these conditions.

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FR-PO325

Cell Surface GRP78 and α2M* Are Important Mediators of Tubulointerstitial Fibrosis in CKD

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Background: Diabetic kidney disease (DKD) is characterized by glomerular accumulation of extracellular matrix (ECM) proteins followed by the development of tubulointerstitial fibrosis. We recently showed the endoplasmic reticulum resident GRP78 translocates to the cell surface (csGRP78) in response to HG, promoting profibrotic responses in mesangial cells. We further implicated activated alpha 2 macroglobulin (α2M*) as an activator of csGRP78 signaling. Based on increased expression of this receptor-ligand pair in both DKD and non-diabetic chronic kidney disease (CKD) mouse models, we thus wanted to elucidate this signaling pathway's influence on other cell types relevant to kidney disease (proximal tubule epithelial cells (PTEC) and renal fibroblasts (RF)) as well as a potential role for TGFβ1-induced signaling.

Methods: PTEC and RF were treated with 30mM HG or 5ng/mL TGFβ1 plus csGRP78 or α2M* inhibitors. Standard molecular biology techniques were used for assessment. Immunohistochemistry staining was conducted on kidney tissues from mouse models of DKD and CKD.

Results: We observed increased localization of GRP78 to the surface of PTEC and RF with either HG or TGFβ1 stimulus. Further, α2M expression and activation were shown to be increased by both HG and TGFβ1. Inhibition of either csGRP78 or α2M* prevented HG and TGFβ1-induced ECM production (fibronectin and collagen IV). By HG treatment, downstream TGFβ1 signaling (measured by activation of Smad3) was attenuated by csGRP78 or α2M* inhibition. Interestingly, we observed no effect on Smad3 activation with csGRP78 or α2M* inhibition with TGFβ1 treatment. We hypothesized a potential role for non-canonical TGFβ1 signaling being mediated by csGRP78/ α2M*. We next assessed the known non-canonical TGFβ1 signaling molecules yes associated protein (YAP) and transcriptional co-activator with PDZ-binding motif (TAZ). Here we observed that inhibition of either csGRP78 and α2M* attenuated YAP and TAZ expression under both HG and TGFβ1 treatment. This implicates Smad-dependent and independent signaling being mediated by csGRP78/ α2M*.

Conclusions: These data support a role for csGRP78/α2M* in mediating HG or TGFβ1-induced profibrotic signaling in PTEC and RF. Inhibition of this signaling pathway represents a novel target for preventing DKD or CKD-associated fibrosis which we are currently evaluating *in vivo*.

Funding: Government Support - Non-U.S.

FR-PO326

Adam17 Inhibition Moderates Interstitial Fibrosis and Macrophage Infiltration in Type 1 Diabetes (TD1) Mouse Model

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Background: ADAM17 participates in the release into circulation of inflammatory and fibrotic molecules, such as TNF-a actively involved in the progression of DN. We studied the effect of specific deletion of ADAM17 in the endothelium and renal tubule in a T1DM mouse model demonstrating its participation in the progression of kidney damage. As ADAM17 is also expressed in other cell types we will study the effect of the complete deletion of Adam17 in T1DM mouse.

Methods: We studied total inducible *Adam17* knockout (ADAM17KO) male mice that were diabetic by STZ injection (DB). Glycemia, mesangial index (PAS staining), number of podocytes and positive area of a-SMA (by immunohistochemistry) were determined. We also studied the protein expression of the cytokine MCP-1 by Western Blot.

Results: The mesangial index value observed in the 20wk-DB group decreased significantly in the ADAM17KO group. Podocyte loss in DB group was not observed in the KO-DB group. For interstitial fibrosis, the intensity and location of a-SMA was significantly lower in the ADAM17KO group. In addition, the total deletion of *Adam17* partly prevented the infiltration of macrophages assessed by the expression of MCP-1 in the protein extract of the renal cortex.

Conclusions: Complete inhibition of Adam17 expression in T1DM mice prevents fibrosis progression and protects the glomerulus from hypertrophy. At the same time, it reduces macrophage infiltration, limiting the inflammatory response induced by diabetes. We demonstrate the influence of Adam17 on macrophages to reduce the expression of TNF-a partly responsible for the progression of diabetic nephropathy.

	Blood glucose (mg/dL)	Mesangial index	% podocytes	α-SMA positive area	MCP1 protein expression
ADAM17WT-NoDB	203,6±6,0	0,23±0,001	0,33±0,01	3,65±0,47	0,84±0,05
ADAM17WT-DB	580,6±17,5*	0,25±0,001*	0,30±0,01#	6,04±0,93*	1,08±0,06*
ADAM17KO-NoDB	181,7±11,3	0,25±0,001	0,33±0,01	2,31±0,28	0,99±0,06
ADAM17KO-DB	575,1±8,8*	0,21±0,001*$	0,35±0,005	3,72±0,37*$	0,92±0,05*
*ps0,05 DB vs NoDB $ps0,05 KO vs WT					

FR-PO327

Functional Coupling of ANXA1 and KCa3.1 Attenuated Renal Tubulointerstitial Fibrosis in Diabetic Kidney Disease

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Background: Tubulointerstitial fibrosis (TIF) is the common pathway and major pathological basis for almost all kinds of renal disease including diabetic kidney disease (DKD) progress into chronic kidney disease, thus it is essential to reveal its pathogenesis. Previous research showed that up-regulation of intermediate-conductance Ca^{2+}-activated K^+ channel (KCa3.1) contribute to TIF. However, targeting the channel directly have unfortunately side-effect in clinic trials.

Methods: Molecular docking and co-immunoprecipitation were used to detect the binding capability between ANXA1 and KCa3.1. HEK293T and HK-2 cell line were cultured and transfected to confirm whether ANXA1 can be modified by SUMOylation. SUMOylation sites were predicted by SUMOsp2.0, and ANXA1 lysine residues K113, K161, K185, K257 and K312 were mutated to test the relative site change. Biotinylation assay were used to evaluate the ANXA1 activation to KCa3.1 surface expression. Western blot was used for evaluate KCa3.1-mediated TGF-β/Smad signaling activation to detect the expressions of α-SMA, fibronectin, collagen matrix and Smads.

Results: We found that ANXA1, an endogenously generated molecules that promote the physiological resolution of inflammation, could interact with KCa3.1. Mechanistic studies demonstrated that intracellular ANXA1 could be modified by SUMOylation and that SUMOylation primarily occurs at three lysine residues K113, K161, and K257 in hyperglycemia/high glucose stimulation, thereby SUMOylated ANXA1 regulating the membrane transport and lysosomal degradation of KCa3.1 channel protein, and ultimately delaying KCa3.1-mediated TGF-β/Smad activation and TIF progression in DKD state.

Conclusions: Our study suggests that ANXA1-KCa3.1 functional coupling may be a promising therapeutic strategy to mitigate DKD-induced TIF.

FR-PO328

Diet Modification to Drive Fibrotic Response in Diabetic Kidney Disease (DKD) Model

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Background: Diabetes is a major cause of chronic kidney disease, affecting approximately 25% of diabetic patients. Several rodent models of Diabetic Kidney Disease (DKD) have been developed; however, drug discovery is hampered by the lack of preclinical rodent models with clinically relevant urinary albuminuria creatinine ratio (UACR) and/or histological fibrosis observed in humans. Here we sought to develop a new translational mouse DKD model incorporating streptozotocin (STZ)-induced hyperglycemia, mild hypertension from nitric oxide synthase inhibition, and dietary modification to drive the fibrotic response, on top of a uninephrectomized (UNx)/ hyperfiltration phenotype.

Methods: UNx Male 129S1 mice (Jackson Labs) were uninephrectomized at 7 weeks old and given STZ injections (5-40mg/kg IP) to induce diabetes. Trimethylamine n-oxide (TMAO) and Choline formulated in D12450J low fat diet (LFD) and D12492 high fat diet (HFD) for rodents (Research Diets). 100mg/L nitroarginine (L-NNA) provided in drinking water. Body weight, food intake and fed blood glucose collected weekly and urine collected biweekly for 8 weeks. At the end of treatment, animals euthanized, kidneys collected for collagen and histological analysis. Terminal plasma analyzed for blood chemistry, TMAO and circulating dietary precursors of TMAO.

Results: STZ-induced hyperglycemia confirmed in the mice (396.3±3.6mg/dL). Daily TMAO and choline intake, both LFD and HFD diet admixtures were similar (Choline: LFD 166.9±7.6g/kg; HFD 178.4±4.6g/kg; TMAO: LFD 54.1±1.8g/kg; HFD 65.2±2.6g/kg). Betaine, Carnitine and Choline dietary TMAO precursors increased in both LFD and HFD choline admixtures. TMAO did not significantly change any dietary precursor levels compared to control. UACR significantly increased after 8 weeks in both Choline supplemented, LFD (p=0.0024; 72.4±13.6) and HFD (p=0.0472; 59.7±8.2). The primary histological lesion observed was tubulointerstitial collagen thickening, seen in LFD TMAO & Choline, and HFD Choline groups.

Conclusions: Refinement of a hypertensive, diabetic, hyperfiltering mouse kidney disease model using dietary supplements to increase renal fibrosis observed to achieve comparable kidney functional impairment to that of human DKD patients, with some evidence of histological damage. This animal model may be used to assess preclinical efficacy of investigational therapies for DKD.

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FR-PO329

Loss of LRG1 Effectively Curbs Diabetes-Induced TGF-β Signaling in Glomerular Endothelial and Mesangial Cells to Attenuate Diabetic Kidney Disease (DKD)

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Background: Despite the immense burden of DKD, optimal therapies remain limited. Although TGF-β is a well-established central mediator of DKD pathogenesis, because of its pleiotropic actions in multiple organ systems, its indiscriminate blockade is not desirable. Moreover, evidence of diverse kidney cell-specific effects of TGF-β, both deleterious and protective, continues to emerge. TGF-β signaling is strongly influenced by cell type- and context-dependent regulators and determinants, and we previously showed that cell surface modulators, such as LRG1 and BAMBI, can significantly influence TGF-β signaling in kidney disease. Since LRG1 is increased in glomerular ECs in DKD, we posited that LRG1 loss may shift the balance away from excessive pathological endothelial TGF-β signaling to attenuate DKD, without a full systemic blockade of TGF-β signaling associated with unwanted side effects.

Methods: Type 1 diabetic OVE26 mice were crossed with *Lrg1*$^{-/-}$ mice to generate OVE26;*Lrg1*$^{-/-}$ mice, and DKD progression was assessed by renal function and histopathologic parameters. scRNA-seq was employed for kidney single-cell gene expression analysis of control and diabetic mice.

Results: scRNA-seq confirmed that increased LRG1 is limited to GECs in early diabetic kidneys. As anticipated, LRG1 loss significantly attenuated diabetic glomerulopathy including podocyte loss, and improved renal function. scRNA-seq analysis showed that LRG1 loss was sufficient to reverse all significant molecular pathway changes in GECs in early DKD, which were associated with the dampening of TGF-β-induced gene expression. Notably, LRG1 loss also led to a significant attenuation of TGF-β-mediated gene expression in mesangial cells of diabetic mice. These results indicate that LRG1 promotes DKD by enhancing TGF-β signaling in GECs and mesangial cells in an autocrine and paracrine manner, and indirectly via glomerular cross-talk.

Conclusions: Our study indicates that increased LRG1 directly enhances TGF-β signaling not only in GECs but also in mesangial cells in DKD, thereby exacerbating subsequent podocyte loss. LRG1 loss, while having no gross defects in mice, significantly attenuated diabetic glomerulopathy in OVE26 mice. Therefore, specific antagonisms of LRG1 may be an effective approach to curb TGF-β signaling in glomerular cells and attenuate DKD.

Funding: NIDDK Support

FR-PO330

Nogo-B Suppresses Endoplasmic Reticulum Stress in Glomerular Endothelial Cells of Diabetic Nephropathy

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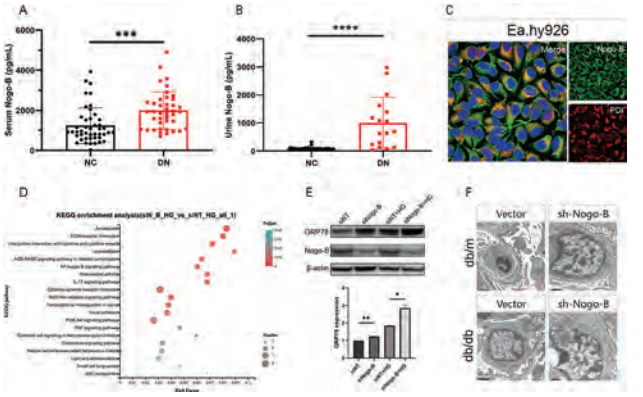
Background: Diadetic vascular injuries contribute to the disease progression and glomerular endothelial cells are the critical targets of injury under hyperglycemia. Nogo-B is an endoplasmic reticulum (ER)-resident protein, which plays an important role in vascular remodeling after injury. Given the location of Nogo-B in the endoplasmic reticulum in glomerular endothelial cells, we set out to investigate whether Nogo-B is involved in the ER stress of endothelial cells in diabetic nephropathy.

Methods: The level of serum and urinary Nogo-B was measured in patients with diabetic nephropathy using ELISA. The expression of Nogo-B in the ER of endothelial cells was detected by immunofluorescence co-staining with the ER marker, PDI. The expression level of ER stress related markers GRP78 was examined using WB analysis. *In vitro*, siRNA was used to knockdown the expression of Nogo-B in Ea.hy926 under high glucose condition and RNA-seq analysis was performed. *In vivo*, AAV-induced knockdown of Nogo-B was performed in *db/db* diabetic mice for 8 weeks. The morphology phenotypes were examined by TEM.

Results: Compared with healthy control subjects, the level of serum (fig.A) and urinary(fig.B) Nogo-B was significantly increased in DN patients. *In vitro*, Nogo-B was co-localized with PDI by immunofluorescent co-labeling (fig.C). The RNA-seq results demonstrated that AGE-RAGE signaling pathway was among the top 10 activated pathways by KEGG analysis (fig.D). In high glucose cultured endothelial cells, knocking down Nogo-B caused an increase in the protein level of GRP78 (fig.E). In *db/db* diabetic mice, knocking down Nogo-B induced glomerular endothelial cell injuries (fig.F) as demonstrated by swollen changes and karyorrhexis of the cells.

Conclusions: Nogo-B, an ER-residential protein, plays a beneficial role in glomerular endothelial cells by inactivating the ER stress. Protecting the vasculature by targeting Nogo-B may serve as a potential therapeutic strategy in the treatment of DN.

Funding: Government Support - Non-U.S.



FR-PO331

Short-Chain Fatty Acids Restore Glomerular Endothelial Cell Stabilization After Exposure to Type 2 Diabetes Mellitus (T2DM) Serum, Circumventing the Reduced CPT1A Transporter

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Background: Renal injury is one of the major consequences for patients with type 2 diabetes mellitus (T2DM). Previously, we observed that diabetic nephropathy (DN) resulted in loss of the endothelial glycocalyx, but the molecular and metabolic mechanisms underlying this loss and in general endothelial dysfunction in T2DM remain largely unexplained. In the present study we tested the mechanistic and metabolic changes in human primary glomerular endothelial cells (huGEnCs) exposed to serum from patients with T2DM.

Methods: HuGenCs have been exposed for 4 days to T2DM serum in either static or laminar flow conditions. Cells were then used for seahorse and ECIS assays, to measure mitochondrial function and monolayer integrity, respectively. In order to visualize the monolayer, cells were stained for VE-cadherin and β-catenin. We also ran qPCR analysis to check the expression levels of endothelial and metabolic genes.

Results: qPCR data showed that huGenCs cultured with T2DM serum have an increased IL-8 mRNA expression while HAS2, HAS3, NOS3 and the fatty acid transporter CPT1A mRNA were reduced. For this reason, we performed a CPT1A knockdown to investigate the effect of the lack of this transporter in huGenCs. Monolayer resistance, either in the presence of T2DM serum or after CPT1A knockdown, was decreased. In each case, administration of the short chain fatty acids (SCFAs) butyrate and acetate restored barrier function. The beneficial effects of SCFAs on the endothelial monolayer were also confirmed when visualizing cell-cell contacts with immunofluorescence staining's for VE-cadherin and β-catenin. Using seahorse assay, we observed that SCFAs also improved fatty acid oxidation which was reduced after T2DM serum exposure.

Conclusions: SCFAs supplementation can rescue endothelial cell integrity after treatment with T2DM serum. Mechanistically, reduction of CPT1A in ECs exposed to T2DM serum revealed the importance of fatty acids for ECs homeostasis, which was confirmed by the knockdown of CPT1A. With butyrate and acetate supplementation we can circumvent this pathway and restore cellular homeostasis by improving fatty acids metabolism.

FR-PO332

L-NAME Accelerates the Onset of Diabetic Nephropathy in Genetically Diabetic Mice

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Background: Diabetic nephropathy (DN) represents one of the major causes of end stage kidney disease worldwide. Despite DN having such a high incidence, mouse models of DN rarely mimic all aspects of the human disease and usually show very slow development of DN phenotype. For this reason, in this project we aimed to develop an accelerated and reproducible rodent model of DN.

Methods: For our experiments we chose 9-week old female and male of the leptin receptor knock-out (BKS.Cg-Dock7m +/+ Leprdb/J) mice as type 2 diabetes model. As these mice are still not prone to develop severe kidney injury despite their diabetic condition, we administered the eNOS inhibitor L-NAME for 6 weeks, in order to aggravate kidney damage. Mice were divided in three groups: one vehicle control group, one receiving 40/mg/kg/day of L-NAME and one receiving 80/mg/kg/day of L-NAME dissolved in drinking water. Blood pressure and glomerular filtration rate (GFR) were measured, besides glycemia and albuminuria. At the end of the experiment, animals were killed and blood and organs collected.

Results: Mice treated with 80mg/kg/day of L-NAME showed an average increase of 10 mmHg in systolic blood pressure, with a peak of 30 mmHg increase at week 4 of treatment. Despite the increased blood pressure, three weeks of L-NAME administration

caused a significant reduction in GFR for both doses of L-NAME, with 5% reduction for the 40mg-group and 23% for the 80mg-group. No change in GFR was observed in the controls. This decrease in GFR was accompanied by a 10-fold increase in urinary albumin for both the experimental groups already after 3 weeks of treatment. PAS staining of kidney sections revealed that in particular mice treated with 80mg of L-NAME have enlarged glomeruli and a reduced glomerular capillary density, coinciding with mesangial expansion. Electron microscopy analysis showed that glomerular basement membrane (GBM) thickening was also occurring.

Conclusions: Our results show that L-NAME considerably accelerates the onset of DN in diabetic mice, with signs of kidney dysfunction already after 3 weeks. This model could be used to assess the therapeutic potential of novel interventions aimed to slow down the progression of DN.

FR-PO333

Protease-Activated Receptor-1 Deficiency Protects Against Glomerular and Endothelial Injury in Type 2 Diabetic Nephropathy

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Background: We recently showed that depletion of protease-activated receptor-1 (PAR-1) confers kidney protection in rodent models of CKD. Whether the same phenomenon may be observed in the diabetic kidney remains unknown.

Methods: We generated a novel double transgenic PAR-1 KO *db/db* mouse and observed its pathophysiology weeks in comparison to the respective wild-type and non-diabetic control animals. Fasting, non-fasting serum and urine were collected for up to week 24 of age. Vascular permeability assay of Evan's blue extravasation was performed to assess endothelial injury in the kidneys. Kidney function and histological damage were determined post-mortem. Six animals were included in each experimental group for analysis.

Results: PAR-1 deficiency significantly reduced fasting blood glucose level and glucose tolerance by OGTT associated with higher serum insulin levels in *db/db* mice. Morphologically, *db/db* control mice developed glomerular hypertrophy and tubulointerstitial damage compared to *db*/+ non-diabetic mice, whereas *db/db*;Par1$^{-/-}$ mice displayed less mesangial expansion and tubular dilation. *db/db*;Par1$^{-/-}$ mice had lower albuminuria with restoration of nephrin and WT-1 levels in the glomerulus compared to db/db controls. PAR-1 deficiency also preserved endothelial integrity and capillary permeability, along with an increase of VEGFA levels in *db/db* kidneys.

Conclusions: PAR-1 depletion confers kidney protection by reducing vascular damage and glomerular injury in experimental type 2 diabetic nephropathy. These novel findings suggest the potential of a PAR-1 targeted therapeutic strategy in diabetic nephropathy. **Funding:** Research Grants Council of Hong Kong (General Research Fund, grant no. 17118720)

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FR-PO334

Effects of a Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP) Blocking Antibody in a Mouse Model of Severe Diabetic Kidney Disease

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Background: Diabetic Kidney Disease (DKD) is a disease with complex pathophysiology wherein endothelial dysfunction plays a central role in disease formation and progression. Emerging evidence emphasizes the critical role of the Tie-2 receptor and Angiopoietin 1 and 2 ligands in DKD. Tie-2 signaling is negatively regulated by the endothelial specific transmembrane Vascular Endothelial Protein Tyrosine Phosphatase (VE-PTP). Recently, it has been reported that the genetic deletion of VE-PTP provided protection from hypertension and diabetes induced renal injury in a mouse model of DKD. In the current study we investigated the efficacy of VE-PTP inhibition in a mouse model of severe DKD with an extracellular domain (ECD) targeting VE-PTP blocking antibody.

Methods: VE-PTP blocking antibody was characterized *in vitro*, *in vivo* in dermal vascular permeability assays, and in pharmacokinetic experiments. The *in vivo* proof-of-concept experiment with the VE-PTP blocking antibody and standard of care lisinopril were performed in hypertensive diabetic mice. Renin overexpression (AAV) was used to induce hypertension in db/db mice following uninephrectomy (Unx). Treatment was initiated 4-weeks after renin AAV administration and continued for another 4 weeks.

Results: Our results showed that VE-PTP inhibition with an ECD targeting VE-PTP antibody induced Tie2-phosphorylation and provided protection against VEGF-A induced vascular permeability both *in vitro* and *in vivo*. Furthermore, treatment with the VE-PTP antibody resulted in decreased kidney gene expression of endothelial activation markers *(Angpt2, Edn1, Icam1 and Vcam1)*. However, the VE-PTP blocking antibody treatment did not alter urinary albumin-to-creatinine ratio (uACR) in a severe mouse model of DKD.

Conclusions: VE-PTP inhibition with an ECD targeting antibody did not ameliorate hypertension- and diabetes-induced albuminuria in a preclinical mouse model of DKD.

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FR-PO335

Renal Lymphatics in Early Diabetic Kidney Disease: Insights from 3D Imaging and Functional Assays

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease, requiring dialysis or kidney transplant for patients' survival. Consequently, new treatments are urgently required. Renal lymphatics have been implicated in DKD pathogenesis, but their specific role in the early stages of disease remains unclear. This study aims to address this need using advanced 3D imaging and in vitro functional assays.

Methods: DBA/2J mice, rendered diabetic by streptozotocin (STZ), were assessed four and twelve weeks post-STZ. We measured body and kidney weight, albuminuria, and inflammatory markers, and quantified lymphatic volume, diameter, and branches using 3-dimensional imaging and computer analysis. Human dermal lymphatic cells were exposed to serum from patients with a 20-year history of Type 1 diabetes, with or without DKD (presence of albuminuria), to study possible changes in their angiogenesis and migration capacities.

Results: Although inflammation was elevated in diabetic mice at week four post-STZ, significant differences in lymphatic vessels, albuminuria, and kidney histology emerged only by week twelve. These changes included a marked expansion in lymphatic volume, diameter, and branches. Human lymphatic cells exposed to DKD$^+$ serum showed longer tube lengths, more branches, and increased migration compared to cells exposed to DKD$^-$ serum.

Conclusions: Through 3D imaging, we identify an early-stage expansion of lymphatics in DKD, coinciding with the initiation of kidney damage. Furthermore, our cellular work indicates this may be a repair response, with enhanced tube formation and migratory capabilities in lymphatic cells exposed to serum from patients with DKD. These insights indicate that modulating kidney lymphatics may represent a novel therapeutic avenue for DKD.

Funding: Private Foundation Support

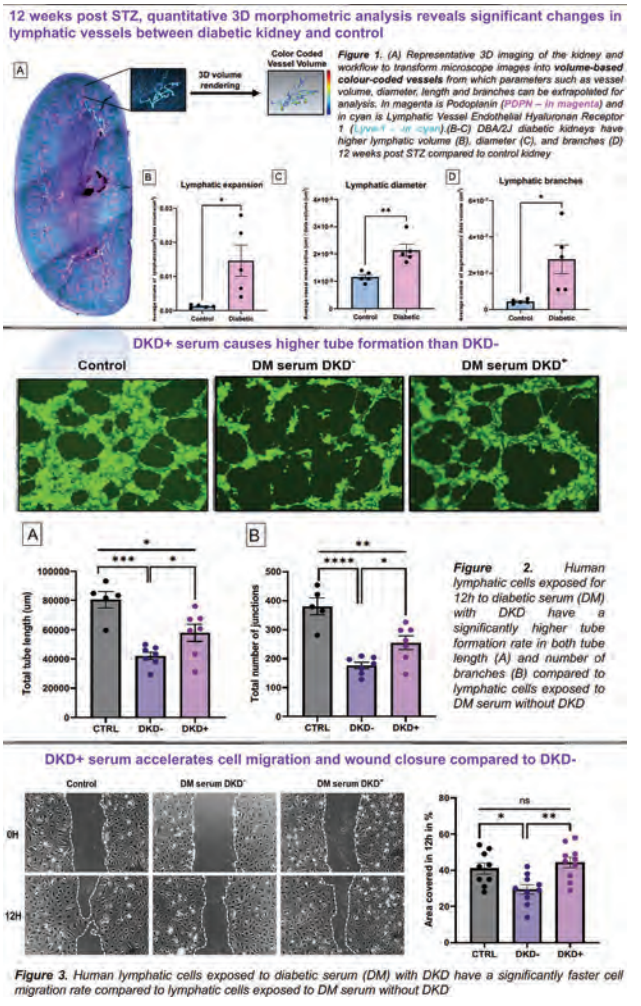

Figure 1. (A) Representative 3D imaging of the kidney and workflow to transform microscope images into volume-based colour-coded vessels from which parameters such as vessel volume, diameter, length and branches can be extrapolated for analysis. In magenta is Podoplanin (PDPN – In magenta) and in cyan is Lymphatic Vessel Endothelial Hyaluronan Receptor 1 (Lyve-1 – In cyan).(B-C) DBA/2J diabetic kidneys have higher lymphatic volume (B), diameter (C), and branches (D) 12 weeks post STZ compared to control kidney

Figure 2. Human lymphatic cells exposed for 12h to diabetic serum (DM) with DKD have a significantly higher tube formation rate in both tube length (A) and number of branches (B) compared to lymphatic cells exposed to DM serum without DKD

Figure 3. Human lymphatic cells exposed to diabetic serum (DM) with DKD have a significantly faster cell migration rate compared to lymphatic cells exposed to DM serum without DKD

FR-PO336

Piezo1 Mediates Vasodilation Induced by Acute Hyperglycemia in Mouse Renal Arteries and Microvessels

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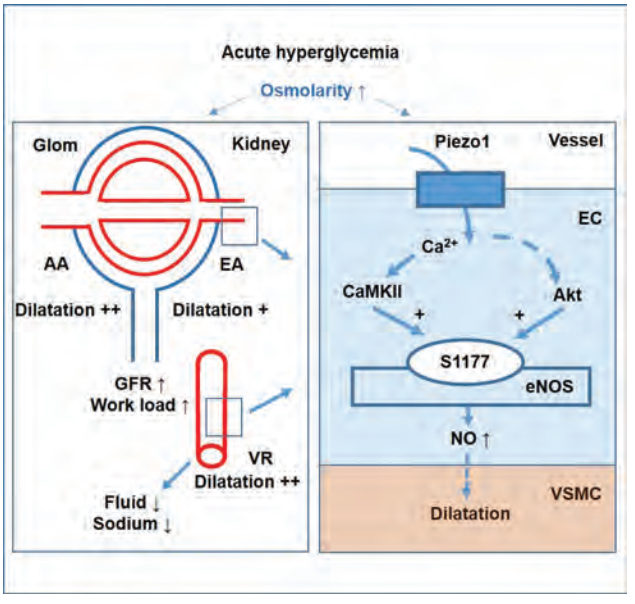
Background: Acute hyperglycemia (HG) is a risk factor for developing acute kidney injury and poor renal outcome in critically ill patients. The role of renal vasculature in this context is not clear. We hypothesize that HG-associated hyperosmolarity facilitates vasodilation through Piezo1-mediated eNOS activation.

Methods: Vasoreactivity of isolated mouse mesenteric (MA) and renal interlobar (ILA) arteries was analyzed using wire myography and that of renal afferent (AA) and efferent (EA) arterioles, and vasa recta (VR) using microvascular perfusion. Immunofluorescence and western blot were used for molecular analyses of isolated mouse blood vessels as well HUVECs.

Results: Pre-treatment with HG (44 mmol L^{-1} glucose; 4 h) increased acetylcholine (ACh)-induced relaxation in ILA and MA, which was prevented by eNOS inhibition using L-NAME. Hyperosmotic mannitol solution had a similar effect. HG induced an immediate, L-NAME-inhibitable dilation in AA, EA, and VR, whereby stronger dilation in AA compared to EA. HG also increased glomerular filtration rate in mice. In HUVECs, HG and the Piezo1 activator Yoda1 increased levels of Piezo1 protein, phosphorylated CaMKII (p-CaMKII), Akt, and p-eNOS. The HG-effect could be prevented by inhibiting Piezo1 using GsMTx4 and CaMKII using KN93. Furthermore, in arteries and microvessels, inhibition of Piezo1 using GsMTx4 prevented the HG-effect, while Yoda1 caused relaxation and dilation, respectively.

Conclusions: Results reveal that Piezo1 mediates renal vasodilation induced by hyperosmolarity in acute HG. This mechanism may contribute to the pathogenesis of renal damage by acute HG.

Funding: Government Support - Non-U.S.



FR-PO337

Podocyte-Specific Regulation of PP2A Worsens Diabetic Kidney Disease (DKD) Progression

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Background: We previously showed a critical role of protein phosphatase 2A (PP2A) in regulation of podocyte function and progression of DKD. However, PP2A is ubiquitously expressed with pleiotropic functions, limiting its role of being a DKD therapeutic target. Here, we investigated the role of a podocyte-specific regulatory subunit of PP2A, PPP2R2B in vitro and in vivo in the context of DKD.

Methods: By using PHEWAS approach, we screened the variants of genes coding for all PP2A subunits to determine their association with renal outcome in DKD patients. Knock-in (KI) mice with one of the clinical worse outcome-related *ppp2r2b* missense variants (T202M) was generated, and diabetes was induced with streptozotocin (STZ). Renal function was assessed every two weeks, and all mice were euthanized at the age of 24 weeks for examination.

Results: By PHEWAS study, several variants of *ppp2r2b* gene were found to be associated with a better or worse renal outcome in DKD patients. Interestingly, single cell transcriptomic data showed that *ppp2r2b* gene expresses mostly in human podocytes. In vitro study confirmed that *ppp2r2b* variants correlated with a better or worse clinical outcome led to an increased or decreased PP2A activity, respectively. We generated KI mice with one of the clinical worse outcome-related *ppp2r2b* missense variants (T202M). In vivo study revealed that diabetic KI mice developed significantly higher level of albuminuria in comparison to diabetic WT mice. Besides, diabetic KI mice also showed worst podocyte injury and loss, and mesangial matrix expansion. As PP2A dephosphorylates p65 NF-κB, we evaluated the phosphorylation level of p65 NF-κB in the glomeruli of these mice. Compared to wildtype mice, KI mice had a higher level of glomerular phosphorylation of p65.

Conclusions: The missense *ppp2r2b* variants were significantly associated with renal outcome in humans with DKD. KI of one of *ppp2r2b* missense variants (T202M) resulted in worsened glomerulopathy in diabetic mice. Thus, PPP2R2B, a podocyte-specific PP2A regulatory subunit, could be a better therapeutic target for DKD.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO338

Critical Role of Serum Response Factor in Podocyte Epithelial-Mesenchymal Transition of Diabetic Nephropathy

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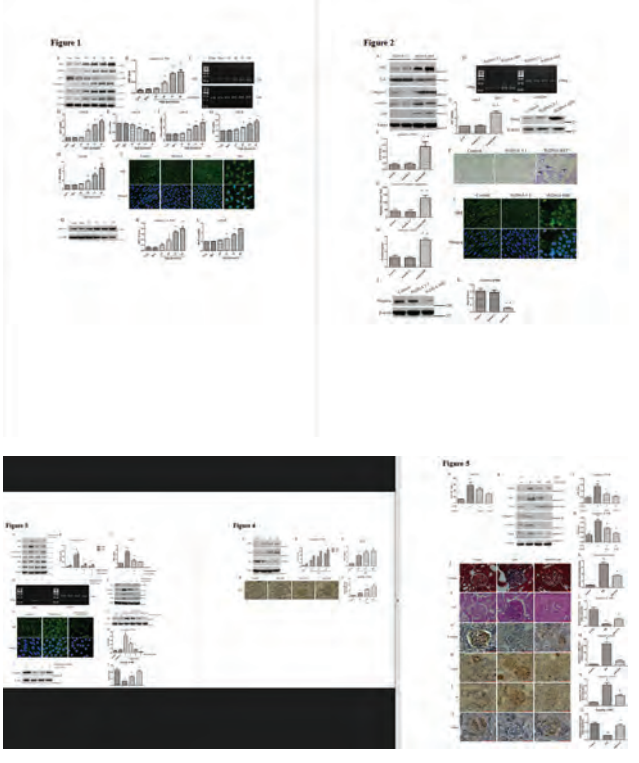
Background: To investigate the expression and function of serum response factor (SRF) in podocyte epithelial–mesenchymal transition (EMT) of diabetic nephropathy (DN).

Methods: Expression of SRF, pSRF, synaptopodin, P-cadherin, ZO-1, α-SMA, FSP-1, fibronectin and collagen-1 were examined in podocytes or renal cortex following high glucose. SRF was upregulated by SRF plasmids and downregulated by CCG-1423 to investigate how SRF influence podocyte EMT in DN. Streptozocin was used to generate DM in rats.

Results: In podocytes after high glucose treatment, SRF, pSRF, α-SMA, FSP-1, fibronectin and collagen-1 increased, while synaptopodin, P-cadherin and ZO-1 declined. In vivo, CCG-1423 significantly abrogated the reduction of synaptopodin expression and the induction of SRF, collagen-1, α-SMA and FSP-1 expression in renal cortex tissues. Masson and PAS staining demonstrated that renal glomerular fibrosis was present in DM group, and after 8 weeks treatment with CCG-1423, renal glomerular fibrosis was dramatically ameliorated. In addition, CCG-1423 significantly preserved P-cadherin expression and suppressed α-SMA and FN expression in DN rats. SRF overexpression in podocytes induced expression of Snail, an important transcription factor that mediates EMT. Blockade of SRF reduced Snail induction, protected podocyte from EMT and improved proteinuria and serum albumin.

Conclusions: Together, increased SRF activity provokes podocytes EMT and dysfunction in DN. Targeting SRF by small molecule inhibitor may be an attractive therapeutic strategy for DN.



FR-PO339

Inhibition of the lncRNA 585189 Prevents Podocyte Injury and Mitochondria Dysfunction by Promoting hnRNP A1 and SIRT1 in Diabetic Nephropathy

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Background: Dysfunction of podocytes has been identified as a crucial pathologic characteristic of diabetic nephropathy (DN), while the regulatory effect of long noncoding RNAs (lncRNAs) in this process has not been fully elucidated.

Methods: We conducted RNA-seq on renal tissues and identified a significantly upregulated lncRNA ENST00000585189.1 (lncRNA 585189) in patients with DN. Subsequently, we assessed its correlation with clinical indicators and demonstrated its localization with RNA-FISH. In high-glucose-induced human podocytes, the expression of lncRNA 585189 was assessed via real-time PCR and RNA-FISH. Subsequently, gain- and loss-of-function experiments detected the effect of lncRNA 585189. The expression of Desmin, ZO-1, hnRNP A1 and SIRT1 were evaluated using real-time PCR, western blot and immunofluorescence assays. Mitochondrial morphologies were evaluated using MitoTracker, while mitochondrial ROS and membrane potential were assessed using MitoSOX Red and TMRM staining. Mechanistically, bioinformatics analysis predicted the interaction between lncRNA 585189 and hnRNP A1, which was confirmed by RIP, pull-down, and EMSA assays. Moreover, the binding of hnRNP A1 to SIRT1 mRNA was validated through RIP and pull-down assays. Additionally, the stability of hnRNPA1 and SIRT1 was assessed by treatment with Cloheximide, MG-132, and Actinomycin D.

Results: lncRNA 585189 displayed a positive correlation with renal insufficiency and was found to be upregulated in both DN patients and high-glucose-induced human podocytes. Silence of lncRNA 585189 decreased the production of ROS, rescued the aberrant mitochondrial morphology and membrane potential, restored the podocyte damage caused by high glucose. Mechanistically, lncRNA 585189 binds to hnRNP A1, inducing destabilization of hnRNP A1 protein and downregulating its expression. Conversely, hnRNP A1 promotes the expression of lncRNA 585189. Furthermore, the interaction between hnRNP A1 and SIRT1 mRNA promotes the stability of SIRT1 mRNA and enhances its expression. Finally, our findings suggested that lncRNA 585189 inhibited SIRT1 expression through hnRNP A1, hindering the recovery of mitochondrial abnormalities and podocyte damage.

Conclusions: In summary, targeting lncRNA 585189 may represent a promising strategy for reversing mitochondrial dysfunction and treating DN.

Funding: Government Support - Non-U.S.

FR-PO340

Stimulator of Interferon Genes (STING) Deletion Alleviates Podocyte Injury Through Suppressing Inflammatory Response in Diabetic Kidney Disease

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Background: The stimulator of interferon genes (STING) is an adaptor protein that can drive noninfectious inflammation and pyroptosis. NLRP3-mediated inflammasome activation is an important type of inflammatory programmed death with strong pro-inflammatory activity and has been confirmed to promote a chronic inflammatory response in DKD. However, the mechanism of STING regulating immune inflammation and the interaction with NLRP3-dependent pyroptosis in the high glucose (HG) state remains unknown. The present study aims to evaluate whether STING contributes to HG-induced podocyte inflammation response through modulating NLRP3-dependent pyroptosis.

Methods: In vivo study, co-localization expression of STING and synaptopodin was evaluated in glomeruli by double immunolabeling. Western blot was performed to assess STING and inflammatory-related protein expression in glomeruli. q-PCR was used to detect inflammatory molecule expression. Transmission electron microscope (TEM) was used to identify ultrastructure changes of podocytes in diabetic mice. Pathological changes were evaluated by periodic acid-Schiff stain (PAS) or hematoxylin and eosin (HE) staining. In vitro study, podocytes were exposed to HG (40mM) for 24 h. Immunofluorescence assay and western blot were performed to evaluate STING expression. Pyroptosis and inflammatory-related molecule expression were detected by western blot and q-PCR. STING siRNA was transfected to podocytes to evaluate the effect of STING inhibition on podocyte inflammatory response under HG stimulation.

Results: Double immunolabeling of STING and synaptopodin in glomeruli was obviously increased in diabetic animals. In addition, STING protein expression was increased in diabetic mice compared with controls. Deletion of STING alleviated podocyte injury, renal dysfunction inflammation, NLRP3 inflammasome activation, and pyroptosis in diabetic mice. In cultured podocytes, STING protein expression was increased in HG-treated podocytes. Modulated STING expression by STING siRNA alleviated pyroptosis and NLRP3 inflammasome activation in HG-treated podocytes.

Conclusions: These results indicate that STING deletion suppresses podocytes inflammation response by targeting NLRP3 and provide evidence that STING may be a potential target for podocyte injury in DKD.

FR-PO341

SrGAP3 Deficiency Mediates Podocyte Injury by Promoting Cdc42 and Rac1 Activity in Diabetic Nephropathy

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Background: Rho GTPase activity plays a key role in cytoskeletal rearrangement and apoptosis of podocytes in diabetic nephropathy (DN). However, the upstream regulatory mechanism directing Rho GTPases in podocytes of DN remains unclear. This study aimed to verify the expression of SrGAP3, a Rho GTPase activating protein, in kidney and its role and mechanism in podocyte injury of DN.

Methods: The level of SrGAP3 expression was analyzed using immunofluorescence in the glomerular podocytes of renal tissue from DN patients and diabetic mice with albuminuria. Albuminuria, podocyte injury and glomerular pathology were evaluated in SrGAP3 overexpression of type 2 diabetic db/db mice and STZ-induced type 1 diabetic mice. The expressions and activities of Cdc42 and Rac1 in the glomerular podocytes in vivo in diabetic mice and in vitro in podocytes exposed to either SrGAP3 knockdown or high glucose treated podocytes with SrGAP3 overexpression were detected by immunofluorescence, western blot and enzyme activity detection. Podocyte marker proteins, cytoskeleton, cell motility and apoptosis were observed in in vitro podocytes under different conditions.

Results: SrGAP3 was markedly reduced in glomerular podocytes from renal tissues of DN patients, db/db mice and STZ-induced diabetic mice with albuminuria. The albuminuria in db/db and STZ-induced diabetic mouse model was markedly attenuated after overexpression of SrGAP3 established by adeno-associated virus. This was accompanied by alleviation of basement membrane thickening, mesangial matrix expansion, and podocyte injury. The decreased expression of SrGAP3 in podocytes cultured with high glucose was upregulated after overexpression of SrGAP3, accompanied by restored decreased podocyte marker proteins, and improved actin cytoskeleton rearrangement, podocyte motility and apoptosis. Further studies found that increased activity of Cdc42 and Rac1 in podocytes in vivo and in vitro under the diabetic state were significantly inhibited after overexpression of SrGAP3.

Conclusions: SrGAP3 deficiency mediates podocyte injury of DN by promoting Cdc42 and Rac1 activation, which may provide a clinical therapeutic target for protecting podocyte injury of DN.

Funding: Government Support - Non-U.S.

FR-PO342

Podocyte-Specific Clusterin Triggers the Activation of Proximal Tubule-Specific CAMK1D Signaling to Attenuate Kidney Injury in Diabetic Kidney Disease

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Background: The role of podocyte-proximal tubule (PT) crosstalk in the progression of Diabetic Kidney Disease (DKD) remains understudied. Podocyte-specific overexpression of Krüppel-like factor 6 (*KLF6*), a zinc finger transcription factor, attenuated proximal tubule (PT) injury in murine DKD model. Initial snRNA-seq studies demonstrated a potential interaction between podocyte Clusterin (CLU), a secretory ligand, and proximal tubule CAMK1D. The aim of this study is to investigate the mechanism by which the podocyte primes the PT to attenuate kidney injury in DKD.

Methods: Conditioned media (CM) was collected from GFP-labeled podocytes obtained from podocyte-specific induction of *KLF6* (*KLF6*^{PODTA}) and control mice to carry out proteomic analysis and in vitro assays in primary (1°) PT. 1° PT cells were treated with control CM as well as CM blocked with CLU antibody. CAMK1D signaling was pharmacologically inhibited using STO-609, an inhibitor of the upstream kinase CAMKK. Oxygen consumption rate (OCR) was measured with seahorse analyzer. Immunofluorescence staining, western blot analysis, and pulldown assay for calmodulin were performed. Single nuclei ATAC (SnATAC) and snRNA sequencing were conducted on the kidney cortex of all mice.

Results: Immunostaining of experimental mice as well as proteomic analysis of the podocyte CM and urine, led to identification of CLU as a potential ligand for PT signaling. *KLF6*^{PODTA} CM-treated 1° PT cells demonstrated an increase in calmodulin binding affinity as well as an increase in OCR compared to control CM-treated cells in high glucose (HG) conditions, and this OCR change was abated by the addition of CLU blocking antibody. CAMK1D expression was unique to the first segment of PT in mouse as well as human tissue. 1° PT cells treated with STO-609 had a decrease in cell viability and OCR in HG conditions, a decrease in p-DRP1, and an increase in fragmented mitochondria. SnATACseq in combination with snRNAseq also validated pathways related to calcium signaling and podocyte-PT communication.

Conclusions: These data suggest that CLU secreted from podocytes attenuates mitochondrial fission in the PT by inducing CAMK1D signaling, thereby priming the PT against injury under diabetic conditions.

Funding: NIDDK Support, Veterans Affairs Support

FR-PO343

High Glucose-Induced Pyruvate Kinase M2 (PKM2) Tyrosine Phosphorylation Drives a Feedback Loop by PDGFRβ to Force mTORC1 Activation for Mesangial Cell (MC) Injury in Diabetic Nephropathy (DN)

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Background: Besides its role in the last step of glycolysis to produce pyruvate, increased expression and tyrosine phosphorylation of PKM2 regulate mitotic checkpoint in many cancers. We investigated the role of PKM2 tyrosine phosphorylation in DN.

Methods: MCs, OVE26 and db/db mice were employed.

Results: Incubation of MCs with 25 mM glucose (HG) increased the expression of PKM2 in a sustained manner. HG induced translocation of PKM2 into the nucleus and increased its phosphorylation at tyrosine-105 residue in both cytosol and nucleus. We have recently shown a role of PDGFRβ in DN. We hypothesized that PDGFRβ may regulate PKM2. JNJ, a PDGFRβ inhibitor, abrogated HG-stimulated PKM2 expression and tyrosine phosphorylation. Interestingly, expression of kinase dead PKM2 K367M and tyrosine phosphorylation deficient PKM2 Y105F mutants inhibited HG-induced MC hypertrophy. In contrast, overexpression of wild type PKM2 induced MC hypertrophy similar to HG treatment. Mesangial matrix expansion is an aspect of DN. Both PKM2 K367KM and PKM2Y105F mutants mitigated HG-stimulated expression of fibronectin, collagen I (α2) and PAI-1 whereas, overexpression of PKM2 had the opposite effects similar to HG. Previously, we reported that Akt/mTORC1 signaling regulates MC pathologies. We found that PKM2 K367M and PKM2 Y105F mutants suppressed HG-stimulated Akt and mTORC1 while overexpression of PKM2 increased their activities. Intriguingly, Akt and mTORC1 inhibitors MK2206 and rapamycin, respectively, suppressed expression and tyrosine phosphorylation of PKM2. While addressing the *in vivo* relevance, we found increased PKM2 expression and tyrosine phosphorylation concomitant with fibronectin, PAI-1 and collagen I (α2) expression in the renal cortex of OVE26 and db/db mice, models of type 1 and type 2 diabetes, respectively.

Conclusions: Our results identify a previously unrecognized HG-stimulated novel positive feedback loop involving PDGFRβ, activated Akt/mTORC1 and tyrosine phosphorylated PKM2 to drive MC pathologies in DN.

Funding: Veterans Affairs Support

FR-PO344

PTEN-Long Suppresses Proximal Tubular Epithelial Cell (PTEC) Injury in Diabetic Nephropathy (DN)

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Background: From the same mRNA, a translational variant with CUG codon (Leu)-initiated PTEN with a 173 amino acids long N-terminus (PTEN-L) compared to canonical PTEN has recently been identified. Both PTENs provide a checkpoint against tumorigenesis. We investigated the hypothesis that PTEN-L acts as a driver of tubular injury in the progression of DN.

Methods: Human PTECs, OVE26 and db/db mice, specific antibodies, immunoblotting, PTEN-L-targeting drugs, measurement of hypertrophy and plasmid expression vector were employed.

Results: 25 mM glucose (HG) time-dependently decreased the expression of PTEN-L. PTECs predominantly express Akt-2 isoform. Concomitant with decreased PTEN-L, HG increased phosphorylation of Akt-2 and its substrate GSK3β. The anti-bacterial chromophore acriflavine (ACR) inhibits initiation from CUG codon. ACR inhibited the expression of PTEN-L. In contrast, aurin tricarboxylic acid (ATA), a potent anti-viral agent, increases translation from CUG codon and increased the expression of PTEN-L. Consequently, ACR increased Akt-2 phosphorylation/activation (p-GSK3β) similar to HG while ATA inhibited these events. These drugs had no effect on canonical PTEN expression. As Akt-2 regulates mTORC1 via phosphorylation/inactivation of tuberin and PRAS40, we determined the effect of these drugs. ACR increased their inactivating phosphorylation, resulting in activation of mTORC1, as judged by phosphorylation of S6 kinase, eEF2 kinase and dephosphorylation of eEF2; these effects were similar to HG. ATA blocked these effects induced by HG. ACR induced PTEC hypertrophy and fibronectin and PAI-1 expression similar to HG while ATA inhibited these HG-induced phenomena. To confirm the results with ATA, we used a plasmid vector expressing PTEN-L. PTEN-L suppressed HG-induced phosphorylation of Akt-2/GSK3b, resulting in inhibition of mTORC1 activity and blocked HG-induced PTEC hypertrophy and, expression of fibronectin and PAI-1. In addressing the *in vivo* relevance of our results, in the renal cortex of OVE26 and db/db mice models of type 1 and type 2 diabetes, we found decreased expression of PTEN-L concomitant with increased phosphorylation of Akt-2/GSK3b, mTORC1 activation, and fibronectin and PAI-1 expression.

Conclusions: We conclude that PTEN-L protects against PTEC injury in DN.

Funding: Veterans Affairs Support

FR-PO345

SIRT3 Activation with Viniferin Treatment Ameliorates Features of Diabetes-Induced Tubular Injury Through Restoration of Mitochondrial Function

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Background: Oxidative stress and mitochondrial dysfunction are key factors inducing diabetic nephropathy. In this study, the role of SIRT3 as a regulator of mitochondrial activity and cell survival and the effect of viniferin as a SIRT3 activator were assessed in diabetes-induced tubular injury.

Methods: In vitro, NRK-52E cells treated with TGF-β-were compared with controls after SIRT3-targeted lentivirus transfection and viniferin treatment to evaluate the effect of SIRT3 overexpression. In an animal study, viniferin was injected to db/db mice for 9 weeks and to C57BL/6 mice given with unilateral nephrectomy and intraperitoneal streptozotocin injection (UNXSTZ) for 4 weeks using osmotic pump, db/m mice and C57BL/6 mice served as controls, respectively.

Results: In NRK-52E cells, TGF-β treatment resulted in decreased expression of SIRT3, in parallel with increased oxidative stress, decreased mitochondrial mass, integrity, and respiration, and increased fibrotic and apoptotic activities. SIRT3 overexpression by lentiviral transfection improved mitochondrial dynamics and cell injury, and similar alterations were observed after viniferin treatment. In kidney of db/db and UNXSTZ mice, diabetes induced downregulation of SIRT3, increased oxidative stress, decreased expressions of mitochondrial dynamic-related genes, and cell injury. SIRT3 activation by viniferin treatment restored these alterations, and tubular degeneration and fibrotic remodeling in diabetic kidney were also ameliorated by viniferin treatment.

Conclusions: This study demonstrates that SIRT3 activation by viniferin treatment improves oxidative stress and impaired mitochondrial metabolism in diabetes-induced tubular injury.

FR-PO346

Single-Cell RNA Sequencing Analysis Reveals Inhibition of Proximal Tubule mTORC1 in Myoinositol Oxygenase Knockout Mice: A Possible Mechanism for Ameliorating CKD

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Background: MIOX is a proximal tubular specific enzyme and it catalyzes the rate limiting step of myoinositol metabolism. MIOX overexpression has been implicated in the progression of chronic kidney disease. Conversely its genetic deletion shows significant amelioration in progression of chronic kidney disease (CKD) in mouse models of diabetes.

Methods: Kidneys harvested from 6-week-old male C57BL/6J (WT) and MIOX-KO mice, fed with normal or high fat diet (HFD, 60% calories from fat) for six weeks, were analyzed. Change in body weight, blood glucose level was estimated. Single cell RNA sequence (scRNA seq) analysis was performed on libraries prepared from whole kidneys of six-week ND (normal diet) and HFD mice. We assessed pS6 level in kidneys of MIOX-KO and WT mice via immunoblotting.

Results: UMAP showed retrieval of 27 clusters which included cells of proximal tubules, loop of Henle, distal convoluted tubules, collecting duct, podocytes, stroma, vasculature, and immune cells. Pathway enrichment analysis with all cells highlighted mTORC1 signaling pathway was substantially downregulated in MIOX-KO HFD mice as compared to MIOX-KO ND mice. Conversely, mTORC1 pathway was significantly upregulated in cells from WT-HFD. Further we narrowed down the pathway enrichment analysis only to proximal tubules (PT) as MIOX is only expressed in PT cells. Beside endoplasmic reticulum stress, hypoxia, apoptosis, mTORC1 pathway was significantly downregulated in MIOX-KO-HFD mice as compared to WT-HFD and MIOX-KO ND. Immunoblotting analysis showed downregulation of p-mTORC1 in MIOX-KO mice fed with normal chow as compared to WT mice. In addition, scRNA showed that mitophagy, which is modulated by mTORC1 signaling, is induced in PT cells of MIOX-KO mice.

Conclusions: MIOX-KO reduced mTORC1 activation compared to WT following HFD. We posit that decreased activation of mTORC1 is one mechanism whereby MIOX inhibition/loss protects the kidney from injury in diabetes.

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FR-PO347

Hic-5 Overexpression Drives Tubular Cell Senescence and Degeneration in Diabetic Kidney Disease

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Background: Emerging data suggest that tubular cell senescence plays a crucial role in the onset and development of diabetic kidney disease (DKD). However, the underlying mechanism responsible for the tubular cell senescence of DKD remains elusive. Hydrogen peroxide-induced clone 5 (Hic-5) has been shown to be associated with senescence-related genes and cell-senescent phenotypes. Ergo, this study investigated the role of Hic-5 in DKD tubular cell senescence.

Methods: The expression of Hic-5 was examined in kidney tissues of DKD patients. The effect of Hic-5 was explored in vitro in cultured tubular epithelial cells by knockdown or by forced expression of Hic-5 in diabetic milieu, or in vivo in mouse models of DKD with knockdown of Hic-5. The cell senescent phenotype, tubular degeneration or kidney injury as well as function were tested.

Results: The tubulointerstitial expression of Hic-5 was markedly increased in kidney tissues of DKD patients, as compared with healthy living donors, which was positively associated with the curated kidney-aging-related gene set "RODWELL_AGING_KIDNEY_UP", as analyzed by gene set enrichment analysis. In vitro in cultured tubular epithelial cells exposed to diabetic milieu, Hic-5 was significantly increased accompanied by increased expression of $p16^{INK4A}$, fibronectin, and increased cell senescence-associated beta-galactosidase activity as well as reduced expression of the epithelial marker E-cadherin. All these senescent phenotypes and degenerative changes were largely abrogated by knockdown of Hic-5 but reinforced by forced expression of Hic-5. In vivo in mouse models of DKD, knockdown of tubular Hic-5 expression mitigated tubular cell senescence and secretion of senescence-associated secretory phenotype including IL6, monocyte chemoattractant protein 1 and plasminogen activator inhibitor 1, concomitant with attenuated kidney function as well as decreased fibronectin and collagen I expression of the kidney.

Conclusions: Hic-5 plays an instrumental role in DKD progression by mediating cellular senescence, and thus is likely a drugable target for halting DKD progression.

FR-PO348

Inhibition of Fatty Acid-Binding Protein 4 Protects Renal Tubular Epithelial Cells and Rescues Diabetic Kidney Disease

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Background: Previous clinical observations have shown that increased circulating fatty acid binding protein (FABP) 4 is associated with the progression of diabetic kidney disease (DKD) in patients with type 2 diabetes. This study aimed to investigate the potential mechanistic role of FABP4 and the direct effects of FABP4 inhibition in experimental DKD.

Methods: To mimic the presence of hyperglycemia in DKD, human renal proximal tubular epithelial cells were cultured with high glucose (25 mM) for 3 days for in vitro study. In addition, Leprdb/JNarl type 2 DM mice were used for a mouse model of DKD. Mice were randomly assigned to receive an oral FABP4 inhibitor, BMS-309403, for 2 weeks.

Results: Administration of FABP4 inhibitor reduced the high glucose-induced apoptosis of renal proximal tubular epithelial cells. Furthermore, FABP4 inhibitor attenuated high glucose-induced inflammatory protein (tumor necrosis factor-α/interleukin-1β/interleukin-6) and fibrotic protein (transforming growth factor-β/collagen-1) expressions in vitro. In in vivo study, treatment of FABP4 inhibitor reduced the increase of serum blood urea nitrogen and creatinine levels in DKD mice. Moreover, the urinary albumin-to-creatinine ratio and kidney-to-body weight ratio were attenuated by FABP4 inhibitor treatments.

Conclusions: Taken together, inhibition of FABP4 could protect renal proximal tubular epithelial cells against the high glucose-induced damage in vitro and improve renal function, renal hypertrophy, and urinary albumin-to-creatinine ratios in DKD mice in vivo. Further molecular mechanistic insights may be explored to provide a novel theoretical basis for the potential therapeutic target of FABP4 in DKD.

FR-PO349

Oxidised IL-33 Mediates Proximal Tubular Injury Through the RAGE/EGFR Pathway

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Background: We previously described IL-33 role in DKD mediating glomerular endothelial inflammation through ST2 signalling and a Ph2b trial in DKD using tozorakimab (anti-IL-33 mAb) is ongoing (FRONTEIR-1). Recently, IL-33 was shown to get oxidised extracellularly ($IL\text{-}33^{ox}$) and exert distinct activity through a novel RAGE/EGFR complex to modulate lung epithelial remodelling. As ST2 and RAGE/EGFR act as putative receptors, we explored $IL\text{-}33^{ox}$ and RAGE/EGFR signalling role in kidney.

Methods: Whilst RAGE is a promiscuous receptor, blockade of RAGE signalling with a neutralising antibody prevented progression of albuminuria in the db/db uninephrectomy model. Mechanistic studies were further developed using primary human glomerular endothelial (GEC) and proximal tubular epithelial cells (PTEC) to address $IL\text{-}33^{ox}$-RAGE/EGFR pathway contribution to human DKD.

Results: GEC but not PTEC expressed ST2 and hence reduced IL-33 ($IL\text{-}33^{red}$) did not display an inflammatory response in PTEC contrary to the effects seen in GEC. However, $IL\text{-}33^{ox}$ stimulation of PTEC promoted EGF receptor activation which was inhibited by antibodies against EGFR and RAGE. $IL\text{-}33^{ox}$ led to phosphorylation of EGFR downstream signalling molecules, like ERK1/ 2 but no other MAP kinases. Data also showed $IL\text{-}33^{ox}$ upregulated epithelial injury markers (KIM-1) and inflammatory cytokine release in PTEC. Preliminary results indicated that $IL\text{-}33^{ox}$ modulates epithelial biological functions that could impact healing and reparative mechanisms in the context of DKD. Under normal culture conditions $IL\text{-}33^{ox}$ but not $IL\text{-}33^{red}$ stimulated PTEC proliferation, while under stress (serum starvation) $IL\text{-}33^{ox}$ prevented this effect. In a PTEC wound closure assay, tozorakimab facilitated wound healing suggesting oxidation inhibition of endogenously secreted IL-33 by the injured epithelium. GEC biology was assessed too. In contrast to the endothelial inflammation caused through the $IL\text{-}33^{red}$/ST2 pathway, minimal effects were observed upon $IL\text{-}33^{ox}$ stimulation.

Conclusions: Although mechanism of action of the $IL\text{-}33^{ox}$–RAGE/EGFR pathway still needs to be fully elucidated, our results suggest that $IL\text{-}33^{ox}$ can contribute to tubular epithelial repair and remodelling. Tozorakimab may therefore be beneficial in DKD by preventing $IL\text{-}33^{red}$ mediated glomerular inflammation and $IL33^{ox}$ mediated tubular injury.

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FR-PO350

microRNA (miR)-299a-5p Promotes Apoptosis of Tubular Cells Through Erk5 Inhibition

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Background: Diabetic kidney disease (DKD) is the leading cause of end stage renal failure in North America. Tubular epithelial cell apoptosis was shown to contribute to the pathogenesis of DKD by promoting interstitial fibrosis. The mechanism involves the release of cytokines and growth factors that promote interstitial inflammation and myofibroblast activation, which leads to the increased production and accumulation of extracellular matrix proteins in the interstitium. Previously, we showed that microRNA (miR) 299a-5p promotes the fibrotic response in mesangial cells. Here we studied the role of this miR in regulating tubular apoptosis.

Methods: Immortalized human kidney proximal tubular cells (HK2) were treated with high glucose (HG); miR299a-5p was detected by qPCR. HK2 cells were transfected with miR overexpression and inhibition plasmids using Transfectamine reagent. Apoptosis was detected using the Annexin V kit. Immunoblotting and immunohistochemistry were used to assess protein expression.

Results: HG increased the expression of miR299a-5p in HK2 cells. A bioinformatics screen of four databases showed that miR299a-5p targets MAP3K2, a protein kinase primarily expressed in the tubules. MAP3K2 is a major activator of extracellular signal-regulated kinase 5 (ERK 5), a known anti-apoptotic and anti-inflammatory kinase. miR299a-5p overexpression reduced the protein expression of MAP3K2 and phosphorylation of ERK5, while augmenting the expression of apoptotic markers and endoplasmic reticulum stress in response to HG. Conversely, miR299a-5p inhibition restored MAP3K2 expression and ERK5phosphorylation to basal levels, while attenuating HG-induced apoptosis. In type-1 diabetic Akita mice overexpressing TGFβ1, a model which accelerates DKD, miR299a was increased in association with reduced expression of MAP3K2 and phosphorylated ERK5.

Conclusions: These data support an important role for miR299a-5p in regulating tubular cell apoptosis in HG. Future studies will determine whether inhibition of this miR *in vivo* attenuates apoptosis and reduces tubulointerstitial fibrosis in DKD. We will also explore whether ERK5 phosphorylation may be a potential therapeutic for interstitial fibrosis.

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FR-PO351

Single Nucleus RNA Sequencing of Sglt2 Knockout Mouse Hearts Reveals Cardiac-Renal Communication

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Background: Sodium glucose cotransporter 2 inhibitors (SGLT2is) are a class of drugs that promote glycosuria and have been shown to provide marked cardiac and renal benefit regardless of diabetes status; however, the precise mechanism of this benefit to the heart is unclear, especially given that the canonical target for SGLT2is is a cotransporter only expressed in the proximal tubule of the kidney. To investigate the broader cardiac effects of chronic Sglt2 inhibition, we conducted the first single-nucleus RNA sequencing (snRNA seq) experiment in the hearts of the SweetPee (SP) mouse model, which carries a missense mutation in the *Slc5a2* gene resulting in loss of Sglt2 expression in the proximal tubule of the kidney.

Methods: 10-week-old male SP and wildtype (WT) control littermates were fed either normal diet (ND) or high fat diet (HFD, 60% calories from fat) for 18 weeks. Hearts were processed using single-nucleus RNA sequencing (snRNA seq) and the resulting data were analyzed through the Seurat pipeline in R to identify differentially expressed genes (DEGs) and to perform pathway enrichment.

Results: Clustering revealed twenty different cell types, no one of which was significantly enriched in any of the four conditions. Replicating prior observations, *Slc5a2* was not expressed in any cardiac cell type under any condition. In the WT HFD group, genes encoding molecules involved in oxidative phosphorylation were upregulated in cardiomyocytes, alongside other metabolic genes. These changes are consistent with altered mitochondrial function. By contrast, the SP HFD showed a downregulation in genes associated with diabetic cardiomyopathy and an upregulation of angiogenic genes. The changes in the WT HFD group are predicted to be deleterious, while those in SP HFD appear to be protective, supporting a model of organ crosstalk whereby renal Sglt2 inhibition results in protective molecular changes in cardiomyocytes.

Conclusions: Here, we demonstrate for the first time that loss of function of the proximal tubule-specific Sglt2 co-transporter results in significant upregulation of cardio-protective pathways, indicating that the cardiac benefit of SGLT2is is secondary to primary effects on the kidney and not a result of off-target pharmacologic effects.

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FR-PO352

SGLT2 Inhibition Causes Methionine Metabolic Modulation in Diabetic Kidney Disease

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Background: Therapeutic inhibition of the sodium glucose cotransporter 2 (SGLT2) protects the kidney although underlying mechanisms are incompletely known. We tested the hypothesis that cell-specific metabolic pathways activated by SGLT2 inhibition in diabetic kidney disease (DKD) underlie benefits.

Methods: Kidneys harvested from 10-week-old male Sglt2 mutant (MT) and wildtype (WT) mice, fed with normal or high fat diet (HFD, 60% calories from fat) for 8 or 18 weeks, were analyzed. Single cell RNA sequence (scRNA seq) analysis was performed on libraries prepared from whole kidneys. Metabolomic analysis of renal cortex was conducted by Metabolon, Inc. Two dosages (10 or 50 mg/kg BW) of Methionine Adenosyltransferase 2A inhibitor (MAT2Ai), an inhibitor of the methionine cycle, was injected into intraperitoneal cavity of WT/MT mice with prior exposure to HFD for 8 weeks. Human proximal tubular cells (HK-2), were exposed to 50 mM of D-glucose with/without 1uM of MAT2Ai or S-Adenosyl methionine (SAM) for 48hr.

Results: HFD-induced obesity was similar in both MT and WT while compensatory hyperphagia was observed in MT. Glucose intolerance occurred in mice fed HFD (WT>MT). Molecular and functional markers of kidney injury including serum creatinine, KIM-1, number of apoptotic cells and albuminuria were higher in WT>MT. Analysis of scRNA seq showed a new class of proximal tubular cells (New-PTC), predominantly found in HFD-fed WT. New-PTC showed increased expression of genes related to epithelial–mesenchymal transition (EMT), apoptosis and inflammation. Pathway enrichment analysis of metabolomic data uncovered differences in WT vs MT renal cortex; metabolites of methionine cycle including SAM were preferentially increased in HFD-fed MT. MAT2Ai abrogated renal protection with anti-inflammatory (reduced IL-6, IL-8, IL-1β and TNF) and fibrotic (reduced αSMA and SM22α) responses in MT. High glucose treatment of HK-2 recapitulated molecular changes observed in New-PTC, including markers of EMT (elevated fibronectin) and inflammation (increased IL-6, IL-8 and TNF) which could be inhibited by SAM supplementation, which enhances methionine metabolism. Conversely MAT2Ai exacerbated EMT and inflammation.

Conclusions: SGLT2 inhibition prevents the emergence of New-PTC with inflammatory and fibrotic phenotypes via methionine metabolic modulation in DKD.

FR-PO353

SGLT2 Inhibition Reveals Kidney Reconfiguration and Metabolic Interorgan Communication

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Background: SGLT2 inhibitors, originally employed for hyperglycemia management, exhibit protective effects against renal and cardiovascular complications, irrespective of diabetes presence. The precise molecular mechanisms underlying these effects remain largely unknown and cannot be solely attributed to their primary function of inhibiting renal glucose re-absorption.

Methods: To gain insights into these mechanisms, we employed LC-MS/MS to investigate various aspects, including the proteome, phosphoproteome, gut metaproteome, metabolome, and SGLT2 interactome. For proteomics/phosphoproteomics analysis, we used TMT16-plex labeling or label-free approaches with an Exploris 480 mass spectrometer (Thermo Fisher Scientific) connected to an UltiMate3000 RSLC (Thermo Fisher Scientific) system. For untargeted metabolomics, we utilized a quadrupole time-of-flight Impact II instrument (Bruker) connected to either a Bruker Elute HPLC or an Agilent 1290 infinity HPLC device. Targeted metabolomics was conducted using a 6495C triple-quadrupole coupled to an Agilent 1290 Infinity HPLC.

Results: We performed an extensive analysis of the proteome, phosphoproteome, and metabolome following one week of SGLT2 inhibitor treatment in non-diabetic and early diabetic mice. We integrated data from multiple metabolic organs and body fluids, including the kidney, liver, heart, white adipose tissue, skeletal muscle, plasma, urine, and gut microbiota. The kidney exhibited the strongest and most significant response to SGLT2 inhibitors in terms of metabolic signaling and transporter reconfiguration. Additionally, the gut microbiome displayed a reduction in bacteria taxa capable of fermenting phenylalanine and tryptophan, resulting in lower plasma levels of uremic toxins. Among the most prominently affected metabolites was p-cresol sulfate, a finding confirmed in cohort studies involving diabetic and heart failure patients with reduced ejection fraction.

Conclusions: The metabolic communication facilitated by SGLT2 inhibitors reduced the presence of circulating waste products such as p-cresol sulfate, consequently reducing the need for renal detoxification. This, combined with decreased glucotoxicity in the proximal tubules and a broad downregulation of apical transport activity, provides a metabolic explanation for the kidney and cardiovascular protection observed.

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FR-PO354

Canagliflozin Greatly Improves Mitochondrial Stress Response in Proximal Tubular Cells (PTCs) of Mice with Combined Hypertension and Type 1 Diabetes

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Background: Canagliflozin (CANA) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor with blood glucose lowering effects. CANA promotes kidney protection in patients with type 2 diabetes (T2D), as well as cardiovascular complications. Both diabetes and hypertension induce mitochondrial dysfunction and oxidative stress. However, it is still unclear whether CANA modulates mitochondrial function in diabetic kidney diseases.

Methods: *In vivo:* Male and female 8 weeks old genetic hypertensive mice (Lin) were subjected to daily intraperitoneal injections of streptozotocin (STZ) for 5 days. 4 weeks after the STZ injections, mice were fed either regular or CANA-infused diet for 1 week. Urinary albumin levels were determined by ELISA and urinary creatinine by colorimetric assay. Proximal tubular epithelial cells (PTCs) isolated from experimental mice were subjected to Seahorse MitoStress test. Kidney OXPHOS complexes were analyzed by Western blotting. *In vitro*: PTCs were isolated from Fvb mice, treated with 100nM Ang II + 30mM glucose for 24h, followed by treatment with 10uM CANA or vehicle for 24h.

Results: Male and females LinSTZ mice had elevated albumin to creatinine ratio (ACR), while CANA reverted the ACR increase in males (23,578 ± 7,937 vs 3,014 ± 492.5, n=4, $P<0.05$) and females (6,758 ± 906.8 vs 623.4 ± 103.8, n=3, $P<0.01$). Overall, PTCs from LinSTZ + CANA greatly improved oxygen consumption rate (OCR) throughout the mitochondrial stress test ($P<0.0001$), with significant increase in OCR after inhibition of complexes I, II, and V in males (n=4, $P<0.05$) and females (n=3, $P<0.05$). A trend to decrease protein levels of OXPHOS complexes were also observed in the kidney of LinSTZ + CANA mice (n=2-3, $P>0.08$). *In vitro*, CANA overall effect on OCR was more pronounced in males, whereas in females there was a higher response to the disruption of mitochondrial oxidative phosphorylation by FCCP ($P<0.001$).

Conclusions: Canagliflozin promoted kidney protection, shown by improvement of albuminuria in hypertensive-diabetic mice. Moreover, we show evidence of improved mitochondria function induced by CANA *in vivo* and *in vitro*. Besides the benefits related to restoration of glucose homeostasis, CANA could play a role on proximal tubular mitochondrial function and remodeling.

Funding: Private Foundation Support

FR-PO355

Combination of SGLT2 Inhibition and ARB Additively Ameliorate High Glucose-Induced Epithelial-Mesenchymal Transition in HK-2 Cells

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Background: Both angiotensin receptor blocker (ARB) and sodium-glucose co-transporter 2 (SGLT2) inhibitors have renal protective effects in diabetic kidney disease; however, their synergistic effects when used in combination are not well understood.

Methods: Human kidney-2 (HK-2) cells were divided into five groups: 1) normal glucose (NG, 5.5 mM), 2) high glucose (HG, 25 mM), 3) HG + candesartan (1μM), 4) HG + dapagliflozin (10 μM), and 5) HG + candesartan + dapagliflozin combination treatment groups. The levels of epithelial-mesenchymal transition (EMT) and inflammation markers were evaluated using real time polymerase chain reaction and western blotting. The changes in the high-mobility group box-1 (HMGB1), receptor for advanced glycation end products (RAGE), and nuclear factor kappa B(NF-kB) signaling pathways were compared among the different groups.

Results: Compared to NG, HG increased mRNA expression and proteins levels of factors associated with renal fibrosis and inflammatory response including transforming growth factor-β (TGF-β), α-smooth muscle actin (α-SMA), connective tissue growth factor (CTGF), collagen type I alpha 1 chain (COL1A1), fibronectin, and tumor necrosis factor-α (TNF-α). In addition, HG decreased the expression of E-cadherin. Treatment with candesartan or dapagliflozin effectively ameliorated these changes in mRNA and protein expressions and the effect was the greatest in combination therapy. These findings suggest that combining SGLT2 inhibitor to ARB therapy holds great promise in suppressing the progression of renal fibrosis through the inhibition of EMT. In addition, the HG group exhibited increased expressions of HMGB1, RAGE, and NF-kB, and treatment with either ARB or SGLT2 inhibitor effectively reversed the upregulation of these molecules. However, combination therapy did not significantly improve HMGB1, RAGG, and NF-kB expression compared to monotherapy.

Conclusions: Our results suggest combining SGLT2 inhibitor to ARB is more effective than the monotherapy for preventing EMT in HG stimulated HK-2 cells.

FR-PO356

Empagliflozin Rescues the Loss of Mitochondrial Mass via ERRα in Proximal Tubular Epithelial Cells from db/db Mice

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Background: It is known that mitochondrial dysfunction of proximal tubular epithelial cells(PTECs) contributes to the pathogenesis of diabetic nephropathy. However, the ultrastructural changes of PTEC mitochondria in diabetic kidneys remain unclear. Empagliflozin(EMPA) protects the diabetic kidney via SGLT2 located only on PTECs. ERRα is highly expressed in PTECs and associated with mitochondrial biogenesis. The present study aimed to investigate the role of ERRα on mitochondrial mass in diabetic tubular injury and the mechanism of the protective effects of EMPA.

Methods: Transmission electron microscopy (TEM) was used to identify ultrastructural changes in the mitochondria of PTECs from diabetic mice and RNA sequences of isolated renal tubules was performed to identify the DEGs related to mitochondria and ERRα. The expression of ERRα was also evaluated by immunohistochemistry(IHC) and Western blot(Wb). EMPA was then administrated to db/db mice for 12 weeks and the mitochondria was assessed by TEM and the expression of ERRα was evaluated by Wb,RT-qPCR and IHC. Wb was also used to assess the expression of Fis1 and PGC1α. In HK-2 cells, High glucose(HG) or ERRα siRNA or pcDNA-ERRα or EMPA were used to modify the expression of ERRα. The mass and function of mitochondria were evaluated by Mitotracker Red and JC-1 in corresponding culture conditions.

Results: PTECs presented less mitochondrial mass and swelling mitochondria with more mitochondrial cristae fracture in 16-week-old db/db mice. RNA-sequences of isolated renal tubules from db/db mice revealed that 110 downregulated genes were related to mitochondrial function or mitochondrial energy metabolism. ERRα is among the genes with prominent changes. The downregulation of ERRα in diabetic kidney was further evaluated by Wb and IHC. In HG exposed HK-2 cells, the expression of ERRα was decreased and the mitochondrial mass and membrane potential(MMP) were inhibited. ERRα gene silencing decreased mitochondrial mass and MMP while ERRα overexpression or EMPA rescued HG-induced loss of mitochondrial mass in HK-2cells. In vivo, EMPA alleviated ultrastructural changes of PTECs and the downregulation of ERRα from db/db mice.

Conclusions: Decreased ERRα contributes to the loss of mitochondrial mass of PTECs in the early stage of diabetes and is a target of EMPA to prevent the progression of diabetes on kidney injury.

Funding: Government Support - Non-U.S.

FR-PO357

Kidney Disease Progression in Obese ZSF1 Rats Treated with the SGLT2 Inhibitor Empagliflozin

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Background: The obese ZSF1 rat is a model of spontaneous diabetic kidney disease. These rats are bred from a zucker diabetic fatty female and a spontaneous hypertensive heart failure male and carry two mutations in the leptin receptor gene: *Lepr^{fa}Lepr^{cp}/Crl*. The control model for this rat is the lean ZSF1 rat (*Lepr^{fa}/Crl*). In contrast to many other animal models of kidney disease, the obese ZSF1 rat model is a slow progressing kidney disease model. In this study, we evaluated kidney disease progression in obese ZSF1 rats and for the first time investigated renal outcomes upon treatment with the SGLT2 inhibitor empagliflozin.

Methods: Lean and obese ZSF1 rats were fed with Purina #5008 diet. In the first sub-study, lean and obese animals were left untreated and regular plasma and urine samples were collected for 36 weeks. In the second sub study, obese animals were treated with empagliflozin (in feed, estimated intake: 30 mg/kg/day) or vehicle at 14 weeks of age for 15 weeks. Plasma and urine samples were collected bimonthly or monthly, respectively. Glomerular filtration rate (GFR) was measured at baseline and upon 14 weeks of treatment. Plasma and urine samples were analyzed for lipid and kidney injury markers using COBAS analysis as well as various ELISAs. Histological analyses were performed on liver and kidney tissue.

Results: Plasma cholesterol, triglycerides, glucose as well as proteinuria increased with age in obese ZSF1 rats. Urinary excretion of the kidney injury markers KIM-1 and NGAL were also elevated with age, reaching maximum concentration at age 34 weeks. Histological analyses revealed severe glomerular damage at 46 weeks of age compared to lean controls. SGLT2 inhibition with empagliflozin indeed reduced plasma glucose and triglyceride levels whereas urine volume and urinary glucose excretion were elevated.

Conclusions: Obese ZSF1 rats were hyperglycemic and hypercholesterolemic. Proteinuria increased with age in these rats, and severe glomerular damage was observed at 46 weeks of age. Empagliflozin reduced blood glucose and increased urine volume as well as glucose excretion. Future analyses investigating proteinuria, GFR as well as histological characteristics of kidney tissue are ongoing and warranted to evaluate renal outcomes upon empagliflozin treatment in obese ZSF1 animals.

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FR-PO358

Expression Profiles of Glucose Transporters Along the Nephron in Non-Diabetic and Diabetic Kidneys

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Background: In non-diabetic kidneys, over 99% of filtered glucose is reabsorbed in the proximal tubule (PT), resulting in limited delivery to the distal nephron. However, in diabetic kidneys, the excessive filtration of glucose surpasses the reabsorption capacity of the PT, leading to its presence in the distal nephron. This may trigger adaptations in the distal nephron to compensate for glucose reabsorption and minimize its excretion in urine. Despite extensive research, the comprehensive expression profiles of glucose transporters along the nephron remains incompletely understood. Hence, this study aims to identify the specific glucose transporters expressed in each tubule segment and investigate alterations in their expression in diabetes.

Methods: We identified glucose transporters expressed in distinct segments of the nephron and compared their gene expression between db/m and db/db mice by analyzing the snRNA-seq data (GEO: GSE184652). Additionally, we conducted microdissection of individual nephron segments from db/m and db/db mice and measured the gene expression of glucose transporters in these isolated tubular segments using RT-PCR and qPCR. To further validate the protein expression of these glucose transporters, we performed immunofluorescence (IF) staining and Western blot (WB) assays on whole kidneys.

Results: We unveiled the expression profiles of glucose transporters in specific segments of the nephron. Specifically, Slc2a4 (GLUT4) is expressed in thick ascending limb (TAL), distal convoluted tubule (DNT), connecting tubule (CNT), and intercalated cells (IC), and Slc2a1 (GLUT1) is expressed in TAL, macula densa, DCT, CNT, pricipal cells, and IC. Furthermore, our analysis revealed an upregulation of Slc2a4 expression in the TAL (27.96%), DCT (6.10%), CNT (53.95%), and IC (6.03%) and a downregulation of Slc2a1 expression in the DCT (-50.98%), CNT (-49.05%), and IC (-10.36%) in db/db mice compared to db/m mice. Additionally, we confirmed these findings through RT-PCR and qPCR in isolated tubular segments, as well as IF staining and WB assays in whole kidneys.

Conclusions: In this study, we identified glucose transporters expressed along the nephron and compared their expression levels in db/m and db/db mice. Notably, the glucose transporter GLUT4 in the distal nephron segments appears to play a significant role in compensating for glucose reabsorption in diabetes.

Funding: NIDDK Support, Private Foundation Support

FR-PO359

Direct Effects of SGLT2 Inhibitors on Proximal Tubule Function

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Background: Sodium glucose transporter 2 inhibitors (SGLT2i) have been shown to have cardiorenal protection in patients with and without T2DM. Inhibition of proximal tubule (PT) sodium/hydrogen exchanger type 3 (NHE3), which is known to regulate endocytosis and fluid transport in the PT, has been suggested to contribute to the SGLT2i renoprotective benefits. Also, some SGLT2i have been demonstrated to activate AMPK. However, the underlying mechanisms behind the beneficial effects of SGLT2i are unknown. To circumvent the challenges of untangling the direct effects of SGLT2i on PT function in vivo, we examined the effects of gliflozins in a well-characterized and highly differentiated opossum kidney (OK) cell culture model of the PT S1 segment.

Methods: The effect of gliflozins vs NHE3 inhibitor S3226 on albumin uptake and fluid transport was quantified in OK cells. Endosomal pH was measured by fluorescence ratio imaging in OK cells treated with cana vs S3226. Effects of gliflozins, S3226, and AMPK pathway perturbants were determined by immunoblotting. 10-week-old male C57BL/6 mice were given cana or empa by oral gavage daily following vehicle gavage. Urine was collected via metabolic cages at baseline and after 24h and 48h. Creatinine and albumin were measured by ELISA.

Results: A subset of SGLT2i (cana and tofo, but not empa) impaired endocytosis and fluid transport in a dose-dependent and glucose-independent manner. Surprisingly, SGLT2i did not recapitulate the effect of S3226 on NHE3 phosphorylation or endosomal pH. Treatment with cana but not empa caused a rapid increase in AMPK phosphorylation and a reduction in phospho-S6 ribosomal protein (pS6), a downstream target of mTOR. These effects were observed at concentrations comparable to plasma levels in humans on standard doses of cana. In our mouse study, both treatment conditions led to increased urine volume compared to baseline, cana treated mice urinated significantly more than emp treated mice.

Conclusions: Differential effects of SGLT2i on fluid transport and albumin uptake in OK cell monolayers may be mediated by off-target effects on AMPK/mTOR activity. These off-target effects could contribute to the differences we observed in mice treated for short periods with cana vs empa, and could impact the renal protective mechanisms of SGLT2i in humans.

FR-PO360

A Human Single-Cell Transcriptomic Atlas Characterizes the Kidney in Diabetic Kidney Disease

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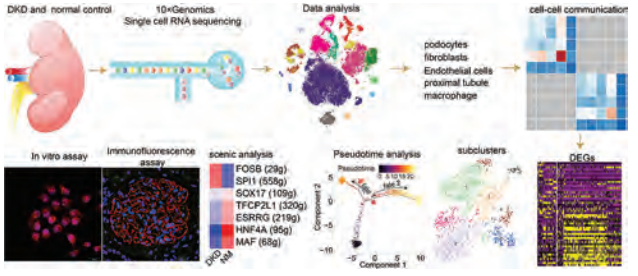
Background: Diabetic kidney disease (DKD), a common and devastating microvascular complication of diabetes, is the leading cause of end-stage renal disease (ESRD). However, the mechanisms of kidney injury in DKD are largely unknown.

Methods: To elucidate the heterogeneity and the underlying mechanisms for DKD progression, we performed single-cell RNA sequencing (scRNA-seq) on human kidneys collected from 3 DKD and 3 normal samples using 10× Genomics.

Results: A total of 51315 cells were enrolled for analyses, and nine kidney cell types and seven immune cell types were identified. The cell-type-specific changes in gene expression and signaling pathways of podocytes, fibroblasts, endothelial cells, proximal tubules and macrophages indicate abnormal regulation associated with inflammation, apoptosis, oxidative stress, extracellular matrix accumulation, fibrosis and immune activation. In particular, we show that podocytes and proximal tubules have a tremendous capacity to regenerate, which is involved in the repair of injury. Extracellular vesicles, important mediators of intercellular communication, might play vital roles in this process. In addition, we identified new candidate transcription factors responsible for the progression of DKD. We also revealed an M1-M2 hybrid pattern, in which M1 and M2 are coupled for activation in macrophages in DKD. Furthermore, we observed an increased intercellular interaction among podocytes, fibroblasts, endothelial cells, proximal tubules, and macrophages in DKD.

Conclusions: Our study advances the understanding of DKD pathogenesis and provides novel therapeutic targets for its treatment in the future.



FR-PO361

Integrative Transcriptome and Proteome Profiling of Insulin-Resistant Kidney Cell Models and Patient Biopsies Reveals Common and Cell Type-Specific Mechanisms Underpinning Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of end stage kidney failure worldwide. It is now clear that cellular insulin resistance is a major driver of this disease.

Methods: Using established human conditionally immortalised podocytes (Pods), glomerular endothelial cells (GECs), mesangial cells (MCs), and proximal tubular cells (PTCs), we modelled both insulin sensitivity and insulin resistance and performed simultaneous transcriptomics and proteomics for integrated analysis. Our data was further compared with bulk- and single-cell transcriptomic kidney biopsy data from early- and advanced-stage DKD patient cohorts.

Results: We identified several consistent changes (individual genes, proteins, and molecular pathways) occurring across all insulin-resistant kidney cell types, which were replicated in human early- and/or advanced-stage DKD biopsies. These included the genes *CTSS*, *NRBF2*, *C3*, *CXCL1*, *TFPI2* and *PFKFB3*, and pathways related to the inflammatory response, ER stress and glycoprotein metabolism. We further identified several cell-line-specific molecular changes occurring in response to insulin resistance, which were replicated in single-cell sequencing data from DKD, together with a selective reduction in mitochondrial function in Pods, MCs and PTC, but not GECs.

Conclusions: This study provides a rich data resource to direct future studies in elucidating underlying kidney signalling pathways and potential therapeutic targets in DKD.

Funding: Government Support - Non-U.S.

FR-PO362

Identification of Novel Noninvasive Biomarkers for Cadmium-Induced Renal Injury Through Transcriptome Profiling and Machine Learning

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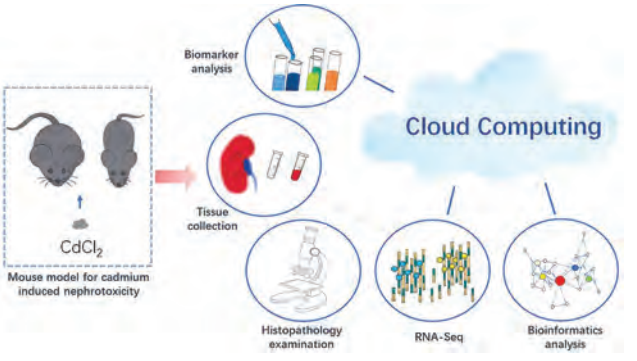
Background: Kidney is the major toxic organ for cadmium. Once entering the body, cadmium accumulates in proximal tubule cells, resulting in the death of renal epithelial cells through necrotic or apoptotic mechanisms. Of particular interest, cadmium is closely associated with diabetes and the diabetic population is more sensitive to cadmium induced cell damage. The molecular mechanisms underlying the chronic cadmium induced toxicity and the increased susceptibly under diabetic conditions are not fully understood.

Methods: In the present study, we optimized an animal model to study chronic cadmium exposure-induced renal injury by using low dose and repetitive CdCl2 treatment. In conjunction with clinical biochemistry and histopathology, we performed whole transcriptome profiling analyses on kidney. Machine learning with cloud computing was applied to identify novel biomarkers indicative of increased susceptibility in diabetic populations with particular focus on secreted molecules.

Results: Repetitive CdCl2 exposure resulted in cadmium accumulation and remarkable renal injuries with the *ob/ob* mice manifesting increased severity of renal injury. RNA-Seq data showed that cadmium treatment induced dramatic gene expression changes correlated with the level of cadmium-induced nephrotoxicity. In order to better understand the increases susceptibility under diabetic conditions, we focused our analyses on the low dose *ob/ob* group. Canonical pathway enrichment analysis revealed key pathways such as Integrin, AP1, IL23, FRA, P53 and TAP63 pathways. Furthermore, a subset of 14 secreted molecules was found to be enriched including Il12b, Ccl2, Il1rn, Gdf15 and Il17f.

Conclusions: A subset of potential sensitive biomarkers which can be measured in peripheral for early diagnosis of cadmium-induced renal injury has been identified. Applicability of these biomarkers in clinical will be tested in human samples.

Funding: Government Support - Non-U.S.



FR-PO363

Cytochrome P450: The Metabolic Pathways and the Genetic/ Epigenetic Regulation Involved in Shaping the Story of Diabetic Kidney Disease (DKD).

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Background: Cytochrome P450 (CYPs) epoxygenases metabolize arachidonic acid (AA) into 20-HETE and EETs. Our group has described the implication of CYPs and their metabolites in the pathogenesis of DKD, in experimental animal model of diabetes. Yet the correlation of these finding in human setting is under investigation. More importantly, CYPs-encoding genes possess polymorphisms that can alter the expression of these key enzymes, affecting the prognosis of patients with DKD. Herein, we hypothesize that alteration in 20-HETE and EETs levels in diabetes leads to kidney injury, and that genetic variants/epigenetic regulation of AA-metabolizing CYPs may potentiate the development of DKD.

Methods: Healthy volunteers, individuals diagnosed with type 2 diabetes (T2DM) with or without clinical manifestation of DKD were enrolled in this study. Levels of 20-HETE and EETs were assessed in the urine and plasma samples of the recruited individuals and correlated with the extent of renal injury. To detect single nucleotide polymorphisms (SNPs) in CYP4A11, CYP4F8 and CYP2B6, TaqMan PCR assay was performed on the DNA extracted from the collected blood samples.

Results: Circulating levels of 20-HETE were increased in patients with DKD when compared to T2DM patients with no clinical signs of DKD, which in turn had higher levels of 20-HETE in comparison to the healthy volunteers. This was associated with an increased expression of CYP4A11 and CYP4F8 in the human kidney biopsies of patients with DKD. In parallel, EETs levels were decreased in patients with T2DM and DKD as compared to patients with T2DM only and this was positively correlated with the decreased CYP2B6 expression in kidney biopsies of patients with DKD. Furthermore, a difference in 2 SNPs for CYP2B6 and 1SNP for CYP4A11 was observed across patients with different conditions, suggesting an increased risk with the mutant allele for diabetes and DKD.

Conclusions: This study may yield important findings about novel regulatory pathways involved in diabetes-induced renal injury and may identify novel prognostic/diagnostic biomarkers associated to CYPs pathways in DKD.

FR-PO364

Deciphering Renal Restoration: Single-Cell Transcriptional Insights from Pre- and Post-Vertical Sleeve Gastrectomy Kidney Biopsies

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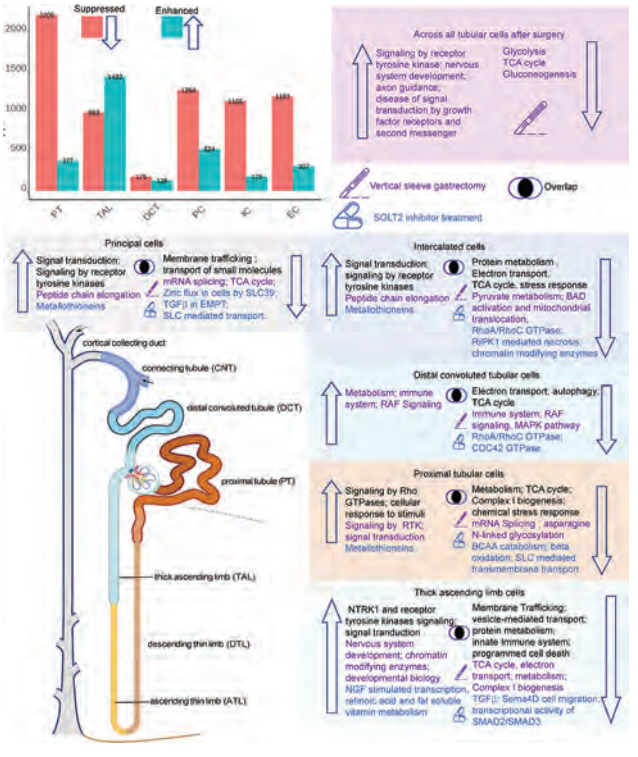
Background: Vertical sleeve gastrectomy (VSG) attenuates the metabolic dysfunction characteristic of obesity and type 2 diabetes. The molecular mechanisms diminishing risk of kidney disease by VSG remain unclear.

Methods: Cell-type-specific differentially expressed genes (DEGs) before and 12 months after VSG (n=5 pairs) were determined from single-cell RNA sequencing (scRNAseq) of kidney biopsies. Top up-and downregulated pathways associated with VSG based on pathway enrichment of DEGs were compared with similarly curated Sodium-Glucose Cotransporter-2 inhibitor (SGLT2i) effects (https://doi.org/10.1172/JCI164486) to identify shared and unique pathways in cell types experiencing significant transcriptional changes.

Results: VSG improved UACR for all, and 75% with initial high albuminuria saw a category stepdown. Glomerular and mesangial volume decreased in the subset with kidney biopsy data. Proximal tubular cells had the most genes suppressed, while thick ascending limb cells the most enhanced, after VSG based on scRNAseq. Metabolic pathways like glycolysis, the TCA cycle, and gluconeogenesis were downregulated, while others like RTK signaling and axon guidance were upregulated across the nephron. Noteworthy transcriptional variations were seen between SGLT2i treatment and VSG (Figure).

Conclusions: scRNAseq provided insights into cell-specific effects of VSG on kidneys. Despite commonalities, VSG and SGLT2i modified distinct cell-specific signaling pathways, offering potential avenues for innovative therapeutic interventions.

Funding: NIDDK Support, Private Foundation Support



FR-PO365

GDF-15 and NETosis Cross-Talk in Diabetes-Induced Renal and Cardiovascular Complications: Unraveling the Molecular Interactions

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Background: Diabetic kidney disease (DKD) and diabetic cardiomyopathy (DCM) are severe complications of diabetes, posing significant risks of renal failure and cardiovascular events. One potential biomarker with promising implications in this context is growth differentiation factor 15 (GDF-15), a cytokine belonging to the transforming growth factor-β (TGF-β) family. Elevated levels of GDF-15 are observed in the presence of tissue injury, inflammation, and stress. Moreover, our research group has focused on exploring the relationship between neutrophil extracellular trap formation (NETosis) and the progression of injury in DKD and DCM. This article aims to elucidate the role and interplay between GDF-15 and NETosis in the development of renal and cardiac injury induced by type 2 diabetes.

Methods: T2DM was induced in C57BL/6J male black mice using the high fat diet/STZ model in two sets of experiments. In the first set, mice were divided into control, PMA-induced NETosis, T2D, and T2D treated with CLA (NETosis inhibitor) groups. In the second set, control mice, GDF-15 antibody AV-380-treated control mice (at 7.5mg/kg or 20mg/kg), T2D mice, and AV-380-treated T2D mice (at 7.5mg/kg or 20mg/kg) were utilized. Functional, histopathological, and molecular studies were performed on kidney and heart tissues from all groups.

Results: Our data demonstrate that inhibiting GDF-15 with AV-380 or NETosis with CLA can restore renal and cardiac homeostasis in T2D mice. This is evident through reduced proteinuria, glomerulosclerosis, collagen deposition in the kidneys and heart, as well as improved cardiac ejection fraction and decreased inflammatory markers in the treated diabetic mice. Importantly, NETosis inhibition attenuated the diabetes-induced overexpression of GDF-15 in kidney and heart tissues, suggesting a crosstalk between these 2 signaling molecules. Intriguingly, inducing NETosis in control mice using PMA resulted in similar renal and heart injuries observed in diabetes.

Conclusions: Our study findings provide valuable insights into the role and interplay between GDF-15 and NETosis in diabetes-related cardiac and kidney injury. Targeting the GDF-15/NETosis signaling cascade through pharmacological interventions offers a basis for future clinical studies that aim to manage diabetes-associated complications.

FR-PO366

Stress Response Protein REDD1 Sustains the Chronic Inflammatory Response in Diabetic Nephropathy

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Background: Diabetic nephropathy (DN) is one of the most common and severe complications of diabetes. We recently demonstrated a role for the stress response protein REDD1 in development of renal complications in DN. However, there remains a significant gap in our understanding of the molecular events whereby REDD1 contributes to the development of renal dysfunction. Herein, we investigated the hypothesis that diabetes-induced REDD1 expression acts to exacerbate pro-inflammatory NF-κB signaling and consequently development of renal inflammation.

Methods: REDD1$^{+/+}$ and REDD1$^{-/-}$ mice were administered low dose streptozotocin to induce diabetes. Kidneys were isolated after 16 weeks of diabetes, weighed, and analyzed for protein and mRNA expression. Spot urine albumin and creatinine levels were assayed. Kidneys were fixed and renal sections were visualized by immunofluorescence microscopy. Complementary analyses were performed with conditionally immortalized human podocyte cultures exposed to hyperglycemic conditions. Inhibition of SLGT2 or GSK3 was achieved by dapagliflozin or VP3.15 administration, respectively. Nuclear NF-κB activity was estimated by luciferase assay.

Results: Diabetes increased REDD1 expression in the kidney and promoted albuminuria and renal immune cell infiltration. In diabetic mice treated with dapagliflozin, blood glucose concentrations were reduced and both REDD1 expression and immune cell infiltration were attenuated. In contrast with REDD1$^{+/+}$ mice, REDD1$^{-/-}$ mice did not exhibit an increase in pro-inflammatory marker expression or renal macrophage infiltration with diabetes. In cultured human podocytes, exposure to hyperglycemic conditions promoted REDD1 expression, which was required for activation of both NF-κB and the NLRP3 inflammasome. Upregulated expression of NF-κB target genes and IL1β production by podocytes exposed to hyperglycemic conditions was prevented by REDD1 deletion. REDD1 acted via an Akt-GSK3β signaling axis, as GSK3β inhibition prevented diabetes-induced NF-κB activation and reduced immune cell infiltration in kidneys of diabetic mice.

Conclusions: These findings demonstrate a role for REDD1-dependent GSK3 signaling in diabetes-induced renal pathology and support the possibility that therapeutics targeting REDD1 or GSK3 could be beneficial in the context of DN.

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FR-PO367

SerpinA3K Deficiency Ameliorates Diabetic Kidney Disease (DKD)

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Background: We showed that SerpinA3K is an early urinary biomarker of Acute Kidney Injury (AKI) to Chronic Kidney Disease (CKD) transition. SerpinA3K or anti-chymotrypsin is a serine protease inhibitor with non-canonical functions such as: antioxidant, anti-inflammatory, and anti-fibrotic in rodent diabetic retinopathy. Nevertheless, we recently showed that AKI is attenuated in SerpinA3K deficient mice by inducing higher expression of antioxidant defense, however, its involvement in CKD remains elusive. This study was designed to evaluate the impact of SerpinA3K absence in DKD.

Methods: Thirty wildtype (WT) [*SerpinA3K*+/+] and thirty knock-out (KO) [*SerpinA3K*-/-] male mice after breastfeeding were randomized in the following six groups: Standard Diet (WT+SD and KO+SD), High Fat Diet (WT+HFD and HFD+KO), and Streptozotocin (STZ) [100 mg/kg] + HFD (WT+DKD and KO+DKD). Glucose monitoring was done every 15 days. A cut-off point was established above 500 mg/dL to receive insulin 2 days per week to increase animal survival. Urine collection was done monthly. After 7 months of follow-up, each group was euthanized for kidney functional, histological, and molecular analyses. Differences between groups were analyzed through ANOVA and post-hoc testing with a significance level of $p<0.05$.

Results: HFD feeding induced obesity, hypercholesterolemia, hyperleptinemia, and hyperinsulinemia, without any differences between genotypes, but increased serum IL6 in the WT+HFD was not evident in the KO+HFD group. In addition, the WT+DKD group exhibited hyperglycemia above 500 mg/dL, since, 15 days after STZ requiring insulin, and exhibited insulin resistance (HOMA-IR). Interestingly, these effects were not seen in the KO+DKD group, in which, glycemia was below 400 mg/dL and non-insulin requirement. GFR measured by fluorescein sinistrin was significantly increased in the WT+DKD but not in the KO+DKD group. Furthermore, the WT+DKD group exhibited an increase in *Hif1a, Il6, and Tgfb1* which was not seen in the KO+DKD.

Conclusions: The absence of SerpinA3K was associated with DKD attenuation. This protective effect seems to be mediated by improving metabolic health against hyperglycemia. Nevertheless, the mechanisms and causes of this protection required further studies to deep into the role of SerpinA3K in DKD induced by STZ.

Funding: Government Support - Non-U.S.

FR-PO368

Specialised Proresolving Mediators Protect the Diabetic Kidney Against Podocyte Loss

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Background: Kidney macrophages are a heterogeneous population of cells that contribute to the chronic unresolved inflammation that underlies diabetic kidney disease (DKD). The macrophage subpopulations initiating and promoting inflammation in DKD, particularly in the glomerulus, have not been characterized. There has also been growing interest in specialised pro-resolving mediators (SPMs) such as Lipoxin A4 (LXA_4) as potential reno-protective agents. The focus of this study was to investigate the effect of LXA_4 on kidney macrophages in a model of DKD.

Methods: Six-week-old male ApoE KO mice were rendered diabetic by five daily IP injections of streptozotocin (55mg/kg). Controls received citrate buffer alone. After 10wks of diabetes, mice were randomly selected to receive twice weekly administration of either vehicle (0.02% ethanol) or LXA_4 (5µg/kg) via IP (n=30/gp) for a further 6 weeks. At endpoint, mice were culled, and kidneys collected for gene expression analysis, single cell RNA sequencing (scRNA-Seq) of glomerular cells, immunohistochemistry and histology.

Results: Diabetic mice had elevated blood glucose, glycated haemoglobin and albuminuria, as well as increased expression of fibrotic (fibronectin, Col 4a3), inflammatory markers (IL1β, TNFα, MCP1, VCAM-1, ICAM-1) compared to control. Interestingly, LXA4 resulted in reduced albuminuria, Collagen IV, inflammatory and fibrotic markers (IL1β, MCP1, ICAM1 and VCAM1) independent of any changes in metabolic parameters. scRNA-Seq of the glomerular cell populations demonstrated an increase in macrophages in kidneys of diabetic mice. These changes were associated with renal injury, including the increased expression of apoptotic markers and depletion of podocytes (reduced by 42% in diabetic versus control). LXA_4 reduced macrophage numbers and prevented podocyte loss in the diabetic kidney.

Conclusions: SPMs protect against DKD by reducing fibrotic and inflammatory signalling, as well as reducing monocyte recruitment and increased macrophage numbers in the diabetic kidney. These effects are accompanied with improved kidney function. These data further support the use of SPMs as typified by LXA_4 as a novel treatment for DKD by targeting macrophages in the kidney.

Funding: Government Support - Non-U.S.

FR-PO369

Mitochondrial Dysfunction-Related Glycogen Synthase Kinase 3β (GSK3β) Overexpression Drives Early Diabetic Tubulopathy

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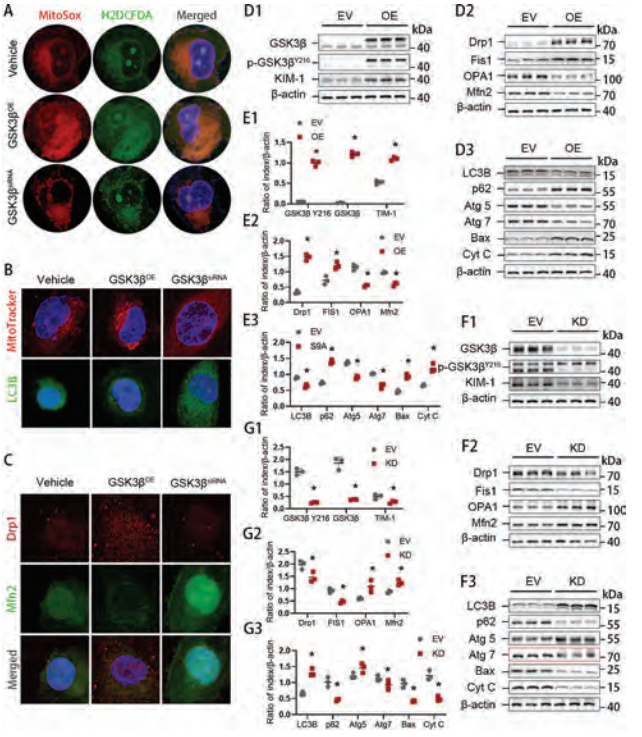
Background: Over these years, the traditional "glomerulocentric" paradigm of DKD has partly shifted to diabetic tubulopathy (DT) because of renal insufficiency and prognosis of patients is closely related to tubular atrophy and interstitial fibrosis. New insights indicate that mitochondria dysfunction represent an early event in DT, but the precise mechanism for such pathological process is not clear.

Methods: The present study was designed by using high-fat diet (HFD)-fed combine with STZ mice as an insulin resistance model of tubular injury in T_2DM. We also reported the expression of GSK3β in human proximal renal tubular (HK-2) cells.

Results: As a potential novel biomarker for predicting a variety of renal diseases, glycogen synthase kinase 3β (GSK3β) is overexpressed and hyperactive with mitochondrial dysfunction in proximal tubular epithelium, correlating with functional and histological signs of renal tubular injury in diabetes mellitus (DM). Moreover, tubule-specific ablation of GSK3β substantially attenuated mitochondrial damage and early tubular lesions in mice. Multiple regulatory mechanisms of mitochondrial damage, such as mitochondrial biology, mitochondrial dynamics, mitophagy and oxidative stress, are closely related to the hyperactivation of GSK3β. In addition, therapeutic targeting of GSK3β by TDZD-8 ameliorated mitochondrial dysfunction and delayed early stage of DT in mice.

Conclusions: Thus, GSK3β appears to play a key role in early DT by modulating mitochondrial dysfunction and may be an actionable target for intervention to delay DKD in advance.



GSK3β hyperactivity exacerbated HG-induced mitochondrial dysfunction in HK-2 cells

FR-PO370

ERRα Acts as a Bridge of Mitochondria and Sodium Homeostasis in Proximal Tubular Epithelial Cells Under Diabetes

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Background: The mechanism of sodium homeostasis in diabetic kidney disease (DKD) is unclear. In previous study, we found that the expression of sodium translocation channels (ATP1A1) and the estrogen-related receptor alpha (ERRα) were decreased only in DKD renal biopsy samples. The present study aims to investigate how ERRα involves in the regulation of mitochondrial loss and sodium homeostasis in proximal tubular epithelial cells (PTEC) under diabetes condition.

Methods: ERRα and ATP1A1 proximal tubule-specific overexpression mice ($ERR\alpha^{ptKI}$, $ATP1A1^{ptKI}$) were constructed and fed with high salt (4% NaCl) or normal diet (0.8%) for 4 weeks. Sodium concentration from isolated PTEC was quantified by ionophore ICPMS analysis. The changes of renal injury markers, proximal tubular sodium-related transport channels were evaluated. In vitro study,HK-2 cells were treated with high glucose (30 mM), high salt (40 mM), and high glucose + high salt for 24 h after overexpression of ERRα and ATP1A1 using adenovirus. Sodium concentration in PTEC was observed by cellular sodium fluorescence probe, morphological changes in mitochondria were observed by TEM, and CHIP-seq analysis was carried out to evaluate the transcriptional regulation of ATP1A1 by ERRα.

Results: High salt diet accelerated the pathological injury and mitochondrial damage in PTEC and provoked sodium accumulation compared with normal diet in wild type mice. STZ-treated $ERR\alpha^{ptKI,}$ and $ATP1A1^{ptKI}$ mice with high salt diet had mild pathological injury and mitochondrial damage and less sodium concentration in PTEC when compared with STZ-treated wild-type mice. In vitro study, CHIP-seq showed that ERRα regulates its transcription by binding to the promoter of ATP1A1. Sodium concentration, mitochondrial damage, and markers of kidney injury were significantly higher in HK-2 cells treated with high glucose or high salt, and further increased in the high glucose + high salt. The above changes were alleviated by overexpression of either ERRα or ATP1A1 in HK-2 cells.

Conclusions: ERRα is an exclusive nuclear transcription factor affected by diabetes in PTEC to integrate the mitochondria and sodium homeostasis via ATP1A1, sodium loading may act as a "second strike" to promote pathological injury in PTEC under diabetic condition.

Funding: Government Support - Non-U.S.

FR-PO371

Promoting Mitochondrial Dynamics by Inhibiting the PINK1/PRKN Pathway to Relieve Diabetic Nephropathy

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Background: Diabetes is a metabolic disorder characterized by high blood glucose levels and a leading cause of kidney disease. Dysfunctional mitochondria have been associated with diabetic nephropathy. However, many questions remain about the exact mechanism; its understanding is important to develop effective therapeutics.

Methods: Structure, function, and molecular pathways are highly conserved between mammalian podocytes and *Drosophila* nephrocytes Thus we used flies on a high sucrose diet to model type 2 diabetic nephropathy. We then investigated the structural and functional effects on the fly nephrocytes and their mitochondria.

Results: The nephrocytes of flies on a high sucrose diet showed remarkable levels of functional decline and decreased cell size; the flies had a shortened lifespan. Structurally, the slit diaphragm—nephrocyte filtration structure—was disorganized. At the cellular level, we found altered mitochondrial dynamics and dysfunction. Regulating mitochondrial dynamics by either genetic modification of the Pink1/Park (mammalian PINK1/PRKN) pathway or treatment with BGP-15, mitigated the mitochondrial defects and nephrocyte functional decline.

Conclusions: These findings support a role for Pink1/Park-mediated mitophagy and associated control of mitochondrial dynamics and health in diabetic nephropathy; and demonstrate that targeting this pathway might provide therapeutic benefits in type 2 diabetic nephropathy.

Funding: Private Foundation Support

FR-PO372

Obesity Augments Urinary Tract Infection Susceptibility by Activating Focal Adhesion Kinase in Kidney Intercalated Cells

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Background: Obesity affects a third of the global population. Among the comorbidities linked to obesity is increased urinary tract infection (UTI) and pyelonephritis risk. The obesity mediated factors that increase UTI risk are unknown. In this study, we assess the impact of diet-induced obesity on UTI susceptibility using male and female mice. Because recent data show intercalated cells (IC) in the kidney have a key role in protecting against UTI and pyelonephritis, we also assess how diet-induced obesity effects murine IC gene expression and antibacterial defenses.

Methods: C57/BL6 male and female mice were fed a high fat diet (HFD; 60 kcal% fat) or standard diet (SD; 10% kcal fat) for 8-12 weeks. Mice were subjected to experimental UTI and infected with UPEC. UPEC burden was quantified 24 hours after infection. ICs from SD and HFD fed mouse kidneys were enriched using FACS and subjected to RNAseq. Differentially expressed genes were used to generate lists of enriched pathways and ontologies. Western blot confirmed pathway suppression or activation. To test how these pathways impact UTI outcomes, ICs were cultured to confluency, treated with target inhibitors, and challenged with UPEC.

Results: Male and female mice fed a HFD showed a 30% increase in body weight, reduced insulin sensitivity measured by glucose tolerance testing, and 10-100-fold greater UPEC burden following UTI. Changes in gene expression in ICs from HFD and SD mice diverged depending on sex. Activation of focal adhesion kinase (FAK) was consistent between sexes when comparing HFD and SD ICs. Western blot confirmed increased FAK signaling in HFD kidneys, as well as increased NFkB, a downstream FAK target. When cultured ICs were treated with the FAK inhibitor PF-573228 and challenged with UPEC, bacterial invasion was abolished.

Conclusions: These results suggest that diet-induced obesity leads to increased UTI susceptibility by activating FAK signaling in ICs. Future studies will investigate the factors regulating FAK as targets for reducing UTI risk.

Funding: NIDDK Support, Other NIH Support - NIH Loan Repayment Program

FR-PO373

Overexpression of Adiponectin, via an Adipocyte Specific Promoter, Confers Metabolic Benefits and Transient Improvements in Urine Albumin-Creatinine Ratio (UACR)

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Background: Adiponectin is an endocrine factor synthesized and released from adipose tissue. Clinical and pre-clinical data have linked low adiponectin levels with the acceleration of kidney disease. However, adiponectin's complex structure and multiple molecular forms have stunted therapeutic approaches to augment adiponectin signalling. We hypothesized that in-vivo overexpression of adiponectin using adipocyte specific AAV vectors would lead to extended increased systemic exposure of functional adiponectin forms.

Methods: We engineered an adipocyte-specific promoter and achieved AAV8 uptake and overexpression of adiponectin in vivo with exposure for up to 12 weeks in plasma. We evaluated the effects of adiponectin overexpression on metabolism and kidney function in the BTBR ob/ob mouse model of dyslipidaemia and diabetic kidney disease.

Results: In human glomerular endothelial cells and iPS differentiated podocytes, protective effects of adiponectin signalling were observed in in vitro disease models. Mice treated with AAV-adiponectin displayed a decrease in body weight change from the first week after treatment up to 9 weeks in BTBR ob/ob mice. In addition, adiponectin overexpression also decreased the urinary albumin to creatinine ratio 3 weeks after treatment; however, this effect was lost at later time points. At termination, AAV-adiponectin-treated obese animals had significantly decreased plasma cholesterol, liver triglyceride levels, and a decreased liver weight as a proportion of body weight. The effect of AAV-adiponectin overexpression on body weight gain was reproduced in a second study in which WT mice were treated with HFD for 10 weeks.

Conclusions: Adiponectin overexpression can reduce body weight gain and improve metabolic parameters in the liver. Overexpression of adiponectin can transiently decrease kidney damage, as assessed by UACR, but further work is required to determine how to maintain the kidney protective effects of adiponectin.

Funding: Commercial Support - AstraZeneca

FR-PO374

Insulin and Glucose Tolerance Assessment in Guanylyl Cyclase/ Natriuretic Peptide Receptor-A Gene-Targeted Mutant Mice

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Background: Atrial natriuretic peptide (ANP), acting through the guanylyl cyclase/ natriuretic peptide receptor-A (GC-A/NPRA), is pivotal in regulating blood pressure and cardiac homeostasis. Ablation of *Npr1* (encoding NPRA) in mice exhibits hypertension and provokes congestive heart failure; however, the underlying mechanisms are not yet precisely determined. The objective of this study was to investigate whether *Npr1* plays a critical role in regulating glucose homeostasis.

Methods: The adult male (14-18 wk) *Npr1* gene-knockout haplotype (*Npr*1+/-, 1-copy), wild-type (*Npr1*+/+, 2-copy), and gene-duplicated (*Npr1*+ +/+ +, 4-copy) mice were fasted overnight (16 h) and given free access to water. The mice were administrated with glucose both orally and intraperitoneally (2 g/kg body weight) to determine the oral glucose tolerance test (OGTT) and intraperitoneal glucose tolerance test (IPGTT). For the insulin tolerance test (ITT), mice were also fasted for 16 h and then received an ip-injection of 1.0 UI/kg of insulin. Blood glucose levels were determined by performing tail bleeds at 0, 15, 30, 60, 90, and 120 min using AlphaTRAK. The non-invasive tail-cuff method determined systolic blood pressure (SBP).

Results: The results showed that administration of glucose resulted in a greater increase in blood glucose levels at 120 mins in 1-copy male mice (OGTT: 237 ± 5 mg/dL, IPGT: 246 ± 6 mg/dL, ITT; 239 ± 7 mg/dL) than 2-copy male (OGTT: 131 ± 3 mg/dL, IPGT: 126 ± 6 mg/dL, ITT; 127 ± 6 mg/dL), respectively. The blood glucose was also significantly lower in 4-copy mice (OGTT: 113 ± 5 mg/dL, IPGT: 108 ± 7 mg/dL, ITT; 107 ± 3 mg/dL) than in 2-copy mice. SBP was significantly greater in 1-copy mice (130 ± 4 mmHg) than in 2-copy mice (100 ± 3 mmHg) and significantly lower in 4-copy mice (90 ± 2) in 2-copy mice. The increase in plasma glucose levels were significantly lower in OGTT than in IPGTT.

Conclusions: NPRA markedly prevented a steep rise in blood glucose levels after glucose challenge and ameliorated glucose intolerance and insulin resistance in 2-copy and 4-copy mice than 1-copy mice. The results suggest that NPRA signaling predisposes to arterial pressure, hyperglycemia, and insulin resistance, thus *Npr1* gene might regulate blood glucose homeostasis. Supported by NIH grant DK133833.

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FR-PO375

Inhibition of Endogenous Adenine Synthesis Ameliorates Kidney Injury in db/db Mice with Type 2 Diabetes

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Background: Elevation of kidney and urine adenine is associated with chronic kidney disease (CKD) including diabetes. Although adenine administration induces CKD in animal models, the effect of endogenous adenine on diabetic kidney disease (DKD) has not been studied. We hypothesize that inhibition of adenine synthesis ameliorates DKD by inhibiting mTORC in mice with type 2 diabetes.

Methods: C57BL6 WT male mice received adenine containing water or control water for 4 weeks. db/db male mice with type 2 diabetes received methylthioadenosine phosphorylase (MTAP) inhibitor or vehicle by drinking water for 8 weeks. Kidney metabolites were measured by ZipChip mass spectrometry. Mouse proximal tubule (MCT) cells were employed for *in vitro* experiments.

Results: Adenine increased albuminuria, blood urea nitrogen (BUN), kidney hypertrophy, kidney KIM-1 expression, kidney matrix protein accumulation, and kidney mTORC1 activity in WT mice. Adenine stimulated senescence-associated secretory phenotype along with reduction in *Klotho* expression in the kidney. Rapamycin (a selective inhibitor of mTORC1) inhibited adenine-induced mTORC1 activation and matrix protein accumulation in the MCT cells. MTAP inhibitor decreased kidney adenine content, serum cystatin C, albuminuria, and urine KIM-1 excretion in diabetic db/db mice.

MTAP inhibitor decreased diabetic kidney hypertrophy, KIM-1 expression, fibrosis, and mTORC1 activation in the kidney of db/db mice without changes in BUN, body weight, blood glucose level, and intake of food or water. Klotho expression was increased by MTAP inhibitor in the kidney of db/db mice. MTAP inhibitor did not affect other diabetes-related metabolites.

Conclusions: Our data suggest that elevation of adenine drives DKD which is ameliorated by inhibiting adenine synthesis in the kidney. Therefore, adenine metabolism could be used for a biomarker and therapeutic target of DKD.

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

FR-PO376

Elucidating NOX5 as a Potential Therapeutic Target and a Biomarker of Kidney Disease in Diabetes

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Background: Diabetes related chronic kidney disease (CKD) is the leading cause of end stage renal failure. Oxidative stress due to excessive production of reactive oxygen species plays a critical role in diabetic kidney disease (DKD). Pro-oxidant enzyme NADPH oxidase-NOX5 is considered as a major contributor of reactive oxygen species (ROS) mediated kidney damage in diabetes. We aim to identify the renoprotective effect of NOX5 inhibition in the in vitro setting of human derived renal cells and organoids exposed to diabetic milieu. We also aim to validate NOX5 as a biomarker for the early prediction of human DKD.

Methods: We examined the effect of NOX5 silencing or inhibition by NOX5-specific inhibitors on ROS formation along with markers of fibrosis, inflammation and ROS-sensitive factors in human renal cells and iPSC derived renal organoids. We assessed the expression of NOX5 in human kidney biopsies as well as in urine and serum obtained from non-diabetic and diabetic individuals by ELISA and FACS. Correlation between NOX5 level and clinical data sets including albuminuria was performed.

Results: Renal NOX5 expression was increased in diabetic patients in comparision to non-diabetic subjects. Increased expression of NOX5 was associated with upregulation of a transcription factor, EGR-1 and down regulation of an endosulfatase, SULF-1 (an enzyme which maintains the integrity of glomerular filtration barrier) in diabetes. Both genetic silencing of NOX5 in renal cells and pharmacological inhibition of NOX5 in renal cells as well as in renal organoids attenuated high glucose induced upregulation of CTGF, MCP-1, TLR-4 and EGR-1 and restored the expression of SULF-1 via reduction in ROS formation. These novel findings suggest the role for NOX5 in renal fibrosis and inflammation as well as in the regulation of EGR-1 and SULF-1 in diabetes like conditions. Moreover, increased level of NOX5 in human urine and serum was observed in diabetic individuals even in the absence of albuminuria.

Conclusions: These findings suggest that NOX5 plays a key role in human DKD by promoting inflammation and fibrosis, thereby providing the fast track validation of NOX5 specific inhibitors to combat DKD in humans. In addition, NOX5 appears to be a potential biomarker for the early detection of DKD.

FR-PO377

Novel Molecular Therapy of Diabetic Nephropathy by Repurposing Niclosamide to Modulate Renal RNA-Binding Protein HuR

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Background: Hu antigen R (HuR) influences the expression of genes involved in pathways critical to the pathogenesis of diabetic nephropathy (DN). We identified a FAD-approved anthelmintic drug, niclosamide (NCS), as a novel inhibitor of HuR. This study sought to determine whether HuR- targeted therapeutics with NCS are therapeutic for DN.

Methods: Four groups of uninephrectomized mice with normal control and diabetic db/db mice without treatment but being terminated at 14 and 22 wks respectively, or treated with NCS (20mg/kg daily via i.p.) from wks 18 to 22 were included.

Results: A significantly increased HuR expression was observed in diabetic kidneys from both patients and db/db mice, while the latter was inhibited by NCS treatment. Immunofluorescent staining for HuR confirmed the Western blot measurement. Untreated db/db mice developed progressive albuminuria and glomerular mesangial matrix expansion between age of weeks 14 and 22, associated with increased renal production of fibronectin and a-smooth muscle actin but decreased glomerular WT-1^{+}-podocytes and nephrin expression. NCS treatment did not affect mouse body weight but reduced blood HbA1c levels (10.8±1.0 in treated db/db vs. 13.4±0.93% in db/db, P<0.05), arrested the increases in albuminuria, markers of glomerulosclerosis and podocyte injury seen in db/db mice. Renal expressions of NF-κBp65, TNF-a, MCP-1, Nox2, and urine TBARS levels, the markers of inflammation and oxidative stress, were increased during disease progression in db/db mice, which were halted by NCS treatment (P<0.05). In addition, a downstream factor of the Wnt signaling pathway, known as WNT1-inducible signaling pathway protein 1 (WISP1), has been identified as one of key downstream mediators of HuR-dependent action and found to be markedly increased by 3.2 fold in db/db mouse kidneys at 22 wks, compared with non-diabetic controls, which was abrogated by NCS treatment, approaching to normal levels.

Conclusions: These results indicate that inhibition of HuR with NCS is therapeutic for DN through improving hyperglycemia and renal inflammation and oxidative stress. The efficacy of NCS in reducing renal WISP1 expression and action may also contribute to its reno-protective effect. Our study provides a proof-of-concept for re-purposing HuR inhibitor as a novel intervention therapy for progressive DN.

Funding: NIDDK Support

FR-PO378

Increased Oxidative Stress with Reduced Renal PON2 in Type 2 Diabetic Nephropathy Mice

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Background: Enhanced oxidative stress with excess accumulation of reactive oxygen species (ROS) triggers progression of type2 diabetic nephropathy (T2DN). However, the effects of antioxidant enzymes including paraoxonase (PON) enzyme family in T2DN are not been studied fully. Therefore, our study was conducted to investigate the alterations in renal oxidative stress, especially antioxidant enzyme expression, in T2DN mice.

Methods: 1. Mouse model: Male 6-week-old C57BL/6J mice were fed a 60% high-fat diet (HFD) for 6 weeks, and then was injected with STZ intraperitoneally at 60 mg/kg/day (T2DN, n=7) or vehicle (controls, n=5) for 3 days. Mice fed a 10% normal-fat diet (NFD) served as the background group (n=5). The mice were sacrificed at 16 weeks of HFD or NFD. 2. Cultured mouse renal proximal tubular cells (mRPTCs): the cells in low-glucose DMEM and 1%FBS were treated with 300μM sodium palmitate (PA) plus 24.5mM D-glucose or mannitol for 24h (n=4). 3. P<0.05 was considered significant for 2 group-comparison by t-test.

Results: Compared with HFD-fed mice, T2DN mice exhibited an elevated blood glucose (26.2±1.0 vs 8.7±0.6,mmol/L) together with polydipsia (13.4±1.6 vs 2.5±0.3,mL), polyphagia (4.9±0.4 vs 3.8±0.2,g), polyuria (10.6±1.5 vs 1.3±0.1,mL) and weight loss (28.2±0.7 vs 38.4±2.5,g). HOMA-IR (239.2±23.3 vs 109.5±7.8,mmol/L) and insulin tolerance test (AUC: 249±23% of control) were increased in T2DN mice with raised urine albumin-to-creatinine ratio (48.5±3.0 vs 20.8±30.7,mg/g), serum creatinine (90.7±26.6 vs 21.9±6.1,mmol/L) and urinary 8-isomeric prostaglandin (1482±86 vs 207±85,pg/mg of Cr). The staining of PAS and Masson's trichrome presented glomerular hypertrophy and collagen deposition while transmission electron microscopy revealed glomerular basement membrane thickening and podocyte fusion. Renal PON2 (66±0.03% of control) by immunoblotting was decreased while NOX1,2,4, PON1, HO1, HO2, and SODs1-3 were not affected. Except a slightly blunted response to insulin, blood glucose and renal ROS enzymes in HFD mice were not altered relative to NFD mice. PON2 was located mainly in NHE3-positive proximal tubules. Similar decrease in PON2 (73±5% of control) was also seen in cultured mRPTCs exposed to high glucose combined with PA.

Conclusions: Decreased renal PON2 may be involved in the pathogenesis of T2DN.

Funding: Clinical Revenue Support, Government Support - Non-U.S.

FR-PO379

A Novel Method for the Analysis of Renal Sympathetic Nerve Activity (RSNA) from Multi-Fiber Nerve Recordings

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Background: Measurement of RSNA via bipolar electrodes from multi-fiber preparations in various species has been used for decades in the context of autonomic regulation research. Traditionally, raw neurograms are usually integrated over short time intervals and this approach works perfectly for the analysis of dynamic RSNA changes due to acute intervention. However, comparability of baseline activities between groups is limited. We present a novel analysis method, based on the raw neurogram sampled at rate of 25 kHz.

Methods: For RSNA-burst analysis a software based programmable algorithm was used. Continuous activities longer than three single spikes (i.e., >8ms) were defined as bursts, followed by silent periods with some single spikes. Approximately 10.000 bursts/rat were analyzed and burst amplitude, burst duration, burst area (i.e., duration integral), as well as the burst frequencies were analyzed.

Results: In rats with myocardial infarction (n=11) we found no difference in integrated baseline RSNA as compared to controls ((n=10). However, the new method revealed higher higher burst rate per cardiac cycle [CC] (2.65 ± 0.39 vs. 1.61 ± 0.38 bursts/CC; P<0.001) and burst frequency (15.09 ± 2.42 vs. 8.52 ±1.54 Hz; P<0.001) compared to healthy controls, indicating increased RSNA.

Conclusions: Our new method of RSNA baseline analysis was able to detect subtle differences between groups of animals that could not be detected by the traditional method of integrated RSNA analysis. Furthermore, this method has the potential to give further insights into RNSA patterns and synchronization to afferent regulatory input form the kidney itself or other organs.

FR-PO380

The Positive Effect of Renal Denervation Persists even Through Regrowth of Afferent Axons Improving Renal Afferent Nerve Activity During High Sodium Intake in Rats

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Background: Previous work of ours suggests that pathologically decreased sensitivity of renal afferent neurons (reduced number of highly active tonic neurons) due to high salt diet is normalized 1 wk after renal denervation (DNX). Now we tested the hypothesis that normalized sensitivity of renal neurons persists after DNX even through regrowth of afferent axons after 12 wk. This morphological regrowth of afferent nerves 12wk after renal DNX (postDNX) was shown in a previous publication (DOI: 10.1152/ajpregu.00227.2014).

Methods: 6 male Sprague Dawley (SD) rats were put on high salt diet (HS; 8% NaCl) for 10 days. In another group of 12 rats on high salt diet (HS) left kidneys were denervated (postDNX) 12 weeks prior to examination. Rats on standard diet were used as controls. Harvested dorsal root ganglion neurons (DRG Th11-L2) with renal afferents were investigated in primary neuronal cell culture using current clamp mode to assess action potential generation during current injection and to characterize neurons as tonic highly active and phasic less active neurons.

Results: In renal neurons from rats on HS the relation of tonic to phasic neurons shifted towards less active phasic units (62% tonic neurons in control vs. 42% on HS, $p<0.05$, z-test). Denervation of the left kidney in rats on high salt diet (HS-DNX) led to a recovery of afferent renal DRG neurons after 1 wk (42% tonic neurons on HS vs. 72% tonic neurons on HS+DNX). Even 12 weeks after renal denervation this regained electrophysiological property of tonic firing persists (42% tonic neurons on HS vs. 69% tonic neurons on HS-postDNX, $p<0.05$, z-test).

Conclusions: The reduced proportion of highly active tonic neurons increased 1 wk after renal denervation to control levels. Even 12 weeks after renal denervation, this effect of renal denervation persisted, and the sensitivity of renal neurons to electrical stimuli did not change despite high-salt diet. Hence, the positive effects of renal denervation persisted even through the regrowth of renal afferent axons to the kidney.

FR-PO381

Mechanosensitive Potassium Channels in the Afferent Limb of the Cardio-Renal Baroreflex

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Background: We have recently shown that the cardiorenal baroreflex (CRB) is impaired already in congestive heart failure with preserved ejection fraction. There might be a number of possibly involved mechano-sensitive channels and receptors in the afferent limb of the CRB. Since cardiac function is dependent on tight control of serum potassium levels, we tested the hypothesis that mechano-sensitive potassium channels are expressed in the afferent limb of the CRB.

Methods: We used inside-out-patches from cultured cardiac nodose ganglion neurons of rats that comprise the first neuron of the afferent limb of the CRB. The channels were activated by applying suction to the patch in a stepwise protocol.

Results: Using the pipette perfusion technique two MS channels could be distinguished: One could be blocked extracellularly with 10 μM gadolinium, a known blocker of MS ion channels. It exhibited a slope conductance of 116.4 ± 5.3 pS in symmetrical potassium concentrations. The other was not affected by gadolinium and had a slope conductance of 76.1 ± 6.5 pS. The channels exhibited also sodium- besides potassium-conductivity. The relative conductivity from potassium to sodium was 3.4 in both groups of channels, which allows membrane depolarization to levels where voltage-activated sodium-channels open.

Conclusions: Hence, through mechano-sensitive cation channels putatively also influenced by extracellular potassium concentrations, the CRB might indirectly influence serum potassium levels via altered salt and water excretion.

FR-PO382

Significance of the Nav 1.8 Voltage-Gated, Tetrodotoxin-Resistant Sodium Channel for Renal Sensoric Innervation in Mice and Rats

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Background: Our previous work repeatedly showed that the sensory innervation of the kidney in rats has a peculiarity containing predominantly (more than 50%) highly active tonic neurons to electrical stimulation. In a previous publication (DOI: 10.1152/ajprenal.00011.2012) we demonstrated an increased mRNA expression of the TTX-resistant sodium channel Nav1.8 in renal sensory neurons. Hence, we tested the hypothesis that tonic firing pattern is related to the specific expression of $Na_v1.8$ on the cell surface of neurons with renal sensoric axons in the dorsal root ganglia (DRG Th12-L2).

Methods: Harvested dorsal root ganglion neurons (DRG Th11-L2) from male Sprague Dawley (SD) with renal afferents were investigated in primary neuronal cell culture using current clamp mode to assess action potential generation during current injection and to characterize neurons as tonic highly active and phasic less active neurons using a Nav1.8 blocker (A-803467) before and after stimulation. Further, renal DRG neurons from a Nav1.8 knock out mouse (C57BL6J-Scn10atm1Jwo) were investigated in a current clamp mode. C57BL6 mice were used as controls.

Results: At a concentration of 0.3μM the maximum AP firing frequency was blocked from 13+/- 1.1 APs/600ms to 7.6+/-1.4 APs/600ms under superfusion with a Nav1.8 blocker. No blocker effects were seen at a concentration of 0.1 μM and due to superfusion with the solvent methanol alone. The firing pattern of renal neurons in the C57BL6 mouse was similar to that in the SD rat with a dominance of the tonic highly active neurons. In a Nav1.8 knock out mouse (C57BL6J-Scn10atm1Jwo) in the population of neurons with dendrites from the kidney only a single cell out of 70 showed tonic firing behavior (control vs Nav1.8 KO mouse, z-test, $p<0.05$).

Conclusions: Under physiological conditions, renal sensory neurons exhibit predominantly a firing pattern associated with higher excitability. Our findings in this study support the significance of the TTX-resistant sodium channel Nav1.8 for the specific tonic firing pattern of neurons with renal projections. That might be of importance for pharmacological interventions to influence renal nerve activity likely involved in the control of blood pressure and cardiovascular function.

FR-PO383

The Minimal Diameter of Renal Artery Stenosis but Not Percentage Diameter Reduction Is Associated with Kidney Perfusion and Function

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Background: Renal Artery Stenosis (RAS) exceeding 50% of the lumen diameter is considered hemodynamically significant. Refractory hypertension or declining kidney function coexistence can contribute to invasive treatment. However, the different diameters of supplying arteries result in different diameters of stenoses, although they all can be estimated at 50% of the lumen diameter reduction. Thus, different diameters of stenoses can be improperly qualified for revascularization on the same decision level. The study aimed to investigate which parameter of Renal Artery Stenosis is associated with kidney perfusion and function.

Methods: Forty kidneys with single, non-hypoplastic supplying arteries were evaluated in a contrast-enhanced multidetector computed tomography (GE Discovery 750 HD) in 25 patients (11F, 14M; age 62 ±16) with hypertension and RAS suspicion. The minimal diameter (MD), percentage of diameter reduction (DR), and lumen cross-sectional area reduction (CSAR) of narrowed renal arteries, renal parenchymal blood flow (RPBF), and kidney function (CKD-EPI) were estimated.

Results: The mean values of investigated parameters were evaluated: MD 2.91 ±1.23 mm; DR 38.8 ±15.2 (range 5-73) %; CSAR 53.7 ±19.0 %; RPBF 187.7 mL/s/100g; CKD-EPI 57.9 ±29.7 ml/min/1.73 m^2. In correlation analysis, only MD was significantly associated with RPBF ($r=0.377$, $p=0.016$) and CKD-EPI ($r=0.346$; $p=0.029$), whereas DR was not correlated with these parameters ($r=-0.134$, $p=0.410$, and $r=-0.229$; $p=0.156$, respectively), and CSAR was significantly connected only with CKD-EPI ($r=-0.290$, $p=0.070$, and $r=-0.335$, $p=0.035$; respectively).

Conclusions: The absolute value of Renal Artery Stenosis minimal diameter is more closely associated with kidney perfusion and function than percentage values of diameter and lumen cross-sectional area reduction. Implementing the minimal diameter of stenosis in the renal artery revascularization criteria could improve the effectiveness of this procedure.

Funding: Government Support - Non-U.S.

FR-PO384

Vascular Dysfunction in the C57Bl/6J;Pkd1RC/RC Mouse Model of Autosomal Dominant Polycystic Kidney Disease Mimics Human Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic nephropathy characterized by progressive cyst growth in the kidney. Patients with ADPKD also present with cardiovascular diseases (CVDs), a leading cause of morbidity and mortality in this population. The majority of CVDs arise due to dysfunction of the arteries. Stiffening of the large arteries (e.g., aorta and carotids) and endothelial dysfunction are manifestations of vascular dysfunction that precede and contribute to CVDs and are often found in patients with early-stage ADPKD, even when kidney function remains preserved. The C57Bl/6J *Pkd1*$^{RC/RC}$ (RC/RC) mouse model mimics the kidney phenotype of patients with ADPKD and is widely used to study kidney pathologies of the disease, but it is unknown if the model also exhibits vascular dysfunction.

Methods: Using male RC/RC mice with mild (4mo) and moderate (8mo) kidney disease severity and age/sex matched C57Bl/6J wildtype (WT) controls, we measured aortic stiffness *in vivo* by pulse wave velocity (PWV). To investigate the contribution of structural changes in the arteries to stiffening, we also measured aortic elastic modulus by stress-strain testing (wire myography) in excised aortic rings. Lastly, we measured endothelial function as endothelium-dependent dilation (EDD) to acetylcholine in isolated carotid arteries by pressure myography.

Results: Aortic PWV was higher in RC/RC mice vs WT at both 4 (440±44 vs 346±26 cm/s, $P<0.01$) and 8mo (428±37 vs 343±30 cm/s, $P<0.01$) of age. Aortic elastic modulus

trended towards being mildly but non-significantly higher in RC/RC vs WT. Carotid artery EDD was impaired at 8mo (peak EDD: 74±6 vs 97±3%, P<0.01) but not 4mo (93±5 vs 94±2%) of age in RC/RC mice vs WT.

Conclusions: Our data suggest that the RC/RC mouse model of ADPKD presents with vascular dysfunction like that observed in patients with ADPKD. Our vascular data is in line with a prior described cardiac phenotype showing cardiac hypertrophy and echocardiographic changes in the heart in RC/RC mouse (FR-PO279 ASN 2022). Thus, this model can be utilized to study mechanisms and test novel interventions aimed to reduce CVD risk in ADPKD.

FR-PO385

The IRE1α/XBP1s Pathway Promotes Vascular Calcification in CKD by Enhancing Oxidative Phosphorylation

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Background: Endoplasmic reticulum stress has been reported to be linked to several vascular diseases. However, whether Inositol-requiring enzyme 1α (IRE1α) participate in vascular calcification in chronic kidney disease remains poorly understood.

Methods: The expression level of IRE1α were measured in the artery tissues of CKD patients and mice. The $Ern1^{flox/flox}$ mice were intercrossed with SMMHC-CreERT2 to obtain VSMC-specific IRE1α knockout mice ($Ern1^{flox/flox}$; SMMHC-Cre). The mice were treated with vitamin D3 to induce vascular calcification. Besides, VSMC were stimulated with high phosphate or human uremic serum to induce calcification. The calcium content and Alizarin red staining were used for analysis of calcification, and the mRNA expression level of IRE1α, XBP1s and regulated IRE1-dependent decay-related genes were measured. After transfected with Ad-XBP1s, transcriptome analysis was performed.

Results: The expression level of IRE1α were upregulated in the artery tissues of CKD patients and mice, and in high phosphate and human uremic serum-stimulated VSMC. Specific knockout of IRE1α in VSMC alleviated vascular calcification both in vivo and ex vivo, and siIRE1α attenuated VSMC calcification in vitro. The mRNA expression level of XBP1s were decreased in the aortic tissues of $Ern1^{flox/flox}$; SMMHC-Cre mice, while the expression level of regulated IRE1-dependent decay-related genes remained unchanged. Knockout of IRE1α inhibits high phosphate-induced calcification, which could be reversed by XBP1s overexpression. Overexpression of XBP1s enhanced oxidative phosphorylation of VSMC.

Conclusions: The IRE1α/XBP1s Pathway Promotes Vascular Calcification in Chronic Kidney Disease by Enhancing Oxidative Phosphorylation.

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FR-PO386

THOC5-Dependent Posttranscriptional Control Maintains Vascular Smooth Muscle Cells Homeostasis Against CKD-Related Vascular Calcification

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Background: Modulation of the vascular smooth muscle cell (VSMC) osteogenic transition plays a fundamental role in CKD-associated VC. Despite transcriptional control mechanisms of VSMC osteogenic transition having been extensively studied, posttranscriptional regulation is still awaiting elucidation. In the present study, we explore the mechanism of THOC5-dependent VSMCs osteochondrogenic switching.

Methods: Von Kossa staining and immunohistochemistry staining were used to detect calcification and expression of THOC5 respectively. Thoc5 shRNA and Thoc5 overexpression lentivirus were used to modulate the expression of Thoc5. RNA-Seq combined with RIP-Seq was used to explore the target mRNAs that directly bind to THOC5, and FISH was used to confirm its subcellular localization.

Results: Immunohistochemical staining showed significantly increased THOC5 expression in the calcified artery of CKD patients. Besides, calcification-induced increase of THOC5 expression was found in both in vivo and in vitro calcification models. The overexpression of Thoc5 relieves the calcification and osteogenic differentiation of VSMCs significantly in vitro, which is mainly manifested by the reduction of calcium ion deposition and the decreased expression of osteogenic markers. Furthermore, RNA-Seq revealed that THOC5 overexpression in osteogenic-induced VSMCs closely resembled the gene expression changes induced on TGF-β treatments in cultured VSMCs. RIP-Seq was selected to detect target genes of THOC5. It was found that THOC5 directly interacts with Guanylate exchange factors (GEFs) mRNAs, and is required for their export. Thereby THOC5 maintaining RhoA GTPase activation contributes to increasing the expression of VSMCs contraction marker, which maintains the contraction phenotype of VSMCs. ROCK (Rho-kinase) inhibitor reversed the protective role of THOC5 on VC.

Conclusions: Our data introduce the binding of THOC5 to GEFs as a novel mechanism contributing to maintaining VSMCs homeostasis and imply THOC5 as a potential intervention node for vascular calcification diseases.

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FR-PO387

The Role and Mechanism of Ubiquitin-Specific Protease 25 in Cardiorenal Syndrome Type 4

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Background: The development of chronic kidney disease will lead to cardiorenal syndrome type 4 (CRS4). At present, there is no research on ubiquitin-specific protease 25 (USP25) in CRS4. The aim of this research was to investigate the function and mechanism of USP25 in CRS4.

Methods: C57BL/6 mice received 5/6 nephrectomy and were fed with high phosphate diet to establish the model of CRS4. The express levels of USP25 in the heart of mice in the CRS4 group and the H9C2 rat cardiomyoblast cell line treated with high phosphate (HP) was detected. The changes of hypertrophic markers and cross-sectional area of H9C2 cells in the siUSP25 + HP group were detected by qPCR and phalloidin staining. qPCR and echocardiography were used to compare the degree of cardiac hypertrophy in *usp25*$^{+/+}$-CRS4 mice and *usp25*$^{-/-}$-CRS4 mice. To prove that USP25 regulated the cardiac hypertrophy in CRS4 through PTEN/AKT signaling pathway, the effect of knockout of USP25 *in vivo* or knockdown of USP25 *in vitro* on the AKT signaling pathway in cardiomyocytes was detected by western blot. The interaction between USP25 and PTEN was verified by immunoprecipitation, and the ubiquitination level and type of ubiquitination of PTEN in cells from the siNC group and siUSP25 group were detected. The degree of cardiomyocyte hypertrophy in the plasmid-USP25+HP+PTEN inhibitor group and plasmid-USP25+HP+DMSO was detected by qPCR and phalloidin staining.

Results: The level of USP25 in the heart of mice in the CRS4 group and the cells in the HP group were increased. In H9C2 cells stimulated by HP, knockdown of USP25 *in vitro* aggravated cardiomyocyte hypertrophy. In CRS4 mice, knockout of USP25 *in vivo* aggravated cardiac hypertrophy. Knockout of USP25 *in vivo* or knockdown of USP25 *in vitro* promoted the activation of the AKT signaling pathway in cardiomyocytes. The results of immunoprecipitation suggested that USP25 interacted with PTEN. The ubiquitination level of PTEN in the siUSP25 group was higher than that in the siNC group, and the increased ubiquitination type was K63-linked ubiquitination. *In vitro*, PTEN inhibitor could attenuate the anti-hypertrophic effect of overexpression of USP25 in H9C2 cells.

Conclusions: USP25 stabilized PTEN by removing the K63-linked ubiquitin chains of PTEN, which inhibited the activation of the AKT signaling pathway and relieved cardiac hypertrophy in CRS4.

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FR-PO388

Aristolochic Acid-Induced Aortic Stiffening in Mice Can Replicate Vascular Dysfunction Seen with CKD

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Background: Cardiovascular disease (CVD) is highly prevalent in CKD and the leading cause of death. Stiffening of large arteries precedes overt CVD and contributes to the pathogenesis. It is unclear if commonly used mouse models of CKD develop arterial stiffness.

Methods: Male and female C57Bl/6J mice (n=3-8/group) received 4 doses of aristolochic acid (AA) at 2 mg/kg and 8 mg/kg, respectively. Aortic pulse wave velocity (PWV), the gold-standard measure of arterial stiffness, was assessed in anesthetized mice 7-9 weeks after AA injections. Serum, aortas, and kidneys were collected at 9 (males) or 11 (females) weeks. To determine if increases in PWV were due to structural changes in the arteries, elastic modulus (EM) was determined in aorta rings by stress-strain testing. We compared CKD-induced fold increases in aortic PWV in mice and carotid-femoral PWV in patients with stage 3-4 CKD (17M/18F; age 66±7; eGFR 38±11 mL/min/1.73 m^2) vs. age-matched controls (17M/18F; 63±7; eGFR 84±12 mL/min/1.73 m^2).

Results: Male mice developed significant CKD as assessed by renal fibrosis (hydroxyproline content 6.3±1.4 mg/g vs. 3.2±0.8 mg/g protein, p<0.05) and renal dysfunction (blood urea nitrogen [BUN] 100±23 mg/dL vs. 33±9 mg/dL, p<0.05). Both aortic PWV (441±64 vs. 342±15 cm/s, p=0.05) and EM (6,525±392 vs. 5,011±898 kPa, p=0.07) were 1.3-fold higher with AA, and this increase in aortic stiffness was comparable to that observed in male CKD patients vs. controls (1.2-fold; 1,014±229 vs. 835±130 cm/s, p<0.01). Female mice also developed renal fibrosis (hydroxyproline 11.8±3.5 mg/g vs. 4.2±0.7 mg/g protein) and renal dysfunction (BUN 41±22 mg/dL vs. 21±4 mg/dL, p< 0.05). Despite less severe renal dysfunction than males, aortic PWV (408±43 vs. 356±16 cm/sec, p=0.08) and EM (7,905±1635 vs. 5,980±1190 kPa, p=0.09) were increased (1.2- and 1.3-fold higher) comparably to male mice and to female CKD patients (1.2-fold; 907±237 vs.789±141 cm/s, p=0.08). The range of aortic stiffening in female mice was wider than males, which was also reflected in our cohort of female patients.

Conclusions: AA administration produces CKD and aortic stiffening in both male and female mice that is similar to that seen in patients with CKD. This model may be a promising pre-clinical model to test vasculoprotective therapies in patients with CKD.

FR-PO389

Histone Deacetylase 9 Contributes to Vascular Calcification in CKD

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Background: Vascular calcification (VC) is a serious chronic kidney disease (CKD) complication. Unfortunately, there is no effective therapy for VC beyond supportive care due to the complex pathogenesis of VC. Histone deacetylase 9 (HDAC9) could regulate the transdifferentiation of vascular smooth muscle cells in atherosclerotic aortic calcification. However, the role of HDAC9 in VC upon CKD is unclear. This study aimed to investigate the role and mechanism of HDAC9 in VC upon CKD.

Methods: Rat aortic smooth muscle cells (RASMCs) were divided into the control and calcification groups. The calcification group was induced with β-glycerophosphate and $CaCl_2$. RASMCs were incubated with Alizarin Red S stain to detect calcification. RT-qPCR and WB were utilized to detect the expression level of HDAC9. 30 male wild-type Wistar rats aged from 6 to 8 weeks were randomly divided into six groups (n=5): 4- and 16-week control groups, and 4-, 8-, 12-, and 16-week VC groups. The VC model of CKD in rats was established by 5/6 nephrectomy combined with high phosphorus chow. Rat aortas were collected and stained with alizarin red to detect VC. Subsequently, the expressions of HDAC9 were detected by third-generation sequencing, immunohistochemical staining, and immunofluorescent staining.

Results: In *vitro*, alizarin red staining showed the calcificated RASMCs had more calcium salt deposits. Both WB and RT-qPCR showed the expression of HDAC9 in calcificated cells was increased. In *vivo*, alizarin red staining of the aorta showedccalcium deposition in the calcification group was significantly higher compared to control group. In the third-generation full-length transcriptome sequencing of rat aorta, the RNA expression of HDAC9 in the calcificated group increased gradually from 4 weeks to 12 weeks, and was significantly higher than that in 4- and 16-week control groups. The immunohistochemical staining and immunofluorescent staining indicated the expression of HDAC9 in the aorta of the 12-week calcification group was significantly increased, compared to the 4- and 16-week control group.

Conclusions: Histone deacetylase 9 could contribute to the development of vascular calcification in chronic kidney disease.

FR-PO390

Autophagy Attenuates Vascular Calcification by Suppressing Ferroptosis

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Background: Vascular calcification (VC) is an independent risk factor for cardiovascular death in chronic kidney disease. Autophagy is reported to be protective in VC, while the mechanism is not fully elucidated.

Methods: RNA-sequencing and metabolomics of aortas from VD3-induced mice VC models (treated with or without Rapamycin) were used to identify potential signalings. RT-qPCR, Western blot (WB), and immunofluorescence staining were performed to confirm our findings, and gain-and-loss-of-function assays were conducted to validate the regulative mechanism of the involvement of ferroptosis in autophagy-mediated protective effect in VC.

Results: We revealed that high phosphate could enhance the autophagy level of vascular smooth muscle cells (VSMCs), and autophagy plays a protective role in VC. Moreover, autophagy mainly occurred on the peroxisome of VSMCs in the high phosphate circumstances, which affects the level of ferroptosis. WB of ferroptosis markers GPX4 and TRF1 in high phosphate treated VSMCs confirmed this finding. Manipulating using ferroptosis inducer can reverse autophagy-mediated VC attenuation, while ferroptosis inhibition rescues Chloroquine induced elevated level of VC.

Conclusions: Our results demonstrated that autophagy attenuates VC via preferable peroxisome inhibition, resulting in ferroptosis suppression.

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FR-PO391

The Effects of Neutrophil Extracellular Traps (NETs) on Endothelial Health and Function

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Background: Neutrophil extracellular traps (NETs) are intricate webs of extracellular DNA, citrullinated histones and granular protein that play an essential role in innate immunity. Dysregulation of NET formation has been implicated in acute kidney injury, lupus nephritis, and diabetic kidney disease. However, the mechanisms by which NETs contribute to kidney injury have yet to be fully elucidated. As the vasculature may represent a common pathogenic target, we examined the effect of NETs on endothelial cells *in vitro* and on *ex vivo* mesenteric artery function.

Methods: The human promyelocytic cell line, HL-60, was used to generate neutrophil-like cells *in vitro*. Differentiation was induced by incubation with 1.25% dimethyl sulfoxide (DMSO) for 5 days. Differentiated cells were then stimulated with 500 nM phorbol 12-myristate 13-acetate (PMA) for 4 hours to induce NET formation. NETs were isolated from the cell culture medium by differential centrifugation. Cultured Human Umbilical Vein Endothelial Cells (HUVECs) were treated with the isolated NETs at 0.5-500 ng/ml for 24 hours. Cell viability and proliferative capacity were measured in the treated HUVECs using an XTT and BrdU assay, respectively. Second-order mouse mesenteric arteries were harvested and mounted to a wire myograph. Vessels were treated with the isolated NETs at 15 ng/mL for 30 minutes, after which we measured vascular relaxation during chemical stimulation with acetylcholine, to assess their effect on endothelium-dependent vasorelaxation.

Results: NETs decreased HUVEC viability ~2-fold at 5 ng/ml (P=<0.0001) and dose dependently decreased proliferative capacity from 0.5-500 ng/ml, with proliferation being decreased by ~80% at 500 ng/ml. NETs also significantly impaired endothelium-dependent vasorelaxation, with relaxation being 43% lower in treated vessels at 10^{-6} M acetylcholine. This was reflected in smaller pD2 values in NET-treated vessels (5.55 vs 6.72 in control vessels) (p=0.0284).

Conclusions: These results show that NETs induce endothelial cell injury *in vitro* and impair endothelial function in intact vessels. Identifying the underlying mechanisms of NET-induced endothelial injury may help further understand their contribution to kidney and cardiovascular injury.

FR-PO392

Circadian Clock Provides Beneficial Effects Against the Endothelial Dysfunction by Regulating Porphyrins Synthesis and Heme Oxygenase-1 Expression

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Background: The circadian clock is a molecular mechanism that confers 24 hours variations in gene expression and function to regulate many physiological functions. Chronic circadian clock disruption is associated with vascular stiffness and dysfunction in endothelial signaling and responses. Heme is a ligand of REV-ERBα and REV-ERBβ which modulate circadian rhythms by binding to the ROR region of CLOCK or BMAL1 to suppress the expression of these genes. 5-Aminolevulinic acid (ALA) is the common precursor of heme. The iron ion is inserted into protoporphyrin IX to form heme in the mitochondria and incorporated into hemoproteins. Heme oxygenase-1 (HO-1) is an intracellular enzyme which catalyzes the oxidation of heme to generate ferrous iron, carbon monoxide, and biliverdin, which is subsequently converted to bilirubin. These products have anti-inflammatory, anti-apoptotic and anti-thrombotic properties. In this study, we observed if the deletion of Bmal1, a critical component of the circadian clock, can influence porphyrins and HO-1generation which play an important part in the protection of vascular diseases.

Methods: Congenic 12- to 16-week-old male, wild-type and Bmal1-KO littermate mice were generated from heterozygote breeding. To synchronize circadian rhythms, serum stimulations were performed. Cells were also pre-incubated with or without 1 mM ALA and 0.5 mM sodium ferrous citrate (SFC). We also knocked down Bmal1 to evaluate the protein levels of HO-1 expression in the knocked down cells.

Results: In aorta from Bmal1 KO mice, there was a reduction in HO-1 expression in mice with a dysfunctional circadian rhythm. Bmal1 KO mice display pre-mature aging to have a dramatic prothrombotic phenotype. This phenotype is linked to the regulation of key risk factors for cardiovascular disease. These include HO-1 which is significantly reduced in Bmal1 KO mice. ALA/SFC co-incubation affected the oscillation and phase of core clock genes to lead to increase of HO-1. HO-1 levels followed a circadian pattern, and this pattern was absent in Bmal1 KO mice.

Conclusions: These findings indicate that circadian clock provides beneficial effects against the endothelial dysfunction to promote atherogenesis by regulating Porphyrins synthesis and HO-1 expression. This study establishes a mechanistic connection between Bmal1 and cardiovascular phenotype.

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FR-PO393

Renal Klotho Safeguards Platelet Lifespan in Advanced CKD Through Restraining Bcl-xL Ubiquitination and Degradation

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Background: Thrombosis and hemorrhage as two opposite pathologies are prevalent within the chronic kidney disease (CKD) population. Platelet homeostasis, which positions centrally in their pathogenesis, varies among the CKD population, while the underlying mechanism is poorly understood.

Methods: The change character of platelet homeostasis and its association with renal Klotho deficiency were determined based on a cohort study as well as CKD mice and Klotho-deficient mice with CKD. The effects on thrombopoiesis and platelet lifespan were examined by flow cytometry and platelet transfer. The underlying mechanism was explored by proteomics, flow cytometry, western blot, and immunoprecipitation.

Results: We show that platelet count declines both in patient and mouse model with advanced CKD (Adv-CKD) and is positively associated with circulating Klotho levels. Mechanistically, we identify that ubiquitin ligase UBE2O governs Bcl-xL ubiquitination and degradation in platelets, whereas Adv-CKD-induced oxidative stress in platelets stimulates p38MAPK to promote Bcl-xL phosphorylation, which facilitates UBE2O binding to Bcl-xL and subsequent Bcl-xL degradation. Consequently, platelet lifespan is shortened in Adv-CKD, culminating in platelet count decline. However, kidney-secreted soluble Klotho protein restricts oxidative stress in platelets, thereby preserving Bcl-xL expression and platelet lifespan.

Conclusions: Our findings uncover the mechanism of platelet count decline in Adv-CKD and identify renal Klotho as a long-range regulator of platelet lifespan, which not only provide a molecular mechanism underlying CKD-associated thrombocytopenia and hemorrhage but also offer a promising therapy choice.

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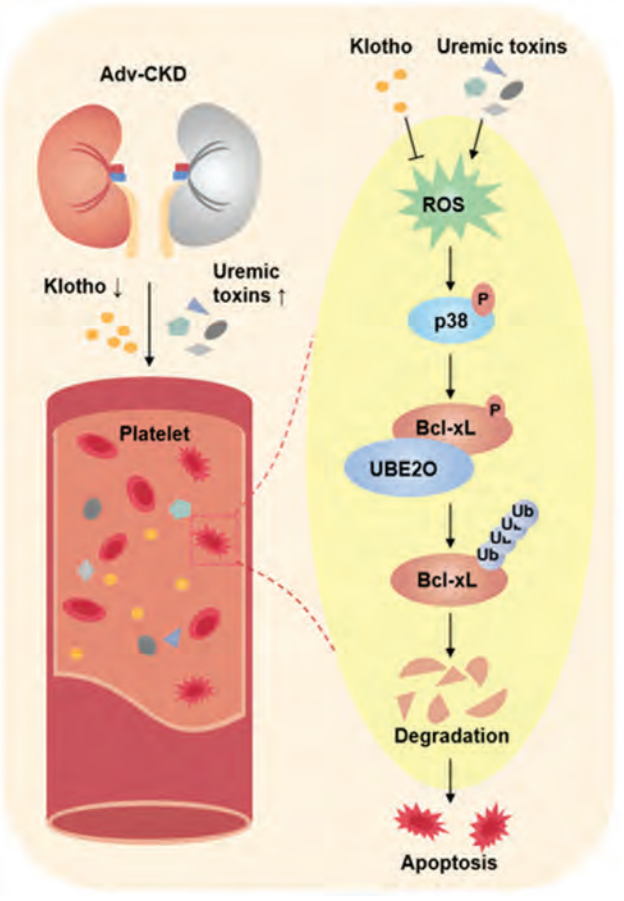

Schematic diagram of the p38MAPK-UBE2O axis-mediated Bcl-xL degradation and apoptosis of platelet.

FR-PO394

Characterization of Cardiac Phenotype in Mouse CKD Models

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Background: Cardiovascular disease (CVD) constitutes ~40-50% of mortality of chronic kidney disease (CKD) patients. Heart injury was described as left ventricular (LV) diastolic dysfunction, cardiac hypertrophy and fibrosis. While CKD rat models partially develop such cardiac phenotype, this is more challenging in mouse models. In this study, we aim to comprehensively examine various cardiac pathologies in two CKD mouse models.

Methods: The Col4a3$^{-/-}$ (Alport) mice, and wild-type (wt) mice on 6- or 12-weeks of mixed adenine diet (0.2% adenine + Western diet + 1.8% P) were examined for LV contractility using Millar-catheter, plasma Troponin I and BNP, and echocardiography (ECHO, Simpson's method). Heart histology, CD31 (endothelial cell) and CD45 (immune cell) were assessed.

Results: Compared to wt mice, the 8-week-old Alport mice developed CKD with histological kidney injury and fibrosis. Alport mice had decreased stroke volume, cardiac output and ejection fraction in ECHO and reduced LV relaxation in Millar-catheter measurement. The mice also showed higher plasma troponin I and BNP, reduced CD31/myocyte area ratio and increased myocardial CD45^{+} cells. Compared to the control diet, mice with mixed adenine diet at both time points showed higher serum cholesterol and phosphate and reduced calcium and histological signs of kidney injury, fibrosis and tubular atrophy. In the heart, mice with mixed adenine diet showed reduced LV contractility (ejection + relaxation phase), increased plasma Troponin I and BNP, and at 12 weeks, LV wall thickening and reduced stroke volume/cardiac output. The mice also showed increased cardiac infiltration of CD45^{+} cells and reduced CD31 expression. No overt cardiointerstitial fibrosis was observed in all models.

Conclusions: Alport mice, and mice fed with mixed adenine diet showed signs of CVD with LV dysfunction, elevated plasma cardiac injury marker, myocardial capillary rarefaction and microinflammation, while no overt fibrosis was observed. Alport mice have short lifespans thus limits the therapeutic time frame. The mixed adenine diet model further accelerates the cardiac injury onset compared to other CKD mouse models, with a good survival rate and similar physiology to CKD-CVD patients. Thus, the mixed adenine diet model with both kidney and heart injury has the potential for CKD-related CVD studies.

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FR-PO395

Dysregulation of Thrombo-Inflammatory Biomarkers in ESRD and Their Potentiation with Heart Failure

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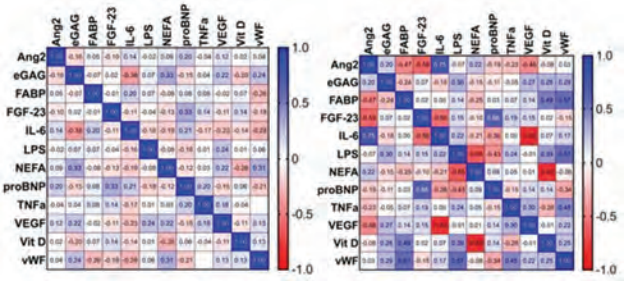
Background: In patients with end-stage renal disease undergoing hemodialysis (ESRD-HD), heart failure with reduced ejection fraction (HFrEF) represents a common comorbidity. Thromboinflammatory processes in both ESRD and HFrEF represent complex pathophysiology, and are demonstrated by dysregulation of thromboinflammatory biomarkers. This study aims to investigate the effects of HFrEF as a comorbidity on these biomarkers in ESRD-HD patients.

Methods: Blood samples from 71 ESRD-HD patients and 40 healthy normal controls were analyzed via commercial ELISA and other chromogenic methods for levels of angiopoietin-2, endogenous glycosaminoglycans, FABP, IL-6, LPS, free fatty acids, proBNP, TNFa, VEGF, Vit D, and vWF. Patient groups were stratified into those with or without HFrEF (EF<50%) in the 6 months prior or following the plasma collection using echocardiography records obtained via chart review.

Results: Compared to ESRD-HD alone, a significant increase ($p < 0.05$) was noted in IL-6 and proBNP, in those with ESRD-HD and HFrEF. Notably, Spearman's rank correlations were compiled for both groups, and markedly stronger correlations were noted in those with both ESRD-HD and HFrEF. Moreover, PAI-1 and tPA were higher in HFrEF group, suggesting the fibrinolytic deficit.

Conclusions: The dysregulation of thrombo-inflammatory biomarkers in ESRD-HD is amplified in comorbid HFrEF. Correlation among biomarkers in this cohort indicates the mechanisms of thrombo-inflammatory biomarker generation have an integrative process that is shared between the two conditions. The role of fibrinolytic deficit is to be further investigated.



FR-PO396

HIF-1α/mTOR/REDD1 Pathway Modulates the Effect of Adipose Tissue-Derived Stem Cells on Kidney Disease Progression in Spontaneously Hypertensive Rats (SHRs) with Induced Visceral Obesity

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Background: The aim of this study was to determine the effect of adipose tissue-derived stem cells (ASC) on the development of renal disease in spontaneously hypertensive rats (SHRs) fed a hypercaloric diet and if their altered lipid profile was dependent on the mTOR/HIF-1α/REDD1 pathway.

Methods: SHRs were divided into groups that received a standard or high-fat diet for 12 weeks and were later treated with ASC for 1 or 2 weeks. Lipid profile and kidney function were evaluated, as well as, the expression and production of the adipocytokines TNF-α, HIF-1α,mTOR and REDD1.

Results: A high-fat diet given to SHRs caused changes in glucose and lipid profiles resulting in insulin resistance, increase in serum levels of triglycerides and low-density lipoprotein cholesterol and decrease in high-density lipoprotein cholesterol values. We also observed an increase in the production of leptin and TNF-α and a reduction in adiponectin, with simultaneous increase in the expression of HIF-1α, mTOR and REDD1 in kidney tissue. Treatment with ASC resulted in the reversal of the kidney and metabolic dysfunction promoted by high-fat diet, with improved glucose and lipid profiles, improved renal function and reduced visceral HIF-1α, mTOR and REDD1 as well.

Conclusions: We found that treatment with ASC resulted in reversal of inflammatory-related kidney damage and metabolic imbalance in SHRs fed a high-fat diet.

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FR-PO397

Role of Ca++ Calmodulin-Dependent Kinase II in Cardiac Pathological Remodeling in Uremia

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Background: Left ventricular hypertrophy is a ubiquitous finding in advanced chronic kidney disease associated (CKD) associated with high risk of heart failure. Our understanding of such pathological hypertrophy in CKD is still evolving. In this study, we set out to test the hypothesis that Ca^{++}- Calmodulin Dependent Kinase II (CAMKII) pathway, a well-recognised downstream mechanism in the genesis of myocardial pathological remodelling, is activated in uremia using a rodent model of experimental uremia.

Methods: Wistar rats had subtotal nephrectomy (STNx, n=10) or sham surgery (sham, n=8) and were followed up for 10 weeks. In vivo and in vitro cardiac assessments were performed. Cardiac tissue was extracted and protein expression of CAMKII, phosphorylated-CAMKII, and myocyte enhance factor 2 (MEF2), the target transcription factor of CAMKII, were quantified using immunoblotting. Data was analysed using an independent sample t-test with Welch's correction and expressed as mean± SEM.

Results: Serum creatinine was elevated in the STNx group (55.00±3.06 vs 32.50±1.44 µmol/L, P<0.01). Echocardiographic left ventricular mass (896.37±54.59 vs 629.81±24.27 mg) and heart weight to tibia length ratio (0.035±0.002 vs 0.027±0.001) were higher in the STNx group (both P<0.01). Furthermore, there was more myocardial fibrosis in the STNx group (4.29±0.79 vs 0.91±0.16 %, P<0.01) (Figure 1). CaMKII signalling was activated in the heart following STNx. An increase in both phosphorylated-CaMKII and total CaMKII was observed. The expression of MEF2 was also increased (Figure 1).

Conclusions: The study shows that experimental uremia induces cardiac pathological hypertrophy and there is associated activation of CAMKII-MEF2 pathway. This novel finding not only offers a mechanism of pathological hypertrophy in uremia but also a potential treatment target to prevent such hypertrophy and the subsequent myocardial dysfunction in CKD.

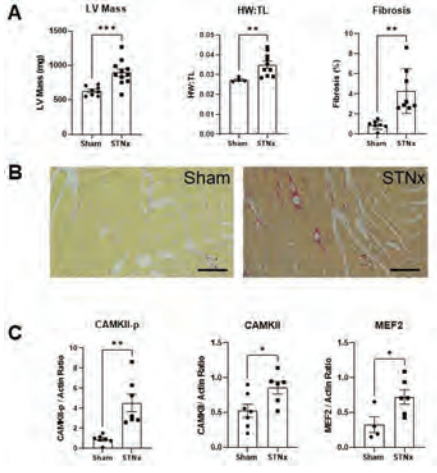

Figure 1: [A] LVmass, HW:TL and percentage cardiac fibrosis were higher in STNx group compared to Sham. [B] Picrosirius red staining of myocardium showing increased fibrosis in STNx. Scale bar 200µm [C] STNx is associated with activation of CAMKII. An increase in both phosphorylated-CAMKII and total CaMKII were observed. The expression of MEF2 was also increased. *P<0.05, **P<0.01 & ***P<0.001 on independent sample t-test. LV: left ventricle, HW:TL: heart weight to tibial length ratio.

FR-PO398

Diabetic Kidney Disease (DKD)-Induced Cardiac Damage Is Characterized and Reduced by Standard-of-Care Treatment in a Translational Diet-Induced Hypertension-Accelerated Mouse Model of DKD

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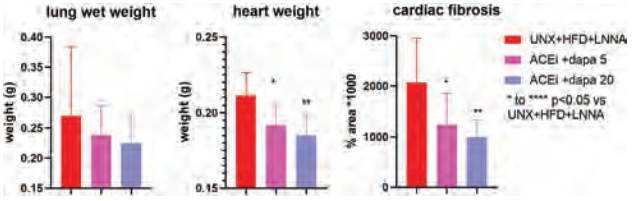
Background: Recently, we developed a diet-induced hypertension-accelerated mouse model of diabetic kidney disease characterized by progressive loss of GFR. Since cardiovascular disease is the major cause of death in CKD, we investigated the occurence of cardiac damage in this model. Additionally, we studied the efficacy of combination therapy with an ACE-inhibitor (Lisinopril) and SGLT2-inhibitor (Dapagliflozin) on cardiac damage.

Methods: Male KKAy mice underwent uninephrectomy. After recovery mice received high fat diet (45% LARD) and drinking water with or without 50 mg/L LNNA (wk0). In the intervention study, at week 4, lisinopril (2,5 mg/kg/day; drinking water) and at week 8 dapagliflozin (5 and 20 mg/kg/day;foodadmix) treatment were started. At week 16 mice were terminated and lung and heart weight and cardiac histology were determined.

Results: Upon termination, macroscopic evaluation of the hearts showed extensive scar tissue formation on the outside of the left ventricle. Histological evaluation showed the presence left ventricular hypertrophy, coronary calcification and myocardial fibrosis in male KKAy mice with UNX, HFD and LNNA. KKAy mice with UNX and HFD but without LNNA also showed myocardial fibrosis, monocyte infiltration and focal mineralization. Treatment with combination therapy reduced lung wet weight, significantly reduced heart weight and significantly decreased cardiac fibrosis. Macroscopically, less scar tissue was observed after treatment.

Conclusions: Cardiac damage is a clear feature in the KKAy mouse model of DKD, either with or without hypertension induction. Combination therapy with Lisinopril and Dapagliflozin reduced cardiac weight and cardiac fibrosis. This indicates cardiac involvement in the DKD mouse model which is clinically relevant. Studies functionally characterizing cardiac damage are currenlty ongoing.

Funding: Commercial Support - Janssen, BPM



Combination therapy with Lisinopril and Dapagliflozin shows reduced lung and heart weight and inhibited cardiac fibrosis.

FR-PO399

Combined Dapagliflozin and Eplerenone Treatment Improve Cardiorenal Function in Rats with CKD

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Background: Patients with chronic kidney disease (CKD) present higher risk of cardiovascular (CV) complications as well as renal function decline. The DAPA-CKD trial showed reduced CV events in diabetic and non-diabetic CKD patients treated with Dapagliflozine (DAPA). Mineralocorticoid Receptor Antagonists (MRAs) have shown similar beneficial effects in diabetic CKD patients (FIDELIO-CKD & FIGARO-CKD trials) but impact in non-diabetic CKD patients is unkown. The aim of this study was to compare DAPA and Eplerenone (EPLE), alone or in combination on renal and CV functions in a non-diabetic rat CKD model.

Methods: CKD was induced in SD rats by 5/6 nephrectomy. Rats were treated with DAPA (10 mg/kg/day PO), EPLE (100 mg/kg/day PO) or the combination during 3 months after CKD induction before cardiorenal function assessment. Renal impact was assessed by histology and creatinine clearance and 24h albuminuria. Cardiac function was evaluated by cardiac echocardiography and left ventricle (LV) hemodynamics (catheterization). LV perfusion was assessed by Magnetic resonance imaging (MRI).

Results: After 3 month kidney fibrosis is decreased in the 3 treated groups compared to untreated CKD. No changes of creatinine clearance were observed while albuminuria increased in the DAPA groups with no significant effects of EPLE. The fractional shortening and the cardiac output were not modified by the treatments (not shown). Cardiac hemodynamic was improved with reduced LV end diastolic pressure (LVEDP) in the CKD rats treated with EPLE or a combination of EPLE and DAPA while LV end diastolic pressure volume relationship (LVEDPVR) was decrease by both DAPA and EPLE and further decreased by DAPA + EPLE. Decreased cardiac perfusion was prevented with EPLE alone or with the combination.

Conclusions: The use of DAPA + EPLE appears to be more effective than DAPA or EPLE alone on diastolic function in non-diabetic CKD rats while cardiac perfusion is improved by EPLE only.

Groups	Kidney fibrosis (%)	Creatinine clearance	Albuminuria (mg/24h)	LV perfusion (ml/min/g)	LV EDP (mmHg)	LV EDPVR (mmHg/RVU)
CKD	0.61±0.05	3.58±0.53	642±128	6.07±0.48	8.65±0.60	3.74±0.18
CKD+DAPA	0.41±0.06	3.61±0.31	2170±316*	7.34±0.49	10.41±0.31	2.21±0.17*
CKD+EPLE	0.39±0.04	4.57±1.49	483±141	9.31±0.89*	6.78±0.28*	2.39±0.21*
CKD+DAPA+EPLE	0.38±0.06*	3.41±0.41	976±268*	9.40±0.87*	7.03±0.41*	1.61±0.15*†

*: p<0.05 vs CKD, †: p<0.05 vs CKD+DAPA or vs CKD+EPLE

FR-PO400

Tryptophan Metabolite 3-Hydroxy Anthranilic Acid Decreases CKD-Associated Atherosclerosis

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Background: The tryptophan catabolism pathway is upregulated in chronic kidney disease (CKD), and tryptophan metabolite 3-hydroxy anthranilic acid (3-HAA) is an anti-inflammatory metabolite that has been shown to decrease atherosclerosis in preclinical and clinical models. However, the mechanistic link between 3-HAA and CKD accelerated atherosclerosis is unknown.

Methods: Twenty-four male LDLr$^{-/-}$ mice underwent 5/6 nephrectomy (CKD) and were placed on a high-fat/high-cholesterol diet (HFD) for 16 weeks. 3-HAA (200 mg/g) was injected intraperitoneally three times a week (3-HAA mice, n=12), while controls (n=12) were injected with PBS for 16 weeks. We quantified atherosclerosis with Oil Red-O staining of *en face* aortic sections at the end of 16 weeks. We used human macrophage cultures that were treated with 10μM 3-HAA and measured changes in transcriptome profiles and macrophage functions like apoptosis, phagocytosis, and cytokine profiles.

Results: 3-HAA treatment increased 3-HAA levels which negatively correlated with aortic atherosclerotic lesions in 3-HAA mice. 3-HAA treatment decreased IL-6 levels and increased IL-10 levels. 3-HAA treatment of human macrophages influences nitric oxide, platelet-derived growth factor, and CXCR3 signaling, while 3-HAA treatment had no effect on T cells. Activated human macrophage cultures reveal that 3-HAA treatment decreases macrophage apoptosis and increases phagocytosis.

Conclusions: In summary, 3-HAA treatment decreases CKD-associated atherosclerosis by its action on macrophage apoptosis, phagocytosis, cytokine profiles, and inflammatory signaling.

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FR-PO401

D4 Dopamine Receptors Regulate Insulin and Salt Sensitivities in Mice

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Background: Insulin resistance associated with dysfunction of dopamine receptors is underlined by multiple metabolic disorders including diabetes and hypertension. Dopamine D4 receptor(D4R) null mice are hypertensive.

Methods: To explore the effects of D4R on insulin resistance and hypertension, we determined the insulin/salt sensitivities, renal insulin pathway and sodium transporters in D4R null mice.

Results: Drd4$^{-/-}$ mice(14mos) had increased fasting blood glucose regardless of sex. Serum insulin levels at fasting were increased in male but not in female Drd4$^{-/-}$ mice. The male and female Drd4$^{-/-}$ mice presented a blunted blood glucose lowering effect at 30, 45 min after insulin injection (0.75U/kg,I.P). Their body weights, fasting serum total and free cholesterols, triglycerides were similar between the mouse strains. D4R agonist(PD168077,1mg/kg) increased but D4R antagonist(L745870,1mg/kg) decreased insulin sensitivity of D4$^{+/+}$ mice via osmotic mini-pumps for a week. Changing the salt intake from low to high increased mean arterial pressure by 25±4% in D4$^{-/-}$ but only by 13±1% in D4$^{+/+}$ mice while switching from high salt to low salt decreased it by 20±1% in D4$^{-/-}$ and by 11±3% in D4$^{+/+}$ mice (tail-cuff, BP-98A, Softron, Tokyo, Japan). The higher salt-sensitivity in KO than WT was also confirmed by telemetry measurements. Less increase in urinary sodium excretion was found in D4$^{-/-}$ than in D4$^{+/+}$ on high salt diet with a right-shift of pressure-natriuresis in D4$^{-/-}$. On normal salt diet Drd4$^{-/-}$ mice had decreased IRβ(19±4, % of controls, n=4)but normal protein expressions of IRα, insulin degrading enzyme, insulin substrate 1, sodium glucose transporter 2 and glucose transporters in renal cortex homogenates. D4R and IRβ were co-immunoprecipitated in immortalized mouse renal distal convoluted tubule cells and the co-immunoprecipitation was increased by D4R agonist and not altered by D4R antagonist. IRβ was co-located with the apical NKCC2 in the thick ascending limbs of the Henle's loop and NCC in the distal convoluted tubules but not with NHE3 in proximal convoluted tubules. NHE3 (126 ± 8), NKCC2 (182 ± 26) and NCC (226 ± 30) were increased in whole kidney homogenates of D4$^{-/-}$ while ENaCs and αNKA were similar between strains.

Conclusions: Therefore, D4R interacts with renal IRβ, NKCC2 and NCC, and may normalize blood pressures via reducing insulin resistance.

FR-PO402

Angiotensin II-Stimulated Superoxide Production Is Increased by a Fructose High-Salt Diet and This Contributes to Salt-Sensitive Hypertension

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Background: Angiotensin II (Ang-II) increases proximal tubule superoxide (O_2^-) production significantly more in rats fed a 20% fructose normal-salt diet compared to rats fed a 20% glucose, normal-salt diet. These data suggest that dietary fructose augments the sensitivity of proximal tubule O_2^- production to Ang-II. A 20% fructose high-salt (3.7% NaCl; FHS) also significantly increases systolic blood pressure (SBP), whereas 20% glucose high-salt (GHS) does not. However, it is unclear whether FHS enhances Ang-II induced oxidative stress in proximal tubules, and whether this contributes to increases in BP in this model. We hypothesized that FHS augments the ability of Ang-II to stimulate superoxide production by proximal tubules, and this contributes to fructose-induced salt-sensitive hypertension.

Methods: We measured SBP in male Sprague Dawley rats fed FHS, GHS, FHS plus 3 mM tempol (a O_2^- scavenger) in the drinking water (FHS+T), and GHS+T for 7 days. Then we measured the effect of 3.7 x 10^{-8} M Ang-II on O_2^- production by proximal tubule suspensions from rats fed GHS, FHS, and FHS+T using the lucigenin assay. This concentration was chosen because it was the lowest concentration that significantly stimulated O_2^- production by proximal tubules from rats fed FHS.

Results: FHS increased SBP by 11 ± 2 mmHg, (Day 0: 131 ± 4, Day 7: 142 ± 5 mmHg; n = 5, p < 0.01), while GHS did not (Day 0: 140 ± 3, Day 7: 137 ± 3 mmHg, n = 5). Rats fed FHS+T and GHS+T showed no significant increases in SBP (FHS+T: Δ-1 ± 5, n = 8; GHS+T: Δ-1 ± 4 mmHg, n = 6). Ang-II increased O_2^- production by 11 ± 1 relative light units (RLU)●μg protein^{-1}●s^{-1} in proximal tubules from FHS-fed rats (Basal: 53 ± 9, Ang-II: 64 ± 8 RLU●μg protein^{-1}●s^{-1}; n = 11, p < 0.01) but not in proximal tubules from rats fed GHS (Basal: 46 ± 3, Ang-II: 43 ± 5 RLU●μg protein^{-1}●s^{-1}; n = 6). Ang-II did not significantly stimulate O_2^- production by proximal tubules from rats fed FHS+T (basal: 53 ± 5, Ang-II: 51 ± 4 RLU●μg protein^{-1}●s^{-1}; n = 6). We did not measure Ang-II induced superoxide production in rats fed GHS+T because there was not a significant change in blood pressure.

Conclusions: We conclude that a FHS diet enhances the sensitivity of proximal tubule O_2^- production to Ang-II, and this contributes to fructose-induced salt-sensitive hypertension.

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FR-PO403

Effects of Mild Hyperuricemia in the Progression of Salt-Sensitive Hypertension and Associated Kidney Damage

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Background: Increased plasma uric acid (UA) (hyperuricemia (HrU)) causes damage via crystal deposition throughout the body in gout. HrU is also a potential causal factor in hypertension (HTN) & chronic kidney disease (CKD). Whether only HrU with crystals, but not asymptomatic HrU (HrU without crystal deposition), drives the progression of HTN & CKD is controversial. Additionally, dietary salt intake is involved in blood pressure & renal function control & may affect UA levels. The renin-angiotensin-aldosterone system (RAAS) activation may trigger HTN during HrU; however, lowering UA did not affect RAAS activity in some clinical studies.

Methods: To answer the question if asymptomatic HrU in the context of salt sensitivity (SS) is a friend or foe, we explored conditions of induced mild HrU & a high salt diet on the development of HTN using Dahl SS rats & administration of either oxonic acid, a uricase inhibitor that prevents the breakdown of UA further into more soluble allantoin &/or probenecid, an inhibitor of the UA transporter Urat1, preventing UA reuptake. 8-week-old male rats were implanted with telemeters to assess mean arterial pressure (MAP). After recovery, SS rats were switched to one of 4 diets: 1) 4% NaCl high salt (HS) diet (control, N=6); 2) HS + 2% oxonic acid (treatment 1, N=7); 3) HS + 750 mg/kg Probenecid (treatment 2, N=4); or 4) HS + 750 mg/kg Probenecid + 2 % oxonic acid (treatment 3, N=3) for 3 weeks.

Results: At the endpoint, treatment group 1 had significantly higher plasma UA levels compared to the control group (2.17±0.34 vs. 0.63±0.07 mg/dl). This mild HrU was associated with attenuated progression of SS HTN while probenecid did not affect MAP & diminished the effect of oxonic acid (MAP for control & treatment 1-3 groups: 156±3, 138±3, 162±3, & 154±4 mmHg). Treatment group 1 also had a lower kidney weight/body weight ratio & lower protein cast accumulation, indicating lower kidney damage. Assessment of circulating RAAS hormones showed no treatment-specific changes.

Conclusions: These results indicate mild HrU in Dahl SS rats attenuates HTN & renal damage without affecting RAAS. Our data suggest that HrU is not inherently detrimental but beneficial to cardiovascular & kidney health under certain conditions.

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FR-PO404

Angiotensin II-Induced Cellular and Transcriptional Remodeling of Mouse Kidney Stroma

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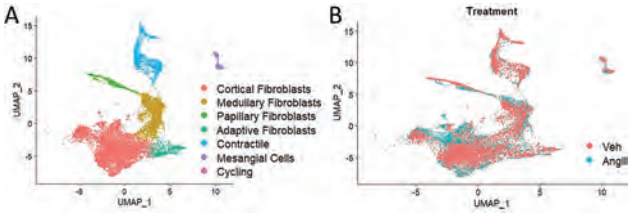
Background: The kidney stroma consists of perivascular cells that play multiple crucial roles. Recent data have shown that murine kidney stromal cells abundantly express the type 1a angiotensin receptor, however, how these cells respond to AngII treatment is poorly understood. Moreover, the cellular heterogeneity of the kidney stroma has been poorly characterized at the molecular level because they comprise a small percentage of kidney cells.

Methods: Pdgfrb-creERT2 mice were crossed with the INTACT mouse to create Pdgfrb-INTACT mice which express GFP connected to the nuclear envelope protein. Pdgfrb-INTACT mice were implanted with osmotic minipumps containing either saline (Veh) or Angiotensin II (AngII, 1000ng/kg/min) for 21 days. Nuclei were extracted from kidneys followed by fluorescence activated nuclei sorting (FANS) and microfluidic partitioning (10X Genomics). After sequencing the resulting cDNA libraries and deconvolution (Cell Ranger) the dataset was dimensionally reduced, integrated, and evaluated for differentially expressed genes (DEGs) with Seurat.

Results: 16449 nuclei were sequenced (9644 from Veh; 6805 from AngII). Nuclei were enriched for expression of Pdgfrb and divided into 7 populations (**Figure A**): cortical fibroblasts, medullary fibroblasts, papillary fibroblasts, adaptive fibroblasts, contractile cells, mesangial cells, and cycling cells. Veh and AngII treated nuclei were present in all cell populations (**Figure B**), but not at the same proportion. Suggestive of AngII inducing myofibroblast remodeling, there was an increase in cycling cells (5 in Veh vs. 31 in AngII) with a concurrent decrease in contractile cells (1394 in Veh vs. 607 in AngII). While each population had a unique set of DEGs, one gene that was more abundant in AngII treated cells was Pde10a.

Conclusions: The mouse kidney stroma is transcriptionally diverse with significant cellular heterogeneity. AngII treatment alters both the cellular composition of the kidney stroma as well as the genes that are expressed within each cell population, highlighting the significant impact of AngII.

Funding: NIDDK Support, Private Foundation Support



Targeted Single-Nucleus RNAsequencing of Kidney Stromal Cells from Mice Treated with Angiotensin II.

FR-PO405

Evidence of Estrogen Biosynthesis in the Rat Distal Nephron

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Background: Estrogenic signaling via renal medullary G protein-coupled estrogen receptor 1 promotes sodium excretion in female, but not male, Sprague Dawley (SD) rats implicating estrogen as a potential female-specific natriuretic factor. Recently we showed that the components of estrogen biosynthesis pathway are expressed in rat kidney suggesting the kidneys can produce estrogen locally to invoke this natriuretic response. However, the renal localization and biological activity of aromatase (ARO), the key enzyme in estrogen synthesis, are still not fully clear. The goal of this study was to determine ARO abundance, localization, binding, and levels of ARO end products in male and female SD rat kidneys.

Methods: We utilized immunohistochemistry (IHC) and immunofluorescence (IF) to determine abundance and localization, a radiotracer to evaluate in vivo binding to ARO, and mass spectrometry to measure estrogens.

Results: IHC analysis revealed ARO was most abundant in cortex (CTX) and outer medulla (OM) with a less intense signaling in the inner medulla (IM) in both sexes (male: CTX 2.4 ± 0.31, OM 1.8 ± 0.19, IM 0.6 ± 0.15 p=0.0002; female: CTX 2.6 ± 0.27 OM 2.0 ± 0.21 IM 1.2 ± 0.31 p=0.0074 Average intensity x total area mM^2). IHC analysis of male and female kidney showed the expression of ARO primarily in the distal nephron with little staining in the proximal tubule and glomeruli. IF staining for ARO and aquaporin 2 showed colocalization indicating that ARO is expressed in the collecting duct. Preliminary positron emission tomography scan of female rats following tail vein injection of [^{11}C]-cetrozole, a radiolabeled ARO inhibitor, revealed binding, indicating ARO-rich regions, within the kidneys, but not the lungs or muscle (2.9 ± 0.16 vs 0.9 ± 0.31 & 0.4 ± 0.04 respectively p=0.0063 Standard uptake value). Estradiol and estrone were present in both male and female OM isolated from flushed kidneys (estradiol; 0.9 ± 0.15 vs 1.0 ± 0.21 p=0.7627, estrone; 0.2 ± 0.05 vs 0.3 ± 0.01 pg/mg tissue p=0.0630).

Conclusions: Overall, our investigation indicates the potential of the rat collecting duct as an extragonadal site for estrogen biosynthesis. Given the critical role of the collecting duct in fine tuning of sodium excretion, improving our understanding of the contribution of kidney-derived estrogens to renal sodium handling and hypertension could reveal novel antihypertensive therapeutic avenues.

Funding: NIDDK Support, Private Foundation Support

FR-PO406

Low Cl- Diet Protects from Hypertension and Cardiac Hypertrophy After AngII Infusion in Mice Preserving Natriuresis

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Background: The increase of blood caused by Angiotensin II (AngII) depends on the expansion of vascular volume and the increase of total peripheral resistance. Besides acting as a vasoconstrictor, AngII increases renal Na^+ reabsorption. Chloride is reabsorbed as the accompanying anion of Na+ and modulates natriuresis, and extracellular Cl^- affects vascular smooth muscle cell contractility. We evaluated if low dietary Cl affected the pressor response to AngII infusion, cardiac hypertrophy, natriuresis, and vascular contractility.

Methods: C56BL/6J mice were allocated to 4 experimental groups: low-Cl diet (Cl replaced by HCO3, phosphate), normal-Cl diet (NaCl), AngII infusion (1.5 mg/Kg/day osmotic minipumps) or vehicle infusion (14 days). We measured systolic blood pressure (SBP) *by* the tail-cuff method. Natriuresis after a saline load (10% of body weight, i.p.) was assessed at baseline 4 and 14 days. Na+, K+ and Cl-excretion were measured (4 hours). We also measured cardiac hypertrophy and isotonic force development in aortic rings (high extracellular K+, phenylephrine) and NO-dependent relaxation.

Results: In normal-Cl^--diet mice, AngII infusion increased SBP from 103.3±9.1 mmHg to. 145.3±3.2 mmHg (n=6 per group, P<0.01 baseline vs. 14 days). In contrast, AngII infusion did not increase SBP in low-Cl diet mice (97.8±3.6 v/s 92.71±4.7 n=6 per group, n.s baseline vs. 14 days). Low Cl diet prevented cardiac hypertrophy after AngIi infusion (14 days). Normal Cl^--diet mice presented hampered natriuretic response after AngII infusion (8.8±1.7 vs. 4.1±2.1 uEq/4h/g BW, baseline vs. 14 days respectively, P<0.01). Low- Cl^--diet prevented the decrease in natriuresis after Ang II infusion (9.6±2.7 vs. 10.69±2.09 uEq/4h/g BW, baseline vs. 14 days respectively, P<0.01). AngII infusion increased the aortic rings maximal tension in response to phenylephrine, irrespective of dietary Cl. No changes in dose response to phenylephrine or Ach-induced NO-dependent vasodilation were observed among the groups.

Conclusions: Low Cl associated to a regular Na^+ content in diet prevented the increase of blood pressure and cardiac hypertrophy in response to AngII infusion. The protective action of a low Cl^- diet may be attributed to the protection of renal natriuretic response without affecting the vascular effects of AngII.

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FR-PO407

Increased Epithelial Sodium Channel (ENaC) Activity Mediates Fructose-Induced Salt-Sensitive Hypertension

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Background: Elevated dietary fructose causes sodium retention and salt-sensitive hypertension. In a preliminary bioinformatics study on kidney cortexes from fructose-fed rats, we found an increase in aldosterone-responsive genes, which included subunits of the Epithelial Sodium Chanel (ENaC). Regulation of ENaC in the aldosterone sensitive distal tubule involves transcriptional and post-translational mechanisms, and is key to maintain electrolyte homeostasis and blood pressure. An important post-translational regulation of α-ENaC and γ-ENaC subunits is cleavage activation by luminal and intracellular proteases. We hypothesized that "dietary fructose increases ENaC subunits expression and cleavage, thereby contributing to sodium retention and salt-sensitive hypertension".

Methods: Sprague-Dawley rats were fed with matched diets containing 4% NaCl and either 20% fructose (FHS) or glucose (GHS) for up to 11 days. Protein expression and RNA transcripts abundance were measured in the kidney cortex by Western blotting and next generation sequencing, respectively. The expression of cleaved α-ENaC and γ-ENaC subunits was measured as surrogate of ENaC activation. The effect of inhibiting ENaC on blood pressure was assessed by tail-cuff plethysmography on rats given oral amiloride for 24h.

Results: Seven days after starting the diets, FHS presented higher abundance of both α-ENaC transcripts (Scnn1a gene; $\log_2$FC = 1.04; p = 0.01, n = 6) and proteins (121±20 vs. 64±10 normalized optical density (OD); Δ 90±34 %, p < 0.03, n = 6) as compared to GHS. No differences in either protein or RNA abundance were found for γ-ENaC or β-ENaC subunits. In addition, the expression of cleaved α-ENaC protein, was higher in FHS than in GHS (85±8 vs. 58±5 OD; Δ 48±16 %, p < 0.01, n = 6). Between days 5 and 10 of dietary intervention, FHS showed significantly higher systolic pressures than GHS (144±5 vs. 127±4 mmHg; Δ17±4 mmHg, p < 0.03, n=6). Oral amiloride from days 10 to 11 reduced systolic pressure in FHS by 10±4 mmHg (paired t-test: p ≤ 0.05), while caused no significant change in GHS (paired t-test: p = 0.23).

Conclusions: Rats consuming a diet rich in fructose and sodium, present increased expression and activity of ENaC than those eating a diet matched with glucose, contributing to the salt-sensitivity of blood pressure seen in this model.

Funding: NIDDK Support

FR-PO408

Deficiency of Peroxiredoxin-4 and Dopamine D5 Receptor Increases NLRP3-Inflammasome Activity

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Background: Dopamine 5 receptor (D_5R) interacts with Peroxiredoxin-4 (PRDX4) to reduce oxidative stress and inflammation. *Drd5* knockout (*Drd5*$^{-/-}$) mice are hypertensive and in a state of oxidative stress and chronic inflammation. However, the gene's specific association with the regulation of inflammasomal activity in the kidney is unknown.

Methods: To investigate inflammasomal activity, the protein expressions of interleukin (IL)-1β, IL-18, and caspase-1 were quantified by immunoblotting. The *PRDX4* gene was silenced in HEK 293 cells overexpressing D_5R. *Drd5*$^{-/-}$ mice were generated as previously reported.

Results: D_5R protein expression was decreased in *PRDX4* siRNA-transfected D_5R-HEK 293 cells (*PRDX4* siRNA: 58.8±6.7% vs Mock: 100.0±9.6%, n=4), and PRDX4 protein was also reduced in the kidney cortices of *Drd5*$^{-/-}$ mice (*Drd5*$^{+/+}$: 100±12.8%, n=3; $D_5R^{-/-}$: 69.2±7.5%, n=4). In D_5R-HEK 293 cells -transfected with *PRDX4* siRNA, the protein expressions of nucleotide-binding oligomerization domain, leucine-rich repeat, and pyrin domain-containing-3 (NLRP3) were increased compared with mock-transfected cells (siRNA: 142.7±8.9%, Mock: 100±1.8%). The protein expressions of cleaved IL-1β (siRNA: 176.3±37.0%, Mock: 100.0±12.7%) and cleaved IL-18 (siRNA:710.0±214.8%, Mock: 100±8.1%) were likewise increased compared with mock- transfected cells, indicating an increase in inflammatory response due to NLRP3 activity. The increase in NLRP3 activity with silenced *PRDX4* was attenuated by tempol, a superoxide dismutase mimetic, in D_5R-HEK293 cells, indicating that oxidative stress was upstream of the increase in NLRP3-associated inflammasomal activity induced by PRDX4 deficiency. Consequently, protein expression of cleaved caspase-1 was increased in renal cortices from *Drd5*$^{-/-}$ mice (*Drd5*$^{+/+}$: 100±2.6%; *Drd5*$^{-/-}$:112.6±3.1%, n=3). Consistent with this increase, the protein expressions of cleaved IL-1β (*Drd5*$^{+/+}$: 100.0±11.1%, n=3; *Ddr5*$^{-/-}$: 152.9±13.5%, n=4), secreted IL-1β (*Drd5*$^{+/+}$: 100.0±1.5%, n=3; *Drd5*$^{-/-}$:137.4±2.2%, n=4), and cleaved IL-18 (*Drd5*$^{+/+}$: 100.0±8.3%; *Drd5*$^{-/-}$:166.0±10.4%, n=3) were also increased compared with their wild-type littermates.

Conclusions: The increase in renal inflammation associated with PRDX4 deficiency in *Drd5*$^{-/-}$ mice is due to the increase in NLRP3-inflammasome activity.

Funding: NIDDK Support

FR-PO409

Renal ABCA1 Deficiency Induces TLR4 that Regulates Epithelial Sodium Channel (ENaC)

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Background: Na sensitive blood pressure (BP) and restricted cholesterol (chol) efflux are risk factors for cardiovascular mortality. In preliminary studies, renal tubular ablation of ABCA1, a chol efflux protein, leads to greater systolic BP (SBP) vs control (WT) mice, while a low Na diet quenches this difference. Moreover, toll-like receptor 4 (TLR4) is stimulated by chol and associated with Na sensitive models. We hypothesize that TLR4 contributes to cation transport in an ABCA1 deficient model.

Methods: Transgenic mice, which express a doxycycline inducible CRE in tubules, were bred with mice expressing floxed ABCA1 to produce mice deficient in ABCA1 (FF). Western blotting of kidney and cortical collecting duct (mpkCCD) cell lysate was performed. Immunofluorescence (IF) was performed on kidneys and amiloride sensitive short-circuit current (*AIsc*) measured in mpkCCD cells.

Results: Mice were fed a 1% chol diet (X 6 weeks), a low Na and a high Na diet for 1 week each and then euthanized and kidneys extracted. TLR4 expression was enhanced in FF (1.9±0.3; n=3; p<0.05) vs. WT (1.0±0.2; n=3) kidneys. Phospho-ERK(pERK) was 2.3±1.3 (p=0.052) fold greater in FF(n=5) than WT(n=5) kidneys. IF of kidneys localized pERK to CDs while TLR4 was seen in CDs and non-CDs. Next, mpkCCD cells were incubated with PSC833 (PSC, 5 μM), an ABCA1 inhibitor, which increased abundance of pERK, (1.7±0.3; n=4; p<0.05) vs. untreated cells (1.0±0.2; n=4). Dual TLR4 antagonist (TAK242 10μM) and PSC suppressed γ-ENAC expression vs. untreated and PSC alone. While TAK242 did not affect *AIsc* in untreated mpkCCD cells, TAK242 repressed *AIsc* in PSC treated mpkCCD (11.2±2.2 μA/cm^2; n=6; p<0.05) vs PSC alone (17.1±3.1 μA/cm^2). Fluid shear stress (FSS) induces pERK, and ERK inhibition suppresses flow-induced in Na absorption (Repetti et al. 2021). The role of TLR4 signaling on FSS mediated Na transport was tested in mpkCCD cells. The *AIsc* in FSS (0.4 dynes/cm^2) exposed cells was greater (40.8±2.1 μA/cm^2;n=20, p<0.05) than in static cells (26.7±1.6 μA/cm^2; n=20) and the FSS induced *AIsc* was reduced (31.5±2.6 μA/cm^2; n=18, p<0.05 vs FSS exposed cells) by TAK242.

Conclusions: ABCA1 deficiency induces TLR4 and pERK abundance in renal CD while in mpkCCD cells exposed to FSS or ABCA1 inhibition sensitizes them to TLR4 dependent *AIsc*. We speculate repression of chol efflux enhances TLR4 dependent activation of pERK and *AIsc*.

Funding: Veterans Affairs Support

FR-PO410

Dysregulation of the Microbiome-Immune Axis Drives Cardiovascular Pathology in Early-Onset CKD

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Background: CKD patients have a high risk for cardiovascular disease (CVD). CKD-related chronic inflammation contributes to the increased CV risk. The underlying mechanisms are incompletely understood, but gut microbial dysbiosis seems to play an important role. Here, we describe the cardiovascular and immune phenotype of children with CKD and investigate the induction of these changes by CKD-typical microbiome alterations.

Methods: We analyzed the CV phenotype by echocardiography, carotid intima-media thickness (cIMT), measurements of blood pressure (BP) and pulse wave velocity (PWV) in 38 children (normal kidney function (HC), CKD stage G3-G4 (CKD), G5 treated by hemodialysis (HD)). Additionally, we performed CITE-seq enhanced single cell RNA sequencing (scRNAseq) and flow cytometry of peripheral immune cells, targeted plasma proteomics (OLINK) and shotgun sequencing of the fecal microbiome. Lastly, from a subset of HC and HD kids, we performed fecal microbiota transplantations into GF mice and analyzed the immunophenotype and vascular function.

Results: Children with CKD showed increased BP and PWV. Our echocardiographic analysis demonstrated increased cIMT, cardiac hypertrophy and diastolic dysfunction. Immune cell analysis by flow cytometry revealed a pro-inflammatory profile with a reduction of circulating regulatory T cells. This finding could be confirmed by scRNAseq. Additionally, we identified a stage-dependent dysregulate of transcriptomes within T cell populations from CKD and HD. Using the targeted proteomics of inflammatory markers, we found 55 out of 92 measured proteins to be dysregulated, with for example an increase in TNF, PD-L1 and MCP-1. Transfer of microbiota from HD patients or HC into germ-free recipient mice (C57BL6/J) promoted early signs of immune aging and a reduced endothelial dependent vasorelaxation.

Conclusions: In the absence of traditional CV risk factors, pediatric CKD leads to a measurable alteration of the CV system. Our analysis revealed a pro-inflammatory immune cell profile. Using fecal microbiome transplantation into germ-free mice, we provide preliminary evidence for a causal role of the microbiota in promoting inflammation and CV risk. Thus, the data highlight the importance of the microbiota-immune axis in CKD.

FR-PO411

Independent Predictors of One-Year Quality of Life Trend in a Large Population of Hemodialysis Patients: Importance of Vascular Access Management

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Background: Health-related quality of life (QoL) is recognized as a relevant patient-centered outcome in hemodialysis (HD). Studies evaluating the trend of QoL with time in large populations are scarce. We aimed to evaluate the changes in QoL over a one-year period in a multinational HD population.

Methods: This was a multicenter prospective observational study using a quality database from a large HD organization. All adult patients that voluntarily responded to KDQOL-36 in 2021 and 2022 were included. Mental (MCS) and Physical Composite Scales (PCS) were analyzed and divided in two groups: Group I, increase in MCS and PCS by more than 5 points; Group II, decrease in both scores. At the time of the first survey, demographic (age, gender) and clinical data (diabetes, comorbidity index - CI, vascular access) were collected. Death was registered until 6 months after the second survey. T-test and z-test were performed for group comparisons. Multivariate logistic regression, Kaplan Meyer and Cox regression for survival analysis were also used.

Results: 20 006 HD patients with valid responses to both KDQOL-36 were included. Increase on both scores was observed in 2381 patients (11.9% of surveys) and decrease in 2051 (10.3%). Group I patients were significantly younger, less diabetic, had a lower CI, higher percentage of fistulas and lower time on dialysis. A significantly higher number of deaths at 6 months were observed in Group II (6.5% vs. 4.2%, p<0.005). In multivariate analysis, age and the presence of a fistula were independently associated with global QoL improvement, whereas female gender and diabetes were independent predictors of QoL decrease. Six-month mortality was associated with worsening of QoL. Males and diabetic patients in Group I and older and diabetic patients in Group II presented significant higher hazard ratios of death.

Conclusions: In our HD population, one-year trend of QoL scores were associated with several demographic and clinical variables, allowing us to define and target specific interventions on a group at risk for rapid QoL decrease. The presence of a fistula was a predictor of QoL improvement, confirming the importance of vascular access management in the global outcomes of HD patients.

FR-PO412

One-Year Quality of Life Trend in a Large Population of Incident Hemodialysis Patients

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Background: Health-related quality of life (QoL) is an important outcome in prevalent hemodialysis (HD) patients, but the evolution in the first months of treatment is still to be explored. We aimed to evaluate the 1-year changes in QoL in incident patients in a large, multinational HD population.

Methods: This was a multicenter prospective observational study. All adult patients with less than 3 months on HD that voluntarily responded to KDQOL-36 in 2021 were selected and included after the response to the 2022 survey. Mental (MCS) and Physical Composite Scales (PCS) were analyzed. At the time of the first survey, demographic (age, gender) and clinical data (diabetes, comorbidity index - CI, vascular access) were collected. T-test, z-test and multivariate logistic regression were used for statistical analysis.

Results: 1 401 HD patients with valid responses to both KDQOL-36 were included. QoL reported on HD admission was low: PCS=36.73±9.05 and MCS=44.07±10.29. In multivariate analysis, female gender and CI were independently associated with a poorer QoL at baseline, whereas diabetes was positively correlated with MCS but not with PCS. In the second survey, a significant increase in QoL was documented: PCS=38.75±9.77, p<0.01 and MCS=46.09±10.20, p<0.01. Increase in both scales after 1-year was observed in 234 patients (16.7% of surveys) and a decrease in 112 (8.0%) with the remaining presenting mixed results. The group with improvement in QoL was significantly younger, had a higher percentage of fistulas and lower prevalence of diabetes, when compared to the group with a decrease in both scales. In multivariate analysis, diabetic status was associated with PCS improvement after 1-year, whereas male gender was an independent predictor of PCS decrease.

Conclusions: In our incident HD patients, QoL was poor at baseline, but increased during the first months on dialysis. Diabetes was associated with QoL improvement, despite the low baseline values normally reported by this population, suggesting that HD may positively impact on QoL of diabetic patients with advanced renal disease. Despite the higher scores at baseline, male patients were more prone to QoL decrease during the first year, alerting for the importance of following QoL through time after the beginning of HD.

FR-PO413

Association Between Perceived Social Support and Health-Related Quality of Life in Hemodialysis Patients: Results from the TACcare Study

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Background: In patients with End Stage Kidney Disease (ESKD), high symptom burden and the demands of thrice weekly hemodialysis (HD) contribute to limitations in their daily lives, including a negative impact on their interpersonal relationships. However, there is limited research exploring associations of social support with symptom burden and health related quality of life (HRQoL) among HD patients.

Methods: The Technology Assisted stepped Collaborative Care (TACcare) was a randomized controlled trial to compare the effectiveness of a stepped collaborative care intervention for symptom management in chronic in-center HD patients. The current study is a secondary, cross-sectional analyses of baseline data to examine the sociodemographic and clinical factors that affect perceived social support (Multidimensional Scale of Perceived Social Support; MSPSS), and its association with symptom burden and HRQoL (SF-12 Mental Component Score (MCS) and Physical Component Score (PCS).

Results: For the 160 randomized patients: mean (SD) age 58 ±14 years; 45% female; 28% Black, 13% American Indian, 18% Hispanic; 88 % high school education; 27% married; 4 ± 4 years on dialysis. Mean baseline levels of MSPSS from family, friends, significant other, and total were: 21.3 (5.5), 19.8 (6.1), 22.0 (5.3), and 63.1 (14.0), respectively, comparable to other chronically ill populations. High school education ($p = .04$) and being married ($p = .05$) were associated with higher total MSPSS scores. Higher MSPSS scores were correlated with lower levels of fatigue ($r = .21$, $p < .01$), pain ($r = -.17$, $p = .03$), depressive symptoms ($r = -.23$, $p < .01$), anxiety ($r = -.23$, $p < .01$), and better sleep quality ($r = -.32$, $p < .001$). Higher family, friend, significant other, and total MSPSS support scores were all associated with higher MCS ($r = .20$, $p = .01$; $r = .25$, $p < .01$; $r = .20$, $p = .01$; and $r = .26$, $p < .001$, respectively); and higher MSPSS friend support was associated with higher PCS ($r = .2$, $p = .04$). After adjusting for age, sex, race, ethnicity, and Charlson comorbidity index, MSPSS total scores were associated with MCS (beta=0.17, $p = .001$).

Conclusions: Because of the associations between MSPSS and HRQoL, particularly mental health, social support appears to be an important intervention target.

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FR-PO414

Quality-of-Life Penalty Associated with Anemia of CKD in a Large Sample of Dialysis Patients

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Background: Anemia of chronic kidney disease (ACD) is a common complication in dialysis and it is associated with fatigue and weakness, possibly leading to quality of life impairment. Previous reports are old and may not account for recent improvement in renal care. We used the Kidney Disease Quality of Life Short Form (KDQOL-36) questionnaire to assessing the health-related quality of life penalty associated with anemia in a large sample of dialysis patients.

Methods: We enrolled 9067 patients from 8 European countries. We assessed the severity of anemia by 5 hemoglobin concentration classes based on the last laboratory assessment available prior to survey administration. We fitted generalized linear models assessing the relationship between each KDQOL-36 subscale and the severity of ACD. We adjusted for age, vintage, gender, country of residence, and comorbidities. We accounted for multicenter design by including a random-intercept parameter. In a secondary analysis we also adjusted for ferritin and inflammatory indexes.

Results: We observed lower KDQOL-36 scores among patients with severe anemia ($p < 0.05$) (see Table 1). We observed a mild, graded association between mental composite, physical composite and symptoms scale and anemia severity. Despite statistically significant, the Quality of Life penalty associated to ACD was modest and barely clinically significant based on MCID standards. No significant differences were found in the BKD and EKD domains among the anemia groups. By adding ferritin and inflammatory indexes as confounding factors, the significance disappears in all scores.

Conclusions: Anemia of CKD is associated with modest quality of life impairment. Our study suggests that this association may be driven by iron deficiency and inflammation.

	Hb: <8 g/dl	Hb: 8-10 g/dl	Hb: 10-12 g/dl	Hb: >12 g/dl & ESA+	Hb: >12 g/dl & ESA-	p-value
QOL score	N=108	N=1122	N=5164	N=1177	N=1501	
BKD	36.4 (30.6-42.1)	38.7 (35.9-41.5)	39.3 (37.0-41.7)	39.5 (36.8-42.3)	39.5 (36.9-42.1)	0.76
EKD	58.6 (53.1-64.1)	63.0 (59.0-67.0)	63.8 (59.9-67.6)	64.0 (60.0-68.0)	64.2 (60.2-68.1)	0.06
MCS12	41.4 (39.1-43.8)	43.8 (42.5-45.1)	44.6 (43.5-45.8)	44.9 (43.6-46.1)	44.7 (43.5-46.0)	<0.01
PCS12	31.2 (28.0-34.4)	33.4 (30.8-35.9)	34.6 (32.2-37.1)	34.7 (32.1-37.2)	34.9 (32.4-37.5)	<0.01
SKD	71.8 (68.0-75.5)	76.2 (73.8-78.6)	77.0 (74.8-79.3)	77.4 (75.0-79.8)	77.3 (74.9-79.7)	<0.01

QOL scores mean values in each level of anemia. Mean values are reported with corresponding confidence intervals (CI).

FR-PO415

Trust in Physicians Among Hospitalized Patients Receiving Maintenance Dialysis: Prevalence and Correlates

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Background: Trust between physicians and patients is crucial for a therapeutic patient-physician relationship and effective healthcare delivery. However, there is limited research on the prevalence and correlates of physician trust in chronic disease populations, especially among acutely ill hospitalized individuals receiving maintenance dialysis.

Methods: We surveyed 223 hospitalized individuals undergoing maintenance dialysis (59% response rate) at Strong Memorial Hospital, an academic tertiary care center. Our sample included 120 patients (53%) over 65 years, 105 women (47.1%), and 91 (41%) White, 82 (37%) Black/African American and 36 (16%) patients from other self-identified racial groups. Patients had been on dialysis for an average of 3.16 years (SD ± 2.369, IQR 1-4). Physician trust was assessed using the validated Primary Care Assessment Survey (PCAS) trust scale. Dependent variables included quality of life measured by Kidney Disease Quality of Life Scale (KDQOL-36) and 30-days self-reported hospitalizations. Co-variates, included age, gender, race, education, annual household income and time on dialysis.

Results: Out of the 223 respondents, 72 (32%) reported not trusting their doctor, and 91 (41%) reported not trusting their doctor's judgments about their medical care. Linear regression analysis revealed a statistically significant correlations between trust and symptom burden subscale (estimate 0.10, CI 0.05-0.016, $p<0.0002$) and number of hospitalizations in the last 30 days (estimate -0.56, CI -1.08, -0.03, $p<0.037$). Female participants reported lower trust scores than their male counterparts (estimate -1.56, CI -3.07, -0.05, $p<0.043$).

Conclusions: Mistrust of physicians is prevalent among hospitalized patients receiving dialysis care. Hospitalized women receiving maintenance dialysis were more likely to mistrust their physicians than men. Higher trust scores were associated with lower symptom burden while lower scores were associated with greater number of hospitalizations in the last 1 month. Interventions to improve patient-physician communication and patients symptoms may improve trust.

FR-PO416

Self- and Observer-Rated Computer-Based Cognitive Function and Abilities Tests Are Valid for Dialysis Patients

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Background: Cognitive Function and Abilities (CFA) are important factors in health-related quality of life (HRQOL) of dialysis patients and a prerequisite for performing hemodialysis (HD) at home. Congruence of self- and observer-reported CFA is debated for assessment in clinical trials. The purpose of the study was to support the use of a CFA measure in Turkish HD patients.

Methods: We translated the 31-item PROMIS (Patient-Reported Outcomes Measurement Information System) CFA (PROMIS-CFA) subset according to FACIT methodology. PROMIS-CFA was filled in electronically by participants, Addenbrooke's Cognitive Examination-Revised (ACE-R) was assessed by psychologists at the same time during dialysis sessions. HRQOL was assessed with KDQOL-SF. Psychologist called participants on the next day for 16-item Telephone Cognitive Screen (T-Cog-S). Among 1164 patients treated in the 7 dialysis clinics, eligible patients were screened, and 151 in-center conventional HD and 26 home HD patients were randomly selected.

Results: The final sample was composed of 63 females and 114 males with an average age of 55.5±13.4. The average time since kidney disease diagnosis was 10.4±8.2 years and the average time on dialysis was 74.4±66 months. Thirty-four patients had mild cognitive impairment based on categorized ACE-R scores. The internal consistency (Cronbach's α) for the PROMIS-CFA was .96 and the observed test-retest intraclass correlation coefficient over approximately 7 days was r=.70. There were significant but low correlations (r=.2-.28) between ACE-R and PROMIS-CFA scores, but higher correlations with HRQOL (r=.15-.44). T-Cog-S significantly correlated with ACE-R (r=.55), but not PROMIS-CFA.

Conclusions: The Turkish translation of PROMIS-CFA is reliable and may support valid inferences regarding cognitive functioning and abilities in this population. Self-rated CFA is more closely related to HRQOL than observer-rated CFA. Future outcome studies should therefore include both assessments in larger samples. Telephone interviewing with T-Cog-S was not an alternative to clinical evaluation in detecting cognitive impairment due to high ceiling effects.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH

FR-PO417

Improved Quality of Life in Postdilution Compared to Predilution Hemodiafiltration in a European Cohort of Dialysis Patients

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Background: Predilution and postdilution hemodiafiltration (HDF) affect solute removal differently, but the effect on patient reported outcomes is not well described. We describe differences in quality of life in prevalent hemodialysis (HD) patients with predilution and postdilution HDF.

Methods: In a cross-sectional study of 18.018 European prevalent HD patients from an international dialysis network, we identified 5.227 patients with HDF. All 317 patients with predilution HDF were compared to 317 propensity-score matched patients with postdilution HDF. KDQOL-36 results were compared between groups. Multivariable regression models were used to identify independent predictors of symptom/problem list, physical health composite (PHC), and mental health composite (MHC).

Results: Patients were comparable with respect to age, gender, diabetes, comorbidity, vascular access, dialysis vintage, and BMI. Patients with postdilution HDF demonstrated better results for symptom/problem list, PHC, MHC, and most KDQOL SF-36 domains (Figure 1). Multivariable regression revealed independent associations of predilution HDF with lower results for symptom/problem list (coefficient B (95% confidence interval) -6.6 (-9.5 - -3.7), p<0.001), PHC (-3.1 (-4.6 - -1.6), p<0.001), and MHC (-2.4 (-4.1 - -0.7), p=0.006).

Conclusions: We demonstrate improved quality of life in postdilution, compared to predilution HDF in a cross-sectional analysis of a multinational European prevalent hemodialysis population.

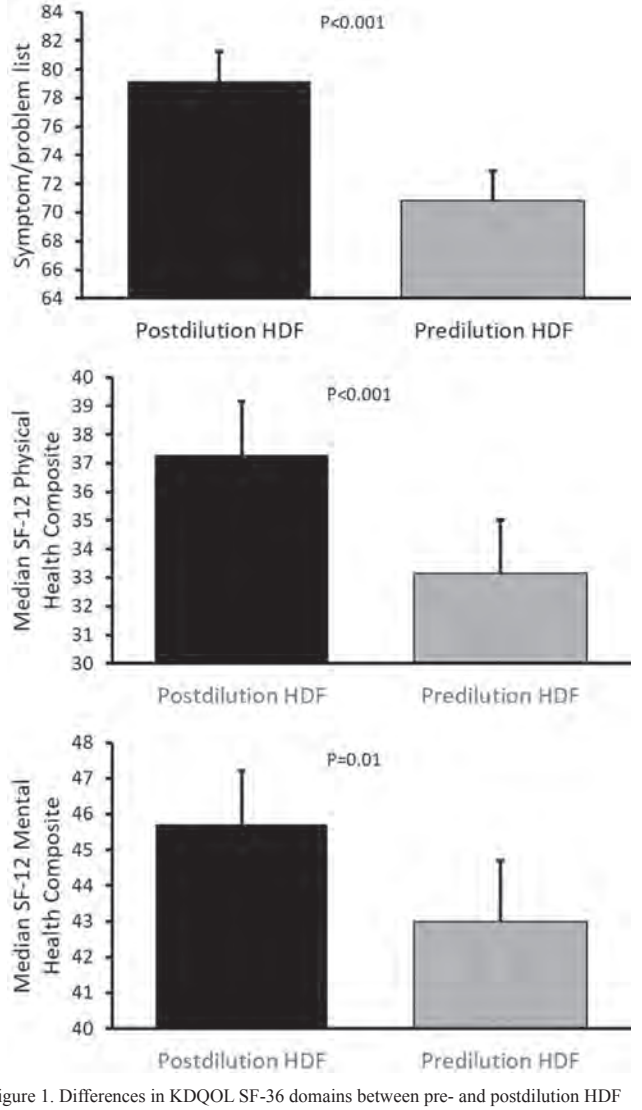

Figure 1. Differences in KDQOL SF-36 domains between pre- and postdilution HDF

FR-PO418

Psychometric Validation of the CONVINCE Inter- and Intradialytic Symptoms Questionnaire

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Background: Symptom assessment, especially from the patient perspective, is crucial in dialysis treatment. A comprehensive questionnaire is needed that covers different symptom types. In the CONVINCE study, we developed a survey based on the KDQOL symptoms scale with an adapted recall period of 7 days for interdialytic symptoms and extended inter- and intradialytic (IDS) items based on literature review and patient interviews.

Methods: Patient-reported outcomes data of 1264 hemodialysis patients were extracted from CONVINCE, an international randomized controlled trial comparing high-dose hemodiafiltration with high-flux hemodialysis, including baseline and quarterly follow-up data up to 24 months. The IDS questionnaire consists of 17 items covering interdialytic symptoms (11 based on KDQOL-36) and 5 newly developed items mainly covering intradialytic symptoms. Reliability, item, and validity analyses were conducted to assess the psychometric properties of the questionnaire. Correlations between IDS and Health-Related Quality of Life (HRQL) domains, measured with the PROMIS questionnaires, were calculated.

Results: Reliability analyses showed high internal consistency, stable over time (Cronbach's α=.86 at baseline, .85-.90 for follow-up visits). Most item-total correlations yielded values from .37-.73, indicating good relationships between individual items and overall score. Item difficulty ranged from .14-.73, revealing a diverse range, ensuring coverage of the symptom spectrum. The survey also showed good validity as correlations between HRQL domains and IDS ranged from .36 to .61. Factor analyses identified 3 symptom clusters (Table 1).

Conclusions: The IDS questionnaire demonstrated good psychometric properties which supports its use in clinical and research settings. By providing a more comprehensive assessment, it is a useful improvement to the KDQOL symptoms scale. Symptoms identified with the questionnaire could be managed in clinical practice and help tailor individualized care.

Funding: Government Support - Non-U.S.

Table 1. Factor Analysis of IDS Questionnaire

IDS Group	IDS	Factor1	Factor2	Factor3
Inter-dialytic symptoms	Soreness in muscles	.75	.01	-.17
	Joint or pain stiffness	.70	.06	-.16
	Numbness in hands or feet	.67	.03	-.13
	Restless legs symptoms	.59	.03	-.01
	Faintness or dizziness	.54	-.05	.09
	Being washed out or drained	.52	.19	.05
	Blurred vision	.50	.01	.04
	Shortness of breath	.47	.07	.10
	Chest pain	.47	-.06	.12
	Headaches	.35	.16	.11
	Cramps	.35	.13	.04
	Nausea or upset stomach	.27	.23	.18
	Lack of appetite	.25	.16	.15
	Problems with sex life	.19	.00	.03
	Dry skin	.01	**.69**	-.02
	Itchy skin	.05	**.63**	-.02
	Hot or cold spells	.24	**.33**	.13
Intra-dialytic symptoms	Cold during dialysis	.02	**.41**	.15
	Blood pressure issues on days without dialysis	.19	-.06	**.61**
	Blood pressure issues during dialysis	.23	-.03	**.54**
	Access site problems	-.09	.14	**.31**
	Smooth dialysis (R)	.12	-.05	-.12

Note. Blue font indicates newly developed items. Factor loadings above .30 are in bold. Reverse-scored items are denoted with an (R).

FR-PO419

Patient-Perceived Benefit of Relief from CKD-Associated Pruritus

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Background: Chronic kidney disease-associated pruritus (CKD-aP) is a substantial burden for the physical and mental well-being of patients with kidney failure. Various instruments have been utilized to assess the impact of itch relief in clinical trials, but regular use in dialysis practice is still uncommon.

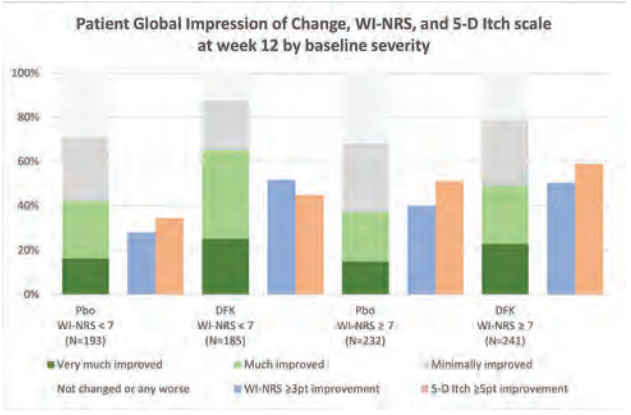
Methods: Phase-3 double-blind, placebo-controlled clinical studies KALM-1 and KALM-2 evaluated the use of IV difelikefalin (DFK) after each dialysis session for 12 weeks compared to placebo (Pbo). Itch intensity at baseline was assessed with the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) and defined as moderate (KALM-1: >4 to <7; KALM-2 ≥5 to <7; N=378) or severe (≥7; N=473). The 5-D Itch scale (range 5 to 25) assessed itch-related quality of life (QoL) and the Patient Global Impression of Change (PGIC) asked patients after 12 weeks how their itch changed (1 [very much improved] to 7 [very much worse]).

Results: A greater percentage of patients achieved a clinically meaningful improvement on the WI-NRS and 5-D Itch with DFK vs. Pbo. More patients with moderate compared to severe CKD-aP at baseline reported an improvement on the PGIC. While PGIC benefit was relatively consistent with WI-NRS and 5-D Itch for severe patients, it was 1.3 to 1.5 times higher for patients with moderate CKD-aP.

Conclusions: While relatively fewer patients with moderate vs. severe CKD-aP reported clinically meaningful improvements on validated scales WI-NRS and 5-D Itch, the share reporting that they feel very much or much improved is notably higher. Asking

patients verbally for their perceived improvement could therefore be more meaningful than clinical scales in daily dialysis practice.

Funding: Commercial Support - CSL Vifor



FR-PO420

Exploring the Skin Symptom Cluster in a Prevalent Hemodialysis (HD) Cohort: The Dominance of CKD-Associated Pruritus and the Association with Fatigue

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Background: Haemodialysis (HD) patients have a high symptom burden. Dominant symptoms may precipitate or intensify others, generating a symptom cluster: the co-existence of ≥2 symptoms. This work explores the *skin symptom cluster* (itching, restless legs, skin changes, difficulty in sleeping) in prevalent HD patients.

Methods: We present prospective symptom data (POS-S Renal) from the CYCLE-HD trial (ISRCTN11299707). Spearman's rank correlations were considered, alongside linear regression (cluster sum score) and proportional odds logistic regression (fatigue sub-score), both adjusted for age, sex, dialysis vintage and BMI.

Results: 118 participants provided symptom data. 77 (65.3%) participants reported ≥2 skin cluster symptoms at baseline. There were positive correlations between each symptom in the skin cluster (all coefficients ≥0.36). A one point difference in baseline itch was associated with a 0.87 increase in total skin cluster score at 6-months; these data, as well as relationships with other symptoms in the cluster, are outlined in Table 1. 70 (59.3%) participants reported fatigue alongside ≥2 skin cluster symptoms at baseline. A unit increase in the skin cluster score at baseline was associated with a 16.1% (3.6-30.1%) higher odds of one unit increase in fatigue at 6-months.

Conclusions: Reporting of symptoms from within the skin cluster is common in the HD population. CKD-aP is the predominant symptom in predicting the persistence and exacerbation of the skin cluster. The skin symptom cluster and fatigue often co-exist and are interdependent. This highlights the importance of elucidating symptom clusters in routine care to improve management of intrusive symptoms.

Funding: Other NIH Support - CYCLE-HD was funded by the National Institute of Health and Care Research (NIHR)

6-month skin symptom cluster score normal linear model

Parameter	Estimate	95% CI	P-value
Intercept	1.36	(-2.29,5.01)	0.4602
BL Itching	0.87	(0.36,1.39)	0.0011
BL Difficulty Sleeping	0.66	(0.19,1.14)	0.0066
BL Restless Legs	0.65	(0.17,1.12)	0.0082
BL Changes in Skin	0.43	(-0.15,1.01)	0.141
Group (ref=Control)	-0.07	(-1.1,0.95)	0.8875
Age	-	-	0.6824
Gender (ref=Female)	0.69	(-0.45,1.83)	0.2307
Dialysis Vintage	-0.03	(-0.23,0.18)	0.7853
BMI	-0.06	(-0.15,0.03)	0.1671

FR-PO421

The Impact of Intradialytic Cycling on the Symptom of CKD-Associated Pruritus

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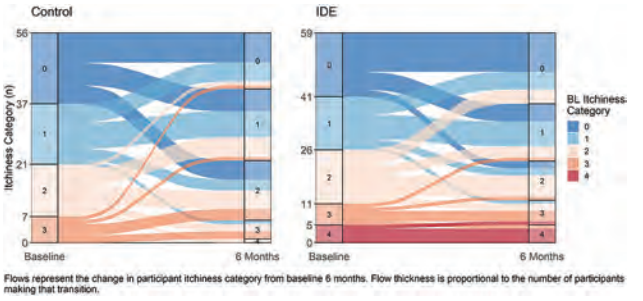
Background: CKD associated pruritus (CKD-aP) is an extremely common symptom amongst haemodialysis (HD) patients. The pathophysiology of CKD-aP is complex and multifactorial; chronic inflammation has been hypothesised as a key contributor. Individuals on maintenance HD experience high levels of chronic inflammation. Previous research has demonstrated that regular intradialytic exercise (IDE) may have an anti-inflammatory effect. This suggests that IDE may reduce levels of CKD-aP in the HD population. This work aimed to ascertain the effect of 6-months of regular IDE on CKD-aP.

Methods: Post hoc analyses of data from the CYCLE-HD (ISRCTN11299707) study. 130 HD patients were randomised to standard care or IDE for 6-months. Data regarding CKD-aP were available from 118 participants who completed the Palliative care Outcome Scale-Symptoms (POS-S) Renal at baseline and 6-months. Statistical testing included proportional odds logistic regression adjusting for baseline itch, age, sex, dialysis vintage and baseline BMI.

Results: At baseline CKD-aP was present in 68.1% of participants (control=66.1%, IDE=70.0%). CKD-aP was classified as mild (27.1%, n=32), moderate (24.6%, n=29), severe (11%, n=13), and overwhelming (3.4%, n=5). There was no statistically significant impact of group assignment on 6-month itchiness; however, the odds of a one category increase in CKD-aP severity was lower (13%) in participants assigned to the IDE group after 6-months (OR=0.87, 95% CI: 0.42, 1.81; p=0.7163). Alluvial plots (Figure) of baseline vs 6-month CKD-aP score categorised by group further demonstrated that group assignment had no marked impact on CKD-aP severity at 6-months.

Conclusions: These results demonstrate that CKD-aP is common in the HD population and 6-months of IDE did not impact on the prevalence or severity. As such, pharmacotherapy should be considered as a primary treatment option.

Funding: Other NIH Support - CYCLE-HD was funded by the National Institute of Health and Care Research (NIHR)



Alluvial plots demonstrating group assignment did not significantly impact CKD-aP severity at 6-months

FR-PO422

The Utilization of Gabapentin and Pregabalin for the Treatment of CKD-Associated Pruritus and Other Indications in Manitoba

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Background: Chronic kidney disease-associated pruritus (CKD-aP) frequently affects patients on dialysis, is associated with reduced quality of life, and was identified as a research priority by patients. Until recently there were no approved treatments for CKD-aP, which was often treated with off-label therapies. Systematic reviews published in 2017-2020 identified GABA (gabapentin, pregabalin) analogues as having evidence for efficacy. This real-world study describes the prescription patterns for GABA over time and their frequency of use for CKD-aP.

Methods: Retrospective cohort study using administrative health data from Manitoba, Canada (>1.2 million residents). We included all adults (≥ 18 years) who received an incident prescription for a GABA between January 1st, 2012, and March 31st, 2022. We calculated the yearly prescription rate per new user for each GABA in total and for each of the following indications: neuropathy, seizure, fibromyalgia, restless legs syndrome (RLS), and chronic pain. Finally, we estimated the total and annual percentage of GABA prescribed for CKD-aP in the chronic dialysis population (defined as dialysis for 90 consecutive days with no gaps >15 days between sessions).

Results: In the study period, there were 125,881 GABA analogue users (adults aged 18 and over). Gabapentin was more commonly prescribed (85%) than pregabalin (15%). The number of new GABA prescriptions increased from 11,301 in 2012 to 12,031 in 2021. Only 0.7% of these were prescribed to treat CKD-aP. There were 4,028 chronic dialysis patients included. Indications for GABA prescriptions in this group were fibromyalgia (24%), seizures (12%), neuropathic pain (9%), RLS (10%) and CKD-aP (19%). Patients receiving GABA for CKD-aP were mostly men (57%) and were older (mean age 60 vs 56 years) than those in the general population. There was a decrease in the proportion of dialysis patients receiving GABA for CKD-aP from 2017 to 2020 (4% to 2.6%) with an increase in 2021 (4%).

Conclusions: GABA are rarely used for CKD-aP (0.7% of all GABA use), despite evidence of efficacy. We speculate that safety concerns may limit GABA use. Further studies of the risks:benefit of GABA analogues in CKD-aP are needed.

Funding: Commercial Support - Otsuka Canada Pharmaceutical Inc.

FR-PO423

Continued Improvement of Itch-Related Quality of Life in CKD-Associated Pruritis (CKD-aP) Patients Treated with Difelikefalin

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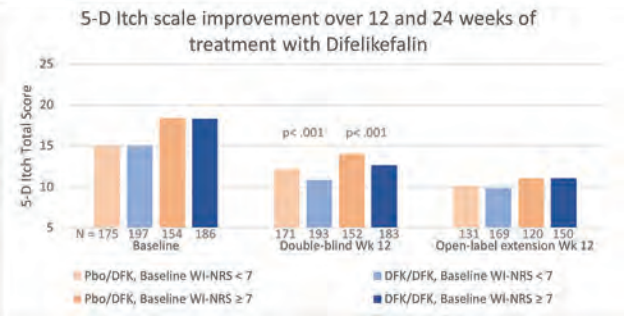
Background: Chronic kidney disease-associated pruritus (CKD-aP) is a serious complication seen in patients with kidney failure. Difelikefalin (DFK) has been approved to treat moderate-to-severe CKD-aP in adults on hemodialysis (HD) based on KALM-1 and KALM-2 randomized, double-blind, placebo (Pbo)-controlled phase-3 trials.

Methods: In KALM trials HD patients received either IV DFK or Pbo 3x per week (wk) for 12 wks followed by an up to 52 wks open-label extension (OLE) with all patients receiving DFK. Baseline itch intensity was defined based on the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) as moderate (KALM-1: >4 to <7; KALM-2 ≥5 to <7) or severe (≥7). Itch-related quality of life (QoL) was assessed by the validated 5-D Itch scale (range 5 to 25). This analysis assesses the 5-D Itch total score at the end of the DB period and wk 12 of the OLE.

Results: At wk 12 patients treated with DFK achieved a significantly greater improvement of QoL compared to Pbo, independent of baseline itch intensity ($p < .001$). After an additional 12 wks therapy in the OLE patients continued to improve, independent of prior exposure to DFK or Pbo and those with severe vs. moderate itch at baseline saw a numerically greater improvement of 5-D Itch scores. Differences between the groups were no longer statistically significant.

Conclusions: Patients with severe CKD-aP benefit from continued treatment with DFK. After an additional 12 wks of treatment they achieve a similar level of benefit as patients with moderate itch severity.

Funding: Commercial Support - CSL Vifor



FR-PO424

Assessing the Quality of Life in Hemodialysis Patients with CKD-Associated Pruritus in Clinical Practice

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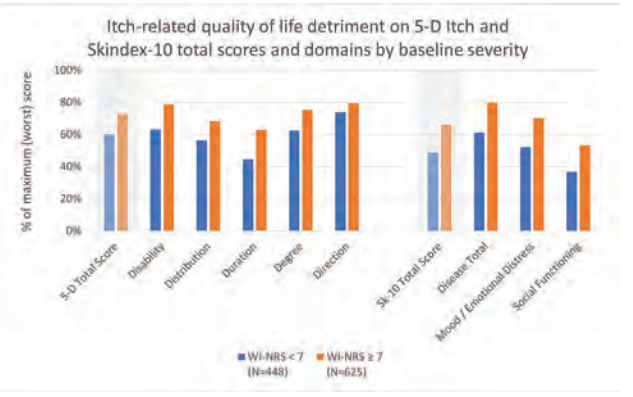
Background: The detrimental impact of chronic kidney disease-associated pruritus (CKD-aP) on the quality of life (QoL) of hemodialysis (HD) patients has been well established in epidemiologic studies. However, diagnosis of CKD-aP and its consequences is not yet routine dialysis practice and no standard instrument is established.

Methods: KALM-1, KALM-2 and 3105 are phase-3 clinical studies evaluating safety and efficacy of difelikefalin in adult HD patients with moderate to severe CKD-aP. Itch intensity at baseline was assessed with the weekly average of the Worst Itching Intensity Numerical Rating Scale (WI-NRS, range 0 [no itch] to 10 [worst itch imaginable]) and defined as moderate (KALM-1: >4 to <7; KALM-2 and 3105 ≥5 to <7; N=448) or severe (≥7; N=625). We set out to compare the association between itch severity and QoL domains in this cohort. Itch-related QoL at baseline was assessed with Skindex-10 (Sk-10; range 0 to 60) and 5-D Itch (5-D; range 5 to 25) scales with higher values indicating worse impact on itch-related QoL.

Results: Patients experiencing moderate / severe itch reported scores of 15.0 / 18.2 (5-D) and 29.3 / 39.7 (Sk-10), equivalent to 60.1% / 72.8% and 48.8% / 66.2% of the maximum for the corresponding scale respectively. Individual domains show a similar pattern. 5-D domains are relatively evenly balanced with Duration being an outlier at the lower end. Sk-10 was most influenced by the disease domain (Figure).

Conclusions: Either instrument can be useful in clinical practice: Sk-10 to complement WI-NRS with a differentiated measure of QoL and 5-D as a standalone option by combining itch intensity and impact on daily activities.

Funding: Commercial Support - CSL Vifor



FR-PO425

Real-World Experience with Difelikeaflin to Treat CKD-Associated Pruritus at a Large Dialysis Organization

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Background: Chronic kidney disease-associated Pruritus (CKD-aP), is a common and burdensome symptom in dialysis patients, however it is often overlooked and underestimated. Difelikefalin (DFK) has been shown in phase 3 clinical trials to decrease pruritus among hemodialysis (HD) patients with moderate to severe CKD-aP after 12 weeks of treatment. The goal of this retrospective database analysis is to assess the effectiveness and prescription pattern of DFK in reducing pruritus in HD pts in routine clinical care.

Methods: Patients (Pts) included in the analysis were Fresenius Kidney Care in-center HD pts aged 18-89 who received >1 dose of DFK before 11/15/2022 and were administered >1 Worst Itching Intensity Numerical Rating Scale (WI-NRS) assessment before first DFK administration. Pts who received >30 DFK administrations within 74-84 days were classified as Complete Regimen Group (CRG), while pts with fewer administrations were Incomplete Regimen Group (IRG). Changes in itch were measured by WI-NRS at 12 weeks compared to the baseline (before DFK start). Safety events were collected through routine post-marketing pharmacovigilance reporting methods.

Results: Patients (Pts) included in the analysis were Fresenius Kidney Care in-center HD pts aged 18-89 who received >1 dose of DFK before 11/15/2022 and were administered >1 Worst Itching Intensity Numerical Rating Scale (WI-NRS) assessment before first DFK administration. Pts who received >30 DFK administrations within 74-84 days were classified as Complete Regimen Group (CRG), while pts with fewer administrations were Incomplete Regimen Group (IRG). Changes in itch were measured by WI-NRS at 12 weeks compared to the baseline (before DFK start). Safety events were collected through routine post-marketing pharmacovigilance reporting methods.

Conclusions: At 12 weeks there is a significant difference in WI-NRS scores between CRG and IRG patients ($p<0.0001$), moreover CRG pts are more likely to continue treatment beyond 12 weeks. Confirming that treatment as prescribed in the pivotal studies ensure more pronounced itch relief and therapy adherence. A better understanding of the reasons for IRG is needed for better patient support.

Funding: Commercial Support - CSL Vifor

FR-PO426

Characterization of Common Adverse Reactions Observed with Intravenous Difelikefalin for the Treatment of CKD-Associated Pruritus in Adults Undergoing Hemodialysis

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Background: Managing side effects associated with medications is critical for optimal outcomes. Here we describe the common adverse reactions with intravenous difelikefalin (IV DFK), a treatment approved in 2021 for chronic kidney disease–associated pruritus (CKD-aP) in adults undergoing hemodialysis.

Methods: Safety data were pooled from two randomized, double-blind, placebo-controlled phase 3 studies (KALM-1, NCT03422653; KALM-2, NCT03636269; DFK=424, placebo=424). The current analysis evaluated the safety of IV DFK administered immediately after dialysis.

Results: Common adverse reactions that occurred in ≥2% of subjects treated with IV DFK and ≥1% higher than with placebo are reported; few were categorized as severe or serious and few led to treatment discontinuation (**Table**). Median time to onset of diarrhea, dizziness, and nausea associated with DFK was 22.5, 22.0, and 39.5 days; median duration

was 3.0, 1.0, and 2.0 days, respectively. Dizziness occurred more often in subjects using concomitant CNS-depressant medications (overall relative risk [ORR] 2.09); hyperkalemia and somnolence were more frequent with concomitant opioids (ORR 1.79 and 2.73, respectively) versus without these medications.

Conclusions: IV DFK was well tolerated with most common adverse reactions reported as mild to moderate, did not lead to discontinuation compared with placebo, and rarely occurred during dialysis sessions. Diarrhea, dizziness, and nausea occurred mostly during the first month of therapy; the duration was ≤3 days, suggesting they typically resolved while IV DFK treatment was ongoing. Concomitant medication use may increase the likelihood of certain adverse reactions. These findings provide additional information to prescribers on the common side effects of IV DFK, which could improve the management of CKD-aP in dialysis patients.

Funding: Commercial Support - Cara Therapeutics

Table.

Common Adverse Reactions	Subjects With Adverse Reactions		Severe		Serious		Leading to Discontinuation	
	Placebo n (%)	DFK n (%)	Placebo n (%)	DFK n (%)	Placebo n (%)	DFK n (%)	Placebo n (%)	DFK n (%)
Diarrhea	24 (5.7)	38 (9.0)	3 (0.7)	4 (0.9)	3 (0.7)	3 (0.7)	1 (0.2)	1 (0.2)
Dizziness	18 (3.8)	29 (6.8)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	1 (0.2)	4 (0.9)
Nausea	19 (4.5)	28 (6.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Gait disturbances[a]	23 (5.4)	28 (6.6)	4 (0.9)	1 (0.2)	1 (0.2)	3 (0.7)	0 (0.0)	1 (0.2)
Hyperkalemia	15 (3.5)	20 (4.7)	2 (0.5)	7 (1.7)	8 (1.9)	8 (1.9)	1 (0.2)	0 (0.0)
Headache	11 (2.6)	19 (4.5)	0 (0.0)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.5)
Somnolence	19 (2.4)	18 (4.2)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.2)	0 (0.0)	0 (0.0)
Mental status change[b]	6 (1.4)	14 (3.3)	1 (0.2)	3 (0.7)	2 (0.5)	6 (1.4)	1 (0.2)	3 (0.7)

N=424 in the placebo treatment group and N=424 in the DFK treatment group.
[a]Gait disturbances include preferred terms of falls and gait disturbances.
[b]Mental status change includes preferred terms of confusional state and mental status change.

FR-PO427

Burden of CKD-Associated Pruritus and Adverse Clinical Outcomes in Patients Receiving Dialysis: The SCREAM Project

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Background: Pruritus, a strong sensation of itching, is a common complain of patients on dialysis, but their prevalence and consequences are not well known. We aimed to quantify the burden of clinically recognized pruritus and associated adverse clinical outcomes in a region-representative cohort of patients on dialysis.

Methods: Observational study of all patients receiving maintenance dialysis in Stockholm, Sweden, during 2006-2021. Pruritus was identified by clinical diagnoses, two consecutive dispenses of pruritus-medications, or use of UV-therapy. Study outcomes were incident diagnoses of depression and sleep disorders, serious infection-related hospitalizations (composite of endocarditis, peritoneal dialysis-related peritonitis, hemodialysis / peritoneal dialysis-related catheter infection, sepsis due to *Staphylococcus Spp.*, or skin infection), and all-cause mortality. Multivariable Cox regression models with time-varying exposures explored the association between prevalent/new-onset pruritus and adverse clinical outcomes.

Results: Among 3281 dialysis patients (median age 64 years, 66% men, 69% on hemodialysis, mean dialysis vintage 2.2 years), 456 (13.8%) had pruritus at enrollment. During median follow-up of 8.3 [IQR: 4.2-13.2] years, additional 637 (22.5%) patients developed pruritus. Prevalent and new-onset pruritus patients were at a higher risk of suffering sleep disorders (N=1294, HR: 2.02 [95%CI 1.70-2.41]), developing depression (N=752, HR: 1.70 [1.40-2.07]) and being hospitalized for serious infections (composite N=872, HR: 1.40 [1.23-1.60]), the latter attributed to higher risk of catheter-related infections, peritonitis and sepsis. No association was observed with endocarditis or all-cause mortality.

Conclusions: At least one third of dialysis patients suffer from CKD-associated pruritus during their lifetime. Patients with pruritus are at increased risk of infections, depression and sleep disorders.

Funding: Commercial Support - Vifor Pharma

FR-PO428

Dialyzer Performance and Associations in Self-Reported Pruritis and Fatigue: Results from the eMPORA III Trial

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Background: eMPORA III was a multi-center crossover trial with 4-week randomized treatment periods comparing dialyzer performance (FX CorAL 600 vs two comparable high-flux dialyzers) in post-dilution online hemodiafiltration (HDF). Primary outcome was beta-2 microglobulin (B2M) removal and self-reported itching and fatigue were also studied.

Methods: Adults on HDF were recruited from 8 centers in Europe (NCT04714281). B2M removal rate (B2M RR) 0 vs 240 min was measured in week 3 (mid-week) of each period. Pruritus Numerical Rating Scale (PNRS) & KDQOL-SF fatigue domain (questions 9a, e, g & i) were captured at baseline & end of periods. Peak/average PNRS surveys capture the worst/average itch in the prior 24 hours on a 0 (no itch) to 10 (worst itch imaginable) point scale. Fatigue survey captures the energy level in the last month on a 0 (least energy) to 100 (most energy) point scale. Analysis used mixed effects model adjusted for center and patient.

Results: Trial enrolled 82 subjects (76 ITT group, mean age 67.0±15.6 years, 26.3% female, 34.2% diabetes). FX CorAL 600 showed a +0.60±0.39% and +1.82±0.38% higher B2M RR vs FX CorDiax 600 (non-inferiority p<0.0001; superiority p=0.0606) and xevonta Hi 15 (non-inferiority p<0.0001; superiority p<0.0001). Mean peak PNRS score was 1.0±1.94, and fatigue score was 63.8±21.41 (**Figure 1**). FX CorAL 600 showed a -0.08 and +0.08 point change in peak PNRS scores vs FX CorDiax 600 (p=0.66) and xevonta Hi 15 (p=0.65); consistent findings were seen for average NRS scores. FX CorAL 600 showed a -0.01 and +0.30 point change in fatigue scores vs FX CorDiax 600 (p=0.95) and xevonta Hi 15 (p=0.86).

Conclusions: FX CorAL 600 provides a higher B2M RR than the comparators. PNRS & fatigue scores were consistent between dialyzer types. Total PNRS & fatigue values indicate mild-to-no itching and reasonable vitality among participants. Nonetheless, some unique patients reported severe itching and fatigue symptoms. Higher middle molecule clearance may not affect these outcomes. However, more studies are needed with longer follow-up should consider focusing on patients with remarkable symptoms.

Funding: Commercial Support - Fresenius Medical Care

Figure 1: Pruritus Numerical Rating Scale and KDQOL-SF v1.3 Fatigue Domain Scores by Dialyzer

Dialyzer		FX CorAL 600	FX CorDiax 600	xevonta Hi 15	Overall
Patient n		74	71	76	82
Observation n		71	71	76	218
Peak PNRS	Mean±SD	0.9±2.03	1.1±1.92	0.9±1.89	1.0±1.94
	Min, Median, Max	0.0, 0.0, 10.0	0.0, 0.0, 8.0	0.0, 0.0, 7.0	0.0, 0.0, 10.0
Average PNRS	Mean±SD	1.0±2.04	1.2±1.94	0.9±1.86	1.0±1.94
	Min, Median, Max	0.0, 0.0, 10.0	0.0, 0.0, 8.0	0.0, 0.0, 8.0	0.0, 0.0, 10.0
KDQOL Fatigue	Mean±SD	63.7±20.35	64.2±22.78	63.6±21.32	63.8±21.41
	Min, Median, Max	10.0, 65.0, 100.0	0.0, 60.0, 100.0	10.0, 60.0, 100.0	0.0, 65.0, 100.0

Max, maximum; min, minimum; N, number of patients; PNRS, Pruritus Numerical Rating Scale; SD, standard deviation.

FR-PO429

Clinical Performance and Patient-Reported Sleep Quality Associated with Dialyzer Types: Results from the eMPORA III Trial

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Background: eMPORA III was a prospective, multi-center, open, crossover trial with 4-week randomized treatment sequences comparing the clinical performance and hemocompatibility of dialyzers (FX CorAL 600 vs FX CorDiax 600 and xevonta Hi 15) in post-dilution online hemodiafiltration (HDF). Primary outcome of beta-2 microglobulin (B2M) removal showed FX CorAL 600 was non-inferior vs its comparators and superior vs. xevonta Hi 15. We assessed the additional patient-reported outcomes on sleep quality per Pittsburgh Sleep Quality Index (PSQI).

Methods: We recruited clinically stable adults on HDF from 8 centers in Europe (NCT04714281). PSQI was measured at baseline and at the end of each 4-week treatment sequence. PSQI survey assesses impairment of sleep quality in the prior month on a 0 (worst) to 21 (best) point scale and has 7 component subscales. PSQI scores >5 points show poor sleep quality. A linear mixed model adjusted for random effects of the center and patient estimated the effect of the dialyzer on PSQI scores.

Results: Study enrolled 82 subjects (76 in the ITT group, mean age 67.0±15.6 years, 26.3% female, 34.2% diabetes). Mean total PSQI score was 5.7±3.77 (**Figure 1**). FX CorAL 600 showed a -0.07 and -0.02 point lower PSQI scores vs FX CorDiax 600 (p=0.75) and xevonta Hi 15 (p=0.93). The 7 PSQI component scores showed consistent patterns with the total score, no differences by dialyzer.

Conclusions: PSQI scores were consistent between dialyzers. Total PSQI values indicate borderline poor sleep quality among trial participants; this appeared to be driven by small additive disturbances in all domains of component scores, especially for subjective sleep quality, latency, duration, and disturbances. FX CorAL 600 has previously shown higher B2M removal vs. comparators. Higher middle molecule clearance may not affect sleep quality outcomes, yet further studies are needed with longer follow-up times and could consider severity of symptoms (i.e., need for improvement).

Funding: Commercial Support - Fresenius Medical Care

Figure 1: Pittsburgh Sleep Quality Index Scores by Dialyzer

Dialyzer		FX CorAL 600	FX CorDiax 600	xevonta Hi 15	Overall
Patient n		74	71	76	82
PSQI observation n		71	71	76	218
Total PSQI score	Mean±SD	5.8±3.75	5.8±3.77	5.6±3.83	5.7±3.77
	Min, Median, Max	0.0, 5.0, 17.0	0.0, 6.0, 17.0	0.0, 5.0, 19.0	0.0, 5.0, 19.0
Subjective sleep quality	Mean±SD	1.0±0.60	1.0±0.73	1.0±0.66	1.0±0.66
	Min, Median, Max	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0
Sleep latency	Mean±SD	1.1±1.07	1.1±1.02	1.0±1.04	1.1±1.04
	Min, Median, Max	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0
Sleep duration	Mean±SD	1.1±0.99	1.0±0.98	1.1±0.99	1.0±0.98
	Min, Median, Max	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0
Habitual sleep efficiency	Mean±SD	0.6±0.92	0.6±0.94	0.6±0.95	0.6±0.94
	Min, Median, Max	0.0, 0.0, 3.0	0.0, 0.0, 3.0	0.0, 0.0, 3.0	0.0, 0.0, 3.0
Sleep disturbances	Mean±SD	1.0±0.55	1.1±0.56	1.0±0.47	1.0±0.52
	Min, Median, Max	0.0, 1.0, 2.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 3.0
Use of sleeping medication	Mean±SD	0.3±0.89	0.4±0.93	0.3±0.86	0.3±0.89
	Min, Median, Max	0.0, 0.0, 3.0	0.0, 0.0, 3.0	0.0, 0.0, 3.0	0.0, 0.0, 3.0
Daytime dysfunction	Mean±SD	0.6±0.74	0.7±0.74	0.6±0.74	0.7±0.74
	Min, Median, Max	0.0, 1.0, 3.0	0.0, 1.0, 3.0	0.0, 1.0, 2.0	0.0, 1.0, 3.0

Max, maximum; min, minimum; N, number of patients; PSQI, Pittsburg Sleep Quality Index; SD, standard deviation.

FR-PO430

Risk Factors for Impaired Cerebral Autoregulation and Its Relationship to Cognitive Decline and Brain Atrophy in Hemodialysis Patients

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Background: The hemodialysis (HD) population has evidence of increased cerebral atrophy and cognitive impairment. Understanding if cerebral vascular function and cerebral perfusion during HD may help us understand the pathophysiology of brain atrophy and cognitive impairment. We evaluate cerebral autoregulation (CA) during HD patients in relationship to cerebral structure and cognitive performance.

Methods: In a cross-sectional study, HD patients age 50 years and older receiving incenter HD were included. Cerebral perfusion during HD was measured using cerebral oximetry and an index of CA was calculated based on the correlation between concurrent cerebral oxygen saturation and intradialytic blood pressure. Potential risk factors for worse CA were measured through linear mixed models including patient-level random effects with a compound symmetry covariance structure to account for the correlation in repeated measures from each patient. Additionally, associations between CA and changes in neurocognitive scores as well as white and gray brain matter volumes over 12 months were measured. P-value < 0.05 was considered significant.

Results: We included 46 participants and 121 HD sessions in our analysis. The mean ± SD decline in cerebral oxygen saturation during HD was 7.02% ± 3.16%. An impaired CA index (> 0.4) was noted in 45% of HD sessions. Only diabetes mellitus as a comorbidity survived the linear mixed model method for predicting impaired CA when adjusting for demographics, albumin, dialysis treatment, and oxygen saturation with an OR 1.35 ($p < 0.01$). The Baseline CA index was negatively correlated with worse picture vocabulary scores at 12 months ($r = -0.44$, $p = 0.03$). There was no association between CA index and brain integrity including white and gray matter volume, gray matter thickness, and abnormal voxels at either baseline or 12 months.

Conclusions: Diabetes is associated with worse CA during HD. A worse (higher) CA index correlated to declining cognitive function in HD patients. Further research is needed to understand these relationships in order to reduce cerebral atrophy and cognitive impairment in HD patients.

Funding: NIDDK Support

FR-PO431

Association of Cognitive Impairment with Subsequent Cardiovascular Disease (CVD) Hospitalization: A Prospective ESKD Cohort Study

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Background: Cognitive impairment (CI) and stroke are common among patients with ESKD receiving hemodialysis. Whether worsened CI can be a clinical indicator of increased risk of stroke and other cardiovascular disease (CVD) events in patients with ESKD is unknown.

Methods: Participants were incident hemodialysis patients from a prospective cohort study, the PACE Study. To assess CI, we used validated tests, the Multiple Mini-Mental State Exam (3MS) and Trail Making Test (TMT) Parts A and B. We used Cox proportional-hazards regression models to evaluate the association of CI at baseline with incident CVD events, adjusting for demographic characteristics, education, depression, and hypercholesterolemia.

Results: Among 568 participants, the average age was 56.3 years (SD: 13.5 years; range: 20-90 years), and most participants are black (n=393; 69.2%) or white (n=161, 28.3%). Over a median follow-up of 2.9 years, 120 (21%) CVD hospitalizations occurred among the 568 participants. Worse TMT-A scores, indicating more severe CI, were associated with subsequent CVD hospitalization on unadjusted analysis (HR=1.08; 95% CI: 1.02-1.06). Similarly, those classified as cognitively "deficient" were at higher risk for subsequent CVD hospitalization, even after further adjustments for a history of diabetes, smoking, prevalent stroke, and atrial fibrillation (HR=1.53; 95% CI: 1.13-2.08). On interaction analysis, the TMT-A scores of patients without diabetes (HR=1.38; 95% CI: 1.02-1.87) were associated with future CVD events. The 3MS test and TMT-B results did not show an association between CI and future CVD hospitalization.

Conclusions: In this study, patients with ESKD new to hemodialysis with worse TMT-A scores were more likely to have future CVD hospitalizations. Further studies should gauge whether this practical bedside test case helps predict a patient's cardiovascular risk.

Funding: NIDDK Support, Private Foundation Support

FR-PO432

Plasma Refill and Changes in Cognition During Hemodialysis

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Background: Rapid ultrafiltration during hemodialysis has been associated with impaired cerebral perfusion. The effects of dialysis-associated hypoperfusion may be enhanced during acute illness due to factors that impair the ability to refill the vascular space (i.e., plasma refill). We sought to investigate whether changes in plasma refill are associated with detectable changes in cognitive function in hospitalized patients receiving intermittent hemodialysis.

Methods: We conducted a prospective pilot study of hospitalized patients receiving intermittent hemodialysis at the University of Pennsylvania. Blood pressure was monitored every 15min throughout hemodialysis. Hematocrit monitoring (using CritLine-IV) and ultrafiltration volumes were used to calculate interval plasma refill rates. Digitized cognitive tests were administered at regular intervals during each session; specifically, the Psychomotor Vigilance Test was used to measure reaction time (delayed reaction defined as the bottom 25% or >50ms slower performance) and the Trail Making Tests A/B were used to measure executive function (impaired function defined as the bottom 25% or >10s difference in completion time). Mixed effects logistic regression was used to examine the relationship between interval change in cognitive function and plasma refill rate.

Results: In interim analysis, among 92 participants enrolled, 60 participants were able to complete at least two sets of cognitive testing. The mean age was 56.9±14.9 yr, 50.5% were female, 53% were Black and 40% were White, and 67% were receiving maintenance hemodialysis versus 33% for acute kidney injury. In the first half of hemodialysis, low plasma refill rate, defined as a plasma refill-to-ultrafiltration ratio < 0.75 was associated with delayed reaction time (OR 4.56, 95% CI 1.11-18.90, $p = 0.035$) and slower executive function but the latter did not reach statistical significance (OR 2.53, 95% CI 0.0.51-12.47, $p = 0.253$). These associations were independent of age, sex, acute versus chronic hemodialysis, and blood pressure.

Conclusions: These preliminary results offer insight into how changes in plasma refill might relate to tissue perfusion leading to detectable changes in cognition, particularly areas affected by the frontotemporal regions of the brain that are particularly susceptible to ischemic injury. Further evaluation in a larger cohort is needed to better evaluate the potential link.

Funding: NIDDK Support

FR-PO433

Sexual Dysfunction in People Treated with Hemodialysis

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Background: End Stage Kidney disease is associated not only with increased mortality, but also with higher symptom burden, particularly for people treated with hemodialysis (HD). Sexual dysfunction (SD) is common but often underrecognized among people with kidney disease. SD is a person's inability to fully engage in sexual activities in one or more categories: desire, arousal, orgasm, and pain disorders. Reported rates of SD vary widely, between 5% - 85%.

Methods: This is a secondary analysis of a project describing symptom burden in patients on HD (Anxiety, Comorbid Depression, and Dialysis Symptom Burden) with a focus on the prevalence of sexual dysfunction. In total, 92 people being treated with hemodialysis in New York City answered questions about their sexual functioning as measured by the Dialysis Symptom Inventory.

Results: The sample was comprised of 44% women (60.8 years ± 14.1) and 56% men (60.0 years ±17.1). 38% of the total sample reported Decreased Interest in Sex (31% of the women, 45% of the men) and 32% reported Difficulty Becoming Aroused (21% of the women and 43% of the men). Of those that indicated Decreased Interest in Sex, 81% of the women and 45% of the men described being significantly bothered by it. Of those that indicated Difficulty Becoming Aroused, 25% of the women and 60% of the men described being significantly bothered by it.

Conclusions: There has been some debate as to whether decreased interest in sex should be categorized as a sexual dysfunction in people with ESKD being treated with HD. Our data find that Decreased Interest in Sex is both present and bothersome in 25% of the women surveyed and 19% of the men. Clinically significant Difficulty Becoming Aroused was reported by 5% of women and 26% of men. More detailed assessments of all the domains of SD are needed, and an exploration of the interest in intervention.

Figure 1: Prevalence and Associated Distress for Decreased Interest in Sex by Gender

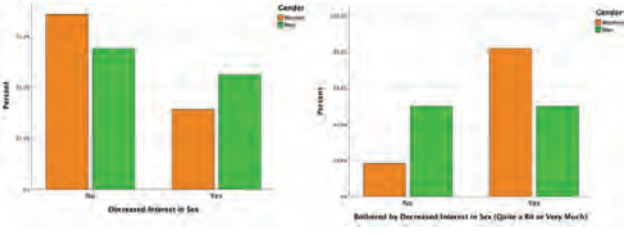
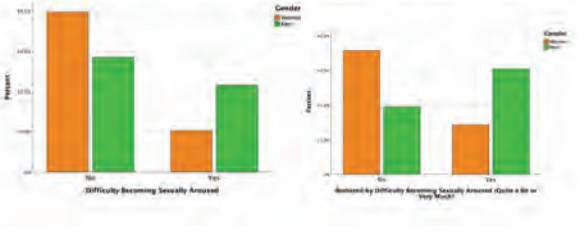


Figure 2: Prevalence and Associated Distress for Sexual Arousal Difficulty by Gender



FR-PO434

Engagement in CBT-I in the SLEEP-HD Trial for People on Long-Term Hemodialysis with Insomnia

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Background: Patients with end-stage kidney disease treated with hemodialysis (HD) experience distressing symptoms including sleep disturbances. Unique aspects of HD treatments and schedules possibly contribute to the high prevalence of insomnia. Cognitive-behavioral therapy for insomnia (CBT-I) is a first-line therapy but largely inaccessible to HD patients, partly due to significant dialysis treatment time. CBT-I delivered by telehealth could overcome barriers to access, but the level of engagement has not been tested for these patients.

Methods: SLEEP-HD was a parallel-group randomized controlled trial (RCT) wherein 126 HD patients treated in community-based dialysis facilities in Seattle and Albuquerque were randomized 1:1:1 to 6-week treatment with telehealth delivered CBT-I, trazodone, or medication placebo. Primary goals were to compare the efficacy of a 6-week treatment with telehealth CBT-I vs. trazodone vs. placebo for the treatment of chronic insomnia at treatment conclusion and follow-up. Herein we describe data available on CBT-I engagement of the study participants.

Results: 43 SLEEP-HD participants were randomized to the 6-week CBTI telehealth intervention with 51% women and 49% men (average age: 60.1 years (SD 15.2)). The protocol called for 6 sessions over 6 weeks and 74% of participants had all 6 sessions, while 5% had none. Participants were asked to keep sleep diaries during the intervention period and 40% kept for all weeks and 19% kept none. After each session, study therapists rated their perception of the participant's level of engagement and effort in following previous week's treatment recommendations ("homework"). Engagement scores across the six sessions indicated that 98% of participants were, on average, at least somewhat engaged during the sessions and 83% were well-engaged. The average homework scores indicated that 18% of the participants were rated as not putting in significant effort, and 43% were rated as putting in considerable effort.

Conclusions: CBT-I can be demanding and patient engagement is an important part of the treatment model. In this telehealth administered CBT-I protocol adapted for people on long-term HD, overall levels of engagement in the sessions seemed high, although the level of skills practice and follow through on sleep recommendations was more limited.

Funding: NIDDK Support

FR-PO435

Reducing Frequency of Surveillance Bloodwork in Chronic In-Centre Hemodialysis (ICHD) Patients from Every Six to Eight Weeks: A Quality Improvement Study

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Background: Regular surveillance bloodwork is vital for hemodialysis patients to monitor complications such as anemia, chronic kidney disease-mineral and bone disorder (CKD-MBD), and electrolyte abnormalities. Previous studies have shown that reducing the frequency of bloodwork from every 4 to 6 weeks did not negatively affect the achievement of anemia and CKD-MBD targets. However, the impact of further reducing routine bloodwork frequency to every 8 weeks has not been explored. This study aims to assess the impact of reducing routine bloodwork frequency from every 6 to 8 weeks in chronic in-center hemodialysis (ICHD) patients on achieving anemia and CKD-MBD targets.

Methods: In this prospective cohort study, the Alberta Kidney Care-South program, which includes 7 hemodialysis centers in Calgary, reduced routine bloodwork frequency for chronic ICHD patients from every 6 to 8 weeks. We compared the impact of this change in the intervention cohort (Dec. 1, 2020 – Nov. 5, 2022) to a control cohort (Oct. 31, 2019 – Oct. 31, 2020). Primary outcomes were proportion of patients within the target range for anemia and CKD-MBD, frequency of hyperkalemia, and cost savings attributable to the change in frequency of bloodwork. Logistic regression mixed models were used to assess the effect of reduced bloodwork frequency on the odds of achieving anemia and CKD-MBD targets, adjusted for demographic and clinical characteristics.

Results: A total of 787 control patients and 956 intervention patients were included. During the intervention period, the odds of achieving target ranges for hemoglobin, calcium, and phosphate decreased by 13% [95% CI: 0.83, 0.91] (P-value < 0.001), 17% [95% CI: 0.76, 0.90] (P-value < 0.001), and 6% [95% CI: 0.89, 1.00] (P-value = 0.050), respectively, compared to the control period. No significant change was observed in achieving target ranges for parathyroid hormone and iron saturation.

Conclusions: Reducing routine bloodwork frequency from every 6 to 8 weeks in chronic ICHD patients was associated with lower odds of achieving anemia and CKD-MBD targets. However, the clinical significance of these findings is unclear. Further studies are needed to elucidate the ideal frequency of surveillance investigations in this patient population.

FR-PO436

Impact of 10-Step Sleep Hygiene Intervention on Insomnia and Muscle Strength of ESRD Patients: A Quasi-Interventional Study

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Background: End-stage renal disease is a significant health issue that affects millions worldwide, the 10 step sleep hygiene interventions is a simple, low-cost strategy for better sleep habits that can potentially enhance the overall health of this patient group. The purpose of this study is to evaluate the impact of a 10-step sleep hygiene intervention on hemodialysis patients and simultaneously evaluate its impact on insomnia severity and muscle power. There is dearth of research in this specific area therefore our study can provide valuable insights in this regard.

Methods: The study used a pre-post quasi-interventional design. Participants' demographic data, sleep quality, physical activity, depression score, medication and addiction history were collected using structured questionnaire before, and 1 month after the intervention. The muscle strength was measured using a handheld dynamometer. The intervention was a validated 10-step sleep hygiene strategy, which was delivered in a face-to-face physician-patient interview.

Results: Out of the 146 patients recruited, 141 completed the study. Majority of the participants were male, married, aged 35-55, had secondary education, and were retired. All of them engaged in mild physical activity, with average dynamometer readings of 10kg, and most were non-smoker with moderate insomnia, sleeping 5-6 hours per night. After the intervention, insomnia scores significantly improved (p=0.004), and muscle power saw a slight improvement. Participants transitioned from moderate to subthreshold insomnia, and average sleep duration increased to 7 hours. However, muscle strength improved in only about 15% of participants and only 8% reported some improvement in depression score.

Conclusions: The study underscores the importance of sleep hygiene in routine care for hemodialysis patients. The 10-step sleep hygiene intervention was found to effectively improve sleep quality and slightly improve muscle strength in this population. The intervention was particularly effective in reducing insomnia in women and improving muscle power in men. Younger participants(18-35 years) showed the greatest overall improvement. This suggests that tailored, age-specific sleep hygiene interventions can yield better results in the future.

FR-PO437

Holographic Biology Theory-Based Auricular Acupoint Therapy Relief Insomnia Symptoms in Hemodialysis Patients

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Background: Insomnia is a common symptom among patients undergoing hemodialysis, which significantly affects their mental and physical well-being. Several studies, including DOPPS have found that sleep quality is not only related to the quality of life but also impacts patient survival rates.

Methods: A total of 42 hemodialysis patients who did not regularly take sleeping pills such as zolpidem were selected as study subjects, including 15 males (35.72%) and 27 females (64.28%), aged 46-83 years with a mean age of (63.76±2.54) years. Following the PFEIO principle, an treatment team was set up to process the treatment. Hamilton Anxiety/Depression Scale (HAMA/HAMD), polysomnography (PSG), and the Pittsburgh Sleep Quality Index (PSQI) and Sleep Rating Scale (SRSS) were used to assess sleep quality and self-rated insomnia severity. Ear acupuncture treatment was proceeded once a week, 4 weeks for a course. The TCM physician carried out a preliminary evaluation of the ears, based on tongue diagnosis, and the senior nurse performed the treatment.

Results: PSG showed that total sleep time (TST), sleep efficiency (SE), NREM stage 2 sleep as a percentage of TST (N2% of TST), NREM stage 3 sleep as a percentage of TST (N3% of TST), and REM sleep as a percentage of TST (REM% of TST) were all increased after treatment, and sleep time was longer than before treatment ($P < 0.05$). Refer to Table 1 for details. PSQI scores showed improvement in sleep quality, increase in sleep duration and efficiency, reduction in sleep disturbances, decrease in the use of hypnotic drugs, and improvement in daytime functioning. The overall score was statistically significant ($P < 0.05$). Refer to Table 2 for details. SRSS showed decrease in insufficient sleep time, significant improvement in sleep quality.

Conclusions: The application of auricular acupoint therapy based on holographic biology theory can relief insomnia symptoms and effectively improve the sleep quality of HD patients with insomnia. The therapy has the advantages of safety, convenience, and low cost, and can be easily promoted and popularized in clinical practice. However, The specific mechanism needs further study.

Comparison of PSG-related data in 42 hemodialysis patients with insomnia.

Number of cases	Group	TST	SE	N1% of TST	N2% of TST	N3% of TST	REM % of TST
42	Before treat	317.64±13.14	65.22±5.70	29.33±4.34	41.24±4.56	10.89±5.11	18.54±6.14
42	After treat	443 .31±12.15	73.83±4.66	21.04±5.02	4 4 .31±4.62	13.63±4.46	22.02±5.47

FR-PO438

Frailty in Patients on Dialysis Surviving for More than 40 Years Is Common and Severe: A Nationwide Study

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Background: The number of end-stage kidney disease (ESKD) patients with a more prolonged dialysis vintage have been increasing. Recently, the Japan Society for Dialysis Therapy (JSDT) survey reporting patients on dialysis for over 40 years has been presented, and there are few reports that describe their characteristics, especially regarding physical function. This study aimed to evaluate the clinical features of ESKD patients on dialysis for 40 years or more and the associations between dialysis vintage and frailty using the JSDT Renal Data Registry database.

Methods: A cross-sectional study was conducted. The analysis included data of 227,136 patients aged over 50 on dialysis in 2018. The dialysis vintage exposure was categorized as: 0–<5 years; 5–<10 years;10–<20 years; 20–< 30 years; 30–<40 years; and above 40 (40–) years. The primary outcome was frailty, defined as grade 2 or higher according to the Eastern Cooperative Oncology Group Performance Status (ECOG PS) scale. The secondary outcome was bedridden, defined as grade 4 on the ECOG PS scale. Modified Poisson regression models adjusted for potential covariates were used to estimate the adjusted prevalence ratios (aPRs) for frailty and bedridden. The clinical characteristics of patients with dialysis vintage of 40 years or more were compared with those in other dialysis vintage categories.

Results: Total 809 (0.36%) ESKD patients were on dialysis for 40 years or more. This group showed a lower proportion of men and presence of diabetes. Histories of fractures and carpal tunnel syndrome were more frequent in the 40– years than in the other groups. The prevalence of frailty was most common in the 40– years group (54.6%), and the prevalence of bedridden was similar (9.9%). The dialysis vintage 40- years vs. 0-<5 years was associated with increased frailty (aPR [95% confidence interval]: 2.41 [2.25-2.58]), and bedridden (aPR [95% confidence interval]: 2.12 [1.72-2.60]).

Conclusions: This large nationwide study found an association between dialysis vintage and frailty in dialysis patients. Long-term dialysis therapy, particularly for over 40 years, may accelerate the decline of physical function, probably due to unmeasured dialysis-related factors.

FR-PO439

"A Ray of Hope": A Qualitative Study of Hemodialysis Patients' Attitudes Toward a Clinic-Based Animal-Assisted Intervention

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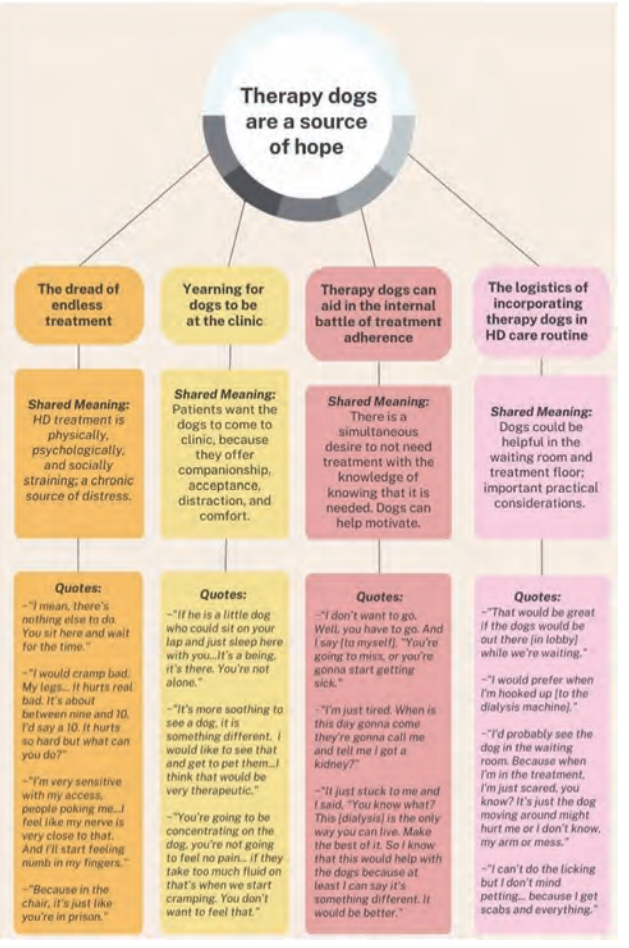
Background: Adherence to one's hemodialysis [HD] regimen is paramount to overall health and well-being for individuals receiving HD in the U.S. Patients may struggle maintaining the strenuous regimen, and ways to effectively reduce rates of missed treatments are needed. The purpose of this study was to explore HD patients' attitudes toward a clinic-based animal-assisted intervention [AAI].

Methods: HD patients from 4 outpatient clinics engaged in 1-on-1 in-depth semi-structured interviews, which were audio-recorded and transcribed verbatim. Interviews took place at the dialysis clinics, including while patients were dialyzing. Within a framework of iterative content analysis, the Matrix Method was utilized in combination with line-by-line coding to thematically analyze data.

Results: Twenty patients aged 57 ± 7.93 years participated in interviews. Their narratives collectively illustrate the perceived value of AAI in the HD setting. Under the larger theme "Therapy dogs are a source of hope", there are 4 subthemes: (i) *The dread and suffering of endless treatment*; (ii) *Yearning for the presence of therapy dogs at the clinic*; (iii) *Therapy dogs can aid in the internal battle of treatment adherence;* (iv) *The logistics of incorporating therapy dogs into the HD care routine*.

Conclusions: This study improves our understanding of how HD patients feel about receiving clinic-based therapy dog visits while also offering helpful insights for implementing this intervention in future research. Incorporating therapy dogs into HD patients' healthcare routine may offer a complementary and integrative approach to improving patient outcomes. Findings highlight the importance of patient-centered care for this population.



FR-PO440

Animal-Assisted Intervention for Hemodialysis Patients' Treatment Adherence, Pain, and Depression

Meredith L. Stensland,[1] Adrian E. Elorriaga,[2] Martha Block,[2] Geoffrey A. Block,[2] Don D. Mcgeary,[1] Jacie Flaman.[3] *[1]The University of Texas Health Science Center at San Antonio, San Antonio, TX; [2]US Renal Care Inc, San Antonio, TX; [3]The University of Texas at San Antonio, San Antonio, TX.*

Background: Maintaining adherence to one's hemodialysis [HD] regimen is paramount to patients' health and well-being. The purpose of this pilot study was to evaluate the feasibility of a clinic-based animal-assisted intervention [AAI] for improving HD patients' treatment adherence, depression, and pain.

Methods: This study used a within-subject repeated measures design at 1 outpatient HD clinic with a primary outcome of unplanned missed HD treatments. Participants were prevalent HD patients, age 18+, who had depression (PHQ-2 ≥ 3), and chronic pain (Pain Enjoyment General activity score ≥ 4). Patients were randomized 1:1 into 2 groups: 1 dog visit (AAI1) or 2 dog visits (AAI2) per week for 10 weeks. The AAI took place in the waiting room immediately prior to HD; it involved socializing with and petting the dog. Patients completed pain and mood assessments before and after each dog visit. A generalized linear mixed effects model was used for data analysis.

Results: A total of 17 patients were enrolled (n= 8 AAI1, n=9 AAI2) who cumulatively received 199 of 240 possible dog visits (83%), averaging 10.8 ± 4.8 minutes each. There were 9 missed HD treatments during the trial (1 in AAI1, 8 in AAI2), while there were 30 missed treatments in the 12 weeks prior to trial (6 in AAI1, 24 in AAI2). All patients who missed at least 1 HD treatment in the 12 weeks pre-enrollment had a decrease of at least 1 fewer missed treatments during the trial. The effect estimate for the reduction in probability of missing an HD treatment in the AAI vs pre-trial was OR 0.23 (95% CI: 0.09 to 0.57), p = 0.002. Pain severity rated 0-10 scores: pre-test = M 4.38 ± 2.63, post-test = M 3.46 ±1.93 (AAI1); pre-test = M 3.52 ± 1.91, post-test = M 3.14 ±2.04 (AAI2).

Conclusions: Including therapy dogs in HD patients' healthcare routine may offer a complementary approach to improving outcomes. This safe and resource-minimal intervention received high patient approval and provides insight for determining the treatment effect of AAI in order to design larger controlled clinical trials on the clinical effectiveness of AAI.

FR-PO441

Motivational Strategies to Empower African Americans to Improve Dialysis Nonadherence

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Background: Compared to whites, African Americans (AA) have four times the risk of ESKD. Hemodialysis (HD) nonadherence is common in AA and driven by low motivation. Motivational interviewing (MI), an evidence-based counseling style increases intrinsic motivation, and if culturally tailored, reduces nonadherence in AA. We hypothesized that culturally tailored MI would be feasible and acceptable for reducing HD nonadherence in AA.

Methods: Parallel arm [usual care (n=15) vs. MI (n=15)] pilot RCT of AA, ≥ 18 years old, who missed HD or shortened HD by 15 minutes/month during the prior 3 months. Patients randomized to MI received 6 sessions over 8 weeks, culturally tailored to prioritize contributors to nonadherence: empowerment; support network; understanding ESKD; communication & trust; mental well-being; transportation; and racial identity. Coaches were assessed via the MI Treatment Integrity (MITI) scale. Coaches and patients provided feedback regarding their experience.

Results: We enrolled 30 AA; 57% male; median age [IQR]= 57[17] years; median HD vintage [IQR] of (6.6[4.3]) and (2.2[4.9]) years in the MI and control groups respectively. Feasibility and acceptability were favorable: 76% enrollment-to-screening ratio; 73% MI attendance; 13% drop-out. Primary outcome was chart-reviewed HD adherence. In month 3 of follow-up, patients were prescribed a median [IQR] of 13 [12, 13] sessions and 2730 [2520, 3120] minutes, and completed 91.7% [80.8%, 99.1%] of prescribed HD. Patients completed 84.6% [63.6%, 92.3%] of prescribed sessions. Empowerment, support network, and understanding ESKD were most frequently discussed during MI per patients' preference. Patients reported variability in the impact of racial identity on HD adherence. Some noted having low trust *in*, and feeling intimidated *by* the health system. Most viewed MI as an effective communication style. Health coaches demonstrated high fidelity on the MITI.

Conclusions: Health coach-delivered culturally tailored MI in AA is feasible and acceptable. Next steps will assess its *efficacy* in reducing HD nonadherence in AA.

Funding: NIDDK Support

FR-PO442

Managed Care Program Improves Hospitalization Rate in ESKD Patients

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Background: Care fragmentation, a lack of coordinated care for patients, is associated with reduced quality of care, increased costs, and poor clinical outcomes. End stage kidney disease (ESKD) patients are at increased risk of care fragmentation due to the complex collection of conditions that often accompany ESKD (i.e., diabetes, hypertension, etc.) and require care from multiple healthcare providers. Recently, managed care programs have started to defragment care for ESKD patients through collaboration across healthcare organizations in order to improve clinical outcomes. However, whether and to what degree these programs are effective is unknown.

Methods: This was a retrospective, observational study of dialysis patients with commercial or Medicare Advantage insurance treating with a dialysis provider in the United States from June 2021- June 2022. The primary exposure was enrollment in a managed care program. Expected hospitalization rates for enrolled patients were estimated by indirect standardization versus the non-enrolled patients.

Results: After accounting for differences in age, comorbidities, insurance type, and geography, we observed that enrolled patients had 0.11 admits per-patient per-year favorable hospitalization rate compared to non-enrolled patients. This resulted in an estimated 961 hospitalizations prevented among approximately 8,500 enrolled patients during the study period. Hospitalization reduction was similar between managed care programs done in partnership with government and private insurers.

Conclusions: A provider managed integrated kidney care program can be effective in improving clinical outcomes for ESKD patients for public or private payors.

FR-PO443

Perspectives on Preventability of Emergency Department Encounters for People Receiving Dialysis: A Qualitative Critical Incident Study

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Background: People receiving dialysis have disproportionately high rates of emergency department (ED) utilization. While certain conditions underlying ED encounters have been characterized as potentially preventable, little is known about how contextual factors may influence perceived need for ED care. We explored the perspectives of patients with kidney failure, their caregivers, and healthcare providers regarding the potential preventability of ED encounters.

Methods: In this qualitative critical incident study, we purposively sampled patients receiving dialysis who had received emergency care in the preceding four weeks for various acute health conditions, their informal caregivers, and healthcare providers working with dialysis patients. We conducted semi-structured interviews in person or virtually, coded transcripts in duplicate across participant roles, and generated themes through an inductive thematic analysis approach.

Results: We completed interviews with 22 patients receiving hemodialysis and peritoneal dialysis, 8 caregivers, and 30 healthcare providers from nephrology, emergency medicine, and primary care disciplines. Across roles, participants discussed aspects of acute illness unique to people receiving dialysis and emphasized coordinated care across disciplines to prevent illness onset, decompensation, and ultimately need for urgent ED management. We characterized perceived preventability of ED encounters in relation to the following themes: (1) Connectedness of the acute condition to kidney failure; (2) Care continuity and engagement; (3) Reactions and behavioural responses to the acute illness experience; (4) Access to urgent care strategies outside of the ED.

Conclusions: Patients, caregivers, and healthcare providers identified how the interplay between kidney failure, the acute illness experience, behaviours, and support structures influence the perceived preventability of ED encounters. Findings will inform coordinated approaches to averting potentially unnecessary ED use among this medically complex population.

FR-PO444

Plasma B Cell-Activating Factor (BAFF) Levels Predict the Upcoming Depressive Symptoms in Hemodialysis Patients

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Background: B cell activating factor (BAFF) is a cytokine that plays a role in B cells' maturation, homeostasis, and differentiation and is associated with mental disorders. Depression can often be caused by inflammation, with various cytokines playing a role. Chronic inflammation is common in hemodialysis (HD) patients, and depression is also prevalent among them. We hypothesize that BAFF may predict upcoming depressive symptoms in HD patients, so we evaluated their association.

Methods: Among 643 subjects who enrolled in a multi-center prospective HD cohort study, we investigated 72 patients who tested plasma BAFF levels, performed initial and follow-up Beck Depression Inventory, and had no depressive symptoms at first. We conducted a univariate and multivariate Cox regression analysis to calculate the hazard ratio (95% confidence interval (CI)) between upcoming depressive symptoms and BAFF levels.

Results: In both univariate and multivariate analyses, a 1 standard deviation (SD) increase in BAFF was significantly linked with a higher risk of future depressive symptoms. The HR was 1.437 (95% CI 1.034-1.996) and 1.699 (95% CI 1.037-2.784), respectively. Patients with higher BAFF levels experienced more depressive symptoms than those with lower BAFF levels for 2 years (p = 0048).

Conclusions: In HD patients, elevated levels of plasma BAFF showed a significant association with depressive symptoms up to two years later.

Hazard ratios of plasma BAFF and APRIL for depressive symptoms

	HR	95% CI	HR	95% CI
BAFF	1.437	1.034-1.996	1.699	1.037-2.784
APRIL	0.843	0.570-1.245		

	Total (N=72)	No depressive symptoms (N=41)	Depressive symptoms (N=31)	P value
Age (years)	57.7 ± 12.9	57.4 ± 13.3	58.0 ± 12.7	0.857
Men (%)	45 (62.5)	15 (36.6)	19 (61.3)	1
Body Mass Index (Kg/m2)	23.3 ± 4.9	22.4 ± 3.5	24.4 ± 6.2	0.122
Diabetes Mellitus (%)	44 (61.1)	25 (61.0)	19 (61.3)	1
Cardiovascular diseases (%)	34 (47.2)	22 (53.7)	12 (38.7)	0.308
Charlson comorbidity index	3.89 ± 1.42	3.71 ± 1.31	4.13 ± 1.54	0.214
Pre-hemodialysis SBP (mmHg)	143.2 ± 18.0	140.8 ± 18.5	146.3 ± 17.2	0.198
Hemodialysis Vintage (months)	60.6 ± 70.3	49.1 ± 57.6	74.5 ± 82.3	0.193
spKt/V	1.58 ± 0.31	1.54 ± 0.27	1.63 ± 0.35	0.22
Ultrafiltration (Liter)	2.35 ± 0.83	2.47 ± 0.79	2.20 ± 0.86	0.18
Residual renal function (ml/day)	283.3 ± 311.8	352.7 ± 327.9	179.1 ± 259.1	0.042
Dialysate Na (mEq/L)				0.125
135 mEq/L (%)	20 (27.8)	8 (19.5)	12 (38.7)	
140 mEq/L (%)	52 (72.2)	19 (61.3)	19 (61.3)	
Calcium (mg/dL)	8.4 ± 0.8	8.39 ± 0.75	8.37 ± 0.90	0.909
Phosphorus (mg/dL)	5.2 ± 1.2	5.24 ± 1.10	5.03 ± 1.35	0.474
Albumin (g/dL)	3.90 ± 0.25	3.96 ± 0.26	3.82 ± 0.21	0.019
hsCRP (mg/dL)	0.80 (0.24, 2.46)	0.45 (0.21, 1.68)	1.33 (0.72, 3.54)	0.009
ALP (U/L)	89.8 ± 31.6	82.5 ± 29.5	99.4 ± 32.1	0.023
Bone specific ALP (µ/L)	16.9 ± 8.39	16.0 ± 8.5	18.1 ± 8.2	0.306
PTH (pg/mL)	288.9 ± 196.1	286.6 ± 188.5	291.9 ± 208.8	0.91
25(OH)VitD (ng/mL)	15.2 ± 9.7	14.9 ± 10.3	15.5 ± 8.9	0.802
BAFF (pg/mL)	800.8 (661.1, 1002.9)	758.2 (603.4, 903.0)	838.9 (706.7, 1130.2)	0.114
APRIL (pg/mL)	564.6 (410.9, 830.2)	563.5 (393.0, 881.2)	565.7 (464.8, 751.1)	0.918

Table 1. The baseline characteristics of all subjects and with or without depressive symptoms

FR-PO445

Effects of Eating Meals During Hemodialysis Treatment on Depressive Symptoms: The FrEDI Randomized Controlled Trial

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Background: Approximately one-third of patients undergoing hemodialysis (HD) suffer from symptoms of depression. HD patients with low serum albumin levels who ingest high- vs. low-protein meals during HD sessions display improved their protein-energy status. We examined whether their depressive symptoms were also alleviated with intradialytic high-protein meals.

Methods: We examined data from participants in the Fosrenol for Enhancing Dietary Protein Intake in Hypoalbuminemic Dialysis Patients (FrEDI) Study (NCT01116947) who were on thrice-weekly HD with serum albumin <4.0 g/dL. Participants were randomized to receive either high-protein (50–55 g) meals or low-protein (<1 g) meals during HD treatments for 8 weeks. The primary outcome was depressive symptoms measured by the Beck Depression Inventory (BDI)-II survey at 8 weeks. Data on change in Mental Component Summary (MCS) as assessed by the SF-36 were also evaluated. Differences between pre-to-post scores within each study arm were examined using Wilcoxon signed-ranks test.

Results: Fifty-seven participants completed the BDI-II assessment. The mean (SD) age was 55 (±15) years; 56 % were female. The BDI-II score showed a statistically significant improvement among 26 participants in the high-protein meals (baseline, 11.5 [IQR, 5-20] vs. 8-weeks, 7 [IQR, 2-13], P=0.01). In the low-protein meals, BDI-II scores among 31 participants showed a trend toward improvement (baseline, 10 [IQR, 4-22] vs. 8-weeks, 6 [IQR, 1-15], P=0.077). The MCS showed no statistically significant changes either among 26 participants in high-protein meals (baseline, 37.2 [IQR, 16.5–48.7] vs. 8-weeks, 39.2 [IQR, 29.6–47.0], P=0.44) or among 31 participants in low-protein meals (baseline, 30.1 [IQR, 15.6–53.3] vs. 8-weeks, 33.4 [IQR, 16.8–48.6], P=0.97). Changes in BDI-II scores were not statistically different across meal composition.

Conclusions: Among HD patients who receive high- versus low-protein meals during thrice-weekly HD, those eating high-protein meals exhibited a significant improvement in depressive symptoms. Further clinical trials are needed to conclusively determine the efficacy and safety of intra-dialytic eating and meal provision in the dialysis clinics on patient-reported outcomes including unpleasant symptoms.

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FR-PO446

Underdiagnosis of Depression in Hemodialysis Patients

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Background: Depression is the most common psychiatric illness among dialysis patients. It has been associated with adverse outcomes in this population, and therefore routine screening is recommended. The Patient Health Questionnaire (PHQ)-9 scale has been validated for depression screening in patients on hemodialysis (HD) in controlled studies, but it is underutilized in dialysis centers. The utility of PHQ-9 in detecting depression in HD patients without an official diagnosis and its association with psychiatric care is not well studied.

Methods: In a single center observational study of HD patients, we used PHQ-9 scores ≥ 10 as an indicator for depression. This was compared to diagnostic code-based depression diagnoses. Two-tailed t-tests were used to compare continuous variables, while Fischer's exact and Chi square tests were used to compare categorical variables.

Results: Among the 98 HD patients analyzed, the mean age was 61.5 years, mean days on HD were 2,005; 91% had hypertension, 59% diabetes and 87% had cardiovascular disease. Eighteen (18.4%) patients were diagnosed with depression using the PHQ-9. Of these, only six (33%) also had a diagnostic code-based depression diagnosis, nine (50%) had a follow-up appointment scheduled with a psychiatrist, and only five (28%) were being treated with an anti-depressant. Patients with depression were also more likely to have comorbid anxiety disorder and a greater number of previous hospitalizations (p<0.05).

Conclusions: Depression is underdiagnosed in HD patients. Better screening for depression will lead to improved medical care and potentially better health outcomes for this vulnerable population.

FR-PO447

"Dialysis Makes You Poor and Keeps You Poor": Patient Perspectives on Health-Related Social Needs and Recommendations for Interventions

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Background: Dialysis patients with low socioeconomic status have worse outcomes, which may be due to health-related social needs. Patient perspectives on the impact of social needs and how to address them have not been explored.

Methods: We interviewed 32 people with low socioeconomic status receiving in-center hemodialysis on barriers and facilitators to care with an emphasis on social needs. The interviews were conducted at three dialysis facilities in Austin, Texas, from April to July 2022. We collected demographic information, and performed thematic analysis using the constant comparative method on interviews after they were audio-recorded, translated and transcribed verbatim.

Results: Participants were mean (SD) age 56 (12) years, 18 (56%) identified as female, 15 (53%) identified as Hispanic/Latino/a/x, 30 (94%) were unemployed, 27 (94%) reported annual income <$25,000, and health-related social needs were common. Themes identified were (1) kidney failure was unexpected, (2) dialysis is detrimental, (3) powerlessness, (4) financial resource strain, (5) motivators, and (6) interventions should promote self sufficiency (Figure).

Conclusions: Dialysis exacerbates financial resource strain, and social needs exacerbate dialysis-related stress. Participants made recommendations to address social needs with an emphasis on increasing financial support and community resources for this population.

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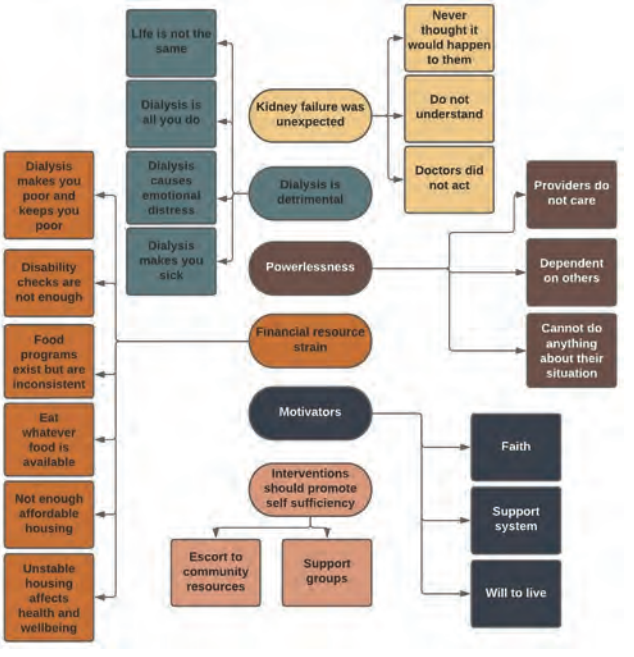

Figure. Themes and subthemes from semi-structured interviews.

FR-PO448

Advance Care Planning in Patients with Advanced CKD on Hemodialysis in the Hospital Setting

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Background: To explore the wishes and preferences of patients with advanced chronic kidney disease (ACKD) who receive hemodialysis through the application of the instrument "Dodecahedron of advance care planning" to improve the approach and medical care of these patients, promote communication between them and the healthcare professionals who attend to them. Advance care planning in patients with advanced chronic kidney disease on hemodialysis in the hospital setting.

Methods: Patients with advanced chronic kidney disease (ACKD) admitted to the Hemodialysis program of the General Hospital of Villalba were included. Demographic variables, knowledge about CAP and conversations about the end of life, comorbidity with the Charlson Index, and cognitive status using the Pfeiffer scale were collected. In addition, the dodecahedron of advance care planning was used as a clinical instrument through an interview.

Results: 70 patients were included; 35 completed PAC, 54.3% men and 45.7% women. Median age 72 years (44-89). Of all with Charlson Index >5, 14.2% had depression. The median dialysis time was 36 months (3-276). 100% had not discussed the end of life with their doctor, and 25.75% had with their main caregiver. 31.4% NECPAL positive. The wishes of the patients were: 91.4% "to be cared for with respect and kindness," 77.7% expect the best to be done at each moment of their illness, 25.4% did not want to talk about the end of life, 77.1% did not want to suffer in pain, 60% "not be a burden to their families," 100% wanted to die accompanied by their family. 48.6% wanted to die at home, 14% in hospital, and 37.1% did not care. 80% wanted to be connected to machines "if their recovery is reasonable," 68.6% wanted palliative sedation for refractory symptoms, 97.1% wanted to be reminded "as a good person," and 85.7% were believers that gave meaning to his illness.

Conclusions: Most patients at the end of life wish not to be a burden to their family, to die accompanied, without pain, and at home. The dodecahedron tool is helpful for CAP in HD; it facilitates communication and decision-making aspects and has a positive impact on the patient.

FR-PO449

One-Year Survival and Hospitalization After Dialysis Initiation in Patients Aged Above 75

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Background: Implementation of dialysis in elderly patients is debated because of an unfavourable short-term prognosis. We therefore analyzed the one-year impact on survival of planned implementation versus emergency dialysis in this population.

Methods: All patients who started maintenance dialysis in our unit during the past 21 years were reviewed. Patient's demographic and clinical characteristics were collected. Emergency implementation of maintenance dialysis was determined if there was no prior referral to a nephrologist one month before dialysis initiation.

Results: From 2000 to the end of 2021, 860 patients started maintenance dialysis in our unit, of whom 231 were aged 75 and above. Mean age was 80 ± 4 years. Hemodialysis was implemented in 83 % of the patients. There were 66% male, 41 % diabetics and median eGFR at start of dialysis was 7± 3 ml/mn. Emergency dialysis was implemented in 36% (n=81) of the patients aged 75 and above. One-year mortality was 18% in patients who had planned dialysis and 36% in patients with emergency dialysis. One-year mean survival was 327+12 days in patients with planned dialysis versus 275± 21days in those who had emergency dialysis ($p< 0.004$). In multivariate analysis including age, gender, comorbidity score and dialysis modality, prior referral was associated with a 33% decline in one-year mortality (HR: 0.67; 95% CI. 048-0.93). Hospitalization-free days within the first year after dialysis start or death were 311+60 days in referred patients versus 280± 74 days in those dialyzed in emergency ($p< 0.005$).

Conclusions: In our dialysis population, one-month referral to nephrologists prior to dialysis implementation significantly increased one-year survival and hospitalization-free days in ESKD patients aged above 75.

FR-PO450

A Nationwide Survey of Conservative Kidney Management in Japan

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Background: Even with our best possible efforts, death is an inevitable endpoint. The age of entering dialysis has reached over 70 years/old in Japan. Withhold and withdrawal dialysis have emerged problem in elderly society. This article explains the selection and current situation of conservative kidney management (CKM) based on nationwide survey in Japan.

Methods: Quetionnaire responses were collected in 2020, based on the 2-year period status from 2018 to 2019. A web-based questionnaire was sent to all members of 4 societies (Japanese Society of Nephrology, Society for Dialysis Therapy, Association for Home Care Medicine, and Society for Pediatric Nephrology), and one response was received from each facility to avoid duplication of cases. Thus, although the exact response rate could not be counted, responses were obtained from 451 facilities.

Results: Among the responses, 299 were from hospitals, 104 were from dialysis clinics, and 37 were from visiting physicians. In the past 2 years (2018-2019), the number of patients who opted for withholding of dialysis was 917, and that for withdrawal from dialysis was 492 (1409 in total). In patients who were 80 years or older, the increase in the number of patients who opted for withholding of dialysis was substantial, with more than twice as many patients than those who opted for withdrawing from dialysis. Among patients who withheld or withdrew from dialysis, the number of patients with poor cognitive function was approximately twice that of those with good, and poor cognitive function was prominent in patients who withheld dialysis. In terms of prognosis after withholding or withdrawal of dialysis, many patients died 1 month after withholding of dialysis and 7-14 days after withdrawal from dialysis. The contents of palliative care varied but pain management was a main component: not many patients were transferred to the palliative ward or home. Relevant confirmation document were obtained, but the explanation of CKM as a therapy option was provided at the time of therapy selection in just 40% of cases.

Conclusions: CKM is not yet as well recognized as renal replacement therapy, and thus, deliberation is still required for consensus-building on CKM, as well as on ACP. Adequate time must be also spent for full SDM in the elderly Japanese dialysis population.

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FR-PO451

Withdrawal from Dialysis: Seven-Year Experience in a Kidney Supportive Care Service

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Background: Withdrawal from dialysis is a common cause of death in patients on dialysis. Kidney Supportive Care (KSC) services have evolved to meet the palliative care needs of patients ceasing dialysis when it is no longer beneficial. This study examines the profile and survival of patients known to a KSC service who withdrew from dialysis.

Methods: Retrospective analysis of patients known to a KSC service between 2016 and 2023 who withdrew from haemodialysis (HD) or peritoneal dialysis (PD). Demographics including age, sex, ethnicity, and Charlson Comorbidity index (CCI) were extracted from medical records. Reason for referral to KSC and patient choices including advance care planning (ACP) documents and preferred place of death were recorded. Date of dialysis withdrawal, date and place of death; and referral to palliative care services were also collected. Results were analyzed descriptively.

Results: Over 7 years, 157 patients withdrew from dialysis with a mean age of 72.4 years (SD 9.88). 38% were female and 3% identified as First Nations people. 132 patients withdrew from HD and 25 from PD. At time of referral to KSC, the median CCI was 7 (IQR 2), 31% had either ischaemic heart or congestive cardiac failure, and 5% had a diagnosis of dementia. Patients withdrew from dialysis a median of 205 days (IQR 440) after KSC referral. Following withdrawal from HD patients survived a median of 7 days (IQR 7.75), and 6 days after withdrawal from PD (IQR 9.5). 50% of people died in an acute hospital, 24% at home and 23% in a palliative care unit (PCU). Of the 74 who had indicated preferred place of death, 35 (47%) wished to die at home; of these 16 (46%) did. Only 16 patients (22%) wished to die in a PCU, but 11 (69%) did. Surprisingly 19 patients (26%) indicated they wished to die in an acute hospital and 14 (74%) of these patients did.

Conclusions: Our results indicate that patients typically survive around one week after withdrawal from dialysis, which is consistent with current literature. Most patients died in acute care settings, which was often not in keeping with their wishes. This may have been due to acute medical complications or sudden deterioration limiting transfer to their preferred place of death. Further work is needed to understand how best to provide care that concords with end-of-life preferences.

FR-PO452

Cultural Tailoring of Motivational Strategies to Improve Hemodialysis Nonadherence in African Americans

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Background: African Americans (AA) make up 33% of patients with ESKD and, compared to white patients, have higher hemodialysis (HD) nonadherence rates. Motivational interviewing (MI) improves nonadherence, and cultural tailoring centered

on racial minorities reduces racial disparities. Informed by key themes derived from prior qualitative research focused on HD nonadherence in AA, we hypothesize that MI can be culturally tailored to improve HD nonadherence in AA.

Methods: During a facilitated community engagement studio, AA community experts (n = 7) with lived experience across each stage of kidney disease, reviewed key themes on HD nonadherence in AA. Themes were obtained from prior focus groups and interviews of 22 AA on HD, and 34 dialysis providers & researchers; mapped onto the PEN-3 cultural model; categorized as **P**erceptions (attitudes), **E**nablers (structural/societal factors), or **N**urturers (support systems); and further categorized as **P**ositive (facilitators), **E**xistential, or **N**egative (barriers). Community experts identified priority targets for an MI intervention. Health equity clinicians and researchers finalized the cultural adaptation process by examining the priority targets and providing additional input.

Results: AA community experts dentified 6 major priority targets: empowerment; support network; understanding kidney disease; communication and health system-related trust/trustworthiness; mental well-being; and transportation. Health equity researchers added racial identity as a priority target. Key themes and illustrative perspectives are shown in Table 1.

Conclusions: Use of the PEN-3 cultural model for the cultural adaptation of MI is novel. Integrating input from AA community experts and content experts with perspectives from AA on HD to identify priority targets of MI, will likely increase the potential efficacy, adoption, and sustainability of MI to improve HD nonadherence in AA.

Funding: NIDDK Support

Mapping of Themes into PEN-3 Cultural Model with Exemplar Quotes

	Perceptions Patient attitudes and beliefs	Enablers Structural and societal factors	Nurturers Patient support systems
Positive Facilitators of dialysis adherence	**SELF-ADVOCACY & EMPOWERMENT …people just understanding how motivational interviewing might empower them to think about their health and put them in the driver	**OPTIMAL MENTAL WELLBEING "Nobody wants to be the person that somebody is pointing their finger at…Because that could be the difference between life and death in some people. Because a person can get bullied for it or talked about it so much…" (Patient) *Cultural Competency	**SUPPORT NETWORK "I'm just to the point where I'm tired and I didn't want to go and I didn't want to interact. But I have a great support system at home as well as patient care to where they were all hovering with me, talking to me, and motivating me to go back to the clinic." (Patient) *Religious Support *Family Support *Peer Support
Negative Barriers to dialysis adherence	**LACK OF UNDERSTANDING OF KIDNEY DISEASE "…I think if [African Americans] were more educated on dialysis and what it does and how it works before they start dialysis, I think they will be more adherent to what	**COMMUNICATION & TRUST There may be a lack of trust… that could be a barrier… all that happened at Tuskegee and not getting the right treatment that they needed. So, there may be a cultural and historical precedent to that, in terms of relying on and believing the medical information we're giving to them now…" (Nephrologist) **TRANSPORTATION "….transportation can be kind of crazy sometimes, when you get off of dialysis, they might come pick you up a couple of hours later, you never know which way transportation's going to go." (Patient) *Finances *Representation in Healthcare	*Stigma *Diet *Lack of Provider Support

*Major themes specific to HD adherence in AA

**Major themes identified as priority targets

FR-PO453

The Impact of Depressive Symptoms on Outcomes in Incident Hemodialysis Patients

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Background: Dialysis is associated with increased physical and psychosocial burden. This study explored the association of depressive symptoms with mortality and hospitalization among incident hemodialysis (HD) patients.

Methods: Incident in-center HD patients who began dialysis between Jan 2017 and Dec 2022 at centers managed by a mid-size non-profit dialysis provider, and who completed the PHQ2 depression screening within 150 days of initiating dialysis, were followed up for one year post-survey completion for death and for hospital admissions. Observation was continued until the end of April 2023. PHQ2 score ≥ 3 was considered positive. For time to event analysis, univariate and age- and sex-adjusted Cox regression were used, while Poisson regression was used to compute rate ratios.

Results: A total of 6,203 patients were included. Mean age was 61 ± 15 years, and 39% were female. The PHQ2 survey was positive in 230 (3.7%) patients. During follow-up, 295 (4.8%) patients died. The hazard ratio (HR) for death was 1.44 (95% CI: 0.86 -2.43) and 1.67 (95% CI: 0.99 – 2.81) in univariate and adjusted analysis respectively. The rates of hospital admissions were 1.88 per patient-year for those with a negative survey, and 1.22 for those with a positive survey (RR: 1.54, 95% CI: 1.38 – 1.72). As shown in the figure, the HR for time to first hospitalization was 1.42 (95% CI: 1.18 – 1.70) for those with a positive survey compared to those with a negative one, in both the univariate and adjusted analyses. Furthermore, patients with a positive survey spent more days in the hospital (13.08 versus 8.15 days per patient-year, RR 1.61, 95% CI: 1.54 to 1.67).

Conclusions: Depressive symptoms appear to be correlated with an increased risk of hospitalization among incident HD patients. This finding provides an opportunity to enhance patient care and potentially reduce associated healthcare costs.

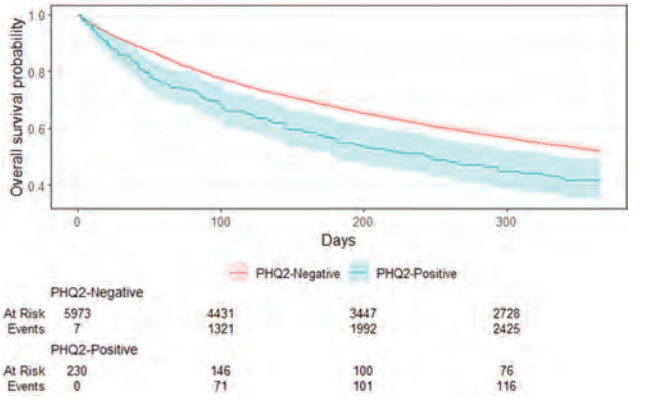

Figure: Survival of incident hemodialysis patients from completion of depression survey to first hospital admission

FR-PO454

Palliative Care and Advance Care Planning Integration into the Dialysis Team: A Quality Improvement Intervention at a Hospital-Based Outpatient Hemodialysis Clinic

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Background: Despite substantial symptom burden and high mortality, adults receiving maintenance hemodialysis (HD) infrequently utilize palliative care (PC). With mostly hospital-based outpatient dialysis clinics, Veterans Affairs (VA) is well-positioned to increase access to PC services. At a large urban VA dialysis unit, we initiated a year-long intervention to improve Life Sustaining Treatment (LST) note and advance care planning (ACP) completion.

Methods: A PC physician was integrated into the dialysis care team at the Jesse Brown VA (JBVA) Medical Center to improve LST and advance directive (AD) completion. The PC physician worked with the dialysis team to provide palliative education and refine and bolster approaches to ACP. The PC physician contacted all patients needing an AD or LST note. After 12 months, we reassessed percentages of patients with LST and AD completion. Change in proportion with note completion pre/post PC intervention was compared.

Results: Among all outpatient HD patients at the JBVA, the average age was 71 years, 85% were Black, 99% were male, and the average time on HD was 4.7 years. Frequent consultation with the dialysis social worker was essential to targeting patients for the intervention. Most patients preferred private phone calls with the PC physician to discuss ACP. Integration of a PC physician into the dialysis care team significantly increased patient completion of an AD and LST note as noted in table.

Conclusions: Integrating a PC physician into the dialysis care team led to a substantial increase in LST and advance directives for maintenance HD patients. Future PC integration plans should build on these gains in advance care planning, measure their impact on subsequent care and also extend to alleviating symptom burden.

	May 2022 (pre-PC intervention)	April 2023 (post-PC intervention)	p-value
Number of Dialysis Clinic Patients	59	70	
Patients with VA Advance Directive	38 (64%)	62 (89%)	<0.01
Patients with LST note	53 (90%)	70 (100%)	<0.01

FR-PO455

Importance of Living with a Spouse for Female Patients Undergoing Hemodialysis

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Background: An increasing number of elderly people are living alone owing to the aging population, and patients undergoing hemodialysis are no exception. Generally, patients living alone have poor prognoses. However, the significance of living with a spouse for patients on hemodialysis has been unclear. Therefore, we aim to clarify such significance among Japanese patients undergoing hemodialysis.

Methods: After excluding patients with an unknown family structure, we included patients undergoing hemodialysis at Nagasaki Renal Center, Japan, during 2011 and 2012. Patients were followed up until 2021. Log-rank tests and multivariate Cox regression analyses were conducted to evaluate the patients' life prognosis.

Results: We included 333 patients undergoing hemodialysis (mean age: 67.2±13.3 years, 57% men, median dialysis vintage: 4.8 years). The proportion of those living with a spouse was 48%. The log-rank test for all patients showed that patients living with a spouse had a favorable prognosis compared with that of patients living alone (P=0.008). Notably, no significant difference was observed among male patients (P=0.22); however,

a significant difference was detected among female patients (P=0.004). Even a patients' background adjusted multivariate Cox regression analysis showed that living with a spouse reduced the risk of death (hazard ratio: 0.74, 95% confidential interval: 0.56–0.98, P=0.04).

Conclusions: Living alone was associated with poor prognosis, especially in female patients undergoing hemodialysis. The precise reason for this remains unknown. However, patients on hemodialysis living alone should not be isolated from society to improve their prognosis.

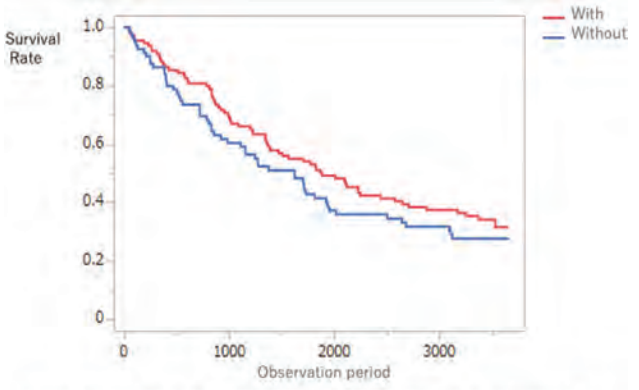

Figure2. Survival rates for those with and without a spouse in male patients undergoing dialysis.

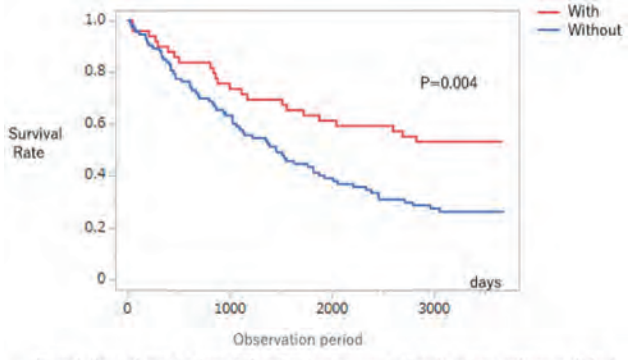

Figure1. Survival rates for those with and without a spouse in female patients undergoing dialysis.

FR-PO456

Impact of Inpatient vs. Outpatient Dialysis Transition on Survival in a National Cohort of Advanced CKD Patients

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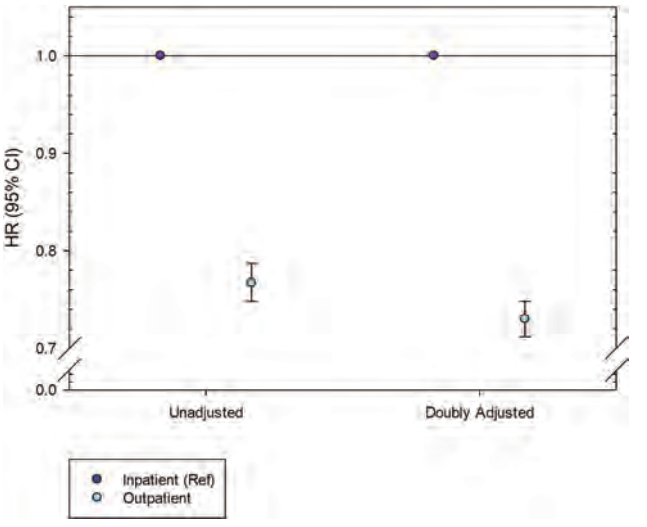
Background: Large population-based studies show advanced CKD patients transitioning to ESKD have high mortality in the first few months of dialysis initiation. It is unclear whether transitioning to dialysis in the inpatient vs. outpatient setting is associated with better survival in incident ESKD patients.

Methods: We examined advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) who transitioned to within 2-years of their 1st (index) eGFR <25 over 1/1/07-6/30/20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/ Medicare Advantage enrollees, and EHR data. We compared all-cause mortality in patients who transitioned to dialysis in the inpatient vs. outpatient setting matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 to address confounding by indication in Cox models.

Results: Among 20,655 patients who were PS-matched to 20,655 patients who transitioned to dialysis in the outpatient vs. inpatient settings, respectively, outpatient dialysis transition was associated with lower mortality risk vs. inpatient dialysis transition: HR (95%CI) 0.77 (0.75-0.79). Similar findings were observed in sensitivity analyses doubly-adjusted for PS-score covariates (ref: inpatient dialysis transition): HR (95%CI) 0.73 (0.71-0.75) for outpatient dialysis transition.

Conclusions: In a national cohort of advanced CKD patients transitioning to ESKD, outpatient dialysis was associated with better survival compared with inpatient dialysis transition. Further studies are needed to determine the factors contributing to differential survival, as well as the comparative effectiveness of inpatient vs. outpatient dialysis transition on other ESKD outcomes (patient-reported endpoints, healthcare costs).

Funding: NIDDK Support



FR-PO457

Use of a Novel Machine Learning Tool ("DoWhy") to Compare Mortality Risk Between High Volume Hemodiafiltration (HV-HDF) and Hemodialysis (HD) Patients in a Large Cohort from Latin America (LA)

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Background: Since hemodiafiltration (HDF) provides higher clearance of middle molecules compared with hemodialysis (HD), several studies showed HDF may result in better outcomes than HD. However, these findings are prone to residual confounding (C) and selection bias (SB). In this study we focused on a methodology that allows to analyze differences in clinical outcomes accounting C and SB.

Methods: We included incident patients (pts) to dialysis in Fresenius Medical Care units in LA between Jan 12-Dec 22, after 90 days of treatment. Pts were classified by modality: HD or HDF (>90% in any modality). High volume HDF (HV-HDF) was considered if infusion volume >21 liters. Values were compared using t-test or Chi-square accordingly. To compare risk of death and odds to reach targets, we use a novel machine learning tool (Python library "DoWhy"), which provides interface for causal inference analysis. A model using "modality" as treatment and baseline variables as covariates was built to estimate "average treatment effect" (ATE) on outcomes of interest using propensity score stratification (PSS), which estimates the risk/odd % change between treatment and control accounting for baseline differences and SB.

Results: 99,496 pts were included (97.1% HD, 2.9% HDF, Table 1). HDF pts were younger, higher vintage and higher prevalence of male gender, diabetes, hypertension and heart disease. After PSS, ATE for mortality showed risk reduction for HDF vs HD of -4.04%, and -5.1% for HV-HDF vs HD. Odds to reach targets were increased on HV-HDF or HDF as compared to HD (Table 2).

Conclusions: Machine learning tools are an alternative when interventional studies are not available and there are unbalanced control/treated cohorts. In our study, after controlling for possible C and modelling using PSS, HDF and HV-HDF showed a reduced risk of dead and increased odds of reaching targets vs HD.

Values expressed as Mean ± SD	Total	HD	HDF	p Value
N	99496	96635 (97.1%)	2861 (2.9%)	
Age (years)	58.4 ± 16.7	58.6 ± 16.7	53.9 ± 16.3	< 0.0001
Gender (Male)	59.5	59.3	65.7	< 0.0001
Vintage (years)	1.45 ± 3	1.4 ± 2.97	3.17 ± 3.78	< 0.0001
Diabetes (%)	35.7	35.7	37.8	0.02
Hypertension (%)	56.3	55.8	73.3	< 0.0001
Ischemic heart diseases (%)	5.8	5.6	10.3	< 0.0001
Other forms of heart diseases (%)	10.5	10.1	25.9	< 0.0001
Cerebrovascular diseases (%)	3	3	9.2	0.5
Amyloidosis (%)	0.17	0.17	0.27	0.23
Neoplasm (%)	4.4	4.4	4.5	0.76
Hb (g/dl)	10.6 ± 1.9	10.6 ± 1.9	11.3 ± 1.6	< 0.0001
Albumin (g/l)	3.8 ± 1.6	3.8 ± 1.6	4 ± 0.9	< 0.0001
Ca (mg/dl)	8.76 ± 0.8	8.76 ± 0.8	8.81 ± 0.7	0.0001
P (mg/dl)	4.7 ± 1.5	4.7 ± 1.5	4.4 ± 1.3	< 0.0001
Effective treatment time (min)	208.7 ± 55.8	207.8 ± 56.2	238.9 ± 23	< 0.0001
TAS [mmHg]	144.3 ± 27.4	144.2 ± 27.5	147.7 ± 26.3	< 0.0001
TAD [mmHg]	74.8 ± 15.2	74.7 ± 15.2	74.9 ± 15.4	0.2

Table1. Patient characteristics

	HDF vs HD	HV-HDF vs HD
N	85465	65240
N HD	82689	62689
N HDF	2776	2551
Risks		
Death	- 4.04%	-5.10%
On target outcomes		
Hb (10-12 g/dl)	7.00%	6.60%
Albumin (≥ 3.5 g/l)	10.50%	15.60%
Ca (8.4 - 9.5 mg/dl)	8.10%	7.40%
P (3.5 - 5.5 mg/dl)	8.40%	10.60%
PTH (130 - 585 ng/ml)	5.80%	3.08%
Kt/V (≥ 1.2)	5.80%	7.20%
TAS pre (≤ 130 mmHg)	6.80%	9.20%
TAD pre (60 - 100 mmHg)	- 1.80%	1.40%

Table2. Model results

Tables 1&2

FR-PO458

A Qualitative Study Exploring the Role and Responsibilities of the Patient Care Technician in US Dialysis Care

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Background: Dialysis patient care technicians (PCTs) provide essential, frontline care for patients on dialysis. We aimed to qualitatively explore perceptions of the PCT job role, responsibilities, and training among current PCTs, other staff on the dialysis care team, and patients receiving dialysis.

Methods: Focus group discussions were conducted in March-May 2023 with U.S. PCTs, dialysis staff, and patients. Participants were recruited via email invitation and social media postings from professional organizations and were purposively sampled to capture diversity in demographics and years of experience. Discussions were audio-recorded and transcribed verbatim and thematic analysis was conducted using inductive and deductive strategies.

Results: Seven focus group discussions (n=36 participants) were conducted (3 with PCTs [n=19], 2 with dialysis staff [e.g., social workers, dietitians; n=6], and 2 with patients [n=11]). Preliminary analyses revealed that, although there is agreement that PCTs play a pivotal role in dialysis care for patients and colleagues, PCTs are often perceived as "helpers" or ancillary rather than an integral part of the care team. Participants reported that PCT job training and qualifications are not standardized and are often not commensurate with job expectations and responsibilities. Additional training and continuing education are needed and desired. Participants reported that the PCT-patient relationship is deeply valued, but boundaries can be fluid and blurred due to the frequency and nature of dialysis care and differences in the perception of relationship boundaries were observed among groups. Finally, it was noted that PCTs are vulnerable to multilevel workplace safety issues (e.g., unsafe staffing ratios, violence) but feel ill-prepared to manage them.

Conclusions: Preliminary findings suggest PCTs play a multifaceted role in dialysis care that is highly valued among patients and staff, but this is not always reflected in the clinic-, organization-, or system-level policies that govern U.S. dialysis care. Future research should prioritize multilevel interventions aimed at equipping PCTs with the needed resources and support to provide quality care for patients and better prepare and integrate these critical members of the dialysis care team.

Funding: Other U.S. Government Support

FR-PO459

A Budget Impact Model (BIM) for Expanded Haemodialysis (HDx) vs. High-Flux Haemodialysis (HF-HD) in Two Major Public Health Sectors, Kingdom of Saudi Arabia (KSA)

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Background: Chronic Kidney Disease imposes economic costs on healthcare systems. The Saudi Center for Organ Transplantation (SCOT) in 2020 estimated that the number of patients undergoing dialysis (all modalities) is expected to increase by 5% per annum. Accumulation of large-size middle molecules/uremic toxins have been shown to be associated with inflammation, vascular calcification, and increased risk of cardiovascular disease. While conventional HD will clear smaller middle molecules adequately; large middle molecules can be reduced by HDx. Theranova (Baxter Healthcare Corporation, Deerfield, IL USA), a medium cut off dialyzer, allows for better clearance of large middle molecules than traditional HF-HD dialyzers.

Methods: An excel-based BIM was assessed the overall cost of HF-HD patients versus those on HDx over five-years from public payers' perspectives. Input data were retrieved via a comprehensive literature search and expert interviews. These included epidemiology data, the costs of healthcare resources utilized in dialysis sessions and dialysis related complications management including physician visits, hospitals stay, and medications.

Results: As per 2021 SCOT report, 1,862 Patients are managed in these health Sectors. HF-HD Therapy total cost per patient per year was $15,947 (US Dollars $, USD, $1 = 3.75 Saudi Riyals [SAR]), while the total cost of HDx Therapy per patient per year was $12,019. The overall cost saving per patient per year of $3,928 were driven by reductions in hospitalization, $3,619, followed by reductions in dose of Erythropoietin Stimulating Agents (ESA), $232, per patient per year. Over 5 Years the cost savings for the patients treated in these health sectors was $3.4m.

Conclusions: This study demonstrated that choosing HDx as alternative line of therapy may result in cost savings. In addition to HDx clinical benefits associated with better clearance of large middle molecules, the increased adoption of HDx with Theranova may provide further economic benefit.

Funding: Commercial Support - Baxter AG

FR-PO460

Assessing the Value of an Integrated Multidisciplinary Patient Centric Program for Patients in Hemodialysis

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Background: Chronic kidney disease (CKD) constitutes a public health concern due to its notable morbidity&mortality and associated costs. The Patient Care Coordination program (PCC) provides comprehensive and personalized care to hemodialysis (HD) patients. This study evaluated the cost-effectiveness of PCC compared to standard of care (SoC).

Methods: The study included patients in 9 HD clinics (5 PCC, 4 SoC) in Catalonia, Spain, in 2020-2021. A comparative effectiveness evaluation was conducted to compare change in Individual Patient Performance Score (IPPS, score 0-100, evaluates parameters such as vascular access, adequacy of HD, anemia, mineral bone disease, arterial hypertension, nutrition/hydration status) and number of hospitalizations of PCC patients vs SoC during the first year in the program. Instrumental variables (IV) regression analysis was performed to address potential confounding; number of interactions with program specialists was a valid IV to estimate degree of PCC use. An incremental cost-effectiveness analysis (iCEA) through microsimulation was performed using the effectiveness data from the previous step, population data from the renal patient registry of Catalonia, and the cost of hospitalizations obtained from the Public Health System.

Results: 127 patients in PCC and 363 patients in SoC were included. The degree of PCC use had a positive impact on IPPS variation during the first year of the program (p= 0.012). In the iCEA the PCC program resulted in a mean gain of 3.4 additional IPPS points, a reduction of 0.2 hospitalizations per patient, and reduced mean costs of €1,265 per patient in the first year compared to SoC, resulting to be a dominant alternative (Figure 1).

Conclusions: Use of PCC resulted in positive impact in outcomes and reduced costs compared to SoC for HD patients. The PCC program represents thus a dominant alternative, with greater effectiveness and total cost savings that could sum up to €5.5 million per year in the region due to reduced hospitalizations. The findings underscore the relevance of comprehensive and personalized care in addressing the challenges of CKD and optimizing healthcare resource allocation.

Funding: Private Foundation Support

FR-PO461

Long-COVID-19 in Hemodialysis Patients: A Prospective Study

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Background: Long-COVID (LC) is defined as persistent symptoms after COVID-19 infection. It has been reported that up to 40% of COVID-19 survivors experience LC (O'Mahoney et al. *The Lancet*, 2023). We aim to determine if hemodialysis (HD) patients experience LC.

Methods: HD patients diagnosed with COVID-19 via RT-PCR test were enrolled from 01 to 04 2022 from 4 clinics in New York City. COVID-19 Yorkshire Rehabilitation Scale (C19-YRS) was administered at baseline, i.e. as soon as possible after diagnosis, and 1 and 6 months after baseline. C19-YRS also asks about pre-COVID symptoms; we used that symptom severity (SS) at baseline as comparator. While SS is graded from 0-10, 10 being the worst, global health score (GH) is reported with 10 being the best. Patient data were obtained from medical records. Paired t-tests were used examine differences in SS pre- and post- COVID-19 infection. Linear and generalized mixed models were used to examine the effect of time on continuous and discrete LC SS, respectively.

Results: We studied 16 patients (58±14 years old, HD vintage 2.7±3.4 years, 56% male, 81% Black, 19% Hispanic, no diabetic, 50 % hypertensive). Baseline C19-YRS was administered 43±23 days (range 9-108) after COVID-19 diagnosis. 5 patients were hospitalized. C19-YRS results are shown in Table 1. Compared to baseline, patients experienced significantly increased dyspnea, anxiety, and PTSD at 1 month and fatigue and inability to perform personal care at 6 months. Decreased mobility and activity of daily living were also observed, though not statistically significant. Lastly, patients reported decreased GH score at months 1 and 6 compared to baseline.

Conclusions: Following COVID-19 infection, patients report worsening LC symptoms. Further studies are warranted to investigate the long-term consequences of LC in HD patients.

Funding: NIDDK Support, Commercial Support - Renal Research Institute

Table 1.

	Pre-COVID n=16	Baseline n = 16	1 month n = 14	6 months n = 14
Global Health¥	6.7 ± 1.7	6.6 ± 2.0	5.6 ± 2.5†	5.5 ± 2.2
Breathlessness				
At rest	1.5 ± 2.1	1.7 ± 2.4	1.8 ± 2.8	2.9 ± 3.1
Getting dressed	0.9 ± 2.2	1.7 ± 2.9	3.4 ± 3.2*†	2.9 ± 3.0†
Walking up flight of stairs	2.6 ± 2.6	4.2 ± 3.4†	4.9 ± 3.1†	4.4 ± 2.5
Laryngeal/ airway complications	N/A	0.7 ± 1.5	1.2 ± 3.1	1.1 ± 3.0
Voice	N/A	0.8 ± 0.9	0.8 ± 2.1	1.1 ± 3.0
Swallowing	N/A	0.3 ± 1.3	0.1 ± 0.5	0.1 ± 0.5
Nutrition	N/A	0.5 ± 1.4	1.6 ± 3.3	0.4 ± 1.6
Mobility	1.2 ± 2.7	1.8 ± 3.0	2.8 ± 4.0	3.1 ± 3.1
Fatigue	1.1 ± 2.5	2.2 ± 3.0	3.4 ± 3.6	4.4 ± 3.2*†
Personal care	0.3 ± 1.0	0.4 ± 1.3	0.8 ± 1.5	1.9 ± 3.1*
Incontinence				
Bowels	N/A	0 (0%)	0 (0%)	0 (0%)
Urinary	N/A	0 (0%)	0 (0%)	2 (13 %)
Activities of daily living	1.3 ± 2.7	2.2 ± 2.8	2.5 ± 2.9	3.9 ± 3.2
Pain	1.0 ± 2.1	1.5 ± 2.8	3.2 ± 4.1	2.6 ± 3.6
Cognition				
Concentration	N/A	3 (19%)	3 (19%)	4 (25%)
Short term memory	N/A	4 (25%)	2 (13 %)	4 (25%)
Communication	N/A	1.4 ± 1.5	0.7 ± 1.8	1.7 ± 3.0
Anxiety	1.3 ± 2.3	1.0 ± 1.8	2.4 ± 3.0*†	2.0 ± 2.8
Depression	0.6 ± 1.4	1.1 ± 2.2	2.6 ± 3.2†	1.4 ± 2.6
PTSD Screen				
Unwanted memories while awake				
Mild	N/A	2 (13%)	2 (13%)	0 (0%)
Moderate	N/A	0 (0%)	0 (0%)	3 (19%)
Severe	N/A	0 (0%)	0 (0%)	0 (0%)
Extreme	N/A	0 (0%)	0 (0%)	0 (0%)
Unpleasant dreams				
Mild	N/A	2 (13%)	1 (6%)	0 (0%)
Moderate	N/A	0 (0%)	0 (0%)	1 (6%)
Severe	N/A	0 (0%)	0 (0%)	0 (0%)
Extreme	N/A	0 (0%)	0 (0%)	0 (0%)
Avoid thoughts				
Mild	N/A	1 (6%)	4 (25%)*	1 (6%)
Moderate	N/A	1 (6%)	0 (0%)	1 (6%)
Severe	N/A	0 (0%)	1 (6%)	0 (0%)
Extreme	N/A	1 (6%)	0 (0%)	1 (6%)
Thoughts about self harm	N/A	1 (6%)	0 (0%)	0 (0%)

*p<0.05, delta between baseline and months 1 & 6
† p <0.05 delta between pre-COVID and baseline, month 1 and month 6
PTSD, Post-Traumatic Stress Disorder
¥ Higher score on Global Health indicates better health status

FR-PO462

Risk of Hospitalization and Mortality Following Extreme Heat Events in Patients Undergoing In-Center Hemodialysis in the Western United States

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Background: Climate change is increasing the frequency of extreme heat events (EHEs) and this trend is projected to continue into the foreseeable future. Previous research indicates that patients undergoing hemodialysis treatment are at an increased risk of both hospitalization and mortality following exposure to EHEs, although earlier analyses were limited in scope to the Northeastern U.S. Here, we investigated the risk of hospitalization and mortality following exposure to EHEs in the Western U.S. among patients that receive in-center hemodialysis treatment.

Methods: We identified EHEs as days where the daily maximum temperature (Tmax) exceeded the 95th percentile distribution of daily Tmax values specific to the location and calendar day over a 20-year baseline (1980-1999). We linked EHE data with health records of 79,963 patients undergoing in-center hemodialysis treatment at Fresenius Kidney Care clinics (*n*=191) in Washington, Oregon, and California during the warm season (May-September) of 2001-2018. We conducted a time-stratified case-crossover analysis with conditional Poisson regression to investigate the association EHE exposure and the risk of hospitalization and mortality.

Results: We observed a total of 7,242 EHE days at the county scale during the study period. EHEs were associated with a 7% higher risk of all-cause hospitalization (rate ratio (RR): 1.07, 95% CI: 1.02, 1.1), and a 6% higher risk of all-cause mortality (RR: 1.06, 95% CI: 1.00, 1.13).

Conclusions: We observed an increase in the risk of both hospitalization and mortality following EHE exposure in the Western U.S., which agrees with earlier findings from the Northeastern U.S. These findings indicate that interventions, such as the implementation of early heat warning systems, are needed to improve outcomes for patients undergoing in-center hemodialysis.

Funding: Other U.S. Government Support

FR-PO463

Global Variability and Patterns of Use in Vascular and Peritoneal Access for Dialysis: Analysis of the ISN-Global Kidney Health Atlas Data

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Background: A well-functioning access (vascular or peritoneal) is key to adequate performance of dialysis. The International Society of Nephrology Global Kidney Health Atlas (ISN-GKHA) survey identified gaps in availability, patterns of use, funding models, and workforce for the provision of vascular and peritoneal accesses across countries.

Methods: Using the second iteration of the ISN-GKHA, countries were categorized by affiliations in the ISN regional boards and by World Bank income classification. Questions focused on availability of surgical aspects of care, access to education and availability of providers for the access creation.

Results: Data was available from 159 countries out of 160 that participated in the survey. Overall, public funding was available for hemodialysis (HD) central venous catheters in 92 countries (57%), for HD fistula or graft creation in 86 countries (54%), and for PD catheter surgery in 85 countries (54%). Public funding for the access types was highest in high-income countries than other country income categories. Overall, and in countries where HD was available, >75% of patients initiated HD with a temporary catheter in 21% of countries compared to patients commencing with a tunneled catheter (5%) or a fistula (5%) (Figures 1). Shortages of surgeons and radiologists were highest in low-income and lower-middle income countries.

Conclusions: There is significant variation in the availability, accessibility and patterns of use of vascular access and peritoneal catheters across countries with significant limitations in the needed workforce. In order to improve the outcomes and survival of patients on dialysis, strategies to increase the uptake of viable access are required.

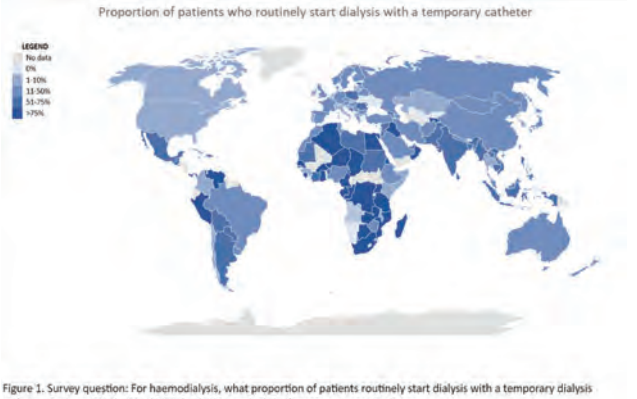

Figure 1. Survey question: For haemodialysis, what proportion of patients routinely start dialysis with a temporary dialysis catheter. Options: 0%, 1-10%, 11-50%, 51-75%, and >75%. Average response is shown.

FR-PO464

Nitric Oxide-Releasing Nanomatrix Gel Inhibits Venous Intimal Hyperplasia and Improves Vascular Remodeling in Porcine Arteriovenous Fistula (AVF)

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Background: Arteriovenous fistula (AVF) is the preferred vascular access for hemodialysis, but a large proportion fails to mature due to venous intimal hyperplasia (IH) formation and impaired outward remodeling. End-stage kidney disease has been linked to endothelial dysfunction characterized by reduced nitric oxide(NO) in the blood vessel. NO delivery during AVF creation may improve AVF maturation. Our study tested an NO nanomatrix gel applied perivascularly during AVF creation in a porcine AVF model.

Methods: AVFs were created in Yorkshire pigs by anastomosing the jugular vein to the carotid artery, treated with NO-releasing nanomatrix or control gel at the anastomosis, and sacrificed at day 35. Immunohistochemistry, histomorphology and hemodynamic changes were evaluated to assess the efficacy of NO gel in reducing intimal hyperplasia and promoting outward remodeling.

Results: NO gel-treated group vs control gel demonstrated significantly reduced IH($p<0.0001$) and type I collagen($p<0.05$). The patency of open lumen within AVF region was significantly higher in NO gel, along with increased blood flow and AVF diameter($p<0.05$). NO gel reduced intimal α-SMA, Vimentin, Desmin, CD68 and CD14 expression($p<0.05$).

Conclusions: AVFs applied with an NO-releasing gel reduce intimal hyperplasia and promote outward remodeling, and could serve as a therapy to promote AVF maturation.

Funding: NIDDK Support

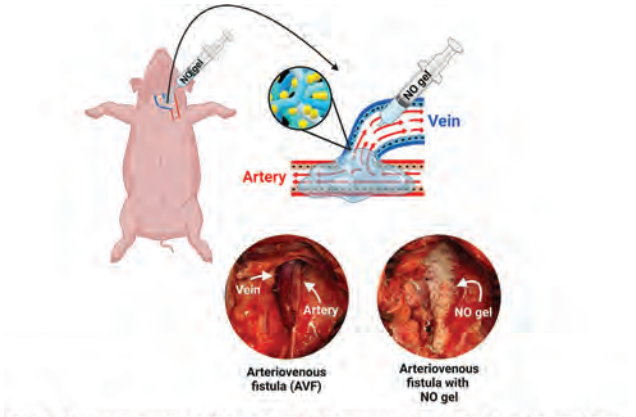

Fig.1. The NO-releasing nanomatrix gel was applied to AVF anastomosis (end jugular vein to side carotid artery)

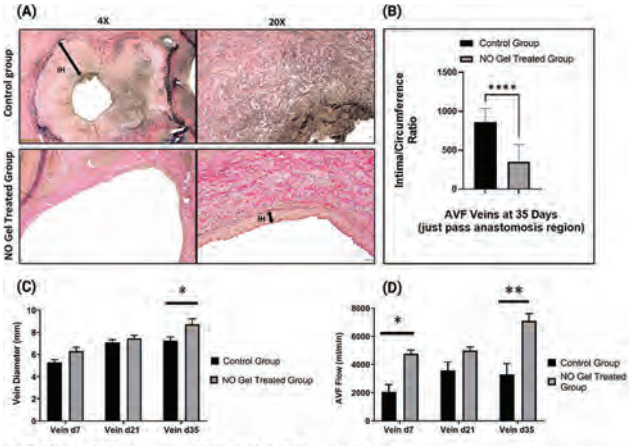

Fig.2. Effects of NO gel treatment 35 days after AVF creation in pigs
(A) Representative Van Gieson-stained cross sections show the development of venous intimal hyperplasia following 35 days post-AVF creation in the control group (note the level of aggressive intimal hyperplasia) and the NO-releasing nanomatrix gel-treated group. A visible increase in intimal thickness is observed when NO gel was not applied. Double-headed black arrows indicate intimal hyperplasia (IH) development.
(B) Morphometric analysis of intimal hyperplasia from AVF veins.
(C)(D) Quantifications of venous diameter (mm) and venous flow (ml/min) 35 days post-AVF.
All data are presented as the mean ± S.E.M. (n=3); *p<0.05 and ****p<0.0001 indicate statistical significance

FR-PO465

Contrast Venography vs. Intravenous Ultrasound in Arteriovenous Access Dysfunction

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Background: Contrast venography, a standard approach for evaluating hemodialysis vascular access dysfunction, has several limitations that may be overcome by intravascular ultrasound (IVUS).

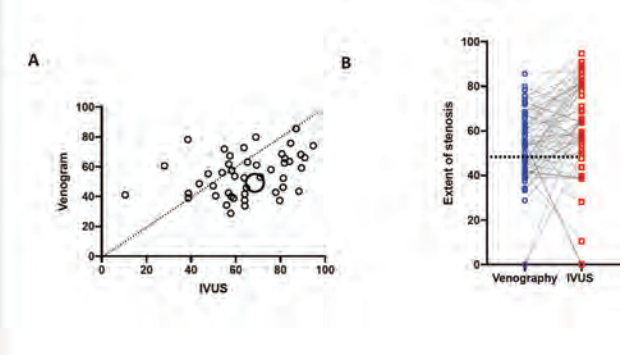
Methods: Venography and IVUS were performed in a prospective study of 41 patients with arteriovenous access dysfunction. Radiologists estimated stenosis on venograms and annotated cross-sectional IVUS images (N=250) that were used to train a deep neural network to analyze a larger set of IVUS images (N=27,315). Two measures were extracted from the IVUS images –eccentricity and homogeneity indices – characterizing stenosis shape and wall texture, respectively.

Results: Among the 33 patients with high quality images, 20 had a single stenosis and 13 had two stenoses of any severity (total of 46 stenoses). Twenty-four stenoses with >50% lumen reduction were detected by both venography and IVUS, and 14 additional stenoses were detected by IVUS but not by venography. A discordance between the two modalities was observed (McNemar ratio 7.11, p=0.0076; kappa 0.163). The severity of stenosis (%) was lower by venography (mean+SD 51.7+14.1) compared to IVUS (64.9+18.1, p=0.002). IVUS image analysis showed higher eccentricity and homogeneity indices for stenotic lesions compared to the reference segments. Metrics comparing stenoses and reference segments demonstrated substantial variability in the distribution of both indices.

Conclusions: Compared to IVUS, venography underestimated severity of stenoses in ~30% of patients presenting with arteriovenous access dysfunction. Further studies are needed to confirm the superiority of IVUS over venography and to establish the clinical utility of morphological indices for predicting stenosis progression and response to intervention.

Frequency distribution of stenoses severity detected by both modalities

Frequency of stenosis by venogram	Frequency of stenosis by IVUS		Total
	<50%	>50%	
<50%	5	14	19
>50%	3	24	27
Total	8	38	46



Disagreement between venogram and IVUS

FR-PO466

Role of Neutrophil Extracellular Traps in Vascular Access Thrombosis in Hemodialysis Patients

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Background: A patent vascular access (VA) is a lifeline for hemodialysis (HD) patients. However, vascular access is prone to thrombosis, which, if left untreated, can lead to permanent vascular access loss and increased mortality. Previous data have shown that neutrophil dysregulation and excessive release of neutrophil extracellular traps (NETs) may be a key mechanism in both venous and arterial thrombosis. The aim of this study is to evaluate the relationship between circulating NETs and VA thrombotic occlusion and their role in predicting permanent VA loss.

Methods: A total of 173 patients (73 arteriovenous fistula [AVF], 100 arteriovenous graft [AVG]) undergoing VA percutaneous transluminal angioplasty (PTA) with or without thrombectomy were included. Circulating nucleosome and myeloperoxidase (MPO)-DNA complexes were measured as markers of NETs. Serum von Willebrand factor (vWF) was measured as a marker of endothelial damage and thrombosis risk. VA loss was defined as access abandonment requiring dialysis catheter placement.

Results: Thrombectomy was performed in 81 patients. Patients who underwent thrombectomy were significantly older than those who underwent PTA only and used AVG more often than AVF. Circulating nucleosome levels were closely associated with MPO-DNA ($r=0.354$, $p<0.001$), serum vWF levels ($r=0.172$, $p=0.025$), and previous coronary artery disease ($r=0.226$, $p=0.003$). Nucleosome and vWF levels were significantly higher in thrombectomy cases than in PTA cases (nucleosome; 0.83 ± 0.70 vs. 0.35 ± 0.26, $p<0.001$, vWF: 9.0 ± 7.6 vs. 7.3 ± 6.2, $p=0.038$). The highest quartile of nucleosomes (Q4) was associated with an 11.4-fold increased risk of VA thrombotic occlusion ($p<0.001$). In addition, the risk of recurrent thrombotic obstruction within 6 months of PTA was also 3.1 times higher in the nucleosome Q4 group than in the Q1-3 group ($p=0.020$). During a median follow-up of 34 months, there were 25 cases of VA abandonment. The nucleosome Q4 was strongly associated with an increased risk of access loss (HR 2.56, 95% CI 1.23-7.44, $p=0.016$) even after adjustment for age, vascular access type, blood pressure, vWF, and duration of access use.

Conclusions: Higher circulating NETs are associated with thrombotic occlusion of VA and subsequent access loss in HD patients.

FR-PO467

Case Series of Real-World Use of Percutaneous Arteriovenous Fistulas in an Urban Predominantly Black US Hemodialysis Population

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Background: Arteriovenous fistula (AVF) is the preferred vascular access for end-stage kidney disease (ESKD), but most patients in the US start hemodialysis (HD) with a tunneled dialysis catheter. Percutaneous (pAVF) creation systems (Ellipsys and

WavelinQ) allow for non-surgical creation of AVFs. Published pAVF studies so far report higher patency rates (85-96%), less interventions, less surgical complications, and greater patient satisfaction compared to surgically created AVF. The percentage of Black patients varies from 0-20.6% in the literature, which vastly differs from our clinical population. We report a case series of real-world outcomes of pAVF in our urban predominantly Black HD patient population.

Methods: Retrospective chart review from 2021-2023 of patients from Emory Dialysis of all patients who received percutaneous AVF.

Results: Eleven patients had pAVF created by four proceduralists using either the Ellipsys or WavelinQ devices. Majority of patients were male (72.7%) and of Black race (91%). Common co-morbidities included hypertension (100%), diabetes mellitus (63.6%), and cardiovascular disease (36.4%). Mean age was 53.6 years, and the mean body mass index (BMI) was 34.6. Dialysis vintage ranged from 0.5 to 9 years, with mean duration of 2.7 years. 91% of patient had a tunneled dialysis catheter before having a fistula. Of 11 patients, 6 (54.5%) had their pAVFs functioning adequately for HD, 4 (36.4%) did not, 1 had 3 angioplasties but her pAVF was not used. Irrespective of ultimate functional patency, all required multiple interventions, with 10 of 11 patients (91%) requiring 2 or more interventions.

Conclusions: Overall, this case series provides real-world data on the use of pAVFs in an urban predominantly Black US dialysis population. To our knowledge, our study has the largest percentage of Black patients in the study population published so far. Our results indicate that though pAVFs can be successfully created in this population, a majority of patients require multiple secondary procedures, and only 54.5% were able to achieve functional patency. Further research with larger sample sizes and longer follow-up is warranted to evaluate the long-term patency rates and complications associated with pAVFs.

FR-PO468

Development of Senescence in the Rat Arteriovenous Fistula: Functional Effects of Heme

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Background: As shown in our previous studies, the murine arteriovenous fistula (AVF) model in the presence of CKD (AVF-CKD) evinces markers of senescence in the venous limb [Am J Physiol Renal Physiol. 315(5):F1493-F1499, 2018]. We now assess whether an AVF fashioned in the rat also exhibits senescence, and whether heme, a prosenescent agent, alters rat AVF function.

Methods: Subtotal nephrectomy was performed in rats after which an AVF was created by anastomosing the femoral artery and vein. At 1 and 2 weeks after AVF creation, the AVF was assessed for evidence of senescence, including increased expression of cell cycle inhibitors (p16 and p21), senescence-associated β-galactosidase (SA-β-Gal) and senescence-associated secretory phenotype (SASP) factors. In additional studies, the effect of heme on AVF blood flow was assessed in the rat.

Results: One week after AVF creation, p16 and p21 mRNA levels were markedly elevated in AVF veins compared to sham veins, as were p21 protein levels; p21 protein in the AVF artery was also increased. At 2 weeks, p21 protein was again upregulated in the AVF vein and artery, and protein levels of p53, an upstream inducer of p21, were significantly increased in the AVF artery, and tended to be higher in the AVF vein ($p = 0.083$). Upregulation of SASP factors was also observed in the AVF vein at 1 week; PAI-1, IL-6, TNF-α and MCP-1 mRNA were all markedly induced compared with sham values. At this time point, miR21, (associated with vascular senescence) was also elevated in the AVF vein. Additionally, SA-β-Gal activity, an established senescence marker, was significantly increased in both the artery and vein compared to their sham counterparts at 1 and 2 weeks post AVF surgery. Finally, heme administration increased AVF blood flow at 5 days after AVF placement, but resulted in lower AVF flow rates at 3 weeks.

Conclusions: We demonstrate that the rat AVF in the presence of CKD exhibits a senescent phenotype, akin to the murine AVF-CKD model. We suggest that heme, administered over 3 weeks, reduces AVF blood flow because of its prosenescent inflammatory effects whereas an early increase in AVF blood flow results from vasodilation that this agent can induce. These results point to the need to further investigate the role of senescence in AVF function/dysfunction, and the biphasic effects of heme treatment.

Funding: NIDDK Support

FR-PO469

Levels of Interleukin 8 and Monocyte Chemoattractant Protein-1 Are Associated with Arteriovenous Fistula Events and Upregulated in the Endothelium by Indoxyl Sulfate and TGF-β Pathway

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Background: Arteriovenous fistula (AVF) failure due to stenosis or acute thrombosis is a major concern in haemodialysis (HD) patients. Intimal hyperplasia responsible for AVF stenosis can be caused by several factors like endothelial dysfunction, uremic toxins, and inflammatory/profibrotic molecules. Studies suggest that endothelium-secreted inflammatory molecules Interleukin 8 (IL8) and Monocyte Chemoattractant Protein-1 (MCP-1) trigger intimal invasion of smooth muscle cells and enhance intimal thickening. We investigated the association of IL8 and MCP-1 serum levels with AVF events in haemodialysis patients and studied the ability of the uremic toxin indoxyl sulfate to upregulate IL8 and MCP-1 expression in endothelial cells.

Methods: We conducted a retrospective observational study in 205 haemodialysis patients with AVF. In vitro, we studied the mRNA expression of IL8 and MCP-1 in endothelial cells incubated with indoxyl sulfate at uremic concentration (200μM).

Results: During the study period of 731 days, 64 patients had an AVF event defined as a composite of the first occurrence of AVF thrombosis or AVF stenosis requiring endovascular treatment. Kaplan-Meier analysis revealed that patients with serum levels of IL8 > 0 pg/ml or MCP-1> 720 pg/ml had significantly more AVF events. Serum levels of IL8 and MCP-1 were positively correlated with the levels of the pro-fibrotic molecule TGFβ1 in HD patients. In addition, serum levels of MCP-1 were positively correlated with indoxyl sulfate. In vitro, indoxyl sulfate upregulated endothelial expression of IL8 and MCP-1 by activating its receptor, aryl hydrocarbon receptor, which in turn activated the non-canonical TGFβ pathway involving TAK1, p38 MAPK, and the transcription factor AP-1. The stimulation of the TGFβ signalling pathway by TGFβ1 amplified indoxyl sulfate-mediated IL8 and MCP-1 expression.

Conclusions: We demonstrated that AVF events are associated with high serum levels of IL8 and MCP-1, which are upregulated in the endothelium by activation of the TGFβ non-canonical pathway by the uremic toxin indoxyl sulfate. Our study could provide therapeutic targets to limit intimal hyperplasia and prevent AVF events in haemodialysis patients.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO470

Uremia and a Lack of Krüppel-Like Factor-2 (KLF-2) Are Responsible for an Inadequate Positive (Outward) Venous Remodeling in a Mouse Model of Arteriovenous Fistula (AVF) Stenosis

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Background: Although AVFs remain the gold standard for dialysis vascular access they have a maturation failure rate of over 50% at 6 months post surgery due to a combination of neointimal hyperplasia and an inadequate positive (outward) remodeling. A central molecule in the mechanotransduction pathways responsible for outward remodeling in response to increased flow is KLF-2. In order to better understand the mechanisms of inadequate outward remodeling in AVF maturation failure we aim to describe the impact of both uremia and the absence of KLF-2 in our mouse model of AVF stenosis.

Methods: AVFs were created between the carotid artery and jugular vein in (a) non-uremic WT C57Bl/6 animals (b) uremic WT animals (c) non-uremic KLF-2 KO animals and (d) uremic KLF-2 KO animals (n=3 in each group). The degree of outward remodeling was assessed by measuring the change in the venous perimeter from the juxta-anastomotic segment (0 microns from the anastomosis) to proximal vein 1200 microns downstream (proximal) to the anastomosis, using Image J morphometry.

Results: Non-uremic WT animals had a 48% increase ($p<0.0001$) in venous perimeter across the length of the venous segment (from 0-1200 microns). In marked contrast both the KLF-2 KO animals and the uremic animals (regardless of KLF-2 presence or absence) completely lost this increase in venous perimeter (outward remodeling).

Conclusions: Our results demonstrate that KLF-2 is likely a strong driver of positive (outward) remodeling in our mouse model of AVF stenosis. At the same time uremia appears to be a strong inhibitor of outward remodeling (likely as a result of endothelial dysfunction) such that the presence or absence of KLF-2 in uremic animals does not have any impact on the remodeling process. Looking to the future our data suggest that (a) creating a local milieu around the AVF which inhibits the impact of uremic toxins and (b) upregulating KLF-2 are two molecular approaches that could reduce AVF maturation failure.

Funding: Private Foundation Support

FR-PO471

Local Sirolimus Delivery Reduces Arteriovenous Graft (AVG) Stenosis in a Pig Model

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Background: Dialysis vascular access is currently the "Achilles Heel" of hemodialysis due to the high rate of stenosis in both arteriovenous fistulae and arteriovenous grafts (AVG). AVG stenosis is due to an aggressive venous neointimal hyperplasia (NH) at the graft-vein anastomosis (GVA). Sirolimus is an anti-proliferative agent which has been shown to reduce NH in the setting of coronary stenting. We have previously developed a local sirolimus (SRL) drug eluting cuff (DEC; 2mg/month) linked to an osmotic pump that can be used to deliver high concentrations of SRL to the GVA with minimal systemic SRL exposure. We herein report on the use of the Sirolimus DEC (SDEC) versus a control solution (CDEC) in the setting of a validated pig model of AVG stenosis.

Methods: 10 AVGs (6 SDEC and 4 CDEC) were created unilaterally in Yorkshire Cross pigs. Animals underwent weekly ultrasound assessments for patency and were sacrificed at 8 weeks post surgery. At the time of sacrifice 1cm of graft downstream to the DEC and 1.5cm of downstream (proximal vein) was collected for analysis of average (avg) and maximal (max) stenosis (including any attached thrombus) across the entire graft-vein segment and also within the individual vein and graft segments, using Image J.

Results: All 10 grafts were patent at the 56 day time point. Systemic SRL levels peaked at between 0.86 and 1.6ng/ml at 3d. Percentage avg. stenosis (SDEC=30.4% vs CDEC=50.8%; p=0.025) and max. stenosis (SDEC=60.1% vs CDEC=80.6%; p=0.02) across the entire graft-vein segment was significantly reduced in the SDEC group. A similar pattern was found in the venous segment for avg. stenosis (SDEC=46.4% vs CDEC=72.9%;p=0.01) and maximal stenosis (SDEC=60.1% vs CDEC=80.6%; p=0.02) but not in the graft only segment for either avg. (SDEC=6.6% vs CDEC=22.7%;p=0.13) or max. stenosis (SDEC=9.9% vs CDEC=27.4%;p=0.19).

Conclusions: Our results (a) demonstrate the technical feasibility of using a SDEC for the local delivery of SRL to the GVA (b) document minimal systemic SRL exposure due to the SDEC device and (c) describe a significant reduction in both avg. and max. stenosis across the entire graft-vein segment. Future clinical development of the SDEC could significantly reduce AVG stenosis and make AVGs the preferred modality for dialysis vascular access.

Funding: Other NIH Support - NIA

FR-PO472

Association Between Vascular Access Type and Health-Related Quality of Life

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Background: The use of arteriovenous fistula (AVF), arteriovenous graft (AVG), or central venous catheter (CC) may differently affect patients' quality of life (QOL). We assessed the association between vascular access (VA) type and Kidney Disease Quality of Life Short Form (KDQOL-36) in a large, multinational sample of dialysis patients.

Methods: We enrolled 10148 European dialysis patients participating in the ePROM improvement program initiated in 8 European countries since September 2021. We assessed the association between the active vascular access type and KDQOL-36 subscales with generalized linear regression. All models were adjusted for potential confounders. We accounted for the multicenter design by including a random-intercept denoting patients' referral center.

Results: Catheter use was associated with statistically significant quality of life penalty in all KDQOL-36 subscales. However, the difference in score was very mild and did not reach clinical significance based on minimal clinically important difference estimation for all scales but the physical composite score (PCS12). Specifically, AVF was associated with 2-point better PCS12 scores, a small effect size difference.

Conclusions: Improving HRQOL of dialysis patients has been an elusive task as it may be associated with a multitude of factors which may require a multifaceted management approach. We found a small PCS12 advantage for AVF users which may be barely perceived as clinical important. Expanding AVF use may contribute to HRQOL improvement in combination with optimization of others modifiable clinical parameters.

QOL score	Catheter (N=2596)	Fistula (N=6379)	Graft (N=220)	p-value
BKD	37.8 (35.3-40.3)	40.3 (37.9-42.7)	37.7 (33.5-41.9)	<0.001
EKD	65.9 (63.9-67.9)	67.8 (65.9-69.7)	66.4 (63.2-69.7)	<0.001
MCS12	44.1 (43.0-45.3)	44.9 (43.7-46.0)	45.0 (43.2-46.7)	<0.05
PCS12	33.6 (31.1-36.0)	35.5 (33.0-38.0)	34.0 (31.2-36.8)	<.0001
SKD	76.2 (73.9-78.5)	77.4 (75.1-79.6)	75.6 (72.7-78.6)	<0.01

FR-PO473

Increase in Hemodialysis Initiation with a Catheter

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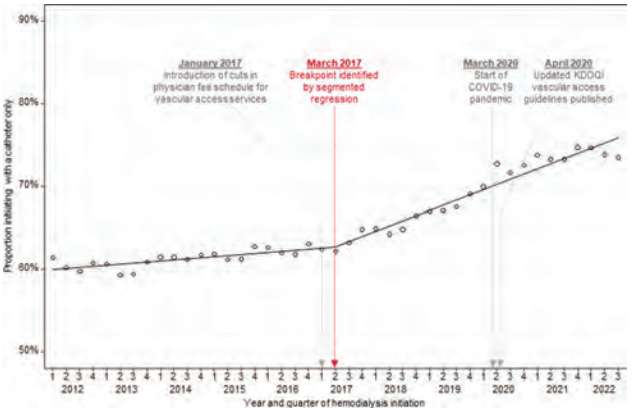
Background: Reliable vascular access is essential for hemodialysis (HD). Initiating HD with an arteriovenous (AV) access rather than a catheter is preferred for most patients. We modeled recent trends in the percentage of patients initiating HD with a catheter and no maturing AV access.

Methods: Using data from the US Renal Data System, we included all adults initiating maintenance HD between January 1, 2012 and September 30, 2022. We estimated the proportion initiating HD with a catheter only in each quarter, identifying a breakpoint in the temporal trend using segmented linear regression. We then fit a generalized piecewise linear model with a binomial distribution and identity link to estimate the temporal trend in catheter use before and after this breakpoint, with adjustment for age, sex, race/ethnicity, and seasonal effects.

Results: The analysis included 1,169,323 adults. A breakpoint was identified in March 2017 (Figure). In 2012, the overall proportion of patients initiating with a catheter only was roughly 60%. This proportion increased by 0.5% (95% CI 0.4-0.6%) per year, on average, until Q1-2017. After the breakpoint, the proportion increased more rapidly, by an average of 2.5% (95% CI 2.4–2.6%) per year, with nearly 75% of patients initiating HD with a catheter and no maturing AV access by 2022. Trends in catheter use before and after March 2017 were similar across categories of age, sex, and race/ethnicity. Other than a transient increase during Q2-2020, there was no enduring change in the pattern of catheter use during the COVID-19 pandemic.

Conclusions: We observed a concerning increasing trend in HD initiation with a catheter in the absence of a maturing permanent access between 2017 and 2022. The emergence of this trend in 2017 coincided with reductions for vascular access services in the Medicare Part B Physician Fee Schedule. Given further reductions in vascular access-related reimbursements occurred in 2023, trends in catheter use should be carefully monitored.

Funding: NIDDK Support



FR-PO474

Trends in Vascular Access Among Incident US Hemodialysis Patients Between 2015 and 2019

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Background: Vascular access guidelines recommend arteriovenous fistula (AVF) placement prior to hemodialysis (HD) initiation to decrease catheter (CVC) dependence. We quantified changes in vascular access between 2015-19.

Methods: Using the USRDS database, we identified 536,667 patients initiating HD from 2015-19. Patients starting HD with an AVF or with a CVC and a maturing AVF were considered to have undergone pre-HD AVF placement. We examined patient demographics, co-morbidities, functional status, insurance status, and duration of pre-HD nephrology care.

Results: AVF use at HD initiation decreased from 17% to 15% (12% relative decline) (**Fig 1**), and occurred across multiple patient subgroups. Pre-dialysis AVF placement decreased from 34 to 28% (18% relative decline). Patients with pre-dialysis AVF placement who used their AVF at dialysis initiation increased from 50 to 54%, indicating a higher AVF maturation rate. CVC use increased from 61 to 68% (11% relative increase) and AVG use remained constant at 3%. As compared to 2015, the adjusted odds ratio for initiation of HD with an AVF was 0.79 (95% CI 0.78-0.81) and for initiation with a CVC was 1.43 (1.20-1.45) in 2019. The best predictor of AVF placement and use was duration of pre-HD nephrology care. However, AVF use decreased and CVC use increased even among patients with prolonged pre-HD nephrology care (**Fig 2**).

Conclusions: AVF use decreased and CVC use increased at dialysis initiation from 2015-19.

Funding: Other NIH Support - NIMHD

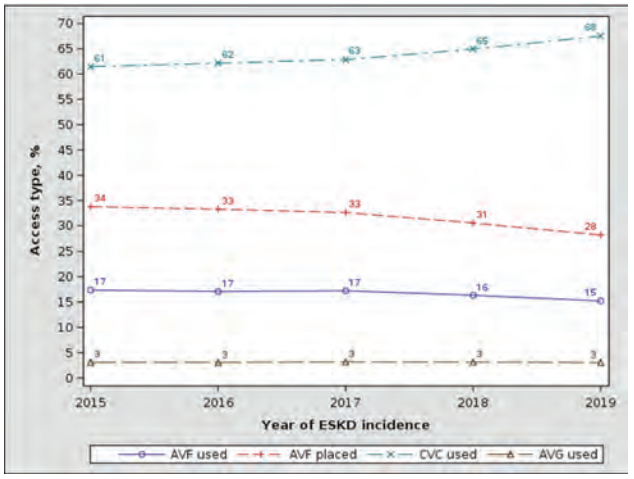

Fig 1

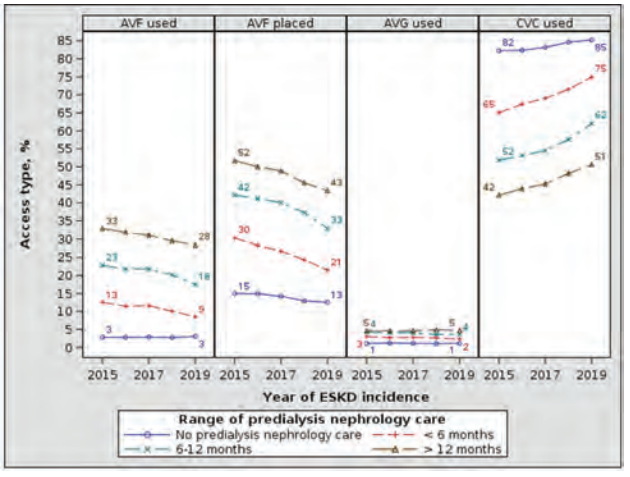

Fig 2

FR-PO475

Dialysis Access: A Post-Code Lottery? A Single-Centre Retrospective Review

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Background: For many chronic diseases there is a clear relationship between social deprivation, health literacy, healthcare access and delayed presentation with disease progression. Outcomes of renal replacement therapy (RRT) may be affected by patient deprivation influencing delays in diagnosis, provision of pre-dialysis education and optimal dialysis access, resulting in line sepsis, central venous occlusion and inferior dialysis clearance. This study explores the influence of patient deprivation on the provision of dialysis access in a cohort of patients, using a 7-point deprivation index linked to patient postcode (IMD2019).

Methods: Data on 1600 haemodialysis patients aged 18+ was gathered from 2015 to present day, from an urban and peri-urban catchment area. Demographic data, initiation date on RRT, mode of dialysis access at initiation and 1 year follow up were analysed with respect to the individual patient's IMD2019.

Results: Data from 308 patients was analysed. Mean age was 64 years, 64% (198) male and 50% Caucasian. A tendency towards lower levels of deprivation was noted, 16% of the cohort belonging to the least deprived decile. 207 (67%) patients commenced dialysis via a tunnelled line. At 1 year of dialysis, 88 (29%) of patients remained using a dialysis line. There was no statistically significant difference between IMD2019 for mode of access at initiation or the probability of having a fistula formed following dialysis initiation ($\chi 2$ 1.6618, p 0.798). The length of time from dialysis initiation to successful fistula formation was 7.5 months for deprivation deciles 1 and 2 (most deprived), 13 months for decile 10 (least deprived). Patients in decile 10 spent on average, 29 months on dialysis, compared to 55 months in decile 2. Deprivation deciles 5 and 6 performed marginally better than deciles 1 and 10 on the rates of access to fistula surgery (relative risk 1.2, p 0.1).

Conclusions: This dataset does not demonstrate a statistically significant impact of deprivation on the first or final mode of vascular access among haemodialysis patients. However, there are significant biases. The study was conducted in a predominantly low deprivation, Caucasian cohort. There is a suggestion that lower decile patients were initiated earlier on dialysis and that middle-decile patients may have better access to fistulas compared to deciles 1 and 10.

FR-PO476

Effectiveness of Custom-Made Under-Table Shield in a Mobile C-Arm Fluoroscopy Unit

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Background: It is emphasized that interventionists should adhere to the "As Low As Reasonably Achievable (ALARA)" principle and radioprotection strategies. However, radioprotection is limited when performing interventional vascular access procedures using mobile C-arm fluoroscopy, because the under-table shields are challenging to be mounted on an arm board of the table in a mobile C-arm angiography unit. We modified commercial tools and implemented custom-made under-table shields to overcome these limitations in the radioprotection strategy. This study aimed to quantitatively analyze the protective effect of the shields using real-time dosimeters.

Methods: Commercial shields were tailored and modified to completely cover the angiography table equipped with an arm board (Figure 1A). Custom-made under-table shields completely covered the table and arm board in all directions to protect operators and assistants (Figure 1B). There was no radiopaque material between the table and arm board, so the shields didn't interfere with the fluoroscopy-guided procedures (Figure 1C). To quantitatively measure the dose equivalent of radiation, real-time dosimeters (RaySafe i2) were located one meter and two meters away from the table (Figure 1D).

Results: Digital subtraction angiography was performed five times with eight pulses per second mode using a mobile C-arm fluoroscopy (GE OEC 9900 system), and the mean radiation doses were compared before and after applying the customized under-table shields. After application of them, the dose equivalent (μSv) was reduced by 34% at a 1-meter distance and 82% at a 2-meter distance, respectively (Figure 2).

Conclusions: Optimizing fluoroscopy settings and implementing radioprotective shields are crucial for ensuring safety. Under-table shields play a significant role in radioprotection strategy and should be emphasized. We customized commercial shields to overcome the limitations of radioprotective strategies in mobile C-arm fluoroscopy settings, and the shields proved effective in reducing the radiation dose.

Figure 1

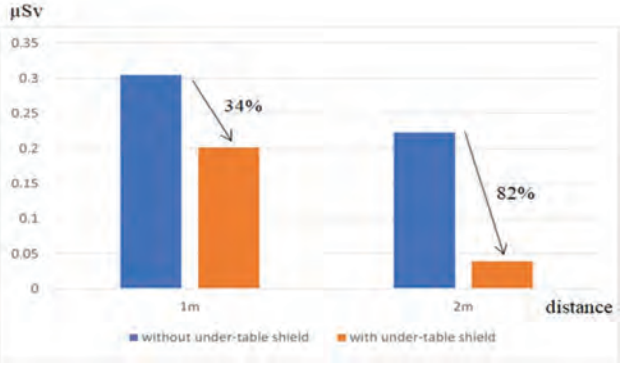

Figure 2

FR-PO477

Hemodialysis Catheter Rewiring vs. Removal and Replacement: Post Hoc Analysis of a National Stepped Wedge Cluster Randomized Trial

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Background: Tunnelled haemodialysis catheters are widely used but often fail prematurely. The optimal replacement strategy is unknown. Rewiring is less burdensome for patients but may predispose to infection. We aimed to quantify variation in tunnelled

haemodialysis catheter rewiring practices among Australian nephrology services, and to determine whether rewiring was associated with infection.

Methods: In a post-hoc analysis of the national stepped wedge cluster randomized REDUCCTION trial, encompassing 37 nephrology services and 6399 adult patients, we examined variation in the service-wide proportion of tunnelled catheters that were replaced by rewiring, for infectious or non-infectious reasons. Given the findings, we compared the absolute risks of, and time to infectious removal between rewired and non-rewired (new exit site) catheters that replaced failing non-infected catheters. Marginal Cox and competing risk proportional hazard models, including catheter, patient, and service-level covariates were used. Confirmed bloodstream infections were assessed in sensitivity analysis. Competing risks included removal for dysfunction and death before removal.

Results: Services universally avoided rewiring infected catheters but varied widely in rewiring non-infected failing catheters (range = 0 – 90% rewired). Among new catheters that replaced failed non-infected catheters, 36 of 480 rewired (7.5%), and 36 of 372 non-rewired (9.7%) were removed for infection. At three months the cumulative incidence of premature infectious and mechanical removals was 5% and 21% for rewired and 7% and 23% for non-rewired respectively. The hazard of infectious removal did not differ between rewired and non-rewired catheters (adjusted HR 0.81, 95% CI 0.46, 1.42). The incidence of confirmed catheter-related bloodstream infections and catheter dysfunction requiring removal were similar between groups.

Conclusions: The practice of rewiring non-infected failing catheters varied widely between services, was not associated with catheter infection, and did not appear to affect the high rate of subsequent catheter dysfunction in this population.

Funding: Government Support - Non-U.S.

FR-PO478

Burden of Haemodialysis Catheter-Related Bloodstream Infections in Australia: A National Data-Linkage Study

Ben Lazarus,[1,2] Kevan Polkinghorne,[1,3] Martin P. Gallagher,[2,4] Nicholas A. Gray,[5,6] Sarah E. Coggan,[2] Girish S. Talaulikar,[7,8] Sradha S. Kotwal.[2,4] REDUCCTION Investigators. *[1]Monash University, Clayton, VIC, Australia; [2]The George Institute for Global Health, Newtown, NSW, Australia; [3]Monash Health, Clayton, VIC, Australia; [4]University of New South Wales, Sydney, NSW, Australia; [5]Sunshine Coast University Hospital, Sunshine Coast, QLD, Australia; [6]University of the Sunshine Coast, Sippy Downs, QLD, Australia; [7]Canberra Hospital, Canberra, ACT, Australia; [8]Australian National University, Canberra, ACT, Australia.*

Background: Haemodialysis catheters are widely used and prone to infection, but the health impact of these infections is unknown. We aimed to quantify the health burden of haemodialysis catheter-related bloodstream infection (HDCRBSI) among chronic haemodialysis patients in Australia.

Methods: Patients who commenced chronic haemodialysis via a catheter in the REDUCCTION trial (Dec 2016- Mar 2020) were followed from first catheter insertion to the later of final catheter removal or end of the trial. Hospitalizations in all States and Territories (except WA) were probabilistically linked and classified using the principal ICD10-AM diagnostic code. Same-day admissions were excluded. Hospitalizations for vascular access infection (VAI) or bacteraemia, with concurrent HDCRBSI reported at time of admission, were characterized.

Results: In REDUCCTION, 4004 patients commenced chronic haemodialysis via a catheter and were followed for 968,783 days, with baseline characteristics comparable to the Australian haemodialysis population. Infection was coded as the primary reason for admission in 1838 (18.1%) of 10,154 non-same-day hospitalizations and accounted for 18,982 (24.1%) of 78,696 total days in hospital. Mean duration of hospitalization for VAI (3649 total bed days, 377 admissions) and bacteraemia (5981 total bed days, 391 admissions) were longer than for pneumonia (2183 total bed days, 361 admissions) or cellulitis (1535 total bed days, 139 admissions; all $p<0.01$). Concurrent HDCRBSI at time of hospitalization was reported in 148 admissions, 122 (82%) with primary code for VAI or bacteraemia. The median length of stay was 9 days (IQR 5-15), 19 (15.6%) admissions required intensive care (median 64 hours, IQR 27 – 110), 10 (8.2%) were complicated by metastatic infection, and 4 (3.3%) resulted in death.

Conclusions: Catheter-related infections are a major source of infectious hospitalization among Australians receiving chronic haemodialysis via a catheter.

Funding: Government Support - Non-U.S.

FR-PO479

The Magnetic Snare Endovascular Catheter System for Central Venous Stenosis

Jonathan G. Owen, Alex Bender. *University of New Mexico Health Sciences Center, Albuquerque, NM.*

Background: Central venous stenosis (CVS) is a common complication in patients with End Stage Kidney Disease undergoing hemodialysis, and most commonly occurs after exposure to tunneled dialysis catheters. CVS can lead to vascular access failure and can become life threatening. Sharp needle recanalization is an option for revascularization when a lesion can be approached bi-directionally, i.e. from the femoral vein and the internal jugular vein, however this procedure carries a high-risk of mediastinal perforation, which can be rapidly fatal. A novel two catheter system, the Magnetic Snare Endovascular Catheter (patent pending PCT/US23/62960), utilizing magnets to approximate either end of the stenosis has recently been developed to address this problem and improve safety of the revascularization procedure.

Methods: Mechanical engineering students at the University of New Mexico were recruited to develop an initial prototype of the catheter system. After initial success, one of the graduates was retained for further work and development of additional working prototypes.

Results: Three distinct prototype catheter systems have been developed for further testing. The first prototype utilizes a neodymium to neodymium magnetic tip and would traverse a central stenosis using thermal or radiofrequency energy. The second catheter design utilized a broad-based neodymium magnet on one catheter, and a needle fashioned from neodymium on the opposite catheter. The final prototype consists of a powerful electromagnetic tip that would be used to attract conventional steel needles and guidewires from the opposing side.

Conclusions: The Magnetic Snare Endovascular Catheter system is a promising new technology to improve safety of central venous stenosis revascularization. Three working prototypes are now developed for additional testing.

Funding: Private Foundation Support

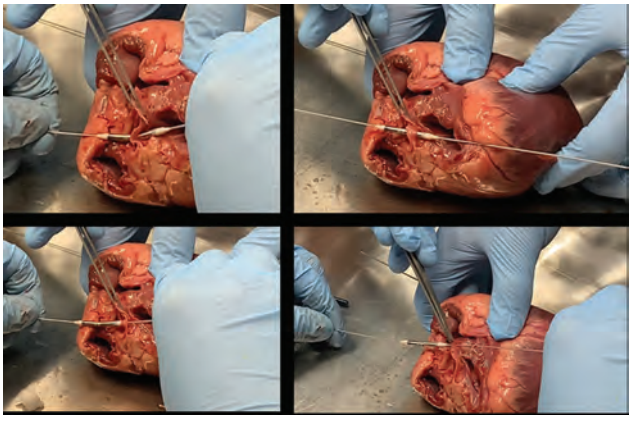

Figure 1: Proof of concept using a pig heart model

FR-PO480

Initial Testing of a Novel Vascular Access Device in a Rabbit Model

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Background: Ideal vascular access for dialysis is the arteriovenous fistula (AVF). However, AVF have delays in maturation or frequently fail to mature. Arteriovenous graft (AVG) mature more quickly but are prone to thrombosis and have higher incidence of infection. Tunneled dialysis catheters (TDC) can be placed rapidly but have the greatest incidence of infection. Recently, a novel vascular access device was created using a titanium needle guide to be inserted around an artery and separately a vein, allowing the placement of a modified removable shunt. The device could be usable for dialysis rapidly and obviate need for AVF or AVG placement. Feasibility of this device was achieved previously in a porcine model. A rabbit model is sought in this study to expand testing and to examine the effects of repeated arterial cannulation.

Methods: A male New Zealand white rabbit was obtained. After a 2-week acclimation, the animal was anesthetized, the right femoral artery dissected, and the vascular access device attached around it. The device was secured with dissolvable sutures, and site closed in three layers. The animal was recovered uneventfully, and after two weeks the site was well healed. The femoral artery was then cannulated via the device twice per week, with 2.5 mL blood withdrawn during each cannulation, for a total of 4 weeks, after which the animal was euthanized and submitted to pathology for examination.

Results: The vascular access device installed easily and without complication. The surgical site healed well with no visible signs of ischemia, trauma, or discomfort. All arterial access cannulations were successful with bright red arterial blood aspirated. After euthanasia, the femoral artery within the device was found to be intact, without neointimal hyperplasia or thrombosis on histologic examination. No visible signs of ischemia in the femoral artery vascular bed were seen. A small amount of neointimal hyperplasia was seen within the adjacent femoral vein, felt most likely secondary to manipulation and dissection from initial surgical implantation.

Conclusions: The novel vascular access device was successfully implantable in a rabbit model. The device allowed for repeated arterial cannulations as intended. No visible damage of the femoral artery was observed after 8 repeated arterial cannulations over four weeks.

FR-PO481

Achromobacter xylosoxidans: A Potentially Serious Occult Dialysis Catheter-Related Infection

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Introduction: Hemodialysis(HD) catheter-related infection is one of the major causes of morbidity and mortality in HD patients. Achromobacter xylosoxidans (AX) is an aerobic, oxidase, and catalase-positive gram-negative bacillus that lives in various

aqueous environments. There are reported cases of AX endocarditis, bacteremia, and an outbreak of AX bacteremia in a hemodialysis unit; however, after a thorough literature review, no case of isolated AX hemodialysis tunneled catheter infection was found. Therefore, we are reporting a case of an AX tunneled dialysis catheter infection causing sepsis.

Case Description: A 50-year-old African American man with a past medical history of end-stage-kidney-disease on hemodialysis for more than one year, hypertension, and hyperlipidemia, who had recently returned from Africa, presented with a low-grade fever, chills, and lethargy. While in Africa, the patient received hemodialysis via a right internal jugular permcath. He was treated with an unknown antibiotic in Africa for 14 days. However, his fever never resolved. On return to the United States, peripheral and tunneled catheter blood cultures revealed no growth, and no other focus of infection was identified. Chest x-ray and CT scan abdomen were unremarkable for any focus of infection. Respiratory PCRs were negative for viruses and atypical bacteria. As an inpatient, in spite of receiving ceftazidime and vancomycin for more than two weeks, he was still febrile despite repeat negative peripheral blood and central line cultures; therefore, a decision was made to remove the tunneled catheter and send the catheter tip for culture, which showed growth of achromobacter xylosoxidans(too numerous to count). It was resistant to a variety of antibiotics; however, sensitive to meropenem. He was treated with meropenem, and his fever resolved following the removal of the tunneled catheter.

Discussion: Achromobacter xylosoxidans is an aerobic, oxidase, and catalase-positive gram-negative bacillus living in various aqueous environments with low virulence. It can cause occult dialysis catheter-related infections and be challenging to identify and treat. Strains of AX are highly resistant to various antibiotics and should be treated with appropriate antibiotics, usually sensitive to antipseudomonal penicillin, levofloxacin, meropenem, and trimethoprim-sulfamethoxazole.

FR-PO482

Should Alcohol Lock Replace Antibiotic Lock in Catheter-Related Bloodstream Infection (CRBSI) Management?

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Background: Catheter related blood stream Infection (CRBSI) is a dreaded complication of Tunneled Cuffed Catheter (TCC), with a reported incidence of 1.1- 5.5 episodes/1000 catheter days. Patients with Staphylococcus aureus, Pseudomonas aeruginosa or fungal growth generally require catheter removal. As per the KDOQI clinical practice guideline for vascular access: 2019, Systemic antibiotics plus antibiotic lock is the current standard of care for CRBSI. This study was done to find the usefulness of 70% alcohol lock (in place of antibiotic lock) in patients with established CRBSI.

Methods: All dialysis patients with TCC as vascular access were the subjects of the study. As per our center's protocol, all patients were given heparin lock after each session of dialysis. CRBSI was diagnosed as per CDC/IDSA criteria. In patients with CRBSI, 70 % alcohol lock (2 ml in each port) was given for 3 consecutive days, in addition to systemic antibiotics. Outcome of these patients was studied and compared with retrospective controls, who were given 'antibiotic lock with systemic antibiotics'.

Results: Over the last two- years 188 TCCs were placed in 181 patients at our center. Our CRBSI rate was 1.38/1000 catheter days. We encountered 31 episodes of CRBSI in 23 patients. There were 16 males and 7 females, with mean age of 57.03 ±11.65 years. Presentation was with fever and chills in 80.6% and hemodynamic compromise in 20%. Relevant investigations showed raised leucocyte count in 23 (74.1%) and procalcitonin in 27 (87%) episodes. The etiological agents were gram positive organisms in 12 (38.7%) and gram negative infections in 19 (61%) episodes ; Staphylococcus aureus was isolated in 11 and albus in 1, Pseudomonas aeruginosa in 6, Klebsiella pneumonie in 8, citrobacter in 3 and E coli in 2 episodes. Only 4 cases required catheter removal. Over a mean follow up period of 145 days after alcohol lock, all catheter have been functioning well. On comparison with our retrospective data of 22 patients with CRBSI who were given antibiotic lock, 15 required catheter removal. The differeence in catheter salvage is statistically significant ($p<0.001$). Our study shows that alcohol lock with systemic antibiotics works as panacea.

Conclusions: Our single center data suggests that alcohol lock works wonder in the management of CRBSI and can be included in the current standard of care.

FR-PO483

Clinical and Demographic Characteristics Associated with Arteriovenous Access-Related Infections in US Patients Initiating Hemodialysis

Sonia J. Pulgar,[1] Mary P. Panaccio,[1] Joanna Willetts,[2] Mohamad A. Hussain,[3] Sheetal Chaudhuri,[2] Len A. Usvyat,[2] Laura E. Niklason.[1] *[1]Humacyte Global Inc, Durham, NC; [2]Fresenius Medical Care Holdings Inc, Waltham, MA; [3]Brigham and Women's Hospital Department of Medicine, Boston, MA.*

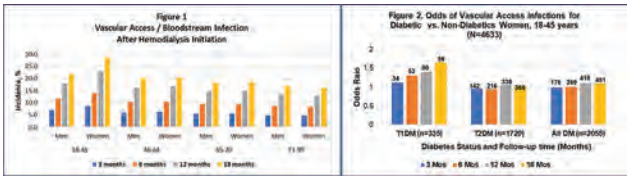
Background: End-stage renal disease (ESRD) patients are dependent on successful arteriovenous (AV) access for continual hemodialysis (HD). Infection risk can be elevated due to AV access type and may vary by patient factors and if severe – this can lead to hospitalization and even death. The study objective was to describe demographic and clinical factors associated with access-related infections (AVI) for patients initiating HD.

Methods: Patients aged 18+ years initiating HD at Fresenius Kidney Care (FKC) clinics from 2016 to 2018 were followed for up to 18 months, with censoring due to death or loss to follow-up. Patient characteristics were compared between those who developed an AVI (defined as graft infection or bloodstream infection) to those who did not. Data were stratified by gender, age range, and diabetes status. Univariate models were constructed and odds-ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Among the 87,707 HD incident patients, 43% were female, 56% were white, with mean age 63 yrs. Incidence of AVI was highest among the youngest age group (18-45), particularly, women (Figure 1). At 18 months, women aged 18-45 (OR: 1.3, CI: 1.2-1.35 vs. aged 45-64) and patients with type 1 diabetes (T1DM) were at high risk for AVI (OR: 1.4, CI: 1.2-1.6 vs. non-DM patients) (Figure 2). AVI risk was highest among younger women with T1DM (OR: 1.65, CI: 1.24 - 2.2 vs similarly aged non-DM patients). Patients with multiple access changes whose initial vascular access was an AV graft were among the highest risk compared to the overall population. Indigenous patients also had elevated AVI risk (23% by month 18) and were more likely to have multiple AV access changes.

Conclusions: Younger women with T1DM had the highest AVI risks compared to those without DM, men, and older patients. Multivariate modeling of this sub-population is required to assess the interplay of other factors mediating the risk of these poorer outcomes.

Funding: Commercial Support - Humacyte, Inc.



FR-PO484

The Vasa Vasorum Is the Gateway to Vascular Inflammation Determining Arteriovenous Fistula Outcomes

Laisel Martinez,[1] Miguel G. Rojas,[1] Zachary M. Zigmond,[2] Simone Pereira-Simon,[1] Marwan Tabbara,[1] Roberto I. Vazquez-Padron.[1] *[1]University of Miami School of Medicine, Miami, FL; [2]Veterans Affairs Medical Center, Miami, FL.*

Background: Postoperative vascular inflammation is believed to contribute to arteriovenous fistula (AVF) maturation failure. However, the cellular mechanisms controlling inflammatory cell recruitment and inflammation resolution after anastomosis remain obscure.

Methods: In this work, we used for the first time a combination of single-cell RNA sequencing (scRNAseq) and histologic validations to reveal the place of entrance of inflammatory cells into the venous wall following AVF creation.

Results: Analyses of vascular tissues collected in the first week after AVF creation demonstrate an extensive infiltration of leukocytes in the media and adventitia and less so in the intima. Interestingly, these AVF showed a notable expansion of vasa vasorum (VV) number and size. Next, we characterized the cellular composition of cells forming the VV of pre-access veins and AVF using scRNAseq and validated our findings by immunofluorescence. Single-cell profiling of endothelial cells (ECs) identified markers for arterioles, capillaries, and venules. Immunofluorescence staining demonstrated an abundance of capillaries throughout the entire wall, venules in the outer media and adventitia, and a comparatively smaller number of arterioles in the outer adventitia. Venular ECs had significant upregulation of adhesion molecules with respect to the other endothelial subsets, indicating that they may act as docking sites for leukocyte infiltration. This work demonstrates a diversity of VV in the walls of veins and constitutes an important foundation for the study of intramural vascularization in vascular access remodeling.

Conclusions: In conclusion, our data strongly support the importance of the VV network, and particularly venules, in postoperative inflammation and AVF outcomes. These results also support the perivascular delivery of drugs targeting neoangiogenesis and microvessel permeability as future treatments to improve vascular access outcomes.

Funding: NIDDK Support, Other NIH Support - NHLBI, Veterans Affairs Support

FR-PO485

Analysis of the Arteriovenous (AV) Fistula Maturation in Eastern North Carolina and Validation of the Failure to Mature Equation

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Background: AVF is the preferred vascular access for hemodialysis patients but has a high maturation failure rate. Lok et al developed a clinical prediction tool to identify AVFs at risk for Failure to Mature (FTM) and it has achieved good prediction accuracy. We aim to examine the AVF success rate at 6 months and validate the FTM equation in patients with AVF in Eastern North Carolina.

Methods: The retrospective cohort study was done to identify patients who received AVF as their first HD access from 12/01/2009 to 12/01/2020. The primary outcome was AVF failed to mature. The FTM equation risk score was retrospectively applied to our patient cohort and compared with the observed clinical outcomes using Receiver Operating Characteristic (ROC) curve. Univariate and multivariate logistic regression analyses were used to assess the association between the clinical predictors and AVF maturation. A nomogram was developed based on the regression coefficients from the multivariable model, and the weight (point) was given based on the regression coefficient.

Results: A total of 162 patients were found; the mean age was 55 years(SD:13.3), 41% were females, and 89% were African American. The failure to maturation rate at 6 months was 53.5%. Compared to the FTM cohort, there were statistically significant differences in age, ethnicity, BMI, presence of diabetes, CAD, and PVD($p<0.05$).

Univariate logistic regression showed PVD was associated with increased arteriovenous fistula failure (OR = 2.07; 95% CI = 1.05–4.09; p < 0.05). When results were adjusted for confounders on multivariate analysis odds ratio was 1.8 with a p-value of 0.08 (CI 0.91-3.8). The failure to maturation equation failed to predict maturation outcomes with the area under the curve performance of 0.587. We also developed a different scoring system by using coefficiency values of Hypertension, PVD, and CAD, calculated with multivariate analysis but AUC on the ROC was 0.63 with the new scoring system.

Conclusions: The failure to mature equation failed to predict fistula maturation failure in our cohort. The difference in characteristics between cohorts is the likely reason. PVD was shown to be significantly associated with fistula failure in univariate analysis but when adjusted for other variables it was no longer significant. Analysis for the rest of the clinical factors did not show any significance.

FR-PO486

Metabolomic Analysis of Plasma Samples Collected Before Arteriovenous Fistula Creation Reveals Metabolome Clusters that Associate with Maturation Outcomes

Xin Wang,[1] Syed S. Zaidi,[4] Cindy Chan,[5] Yan Yi Cheung,[2] Nadja Grobe,[1] Peter Kotanko,[1,3] Sandip Mitra,[4] Milind Nikam.[2] *[1]Renal Research Institute, New York, NY; [2]Global Medical Office, Fresenius Medical Care, Singapore, Singapore; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Manchester Royal Infirmary, Manchester University NHS Foundation Trust, Manchester, United Kingdom; [5]Fresenius Medical Care Asia Pacific Ltd, Hong Kong, Hong Kong.*

Background: The Manchester Vascular Access study was a prospective observational study intended to investigate the natural history and maturation of arteriovenous fistulas (AVF). We aimed to identify biomarkers that predict maturation success already before AVF creation.

Methods: Plasma samples were obtained before AVF creation. Unassisted maturation was defined either by successful hemodialysis or a combination of ultrasound features (vein size > 4 mm with fistula flow ≥ 500 ml/min) and clinical assessment. Untargeted metabolomic analysis employed liquid chromatography-mass spectrometry. Hierarchical clustering and principal component analyses were performed to cluster patients using 819 metabolite features. We used Chi-square test to explore differences in demographics, comorbidities, and AVF maturation between clusters.

Results: We studied 44 patients. Metabolomic analysis revealed 2 clusters (Cluster 1: 21 patients, Cluster 2: 23 patients) with diverse levels of plasma metabolites (Fig. 1). There was a significant statistical difference in unassisted maturation rates between the two clusters (Cluster 1: 85.7% vs. Cluster 2: 43.5%; p=0.0095). No significant differences between the clusters were found with respect to variables commonly associated with maturation (age, sex, diabetes, and cardiovascular disease).

Conclusions: In this cohort, we observed 2 clusters of metabolomic signatures associated with successful and unsuccessful AVF maturation, respectively. If corroborated in a larger cohort, metabolomic analysis could help identify biomarkers that predict AVF maturation success or failure already prior to AVF creation, thus allowing individualisation of vascular access planning. Future targeted metabolomic analysis may also shed light on biological pathways related to AVF maturation.

Funding: Commercial Support - Fresenius Medical Care

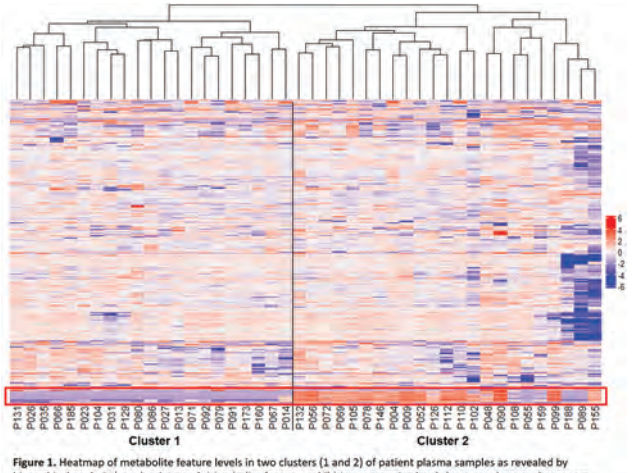

Figure 1. Heatmap of metabolite feature levels in two clusters (1 and 2) of patient plasma samples as revealed by hierarchical analysis (top dendrogram). Metabolite features exhibiting contrasting levels between the two clusters are highlighted within a red rectangle.

FR-PO487

Deficient Endothelial Autophagy Promotes Accelerated Atherosclerosis and Impaired Arteriovenous Fistula (AVF) Remodeling

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Background: Arteriovenous fistulas (AVFs) are the preferred vascular access for hemodialysis patients. Atherosclerosis is highly prevalent in arteries of patients with Chronic Kidney Disease undergoing hemodialysis. We investigated the role of macroautophagy in the venous region of the AVF in an atherosclerotic mouse model.

Methods: At 8-12 weeks of age endothelial cell autophagy-related 7 gene knockout mice with LDLR gene deletion (ecAtg7$^{-/-}$/LDLR$^{-/-}$) and mice where the LDLR gene was deleted (LDLR$^{-/-}$) were introduced to a high fat diet for 3 months before AVF creation surgery. Subsequently, mice underwent AVF surgery using the carotid artery and jugular vein. At day 7 blood flow in the AVF vessels was measured and mice were sacrificed, and histology and oil red staining were performed.

Results: Intimal hyperplasia was significantly greater in the AVF vein in ecAtg7$^{-/-}$/LDLR$^{-/-}$ mice compared to LDLR$^{-/-}$ mice ($p<0.04$). Collagen deposition was significantly greater in the AVF arteries and veins in the ecAtg7$^{-/-}$/LDLR$^{-/-}$ mice compared to LDLR$^{-/-}$ mice ($p<0.01$). Oil red staining in the AVF was significantly greater in ecAtg7$^{-/-}$/LDLR$^{-/-}$ mice compared to LDLR$^{-/-}$ mice ($p<0.01$). There was a trend towards increased blood flow in AVF vein and arteries in LDLR$^{-/-}$ mice compared to AVF vessels in ecAtg7$^{-/-}$/LDLR$^{-/-}$.

Conclusions: Autophagy may play an important role in AVF maturation by worsening atherosclerosis and arterial remodeling, which subsequently impacts vein remodeling.

Funding: NIDDK Support, Other NIH Support - NHLBI

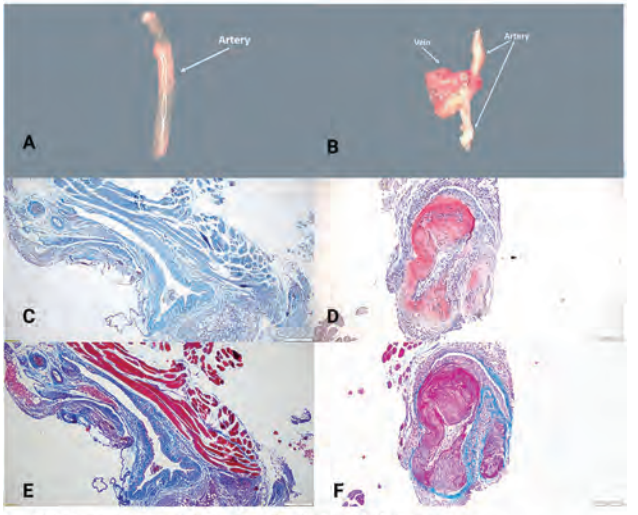

Fig. Histology and Morphology ATG7$^{-/-}$/LDLr$^{-/-}$ and LDLr$^{-/-}$ vessels.
A: Aorta from ATG7$^{-/-}$/LDLR$^{-/-}$ mouse. B: AVF from ATG7$^{-/-}$/LDLR$^{-/-}$ mouse after surgery. C and E: Oil Red O and Masson's Trichrome staining of LDLR$^{-/-}$ vein respectively. D and F: Oil Red O staining and Masson's Trichrome of ATG7$^{-/-}$/LDLR$^{-/-}$ vein respectively.

FR-PO488

Phenotypic Switch Study in Cultured Arterial and Venous SMCs: Messages for the Future Development of Novel Therapies for Vascular Access Dysfunction

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Background: Smooth muscle cell (SMC) dedifferentiation, proliferation, migration, and extracellular matrix protein secretion are key events in the progression of SMC phenotypic switch and the development of intimal hyperplasia (IH) as well as negative vascular remodeling, which is responsible for arteriovenous access (AVF and AVG) failure. Previous studies have demonstrated differences in proliferation between venous (vSMC) and arterial SMCs (aSMC) but have not attempted to characterize specific pathways in this process. We herein aim to characterize the role of IRS-1/KLF-4/p53 pathway and other dedifferentiation related pathways regulating SMC phenotypic switch in pig vSMCs and aSMCs.

Methods: To reach the SMC differentiation stage before applying phenotypic switch stimuli, confluent cells were exposed to differentiation medium (DM, containing 1%FBS, 1% P/S and 30ug/ml heparin) for different time periods. A hyperglycemic milieu was created through the addition of 20 mM glucose 24-48hr before harvesting/treatments. PDGFBB or IGF-1 was applied to create a dedifferentiation milieu for different durations. Cellular expression of proteins of interest were assessed using either immunofluorescence (IF) staining or Western blots.

Results: Hyperglycemia significantly suppressed myocardin expression and enhanced KLF-4 expression in both cell types. IRS-1 suppression in response to hyperglycemia,

however, only occurred in aSMCs. Exposure to DM resulted in a suppression of proliferation and an increase in SMC differentiation marker expression (calponin and myocardin), in both cell types. IF staining demonstrated that Thrombospondin-1 was highly expressed over time in vSMCs under both hyperglycemic and normoglycemic conditions whereas, in aSMCs, this only occurred in the setting of hyperglycemia. Finally, PDGFBB was able to induce dedifferentiation under either normal or hyperglycemic conditions in both cell types while IGF-I was able to induce SMC dedifferentiation only under hyperglycemic conditions.

Conclusions: Arterial and venous SMC appear to have both similarities and differences regarding dedifferentiation/phenotypic switch pathways in response to hyperglycemia or growth factors. Hyperglycemia and PDGFBB are potent stimuli for SMC dedifferentiation.

Funding: NIDDK Support

FR-PO489

Comparative Prognostic Accuracy of Vascular Access Flow and Artificial Intelligence (AI)-Based Arteriovenous Fistula (AVF) Failure Risk Score

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Background: Technical surveillance based on vascular access blood flow (Qa) measurement it is time consuming, requires training, and specific equipment. We developed a risk score which accurately and reproducibly predicts AVF failure within 3 months. The risk score may offer a cheap and automated alternative to Qa measurement. We compared the prognostic accuracy of Qa measurement and AVF failure risk score.

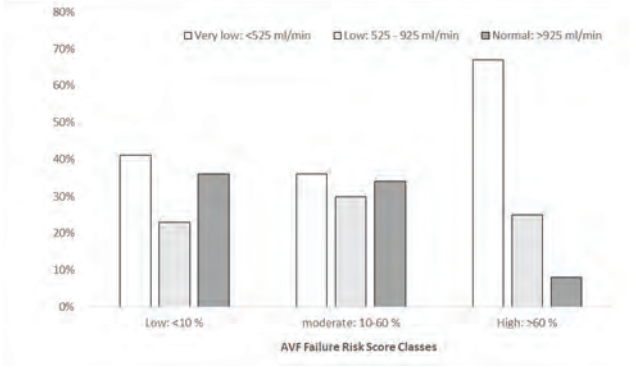
Methods: We included 8,969 AVF Qa measurements from 1,116 dialysis patients in 4 European countries. We used the AVF failure risk score to classify patients into 3 classes (low:<10%, moderate: 10%-60%, high:>60%) representing AVF failure risk within 3 months. Qa was measured with the thermodilution method and classified in very low (<525 ml/min), low (525-925 ml/min), normal (>925 ml/min). We computed the incidence of observed AVF failures by Qa levels and AVF risk classes to assess the overlap between the two metrics.

Results: A large share of patients was classified in the low-risk class by the AVF failure risk model (44%) whereas a tiny proportion were considered high risk (0.5%). We observed 907 AVF failures (10.1 %). There was a weak correlation between Qa and AVF failure risk score ($p>0.05$; Figure 1). The AVF failure risk score showed stronger association with AVF prognosis over a 3-month horizon compared to Qa measurement ($p<0.05$; Table 1).

Conclusions: Our study suggests that AVF failure risk may represents a valuable, cheap, automated alternative to Qa measurement for AVF technical surveillance.

	AVF Failure Risk		
Qa	low: <10 %	High: 10-60 %	Very high: >60 %
very low: <525 ml/min	4% (58)	21% (373)	83% (20)
low: 525 - 925 ml/min	5% (46)	17% (245)	67% (6)
normal: >925 ml/min	2% (31)	8% (127)	33% (1)

Incidence of AVF failures ("number of failures"/"number of Qa measurements" × 100) stratified by Qa and AVF failure risk levels.



Percentage of Qa measures for each AVF failure risk class.

FR-PO490

Impact of Arteriovenous Fistula (AVF) Dysfunctional and Repeated Endovascular Procedures on AVF Intervention-Free Survival

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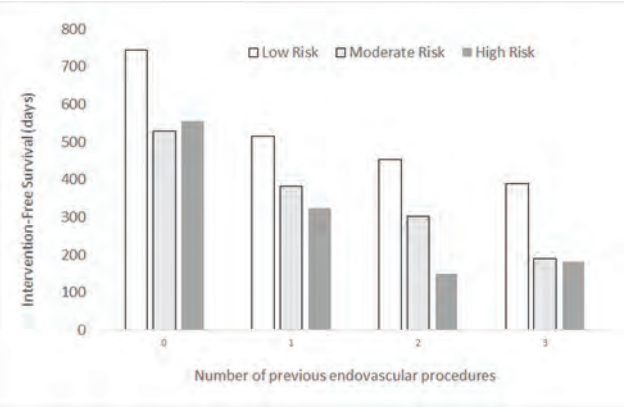
Background: Endoluminal and surgical procedure effectively re-establish patency of disfunctional Arteriovenous Fistulas (AVF); however, repeated intervention may reduce overall vascular access survival. We previously developed a risk score predicting AVF failure within 3 months that shows high accuracy and reproducibility. To enhance score interpretability we sought to assess its association with AVF intervention-free survival among patients with previous intervention to re-establish vascular access patency.

Methods: We included all patients receiving in-center hemodialysis therapy with an AVF in Nephrocare Portugues network between January 1st, 2015 and December 30th, 2022. We abstracted data from the European Clinical Database (EuCliD). We used generalized linear models to assess the association between the AVF failure risk score and intervention-free survival by the number of previous endoluminal interventions.

Results: We included 4,668 AVFs from 4,355 patients in the analytical dataset. Whereas patients with previous multiple endovascular procedures were common, only a small minority had more than 3 procedures. Both the AVF risk score class ($p<0.01$) and the number of previous endoluminal interventions ($p<0.01$) independently predicted AVF intervention-free survival (Fig. 1).

Conclusions: AVF intervention-free survival was associated with both AVF risk score classes and the number of previous endovascular procedures; both factors should be considered in evaluating the risk-benefit ratio of additional endoluminal procedure against alternative interventions for dysfunctional AVFs.



AVF intervention-free survival (in days) with respect to the number of previous endovascular procedures and AVF failure risk class

FR-PO491

Initial Vascular Access Flow Rate for Early Prediction of Need for Intervention: A Retrospective Cohort Study

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Background: Arterio-venous fistula (AVF) or graft (AVG) are lifelines for most hemodialysis (HD) patients. Low access flow rate (AFR) often requires intervention to prevent access failure. This study examines if AFR, measured at initial AVF/AVG cannulation, predicts need for intervention in the first year.

Methods: From 2012 to 2021, 52 (30.7%) of 169 patients with surgical AVF/AVG creation had AFR measurements. Up to three values were collected per subject. Need for intervention within one year was documented.

Results: Of 52 subjects, 28 (53.8%) required access intervention. After stratification by need for intervention (data not shown), patient characteristics were not significantly different. However, *first* AFR was significantly lower in the group with access intervention (898±495 vs. 1471±777mL/min; P=0.003), as was *average* AFR (841±399 vs. 1506±700mL/min; P<0.001). Receiver-operating characteristic (ROC) curve analyses (Figure1 and Table1) showed that *first* AFR (area-under-the-curve [AUC] 0.743; 95% CI 0.608, 0.877) and *average* AFR (AUC 0.775; 95% CI 0.648, 0.903) predicted need for access intervention within one year.

Conclusions: In HD patients, early AFR measurements can predict access intervention within one year after initial access cannulation. Our results are limited by single center setting and small sample size. Further studies are needed to determine optimal AFR cut-offs that indicate AVF/AVG at higher risk of early stenosis.

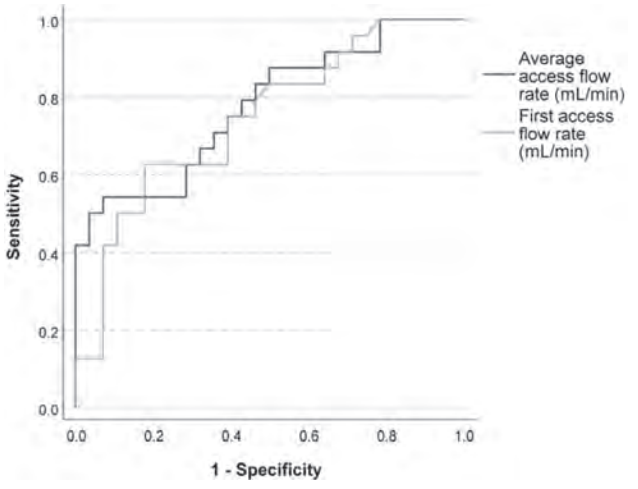

Figure 1. Receiver operating characteristic (ROC) curve showing diagnostic performance of *first* and *average* access flow rates (AFR) in new arterio-venous fistulas (AVF) and grafts (AVG) for predicting need for intervention within one year.

Receiver-operating characteristic (ROC) curve analyses

Vascular access type	Area-under-the-curve	95% confidence interval	P value
AVF and AVG combined (*n* = 52)			
***First* vascular access flow rate**	0.743	0.608, 0.877	< 0.001
Average* vascular access flow rate	0.775	0.648, 0.903	< 0.001
AVF only (*n* = 31)			
***First* vascular access flow rate**	0.696	0.508, 0.884	0.04
Average* vascular access flow rate	0.746	0.574, 0.918	0.005
AVG only (*n* = 21)			
***First* vascular access flow rate**	0.865	0.702, 1.000	< 0.001
Average* vascular access flow rate	0.856	0.695, 1.000	< 0.001

* Average of the first 3 consecutive measurements derived from the Transonic vascular access flow methodology; AVF, arteriovenous fistula; AVG, arteriovenous graft.

Table 1. Area-under-the-curve (AUC) shows good diagnostic performance of access flow rate (AFR) for predicting patency-assisted intervention within one year.

FR-PO492

Be Positive: Breaking the Cycle of Recurrent Vascular Access Thrombosis

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Introduction: Vascular access failure is a major cause of morbidity in patients on haemodialysis. Thrombosis and stenosis can occur due to shear stress on the vessel wall and formation of a thrombus or fibrin sheath. Recurrent episodes of vascular access failure in the absence of anatomical factors such as a venous stenosis or haemodynamic factors such as hypotension raise the possibility of an underlying hypercoagulable state.

Case Description: A 28-year-old Irish male was commenced on haemodialysis via a tunnelled catheter following presentation with severe renal impairment with advanced chronic tubulointerstitial nephritis on biopsy. One year into diagnosis he began to experience repeated episodes of vascular access failure. Over the course of three months, he had five different malfunctioning catheters, including three right internal jugular tunnelled lines, one right internal jugular non-tunnelled line and one right femoral non-tunnelled line. This was despite use of catheter-locking solutions and heparin with dialysis. His left side was being saved for an arteriovenous fistula. He was screened for antiphospholipid syndrome as a cause of recurrent thromboses. He was found to have significant positivity for IgG anticardiolipin antibodies, IgG antibeta2 glycoprotein1 antibodies and lupus anticoagulant, persistent on two occasions more than twelve weeks apart. Triple antiphospholipid antibody positivity is associated with a high risk for thrombosis. He was commenced on warfarin with an INR target of 2-3. Seven months later he has had no further vascular access complications with a functioning right internal jugular tunnelled catheter and recent formation of a left arteriovenous fistula which is maturing well.

Discussion: In this case a thrombophilia screen critically altered management, halting the cycle of recurrent access failures in a young patient on haemodialysis. It has been reported that there is a higher prevalence of antiphospholipid antibodies in the haemodialysis population and some studies suggest that these are associated with a higher incidence of vascular access thrombosis. Our patient was strongly positive for all three antiphospholipid antibodies, idenitifying him as of particularly high risk. This case highlights the need to consider thrombophilia as a cause of recurrent vascular access failure, particularly in cases without an identifiable stenosis.

FR-PO493

Autosomal Dominant Polycystic Kidney Disease Results in Increased Flow in Murine Arteriovenous Fistulas

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a renotubular disease caused by mutations in the *PKD1*-gene. ADPKD is the most common monogenic kidney disorder, affecting 10% of end-stage kidney disease (ESKD) patients. The arteriovenous fistula (AVF) is the gold standard of hemodialysis vascular access, although non-maturation due to inadequate vascular remodeling is a major limitation of these conduits. Polycystins are expressed in endothelial and vascular smooth muscle cells, and involved in production of extracellular matrix supporting the vessel wall and mechanosensation. In the present study, we investigated whether reduced expression of *Pkd1* impacts vascular remodeling in a murine model of AVF failure.

Methods: Unilateral jugular-carotid AVFs were created in adult B6Ola*Pkd1*$^{nl/nl}$ mice and wild-type litter mates. Blood pressure was measured using a tail cuff, before and six days after AVF-surgery. Flow volume was measured weekly over three weeks post-AVF creation using doppler ultrasound. After three weeks, the mice were sacrificed and AVFs were used for histological analysis and collagen analysis through multiphoton microscopy. Longitudinal flow data was analyzed using Mixed-effects model, histological data using the Mann-Whitney U test.

Results: B6Ola*Pkd1*$^{nl/nl}$ mice show signs of renal failure, with cystic kidneys and elevated blood urea levels throughout the study. *Pkd1*$^{nl/nl}$ mice had elevated mean arterial blood pressure at both timepoints compared to WT mice (1.2 and 1.3 fold increase in ADPKD mice). Whereas arterial flow was comparable in both groups before surgery, AVF flow in *Pkd1*$^{nl/nl}$ mice was consistently higher post-AVF creation (1.9 fold difference, p=0.0002, at all time points). There was no difference in luminal area between the two groups, nor aneurysm formation in the afferent artery. Histological analysis revealed a reduction of collagen deposition in the venous outflow tract in *Pkd1*$^{nl/nl}$ mice at 21 days post-surgery.

Conclusions: AVFs in mice with ADPKD are characterized by a higher flow and reduced collagen deposition in the venous outflow tract, when compared to wild type mice. Clinical studies should reveal if ADPKD patients have better primary patency rates of their AVFs compared to patients with other causes of ESKD.

FR-PO494

Arterio-Venous Shunt and Right Heart Function and Structure

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Background: Emerging evidence suggests that right ventricular dysfunction (RVD) is a major determinant of adverse health outcomes. Data regarding the effect of AV shunt (AVS) placement on right heart function (RHF) and right heart structure (RHS) are sparse.

Methods: We conducted a cross-sectional study on patients with advanced CKD or ESRD who were followed by URMC nephrology faculty. We identified subjects who underwent an ambulatory echocardiogram within 90 days of AVS creation (Pre) and another ambulatory echocardiogram at least six months after AVS creation (Post). Original echocardiographic images were re-read to focus on RHF and RHS. Measures of RHF included: Tricuspid annular plane systolic excursion (TAPSE) and right ventricular fractional area change (RVFAC). Measures of RHS included length and diameter in systole and diastole. Changes between first and second echocardiograms were assessed. Continuous variables were analyzed by paired T-test. Categorical variables were analyzed by the McNemar test.

Results: Between 1/1/2010 and 12/31/2022, 1319 advanced CKD or ESRD patients under our care underwent at least one echocardiogram and/or underwent AVS construction. Thus far we have identified 39 subjects who met the criteria of having Pre and Post ambulatory echocardiograms that have interpretable measurements for the right heart. Selected subject characteristics are summarized in table 1. Selected echocardiographic changes are summarized in table 2.

Conclusions: Changes consistent with worsening RHF and RHS are observed in patients who underwent AVS construction. The observed population deterioration may have been attenuated due to survival bias as only subjects with two ambulatory echocardiograms at least six months apart were considered for analysis. Future efforts include adding a comparator group of failed AVS creation.

Table 1. Baseline Characteristics of Group (N=39)		Count or Mean (Std)	%
Male Sex		26	66.7%
Black Race		15	38.5%
Hispanic Ethnicity		6	15.4%
Age in years		59 (14.8)	
Days between Echocardiograms		1193 (920)	
Obese (BMI > 30)		17	43.6%
Diabetes		23	59.0%
Coronary Artery Disease		10	25.6%
Never Received Dialysis		4	10.3%
Table 2 Echocardiographic Findings	**Pre**	**Post**	**p**
	Count or Mean (Std)	Count or Mean (Std)	
E.F. < 50%	8	10	0.3173
Grade 2 or 3 Diastolic Dysfunction	16	17	0.405
Peak Pulmonary Pressure ≥ 50 mm hg	1	6	0.059
Mean TAPSE (cm)	2.40 (0.36)	2.26 (0.43)	0.0139
TAPSE < 1.7 cm	1	3	0.157
Mean RVFAC (%)	48.9 (7.3)	45.3 (7.1)	0.0005
RVFAC < 35%	1	4	0.0263
TAPSE < 1.7 cm or RVFAC < 35%	2	6	0.0455
Mean Systolic Diameter (cm)	2.24 (0.63)	2.44 (0.603)	0.0729
Mean Diastolic Diameter (cm)	3.11(0.63)	3.38 (0.722)	0.0219
Mean Systolic Length	6.098 (0.859)	6.33 (0.822)	0.0995
Mean Diastolic Length	7.14 (0.83)	7.35 (0.88)	0.1961

FR-PO495

Time-Dependent Efficacy of Percutaneous Angioplasty with Drug-Coated Balloon in the Treatment of Stenosis of Artero-Venous Fistulae: A Retrospective Study

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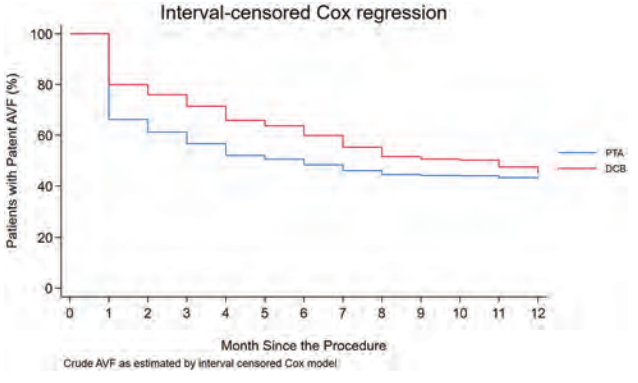
Background: Percutaneous transmural angioplasty (PTA) is the first-line treatment for stenosis of the arteriovenous fistulae (AVF). Even if paclitaxel drug-coated balloon (DCB) has become the standard of care, trials testing efficacy in comparison with standard PTA has provided conflicting results. We tested the hypothesis that conflicting findings from trials may result from the effect of DCB being short-lived.

Methods: We enrolled all patients undergoing angioplasty AVF stenosis with PTA or DCB 01/2011 to 04/2022 at the Parma dialysis centre. The choice of PTA vs. DCB depended on the temporary supply of each device. AVF patency was assessed after the procedure and at monthly intervals until month 12. We compared the hazard of AVF failure using interval-censored Cox-multiple regression model, with the procedure (DCB vs. PTA) being included as a time-varying effect (i.e. interacted with time), and the standard errors adjusted for accounting of multiple procedures within the same patient.

Results: We retrospectively examined 146 procedures (in 143 subjects), 69 with PTA and 77 with DCB. Baseline features were similar between groups, apart from DCB performed most often in patients with multifocal stenosis (22.1 vs. 1.4%; P<0.001) and with previous AVF (76.6 vs. 58%; P=0.021), but less often with cardiovascular disease (46.8 vs. 69.6%; P=0.007). Figure 1 shows crude AVF patency over the follow-up: survival curves diverged shortly after the procedure and eventually converged. Adjusted for different variables, the hazard of AVF failure was halved with DCB compared to PTA after the procedure (adjusted hazard ratio aHR 0.48 [95%CI: 0.26-0.97; P=0.016]); then, benefit vanish over time and aHR increasing (toward the null value of 1) by 1.20 per every month elapsed since the procedure (95%CI: 1.07-1.34; P=0.001).

Conclusions: Compared to PTA, DCB provides significant short-term benefit which vanishes by 12 months after the procedure.



FR-PO496

Differences in Vascular Access Can Influence the Level of Thrombo-Inflammation and Oxidative Stress in Patients with Hemodialysis

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Background: Patients undergoing hemodialysis require vascular access which includes arteriovenous (AV) fistula, AV graft, and tunneled catheter. At these sites changes in the vessel wall result in a positive feedback loop that propagates inflammation and cell proliferation which can progress to stenosis and thrombosis. This study was designed to compare the levels of biomarker of thrombo-inflammation and oxidative stress in patients with ESRD requiring different vascular access sites.

Methods: A prospective cohort of 95 patients undergoing hemodialysis at Loyola University Chicago were compared to 50 normal healthy individuals. The ESRD patients were stratified according to the vascular access sites. All plasma samples were analyzed for D-Dimer, PAI-1 antigen, vWF, CRP, annexin V, MPO, nitotyrosine, eNOs, IL4, IL6, IL10, VEGF, and EGF by using Sandwich ELISA methods and Randox Biochip Array.

Results: The ESRD patient cohort included 48 male and 47 female, with the median age 66-years, weight 77-kg and BMI 27.2-kg/m^2. The levels of thrombo-inflammation and oxidative stress marker were significantly ($p < 0.05$) higher in ESRD patients while MPO, IL4, and IL10 were significantly ($p < 0.05$) lower in ESRD patients compared to normal controls. The biomarker profiles demonstrated that various markers of thrombo-inflammation and oxidative stress were significantly elevated in patients with various vascular access types (table 1).

Conclusions: These studies suggest that ESRD patients with the AV fistula are at high risk of fibrinolytic deficit, inflammation, and oxidative stress they are at low risk of thrombosis. Patients with AV graft and tunneled catheter are at high risk of inflammation, oxidative stress, and thrombosis.

Table 1: Comparison of the level of thrombo-inflammation and oxidative stress in hemodialysis patients with different vascular access.

A. Comparison between AV Fistula and AV Graft			
Biomarkers	**AV Fistula N=49 (median)**	**AV Graft N=32 (median)**	**P Value**
D-Dimer (ng/ml)	683.9	1361.8	<0.001
PAI-1 (ng/ml)	16.8	12.7	0.049
CRP (ug/ml)	13.1	7.9	0.026
Annexin V (ng/ml)	7.7	4.4	0.001
MPO Activity (%)	96.1	92.4	0.047
IL-10 (pg/ml)	0.4	0.5	0.043
EGF (pg/ml)	2.9	2.1	0.035
B. Comparison between AV Fistula and Tunneled Catheter			
Biomarkers	**AV Fistula N=49 (median)**	**Tunneled Catheter N=14 (median)**	**P Value**
D-Dimer (ng/ml)	683.9	1213.4	0.033
Nitrotyrosine (nM)	107.6	58.7	0.035
VEGF (pg/ml)	8.4	5.1	0.011
C. Comparison between AV Graft and Tunneled Catheter			
Biomarkers	**AV Graft N= 32 (median)**	**Tunneled Catheter N= 14 (median)**	**P Value**
vWF (%)	212.1	194.0	0.033
MPO Activity (%)	92.4	102.2	0.032
eNOS (pg/ml)	542.5	271.7	0.008
IL-6 (pg/ml)	2.0	4.9	0.049
VEGF (pg/ml)	7.6	5.1	0.017
EGF (pg/ml)	2.1	3.5	0.034

Abbreviations: AV Fistula: Arteriovenous Fistula; AV Graft: Arteriovenous Graft; CRP: C-Reactive Protein; PAI-1: plasminogen activator inhibitor-1 antigen; MPO: Myeloperoxidase; IL-10: Interleukin 10; EGF: Epidermal Growth Factor; VEGF: Vascular Endothelial Growth Factor; eNOS: Endothelial Nitric Oxide Synthase; vWF: von-Willebrand Factor; IL-6: Interleukin-6.

FR-PO497

Outcome of Central Venoplasty and AVFistuloplasty in a Tertiary Care Centre in Eastern India

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Background: Access crisis is the Achilles heel of dialysis in ESRD patients. Central vein stenosis and stenosis in mature AVfistulas are common and negatively impact the quality of hemodialysis. Here we report the outcome of central venoplasty and fistuloplasty in our centre.

Methods: This was an retrospective observational study. Study period january21 to april22. Minimum follow up was 6 months. Central venoplasty was preceded with venography. Right/left common femoral, internal jugular/venous limb of fistula were used as access, followed by gradual balloon dilatation and stent placement if required. For fistuloplasty, arterial/venous limb was used as access, followed by balloon dilatation.

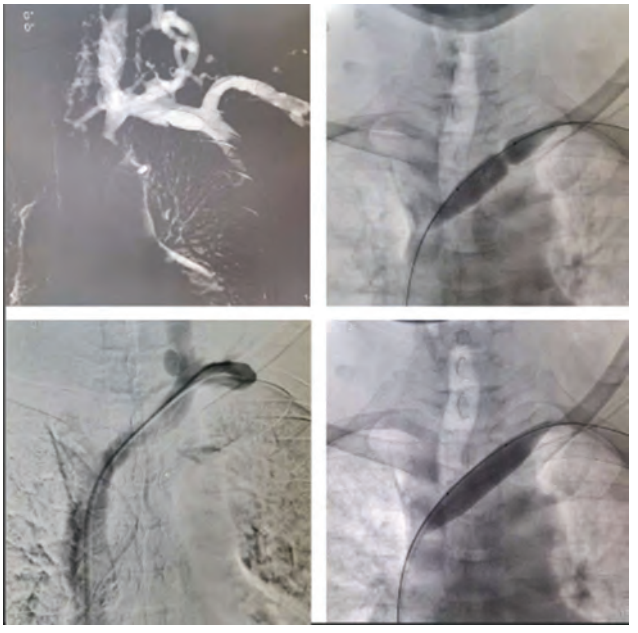
Results: Total 38 primary and 5 secondary venoplasty performed. 42.1% patients had tunneled catheter, 52.6% had AVF and 5.3% had temporary catheter.73.7%patients had access failure, 26.3%- upper limb swelling.73.7% had CRBSI episodes>3. Mean duration to develop CVS-34.5m(SD-13.6m). 32(84.2%) were successful and 15.8% failed. Restenosis developed in 7(18.4%). Mean duration to develop restenosis-

105.3d(SD-53.6d). 21 patients undergone Fistuloplasty. Mean patency of AVF -1.03Yr. perianastomotic stenosis -71.4% outflow stenosis -19.04%, inflow stenosis-9.52%. Fistuloplasty was successful in 85.7% cases. Mean fistula flow volume-110.47ml/min(SD-79ml/min)(pre) 438ml/min(SD-244.9 ml/min)(post). 4 cases developed restenosis. complications-minor bleeding-6 cases, venous rupture in 2 and brachial artery pseudoaneurysm in 1 case.

Conclusions: This outcome analysis suggests that central venoplasty and fistuloplasty have very good outcome in the management of access issues in ESRD patients, but cost and restenosis are the main limiting factors.

Types of AVF

radiocephalic	brachiocephalic	brachiobasilic
57.14%	28.57%	14.28%



FR-PO498

Safety and Efficacy of a Novel Compression Hemostatic Device for Vascular Access: A Quality Improvement Study

Mohamed Modar Abidian,[1] Rodella Broxton-Key,[2] Forest Rawls,[2] Vandana D. Niyyar.[1] *[1]Emory University School of Medicine, Atlanta, GA; [2]Emory Healthcare, Atlanta, GA.*

Background: Arteriovenous fistulas (AVF) and arteriovenous grafts (AVG) are common types of vascular access for chronic hemodialysis (HD) patients that require frequent needle cannulations. Proper cannulation and decannulation techniques are important for achieving hemostasis and preventing complications from bleeding. After decannulation, most protocols require manual pressure at vascular access sites to prevent bleeding. A novel compression device with a simple manual inflation/deflation pump has been developed to achieve post decannulation hemostasis. The purpose of this quality improvement (QI) study was to assess the safety and effectiveness of such a device in our clinical practice.

Methods: Our protocol for using the device is detailed in Figure 1. All patients who had HD with either AVF or AVG and were holding manual pressure for hemostasis were eligible for the study. Efficacy outcome was achieving post decannulation homeostasis within 15 minutes. Safety outcome measures were prolonged bleeding (more than 15 minutes), access thrombosis, and local infection. Patient satisfaction surveys were performed using the Likert scale.

Results: We evaluated 166 HD sessions using the compression device in 28 patients. There were no access infections or thrombosis. Only 1 (0.03%) episode of prolonged bleeding post decannulation in a patient who was on warfarin therapy. Almost all patients preferred the device to manual compressions and the average satisfaction rate was 4.6/5.

Conclusions: This novel device was safe and effective in achieving post-cannulation hemostasis and was preferred to manual compression by patients at our center.

Funding: Commercial Support - No financial payment was received by the manufacturing company Sun-Scientific as the device was donated free of cost

Table 1. Incidence Rate of Complications

No. of patients	Total No. (average per patient) of HD sessions performed using the device	No. of prolonged bleeding >15 min per patient	No. of access thrombosis	No. of local infection	Average patient satisfaction (1-5)
28	166 (5.8 per patient)	1 (0.03%)	0 (0%)	0 (0%)	4.6

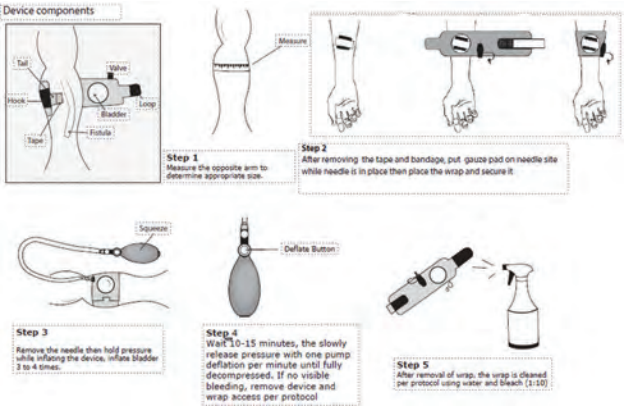


Figure 1: Instructions

FR-PO499

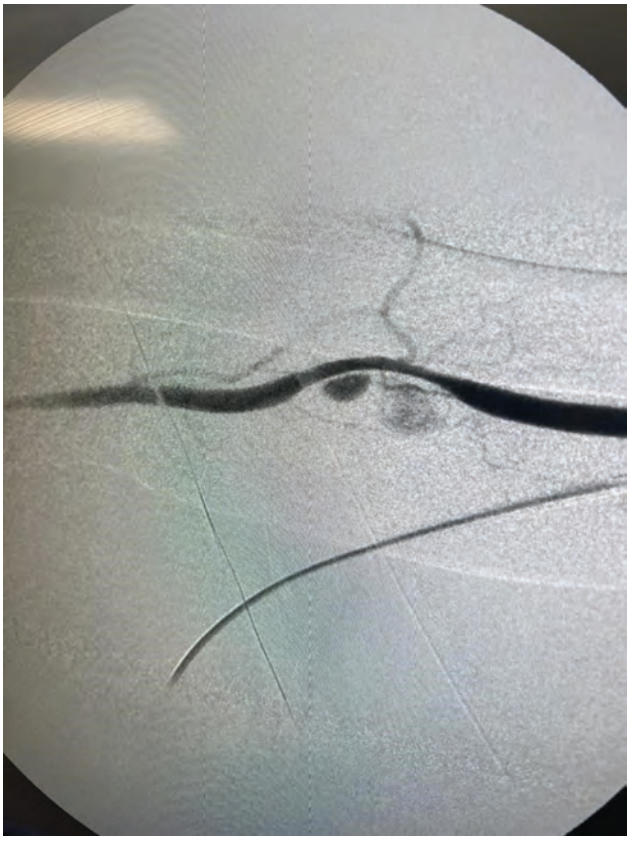
Brachial Artery Pseudoaneurysm (BAP): A Rare Cause of Median Nerve Neuropathy

Huy Truong, Hira H. Al-adroos, Mohamed Z. Ghyaz, Dalia Dawoud. *Riverside Community Hospital, Riverside, CA.*

Introduction: BAP, a complication in long-term hemodialysis (HD) patients, often develops without symptoms but can rarely lead to median nerve neuropathy. Differentiating between causes of the neuropathy is crucial due to distinct treatment approaches, but it is challenging and can result in severe consequences. This case report aims to raise awareness of BAP as a possible diagnosis for HD patients with the neuropathy.

Case Description: A 53-year-old man with end-stage renal disease undergoing HD via a left brachiobasilic arteriovenous fistula (AVF) presents to the hospital with pain and weakness in his left first three fingers for three weeks. Patient had a history of difficulty with AVF cannulations, but his HD sessions were able to be completed fully. During a thrombectomy for AVF thrombosis outpatient, a brachial artery pseudoaneurysm was incidentally discovered through a retrograde arterial angiogram. The patient underwent surgical intervention, which relieved the pain but did not fully restore motor function due to prolonged compression of the median nerve.

Discussion: BAP warrants prompt recognition in patient's presenting with median nerve neuropathy or pain at AVF sites. Symptoms may mimic other etiologies such as distal hypoperfusion ischemic syndrome. However, BAP can develop when there is arterial infiltration, especially in the patient whose AVF body overlaps with the feeding arteries. Therefore, it is crucial to educate dialysis staff not only on proper cannulation techniques but also on the mentioned anatomical variation. Additionally, physicians should consider arteriography to exclude the presence of arterial pseudoaneurysm in patients with progressing neuropathy, particularly those who have a history of difficulty with cannulation, to prevent prolonged nerve ischemia.



BAP in a retrograde arterial angiogram

FR-PO500

Pseudoaneurysms in Arteriovenous (AV) Fistulas: A Common Complication or a Rare Occurrence?

Nicole Wyatt, Naief N. Abudaff, Megha Salani. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Although pseudoaneurysms are primarily a complication seen with arteriovenous grafts (AVGs) with repeated localized cannulation, they can more rarely be seen in arteriovenous fistulas (AVFs). The incidence of AVF pseudoaneurysms remains largely unknown and there is limited quality evidence to guide management. We present a case of pseudoaneurysm in a native AVF that required surgical correction.

Case Description: A 56-year-old male with end stage kidney disease on hemodialysis via right brachiobasilic (BB) AVF presented with two days of shortness of breath and right upper extremity (RUE) swelling. He denied any inciting event or prior difficulty with AVF cannulation. Exam revealed unilateral RUE swelling and a tortuous right BB AVF with palpable thrill and audible bruit. There was no bleeding, ulcerations, or skin breakdown noted. A RUE ultrasound revealed a superficial thrombosis of right basilic vein and a saccular outpouching concerning for a pseudoaneurysm. A fistulagram revealed severe stenosis of right innominate vein requiring venoplasty/stenting, as well as two pseudoaneurysms in the cannulation zone, the largest of which was 2.8 x 2.2 x 1.5cm. Surgery was consulted and recommended against cannulation of AVF given risk of rupture. The pseudoaneurysms were deemed too large for non-invasive treatment, therefore he had a tunneled dialysis catheter placed and underwent prompt AVF revision including pseudoaneurysm resection and conversion to AVG.

Discussion: This case highlights an important complication of AVFs which impacts patient safety. Though many AVF pseudoaneurysms may be asymptomatic, they pose risks such as rupture and infection. Despite this, the incidence of AVF pseudoaneurysms is scarcely reported and ranges from 0.3% to over 15% in available literature. In addition, there is insufficient literature on treatment results with poorly available evidence and no randomized control trials to guide recommendations for management. Treatment decisions are largely based on access type and etiology of underlying problem, with options including ultrasound-guided manual compression, direct thrombin injection, or surgical options such ligation and excision/repair with graft interposition. We present this case to encourage further research to define AVF pseudoaneurysm classifications, natural history, and optimal treatment guidelines.

FR-PO501

mTORC2 Coordinates Renal Gluconeogenesis and Glucose Reabsorption

John E. Demko, Bidisha Saha, Enzo Takagi, David Pearce. *University of California San Francisco, San Francisco, CA.*

Background: The proximal tubule is uniquely responsible for both gluconeogenesis (GNG) and glucose reabsorption from the filtrate. Insulin signaling in the proximal tubule suppresses gluconeogenesis and stimulates glucose transport. However, the coordinated regulation of these processes is poorly understood. The kinase mTORC2 is regulated by insulin signaling in multiple cell types, but its mechanistic role in proximal tubule glucose homeostasis is unknown.

Methods: Rictor is a critical component of the mTORC2 complex. Inducible tubule-specific Rictor knockout (TRKO) mice were made with Pax8-rtTA TetOCre Rictor$^{flox/flox}$. Male and female TRKO mice and wild-type (WT) littermates were fasted for 18 hours then refed 4 hours before sacrifice. Whole kidney relative mRNA was measured via RT-PCR. Kidney plasma membrane and cytosolic proteins were separated using the BioVision Plasma Membrane Protein Extraction Kit, and protein abundance was measured with western blotting.

Results: There were no differences in serum glucose between TRKO and WT mice during refeeding (n=6–10 per group for all experiments). However, the mean ± standard error of the mean urine glucose excretion was 1824.9±768.5 µg in TRKO mice compared to 69.2±15.0 µg in WT animals during refeeding ($p<0.05$). TRKO kidneys compared to WT had significantly higher relative PEPCK protein abundance (0.54±0.05 vs 0.28±0.03 AU; $p<0.001$) and mRNA levels (0.54±0.17 vs 0.17±0.01 AU; $p<0.05$). TRKO kidneys compared to WT had statistically similar G6Pase protein abundance and significantly higher relative mRNA levels (0.58±0.17 vs 0.18±0.05 AU; $p<0.05$). Refed TRKO kidneys showed a decrease in plasma membrane SGLT2 after refeeding (0.64±0.07 vs 1.22±0.24 AU; $p<0.05$) and no significant difference in SGLT2 mRNA levels compared to WT mice. There were no significant differences in plasma membrane protein abundance or mRNA levels for SGLT1 or GLUT2 between TRKO and WT kidneys.

Conclusions: TRKO mice have glycosuria with normal serum glucose. TRKO mice fail to suppress renal GNG and have decreased plasma membrane SGLT2. Coordinated suppression of GNG and stimulation of glucose reabsorption by mTORC2 is critical to conserve energy by preventing excess glucose production and urinary glucose loss. Future studies will examine changes in the insulin and mTORC2 signaling pathways which mediate these findings.

Funding: NIDDK Support, Private Foundation Support

FR-PO502

High Potassium Suppresses Glycosuria in Tubule-Specific mTORC2 Knockout Mice

John E. Demko, Bidisha Saha, Enzo Takagi, David Pearce. *University of California San Francisco, San Francisco, CA.*

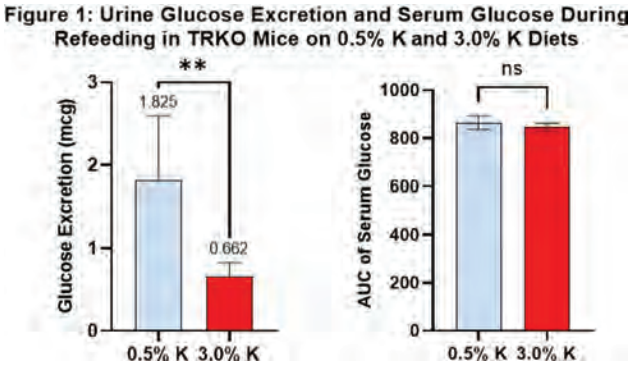
Background: Insulin signaling promotes proximal tubule glucose reabsorption and suppresses gluconeogenesis (GNG). mTORC2 is critical to insulin signaling in multiple cell types and there is emerging evidence for its importance in the proximal tubule. Potassium (K) has also been shown to regulate GNG in the kidney. However, the mechanism and overall significance of the relationship between K and glucose homeostasis is poorly understood.

Methods: Rictor is an essential component of the mTORC2 complex. Inducible tubule-specific Rictor knockout (TRKO) mice were made with Pax8-rtTA TetOCre Rictor$^{flox/flox}$. Mice were fasted for 18 hours then refed 4 hours before sacrifice. Mice were adapted to a 0.5% K diet prior to refeeding and then switched to either a 0.5% K or 3% K diet for refeeding. Data were obtained in metabolic cages during refeeding.

Results: Figure 1 shows a significant decrease in urine glucose excretion after refeeding on a 3.0% K diet compared to a 0.5% K diet despite no difference in area under the curve (AUC) of serum glucose (n=6–10 per group for all experiments). TRKO mice refed with a 3.0% K diet compared to 0.5% K diet had higher serum K (mean ± standard error, 7.3±0.4 vs 4.7±0.2mEq/L; $p<0.001$), higher hematocrit (42.0±0.8 vs 35.7±0.6%; $p<0.001$), decreased refeeding weight gain (0.70±0.09 vs 2.25± 0.24g; $p<0.001$), decreased food intake (1.02±0.08 vs 1.92±0.19g; $p<0.001$), and higher urine output (0.87±0.10 vs 0.39±0.05mL; $p<0.001$). There were no differences in baseline weight, refeeding water intake, or BUN between TRKO mice on either diet.

Conclusions: High dietary K rapidly suppressed glycosuria without changing serum glucose in TRKO mice. A change in GFR or filtered load of glucose is less likely to explain the reduction in glycosuria in these short-term experiments. Dietary K appears to act through an mTORC2-independent pathway to regulate renal glucose reabsorption. Future studies will examine the role of dietary K on GNG, glucose transporters, and insulin signaling pathways.

Funding: NIDDK Support, Private Foundation Support



**p<0.01; ns, not significant by t-test.

FR-PO503

Mechanisms of Renal Potassium Handling Sexual Dimorphism Resolved at Single-Cell Level

Hyun Jun Jung, Rick Grimm, Paul A. Welling, Lama Al-Qusairi. *The Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: A recent study revealed a rising trend of hypokalemia in the US general population, with women being more prone to hypokalemia. Our previous study revealed that the response to potassium (K^+) deficiency in mice phenocopies the human condition, with females being more susceptible to hypokalemia than males upon dietary K^+ deprivation.

Methods: C57BL6J wild-type male and female mice were randomized to a control or K^+-free diet for 8 days. K^+ balance and key transporters involved in renal K^+ secretion were analyzed. The sexual dimorphic transcriptional responses to K^+ deprivation were assessed using single nucleus RNA-Seq (snRNA-Seq) in whole kidneys.

Results: Males exhibited a more robust reduction in renal K^+ excretion in response to K^+ deprivation compared with females. The apical localization of K^+-secretory ROMK channel in the early distal nephron was less abundant in males under basal conditions and decreased to a greater extent than in females in response to K^+ deprivation. snRNA-Seq of whole kidneys from both sexes defined 45 cell-type clusters. Given the key role of the distal nephron in K^+ regulation, we initially analyzed distal tubular cells. Cell type-dependent transcriptome profiling revealed that connecting tubule (CNT) cells exhibited striking sex-dependent changes in response to K^+ deprivation. Pathway enrichment analysis of the CNT differentially expressed genes (DEGs) between control and K^+-deprived animals revealed that cellular processes associated with the cytoskeleton and actin organization were mostly reprogrammed in females, while ion channel regulating pathways exhibited more active reprogramming in males. Among the DEGs, transcript abundance of the *Kl* gene encoding for Klotho protein, a positive regulator of ROMK, was significantly decreased in K^+-deprived males only. Similar to the transcript levels, Klotho protein was significantly decreased in response to K^+ deprivation only in males, consistent with more robust reduction in ROMK, leading to more efficient K^+ conservation in males.

Conclusions: Females are more susceptible to hypokalemia due to urinary K^+ loss. This sexual dimorphism is mediated by sex-dependent gene reprogramming of the CNT. Specifically, ROMK and its regulatory network, including Klotho, are involved in shaping the sexual dimorphism of K^+ regulation.

Funding: Other NIH Support - O'Brien Centers, Private Foundation Support

FR-PO504

Changes in Renal Acid-Base Handling in Megalin-Knockout Mice

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Background: Megalin is a ~600 kDa receptor abundantly expressed in the renal proximal tubules. It facilitates reabsorption of a great variety of proteins avoiding their loss in the urine. Lack of megalin therefore leads to insufficient reuptake of its substrates, and thus low-molecular weight proteinuria. In addition, our preliminary data suggest that lack of megalin also causes impaired regulation of renal acid-base excretion.

Methods: Kidney specific mosaic megalin knockout mice Immunofluorescence Western blotting Liquid chromatography/mass spectrometry Biochemistry of mouse blood and urine

Results: Immunofluorescence showed a very marked increase of brush border carbonic anhydrase 4 (CA4) in proximal tubular cells lacking megalin compared to megalin-positive cells (Figure 1). This was confirmed by western blotting of cortex homogenates. To investigate if other proximal tubular proteins involved in acid-base handling were changed, we applied proteomics. We found a significantly decreased abundance of NBCe1A (-20%), V-ATPase and NHE3 (-20%) and confirmed an increased abundance of CA4 (324%) in megalin KO mice. Megalin knockout mice showed mild alkalosis during baseline conditions. Urine analyses showed a very unusually combination of high NH4+ excretion concomitant with reduced titratable acid excretion and increased bicarbonate excretion. Despite high NH4+ excretion net acid excretion was reduced.

Conclusions: Our data suggest that the absence of megalin has major effects on renal acid-base handling. We suggest that megalin KO mice have increased ammoniagenesis in PT-cells and that this causes a compensatory reduction in TA excretion and increase in bicarbonate excretion. Further experiments are necessary to solidify this hypothesis.

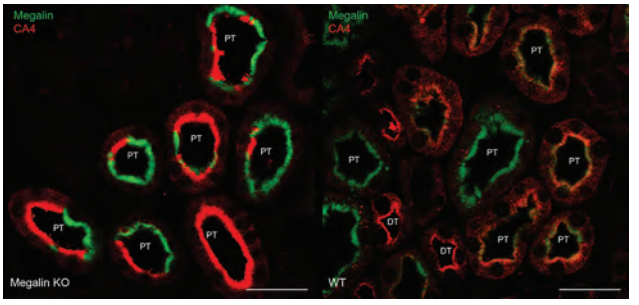

Figure 1. Micrograph showing double labeling of megalin (green) and CA4 (red) in a megalin KO (left) and a WT mouse (right). The megalin KO is mosaic, which means that it still has megalin in a few percentage of cells. Distal tubules (DT). PT=proximal tubule. Scale bar = 50 mm.

FR-PO505

LRBA Signalosomes Activate Vasopressin-Induced AQP2 Trafficking at Recycling Endosomes

Yu Hara, Fumiaki Ando, Hideki Yanagawa, Soichiro Suzuki, Tamami Fujiki, Shintaro Mandai, Yutaro Mori, Koichiro Susa, Takayasu Mori, Eisei Sohara, Shinichi Uchida. *Tokyo Ika Shika Daigaku, Bunkyo-ku, Japan.*

Background: In dehydrated states, increased plasma osmolarity stimulates the release of the antidiuretic hormone vasopressin from the posterior pituitary gland. Subsequently, vasopressin binds to vasopressin type 2 receptor in renal collecting ducts and then activates protein kinase A (PKA)/aquaporin-2 (AQP2) water channels signaling, which increases water reabsorption from urine. Lipopolysaccharide-responsive beige-like anchor protein (LRBA) is a protein kinase A (PKA) anchoring protein localized at renal intracellular endosomes that creates compartmentalized PKA signaling responsible for AQP2 phosphorylation. cAMP/PKA signaling phosphorylates AQP2, promoting AQP2 trafficking from intracellular endosomes to the apical plasma membrane; however, the molecular mechanisms by which LRBA mediates vasopressin-induced AQP2 phosphorylation remain unknown.

Methods: To elucidate the *in vivo* role of LRBA in vasopressin-induced AQP2 phosphorylation and endosomal trafficking, a density gradient ultracentrifugation technique was combined with an *in situ* proximity ligation assay (PLA) and superresolution structured illumination microscopy (SIM). *Lrba*$^{-/-}$ mice were used as negative controls for vasopressin-induced AQP2 activation.

Results: Sucrose density gradient and SIM revealed that AQP2 was stored in the recycling endosome under resting conditions. Desmopressin phosphorylated AQP2, translocating it from the recycling endosome to the apical plasma membrane. In contrast, SIM and PLA demonstrated that LRBA was constitutively localized on Rab11-positive recycling endosomes in WT mice regardless of vasopressin stimulation. Therefore, LRBA and AQP2 were well-colocalized in the absence of vasopressin stimulation. The loss of LRBA/PKA signaling by *Lrba* knockout impaired vasopressin-induced AQP2 phosphorylation, resulting in AQP2 retention at the recycling endosome. Defective AQP2 trafficking reduced urinary concentrating ability in *Lrba*$^{-/-}$ mice.

Conclusions: AQP2 was found to be stored on the LRBA-containing recycling endosome, and LRBA-induced compartmentalized PKA signaling efficiently phosphorylated AQP2 in response to vasopressin.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO506

Ghrelin Enhances Tubular Magnesium Absorption in the Kidneys

Matthias T. Wolf, Mingzhu Nie, Jing Zhang, Manjot S. Bal, Michel G. Baum. *The University of Texas Southwestern Medical Center, Dallas, TX.*

Background: In animal models mimicking bariatric procedures, bone disease, decreased serum levels of Ca^{2+}, Mg^{2+} and the gastric hormone Ghrelin were described. Ghrelin binds to the growth hormone secretagogue-receptor (GHSR) which is expressed in renal tubules. We tested if Ghrelin modifies tubular calcium or magnesium absorption via the ion channels TRPV5 or TRPM6.

Methods: We expressed GHSR1 with TRPV5 or TRPM6 channel in HEK293 cells and treated them with purified Ghrelin. Whole-cell current density was analyzed by patch-clamp recording. Nephron-specific gene expression of Ghrelin, GHSR, and Trpm6, was determined in microdissected tubules. Tubular localization of GHSR was examined by immunofluorescent (IF) imaging of GHSR-GFP mice. As there is more Ghrelin secreted with fasting, we elucidated the effect of Ghrelin in tubular magnesium homeostasis in GHSR-null mice at baseline and after starvation.

Results: After Ghrelin exposure whole-cell current density did not change for TRPV5 but increased for TRPM6 in a dose-dependent fashion. While a Ghrelin-mimetic also increased TRPM6 current density, addition of a GHSR antagonist inhibited the effect. GHSR signals via protein kinase A (PKA) and applying the PKA inhibitor H89 abrogated TRPM6 stimulation by Ghrelin. In microdissected tubules of wild-type (WT) mice there was abundant Ghrelin and GHSR mRNA in the TAL with 50% lower levels

in microdissected DCTs. TRPM6 was highly expressed in the DCT. Unexpectedly, we also detected TRPM6 mRNA in the TAL at 15% expression compared to DCT. IF studies of GHSR-GFP mice confirmed a GFP signal in the TAL but not in the DCT. In 3, 6, and 9 month-old GHSR-null and WT mice, baseline serum magnesium and 24-hour urinary excretion of magnesium was not significantly different. Starved GHSR-null mice, displayed a significantly higher urinary magnesium excretion and lower serum magnesium levels with downregulation of tubular magnesiotropic genes *Hnf1b*, *Cldn-16*, *Cldn-19*, *Fxyd-2b*, and *Parvalbumin*.

Conclusions: Ghrelin stimulates TRPM6 via GHSR and $G\alpha_s$-PKA signaling *in vitro*. The physiological significance of this mechanism is unclear given the higher GHSR mRNA abundance in the TAL compared to DCT. Starved GHSR-null mice had increased urinary magnesium excretion and lower serum magnesium levels. This may be mediated by Ghrelin-upregulation of TRPM6 in the TAL and/or upregulation of other magnesiotropic genes.

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FR-PO507

Lithium-Associated Tubulointerstitial Nephropathy, Role of Collecting Duct Cell Proliferation

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Background: Lithium salts are the main treatment for bipolar disorder, a common and serious illness. However, their effectiveness is offset by their renal toxicity, especially microcystic tubulointerstitial nephropathy, which can lead to end-stage renal failure. The aim of this project is to determine the mechanisms involved in this nephropathy, and to identify predictive biomarkers of renal outcome, especially GDF15, a growth factor known to be involved in the proliferation of intercalary A cells in an acid environment.

Methods: The project is based on a model of lithium exposure, for 1 month, of mice expressing or not GDF15, followed prospectively in a metabolic cage, allowing the analysis of urine, including the dosage of GDF15, by ELISA test. Cell proliferation was studied by immunofluorescence analysis of mouse kidneys collected at sacrifice. The role of GDF15 was also clarified in humans, from a prospective cohort of lithium treated patients, in whom GDF15 was measured in the urine and correlated with the clinico-biological phenotype.

Results: Plasma levels of GDF15 are increased in lithium treated mice ($p=0.019$). The phenotype of GDF15-/- mice is not different from WT lithium carbonate treated mice, while in lithium chloride treated mice, diuresis and cell proliferation are significantly lower in GDF15-/- mice ($p=0.0159$ and $p=0.0147$ respectively). In patients, GDF15 urinary excretion is positively correlated with diuresis ($p<0.0001$) and natremia ($p<0.0001$), but negatively with eGFR ($p<0.0001$).

Conclusions: GDF15 is both increased in lithium treated mice and patients, suggesting it as a prognostic marker of nephropathy. There is a differential causal relation depending on the associated anion, requiring more investigations. It could be a protective mechanism to limit polyuria by increasing the proliferation of the principal cells.

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FR-PO508

WNK1 Is a Central Osmolality Sensor for Arginine Vasopressin Release and Acts Through OSR1/SPAK Kinase Cascade

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Background: Terrestrial animals are subject to constant stress of water deprivation. Maintaining internal osmolality constancy is essential for life. The circumventricular organs (CVO's) of brain including the organum vasculosum of the lamina terminalis (OVLT) and subfornical organ (SFO) lack a blood-brain barrier. Neurons in OVLT and SFO detect increases in serum osmolality that stimulates the production of AVP in paraventricular nuclei (PVN) to be released in the posterior pituitary. We have recently reported that WNK1 in sensory neurons in CVOs functions as an osmolality sensor for AVP release (Xin et al., JCI, 2023). WNK1 activates Kv3.1 to increase action potential travelling down to PVN to increase AVP synthesis for release from the posterior pituitary. Here, we further investigated the hypothesis that OSR1/SPAK acts as the downstream kinase for WNK1 in regulating AVP release.

Methods: PVN nuclei from control mice and Spak-null mice with homozygous Osr1-floxed allele ($Spak^{-/-}$;$Osr1^{flox/flox}$) were stereotaxically injected with Cre-recombinase-carrying retrograde AAV virus. Metabolic cage studies were performed in mice. Urine output, water intake, serum, urine osmolality, serum AVP and copeptin levels were measured.

Results: Increased osmolality either by water restriction or mannitol injection activated OSR/SPAK in OVLT as evident by increased serine-373 phospho-SPAK/serine-325 phospho-OSR. Like Wnk1 deletion, double deletion of OSR/SPAK in OVLT caused polyuria with decreased urine osmolality that persisted in water restriction. Circulating levels of AVP and copeptin were increased by water restriction in control mice. In contrast, water restriction failed to increase the levels in OSR/SPAK-deletion mice. Knockdown of Kv3.1b channel in OVLT by shRNA reproduces the phenotypes.

Conclusions: WNK1 in osmosensory neurons in CVOs detects extracellular hypertonicity and mediates the increase in AVP release by activating Kv3.1 and increasing action potential firing from osmosensory neurons. OSR1/SPAK acts downstream of WNK1 to regulate AVP release. Our findings reveal that an intracellular protein acts as a sensor for extracellular tonicity and provide fresh insights into mechanism how body maintains osmolality constancy. Future studies will investigate how OSR1/SPAK regulates Kv3.1 channels.

Funding: NIDDK Support

FR-PO509

Replacing the Brattleboro Rat: Generation of an Inducible Avp Knockout Mouse Line Using CRISPR/Cas9 and Cre/LoxP

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Background: Arginine vasopressin (AVP) is a peptide hormone coded by the *Avp* gene, synthesized in the hypothalamus and secreted by the posterior pituitary. Dysregulation of AVP secretion contributes to a variety of human diseases. Previous studies of functional roles of AVP have been largely dependent on the use of Brattleboro rats, which manifest a spontaneous mutation in the *Avp* gene and lack circulating AVP. Despite their utility, Brattleboro rats are difficult to breed owing largely to the fixed nature of the *Avp* mutation, resulting in increased neonatal death and behavioral effects in the adults. Consequently, commercial breeders have ceased production, despite a continued need. To fill this need, we have now created a mouse model with tamoxifen-inducible deletion of AVP.

Methods: We employed CRISPR/Cas9 to flox a portion of exon 2 of the *Avp* gene. Successful insertion of the two loxP sites was confirmed by PCR using primers flanking the targeted regions. Restriction enzymes *Bam*HI or *Eco*RI were used to confirm correct targeting. For additional confirmation, PCR products were cloned into the TA-cloning vector and sequenced. Mice harboring the floxed allele were mated to mice that globally express a tamoxifen-inducible *Cre* recombinase.

Results: The resultant homozygous conditional knockout mice ($Cre^{+}Avp^{flx/flx}$) are viable, fertile and show no signs of polydipsia or polyuria prior to induction, indicating that the conditional alleles retain their wild-type function. Induction of *Cre*-mediated recombination by administration of tamoxifen (2-3 mg q.d., i.p. for 5 days) in 8-week-old mice resulted in a decrease in urine osmolality from 2076±138 to 122±6 mOsm/kgH_2O on day 31 after induction ($P<0.0001$). Sanger sequencing demonstrated the expected 1245 bp deletion at the *Avp* locus. The kidney parenchyma was structurally normal with no evidence of medullary atrophy 6 weeks after induction. Immunoblotting of AQP2 in the inner medulla showed a significant decrease in AQP2 band density in $Cre^{+}Avp^{flx/flx}$ mice to 27±14% of values in Cre^{-} floxed control mice ($P<0.05$).

Conclusions: We developed an inducible AVP knockout mouse line $Cre^{+}Avp^{flx/flx}$ that will be shared with the research community and are likely to be useful for further study of regulation of water balance and polycystic kidney disease, as well as neural, vascular, and metabolic roles of AVP.

Funding: Other NIH Support - NHLBI

FR-PO510

Acute and Chronic Modulation of Kidney Proximal Tubule Endocytic Capacity by Fluid Shear Stress

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Background: The kidney proximal tubule (PT) is uniquely specialized for efficient apical uptake of proteins that escape the glomerular filtration barrier. These proteins bind to the multiligand receptors megalin and cubilin and are internalized into apical early endosomes that rapidly mature into larger apical vacuoles (AVs). Dissociated ligands are delivered from AVs to lysosomes for degradation, while receptors are collected into dense apical tubules for recycling to the cell surface. We have extensively characterized an opossum kidney (OK) PT cell model cultured under continuous fluid shear stress (FSS) that has several-fold higher levels of megalin, cubilin, and endocytic capacity compared with static-grown cells. Additionally, cells cultured in this manner rapidly and reversibly adjust their endocytic capacity in response to acute changes in FSS. We hypothesize that flow-dependent modulation of endocytic capacity enables PT cells *in vivo* to preserve uptake efficiency in response to changes in glomerular filtration, though these mechanisms are unknown.

Methods: We combined biochemical, imaging, and mathematical modeling approaches to compare the effects of chronic vs acute changes in FSS on megalin trafficking. Biochemical measurements of surface expression, endocytic kinetics, and half-life were combined with quantitative imaging to determine subcellular distribution of megalin with markers of endocytic compartments. Data were fit to a previously validated mathematical model.

Results: Cells cultured under continuous FSS have faster megalin endocytic and recycling rates and slower degradation rates compared with static grown cells. These cells also have reduced steady state fraction of surface megalin due to the enhanced endocytic flux. By contrast, surface expression and endocytic kinetics of megalin were not significantly altered when cells were removed from FSS for 1h, despite an overall reduction in endocytic capacity. Our model predicts that this decrease reflects slower endosomal maturation and megalin recycling.

Conclusions: Chronic vs acute changes in FSS mediate alterations in endocytic capacity via distinct mechanisms. Whereas the primary rate affected when cells are cultured under continuous FSS is megalin internalization, acute drops in FSS preferentially alter intracellular trafficking steps to reduce endocytic uptake.

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FR-PO511

The Effects of Hypoxia-Inducible Factors on Water Regulation in the Kidneys

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Background: Hypoxia-inducible factor (HIF) is one of important cellular responders when facing decreased oxygen tension or under hypoxia. HIF stabilization can improve anemia through erythropoietin production from kidneys; however, its overexpression could be seen in different cancer types, such as clear cell renal cell carcinoma. Previous studies have shown wide-spread HIF-1a-dependent hyperplastic, inflammatory and fibrotic lesions in the kidney of mice with von Hippel-Lindau gene (*Vhlh*) deletion in Hoxb7-expressing renal collecting duct (CD) epithelia. Interestingly, *Vhlh* deletion in Ksp1.3-expressing renal tubular epithelia has also been reported to cause HIF-1a dependent diuresis in mice.

Methods: *Tg(Hoxb7-cre);Vhlh$^{F/F}$* (*Vhlh* KO), *Tg(Hoxb7-Cre);Vhlh$^{F/F}$;Hif1a$^{F/F}$* (*Vhlh*;*Hif1a* DKO), and *Tg(Hoxb7-Cre);Vhlh$^{F/F}$;Hif2a$^{F/F}$* (*Vhlh*;*Hif2a* DKO) mice were bred to study the effect of HIF stabilization in Hoxb7-expressing renal CD epithelia. Littermate without *Hoxb7-cre* transgene was used as the control to compare body weight, blood and urine biochemistry, gene/protein expression and histology in kidney.

Results: Compared to littermate control, *Vhlh* KO mice exhibited higher 24-hour urine volume and lower urine osmolality which could be partially ameliorated by water deprivation. Water deprivation-induced, vasopressin-dependent urine concentration was not different between *Vhlh* KO mice and littermate control. *Vhlh* KO mice exhibited higher food intake and solute diuresis, but decreased body weight. Food restriction led to similar excretion of urine solutes, but *Vhlh* KO mice consistently exhibited higher urine volume and lower urine osmolality than littermate control. *Vhlh*;*Hif2a* DKO mice exhibited higher urine volume and lower urine osmolality, but no more solute diuresis. *Vhlh*;*Hif1a* DKO mice did not exhibit abnormality in urine volume and osmolality. Histologically, *Vhlh* KO mice exhibited substantial tubulointerstitial injury.

Conclusions: *Vhlh* KO and hence HIF-1a/HIF-2a overexpression in renal CD epithelia led to HIF-1a-dependent decrease in renal concentrating ability. However, increase of solute diuresis was HIF-2a-dependent. Water deprivation-induced, vasopressin dependent urine concentration was not impaired in *Vhlh* KO mice. HIF-1a-dependent diuresis might be caused by destructed renal interstitium. But the mechanisms underlying HIF-2a-dependent solute diuresis need further study.

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FR-PO512

Hyperosmolarity-Induced Cell Shrinkage in Renal Cells: What a Role for RhoB?

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Background: The small Rho GTP-binding proteins are important regulators of cell morphology, function, and apoptosis. Unlike other Rho proteins, RhoB can be subjected to either geranylgeranylation (RhoB-GG) or farnesylation (RhoB-F), making that the only target of the farnesyltransferase inhibitors (FTIs). This study evaluated the involvement of RhoB farnesylation in the mechanism that regulates cell volume changes.

Methods: Mouse collecting duct MCD4 cells and human proximal tubule HK-2 cells were used as experimental models. Fluorescence Resonance Energy Transfer (FRET) studies were applied to evaluate the activity of RhoB. Cell volume was detected using an automated cell counter (Luna, Logos Biosystem), a calcein-based assay, and laser-scan confocal microscopy followed by 3D reconstruction and cell-volume analysis (3D-LSCM).

Results: Treatment with FTI-277 significantly reduced the cell volume in MCD4 and HK-2 cells. Compared to untreated cells, FTI-277 treatment altered hyperosmotic-dependent cell shrinkage response. FRET experiments revealed that RhoB was activated by hyperosmolarity regardless of FTI exposure. By contrast, hyposmolarity did not alter the activity of RhoB. To evaluate whether RhoB plays a role in volume reduction, cells were transiently transfected with RhoB-wt-EGFP and RhoB-CLLL-EGFP which cannot undergo farnesylation. Notably, hyperosmolarity caused a significant reduction in cell volume in mock and RhoB-wt-EGFP-expressing cells. By contrast, cells treated with FTI-277 or expressing the RhoB-CLLL-EGFP mutant did not properly respond to hyperosmolarity compared to mock and RhoB-wt-EGFP expressing cells. These findings were further confirmed by 3D-LSCM. Additionally, RhoB-CLLL-EGFP expressing cells showed relevant staining for Annexin-V compared to cells expressing EGFP and RhoB-wt-EGFP.

Conclusions: Together, these data suggest that: i) RhoB is sensitive to hyperosmolarity but not to hyposmolarity; ii) inhibition of RhoB farnesylation associates with an increase in cell apoptosis, likely suggesting that RhoB might be a paramount player controlling apoptosis by interfering with responses to cell volume change.

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FR-PO513

Tamoxifen Attenuates the Lithium-Induced Decrease in Necroptosis in Renal-Collecting Duct Cells

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Background: Lithium is recommended for bipolar disease, but it generally displays adverse effects including chronic kidney disease and acquired nephrogenic diabetes insipidus, a disorder characterized by a defective renal concentrating ability that leads to massive water loss. Several data demonstrated that tamoxifen attenuates the development of lithium-induced NDI by modulating AQP2 and AQP3 expression and function. Recent studies revealed that lithium promotes proliferation and autophagy in renal cells. Here, we identify the heat-shock-protein 90 (HSP90) as a novel player involved in signaling activated by lithium treatment and leading to the inhibition of cell necroptosis. Inhibition of HSP90 may lead to conformational changes and degradation of RIP3 which is a key protein promoting necroptosis via MLKL.

Methods: Renal collecting duct MCD4 cells were used as an experimental model. Western Blotting analysis was applied to evaluate the expression and function of proteins.

Results: Exposure of MCD4 cells to lithium (10mM for 48 hours) significantly reduced the expression of HSP90, RIP3, and MLKL. A relevant decrease in phosphorylated MLKL was also detected. A decrease in the expression of BID and an increase of beclin, selective markers of apoptosis and autophagy respectively, were found as well. The effect of tamoxifen on necroptosis was evaluated considering that tamoxifen enhances the client activity of HSP90. Notably, either tamoxifen or IP6, a known activator of necroptosis, reversed the effect of lithium on HSP90 and RIP3 expression. Importantly, preliminary in vivo data showed that lithium decreased the expression of RIP3. By contrast, tamoxifen reversed the lithium-induced RIP3 reduction.

Conclusions: Together, these findings revealed for the first time that exposure of renal collecting duct cells to lithium resulted in a significant reduction in the expression level of selective markers of necroptosis possibly through HSP90 inhibition. Treatment with tamoxifen counteracts the lithium-induced downregulation of HSP90 and RIP3.

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FR-PO514

Gut Dysbiosis and Hyperoxaluria in Nephrolithiasis

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Background: Nephrolithiasis is a urologic disease with high recurrence rate. Hypercalciuria, hypocitraturia and hyperoxaluria are common risk factors. Previously studies reviewed gut dysbiosis in patients with nephrolithiasis, including increased *Bacteroidota*, although no evidence showed that gut dysbiosis is the cause or consequence of nephrolithiasis. We underwent human-to-animal fecal microbiota transplant (FMT) to elucidate this gut-kidney axis.

Methods: Five nephrolithiasis patients and 5 healthy adults with age- and gender-matched were enrolled. Urine was collected for calcium, oxalate, citrate, and magnesium measurement, while feces were analyzed for gut microbiome, and feces were mixed and extracted for microbiota. Rats with intestinal microbial eradication by antibiotics for 1 week were divided into (a) Control, (b) Healthy-FMT (hFMT) and (c) Nephrolithiasis-FMT (nFMT) (n=6 each). The hFMT and nFMT were gavaged with fecal microbiota from Healthy and Nephrolithiasis group, respectively, twice a week for 4 weeks. Blood and urine were collected at Week-0 and Week-4 to measure calcium, oxalate, citrate, and magnesium, and feces for fecal microbiome.

Results: Compared with Healthy control, participants with nephrolithiasis had higher urinary calcium and oxalate excretion rate (p=0.043 and p=0.005) and lower citrate excretion rate (p=0.031). Tiselius supersaturation index is higher in Nephrolithiasis (p=0.027). Fecal microbiota showed increased *Bacteroidota* spp in Nephrolithiasis group. In rats, nFMT had insignificant increases in gut *Bacteroides*, and increased urinary oxalate excretion rate in post-FMT compared to pre-FMT (p=0.020), while hFMT rats had no significant change (p=0.625). Higher Tiselius index in nFMT rats (p=0.032) was detected. Moreover, nFMT rats had higher renal NF-kB expression than hFMT, suggesting renal inflammation. In addition, intestinal expression of oxalate transporter was higher, and zonula occluden-1 was lower in nFMT rats, indicating increased gut permeability to oxalate in nFMT rats.

Conclusions: Our study reviewed hypercalciuria, hyperoxaluria and hypocitraturia and gut dysbiosis in patients with nephrolithiasis. FMT from nephrolithiasis to rats induced hyperoxaluria, renal inflammation and higher risk of stone formation, possibly due to increased intestinal oxalate absorption from gut leakage and oxalate transporter overexpression.

Funding: Government Support - Non-U.S.

FR-PO515

RNAseq of Microdissected Collecting Ducts Revealing the Early Signaling Mediating the Loss of Aquaporin 2 After K+ Deprivation

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Background: Potassium (K^+) deficiency could cause a reduction in urinary concentrating ability, resulting in nephrogenic diabetes insipidus (NDI), but the detailed mechanism remains unclear. Recently, transcriptomic and proteomic data from acquired NDI models reveals that oxidative stress, apoptosis, and inflammatory signaling are associated with AQP2 loss. We aim to explore the early signaling after K^+ deprivation in cortical collecting ducts (CCDs).

Methods: Immunoblotting and bulk kidney RNAseq were performed at 0, 12, 24, and 48 hours after K^+ deprivation in rats. Serum and urine biochemistry were also recorded. Based on immunoblotting and bulk kidney RNAseq, CCDs were microdissected from rats at 6 hrs after K^+ deprivation versus time controls. Single-tubule RNA-Seq was carried out independently in K^+ deprivation rats versus controls (n=4).

Results: Immunoblotting of bulk kidney showed a decrease in AQP2 protein abundance at 12 hours of K^+ deprivation diet, and urine osmolality was significantly decreased at 24 hours, confirming the animal model of K^+ deprivation-induced NDI. Preliminary bulk kidney RNA-Seq time course experiments also revealed that *Aqp2* and other collecting ducts markers such as *Aqp3, Aqp4,* and *Fxyd4* mRNA started to decrease at 12 hrs. Single-tubule RNA-Seq data of CCDs at 6 hrs after K^+ deprivation showed *Aqp2, Aqp3,* and *Atp1a1* were significantly downregulated. It also revealed that chemokine transcripts (*Ccl20* and *Ccl28*) were increased significantly. We also carried out analysis of *Gene Ontology Biological Process* terms that are statistically over-represented in the list of 88 "Increased Transcripts"at 6 hrs of K^+ deprivation in CCDs, and many of the terms are related to glutathione metabolic process (*Gstm1, Gsta1, Gstt3, Txnrd3*), positive regulation of ERK1 and ERK2 cascade (Nrp1, *Ccl20, Ripk2, Fgfr4, Fgfr3*), cell chemotaxis (*Ccl20, Ccl28, Hbegf*), cellular response to lipopolysaccharide (*Ccl20, Ripk2, Cd14, Tfpi*), consistent with an inflammatory response.

Conclusions: Our small samples RNA-Seq from microdissected CCDs in rats showed early cellular signaling changes in activation of oxidative stress and inflammatory signaling causing loss of aquaporin-2 in K^+ deficiency induced NDI.

FR-PO516

Role of Paraoxonase 3 (PON3) in Regulating Epithelial Sodium Channel (ENaC)-Mediated Na+ Transport in Distal Nephron

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Background: PON3 is expressed in the aldosterone-sensitive distal nephron, where ENaC plays an essential role in maintaining Na^+/ K^+ homeostasis in the kidney. The aims of our study were to determine the physiological roles of PON3 in renal Na^+ and K^+ handling. We hypothesize that PON3 functions as a molecular chaperone to regulate ENaC expressionand Na^+ reabsorption in the kidney.

Methods: We have obtained a *Pon3* global knockout mouse model and examined the effect of PON3 on ENaC functional expression using several approaches, including biochemistry, immunohistochemistry, electrophysiology, and whole animal metabolic cage studies.

Results: *Pon3* KO mice have normal kidney histology without evidence of inflammation or injury. At baseline, *Pon3* KO mice have a significantly lower blood [K^+] and higher blood [Na^+] when compared to WT littermates. Amiloride-induced natriuresis was significantly greater in the KO mice, reflecting, in part, an upregulation in ENaC-dependent Na^+ reabsorption in the absence of the PON3. Immunoblotting of whole kidney lysates indicated that the total abundance of ENaC subunits was not altered in KO mice. However, γENaC was more apically distributed within the cortical collecting ducts (CCD) of the KO kidneys. Single channel recordings of ENaC in split-open tubules freshly isolated from WT or *Pon3* KO mice kidneys demonstrated that open probability (P_O) was similar between the two groups of animals. However, the number of active channels per patch (*N*) was significantly higher in the KO kidneys, resulting in a higher ENaC activity (NP_O) in the distal nephron segments of *Pon3* KO mice. Consistent this notion, we found that γENaC surface abundance was increased in mCCD cells when PON3 expression was knocked down by siRNA.

Conclusions: Together, our data suggest that *Pon3* KO mice have upregulated Na^+ reabsorption and K^+ secretion, likely a result of increased ENaC functional expression in the absence of PON3.

Funding: NIDDK Support

FR-PO517

Circadian Rhythm Misalignment Induced Differential Expression of Mineralocorticoid Receptor Type I and Aldosterone in Kidneys and Urine of Male Rats

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Background: Circadian rhythm misalignment (CRM) adversely impacts health and increases blood pressure (BP), especially in shift workers. Aldosterone (ALD) acting through mineralocorticoid receptor-1 (MCR1) causes sodium retention and water reabsorption to increase BP. The aim of this study was to determine if CRM alters the expression of MCR1 in the kidneys and aldosterone levels in the urine of rats.

Methods: 32 young male rats were divided into control (CTL) and CRM groups. CTLs experienced normal light/dark cycles but CRMs were phase-advanced every 2 days for 22 days after which BPs were measured at 6-hour intervals. Rats were sacrificed and kidney tissue and urine stored at 80°C. RNA was extracted and Real-Time PCR conducted. ELISA was utilized to quantitate urine ALD. The MCR1 expression was normalized to 18s ribosomal RNA. An independent sample two-tailed t-test was used to determine effects of variance in both directions for both ELISA and RT-PCR data.

Results: Overall MCR1 expression was ~7.5-fold higher in combined CRM groups compared to CTL ($p = 0.00019$). Subgroup analyses revealed significance in the 9AM CRM group with an ~18-fold higher MCR1 expression ($p = 0.20$). The 3PM, 9PM and 3AM CRM groups also exhibited higher expression but did not reach statistical significance (Fig. 1). ALD was ~1.8-fold higher in combined CRM compared to CTL groups ($p < 0.0035$). Subgroup analyses revealed the 9AM, & 3PM CRM groups with significantly higher ALD expression (~2.96-fold ($p = 0.005$) and ~ 2.87-fold ($p = 0.011$), respectively). 3AM also showed higher expression but the 9PM CRM subgroup did not differ from CTL.

Conclusions: MCR1 expression and ALD are upregulated in kidneys and urine of rats after CRM and may be a potential mechanism for CRM-induced renal and cardiovascular dysfunction (CVD). Additionally, MCR1 expression and ALD levels appear to vary over a daily 24-hour cycle. Shift workers, have an increased risk of impaired sodium excretion and water retention. We hypothesized that this impaired cycle is due to the improper activation of the renin-aldosterone-angiotensin system thus resulting in hypertension, renal dysfunction, and CVD.

	9AM	9PM	3AM	3PM	Overall
PCR data					
MCR1 gene expression fold change	18.252	10.880	2.042	7.681	7.52
P-value	**0.020**	0.076	0.407	0.095	**0.00019**
Elisa data					
Aldosterone hormone expression fold change	2.956	1.072	1.871	2.871	1.794
P-value	**0.005288**	0.8587	0.07717	**0.01146**	**0.00352**

FR-PO518

Proximal Tubule Regulates the Collecting Duct Response to Hypokalemia

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Background: Hypokalemia induces phenotypic and remodeling responses in the collecting duct that increase net acid excretion. We showed recently that the proximal tubule, through an NBCe1-A-dependent signaling pathway likely involving ammonia, regulates the collecting duct response to metabolic acidosis. Because hypokalemia stimulates proximal tubule NBCe1-A-dependent ammoniagenesis, we postulated that a similar mechanism would control the collecting duct response to hypokalemia.

Methods: Male and female NBCe1-A knock-out (KO) and wild-type (WT) mice were studied either on a K-control diet or a nominally K-free diet (KFD). Immunoblot analysis, immunohistochemistry, and cell counting evaluated phenotypic and remodeling responses.

Results: KO mice tolerated only four days of KFD before developing life-threatening hypokalemia. After four days, KFD increased the number of Type A intercalated cells (A-cell) in the inner stripe of the outer medullary collecting duct (OMCDis) and decreased the number of Type B intercalated cells (B-Cell) in the cortical collecting duct (CCD), and KO significantly blocked these remodeling responses. KFD increased the number of A-cells in the CCD, and KO did not alter this response. Immunoblot analysis showed KFD decreased cortical pendrin expression, and KO did not alter this response. In the inner stripe of the outer medulla (ISOM), KFD did not significantly alter either AE1 or Rh B Glycoprotein (Rhbg) expression, and NBCe1-A deletion did not alter the response to KFD. ANOVA analysis showed no significant effect of sex on these immunoblot responses.

Conclusions: We conclude: (1) the CCD B-Cell and OMCDis A-cell remodeling responses to hypokalemia are present at four days and involves a proximal tubule NBCe1-A-dependent response likely involving ammonia; (2) the ISOM collecting duct phenotypic response to hypokalemia that involves AE1 and Rhbg requires more than four days to develop; and, (3) the CCD pendrin response to hypokalemia occurs more rapidly than ISOM responses, and is independent of proximal tubule NBCe1-A expression.

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FR-PO519

Distal Convoluted Tubule-Specific Disruption of the COP9 Signalosome and CUL3 Activates the WNK4-SPAK-NCC Pathway

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Background: The disease Familial Hyperkalemic Hypertension (FHHt; also known as Gordon Syndrome) is caused by aberrant accumulation of WNK4 activating the NaCl cotransporter (NCC) in the distal convoluted tubule (DCT) of the kidney. Mutations in cullin 3 (CUL3) cause FHHt by disrupting interaction with its regulator, the COP9 signalosome (CSN). Deletion of *Cul3* and *Jab1* (the catalytically active CSN subunit) along the entire nephron causes an FHHt phenotype with activation of the WNK4-SPAK-NCC pathway.

However, only a partial FHHt phenotype develops due to kidney injury. We hypothesized that DCT-specific deletion would more accurately model the disease.

Methods: We utilized NCC-Cre-ERT2 mice to delete *Cul3* (DCT-*Cul3*$^{-/-}$) and *Jab1* (DCT-*Jab1*$^{-/-}$) only in the DCT. Blood was collected for plasma electrolyte analysis, and kidneys were collected for Western blotting and immunofluorescent staining.

Results: Both DCT-*Cul3*$^{-/-}$ and DCT-*Jab1*$^{-/-}$ mice showed an FHHt-like phenotype, with increased WNK4, SPAK, and pNCC abundance. CUL3 inactivation in the DCT-*Cul3*$^{-/-}$ mice caused an increase in both KLHL3 (the CUL3 substrate adaptor for WNK4) and WNK4 abundance. WNK4 accumulated in DCT-*Jab1*$^{-/-}$ mice due to hyperactivation of CUL3, which caused decreased CUL3 and KLHL3 abundance. Both genotypes showed formation of pSPAK and WNK4 puncta, however, the number of WNK4 puncta was higher in DCT-*Cul3*$^{-/-}$ mice. Contrasting the disease, both genotypes showed no change in plasma K^+, Cl^-, or HCO_3^- at baseline, but the DCT-*Jab1*$^{-/-}$ mice became hyperkalemic when challenged with a high K^+ diet. Additionally, over time DCT-*Jab1*$^{-/-}$ mice showed a large decrease in NCC abundance, which was not observed in the DCT-*Cul3*$^{-/-}$ mice. Interestingly, although *Jab1* was deleted only in the DCT, the mice had increased abundance of KIM-1, a marker of proximal tubule injury.

Conclusions: DCT-specific knockout of both CUL3 and the cullin-RING-ligase regulator JAB1 led to an FHHt-like phenotype. Chronically, only DCT-*Jab1*$^{-/-}$ mice developed a large reduction in NCC abundance, suggesting the decrease is due to a direct JAB1 effect, or effects of JAB1 on other cullins.

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FR-PO520

Regulation of NKCC1, NKCC2, and NCC69 by TSC1/TSC2 Complex

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Background: Na-K-2Cl cotransporters NKCC1 and NKCC2 play important roles in numerous physiological processes and several human diseases such as salt losing tubulopathies, hypertension and cancer. In the kidney, NKCC1 plays a pivotal role in K+ secretion in the collecting duct while NKCC2 is the pacemaker of NaCl reabsorption in the thick ascending limb. Using the two-hybrid system, we identified tuberin (TSC2) as a binding partner of NKCC2. We therefore sought to characterize the mechanism by which TSC2, with or without hamartin (TSC1), could regulate NKCC2 and / or NKCC1.

Methods: NKCC1 and NKCC2 protein expression was monitored in HEK cells transiently or stably transfected with the cotransporters using immunoblot and confocal imaging. The stability of the cotransporters was assessed by cycloheximide chase assay. NCC69 function was evaluated in *Drosophila* Malpighian tubules overexpressing TSC1 and/or TSC2 in a control of *Ncc69* mutant background.

Results: Co-immunoprecipitation experiments showed robust interaction between TSC2 and the complex-glycosalyed form of NKCC2 suggesting that the interaction takes a place at the post-Golgi level. TSC2 and/or TSC1 knock-down (KD) similarly increased total NKCC2 protein. Cycloheximide assays and leupeptin treatment (lysosome inhibitor) revealed that TSC1/2 KD upregulate NKCC2 by increasing its stability and maturation. Interestingly, similar to NKCC2, the KD of TSC1/TSC2 reproduced the same effects on NKCC1. To elucidate *in vivo* the role of TSC1/TSC2 in the regulation of NKCC, we took advantage of the expression of NCC69, the fly NKCC **in** the Drosophila melanogaster renal tubule. Importantly, while overexpression of either TSC1 or TSC2 alone had no effect, overexpression of TSC1 and TSC2 together resulted in decreased tubule K^+ secretion in control tubules, but not in tubules lacking NCC69, strongly indicating that the two TSC function together to regulate NCC69 function.

Conclusions: We identified TSC1/TSC2 complex as a novel key player in the post-Golgi regulation of NKCCs. Our results are consistent with a model whereby TSC1 and TSC2 function together to decrease the expression of the cotransporters via the lysosome pathway. A better understanding of the regulatory pathways acting on NKCC1 and NKCC2 will ultimately help to identify new "druggable" targets to prevent and/or treat several disorders in which these two cotransporters are involved.

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FR-PO521

Chloride-Induced Monomer to Dimer Transition Controls WNK1 Scaffold Activity

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Background: Although it is well established that WNK kinase activity is involved in controlling cation-chloride co-transporters, such as NCC and NKCC, recent findings demonstrate that WNK1 can also act as a scaffold, independent of its kinase function. It facilitates the interaction between mTORC2 and SGK1 and stimulates SGK1 phosphorylation thereby enhancing ENaC activity. Extracellular K^+ stimulates this non-kinase scaffolding activity at the same time that it inhibits WNK kinase activity. Both of these effects are mediated by intracellular Cl^-, which directly binds to WNKs. Previous studies have identified two conformational states of WNK kinases: a kinase inactive, unphosphorylated chloride-bound dimer and a kinase active monomer, which is not chloride-bound. The dimer conformation is maintained by salt bridges between the monomers, which dissociate in low chloride conditions. This study explores the conformational changes in WNK1 that contribute to its catalytic and non-catalytic functions.

Methods: Salt bridge mutations were generated using site-directed mutagenesis. WNK1 knockout (WNK1 KO) HEK293 cells were transfected with either wild-type (WT) WNK1 or the salt bridge mutants of WNK1. Subsequently, the cells were adapted to 1 mM [K^+] and then subjected to an increase in [K^+] to 5 mM. Following this, the cells were processed for co-immunoprecipitation (co-IP) and immunoblot analysis. Whole cell lysates were also assayed for OSR1/SPAK and SGK1 phosphorylation.

Results: In cells transfected with wild-type (WT) WNK1, extracellular K^+ stimulated mTORC2-dependent SGK1 phosphorylation, while inhibiting WNK kinase activity-dependent SPAK phosphorylation. In contrast, mutations disrupting the salt-bridge interface of WNK1 blocked the effect of K^+ on mTORC2-dependent SGK1 phosphorylation but not SPAK phosphorylation, which became insensitive to changes in extracellular [K^+]. Additionally, extracellular [K^+] stimulated dimer formation in the WT WNK1, but it was significantly reduced or absent in mutant forms of WNK1.

Conclusions: Our data suggest that the Cl^- induced shift of WNK1 from monomer to dimer conformations both inhibits WNK kinase activity and enhances scaffolding activity, providing a parsimonious mechanism for its opposite regulation of cation-chloride cotransporters and ENaC.

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FR-PO522

Sexual Dimorphism in Vasopressin Signaling

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Background: Hyponatremia is a life-threatening condition characterized by decreased body natrium (sodium) concentration due to water retention. For reasons not yet understood, women are more prone to hyponatremic conditions, including exercise-associated hyponatremia, post-operative hyponatremia, and ecstasy-associated hyponatremia. Recent reports suggest that compared to males, female mice concentrate their urine more effectively due to enhanced AQP2 apical membrane localization. It has been suggested that sex hormones affect water balance; however, it is unknown if vasopressin signaling itself exhibits sex-dependent differences.

Methods: The sexual dimorphism in water balance was analyzed in C57BL6J wild-type males and females at basal conditions and after 12 hours of water deprivation. The *in-vivo* activation of vasopressin signaling was assessed using western blot (WB) and confocal imaging. Plasma copeptin, a surrogate marker of vasopressin secretion, was analyzed using ELISA.

Results: Our data revealed that females exhibit higher urine osmolality at baseline and have an enhanced ability to further concentrate their urine following 12 hours of water deprivation. Plasma copeptin was higher in females compared to males under basal conditions. WB analysis of the renal cortex and medulla in both sexes under basal conditions revealed AQP2 total protein levels were similar between males and females. However, AQP2 phosphorylation at Ser256, in a protein kinase A (PKA) consensus site, was more enhanced in the renal cortex and medulla of females. This is consistent with higher AQP2 apical localization in females as revealed by confocal imaging. To assess a potential sex-dependent activation of vasopressin signaling in the principal cells, we analyzed phospho-PKA substrates in the AQP2-positive cells using phospho-PKA substrate (RRXS/T) antibody. Quantitative analysis of confocal images revealed PKA-substrates were more phosphorylated in the principal cells of females compare to males, indicating more enhanced vasopressin signaling in females.

Conclusions: The sexual dimorphism in water balance is mediated, at least in part, by higher circulating vasopressin levels in females. Subsequently, vasopressin signaling in the collecting duct was more enhanced in females resulting in more robust AQP2 apical translocation.

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FR-PO523

α-Epithelial Sodium Channel (ENaC) Proteolysis Regulates Channel Function In Vivo in a Sex- and Tissue-Specific Manner

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Background: Epithelial Na^+ channels (ENaCs) facilitate Na^+ and water reabsorption in the distal nephron and distal colon, while also controlling K^+ secretion in the distal nephron. ENaC activity is regulated, in part, by proteolysis of the channel's α and γ subunits. *In vitro*, α-ENaC is typically cleaved twice by furin proteases during synthesis. As a result, an autoinhibitory peptide sequence is excised, thereby increasing the channel's open probability (P_O). However, the importance of α-ENaC cleavage with respect to Na^+ and fluid handling *in vivo* is unknown.

Methods: We tested the hypothesis that α-ENaC cleavage is necessary for channel function *in vivo* by generating mice that lack a key furin cleavage site (^{229}RSAR^{232} > ^{229}QSAQ^{232}; α^{Fm} = α furin site mutant). We assessed ENaC function in α^{Fm} versus wild-type (WT) littermates via electrophysiological and systemic analyses under normal and Na^+-restricted dietary conditions.

Results: At baseline, male α^{Fm} mice had elevated blood K^+ versus WT littermates (α^{Fm} vs. WT: 4.7 ± 0.1 vs. 4.3 ± 0.1 mM; p=0.03), but this was not observed in females (α^{Fm} vs. WT: 4.8 ± 0.1 vs. 5.0 ± 0.2 mM; p=0.8). Otherwise, α^{Fm} mice of either sex exhibited no baseline phenotype regarding blood electrolyte or metabolic parameters. Western blot analysis showed no differences in ENaC subunit expression in the kidney or distal colon. Patch clamp experiments revealed no differences in ENaC activity (P_O) in isolated kidney tubules. However, short-circuit current (I_{SC}) measurements revealed that male α^{FM} mice had diminished ENaC activity in the distal colon (α^{Fm} vs. WT ΔI_{SC}(amiloride): -0.2 ± 2.3 vs. -17.7 ± 4.4 μA/cm^2; p<0.01). Colonic ENaC activity in both genotypes was stimulated by dietary Na^+ restriction (α^{Fm} vs. WT ΔI_{SC}(amiloride): -104 ± 38 vs. 64 ± 19 μA/cm^2;

p=0.4) and plasma aldosterone levels were also similar following treatment (α^{Fm} vs. WT: 2,910 ± 323 vs. 2,275 ± 584 pg/mL). Body composition analysis showed that during Na^+-restriction, α^{FM} mice maintained body water content, but lost total body weight more rapidly than WT littermates.

Conclusions: α subunit cleavage is required for full ENaC function in male mice. However, loss of α-ENaC cleavage can be compensated by elevated aldosterone under Na^+-restricted conditions to maitain salt and fluid balance.

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FR-PO524

Inhibition of Calcium-Sensing Receptor in Mice Proximal Tubule Leads to Calcium Phosphate Crystalluria

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Background: The proximal tubular (PT) Ca^{2+} transport is crucial for maintaining tubular Ca^{2+} levels to prevent downstream calcium phosphate (CaP) crystal formation. While PT Ca^{2+} transport is often described as paracellular, we found a transcellular Ca^{2+} transport pathway in the PT that is mediated by the interaction of calcium-sensing receptor (CaSR) and transient receptor potential canonical type 3 (TRPC3) channel. TRPC3 knockout mice exhibited hypercalciuria and microcalcifications arguing for a protective role of TRPC3 in preventing nephrocalcinosis. However, the role of CaSR in CaP crystal formation is unclear. Thus, we used a renal-selective knockdown of CaSR by the renal subcapsular infusion of CaSR siRNA to sort out the CaSR-mediated Ca^{2+} transport in the PT and its contribution to urinary CaP formation.

Methods: Adult male C57BL/6J mice were uninephrectomized 1 week before the renal implantation of osmotic minipumps. Osmotic minipumps (100 μL; flow rate 0.5 μL/h for 7 days) were filled with previously validated CaSR or non-silencing siRNA as control. siRNAs were dissolved in an *in vivo* transfection reagent under sterile conditions and was delivered via the osmotic minipumps into the renal cortex of each mouse. 24h urine collection and ion measurements were performed and collected urine were stained with AR pH 4.3 to detect CaP. Real time intracellular Ca^{2+} was measured in siRNA- or scramble-transfected isolated mice PT cells.

Results: In mice that underwent renal subcapsular infusion with siRNA for two weeks, 24h urine showed notable CaP crystal formations compared with that of control and scramble siRNA- infused mice. Renal cortical knockdown of CaSR did not significantly affect Na^+, Cl^-, and K^+ excretion (normalized by creatinine) except for Ca^{2+}. Fura-2 intracellular Ca^{2+} measurements in CaSR siRNA-transfected PT cells revealed decreased or nearly complete absence of Ca^{2+} entry after application with L-phenylalanine (CaSR agonist), confirming the effects of the siRNA.

Conclusions: The decreased Ca^{2+} influx due to CaSR inhibition suggest diminished tubular Ca^{2+} reabsorption confirming CaSR's involvement in PT Ca^{2+} regulation. This study thus enhances our understanding about transcellular regulation of PT Ca^{2+} and its role in regulating urinary Ca^{2+} levels and subsequently CaP stone formation.

Funding: NIDDK Support

FR-PO525

Mice Lacking P300/CBP-Associated Factor Have a Resistance to Salt-Induced Hypertension Probably Through Dysregulation of NKCC2 and Aquaporin 2

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Background: P300/CBP-associated factor (PCAF), a member of the GNAT acetyltransferase family, is involved in the modulation of differentiation and cell cycle progression. Several neurodegenerative conditions have been thought to be associated with an alteration of PCAF activity and subsequent histone acetylation, and patients with neurodegenerative diseases often experience hypotension although the consequence of dysfunctional PCAF on blood pressure remains unknown. This study investigated a potential role of PCAF in the relationship between blood pressure and urinary sodium and water excretion in the kidney.

Methods: PCAF knockout (KO) mice and wild-type (WT) mice received 8% or normal NaCl salt diet for 2 weeks.

Results: WT mice had higher blood pressure on a high-salt diet than on a normal salt diet, but changes of dietary salt did not affect the blood pressure of PCAF KO mice. Free water clearance (FWC) and electrolyte free water clearance (EFWC) in PCAF KO mice on a high-salt diet were higher than those of WT mice on a high-salt diet. Both PCAF KO and WT mice on a high-salt diet had higher expression of Na^+/H^+ exchanger isoform 3 (NHE3) compared with normal salt-fed groups. In PCAF KO mice fed a high-salt diet, there was an increase in renal expression of Na^+-Cl^- cotransporter (NCC) and a decrease in renal expression of Na^+-K^+-$2Cl^-$ cotransporter (NKCC2) compared with WT mice fed a high-salt diet. Although renal mRNA expression of aquaporin 2 (AQP2) was upregulated in all groups on a high-salt diet, the phosphorylated protein level of AQP2 at serine 261 was significantly increased only in PCAF KO mice on a high-salt diet.

Conclusions: A deletion in PCAF expression makes blood pressure less sensitive to salt probably via inappropriate downregulation of NKCC2 and AQP2 in kidneys, indicating that genetically impaired PCAF activity is likely to affect how blood pressure responds to changes in dietary salt.

FR-PO526

TGR5 Activation Ameliorated Hypertension Through Inhibiting Epithelial Sodium Channel (ENaC) Expression in the Kidney of Deoxycorticosterone Acetate (DOCA) Salt-Treated Mice

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Background: Epithelial sodium channel (ENaC), located in the collecting duct principal cells of the kidney, plays a critical role in regulating sodium balance and blood pressure in the body. The G protein-coupled bile acid receptor (TGR5) is a cell-surface receptor mediating bile acid effects and is implicated in several kidney diseases. The current study aims to investigate whether activation of TGR5 by lithocholic acid (LCA) regulated renal ENaC expression and blood pressure in deoxycorticosterone acetate (DOCA)-salt induced hypertensive mice.

Methods: Hypertension was induced in mice by subcutaneous implantation of DOCA pellets with 1% NaCl in drinking water. LCA was given by gavage.

Results: LCA markedly decreased blood pressure induced by DOCA-salt in mice, which was associated with decreased expression levels of ENaC mRNA and protein in the kidney. Compared with wild type group, TGR5 knockout mice developed increased blood pressure and ENaC protein expression in the kidney after DOCA-salt treatment. Bioinformatic indicates H3K4me1, 2, 3 enrichment in the promotor of ENaC. DOCA-salt treatment was associated with increased H3K4me3 expression in the kidney cortex which was markedly inhibited by LCA, while TGR5 knockout caused further increased H3K4me3 expression mice with DOCA-salt. Interestingly the mRNA and protein expression of KDM5A, a lysine demethylase, was significantly decreased in the kidney of mice with DOCA-salt, which was also significantly prevented by LCA. These data likely suggests that TGR5 activation decreased H3K4me3 enrichment of ENaC thus downregulated ENaC mRNA and protein expression. In immortalized mouse cortical collecting duct cells (mpkCCD) cells treated with either Ang II or aldosterone, the protein and mRNA expression levels of ENaC subunits were dramatically increased in association with increased protein expression of H3K4me3 and decreased mRNA and protein abundance of KDM5A, which were all inhibited by LCA treatment. Inhibition of KDM5 or KDM5A knockdown in mpkCCD cells treated with Ang II or aldosterone prevented the downregulation of ENaC expression induced by LCA.

Conclusions: In conclusion, LCA decreased blood pressure and ENaC protein expression in the kidney of mice with DOCA-salt, likely through increased KDM5A-mediated H3K4me3.

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FR-PO527

Metabolic Reprogramming of Renal Epithelial Cells Contributes to Lithium-Induced Nephrogenic Diabetes Insipidus

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Background: Lithium, mainstay treatment for bipolar disorder, frequently causes nephrogenic diabetes insipidus (NDI). However, the detailed mechanism remains unclear. Metabolic reprogramming is not only a hallmark of disease progression, but also an important pathogenic cause and therapeutic target in diseases. But its role in Li-NDI is unknown. Rotenone (ROT), an inhibitor of electron transport complex I, has a strong protective effect in various renal diseases. Whereas, the effect of ROT on metabolic status of kidney during Li-NDI remains unknown.

Methods: Mice were treated with lithium chloride (40 mmol/kg chow) and ROT (100 ppm) in diet for 28 days. Transmission electron microscopy was performed to evaluate structural changes of nephron. Metabolomics and transcriptomics were applied to examine metabolic status during Li-NDI.

Results: ROT treatment markedly ameliorated lithium-induced NDI and mitochondrial structural abnormalities. Metabolomics and transcriptomics data demonstrated that lithium resulted in metabolic over-activation in the kidney, which were significantly ameliorated by ROT intervention.

Conclusions: Mitochondrial abnormalities and metabolic reprogramming play a key role in Li-NDI, thereby serving as a novel therapeutic target.

Funding: Government Support - Non-U.S.

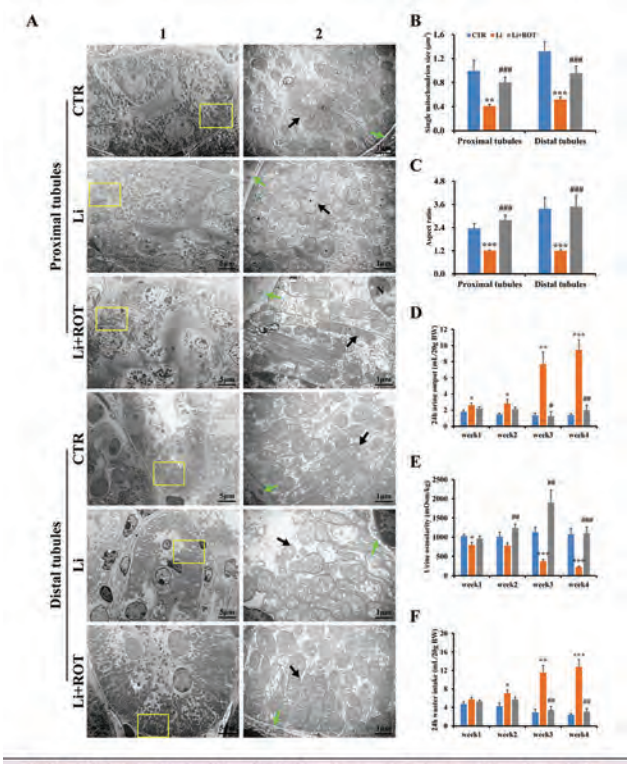

Fig.1 Effect of ROT on lithium-induced renal injury and NDI. (A) Representative transmission electron microscopic images of proximal tubules and distal tubules in mice after lithium with or without ROT treatment. (B) Single mitochondrion size (μm²). (C) Aspect ratio of single mitochondrion. The number of examined mitochondria was 15-20 in each group. (D) 24h urine volume (mL/20g BW). N=5-6 per group. (E) Urine osmolarity (mOsm/kg). N=5-6 per group. (F) 24h water intake (mL/20g BW). N=5-6 per group. CTR: Control; Li: Lithium treatment; Li+ROT: Lithium plus rotenone treatment.Data are represented as means ± SE. * denotes p<0.05, ** denotes p<0.005 and * denote p<0.0005 compared to CTR group while # denotes p<0.05, ## denotes p<0.005 and ### denotes p<0.0005 compared to Li group.**

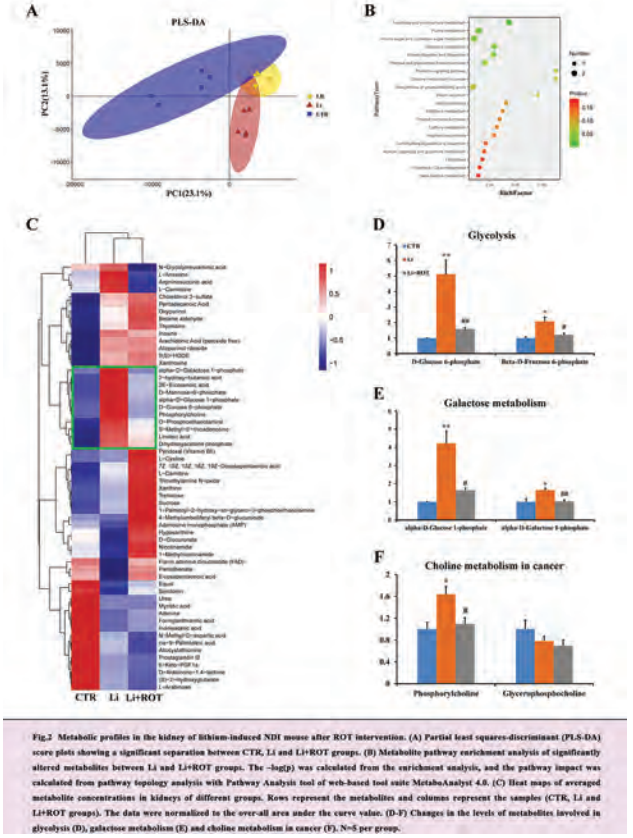

Fig.2 Metabolic profiles in the kidney of lithium-induced NDI mouse after ROT intervention. (A) Partial least squares-discriminant (PLS-DA) score plots showing a significant separation between CTR, Li and Li+ROT groups. (B) Metabolite pathway enrichment analysis of significantly altered metabolites between Li and Li+ROT groups. The –log(p) was calculated from the enrichment analysis, and the pathway impact was calculated from pathway topology analysis with Pathway Analysis tool of web-based tool suite MetaboAnalyst 4.0. (C) Heat maps of averaged metabolite concentrations in kidneys of different groups. Rows represent the metabolites and columns represent the samples (CTR, Li and Li+ROT groups). The data were normalized to the over-all area under the curve value. (D-F) Changes in the levels of metabolites involved in glycolysis (D), galactose metabolism (E) and choline metabolism in cancer (F). N=5 per group.

FR-PO528

Deletion of Kcnj16 Disturbs Acid-Base Homeostasis in Dahl Salt-Sensitive Rats

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Background: The role of renal inwardly-rectifying potassium (K_{ir}) channels in regulating acid-base homeostasis has been suggested by various studies. Previous studies demonstrated that patients with loss-of-function variants of *Kcnj16* (the gene encoding $K_{ir}5.1$) presented with disturbed acid-base homeostasis. However, the underlying mechanisms are still not fully understood. Here, we aim to investigate the renal handling of acid-base balance under the deletion of $K_{ir}5.1$ in Dahl salt-sensitive rats ($SS^{Kcnj16-/-}$).

Methods: To evaluate the baseline acid-base status of $SS^{Kcnj16-/-}$ rats, 12-week-old male SS^{WT} and $SS^{Kcnj16-/-}$ rats were used (N=5 per group). 24 hrs urine and blood were collected for measurement of blood pH, $HCO3^-$ and urinary pH, $NH4^+$, titratable acid, and net acid excretion (NAE). At the end of the experiments, RNA-Seq and Western blot analysis were performed on extracted kidneys to evaluate the expression of key transporters related to renal $HCO3^-$, H^+, and $NH4^+$ handling.

Results: At baseline, $SS^{Kcnj16-/-}$ rats showed significantly lower blood pH and $HCO3^-$, but higher urinary $NH4^+$, titratable acid and NAE than SS^{WT} rats. RNA-Seq and Western blot analysis revealed altered expression of several transporters essential for renal handling of $HCO3^-$, H^+ and $NH4^+$. For example, for $HCO3^-$ transport, both RNA-seq and Western blot analysis demonstrated increased expression of NBCe1 while decreased expression of pendrin, which may suggest enhanced $HCO3^-$ reabsorption in the proximal tubule while inhibited $HCO3^-$ excretion in the collecting duct of $SS^{Kcnj16-/-}$ rats. For $NH4^+$ transport, increased mRNA expression of *Rhbg* and *Rhcg* may indicate enhanced $NH4^+$ excretion in the kidney of $SS^{Kcnj16-/-}$ rats. For H^+ transport, elevated mRNA and protein expression of NHE3 may suggest enhanced H^+ secretion in the proximal tubule. Additionally, although the RNA-Seq suggested increased expression of various subunits of V-ATPase, we didn't observe any differences at protein levels.

Conclusions: Our data suggested that at baseline, loss of $K_{ir}5.1$ initiated metabolic acidosis and altered the renal transport of $HCO3^-$, $NH4^+$, and H^+ in Dahl SS Rats. The following analysis will further investigate the phenotype after the NH_4Cl challenge test in both genders.

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FR-PO529

Physiologic Importance of Proteolytic Cleavage of Epithelial Sodium Channel (ENaC)'s γ Subunit in Na+ and K+ Handling

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Background: Proteolytic removal of a peptide inhibitory tract (IT) from the epithelial Na^+ channel (ENaC) γ subunit's extracellular domain increases channel open probability (P_O) *in vitro*. IT removal requires cleavage at a furin recognition sequence (^{140}RKRR^{143}) proximal to the inhibitory tract *and* a site distal to the IT. We hypothesized that mice with impaired IT removal would exhibit diminished distal nephron ENaC P_O, decreased Na^+ transport, and increased susceptibility to hyperkalemia and body fluid volume depletion.

Methods: We disrupted the γ subunit furin cleavage site in mice (^{140}QQQQ^{143}, or "Q4"), reducing furin cleaved / full length γ subunit in Q4 mouse kidneys compared to wild-type (WT) littermates.

Results: Q4 mice exhibited no significant difference in blood Na^+, K^+, tCO_2, BUN, Hb, and Ca^{2+} on a standard, low Na^+, or high K^+ diet and no difference in plasma aldosterone on a low Na^+ diet. Collecting duct patch clamp experiments revealed an 8 pS channel, consistent with canonical heterotrimeric ENaC, that exhibited no difference in P_O or NP_O. A 17pS ion channel also showed no change in P_O or NP_O. In isolated, perfused collecting ducts from low Na^+-diet fed mice, Na^+ flux (J_{Na}) was not different between Q4 and WT animals at low or high luminal fluid flow rates (1 or 5 nl min^{-1} mm^{-1}). K flux (J_K) was also not different at a low flow rate. At a high flow rate, the J_K magnitude was greater in WT than Q4 collecting ducts (6.0 ± 1.1 vs 3.8 ± 0.6 pmol min^{-1} mm^{-1}, $p \leq 0.01$). In colonic epithelium, we observed no difference in amiloride-sensitive short-circuit currents (I_{SC}) in Q4 vs. WT. Total body water (TBW), measured via quantitative magnetic resonance and normalized to starting TBW, declined more in Q4 than WT males. TBW change was not different in female Q4 mice compared with WT mice.

Conclusions: Impaired furin site cleavage in ENaC's γ subunit did not influence blood electrolytes, colonic I_{SC}, or collecting duct channel P_O or J_{Na}, but diminished flow-induced stimulation of J_K in the collecting duct, and impaired body fluid conservation in males. Differences, where observed, were relatively subtle, indicating that additional factors influence ENaC activity and Na^+ and K^+ balance in live animals.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO530

FXR Modulates the Epithelial Sodium Channel Expression Through WNK1/SGK1/NEDD4-2 Signaling in the Kidney

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Background: Epithelial sodium channel (ENaC), located in the aldosterone sensitive nephron, is essential for renal salt handling and blood-pressure homeostasis. The farnesoid X receptor (FXR) signaling is involved in various important physiological and pathophysiological processes in the kidney such as energy metabolism, immune responses and fluid homeostasis. Here, we aimed to investigate whether FXR is involved in regulating renal ENaC expression and the potential roles in angiotensin II-induced hypertension.

Methods: Immortalized mouse cortical collecting duct ($mpkCCD_{c14}$) cells and mice were treated with FXR agonists or antagonists. To induce hypertension, mice were infused with angiotensin II (300 ng/kg/min) for 2 weeks by osmotic minipump.

Results: We found that FXR activation by CDCA and INT-747 markedly decreased, whereas FXR antagonist guggulsterone increased the protein and mRNA expression levels of ENaC in the $mpkCCD_{c14}$ cells. CDCA reduced the amount of ENaC at the plasma membrane of $mpkCCD_{c14}$ cells, which indicated FXR activation inhibits the trafficking of ENaC to the cytomembrane. Interestingly, CDCA significantly reduced With-No-Lysine 1 (WNK1) and SGK1 expressions, whereas induced the E3 ubiquitin ligase NEDD4-2 expression. Additionally, immunofluorescence and immunoprecipitation revealed that the level of ubiquitin binding to ENaC was increased as a result of FXR activation. Consistent to the in vitro study, CDCA downregulated the expressions of ENaC in the kidney of mice, which was associated with increased abundance of WNK1 and SGK1 and decreased abundance of NEDD4-2. In angiotensin II-induced hypertension, CDCA treatment lowered the systolic and diastolic blood pressure in mice. The increased expressions of ENaC in the kidney induced by angiotensin II were prevented by CDCA through activation of NEDD4-2 signaling.

Conclusions: Our findings demonstrated FXR activation decreased renal ENaC expression likely through WNK1/SGK1/NEDD4-2 signaling and thus reduced blood-pressure in angiotensin II-induced hypertensive mice. FXR represents a promising target for the treatment of hypertension.

Funding: Government Support - Non-U.S.

FR-PO531

Extracellular Flux Analysis Reveals that Transport Activity Regulates Mitochondrial Bioenergetics in Thick Ascending Limbs and Distal Convoluted Tubules

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Background: Alterations of mitochondrial functions and substrate oxidation have been proven pathogenic in many renal tubulopathies. Traditional assays using kidney slices or cultured cells do not provide tubule-specific resolution because of cell heterogeneity and rapid dedifferentiation in vitro. Understanding mitochondrial respiration and energy metabolism in renal tubules offers deeper insights into the metabolic adaptations of renal tubules to stimuli.

Methods: We applied extracellular flux analysis (EFA) to investigate mitochondrial respiration and energy metabolism in isolated renal tubules. Briefly, after mice were sacrificed and perfused, renal tubules were microdissected and incubated at 37°C for 1 hour. The dynamic oxygen consumption and extracellular acidification rates (OCR/ECAR) following the sequential injection of mitochondrial/metabolic inhibitors were measured by Seahorse XFp analyzer.

Results: Isolated renal tubules remained metabolically active and energetically dependent on mitochondrial oxidative phosphorylation (OXPHOS) during the assay. EFA detected significant OCRs/ECARs linearly correlated with sample sizes in millimeter-length renal tubules. Mitochondrial electron transport chain inhibitors suppressed OCRs and induced a simultaneous increase of ECARs in thick ascending limbs (TALs) and distal convoluted tubules (DCTs), indicating compensatory glycolysis. However, the proximal tubules (PTs) lacked noticeable compensatory glycolysis when OXPHOS was shut off. TALs and DCTs relied on glucose/pyruvate oxidation for ATP production in the basal state, and stimulation of oxygen consumption by mitochondrial uncoupler did not provoke the utilization of glutamine or long-chain fatty acids. Two-hour ouabain treatment reduced basal and ATP-linked mitochondrial respiration in isolated TALs. Besides, two-week furosemide treatment or deletion of with-no-lysine (WNK) kinase 4 further decreased the maximal and spare capacity of mitochondrial respiration in TALs via downregulating mitochondrial biogenesis.

Conclusions: EFA successfully provides tubule-specific metabolic features, showing differential glycolysis capacity and substrate utilization in PTs, TALs and DCTs. The transport activity can acutely regulate ATP turnover rate and chronically modulate mitochondrial biogenesis in TALs and DCTs.

Funding: NIDDK Support

FR-PO532

CREB and ATF1 Transcription Factors Are Not Required for the Vasopressin-Mediated Increase in AQP2 Abundance in Collecting Duct Cells

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Background: Aquaporin-2 (AQP2) abundance is regulated by arginine vasopressin (AVP), largely by increasing *Aqp2* gene transcription. In both native collecting duct and cultured mpkCCD cells, long-term exposure to AVP increases AQP2 abundance by 10-fold or more. Most review articles and textbook chapters on AQP2 regulation attribute the increase to PKA-mediated activation of the transcription factor CREB, by phosphorylation of S133 at the Kinase Inducible Domain (KID). Two KID-containing transcription factors are strongly expressed in collecting duct principal cells, namely ATF1 and CREB. Here, we investigated their potential roles in the AVP-mediated increase in AQP2 abundance.

Methods: PKA knockout (PKA-KO) and WT mpkCCD cells were utilized. CREB and ATF1 phosphorylation was analyzed by immunoblotting. *Atf1* and *Creb1* genes were deleted by CRISPR/Cas9 in WT mpkCCD cells and verified by immunoblotting (using a custom mouse ATF1 specific antibody and a commercial CREB antibody) and Sanger sequencing. RNA-seq was performed in *Atf1*-KO cells and AQP2 protein levels were analyzed by immunoblotting in *Atf1*-KO cells as well as *Atf1/Creb1*-KO cells, with or without desmopressin (dDAVP), an AVP analogue.

Results: Basal phosphorylation levels of CREB-S133 and ATF1-S63 were similar between WT and PKA-KO cells, however the dDAVP-mediated increase was blunted in PKA-KO cells. In WT cells, dDAVP (0.1nM for 72 hours) produced a 15-fold increase in AQP2 band density ($P < 0.005$), whereas it increased AQP2 17-fold in *Atf1*-KO cells ($P < 0.0005$) and 14-fold in *Atf1/Creb1* double KO cells ($P < 0.01$). RNA-seq analysis found only 11 differentially expressed genes comparing WT and *Atf1*-KO cells in the presence of dDAVP ($P_{adj} < 0.05$ and $|\log_2 KO/WT| > 1$), and *Aqp2* mRNA was not affected.

Conclusions: We conclude that CREB and ATF1 are not necessary for the action of dDAVP to increase *Aqp2* gene expression, contrary to the conventional belief in the literature. Future studies will assess whether other dDAVP-responsive genes are regulated by KID transcription factors, and what other transcription factors might be modulated by vasopressin-mediated signaling to explain the upregulation of AQP2.

Funding: Other NIH Support - NHLBI

FR-PO533

MEF2A Is a Novel Osmoregulatory Transcription Factor

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Background: Osmoregulation is a complex component of cell physiology, yet the initial transcriptional regulators of the osmotic stress response remain to be fully characterized. Here we studied the regulation of promoter-proximal RNA polymerase pausing after osmotic stress and uncovered MEF2A as a tonicity-responsive transcription factor.

Methods: We identified tonicity responsive genes by expression profiling in skin fibroblasts and inner medulla collecting ducts cells following osmotic stress. To identify genes with paused RNA polymerase we used the Precision nuclear Run-On and Sequencing assay (PRO-seq) to determine the locations of actively transcribing RNA polymerases.

Results: Aldose reductase (*AKR1B1*) and sodium myoinositol transporter (*SLC5A3*) are tonicity-responsive genes marked by abundant paused RNA Pol II at baseline. Both genes are induced by hypertonic stress, but induction is abrogated in the presence of a small molecule that stabilizes paused RNA Pol II. While *AKR1B1* and *SLC5A3* require pause-release for gene induction, not all genes with paused polymerase are induced by hypertonic stress, indicating specificity to pause-release. To identify other pause-dependent tonicity-responsive genes, we performed RNA sequencing and Precision Nuclear Run-On sequencing (PRO-seq) to measure gene expression and nascent transcription. We observed pause-dependent induction of 335 tonicity-responsive genes. To ask how pausing at these genes is regulated, we searched for transcription factor binding sites and identified motifs for MEF2A at 48% of the induced genes. We then performed CUT&Tag in fibroblasts and found tonicity-dependent binding of MEF2A at 1230 sites, including the *SLC5A3* promoter. Next, we knocked down MEF2A using siRNA and found *SLC5A3* and *AKR1B1* expression is significantly reduced following hypertonic stress. Finally, we water restricted mice to test if MEF2A responds to physiologic hypertonic stress. We observed increased MEF2A staining in the nuclei of renal collecting duct cells of water restricted mice compared to controls.

Conclusions: Together, we show MEF2A exhibits osmotic stress-dependent nuclear localization and chromatin binding, and that it regulates expression of *SLC5A3* and *AKR1B1*. We suggest MEF2A mediates RNA Pol II pause release to induce transcription of tonicity-responsive genes.

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FR-PO534

Activation of BKα Channel Prevented the High Glucose-Induced Oxidative Stress in Human Proximal Tubular Cells

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Background: Hyperglycemia stimulates the production of reactive oxygen species (ROS) leading to oxidative stress. Oxidative stress could cause inflammation or fibrosis. Our previous study found that activation of the large conductance, calcium-activated potassium channels (BK channels) attenuated renal fibrosis in mice. We hypothesized that upregulation BK channel activity would suppress the high glucose (HG)-induced oxidative stress.

Methods: Human proximal tubular epithelial cell (HK-2) was cultured in DMEM/F12 medium. HEK-BKα cells (HEK293 stably expressing BKα) were maintained in DMEM with G418. Cells were cultured in the low glucose DMED (5.5mM glucose) for 24 hours before treatments. NS1916 (Sigma) was used to activate BKα channel. Two ROS products were measured: 1-hydrogen peroxide (H2O2) was tested by Amplex Red Hydrogen Peroxide Kit (cat # A22188, Molecular Probes): 2- DHE (Dihydroethidium) Assay (Abcam ab236206) was used to detect superoxide. Superoxide Dismutase (SOD), a defense of oxidative enzyme, was measured using colorimetric activity kit (Invitrogen EIASODC). Single channel recordings were used to analyze the activity of BKα channel.

Results: Using single channel recordings we showed that high glucose (HS, 25 mM D-glucose) inhibited BKα channel activity in HEK-BKα cells. As an osmolarity control, 25 mM mannitol does not change the BKα activity. To determine the effect of BKα activation on HG-induced ROS production HK2 cells was treated with HS (25mM) with or without NS1916 (BKα channel opener). H2O2 and superoxide productions were significantly increased with high glucose treatment, whereas NS1916 (20mM) prevented the HG-induced upregulation of H2O2 and ROS. In addition, HS treatment (25 mM) significantly decreased SOD activity in HK2 cells, whereas activation of BKα activity with NS1916 reversed the decreased SOD activity induced by HS.

Conclusions: High glucose inhibited BKα activity while increasing H2O2 and superoxide productions in HK2 cells. Activation of BKα channel activity attenuated HS-induced the ROS production. In addition, BKα reversed HS-induced down-regulation of SOD. These results suggest that activation of BKα channel has novel roles in preventing oxidative stress.

Funding: Veterans Affairs Support

FR-PO535

Neuropeptide FF Increases Na+/K+-ATPase Activity in Live Renal Proximal Tubule Cells

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Background: Neuropeptide FF (NPFF), an amidated peptide, acts as a pain-modulator. However, the effects of NPFF on renal Na^+ transport and blood pressure are unknown.

Methods: Intracellular Na^+ concentration in renal proximal tubule cells (RPTCs) was measured using the lifetime Na^+-binding of NaTRIUM Green-2 (Green-2), monitored by fluorescence lifetime imaging (FLIM) and Na^+ green tetraacetate, monitored by spectrometry. Blood pressure and sodium excretion were also studied in mice.

Results: In glass bottom-cultured RPTCs, Green-2 (5 μM/1 hr) had a biexponential decay in time-resolved fluorescence measurements in randomly selected regions of interest (ROI) in the cytoplasm of these RPTCs. In the basal state, the lifetime t_2 (Na^+-binding decay time component, nanoseconds) was 3.44±0.05 (n=8). NPFF (100 nM) sequentially decreased the lifetime t_2: 3.44±0.04 (5 min), 3.35±0.07 (10 min), 3.31±0.07 (15 min), and 3.25±0.06 (20 min), analyzed from the ROIs (n=8-20). The decrease in t_2, Na^+-binding decay time component, due to NPFF was associated with a decrease in intracellular Na^+ concentration (NPFF: 79.0±4.7%, n=4 vs vehicle: 100.0±9.4%, n=4). The NPFF-mediated decrease in intracellular Na^+ was due to an increase in Na^+/K^+-ATPase activity, because ouabain (50 μM) which inhibits Na^+/K^+-ATPase activity increased intracellular Na^+ (125.9±6.1%, n=4) and prevented the NPFF-mediated decrease in intracellular Na^+ concentration (124.3±4.9%, n=4). The effect of NPFF on other sodium transporters and exchangers was not determined. The stimulatory effect of NPFF on Na^+ transport has physiological significance because in anesthetized C57Bl/6 mice (n=4), the acute bilateral renal subcapsular injection of NPFF (10 μg/100 μL) increased systolic blood pressure (SBP, mm Hg), 15 min post injection (138.5±12.8 vs basal, 99.5±1.3, $P < 0.05$), peaked at 25 min (148.3±8.3), and gradually returned to baseline at 60 min. The chronic bilateral renal subcapsular infusion of NPFF (9.25 mM, 0.5 mL/hr, n=4) for 7 days also increased SBP and decreased urinary sodium excretion that were prevented by RF9, an NPFF antagonist.

Conclusions: NPFF decreased intracellular Na^+ concentration in RPTCs by stimulating Na^+/K^+-ATPase activity, decreased Na^+ excretion, and increased blood pressure in C57Bl/6 mice.

Funding: NIDDK Support, Other NIH Support - NHLBI

FR-PO536

Cell Volume-Sensitive Transcription Factor(s) Regulate Claudin-2 Expression in Epithelial Cells

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Background: The basolateral Na^+-K^+-$2Cl^-$ cotransporter (NKCC1) plays a critical role in maintaining the intracellular concentrations of Na^+, K^+, and Cl^- ions, and cell volume. While it is well recognized that NKCC1 is critically important for vectorial transport of Na^+, K^+, and Cl^- across epithelia, its role in transcellular ions transport and epithelial barrier function is not well understood. Here we ask whether loss of NKCC1 function affect kidney and intestinal epithelial tight junction permeability.

Methods: Wild-type MDCK I and NKCCC1-deficient clones LKA3 and LKC1 were plated and polarized on transwell filters, and their TER was measured. Tight junction protein expression and localization was assessed by western blotting and immunofluorescence.

Results: The TER values of NKCC1-deficient MDCK I cells decreased by more than 20-fold, from 8000 Ω.cm² in parental MDCK I to 300-500 Ω.cm² in LKA3 and LKC1 clones. Western blot analysis showed that genetic ablation or pharmacologic of NKCC1 function increases the expression of the cation selective claudin-2. This is consistent with the observed decreased TER. In addition, growing MDCK I cells in Cl^--free, Na^+-free or both Cl^- and Na^+-free media upregulates claudin-2 expression.

Conclusions: Our data indicate that loss of NKCC1 function affects tight junction protein expression without affecting their localization. Particularly, claudin-2 was significantly upregulated. This led to an increase in paracellular flux of positively charged ions across the MDCK epithelial cell monolayers. Notably, this phenomenon is not unique to kidney epithelial cells cells, as loss of NKCC1 function in intestinal HT29 cells also led to significant decrease in TER and upregulation of claudin-2 expression.

Funding: NIDDK Support, Private Foundation Support

FR-PO537

Resveratrol Inhibits Proximal Tubular Sodium Reabsorption and Suppresses the Progression of Renal Injury

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Background: Resveratrol(RSV), a natural polyphenol compound, has demonstrated anti-inflammatory, anti-cancer, anti-oxidant, and anti-aging effects in vitro and in vivo studies. However, its effects on the proximal tubules (PTs) and kidney disease remains unknown. In this study, we evaluated the effect of RSV on Na transport in isolated PTs and its potential to inhibit the progression of chronic renal injury in rat models.

Methods: By using a pH-sensitive dye BCECF we measured the basolateral Na^+-HCO_3^- Cotransporter (NBCe) 1 activity and apical Na^+-H^+ Exchanger (NHE) activity in freshly-isolated rat PTs. To evaluate the effect of RSV on the progression of kidney disease, 6-week-old OLETF rats that had undergone unilateral nephrectomy were fed a high-salt diet, administered aldosterone (Ald) continuously by osmotic pump, and compared to a group receiving 50 mg/kg BW RSV orally daily for four weeks. Comparisons were made by serum biochemical, histological tests and protein expression. Protein expression was determined by Western blot.

Results: In a concentration-dependent manner, RSV significantly inhibited the stimulatory effects of insulin on Na reabsorption on PTs, and inhibited insulin-induced phosphorylation of Akt. Moreover, continuous Ald administration resulted in severe albuminuria and renal dysfunction, whereas those treated with RSV exhibited a significant reduction in both albuminuria ($p < 0.05$) and renal dysfunction ($p < 0.05$). In the renal cortex, phosphorylation of Akt and expression of Rictor and Raptor were significantly decreased ($p < 0.05$).

Conclusions: RSV inhibits insulin-induced sodium reabsorption in PTs, and it could have a renoprotective effect.

Funding: Government Support - Non-U.S.

FR-PO538

Exposure of Junctional Claudin-3 Epitopes in the Thick Ascending Limb of Cldn19-Deficient Mice

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Background: The kidney plays a vital role in maintaining mineral balance. The reabsorption of calcium and magnesium in the renal thick ascending limb (TAL) is facilitated by CLDN16 and CLDN19 and mutations in either gene results in severe calcium and magnesium loss. *Cldn3* is also expressed in TAL RNAseq databases, however some but not all studies localize the CLDN3 protein to the TAL. In our hands, using 3 distinct antibodies, we have been unable to detect CLDN3 expression in the TAL.

Methods: The pattern of expression of CLDN3 was evaluated using 3 distinct CLDN3 antibodies: 1. Anti-CLDN3 antibody (HPA014361 Sigma-Aldrich), 2. Anti-CLDN3 antibody (STJ23159, St John's Laboratory), and 3. Anti-CLDN3 Antibody (34-1700, Invitrogen), all produced in rabbit. Using these antibodies, we investigated the localization of CLDN3 in the kidneys of both wild-type and Cldn19 deficient mice on 2 um paraffin sections.

Results: All antibodies showed immunoreactivity towards epitopes situated in the tight junctions of the renal tubular cells. In addition, the Sigma antibody labeled epitopes in the intercalated cells and the Invitrogen labelled epitopes in the perinuclear region of epithelial cells. With respect to the tight junction, CLDN3 was expressed in portions of the proximal tubule as well as distal nephron cells but was absent from the TAL in wild-type animals using all three antibodies. In contrast, in *Cldn19* deficient animals, immunoreactivity was also found in the TAL in a mosaic pattern.

Conclusions: These findings suggest that CLDN3 localizes to the TAL where it may play a direct role in determining the permeability. Why immunoreactivity in the TAL is only seen in Cldn19 deficient animals remains to be elucidated. The findings could suggest that CLDN19 shields the epitope towards which CLDN3 binds in fixed tissue.

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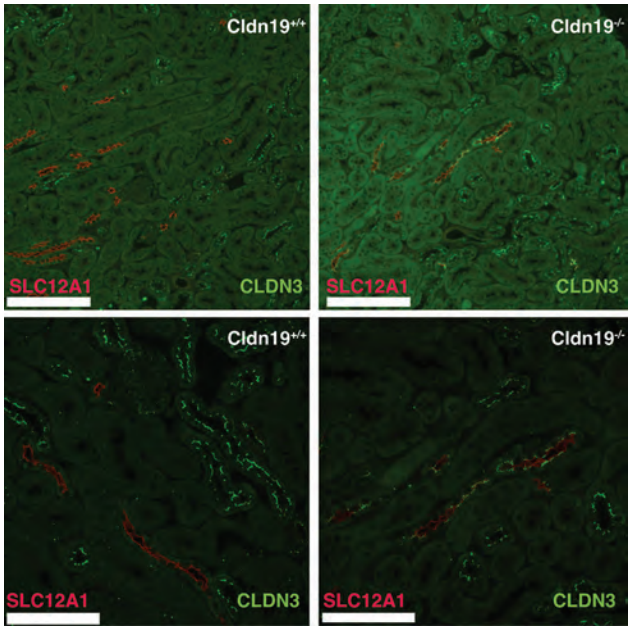

FR-PO539

A Novel R881S Mutant of Transporter NBCe1 Has Cytosolic Retention and Lacks Dominant Negative Effect

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Background: The electrogenic Na^+/HCO_3^- cotransporter NBCe1 is expressed in many organs including the brain, eye, and the kidney, where it controls sodium and bicarbonate reabsorption. NBCe1 homozygous mutation causes not only severe hypotension but also proximal renal tubular acidosis (RTA) in human and rodents. Here we characterized the functional significance of SNVs reported from NCBI database.

Methods: We identified the missense mutation R881S in NBCe1 variant A (kidney type) from the database. Given the report of R881C mutation in patients with RTA (JASN 2005), we conducted a comparative analysis of cellular localization and cell protein expression between R881S and R881C using confocal microscopy and Western blotting.

Results: Immunofluorescence analysis with confocal microscopy revealed that the R881S variant was present exclusively in the cytoplasm in both HEK293 cells and MDCK cells. Biotinylated western blotting in HEK293 cells confirmed that the cell-surface expression was completely abolished in R881S mutant. In total cell lysates, R881S-NBCe1 showed a lower molecular weight compared with wild-type, and deglycosylation study confirmed that R881S substitution impaired N-glycosylation. Moreover, co-immunoprecipitation study revealed that the interaction with wild-type NBCe1 was severely impaired in R881S compared with R881C.

Conclusions: R881S mutation inactivates the NBCe1 function without lack of dominant-negative effect. These data illustrate the diverse physiological consequences of distinct SNVs and underscore the importance of functional characterization in membrane transport proteins.

Funding: Government Support - Non-U.S.

FR-PO540

Estimation of Plasma Vasopressin Activity by AQP2 in Urinary Extracellular Vesicles

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Background: The antidiuretic hormone, vasopressin (AVP), activates protein kinase A (PKA) in the principal cells of the collecting duct via the V2 receptor. Activated PKA is known to phosphorylate the amino acid residues (S256 and S269) on the water channel, aquaporin 2 (AQP2). These phosphorylations are considered to promote water reabsorption by increasing the trafficking of AQP2 into the apical membrane. The measurement of the blood AVP concentration is difficult because of its instability and binding to the platelets. It has been shown that urinary extracellular vesicles (uEVs) contain AQP2 protein. Therefore, in this study, we investigated whether AVP activity could be inferred by measuring the total or phosphorylated form of AQP2 in uEVs.

Methods: In experiment I, male SD rats were divided into three groups: a control group (free-drinking tap water), a dehydration group (water deprivation; DH group), and a hydration group (free-drinking 20% sucrose; HY group). In experiment II, male SD rats were divided into two groups: a vehicle group (50% of 5% glucose, 50% of saline, s.c.) and a dDAVP group (300 ng/kg desmopressin, V2 agonist, s.c.). Urine samples were collected for 12-24 hrs, and blood and kidney samples were collected at 24 hrs after the treatment. Total and phosphorylated (pS256, pS269) AQP2 protein levels in uEVs were evaluated by immunoblot analysis.

Results: In experiment I, urine volume was decreased in the DH group and was increased in the HY group. Moreover, urine osmolality was elevated in the DH group and reduced in the HY group. Total and phosphorylated AQP2 levels in uEVs were increased in the DH group, and only the pS269-AQP2 level was decreased in the HY group. In experiment II, urine osmolality in the dDAVP group significantly increased in comparison with the control group. The total AQP2 level showed an increasing tendency, and the pS269-AQP2 level was significantly increased in the dDAVP group. On the other hand, the pS256-AQP2 level was not altered.

Conclusions: These results indicate that the pS269-AQP2 level in uEVs responded well to the physiological and pharmacological changes in V2 receptor activation. Therefore, pS269-AQP2 in uEVs may be a potential non-invasive biomarker to estimate plasma AVP activity.

FR-PO541

Elucidating the Diuretic Effect of Corticosteroids in Rats

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Background: Corticosteroids are widely used to treat kidney diseases such as nephrotic syndrome. A few cases of polyuria following corticosteroid treatment have been reported in human patients with heart failure or hypopituitarism. In dogs, corticosteroids frequently cause polyuria and polydipsia (Elkholly DA et al., *Front Vet Sci.* 2020). In experimental rat models, acute corticosteroid treatment is known to cause a potent diuretic effect (Tunhorst RL et al., *Am J Physiol Regul Integr Comp Physiol* 2007). However, the mechanisms by which corticosteroids cause polyuria is largely unknown. Here, we investigated the mechanism of corticosteroid-induced polyuria in rats treated with prednisolone (PSL).

Methods: Male SD rats aged 10 weeks were treated with PSL (0.3 or 1.0 mg/kg, s. c.) or vehicle (25% DMSO/75% Corn Oil, s. c.). Urine was collected for 6 hours after the treatment. Blood and kidneys were isolated at 6 hours post-treatment. The levels of electrolyte and osmolality in urine and blood were measured. Free water clearance was also calculated. The gene expression levels of sodium-dependent transporters and water channels were investigated by real-time PCR.

Results: The urine volume was significantly increased and the urinary osmolality was significantly decreased after the treatment of PSL, in a dose-dependent manner. The total excretion of Na^+, K^+, Cl^- and inorganic phosphorus was significantly higher in rats treated with PSL than in without it. The free water clearance value was negative in the PSL-treated rats. Real-time PCR revealed that mRNA levels of sodium/chloride cotransporters (NKCC2/Slc12a1 and NCC/Slc12a3), sodium/phosphate cotransporters (Slc34a1 and Slc34a3) and a water channel (AQP2) were decreased in the PSL group. In addition, significant negative correlations were observed between urinary sodium excretion and the gene expression of NKCC2 and NCC.

Conclusions: These results indicate that reduced renal expression of sodium-dependent transporters in response to PSL may contribute to the suppression of electrolyte reabsorption, leading to the diuretic and natriuretic effects in rats. Since the free water clearance value was negative, the contribution of AQP2 was considered modest in the diuretic effect of PSL.

FR-PO542

Colistin-Induced Acute Tubular Dysfunction: Toxicity Beyond Creatinine

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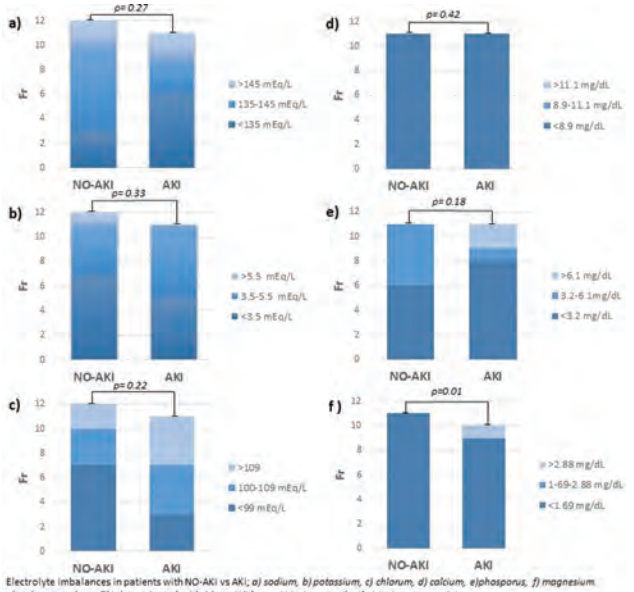
Background: Colistin is a relevant antibiotic for infections by multiresistant microorganisms. However, it is not exempt from serious renal adverse events, e.g.: acute kidney injury (AKI). The present study describes the hydroelectrolytic disorders associated with the prescription of colistin.

Methods: Retrospective cohort design. Data were obtained from January 2021 to December 2022. Patients who received colistin for at least 48 hours were included. Patients with chronic renal support therapy or acute kidney injury prior to starting colistin were excluded.

Results: 23 patients were evaluated, with an average age of 55.96 years, men 60.86%. The most frequently isolated microorganism was *P. aeruginosa* (56.52%). The reported findings were: euvolemic hyponatremia (39.13%), hypochloremia (43.47%), hypokalemia (52.17%), hypocalcemia (100%), hypophosphatemia (63.63%), and hypomagnesemia

(95.23%). 11 patients (47.82%) developed AKI. When comparing the development of electrolyte disturbances between patients with and without AKI, hypomagnesemia was more frequent in the AKI group. There was a constant increase in the renal elimination of potassium, phosphate, and magnesium.

Conclusions: A high incidence of hydroelectrolytic imbalance associated with colistin was found. Interestingly, 100% of patients developed hypocalcemia and the majority had hypomagnesemia and hypophosphatemia. Urinary biochemical evaluation for potassium, phosphate and magnesium provides data highly suggestive of acute tubular dysfunction, an event rarely reported in the literature, which causes high comorbidity if the imbalance is not treated.



Electrolyte imbalances in patients with NO-AKI vs AKI; *a) sodium, b) potassium, c) chlorum, d) calcium, e)phosporus, f) magnesium.* α level accepted was 5% determinated with *Mann-Withneyy U test or student's t test as appropriate .*

Renal elimination of potassium, phosphate and magnesium

	Electrolyte disorders	KuOrU (mEq/g)	EF-P[i] (%)	TRP (%)	EF-Mg2+ (%)
Patient without AKI	↓K+	80.13*			
Patient with AKI #1	↓Mg2+ and ↓P-	89.89*	41*	50%	8%*
Patient with AKI #2	↓K+ ↓P- and ↓Mg2+	133.7*	8	92%	48%*
Patient with AKI #3	None	168*			
Patient with AKI #4	↓K+	165*			
Patient with AKI #5	↓K+	29.76*			

*High elimination for the electrolyte disorder in a normal serum electrolyte. KuOrU: Urinary potassium. Urinary creatinine index. EF-P: (%) Fractional excretion phosphate. TRP: Tubular reabsorption of phosphate. EF-Mg2+: Fractional excretion of Magnesium

FR-PO543

Mechanisms of Thiazide-Induced Magnesium Wasting and Calcium Retention at Single-Cell Resolution

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Background: States of NCC inhibition, as in Gitelman syndrome and chronic thiazide treatment, present with hypokalemia, alkalosis, hypomagnesemia, and hypocalciuria. The mechanism by which loss of NCC function affects Mg and Ca handling remains very unclear. Here we combined single nucleus RNA sequencing with physiologic and morphometric analysis to unravel the causes of hypomagnesemia and hypocalciuria secondary to NCC inhibition.

Methods: 8 to 10-week-old male NCC-Cre-INTACT mice received 50 mg/kg/day metolazone (MTZ) orally for 4 days. Fluorescence-activated nuclei sorting was performed to select for DCT nuclei. Sequencing was done using 10X Chromium. Reads were analyzed using a transcriptomic bioinformatics pipeline with Seurat. We also performed tubule morphometrics.

Results: MTZ-treated mice had lower plasma Mg and lower urinary Ca excretion compared to controls, consistent with NCC inhibition. Our snRNA-seq dataset showed 2 clusters, DCT1 and DCT2, based on canonical markers consistent with published transcriptomic atlases. We curated Mg and Ca cassettes from known magnesiotropic and calciotropic genes and defined Mg and Ca scores from the pooled expressions of the genes and used them to indicate Mg and Ca handling capacity. The analyses showed that Mg handling is primarily a DCT1 process and Mg score was lower in the MTZ group. We also found that the DCT1 undergoes dedifferentiation leading to reduction in magnesiotropic gene expression. Additionally, 3D morphometrics showed that DCT1 was shorter in the MTZ group. Ca handling is primarily a DCT2 process and Ca score was lower in the MTZ group consistent with low distal delivery due to enhanced proximal Ca reabsorption. Yet, DCT2 cells maintained their cell state and were less vulnerable to NCC inhibition compared to DCT1 cells. Lastly, MTZ-treatment caused hypertrophy of the Ca-transporting connecting tubule (CNT).

Conclusions: The results indicate that hypomagnesemia secondary to NCC inhibition results both from a disruption of genes involved in Mg handling and from DCT1 dedifferentiation and atrophy. While increased proximal tubule Ca reabsorption is required for hypocalciuria, our results also indicate that aldosterone-induced hypertrophy of the CNT and relative preservation of DCT2 contribute to calcium retention.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO544

WNT Ligands Drive PKD1-Mediated G Protein Signaling and Receptor Internalization and Downregulation

Emily P. Hardy, Leonidas Tsiokas. *The University of Oklahoma Health Sciences Center, Oklahoma City, OK*.

Background: Autosomal Dominant Polycystic Kidney Disease is a genetic disorder caused by mutations in *PKD1* or *PKD2*, which encode PKD1 and PKD2, respectively. PKD2 is a nonselective cation channel and forms a complex with PKD1 in which the channel is activated upon WNT binding to PKD1. Independently, PKD1 is proposed to act as an atypical G protein-coupled receptor (GPCR) for which the activating ligand is unknown. Here, we investigated the role of WNTs in PKD1-mediated G protein signaling and receptor internalization and downregulation.

Methods: An interaction between PKD1 and G_q has been previously established and was used to investigate PKD1-mediated signaling in response to WNTs. Using wild type and PKD1 knockout IMCD3 cells, single-cell calcium imaging was employed to test whether PKD1-G_q coupling is functional and occurs in response to WNTs. To determine if WNTs induce downstream PKD1 internalization and downregulation, pull down assays in combination with BRET (Bioluminescence Resonance Energy Transfer) were used. HEK293T cells were either singly- or co-transfected with PKD1 and WNT/empty vector, and assayed following co-expression or co-culture. Co-immunoprecipitation and western blot techniques coupled with a BRET titration approach were used to assess GPCR kinase (GRK) and β-arrestin recruitment to PKD1.

Results: Compared to wild type cells, PKD1 knockout IMCD3 cells showed a significant reduction in the rise of intracellular Ca^{2+} following WNT5A stimulation, suggesting a role for WNT5A in PKD1-dependent downstream Ca^{2+} transients. Following co-expression/co-culture, our western blot and BRET analysis revealed a significant decrease in whole cell and cell surface levels of PKD1 in cells transfected with WNT5A/9B, but not empty vector. This data suggests requirement for WNT in PKD1 internalization and downregulation. Supporting the notion that this process occurs as GPCR desensitization, GRK2/6 and β-arrestin1/2 were found to interact specifically with PKD1.

Conclusions: Our findings highlight an important role for WNTs in the GPCR-function of PKD1 for both receptor activation and desensitization. WNTs have been shown to interact with PKD1 to activate PKD2 channel activity, andtogether with our findings suggest a model whereby WNT-induced activation of PKD1 leads to intermediary G protein signaling and downstream activation of PKD2 channel activity.

Funding: NIDDK Support

FR-PO545

Addition of an N-Terminal SNAP-Tag Induces a Novel Hypomorphic Pkd1 Allele

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Background: We engineered mice that express endogenous polycystin-1 (PC1) with an N-terminal, self-labeling SNAP-tag to facilitate the *in vivo* visualization of PC1 trafficking and co-immunoprecipitation of multiprotein complexes. While initial reports indicated that the allele is normal, follow-on work has demonstrated that addition of SNAP results in a hypomorphic cystic phenotype that is variable depending on the nature of the second *Pkd1* allele.

Methods: A repair construct encoding SNAP fused in-frame with the first exon of *Pkd1* was injected into C57 pronuclei for homology-driven repair using CRISPR. Resulting $Pkd1^{N\text{-}SNAP}$ mice were crossed to homozygosity and also crossed with non-functional $Pkd1^{NdL}$ (truncation) mice, and hypomorphic $Pkd1^{V}$ and $Pkd1^{RC}$ mice, to generate compound heterozygotes. Mice were maintained up to 26-weeks of age, then sacrificed for analysis.

Results: Compound heterozygous $Pkd1^{N\text{-}SNAP/NdL}$ pups had severely cystic kidneys at 2 weeks of age, with an average percent kidney weight to body weight (%KW/BW) of 9.4%. Homozygous $Pkd1^{N\text{-}SNAP/N\text{-}SNAP}$ mice had moderately cystic kidneys with a %KW/BW of 2.6% at 8 weeks, progressing to 5.2% at 23-26 weeks. In contrast to compound heterozygous $Pkd1^{V/RC}$ mice, which are severely cystic by 3 weeks, compound heterozygous $Pkd1^{N\text{-}SNAP/V}$ and $Pkd1^{N\text{-}SNAP/RC}$ mice had kidneys with only a few very small cysts with a %KW/BW of 1.4% at 23-26 weeks. Interestingly, a female $Pkd1^{N\text{-}SNAP/V}$ mouse and a female $Pkd1^{N\text{-}SNAP/RC}$ mouse used as breeders had a few large cysts at 23-26 weeks.

Conclusions: Addition of SNAP to the N-terminus of PC1 generates a hypomorphic $Pkd1^{N\text{-}SNAP}$ allele. The cystic phenotypes in $Pkd1^{N\text{-}SNAP/NdL}$ and $Pkd1^{N\text{-}SNAP/N\text{-}SNAP}$ mice suggest that the tag affects PC1 trafficking, stability, and/or a critical function of the polycystin complex. However, the very mild phenotype in $Pkd1^{N\text{-}SNAP/V}$ and $Pkd1^{N\text{-}SNAP/RC}$ mice suggests complementation between the SNAP allele and the V or RC alleles. This suggests the PC1-SNAP defect is functionally distinct from that of the defects caused by

the V and RC mutations, allowing partial preservation of PC1 function when present *in trans* within the same animal. Future experiments will determine the functionality of the SNAP-tag, the localization of the $PC1^{N\text{-}SNAP}$ protein, and the nature of the defect caused by the SNAP-tag.

Funding: NIDDK Support

FR-PO546

Cleavage of PC1 Is Not Required for Embryonic Vasculature Development

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Background: Polycystin 1 (PC1) is a large membrane protein that undergoes an autoproteolytic cleavage at a G protein coupled receptor (GPS) site. PC1 cleavage at the GPS is essential for trafficking of the PC1/PC2 complex to the primary cilium. While homozygous *Pkd1* or *Pkd2* knock-out mice die at mid-gestation due to vascular and lymphatic abnormalities homozygous $Pkd1^{V/V}$ mutant embryos, harboring a mutation that abolishes PC1 cleavage, survive embryogenesis, suggesting that uncleaved PC1 ($PC1^{V}$) might play a role in embryonic vascular development.

Methods: We analyzed the vascular phenotype of $Pkd1^{V/V}$, $Pkd1^{-/-}$ and control E14.5 embryos including placenta branching morphogenesis and epidermal lymphatic vessel development. Rescue experiments were performed using a transgenic BAC expressing HA-tagged-$PC1^{V}$ ($PC1^{V\text{-}F/H}$). We evaluated the impact of PC1 cleavage on cell migration/polarity via wound healing assay. Trafficking of $PC1^{V}$ and the PC2/$PC1^{V}$ complex was assessed by N-glycosylation studies and biotinylation assays. Localization of PC1 and $PC1^{V}$ in the cilia was performed using immunofluorescence in endothelial cells (EC).

Results: $Pkd1^{V/V}$ embryos lacked the vascular abnormalities observed in $Pkd1^{-/-}$ embryos including hemorrhage, edema and polyhydramnios. The complexity of the placental labyrinth vasculature and the lymphatic vasculature were similar between $Pkd1^{V/V}$ and controls but reduced in $Pkd1^{-/-}$ embryos. Transgenic expression of $PC1^{V\text{-}F/H}$ was sufficient to rescue the vascular phenotype observed in $Pkd1^{-/-}$ mutants. Using wound-healing assays we observed that $Pkd1^{V/V}$ cells migrated properly and that front-rear polarity was similar to controls. We confirmed that PC1 and PC2 colocalized in the primary cilia of cultured ECs. In contrast, PC2 was undetectable in cilia from $Pkd1^{V/V}$ cells. In addition, we showed that the pool of PC2 protein that co-immunoprecipitated with $PC1^{V}$ was Endo H sensitive, indicating that PC1 cleavage is a pre-requisite for the protein complex to traffic beyond the Golgi in ECs. $PC1^{V}$ was partially resistant to Endo H and able to reach the cell surface.

Conclusions: Our data suggests that expression and localization of PC1 and/or PC2 in the primary cilia of ECs is not required for a proper vascular/lymphatic vessel development. This is the first time that an extraciliary role for full length PC1 has been identified.

Funding: NIDDK Support

FR-PO547

Involvement of Glycolipids in Cyst Formation in Cystic Kidney Disease

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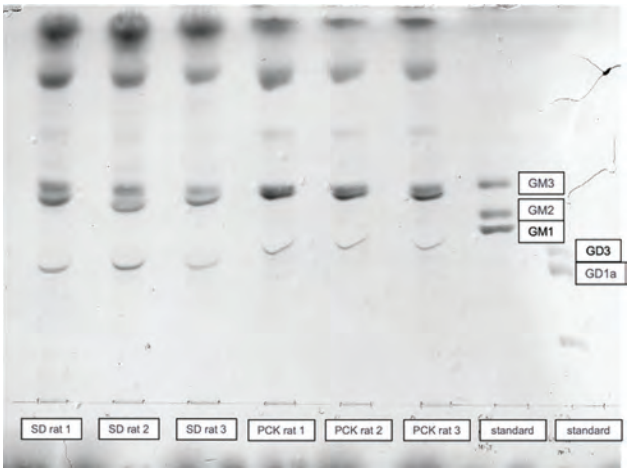
Background: ADPKD is an important disease that can lead to end-stage renal failure, yet many aspects of the mechanism of cyst enlargement remain unclear. In this study focusing on cystic kidney diseases, we examined the differences in glycolipids, a post-translational modification of proteins. Previous studies have demonstrated the accumulation of sphingolipids, such as GlcCer, LacCer, and GM3, in cystic kidney diseases. However, their direct involvement in cyst formation has not been established.

Methods: Glycolipids were extracted from the kidneys of PCK rats, a model of ARPKD, and developed by thin layer chromatography. Total RNA was extracted from the kidney tissue of the model animals and expression of glycosyltransferase was confirmed by qPCR. The same was also confirmed by WB.

Results: Thin layer chromatography of glycolipids extracted from renal tissue revealed changes in gangliosides including GM3, an acidic glycolipid. In cystic kidney tissue, GD3 with malignant phenotype was detected. qPCR and WB showed decreased expression of B4galnt1, a glycosyltransferase, in the medullary tubules of cystic kidney tissue. Primary culture of kidney cells from ADPKD patients also showed decreased expression of *B4GALNAT1*.

Conclusions: In the kidneys of mouse models of cystic kidney disease, disturbance in the composition of glycolipids was observed. Accumulation of GD3 is said to be involved in signaling of cell proliferation and may contribute to cyst enlargement. Decreased expression of B4galnt1 could explain these disturbed glycolipids change.



FR-PO548

Role of FBW7 in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

Maulin M. Patel, Leonidas Tsiokas. *The University of Oklahoma, Oklahoma City, OK.*

Background: ADPKD, caused by mutations mostly in *PKD1* or *PKD2* genes, is a leading cause of end-stage renal disease. Deleting structural components/proteins of cilia in mouse models of *Pkd1* inactivation ameliorates ADPKD progression, highlighting the importance of cilia regulation in ADPKD. Our lab has shown that FBW7, a substrate recognition receptor of the SCF^{FBW7} Ubiquitin E3 ligase, can regulate ciliogenesis. It recognizes proteins with a specific phosphorylated sequence called "phospho-degrons" and targets them for degradation via the ubiquitin-proteasome system. In this study, we sought to investigate the role of FBW7 in ADPKD.

Methods: We adopted an early-onset ADPKD mouse model where we induced *Pkd1* and/or *Fbxw7* deletion in postnatal mice using a global tamoxifen-inducible *Ubc-*Cre^{ERT2}.

Results: We found that *UbcCre*^{ERT2}*; Pkd1*$^{f/f}$ P16 pups develop cysts and significantly increased the Two kidney weight/body weight (2KW/BW) and cystic index, along with the loss of kidney function measured by levels of three different markers, BUN, Creatinine, and cystatin C in the blood serum compared to the WT pups. Furthermore, *UbcCre; Pkd1*$^{f/f}$*; Fbxw7*$^{f/+\ \&\ f/f}$ p16 pups also developed cysts and increased 2KW/BW and cystic index similar to *UbcCre*^{ERT2}*; Pkd1*$^{f/f}$ P16 pups. However, surprisingly, *UbcCre; Pkd1*$^{f/f}$*; Fbxw7*$^{f/+\ \&\ f/f}$ p16 pups showed significant rescue in the kidney function based on BUN, Cystatin C, and Creatinine levels in the serum compared to *UbcCre*^{ERT2}*; Pkd1*$^{f/f}$ P16 pups. Although the kidney function parameters in *UbcCre; Pkd1*$^{f/f}$*; Fbxw7*$^{f/+\ \&\ f/f}$ p16 pups were still significantly higher compared to the WT pups, the fact that the *UbcCre; Pkd1*$^{f/f}$*; Fbxw7*$^{f/f}$ p16 pups displayed improved kidney function despite having no significant changes in 2KW/BW, and cystic index compared to *UbcCre*^{ERT2}*; Pkd1*$^{f/f}$ P16 pups was exciting. This protective effect on kidney function upon loss of FBW7 was persistent when we analyzed P21 pups. *Ubc-*Cre^{ERT2}*; Fbxw7*$^{f/f}$ pups do not show any apparent kidney phenotype.

Conclusions: Loss of FBW7 ameliorates ADPKD progression via proteomic reprogramming that perhaps partially uncouples the kidney function and cystogenesis, challenging the prevailing dogma that kidney function is secondary to defects/cysts in kidney architecture.

Funding: NIDDK Support

FR-PO549

Anoctamin 3 Enhances Cystogenesis and Ciliary Dosage of Polycystins by cAMP Signaling in Renal Cilia

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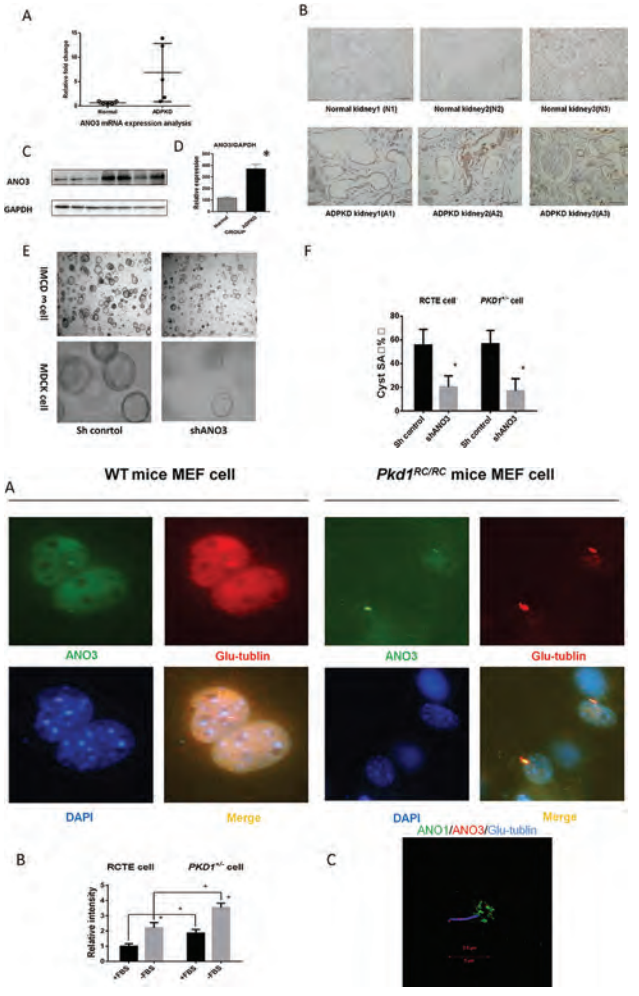
Background: Autosomal dominant polycystic kidney disease (ADPKD) is a ciliopathy which is characterized by abnormal tubular epithelial proliferation and fluid secretion. We reported Anoctamin1(ANO1), one of chlorine channels family could accelerate both cilia formation and cilia trafficking of polycystins. Anoctamin3(ANO3) was recently shown to be involved in ADPKD progression in our research.

Methods: 1.Real-time RCR, IHC and Western blot to detect expression of ANO3 in kidney tissue of ADPKD patients and normal kidndy. 2.3D culture to vertify the function of ANO3 in cysts formation with siANO3. 3.Super-resolution 3D structured illumination microscopy and co-IF to investigate ANO3 location and the impact of ANO3 on PC2 by siRNA in cilia. 4.MQAE to detect chloride ion flow by shANO3 and ad-ANO3 treating in ADPKD cells. 5.MRI to calculate the separates normal tubule space from cystic fluid area (Cyst fluid SA) in *PKD1* $^{flox/flox}$*CAG-creER*$^{+}$ mice.

Results: 1.ANO3 located in renal tubules and cyst and upregulated in human and mouse ADPKD kidneys. 2.siANO3 could inhibited cysts formation. 3.ANO3 was puncta-like localization on cilia membrane and siANO3 increased the cilia length and the expression of PC2. 4.Chloride ion flow was lower by shANO3 treating than ad-ANO3 in ADPKD cells. 5.Cyst fluid SA in *PKD1* $^{flox/flox}$*CAG-creER*$^{+}$ mice was significantly decrease than which in $PKD1^{RC/RC}$ mice.

Conclusions: ANO3 may aggravate ADPKD by regulating the renal cilia length and PC2 expression through cAMP signaling and provide mechanistic insights regarding the therapeutic potential of ANO3 pathway.



FR-PO550

The Cilia-Enriched Oxysterol 7β,27-DHC Is Required for Polycystin Activation

Kotdaji Ha, Nadine Mundt, Aide Pinedo, Gabriel Loeb, Jeremy Reiter, Markus Delling. *University of California San Francisco, San Francisco, CA.*

Background: The polycystin complex (PC-1 and PC-2) forms a non-selective cation channel and mutations within the polycystin complex cause Autosomal Dominant Polycystic Kidney Disease (ADPKD). The spatial and temporal regulation of the polycystin complex within the ciliary membrane is poorly understood, partially due to technical limitations studying the electrical properties of this tiny cellular compartment.

Methods: In this study, we used both whole-cell and ciliary patch-clamp recordings to measure the polycystin activity in the plasma or ciliary membrane. For carbenoxolone (CNX) injection study, we used intravenous and intraperitoneal injections to C57BL/6 strain mice from postnatal day 0.5 to 17.

Results: We identified a novel oxysterol binding pocket within PC-2 to modulate channel activation and showed that mutations within the oxysterol binding pocket disrupt 7β,27-DHC dependent polycystin activation. Pharmacologic and genetic inhibition of 11B-HSD enzyme that synthesizes oxysterol deplete channel activity in primary cilia and result in renal tubular dilation *in vivo*.

Conclusions: Our results identify the oxysterol binding pocket in PC-2 as an allosteric regulatory site in the polycystin complex, which may provide a specific target for novel ADPKD therapeutics.

Funding: NIDDK Support

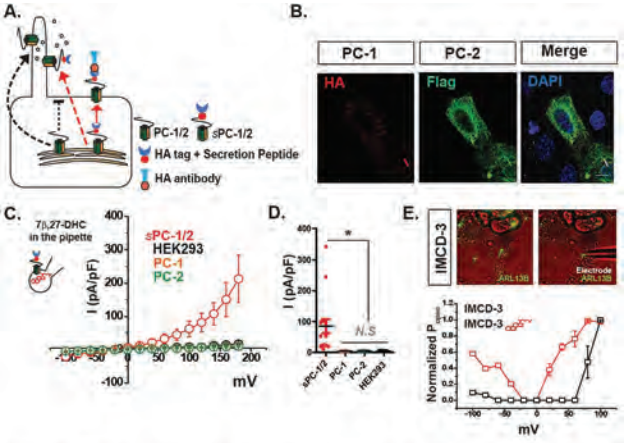


Figure 1. 7β,27-DHC activates the polycystin complex on the plasma membrane.

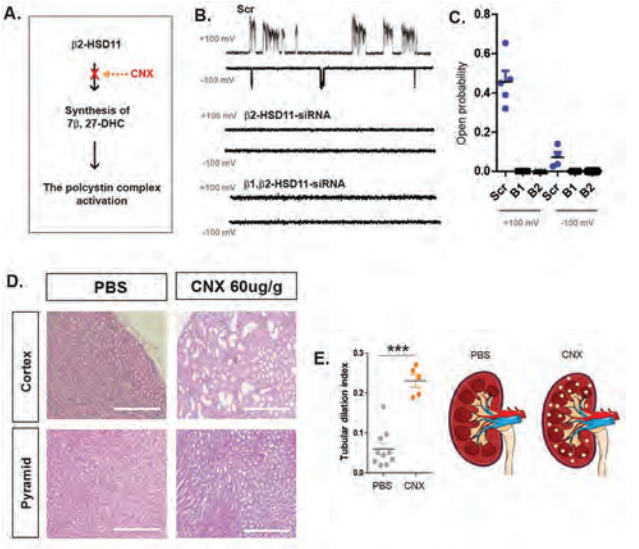


Figure 2. 7β,27-DHC synthesis is critical for basal activity of polycystin channels.

FR-PO551

Ouabain Enhances Renal Cyst Growth in a Slowly Progressive Mouse Model of Autosomal Dominant Polycystic Kidney Disease

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Background: Renal cyst progression in autosomal dominant polycystic kidney disease (ADPKD) is highly dependent on agents circulating in blood. We have previously shown, using different *in vitro* models, that one of these agents is the hormone ouabain. By binding to Na,K-ATPase (NKA), ouabain triggers a cascade of signal transduction events which enhance ADPKD cyst progression by stimulating cell proliferation, fluid secretion, and dedifferentiation of the renal tubular epithelial cells, all effects not seen in normal human kidney cells. The potential mechanism behind these effects is the abnormally high affinity that ~25% of the NKA of ADPKD cells have for ouabain. Here, we validate ouabain's effects *in vivo* and show that NKA ouabain affinity is critical for these effects.

Methods: Low dose ouabain (0.01 or 0.03 mg/g) or saline was injected intraperitoneally to mice daily, starting at postnatal day 9 and continuing for 1-5 months. The mouse models used include wildtype (WT), a slowly progressive ADPKD model ($Pkd1^{RC/RC}$), and an ADPKD mouse model in which all NKA has a high ouabain affinity ($Pkd1^{RC/RC}NKA\alpha1^{OS/OS}$). Kidney weight to body weight ratio (%KW/BW), blood urea nitrogen (BUN), renal percent cystic area (% cyst area), cyst number, and percent fibrosis were measured.

Results: Ouabain augmented % cyst area, cyst number, and renal fibrosis in $Pkd1^{RC/RC}$ mice when compared to saline-administered controls. By contrast, ouabain had no significant effect on WT mice. $Pkd1^{RC/RC}NKA\alpha1^{OS/OS}$ mice receiving saline had significantly increased % cyst area, cyst number, %KW/BW, and % fibrosis than $Pkd1^{RC/RC}$ mice receiving saline. Ouabain administration to $Pkd1^{RC/RC}NKA\alpha1^{OS/OS}$ mice did not alter any of the cystic parameters studied when compared to the saline-administered controls, and when compared to $Pkd1^{RC/RC}$ mice receiving ouabain, only % cyst area and renal fibrosis were increased over the study period.

Conclusions: These findings demonstrate that ouabain at levels similar to those circulating in plasma stimulates kidney cyst progression in ADPKD *in vivo* as well as *in vitro*. Additionally, the ouabain affinity of NKA plays a key role in the hormone's cystogenic effects.

Funding: NIDDK Support

FR-PO552

Cytoplasmic Domain of Fibrocystin/Polyductin Suppresses cAMP-Induced Cyst Formation of Pkhd1 Knockout (KO) Cells

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Background: Loss of ciliary protein function leads to defective control of epithelial homeostasis in hereditary polycystic kidney diseases. To address molecular aspects of epithelial function, monolayered epithelial spheroids can be used to analyze consequences of protein expression and pharmacological intervention. Here, we employed epithelial cell clones deficient for the protein fibrocystin/polyductin (FPC), the cause of ARPKD, to study the impact of FPC cytoplasmic domain expression on cAMP/Src-induced cyst formation.

Methods: We used pl-MDCK, sub-cloned principal-like cell lines, with CRISPR/Cas9-based genetic knockout (KO) of *Pkhd1* / FPC, and corresponding controls. Cells were grown in matrigel to allow formation of epithelial spheroids within 3 days. Forskolin (Fsk) treatment was employed to induce cAMP-mediated cyst growth mimicking disease conditions. Proportional lumen, i.e. the ratio of lumen to spheroid area, provided the measure to detect the enhanced water / ion transport across the barrier that is characteristic for cystic epithelia. Cellular signals known to stimulate cyst formation were modulated by viral expression of the FPC C-terminal domain and/or interventional treatment.

Results: In *Pkhd1*-KO cell lines, enhanced cAMP levels resulted in massive lumen expansion of epithelial spheroids with no increase in cell number. Cyst induction was sensitive to inhibition of Src kinase and led to activation and increased Y705 phosphorylation of STAT3. To address the contribution of FPC to cyst signaling, expression of a membrane-bound FPC C-terminal protein domain was studied, and its processing and intracellular localization determined. Controlled expression of the FPC cytoplasmic domain in *Pkhd1*-KO cell lines suppressed the Fsk-induced increase of proportional lumen / cyst formation, and furthermore, reduced activation of Src and STAT3 as well as STAT3-dependent transcription.

Conclusions: In FPC-deficient pl-MDCK cells, cyst formation stimulated by high cAMP levels is associated with enhanced Src/STAT3 signaling. Expression of the FPC cytoplasmic domain can correct control of the epithelial barrier in *Pkhd1*-KO and inhibit cyst growth *in vitro*. Therefore, expression of FPC domain constructs can lead to a gain-of-function and limit cyst promoting signals, a proposed cellular function of FPC protein.

Funding: Government Support - Non-U.S.

FR-PO553

Transcriptomics Analysis of ADPKD Cysts Shows Remodeling of Purinergic Receptors in Pkd1RC/RC Mice

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Background: Polycystic kidney diseases (PKD) are characterized by development of multiple cysts, dilations of nephron segments, which replace normal tissues and lead to kidney insufficiency.

Methods: To identify new gene pathways affected by cyst development in collecting ducts, we used a bulk RNAseq approach comparing gene expression of normal microdissected cortical collecting ducts (n=3) vs cysts (n=4) microdissected from the same *Pkd1*$^{RC/RC}$ mice.

Results: Bulk-RNA analysis identified 18,000 genes and allowed statistical comparison of over 15,000 genes. Our data reveals that although cysts originate from normal collecting ducts, cystic epithelium show 2692 down-regulated and 2278 up-regulated genes ($p<0.05$ pAdj. FDR). Ingenuity Pathways Analysis identifies the following intracellular mechanisms mostly affected by transition: Rac and Rho signaling, fibrosis signaling, epithelial-to-mesenchymal transition, cytoskeleton rearrangement and ERK/MAPK signaling. Our previous publication reported that development of cysts in an autosomal recessive model of PKD is associated with a shift of P2Y to P2X receptor abundance. In the current study we found that in the autosomal dominant *Pkd1*$^{RC/RC}$ mice model purinergic signaling undergoes similar remodeling. The most abundant ionotropic receptors with reduced expression were *P2ry2* and *P2ry4*, whereas ionotropic receptors *P2rx5* and *P2rx7* increased expression (2.88 and 1.53, log2). Additionally, analysis detected elevated abundance of *P2ry6*, *P2ry12* and *P2ry13* RNA level. We hypothesize that the physiological significance of the predominant P2X signaling in the cysts include their role in regulation of ATP release via pannexin-1 channels. Abnormal ATP accumulation in the cyst space was shown earlier to contribute in cystogenesis and we previously showed that pannexin-1 mediates ATP release to the cyst lumen. In the presented study, RNAscope confirms hyperexpression of *P2rx7* mRNA in cysts. In a heterologous CHO cells system, interaction of P2X7 with pannexin-1 upregulates channel activity and both proteins co-immuno precipitate.

Conclusions: Development and establishment of ADPKD cysts involves massive transcriptome remodeling of collecting ducts which include a shift in purinergic signaling that facilitates pathogenic pannexin-1 hyperactivity.

Funding: NIDDK Support

FR-PO554

Early Transcriptional Changes in Distal Convoluted Tubule Cells Are Evident in PKD1 (Polycystin 1) Mutant Mice Prior to Cyst Development

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is due to mutations in PKD1 and PKD2 and is not diagnosed in patients until cyst formation has already occurred. Cysts arise mainly from distal portions of renal tubular segments but the mechanism of cyst formation is still unclear, and there are no treatment strategies to prevent formation of cysts. The PKD1 p.R3277C *Pkd1*$^{tm1.1Pcha}$ knockin mouse (RC/RC) develops gradual cystogenesis mimicking the features of ADPKD (Hopp K et al., JCI 2012). Here, we use this model to identify transcriptional changes at early timepoints; post-natal day 10 (p10), before gross cyst formation and p20, after cystic changes occur in the kidney.

Methods: Single nuclei RNA-seq was performed on kidneys from RC/RC and age matched control mice at p10 (n=3) and p20 (n=3). Sequencing data within the same condition were aggregated. Cluster identities were assigned using expression of known cell markers. Differentially expressed genes between p10 and p20 with correlating controls was performed on distal convoluted tubule (DCT) cell clusters using regression analysis with a cutoff of log2 fold change.

Results: Cells with unique molecular identifiers (UMI) > 1000 ranged between 7000 to 10,000 for controls and 25,000 to 31,000 for kidneys from RC/RC mice. There were 20-26 clusters for each condition covering 12 kidney cell types, including >1500 DCT cells per condition. Genes with significant differential expression in the RC/RC mouse at p10 included genes associated with cystic disease (*Nek1* and *Pde1a*) in addition to 34 other genes. Genes with differential expression within DCT cells at p20 include *Hsf2bp* in addition to 5 other genes.

Conclusions: This work identifies genes within distal convoluted tubule cells implicated in cyst formation in polycystic kidney disease caused by mutations in PKD1. The transcriptional landscape of the pre-cystic kidney is significantly different than control, indicating that molecular pathways are activated at early timepoints before structural changes in the tissue. Further characterization of differentially expressed genes at early timepoints will address an important gap in field of ADPKD by identifying pathways leading to cyst formation and potential targets for therapeutics before cysts occur.

Funding: NIDDK Support, Private Foundation Support

FR-PO555

Dynamics of the Renal Transcriptomic Profile Through the Course of the Disease in Experimental ADPKD

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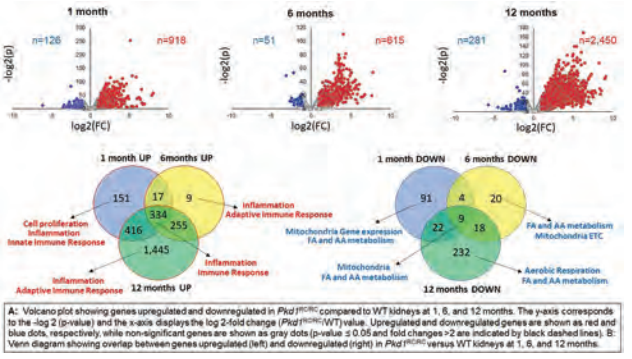
Background: Autosomal dominant polycystic kidney disease (ADPKD) is a chronic disease spanning an affected individual's life where earlier stages are marked by cyst development and kidney enlargement with preservation of renal function and later stages by increased kidney fibrosis and renal function decline. To understand the underlying molecular processes accompanying the dynamics of the disease phenotype, we comprehensively characterized the kidney transcriptomic profile in the slowly progressive hypomorphic *Pkd1* mutant mouse (p.Arg3277Cys, *Pkd1*$^{RC/RC}$) across the course of the disease.

Methods: *Pkd1*$^{RC/RC}$ and wild type (WT) mice (n=10, 5 males and 5 females each) were studied longitudinally, and their renal mRNA profiles were analyzed using high-throughput mRNA-sequencing (seq) at 1, 6, and 12m (n=5 each). Disease severity and progression were evaluated by kidney weight/body weight (KW/BW), cystic index (CI), fibrotic index (FI), and BUN. Renal tubular cell proliferation, inflammation, mitochondrial morphology, and metabolic function were assessed by immunostaining, western blot, electron microscopy, and metabolomics at all time points.

Results: KW/BW and CI were higher in *Pkd1*$^{RC/RC}$ from 1m and FI from 6m, but BUN was similar until 12m. mRNA-seq identified an important number of differentially expressed (DE) genes [fold-change ≥ 2, and false discovery rate (FDR) ≤ 0.05] in *Pkd1*$^{RC/RC}$ versus WT kidneys, which was higher at 1- compared to 6-, but further increased at 12m (Figure). Functional analysis showed that while DE genes were primarily implicated in inflammation, immune response, and mitochondrial functions, different signatures characterize each timepoint. Confirmatory studies on cell proliferation, inflammation, mitochondria, and kidney metabolism agreed.

Conclusions: Our findings that the renal phenotype and transcriptomic landscape varied across the course of ADPKD may have significant clinical implications and suggest that different therapeutic strategies might be beneficial throughout the disease.

Funding: NIDDK Support



A: Volcano plot showing genes upregulated and downregulated in *Pkd1*^{RCRC} compared to WT kidneys at 1, 6, and 12 months. The y-axis corresponds to the -log 2 (p-value) and the x-axis displays the log 2-fold change (*Pkd1*^{RCRC}/WT) value. Upregulated and downregulated genes are shown as red and blue dots, respectively, while non-significant genes are shown as gray dots (p-value ≥ 0.05 and fold changes >2 are indicated by black dashed lines). B: Venn diagram showing overlap between genes upregulated (left) and downregulated (right) in *Pkd1*^{RCRC} versus WT kidneys at 1, 6, and 12 months.

FR-PO556

CRISPR Activation of PKD1 in Immortalized Cell Lines Is Limited by Its Heterochromatinized Proximal Promoter

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Background: Loss of function mutations in *PKD1* are the predominant causes of autosomal dominant polycystic kidney disease (ADPKD). ADPKD is characterized by the progressive enlargement of renal cysts which leads to a decline in renal function. Cysts form when the functional levels of polycystin 1 (PC1), the protein product of *PKD1*, decrease below a critical threshold. We hypothesize that increasing the expression of *PKD1* could potentially restore functional levels of PC1 and rescue the disease.

Methods: To increase the expression of *PKD1* using CRISPR activation (CRISPRa), we designed and screened several guide RNAs (gRNA) targeting the proximal promoter of the gene in mouse renal cortical collecting duct (M1) and HEK293T cell lines. We measured the abundance of *PKD1* transcripts in these cell lines using qRTPCR and assessed the chromatin accessibility of the *PKD1* proximal promoter.

Results: CRISPRa-mediated *PKD1* upregulation in M1 or HEK293T cells reached a maximum of 2-2.5-fold ($p<0.001$) using pooled gRNAs targeting the 100 bp region upstream of the transcriptional start site. In contrast, positive control genes (*Klf1*, *Nkx2*, *Oct4*, *INS*, and *TTN1*) displayed substantially greater increases in expression (5-6000-fold). Both cell lines exhibited low *PKD1* mRNA abundance (~10 copies/cell). PCR-based chromatin accessibility assay showed less than a 4-fold enrichment in the *PKD1* proximal promoter (in both cell lines), indicating a heterochromatinized region. Additionally, H3K27 acetylation and DNase hypersensitivity data from ENCODE showed that heterochromatization of the mouse or human *PKD1* proximal promoter is common to most immortalized cell lines.

Conclusions: Our findings suggest that the heterochromatinized *PKD1* proximal promoter poses a limitation on the extent to which the gene can be effectively upregulated by CRISPRa. Understanding these constraints is crucial for developing strategies to overcome heterochromatinization and enhance *PKD1* expression, potentially enabling therapeutic interventions for ADPKD.

FR-PO557

Identification of Paracrine Factors in the Early Cyst Microenvironment in Polycystic Kidney Disease

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Background: Initial cysts that are formed upon *Pkd1* loss in mice impose persistent stress on surrounding tissue and trigger a cystic snowball effect, leading to the activation of PKD-related signaling which increases the likelihood of new cyst formation and disease progression. In the present study, we profiled transcriptomic changes that occur in the cyst microenvironment in PKD mice and identified paracrine factors with increased activity in PKD mice and in human ADPKD cyst cultures.

Methods: To perform an unbiased analysis of transcriptomic alterations that occur in the cyst microenvironment, microdomains were collected from *iKsp-Pkd1*^{del} mice with scattered *Pkd1*-deletion using Laser Capture Microdissection. Based on F4/80 staining, collected microdomains were defined as either macrophage (MΦ)-low cystic, representing early alterations in the cyst microenvironment, MΦ-high cystic, with more advanced alterations, or non-cystic. Pathway and upstream regulator analyses were applied to identify dysregulated pathways and secreted factors that may play a key role in altered signaling. Finally, supernatants from 3D cultures of primary ADPKD cells were harvested to analyze secreted paracrine factors using a Bio-Plex assay.

Results: When compared to the non-cystic microdomains, 953 and 8088 genes were dysregulated in MΦ-low and MΦ-high regions, respectively. Several injury-repair, growth, and tissue remodeling-related pathways were activated in MΦ-low microdomains, accompanied by mild metabolic alterations. In the more advanced MΦ-high microdomains, these pathways were strongly potentiated and the metabolism was more dysregulated. Using upstream regulator analysis, paracrine factors were identified with increased activity in the early cyst microenvironment, including IFNG, TNF, IL1B, TGFB1, AGT, and PDGFB. In addition, we identified TNF-α, PDGF-β, and several other factors that were secreted by primary ADPKD cells in the culture medium.

Conclusions: Collectively, our data provide an overview of molecular alterations that occur specifically in the MΦ-low and MΦ-high cyst microenvironment. Also, paracrine factors were identified that may drive early epithelial cell-induced alterations and tissue remodeling, which potentially give rise to the formation of more cysts.

Funding: Private Foundation Support

FR-PO558

Identification of Early Transcriptional Markers of ADPKD Cystic Epithelial Cells

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Background: Mechanisms driving ADPKD cystogenesis are not well understood, and reliable biomarkers are scarce. To explore molecular changes in cystogenesis, we performed single cell RNA sequencing on kidneys from an ADPKD mouse model at an early stage of cyst formation and from a model in which cystic disease was suppressed by expression of the polycystin-1 C-terminal tail (PC1-CTT).

Methods: Doxycycline inducible *Pkd1*$^{fl/fl}$*;Pax8*^{rtTA}*;Teto-Cre* ADPKD C57BL/6N mice expressing CTT (*Pkd1*-KO+CTT) or not (*Pkd1*-KO) were induced between 4-6 weeks and aged to 10 weeks. Single cell kidney suspensions from biological replicates were pooled and processed for cDNA synthesis and library preparation with 10X Chromium technology. Reads were aligned using the 10X Genomics CellRanger pipeline and further processed using Seurat v4.3.

Results: Clusters corresponding to tubule segments were identified using established annotations. Several novel clusters defined by expression of multiple markers, including *Jarid2*, *Tmtc2*, and *Filip1l*, were identified in the *Pkd1*-KO model. These clusters were sparsely populated in *Pkd1*-KO+CTT samples, suggesting that they may correspond to cyst epithelial cells that are suppressed by PC1-CTT expression. Each of these novel clusters included cells whose markers identified them from distinct tubule segments (e.g. *Sglt2*, *Umod*, *S100g*), suggesting that cells of different segments are clustered together by virtue of sharing the putative cyst cell transcriptional signature. The single cluster observed in *Pkd1*-KO+CTT model and not in the *Pkd1*-KO model is enriched in markers associated with metabolic processes including *Ugt1a2*, *Cbr1*, and *Pck1*. Importantly, at 10 weeks, there are no significant differences in %KW/BW or kidney morphology between the *Pkd1*-KO+CTT and *Pkd1*-KO models, suggesting that the cells belonging to the cystic epithelial cell clusters exhibit early identifiable differences in transcriptional programming.

Conclusions: scRNA-seq at an early timepoint reveals novel transcriptional makers of putative cystic epithelial cells. The protein expression levels of individual markers are being assessed. These results suggest that there are epithelial cells early in disease progression exhibiting a unique transcriptional signature that may elucidate the mechanisms of cyst formation and that may provide new candidate biomarkers.

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

FR-PO559

Repression of Foxo3-Gatm Accelerates Cystogenesis by Increasing Reactive Oxygen Species (ROS) in ADPKD

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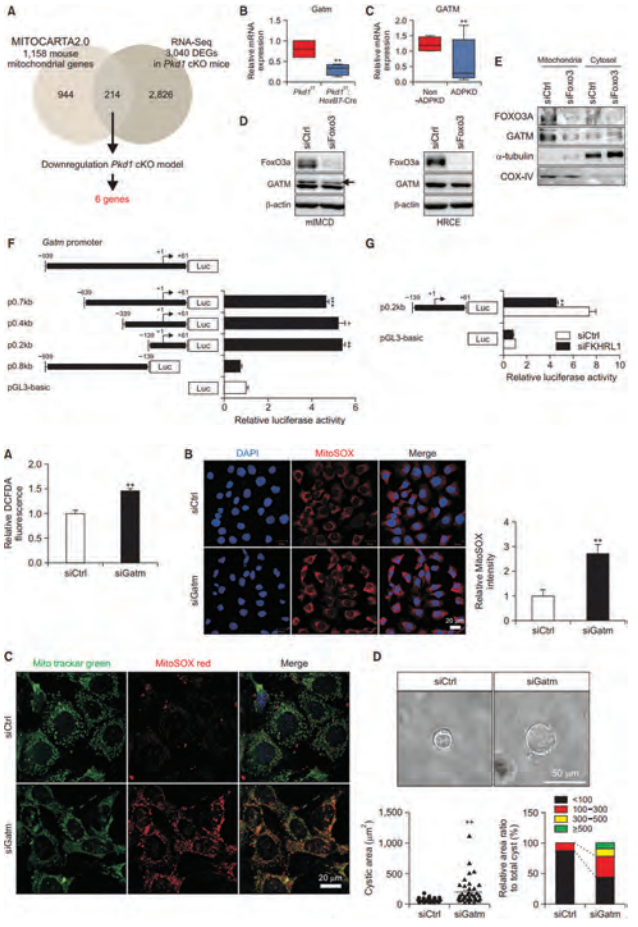
Background: The most common inherited renal disorder and leading cause of genetic end-stage renal disease is ADPKD. The relationship between ADPKD and oxidative stress have reported in in the early stage with disease progression, however the mechanism of correlation remains unclear.

Methods: We generate *Pkd1*^{flox}:HoxB7-Cre and performed integrative analysis. 3D cell culture produced *in vitro* cyst formation, and we observed differences in cyst formation.

Results: We explored the mechanisms associated with FOXO3 in ADPKD through screening by integrative analysis since FOXO3 regulates mitochondrial gene expression. And notably, GATM were significantly reduced in ADPKD patients. Furthermore, GATM was decreased by FOXO3 knockdown. Additionally, Inhibition of FOXO3 decreased GATM in the mitochondria. Therefore GATM is regulated by FOXO3 in the mitochondria. To verify the effect of Gatm on oxidative stress in ADPKD, we measured cellular ROS, DCFDA fluorescence intensity is elevated in Gatm knockdown. More specifically, Gatm silencing increased mitochondrial superoxide levels. This Gatm-mediated increase in superoxide levels was confirmed by co-staining with MitoSOX Red. To investigate the effect of Gatm on cyst formation in ADPKD, we experimented 3D cell culture and observed significantly promoted cyst progression with Gatm silencing.

Conclusions: We suggest a novel insight of cystogenesis, in which inhibited Foxo3 reduces Gatm expression, thereby increasing ROS and oxidative stress, consequently progressing cyst enlargement in ADPKD.



FR-PO560

Enhancing Intracellular Cholesterol Biosynthesis Slows PKD Progression

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Background: Metabolic reprogramming is a hallmark of ADPKD but remains incompletely understood. Cholesterol is a building block for cell membranes and functions in signaling pathways. Abnormal activation of cholesterol biosynthesis has been implicated in the pathogenesis of proliferative diseases such as cancer. However, the role of cholesterol biosynthesis in ADPKD is unknown.

Methods: We used transgenic mouse models to manipulate the activity of the transcriptional regulators of cholesterol/lipid synthesis: sterol regulatory element binding proteins (*Srebp1/2*). We inhibited cholesterol biosynthesis by deleting *Scap* in *Ksp*rtTA;TetOCre;*Pkd1*$^{F/F}$; *Pkhd1*Cre;*Pkd1*$^{F/F}$ and *Pkd1*$^{RC/RC}$ mouse models. To enhance cholesterol biosynthesis we inactivated *Insig1/2* in *Ksp*rtTA;TetOCre;*Pkd1*$^{F/F}$; *Ksp*Cre;*Pkd1*$^{F/F}$ and *Ksp*Cre;*Pkd1*$^{F/RC}$ mouse models. Mice were sacrificed at pre-determined timepoints for histological and molecular analysis or monitored for survival. 3D cyst assay was performed on human ADPKD kidney cell lines treated with scramble or *Insig1/2* siRNA. Western blot and sterolomics was completed on 10 and 18 day old *Ksp*Cre;*Pkd1*$^{F/RC}$ and control mice kidneys to assess baseline Srebp1/2 activity and cholesterol levels.

Results: Total cholesterol was reduced in *Ksp*Cre;*Pkd1*$^{F/RC}$ kidneys compared to controls. Western blot showed reduced nuclear Srebp2, the primary transcriptional driver of cholesterol synthesis, in early cystic *Ksp*Cre;*Pkd1*$^{F/RC}$ kidneys. Inhibition of cholesterol synthesis (*Scap* deletion) increased kidney-weight/body-weight ratio and reduced kidney function in 3 mouse models of PKD. Conversely, augmentation of cholesterol synthesis pathway (knockout of *Insig1/2*) reduced kidney weight/body weight ratio reduced serum creatinine and prolonged survival in multiple mouse models of PKD. RNA-seq confirmed appropriate inhibition or activation of cholesterol biosynthesis pathway. Finally, *Insig1/2* siRNA reduced cyst growth in 2 human ADPKD cell lines.

Conclusions: Srebp2 and cholesterol are reduced in *Pkd1* mutant mice. Inhibition of cholesterol biosynthesis markedly aggravates cyst growth. Surprisingly, activation of cholesterol biosynthesis slows cyst growth in 3 mouse models of PKD and in human ADPKD cell lines. Further studies are needed to understand how enhancing intracellular cholesterol reduces PKD progression and determine if this pathway can be targeted therapeutically.

Funding: NIDDK Support, Private Foundation Support

FR-PO561

Progressive Cellular Senescence Promotes and Senolytic Therapy Delays Cyst Growth in ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is one of the most common, life-threatening inherited kidney disease. Cellular senescence is permanent proliferative arrest, which accumulates with the progression of a variety of chronic diseases and age in response to endogenous and exogenous stresses. However, the roles and mechanisms of cellular senescence in ADPKD remains elusive.

Methods: To investigate the roles of senescence in ADPKD and evaluate the senescence removal therapy on cyst growth, we treated two *Pkd1* mutant mouse models with senescent inducer D-galactose (D-gal) or senolytics. To understand senescence-associated mechanisms in promoting cyst growth, we performed H&E staining, Western blot, qRT-PCR and TUNEL analysis *in vitro* and *in vivo*. We also identify SASP produced by *Pkd1* mutant cells by mass spectrometry.

Results: Cellular senescence was increased in *Pkd1* mutant mouse and human ADPKD kidneys characterized by the increase of the expression of SA-β-Gal and p16. Treatment with senolytics, including dasatinib (D) (7.5mg/kg), quercetin (Q) (75 mg/kg) and D plus Q, delayed cyst growth in kidneys of two *Pkd1* mutant mouse models as seen by decrease of cyst index, KW/BW ratios, BUN levels as well as cyst lining epithelial cell proliferation and the release of senescence-associated secretory phenotype (SASP), but increase cystic renal epithelial cell apoptosis. Co-treatment with D plus Q had synergized effect on cyst growth compared to that in kidneys treated with either D or Q alone. The release of SASP from *Pkd1* mutant renal epithelial cells stimulated the proliferation of nearby renal epithelial cells and activated renal fibroblasts characterized by the increased the phosphorylation of Akt, S6 and Stat3 and the expression of fibrotic markers (Fibronectin, α-SMA and Col-1). In addition, treatment with senescent inducer, D-gal, promotes cyst growth in *Pkd1* mutant kidneys. The clearance of senescence-associated P16^{INK4a}-positive cells by treating *Pkd1*$^{RC/RC}$*:INK-ATTAC* and *Pkd1*$^{fl/fl}$*:Pkhd1-Cre:INK-ATTAC* mice with AP20187 delays the cyst growth in ADPKD.

Conclusions: Senescence was increased in *Pkd1* mutant mouse and ADPKD kidneys, which is mediated by p16 associated signaling pathways, and the senescence removal therapy with senolytics is a novel therapeutic strategy for ADPKD treatment.

FR-PO562

Total and Phosphoproteomic Analyses in Kidneys from an Authentic Mouse Model of Human Autosomal Dominant Polycystic Kidney Disease

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Background: ADPKD (Autosomal Dominant Polycystic Kidney Disease) is a genetic disorder characterized by the development of multiple cysts in the kidneys. The disease is caused by mutations in PKD1 and PKD2, encoding PC1 and PC2 respectively. To date, PC1 and PC2 have been implicated in modulating a number of cellular events such as Ca^{2+} signaling, mTOR, cyclic AMP, Wnt, PCP, and STAT3 pathways. How the polycystins modulate these pathways remains elusive, however. While transcriptome studies provide essential insights into gene expression patterns, proteomic studies offer a more comprehensive understanding of the functional proteome, including protein abundance, alternative splicing and posttranslational modifications. Integrating both transcriptome and proteome data can provide a more holistic view of biological systems and diseases, complementing each other's strengths and limitations.

Methods: Mice homozygous with an inducible mutation in *Pkd1* gene were generated by intraperitoneal injection of tamoxifen. Kidneys from *Pkd1* knockout mice and controls were isolated at different stages and subjected to multiplexed proteomics and phosphoproteomics. Various bioinformatic techniques, RT-PCR, immunostaining, and western blotting were used for analysis and validation.

Results: To determine the cystogenic total and phosphoproteome, we performed multiplexed quantitative mass spectrometry analysis in Pkd1 knockout mouse kidneys at pre-/early disease and disease stages. Several thousands of proteins were quantified and hundreds of phosphorylation events were measured. MS/MS data were searched against a Uniprot mouse database with both the forward and reverse sequences using the SEQUEST algorithm, MS3 data was used for quantification. Phosphopeptides were processed separately but taken through a similar software pipeline with an additional phosphorylation site localization step using the Ascore algorithm. Several significant pathways were identified. A specific selection of proteins identified in the total and phosphoproteomic studies are being validated and further analyzed.

Conclusions: We have identified several pathways that are changed in an authentic mouse model of human ADPKD and determined the sequence of change of specific pathways in relation to disease development.

Funding: Other NIH Support - PKD Foundation

FR-PO563

Tubular Obstruction-Induced Polycystin Upregulation is Profibrotic and Induced a Severe Cystic Phenotype in Adult Mice with ADPKD

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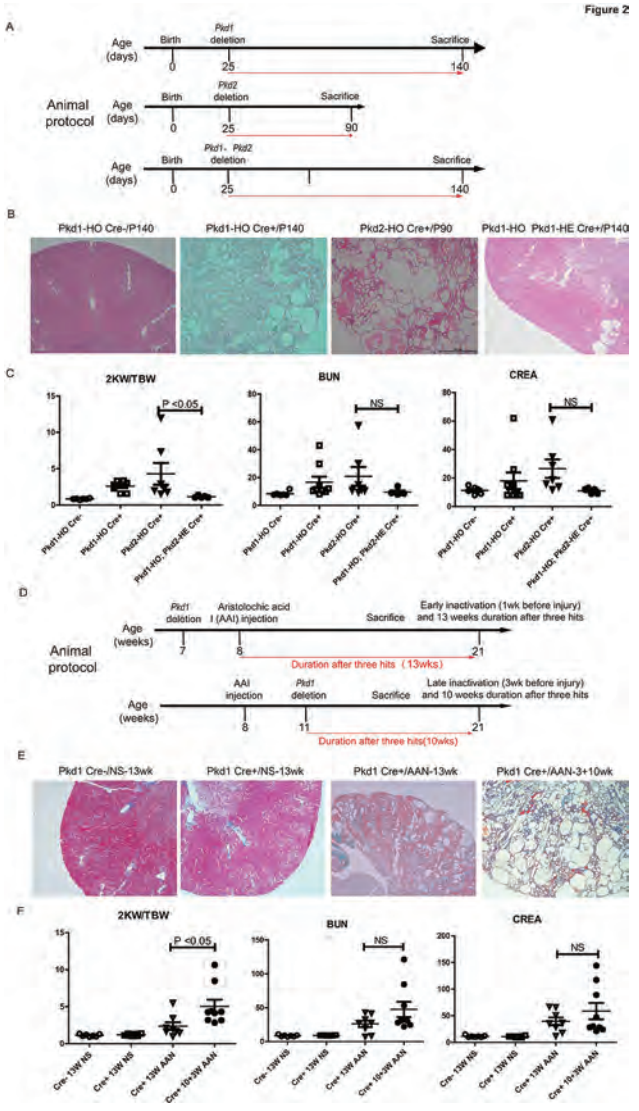
Background: Mutations in *PKD1* or *PKD2* gene cause ADPKD, however high levels of polycystins are detected in renal tissues of ADPKD patients. Animal studies showed that loss and gain of function of polycystins are both pathogenic and can induce cystic phenotype in the kidney, which are associated with enhanced renal fibrosis.

Methods: UUO or aristolochic acid I (AAI) induced mouse nepropathy was established for renal fibrosis study. Pkd1 or Pkd2 gene was inactivated in mice.

Results: We demonstrated that polycystin-1 or polycystin-2 was highly expressed in fibrotic mouse kidneys and positively correlated with expression of collagen-I. Inhibition or deletion of polycystin-2 reduced the deposition of extracellular matrix proteins in fibrotic kidneys. Similarly, knockout of *Pkd1* gene attenuated renal fibrosis in fibrotic mouse models. We further hypothesized that inhibition of polycystins delays cyst growth by mitigating renal fibrosis. Here, we showed that polycystin-1 or polycystin-2 was up-regulated in *Pkd2* or *Pkd1* mice respectively and tightly correlated with the growth of renal cysts and fibrosis development. Genetic deletion of both polycystin-1 and polycystin-2 retarded cyst growth in adult ADPKD mice. Finally, we inactivated Pkd1 gene in a fibrosis triggered adult ADPKD mouse model at different time point before or after the fibrotic injury. We showed that early and long-term inactivation of *Pkd1* delayed fibrosis triggered renal cyst growth in adult *Pkd1* mice as compared with mice with late and short-term inactivation of *Pkd1* gene.

Conclusions: We conclude that tubular obstruction induced polycystin up-regulation is pro-fibrotic and accelerates cyst growth through enhancing renal interstitial fibrosis in ADPKD mice. Our study indicates that ADPKD is caused by the coexistence of loss and gain function of polycystins.



FR-PO564

CDK6 Suppresses Tubulin Polyglutamylation in Primary Cilia and Promotes Renal Cystogenesis in ADKPD

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Background: Polycystin-1 (PC1) and Polycystin-2 (PC2) hypothetically forming an ion channel complexes localize on primary cilium to inhibit renal cyst growth. Polyglutamylation (PG) is one of the tubulin posttranslational modifications (PTMs) predominantly occurs on cilia axoneme which controls the ciliary localization of PC1/2. Defective axoneme PG has been correlated with ciliopathies that usually manifest syndromic forms of PKD. We recently discovered an uncanonical CDK6-mediated pathway that specifically inhibits axoneme PG by engaging the ciliary import of tubulin glutamylases. Intriguingly, CDK6 is strongly upregulated in the renal tubules of ADPKD mice and human patients. In agreement with the inhibitory role of CDK6 in ciliary import of tubulin glutamylases, defective axoneme PG was observed in ADPKD cells. Remarkably, pharmacologic inhibition of CDK6 restores defective axoneme PG, increase ciliary dosage of PC2 in ADPKD cells, and significantly suppressed the cyst growth in the *ex vivo* model of ADPKD. These data suggest that targeting axoneme PG could be a novel therapeutic approach for ADPKD. To identify novel small molecules/drugs to specifically target axoneme PG, we established high-content image-based strategy to screen drug-repurposing compound library and kinase inhibitor library. We will further access the therapeutic potential of drug hits in ADPKD, using *in vitro, ex vivo* and *in vivo* ADPKD models.

Methods: Cell-imaging Drug screening Biochemstry and Molecular Biology Ex vivo renal cystogenesis

Results: 1. CDK6 suppresses tubulin polyglutamylation by inhibiting ciliary import of tubulin glutamylases. 2. CDK6 is strongly upregulated in renal tubules of ADPKD mice and human patients. 3. ADPDK cells exhibit defective tubulin polyglutamylation in primary cilia. 4. Inhibition of CDK6 suppresses cyst growth in ex vivo ADPKD model.

Conclusions: Targeting axoneme PG could be a novel therapeutic approach for ADPKD.

Funding: NIDDK Support, Private Foundation Support

FR-PO565

Eliosin, A Protein Encoded by a Transcript from the HmPKD Locus, Is a Component of Mitochondria-ER Contact Sites/Mitochondria-Associated Membranes (MAMs)

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Background: The HmPKD1 gene locus is predicted to produce multiple transcripts whose functions are largely unknown. We studied one alternative transcript that starts at intron 40 but has a protein start site in exon 41. This transcript has a splice from the 3' end of exon 41 to the 5' end of exon 43 of the HmPKD1 gene. Subsequent splices follow the same splicing pattern found in the full-length polycystin-1 mRNA. The subcellular localization and function of this alternative transcript is not known.

Methods: PCR primers are designed to detect the transcript's unique splice features that are not found in full-length HmPKD1 transcripts. RT-PCR studies were conducted to identify the alternative transcript. cDNA encoding the alternative transcript and its product (Eliosin) were expressed in COS-1, 293, and NIH 3T3 cells for immune-blot and light microscopy analysis. Co-localization studies were performed with mCherry-Eliosin fusion protein and dynamin-related protein (DRP-1) or mitofusin-1 (MFN-1). Analysis of mitochondria morphology in co-transfection studies was performed in 293 and PKD 9-7 cells.

Results: RT-PCR reactions performed using human kidney RNA confirmed that a shortened PCR fragment from the PKD1 gene's exons 41/43 splice is expressed. Immune blot analysis revealed that the protein, we name Eliosin is a 48 kDa protein and it is expressed by a cDNA isolated from human testes. Fluorescence microscopy studies show co-localization between Eliosin and Inositol-3-phosphate receptor or MFN-1, known components of MAMs. However, when Eliosin and DRP-1 are co-expressed, DRP-1 is found in the cytosol. Since DRP-1 mediates mitochondria scission, we reasoned that the mutation in Eliosin leads to unopposed mitochondria scission in PKD 9-7 cells. We find that untransfected PKD 9-7 cells have fragmented mitochondria while Eliosin-transfected PKD 9-7 cells have normal-appearing mitochondria.

Conclusions: Eliosin is a 48 kDa protein that is a component of mitochondria-ER membrane contact sites, and it acts to displace dynamin-related protein-1 from MAMs. We conclude that Eliosin plays a role in altering the balance between mitochondria fusion and scission. This finding extends the HmPKD1 locus' role in mitochondria metabolic physiology.

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FR-PO566

Manipulation of Autophagy in PKD Mice

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Background: 2-Deoxyglucose (2DG) and Chloroquine (CHLQ) are known to potentially induce or inhibit autophagy, respectively. Aim of the study was to determine the effect of pharmacological and genetic manipulations of autophagy on tubular cell proliferation and cyst growth.

Methods: Pkd1$^{RC/RC}$ (RC) male mice. 2DG (100 mg/kg) or CHLQ (60 mg/kg) from 50 - 120d of age. Kidney specific *Pkd1, Atg7* double knockout mice generated by Ksp 1.3 Cre-lox recombination. Autophagic flux measured by increase in LC3-II (autophagosomes) with the lysosomal inhibitor, bafilomycin. Autophagy proteins measured by immunoblot. Cyst index (%) number and area determined on kidney cross sections by a computerized algorithm.

Results: See table. 2DG significantly reduced two kidney/body weight ratio (2K/BW), cyst index, cyst count, cyst area, BUN. 2DG significantly (P<0.05) reduced PCNA + cells lining cysts. 2DG decreased autophagy-related proteins (ATG12-5 complex, ATG3) and suppressed autophagic flux in RC kidneys. p-ERK and p-AMPK known to activate autophagy were decreased by 2DG. 2DG from 150-350d of age (later stage of PKD) had no effect on cyst growth. CHLQ had no effect on PKD or proliferation in the cells lining the cysts. CHLQ resulted in decreased expression of pBeclin (critical regulator of autophagy) and suppressed autophagic flux in RC kidneys. Next autophagy (ATG7) was knocked out in PKD mice. In a rapid PKD model, 2K/BW and BUN at 28 d old was the same in Pkd-/- vs Pkd1-/- ATG+/- vs Pkd1-/- ATG7-/- mice. In a slow PKD model, at 120 d, double knockout RC ATG7 mice had higher cyst indices than RC mice.

Conclusions: 2DG suppressed autophagy, decreased proliferation, slowed PKD and improved kidney function. CHLQ suppressed autophagy but had no effect on PKD. Knockout of autophagy (ATG7) had no effect on PKD in a rapid severe model and worsened PKD in a slowly progressive model. Pharmacological suppression of autophagy had variable effects on proliferation and cyst growth and genetic knockout of autophagy worsened PKD in a slowly progressive PKD model.

Funding: Veterans Affairs Support

Cyst indices

	Veh	2DG	Veh	CHLQ	Pkd1-/-	Pkd1-/-ATG7+/-	Pkd1-/-ATG7-/-	RC	RC ATG7-/-
2K/BW (%)	2.4	2*	2.2	2.5	39	35	37	2.2	3.3*
Cyst index	8	4*	16	12	ND	ND	ND	13	21*
Cyst No	211	161*	233	190	ND	ND	ND	197	455*
Cyst size μm^2	6414	5385*	8500	8647	ND	ND	ND	6794	6492
BUN	35	27*	33	27	77	79	75		

ND=Not determined as kidney completely replaced by cysts. *P<0.05

FR-PO567

Pkd1 Mutation Causes Memory Impairment Driving by Cellular Senescence in ADPKD

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Background: Cellular senescence is a hallmark of aging. It plays a crucial role in a wide variety of age-related diseases and neuronal disorders. Accumulation of senescent cells in the brain leads to structural and functional changes and result in memory impairment. It is not clear whether *Pkd1* mutation results in memory impairment in ADPKD patients. We hypothesize that *Pkd1* mutation impairs memory in mice through cellular senescence signaling.

Methods: To test our hypothesis, we performed behavioral experiments (Y-maze and novel object recognition test) to evaluate the memory deficit in wild type and *Pkd1$^{RC/RC}$* mice. To understand the underlying molecular mechanisms, we isolated cerebral cortex and hippocampus from wild type and *Pkd1$^{RC/RC}$* brain and then performed Western blot, qRT-PCR, and immunostaining analysis.

Results: We observed an impairment of hippocampal and cortical dependent memory with novel object recognition and Y-maze test in *Pkd1$^{RC/RC}$* mice. To understand the underlying molecular mechanisms, we found that the expression of PSD-95, a synaptic marker, and neural growth factor BDNF was decreased in *Pkd1* mutant brains compared to wild type controls, and thus resulting in synaptic dysfunction and memory impairment. The downregulation of PSD-95 and BDNF was regulated by the RE-1 silencing transcription factor (REST), which was downregulated in *Pkd1* mutant mouse brain. Mutation of *Pkd1* also resulted in the accumulation of macrophages in mouse brain as examined with F4/80 staining. We further found that cellular senescence was increased in *Pkd1* mutant mouse brain as seen by the increase of p16. The mRNA levels of senescence associated secretory proteins (SASP), including CCL2, IL1-β, IL6, and TNF-α, were upregulated, which contribute to neuroinflammation as seen by the increase of the accumulation of activated microglial cells in *Pkd1* mutant mouse brain. The increased SASP level was regulated by the activation of JAK/STAT signaling in *Pkd1* mutant mouse brain.

Conclusions: This is the first study to show that *Pkd1* mutation causes memory loss and cognitive impairment in mouse brain via the accumulation of senescent cells to increase SASP production, which causes activation of microglial cells and downregulation of REST, resulting in synaptic dysfunction.

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FR-PO568

Dephosphorylation Facilitates Trafficking of Mutant Polycystin-2 to Cilia

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Background: ADPKD is characterized by mutations in polycystin-1 (PC1) and polycystin-2 (PC2) that result in progressive cyst formation in the kidneys and liver. The steady state expression and ciliary trafficking of PC1 requires the presence of PC2. Missense mutations resulting in alterations in trafficking properties of PC1 and PC2 underlie a subset of cases of ADPKD. Here, we investigate the role of phosphorylation of PC2 in its localization to cilia.

Methods: Unbiased phosphoproteomic analysis of mouse kidney lysates was performed to identify the phosphorylation sites of native PC2. mNeonGreen-tagged PC2 (PC2NG) constructs of wild type or dephosphorylated forms were generated and expressed in IMCD3 cells lacking endogenous *Pkd1* or *Pkd2* or both. Ciliary expression of PC2 was analyzed via live-cell imaging and by immunofluorescent cell staining. Knock-in mice carrying dephosphorylated *Pkd2^{S829A}* and a novel anti-phospho-specific PC2 antibody were generated and utilized as part of this study.

Results: Two phosphorylation sites in native PC2 were identified from native protein in mouse kidneys: Ser812 and Ser829. We investigated the functional effects of Ser829 phosphorylation. We found that expression of PC2 in cilia was regulated by phosphorylation at Ser829. While dephosphorylation at the Ser829 was not a prerequisite for PC2 ciliary expression, the phosphorylation deficient Ser829Ala (S829A) form of PC2 showed quantitatively enhanced expression in cilia that did not require the presence of PC1. Mice carrying a homozygous knockin phosphorylation deficient *Pkd2^{S829A}* allele have no phenotype indicating that the absence of phosphorylation at Ser829 does not result in reduced PC2 function. Introduction of S829A into a PC2 construct containing a human pathogenic mutant that otherwise does not appear cilia resulted in expression in cilia, indicated that dephosphorylation rescued the trafficking defect of the human mutation.

Conclusions: Dephosphorylation of PC2 at Ser829 retains normal function in vivo. Dephosphorylation at Ser829 enhances the steady state expression of PC2 in cilia and it overcomes cilia trafficking defect of a human pathogenic missense mutant of PC2. The phosphorylation state of PC2 has a functional role in expression of the polycystin complex in cilia.

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FR-PO569

Pkd2 Deficiency in Embryonic Aqp2+ Progenitor Cells Is Sufficient to Cause Severe Polycystic Kidney Disease

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Background: Most cases of autosomal dominant polycystic kidney disease (ADPKD) are caused by mutations in *PKD1* or *PKD2*, which encode polycystin-1 and polycystin-2, respectively. The mechanism for renal cyst formation remains unclear. We showed that embryonic Aqp2$^+$ progenitor cells (AP) give rise to principal cells (PC) and intercalated cells (IC) to generate the distal renal segments consisting of the late distal convoluted tubules (DCT2), connecting tubules (CNTs), and collecting ducts (CDs). Adult AP also contribute to the renal tissue maintenance and injury repair by regenerating DCT2/CNT/CD cells. Here, we tested the hypothesis that ablation of *Pkd2* in embryonic AP is sufficient to induce PKD.

Methods: *Aqp2Cre Pkd2$^{f/f}$* mice were generated to disrupt *Pkd2* in embryonic AP. *Aqp2$^{ECE/+}$ Pkd2$^{f/f}$* mice were tamoxifen-inducted at P1 or P60 to disrupt *Pkd2* in neonate or adult AP and PC, respectively, and sacrificed 7 months after Cre induction. Immunofluorescence was done to assess cell types that lined the cysts. Cells were categorized and quantified. We also analyzed cyst-lining cells in four other PKD mouse models (cpk, *Six2creFrs2αKO, Pkd1$^{RC/RC}$* and *Thm1CKO),* and compared staining between ADPKD patients and normal controls.

Results: *Pkd2* is expressed in all segments from proximal tubule to CD, and in all CNT/CD cell types. *Pkd2$^{f/f}$ Aqp2Cre* mice developed severe PKD and died ~P17. The kidneys showed a reduced IC to PC ratio and a complete lost of α-IC by P12. Cysts extended from the CD to DCT1 and possibly to the loop of Henle, but not to the proximal tubules. *Pkd2$^{f/f}$ Aqp2Cre* mice had obvious cysts by P6 with rare α-IC. IC were more apoptotic than PC. Ablation of *Pkd2* in neonate or adult AP and PC in *Aqp2$^{ECE/+}$ Pkd2$^{f/f}$* mice did not cause PKD. Cyst-lining α-IC were found in the other PKD models. AQP2$^+$ cells were found in the cysts of only 13 out of 27 ADPKD samples, which had a diminished IC to PC ratio. None of the ADPKD kidneys had α-IC within the AQP2$^+$ cysts.

Conclusions: *Pkd2* deletion in embryonic AP, but not in neonate or adult Aqp2$^+$ cells (PC and AP), was sufficient for PKD development. IC, particularly α-IC, were selectively depleted in *Pkd2$^{f/f}$ Aqp2Cre* mice and ADPKD patients. We proposed that *Pkd2* is critical for maintenance of cystic α-IC.

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FR-PO570

The Direct Physical Interaction Between Calcium-Sensing Receptor and Polycystin-2: Implication in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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Background: ADPKD is a ciliopathy caused by mutations in *PKD1* or *PKD2* genes, encoding polycystin-1 (PC1) and polycystin-2 (PC2), respectively, which form a complex localized to the primary cilium. PC2 is a member of the transient receptor potential polycystic (TRPP) family of cation channels acting as a non-selective cation channel which, in the primary cilium of renal epithelial cells, preferentially conducts K^+ and Na^+ over Ca^{2+} ions. In this study, we explored the possibility that the Calcium Sensing Receptor (CaSR) is involved in PC2 functional regulation.

Methods: Human conditionally immortalized Proximal Tubular Epithelial cells isolated from urine sediments (ciPTECwt) and with stably down-regulated *PKD2* (ciPTEC-PC2KD), expressing endogenous CaSR, were used as experimental tools.

Results: Immunofluorescence experiments showed the expression of both CaSR and PC2 on the primary cilium. CaSR and PC2 co-immunoprecipitated both in ciPTEC and mouse kidney. Worthy of note, Proximity Ligation Assay demonstrated the direct interaction between CaSR and PC2 in both ciPTEC and mouse kidney slices. Preliminary electrophysiological measurements demonstrated that, in ciPTEC, CaSR activation caused plasma membrane hyperpolarization, consistent with modulation of cation channels. Interestingly, the membrane hyperpolarization induced by the activation of CaSR in ciPTEC-PC2KD was significantly lower with respect to ciPTECwt.

Conclusions: These studies underline the functional coupling of CaSR with PC2, providing a rationale for the amelioration of the principal cellular ADPKD dysregulations observed in our previous studies in ciPTEC-PC1KD exposed to calcimimetics (CaSR allosteric modulators) as well as in animal models of ADPKD.

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FR-PO571

Molecular Basis of the Regulation of a Gain-of-Function Polycystin-2 Channel by Small Molecule Ligands

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Background: Mutations in PKD2 gene lead to autorsomal dominant polycystic kidney disesae (ADPKD). PKD2 encodes polycystin-2 (PC2) protein. As a member of the transient receptor potential (TRP) channel superfamily, PC2 functions as a non-selective cation channel. The activation and regulation of PC2 channel is largely unknown and no small molecule ligand of PC2 has been reported.

Methods: We expersssed human PC2 channel in *Xenopus oocytes*, and used two-electrode voltage clamp (TEVC) method to record the ion channel function.

Results: In this work, we tested the effect of a group of know TRP channel small molecule agonists on PC2 channel funciton, and found that while most of them inhibit the activity of PC2_F604P, a gain-of-function PC2 mutant PC2 channel, some others have a dual regulating effect with low concentration further activates PC2_F604P, and high concentration leads to inactivation of the channel. We identified two distinct binding sites of the ligand in PC2_F604P that are responsible for activation and inactivation respectively. Our results also suggest that Ca^{2+} binding at the outer pore region is essential for ligand-induced inactivation.

Conclusions: These results provide structural and functional views of the interaction between PC2 and small molecule ligands and showcase how ligands can regulate channel function in unusual mechanisms.

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FR-PO572

Transcriptomic Analysis of Pkd2-Deficient Kidneys Shows Altered Metabolic and Cytoskeleton Pathways Similar to Pkd1 Models and Evidence of an Increased Inflammatory Response

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is characterized by fluid-filled cysts and progressive enlargement of the kidney. Mutations in either *PKD1* or *PKD2* genes, encoding polycystins 1 and 2, are responsible for the disease. Despite advances in understanding polycystins structure and function, how mutations in PKD genes lead to cystogenesis is still unknown. While dozens of studies have investigated the transcriptome of human and mouse *PKD1* mutant kidneys, none focused on *PKD2* deficient kidneys. Here we report RNAseq from *Pkd2* cystic kidneys from a slow progression model.

Methods: We induced *Pkd2* deletion at P27 (postnatal day 27) in a strain that inactivates *Pkd2* in the renal epithelium. We isolated RNA from kidneys at P125 from 10 males and 10 females (5 *Pkd2$^{fl/fl}$; Pax8rtTA-Cre* (+) and 5 littermate *Pkd2$^{fl/fl}$; Pax8rtTA-Cre* (-) per set) and sequenced using and Illumina NovaSeq 6000 S4 system. Sequence reads were mapped to mm10 mouse genome and counted using STAR. Differential gene expression and pathway analyses were done in R using DESeq2, clusterProfiler and fgsea.

Results: Transcriptomic analysis identified ~1976 significantly differentially expressed (DE) genes (adjusted $p < 0.05$), of which 622 were only DE in males and 229 in females. In both sexes, injury markers were up-regulated and pathway analyses suggested increased chemokine activity. Gene set enrichment analysis suggested enrichment of up-regulated genes in inflammatory pathways and down-regulated genes in oxidative phosphorylation and fatty acid metabolism, similar to what is observed in *Pkd1* knockout kidneys. Approximately 700 DE genes in *Pkd2* knockout kidneys were also DE in *Pkd1* knockout kidneys. Pathway analysis of DE genes in both *Pkd1* and *Pkd2* models showed enrichment of genes involved in cytoskeleton, actin biding and encoding proteins in the kinetochore.

Conclusions: The data suggest an increased inflammatory response in *Pkd2* knockout kidneys and some of the transcriptional changes previously reported in *Pkd1*. The presence of injury markers suggests that some of these differences could be secondary to kidney injury. Meta-analysis of *Pkd1* and *Pkd2* knockout kidneys implicate changes in cytoskeleton and actin signaling as common pathways.

FR-PO573

Generation of a New Mouse Model Harboring the Polycystin-2 Loss-of-Function D511V Patient Variant

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is one of the most frequent renal genetic disorders caused by genetic mutations in either *PKD1* or *PKD2* genes, which encodes for protein products polycystin-1 (PC1) and polycystin-2 (PC2), respectively. The molecular pathogenesis of ADPKD and the function of polycystins is an area of active research. PC2 subunits can form ion channels within organelle membranes such as the ER and primary cilia, or it can form channel complexes with PC1. There remains a need to develop novel animal models to mimic mutations observed in humans to study the allelic contributions of PKD genes, and to understand the impact of ADPKD-causing variants. To date there are no mouse models with *Pkd2* missense variants.

Methods: We used CRISPR/Cas9 gene editing to engineer a new *Pkd2* mouse model with the human pathogenic variant D511V (D509V in the mouse, *Pkd2^{D509V}*). This *Pkd2* variant affects a highly conserved region in the voltage-sensor domain (VSD). Prior studies in cell models showed that PKD2^{D511V} encodes a temperature sensitive mutant protein that is more stable at 27°C versus 37°C, interacts with PC1 and can traffic to cilia. Nonetheless this protein is "channel-dead" in ER vesicles.

Results: We found that heterozygous *Pkd2^{D509V}* mice are viable and fertile but initial studies suggest that homozygous carriers are embryonically lethal, as no homozygotes were alive at P0 (postnatal day 0). We are in the process of determining the cause of embryonic lethality and of measuring PC2^{D509V} protein abundance and ciliary localization *"in vivo"* and *"in vitro"*. We will examine the functional role of the PC2^{D509V} variant in maintaining kidney homeostasis in adult and postnatal kidneys by crossing it to a renal tubule specific inducible *Pkd2* mouse model.

Conclusions: The generation of this new *Pkd2^{D509V}* model provides a relatively rapid system to: 1) study the roles of PC2 *"in vivo";* 2) decipher the pathogenic mechanisms leading to cyst formation after inactivating the channel activity of PC2 and 3) may be useful for precision medicine applications using patient-derived variants.

Funding: NIDDK Support

FR-PO574

Epigenetic Age Is Accelerated in ADPKD Kidneys and Is Regulated by Autophagy-Mediated DNA Methyltransferase

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Background: The epigenetic clock (DNA methylation age) is characterized by changes in DNA methylation (DNAm) levels across specific CpG sites that are associated with chronological age, diseases and mortality. Epigenetic age acceleration (EAA), the residual variation in DNAm age, indicates whether individuals and specific organs are aging faster or slower than their chronological age in response to endogenous and exogenous factors. Whether epigenetic age is regulated by autophagy and accelerated in ADPKD kidneys remains unknown.

Methods: To investigate an association between epigenetic clock/EAA and autophagy in ADPKD, we performed single cell RNA sequencing (scRNA-seq), whole-genome bisulfite sequencing (WGBS), Western blot and qRT-PCR analysis.

Results: We found that 353 human and 329 mouse CpG dinucleotide DNA methylation markers correspond to 309 human genes and 224 mouse genes. Our scRNA-seq analysis

indicated that the numbers of dysregulated epigenetic clock associated genes were 48, 33 and 70 in collecting duct cells; 8, 14 and 44 in macrophages; and 2, 14 and 57 in fibroblasts in day 7, 14 and 21 *Pkd1* homozygous kidneys compared to the same cell types in age matched *Pkd1* heterozygous kidneys. The differential methylation status of these epigenetic genes and the specific methylation sites on these genes were identified in ADPKD kidneys compared to normal individuals as examined by WGBS. The dysregulation of epigenetic clock genes is associated with a gradual upregulation of DNA methyltransferase1 (DNMT1), the only DNMT responsible for maintaining DNA methylation, in day 7, 14 and 21 *Pkd1* homozygous kidneys. DNMT1 interacted with ATG7, a key player of autophagy. Treatment with the autophagy inhibitor, Lys05, increased DNMT1 protein, whereas treatment with autophagy inducer decreased DNMT1 protein in kidneys, supporting that autophagy is involved in DNMT1 mediated epigenetic age acceleration in ADPKD. We also found that the methylation status of four epigenetic clock genes, including *Apoe, Cldn4, Mgp* and *Slc38a2,* are potential biomarkers that indicate epigenetic age acceleration in ADPKD kidneys.

Conclusions: Autophagy is a key player of DNMT1 mediated epigenetic age and cyst growth in ADPKD kidneys. Targeting DNMT1 and inducing autophagy should have a synergistic effect on decreasing cyst growth and epigenetic age acceleration.

FR-PO575

Tumor-Associated Calcium Signal Transducer 2 (Tacstd2) Expression Is Increased in Early Polycystic Kidney Disease

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is caused by polycystin gene mutations, leading to kidney cysts. Cysts grow via abnormal epithelial proliferation and secretion. Despite known mutations and pro-cystic pathways, the initiating transcriptional events in cyst formation are unclear. By studying pre-cystic ADPKD mice, we found new candidate genes for cyst initiation.

Methods: *Pkd2^{fl}; CAG-Cre^{ERT2}* pups received tamoxifen via IP injection on postnatal day 2 (P2). RNA was isolated on P6 and P10, followed by library preparation and analysis. Results were compared to published data and mouse and human kidney tissues were stained to confirm epithelial candidate localization.

Results: We found 91 differentially expressed genes (DEGs) in pre-cystic kidneys (P6) and 5,309 DEGs at the early cystic timepoint (P10) (FDR<0.05). P6 and P10 overlapping DEGs include 74 genes, defined as cyst initiation candidates (CICs). We characterized CICs using published datasets (bulk RNAseq from alternative early ADPKD models, single-cell RNAseq from healthy mouse kidney and human ADPKD patients). Tacstd2 emerged as a promising candidate due to its epithelial specificity. Experiments showed high Tacstd2 expression in cystic-lining epithelium in mouse and human tissue.

Conclusions: 74 candidate cyst initiation genes warrant further investigation. Tacstd2 selectively labels cystic epithelium in *Pkd2* mice and humans with ADPKD. Antibody drug conjugates targeting Tacstd2 in human epithelial tumors have been approved by the FDA for treatment of metastatic triple-negative breast cancer and urothelial cancer. Adapting this technology may prove efficacious in ADPKD.

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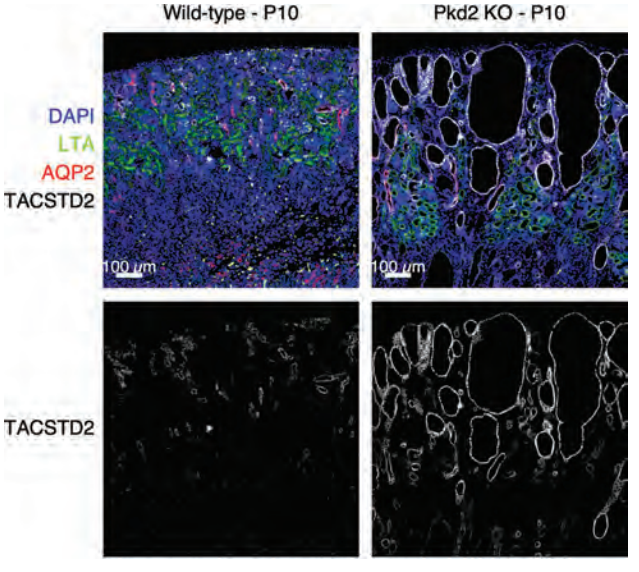

Mouse kidney probed for Tacstd2, collecting duct marker AQP2, proximal tubule marker LTA. Nuclear marker DAPI.

FR-PO576

Heterozygous PKD Organoids Show Increased Sensitivity to Forskolin-Stimulated Cystogenesis

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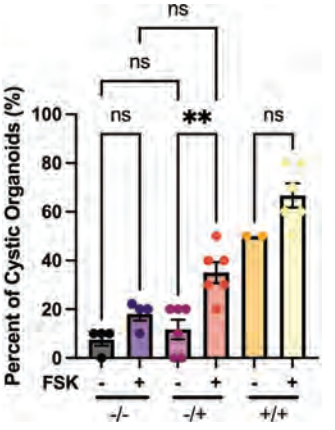
Background: Polycystic kidney disease (PKD) is inherited as a single heterozygous loss-of-function mutation, but theorized to require additional loss-of-function to cause cystogenesis. Activation of cAMP can stimulate cystogenesis, but whether this happens in heterozygotes is not well understood. We set out to test this in human kidney organoids.

Methods: We established human pluripotent stem cells in allelic series using CRISPR base editing to introduce nonsense mutations previously documented in ADPKD patients – *PKD1* R2430X and Q3838X and *PKD2* R186X and R872X. Mutations were confirmed by sequencing and protein changes by immunoblot. Homozygous mutant, heterozygous mutant, and isogenic control stem cells were differentiated into kidney organoids to determine if nonsense mutations conferred a cystic phenotype. Each genotype was treated with 0 uM or 30 uM forskolin, a stimulant of the cAMP pathway.

Results: Heterozygous cells expressed ~50% of PC1 or PC2 protein compared to controls. When differentiated into human kidney organoids, homozygous mutants spontaneously formed cysts whereas heterozygous mutants expressed no detectable phenotype, similar to non-mutant controls. Following forskolin treatment, heterozygous organoids showed a significant increase in the number of cysts formed which was not observed in homozygous mutant or non-mutant organoids (Figure 1).

Conclusions: Heterozygosity alone is insufficient to cause expression of PKD phenotypes in human kidney organoids. However, when treated with forskolin, heterozygosity sensitizes tubules to become cystic. Thus, even partial loss of function may enhance the PKD phenotype in the context of high levels of cAMP.

Funding: NIDDK Support



Control (+/+), heterozygous (+/-), and homozygous (-/-) organoids ± forskolin (FSK). Mean ± s.e.m. n = 4 independent experiments, ** $p < 0.01$

FR-PO577

Organoid Model of Polycystic Kidney Disease Recapitulates Clinically Relevant Symptoms and Identifies Candidate Drugs

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Background: Polycystic kidney disease (PKD) is one of the most common genetic kidney diseases, characterized by the progressive expansion of fluid-filled cysts in the kidney. Currently, there are limited treatment approaches for PKD. Advances in generating kidney organoids from human pluripotent stem cells (hPSCs) have helped overcome many of the drawbacks of the traditional mouse and 2D cell culture models. Alongside genetic editing, these organoids have been used to investigate the pathogenic mechanisms of PKD and to screen for potential drugs.

Methods: Herein, we have generated a collection of kidney organoids from both ARPKD and ADPKD patient-derived iPSCs, as well as genetically engineered hPSCs. Subsequently, we employed stress paradigms to modulate intracellular levels of cAMP or Ca^{2+} for inducing cystogenesis. We further characterized the structural and functional abnormalities in PKD kidney organoids using a multitude of analyses, including cell biology, molecular biology, biochemistry, and single nuclei RNA-sequencing. Finally, we performed a small-scale drug screening to identify candidate drugs.

Results: PKD kidney organoids developed tubular cysts in response to upregulation of intracellular cAMP or downregulation of Ca^{2+} homeostasis. Multiple structural and functional abnormalities were observed in PKD organoids, including hyper-proliferation of cystic epithelial cells, increased fluid secretion, tubular injury and dedifferentiation, as well as aberrant renin release which are commonly observed in PKD patients. Employing cystic index as the readout, we identified two candidate drugs that can effectively attenuate cyst formation in PKD organoids.

Conclusions: hPSCs derived organoid model of PKD can faithfully recapitulate critical structural and functional characteristics of PKD which would serve as an invaluable tool to investigate PKD pathogenesis and to discover potential therapeutics.

Funding: Government Support - Non-U.S.

FR-PO578

Epithelial-Mesenchymal Cross-Talks in Murine Models of Renal Ciliopathy

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Background: Ciliary defects underpin a variety of renal ciliopathies, including polycystic kidney disease and Nephronophthisis (NPHP). Both epithelial and stromal abnormalities are manifested in these diseases. Previously, to clarify the role of different cell types in disease progression, we utilized tissue specific mouse models of *Arl13b*, a cilia biogenesis gene, and *Invs/Nphp2*, a NPHP gene that encodes a protein localized to the proximal part of the cilium. Our results showed that epithelial specific knockout of *Arl13b* or *Invs/Nphp2* was sufficient to cause both epithelial cyst and interstitial fibrosis. By contrast, stromal specific knockout of *Invs/Nphp2* showed no obvious renal phenotypes up to the young adult stage, suggesting that epithelial cells are the main driver of the phenotypes and abnormal signaling from epithelial cells triggers interstitial fibrosis. Moreover, when *Arl13b* was specifically deleted in epithelial cells, Hedgehog signaling (HH) was activated non-cell autonomously in stromal cells and global pharmacological inhibition of HH signaling ameliorated fibrosis, kidney function decline and cyst progression, revealing a critical role of epithelial-mesenchymal crosstalk in disease progression. Combined, these results highlighted not only the importance of epithelial cells, but also epithelial-mesenchymal communications that include HH signaling in the molecular etiology of renal ciliopathy. However, the role of cilia in stromal response to epithelial signaling remains unclear.

Methods: In this study, we generated genetic mutants with *Invs/Nphp2* and cilia biogenesis genes deleted in both epithelial and stromal cells and will investigate the renal phenotypes of the mutant mice. We further investigated cilia distribution in stromal cells.

Results: Our results suggest that cilia are present on stromal cells. Further phenotypic analysis will reveal whether cilia and *Invs/Nphp2* in stromal cells modify the phenotypes triggered by defective epithelial cells.

Conclusions: Tissue specific function of cilia and ciliary genes plays a role in epithelial-mesenchymal crosstalks in renal ciliopathy.

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FR-PO579

Lyve1+ Macrophages Play No Role in Initiating Polycystic Kidney Disease

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Background: Recent studies show macrophages modulate progression of polycystic kidney disease (PKD). As examples, depletion of macrophages chemically with clodronate or genetically by deleting macrophage chemoattractant protein 1 (MCP1) reduces PKD severity. We hypothesised that a specific population of macrophages may be needed to initiate kidney cystogenesis.

Methods: We characterised macrophage subpopulations in cystic *Cpk* and *Pkd1*^{RC} mouse kidneys from the embryonic period. Additionally, we specifically depleted Lyve1^{+} macrophages by crossing *Lyve1-Cre* with *Csf1r-floxed* mice in the context of wild type and *Cpk* mice.

Results: Using macrophage-specific markers F4/80 and CD11b, we identified two populations of macrophages (F4/80^{hi}CD11b^{lo} and F4/80^{lo}CD11b^{hi}) by flow cytometry. CD206, Lyve1, TIMD4 and CCR2 markers were used to further characterise the subpopulations. Renal F4/80^{hi}CD11b^{lo} macrophages were CD206^{+}, some expressed Lyve1 and some were TIMD4^{+}. F4/80^{lo}CD11b^{hi} macrophages were CCR2^{+} and negative for the other markers. At embryonic day 18.5, when homozygous *Cpk* and *Pkd1*^{RC} mutant mice have dilated tubules, there was a significant increase in the proportion of Lyve1^{+} macrophages in mutant compared with wild-type kidneys, with no changes in other populations. By studying a detailed time course of *Cpk* disease progression, we observed the initial accumulation of Lyve1^{+} macrophages was followed by an increase in F4/80^{hi}CD11b^{lo} macrophages in kidneys as cysts initiate. All macrophage populations were significantly increased in severely cystic kidneys. Depleting Lyve1^{+} macrophages did not compromise kidney development in non-PKD-mutant mice, with no significant change in glomerular numbers in *Lyve1-Cre Csf1r*$^{fl/fl}$ embryos. There were no differences in PKD severity between *Cpk*$^{-/-}$ and Lyve1^{+} macrophage-depleted *Cpk*$^{-/-}$ mice based on kidney/body weight, renal cystic index and blood urea nitrogen two weeks after birth.

Conclusions: Lyve1^{+} macrophages accumulate before PKD cysts initiate during embryonic development. Genetic depletion of Lyve1^{+} macrophages from this period, however, does not affect the severity of PKD.

FR-PO580

The Immune Checkpoint Protein PD-L1 Interacts with BBS5 to Regulate Ciliogenesis and Hedgehog Signaling

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Background: Programmed cell death 1 ligand 1 (PD-L1) is an immune checkpoint protein regulates the immune synapse, a structure formed between immune cells and share structural and functional homology to primary cilium. However, whether and how PD-L1 regulates ciliogenesis remains elusive.

Methods: To investigate the role of PD-L1 on ciliogenesis, we performed immunostaining, Western blot, and qRT-PCR analysis in mouse NIH3T3 fibroblasts and human retinal pigment epithelium (RPE) cells. We also performed co-immunoprecipitation analysis to examine the interaction between PD-L1 and cilia associated proteins.

Results: We found that PD-L1 is located at the basal body and the Golgi apparatus as seen by its co-localization with centrosome marker γ-tubulin, Golgi associated protein Ift20, and Golgi marker Giantin. Knockdown of PD-L1 resulted in an increase in percentage of ciliated cells and average cilia length in 3T3 and RPE cells, whereas that overexpression of GFP-PD-L1 inhibited ciliogenesis in those cells. Consistent with this result, we found that serum starvation, which induces ciliogenesis, resulted in the downregulation of PD-L1 levels. Knockdown of PD-L1 increased the accumulation of Rab8a, BBS5 and polycystin 2 along the cilia axoneme in 3T3 cells but decreased the accumulation of Ift140 along the cilia in 3T3 cells and RPE cells. In addition, we found that the protein levels of BBS5, IFT20 and Rab8a were upregulated in PD-L1 knockdown 3T3 and RPE cells. We also found that PD-L1 formed a complex with BBS5 by co-immunoprecipitation analysis, and that knockout of BBS5 in PD-L1 knockdown 3T3 cells decreased the accumulation of polycystin 2 along the cilia. However, knockdown of BBS5 did not affect the localization, or protein level of PD-L1. We further found that knockdown of PD-L1 resulted in 1) the accumulation of the components of the hedgehog signaling pathway, including Smoothened (Smo) and Gli3, on cilia axoneme in 3T3 cells, 2) the upregulation of mRNA and protein levels of Gli1 and Gli3, and 3) the downregulation of Smo, Gli2 and Ptch1 proteins but not their mRNAs.

Conclusions: This study shows that PD-L1 is a novel basal body/Golgi component to regulate ciliogenesis and polycystin 2 ciliary trafficking through BBS5 and connects for the first time an immune checkpoint protein with ciliopathies, and possibly immune response.

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FR-PO581

Role of Interferon-Gamma in Cyst Formation After AKI

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Background: Acute kidney injury (AKI) is known to accelerate cystogenesis in conditional ciliopathy (*Ift88*) mice. Our lab previously showed that genetic deletion of adaptive immune cells significantly reduced cystic disease in *Ift88* mice after AKI. Additionally, using single-cell RNA sequencing, we found that T cells isolated from conditional *Ift88* mice after AKI had enriched expression of the cytokine interferon-gamma (IFN-γ). Based on these data, we hypothesize that T-cell-derived IFN-γ is a significant contributor to the accelerated cystogenesis that is seen following AKI in ciliopathy mice.

Methods: To test this hypothesis, we crossed conditional *Ift88* mice to mice lacking IFN-γ. At 8 weeks of age, we induced loss of *Ift88* and primary cilia through tamoxifen injection followed by administration of folic acid to induce AKI at 11-12 weeks of age; sodium bicarbonate solution was used as a vehicle-only control. Kidneys were harvested 56 days post-injury and cystic severity was measured by quantifying cystic index. We also analyzed changes in immune cell populations at the same time point using flow cytometry.

Results: Analyses of cyst severity 56 days post AKI indicate that conditional *Ift88* IFN-γ knockout mice had a significant reduction in the severity and number of renal cysts compared to conditional *Ift88* IFN-γ control mice. Analysis of flow cytometry data indicates a correlative reduction in the number of kidney resident macrophages and neutrophils in the conditional *Ift88* IFN-γ knockout AKI mice compared to conditional *Ift88* IFN-γ control AKI mice.

Conclusions: Collectively, our data indicate that T-cell-derived IFN-γ is a major contributor to accelerated cystic disease that is observed in conditional *Ift88* mice post AKI. Ongoing studies are addressing the specific T cell subset involved in injury-accelerated disease and the potential mechanism through which IFN-γ accelerates cystic disease in conditional *Ift88* mice following AKI.

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FR-PO582

The CPLANE Protein Fuzzy Regulates Primary Ciliogenesis Through Actin Remodeling

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Background: Defects in primary cilia cause a set of diseases termed ciliopathies manifesting in developmental defects including cystic/dysplastic kidneys. Mutations in ciliogenesis and planar cell polarity (CPLANE) genes *FUZZY*, *INTURNED*, and *WDPCP* lead to a ciliopathy spectrum with abnormal kidney phenotypes. Although Fuzzy ortholog in *D.Melanogaster* was identified as a part of the planar cell polarity and actin regulatory pathway, its functions in primary cilia assembly and ciliopathies remain largely unknown. We hypothesize that Fuzzy modulates actin-assembly involved in primary cilia formation.

Methods: The interactions between Fuzzy-Flag, p190A RhoGAP and IQGAP1-GFP were assessed by co-Immunoprecipitation. Rhotekin G protein-binding domain-eGFP biosensor in mutant and control mouse embryonic fibroblast (MEF) cells was used to measure RhoA activity. IQGAP1 was knocked down by siRNA in Retinal Pigmented Epithelial cells (RPE-1). Overexpression of Fuzzy-GFP was done by stable transfection in MDCK cells. Immunofluorescence with gamma-tubulin, Arl13b and phalloidin was used for cilia assessment.

Results: We established that Fuzzy interacts with p190A RhoGAP and controls its localization to the basal body. Normally, p190ARhoAGAP localizes to the primary cilia base and inactivates the actin-regulating protein RhoA. However, in Fuzzy mutant cells, RhoA is excessively activated. We also demonstrate that Fuzzy interacts with IQGAP1 – a protein that facilitates the interaction between p190ARhoGAP and RhoA. siRNA-mediated knockdown of IQGAP1 negatively affected ciliogenesis in RPE-1 cells. On the other hand, we show that Fuzzy is involved in regulation of the early stages of ciliogenesis: the overexpression of Fuzzy in MDCK cells triggered earlier cortical actin clearing at the apical membrane and earlier ciliogenesis.

Conclusions: We conclude that Fuzzy regulates the actin cytoskeleton at the primary cilium during the early and later stages of ciliogenesis. Fuzzy recruits p190A RhoGAP to the ciliary base and interacts with IQGAP1 resulting in the inhibition of RhoA and the suppression of excessive actin polymerization at the base of the cilium. Fuzzy is also involved in the process of actin clearing during the early stages of ciliogenesis, but the exact mechanism is yet to be elucidated.

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FR-PO583

Identification of Novel Targets for Autosomal Dominant Polycystic Kidney Disease Using a Patient Cell-Derived Cyst Model

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Background: Autosomal dominant polycystic disease (ADPKD) is the most common potentially lethal monogenic disorder and the most inherited kidney disease. Therapeutic development in ADPKD has been hampered by the lack of understanding of how mutations in polycystin 1 or 2 lead to uncontrolled cyst growth and ultimately end-stage renal disease.

Methods: We developed a 3-dimensional *in vitro* cyst model consisting of primary human epithelial cells derived from the cyst walls of ADPKD patients. The cells progressively form fluid-filled cysts within a collagen-rich gel in the span of 5-10 days and can be quantified through high-content imaging. To validate this model, a transcriptomic time course was obtained during cyst development and compared to transcriptomic signatures obtained from normal versus ADPKD biopsy tissue and secreted protein analysis of patient cyst fluid. Using data from these analyses, novel targets were assessed alongside established industry targets for their ability to inhibit cyst formation in the *in vitro* model.

Results: Comparing the transcriptomic signatures from the human *in vitro* model to patient tissue showed a high degree in overlapping responses and pathways that were consistent with the growth factors and chemokines confirmed to be present in patient cyst fluid. Clinical targets such as V2R, CFTR, and NRF2 showed varying effects in their ability to inhibit cyst formation. From our analysis, we hypothesized new targets based on the unbiased bioanalyses of the transcriptomic signatures, which showed equal or better inhibition of cyst formation in the model.

Conclusions: Mapping the response profile of over 50 therapeutic targets spanning diverse mechanisms of actions in the validated ADPKD patient-derived cyst model has enabled prioritization of key signaling hubs that may represent promising new therapeutic targets for ADPKD.

FR-PO584

Primary Cilia Change Protein Composition in Response to Glutamine Deprivation

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Background: ADPKD is a genetic disorder in majority of cases caused by mutations in PKD1 and PKD21. Genes encode for Polycystin 1 and 2 which form a receptor-complex located to primary cilia. Primary cilia are sensory organelles that protrude from the cell membrane. From this extroverted position it responds to changes in the cellular environment and convey various signaling pathways to control cell function, such as cell maintenance. Our lab previously published that loss-of-function of Pkd1 leads to metabolic reprogramming. Recently we published the importance of glutamine availability during nutrients-stress conditions on cilia length. Demonstrating that primary cilia respond to nutrients availability and particularly to glutamine. We also showed that the glutamine response of cilia requires the presence of Asparagine Synthetase (ASNS), which localizes to the cilia-centrosome complex.

Methods: To follow up on these findings we set up a large-scale proteomics study using mIMCD3 cells expressing a ciliary target fused to the proximity labelling tag, BioID. We affinity purified biotinylated proteins specific to the cilium by taking advantage of the high affinity of streptavidin coupled to beads. IP samples were analyzed with LC-MS. We generated an expression vector with ASNS fused to mNeonGreen fluorescent-tag and generated stable transfectants in IMCD3s.

Results: A first LC-MS analysis of proteins exclusively observed in cilia of cells grown in medium with or without glutamine revealed a total of 22 proteins significantly changing with removal of glutamine. A few proteins were found to change both in expression levels and in ciliary abundance. Among these, ASNS was upregulated with removal of glutamine in both the cytoplasm, and in the cilium. In line with these findings live imaging and IF performed with mNG-ASNS IMCD3s showed ASNS localizing not only at the base of the cilium, as we reported, but also within the axoneme. To accumulate ASNS in the cilium we treated mNG-ASNS cells with CilioBrevin D which inhibits dynein proteins and found that ASNS accumulates at the tip of the cilium.

Conclusions: Our data demonstrate that primary cilia respond to glutamine removal by changing their protein composition. And that the enzyme ASNS is among the proteins responding to glutamine availability.

FR-PO585

Dissecting Heterogeneity and Common Pathogenetic Pathways in Autosomal Dominant Tubulointerstitial Kidney Disease due to Mutations in REN

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Background: Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD) is a rare genetic disorder characterised by renal tubulointerstitial fibrosis and progressive chronic kidney disease. ADTKD is caused by mutations in different genes including *REN* encoding renin, a key player in the regulation of salt and blood pressure homeostasis. Renin is a secreted protein composed of 3 domains: the leader peptide allowing its insertion in the endoplasmic reticulum (ER), a pro-segment regulating its aspartyl protease activity, and the mature part. Mutations in mature renin lead to ER retention of mutant protein and to a late onset disease, while mutations in the leader peptide, associated with defective ER translocation, and mutations in the pro-segment, accumulating in the ER-to-Golgi compartment, lead to early onset disease.

Methods: We used transiently and stably transfected cells as well as an inducible system of renin expression to investigate the effect of mutations on renin trafficking.

Results: We demonstrated an unprecedented effect of mutations in the leader peptide and pro-segment leading to full or partial mistargeting of mutated protein to mitochondria. By studying GFP-fusion constructs we observed that the pre-pro sequence of renin, carrying mutation in either the leader peptide or the pro-segment, is necessary and sufficient to drive mitochondrial rerouting. In turn, this leads to mitochondrial import defect and mitochondria fragmentation. Induction of the 3 branches of the Unfolded Protein Response is observed in cells expressing renin mutated in the mature part, while induction of the IRE1 branch only is observed for the other mutants. Interestingly, the chronic expression of all mutants leads to toxicity and cell death.

Conclusions: Our results unravel a common cellular phenotype for mutants in the leader peptide and pro-segment (i.e. mitochondrial mistargeting) associated with an early-onset disease that differs from the one associated with mutants in the mature part (i.e. ER retention) that lead to a late onset disease. We currently aim at understanding how expression of these different mutants eventually converges to kidney inflammation and fibrosis by characterising stress signals emerging from the ER and mitochondria.

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FR-PO586

Antisense Oligonucleotide Knock Down of Uromodulin: A Potential Treatment Autosomal Dominant Tubulointerstitial Kidney Disease (ADTKD)

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Background: Autosomal Dominant Tubulointerstitial Kidney Disease-Uromodulin (ADTKD-UMOD) is a genetic disease caused by destabilizing mutations in the uromodulin (UMOD) or Tamm-Horsfall protein. Misfolded UMOD protein aggregates and accumulates inside the loop of Henle and the distal convoluted tubule, leading to progressive and irreversible chronic kidney disease. We hypothesized that peptide-conjugated phosphorodiamidate morpholino oligomers (PPMOs) could knock down *UMOD* expression and potentially reduce the disease-causing UMOD aggregation inside the cells.

Methods: A library of PPMOs was designed to bind to the complementary sequences of the mouse *Umod* gene and induce nonsense-mediated decay. These PPMOs were screened in mIMCD-3 cells, which express endogenous transcript to identify the most active compounds. The most efficacious PPMO compound was tested in both wildtype and UMOD C93F mice, a well characterized disease model of ATDKD, to determine the ability of the PPMO to reduce UMOD expression at the transcript and protein levels.

Results: A single dose of lead PPMO resulted in a 70% knockdown of *Umod* transcript that led to protein reduction that was sustained for at least 28 days. Furthermore, UMOD protein expression was reduced in the UMOD C93F animals after a single dose of PPMO.

Conclusions: This study shows the ability of PPMO technology to reduce UMOD transcript and protein levels *in vitro* and *in vivo.*

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FR-PO587

Retinal Oxalosis: An Unusual Presentation of Hyperoxaluria

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Introduction: Hyperoxaluria can be primary due to inherited disorders of enzymatic defects in the glyoxylate pathway causing decreased oxalate metabolism, or secondary from increased intestinal absorption. Type 1 primary hyperoxaluria (PH) is typically diagnosed in infancy/childhood, leading to kidney failure by the fourth decade of life with more mild presentation in types 2 and 3. Retinal oxalosis is a rare finding, especially in adults. Herein we describe a case of suspected primary hyperoxaluria diagnosed late in life causing rapid decline in kidney function and vision loss.

Case Description: An 81-year-old woman with history of coronary artery disease, melanoma, hypertension, CKD stage 2 was referred to kidney clinic for rapid worsening of kidney function. History was pertinent for left nephrectomy at age 15 presumably from kidney stones/pyelonephritis. Kidney function began rapidly deteriorating 6-8 months prior to the referral with minimal proteinuria (random urine protein creatinine ratio of 0.22) and no hematuria. Kidney biopsy was performed which showed calcium oxalate crystal deposition. Except for 4-6 glasses of iced tea daily, no other risk factors could be identified. Despite dietary restriction of oxalate, her kidney function decline continued, warranting peritoneal dialysis (PD) initiation. Four months post PD initiation she developed sudden worsening of vision and was found to have oxalate retinopathy after extensive evaluation ruling out other causes. Primary hyperoxaluria was suspected and she was referred for genetic testing at the kidney genetics clinic at our institution.

Discussion: Dialysis patients are at high risk of systemic oxalosis due to poor oxalate removal by dialysis. Treatment for PH Type 1 includes combined liver and kidney transplant in those with kidney involvement. Other treatment options include high dose pyridoxine, oral citrate and hydration. Lumasiran -an RNA interference agent- has been approved for PH Type 1. In those with ESKD, daily dialysis/dialysis with high flux dialyzers has been attempted with limited benefit. Our patient refused to switch to hemodialysis. Genetic testing was performed, and results are pending. Despite aggressive treatment oxalate retinopathy is known to be irreversible. Hyperoxaluria is a rare cause of nephrolithiasis and kidney failure yet should remain on the differential in the setting of rapid decline of kidney function with no clear cause.

FR-PO588

Better Oxalate than Never: A Diagnosis of Primary Hyperoxaluria Made After Renal Transplantation

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Introduction: Primary hyperoxaluria (PH), a genetic impairment of glycoxylate metabolism, causes kidney injury and end-stage renal disease (ESRD) when left untreated. We present a case of PH diagnosed following deceased donor renal transplantation (DDRT).

Case Description: A 60 year old woman with ESRD on hemodialysis (HD) thought to be from hypertension with no prior kidney stones underwent DDRT. Post-reperfusion biopsy of the transplant showed mild tubular atrophy and interstitial fibrosis occupying 10-15% of the sampled cortex. Immunosuppression was induced with thymoglobulin and methylprednisolone and has been maintained on prednisone, belatacept and mycophenolic acid. Four years later, kidney stones were identified in the transplant. Cystoscopy and lithotripsy were performed with retrieval of a 100% calcium oxalate stone by analysis, prompting initiation of potassium citrate and pyridoxine. A 24-hour urinary oxalate collection revealed markedly elevated oxalate levels. Genetic testing revealed heterozygosity of the GRHPR alleles. One allele contained a known mutation for PH2. The other allele contained a mutation that likely rendered it nonfunctional. Pyridoxine has since been held and potassium citrate dose increased. The patient was counseled on adequate hydration and low oxalate intake. Nedosiran is being considered for this patient.

Discussion: PH is characterized by deranged metabolism of glycoxylate, causing accumulation of oxalate. Calcium oxalate then precipitates in the urine and deposits in the kidneys, causing inflammation and cortical scarring. While PH1 is more prevalent and classically thought to cause more rapidly-progressive disease, PH2 can also cause significant kidney injury despite its relative indolence. The condition is diagnosed by detection of increased urinary oxalate followed by confirmatory genetic testing. In the post-transplantation phase, kidney dysfunction secondary to hyperoxaluria can be confused for delayed graft function, defined as the use of HD in the seven days post-transplantation. In the absence of a clear etiology for the underlying native renal function, and with genetic testing becoming affordable, it may be worthwhile to consider genetic testing for underlying renal diseases that could affect a transplanted kidney with the intention of increasing the longevity of transplanted kidneys in the post-transplantation phase.

FR-PO589

Heart Failure Recovery After Lumasiran and Isolated Kidney Transplantation in Primary Hyperoxaluria Type 1

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Introduction: Primary hyperoxaluria type 1 (PH1) is characterized by oxalate stones leading to kidney failure. In advanced PH1, systemic oxalate deposition may lead to heart failure. Lumasiran, a small interfering RNA, reduces oxalate load and may improve organ dysfunction in systemic oxalosis.

Case Description: A kidney biopsy revealed diffuse interstitial nephritis with massive oxalate deposition. Genetic testing confirmed two compound heterozygous Alanine-Glyoxylate Aminotransferase (AGXT) gene mutations. Our patient had peritoneal dialysis (PD) for 6 months. In addition, he suffered from severe heart failure (NYHAIII) with a left ventricular ejection fraction (LVEF) of 25%, marked left ventricular hypertrophy and a NTproBNP of >50,000pg/mL. A cardiac biopsy revealed severe oxalate deposition. Hemodialysis (HD) therapy was commenced to optimize volume overload and lower plasma oxalate (POx) levels. The initial POx level of 141.3µmol/L decreased to less than half after combined PD and HD. After starting lumasiran and high dose pyridoxine, POx levels further decreased to 29.2µmol/L. Subsequently, cardiac output improved to an LVEF of 35-40%. He received a living kidney donation from his father using standard immunosuppression and intensive hydration post transplantation. Daily oral pyridoxine and 3 monthly subcutaneous lumasiran was continued. At 3 months follow up, allograft function stabilized at a creatinine of 2.0 mg/dL. An allograft biopsy showed no oxalate deposition. His cardiac function improved further (NYHAI, LVEF 55%, NTproBNP of 449pg/mL) with a recent POx level of 11µmol/L.

Discussion: To our knowledge, this is the first case demonstrating complete remission of heart failure in a patient with PH1 following lumasiran therapy and isolated kidney transplantation. This underscores the utility of lumasiran and the conclusion that cardiac dysfunction related to PH1 is potentially reversible.

FR-PO590

Genetic Prevalence Estimates for All Types of Primary Hyperoxaluria

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Background: Primary hyperoxaluria is a rare disorder caused by biallelic pathogenic changes in 3 known genes (*AGXT* (PH1), *GRHPR* (PH2), *HOGA1* (PH3)). Affected patients have marked hyperoxaluria, frequent kidney stones, and are at high risk for kidney failure. Patients are often diagnosed late after they have developed severe disease complications, including systemic oxalosis. Given approved and emerging therapies for these diseases, it is important to understand the genetic prevalence of PH to determine the magnitude of missed diagnoses/reduced penetrance and develop strategies to improve patient outcomes.

Methods: Variants from all 3 genes were curated from OxalEurope, Rare Kidney Stone Consortium, ClinVar, and GnomAD registries in addition to an extensive literature review. Variants were scored as Pathogenic or Likely Pathogenic according to the 2015 ACMG guidelines using Intervar. Allelic frequencies were determined from GnomADv.2.1.1 after all identified variants were curated/reclassified and used to calculate the lifetime genetic prevalence of disease.

Results: The number of Pathogenic or Likely Pathogenic variants studied following comprehensive curation or reclassification of variants were 89 *AGXT*, 45 *GRHPR*, and 74 *HOGA1*. The following overall estimated genetic prevalence was determined: PH1 (1:209,357), PH2 (1:863,028), and PH3 (1:90,834) resulting in an estimated 17 per 1M individuals (136,000 individuals worldwide) with a lifetime possibility of developing PH regardless of ethnicity. The estimated carrier frequency is the following: PH1 (1:229), PH2 (1:465), and PH3 (1:151). Furthermore, ethnic groups were examined using post-curated variants showing the genetic prevalence is most predominant for PH1, PH2, and PH3 in the following populations respectively: East Asian (1:84,574), South Asian (1:390,788), and Ashkenazi Jewish (1:5,633).

Conclusions: Based on analysis of available genetic data, the estimated lifetime prevalence of PH is approximately 1:58,823 individuals globally. This is more common than currently diagnosed by at least an order of magnitude. The extent to which this is due to reduced disease penetrance or underdiagnosis is to be determined. Increasing access to diagnostic testing and continued curation of variants to the ClinVar registry is important to improve outcomes for all patients.

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FR-PO591

Unlocking the Potential of Genetic Testing: Insights into Primary Hyperoxaluria and Monogenic Kidney Stone Disease

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Background: Primary Hyperoxaluria (PH) is an autosomal recessive disorder that results in kidney stone disease and/or nephrocalcinosis affecting both pediatric and adult patients. Over time, the chronic disease progresses to end stage kidney disease (ESKD) necessitating a kidney and liver transplant. PH is divided into three types: PH1, PH2, and PH3, caused by mutations in *AGXT*, *GRHPR*, and *HOGA1* genes resulting in reduced enzyme activity and excess oxalate production. Nedosiran is an investigational RNA interference therapy holding the promise of mitigating excessive oxalate production and offering potential therapeutic benefits to patients suffering from this debilitating condition.

Methods: Novo Nordisk and PerkinElmer Genomics have partnered to provide sponsored genetic testing for patients with high-risk clinical symptoms for monogenic kidney stone diseases (MKSD) including PH. Two panels were offered: a 3-gene panel for PH and a 35-gene panel for MKSD. Results were categorized as the following: 1) Positive Genetic Diagnosis (Pathogenic or Likely Pathogenic variants in autosomal dominant (AD)/autosomal recessive (AR) genes), or 2) Possible Genetic Diagnosis (Pathogenic, Likely Pathogenic, or Variant of Uncertain Significance) in AD/AR genes.

Results: Out of 209 patients tested globally, 27 had PH1, 1 had PH2, and 2 had PH3, resulting in a 14% diagnostic yield for PH. An additional 15 patients received a positive diagnosis for MKSD, leading to a 22% overall diagnostic yield. Furthermore, 2 patients had a possible genetic diagnosis of PH2, 1 patient had a possible genetic diagnosis of PH3, and 27 patients received possible genetic diagnoses for MKSDs in addition to PH.

Conclusions: Genetic testing is vital for accurate diagnosis and treatment of patients who are at high risk for underlying MKSD including PH. In this study, genetic testing in pediatric and adult patients with high-risk clinical symptoms resulted in a positive genetic diagnosis in 45 of 209 patients. It is worth noting that genetic testing also yields valuable information beyond definitive diagnoses. An additional 30 patients obtained a possible genetic diagnosis, indicating the need for further metabolic and/or familial genetic testing.

Funding: Commercial Support - Dicerna Pharmaceuticals Inc., a Novo Nordisk Company

FR-PO592

Lumasiran for Primary Hyperoxaluria Type 1 and Impaired Kidney Function: 24-Month Analysis of the Phase 3 ILLUMINATE-C Trial

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Background: Primary hyperoxaluria type 1 (PH1) is a rare genetic disorder in which hepatic oxalate overproduction can lead to chronic kidney disease (CKD). Plasma oxalate (POx) increases with declining kidney function, leading to systemic oxalosis. Lumasiran, an RNA interference therapeutic that reduces hepatic oxalate production, administered to patients with PH1 and CKD 3b–5 in the ILLUMINATE-C trial (NCT04152200), resulted in decreased POx at month (M) 6 and 12 with acceptable safety. Here we present M24 results.

Methods: ILLUMINATE-C is an ongoing, single-arm study evaluating lumasiran in patients of all ages with PH1, eGFR ≤45 mL/min/1.73m^2 including hemodialysis (HD), and POx ≥20 μmol/L. The 6M primary analysis period is followed by a 54M extension period.

Results: Of 21 patients who entered the study, 5 of 6 (83%) assigned at study start to Cohort A (no HD) and 12 of 15 (80%) assigned to Cohort B (on HD) completed the M24 visit. Mean reduction from baseline in POx at M24 was 60.5% (Cohort A) and 30.6% (Cohort B). Two Cohort A patients with low baseline eGFR (8.6, 16 mL/min/1.73m^2) initiated HD. Two Cohort B patients who underwent kidney-only transplantation remained in the study with a functional graft after 16 and 21 months and comparable POx levels to 2 patients who underwent combined liver-kidney transplant. In patients with an ejection fraction (EF) <55% at baseline, 2 of 3 had improvement of ≥5% at M24; none met criteria for EF worsening. Mild injection site reactions were the most common lumasiran-related AEs, occurring in 5 of 21 (24%) patients overall. No deaths or lumasiran-related serious/severe AEs, discontinuations, or withdrawals occurred.

Conclusions: POx reductions with lumasiran were maintained at M24 with an acceptable safety profile in PH1 patients with CKD 3b–5, including those on HD, and in patients with an isolated kidney transplant. Noninvasive indicators of systemic oxalosis including EF appear stable or possibly improving after 2 years of treatment in this study population.

Funding: Commercial Support - Alnylam Pharmaceuticals

FR-PO593

Functional Analysis of AGXT1 Missense Variants of Uncertain Significance in HepG2 Cells: Association with Primary Hyperoxaluria Type I

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Background: Primary Hyperoxaluria Type I (PH1) is caused by functional deficit of alanine:glyoxylate aminotransferase (AGT1), a liver enzyme that detoxifies glyoxylate, thus preventing its conversion into oxalate. The hallmark of PH1 is the progressive deposition of calcium oxalate resulting in kidney stones leading to ESRD and systemic oxalosis. The diagnosis is established on a proband with hyperoxaluria or hyperoxalemia by the presence of biallelic pathogenic or likely pathogenic variations in the *AGXT1* gene encoding AGT1, 67% of which are missense. Although the pathogenicity of some genetic variants has been clearly defined, the clinical assessment of variants of uncertain significance (VUS) represents a big challenge. Our work is aimed at determining pathogenicity of *AGXT1* missense variants in a cellular model of disease.

Methods: We used hepatocarcinoma-derived human HepG2 cell line knocked-out for the *AGXT1* gene utilizing CRISPR/Cas9 technology, since they exhibit conserved glyoxylate/oxalate metabolism. By lentiviral infection we created and analyzed stable clones of *AGXT1*-KO HepG2 cells expressing the two polymorphic forms of AGT1 (AGT1-Ma and AGT1-Mi). Eight VUS were expressed on the AGT1-Ma background and three on the AGT1-Mi background. We validated our experimental setting to mimic the liver expression of AGT1 and investigated the effects of amino acid changes at the protein level.

Results: The p.Pro28Ser, p.Arg118Cys, p.Asp129His, p.Ala248Val, p.Arg317Trp mutations on AGT1-Ma, and the p.Glu274Asp, p.Ile279Thr, p.Arg289Cys mutations on AGT-Mi led to a biologically meaningful reduction in protein levels and activity, denoting the variants are likely pathogenic. On the other hand, the p.Pro314= mutation did not significantly affect AGT1 protein levels and activity, while p.Ala186Val and p.Arg197Gln cause only a partial reduction, thus suggesting that they could be benign or likely-benign.

Conclusions: We developed a platform to predict the pathogenicity of newly identified *AGXT1* variants that could have a significant clinical implication as potential tool to support the diagnosis of PH1 and establish genotype/phenotype correlations.

Funding: Commercial Support - Novo Nordisk Inc.

FR-PO594

An Un-Hex-Pected Cause of Crystalluria

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Introduction: Cystinuria, a genetic cause of kidney stones, is present in 1/7000 births, and 75% present in childhood. Cystinuria should be suspected in those with childhood kidney stones, staghorn calculi, or family history of stones. Diagnosis is confirmed by cystine calculi on analysis, hexagonal cystine crystals on microscopic urinalysis, or genetic testing. Patients are at increased risk of developing chronic kidney disease.

Case Description: A 21-year-old man with no significant past medical history presented with acute onset chest pain and dyspnea following a strenuous run. He had a nagging cold and took guaifenesin and half a scoop of workout supplement prior to running. Immediately afterward, he had lightheadedness, paraesthesias, headache, and progressive dyspnea. He had an anion gap of 28, elevated troponin, normal pro-BNP, HCO3 11 meq/L, sCr 1.6 mg/dl (no prior), Ca 10.6 mg/dl, and glucose 277 mg/dl. His symptoms were transient, and although he had acute myocardial injury, cardiac workup was negative. Creatinine peaked at 2.3 mg/dl. Urinalysis was notable for hemoglobinuria and proteinuria; microscopy showed hexagonal crystals. Two 24hr urine collections, 1 month apart, showed elevated cystine and low citrate. He was found to have a heterozygous pathogenic variant in the gene SLC7A9, c.997C>T, p.Arg333Trp consistent with autosomal dominant cystinuria. His father had a stone in his 40s, attributed to diet. While the patient has never had nephrolithiasis, he is at increased risk. He was started on potassium citrate and counseled to increase fluid intake and reduce dietary sodium and animal protein, with a goal urine cystine <250mg/L and urine pH >7.

Discussion: SLC7A9 variants are associated with autosomal dominant and recessive cystinuria, with variable penetrance. Heterozygotes often have increased urine excretion of cysteine and dibasic amino acids, which can lead to nephrolithiasis. Cystinuria was

unexpected in this patient, and upon renal recovery urine cystine crystals were absent. The combination of his mild cold, supplement use, and strenuous exercise predisposed him to acute kidney injury and revealed his otherwise quiescent cystinuria. Continued monitoring and treatment is warranted to prevent nephrolithiasis and chronic kidney disease. *The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

FR-PO595

Clinical Characterization of a Cohort with Suspected Monogenic Stone Disease

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Background: Monogenic stone diseases (MSDs) result from pathogenic variants in ~40 genes, displaying early onset, frequent stone events, chronic kidney failure, and positive family history. Targeted next-generation sequencing (tNGS) is a valuable approach for identifying genetic causes. Here, we share tNGS panel analysis results from a large cohort with suspected MSDs.

Methods: Subjects were recruited by Rare Kidney Stone Consortium (RKSC) collaborators with features suggestive of a possible MSD. Genotyping with a tNGS panel that includes 149 known and candidate causes of MSD. All variants were scored for pathogenicity using ACMG criteria. Clinical features were extracted from the RKSC registries and medical records. Urine parameters and eGFR were adjusted for age and sex. Data are reported as medians for continuous variables and percentages for categorical variables. Non-parametric and proportional tests were used for analysis.

Results: A total of 374 families (540 patients) were enrolled and screened. Of these, 131 families (40%; 216 individuals) were resolved with an identified pathogenic change in a total of 20 different genes, while in 243 families no mutation was detected (NMD) (60%, 324 individuals). Families were categorized based on the reason for recruitment into the following groups: Hyperoxaluria, hypercalciuria, cystinuria, and Stones without urine abnormalities. Table 1- shows a summary of the clinical features of resolved cases. Resolved hypercalciuria cases had a lower eGFR ($p<0.01$). Dent disease patients had a higher urinary calcium excretion than other resolved cases, and primary hyperoxaluria patients manifested hyperoxaluria as expected. Patients with SLC34A1 and SLC34A3 variants required more stone surgeries ($p=0.03$).

Conclusions: Despite a wide range of etiologies, the clinical characteristics of MSD show an overlap, yet kidney stones, nephrocalcinosis, and kidney failure are prevalent. A candidate gene panel is efficient to screen for the many causes of MSD with a high resolving rate improving diagnostics and allowing appropriate management and treatments.

Funding: NIDDK Support, Private Foundation Support

	N.	Age at last Follow-up	eGFR last F/U	N. Stone events	NC (%)	ESKD (%)
PH	46	16[12-28]	49[21-63]	9.5[3.5,10.5]	50%	28%
CYS	16	27.5[40.2,14.8]	69[59,82]	6[1.5,13]	26%	10%
Dent	12	14[12,24]	48[29,80]	3[1,5]	60%	14%
SLC34A3/SLC34A1	24	35[23,44]	55(46,61]	10[8,18]	65%	21%
CYP24A1	16	57[35,68]	59[48,68]	4[2.5,11]	62%	18%

Table-1 resolved cases with their clinical characteristics

FR-PO596

Understanding the Clinical Genetics of Kidney Stone Disease Using a Kidney Disease-Specific Genetic Test Panel

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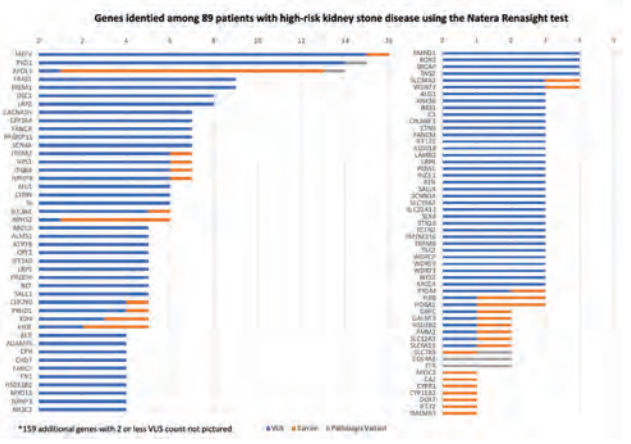
Background: The etiology of kidney stone disease (KSD) is multifactorial. Emerging data suggest that genetics may play a larger role than previously thought. 11% to 56% of KSD has heritable stone-related genetic mutations. We aimed to better understand the genetics of KSD using a kidney disease focused genetic test at our diverse, urban academic center.

Methods: A single-center, prospective study was conducted on patients with recurrent stones or a single stone with family history. Those with known causes of urolithiasis, active UTI or acutely passing a stone were excluded. All underwent standard stone analysis, serum metabolic evaluation, 24-hour urine studies and buccal DNA screen for 385 kidney disease-linked genes using the Natera Renasight™ kit. Variants were categorized as "positive" if pathologic, "carrier" if autosomal recessive, or of "uncertain significance" (VUS).

Results: 89 patients were enrolled. 55% were female, 60% were Hispanic, and 30% reported a first-degree family history. Median (IQR) patient age was 49 years (IQR 41-60) with 2 (IQR 1-3) stone episodes in the prior 5 years. 61% formed calcium oxalate stones. 7 (8%) subjects were positive for amyloidosis (*TTR*), Alport syndrome (*COL4A3*), cystinuria (*SLC7A9*), polycystic kidney disease (PKD1), or FSGS (*APOL1*). 39 (44%) were carriers for 30 unique genes and all patients had multiple VUS spanning 247 unique genes. Positive/carrier patients were similar to negative patients in demographics, comorbidities, stone analysis and 24-hour urine studies. They had lower median vitamin D (22.3 vs 29.7 ng/ml; $p=0.041$) and higher potassium (4.4 vs 4.2 mEq/ml; $p=0.090$).

Conclusions: Our study sheds light on potential genetic variants in recurrent stone formers in our diverse patient population. The initial wide range of results support the complex and polygenetic expression of KSD.

Funding: Commercial Support - Natera



FR-PO597

A Rare Cause of Proteinuria and Nephrolithiasis: Biallelic SLC26A1 Variants

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Introduction: Up to 2% of adult nephrolithiasis cases are attributable to a monogenic disease, a clinically and genetically heterogeneous group. Although high-throughput sequencing has identified >90 nephrolithiasis-causing genes, some of these genes are understudied.

Case Description: This Irish family consists of 2 affected siblings. The proband (W94_1), a 63-year-old woman, presented with recurrent non-obstructive nephrolithiasis, urinary infections, and proteinuria. Sonography revealed normal-sized kidneys. In addition, she reported bilateral sensorineural deafness since childhood, indicating hearing aids at age 50 years. No further evidence of systemic involvement was identified. At the last follow-up, aged 63 years, she exhibited reduced estimated glomerular filtration rate (eGFR). Despite recurrent nephrolithiasis, the kidney function of her 61-year-old brother (W94_2) is adequate (eGFR = 88 mL/min). At the time of genetic analysis, oxalate and calcium excretion in the urine were normal, with normal serum bicarbonate. Genetic testing revealed both harbor biallelic variants in The Solute Carrier Family 26-Member 1 (*SLC26A1*) gene (NM_022042:c.C1073T; p.S358L and c.C554T; p.T185M) associated with monogenic calcium oxalate nephrolithiasis. The *SLC26A1* gene encodes for an anion transporter critical in oxalate and sulfate hemostasis. These reported *SLC26A1* variants (p.S358L and p.T185M) occurred at conserved resides and reported at a low frequency in population databases, such as the Genome Aggregation Database (gnomAD). It is localized into the basolateral membrane of proximal tubules. Functional studies of similar reported variants demonstrate a dysfunctional process of protein and impaired transporter activity. However, the effect of *SLC26A1* on oxalate homeostasis, which causes hyperoxaluria and urolithiasis, remains controversial. Nevertheless, its role in sulfate homeostasis in humans has only recently been established.

Discussion: Clinical features of kidney stone formers harboring *SLC26A1* variants can vary, indicating the potential expressivity. Awareness of monogenic nephrolithiasis, especially in families with history, should allow early diagnosis, treatment, and personalized counseling.

FR-PO598

Characterization of Monogenic Kidney Disease in Patients over 60 Years of Age

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Background: Approximately 10% of adults with chronic kidney disease (CKD) have monogenic forms of the disease. However, the prevalence of monogenic kidney diseases in the over-60 population is not well characterized.

Methods: For genetic screening in this cohort with suspected monogenic kidney disease, excluding polycystic kidney disease, we utilized gene-panel and exome sequencing. The purpose of this study was to assess the diagnostic yield of clinically validated disease-causing variants and to compare the clinical characteristics of solved and unsolved cohorts.

Results: Genetic testing was performed for 113 adults (*n*= 93 families) with a median age at recruitment of 69 years (IQR: 64 - 73). 83.3% participants reported a family history of CKD and 52.2% were females. At last follow up, 84 (75.7%) individuals progressed to kidney failure at a median age of 57 years [IQR: 41.5 – 65]. We were able to demonstrate likely-pathogenic/pathogenic variant in 37/113 (32.7%), encompassing 13 distinct monogenic entities. Disease-causing variants in three phenotypes accounted for up to 76% of solved cases. These included *MUC1* (*n*=6), *UMOD* (*n*=3), *HNF1B* (*n*=5) and *DNAJB11* (*n*=1) associated with tubulointerstitial kidney disease; *COL4A5* (*n*=4) and monoallelic *COL4A3* (*n*=4) associated with Alport–related kidney disease; and *INF2* (*n*=5) associated with focal segmental glomerulosclerosis. We identified disease-causing variants in the *CLCN5* gene associated with Dent disease type 1 in an additional 3 (2.6%) individuals. In 32% (*n*=8) of the 25 patients referred with *a priori* diagnosis of CKD of undetermined cause were found to have a known monogenic cause. There was no difference in age at initial presentation [45.4 vs. 46 years; $p = 0.863$] and age at kidney failure [52.8 vs. 52.8 years; $p = 0.747$] between individuals with monogenic disease and those without. A family history of CKD was an independent predictor of a genetic diagnosis [odds ratio: 5; 95% CI: 1.1 - 23.3, $p = 0.040$], with a higher proportion of solved cases than unsolved cases [94.4% vs. 77.7%, $p = 0.02$].

Conclusions: We estimated that about a third of this cohort over 60 years old with suspected inherited CKD would have a monogenic nephropathy. Awareness of monogenic nephropathies, particularly in this population group, should permit family counselling and individualized treatment.

FR-PO599

Comprehensive Genetic Analysis Reveals Novel Variants in Nephrolithiasis and Nephrocalcinosis

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Background: Renal stones or nephrolithiasis (NL) and nephrocalcinosis (NC) are clinically heterogeneous conditions. The etiology of renal stone disease is multifactorial and influenced by a combination of genetic and environmental factors. 33 monogenic causes of NL/NC have been identified to date; we have shown that a genetic cause of NL/NC can be identified in approximately 11 % of adults and 16-20% of children (Halbritter *JASN* 26:543, 2015; Braun *CJASN* 11: 664, 2016). Several investigations have been conducted using next-generation sequencing (predominantly targeted sequencing). Nonetheless, a comprehensive genetic analysis of NL/NC, particularly in terms of copy number variation (CNV), is yet to be done.

Methods: Individuals with a history of at least one renal stone or NC before the age of 25 years were recruited from international stone clinics between January 2013 and December 2020. Affected individuals with NL/NC from 285 families were enrolled in this study. Exome sequencing (ES) was performed to determine the genetic cause of NL/NC. Detected variants were assessed using a population database, evolutionary conservation, and *in silico* pathogenicity prediction scores, and categorized according to the American College of Medical Genetics (ACMG) guidelines. Furthermore, CNVs were analyzed using sequencing coverage data.

Results: 37 Likely disease-causing variants were detected in 42 families, leading to genetic diagnosis in 14.7% (42/285) of all cases. Of the 37 detected variants, 20 were novel. The *CTNS* gene was the most frequent (n=8), followed by AGXT (n=5), *SLC3A1* (n=4), *ATP6V1B1* (n=3), and *ATP6V0A4* (n=2). The other genes included *CLCN5, CLDN16, CLDN19, MOCOS, SLC4A1, SLC7A9, SLC12A1, SLC34A1,* and *BSND*. CNVs were detected in three cases. Homozygous deletions in *SLC3A1* were detected in two cases: one showed deletion in exon 4-9, and the other showed a deletion involving only exon 7.

Conclusions: Our data represent a comprehensive analysis of the monogenic causes of renal stone disease. In-depth analysis at the single-exon level is beneficial. Simultaneous analysis of CNVs and SNVs based on ES has potential as a first-choice diagnostic approach for renal stone disease.

FR-PO600

Heterozygous Pathogenic Variants in SLC34A3 in Patients with Recurrent Calcium Phosphate Kidney Stones

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Introduction: The solute carrier family 34-member 3 (SLC34A3) gene encodes the renal type 2c sodium-phosphate cotransporter and mutations in SLC34A3 cause an autosomal recessive disorder known as hereditary hypophosphatemic rickets with hypercalciuria (HHRH). Disease onset is typically observed in infancy/childhood and is associated with hypophosphatemia, growth retardation, rickets and/or osteomalacia. There is also an adult-onset form recognized in heterozygous carriers of SLC34A3 variants with manifestations of reduced bone density and multiple fractures. Here we describe two adult patients with heterozygous pathogenic variants in SLC34A3, who presented with recurrent calcium phosphate nephrolithiasis without hypophosphatemia or bone disease.

Case Description: Case 1: A 47-year-old female with type 2 diabetes mellitus, migraine headaches on topiramate and a paternal history of nephrolithiasis was evaluated by renal genetics for recurrent kidney stones. As shown in Table 1, she had hypercalciuria, hypocitraturia and urine pH of 6-7. Calculus analysis revealed 90% calcium phosphate composition. Genetic testing showed a heterozygous pathogenic variant in SLC34A3 (c.1304del). **Case 2:** A 46-year-old female with morbid obesity S/P sleeve gastrectomy 4 years ago presented for renal genetics evaluation for recurrent kidney stones since age 18. As shown in Table 1, she had hypercalciuria, hypocitraturia despite potassium citrate, hyperoxaluria and urine pH of ≥7. Multiple calculi analyses revealed 78-90% calcium phosphate composition. Genetic testing showed a heterozygous pathogenic variant in SLC34A3 (c.1046_1047del).

Discussion: Our patients seemed to have a predilection for developing calcium phosphate stones, and to our knowledge, this has not been previously recognized in the literature in patients with heterozygous pathogenic variants in SLC34A3. Both cases presented with hypercalciuria, hypocitraturia and alkaline urine pH. The association of SLC34A3 gene variants with calcium phosphate stone formation deserves further investigation.

Table 1

Laboratory Data	Case 1	Case 2
Urine Calcium / 24 hours (mg) (range)	390 - 450	232 - 315
Urine Citrate / 24 hours (mg) (range)	207 - 454	< 40
Urine Oxalate / 24 hours (mg) (range)	22 - 30	52 - 60
Urine pH (range)	6 - 7	≥ 7
Serum Phosphorus (mg/dL) (range)	3.0 - 3.5	3.2 - 3.4

FR-PO601

A Canine Model Implicates Uromodulin Peptides in Calcium Oxalate Urinary Stone Risk

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Background: Dogs offer a spontaneous model of calcium oxalate (CaOx) urinary stone formation. Our previous research identified a pathogenic variant (PV) in the canine uromodulin gene (*UMOD*) that is associated with a dramatic risk for CaOx stones. This stone-risk PV resides in the external hydrophobic patch (EHP) of uromodulin, which is cleaved from the mature protein before secretion into tubular fluid. In this study, we characterized urinary excretion of EHP-containing peptides from CaOx stone former (SF) dogs with and without the *UMOD* PV.

Methods: Urinary uromodulin peptides were measured in urine samples from SFs with (n=4) and without (n=4) the *UMOD* PV plus healthy control dogs (n=7) and normalized to urinary creatinine. Dogs with kidney disease were excluded. Uromodulin peptide abundances were summed for comparisons of total excretion. For individual peptides, abundance was calculated relative to the sum of all uromodulin peptides to obtain a percentage. Cleavage patterns were compared between groups.

Results: Total uromodulin peptide abundance was reduced in SF dogs with the *UMOD* PV. Urine from PV SF dogs lacked a peptide cleavage site, resulting in longer peptides compared to healthy controls. Total uromodulin peptide abundance did not differ between non-PV SF and healthy dogs. However, non-PV SF dogs had decreased abundance of specific EHP-containing peptides that was intermediate between healthy and PV SF dogs (**Figure 1**).

Conclusions: Reduced urinary excretion of specific uromodulin peptides in CaOx SF dogs with and without the *UMOD* PV implicates these peptides in stone risk. Previous research has demonstrated bioactivity of uromodulin peptides. The peptides that are decreased in the urine of SF dogs may have a protective effect against stone formation.

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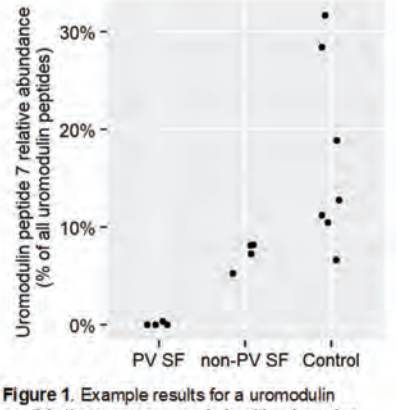

Figure 1. Example results for a uromodulin peptide that was common in healthy dog urine but nearly absent in SF dogs with the *UMOD* PV and decreased in SF dogs without the PV.

FR-PO602

Novel Therapy for Cystinuria Using Genetic Tools

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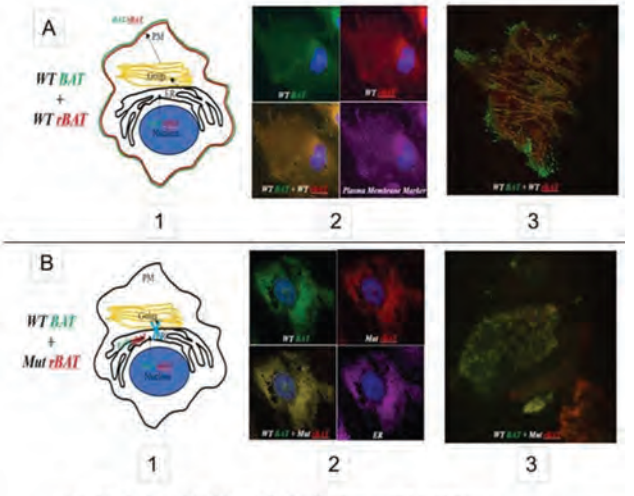
Background: Available drug treatment for Cystinuria is still imposes huge disadvantages to patients through harmful side-effects. This fact necessitates the need for other therapeutic approaches without causing major side-effects. Cystinuria is caused by a mutation of $b^{0,+}AT$ *(SLC7A9)* or *rBAT (SLC3A1)* Proteins. Mutations result in the mis-localization of functioning channles at the plasma membrane (PM) leading to a disruption in cystine reabsorption that results in the accumulation of cystine stones. This research hypothesizes that repurposing established drug compounds to re-direct both proteins into the PM is a new and improved therapeutic approach.

Methods: In this study, we utilised constructed transduced human PTEC to investigate the localisation of $b^{0,+}AT$ and *rBAT* in wildtype and four mutated cell lines: *p. Met467Thr, p. Thr216Met, p. Gly458Arg,* and *p. Asn254Thr* using various imaging systems. Primary investigation was done using ICC/IF followed by Widefield Fluorescence Microscopy. Follow-up investigations were done using Confocal Microscopy and co-localisation analysis of obtained data. Findings were confirmed by TIRF Microscopy. Currently, the INCELL analyser is being used to optimise the LOPAC 1280 in these cell lines.

Results: All localisation studies done using different imaging systems showed the same results. Firstly, both proteins were found to be trafficked together. Secondly, in the wild-type cell line, both proteins were located at the PM. Thirdly, in mutated cell lines, both proteins were trapped in the ER. Morphological changes of PTEC were supportive of the co-localisation studies.

Conclusions: Both proteins were trapped in the ER in all four mutants in contrary to wild-type cell line. These findings allow testing of LOPAC 1280 drugs to show their efficacy in re-locating proteins into the PM. Radiation testing will followed to confirm functionality of both proteins.



(The Localization of $b^{0,+}AT$ and *rBAT* in Wildtype and Mutated Genes)

The figure A-1 illustrates the trafficking of $b^{0,+}AT$ and *rBAT* in the Wildtype gene from the nucleus to the plasma membrane (PM) of the cell, while in mutated *rBAT* both proteins are trapped in the Endoplasmic Reticulum (ER) as illustrated in B-1. A-2 displays Widefield microscope images for the colocalization of both protein at the plasma membrane in the Wildtype gene (*BAT* tagged with E-GFP, *rBAT* tagged with mCherry, Far-red is CellMask plasma membrane stain from Invitrogen), while in mutated *rBAT* both proteins colocalize in ER as seen in B-2 (ER marker is Anti-KDEL antibody from abcam). A-3 displays TIRF microscope image which confirms clear localization of both proteins at the plasma membrane in the Wildtype gene, while in the mutated gene of *rBAT* only a slight shadow is observed which suggest a modest degree of localisation for both proteins at the PM.

FR-PO603

Gordon Syndrome in an Elderly Adult: A Rare Presentation

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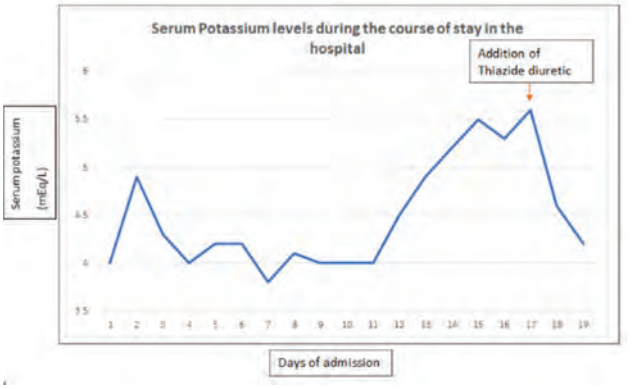
Introduction: Gordon syndrome (GS) is a rare autosomal dominant condition with a loss of function mutation of WNK1, WNK4, KLHL3, and CUL3 genes. This affects the thiazide-sensitive sodium-chloride channels (NCC) in the distal convoluted tubule. Being a hereditary disease, it is expected to present at a young age, but may rarely present in adults as well.

Case Description: A 70-year-old male with obstructive uropathy, indwelling Foley catheter and right nephrostomy tube, CKD stage G3B/A3, and persistent atrial fibrillation (AF), presented to the ER with generalized weakness. He developed urosepsis, metabolic acidosis and AKI, for which empiric antibiotics and IV fluids with sodium bicarbonate were started. Development of fluid overload secondary to chronic heart failure prompted the addition of 40mg IV daily of furosemide. He was started on metoprolol tartrate 100 mg PO b.i.d. for AF with rapid ventricular rate. Bicarbonate drip was stopped on day 5 when levels normalized. IV furosemide had to be decreased to 20 mg daily along with addition of IV acetazolamide, due to development of contraction alkalosis on day 12. While alkalemia improved, serum potassium (K) surprisingly rose, with levels not improving even with lowering the metoprolol dosage. This paradoxical trend of K led to clinical suspicion of GS. Lo and behold, administering hydrochlorothiazide after discontinuing the previous diuretics resulted in immediate and sustained decline of K back to normal.

Discussion: Hyperkalemia can be attributed to various factors, with beta-blockers, metabolic acidosis, and insulin deficiency being some of them. True hyperkalemia is rare unless there is a large K load, marked exercise, or a defect in K handling that prevents the excretion of the excess extracellular K. GS, a rare cause of hypertension and hyperkalemia, can be missed, especially in adults, without vigilance for electrolytes and acid-base abnormalities. It should therefore be included in the differential diagnosis of patients presenting with unexplained hyperkalemia.



FR-PO604

Clinical Features and Genotype-Phenotype Correlation of Bartter Syndrome Type 1 and 2

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Background: Bartter syndrome type 1 and 2 (T1/T2BS) are autosomal recessive hereditary salt-losing tubulopathy (SLT) caused by loss-of-function variants of *SLC12A1* (NM_000339) and *KCNJ1* (NM_000220) respectively. Although the typical case of both diseases presents severe clinical manifestation at the perinatal period, they are very rare diseases and there are few reports on their clinical course and genotype-phenotype correlations.

Methods: Of 651 patients with suspected SLT who underwent comprehensive genetic testing of 124 genes related to the renal disease by next-generation sequencing at our department, T1BS: 16 and T2BS: 10 cases genetically diagnosed were evaluated retrospectively.

Results: In T1BS, 23 variants (novel:15) were found in the *SLC12A1*, and in T2BS, 11 variants (novel:7) were identified in the *KCNJ1*. The median age at the time of genetic testing was 0 years for both diseases. The mean serum potassium level at diagnosis was 2.9 mEq/L in T1BS, but all T2BS patients showed transient hyperkalemia (mean 7.5 mEq/L) in the early postnatal period, followed by hypokalemia (mean 3.2 mEq/L). All patients with T1BS required continuous treatment with potassium products, potassium-retaining diuretics, and/or NSAIDs as a treatment for hypokalemia, whereas only 5 patients (50%) with T2BS required these treatments. Concerning renal prognosis, 3 patients with T1BS and 5 patients with T2BS had deteriorated renal function at the time of genetic testing. Regarding the genotype-phenotype correlation, some of the missense variants of both T1 and T2BS did not show polyhydramnios and presented an atypical mild clinical manifestation without any symptoms in neonatal age. As for the *KCNJ1* gene, serum potassium levels tended to be high (mean 3.3 mEq/L) in patients with the large deletion variant including the promoter region that has been previously reported, and this variant may present with mild manifestation.

Conclusions: T2BS shows significant hyperkalemia in the early postnatal period, but the severity of hypokalemia after infancy is milder than that of T1BS, and some cases did not require potassium supplementation. The correlation between the genotype-phenotype is not yet clear, but there were some clinically atypical cases, and further research is needed.

Funding: Government Support - Non-U.S.

FR-PO605

Adrenal Mass in Bartter: Incidentaloma or Adenoma?

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Introduction: Bartter's syndrome is rare, characterized by salt wasting caused by impaired absorption of sodium in the thick ascending limb of the loop of Henle. Young patients present with hypokalemia, metabolic alkalosis, and hyperaldosteronism. Our case presents a patient with Bartter's syndrome with an incidental adrenal mass.

Case Description: A 39 yo F with hx of Bartter's syndrome type III (heterozygous for CLCKNB) and Sjogren's syndrome presents for an office visit for evaluation of incidental right adrenal complex mass 1.5cm X 1.7cm with a question of whether the hyperaldosteronism was because of Bartter's syndrome or a hypersecretory adrenal nodule. She denies any h/o Hypertension. She was diagnosed at the age of 5 months with Bartter's syndrome, hypokalemia, and hypomagnesemia. Vitals - temp 97.3, pulse 80, BP 120/81. The physical exam was unremarkable. Her daily medications include Losartan 50 mg, Amiloride 10 mg BID, and Potassium and Magnesium supplements. Labs: BMP: Na 138, K 4.9, Cl 103, bicarb 23, BUN 10, Cr 0.8, Mg 1.7, Hb 12.6, WBC 9.2, Plt 419. Renin 48ng/mL/h, aldosterone 1100ng/dL.

Discussion: Bartter syndrome presents as hypochloremic, hypokalemic metabolic alkalosis. It is diagnosed in young individuals with an incidence of 1/1000000. Hyperaldosteronism and high rennin levels occur secondary to compensation mechanisms that cause macula densa hypertrophy. An adrenal mass occurring in Bartter syndrome has not been reported in the literature. This patient was normotensive with an elevated renin and aldosterone level. Our case makes us wonder if the elevated aldosterone was compensatory vs hypersecretory. An adrenal adenoma in this case would present with suppressed renin, elevated aldosterone with hypertension. Primary hyperaldosteronism would have suppressed renin levels in addition to elevated aldosterone levels. A salt suppression test could be used to differentiate between the etiology of primary vs secondary hyperaldosteronism if renin levels are suppressed. In conclusion, Bartter syndrome causes compensatory hyperaldosteronism with high renin levels.

FR-PO606

Knocking out the Sweetest Urine

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Introduction: SGLT2 inhibitors—which act on a Na-glucose co-transporter in the apical membrane along the proximal tubule—lead to natriuresis and glycosuria, and have been shown to have an astonishing salutary effect on slowing CKD, perhaps in part by stimulating tubuloglomerular feedback. Here, we present siblings with a naturally occurring loss-of-function mutation of the SGLT2 co-transporter.

Case Description: A 44-year-old male presented to the clinic for glucosuria first discovered at age 10. He reported concurrent polyuria and polydipsia since childhood. He denied history of UTI, dysuria, urinary retention, change in appetite, or change in vision. His biological sister was found to have glucosuria as well. Both have enjoyed perfect health with normal blood pressure, electrolytes, and kidney function; both have normoglycemia and neither have diabetes. A 24-hour urine demonstrated 29 g glucose in 3.1 L (935.5 mg/dL). Genetic testing revealed a mutation in SLC5A2, the gene encoding the SGLT2 co-transporter.

Discussion: In these siblings, an SLC5A2 loss-of-function variant c. 1152_1163del (p.Val385-Ala288del) is the cause of their familial renal glucosuria. While the SGLT2 inhibitor class of medication is growing in popularity for its known benefits at reducing CV disease and progression of CKD, few studies have evaluated the effect of the gene mutation induced glucosuria. One study of 13 family members in Finland with a SLC5A2 genetic mutation was followed over 30 years. While they were at increased risk of urinary tract infections and postprandial hypoglycemia, there has been no effect on glucose tolerance and they maintain normal kidney function. We conclude that, as has been the case with other genetic abnormalities of transporters along the nephron, individuals and families with SLC5A2 mutations should be studied in an effort to elucidate the potential mechanisms that underlie the beneficial effects of SGLT2 inhibitors in patients with kidney disease.

FR-PO607

Clinical and Genetic Characterization of Patients with CUBN Variants

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Background: Isolated persistent proteinuria caused by *CUBN* variants is rare with only a few cases reported and even fewer have had phenotypic characterization with a kidney biopsy and electron microscopy.

Methods: We retrospectively reviewed all cases undergoing genetic testing in the Mayo Clinic Nephrology Genomics Clinic with *CUBN* variants identified and described their clinical, pathological, and molecular genetic characteristics.

Results: We identified one patient with two *CUBN* variants who developed subnephrotic-range proteinuria after a urinary tract infection at 4 years and 9 months of age (UPCR 1.51 mg/mg; current cystatin eGFR 97 ml/min/1.73 m^2). A kidney biopsy revealed minimal change disease (MCD) and minimal mesangial hypercellularity. A exome-based panel testing detected a variant of uncertain significance (VUS) in *CUBN* (NM_001081.4:c.9079G>A, p.(Gly3027Arg)) which has been reported in the homozygous or compound heterozygous state in at least one affected individual (PMID: 31613795) (PM3_Supporting) and it is predicted to have a deleterious effect to the protein (PP3). Also, this variant has a 0.0402% allele frequency in population databases (PM2_Supporting). Subsequent genome-based panel (432 kidney-related genes) identified a pathogenic deep intronic *CUBN* variant (NM_001081.4:c.3330-439C>G) predicted to impact splicing (PP3) and result in loss of function, a known disease mechanism for CUBN-related diseases (PMID: 10080186, 15024727, 24156255). This variant has been reported in the homozygous or compound heterozygous state in at least 3 affected individuals (PMID: 10080186, 22929189) (PM3_strong), segregated with disease in one family (PMID: 10080186), and it is absent in population databases (PM2_Supporting). Treatment with RAAS blockade, resulted in partial improvement of albuminuria. B12 levels were normal. Additionally, we identified single *CUBN* VUSs in 8 patients with FSGS and 1 patient with MCD. Among those, 3 required renal replacement therapy and one had a pathogenic variant in the *INF2* (NM_022489.4:c.641G>A, p.(Arg214His)) associated with autosomal dominant proteinuric kidney disease.

Conclusions: We confirm the rarity of *CUBN* related kidney disease in our nephrology practice and highlight the utility of genome sequencing to identify non-coding variants, improving genetic diagnostic yield when targeted or exome-based panels are inconclusive.

FR-PO608

SLC5A2 Mutation in a Patient Presenting with Volume Depletion

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Introduction: We present a patient found to have a heterozygous SLC5A2 mutation in the absence of glucosuria with volume depletion and underlying tubulopathy.

Case Description: 30 year old African American male, no prior medical history with chief complaint of fatigue and persistent alkalemia on bloodwork. Evaluation of fatigue included a sleep study negative for central/obstructive sleep apnea, pulmonary function testing without obstruction/restriction. He stated the fatigue had been worsening over the past year, prior asymptomatic, water intake 4L/day. He denied the use of laxatives, diuretics, antacids, herbals and medications. ROS was positive for orthostasis, palpitations, denied: poor oral intake, nausea, vomiting, diarrhea, polyuria. Family history unknown, and he never had surgery. Exam revealed BP: 89/60 mmHg, HR 88 bpm, RR 16 bpm, small/thin stature, positive orthostatics, moist mucous membranes. Labs remarkable for *Serum*: bicarbonate 34 mmol/L, normal: sodium, potassium, chloride, magnesium, phosphorus, creatinine, glucose, elevated plasma renin 58.9 pg/ml. Fractional excretions of: Sodium 0.3%, Chloride 0.5% Magnesium 5%, Potassium 17%, and *urine* significant for K/Cr 9 and Ca/Cr 0.05, no glucosuria on urinalysis, diuretic screen negative, Uosm 685 mOsmol/kg. Renal US: 1 simple cyst, absence of nephrocalcinosis. Differential included volume depletion on background of salt wasting tubulopathy. Genetic testing performed which revealed SLC5A2 heterozygous mutation (c.1024G>T, p.Glu342*). He was counseled to intake copious fluids and sodium chloride to mitigate the effects of volume depletion and symptoms improved.

Discussion: SLC5A2 encodes the renal sodium/glucose transporter, responsible for renal glucose reabsorption. While homozygous mutations result in glucosuria which may lead to volume depletion, heterozygous mutations are variable with differing phenotypes, and many do not manifest with overt volume depletion in the absence of glucosuria. Here we present a patient with a heterozygous mutation in the SLC5A2 gene without glucosuria, who presented with evidence of volume depletion and electrolyte wasting tubulopathy. This case emphasizes the need for phenotyping various mutations in the SLC5A2 gene, to aid in the differential of metabolic alkalosis and altered tubular handling of electrolytes in the setting of such mutations.

FR-PO609

Juvenile Nephronophthisis Caused by Two New XPNPEP3 Gene Mutations: A Case Report

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Introduction: Nephronophthisis(NPHP) is an autosomal recessive disease that mainly involves the tubulointerstitium. This article reports a case of a juvenile type of Nephronophthisis with a small proportion of urine, an increase in serum creatinine and anemia of uric acid, as the main clinical manifestations, renal pathological features of renal tubule atrophy, renal tubule membrane thickening, fibrosis, and inflammatory cell infiltration. The whole exome of the XPNPEP3 gene showed two mutations: CHR22:41278058,c.466(exon 3) C>T, and Chr22:41253249,c.64(exon 1) G>A, which caused Nephronophthisis. These two mutations are novel mutations of the XPNPEP3 genes.

Case Description: The patient, a 14-year-old male, was admitted to the hospital because of "abnormal renal function for 3 years." Pathological diagnosis: Proliferative sclerosing glomerulonephritis with chronic renal tubulointerstitial nephropathy is initially considered, and genetic screening is recommended. The whole exome of the XPNPEP3 gene showed two mutations: CHR22:41278058,c. 466(exon 3) C>T, and Chr22:41253249,c. 64(exon 1) G>A. Mutations in this gene can lead to Nephronophthisis. The clinical diagnosis was: 1. Nephronophthisis 2. Chronic renal insufficiency 3. Metabolic syndrome, Category 1 high blood pressure, high-risk glucose tolerance, abnormal abdominal obesity 4. Hyperuricemia 5. mild anemia. At present, the patient is still under regular follow-up.

Discussion: Nephronophthisis(NPHP) is an autosomal recessive disease that primarily involves the renal tubulointerstitium. NPHP is characterized by normal or reduced renal size, renal cysts concentrated at the corticomedullary junction, and tubulointerstitial fibrosis. Whole exome sequencing of the XPNPEP3 gene showed two NPHP-causing variants, Whole exome sequencing of the patient's father and mother confirmed the existence of compound heterozygous mutations. The clinical manifestations of the patient were partially consistent with Nephronophthisis type 1. At present, there is no specific drug for the treatment of Nephronophthisis, and the principle of clinical treatment is supportive therapy. Risk factors leading to renal injury and complications should be controlled. Hormones should be avoided in patients with hypertension, worsening renal function, edema, or hyperkalemia.

FR-PO610

In Vivo Disruption of pH Gradients Alters Endo-Lysosomal Dynamics in the Proximal Tubule

Imene B. Sakhi,[1] Monika A. Kaminska,[1] Nevena Jankovic,[1] Andrew Hall.[1,2] Structural and Functional Imaging of the Kidney. *[1]Universitat Zurich, Zurich, Switzerland; [2]Universitatsspital Zurich Klinik fur Nephrologie, Zurich, Switzerland.*

Background: The proximal tubule (PT) displays an apical endo-lysosomal system (ELS) that reabsorbs and degrades filtered plasma proteins. Defects in this process result in proteinuria. Vesicular acidification is integral to endocytotic function and is impaired in some genetic kidney disorders, such as Dent disease; but the nature of pH gradients in the PT ELS and their functional relevance to dynamic processes were not well understood. Data from partially differentiated *in vitro* models suggest that pH decreases progressively through early endosomes (EEs), late endosomes (LEs) and lysosomes, but whether it is also the case in PTs *in vivo* was unclear.

Methods: We have used small molecules as carriers to target pH dependent and independent fluorescent sensors to the PT ELS in living mice and provide ratiometric readouts of intracellular pH. We have applied intravital multiphoton microscopy to track probes through ELS components in real-time, and have mapped changes in pH to specific structures identified by antibody labeling in fixed tissue. The lipophilic weak base hydroxychloroquine (HCQ) was injected intravenously to explore the effects of rapidly de-acidifying ELS vesicles.

Results: The ratiometric technique was shown to provide a readout of pH across the physiological range in a PT cell line. Clear decreases in pH were identified within PTs *in vivo* in both EEs and lysosomes, but surprisingly not in LEs. Abolishing these pH gradients with HCQ disrupts recycling of megalin and reroutes it to the degradative pathway, resulting in a severe defect in protein uptake. However, HCQ treatment did not recreate characteristic defects in endosomal maturation described previously in Dent disease models. Meanwhile, de-acidification of lysosomes inhibits dissociation from LEs and prevents their trafficking into the basal, mitochondrial-rich region of the cell.

Conclusions: By using an innovative intravital imaging approach, we have generated the first functional map of ELS pH changes within working PTs, which differs significantly from the previous textbook paradigm. Moreover, we show that vesicular acidification is critical for endocytotic receptor recycling and lysosomal dynamics. However, our results suggest that endosomal alkalinization alone does not fully explain the pathogenesis of Dent disease, meaning that pH-independent mechanisms still need to be considered.

Funding: Government Support - Non-U.S.

FR-PO611

Hypokalemia in an Older Adult due to Heterozygosity for a Novel Pathogenic Variant that Causes Gitelman Syndrome

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Introduction: Gitelman Syndrome (GS) is a rare autosomal recessive disorder due to a mutation in the *SLC12A3* gene that encodes thiazide-sensitive sodium-chloride cotransporter (NCCT) in the distal convoluted tubule. GS classically presents as a salt-losing tubulopathy characterized by low-normal blood pressure, hypokalemia, hypomagnesemia, and metabolic alkalosis and is typically diagnosed in childhood or adolescence. We present an unexpected case of isolated hypokalemia in an older adult with HIV due to a heterozygous *SLC12A3* variant mutation.

Case Description: A 63-year-old male with well controlled hypertension, coronary artery disease and HIV with undetectable viral load was referred for hypokalemia. He had intermittent hypokalemia for at least 15 years with potassium as low as 2.7 mEq/L. He had no symptoms of gastrointestinal loss of potassium or family history of hypokalemia. Medications included losartan 50 mg daily, metoprolol 50 mg daily, and amlodipine 10 mg daily, potassium chloride 10 mEq thrice daily, emtricitabine-tenofovir alafenamide 200-25 mg daily, and dolutegravir 50 mg daily. His blood pressure was 110/75 mmHg. Serum magnesium and phosphate were normal and serum bicarbonate ranged from 25-28 mEq/L. Urine spot potassium was 43 mEq/L and fractional excretion of potassium was 11%, indicating renal potassium wasting. Screening for hyperaldosteronism was negative. A prior computed tomography showed a hyperdense appearance to the renal medullary pyramids and several non-obstructing kidney stones. Due to concern for an underlying genetic etiology of his hypokalemia, genetic testing was performed which revealed a heterozygous single amino acid substitution of *Glu* to *Asp* at codon 121 in exon 2 of the *SLC12A3* gene.

Discussion: Our patient was heterozygous for a pathogenic variant in the *SLC12A3* gene that causes GS. Though the inheritance pattern of GS is autosomal recessive, we believe our patient's isolated renal potassium wasting reflects an intermediate disease phenotype that may be seen in heterozygous carriers. A prior study found heterozygosity for the *p.R642G* variant was associated with lower serum potassium but to our knowledge, this is the first report of hypokalemia associated with the *c.363G* variant. This case supports the concept that pathogenic variants, known to cause many recessive disorders, contribute to complex traits.

FR-PO612

Syntaxin 3 Is Essential for Renal Proximal Tubular Reabsorption

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Background: Transporters at the apical membrane of renal proximal tubular epithelial cells (PTEC) are essential for reabsorbing water and electrolytes from primary urine. However, how these transporters are trafficked to the apical membrane remains uncertain. Syntaxin 3 (STX3) is a molecule that belongs to the membrane fusion-associated protein superfamily. The study aims to investigate the role of STX3 in the trafficking of transporters to the apical membrane in PTEC.

Methods: Localization of STX3 in mouse and human kidneys were analyzed by immunohistochemistry. Mice with floxed *Stx3* were crossed with tamoxifen (Tam)-inducible PTEC-specific Cre-expressing mice (*Ndrg1-CreERT2 Stx3$^{fl/fl}$* (*Stx3* cKO)). Samples of the *Stx3* cKO mice were analyzed 1, 2, and 6 months after tamoxifen injection. Urinary electrolytes, urinary glucose, and urinary low molecular weight proteins were quantified to determine the presence of a Fanconi syndrome-like phenotype. The expression levels and localization of various transporters of PTEC were examined by immunohistochemistry. The localization of transport vesicles and brush border in PTEC were analyzed by electron microscopy.

Results: STX3 was localized at the apical membrane of PTEC, both in humans and mice. Increased urinary excretion of phosphate, glucose, and low molecular weight proteins were found in *Stx3* cKO mice compared to control (Ctrl) mice. Urinary calcium excretion and serum creatinine levels in *Stx3* cKO mice were similar to those in Ctrl mice. Immunohistochemical analyses revealed that sodium phosphate transporter 2a was distributed intracellularly and sodium-glucose transporter 2 expression was reduced in the PTECs of *Stx3* cKO mice. Apical brush border membranes were diffusely shortened, and intracellular vesicles were accumulated in the sub-apical areas of the PTECs in *Stx3* cKO mice.

Conclusions: These results suggest that STX3 is critical for the apical trafficking of various transporters that regulate urinary reabsorption in PTEC.

Funding: Private Foundation Support

FR-PO613

Natural History of Advanced Primary Hyperoxaluria Type 1: A Retrospective Study

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Background: Primary hyperoxaluria 1 (PH1) is a genetic disease of oxalate overproduction that can cause progressive kidney damage and systemic oxalosis. We aimed to characterize the natural history of advanced PH1 in the context of standard of care.

Methods: In this retrospective, multinational chart review study, eligible patients had ≥4 healthcare visits related to PH1 spanning ≥6 months (except deceased patients) on or after January 1, 2000, and ≥2 eGFR values ≤45 mL/min/1.73m^2 (or, if age <12 months, 2 serum creatinine values elevated for age [>ULN]). Diagnosis details, laboratory values, clinical events, and imaging data were collected. Patients were assigned to one or both of 2 cohorts, nondialysis (Cohort A) and hemodialysis (Cohort B). Censoring events included participation in a therapeutic clinical trial or initiation of lumasiran. Bone x-ray images were evaluated centrally for evidence of systemic oxalosis and graded using a novel bone oxalosis grading scale.

Results: Fifty-four patients met criteria for Cohort A and 53 for Cohort B; in total, 70 patients were analyzed with up to 21 years of data. Median age at cohort entry was 11.8 years and 12.2 years (Cohorts A and B, respectively); 28 and 13 patients, respectively, met cohort entry criteria prior to PH1 diagnosis. In Cohort A, eGFR slope was –2.8 mL/min/1.73m^2/y (n=25). In Cohort B, patients underwent hemodialysis a median of 6 days/week (range 3–7; n=41) and 3.8 hours/session (range, 2–8; n=31). Overall, 42 patients underwent liver and/or kidney transplantation at least once (median age at first transplant, 15.3 years). Nineteen patients died at a median age of 3.9 years (range, 2.2–34.9); systemic oxalosis was evident in all. Among these, the primary cause of death was transplant-related or occurred within 6 months of transplant in 6 patients. Skeletal oxalosis grade improvement after liver-kidney transplantation generally took more than a year.

Conclusions: Advanced PH1 is associated with high morbidity and mortality; liver and/or kidney transplantation have frequently been pursued. Although liver transplantation corrects the metabolic defect, it also carries significant risk.

Funding: Commercial Support - Alnylam Pharmaceuticals

FR-PO614

The Effect of Slc7a9 Knockout in Dahl SS Rats on Blood Pressure, Metabolism, and Kidney Function

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Background: Amino acid balance plays a crucial role in regulating blood pressure and kidney function, impacting overall cardiovascular health. Mutations in the *Slc7a9* gene, which encodes b(0,+)-type amino acid transporter 1 (b(0,+)AT1) responsible for transporting dibasic amino acids (AA) and cystine, are associated with chronic kidney disease (CKD) and reduced glomerular filtration rate. Patients with cystinuria have a higher risk of developing hypertension due to renal impairment. However, the precise role of AA balance in the development of hypertension and CKD remains incompletely understood. We hypothesized that knockout of *Slc7a9* on the Dahl salt-sensitive background (SS$^{Slc7a9-/-}$) will enhance the excretion of dibasic AAs and disrupt AA homeostasis, thereby affecting blood pressure and kidney function.

Methods: The *Slc7a9*$^{-/-}$ rat model was generated on the Dahl SS background by CRISPR/Cas9. The mutation was confirmed by RT-qPCR and Western blotting. Transcriptomic, proteomic, and targeted metabolomic analyses were performed.

Results: Both male and female knockout rats exhibited reduced body weight, hepatic steatosis, lower diuresis, and both hexagonal and needle crystals in urine sediments. Loss of function of b(0,+)AT1 increased the fractional excretion of several AAs, most notably arginine (0.25 ± 0.1 & 76 ± 18 %, p<0.003), lysine (0.13 ± 0.03 & 39 ± 9 %, p<0.003), 3-methylhistidine (1.3 ± 0.5 & 36 ± 9 %, p<0.003) and ornithine (0.1 ± 0.04 & 21 ± 5 %, p<0.002). Regarding urine metabolites related to the tricarboxylic acid cycle, we observed a decrease in acetoacetic acid and an increase in glutaric and citric acid in *Slc7a9*$^{-/-}$ rats. Following the high salt (4% NaCl) diet for 3 weeks, female Slc7a9$^{-/-}$ rats but not male Slc7a9$^{-/-}$ rats displayed higher mean arterial pressure compared to Slc7a9$^{+/+}$ (184 ± 10 & 144 ± 6 mmHg). The following proteomic and transcriptomic analyses uncovered several pathways that exhibited differential regulation between *Slc7a9*$^{+/+}$ and *Slc7a9*$^{-/-}$. For instance, it was found that "α-amino acid-", "cellular-" and "glutamine family AA" metabolic processes were targeted.

Conclusions: Based on our data, it can be inferred that the knockout of Slc7a9 disrupts AA metabolism, which likely contributes to the effects on blood pressure and metabolic processes.

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FR-PO615

Nine New Genetic Associations with Medullary Sponge Kidney (MSK) and Successful Pain Therapy with Rimegepant

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Background: MSK has been associated with glial derived neurotrophic factor(GDNF) mutations in 15 % of patients(pts). Chronic kidney pain occcurs in 80% of MSK pts (D Goldfarb, J Nephrol 81: 537, 2018).

Methods: We studied 15 consecutive radiologically confirmed MSK pts, 2 male and 13 female. 24 hour urinary metabolic changes were studied & gene mutations using Renasight, (Natera, Austin, TX).were performed. Since the kidney sensory afferent nerve fibers in the tubules, pelvis, & ureters are mediated by calcitonin gene-related peptide(CGRP) we studied the effects of eresumab 70 & 140 mg/month subcut & rimegepant(R) 75 mg po qod (both block CGRP activity) to relieve kidney pain in the 6 pts with migraines & MSK. Eresumab caused GI upset in all 6. Chronic kidney pain was assessed before R & after 3 & 6 months of R utilizing the numeric pain rating scale.

Results: Urine studies revealed hypercalciuria > 250 mg/d in 5/15, hypocitraturia < 200 mg/d in 6/15 pts, hyperuricosuria > 700 mg/d in 4/15 pts and none had hyperoxaluria. 13 pts had at least 1 urine abnormality & 14/15 had normal electrolytes without acidosis. Two pts had no mutations & none had GDNF mutations. 13 pts have new mutations associated with MSK: Two pts have Cystinuria: SLC7A9 & SLC3A1. Two pts have Alport's syndrome : COL4A4. One pt has Ehler Danlos Syndrome: COL5A1 One pt has Noonans's Syndrome: PTPN11 Two pts have Smith Lemli Opitz Syndrome: DHCR7. One pt has Pallister Hall Syndrome: CLI3. Two pts have nephronopthisis: NPHP2 & NPHP3. One pt has a defect in both FGFR-2 & Xanthinuria: MOCOS. One pt has proximal renal tubular acidosis: SLC4A4. Six pts had refractory migraines. The X +SEM pain score before R was 8.9+/- .4 & was reduced to 5.7+/-.3 at three & 6 months of R therapy, respectively, (p<0001) allowing 3 pts to lower their chronic opioids.

Conclusions: We conclude: all nine new gene mutations associated with MSK can cause structural renal changes especially in the interstitium and medulla & no pt had GDNF mutations. If MSK pts have migraines R can be a promising new successful chronic pain therapy confirming that CGRP is an important mediator of kidney pain in MSK.

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FR-PO616

A New Mouse Model for Dent Disease 1 with Impaired Mitochondrial Metabolism Develops CKD

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Background: Dent disease 1 is a rare tubular disorder characterized by low-molecular-weight (LMW) proteinuria, hypercalciuria, and progressive renal failure. It is caused by inactivating mutations of the *CLCN5* gene encoding for the 2Cl$^-$/H$^+$ exchanger ClC-5. In the kidney, ClC-5 is mainly expressed in early endosomes of proximal tubules (PT) cells where it is thought to optimize the function of the vacuolar H$^+$-ATPase to ensure the proper endocytosis of LMW proteins. To better understand the cellular mechanisms involved in Dent disease, we have generated a *Knock-In* (KI) mouse model carrying a patient mutation of ClC-5. Preliminary data from the lab show altered PT endo-lysosomal function and consequent impaired autophagy. Whether this altered pathway could impact mitochondrial metabolism was previously unknown. Therefore, we used this novel mouse model to evaluate the contributing factors of the progressive metabolic disorder observed in Dent disease.

Methods: The renal phenotype of WT and KI ageing mice was explored using metabolic cages. Their mitochondrial distribution and function were assessed with immunofluorescence, western blot, transmission electronic microscopy, and targeted urinary metabolomic analysis.

Results: 10-month-old KI showed an impaired general renal function accompanied by increased fractional excretions of calcium, phosphate, magnesium, indicating a PT dysfunction. KI mice expressed more Lipocalin 2, a tissue damage marker, in their kidneys and showed its increased excretion. These changes were associated with renal fibrosis and inflammation. The renal expression of PGC1 alpha, a marker of mitochondrial biogenesis, was increased between 4 to 10 months in KI mice. It was associated to an increased mitochondrial mass at 10 months. The shape of PT mitochondria from KI mice was altered even at young stages. Additionally, the loss of metabolites crucial for mitochondrial metabolism (alpha ketoglutarate, oxaloacetic acid, etc.) was highlighted in KI mice.

Conclusions: In conclusion, our mouse model suggests that altered endocytosis, consequent to ClC-5 mutation, impairs autophagy and leads to the accumulation of defective mitochondria. This would therefore potentiate renal damages of various origins with age, and a subsequent renal failure. This study opens up new perspectives for the development of therapeutic strategies.

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FR-PO617

Phosphor-Modified KLHL3 Knockin Mice Reveal WNK1/4-Independent SPAK/OSR1-NCC Activation in Pseudohypoaldosteronism Type II (PHAII)

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Background: We have successfully created missense *Klhl3*$^{M131V/+}$ knockin (KI) mice (human *M78V* mutation in BTB domain) and nonsense *Klhl3*$^{W523X/+}$ KI mice (human *W470X* mutation in Kelch domain) to decipher the molecular mechanisms of PHAII. However, the phosphorylation site (S433) on *KLHL3* regulated by several stimuli such as angiotensin II, insulin, and calcineurin inhibitors in PHAII have not been examined *in vivo*.

Methods: We generated and analyzed two missense *Klhl3* KI mice with phosphor-modified at *S486* site. The phenotypes of phosphomimetic *Klhl3*$^{S486D/+}$ mice (human *KLHL3* S433D mutation) and phosphodefective *Klhl3*$^{S486G/+}$mice (human *KLHL3* S433G mutation) were examined. The associated protein expression of their kidney tissue was evaluated by western blot and immunofluorescence.

Results: Unlike the Wnks-dependent Spak/Osr1-Ncc activation in *Klhl3*$^{M131V/+}$ and *Klhl3*$^{W523X/+}$ KI mice, both *Klhl3*$^{S486D/+}$ and *Klhl3*$^{S486G/+}$mice recapitulating typical phenotypes of PHAII exhibited an enhanced phosphorylation of Spak/Osr1-Ncc but the "unchanged" Wnk1/4 and Klhl3 expression. Both phosphor-modified *Klhl3* KI mice demonstrated a significantly increased expression of calcium binding protein 39 (Cab39) known to interact and stimulate Spak/Osr1, as compared to those in WT littermates, *Klhl3*$^{M131V/+}$ and *Klhl3*$^{W523X/+}$ mice. *In vitro* study showed that endogenous Cab39 interacted with KLHL3 and Cul3 complex, but not with WNK1/4. The simulation model demonstrated that KLHL3-WT and phosphor-modified KLHL3 mutants had different binding regions with Cab39.

Conclusions: Phosphor-modified *KLHL3* KI mice exhibiting PHAII reveal a novel Wnks-independent Spak/Osr1-Ncc activation. Whether the phosphorylated status of KLHL3 S433 could affect its binding ability with Cab39 as a substrate for ubiquitination needs to be well validated.

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FR-PO618

Tracking Molecular and Phenotypic Changes in Kidney Cells in 2D and 3D Cultures Following DHA Exposure: An Approach to Understand Cellular Changes in Adenine Phosphoribosyltransferase (APRT) Deficiency

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Background: Adenine phosphoribosyltransferase (APRT) deficiency is a rare autosomal recessive disorder of adenine metabolism that results in the generation and renal excretion of 2,8-dihydroxyadenine (DHA), leading to kidney stones and crystal nephropathy characterized by inflammation and fibrosis. The aim of this study was to create a cell culture model to investigate DHA crystal-induced kidney injury in order to identify potential targets for clinical intervention.

Methods: Three kidney cell lines, MDCK, HK-2, and HEK293, were used in this study. All cell lines were treated with DHA at concentrations comparable to those found in the urine of untreated humans with APRT deficiency, both in monolayer and 3D assays. Furthermore, siRNA against *APRT* was used to knock down the gene in HEK293 and HK-2 cells. The readout assays included cell viability, RT-PCR, western blotting, and immunostaining.

Results: Following DHA exposure, decreased viability was observed in all cell lines. HEK293 cells exhibited increased expression of IL-8 following DHA treatment, indicating an inflammatory response. MDCK cells showed increased expression of N-cadherin when treated with high concentrations of DHA compared to the control, suggesting an epithelial–mesenchymal transition (EMT) response. Additionally, both HEK293 and MDCK cells showed increased CD44 expression, which is believed to be important for crystal binding to renal epithelial cells, upon exposure to higher DHA concentrations. When cultured in 3D condition with the addition of DHA, MDCK cells were still able to form polarized structures, and DHA accumulated within and around the structures. HEK293 cells form solid colonies and with the addition of DHA, the DHA accumulates inside the colonies. APRT expression was significantly reduced in HEK293 and HK-2 cells after successful knockdown, and HEK293 cells exhibited elongated protrusions.

Conclusions: We have established a cell culture model that captures kidney cell alterations observed in APRT deficiency. Data suggest that DHA treatment of these cell lines *in vitro* induces an inflammatory response, EMT, and reduces cellular viability. This cell culture model provides insights into the inflammatory response and potential disease-specific targets for clinical intervention.

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FR-PO619

Acyl-CoA Synthetase Short-Chain Family 2 Is a Renal Disease Risk Gene: Controlling De Novo Lipogenesis in Kidney Tubules

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Background: Worldwide, over 800 million people are affected by kidney disease, yet its pathogenesis remains elusive, hindering the development of novel therapeutics.

Methods: In this study, we employed kidney-specific expression of quantitative traits and single-nuclear open chromatin analysis to show that genetic variants linked to kidney dysfunction on chromosome 20 target the acyl-CoA synthetase short-chain family 2 (ACSS2). By generating ACSS2 knock-out mice, we demonstrated their protection from kidney fibrosis.

Results: Our analysis of primary tubular cells revealed that ACSS2 regulates de novo lipogenesis (DNL), causing NADPH depletion and increasing ROS levels, ultimately leading to NLRP3-dependent pyroptosis. Additionally, we discovered that pharmacological inhibition or genetic ablation of fatty acid synthase safeguarded kidney cells against profibrotic gene expression and prevented kidney disease in mice. Lipid accumulation and the expression of genes related to DNL were elevated in the kidneys of patients with fibrosis.

Conclusions: Our findings pinpoint ACSS2 as a critical kidney disease gene and reveal the role of DNL in kidney disease.

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FR-PO620

Mitochondrial Reactive Oxygen Species (ROS) Triggers Karyomegalic Interstitial Nephritis (KIN) Pathogenesis in FAN1-Deficient Kidneys

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Background: Karyomegalic interstitial nephritis (KIN) is a genetic adult-onset chronic kidney disease (CKD) characterized by genomic instability and mitotic abnormalities in the tubular epithelial cells. KIN is caused by recessive mutations in the FAN1 DNA repair enzyme. However, the endogenous source of DNA damage in FAN1/KIN kidneys has not been identified.

Methods: KIN was induced in 12-week-old *Fan1* KO mice by employing low dose cisplatin injury models: one mimicking AKI (1 x 2 mg/kg cisplatin), and another CKD (weekly 5 x 2 mg/kg cisplatin). Coincident with cisplatin, mice were administered a novel mitochondrial ROS and electron scavenger JP4-039 at a dose of 10 mg/kg. Histological analysis was performed using PAS and HE. Markers of tubular injury, DNA damage and fibrosis were assessed by IF and IHC. Human kidney proximal tubular cells (PTECs) were used to model FAN1 loss of function *in vitro*. RNA-seq analysis was performed to identify transcriptional changes in KIN. Mitochondrial OXPHOS was measured using the Oroboros Oxygraph-2k System. Metabolite measurements were preformed using YSI 7100 Bioanalyzer.

Results: Transcriptional profiling of kidneys with KIN revealed a significant downregulation of genes involved in mitochondrial energy metabolism - OXPHOS, fatty acid oxidation (FAO) and peroxisomal function. Metabolic analysis of FAN1KO PTECs showed a defect in respiratory chain, increased oxidative stress and a shift to increased lactate secretion. Similarly, *Fan1* KO kidneys revealed marked increase in oxidative DNA damage (8-OHdG), lipid peroxidation (4-HNE) and tubular lipotoxicity (OilRedO) after AKI or CKD. Treatment with mitochondrial ROS scavenger reduced the level of oxidative lesions in *Fan1* KO kidneys, mitigated tubular damage and blocked the formation of KIN.

Conclusions: Loss of *FAN1* causes defective mitochondrial metabolism and increased ROS generation in the kidney which give rise to oxidative DNA lesions and results in KIN. Blocking mitochondrial ROS protects *Fan1* KO kidneys from DNA damage accumulation, mitigates tubular injury and improves kidney function in mice.

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FR-PO621

A Novel Renal Collecting Duct Model to Study Secondary Nephrogenic Diabetes Insipidus Associated with Cystinosis

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Background: Cystinosis is a severe lysosomal disorder caused by mutations in the *CTNS* gene, encoding for the lysosomal transporter cystinosin, resulting in the accumulation of cystine throughout the body. It manifests as Renal Fanconi syndrome in the first months of life, and lastly progresses into end stage renal failure. Secondary Nephrogenic Diabetes Insipidus (NDI) has been reported as a secondary complication of cystinosis due to the resistance to vasopressin, a key hormone that, in the collecting duct activates the vasopressin-sensitive water channel Aquaporin-2 (AQP2), regulating water reabsorption. Over the past years, the development of several *in vivo* and *in vitro* models of cystinosis has contributed to understand the pathophysiology of this severe disease. Nevertheless, the molecular mechanisms causing the secondary NDI phenotype have not been investigated due to the lack of collecting duct cellular models.

Methods: A CRISPR/Cas9 *CTNS* knock out model derived from MCD4 cells, a mouse renal collecting duct cell line, stably expressing human AQP2 and vasopressin receptor 2 (V2R), was established and validated by Sanger sequencing, qPCR and mass spectrometry (MS). Osmotic water permeability measurements in presence or absence of Desmopressin (DDAVP), a synthetic vasopressin analog to investigate AQP2 function were carried out.

Results: Sanger sequencing analysis demonstrated that *CTNS* was efficiently CRISPRed. This result was further confirmed by a significant reduction of *CTNS* transcript levels, up to 65%, and a significant accumulation of cystine by MS in CRISPRed *CTNS* KO cells with respect to wt. Preliminary studies on osmotic water permeability indicate that, compared to control, in *CTNS* CRISPR cells, the osmotic water permeability does not significantly increase in response to DDAVP treatment, consistent with an impairment of the vasopressin-AQP2 pathway.

Conclusions: We provide here the first *CTNS* KO collecting duct *in vitro* model useful for the study of secondary NDI in cystinosis.

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FR-PO622

Sox2/CD63-GFP Transgenic Rat: A Novel Model for Nephrogenic Diabetes Insipidus

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Background: Tetraspanins are transmembrane proteins with four membrane domains that form complexes with other membrane proteins, playing diverse roles in physiological functions. The tetraspanins CD9, CD63, and CD81 are well-established exosome markers, while CD151 variants have been associated with glomerular disease. Previous studies using transgenic (Tg) rats expressing CD63-GFP under the Sox2 promoter, aimed at visualizing exosomes, revealed prominent symptoms of polydipsia and polyuria (Yoshimura et al., Disease Models & Mechanisms, 2018). This study aims to explore the pathophysiological characteristics of Tg (Sox2/CD63-GFP) rats.

Methods: We assessed body weight, food consumption, water intake, blood pressure, serum urea nitrogen (UN), creatinine (Cre), urine volume, and urine osmolality in Sox2/CD63-GFP rats, along with age- and sex-matched normal littermates. Histological and immunohistochemical analyses of the kidneys were conducted.

Results: Tg rats exhibited lower body weight compared to normal rats, along with approximately 7-8 times higher water intake and urine volume. Serum biochemical analysis indicated elevated UN and Cre levels in Tg rats, suggesting deteriorating renal function. Tg rat kidneys showed significant enlargement and symptoms of hydronephrosis. In normal rat kidneys, AQP3 was distributed laterally, while AQP2 was distributed apically in the collecting ducts. In contrast, Sox2/CD63-GFP rats exhibited reduced AQP2 expression in both the plasma membrane and cytoplasm of the cortical collecting ducts.

Conclusions: Nephrogenic diabetes insipidus, one of the two primary types of diabetes insipidus, primarily results from mutations in the vasopressin receptor or AQP2 in the collecting ducts. The observed symptoms in Sox2/CD63-GFP rats resembled those of diabetes insipidus, characterized by impaired water reabsorption in the kidneys and severe renal manifestations such as polydipsia, polyuria, and hydronephrosis due to excessive urinary output. CD63-GFP expression may disrupt intracellular trafficking of AQP2, given CD63's involvement in intracellular trafficking and protein localization at the plasma membrane.

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FR-PO623

Renal Failure from Bladder Acontractility in Untreated X-Linked Nephrogenic Diabetes Insipidus

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Introduction: A lot is known about about the genetics and molecular pathophysiology of hereditary nephrogenic diabetes insipidus (DI) but there is little information on the long term renal outcome of this condition. Case series show that nephrogenic DI can lead to CKD but the mechanism is unclear. Here we report a patient with untreated x-linked nephrogenic DI who developed renal failure from bladder acontractility.

Case Description: A 45 year old man presented to the emergency room with a distended abdomen and 10lbs weight gain over several weeks. Ultrasound showed a large bladder and bilateral severe hydronephrosis. His serum creatinine was 1.36mg/dl, increased from a 1.2mg/dl previously. Bladder catheterization produced immediate drainage of 7.5L of urine. In the following hours large urine output was noted. The next morning the patient's serum creatinine was 1.5mg/dl, serum sodium 149mEq/L and serum osmolality 307mOsm/L. The urine osmolality was 84mOsm/L, sodium <20 and specific gravity 1.003. An ADH level was elevated at 16.3pg/ml. The patient was diagnosed with nephrogenic DI at birth and lost to follow up since his early teenage years. He has three brothers with DI and an adult son who is not affected. X-linked nephrogenic DI was confirmed by genetic testing showing substitution of guanosine by adenosine at codon 296 of the AVP Receptor 2 gene, introducing an early stop codon. Imaging showed a normal sized prostate, cystoureteroscopy was normal except large bladder capacity and urodynamic studies revealed detrusor acontractility. The patient received fluids and was discharged on HCTZ and with an indwelling Foley catheter. He learned to self-catheterize and four months later his serum creatinine was 1.02mg/dl and his urine output 7 L per day.

Discussion: Patients with nephrogenic DI produce urine volumes in the range of 10-12 L and with a bladder volume of 400ml, they will have to urinate at least 25 times in 24 hours, night and day. Because of Poiseuille's law, increased urine flow leads to increased pressure, causing hydronephrosis and bladder distention which in turn leads to detrusor dysfunction and ultimately bladder acontractility. We suspect this chain of events is a frequent cause of renal failure in DI, preventable by flow reduction via diuretic treatment and reduced osmole diet. Straight catheterization can improve renal function in patients with bladder acontractility.

FR-PO624

A Rare Case of Pseudohypoparathyroidism Type 1B Diagnosed by Methylation-Specific Multiplex Ligation-Dependent Probe Amplification (MS-MLPA)

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Introduction: Pseudohypoparathyroidism (PHP) is a rare disorder characterized by hypocalcemia, hyperphosphatemia, and increased serum parathyroid hormone (PTH). Pseudohypoparathyroidism type 1B (PHP1B) is a subtype of PHP characterized by isolated renal PTH resistance, usually without physical abnormalities such as Albright hereditary osteodystrophy or other endocrine abnormalities. We present a rare case of PHP1B presented as hypocalcemia with elevated PTH.

Case Description: A 33-year-old man visited the nephrology department outpatient clinic with abnormal laboratory finding. His serum calcium level was 5.9 mg/dL in recent health exam. He had a history of dyslipidemia without any medication. He complained of tingling sensation in hands and eyelid twitching. On physical examination, he showed Chvostek's sign. His laboratory findings included a serum calcium level of 7.7 mg/dL, a serum ionized calcium level of 1.74 mEq/L, a serum phosphorus level of 4.7 mg/dL, a serum creatinine level of 0.9 mg/dL and a serum PTH level of 284.2 pg/mL. A serum 25-hydroxyvitamin D level of 27.5 ng/mL and a serum 1,25-dihydroxyvitamin D level of 28.2 pg/mL. Under strong suspicion of PHP, DNA sequence analysis and methylation specific multiplex ligation-dependent probe amplification (MS-MLPA) of the GNAS and STX16 genes was performed. MLPA analysis of GNAS gene revealed methylation abnormality in multiple differentially methylated region (DMR). Finally, he diagnosed as PHP1B. He is on outpatient follow-up with adequate calcium replacement and no specific symptoms.

Discussion: The exact prevalence of PHP is not yet known. PHP1B can be sporadic or familial. The genetic characteristics of most sporadic PHP1B is still not well-known but GNAS imprinting abnormalities, hypomethylation at A/B DMR has been reported. Symptoms of PHP1B usually begin in childhood due to low calcium levels and may include numbness, seizures, tetany, cataracts, and dental problems. However, as in our case, specific symptoms may not occur until adulthood. Therefore, when evaluating the cause of hypocalcemia, it is necessary to differentiate PHP1B even in adults, especially in cases with hyperphosphatemia and high PTH levels.

FR-PO625

Effects of N-Acetylcysteine on Evolution of Kidney Function in Patients with Acadian Variant Fanconi Syndrome

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Background: Acadian variant of Fanconi syndrome (AVFS) is an autosomal recessive disease that leads to chronic kidney failure, proximal tubule dysfunction and pulmonary fibrosis, and is present only in the Acadian people. This condition is caused by a mutation in the NDUFAF6 gene which results in mitochondrial dysfunction and oxidative damage to the kidneys. The objective of this study is to evaluate the effect of N-acetylcysteine (NAC), an antioxidant, on the progression of loss of renal function in patients with AVFS.

Methods: A retrospective self-controlled study was conducted with 4 individuals diagnosed with AVFS, comprising 100% of the known active population who were neither transplanted nor on dialysis. Medical records were reviewed to obtain information regarding glomerular filtration rate (eGFR), serum creatinine, blood pressure, and medications. eGFR was calculated using the Schwartz formula for patients under 18 years of age and the MDRD formula for adults. The changes in GFR before and after NAC prescription were analyzed for each patient to assess the effect of NAC on disease progression, and these changes were also compared with past AVFS patients who had never received NAC.

Results: NAC was projected to delay the need for kidney replacement therapy by an average of 135 months in the treated patients who otherwise would have required it by a mean age of 28 years, which is comparable to past patients who underwent kidney replacement therapy at an average age of 30.

Conclusions: This study demonstrated that NAC appears to have a beneficial effect on the progression of GFR in patients with AVFS, delaying the projected need for kidney replacement therapy by over 11 years. Further studies are needed to evaluate the potential benefits of NAC in other chronic kidney conditions.

FR-PO626

ABCC6 and CKD: The Phenotypic Expansion of Pseudoxanthoma Elasticum

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Background: Adenosine triphosphate (ATP) Binding Cassette Subfamily C Member 6 *(ABCC6)* is a transporter nucleotide that mediates cellular efflux of ATP, which is hypothesized to prevent calcification. In chronic kidney disease (CKD) patients, vascular calcification is prevalent but not completely understood. Monogenic cause occurs in 10% of CKD patients, however monogenic causes of vascular calcification in CKD have yet to be identified. Both recessive and dominant variants in *ABCC6* are known to cause Pseudoxanthoma Elasticum (PXE), a heritable disorder characterized by the accumulation calcium deposits and subsequent vascular calcification involving elastic fibers in the skin, eyes, and cardiovascular system. Data suggests PXE is associated with nephrolithiasis and nephrocalcinosis, with reports also suggesting higher prevalence of end-stage kidney disease (ESKD), glomerulonephritis, and renovascular hypertension. This is hypothesized to be secondary to elastic fiber fragmentation and mineralization in renal arteries. In addition, knockout mice models in *ABCC6* developed calcification in the blood vessels, prominently in the renal cortex, in association with papillary calcification.

Methods: To identify monogenic kidney disease associated with vascular calcification phenotype, we performed whole exome sequencing (WES) in 94 families with CKD, looking for pathogenic variants in the gene *ABCC6*.

Results: We identified 2 heterozygous, loss of function variants in *ABCC6* in 2 families with CKD of unknown etiology (c.1999delG p.A667fs and c.C3421T:p.R1141X). No formal diagnosis of PXE was established prior to analysis. Affected individuals were reviewed post exome analysis and were found to exhibit a broad spectrum of extra-renal phenotypes including eye and skin pathology, and severe peripheral vascular disease. Renal phenotype included a history of kidney stones along with CKD of unknown etiology progressing to ESKD in multiple family members.

Conclusions: We identified loss of function variants in *ABCC6* in two families with CKD by reverse phenotyping for PXE. This report suggests the need for phenotype expansion of PXE to include CKD. Further work is required to establish the exact role in disease pathogenesis but preliminary data suggests that heterozygous variants in ABCC6 may lead to multi-system vascular calcification disease, also affecting the kidney.

FR-PO627

Utility of a Renal Genetics Clinic: A Canadian Prospective Cohort

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Background: Genetic kidney disease (GKD) is more prevalent than previously considered, with 1 in 10 chronic kidney disease (CKD) patients affected. When correct inclusion criteria for GKD is used, 34-67% of patients can have a genetic diagnosis. Genomic testing using gene-panel or exome sequencing (ES) can confirm GKD through detection of mutations in genes known to cause CKD. Unfortunately, widespread integration into clinical practice has been hampered by small studies and highly selective populations predominately performed in research rather than clinical settings. This study aims to prospectively demonstrate the utility of a renal genetics clinic in a Canadian cohort.

Methods: We analyzed data from a cohort of patients (n=174 families, n=209 affected patients) referred to a renal genetic clinic between September 2019 and April 2023. Testing strategy was firstly to perform gene-panel testing, and if negative or unsuitable, ES was performed. Testing was performed for the detection of mutations in genes suspected to cause the specific subtype of CKD. Mutations are classified according to the American College of Medical Genetics guidelines, with pathogenic and likely pathogenic variants being causative.

Results: We identified a causative mutation in a gene known to cause CKD in 38% of patients (n=80/209). Gene panel testing, performed as the first line of investigation, detected the underlying molecular cause of CKD in 31% of patients tested (n=44/142). Primary ES was performed as the first test in patients with CKD of unknown etiology (CKDu) and had a solve rate of 18% (n=8/45). In patients whom gene-panel was negative or not possible (n=82), secondary ES analysis was performed and confirmed the suspected clinical diagnosis in 26% of patients (n=21/82). For solved patients (n=80), there were many clincial outcomes, including change of diagnosis. Of note, 48% of solved patients had a pre-priori diagnosis of CKDu, but all receied a diagnosis after testing. Other important clinical outcomes include, avail of genetic counselling, resolved diagnostic confusion, and correction of diagnosis.

Conclusions: We show that in a Canadian cohort of adults referred to a renal genetic clinic, genomic testing has utility by confirming the cause of genetic kidney disease in 38% of patients. Genetic sequencing also has significant impacts on clinical management and patient outcomes.

FR-PO628

Diagnostic Utility and Clinical Impact of Genomic Testing in Adolescent and Adult Kidney Disease Patients with Suspected Monogenic Etiology by Establishing an Integrated Kidney Genetics Service

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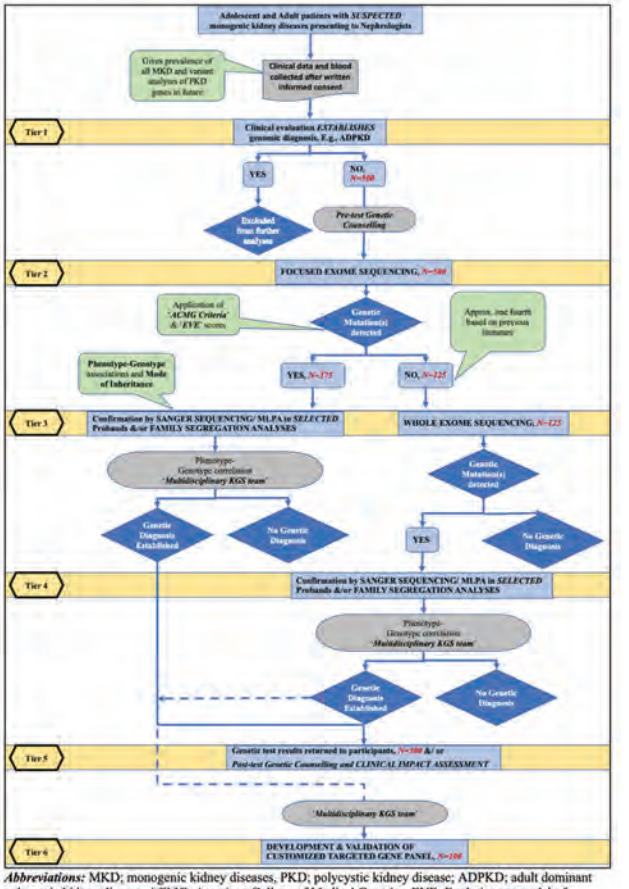
Background: Though studies have shown positive impact of genomic testing in pediatric population, the diagnostic utility and the clinical impact in real world situations faced by nephrologists when managing adolescent and adult patients with suspected monogenic kidney disease is not known.

Methods: It is a prospective observational pragmatic cohort study. Consecutive patients satisfying the inclusion and exclusion criteria was recruited after written informed consent and pre-test genetic counselling. Genetic testing was by exome sequencing and results returned with post- test genetic counselling. The whole exome sequencing was done for all probands and the bio-informatics was performed using in-house and commercial (VarSeq, Golden Helix) pipeline to identify diagnostic variants for patients' renal disease by data scientist and nephrologist trained in genetics. Segregation testing was done on parents of probands to confirm inheritance pattern if required. The diagnostic utility and the clinical impact was assessed at 3 months of patient follow-up following detailed phenotype-genotype correlations.

Results: More than 100 patients were prospectively recruited for this study. Diagnostic utility was 60% and covered the whole spectrum of renal diseases. Phenotypic enrichment prior to recruitment is essential for optimum test usage. There was definite clinical impact and cascade testing could be offered to family members. Cost was significantly decreased with in-house bioinformatics pipeline.

Conclusions: In-house generation of database and bio-informatics performed together nephrologist in the team, helps to correlate the phenotype and genotype tightly and identify disease causing variants by ACMG criteria.

Funding: Government Support - Non-U.S.



Abbreviations: MKD; monogenic kidney diseases, PKD; polycystic kidney disease; ADPKD; adult dominant polycystic kidney disease, ACMG; American College of Medical Genetics, EVE; Evolutionary model of Variant Effect, KGS; Kidney genetics service, MLPA; Multiplex Ligation-dependent Probe Amplification

FR-PO629

Developing Best Practices for Returning Genetic Results to Participants in Nephrology Research: A Study of the CureGN Network

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Background: Returning genetic results (RoR) from research is a growing practice aiming to improve patient care and to serve as a trust-building measure by showing reciprocity in health research. No guidelines for RoR in nephrology research currently exist, leading to diverse practices across research sites which limits the ability to understand the impacts of RoR on research participants. We developed a workflow for RoR in the Cure Glomerulonephropathy Network (CureGN) and a study to assess its implementation and the medical and psychosocial impacts of RoR.

Methods: Genome sequencing was performed on 1957 CureGN participants. We identified 3 variants' groups: variants consistent with kidney diseases; APOL1 high risk genotypes; and variants in actionable genes per ACMG/AMP's guidelines. A multidisciplinary team developed a framework for RoR, assessed its acceptability and barriers via a survey with nephrologists, followed by webinars with nephrologists, research participants and parents of pediatric participants, refined and finalized the workflow. We developed pre- and post-RoR surveys for parents, research participants (adults and adolescents), and treating nephrologists to assess satisfaction, medical and psychosocial impacts of the RoR, and barriers for Post-RoR care. With an NIDDK grant, the RoR is free to CureGN participants.

Results: Based on findings from the nephrologists' survey and webinars, we will return the 3 variants' groups. A centralized RoR workflow is implemented by Columbia University (CU) and the CureGN Data Coordinating Center (DCC) at the University of Michigan. Given privacy protections, we instituted a multistep process to inform participants with positive results (n=270): CU will share relevant CureGN IDs with the DCC to inform sites on who to invite for RoR. Interested participants will contact CU's genetic counselors (GCs) to discuss the RoR study, consent and provide a DNA sample for clinical confirmation. GCs will return the results to participants and their nephrologists, add them to the medical records, and send out the surveys.

Conclusions: Findings will inform about the feasibility of, and best practices for, RoR in a large, racially and ethnically diverse Network and will be generalizable to other consortia.

Funding: NIDDK Support

FR-PO630

Pathogenic Genes in the Mesoamerican ESRD Population

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Background: Dialysis clinics in the New York area treat a large population of immigrants originating from Central and Northern South America. Many do not have an etiology for ESRD, which may result from Mesoamerican (MA) Nephropathy, a pathology not well understood. This study assesses if there are underlying diseases due to genetic variances that predispose these patients to ESRD.

Methods: MA subjects were recruited prospectively from Atlantic Dialysis Management Services units in New York City and Dialysis Clinic Inc. from Westchester Medical Center, along with Non-Mesoamerican subjects (n-MA). Saliva swabs were acquired and processed via Renasight genetic kits. 385 genes were assessed for pathogenic or likely pathogenic variants.

Results: 228 subjects were recruited, of which 123 were MA. 11% of MAs were found to have 23 pathogenic or likely pathogenic variants of positive genes. Of these 23 cases, the most common variants were identified in genes associated with Alport Syndrome (*COL4A3* and *COL4A4*) at a frequency of 26% (6/23). The variants in genes associated with Polycystic Kidney Disease (PKD) (*PKD1* and *PKD2*) also had a frequency of 22% (5/23). Of the 105 n-MA subjects, 20% of them were found to have 39 pathogenic or likely pathogenic variants of positive genes. The frequency of pathogenic variants of genes encoding for Alport Syndrome is 10%, and the frequency of PKD is 8%. The frequency of pathogenic variants of genes encoding for Alport Syndrome is 10% (4/39), and the frequency of PKD is 8% (3/39). The incidence of the APOL1 risk allele in the n-MA population was 28% (11/39), compared to 4% (1/23) in the MA population.

Conclusions: The frequency of genes related to Alport's Syndrome and PKD were increased in MAs. The higher frequency of APOL1 risk alleles in the n-MA contributes to a higher incidence of variants of positive genes, but it is unclear if this led to an underlying genetic cause of kidney disease. Although pathogenic variants were found, their presence does not clearly point to genetic etiologies for MA Nephropathy.

Funding: Commercial Support - Natera

Left: n-MA pathogenic variantsRight: MA pathogenic variants

FR-PO631

Association Between Sickle Cell Disease and Mortality and Hospitalizations Among In-Center Hemodialysis Patients

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Background: Sickle cell disease (SCD) is the most common hemoglobinopathy and genetic disorder worldwide, and a significant cause of end stage kidney disease (ESKD). Despite this, our understanding of adverse outcomes in SCD patients undergoing in-center hemodialysis (ICHD) is limited by small sample sizes, non-granular data and significantly different control groups resulting in residual confounding. The purpose of this preliminary study was to assess mortality and hospitalizations within a SCD patient population treated with ICHD for at least 6 months.

Methods: This retrospective study identified SCD and non-SCD patients receiving ICHD treatment from Fresenius Kidney Care (FKC) between 1-1-2017 and 12-31-2021. The baseline period was considered the first 6 months of treatment at FKC. Incident and prevalent ESKD status was defined as less than or more than 4 months since first dialysis date at the start of baseline, respectively. 602 incident and 541 prevalent SCD patients were matched to non-SCD controls using propensity score matching with confounders including incidence/prevalence status (exact match), sex, race, ethnicity, age, and vascular access type. All-cause mortality was analyzed using the Cox proportional hazards model, with the number and duration of hospitalizations being modeled using generalized estimating equations with a Poisson distribution and log link function.

Results: a) Incident Patients: Compared to matched controls, incident SCD patients were 45% more likely to pass away at any given time point ($p<0.001$). SCD patients also had higher rates of hospitalizations per year (2.8 vs 1.6, $p<0.001$) and days hospitalized per year (8.2 vs 4.2, $p< 0.001$) than controls. **b) Prevalent Patients:** Compared to matched controls, prevalent SCD patients were 23% more likely to pass away at any given time point ($p< 0.023$). SCD patients also had higher rates of hospitalizations per year (2.8 vs 1.6, $p<0.001$) and days hospitalized per year (9.6 vs 5.0, $p< 0.001$) than controls.

Conclusions: This preliminary study provided evidence that SCD patients who have received ICHD treatments for at least 6 months remain at an elevated risk for all-cause mortality and hospitalizations compared to similar, non-SCD patients. The all-cause mortality risk was attenuated by prevalent status.

FR-PO632

Patient Mortality and Graft Failure Risks in Transplant Recipients with Kidney Failure Secondary to Genetic Kidney Disease Compared to People with Other Kidney Diseases

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Background: There is limited population-level data on long term outcomes of people with genetic kidney disease (GKD) after kidney transplantation. This study aimed to characterise clinical outcomes in people with GKD after kidney transplantation and compare them to those of people with other kidney diseases.

Methods: Data on first kidney transplants between 1 January, 1989 and 31 December, 2020 were extracted from the Australia and New Zealand Dialysis and Transplant (ANZDATA) registry. GKDs were classified as majority or minority monogenic. People with other primary kidney diseases were included as the comparator group. Outcome measures were mortality and graft failure. Unadjusted and adjusted hazard ratios (AHRs)

were calculated using Cox proportional hazard regression models. Sensitivity analyses were completed to test the effect of major diagnoses (e.g. autosomal polycystic kidney disease and reflux nephropathy) within GKD groups.

Results: 21,860 transplant recipients were included. GKDs were associated with reduced mortality in kidney transplant recipients on univariable analyses. This correlation was not statistically significant on multivariable analyses (majority monogenic AHR 0.92, 95% CI 0.84-1.00; minority monogenic AHR 0.91, 95% 0.82-1.02). Majority monogenic GKDs correlated with reduced graft failure compared to other kidney diseases on univariable (Figure 1) and multivariable analyses (AHR 0.79, 95% CI 0.71-0.87). This result was attributed to reduced graft failure in recipients with polycystic kidney disease which constituted 91.9% of the majority monogenic GKD group.

Conclusions: This binational registry analysis found that people with GKD had similar mortality but reduced graft failure after kidney transplant. This is the first study to provide a broad longitudinal overview of clinical outcomes in kidney transplant recipients with GKD.

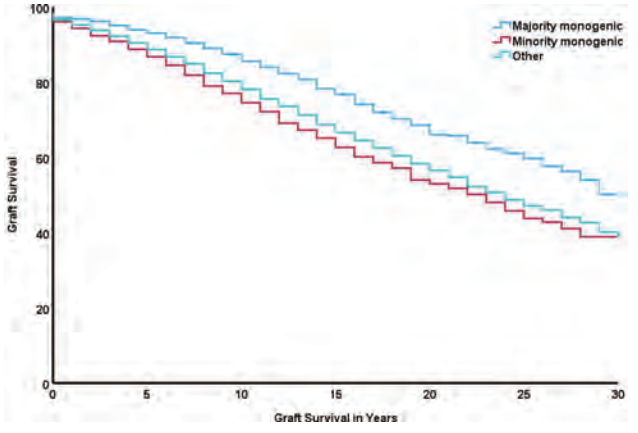

Figure 1 – Kaplan Meier curve for graft failure in kidney transplant recipients

FR-PO633

Evaluating the Association Between Maternal Dietary Vitamin A Status and Fetal Kidney Development

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Background: Vitamin A is a fat-soluble vitamin that plays a crucial role in the development of fetal organs. In vitro, studies have indicated that the number of nephrons, which are functional units in the kidney, is impacted by the presence and quantify of vitamin A. However, the effect of maternal dietary vitamin A status on fetal kidney development remains unknown. As abnormal kidney development can contribute to later renal disease, it is important to identify modifiable factors impacting kidney development, such as dietary intake of vitamin A.

Methods: An IRB-approved study recruited pregnant women who completed a food survey (DHQ III) to evaluate dietary vitamin A intake between 24-28 weeks of gestation. Vitamin A intake was measured in retinol activity equivalents (RAE, mcg/day), with <770 mcg/day being deemed inadequate. Fetal ultrasound between 16-20 weeks gestation measured bilateral fetal kidney size and volume. A post-natal retroperitoneal ultrasound was performed 24-48 hours after birth. Kidney length and volume were compared between maternal vitamin A sufficient and deficient groups using the Mann-Whitney U test. A p-value of <0.05 was considered statistically significant.

Results: A total of 39 women were included in this analysis, with a median age of 32 years. The median RAE was 661.50 RAE (without supplements) and 1200.00 RAE mcg/day (with supplements). There were no significant differences in fetal right kidney measurements, length, and volume ($p = 0.94$ and $p = 0.44$), infant right kidney length and volume ($p = 0.94$ and $p = 0.57$) and change in right kidney length and volume ($p = 0.78$ and $p = 0.62$) across two groups. Similarly, no significant differences were noted in fetal left kidney length and volume ($p = 0.39$ and $p = 0.10$), infant left kidney length and volume ($p = 0.20$ and 0.10) and change in left kidney length and volume ($p = 0.72$ and 0.43) across two groups.

Conclusions: Our study did not find any difference in fetal or infant kidney measurements between maternal vitamin A status and fetal and infant kidney measurements. Furthermore, maternal vitamin A status did not impact kidney growth reported as a change in kidney length or volume. Larger, adequately powered studies should be conducted.

FR-PO634

The Underappreciated Renal Phenotype of EGFR Deficiency: Could It Be that Complex?

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Introduction: Epidermal Growth Factor Receptor (EGFR) is a cell signaling receptor implicated in cell proliferation, survival, and tissue growth. Neonatal inflammatory skin and bowel disease type 2 is caused by EGFR recessive deficiency (OMIM 616069). Among the 22 known cases, nephromegaly is the only notable renal phenotype. A review of published cases and a new case suggests NISBD2 is frequently associated with tubulopathy.

Case Description: A 10-year-old girl was diagnosed with NISBD2 caused by homozygous pathogenic EGFR variants (NM_005228.3: c.1283G>A; p.G428D). Ultrasound revealed large echogenic kidneys with poor corticomedullary differentiation and many small cysts. We documented hypomagnesemia 0.5 mmol/L and hypokalemia 2.6 mmol/L caused by excessive urinary magnesium wasting FeMg 14%. We also observed mild chronic hypernatremia 155 mmol/L due to a urinary concentration defect UOsm 400 mOsm/kg water. Finally, low-molecular-weight proteinuria and glucosuria without hyperphosphaturia or aminoaciduria suggest partial proximal tubulopathy.

Discussion: In EGFR signaling, there are various downstream pathways, so mutations affect cell proliferation and homeostasis. We will discuss with an in-depth insight into the disease, the potential pathophysiology of the associated tubulopathy and PKD, and its presence in previously reported under-recognized cases. Conclusion: Hypomagnesemia is well-known in EGFR inhibitors but not in EGFR deficiency. Additionally, EGFR deficiency causes enlarged kidneys. The renal phenotype, however, is much more complex, involving hypokalemia, hypernatremia, cystic disorder, and tubulopathy. Electrolytes can be monitored more precisely in cases of EGFR deficiency to determine the significance of this association.

FR-PO635

Müllerian Anomalies in Girls with Solitary Functioning Kidney

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Background: Patients with Müllerian anomalies have a 30-50% increased prevalence of congenital renal anomalies and solitary functioning kidney (SFK) is the most common. However, the prevalence of Müllerian anomalies among patients with SFK is not well defined. A delay in diagnosis of obstructive Müllerian anomalies can increase the risk of poor clinical outcomes. This study describes the prevalence of Müllerian anomalies in patients with congenital SFK.

Methods: A retrospective review was performed of patients within the Nationwide Children's Hospital system with ICD9 or ICD10 diagnostic codes for SFK. Analysis focused on girls with congenital SFK defined as either unilateral renal agenesis (URA) or multicystic dysplastic kidney (MCDK). Patients with complex urogenital pathology, such as, cloaca, urogenital sinus, or bladder exstrophy were excluded. Renal anomaly, Müllerian anomaly, reason for and type of pelvic evaluation, and age of diagnosis of anomalies were evaluated.

Results: Diagnostic codes identified 400 patients; 97 were excluded for complex urogenital anatomy. SFK was confirmed in 204 girls and 169 (82%) were congenital. There were 115 patients with URA and 54 with MCDK. Additional anomalies of the SFK were pelvic/ectopic (4), dysgenesis/hypoplasia (8), cystic (2), and other (19). Of patients with congenital SFK, 85 (50%) had a pelvic evaluation, most frequently in response to abdominal pain/dysmenorrhea (39%). Ultrasound was the most common imaging modality (74%). 49 (29%) patients had a Müllerian anomaly with the majority having combined uterine and vaginal anomalies (28) or isolated uterine anomaly (18). In 59% of patients, the renal anomaly was diagnosed prior to the Müllerian anomaly, at a median age of 6.5 years. In 24 patients, an obstructive Müllerian anomaly was found, including 11 who had a known renal anomaly.

Conclusions: The prevalence of Müllerian anomalies in patients with congenital SFK was 29%. Only half of patients with a congenital SFK had a pelvic evaluation. A Müllerian anomaly was found in about 60% of patients evaluated and it was obstructive in about one third of cases. Over half of the girls with Müllerian anomalies had a prior renal anomaly diagnosis. The high prevalence of Müllerian anomalies in patients with congenital SFK justifies routine screening pelvic ultrasound to improve early diagnosis.

FR-PO636

Pparg Pathway Drives Renal Uroplakin Cell Formation and Parenchymal Preservation During Urinary Tract Obstruction

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Background: Urinary Tract Obstruction (UTO) is a leading cause of chronic and end stage kidney disease in children. While no current treatments prevent obstruction-induced kidney disease, future therapies may be identified by understanding how the kidney adapts to obstruction. We previously reported that obstruction triggers the formation of protective uroplakin (Upk) cells which preserve renal parenchyma during congenital and acquired UTO. The molecular program that governs Upk cell formation in the renal urothelium is unknown. In bladder, the *Pparg* signaling pathway drives urothelial differentiation. Thus, we hypothesized that*Pparg* drives renal Upk cell formation during UTO.

Methods: Kidneys from embryonic (E-) and postnatal (P-) female and male mice were collected. We modeled UTO using congenital and surgical models. We conditionally manipulated Pparg in Upk cells using inducible Pparg deletion ($Upk2^{iCre}$;$Pparg^{LOF}$) and gain-of-function ($Upk2^{iCre}$;$Pparg^{GOF}$) mouse lines. Immunofluorescent Analysis (IF-A) and renal ultrasound were used to evaluate the effect of *Pparg* pathway manipulation on UTO-induced Upk cell formation and renal parenchyma, respectively.

Results: Pparg was expressed by renal Upk cells at E17 - P7, but was absent in adult mice ≥P42. Both congenital and surgical UTO triggered Upk cells to re-express Pparg and its targets, Grhl3 and Fabp4. During UTO, $Upk2^{iCre}$;$Pparg^{LOF}$ mice showed a significant reduction in Upk expression (10% Vs 3.1%, P=0.008) accompanied by

significantly thinned renal parenchyma (30.9% Vs 25.9%, P=0.039), compared to Cre(-) mice. However, *Upk2*^{iCre};*Pparg*^{GOF} mice induced a significant upregulation of Upk (10% Vs 17.42%, P=0.006) and exhibited significantly greater parenchymal preservation (30.9% Vs 44.4%, P=0.002), compared to Cre(-) mice.

Conclusions: Our results reveal that UTO-induced *Pparg* signaling is a recapitulation of a renal urothelium developmental program, and that *Pparg* signaling promotes Upk cell formation to preserve renal parenchyma during UTO. Our findings advance our understanding of renal adaptation to UTO and reveal a potential mechanism, such as *Pparg* signaling, with therapeutic utility for mitigating obstructive kidney disease in children. Future studies will investigate the utility of synthetic Pparg agonists during UTO.

Funding: NIDDK Support

FR-PO637

Selected Renal Cells Exhibit Renal Tubule Formation Associated with Transforming Growth Factor B2 Expression

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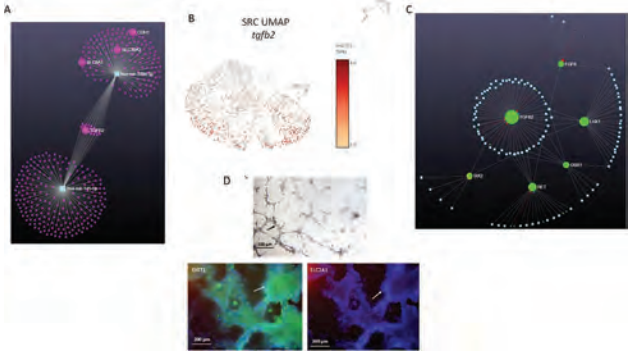
Background: TGFB2 mediates interactions between the ureteric bud and the metanephric mesenchyme resulting in renal tubule formation. Selected renal cells (SRCs) express ureteric bud markers RET and FGF8, and cap mesenchyme markers, LHX1, OSR1 and SIX2, their administration is therapeutic in models of chronic kidney disease. We tested the hypothesis that SRCs express *tgfb2* and assemble into renal tubules.

Methods: Human SRCs (sourced from NDRI kidneys) were submitted to miRNAseq and mRNAseq, differentially expressed nodes identified and seeded into miRNet for interactome visualization. SRCs were submitted to scRNA-seq to map gene expression. SRCs were placed in culture, and secreted TGFB2 measured using ELISA, and evidence of renal tubule formation confirmed by antibody staining for epithelial markers GGT1 and SLC12A1.

Results: Compared to the source biopsy hsa-miR-145-5p (log2FC=-6.9) and hsa-miR-199a-5p (log2FC=-5.7) were downregulated in SRCs (p_{adj}<0.01). Gene ontology revealed that these miRNAs regulate expression of *tgfb2* together with renal epithelial markers (A). SRCs overexpressed *tgfb2* (log2FC=2.5, p_{adj} <0.01). scRNA-seq confirmed *tgfb2* expression (B) and SRC secreted TGFB2 exhibited 12-fold increase vs. control; p<0.01). Gene ontology revealed that *tgfb2* forms an interactome with *ret*, *fgf8*, *lhx1*, *osr1* and *six2*, ureteric bud and cap mesenchyme markers expressed by SRCs (C). Placed in culture, SRCs assembled into GGT1- and SLC12A1-positive renal tubules (D).

Conclusions: These data suggest that therapeutic activity of SRCs may be mediated in part via formation of renal tubules and maintenance of electrolyte balance, fluid homeostasis, reabsorption of essential nutrients, urine concentration and Cystatin C metabolism.

Funding: Commercial Support - ProKidney



(A) hsa-miR-145-and hsa-miR-199a-5p regulate expression of *tgfb2* and renal epithelial markers. SRCs express *tgfb2* (B) which forms an interactome with ureteric bud and cap mesenchyme markers (C). Placed in culture, SRCs assemble into GGT1-and SCL12A1-positive renal tubules (D, arrows).

FR-PO638

Notch Signaling Regulates Renal Urothelium Differentiation

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Background: Children with congenital urinary tract obstruction (UTO) face limited treatment options and experience high rates of ESKD. The renal urothelium undergoes a protective adaptation during UTO by forming differentiated Uroplakin (Upk) cells. However, little is known about signaling pathways that govern Upk expression and urothelial differentiation within the kidney. The Notch signaling pathway regulates bladder urothelial differentiation and single cell RNAseq data suggest a role in renal urothelium development. The objective of this study was to test the hypothesis that Notch signaling regulates Upk expression and urothelial differentiation in the kidney.

Methods: We generated *Hoxb7*^{Cre};RBPJ$^{fl/fl}$ (RBPJ$^{UB\text{-}KO}$) mice and RBPJ$^{fl/fl}$ (controls) to conditionally disrupt Notch signaling. We collected kidneys and bladders from RBPJ$^{UB\text{-}KO}$ and controls at embryonic, neonatal, juvenile, and adult time points. We confirmed tissue-specific depletion of RBPJ and Notch abrogation using immunofluorescent analysis (IF-A) and RNAscope, respectively. We used IF-A to evaluate markers of urothelial differentiation.

Results: IF-A confirmed efficient RBPJ depletion in renal urothelium and collecting ducts, but not bladder urothelium at all time points in RBPJ$^{UB\text{-}KO}$ mice. RNAscope confirmed that Notch targets, *Hes1* and *Hes6*, were significantly decreased in RBPJ$^{UB\text{-}KO}$ renal urothelium compared to controls. IF-A showed that RBPJ$^{UB\text{-}KO}$ kidneys had significant decreases in Upk at each stage. Ppar-γ - a transcription factor that regulates Upk expression - and its targets were also significantly decreased in RBPJ$^{UB\text{-}KO}$ kidneys compared to controls.

Conclusions: We have demonstrated that Notch signaling is key to the formation and maintenance of Upk cells in the renal urothelium. Our data also suggest that Ppar-γ signaling in the renal urothelium may be regulated by Notch. Future studies will investigate whether the Notch signaling directly regulates Upk expression or whether Upk expression is regulated by a Notch-dependent Ppar-γ signaling axis.

Funding: NIDDK Support

FR-PO639

Dot1/H3K79 Pathway Mediates Defective Ureteric Bud (UB) Branching Leading to Renal Hypodysplasia (RHD) in Prorenin Receptor (PRR) PRRUB-/- Mice

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Background: Dot1 is histone methyltransferase specific for Histone 3 lysine 79 (H3K79) that is important for differentiation of collecting duct (CD) cells. Targeted deletion of the *Dot1* in the CD principal cells (PCs) in mice represses the acquisition of PC phenotype resulting in polyuria (Wu. JASN, 2013). We tested the hypothesis that RHD and polyuria observed in mice that lack the *PRR* in the UB lineage (*PRR*$^{UB\text{-}/\text{-}}$) (Song. PLoS ONE, 2013) is due to reduced Dot1/H3 dimethyl K79 (H3m2K79) expression.

Methods: Mutant [*Hoxb7*$^{Cre+}$/*PRR*$^{flox/flox}$ (*PRR*$^{UB\text{-}/\text{-}}$), n=3] and control (*PRR*$^{UB+/+}$, n=3) mice were studied on embryonic (E) day E17.5. Dot1 mRNA and protein expression in the kidney was studied by real-time qRT-PCR and immunohistochemistry, respectively. H3m2K79 protein expression was determined by immunohistochemistry and Western blot analysis. The intensity of H3m2K79 and Dot1 immunoreactivity, normalized for surface area of the kidney section, was examined by Slidebook 4.1 software.

Results: Kidney section surface area was smaller in the mutant compared to control mice (220600±20120 vs.533800±72170 pixels, p<0.05). Dot1 mRNA levels were decreased in mutant compared to control mice (0.68±0.06 vs. 1.0±0.01, p<0.01). Dot1 and H3m2K79 immunostaining was reduced in the mutant vs. control kidneys (Dot1: 0.62±0.03 vs. 1.0±0.01, p<0.05; H3m2K79: 0.64±0.04 vs.1.1±0.01. p<0.05.). Western blot analysis revealed decreased H3m2K79 protein levels in mutant compared to control kidneys (1.0±0.06 vs. 1.5±0.02, p<0.05).

Conclusions: We conclude that reduced H3m2K79 methylation by Dot1 in the UB of *PRR*$^{UB\text{-}/\text{-}}$ mice contributes, in part, to RHD and polyuria observed in these mice.

FR-PO640

Roles of microRNA in Development and Maintenance of Urothelium

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Background: MicroRNA (miRNA) serve essential roles in epithelial cell development, maintenance, and response to injury by modulating mRNA and protein expression, but their function in urothelium remains largely unexplored. To address this knowledge gap, we engineered mice with urothelium-specific constitutive and inducible inactivation of *Dicer*, an exonuclease required for miRNA biogenesis.

Methods: We generated urothelial *Dicer* conditional knockout mice by crossing *Dicer*$^{fl/fl}$ and *Upk2*Cre or *Upk2*CreERT$_2$ animals. A tdTomato (tdT) fluorescent protein was expressed in a Cre/LoxP dependent manner from the *Rosa26* locus to identify cells in which *Dicer* inactivation had occurred. Urothelial lineage markers were evaluated by immunofluorescence microscopy, Western blotting and QRT-PCR.

Results: Bladders from control animals displayed the expected urothelial morphology with sequential layers of Krt5+ basal (B) cells, Upk+ intermediate (I) cells, and Upk+; Fabp4+ superficial (S) cells. In contrast, bladders from 3-week-old mice with biallelic inactivation of *Dicer* exhibited rounded S cells appearance with patchy/discontinuous Fabp4 expression and frequent exfoliation into the bladder lumen. This was increasingly evident at 6 and 9 weeks of life and associated with expansion of Krt14+ progenitor cells and thickening of the B and I cell layers. Conditional inactivation of *Dicer* in Upk+ cells of 3-week-old mice recapitulated the phenotype of S cell loss and expansion of the remaining urothelial cell layers.

Conclusions: *Dicer* is dispensable for urothelial formation but serves an essential role in its structural integrity. Ongoing efforts will identify the specific microRNAs responsible for S cell maintenance.

Funding: NIDDK Support

FR-PO641

Defining the Expression and Functions of SLPI, an Antibacterial Peptide Produced by Kidney Intercalated Cells

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Background: Mounting evidence suggests intercalated cells (IC) in the kidney collecting duct have antibacterial defenses that prevent pyelonephritis. In part, ICs prevent uropathogenic *E. coli* (UPEC) infections by expressing antimicrobial peptides and secreting them into the urine. The goal of this project is to define the expression, regulation, and antibacterial capacity of secretory leukocyte protease inhibitor (SLPI), a peptide that prevents infections in other organ systems by killing Gram-positive and negative bacteria. SLPI expression in the kidney has not been tested and its antibacterial activity against UPEC is unclear.

Methods: To evaluate SLPI expression, human kidney samples were obtained from people with and without a history of pyelonephritis. Mouse kidney samples were collected before and after mice were transurethrally infected with UPEC. ICs were enriched from mouse kidneys using FACS, cultured to confluency, and challenged with UPEC. SLPI expression was defined using qRT-PCR and Western blot. To test how SLPI is transcriptionally regulated, chromatin immunoprecipitation was performed. The antibacterial activity of SLPI was defined by performing UPEC bactericidal assays.

Results: qRT-PCR and Western blot identify SLPI expression in human and mouse kidneys and show SLPI expression increases with pyelonephritis. Within ICs, *Slpi* transcript expression increases 1.7-fold following UPEC infection. With UPEC infection, we observed increased NF-kB binding to the *SLPI* promoter. Recombinant human and mouse SLPI exhibit dose-dependent killing of UPEC, including multi-drug resistant UPEC.

Conclusions: These findings are the first to demonstrate that SLPI is expressed in human and mouse kidneys and ICs. Its expression is augmented during pyelonephritis, perhaps via NF-kB activation. They also show that SLPI has antibacterial activity against UPEC and multi-drug resistant UPEC. Future studies are needed to assess the utility of SLPI as a pyelonephritis biomarker and define its IC antimicrobial activity in model systems.

Funding: NIDDK Support

FR-PO642

Stat3-Driven Urothelial Programming Prevents Urinary Tract Infection (UTI) Chronicity

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Background: Uropathogenic E. Coli (UPEC) can evade host immunity resulting in urinary tract infection (UTI) chronicity. We have previously demonstrated that STAT3 limits chronic UTI at 7 days. STAT3 controls several cellular processes by regulating gene transcription. Persistent activation of STAT3 has shown to be oncogenic however not much is known about its impact in UTI. We hypothesize that constitutive STAT3 activation has direct effects on urothelial integrity and epithelial immunity.

Methods: 6-8 weeks old female FVB/N wild type controls (WT) and constitutively active Stat3 (Stat3C) mice underwent experimental UPEC UTI. Serial bladder tissue and urine were collected up to 7 days post infection (dpi). Cytospins were performed on urine. Immunofluorescent staining was performed on bladders for Keratin 5, pStat3, Ly6G, and Iba-1. TUNEL staining was also performed. A Qiagen RT^2 profiler PCR microarray for the IL-6/ STAT3 signaling pathway was also performed on bladders. Results were evaluated by Mann-Whitney U test with $p<0.05$ being significant.

Results: Stat3C and WT urothelium demonstrated induction of pStat3 after infection, with Stat3C urothelium showing persistent activation at 7 dpi. TUNEL staining demonstrated more signs of cellular apoptosis in the WT compared to Stat3C bladders at 24hpi and 7dpi, with cellular shedding on WT cytospins at corresponding time points. There was an earlier infiltration of neutrophils in the urothelium of WT mice with a later infiltration of macrophages in STAT3C mice. RT^2 profile PCR arrays shows altered expression of genes involved in cell cycle regulation, immune cell recruitment, cytokine expression at 24hpi and 7dpi.

Conclusions: Urothelial STAT3 overexpression directly impacts its viability in response to UTI and the recruited inflammatory milieu. Manipulation of this signaling pathway can alter susceptibility to chronic UTI.

Funding: NIDDK Support

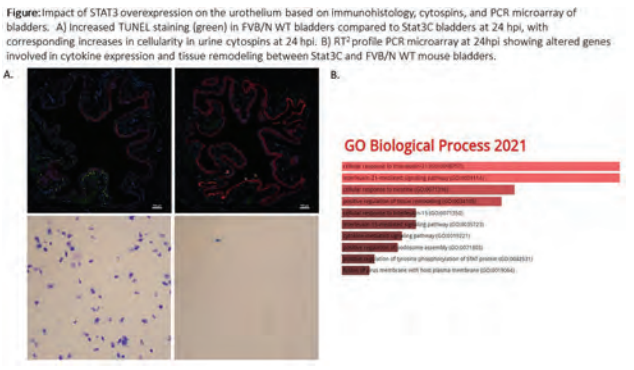

Figure: Impact of STAT3 overexpression on the urothelium based on immunohistology, cytospins, and PCR microarray of bladders. A) Increased TUNEL staining (green) in FVB/N WT bladders compared to Stat3C bladders at 24 hpi, with corresponding increases in cellularity in urine cytospins at 24 hpi. B) RT^2 profile PCR microarray at 24hpi showing altered genes involved in cytokine expression and tissue remodeling between Stat3C and FVB/N WT mouse bladders.

FR-PO643

The Renal Urothelium Serves Essential Roles in Host Defense and Pathogenesis of Pyelonephritis

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Background: Uropathogenic *Escherichia coli* (UPEC) causes over 90% of acute pyelonephritis cases in humans. The urothelial lining of the pelvicalyceal system serves a proposed gatekeeper role in limiting renal parenchymal invasion by UPEC, but the exact mechanisms that account for this function are unclear. In this study we utilized spatial transcriptomics to map host-pathogen interactions within renal urothelium during pyelonephritis.

Methods: We established acute pyelonephritis in female C3H/HeOuJ mice by transurethral inoculation of UPEC strain CFT073. We profiled transcriptional changes in renal pelvic urothelium through spatial transcriptomics at baseline and 7 days post infection (dpi). We validated these changes by QRT-PCR and immunofluorescence microscopy. *Upk1b* knockout mice were used to investigate the role of the urothelial plaque in the initiation of pyelonephritis.

Results: Spatial transcriptomics identified induction of transcripts with roles in barrier function, leukocyte recruitment, and bactericidal activity in infected renal urothelium. Conversely, transcripts encoding Uroplakin subunits that comprise the urothelial plaque were decreased following infection. *Upk1b* deletion results in absent urothelial plaque formation. Following transurethral UPEC inoculation, *Upk1b*$^{-/-}$ mice exhibited reduced renal bacterial burden and decreased neutrophil infiltration, when compared to *Upk1b*$^{+/+}$ mice.

Conclusions: The renal pelvis engages multiple antimicrobial mechanisms in response to *E. coli* pyelonephritis – including the downregulation of urothelial plaque formation, which serves to limit parenchymal invasion by UPEC. This study identifies a foundational role for the urothelial plaque in Gram-negative pyelonephritis and further strengthens the rationale for the development of antimicrobial agents that disrupt UPEC-plaque interactions in preventing pyelonephritis.

Funding: NIDDK Support

FR-PO644

Gain- and Loss-of-Function Approaches Substantiate Roles for Ribonuclease 6 in Pyelonephritis

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Background: Acute pyelonephritis (APN) episodes can result in urosepsis, acute kidney injury, and renal scarring. Identifying mechanisms of host defense against APN is a priority to mitigate these sequelae, particularly in an era of mounting antibiotic resistance. Ribonuclease 6 (RNase 6) is a cationic protein with potent bactericidal activity toward uropathogenic *Escherichia coli* (UPEC). We took complementary approaches to examine roles for RNase 6 in experimental APN.

Methods: We utilized a novel *Rnase6*$^{EGFP/+}$ knockin allele to identify the cellular sources of RNase 6 and the impact of its deficiency on APN susceptibility in mice. As a complementary approach we generated human *RNASE6* transgenic mice. Flow cytometry, immunofluorescence microscopy, and scRNAseq identified cellular sources of RNase6 within the kidney. The role of RNase 6 in intracellular UPEC killing was identified in a gentamicin protection assay using bone marrow derived macrophages (BMDM).

Results: Mouse and human RNase 6 are expressed by resident mononuclear phagocytes and circulating monocytes that are recruited to the infected kidney during APN. *Rnase6* deficient mice are more susceptible to APN, whereas *RNASE6* transgenic mice exhibit reduced renal UPEC burden. *Rnase6* deficiency is associated with increased intramacrophage UPEC survival, while human *RNASE6* transgenic macrophages are more adept at killing phagocytosed UPEC.

Conclusions: RNase 6 is an essential antimicrobial protein within the renal mononuclear phagocyte system that promotes UPEC clearance during APN.

Funding: NIDDK Support

FR-PO645

Long-Term Complications and Outcomes of Augmentation Cystoplasty in Children with Neurogenic Bladder

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Background: Controversy still exists regarding complications especially malignancy and long-term outcomes of augmentation cystoplasty (AC) in children with neurogenic bladder.

Methods: Pediatric patients <18 years underwent AC between 2000 and 2020 were enrolled. Early postoperative complications, long-term outcomes and histopathologic changes in mucosal biopsies of native bladder and the augmented intestine after AC were reviewed.

Results: Twenty-two patiients with mean age of 7.6±4.4 years were included. The ileum was used in 19 patients and the sigmoid colon in 3 patients. The length of hospital stay was 14.8±6.8 days. Post-operatively, urinary continence rate improved from 22.7% to 86.4% (p<0.001). Vesicoureteral reflux resolved in 16 (64.0 %) of the refluxing ureter units and was downgraded in 8 (32.0%). Hydronephrosis resolved in 17 of 19 patients. Grades of reflux and hydronephrosis significantly improved following AC (p<0.001). The estimated glomerular filtration rate also significantly increased (p=0.012). Formation of urinary tract stones was the most frequent late complication (in 8 patients, 36.4%). After a mean follow-up of 13.4±5.9 years, there were no cases of mortality, new-onset symptomatic metabolic acidosis, or effects on serum electrolytes. No cases of malignancy or metaplastic changes were identified in the native bladder or augmented bowel epithelium.

Conclusions: AC is a safe and effective procedure with low surgical and metabolic complication rates. AC provides a satisfactory continence rate and long-term protection of renal function, increases functional capacity, and regresses reflux and hydronephrosis. Individualized surveillance is recommended for the early identification of urolithiasis and metabolic disturbance.

Funding: Government Support - Non-U.S.

Table 1 The demographic data and clinical characteristics of the children who underwent augmentation cystoplasty

Variables	n (%)
Sex	
Male	6 (27.3%)
Female	16 (72.7%)
Age at surgery (years)	7.6±4.4
Age at the last follow-up (years)	20.9±6.9
Follow-up period (years)	13.4±5.9
Indication for augmentation	
Neurogenic	
Myelomeningocele	19 (86.4%)
Transverse myelitis	1 (4.5%)
Anorectal malformation with vertebral anomalies	1 (4.5%)
Non-neurogenic	
Posterior urethral valve	1 (4.5%)
Preoperative urodynamic diagnosis	
Small capacity	14 (63.6%)
Low compliance	17 (77.3%)
Detrusor hyperactivity	10 (45.5%)
Detrusor areflexia	6 (27.3%)
Detrusor sphincter dyssynergia	2 (9.1%)

Table 2 Perioperative outcomes and complication profile

Variables	Mean (SD) or n (%)
Hospital stay (days)	14.8±6.8
Type of bowel segment	
Ileum	19 (86.4%)
Sigmoid	3 (13.6%)
Ancillary surgical procedures	
Ureteric reimplantation	
Unilateral	3 (13.6%)
Bilateral	3 (13.6%)
Complications	
Early complication	
Postoperative UTI	3 (13.6%)
AKI	2 (9.1%)
Bowel-bladder anastomotic leak	1 (4.5%)
Ileus	1 (4.5%)
Small bowel obstruction	1 (4.5%)
Late complications	
Small bowel obstruction	0 (0%)
Metabolic complications	
New-onset hyperchloremic metabolic acidosis	0 (0%)
Electrolyte disturbances	0 (0%)
Urinary stone	
Kidney	5 (22.7%)
Urinary bladder	3 (13.6%)
Malignancy	0 (0%)
Bowel disturbance	0 (0%)
Perforation	1 (4.5%)
Intra-abdominal fluid collection	1 (4.5%)

AKI, acute kidney injury; UTI, urinary tract infection

Table 1 & 2

Table 3 Renal and functional outcomes after augmentation cystoplasty

Variables	Preoperatively	Postoperatively	p value
Hydronephrosis			<0.001
No hydronephrosis	3 (13.6%)	19 (86.4%)	
Mild hydronephrosis	4 (18.2%)	1 (4.6%)	
Moderate hydronephrosis	5 (22.7%0	0 (0%)	
Severe hydronephrosis	10 (45.5%)	2 (9.1%)	
Number of renal units with VUR			<0.001
No VUR	19 (43.2%)	35 (72.7%)	
Grade I	4 (18.2%)	4 (18.2%)	
Grade II	0 (0.0%)	2 (9.1%)	
Grade III	4 (18.2%)	1 (4.6%)	
Grade IV	9 (40.9%)	2 (9.1%)	
Grade V	8 (36.4%)	0 (0%)	
Renal function outcome			
Creatinine (mg/dL)	0.78 ±0.57	0.90 ±0.80	0.477
eGFR (mL/min/1.73 m^2)	80.6 ±33.9	98.2 ±39.5	0.012
CKD stage			0.115
Normal eGFR (>90 mL/min/1.73 m^2)	8 (36.4%)	13 (59.1%)	
CKD stage 2	8 (36.4%)	6 (27.3%)	
CKD stage 3	5 (22.7%)	2 (9.1%)	
CKD stage 4	1 (4.6%)	0 (0%)	
CKD stage 5	0 (0%)	1 (4.6%)	
Urinary incontinence	5 (22.7%)	19 (86.4%)	<0.001

CKD, chronic kidney disease; VUR, vesicoureteral reflux; CIC, clean intermittent catheterization

Table 3 Renal and functional outcomes after augmentation cystoplasty

FR-PO646

Kidney and Urinary Manifestations in Kabuki Syndrome

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Background: Kabuki syndrome (KS) is a rare genetic disorder caused by pathogenic variants in *KMT2D* (formerly *MLL2*) or *KDM6A*. It is characterized by multiple abnormalities including typical facial features, growth delays, varying degrees of intellectual disability, skeletal abnormalities, and short stature. Kidney and urinary manifestations of this syndrome include congenital anomalies of the kidneys and urinary tract (CAKUT), and there were some reports of kidney stone and kidney failure. This study aimed to describe the clinical features and prevalence of renal manifestations in KS patients.

Methods: All genetically confirmed KS patients who visited the Seoul National University Children's Hospital during the period of 2000 to 2023 were included. Medical records were retrospectively reviewed for clinical and laboratory findings.

Results: Sixty-one patients (28 males) were reviewed in this study. Their median age at diagnosis was 32 months (interquartile range (IQR) 9-110). Causative gene of KS were *KMT2D* in 58 cases and *KDM6A* in 3. CAKUT were found in total of 16 (26.2%) patients, including horseshoe kidney (n=6), ectopic kidney (n=5), vesicoureteral reflux (n=2), hypoplastic kidneys (n=2), multicystic dysplastic kidney (n=1), duplex kidney (1), unilateral renal agenesis (n=1), and hydronephrosis (1). In addition, 4 (6.6%) patients had kidney stones or nephrocalcinosis and two had ureter stones. Kidney function at diagnosis was normal in all patients, and one had proteinuria of tubular origin. After median follow-up of 5 years (IQR 2.5-7.5), kidney function did not decrease except for one patient, whose estimated GFR at age of 15 was 59 after partial nephrectomy due to complicated cysts.

Conclusions: More than one third of patients of KS had kidney or urinary involvement, and some of them progress to CKD. Therefore, screening for kidney or urinary problems and regular follow-up would be necessary for KS patients.

FR-PO647

Long-Term Kidney Outcomes in Children with Posterior Urethral Valves: A Population-Based Cohort Study

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Background: Posterior urethral valves (PUV) are a common cause of urinary tract obstruction in male infants. However, the long-term kidney outcomes of PUV are uncertain. We aim to determine the risk of major adverse kidney events (MAKE) among PUV patients.

Methods: Retrospective cohort study of all male infants (0-2yr) diagnosed with PUV from 1991-2021 in Ontario, Canada, identified by provincial administrative health databases. We chose two comparator cohorts of males (0-2yr) without PUV: 1) general pediatric population and 2) pyeloplasty patients. Patients were followed until death, provincial emigration, or March 2022 (89%). The primary outcome was modified MAKE (composite of death, chronic kidney replacement therapy (KRT), or *de novo* chronic kidney disease (CKD)).

Results: We included 727 PUV patients, 855 pyeloplasty patients, and 1,013,052 general pediatric comparators. Median age at PUV diagnosis was 40 days (IQR 10-196). Median follow-up was 16.6 years (IQR 8.6-24.5). During follow-up, 32.3% of PUV patients developed MAKE vs. 5.8% of pyeloplasty patients and 0.8% of general comparators. The adjusted HR for MAKE throughout follow-up was 36.6 (95%CI 31.6-42.4, p<0.001) in PUV patients vs. general comparators. The cumulative incidence of CKD, chronic KRT, hypertension, and incident acute kidney injury were also higher among PUV patients.

Conclusions: PUV patients are at a substantially increased risk of long-term kidney sequelae vs. those without PUV. This justifies enhanced kidney function and blood pressure surveillance among those with a history of PUV.

Table. Cumulative incidence of outcomes

Outcome	PUV patients, incidence rate per 1000py (95%CI)	Pyeloplasty patients, incidence rate per 1000py (95%CI)	General pediatric comparators, incidence rate per 1000py (95%CI)
Major adverse kidney event (MAKE)	28.4 (25.0-32.2)	4.5 (3.4-5.9)	0.49 (0.48-0.50)
Kidney replacement therapy (chronic dialysis or kidney transplant)	6.1 (4.7-7.8)	0.5 (0.2-1.1)	0.01 (0.01-0.01)
Chronic kidney disease	26.2 (22.8-30.1)	4.0 (3.0-5.7)	0.24 (0.23-0.25)
Hypertension	14.6 (12.3-17.3)	4.3 (3.2-5.7)	1.79 (1.77-1.81)
Acute kidney injury	15.8 (13.4-18.6)	2.8 (2.0-4.0)	0.27 (0.26-0.28)

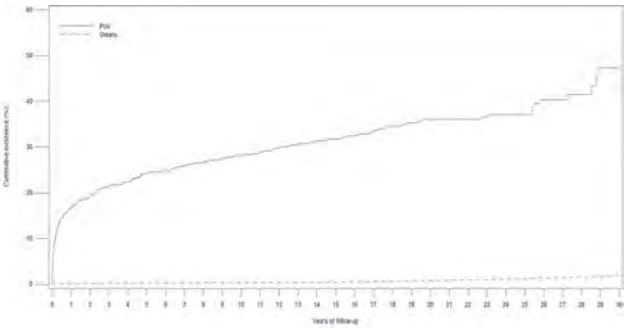

Figure. Cumulative incidence of MAKE among PUV patients vs general pediatric comparators

FR-PO648

Incidence and Risk Factors for Obesity and Short Stature in Childhood Nephrotic Syndrome: A Prospective Cohort Study

Cal Robinson,[1] Nowrin F. Aman,[1] Rahul Chanchlani,[2] Vaneet Dhillon,[1] Christoph Licht,[1] Damien G. Noone,[1] Rachel J. Pearl,[1] Seetha Radhakrishnan,[1] Chia Wei Teoh,[1] Rulan S. Parekh.[1,3] *[1]The Hospital for Sick Children, Toronto, ON, Canada; [2]McMaster Children's Hospital, Hamilton, ON, Canada; [3]Women's College Hospital, Toronto, ON, Canada.*

Background: Children with nephrotic syndrome are at risk of obesity and short stature from repeated steroid treatment. The incidence, timing, and risk factors for these outcomes remain uncertain.

Methods: We evaluated longitudinal growth and obesity in children (1-18yr) enrolled in Insight into Nephrotic Syndrome: Investigating Genes, Health, and Therapeutics (INSIGHT). We included nephrotic syndrome cases diagnosed from 1996-2019 in Greater Toronto. Growth parameters were measured at annual clinic visits. Primary outcomes were *de novo* obesity (body mass index (BMI) Z-score ≥+2) and short stature (height Z-score ≤-2). We calculated hazard ratios (HR) using Cox proportional hazards models.

Results: We included 531 children with nephrotic syndrome (24% frequently relapsing (FRNS) by 1-year). At their initial clinic visit (within 1-year of diagnosis), 23.5% of cases were obese, 51.8% were overweight (BMI Z-score ≥+1), and 4.9% had short stature. At the last clinic visit, the prevalence of obesity had decreased (17.3%) and short stature was unchanged (3.8%). During median 4.2-year follow-up, 69 (17.7%) children developed obesity and 16 (3.3%) developed short stature, among those without obesity or short stature initially. Total relapse count was a significant predictor for *de novo* obesity (adjusted HR 1.03, 95%CI 1.01-1.06, p=0.01) and short stature (unadjusted HR 1.06, 95%CI 1.02-1.10, p=0.01). Children with >6 and >12 total relapses were more likely to develop obesity and short stature, respectively.

Conclusions: Obesity is common among children with nephrotic syndrome early after diagnosis, but prevalence decreases over time. Effective relapse prevention may reduce steroid exposure and the risks of *de novo* obesity or short stature.

Funding: Government Support - Non-U.S.

Obesity and height outcomes, by FRNS classification within 1-year of diagnosis

Outcome	Overall (n=531)	Non FRNS (n=404)	FRNS (n=127)
Prevalent obesity at initial clinic visit, n (%)	125/531 (23.5)	89/404 (22.0)	36/127 (28.4)
De novo obesity during follow-up, n (%)	69/390 (17.7)	46/302 (15.2)	23/88 (26.1)
Prevalent obesity at last clinic visit, n (%)	91/526 (17.3)	65/399 (16.3)	26/127 (20.5)
Prevalent short stature at initial clinic visit, n (%)	26/531 (4.9)	21/404 (5.2)	5/127 (3.9)
De novo short stature during follow-up, n (%)	16/488 (3.3)	8/369 (2.2)	8/119 (6.7)
Prevalent short stature at last clinic visit, n (%)	20/525 (3.8)	13/398 (3.3)	7/127 (5.5)
Change in BMI Z-score during follow-up, mean (SD)	-0.52 (1.23)	-0.48 (1.19)	-0.65 (1.34)
Change in height Z-score during follow-up, mean (SD)	+0.19 (0.84)	+0.22 (0.79)	+0.09 (0.97)

FR-PO649

Associations Between Monogenic Causes of Nephrolithiasis and Initial 24-Hour Urine Studies in Pediatric Patients

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Background: In children, testing for monogenic causes of nephrolithiasis offers the potential for early identification of high-risk individuals. The association between positive genetic tests for nephrolithiasis and 24-hour urine (24HU) findings in pediatric patients is unclear. We examined pediatric stone formers at our institution aiming to identify associations between 24HU parameters and the presence of lithogenic genetic variants.

Methods: We performed retrospective review of patients <18 years with nephrolithiasis who underwent genetic testing between 2019-2023 (Invitae Nephrolithiasis Panel, San Francisco, USA). We classified genetic tests as negative, variants of uncertain significance (VUS), and pathogenic (P) variants. Demographic and initial 24HU data were collected. Descriptive and comparative analyses were performed, including Kruskal-Wallis, Mann-Whitney-U and Spearman's tests, with p<.05 considered significant.

Results: We identified 25 patients with nephrolithiasis who underwent both genetic and 24-hour urine testing, with 57% male and 43% female. The median age at the time of genetic test was 10.4 years. There 21 (60%) positive tests, with 19 (54%) VUS and 2 (6%) P variants (Table 1). Mean 24HU results from the cohort are shown (Table 2). On 24HU, all patients had 1 abnormal metabolic parameter. Six had abnormal values >2 standard deviation from mean for age/sex. There were no significant differences in values on 24HU studies between groups.

Conclusions: In this first study of associations between 24HU and nephrolithiasis genetic testing, we found no differences between pediatric stone formers with known variants and those with negative genetic tests. This suggests that genetic testing should not have an immediate impact on preventive care strategies, excluding conditions like primary hyperoxaluria. However, our study did not measure longitudinal outcomes; genetic disposition to stone disease may require more aggressive preventive care and metabolic management over time, so we recommend larger, longitudinal studies of pediatric patients with monogenic causes of nephrolithiasis.

Table 1. Frequency and association of genetic testing results.

Significance Frequency	Gene	Association
6 VUS, 1 Pathogenic	SLC34A3	Hereditary hypophosphatemic rickets with hypercalciuria
1 Likely Benign, 1 VUS	SLC26A1	Autosomal recessive calcium oxalate urolithiasis
1 Pathogenic	SLC7A9	Autosomal recessive cystinuria type B
1 VUS	CYP24A1	Infantile hypercalcemia
1 VUS	XDH	Autosomal recessive xanthinuria type I
1 VUS	UMOD	MCKD2
1 VUS	CLCNKB	BSND
1 VUS	ATP6V0A4	dRTA
1 VUS	SLC3A1	Calcium oxalate urolithiasis
1 VUS	SLC12A1	Bartter syndrome type 1
1 VUS	AQP1	Primary hyperoxaluria, type 1
1 VUS	VDR	VDDR2A
1 VUS	ADCY10	Familial idiopathic hypercalciuria
1 VUS	SLC4A1	dRTA
1 VUS	CASR	Multiple CASR-related conditions
1 VUS	SLC9A3R1	Hypophosphatemic nephrolithiasis and osteoporosis
1 VUS	PREP1	Congenital myasthenic syndrome 22

Table 2. Mean results of 24-hour urine studies.

Parameter	Total (N=25)	Negative (n=19)	VUS (n=13)	Pathogenic (n=2)	P-Value
Total Volume (L)	1.1	1.0	1.1	1.3	.444
Calcium (mg)	137	153	131	91	.538
Oxalate (mg)	26	24	28	28	.905
Citrate (mg)	648	453	443	456	.722
pH	6.5	6.4	6.4	7.1	.196
Uric Acid (g)	0.47	0.46	0.45	0.63	.266
Sodium (mmol)	114	117	110	120	.975
Potassium (mmol)	33	36	30	35	.652
Magnesium (mg)	88	87	93	66	.601
Phosphorus (g)	0.6	0.7	0.7	0.4	.677
Ammonium (mmol)	26.7 (n=22)	24.8 (n=8)	27.5 (n=12)	28.8	.753
Chloride (mmol)	106 (n=22)	114 (n=8)	104 (n=12)	85	.778
Sulfate (meq)	25	26	23	34	.682
Creatinine (mg)	910	921	914	830	.973

FR-PO650

Clinical and Metabolic Findings in Children with Nephrolithiasis: A Single-Center Experience

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Background: Prevalence of nephrolithiasis in children has increased in recent decades and is associated with high risk of recurrence. Over 50% of children with nephrolithiasis may have a metabolic, genetic, or anatomic cause, making the epidemiology of the disease notable. The epidemiology of stones, including etiology, may better inform future treatment and prevention in at-risk populations. This study aims to describe clinical and metabolic findings in children with nephrolithiasis followed at a multidisciplinary stone clinic within a tertiary children's hospital.

Methods: This is a retrospective study that included all children (n=330) with nephrolithiasis followed in the stone clinic from 5/2013-5/2023. Demographic, clinical, and metabolic variables were recorded from the patient's first encounter in the clinic. Descriptive statistics were utilized.

Results: A total of 82 patients were reviewed at the time of reporting. Majority of patients were male (59%, n=48). Roughly 37% (n=30) of patients were Hispanic and 48% (n=39) were non-Hispanic White. The median age of presentation with first kidney stone was 11 years (range: 6 months–18 years). Almost half of patients had a family history of stone disease (48%, n=39), with the most common relative being the patient's mother (33%, n=13). For patients who underwent a 24-hour urine collection (73%, n=60), 78% had metabolic abnormalities (n=47). The most common metabolic abnormalities were hypocitraturia (77%, n=36) and hypercalciuria (40%, n=19). A fifth of patients with hypocitraturia (22%, n=8) had bilateral nephrolithiasis. Almost a third of patients had hydronephrosis (30%, n=25) and required surgical stone removal (36%, n=9). Majority of patients had spontaneous passage of a stone (56%, n=46). For patients that completed stone analysis (38%, n=31), 71% (n=22) contained calcium, with the most common composition being calcium phosphate (73%, n=16). Being wheelchair bound (15%, n=12), having cerebral palsy (13%, n=11), or taking Zonisamide (10%, n=8) were frequent risk factors for stone formation.

Conclusions: Almost half of patients had a family history of stone disease, suggesting a genetic aspect to nephrolithiasis and importance of genetic testing in this subset of patients. Metabolic abnormalities were frequent among children with stone disease, with hypocitraturia being the most common.

FR-PO651

Nephritic Factor-Like Autoantibodies Are Present in Unaffected Children

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Background: We previously reported that C3-convertase targeted autoantibodies (nephritic factor-like antibodies) were highly prevalent in normal young adults (publication pending). In this study, we explore the prevalence of these convertase-directed antibodies in the pediatric population.

Methods: We measured the binding and stabilization of the C3-convertase and it's proenzyme by normal human IgG purified from plasma samples. We selected samples for three age cohorts: one, five, and ten-year-olds. Binding was determined using surface plasmon resonance with C3b was immobilized as the surface ligand. Each purified antibody was tested in four analyte conditions: IgG alone, IgG with FB (proconvertase), IgG with FD, and IgG with FB and FD (convertase). These conditions were compared to four control conditions: buffer alone, FB alone, FD alone, and FB with FD. Response (in RUs) was recorded at 20 seconds post-injection to measure binding and at 200 seconds post-injection to evaluate stabilization.

Results: Binding and stabilization results were mixed. All three age cohorts (1, 5, 10 years) show a statistically significant increase in binding for IgG+FB (proconvertase) vs FB

alone at 20 seconds post-injection (two-tailed students t-test values of 0.002, 0.004, and 0.007, respectively). However, none of the cohorts show statistical significance at 200 seconds (t-test results of 0.49, 0.13, and 0.41). Significant binding was observed in the IgG+FB+FD samples compared to FB+FD at both 20- and 200-seconds post-injection for all age groups. Review of the data shows strong positive results (increasing reagent response by >20%) in 16 individuals for the convertase and 20 individuals for the proconvertase.

Conclusions: Our data suggests that convertase- and proconvertase-directed antibodies exist in pediatric cohorts. The prevalence is less than what we previously reported in adults (29/30 individuals were positive for both antigens). Whether this indicates the *de novo* emergence of this antibody over time or class switching of an IgM to an IgG over time is currently under investigation. Determining an origin for nephritic factors is an important research goal in complement-mediated kidney disease. Identifying non-pathogenic antibodies that share the convertase antigen may provide an origin for nephritic factors.

Funding: NIDDK Support

FR-PO652

Identification of Patients with Potential Undiagnosed Atypical Hemolytic Uremic Syndrome (aHUS) in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry

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Background: Atypical Hemolytic Uremic Syndrome (aHUS) is a rare disease characterized by thrombocytopenia, microangiopathic hemolytic anemia, and impaired kidney function. Diagnosis of aHUS is complicated by its similarity to other forms of thrombotic microangiopathy (TMA). The recognition of aHUS has become more commonplace in the last 10 years due to advancements in laboratory diagnostics and targeted complement inhibition. Although acute presentation with fulminant TMA are readily diagnosed, more indolent presentations may not be recognized as aHUS but may progress if untreated to end-stage kidney disease.

Methods: Potential participants were identified from the 3 NAPRTCS registry arms through a query of underlying diagnoses that could be associated with TMA or unknown etiology and transplant eligibility (defined as eGFR <30 ml/min/1.73m^2, history of maintenance dialysis or kidney transplant). Identified participants were eligible if they had evidence of TMA (thrombocytopenia, schistocytes, decreased hemoglobin levels, elevated lactate dehydrogenase, and/or decreased haptoglobin levels). Enrollees were evaluated for evidence of thrombocytopenia and severe anemia as a marker of microangiopathic hemolysis. Major organ symptoms and growth factors (height or weight z-score <-2.0), were also reviewed at the time of potential TMA.

Results: Ninety-five participants were identified in the query of diagnosis and transplant eligibility. Thirty-three (35%) participant records from 9 NAPRTCS centers were available for retrospective review and had at least one marker of potential TMA. The most common CKD diagnoses were AKI (27%), Lupus (27%) and unknown (22%). They were 55% biological female and median age at enrollment was 15 years. Thrombocytopenia OR microangiopathic hemolysis were each suspected in 74% of participants, while 42% had evidence of both. Major organ involvement most frequently identified at time of suspected TMA episodes included cardiac (hypertension; 31%) and gastrointestinal (19%), while 44% of participants had evidence of growth failure or were underweight.

Conclusions: This analysis shows that there may be a higher prevalence of aHUS in the NAPRTCS registries than was previously thought.

Funding: Commercial Support - Alexion Pharmaceuticals, Inc.

FR-PO653

Shiga Toxin-Producing Escherichia coli (STEC) Infection in a Pediatric Patient with Compound Heterozygous Deletion of CFHR1-3 and CFHR1-4

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Introduction: Hemolytic uremic syndrome (HUS) is classified into typical and atypical (aHUS). Typical HUS is secondary to a Shiga-toxin infection as E. Coli (STEC-HUS), whereas aHUS is secondary to complement gene mutation and/or complement factor H (CFH) antibodies. aHUS is diagnosed once ADAMTS13 deficiency and STEC infection have been ruled out. aHUS can be triggered by different conditions also STEC infection. We present a pediatric case firstly diagnosed as STEC-HUS afterward diagnosed as aHUS following a sudden relapse of the thrombotic microangiopathy (TMA) who favorable response to Eculizumab.

Case Description: A 9 years old child developed TMA, acute kidney injury (AKI) and posterior reversible encephalopathy syndrome (PRES). Eculizumab was administered leading to clinical improvement. The patient was initially diagnosed with STEC-HUS based on positive fecal test for STEC O157. After 4 weeks, a severe relapse of TMA occured. Thus, Eculizumab treatment was restarted. Genetic analysis revealed compound heterozygous deletion of CFHR3-CFHR1 and CFHR1-CFHR4, along with high serum titer anti-CFH antibodies (222 U/mL). aHUS diagnosis was made and Eculizumab was continued.

Discussion: STEC infection does not ruled out aHUS diagnosis and early use of Eculizumab might be reasonable in severe HUS cases. Investigations for autoantibodies and genetic factors should be pursued to identify aHUS-related factors and enhance patient outcomes.

Biochemical analysis

	Admission	Discharge
Platelets (n°/uL)	48000	293000
Hemoglobine (g/dL)	7.4	12.6
Aptoglobine (mg/dL)	2	100
Lactate dehydrogenase (U/L)	1585	244
Creatinine (mg/dL)	9.86	0.96
Bood urea nytrogen (mg/dL)	355	73
C3 (mg/dL)	59	106
C4 (mg/dL)	26	41
CH50 (%)	-	2

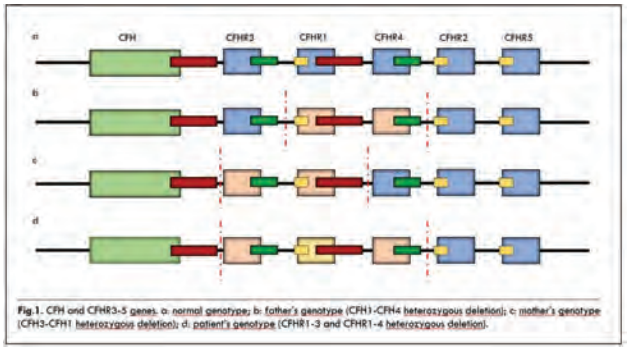

Fig.1. CFH and CFHR3-5 genes. a: normal genotype; b: father's genotype (CFH)-CFH4 heterozygous deletion); c: mother's genotype (CFH3-CFH1 heterozygous deletion); d: patient's genotype (CFHR1-3 and CFHR1-4 heterozygous deletion).

FR-PO654

Successful Voclosporin Treatment of Lupus Nephritis in an Adolescent

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Introduction: Lupus nephritis (LN) flare is a common cause of kidney injury. Rituximab (RTX) is a widely employed treatment for children with LN flare, though Its use may be limited by severe hypersensitivity reaction. We report here a 17-year-old AA girl with LN flare who had severe hypersensitivity to RTX, who showed significant improvement of proteinuria after introduction of Voclosporin (VCS). We believe this is the first reported case of the use of VCS in an adolescent with LN.

Case Description: 17 yo AA girl diagnosed with LN class V in 2016 after she presented with facial rash, proteinuria, joint stiffness, and weight loss. She was treated with Prednisone and mycophenolate mofetil leading to complete remission. In 2019, she developed increasing proteinuria with flare and required 2 cycles of RTX with remission of LN. Cyclophosphamide (CYC) was not used due to parental refusal. She remained on hydroxychloroquine, prednisone, enalapril and aspirin. In late 2022, she had a symptomatic LN flare with hypoalbuminemia, edema, and serum creatinine of 0.5mg/dL. Repeat RTX infusion led to a severe hypersensitivity reaction characterized by chest pain, SOB and generalized rash which required epinephrine, antihistamine and O_2. Due to severe anaphylaxis, it was decided not to use further RTX. VCS 23.7mg BID was initiated starting Feb 2023. Results: With the use of VCS, patient had rapid improvement in her serum albumin and reduction of proteinuria within 2 weeks, which has been maintained to 12 weeks. At last visit her serum albumin improved to 3.3 gm/dL from 2.1gm/dL and UPCR (mg/mg creatinine) improved to 1.4 from 7.5 at the start of VCS. Her lipid profile (Total cholesterol, LDL, TG) at follow up improved to (157,96,113) from (284,197,162) at start of VCS. No other significant changes in BP, hematologic parameters or eGFR. No adverse events from the use of VCS.

Discussion: Treatment options in children with LN are limited and mostly involve RTX and calcineurin inhibitors. Severe RTX hypersensitivity in our patient precluded its use. We have shown significant improvement of proteinuria with use of VCS in pediatric age group, suggesting it may be a useful option especially if other medications like RTX are not effective or contraindicated. Further controlled trials should be done to evaluate safety and efficacy of VCS in children.

FR-PO655

Clinicopathological Characteristics of the Pediatric IgA Nephropathy with eGFR <90 mL/min/1.73 m2 at Onset

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Background: The pediatric IgA nephropathy (IgAN) cases with eGFR<90 ml/min/1.73m^2 (eGFR<90) at onset are regarded as a type of severe case in the Japanese Clinical Practice Guidelines for Pediatric IgA Nephropathy 2020. However, clinicopathological characteristics of those patients are not clarified. So, the purpose of this study is to clarify the clinicopathological features of those with eGFR<90 at onset.

Methods: From July 1976 to December 2018, among 560 children with biopsy-proven IgAN at Kobe University and Wakayama Medical University, Cr-eGFR at onset was available in 555. We investigated clinicopathological differences in 107 (19.3%) patients with eGFR<90 at onset and the other 448 patients.

Results: About 30% of eGFR<90 cases were detected as with gross hematuria. And there were significant differences in the proportion of boys (69.2 vs. 51.8%, p=0.001), onset age (9.6 vs. 11.0 years, p<0.0001), the prevalence of nephrotic syndrome (10.3 vs. 4.9%, p=0.004), proteinuria (1.2 vs. 0.9 g/gCr, p=0.03), and renal biopsy before 1990 vs. after 1990 (73.8 vs. 33.7%, p<0.0001). There was no significant difference in pathological findings. The renal survival rate in the eGFR<90 group was significantly lower (77.9 vs. 93.3% at 15 years; 95%CI: 53.3-91.6 vs. 83.8-97.0%, p=0.006). In patients with eGFR<90 at onset, when irreversible eGFR<60 state is defined as kidney failure, the patients who progressed to kidney failure showed lower eGFR at onset (64.7 vs. 78.2 ml/min/1.73m2, p=0.0001), heavier proteinuria (2.6 vs. 1.0 g/gCr, p=0.008), and no remission of proteinuria after treatment (0.0 vs. 52.6%, p=0.001).

Conclusions: Cases with eGFR<90 at onset are clinically severe cases with various histopathological features, and some of them do not respond to treatment and have poor renal prognoses.

FR-PO656

DNASE1L3-Associated Nephropathy in Two Siblings Presenting C1q Nephropathy and Membranoproliferative Glomerulonephritis

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Introduction: Deoxyribonucleases are in charge of extracellular DNA degradation, limiting inflammatory response. Deoxyribonuclease 1 like 3 (*DNASE1L3*) of DNase I family is known to be essential for the prevention of autoimmune disorders by sustaining plasma extracellular DNA homeostasis. Therefore, DNase1L3 gene mutation might cause autoimmune disorders, although only the cases of systemic lupus erythematous (SLE) had been reported previously. Here we report two siblings, sharing same compound heterozygote pathogenic variants of *DNASE1L3*, who were diagnosed with two different chronic glomerulonephritis.

Case Description: An eight-year-old boy presented hematuria with proteinuria and diagnosed as C1q nephropathy after kidney biopsy. Past medical history and family history were unremarkable. Despite treatment with immunosuppressive agents including steroid and tacrolimus, his kidney function deteriorated and lost at his age of 12. After living-donor kidney transplantation (KT), his allograft function has been well maintained until the last follow-up after 2 years of KT without proteinuria or any other extra-renal symptoms. His brother also presented hematuria and proteinuria at his age of 6 and diagnosed as membranous nephropathy at his first kidney biopsy. Steroid and weekly rituximab treatment led to partial remission, but became resistant to immunosuppressant treatment. Follow-up biopsy revealed membranoproliferative glomerulonephritis type 2 and now he has been managed with medications including tacrolimus and mycophenolate. At his last follow-up on age of 13, his eGFR was 110mL/min/1.73m^2 but nephrotic range proteinuria still persisted. On multiple parallel sequencing, both siblings were found to have same compound heterozygote likely pathogenic variants of *DNASE1L3*, c.401_402dup and c.556A>G, which were inherited from their father and mother, respectively.

Discussion: Here we report sibling cases of *DNASE1L3* associated nephropathy, suggesting that dysfunction of deoxyribonucleases and predisposition to autoimmune diseases can be one of the pathogenic mechanisms of chronic glomerulonephritis. Interestingly, two siblings with same genetic predisposition showed different spectrum of nephropathies with distinct clinical courses, implying that there might be other modifying factors than the genetic predisposition.

FR-PO657

Persistent Proteinuria Associated with CUBN Variants in Korean Children

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Introduction: Persistent proteinuria is a risk factor of progression for chronic kidney disease (CKD). However, the recent discovery suggests that not all proteinuria is damaging. *CUBN*, encoding the membrane glycoprotein cubilin, forms cubilin-amnionless-megalin complex that is responsible for the receptor-mediated endocytosis of albumin in the proximal tubules. A defect of cubilin decreases albumin reuptake, consequently resulting in proteinuria. Interestingly, variants located at the N-terminal of *CUBN* result in severe proteinuria and megaloblastic anemia, whereas variants at the C-terminal are associated with benign, isolated proteinuria.

Case Description: Here, we report 6 Korean patients (M:F=3:3) presented with persistent proteinuria with homozygous or compound heterozyous C-terminal *CUBN* variants. All patients presented with incidentally found isolated asymptomatic proteinuria, at their median age of 5 years (range 18 months ~ 9years). Their mean urine protein creatinine ratios was 1.13 (range 0.94 ~ 1.5) mg/mg at presentation and laboratory findings were unremarkable at presentation for eGFR, serum albumin, lipid, hemoglobin, urine 2-microglobulin and N-acetyl-beta-D-glucosaminidase. None had hypertension, and kidney ultrasound was normal. Two patients underwent kidney biopsy, which revealed non-specific findings. Their median follow-up duration was 4 years (range 6 months ~ 12 years), median age at the last follow-up was 8.5 years (range 2 years ~21 years) and the amount of proteinuria and the kidney function did not change significantly over time regardless of renin-angiotensin-aldosterone system (RAS) inhibition with mean urine protein creatinine ratio at the last follow up of 0.965 (range 0.75 ~ 1.175).

Discussion: These cases are similar to previously reported cases, indicating that asymptomatic subnephrotic range proteinuria patients should be suspected of C-terminal variants of *CUBN* gene. There are still debates on whether *CUBN* C-terminal mutation is truly benign proteinuria, and whether clinicians should treat these patients with RASi.

	Patient #1	Patient #2	Patient #3	Patient #4	Patient #5	Patient #6
1st Presenting age / gender	9yr / F	8yr / F	3yr / F	18month / M	7yr / M	20 months/M
UPCR, mg/mg	0.94	1.13	1.5	1.14	0.63	1.46
cDNA	c.4402del c.6821+3A>G	c.205G>T c.6821+3A>G	c.6118C>T c.4855+2C>G	c.4855+2C>G c.4855+2C>G	c.8579G>A c.6821+3A>G	c.4855+2C>G c.9079G>A c.4770C>G
Protein	p.Q1468Rfs*17 -	p.G69* -	p.R2040* -	- -	p.C2860Y -	- p.G3027R p.I1590M

FR-PO658

Anti-Nephrin Antibodies in Idiopathic Nephrotic Syndrome in Japanese Children

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Background: Many patients with childhood idiopathic nephrotic syndrome are steroid-sensitive, suggesting the involvement of the immune system in the pathogenesis. Several genome-wide association studies have suggested a polygenic contribution, particularly in the *HLA DR/DQ* region and a locus including *NPHS1*, but the etiology remains unclear. Anti-nephrin antibodies have recently been reported in both adults and children with biopsy proven minimal change disease (MCD), but the presence of anti-nephrin antibodies in Japanese childhood idiopathic nephrotic syndrome (INS) has not been investigated.

Methods: Anti-nephrin antibodies were measured by ELISA in paired plasma samples obtained from 14 Japanese pediatric patients with INS (male/female: 8/6), at initial disease onset (active disease) and following steroid monotherapy. Clinical characteristics were compared between the anti-nephrin antibodies positive and negative groups.

Results: The median age at the onset was 75.5 months (interquartile range (IQR): 45-113). Steroid sensitivity resulted in complete remission in 13 patients and almost complete remission in one patient after 4 weeks of glucocorticoid monotherapy. Circulating anti-nephrin antibodies were detected in seven of 14 patients during active disease. In all cases, anti-nephrin antibodies were significantly reduced following treatment concordant with clinical response. There were no differences between the positive and negative groups in pre-treatment parameters. Of the 13 patients who achieved complete remission, nine had at least one relapse during a median follow-up of 851 days (IQR: 808-973). There was also no significant difference in the relapse-free period after the onset between the two groups (P=0.658).

Conclusions: We have identified circulating anti-nephrin antibodies at initial presentation in half of Japanese pediatric INS, which is a higher proportion than previously reported for a North American cohort of adults and children with biopsy proven MCD. Further studies are needed to establish the prognostic implications of anti-nephrin antibodies in childhood INS and the relationship with the *NPHS1* risk variants in this population.

Funding: Government Support - Non-U.S.

FR-PO659

Metabolic Acidosis in Pediatric Participants with Glomerular Disease in the NEPTUNE and CureGN Cohorts

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Background: Metabolic acidosis (MA) has been associated with a more rapid decline of kidney function in cohorts of children with chronic kidney disease (CKD) and children with glomerular (vs. non-glomerular) CKD were more likely to have untreated acidosis. To date, no study has systematically examined MA in children with varying types of glomerular disease.

Methods: Children ages 1-17 y/o, enrolled in the NEPTUNE or CureGN studies with ≥1 serum bicarbonate and eGFR measurement were included. MA was defined as serum bicarbonate <22mEq/L, unresolved acidosis was acidosis at baseline that remained <22 mEq/L whereas resolved acidosis was baseline acidosis that improved to ≥22 mEq/L on repeated measures. The primary outcome of interest was eGFR slope (ml/min/1.73m^2 per year) which was examined using an adjusted linear mixed-effects model.

Results: In the 786 participants eligible for study inclusion, the mean baseline serum bicarbonate was 24.8±3.15 meq/L. 12.2% (n=96) of the cohort were acidotic and only 1.4% (n=11) were receiving alkali therapy. In the adjusted longitudinal analysis, patients with unresolved acidosis had an eGFR slope difference per year of -12.4 ml/min/1.73m^2 compared to those with resolved acidosis (95%CI: -17.5, -7.4) (Table 2).

Conclusions: Untreated MA is common in children with glomerular disease. Patients with unresolved MA had faster eGFR loss when compared to those with resolved acidosis from baseline. Future analyses will examine mechanistic pathways by which MA is proposed to contribute to disease progression through gene expression analysis.

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Table 1: Baseline demographic and clinical characteristics for 786 children in the NEPTUNE and Cure GN cohort

Characteristics	Overall (n= 786)	Serum Bicarbonate (<22 meq/L) (n=96)	Serum Bicarbonate (22-25 meq/L) (n= 461)	Serum Bicarbonate (>25 meq/L) (n= 229)	p-value
Demographics					
Age (years)	10 (6, 14)	6 (3, 11)	9 (5, 14)	13 (9, 15)	**<0.001**
Male sex	453 (58)	50 (52)	261 (57)	142 (62)	0.20
Race					0.15
White/Caucasian	479 (61)	63 (66)	280 (61)	136 (59)	
Black/African American	164 (21)	18 (19)	88 (19)	58 (25)	
Other	101 (13)	10 (10)	68 (15)	23 (10)	
Unknown/missing	42 (5)	5 (5)	25 (5)	12 (5)	
Hispanic Ethnicity	116 (15)	17 (18)	70 (15)	29 (13)	0.44
Clinical Characteristics					
Glomerular Disease					0.42
Minimal Change Disease	312 (40)	43 (45)	184 (40)	85 (37)	
FSGS	200 (25)	27 (28)	117 (25)	56 (24)	
Other	274 (35)	26 (27)	160 (35)	88 (38)	
Hypertension	156 (20)	22 (23)	93 (20)	41 (18)	0.56
Height (cm)	140 (115, 162)	120 (104, 143)	135 (111, 159)	156 (134, 169)	**<.0001**
BMI Percentile					0.29
Obese (>95th)	246 (31)	37 (39)	149 (32)	60 (26)	
Overweight (85th-95th)	161 (20)	18 (19)	95 (21)	48 (21)	
Normal weight (5th-84th)	338 (43)	36 (38)	192 (42)	110 (48)	
Underweight (<5th)	14 (2)	1 (1)	7 (2)	6 (3)	
Unknown/missing	27 (3)	4 (4)	18 (4)	5 (2)	
eGFR (ml/min/1.73m^2)	97 (81, 117)	92 (75, 120)	98 (83, 119)	96 (80, 113)	0.27
Hemoglobin (g/dL)	12.0 (12.0, 14.0)	12.5 (11.6, 13.4)	13.1 (12.0, 14.0)	12.3 (12.2, 14.2)	**0.005**
Albumin (g/dL)	3.6 (2.7, 4.1)	3.4 (2.3, 4.1)	3.7 (2.8, 4.2)	3.5 (2.6, 4.0)	0.07
Urine protein/creatinine (mg/mg)	0.6 (0.2, 3.8)	1.2 (0.2, 5.4)	0.6 (0.1, 3.7)	0.9 (0.2, 3.8)	0.14
Medications					
Alkali therapy	11 (1)	4 (4)	4 (1)	3 (1)	**0.04**
Carbonate	30 (4)	8 (4)	18 (4)	8 (3)	0.95
ACE inhibitors/ARBs	333 (42)	41 (43)	185 (40)	107 (47)	0.26
Diuretics	84 (11)	12 (13)	39 (8)	33 (14)	**0.05**
Other	271 (34)	40 (42)	165 (36)	66 (29)	0.06

Frequencies are presented as N (%) and continuous variables as median (interquartile range)

Table 2: Association of unresolved metabolic acidosis with estimated GFR slope (ml/min/1.73m^2 per year) over follow-up

	Estimate	95% Confidence Limits		P-value
Unresolved acidosis*yearly eGFR slope *(ref=resolved acidosis)*	-12.4	-17.5	-7.4	**<0.001**

Linear mixed effects model adjusted for baseline age, sex, race, and eGFR as well as for the effect of time with each covariate.

FR-PO660

Mitochondrial DNA in Urinary Large Extracellular Vesicles as a Marker of Relapse in Children with Nephrotic Syndrome

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Background: Nephrotic Syndrome (NS) is one of the most common causes of glomerulopathy in children. There has been an increased focus on reactive oxygen species (ROS) and mitochondrial injury in podocytes as drivers of proteinuric disease. We recently showed that podocyte-specific large extracellular vesicles (LEVs; 0.1-1.0 um) are increased in the urine of children with NS. The aim of this study was to characterize LEV mitochondrial DNA (mtDNA) content from those same children. We investigated this relationship further using cultured podocytes exposed to toxins *in vitro*.

Methods: We analyzed urine samples from a prospective cohort enrolling children 1-18y with NS. Podocyte specific LEVs were quantified using flow cytometry and nanoparticle tracking (NTA). Urinary LEV mtDNA was assessed using qPCR. Human immortalized podocytes (hPod) were used in cell culture experiments. Puromycin aminonucleoside (PAN; 25 ug/mL; 24 hours) and lipopolysaccharide (LPS; 25 ug/mL; 24 hours) were used as podocyte toxins.

Results: We analyzed 28 samples from 14 patients. Podocyte LEVs were significantly lower in remission vs. nephrosis ($p<0.01$). Urine protein to creatinine ratio correlated with elevated LEVs ($p=0.0005$). Patient urinary LEV mtDNA was higher in NS relapse compared to remission ($p=0.04$). In hPod cells, PAN treatment resulted in a 2.5-fold increase in hPod LEVs ($p=0.03$) while LPS caused a 3.5-fold increase ($p=0.0004$). The impact of PAN and LPS treatment on *in vitro* LEV production was abrogated by the antioxidant MITO-Tempol. Following treatment with PAN or LPS *in vitro*, we observed an ~25-fold increase in LEV mtDNA content ($p<0.01$).

Conclusions: In summary, LEVs may serve as a biomarker of podocyte injury in nephrotic syndrome in children and their mtDNA content can differentiate remission from relapse. hPods show similar characteristics when treated with common podocyte toxins, and ongoing studies aim to characterize this further.

FR-PO661

Urine Biomarker Analysis of Pediatric Nephrotic Syndrome

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Background: The molecular underpinnings of pediatric nephrotic syndrome remain unclear. Response to immunosuppressive therapy is relatively poor in many patients with Focal Segmental Glomerular Sclerosis (FSGS) as compared to children with Minimal Change Disease (MCD). Elucidation of glomerular disease biomarkers that predict treatment response would be critical towards improved outcomes in pediatric nephrotic syndrome. Identification of subpopulations of nephrotic syndrome by proteomics could indicate differences in patient outcomes. We addressed the hypothesis that comparison of urine proteomes in children with MCD and FSGS could distinguish disease activity and molecular mechanisms of disease progression.

Methods: Proteomic analysis was conducted on urine from children with MCD and FSGS enrolled in the CureGN Consortium to determine differences in disease activity. Urine specimens from 216 patients were analyzed by 2D-LC-MS/MS. MetaboAnalyst 5.0 was employed to perform statistical analyses to identify candidate urine biomarkers of disease activity in pediatric FSGS and MCD. Confirmation ELISA assays were performed for ORM1 and C3. K-means clustering was conducted on nephrotic urine proteome to identify patient clusters.

Results: Proteomic profiles in complete remission urine were dramatically different from nephrotic specimens. ORM1 and C3 levels are significantly higher in nephrotic urine vs complete remission. Unsupervised clustering of nephrotic proteomes showed two distinct clusters suggesting subgroups of patients.

Conclusions: Our findings indicate the potential for ORM1 and C3 to be biomarkers of disease activity. Unsupervised clustering analysis of nephrotic urine proteome indicated a cluster with increased immune response and complement proteins.

Funding: NIDDK Support

FR-PO662

Multi-Omic Serum Profiling in Children and Young Adults Affected by Steroid-Dependent Nephrotic Syndrome

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Background: Idiopathic nephrotic syndrome (INS) is the most common cause of proteinuria in children and young adults. The mainstay of therapy is steroids and based on treatment response, patients can be classified as dependent or resistant. However, there

are no validated biomarkers able to predict treatment response or even to identify the biochemical pathways involved in the pathogenesis of INS.

Methods: We performed a proteomic and lipidomic analysis on serum samples of 82 children and young adults with steroid-dependent INS enrolled in a randomized clinical trial (NCT02394119). With the aim to limit confounding factors due to protein and lipid dysregulation that characterized the acute phases of INS, serum samples were collected during remission. Therefore, all patients had no proteinuria. As control group, we used 26 healthy donors matched for age and sex.

Results: Multi-omics analysis identified a total of 307 and 3.027 unique gene proteins and lipids respectively. Statistical analysis revealed the upregulation of 8 proteins and 38 lipids and the downregulation of 20 proteins and 18 lipids. Moreover, by combining multiple algorithms, including machine learning analysis, we identified a core panel of features able to clearly distinguish between INS patients and healthy donors. In addition, functional analysis of these panel of features revealed the main biological processes associated to steroid-dependent INS patients.

Conclusions: This study confirmed that the multi-omics approach allows to identify a core panel of biomarkers specific for steroid-dependent INS. As a strength point, we emphasize that INS patients had no proteinuria. Therefore, our findings may suggest that INS is characterized by several protein and lipid fingerprints not related to the remission or recurrence phases. Our results may represent the base for further investigation into the still unknown pathogenetic mechanisms of INS.

Funding: Government Support - Non-U.S.

FR-PO663

Genotype-Phenotype Associations in Patients with Congenital and Infantile Nephrotic Syndrome

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Background: Congenital nephrotic syndrome (CNS) and infantile nephrotic syndrome (INS) are disorders of the slit diaphragm of podocytes in the glomerular basement membrane. CNS manifests during the first three months of life, and INS between 3-12 months. The clinical features of the diseases include nephrotic-range proteinuria, hypoalbuminemia, and edema. The most common causes of CNS and INS are mutations in the *NPHS1* and *NPHS2* genes encoding nephrin and podocin, respectively. This study aimed to establish specific genetic characteristics of CNS and INS and their clinical correlations in the North American population.

Methods: Nine Pediatric Nephrology Research Consortium (PNRC) sites retrospectively reviewed charts of 36 patients born between 1998 and 2019 with CNS or INS and underwent genetic testing. ClinVar, SNP, and Human mutation database confirmed the mutation's pathogenicity.

Results: *NPHS1* mutations were more often seen in CNS patients (27/36; 75%), whereas the INS group had more frequent mutations of *WT1* (3/11;27.2%) and *NPHS2* (4/11;36.3%) genes. Among patients with *NPHS1* mutations, the splice site had more mutations than the gene coding region, irrespective of the group. Among these mutations, IVS17-1 G>A splice mutation was found in 4 subjects that showed aggressive features of CNS. Interestingly, the mutation's pathogenicity was confirmed by ClinVar, SNP, and Human mutation database. In patients with CNS, the frequency (9/18;50%) of multiple mutations of the *NPHS1* gene was higher than in the INS group (2/5;40%) and significantly associated with hyperproteinemia (p=0.021) and hypoalbuminemia (p=0.03). Albumin infusions were much more effective in CNS patients with *NPHS2/WT1* mutations than those with *NPHS1* mutations. In INS patients with *WT1* mutations, albumin infusions were less effective in supporting serum albumin levels.

Conclusions: Variations in splice sites, especially IVS17-1 G>A, and multiple mutations in the *NPHS1* gene were associated with a more aggressive course of CNS in infants.

FR-PO664

Pediatric Nephrotic Syndrome in Brazil: Results from a National Cohort of 772 Cases

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Background: Characterizing pediatric nephrotic syndrome (NS) is crucial to predict long-term outcomes. However, data on this disease condition are yet scarce in developing countries.

Methods: We conducted a retrospective epidemiological study using a nationwide representative sample comprising 16 centers and 772 cases. Cox regression was used to model stage 5 chronic kidney disease (CKD)-free survival, with response to steroid therapy as the explanatory variable, and sex, ethnicity, and family history of nephrotic syndrome as covariates.

Results: There was a slight male predominance in the cohort (436 cases, 56% of the total). The median age at disease onset was 3.3 years (IQR: 2.2 to 5.7), and the follow-up period for the sample was 5.4 years (IQR: 2.8 to 9.1). A family history of NS was reported in 55 cases (9.7% of valid responses to this question). The final classification of the response to steroid treatment revealed 317 (42%) cases of steroid-sensitive NS, 238 (31%) patients with steroid-dependence/frequent relapses, 167 (22%) cases of steroid-resistant NS, and 39 (5%) patients with secondary steroid resistance (initial positive response to steroids followed by subsequent resistance). Considering the whole sample, 317 (41%) underwent a kidney biopsy and only 15 (2%) children had a genetic test, yielding a low molecular genetic diagnostic rate. At the end of the follow-up, 57 children (7.7%) had progressed to stage 5 chronic kidney disease (CKD). CKD stage 5-free survival over a ten-year follow-up period was estimated to be 90% (95% CI: 87% to 94%) and the median time to the event was 5 years. According to the response to steroids, resistance (HR: 63, $p < 0.001$) and secondary resistance (HR: 11, $p = 0.031$) were associated with a worse prognosis. A multivariable model adjusted for sex, ethnicity, and family history of NS did not alter the magnitude or direction of the associations with steroid responses.

Conclusions: Steroid resistance was observed at a higher frequency than typically reported in the literature, and there is low access to molecular diagnosis in the whole country. Moreover, our data reaffirm the negative impact of resistance and secondary resistance to steroids on the prognosis of pediatric nephrotic syndrome.

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FR-PO665

Nephrotic Syndrome in a Child with R138Q NPHS2 Mutation

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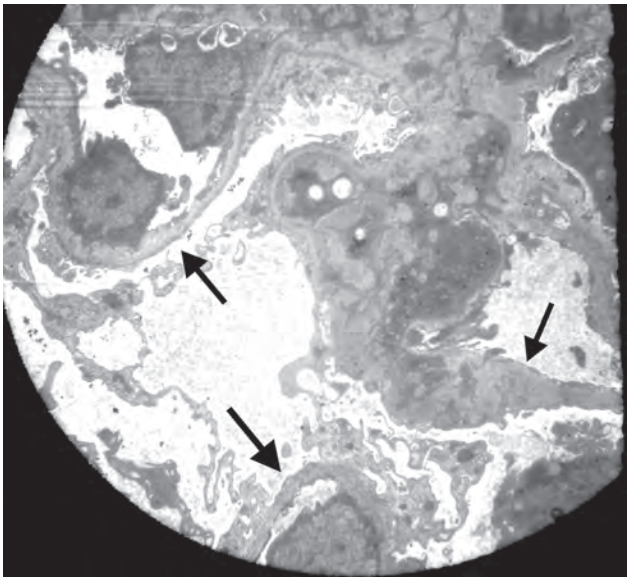
Introduction: Steroid resistant nephrotic syndrome (SRNS) accounts for 30% of all cases of nephrotic syndrome (NS) in children and frequently leads to end stage kidney disease (ESKD). 30% of children with SRNS demonstrate identifiable causative mutations in podocyte-associated genes. Early identification of genetic forms of SRNS is critical to avoid potentially harmful immunosuppressive therapy.

Case Description: A 2-year-old male patient with NS (plasma creatinine of 0.7 mg/dL, serum albumin of 0.6 g/dL, urine protein/creatinine ratio of 18.0 mg/mg) and negative family history of renal disease did not respond to 4-week steroid treatment. Infectious and immune workup for secondary NS was negative. Kidney biopsy showed mesangial proliferative glomerulonephritis, focal membranoproliferative pattern, global glomerulosclerosis (3/50), mild interstitial fibrosis, foot process fusion and basement membrane dysmorphism. Tacrolimus and lisinopril were added to therapy pending results of genetic testing. Genetic panel showed *NPHS2* c.413G>A (p.Arg138Gln) homozygous pathogenic variant. A diagnosis of autosomal-recessive form of nonsyndromic SRNS due to *NPHS2* causative variant was made. Immunosuppressive therapy was stopped, lisinopril dose was increased and weekly infusions of albumin/furosemide were initiated to manage edema.

Discussion: A diagnosis of SRNS due to NPHS2 causative variant was made. Immunosuppressive therapy was stopped, and lisinopril dose was increased. Weekly infusions of albumin/furosemide were initiated to manage edema and prevent complications from hypoalbuminemia. The patient is being managed expectantly until a time when a kidney transplant is necessary. This case demonstrates the importance of early genetic testing in children with SRNS to avoid prolonged potentially harmful immunosuppressive therapy, provide timely genetic family counseling and discuss considerations for future living related donor kidney transplantation.



FR-PO666

Improving PPSV23 Vaccination Rates in Children with Nephrotic Syndrome

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Background: Children with nephrotic syndrome (NS) are at high risk for pneumococcal infections and the PPSV23 vaccine is recommended as part of the pneumococcal vaccine series. Barriers such as lack of availability in pediatrician clinics, inability to verify primary series status, and not addressing vaccinations has led to an inadequate rate of PPSV23 vaccination.

Methods: This is a quality improvement (QI) study that aims to increase PPSV23 vaccination rate among eligible NS patients admitted to the renal service to 75% by September 2023. An H&P template was created that includes a smart phrase prompting residents to review eligibility criteria for PPSV23 vaccination and vaccinate if appropriate. Patients older than 2 years of age that have completed primary pneumococcal vaccine series, and had not received Rituximab in the last 6 months were included. Pediatric residents were educated on QI study at the beginning of their renal rotation by fellows and sign placed in workroom to serve as a reminder. Process metrics included resident use of H&P and percent of eligible patients that refused vaccinations.

Results: In 2-month period, 12 patients with NS were admitted to the renal service. 8 patients were up-to-date and 4 were eligible for PPSV23. Of eligible patients, 3 were identified, 2 received PPSV23 prior to discharge and 1 family declined. The H&P template was used for 7/12 (58%) of admissions and at hospital discharge 2/4 (50%) of eligible patients were up-to-date.

Conclusions: Increasing PPSV23 vaccination is important in decreasing serious pneumococcal infections. Our project showed improvement in identifying eligible NS patients with the implementation of the new H&P template. The participation from pediatric residents underscores value of simple interventions woven into work flow and work space.

FR-PO667

Homeostatic Model Assessment (HOMA) in Pediatric Patients with Nephrotic Syndrome Receiving Tacrolimus

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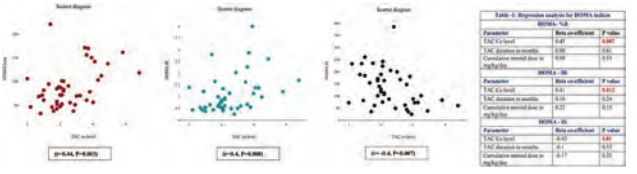
Background: Children with nephrotic syndrome receive diabetogenic drugs like tacrolimus (TAC) and steroids. TAC is toxic to pancreatic β-cells and suppresses insulin production in a time and dose dependent manner. Post transplant diabetes mellitus due to TAC and or steroids is well documented in renal transplant patients. Although overt diabetes is rare in children receiving TAC with or without steroids for nephrotic syndrome (NS), the subclinical effect on β cell function has not been studied.

Methods: We prospectively followed children with NS who received TAC therapy at least for 1 year. We noted patient demographics, clinical and histologic pattern of NS, cumulative steroid dose (mg/kg/day) received 90 days prior and TAC C_0 levels. Fasting insulin, blood sugar to calculate HOMA indices for IR (insulin resistance), HOMA % β for beta cell function, HOMA-IS (insulin sensitivity), C-peptide and HbA1C were done once at study inclusion and yearly intervals when required. Statistical analysis included Pearson's correlation, paired t test and regression analysis.

Results: We performed HOMA indices in 37 patients between September 2021-February 2023. Six patients had 2 measurements during the study period. The mean TAC duration, TAC Co level and mean cumulative steroid dose were 27 months (95% CI[22;32]), 4.54 ng/ml (95% CI[4.12;4.97]) and 0.36 mg/kg/d (95% CI[0.28;0.44]) respectively. In Pearson's correlation analysis we found positive correlation between TAC Co level, HOMA IR (r=0.4, P=0.008) and TAC Co, HOMA %β (r=0.44, P=0.003) and cumulative steroid dose, fasting blood glucose (r=0.3, P=0.46). There was negative correlation between TAC Co level, HOMA IS (r =-0.4, P=0.007). In regression analysis, only TAC Co level significantly influenced all HOMA indices including insulin resistance, insulin sensitivity and beta cell function. A HbA1C of > 5.7 (pre-diabetes range) was found in 32.4% (12/37) patients which warrants further monitoring. C-peptide levels were significantly higher after 12 months of TAC therapy in 6 patients who had two measurements (p=0.032).

Conclusions: Tacrolimus therapy for nephrotic syndrome in children can affect pancreatic beta cell function as assessed by HOMA indices.



FR-PO668

Using Degree of Foot Process Effacement to Predict Outcome in Paediatric Steroid-Resistant Nephrotic Syndrome: A Multi-Centre Analysis

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Background: Steroid resistant nephrotic syndrome (SRNS) is a common cause of paediatric end-stage renal failure requiring transplantation. Recurrence post-transplantation is high in those with no identified pathogenic variant, but those with pathogenic mutations rarely develop recurrence post-transplantation. Previous work suggests that degree of native renal biopsy podocyte foot process effacement (FPE) may distinguish genetic and non-genetic causes of SRNS, but the studies are limited by small samples and single-centre recruitment. This suggests that degree of native biopsy FPE may detect risk of post-transplant recurrence. We hypothesised that diffuse FPE is a marker of circulating factor disease and predicts post-transplant recurrence, while segmental FPE is a marker of non-recurrent disease.

Methods: We analysed a multi-centre nationwide cohort of paediatric SRNS patients (RADAR) to assess if FPE degree can predict disease recurrence. 138 paediatric Nephrotic Syndrome patients had transplantation between 2007-22. 28 with native biopsy electron microscopy (EM) reports available were included. We quantified FPE as diffuse or segmental from report language.

Results: 9/28 patients developed disease recurrence. 27 patients had genetic testing, of which 11 had a causative genetic mutation. No patients with pathogenic genetic variants developed recurrence (recurrence if pathogenic variant 0/11; recurrence if no pathogenic variant 9/17, p=0.0039). 9/11 patients with pathogenic variants show diffuse FPE on EM while 9/17 without identified genetic mutations show diffuse FPE (p=0.2264). All 7 patients with slit diaphragm protein pathogenic mutations had diffuse FPE. Patients with diffuse FPE (recurrence 4/18) trended towards lower recurrence rates than those with segmental FPE (recurrence 5/10, p=0.2096).

Conclusions: In this multi-centre cohort we show trends between genetic causes of SRNS and FPE, and the direction of the association contrasts with literature. We show that slit diaphragm protein mutations are associated with diffuse FPE. We show a not statistically significant trend towards diffuse FPE and lower recurrence post-transplant. This study is limited by small numbers and its retrospective nature, but the trends justify further investigation in larger groups of patients.

FR-PO669

A Pediatric Patient with Proteinuria and Hepatic Steatosis

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Introduction: Frasier syndrome is a rare but well described disorder arising from a donor splice site mutation in intron 9 of the Wilms Tumor 1 (*WT1*) gene. It is associated with steroid resistant nephrotic syndrome and progression to ESRD. Patients with Frasier syndrome are characteristically phenotypic females with an XY genotype, streak ovaries and a risk for gonadoblastoma. Here we describe an XX pediatric patient with *WT1* mutation characteristic of Frasier syndrome and an incidental finding of hepatic steatosis.

Case Description: A six year old obese female was referred to nephrology after two years of progressive isolated proteinuria; dipstick of 3+ and UPC of 2.5 mg/mg at time of referral. She had no overt edema. Her serum albumin and creatinine were normal at 4.0 g/dL

and 0.48 mg/dL respectively, and labs were notable for transaminitis with AST 56/ ALT 126. Ultrasound demonstrated normal kidneys but incidentally an echogenic liver. Renal biopsy was consistent with FSGS: 1/24 glomeruli had global sclerosis, EM had diffuse podocyte foot process effacement, and IF was unrevealing. Genetic panel testing was then completed and revealed a pathogenic mutation in *WT1* (IVS9+4C>T) and a separate pathogenic mutation in HNF1A which portends a risk to Mature Onset Diabetes of the Young (MODY) and in some cases hepatic steatosis. Normal uterus and ovaries as well as XX genotype were confirmed on this patient. She was initiated on ACEI therapy with no improvements in proteinuria over two years (recent UPC of 4.7 mg/mg), but renal function has remained stable. She is followed by Hepatology for hepatic steatosis. Parental genetic testing is pending, but father has a history of type 2 diabetes at age 18 years.

Discussion: This case highlights the value of genetic testing in pediatric patients who present with isolated nephrotic range proteinuria without nephrotic syndrome, and whether a renal biopsy can be avoided if genetic results are available. Our patient is unique in that she is an XX female with normal ovarian development thus we question the need for gonadal monitoring as the risk for gonadoblastoma is seen in those XY females with streak ovaries. With regards to proteinuria and progression to ESRD, therapy is mainly limited in pediatrics to ACEI and ARB. In this patient with an HNF1A associated risk of metabolic syndrome, we consider the role of an SGLT-2 inhibitor for its nephroprotective and antiproteinuric effects.

FR-PO670

Improving Polygenic Risk Scores for Steroid-Sensitive Nephrotic Syndrome by Integrating Relevant Traits

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Background: Polygenic risk scores (PRS) have been widely applied in research studies to identify associations of a person's overall genetic profile with diseases/traits. We are in the early stages of developing PRS for steroid sensitive nephrotic syndrome (SSNS). PRSmix and PRSmix+ have been created to incorporate additional PRS for both the same disease and correlated traits to improve PRS prediction accuracy. Here, we tested the hypothesis that the prediction accuracy of an SSNS PRS would be increased using these strategies.

Methods: Using our previously created SSNS PRS (Barry et al.), we applied PRSmix and PRSmix+ in a European SSNS cohort. Candidate PRSs were obtained from the Polygenic Score Catalog. Individuals in our European SSNS cohort were randomly assigned to a training/testing cohort. Three models were created to assess the additive benefit of combining multiple PRS and correlated traits: the "best PRS" model only includes our SSNS PRS as a predictor, the "PRSmix" model incorporates all SSNS PRS, and the "PRSmix+" model adds high-power PRS from correlated traits to the PRSmix model. The Likelihood-Ratio test (LRT) was used to compare the goodness of when adding a PRS to the model. The Matthews Correlation Coefficient (MCC) was used to evaluate binary classifications; it ranges from –1 to 1, with extreme values 1 reached in case of perfect classification. Comparative predictive accuracy in the testing dataset was assessed using a two-sample z test.

Results: In a 100-fold cross validation study, adding another SSNS PRS (PRSmix) always significantly improved model fit (LRT<0.05) compared to the best PRS. Furthermore, adding high-powered traits (PRSmix+) always significantly improved model fit (LRT<0.05) compared to the PRSmix. The average case prediction accuracy (as measured by MCC) was slightly improved for both the PRSmix (MCC=0.499) over bestPRS (MCC=0.477; p=0.38) and the PRSmix+ (MCC=0.502) over best PRSmix (p=0.36). For PRSmix+, the PRS traits with highest inclusion across 100 models were eosinophil (100%), asthma (79%), and white blood cell counts (72%).

Conclusions: We improved the prediction capability of SSNS PRS using PRSmix and PRS mix+. PRS of other diseases/traits can increase the accuracy of predictive models, may ultimately improve clinical inference, and could provide a better understanding of SSNS disease etiology.

FR-PO671

Trends from 2010 to 2022 in the Utilization of Anti-CD20 Antibodies to Treat Childhood Nephrotic Syndrome

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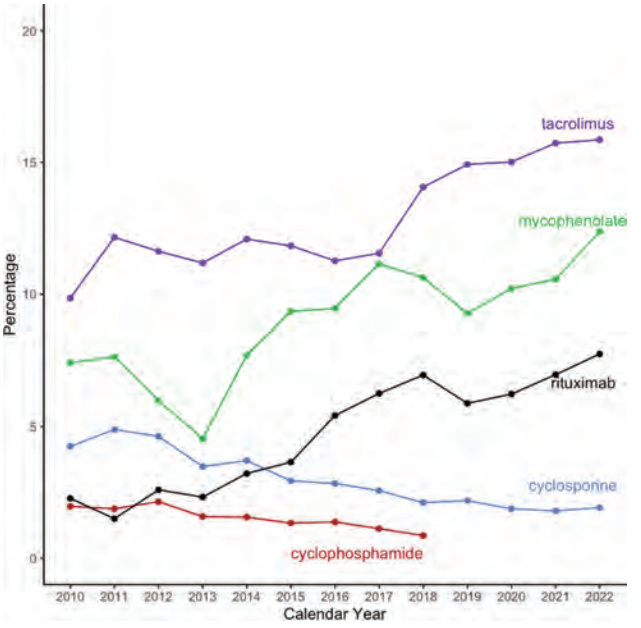
Background: A growing body of evidence supports the efficacy of the type I anti-CD20 monoclonal antibody, rituximab, in the management of children with frequently relapsing or steroid dependent nephrotic syndrome (NS). We examined trends in the use of anti-CD20 antibodies in a multi-institutional population of children with NS.

Methods: Data came from PEDSnet, a clinical research network that aggregates electronic health record (EHR) data at several children's healthcare organizations (database version 4.8). Patients were aged 2-21.99 years, had ≥2 outpatient visits ≥1 year apart, and met our published EHR-based computable phenotype algorithm for nephrotic conditions between January 2010-November 2022. Children with systemic lupus erythematosus (SLE) or congenital or genetic nephrotic diagnoses were excluded. Treatments were measured from NS diagnosis to kidney transplant or most recent in-person encounter. We stratified the cohort by presence of native kidney biopsy.

Results: Among 6,880,824 patients across 6 centers, 3,021 met criteria for nephrotic conditions. 953 (32%) had at least one kidney biopsy. Rituximab utilization increased over time, with a sustained increase since 2019 from 5.9% to 7.8%. Similar trends were observed for mycophenolate and tacrolimus. Concurrently, use of cyclosporine and cyclophosphamide decreased. Tacrolimus was most frequently used.

Conclusions: Use of rituximab to manage NS has steadily increased. PEDSnet provides the ability to collect real-world data and enhance our understanding of long-term efficacy and trends in steroid-sparing medication use for rare diseases such as NS.

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



Drug exposure trends in NS patients; counts <11 not shown

FR-PO672

Efficacy and Safety of Single-Dose Rituximab Biosimilar in the Initial Episode of Paediatric Steroid-Sensitive Nephrotic Syndrome

Liu Jialu, Hong Xu, Qian Shen. *Children's Hospital of Fudan University, National Children's Medical Center, Shanghai, China.*

Background: The 12-month relapse-free survival rate is less than 30% in steroid-sensitive nephrotic syndrome (SSNS) children after the standard corticosteroid therapy. Rituximab is effective in reducing the relapse in children with frequent relapse or steroid dependent NS. Accordingly, we hypothesize rituximab added to guideline-recommended corticosteroid therapy is effective for maintaining remission for the first year of onset.

Methods: An open-label, single-arm, multicentre trial was performed at eight centers in China with a 12-month follow-up (NCT04783675). The first episode of SSNS children treated with standard corticosteroids was eligible for inclusion. Eligible patients received a single dose of 375 mg/m^2 rituximab biosimilar within one week after achieving remission. The primary outcome was the 12-month relapse-free survival rate after rituximab was added to corticosteroid therapy, was compared with historical controls treated without rituximab on NCT03878914.

Results: Totally, 44 children were treated with rituximab and all but one patient completed one year of follow-up. Rituximab therapy was associated with a significantly higher 12-month relapse-free survival rate than the historical control (32 [74.4%] vs 10 [30.3%] children; P <0.001; hazard ratio, 1.89; 95%CI, 1.15-3.11). The median time to first relapse was 123 days (95%CI, 73 to 201 days). The treatment was well tolerated. During infusion, three participants reported throat irritation. Besides two patients with a decreased neutrophil count, all other adverse events were fully resolved.

Conclusions: In children with the initial episode of SSNS, rituximab appears to be an effective and safe treatment for maintaining disease remission. It provides evidence for the initial treatment strategy of SSNS in children to prevent the recurrence.

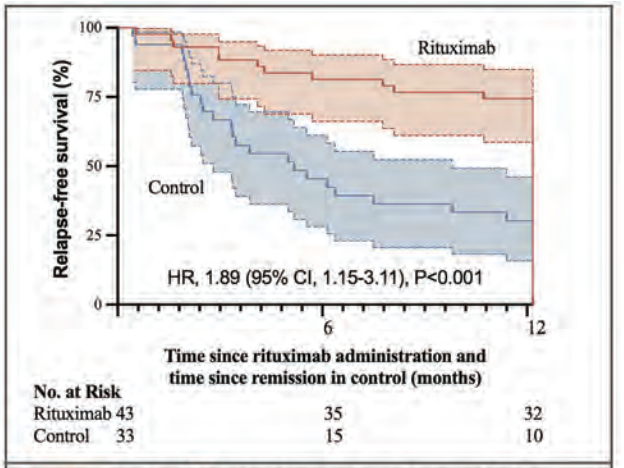


Figure 1. Kaplan-Meier curve of relapse-free survival in patients with rituximab and historical controls
Kaplan–Meier curves indicating the percentage of patients who maintained remission at 6 months and 12 months after rituximab biosimilar (HANLIKANG) infusion and in control. Shading indicates 95% CIs.

FR-PO673

The Genetic Background of Persistent Hypogammaglobulinemia After Rituximab Treatment in Refractory Nephrotic Syndrome

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Background: Rituximab (RTX) has been proven to be effective for refractory nephrotic syndrome(rNS); however, persistent severe hypogammaglobulinemia (HGG) is occasionally observed and causes health problems in some patients. We suspected the coexistence of common variable immunodeficiency (CVID) in these patients, and we proved that they had either genetic mutations associated with CVID or *FCGR3A* F176V polymorphism, that is, a missense variant, c.526T>G (p.Phe176Val) in *FCGR3A* gene (NM_000569.8).

Methods: We performed whole genome sequence analysis on patients who developed persistent HGG (<400 mg/dL, more than two years) after the last RTX therapy.

Results: Five patients were recruited (table). All of them developed rNS and were treated with repeated RTX <18 years old. Their HGG was persistent for more than five years after the last RTX therapy. Among the five patients, three (No.1-3) showed severe (<200 mg/dL) HGG, pan hypoimmunoglobulinemia, and susceptibility to infection. The other two (No.4 and 5) showed relatively mild HGG, normal to high levels of other types of immunoglobulin, and no clinical symptoms. Genetic analysis revealed that No.1 had a novel heterozygous mutation in *NFKB1*, and No.3 had a heterozygous mutation in *TNFSF12*. Both genes were associated with CVID. *FCGR3A* F176V polymorphisms were found in No.2 and 3. Thus, patients who developed severe and symptomatic pan hypoimmunoglobulinemia had either a genetic mutation associated with CVID or *FCGR3A* F176V polymorphism.

Conclusions: Severe and symptomatic pan hypoimmunoglobulinemia after RTX treatment was accompanied by genetic alterations in CVID-associated genes or in FCGR3A genes. Advanced analysis of these genes before RTX administration could prevent, or at least delay, the development of symptomatic pan hypoimmunoglobulinemia.

No.	gender	IgG level (mg/dL)	other Ig	genetic mutation	FCGR3A F176V	clinical symptoms
1	female	<100	IgA↓, IgM↓	NFKB1	N.A.	otitis media, respiratory infection
2	female	<100	IgA↓, IgM↓	–	+	otitis media, sinusitis
3	male	100-200	IgA↓, IgM↓	TNFSF12	+	rota virus-associated encephalitis
4	female	200-300	IgA↑, IgM→	–	–	no symptoms
5	female	200-300	IgA↑, IgM↑	–	–	no symptoms

FR-PO674

Genetic Insights into Pediatric Polycystic Kidney Disease

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Background: Pediatric polycystic kidney disease (PKD) exhibits genetic heterogeneity, including autosomal dominant and recessive PKD, as well as ciliopathies with syndromic involvement. Relying solely on gene-specific analyses may lead to missed diagnoses. Our objective was to summarize genetic findings in pediatric patients (pts) with bilateral kidney cysts seen at our clinic, emphasizing unique cases.

Methods: We reviewed resolved cases from Jan 2020 to Apr 2023 involving clinical or research genetic testing. Targeted next-generation sequencing, encompassing known and candidate PKD/ciliopathy genes, was performed at our research lab. Variants were assessed using disease-specific and population databases, along with in silico variant assessment tools. Categorization followed ACMG guidelines.

Results: Genetic screening identified pathogenic changes in 9 genes, accounting for 49 pts (45 families): 40 with monoallelic and 9 with biallelic variants. Monoallelic genes included *PKD1* (n=18), *HNF1B* (n=9), *PKD2* (n=5), *PKHD1* (n=2), *IFT140* (n=2), *NEK8* (n=1), *GANAB* (n=1), *TSC2* (n=1), and *TSC2/PKD1* deletion (n=1). Biallelic genes were *PKHD1* (n=6) and *NPHP1* (n=3). Among PKD1 pts, 83% (15/18) had a positive family history, while 60% (3/5) of PKD2 pts did. Incident discovery or family screening diagnosed 67% (12/18) of PKD1 pts, 28% (5/18) had prenatal presentation, and one case involved an early onset intracranial aneurysm rupture. PKD2 pts were all incidentally diagnosed. Children with monoallelic variants in *IFT140*, *GANAB*, or *PKHD1* exhibited mild PKD phenotypes and were incidentally diagnosed through abdominal imaging. The NEK8 variant pt presented with severe neonatal PKD and kidney failure requiring dialysis at 6 years old, representing a novel manifestation for this gene. Nearly all HNF1B variant/deletion pts (8/9) presented in utero with kidney cysts and/or hyperechoic kidneys.

Conclusions: Comprehensive analysis of clinical and research-related genetic screening reveals the complexity of monogenic causes of PKD. This study reports the first pathogenic variant in *IFT140* found in pediatric pts, an additional case involving *GANAB*, and a new monoallelic NEK8 disorder. Genetic screening in pediatric PKD pts, irrespective of family history, offers a definitive diagnosis, informs prognosis and therapy discussions, and facilitates enrollment in clinical trials.

Funding: NIDDK Support

FR-PO675

Kidney Survival in Pediatric Patients with Pathogenic Hepatocyte Nuclear Factor 1β Variants

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Background: Hepatocyte nuclear factor 1β (*HNF1B*) gene variants represent the most common monogenic cause of developmental kidney disease. Identification of specific genotype-phenotype associations in *HNF1B* disease would inform genetic counselling. The objective of this study was to determine whether the *HNF1B* mutation type is associated with kidney survival.

Methods: This was a retrospective observational study involving 521 patients from 14 European countries using the European ERKNet-ERN network. Mean follow-up time was 7.7 years with 6.2 visits per patient. The primary end point was progression to chronic kidney disease (CKD) stage 3 (eGFR<60 mL/min/1.73m^2). Secondary endpoints were the development of extra renal abnormalities including hypomagnesemia, hyperuricemia and hyperglycemia.

Results: Progression towards CKD-stage 3 was significantly delayed in patients with the 17q12 deletion compared to patients with other pathogenic *HNF1B* variants (HR 0.31 (95%CI: 0.20-0.47), p<0.001). Presence of only one functional kidney due to a contralateral multicystic dysplastic kidney or agenesis was associated with accelerated CKD progression (p=0.028). Interestingly, the 17q12 deletion conferred a significant better kidney function than the other *HNF1B* variants already in the neonatal period. Finally, the 17q12 deletion was associated with hypomagnesemia (HR 2.49, 95%CI:1.57-4.03, p<0.001), but not with hyperuricemia or hyperglycemia.

Conclusions: Pediatric patients with the 17q12 deletion and two functional kidneys display a significantly better kidney survival than patients with other pathogenic *HNF1B* variants. We identified the first clinically relevant *HNF1B* genotype-phenotype correlation that informs genetic counselling of pediatric patients.

FR-PO676

Characteristics of Kidney Resident IgA Antibody-Secreting Cells in IgA Nephropathy

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Background: The trigger and sources of pathogenic IgA in IgAN are not established. Prevailing theories suggest that circulating polymeric nephritogenic IgA is produced by either antibody secreting cells located within the mucosa-associated lymphoid tissue or the bone marrow. Our recent work demonstrated that in experimental IgAN mice (BAFF-Tg), mucosal pathobiont-directed IgA antibody secreting cells (APC) are identified within the kidney. In the current study we aimed to characterize kidney IgA APC in experimental IgAN, and to elucidate the factors that foster migration to and residence within the kidney and explore cell-cell interactions within the kidney niche.

Methods: Flow cytometry was used to identify IgA APC in the kidneys of the male BAFF-Tg and C57/BL6 (WT). Single-cell mRNA sequencing (scRNA-seq) was performed in 4 BAFF-Tg and 4 WT at 20 weeks of age to characterize immune cells within the kidney.

Results: We identified an age-dependent increase in IgA-producing plasma cells (PC) by flow cytometry (CD45+, B220-, CD98+, IRF4+, IgA+) within the kidneys of BAFF-Tg but not WT mice; these PC were detectable at 6 weeks of age, and numbers continued to rise by 20 weeks of age. scRNA-seq confirmed a population of IgA APC in the BAFF-Tg kidneys. Analysis of differential gene expression supported phenotypically different subpopulations of IgA APC in kidneys of BAFF-Tg. Ligand-receptor pair analysis suggests

cell-cell interaction patterns between IgA APC, macrophages and endothelial cells that may support migration of IgA APC and proliferation of these cells within the kidney.

Conclusions: Our mouse data support the concept that pathogenic IgA production in experimental IgAN can occur within the kidney. We have confirmed the age-dependent presence of IgA-producing PC within the kidneys of the BAFF-Tg by flow cytometry and these cells may be initially proliferating within the kidney. We have further characterized the immune cell populations within the kidney in experimental IgAN using scRNA-seq, and identified possible cell-cell interactions that may foster the migration and support of mucosal derived IgA APC within the kidney, potentially resulting in kidney pathology. Elucidation of the ligands and receptors involved in kidney IgA APC migration and residence will inform therapeutic interventions for the treatment of IgAN.

FR-PO677

Gut Microbial Variation and Disease Status in IgA Nephropathy

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Background: The pathogenesis of IgA nephropathy (IgAN) is ill-defined. Recent evidence suggests involvement of the gastrointestinal lymphoid tissue in association with the gut microbiome. We hypothesized that patients with IgAN have alterations in gut microbial composition compared to healthy controls (HC), especially during disease activity.

Methods: We performed a case-control study of adult patients with primary IgAN, and age-sex-gender-BMI matched healthy controls (HC). Patients with IgAN were sub-divided based on disease activity (active - UPCR > 1.5 g/g ; remission - UPCR < 1 g/g) and immunosuppressive therapy status (IS, on/off). DNA isolated from stool sample underwent 16S rRNA amplicon sequencing of the V4 variable region. The QIIME2 pipeline was used for analysis. Kruskal-Wallis and PERMANOVA tests were used to compare alpha- and beta-diversity between groups, respectively. ANCOM-II was used to assess taxonomic abundance between groups, and accounted for multiple testing.

Results: The gut microbiome composition of patients with IgAN in remission, off IS, showed significant differences from HC as measured by alpha-diversity index: a decrease in both Chao1 index (p=0.03) and observed features (p=0.02). No significant difference in beta diversity metric found. The genus Muribaculaceae was estimated to occur only in HC whereas Bacteroidales was estimated to occur only in patients in remission, off IS. Although the gut microbiome composition of patients with active IgAN, off IS, showed no significant differences from HC as measured by diversity indices, there were significant alterations in the differential abundance of taxa among the different groups (Table1).

Conclusions: IgAN is associated with changes in the gut microbial composition. Megasphaera, a commensal of healthy gut, was present in HC and patients with IgAN in remission, off IS. Bacteriodales was present only in patients in remission status, off IS. Higher abundance of Enterobacteriaceae genus may reflect bacterial overgrowth due to IS.

Table 1	Healthy Control (N= 23)	Active off IS (N = 14)	Remission off IS (N = 19)	Remission on IS (N = 15)
UPCR, g/g Median(Q1, Q3)		2.2 (1.5,3.3)	0.6 (0.2,0.8)	0.7 (0.4,1.4)
eGFR, ml/min/1.73m2 Median(Q1 , Q3)		72 (36,108)	67 (46,78)	58 (41, 87)
Differential abundance of gut microbial taxa				
Megasphaera (genus)				
Enterobacteriaceae (genus)				
Rhodospirillales (order)				
Gastranaerophilales (family)				
Bacteroidales (order)				

Red color = taxa absent ; Green color = taxa present

FR-PO678

Dihydroartemisinin Inhibits Mesangial Cell Proliferation in IgA Nephropathy by Regulating PGC1α-Mediated Glycometabolism

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Background: Mesangial cell proliferation is the basic pathological feature of IgA nephropathy (IgAN), but the mechanism of glucose metabolism in mesangial cell proliferation has not been studied. It has been reported that artemisinin analogues can effectively regulate cellular glucometabolic enzymes and improve autoimmune diseases, but their efficacy on IgAN remains unclear. The aim of this study was to clarify the changes of glucose metabolism in IgAN, and to explore the therapeutic effect of dihydroartemisinin (DHA) on IgAN.

Methods: The expression of glucometabolic enzymes, and the relationship between enzymes and clinicopathology in IgAN patients were analyzed using GEO datasets and renal biopsy specimens. The expression of glucometabolic enzymes, energy metabolic pathway, cell proliferation, apoptosis were evaluated in mesangial cells after PGC1α agonist/ inhibitor/DHA intervention. Enrichment pathways was analyzed and the metabolites of glucose metabolism were detected after DHA intervention. The IgAN mouse model was administrated with DHA, renal function and pathology, as well as the expression level of glucometabolic enzymes in glomeruli were detected.

Results: The expression of glycolytic enzyme HK1 was increased, and the expression of gluconeogenic enzyme (PCK1, FBP1) were decreased in IgAN glomeruli. The expression of glycometabolic enzymes were significantly correlated with renal clinical indicators. PGC1α was significantly correlated with differentially expressed glucometabolic enzymes, and its expression was lower in IgAN patients with heavy mesangial cell proliferation. DHA upregulated PGC1α expression, inhibited glycolysis and suppressed mesangial cell proliferation. In vivo, DHA reversed the expression of glucometabolic enzymes and alleviated kidney injury in IgAN mice.

Conclusions: This study demonstrated the alteration of glucose metabolism in glomeruli, and the therapeutic effects of DHA in regulation of PGC1α and glucose metabolism in IgAN. These results provide new strategies for renal protection, as well as theoretical basis and intervention targets for DHA therapy of IgAN.

Funding: Other NIH Support - This work was supported by the National Natural Science Foundation of China 82070737, 82270752

FR-PO679

Spatially Resolved Transcriptomics Reveals Golgi-Endoplasmic Reticulum (ER) Network-Associated Differentially Expressed Genes in Membranous Lupus Nephritis

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Background: Class V lupus nephritis (LN) shares histological similarities with membranous nephropathy (MN) characterized by subendothelial immune complex deposits. However, the differences in pathogenesis between class V LN and other LN classes or anti-PLA2R-associated MN are largely unknown.

Methods: Spatial transcriptomic profiling was conducted using GeoMx Digital Spatial Profiler on formalin-fixed paraffin-embedded kidney biopsy specimens obtained from control (n = 7), LN class I to V (n = 24), and anti-PLA2R-associated MN (n = 16). LN and MN specimens were collected at proteinuric status. Differentially expressed genes (DEGs) between (1) each class of LN (I-V) vs. control and (2) class V LN vs. MN were identified. Gene Ontology (GO) terms for DEGs were annotated using the ToppGene suite.

Results: A total of 128 DEGs were downregulated in class V LN compared to MN. These genes were also downregulated in class V LN when compared to control samples, while no significant expression differences were observed in other LN classes compared to controls. Eleven of 128 downregulated DEGs were annotated with biological process GO terms related to Golgi vesicle transport. Regarding cellular component GO terms, Golgi apparatus (30/128 DEGs), endoplasmic reticulum (ER) membrane (19/128 DEGs), and ER-Golgi intermediate compartment (6/128 DEGs) were among the annotated GO terms associated with the DEGs. DEGs in annotation included GOLGA3, TMED7, BET1L, and RAB10.

Conclusions: The ER-Golgi network and related molecular pathway may be involved in the distinct pathogenesis and clinical features of class V LN.

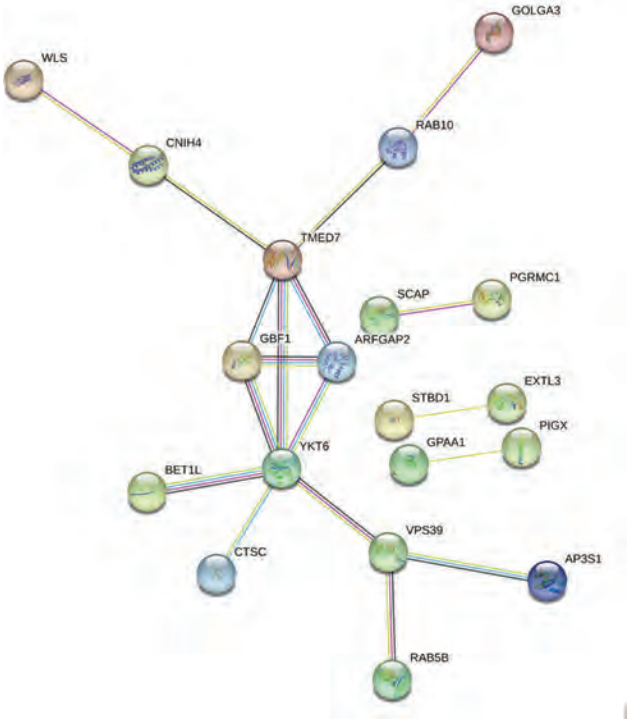


Figure 1. Visualization of Gene Ontology terms annotated differentially expressed genes

FR-PO680

Spatially Resolved Transcriptomic Profiling for Glomerular and Tubulointerstitial Gene Expression in C3 Glomerulonephritis

Jung Hun Koh,[1] Sehoon Park,[1] Jeongmin Cho,[1] Yaerim Kim,[2] Dong Ki Kim.[1]
[1]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea; [2]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea.

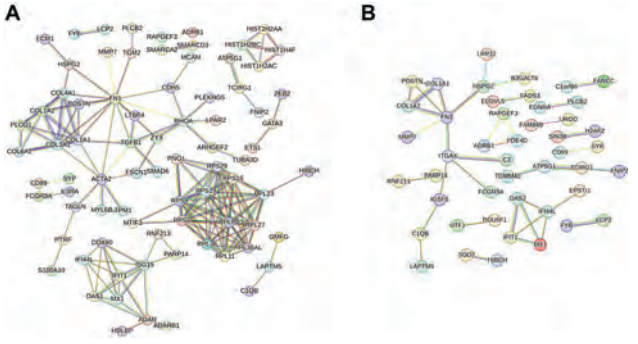
Background: C3 glomerulonephritis (C3GN) is a rare but clinically significant primary glomerulopathy. However, little is known about its transcriptomic profile. We aimed to investigate the substructure-specific gene expression profile of C3GN using the recently introduced spatial transcriptomics technology.

Methods: We performed spatial transcriptomic profiling using GeoMx Digital Spatial Profiler with formalin-fixed paraffin-embedded kidney biopsy specimens of three C3GN cases and eight donor kidney controls. Profiles from other glomerular diseases, including focal segmental glomerulosclerosis, membranous nephropathy, and minimal change disease, were included as disease controls. Gene expression levels between C3GN and the controls were compared by DESeq2 method, and differentially expressed genes (DEGs) were identified with a false discovery rate threshold of 0.05. We performed gene ontology (GO) annotation by the ToppGene Suite and mapped interaction networks among the DEGs using the STRING database.

Results: We identified 229 and 157 highly expressed DEGs in the glomeruli of C3GN compared to those of donor and disease controls, respectively, with consistently highest fold changes seen in POSTN, COL1A2, IFI44L, and TAGLN. Protease binding, structural molecule activity, and extracellular matrix constituent were the top enriched GO terms in the glomeruli of C3GNs, with consistent features seen in the network analysis. In contrast, no significant GO enrichment was found among the 563 and 347 lowly expressed DEGs in the glomeruli of C3GN compared to donor and disease controls. The tubular transcriptome profiles of C3GN were similar to those of the controls.

Conclusions: This is the first report of kidney substructure-specific transcriptomic profile of C3GN to date. Significant disease-specific transcriptomic alterations occur in the glomerulus of C3GN, providing potential insights into the pathophysiology.

Funding: Government Support - Non-U.S.



STRING network analysis of highly expressed DEGs in C3GN glomerulus compared to (A) donor and (B) disease controls.

FR-PO681

Toll-Like Receptors (TLRs) Regulate the Production of Galactose-Deficient IgA1 in Human Renal Mesangial Cells

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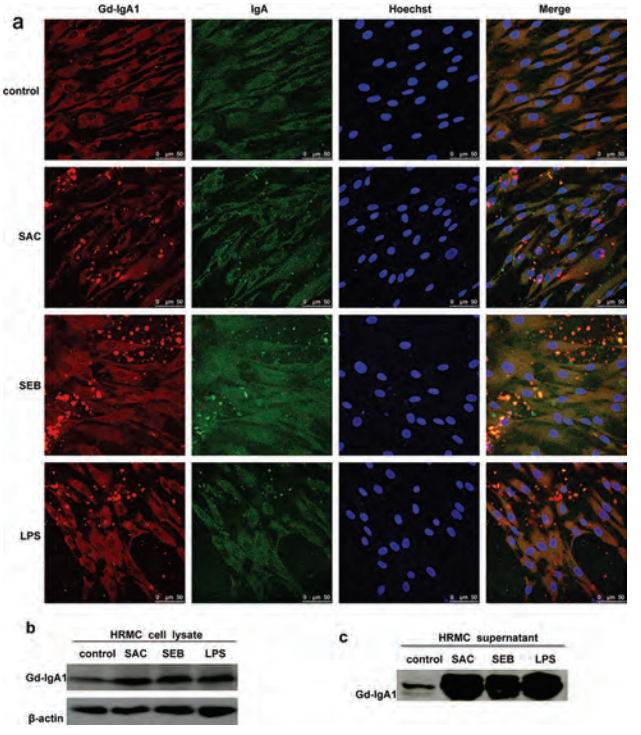
Background: Galactose-deficient IgA1 (Gd-IgA1) is the core factor in the pathogenesis of IgA nephropathy (IgAN). Our group found that glomerular mesangial cells (GMC) could express and secrete IgA1. The aim of this study is to investigate whether Gd-IgA1 can be expressed in normal cultured GMC, upregulated by pathogenic factors, and to explore the regulatory mechanisms between Gd-IgA1 production and pathogen infection.

Methods: Immunofluorescence and western blot were used to confirm Gd-IgA1 expression under normal or stimulated condition. RT-PCR was used to verify the TLRs transcripts.

Results: In this study, we confirmed that Gd-IgA1 can be produced and secreted by mesangial cell lines under normal culture condition, and significantly increased by staphylococcus aureus (SAC), staphylococcal enterotoxin B (SEB), lipopolysaccharide (LPS) and angiotensin II (Ang II). Evidently, SAC and SEB promoted secretion and extracellular granular deposition of Gd-IgA1 in mesangial cells, consistent with renal pathology. Interestingly, mesangial cells constitutively expressed multiple TLRs, and that engagement of mesangial cell TLRs led to produce of Gd-IgA1 and release of proinflammatory cytokines, which can be inhibited by specific repressor of TLRs.

Conclusions: In short, we reported, for the first time, that mesangial cells can produce Gd-IgA1 and regulated by TLRs. This discovery subverted our current understanding for the pathogenesis mechanism of IgAN and hopefully change the current lack of effective treatment for IgAN.

Funding: Government Support - Non-U.S.



FR-PO682

Single-Cell Spatial Profiling of Glomerular Structures in Alport Syndrome

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Background: Many transcriptomics studies have described the molecular mechanisms underlying the progression of glomerular diseases, but very little is known about the gene spatial map of the different cell types, the heterogenous tissue niche composition, and how each glomerulus is affected during progressive CKD. Here we report the spatial characterization of gene expression at the single-cell level in renal biopsies of Alport Syndrome (AS) patients and from healthy subjects.

Methods: Using the Nanostring CosMX Spatial Molecular Imager (SMI) platform, and the human 1000-plex RNA panel we generated spatial maps of gene expression of kidney biopsies from AS patients (n=3) vs healthy subjects. Using H&E images we selected 29 fields of view (FOV) with dimensions of 0.9mm x 0.7mm for analysis. After data QC and normalization steps, we supervised cell typing. Spatial data analysis was achieved using different software and integrated with histopathology.

Results: We identified 36 clusters corresponding to different renal cells including glomerular, tubular, interstitial, and immune cell types. A spatial map of cell types in each FOV was reconstructed. Localization of podocytes, glomerular endothelial cells, and mesangial cells could be visualized. Color-coded gene expression maps of each cell type could be visualized at a single-cell resolution. Our analysis indicated the cellular composition varied between the different AS biopsies, revealing the presence of different cell types in the AS glomerulus not previously described including 3 different types of fibroblasts. We could also identify specific "glomerular immune niches."

Conclusions: CosMx SMI analysis revealed significant differences in gene expression between AS and healthy biopsies at a single-cell level. These preliminary data using this technology may allow the discovery of potential new therapeutic targets for patients with AS, and other CKDs.

FR-PO683

Transplanted Immune Competent Bone Marrow or Spleen Stem Cells Prevent Myeloperoxidase (MPO)-ANCA Glomerulonephritis in Immune-Deficient Mice

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Background: ANCA disease patients cannot suppress the ANCA autoimmune response. Immune deficient *Rag2* knock out (KO) mice also cannot suppress ANCA. We hypothesized that transplantation (Tx) of wild type (WT) bone marrow (BM) or spleen cells would provide Rag-2 KO mice with stem cells capable of defending against Tx of

syngeneic MPO-ANCA B cells. This model could be used to identify specific stem cells for targeted therapy of autoimmune disease.

Methods: As previously described (Xiao H, et al. J Clin Invest 2002; 110:955-963), B6 *Mpo* knockout (KO) mice were immunized with mouse MPO and used as donors of splenocytes (SC) containing B-cells producing pathogenic MPO-ANCA. All B6 WT or B6 *Rag2* KO mice received anti-MPO SC on day 0 (Table G1-8). G3, 7 and 8 *Rag2* KO mice also received normal WT B6 BM or SC Tx on day 0 (G6) or 2-6 weeks before anti-MPO SC Tx. Serum MPO-ANCA was measured on days 0, 4, 7, 11 and 14; and mice were euthanized on day 14 for pathology evaluation.

Results: No male (G1) or female (G4) WT mice developed MPO-ANCA or GN 14 d after injection of MPO-ANCA SC. All male (G2) and female (G5) Rag2 KO mice developed MPO-ANCA and GN by day 14. WT BM Tx into *Rag2* KO mice 6 wks prior to anti-MPO SC (G3) prevented MPO-ANCA and GN. Similarly, Tx of WT SC 2 or 4 wks prior to MPO-ANCA SC (G7,G8) prevented MPO-ANCA and GN. However, Tx of WT SC on 0d (G6) did not prevent MPO-ANCA and GN.

Conclusions: Transplanted immune-competent stem cells from B6 WT BM or spleen prevent MPO-ANCA GN in *Rag2* KO B6 syngeneic mice. Delay in developing autoimmune defense indicates that Tx stem cells require time to proliferate and differentiate to establish autoimmune defense (G6 vs G7 & G8). This model system will be used to identify specific stem cells that are effective in suppressing autoimmunity and effective for targeted immunotherapy.

Funding: NIDDK Support

Table: All mice received anti-MPO SC on day 0. G3,6,7, and 8 also received WT SC or BM cells.

Group	B6 Strain	Sex	n	WT SC or BM Tx	D14 MPO-ANCA (OD)	P vs WT	Crescents %	P vs WT
G1	WT	M	5	None	0.23		0.0	
G2	Rag2 KO	M	5	None	2.04	<0.01	4.6	<0.0001
G3	Rag2 KO	M	5	BM -6 wks	0.16	ns	0.0	ns
G4	WT	F	8	None	0.24		0.0	
G5	Rag2 KO	F	8	None	2.05	<0.0001	6.5	<0.0001
G6	Rag2 KO	F	6	SC day 0	2.12	<0.0001	6.6	<0.0001
G7	Rag2 KO	F	3	SC -2 wks	0.39	ns	1.7	ns
G8	Rag2 KO	F	4	SC -4 wks	0.24	ns	1.5	ns

FR-PO684

Regulatory Function of FcγRIIB Involving the NLRP3 Inflammasome in a Mouse Model of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common form of glomerulonephritis and represents a leading cause of end-stage renal disease. Ample evidence confirms the deposition of IgA and IgG and filtration of mononuclear leukocytes in IgAN patients. Previously, we established an experimental IgAN model in B cell-deficient mice, which implicated interactions between Fcγ receptors (FcγRs) in the pathogenesis of IgAN. Although it is generally accepted that FcγRIIB plays a regulatory role in humoral responses, it remains unknown whether this function and the cell type-specificity of FcγRIIB are reno-protective in IgAN.

Methods: We observed a dramatic increase in albuminuria, renal function impairment, and renal injury in FcγRIIB knockout mice with induced IgAN. Utilizing a mouse model of IgAN and three different types of FcγRIIB-deficient mice, including CEBP/α Cre (myeloid cells), CD11c Cre (dendritic cells) and CD19 Cre (B cells) in floxed FcγRIIB mice, as well as several specific cell models.

Results: We demonstrated that macrophage- and dendritic cell-specific FcγRIIB deficiency blunted the activation of the NLRP3 inflammasome and inhibited the development of IgAN. Moreover, activation of the inflammasome was induced by IgA immune complexes dependent on TLR4/MyD88 signaling, associated with crosstalk between TLR4 and Dectin-2.

Conclusions: These results suggest that activation of FcγRIIB and its downstream signaling pathways could moderate progression of IgAN involving the suppression of the NLRP3 inflammasome. A cell type-specific targeting of FcγRIIB may help the establishment of therapeutic strategy for the renal disease.

FR-PO685

Group 3 Innate Lymphoid Cells (ILC3s) Accelerate Lupus Nephritis Development by Promoting B Cell Activation in Kidney Ectopic Lymphoid Structures

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Background: Group 3 innate lymphoid cells (ILC3s), a novel subset of immune cells with the features of both innate and adaptive immunity, have emerged as important players in autoimmune diseases. However, whether they participate in lupus nephritis (LN) remains elusive. Here, we investigated the role of ILC3s in the pathogenesis of LN.

Methods: Systemic and renal ILC3s were detected by flow cytometry or confocal microscopy in LN patients and spontaneous lupus model MRL/*lpr* mice. The distribution of ILC3s in human and murine kidneys were characterized by immunofluorescence, and the characteristics of ILC3s in different organs of MRL/*lpr* mice were revealed by transcriptome sequencing. Furthermore, ILC3s were adoptively transferred into LN mice to explore their roles in disease. *In vitro*, ILC3s were co-cultured with or without B cells to clarify their function in antibody formation.

Results: The frequencies of ILC3s in blood and kidneys of LN patients were found significantly higher than normal control, and positively associated with serum anti-dsDNA, ANA and total IgG. The elevation of ILC3s and their correlations with autoantibodies were also observed in MRL/*lpr* mice. In the kidney, ILC3s were mainly localized within perivascular ectopic lymphoid structures, showing low expression of resident and proliferative markers. Interestingly, renal ILC3s shared high transcriptomic similarity with gut-derived ILC3s, implying that the small intestine may be a potential source of renal ILC3s. After adoptive transfer of ILC3s into LN mice, both systemic autoimmune manifestations and renal damage were significantly exacerbated. Meanwhile, there were remarkable increases in the proportion of plasma cells and IgG^+ B cells in the kidney after ILC3s transfer. Mechanistically, *in vitro* studies showed that ILC3s promoted the differentiation of B cells into plasma cells and antibody formation.

Conclusions: Our results showed that ILC3s were increased in LN, and accelerated the progression of LN by promoting B cell activation in the kidney.

Funding: Government Support - Non-U.S.

FR-PO686

A Kidney Organoid-Derived Hypoxic Transcriptional Signature Correlates with Tubular Injury and Disease Progression in Focal Segmental Glomerulosclerosis (FSGS)/Minimal Change Disease (MCD)

Akihiro Minakawa, Celine C. Berthier, Matthew Fischer, Jamal El Saghir, V. Vega-Warner, Rajasree Menon, John R. Hartman, Felix H. Eichinger, Jennifer A. Schaub, Matthias Kretzler, Jennifer L. Harder. *University of Michigan Division of Nephrology, Ann Arbor, MI.*

Background: Alterations in kidney tissue hypoxia are thought to contribute to kidney disease but the pathomechanism is unclear. The aim of our study was to investigate the relevance of a hypoxia molecular signature derived from a kidney organoid model to human kidney disease.

Methods: Kidney organoids (K-Orgs) were treated with 1% O_2 for 24 h, and assessed by qPCR, bulk and single cell (sc) RNA-seq, IF and ELISA. A hypoxia signature was extracted from the differentially expressed genes in hypoxic vs. control K-Orgs. This signature was evaluated in bulk RNA-seq the kidney tissue expression profiles in the molecularly characterized FSGS/MCD NEPTUNE cohort (PMID: 36442540) and accompanied with morphometric scores of tubular injuries and the 3 previously computationally derived disease subclusters (C1~C3) and Living donors (LD).

Results: In hypoxic K-Orgs, IF confirmed HIF-1α nuclear accumulation, along with GLUT1 (IF) and secreted VEGFA (ELISA), and genes related to glycolysis and lactate synthesis (qPCR). sc RNA-seq confirmed HIF-1's target gene expression in kidney cell types (e.g. podocytes), and bulk RNA-seq revealed a total of 380 genes identified a hypoxia signature in hypoxic organoids. As shown in the figure, this signature was significantly higher in C3 that was identified with the poorest outcome. Tubular injury scores also correlated with hypoxic gene signature scores.

Conclusions: A transcriptional signature of hypoxic cell stress generated from a hypoxic K-Orgs was higher in the tubulointerstitial compartment of FSGS/MCD patients with poor outcome and correlated with morphometric evidence of tubular injury. These results suggest that kidney cell hypoxia is contributing to FSGS/MCD disease activity and progression.

Funding: NIDDK Support, Other NIH Support - NCATS, Commercial Support - Eli Lilly, Private Foundation Support

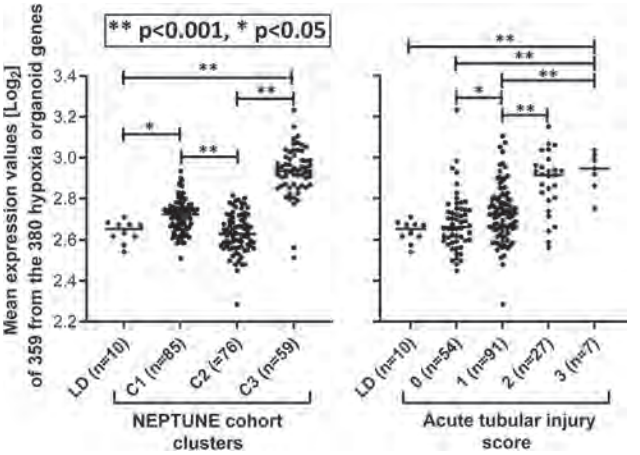

Figure. NEPTUNE cohort

FR-PO687

Mechanistic Study of Celastrol-Mediated Inhibition of Macrophage M1 Polarization in IgA Nephropathy via Downregulating ECM1

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Background: Macrophages play a vital part in amplifying the inflammatory cascade in IgA nephropathy (IgAN), but the potential mechanism and targeted treatment strategies still need to be explored. The aim of this study is to investigate the therapeutic effect of celastrol (CLT) on IgAN, as well as the mechanism of celastrol-mediated inhibition of macrophage M1 polarization in IgA Nephropathy via down-regulating ECM1.

Methods: We established an IgAN mouse model treated with CLT and an M1 macrophage model induced by LPS in Raw 264.7 in vitro. The proteinuria, serum creatinine levels, renal lesions, and infiltration of M1 macrophages in mice were detected. The macrophage markers such as M1 (iNOS) and M2 (Arg-1) expression levels in vitro were checked, as well as expression situation of inflammatory factors such as IL-6 and TNF- α. The expression of ECM1 in renal biopsy of patients was observed and its clinical significance was analyzed. We detected the activation of the ECM1/STAT5 pathway in IgAN mice and M1 macrophage models. And we constructed stable transfected cells with ECM1 overexpression to detect the changes in macrophage M1 polarization after CLT treatment, as well as the expression of ECM1 and STAT5/p-STAT5.

Results: CLT effectively alleviated renal lesions and macrophage infiltration in IgAN mice, and improved renal function. In addition, after CLT intervention, the expression of iNOS, IL-6, TNF- α was decreased and the expression of Arg-1 was increased. ECM1 was obviously expressed in IgAN patient's renal tissue and it was negatively correlated with eGFR, while positively correlated with 24-hour proteinuria. ECM1 was also highly expressed in IgAN mice and in M1 macrophage models. In the M1 macrophage model with overexpression of ECM1, CLT inhibits macrophage M1 polarization and the production of inflammatory factors by downregulating the ECM1/STAT5 pathway.

Conclusions: CLT can effectively alleviate IgAN renal inflammatory damage, inhibit macrophage M1 polarization, and reduce the production of inflammatory factors. ECM1 was obviously expressed in IgAN renal macrophages, and the increase in ECM1 expression is related to the severity of clinical indicators in IgAN patients. The therapeutic effect of CLT on IgAN may be related to its inhibition of macrophage ECM1/STAT5 pathway.

Funding: Other NIH Support - This work was supported by the National Natural Science Foundation of China (82070737) and (81770714)., Government Support - Non-U.S.

FR-PO688

Spatialomic Profiling of Human Kidney Tissues Stratifies Disease Pathology

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Background: To make any scientific advancements, there should be an in-depth understanding of pathophysiology of tissue microenvironment. Newer multiplex imaging-based methods are providing important insights into cytoarchitecture of tissue. We recently developed a novel tissue imaging method, termed SeqStain, that allows rapid and easy immunofluorescence based multiplexed tissue imaging and analyses. Here, we utilize this approach to understand the complex assemblage of cells and their correlations with each other in both healthy subjects and patients with various glomerular diseases.

Methods: We synthesized fluorescently-DNA-tagged antibodies for analyzing multiple kidney-specific antigens using cycles of staining and de-staining on a single tissue section. We probed different histological regions relevant to the kidney and used conventional fluorescence microscopy for imaging the tissues and HALO software for image analyses.

Results: We analyzed both paraffin-fixed and frozen tissue sections using off-the-shelf reagents and a confocal microscope. We were able to accurately image tens of antigens on single tissue specimens for healthy subjects, and from patients with lupus nephritis (LN) and diabetic nephropathy (DN). Analysis of various cellular biomarkers indicated enrichment of specific cellular clusters into distinct neighborhoods.

Conclusions: SeqStain proved to be a versatile, gentle, and easily adaptable method for multiplex imaging that can be highly effective in obtaining a spatial map of kidney. Generated spatial maps will provide important new insights about the disease pathobiology and improve future diagnostics and therapeutics for LN and DN.

FR-PO689

Lisinopril-Mediated ACE Inhibition Reduces Proteinuria and Sclerosis in the G1/G1 but not the G2/G2 APOL1 Mouse Model of FSGS

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Background: APOL1 gene variants G1 and G2 account for the 3 to 4-fold elevated risk of kidney disease in individuals of recent African ancestry. These variants confer protection against Trypanosomal disease, but individuals with two high-risk alleles are at higher risk of developing FSGS and renal failure. Molecular disease mechanisms remain controversial and targeted treatments for APOL1 kidney disease remain an unmet need.

Methods: Our lab has created APOL1 BAC transgenic mice that develop proteinuria and glomerulosclerosis upon injection of pCpG-free plasmid DNA encoding murine IFNg. After injection of G1/G1 and G2/G2 mouse groups with IFNg plasmid, mice were randomized on post-injection day 7 (after confirming proteinuria) to treatment with Lisinopril in the drinking water at 75 mg/L or to a no drug control group. Urinary albumin/creatinine ratio was measured biweekly. At time of sacrifice, kidney tissue was harvested, paraffin-embedded, and 4μm sections were stained with periodic acid-Schiff (PAS) stain. An FSGS score was computed from 30 glomeruli per mouse, each scored in a blind manner as normal or displaying segmental or global sclerosis.

Results: Treatment with the ACE inhibitor lisinopril reduced proteinuria by ~100-fold in APOL1 G1/G1 BAC-transgenic mice and greatly reduced severity of FSGS by histological criteria. In contrast, lisinopril treatment of G2/G2 mice produced improvement neither in proteinuria nor in the likelihood of developing severe FSGS in G2/G2 mice.

Conclusions: Lisinopril-mediated inhibition of ACE modified disease phenotype in the BAC-transgenic APOL1 G1/G1 mouse model of FSGS, but not in the G2/G2 model. These findings add to our understanding of APOL1 disease mechanisms in mouse models of FSGS and may provide insight into APOL1-associated human kidney disease. Early genotyping should in future allow trials of inhibition of the renin-angiotensin-aldosterone system starting before clinical onset of glomerular disease in patients with high-risk APOL1 alleles.

Funding: Other U.S. Government Support, Private Foundation Support

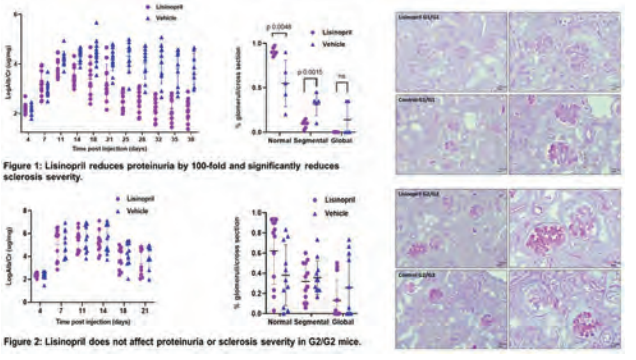

Figure 1: Lisinopril reduces proteinuria by 100-fold and significantly reduces sclerosis severity.

Figure 2: Lisinopril does not affect proteinuria or sclerosis severity in G2/G2 mice.

FR-PO690

YBX1 Alleviated Kidney Injury as a "Reader" of m5C Methylation in Adriamycin-Induced FSGS Mice

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Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of adult nephrotic syndrome. Currently, effective treatments lack due to unclear understanding of its pathogenesis. Recently, Y-box binding protein 1 (YBX1) has been found as a 5 methylcytosine (m5C) 'reader' to stabilize mRNA and promote protein translation. However, the role of YBX1 in FSGS remains unknown.

Methods: FSGS was induced by adriamycin (ADR) in BALB/c mice. Adeno-associated virus 9 (AAV9) containing YBX1 was delivered to FSGS mice for overexpressing YBX1. Mice (n=24) were randomly divided into four groups: normal control (NC), ADR, ADR + AAV9-control, and ADR + AAV9-YBX1. Urine protein creatinine ratio (UPCR), serum creatinine (Scr), and blood urea nitrogen (BUN) were examined by biochemistry. Histological damages were evaluated by PAS and Masson staining and transmission electron microscopy (TEM). YBX1; podocyte biomarkers WT1, synaptopodin, and podocin; profibrotic proteins α-smooth muscle actin (α-SMA), vimentin, and fibronectin (FN) were analyzed by Western blotting and immunofluorescence (IF) staining. The *synaptopodin* and YBX1 were double stained by fluorescence in situ hybridization and IF. Finally, these proteins were stained in renal biopsies from FSGS patients and NC kidneys.

Results: In FSGS mice, UPCR, BUN, and Scr were increased; WT1, synaptopodin, podocin were decreased; α-SMA, vimentin, and FN were overproduced. Importantly, renal YBX1 was decreased. In YBX1 overexpressed FSGS mice, UPCR, Scr, and BUN levels were improved. Meanwhile, the percentage of sclerotic glomeruli was decreased on PAS and Masson. The degree of foot processes fusion was alleviated under TEM. The levels of podocytic WT1, synaptopodin, and podocin as well as profibrotic α-SMA, vimentin, and FN were reverted by delivering YBX1. The co-localization of *synaptopodin* mRNA and YBX1 protein was shown in the cytoplasm of podocytes. The same change directions of podocytotic and profibrotic proteins were seen in renal biopsies from FSGS patients compared to NC kidneys.

Conclusions: YBX1 may play an important role in pathogenesis of FSGS by regulating synaptopodin mRNA and further alleviating glomerulosclerosis through serving as a m^5C 'reader'. YBX1 might be a novel therapeutic target for FSGS.

Funding: Government Support - Non-U.S.

FR-PO691

CD4+ T Cell Egress in Crescentic Glomerulonephritis Is Regulated by a Converse Expression of S1PR1 and CXCR6

Jonas Engeßer,[1] Hans-Joachim Paust,[1] Yu Zhao,[2] Catherine Meyer-Schwesinger,[1] Thorsten Wiech,[1] Stefan Bonn,[2] Christian F. Krebs,[1] Ulf Panzer.[1] Panzer Lab. *[1]Universitatsklinikum Hamburg-Eppendorf, Hamburg, Germany; [2]Universitatsklinikum Hamburg-Eppendorf Zentrum fur Molekulare Neurobiologie Hamburg, Hamburg, Germany.*

Background: Autoimmune diseases such as crescentic glomerulonephritis (cGN) are characterized by a dramatically increased migration of leukocytes to the inflamed tissue. Infiltration of CD4$^+$ T cells play a key role in orchestrating the immune response during inflammation. However, little is known about the function and mechanisms of T cell exit out of the kidney. The aim of this study is to characterize the CD4$^+$ T cell retention and emigration receptors and their implication on tissue injury, especially in the context of restitutio vs chronification of tissue inflammation.

Methods: Lymph vessel staining of renal biopsy cores was performed by immunohistochemistry (IHC). For leukocyte trafficking analysis cGN was induced in *Kaede*-mice, ubiquitously expressing the photoconvertible *Kaede* protein. Photoconversion of intrarenal leukocytes was performed by UV-A light (385 nm) exposure of the left kidney. Leukocytes from kidneys, blood and dLN were analyzed by scRNAseq, flow-cytometry and IHC. For analysis of the chemokine receptor *CCR7* a *CCR7*$^{-/-}$ deficient mouse model was used, for analysis of *CXCR6* a depleting antibody of its sole ligand *CXCL16* was used. *S1PR1* signaling was blocked using FTY720.

Results: In human biopsy cores an exit of CD4$^+$ T cells but not CD68$^+$ macrophages via the lymphatics could be shown. Murine analysis of emigrated CD4$^+$ T cells revealed a set of differentially expressed genes compared to resident CD4$^+$ T cells, mainly a downregulation of the chemokine receptor *CXCR6* and an upregulation of *S1PR1*. *CCR7*, although upregulated on CD4$^+$ T cells showed to be dispensable for T cell egress. Depleting *CXCL16* resulted in an increased migration of CD4$^+$ T cells to dLN, while blocking *S1PR1* signaling led to an increased retention of CD4$^+$ T cells in the kidney and a marked increase in tissue damage.

Conclusions: CD4$^+$ T cells egress via the lymphatics out of the inflamed kidney is tuned by the downregulation of *CXCR6* and upregulation of *S1PR1*. Blocking T cells egress leads to an increase in tissue damage, thus promoting the idea that T cell egress to the dLN alters organ-specific immunity.

Funding: Government Support - Non-U.S.

FR-PO692

The Serine Protease HTRA1 Mouse Model: A Gateway to Identify the Cellular Origin of New Antigens

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Background: While initial membranous nephropathy (MN) autoantigens like PLA2R were found to be transmembrane podocyte proteins, more recently identified antigens are secreted proteins or not clearly derived from podocytes. Whether immune complexes in these cases assemble *in situ* or are deposited after forming in the circulation remains unclear.

Methods: WT and HTRA1 KO mice were immunized with full-length human HTRA1. Immunofluorescence, confocal microscopy and RNAscope were used to identify the origin of autoantigen in HTRA1-associated MN.

Results: As shown in **Figure 1**, MN pathology with mouse HTRA1-mouse IgG immune complexes in a membranous loop pattern and more significant proteinuria was observed in WT, but not HTRA1 KO, mice that were previously immunized with recombinant human HTRA1, despite the presence of circulating anti-human HTRA1 in both animals. This finding suggested that mouse HTRA1 autoantibodies were formed against a shared epitope between human and mouse proteins, leading to *in situ* immune complex formation at the GBM. Furthermore, RNAscope (**Figure 2**) demonstrated podocytes to be the cellular source of HTRA1.

Conclusions: The presence of HTRA1-mIgG deposits in actively immunized WT but not KO mice, along with increased podocyte expression of HTRA1 by podocytes, argues against deposition of circulating immune complexes and instead argues for a podocyte origin of this secreted autoantigen and formation of *in situ* immune deposits. We will further confirm this hypothesis using a podocyte-specific HTRA1 KO.

Figure 1

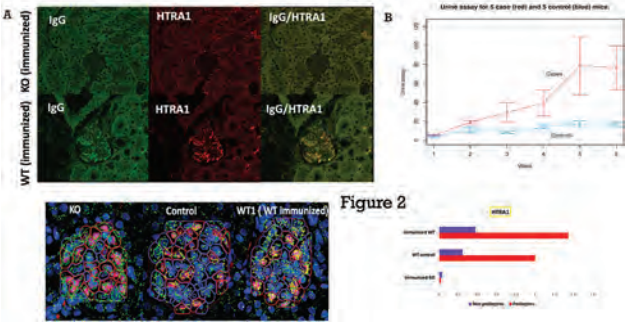


Figure 2

FR-PO693

The Impact of Exposure to Air Pollution on the Progression of Primary Glomerular Disease

Howard Trachtman,[1] Jonathan P. Troost,[1] Jennifer D'Souza,[1] Sara Adar,[1] Miatta Buxton,[1] Abhijit V. Kshirsagar,[2] Lawrence S. Engel,[2] Cassandra R. O'Lenick,[2] William E. Smoyer,[3] Jon B. Klein,[4] Wenjun Ju,[1] Laura H. Mariani,[1] Matthias Kretzler.[1] *[1]University of Michigan, Ann Arbor, MI; [2]University of North Carolina Research Opportunities Initiative, Chapel Hill, NC; [3]Nationwide Children's Hospital, Columbus, OH; [4]University of Louisville, Louisville, KY.*

Background: Exposure to air pollution is linked to chronic disease. Air pollution stimulates injury pathways that contribute to organ damage. However, there is limited information about its impact on the course of kidney disease or the molecular pathways involved.

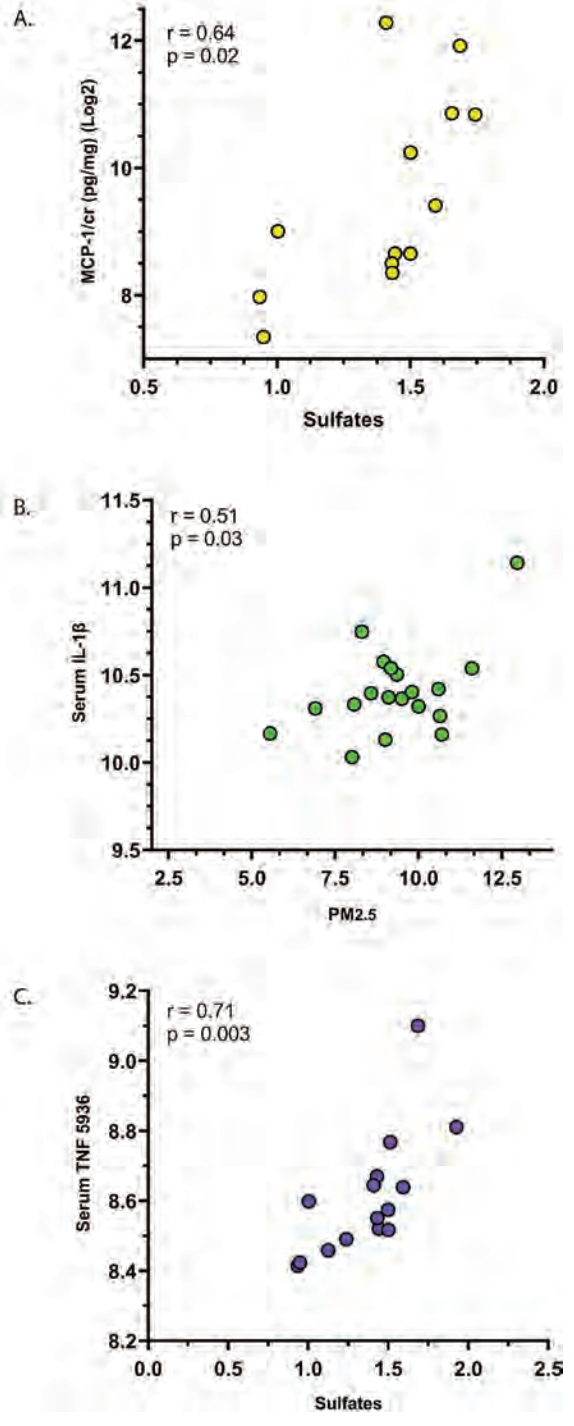
Methods: Patients enrolled in the Nephrotic Syndrome Study Network (n=228) and Cure Glomerulonephropathy (n=697) studies with residential census tract data and ≥2 yr of follow-up were included. Three indices of air pollution exposure were assessed: (1) $PM_{2.5}$; (2) Black carbon; and (3) Sulfates. The primary outcome was the hazard ratio for >40% decline in eGFR or end-stage kidney disease (eGFR<15 ml/min/1.73 m^2, initiation of dialysis, or kidney transplantation). Air quality was categorized by census tract and assessed using modeled concentrations.

Results: $PM_{2.5}$, black carbon, and sulfate exposure were comparable in the two cohorts but higher in Black participants (p<0.005). Baseline eGFR was lower and proteinuria higher in those with exposure above the median for all three pollutants. Among patients with disease duration ≥1 year, in an adjusted analysis, $PM_{2.5}$, HR 1.23 [95% CI:1.02, 1.49], p=0.029, and black carbon, HR 1.42 [95% CI:1.18, 1.71], p=0.0002, were associated with increased likelihood of worsening kidney disease. Sulfate exposure was associated with increased urinary MCP-1 excretion (p=0.018) and increased serum TNF levels (p=0.003), while $PM_{2.5}$ exposure was associated with increased serum IL-1β levels (p=0.025) (Figure 1).

Conclusions: In patients with primary glomerulopathies, exposure to air pollution is associated with an elevated risk for disease progression and increases in systemic biomarkers of inflammation.

Funding: NIDDK Support

Figure 1



FR-PO694

Determining Individual Glomerular Proteinuria and Periglomerular Infiltration in a Cleared Murine Kidney by 3D Fast-Marching Algorithm

Christian Kurts,[1] Alexander M. Böhner,[1] Karin A. Böhner,[1] Sebastian Braehler,[2] Ulrike Attenberger,[1] Martin Rumpf,[3] Alexander Effland.[3] *[1]University Clinic of Bonn, Bon, Germany; [2]Universitat zu Koln, Koln, Germany; [3]Rheinische Friedrich-Wilhelms-Universitat Mathematisch-Naturwissenschaftliche Fakultat, Bonn, Germany.*

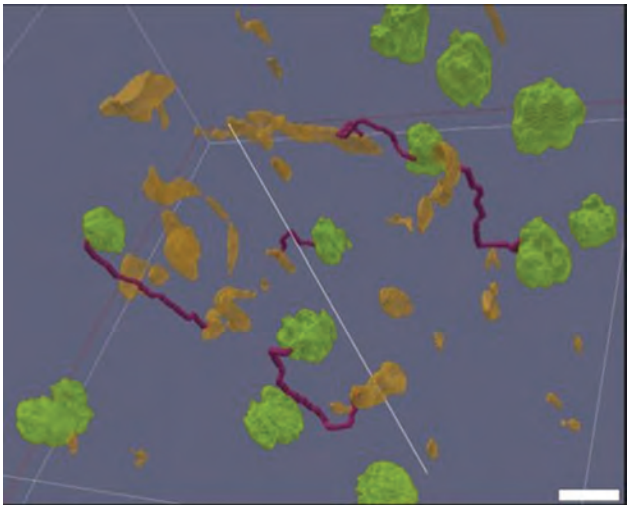
Background: Research in organs with a complex architecture like the kidney benefits from 3D image analysis. However, limited resolution and imperfections of real-world 3D image material often preclude algorithmic image analysis. We here present a methodical framework to overcome these obstacles.

Methods: We optimized our optical tissue clearing protocol to preserve fluorescence signals for light-sheet-fluorescence-microscopy and compensated attenuation effects using adjustable 3D correction fields. Next, we adapted the Fast-Marching algorithm (FMA) to conduct backtracking in 3D environments. Furthermore, we designed a local concentration measure termed Volumetric impact factor (VIF) to quantify extractable objects in 3D microenvironments.

Results: We applied this framework to cleared kidneys of mice with nephrotoxic nephritis, a model for human crescentic glomerulonephritis. Our framework generated a list of anatomical and functional parameters of each individual glomerulus of a murine kidney. Using FMA, we determined and visualized the individual proteinuria (Figure 1). Using VIF, we quantified the individual periglomerular dendritic cell infiltration in nephritic kidneys. By correlating these parameters, we disprove the intuitional assumption that the most infiltrated glomeruli are the most proteinuric. Instead, the glomerular density predicted proteinuria.

Conclusions: Our framework allows multiparameter image analysis and advanced 3D analysis of all nephrons of a murine kidney and facilitates understanding of renal immunopathology.

Funding: Government Support - Non-U.S.



Visual verification of the FMA as a slice-by-slice reduction. Glomeruli in green and intratubular albumin deposits in orange. Shortest intratubular path between protein deposit and causative glomerulus is in purple.

FR-PO695

Dense Deposit Disease: What Makes the Deposits Dense

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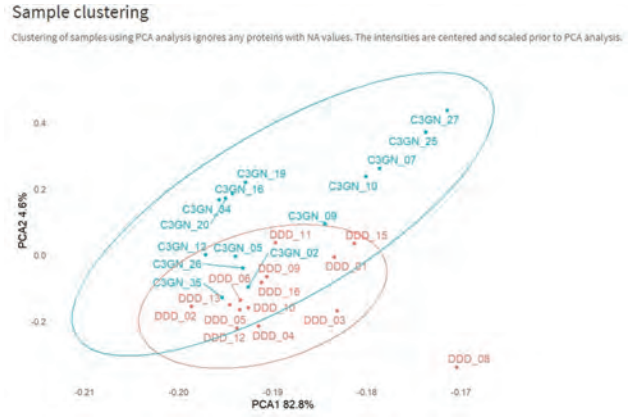
Background: C3 glomerulopathy (C3G) is a disease resulting from dysregulation of the alternative pathway (AP) of complement. C3G includes C3GN and DDD; both are characterized by bright glomerular C3 staining. However, on EM, DDD is characterized by dense osmiophilic mesangial and intramembranous deposits, while the deposits of C3GN are not dense.

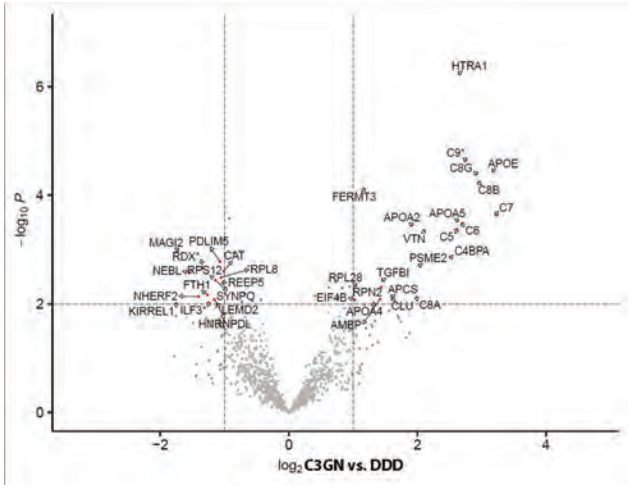
Methods: We performed laser microdissection of glomeruli followed by mass spectrometry in 15 cases of DDD and 29 cases of C3GN to determine the proteomic profile and differences between C3GN and DDD.

Results: As expected, there was overlap in the proteomic profile of C3GN and DDD (figure 1). Both diseases showed high total spectral counts (TSC) of C3, CFHR5, CFHR1, CFHR2 and CFH. Although high TSC of terminal complement proteins (C5-C9) were present in C3GN and DDD, there was a 6-9-fold increase of C5-9 in DDD compared to C3GN. An unexpected finding was the 7-9-fold increase of apoliproteins (APO): APOE, APOA5, APOA2 and APOA4, in DDD compared to C3GN (figure 2). Controls cases showed no accumulation of APO. We also detected increased accumulation of HTRA1, C4b binding protein and SAP proteins in DDD. Immunohistochemistry is being performed to confirm and localize APO in the dense deposits of DDD and compare them with deposits in C3GN.

Conclusions: There is a higher burden of terminal complement pathway proteins in DDD compared to C3GN. In addition, extensive deposition of APOE and APOA5 likely cause the deposits to appear dense in DDD.



Overlap in the proteomic profile of C3GN and DDD.



Differences in protein expresion in DDD compared to C3GN.

FR-PO696

Glomerular Spatial Transcriptomics and Integrated Gut Microbiome Analysis Reveals Pathogenetic Importance of Short-Chain Fatty Acid in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis, and the pathogenesis has been reported to be related to the gut microbiome. Additional studies focusing on the linkage between intra-glomerular transcriptomic alterations and associated microbial signals are warranted.

Methods: We performed glomerular spatial transcriptomic profiling of various glomerulopathies without a profound eGFR decrease and healthy controls using the GeoMx Digital Spatial Profiler. This included 8 IgAN, 10 donor kidney biopsy, 6 diabetic nephropathy, 7 focal segmental glomerulosclerosis, 13 minimal change disease, and 16 membranous nephropathy cases. The glomerular transcriptome was compared between the IgAN and each control group using the DeSeq2 method, and gene ontology annotation was performed. For microbial profiling, fecal samples were collected from 247 IgAN, 52 diabetic nephropathy, 27 lupus nephritis, 42 minimal change disease, 72 membranous nephropathy, and 51 healthy control cases and underwent 16S-sequencing. PICRUSt2 analysis was used to predict metagenome functions, which were compared by ALDEx2 between the groups.

Results: We identified 1209 consistently highly expressed genes in the IgAN glomerulus, mainly annotated in major histocompatibility protein binding, immune cell adhesion, and extracellular matrix formation gene ontologies. On the other hand, 1050 genes were consistently lowly expressed in the IgAN glomerulus. Notably, the annotated gene ontologies included beta 1, 3 galactosyltransferase and short-chain fatty acid transporters or G protein-coupled receptor signaling pathways. Although there was an absence of a single taxa consistently showing a significant difference in the IgAN microbial community, the pathway analysis indicated that the methanogenesis from acetate pathway was significantly abundant in the IgAN gut microbiome.

Conclusions: We identified that short-chain fatty acid and related signal receptors, G-protein-coupled receptors, were significantly lowly expressed in the IgAN glom, linked to the alteration of acetate, a representative short-chain fatty acid, metabolism pathway in the IgAN microbiome. Further experimental validation studies are ongoing to investigate the pathogenetic significance of the current findings.

FR-PO697

Development and Application of Multiplexed Proteomics to Investigate Protein Complexes in Kidney Aging and Disease

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Background: Kidney aging is a complex process associated with a decline in renal function. This decline is due to several factors, including changes in cellular states driven by protein expression and their composition in complexes. Proteins rarely function alone, and their activity is often determined by their interactions with others. However, owing to the technical challenges, no attempt has been made to profile the global changes in protein complexes composition and abundance in the kidney as a function of age or disease.

Methods: Co-fractionation mass spectrometry (CF-MS) is an emerging unbiased method that identifies protein complexes in cell or tissue lysate. CF-MS first separates the proteins in a sample by chemical properties such as size and charge using native chromatography, and thereby proteins from the same complexes will co-elute into the same fractions. All the proteins in each fraction are then identified and quantified by MS and the complexes can be inferred using downstream bioinformatics analysis. In a classical CF-MS set-up, one fraction per sample is processed and analyzed by the MS at a time. As samples are fractionated into tens or hundreds of fractions, with each fraction requiring analysis, the large number of samples results in a highly time-consuming process both in sample preparation as well as data acquisition time. To address this bottleneck, we have explored using a multiplexed isobaric labeling strategy (Tandem Mass Tags, TMT) that can significantly reduce the acquisition time. We have applied this approach to analyze young and old human kidneys as well as kidneys from chronic kidney disease patients.

Results: We present the first comparison of profiling global changes in protein complexes in young vs old vs CKD human kidneys. We validate our novel TMT proteomics approach using known complexes before applying the technique to profile complexes in precious human kidneys. Our preliminary results suggest that the method is a promising high throughput tool for comprehensively studying protein complexes in kidney aging and disease.

Conclusions: Our approach of using CF-MS combined with TMT-MS offers a novel direction to explore changes in protein complexes with a great potential to identify new drug targets and therapies for kidney aging and diseases.

FR-PO698

Involvement of Kynurenine Metabolizing Enzymes and Its Metabolites in Antibody-Mediated Glomerulonephritis

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Background: Tryptophan (TRP) is eventually metabolized to NAD in kynurenine pathway (KP), and its metabolites (Figure) potentially exert many biological activities in immune system. The objective of the current study is to elucidate the role of TRP metabolism in the progression of glomerulonephritis.

Methods: We introduced antibody mediated glomerulonephritis by administration of rabbit anti-mouse nephrotoxic serum (NTS-GN) in mouse strains deficient in KP-related enzymes including indoleamine 2,3-dioxygenase 1, 2 (IDO1$^{-/-}$, IDO2$^{-/-}$), and kynurenine 3-monooxygenase (KMO$^{-/-}$) and performed functional and histological analyses in diseased kidneys. For the therapeutic intervention, we administrated kynurenic acid (KYNA) into IDO1$^{-/-}$ with NTS-GN. In vitro, we analyzed morphology of bone marrow derived neutrophils on immune complexes (ICs).

Results: IDO1$^{-/-}$ demonstrated severe renal dysfunction and histological glomerular damage than WT, while those in IDO2$^{-/-}$ were comparable with WT. Conversely, crescent formation was significantly less in KMO$^{-/-}$ mice. Glomerular accumulation of neutrophils was significantly more in IDO1$^{-/-}$ mice, but less in KMO$^{-/-}$ mice. Neutrophils presenting "spread" morphology among attaching cells on ICs was significantly increased in IDO1$^{-/-}$, whereas it was reduced in KMO$^{-/-}$. Administration of KYNA into the diseased IDO1$^{-/-}$ significantly diminished glomerular crescent formation, which associated with the amelioration of renal dysfunction. Moreover, KYNA treated IDO1$^{-/-}$ neutrophils demonstrated less percentage of "spread" cells on IC-coated dishes than non-treated cells.

Conclusions: IDO1/KMO-mediated alterations of TRP metabolism involve in the disease activity of NTS-GN. Of note, KYNA negatively regulates to the disease pathogenesis by the alteration of IC-mediated neutrophil activity.

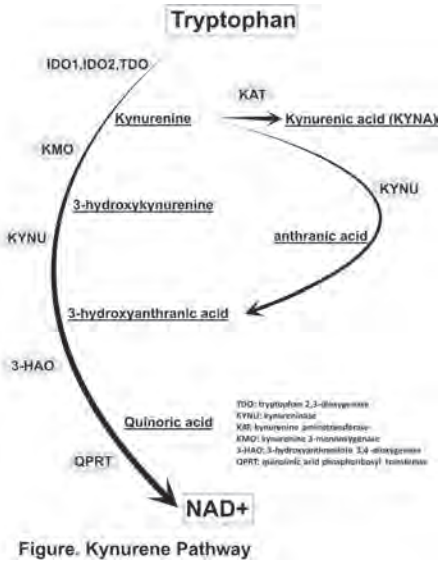

Figure. Kynurene Pathway

FR-PO699

Quantitative Ultrasound for Glomerulosclerosis in Ex Vivo Murine Kidneys

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Background: Focal segmental glomerulosclerosis (FSGS) is a condition that can lead to kidney function loss over time, making early detection and diagnosis essential for effective treatment and management. The glomeruli are the main source of ultrasound scattering in the kidney. This study proposes a novel approach to detecting FSGS using a multi-parametric quantitative ultrasound (QUS) approach in ex-vivo murine kidney models. QUS analyzes the spectral content of radiofrequency data in ultrasound to provide user- and system-independent quantifiable measurements, such as backscatter. We hypothesize that as FSGS progresses, there is a measurable increase in backscatter.

Methods: Five mice were recruited to each cohort of a podocalyxin knockout (PKO) model, a puromycin aminonucleoside (PAN) model and healthy controls. QUS was performed using a 128-element linear transducer at 15.625 MHz. From radiofrequency data, we extracted 16 parameters. To avoid overfitting, principal component analysis was used to create a reduced set of three parameters. These were inputs to a support vector machine for multi-class classification using a 5-fold cross validation scheme. Histopathologic analysis, performed by two expert pathologists, was used to determine the burden of FSGS as the ground truth.

Results: The average PKO case had 7% global segmental glomerulosclerosis and 19% FSGS, while the average PAN case had 20% global segmental glomerulosclerosis, 17% FSGS, and 7% total inflammation. Across all spatial locations or views, no significant differences in QUS parameters were found within a cohort. The mean classification accuracy was 80% across the three groups, with the mean precision, recall, and F1 scores being 0.86, 0.80, and 0.78, respectively. Misclassification only occurred in three PKO cases that were considered normal by the algorithm. The Nakagami scale parameter showed significant differences between the PAN model and the others, while the shape parameter showed significant differences between the PKO model and the others.

Conclusions: This study demonstrates that ultrasound measurements alone can effectively discriminate between healthy and diseased models of FSGS in mice. The results provide a foundation for further research into the quantification of kidney disease burden and its eventual use in humans.

Funding: Government Support - Non-U.S.

FR-PO700

Analysis of CD169 (Sialoadhesin)-Positive Activated Macrophages in Kidney Damage in Lupus Nephritis

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Background: CD169 (sialoadhesin; Sn)$^+$ activated macrophages (MQ) are associated with renal lesions in lupus nephritis (LN). However, the function of Sn$^+$ MQ is unclear as Sn does not fit into the M1/M2 paradigm of MQ activation, and little is known of how steroid therapy affects Sn expression. This study examined the activation status of Sn$^+$ MQ in biopsies of LN and in cultured MQ.

Methods: Biopsies from 32 patients diagnosed as LN with ISN/RPS classification III or IV were examined for accumulation of Sn$^+$ MQ by immunofluorescence staining, and correlated with clinico-pathological findings. For in vitro studies, normal human monocyte-derived MQs were incubated with IFNγ+LPS, with or without dexamethasone (DEX), and transcriptomic changes analysed by DNA microarray.

Results: In vitro, IFNγ+LPS induced an M1 pro-inflammatory MQ response with significant up-regulation of Sn mRNA levels. Dex suppressed the IFNγ+LPS induced M1-type response, but did not affect the increased Sn expression. In addition, Dex drove an M2-type response with up-regulation of the M2 marker CD163. Biopsies showed marked glomerular and interstitial infiltration of Sn$^+$ MQ in all cases, which correlated with glomerular active lesions such as endocapillary proliferation and cellular or fibro-cellular crescents ($p<0.0001$) or interstitial fibrosis ($p<0.05$), respectively. Separating patients into those who did (n=15), or did not (n=17) have steroid therapy before biopsy; there was no difference in the number of glomerular or interstitial Sn$^+$ MQ. However, the number of glomerular (but not interstitial) CD163$^+$ M2-type activated MQ was significantly higher in steroid treated patients ($p<0.0001$). Furthermore, Sn$^+$ MQ co-localized with T lymphocytes in glomerular, periglomerular and interstitial areas.

Conclusions: Sn may be a common activation marker for both M1 and M2 MQ in LN. Sn$^+$ MQ infiltration correlates with disease activity and may play a role in regulating T lymphocytes in LN. The lack of impact of steroids on the Sn$^+$ MQ subset indicates that alternative strategies are needed to target this mechanism of kidney injury.

FR-PO701

Cytokine Profiling in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) is a multisystem autoimmune disease that often affects the kidneys. It is unclear why some patients with AAV have kidney involvement while others do not. To investigate the mechanisms underlying these phenotypes, this study examined plasma and urine cytokine profiles in patients with active renal and non-renal AAV (AAGN and NR-AAV, respectively), and healthy controls (HC).

Methods: Levels of 200 cytokines were measured in the plasma and urine of 6 patients with active AAGN, 9 patients with NR-AAV, and 3 HC using a human cytokine array. Urine cytokine levels were corrected to urine creatinine and an analyte-to-creatinine ratio was utilized for analysis. Levels in the three groups were compared using ANOVA. Analytes with false discovery rate (FDR)-corrected p-values <0.05 were further compared using Tukey HSD post-hoc test.

Results: Patient Characteristics are depicted in Table 1. Most cytokines measured were similar between HC and NR-AAV patients. Compared to patients with NR-AAV, patients with AAGN had higher levels of plasma and urine cytokines that are involved in involved in Th17 signaling (IL-17A, IL-17F, IL-17R, IL-23, IL-6), Th1 response (IL-12, GM-CSF, IFNg, TNFa), chemotaxis (especially for T-cells, monocytes, and dendritic cells - eotaxin-2, I-TAC, Lymphotactin, MCP-3, MIP-3a, CCL23), B and T-cell crosstalk (B7-1, CD40, CD40L), and angiogenesis (VEGFR1, FLT4, VEGF-C, VEGF-D, SDF1a) (Figure 1).

Conclusions: Compared to NR-AAV, AAGN is associated with an increase in plasma and urine levels of many pro-inflammatory cytokines. T-cell differentiation, signaling, and crosstalk seem to be the most prominent molecular processes that are active in patients with AAGN. These data suggest a prominent role of T-cells in AAGN which have the potential of being leveraged therapeutically.

Funding: Private Foundation Support

Table 1. Patient Characteristics

Patient ID	Flare	Tissue available	Ethnicity	Age	Sex	Phenotype	ANCA type IF	ANCA type ELISA	Organ	ESR	CRP	sCr	UPCR	Urine RBC	Intervention
1	NR	P+U	Caucasian	63	F	MPA	p-ANCA	MPO	Arthritis, rash, fatitue	10	1	0.93	NA	None	Restart RTX
2	NR	U	Caucasian	61	M	GPA	c-ANCA	PR3	Sinus	99	16.5	1.52	NA	None	Restart RTX
3	NR	P	Caucasian	41	M	GPA	c-ANCA	PR3	Sinus	28	11.5	0.94	0.73	None	Start MMF
4	NR	U	South Asian	53	F	GPA	c-ANCA	PR3	Lung	15	38.9	0.69	NA	None	Start CYC
5	NR	U	Caucasian	53	M	GPA	c-ANCA	PR3	Mononeuritis multiplex	30	9.3	1.08	0.43	None	Start IVIG
6	NR	P	Caucasian	78	M	GPA	c-ANCA	PR3	Sinus, Lung	37	45.3	1.23	NA	None	Start RTX
7	NR	P+U	Caucasian	73	F	GPA	c-ANCA	PR3	Lung	58	43.7	0.70	NA	None	Start RTX
8	NR	P	Caucasian	38	F	EGPA	p-ANCA	MPO	Skin	4	1	0.83	0.40	6-9	Start RTX
9	NR	P+U	Caucasian	60	F	GPA	c-ANCA	PR3	Sinus	4	10.8	0.90	NA	None	Increase steroids
10	R	P+U	Caucasian	59	F	GPA	c-ANCA	PR3	Renal (focal, mild activity)	6	1	0.88	0.39	20	Start RTX
11	R	P+U	Caucasian	45	F	MPA	p-ANCA	MPO	Renal, Lung	42	18.1	1.93	0.69	20	Start CYC
12	R	P+U	Caucasian	31	M	EGPA	c-ANCA	PR3	Renal, Asthma	41	34.6	1.94	1.74	20	Start CYC
13	R	P+U	Caucasian	73	M	MPA	p-ANCA	MPO	Renal	32	2.8	3.04	10.90	10-19	Start CYC
14	R	P+U	Caucasian	68	F	MPA	p-ANCA	MPO	Renal	11	1	2.25	2.30	NA	Start RTX
15	R	P+U	Caucasian	58	F	MPA	p-ANCA	MPO	Renal, Lung	NA	NA	3.79	3.20	10-19	Start CYC

Abbreviations: NR: non-renal, R: renal, P: plasma, U: urine, F: female, M: male, MPA: microscopic polyangiitis, GPA: granulomatosis and polyangiitis, EGPA: eosinophilic GPA, ANCA: anti-neutrophil cytoplasmic antibody, MPO: myeloperoxidase, PR3: proteinase 3, NA: not available, ESR: erythrocyte sedimentation rate, CRP: Creactive protein, sCr: serum creatinine, UPCR: urine protein-to-creatinine ratio, RBC: red blood cell, RTX: rituximab, MMF: mycophenolate mofetil, CYC: cyclophosphamide, IVIG: intravenous immunoglobulin.

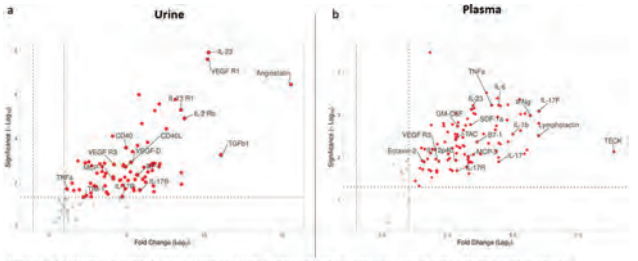

Figure 1. Differences in urine (a) and plasma (b) levels of cytokines in patients with active renal and non-renal vasculitis. Fold change: log2(renal – non-renal)

FR-PO702

Proteinuria Induces Tubular Cell Proliferation in Nephrotic Syndrome Model Mice Without Causing Tubular Injury

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Background: Proteinuria exhibits a robust association with the progression of kidney diseases and causes pathological effects on tubular cells. Nevertheless, the precise molecular mechanisms underlying tubular injury induced by proteinuria remain largely unknown. To elucidate the transcriptome alterations in the kidney resulting from proteinuria, we conducted an RNA sequencing (RNA-seq) analysis on a mouse model of nephrotic syndrome.

Methods: We used NEP25 mice, which express the human CD25 receptor on podocytes. Proteinuria was induced in these mice through the administration of an immunotoxin targeting the human CD25 receptor, LMB2 (0.625 ng/g body weight). After a period of seven days following LMB2 injection, the mice were euthanized, and RNA was extracted from the whole kidney. RNA-seq was performed using Illumina NovaSeq, and differential expression genes (DEGs) were identified using the DESeq2 package in R. Subsequently, we conducted multiple immunostaining and in situ hybridization (ISH) of the DEGs to determine their cellular localization and specific cell types.

Results: Following the administration of LMB2, Nep25 mice exhibited significant proteinuria without exhibiting kidney disfunction or histological damage. Through our kidney RNA-seq analysis of Nep25 mice, we identified 562 up-regulated and 430 down-regulated genes. Enrichment analysis revealed a notable up-regulation of genes associated with cell proliferation, such as Mki67. Notably, we observed a significant up-regulation of the transcription factor Foxm1, known to be involved in cell proliferation. Immunostaining and ISH confirmed the co-expression of Ki67 and Foxm1 in various tubular cells, including the proximal tubule, loop of Henle, distal tubule, and collecting duct.

Conclusions: The RNA-seq analysis of nephrotic syndrome model mice revealed that tubular cell proliferation was triggered by extensive proteinuria without causing kidney dysfunction or histological damage. The up-regulated genes, including Foxm1, have been previously associated not only with cell proliferation but also with tissue fibrosis. Consequently, the modulation of these gene functions is possible to serve as novel targets for chronic kidney disease treatment.

FR-PO703

Gnaq Deficiency Enhances Ifi202b/IFI16 and NF-kappaB Pathway in Kidney Endothelial Cell and Lupus Nephritis Pathology

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Background: Lupus nephritis (LN) is a serious complication of systemic lupus erythematosus (SLE), the heterogeneity is still a great major challenge to study. Our previous study revealed a negative correlation between Gnaq (G protein subunit alpha q) and autoimmune diseases. As Gnaq was also relatively enriched in the kidney glomerular endothelium, in addition, Gnaq heterozygous knockout mice exhibited an aberrant glomerular endothelial phenotype. Hereon we found the role of GNAQ in LN remains unclear.

Methods: LN was induced by pristane administration in female appropriate age C57BL/6 *Gnaq*$^{+/-}$ and littermate *Gnaq*$^{+/+}$ mice. Renal disease was assessed by the quantification of proteinuria and histologic analyses. Transcriptomic analysis was conducted on leukocytes and glomeruli obtained from *Gnaq*$^{+/+}$ and *Gnaq*$^{+/-}$ mice for differentially expressed genes.

Results: Treatment with pristane induced diffuse proliferative LN characterized by kidney morphology and persistent albuminuria at 16 weeks follow-up in *Gnaq*$^{+/-}$ mice. Mechanistically, levels of the Interferon activation protein 202b (Ifi202b) were significantly elevated in the glomeruli when Gnaq was deficient and followed lupus. Moreover, GNAQ knockdown endothelial cell increased the expression of IFI16 (Ifi202b human ortholog) and activation of the NF-kappaB pathway, which was associated with enhanced endothelial cell adhesion. Furthermore, by transferring bone marrow from WT-Gnaq$^{+/-}$, mice (WT-Gnaq$^{+/-}$) developed macroproteinuria and diffuse proliferative nephritis induced by pristane when compared with other groups. Last but not the least, increased expression of IFI16 was shown to be associated with proliferative LN on human biopsy among CKDs.

Conclusions: The findings of this study reveal that Gnaq heterozygous loss mice were prone to develop proliferative nephritis by pristane induction. GNAQ acts as an inflammatory regulator in kidney endothelial cells through IFI16-NF-kappaB. The endothelial IFI16 expression level is correlated with human LN among CKDs. These findings offer valuable insights for diagnosing against LN and potential mechanisms behind GNAQ and autoimmune diseases.

Funding: Government Support - Non-U.S.

FR-PO704

The Correlation Between Urinary microRNA-5195 and Renal Parameters in Patients with IgA Nephropathy

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Background: The microRNA-5195 (miR-5195) modulates cell proliferation by targeting *the Cyclin L1* gene that regulates the cell cycle. In this study, we examined whether the urinary concentration of miR-5195 is related to clinicopathological parameters and short-term changes in renal function in patients with IgA nephropathy.

Methods: We extracted and quantified microRNAs in morning spot urine in 80 patients with IgA nephropathy at biopsy and four control subjects. Then we examined the relationship between clinical and histological parameters, one-year changes in eGFR, and urinary miR-5195. The concentrations of microRNAs and proteins were corrected to the concentration of urinary creatinine and were log-transformed for simple correlation analysis.

Results: The urinary excretion of miR-5195 was detected in all subjects, and the urinary concentration of miR-5195 in patients with IgA nephropathy was significantly higher than in controls. Among 80 patients with IgA nephropathy, urinary miR-5195 levels showed a significantly positive correlation with the urinary concentration of total microRNA (r=0.57), total protein (r=0.46), beta2-microglobulin (r=0.46), and N-*acetyl*-beta-D-glucosaminidase (NAG) (r=0.39), but not with baseline GFR, and urinary red blood cells. Concerning the histological parameters, the urinary miR-5195 levels showed a significant positive correlation with glomerular proliferation (r=0.24) but not with glomerular sclerosis and tubulointerstitial fibrosis. The one-year changes in eGFR after biopsy showed a significant inverse correlation with the urinary concentration of miR-5195 (r= -0.39) and total protein (r=-0.37) but not total microRNA, beta2-microglobulin, and NAG. The correlation between urinary miR-5195 and one-year eGFR change was stronger in the subjects without steroid treatment (r=0.47) than those with steroid treatment (r=0.38).

Conclusions: In this study, the urinary excretion of miR-5195 was correlated with clinical and histological parameters and one-year changes in renal function in patients with IgA nephropathy, suggesting that urinary miR-5195 might be a useful biomarker of IgA nephropathy.

Funding: Government Support - Non-U.S.

FR-PO705

Unprecedented Rise in ANCA Vasculitis: Unveiling Patterns, Phenotypes, and Etiological Factors

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Background: There has been a perceived increase in the incidence of patients presenting with ANCA associated vasculitis (AAV). We aim to quantify the extent of this increase and identify trends and associations.

Methods: The incidence of newly diagnosed AAV was observed from two renal centres in the North West of England from 1st January to 30th April 2023. Retrospective data collection included demographics, serology, AAV phenotype and COVID-19 vaccination status. This data was compared to previous annual incidence rates of AAV diagnosis.

Results: A total of 25 new AAV patients were diagnosed across the two centres. The mean age was 56 and there was a slight male predominance (Fig. 1). Nineteen new cases from centre one suggests a greater than four-fold increase in the incidence of AAV, as compared to data averages from the same centre for the previous decade (Fig. 2). 62.5% of centre one patients had received ≥2 viral vector vaccines for COVID-19, whereas 83.3% of the centre two cohort received mRNA vaccines.

Conclusions: Our data shows a significant increase in AAV this year at one centre. More diagnoses were of the MPA phenotype, contradicting previous studies suggesting a higher prevalence of GPA in northern Europe. Possible explanations for the increase include autoimmune responses triggered by viral illnesses and COVID-19 vaccinations. Although not statistically significant, our data suggests a link between viral vector vaccines for COVID-19 and increased AAV incidence. Environmental factors such as air pollution have also been associated with higher autoimmune risk. The rising incidence necessitates further research into the cause and raises questions about service provision, health promotion and management.

	Total *(n=25)*	Centre 1 *(n=19)*	Centre 2 *(n=6)*
Mean age, years *(IQR)*	58 (42-76)	59 (43-76)	56 (32-72)
Sex *(M:F)*	3:2	12:7	1:1
Serology *(MPO:PR3)*	3:2	11:8	2:1
MPA *(n)*	15 (60.0%)	11 (57.9%)	4 (66.7%)
GPA *(n)*	9 (36.0%)	7 (36.8%)	2 (33.3%)
EGPA *(n)*	1 (4.0%)	1 (5.3%)	0 (0.0%)
(n) **receiving ≤2 vaccines**	7 (28.0%)	4 (21.1%)	3 (50.0%)
(n) **receiving ≥3 vaccines**	13 (52.0%)	11 (57.9%)	2 (33.3%)
Total number of mRNA vaccines	20	20	0
Total number of viral vector vaccines	44	30	14

Fig. 1: Data from 1 January to 30 April 2023

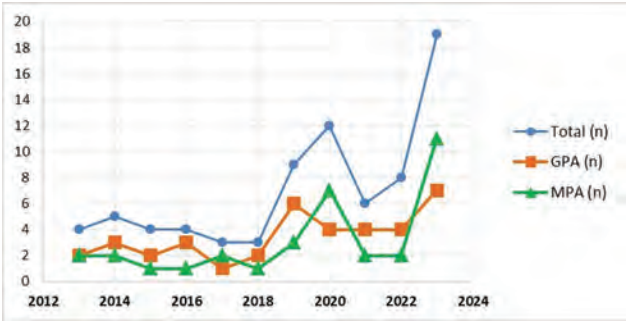

Fig. 2: New AAV diagnoses over the last decade

FR-PO706

Further Insights into Iptacopan Mode of Action in IgA Nephropathy Through Protein Profiling

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Background: IgA nephropathy (IgAN) can lead to progressive loss of kidney function, with ~30% of patients with proteinuria 1-2 g/day progressing to kidney failure within 10 years. Iptacopan is a proximal complement inhibitor that specifically binds factor B and inhibits the alternative complement pathway (AP). In a Phase 2 study (NCT03373461), iptacopan treatment led to a dose-dependent reduction in proteinuria and inhibition of the AP in patients with IgAN (1, 2).

Methods: SomaScan, a large proteomics platform, and statistical analysis were used to examine iptacopan's impact on plasma proteins. Statistical threshold for biomarker definition was set to adjusted p-value < 0.05 and absolute log Fold Change > 0.1.

Results: Iptacopan resulted in a significant modulation of 81 distinct plasma proteins in IgAN patients after 90-days treatment, persisting at the 180-day timepoint. Except for four, proteins were downregulated. Approximately two-thirds of the proteins are likely originated from the kidney (Fig.1), amongst which 4 proteins were reported to have increased expression in kidney from IgAN patients (BCL2L1, HES1, LTbR, C8). These proteins are thought to be released by cellular mechanisms like necrosis, apoptotic vesicles, proteolysis, and cell activation (Fig.1). From scientific literature, the findings are implicating changes in key biological pathways like inflammation, hypercellularity, fibrosis and atrophy. This underscores the potential of iptacopan to modulate protein expression across these pivotal biological processes in the context of IgAN patients.

Conclusions: This data suggests that iptacopan may contribute to reduction of renal inflammation, hypercellularity, fibrosis and atrophy in patients with IgAN. The relevance of these encouraging early findings will necessitate confirmation in a larger data set and at tissue level.

Funding: Commercial Support - Novartis Pharma AG

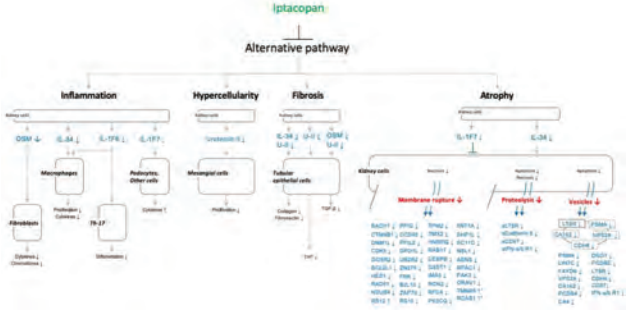

Fig1: Mapping plasma proteins likely originated from kidney to biological functions.

FR-PO707

Anti-Glomerular Basement Membrane (GBM) Serum Effects on Kidney Function and Glomerulosclerosis in Mice

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Background: Antibody-induced glomerulonephritis (GN) is a condition characterized by caused by an inappropriate autoimmune response to renal antigens, such as the glomerular basement membrane (GBM), leading to progressive glomerulosclerosis and rapidly declining renal dysfunction for which there exist only few treatment options. Understanding the underlying mechanisms of GN is crucial for developing effective therapeutic strategies. In this study, we aimed to investigate the induction of antibody-induced GN by anti-GBM serum on kidney biomarkers, histology and transcriptome signatures.

Methods: Male C57BL/6J mice (n=15) were randomized into three groups (n=5 per group) and received either vehicle injection, 100, or 200 µl of anti-GBM serum. We measured urine albumin-to-creatinine ratio (ACR) as an indicator of renal function. Renal endpoints included urine albumin-to-creatinine ratio (ACR), AI-assisted glomerulosclerosis scoring, histomorphometric analysis of fibrosis (Col3a1), and RNA sequencing (RNA-seq) analysis.

Results: Compared to vehicle controls, both doses of anti-GBM serum significantly increased urine ACR, indicating renal dysfunction and glomerular injury. AI-assisted based histopathological scoring confirmed significant glomerulosclerosis in anti-GBM serum-treated groups. Additionally, IHC image analysis indicated renal fibrotic injury. Correspondingly, RNA-seq analysis revealed upregulated gene expression programs signifying renal extracellular matrix remodelling (e.g., *Col1a1, Col3a1, Col4a1)* inflammation (e.g., *CD68, Ccl2, Il1b).*

Conclusions: Anti-GBM serum induces fast onset of renal dysfunction, glomerulosclerosis, and fibrosis in the mouse model of antibody-induced GN. The antibody-induced GN model in mice is highly applicable for probing test compounds with potential nephroprotective effects autoimmune GN.

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FR-PO708

Successful Use of Intravenous Immunoglobulin (IVIG) in Severe Life-Threatening Hypoalbuminemia in a Young African American (AA) Male with FSGS

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Introduction: Nephrotic syndrome (NS) relapses are common and are mostly managed by intensified doses of steroids with or without IV albumin infusion. In some instances, the relapses may be steroid resistant thereby warranting alternative immunosuppressive modalities. IVIG therapy has shown beneficial effects in patients with certain forms of glomerulonephritis but has been rarely used in steroid resistant NS patients. We hereby report an AA male adolescent with long standing FSGS who presented with NS relapses that are characterized by unusual severe life-threatening hypotensive crisis that was successfully treated with IVIG therapy.

Case Description: A 21-year-old AA male with known history of infrequent relapses of steroid resistant NS since the age of 3 yrs. At the age 18 years, he started having frequent relapses (9 events per year) and a repeat renal biopsy showed FSGS with 40% tubular atrophy and scarring. Relapses were characterized by precipitous events of heavy proteinuria (10-20 gm/day), severe hypoalbuminemia (< 1 gm /dL), and a peripheral circulatory failure. The latter was complicated by cerebral hypoperfusion with a syncope and atrial fibrillation. He was not responsive to Mycophenolate Mofetil and Rituximab. There was an interval event of COVID-19 infection that warranted monoclonal antibody. Patient was reluctant to undergo a proposed medical and surgical nephrectomy. Given a concurrent severe hypoalbuminemia and hypogammaglobinemia, an empirical treatment with a sequential IVIG was commenced. Consequently, frequency and severity of relapses had reduced for the past 10 months with no subsequent ICU admissions. His serum creatinine has always been normal (0.4-0.7 mg/dl). Genetic studies showed heterozygous APOL1 haplotypes of G1 and G2 variants.

Discussion: We present a rare case of life-threatening episodes of severe NS relapses in a patient with FSGS and G1/G2 APOL1 gene mutation who had a superimposed COVID-19 infection that responded to serial doses of IVIG therapy. We believe the beneficial effect of IVIG might be related to an increase in intravascular oncotic pressure and immunologic effects. IVIG therapy may be considered in patients with staroid resistant NS that failed to respond to conventional immunosuppressive modalities.

FR-PO709

Membranoproliferative Glomerulonephritis Associated with Coeliac Disease and Autoimmune Thyroiditis

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Introduction: Membranoproliferative glomerulonephritis (MPGN) is a pattern of glomerular injury which can be related to immune complex deposition from infections, paraproteinemia and autoimmune diseases. Rarely, there has been associations between MPGN and coeliac disease and MPGN and autoimmune thyroiditis described in literature.

We present a case of a patient who had all three diagnoses and treated with a Sodium/glucose cotransporter-2 inhibitor (SGLT2i).

Case Description: A 21 year old female presented with four month history of leg oedema, and subsequently confirmed nephrotic syndrome. She had recent diagnosis of hypothyroidism and coeliac disease prior to this presentation, and was established on gluten free diet and levothyroxine. At presentation, urine protein creatine ratio was 403.4mg/mmol with serum albumin of 2.9 g/dL. Complements C3 and C4 were normal, with no detected paraprotein and negative immunology (ANA, cryoglobulins, ANCA) and virology screen. Thyroglobulin and TSH receptor antibody levels were raised. Percutaneous kidney biopsy was performed which showed immune complex glomerulonephritis with MPGN pattern. She was commenced on maximally tolerated Angiotensin-converting enzyme inhibitor (ACEi) and SGLT2i. After 8 months, there was resolution of oedema, and marked improvement of proteinuria (123.5 mg/mmol) without need for immunosuppressive therapy.

Discussion: There have been five case reports of MPGN with nephrotic syndrome, associated with autoimmune thyroiditis. There have been biopsy studies showing thyroid antibody deposition in glomeruli, supporting this association. There have been four case reports of MPGN associated with coeliac disease. In these cases, a mix of pediatric and adult patients, hypocomplementemia was observed. In all the cases, gluten-free diet was sufficient to improve gastrointestinal symptoms, resolution of oedema and reduction in proteinuria. As we did in this case, we believe supportive therapy for MPGN associated with coeliac disease and/or autoimmune thyroiditis should include management of the associated conditions with gluten-free diet and maintaining euthyroid state. In addition, ACEi and SGLT2i have a role in managing MPGN, and may help avoid need for immunosuppression in such cases.

FR-PO710

Atypical Presentation of Atypical Anti-Glomerular Basement Membrane Disease

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Introduction: Anti-glomerular basement membrane (anti-GBM) disease is a rare aggressive autoimmune disorder characterized by circulating anti-GBM Antibodies (Ab) leading to crescentic necrotizing glomerulonephritis with linear deposits of immunoglobulin G (IgG) along the GBM. As opposed to the classic anti-GBM disease, atypical anti-GBM glomerulonephritis is characterized by an indolent clinical course, undetectable circulating anti-GBM Ab, endocapillary proliferation with only few crescents and linear IgG staining of the GBM. Herein, we present a case of atypical manifestation of atypical anti-GBM disease and emphasize the therapeutic dilemmas and challenges.

Case Description: 24-year-old male with a 3 weeks history of vomiting, was admitted to the hospital with severely impaired kidney function (creatinine 17 mg/dl), massive proteinuria without pulmonary involvement. Anti-nuclear, anti-neutrophilic cytoplasmic, and anti-GBM Ab were negative (anti-GBM was examined by indirect immunofluorescence (IF) assay, and enzyme-linked immunosorbent assay (ELISA)). Kidney biopsy demonstrated 100% cellular crescents with linear polytypic IgG staining of the GBM and C3 on IF. Hemodialysis was started. The patient was treated with high-dose steroids, cyclophosphamide and plasma exchange, as for classic anti-GBM disease. As opposed to classic anti-GBM disease, duration of plasmapheresis could not be dictated in the absence of detectable anti-GBM antibodies. The clinical course was ominous without improvement of his kidney function.

Discussion: The patient's clinical course and pathological findings were consistent of classic anti-GBM disease. Therefore, the absence of circulating anti-GBM Ab was surprising and did not suit the aggressive course of his kidney disease and pathological findings. Several theories had been proposed to explain the undetectable anti-GBM Ab including autoantibodies directed against GBM epitopes other than a3NC1, quaternary epitopes of native a345NC1 hexamers or high avidity for anti GBM ab along the glomeruli leading to undetectable circulating ab. Modified assays to detect a wide range of antigens or epitopes, using more sensitive techniques like biosensors, can unmask circulating anti-GBM antibodies and help in making therapeutic decisions regarding duration of plasmapheresis and immunosuppression therapy well as timing of kidney transplantation.

FR-PO711

Anti-Glomerular Basement Membrane Disease Overlap with Pauci-Immune Glomerulonephritis: Temporal Concurrence at a Single Center

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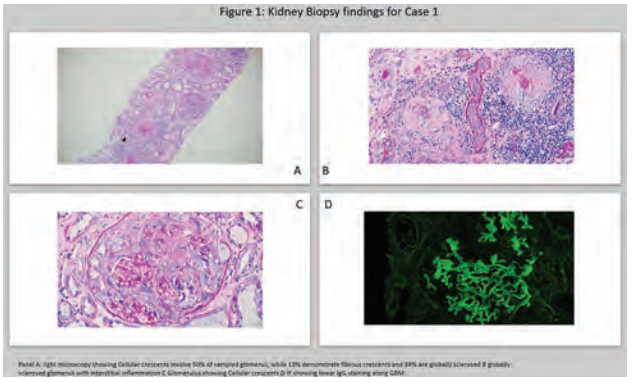
Introduction: Anti-GBM and pauci-immune vasculitis are small vessel vasculitis and cause RPGN with diffuse alveolar hemorrhage (DAH). Overlap between these entities is rare. Upto 38% of the individuals with anti-GBM disease demonstrate double-positivity and approximately 10% of patients with ANCA vasculitis have positive titers of anti-GBM antibodies. We present two double-positive cases diagnosed within 6 weeks at our institution.

Case Description: Case 1:A 74-years-old white male with h.o SARS-COV19 two months ago presented with cough and metallic taste, BUN 60 with S/Cr 5.05 mg/dl, p-ANCA 1:640 and anti-GBM+. Kidney biopsy showing Diffuse crescentic GN with cellular crescents involve 50% of the glomeruli, IF linear IgG staining. Patient was started on PLEX, IV Methylprednisolone and Cyclophosphamide. Patient remains HD dependent. Case 2:A 71-years-old white male with recently diagnosed lung biopsy proven GPA 4 months ago. Patient was admitted with SARS-COV-19 infection, serum creatinine 6.42mg/dl (baseline 0.9mg/dl few months ago). Kidney biopsy showing Crescentic glomerulonephritis with overlapping anti-glomerular basement membrane disease and pauci-immune glomerulonephritis. Patient was started on iv methylprednisolone, PLEX and cyclophosphamide. Patient needed hemodialysis for 2.5 months and has come off with most recent s/cr 3.54 mg/dl.

Discussion: In anti-GBM disease DAH can be the predominant presenting feature and will prompt early diagnosis necessitating early intervention. Hallmark for diagnosis is linear IgG staining of GBM on immunofluorescence. ANCA-associated vasculitis, in contrast, is pauci-immune with few or no immune deposits on IF. Given rarity of the overlap disease and paucity of literature standard treatment strategy is not established. Approach remains similar to treatment of anti GBM disease with PLEX and induction immunosuppression with cyclophosphamide. However longer and closer follow-up is required for double-positive disease due to more frequent relapses.

Figure 1: Kidney Biopsy findings for Case 1



Panel A: light microscopy showing Cellular crescents involve 50% of sampled glomeruli, while 13% demonstrate fibrous crescents and 34% are globally sclerosed & globally sclerosed glomeruli with interstitial inflammation C: Glomerulus showing Cellular crescents @ IF showing linear IgG staining along GBM

FR-PO712

Hydralazine-Induced ANCA Vasculitis Presenting with Pulmonary-Renal Syndrome

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Introduction: Hydralazine, an arterial vasodilator, is a frequently used medication for the management of hypertension and heart failure. It is generally well-tolerated and has a safe profile; however, hydralazine can induce immune-mediated complications. There are rare reports of hydralazine-induced ANCA associated vasculitis (AAV) with pulmonary manifestations, also known as hydralazine-induced pulmonary-renal syndrome (PRS). Here we report a case of hydralazine-induced alveolar hemorrhage and anti-neutrophil cytoplasmic antibody (ANCA)-positive pauci-immune glomerulonephritis.

Case Description: A 75-year-old female with history of hypertension treated with hydralazine 75 mg TID for seven years, presented with five months of dyspnea on exertion, blood tinged sputum and unintentional weight loss. CT scan showed a cluster of pulmonary nodules with mediastinal lymphadenopathy. Transbronchial lung biopsy revealed alveolar hemorrhage. Serum creatinine was 2.8 mg/dL from baseline 1.0 mg/dL and urinalysis showed 2+ blood, 30-50 RBC/hpf and red blood cell casts. Urine protein to creatinine ratio was 0.7 gr/day. Given the complaint of hemoptysis, a vasculitis work-up was pursued. Work-up revealed p-ANCA > 1: 1280, elevated MPO antibodies, elevated PR-3 antibodies, and elevated inflammatory markers. Anti-histone antibodies were present. Additional immunologic and serologic work up was unremarkable. Renal biopsy was consistent with pauci-immune ANCA associated vasculitis with crescents. Given concern for drug induced vasculitis, hydralazine was discontinued. She received 1 gm methylprednisolone for three days and received two doses of Rituximab followed by prednisone taper per the PEXIVAS trial. Hemoptysis resolved after treatment. She has remained off prednisone with stable renal function and minimal proteinuria.

Discussion: This case demonstrates a case of hydralazine-induced small vessel vasculitis. While immune-mediated complications have been frequently reported with the use of hydralazine, drug-induced ANCA vasculitis is rarely reported. This diagnosis should be considered in patients on hydralazine who develop pulmonary-renal syndrome. Diagnosis relies on serologic work-up and renal histopathology. Discontinuing hydralazine is the first step in treatment and this alone might be sufficient; however, more aggressive management including immunosuppression is frequently needed.

FR-PO713

Wrist Drop: An Unusual Initial Presentation of ANCA-Negative Pauci-Immune Glomerulonephritis

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Introduction: Pauci-immune glomerulonephritis (PING) is often associated with the presence of antineutrophil cytoplasmic antibodies (ANCA). ANCA-negative PING is a rare variant, which primarily affects the kidneys, with fewer extrarenal manifestations as compared to ANCA-positive PING. Our case highlights the initial presentation of progressive neurological weakness in ANCA negative PING.

Case Description: A 77-year-old male with medical history of hypertension and monoclonal gammopathy of undetermined significance (MGUS) presented with acute left wrist drop and progressive muscle weakness for six months. The weakness started in

the lower extremities, and gradually involved the upper extremities. He denied numbness, tingling, rash, fever and gastrointestinal symptoms. Vital signs were stable. Neurological exam was positive for bilateral foot drop, left wrist drop, decreased sensation in all extremities, decreased deep tendon reflexes, and an unsteady steppage gait. Laboratory tests showed elevated creatinine 1.82 mg/dL (baseline 0.7-0.9), low albumin 1.9 g/dL, and elevated CRP 7.5 mg/dL. Lumbar puncture and MRI spine was normal. Electromyography showed moderate acute-on-chronic symmetrical sensory motor polyneuropathy and left radial mononeuropathy. Subsequent sural nerve biopsy revealed marked axonal neuropathy. Patient's kidney function continued to worsen with creatinine peaking at 2 g/dL. 24 hour urine collection revealed 2.5 g proteinuria, with an elevated urine albumin-creatinine ratio of 1300. Therefore, a renal biopsy was performed revealing pauci-immune proliferative and necrotizing glomerulonephritis with crescent formation, negative immunofluorescence with no amyloid and immune deposits. Treatment with intravenous steroids followed by rituximab was initiated, resulting in improved renal function with creatinine of 1.77 at discharge. He demonstrated further renal recovery on outpatient follow up with serum creatinine down to 1.32.

Discussion: ANCA-negative PING is a severe vasculitis with high morbidity and mortality. This is the first case to report severe neurological weakness as the initial presentation of ANCA-negative PING. It highlights the importance of considering PING in the differential diagnosis for patients presenting with neurological weakness and elevated creatinine, as prompt diagnosis and treatment can prevent adverse patient outcomes.

FR-PO714

A Case of Lupus-Like Nephritis in a Patient with a Negative Antinuclear Antibody (ANA)

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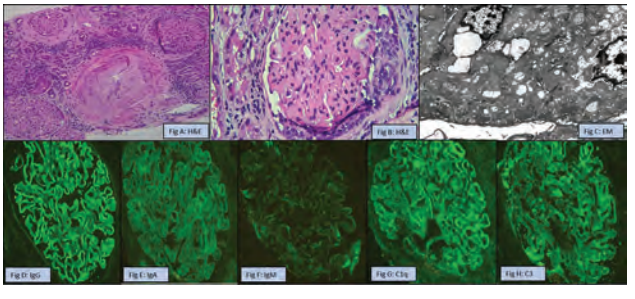
Introduction: Diagnosis of SLE cannot be made based only on kidney biopsy, however the histopathologic findings is one of the important cornerstone for the diagnosis of lupus nephritis.

Case Description: A 60-year-old male with PMH of HTN presented with worsening bilateral lower extremity edema with hematuria & heavy proteinuria for 4 months. Other symptoms significant of dyspnea on exertion & a strong family history of kidney disease. Labs showed S. Cr 1.80 mg/dL (previous 0.86) & urine protein/creatinine >7.96 g/g. Workups including ANA, ANCA, C3 (160), C4 (36), and ds-DNA (<1) were negative. Serum protein electrophoresis revealed two small oligoclonal bands without monoclonal paraprotein. CXR, TTE & renal ultrasound were within normal limit. HBsAg, anti-HCV, RPR & HIV were also negtive. A kidney biopsy revealed marked (>50%) endocapillary proliferation, mesangial sclerosis, GBM thickening with two cellular crescents. Immunofluorescence (IF) studies showed full house positivity on immunoglobulins (Ig A, Ig G and Ig M) & complement deposit. Electron microscopy (EM) showed subendothelial & mesangial electron dense depositions with no tubuloreticular inclusion identified. Patient was initially treated with IV methylprednisolone followed by prednisone with improvement in renal function. Patient was discharged on mycophenolate for outpatient follow up and monitoring.

Discussion: Here we presented a case of renal-limited, lupus-like nephritis in a patient with absent extrarenal manifestations & negative lupus serology. As per American Rheumatism Association (ARA) criteria, our patient did not fit into the diagnosis of SLE. However, the presence of immune-complex mediated glomerulonephritis and "full house" IF staining and EM showing subendothelial and mesangial electron dense deposits on kidney biopsy are highly suggestive of the lupus nephritis. There is a need for proper characterization of this disease pathogenesis, precise diagnostic criteria, standardization of treatment protocols & long term follow up studies to identify the true prognosis of this challenging clinical entity.



Histopathologic images of a kidney biopsy

FR-PO715

Mixed Cryoglobulinemic Glomerulonephritis Triggered by Influenza Vaccination

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Introduction: Mixed cryoglobulinemia is associated with viral infections such as hepatitis B or C virus, lymphoproliferative and autoimmune disorders. Influenza vaccine-induced cryoglobulinemia has been rarely reported. We present a rare case of cryoglobulinemic vasculitis following influenza vaccination with new onset renal involvement.

Case Description: A 68-year-old male with history of atrial fibrillation and chorioretinopathy presented in fall 2022 for a rash and edema of the lower extremities and thrombocytopenia after influenza vaccination. Prior, in both 2020 and 2021, he had similar presentation of rash and edema following annual influenza vaccine. His illness was self-limited, but evaluation had shown mixed cryoglobulins. A bone marrow biopsy was unremarkable and viral etiologies were negative. He was diagnosed with idiopathic mixed cryoglobulinemic vasculitis. For recent presentation, in addition to the edema and rash, he had thrombocytopenia and a positive rheumatoid factor (RF). Patient received intravenous immunoglobulin (IVIG) with improvement of rash and platelet count, but his edema persisted. Soon after, he was readmitted and found to have acute kidney injury (AKI) (creatinine of 2.89 mg/dL; baseline 1.2 mg/dL), hematuria, proteinuria, and labs showing RF elevation and low complements. An evaluation for paraprotein revealed IgM kappa and IgA lambda paraproteins, with cryoglobulin elevation in polyclonal fashion including IgG, IgA, but predominately IgM. He received IVIG and creatinine improved. A kidney biopsy showed endocapillary proliferative glomerulonephritis with organized deposits, consistent with mixed-type cryoglobulinemic glomerulonephritis treated with rituximab infusions, resulting in improvement in cryoglobulins and complement levels and renal function, with creatinine at 1.46 mg/dL in May 2023. Of note, plasmapheresis was given for rash from IVIG.

Discussion: Our patient had a favorable outcome after rituximab, IVIG, and plasmapheresis for diagnosis of mixed cryoglobulinema triggered by the influenza vaccine, noting a reduction of cryoglobulins, improved renal function, and resolution of rash. Cryoglobulins can form as an immune response to infections though it is unclear why cryoglobulins are produced as a response to a vaccination. Understanding this novel association and interaction is important for prompt diagnosis and management.

FR-PO716

Polycythemia and IgA Nephropathy: An Interesting Association

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Introduction: IgA nephropathy (IgAN) is often associated with chronic kidney disease (CKD) which usually presents with anemia. We present a case IgAN-associated polycythemia.

Case Description: A 46-year-old patient with known hypertension (HTN) was evaluated for progressive CKD. Serum creatinine (sCr) increased from 1.2 to 1.7 mg/dL over 5-6 years. Urinalysis showed microscopic hematuria and proteinuria of 1g/g of creatinine. A kidney biopsy showed IgAN with an Oxford classification score of M1E0S1T1-C0. He was treated with RAAS blockade and a 6 months course of steroid followed by dapagliflozin and currently with stable sCr and proteinuria of 0.13 g/g. In conjunction to IgAN, polycythemia was noted for several years with Hematocrit (Ht) levels between 50-60%. The most recent Hemoglobin was 18.6 g/dL with normal platelets and white blood cell counts. Abdominal imaging showed normal sized kidneys and no splenomegaly or hepatomegaly. Polycythemia evaluation was unrevealing. The patient had no smoking history, and sleep study was negative. Genetic testing for Janus kinase 2 (JAK2) mutation as well as other polycythemia-associated mutations was negative, excluding Polycythemia Vera. The final diagnosis from hematology was polycythemia associated with IgAN with a recommendation for observation.

Discussion: The 4-hit hypothesis for IgAN pathogenesis involves galactose-deficient IgA1 targeting the hinge region, being recognized by IgG autoantibodies, leading to immune complexes which deposit in kidney mesangium. High polymeric IgA (pIgA1) and IgA1 complexes can stimulate red blood cell formation in some patients. In vitro study showed that the serum of patients with IgAN and unexplained polycythemia increased the number of erythroid burst forming unit (BFU-E)-derived colonies from human progenitor CD34+ cells. Removal of IgA1 from IgAN-Polycythemia patients normalized the number of colonies. Mice studies have shown that increased expression of Polymeric IgA (pIgA1) was associated with increased hemoglobin levels without raising EPO levels likely by sensitizing cells to Epo through activating the transferrin receptor 1 (TfR1). We report an interesting association of IgAN and polycythemia that is supported by in vitro findings of polygenic IgA1 stimulating RBC formation. Evaluation for other etiologies of polycythemia needs to be done before considering the IgAN as the plausible etiology of polycythemia.

FR-PO717

Outcomes from Acute Co-Infection of HIV and Hepatitis B Infection Nephritic Syndrome

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Introduction: We present a unique case of a previously untreated combined HIV and HBV coinfection presenting as HD requiring AKI with Nephritic syndrome and significant lymphoplasmacytic interstitial inflammation with dominant for CD8 T lymphocyte.

Case Description: 40-year-old AA male with no past history who presented with anasarca, 3+ proteinuria and uremic symptoms of nausea/vomiting for 1-2 weeks. Labs significant for BUN/Cr 56/5.1, Alb <1.5, Urine Prot >500, Hgb 5.8, C3 64, C4 122, CD4 141. SPEP and UPEP negative. Hep B and HIV viral quantitative PCR were 7.7million virions and 280,000. Negative for other serologies. Biopsy showed HIVAN with FSGS and microcystic tubular changes, MPGN, diffuse interstitial lymphocytosis syndrome (DILS) with dominant CD8 cells along with lymphoplasmacytic infiltration. He needed emergent HD for AKIN Stage 3 and anasarca unresponsive to diuretics, on retrovirals without renal response until he was started on a course of steroids, serendipitously for high intracranial pressures from Acute Toxoplasmosis on his second admission.

Discussion: DILS is a rare multisystemic syndrome characterized by CD8+ lymphocytosis associated with a CD8+ T-cell infiltration of multiple organs, usually seen in uncontrolled or untreated viral infections but can also manifest itself independently of CD4+ T-cell counts. The rarity of DILS cases explains the lack of studies describing treatment options but the consensus is that the primary treatment line should be HAART. Specifically, for the renal condition, several case reports suggest the use of corticosteroid therapy. This is congruent with other studies showing initial response may be dramatic with corticosteroids adjunct to ART +/- ACEi/ARB, even reversing dialysis dependence, but transient. Comorbid kidney disease in the setting of HIV/HBV is challenging to manage clinically because the preferred antiretroviral agent in coinfection, tenofovir disoproxil fumarate (TDF), is potentially nephrotoxic. However, in immune-tolerant HBV, steroids could reactivate severe infection. In the current era of retroviral availability, it is extremely rare to see a case of classical HIVAN and DILS. Our case is unique as the patient had 2 viral infections and lymphocyte pattern of CD8 lineage that coincidentally responded to high-dose steroids which were given for other reasons.

FR-PO718

Lactobacillus Endocarditis-Associated Crescentic Glomerulonephritis

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Introduction: Infection-related glomerulonephritis (IRGN) encompasses a wide range of clinical and pathologic manifestations. Up to 50% of patients can develop persistent kidney impairment and 1/3 can progress to kidney failure. (Medjeral-Thomas et al. Clin J Am Soc Nephrol. 2014.) Staphylococcus and Streptococcus are the most common pathogens isolated however IRGN in the setting of lactobacillus is considered rare.

Case Description: A 79-year-old male with history significant for heart failure with preserved ejection fraction, bioprosthetic AVR, and chronic kidney disease (CKD) IIIb thought to be secondary to uncontrolled hypertension and recurrent AKI presented with dyspnea on exertion. Physical exam revealed signs of volume overload and a new systolic murmur. Echocardiogram showed vegetation consistent with bioprosthetic valve endocarditis. Blood cultures grew Lactobacillus species and upon reviewing his medication list probiotics was noted. His course was complicated by acute on chronic kidney injury requiring dialysis. Workup included a 24-hour urine collection showing 2.4g of protein and 1.3g of albumin, normal serum free light chain ratio, normal serum protein electrophoresis, and normal C3 and C4 levels. Kidney biopsy performed revealed necrotizing and crescentic glomerulonephritis with immunofluorescence positive for IgG, IgM and C3; consistent with IRGN. Patient was started on ampicillin and a steroid course was proposed. However, the patient and his family declined given risk of exacerbation of infection and decision was made to pursue conservative management with antibiotics and dialysis which the patient is still on.

Discussion: The pathogenesis of IRGN involves glomerular immune complex deposition along with classical complement pathway activation. This is frequently associated with a reduction in serum C3 and normal C4 levels, but as illustrated in our case C3 levels can be normal. The mainstay of treatment is withdrawal of enticing agent (probiotics), treatment of the underlying infection and supportive care. The utilization of systemic steroids in these patients is highly controversial given no evidence of efficacy in IRGN patients at low risk for progression (Arivazhagan et al. Kidney Int Reports. 2022). They can be considered in specific cases, such as patients with diffuse crescentic and rapidly progressive GN.

FR-PO719

Hepatitis C Negative Type II Cryoglobulinemic Glomerulonephritis

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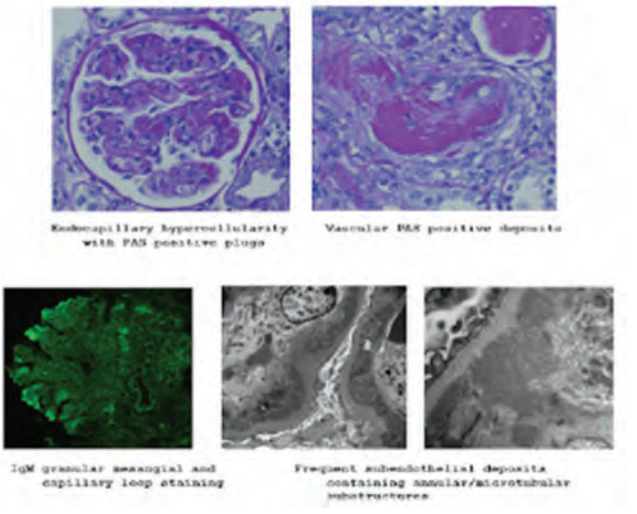
Introduction: Mixed cryoglobulinemia typically follows a chronic, smoldering course. Here we present a case of rapidly progressive mixed cryoglobulinemic glomerulonephritis (GN) in a hepatitis C negative patient.

Case Description: A 67-year-old female with a history of chronic kidney disease stage III and ophthalmologic Sjogren's syndrome presented to the emergency department for labile blood pressures. Labs were notable for serum creatinine 1.49 mg/dL, positive anti SS-A, anti-B. C3 28 (low), C4 < 3, and negative hepatitis panel. Urine protein: creatinine ratio was 2.2 g/day. Additional labs showed cryoglobulin level < 10% and was identified as Type II cryoglobulinemia monoclonal IgM kappa and polyclonal IgG. A kidney biopsy showed diffuse proliferative GN consistent with cryoglobulinemic GN. The patient's condition continued to decline with worsening creatinine and raising concern for rapidly progressive GN secondary to cryoglobulinemic GN. Patient was initiated on high-dose steroids and plasmapheresis (PLEX). Subsequently, she received Rituximab. Despite these aggressive measures, oliguria and uremia persisted requiring dialysis.

Discussion: Mixed cryoglobulinemic GN is a rare cause of rapidly progressive GN that is commonly associated with hepatitis C viral infections. Sjogren disease is responsible for <10% of HCV-negative mixed cryoglobulinemias. Prompt treatment with steroids, PLEX, cyclophosphamide, or rituximab is essential due to the significant morbidity and mortality associated with this condition.



FR-PO720

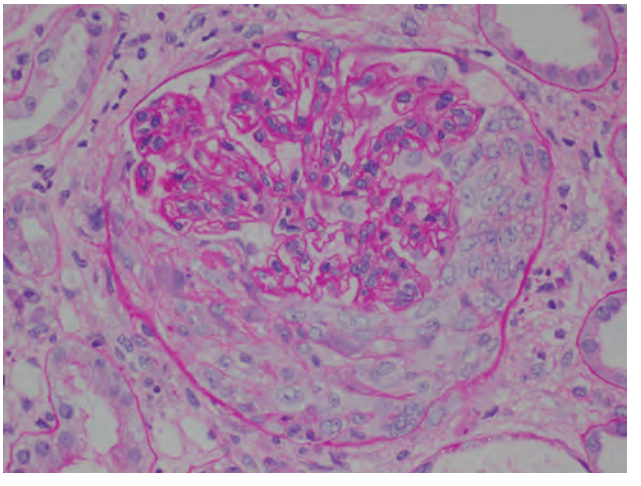
Infection-Related Rapidly Progressive Crescentic Glomerulonephritis

Jacob R. Henderson, Karl B. Pembaur. *The Christ Hospital, Cincinnati, OH.*

Introduction: Rapidly progressive crescentic glomerulonephritis (RPGN) is characterized by progressive loss of renal function. Most cases are diagnosed with a renal biopsy. Here we examine a subtype of RPGN in the setting of IV drug abuse, hepatitis C, and tricuspid valve (TV) MRSA endocarditis.

Case Description: A 32 year-old male with a PMHx significant for IVDU presented with fever, chills, lower extremity edema, and a dark discoloration to his urine. The patient had a new acute kidney injury (AKI) (Cr 1.66, BUN 35), anemia (Hgb 11.2), and leukocytosis (WBC 16.8k). Total protein and albumin were low. Urinalysis revealed hematuria (30 RBC's and RBC casts), proteinuria (300mg/dL), small leukocyte esterase, 41 WBC's and a urine protein to creatine ratio of 4.4mg/g. Blood cultures were positive for MRSA, and TEE revealed TV endocarditis. Hepatitis testing revealed a chronic, active hepatitis C infection and a cleared hepatitis B infection, HIV testing was negative. He underwent TV thrombectomy for vegetation removal and was initiated on antibiotics. Renal function worsened and an ANA, dsDNA, Anti-GBM, SPEP, and cryoglobulin were negative. An atypical P-ANCA was positive with a 1:40 titer, complements C3 and C4 were low. Renal biopsy was performed, and light microscopy revealed 61% crescents with focal segmental necrosis, and mesangial expansion. IF microscopy revealed mesangial staining of 1+ IgG/IgA/IgM/C1q, 3+ C3, and 3+ kappa & lambda.

Discussion: The biopsy was consistent with a necrotizing, crescentic glomerulonephritis with mild interstitial fibrosis. The atypical P-ANCA seropositivity was thought to be due active hepatitis C infection. In the context of MRSA bacteremia, active hepatitis C infection, and chronically inactive hepatitis B infection with rapid progression of renal impairment, the patient was diagnosed with an infection related RPGN. Treatment was directed at the underlying cause of infection, however due to rapid progression of renal injury, and degree of proteinuria, he was started on a steroid taper. This patient will be treated for hepatitis C in the outpatient setting. In the context of an active infection and clinical evidence of RPGN, a renal biopsy should be performed for a definitive diagnosis. While treating the underlying infection is appropriate, immunosuppression should be considered in the right clinical context, in this case, rapidly progressive renal failure.



FR-PO721

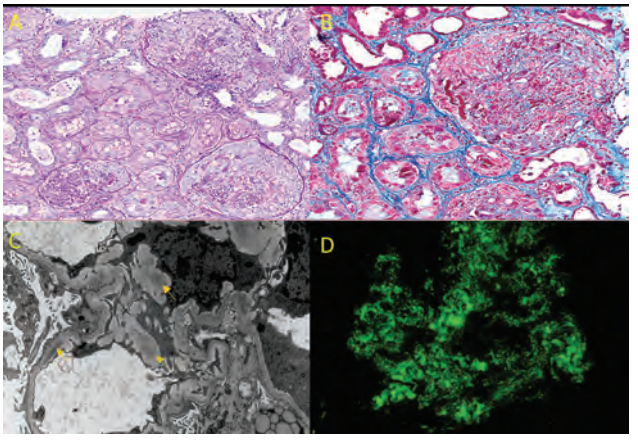
Looks Can Be Deceiving: A Case of C3 Glomerulopathy

Kevin Dao, Robin Edwin, Mohid Mirza, Richard G. Macneil, Alexei V. Mikhailov, Pirouz Daeihagh. *Atrium Health Wake Forest Baptist, Winston-Salem, NC.*

Introduction: Complement 3 glomerulopathy (C3G) is caused by an acquired or genetic dysregulation of the complement alternative pathway. It can be further classified into dense deposit disease (DDD) or C3 glomerulonephritis (C3GN). We present a case of a middle age male who presented with suspected infection-related glomerulonephritis (IRGN). However, his renal functions did not significantly improve with antibiotics. Renal biopsy was performed and he was diagnosed with C3GN.

Case Description: 55-year-old male with past medical history of untreated hepatitis C and former intravenous drug use presented for evaluation of oliguric acute kidney injury, hematuria, and rash in the setting of MSSA empyema and chest wall osteomyelitis. He was septic and had acute renal failure requiring broad spectrum antibiotics and renal replacement therapy. Further GN work up was significant for proteinuria 11g/g, elevated Anti-DNASE, cryoglobulins 1.0%, undetectable C3, low C4 and M spike on SPEP. Patient was treated with prolonged course of antibiotics for presumed endocarditis. Differential included IRGN but due to multiple abnormal serological markers a renal biopsy was performed which revealed C3GN. He was started on steroid taper and mycophenolate mofetil with rapid improvement in edema and renal functions. Dialysis was discontinued and patient was discharged on immunosuppressive therapy.

Discussion: C3G is a difficult diagnosis and may often require immunosuppression (IS). Our patient above was requiring routine dialysis until the initation of IS and was able to stop dialysis shortly after. Patients who are suspected to have IRGN that are not improving with antibiotics should have C3GN included in the differential. Biopsy is warranted in these patients and IS may help with improving outcomes.



Diffuse global crescents on LM(A). Fibrinoid necrosis on LM(B). Mesangial subendothelial dense deposits (arrow) on EM(C). C3 4+ on glomerular capillary walls on IF(D).

FR-PO722

Mesangial Proliferative Glomerulonephritis and Neurocysticercosis: A Novel Association

Jinlan Liao,[1,4] Brendan Smyth.[2,3] *[1]Peking University Shenzhen Hospital, Shenzhen, China; [2]The George Institute for Global Health, Newtown, NSW, Australia; [3]St George Hospital, Kogarah, NSW, Australia; [4]The First Affiliated Hospital of Anhui Medical University, Hefei, China.*

Introduction: The etiology of nephrotic syndrome is diverse, and parasitic infections typically do not cause this condition. Here, we present a case of nephrotic syndrome associated with parasitic infections.

Case Description: A 21-year-old man with a habit of eating raw fish presented with a 6-week history of bilateral limb edema, back pain and nausea. Nephrotic syndrome with acute kidney injury was diagnosed after finding a creatinine of 163 umol/L, albumin of 19.7 g/L, and proteinuria (9.4 g/day). Peripheral blood eosinophilia was noted (5.78 x10^9 cells/L). A renal biopsy revealed mesangial-proliferative glomerulonephritis and eosinophils within the renal interstitium. Serum was strongly positive for anti-*Taenia solium* antibodies (by enzyme linked immunosorbent assay). Cranial magnetic resonance imaging revealed a 9.8 x 12.8mm mass in the fourth ventricle. A specimen of cerebrospinal fluid was also weakly positive for anti-*Taenia solium* antibodies. On the basis of these findings, a diagnosis of neurocysticercosis was made. The patient did not consent to surgical exploration and removal of cyst in the fourth ventricle. Medical therapy was commenced with albendazole and glucocorticoids. Two months later, 24-hour urinary protein excretion had reduced to 0.8 g/day, and the blood eosinophil level was normal. At a follow-up visit 1 year later, the patient's renal recovery was found to be complete. MRI of the brain revealed no change in the fourth ventricular cyst and he remained asymptomatic.

Discussion: This is the first reported case of mesangial-proliferative glomerulonephritis with eosinophilic infiltrate associated with cysticercosis. We hypothesize that this patient's infection resulted from cross-contamination in the preparation of raw seafood. Cysticercosis should be considered in the differential diagnosis of nephrotic syndrome in areas where *Taenia solium* is endemic.

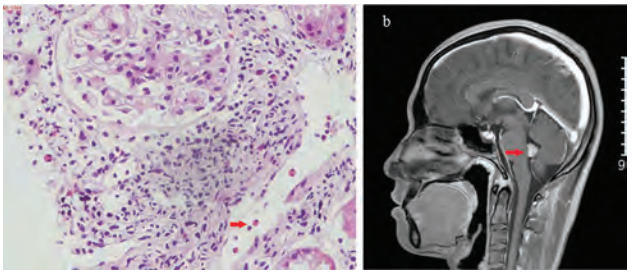


Figure 1: Image a is from a renal biopsy, the arrow indicates eosinophils. Image b is from cranial MRI revealed a mass in the fourth ventricle.

FR-PO723

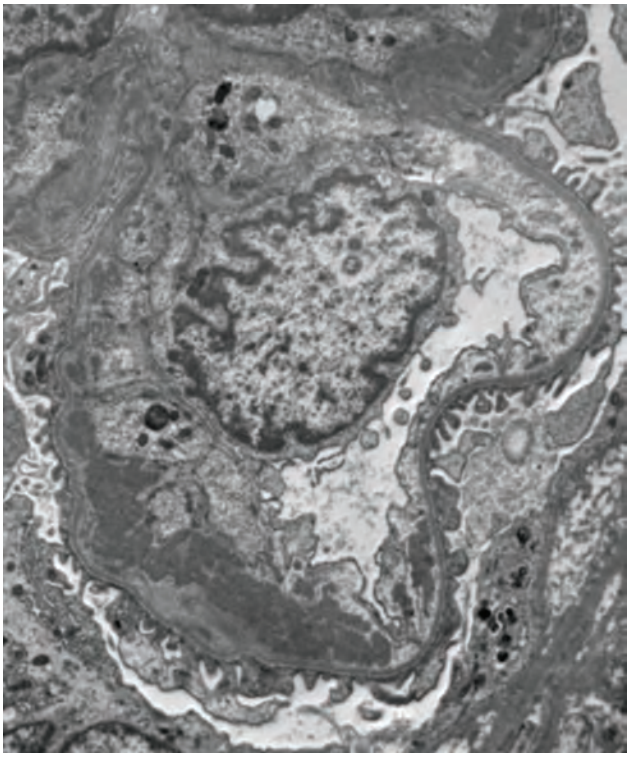
Anti-Tumor Necrosis Factor Antibody-Induced Lupus-Like Glomerulonephritis

Luis B. Caraballo, Hima B. Doppalapudi, Amar Pandit, Vijay K. Vanguri. *University of Massachusetts Chan Medical School, Worcester, MA.*

Introduction: Anti-TNF agents can lead to expression of autoantibodies resulting in symptoms similar to systemic lupus erythematosus (SLE). This autoantibody expansion can be reversible with the discontinuation of the offending agent. We present a case of a 35-year-old female patient with drug-induced lupus nephritis caused by adalimumab.

Case Description: A 35-year-old female was evaluated for worsening renal function and microscopic hematuria. Her medical history was significant for RA on weekly adalimumab since 2011. Her serum creatinine increased from 0.8-1.7 mg/dL over a period of 2 years. Urine sediment demonstrated dysmorphic RBC's. Urine protein to creatinine ratio (UPCR) was 3.7 g/g. Elevated proteinase 3 antibody, and anti-double stranded DNA antibody. She underwent a renal biopsy to determine the etiology of her worsening renal function. The biopsy revealed immune complex-mediated glomerulonephritis with a focal proliferative and membranoproliferative patterns of injury, as well as a background of 40-50% chronicity. Her findings were compatible with a lupus-like immune complex-mediated glomerulopathy, and were believed to be secondary to adalimumab. Adalimumab was discontinued and she was started on prednisone 1 mg/kg. Her most recent creatinine downtrended to 1.5 mg/dL, with UPCR 1.5 g/g.

Discussion: Anti-TNF drug induced lupus nephritis mechanism is unknown, is believed that this agents promotes anti-dsDNA antibody by inducing cellular apoptosis. Adalimumab has been associated with focal and diffuse membranoproliferative glomerulonephritis similar to our biopsy findings. In our case, the patient had significant renal function improvement after completing four weeks of prednisone therapy.



Glomerular capillary loop with large subendothelial electron dense deposit incorporated into an evolving double contours

FR-PO724

Double Insult: Secondary IgA and Anticoagulant-Related Nephropathy

Elizabeth Pabon-Vazquez, George N. Thomas, Bogdan Anea, Vatsalya Kosuru. *Augusta University Medical College of Georgia, Augusta, GA.*

Introduction: Acute kidney injury represents the most frequent nephrology consultation. In select cases, AKI is the result of series of cumulating insults overlapping previously undiagnosed conditions. These usually carry a significant negative impact towards renal recovery.

Case Description: This is the case of a 62-year-old male with a past medical history of peripheral artery disease, s/p right below the knee amputation, severe ischemic cardiomyopathy s/p intra-cardiac device, atrial fibrillation on apixaban, diabetes mellitus and hypertension, who was admitted for cellulitis in the amputated stump. In addition to cellulitis, the patient reported a non-blanching petechial rash on the left arm which was present for several months. Hospitalization was complicated by AKI;and initial workup revealed a history of daily NSAID use and elevated vancomycin levels with granular casts noted on urine microscopy. An initial diagnosis on acute tubular necrosis due to intrinsic etiology was suspected. However, renal function continued to worsen, and given the patient's rash, we suspected for acute interstitial nephritis or vasculitis. Skin biopsy revealed leukocytoclastic vasculitis that was negative for IgA deposition. Further immunologic workup was negative. No peripheral eosinophilia was observed, and blood cultures were positive for Staphylococcus Aureus. A renal biopsy was performed, which showed IgA-dominant immune complex deposition, likely secondary to infection, and numerous cortical and medullary RBC casts out of proportion to the degree of glomerular injury, concern for anticoagulant associated nephropathy. Moderate interstitial fibrosis and tubular atrophy with no crescents was described. Due to active infection, steroids were not recommended, and the patient's anticoagulation was placed on hold. Unfortunately, due to significant renal injury the patient was initiated on hemodialysis and subsequently, did not show signs of renal recovery.

Discussion: Our patient has dialysis-dependent AKI complicated by secondary IgA nephropathy associated with infection along with anticoagulant-associated nephropathy, related to eliquis. Comorbidities such as diabetes, hypertension, and advanced age can negatively impact the response to therapy. In our case, the patient was also diagnosed with anticoagulant-associated nephropathy which further decreased his chances of recovery.

FR-PO725

A Case of Cronkhite-Canada Syndrome-Associated Membranous Glomerulonephritis: Can Lightning Strike Thrice?

Benjamin J. Strimaitis, Shaun P. Chandler, Leo Francis, Rachna V. Pagnis, Dwarakanathan Ranganathan, Eoin D. O Sullivan. *Royal Brisbane and Women's Hospital, Herston, QLD, Australia.*

Introduction: Cronkhite-Canada Syndrome (CSS) is a rare disorder with less than 500 reported cases, characterized by extensive gastrointestinal polyposis and ectodermal abnormalities. It has been rarely associated with membranous nephropathy (MN). Of the 5 cases of MN associated with CSS in the literature, 3 have been in the context of malignancy, and none have tested PLA2R or thsd7a antibodies.

Case Description: A 60-year-old female of Aboriginal heritage presented for evaluation of proteinuria with an Albumin Creatinine ratio (ACR) of 123 mg/mmol and Protein Creatinine ratio (PCR) of 108 mg/mmol on the background of CCS. Her renal function was reduced with a creatinine-based eGFR of 58mL/min/1.73m2 and a blood pressure of 128/78mmHg. She had a history of bilateral hearing loss since her teens requiring hearing aids but no visual impairment. Her brother had been diagnosed with thin basement membrane disease (TBM) and a maternal aunt with a similar presentation. Serological tests and ultrasonography were unremarkable, and a kidney biopsy demonstrated a classical appearance of MN – which was confirmed to be PLA2R and Thsd7a negative. Electron microscopy confirmed TBM with a mean basement thickness of 180nm. No malignancy suggested by history or examination, nor full body CT imaging or colonoscopy. She was treated with ACE inhibition and proteinuria improved to an ACR of 58 mg/mmoL and PCR of 73 mg/mmoL by six months.

Discussion: This case is the first time that contemporary MN associated antibodies have been tested for in CCS, and suggests MN associated with CCS is not caused by PLA2R and thsd7a antibodies as previously suggested. Hiccum's Dictum is the counter to Occam's Razor, which argues a patient may have as many rare diagnoses as they please. This patient was one of 500 reported cases of CCS, one of 5 reported cases of associated MN and is the only reported case with concurrent active TBM disease. This case highlights the careful consideration which should be give to pre-test probabilities when deciding whether to pursue kidney biopsy (isolated TBM was more likely the diagnosis at initial presentation given the confirmed family history) while acknowledging that lightning can indeed strike thrice.

FR-PO726

Molecular Similarity Between Chronic Active Antibody-Mediated Rejection (CA-ABMR) and Acute T Cell-Mediated Rejection (TCMR) of Human Kidney Allografts

Yajas Shah, Carol Y. Li, Sheavonnie Wright, Alex Devito, Thalia Salinas, Steven Salvatore, Deirdre L. Sawinski, Darshana M. Dadhania, Surya V. Seshan, Manikkam Suthanthiran, Thangamani Muthukumar. *Weill Cornell Medicine, New York, NY.*

Background: CA-ABMR, even without concomitant histological TCMR, is characterized by an increased abundance of NK Cells and T cells. We RNA-sequenced kidney allograft biopsies to test the hypothesis that CA-ABMR, but not active-ABMR, is exemplified by the overexpression of key gene sets that are similar to TCMR.

Methods: We did RNA-seq of 57 biopsies from 57 kidney transplant recipients; 39 for-cause biopsies (15 CA-ABMR, 17 TCMR, & 7 active-ABMR), and 18 surveillance biopsies (no rejection [NR]). All biopsies were evaluated independently by two transplant pathologists. We isolated total RNA from stored biopsy samples, prepared cDNA libraries, and sequenced pooled libraries on an Illumina sequencer. After appropriate quality checks, we used standard bioinformatic tools for data analysis.

Results: There were 1425 genes increased and 29 reduced between CA-ABMR and NR biopsies (FC≥2 & P-FDR<0.05); 1829 were increased and 164 were reduced between TCMR and NR biopsies. T and NK cells were the top cell types and pathways in CA-ABMR and TCMR (Fig.1). Differential gene expression analysis between CA-ABMR and TCMR biopsies yielded only one gene, *MARCHF4*, that was significantly different. Cellular deconvolution revealed a similar proportion of immune cells in the three rejection categories; principal component analysis of deconvolved immune cell transcriptomes separated CA-ABMR and TCMR from active-ABMR and NR biopsies (Fig.2).

Conclusions: CA-ABMR exhibits an immune transcriptome profile that resembles TCMR biopsies. Our findings, besides advancing our knowledge of the pathogenesis of CA-ABMR, provide a compelling argument for the pharmacological targeting of T cells and NK cells in CA-ABMR.

Funding: Other NIH Support - NIAID

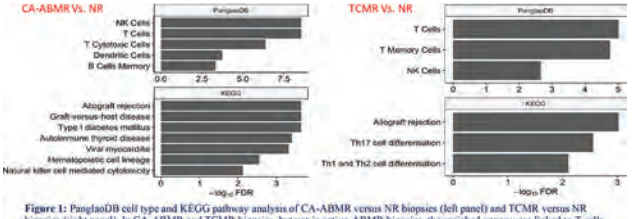


Figure 1: PanglaoDB cell type and KEGG pathway analysis of CA-ABMR versus NR biopsies (left panel) and TCMR versus NR biopsies (right panel). In CA-ABMR and TCMR biopsies, but not in active-ABMR biopsies, the enriched genes were linked to T cells and NK cells, as well as with the allograft rejection pathway.

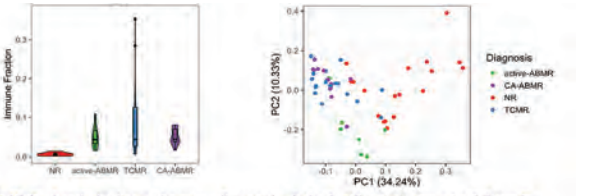


Figure 2: Violin plots depict the total immune cell proportion in the four diagnostic categories (left panel). The proportion of total immune cells in the allograft was not significanly different among the three rejection categories. The total immune cell proportion in each of the three rejection categories was significanlt different when compared to NR. Principal component analysis of the deconvolved immune cell transcriptomes (right panel). Each colored dot represents a biopsy sample. The two principal components, based on deconvolved immune cell transcriptomes, separated CA-ABMR and TCMR from ABMR and NR biopsies.

FR-PO727

Unbiased Proteomics Analysis Shows Distinct Graft Protein Expression in Donor-Specific Antibodies (DSA+) Kidney Transplant Recipients with Antibody-Mediated Rejection

Kieran Manion, Maya A. Allen, Sergi Clotet Freixas, Rohan John, Ana Konvalinka. *University Health Network, Toronto, ON, Canada.*

Background: Nearly 1,000,000 North Americans have end-stage renal disease (ESRD), where the kidneys no longer function. Transplantation is the best treatment for ESRD; however, 50% of grafts fail by 10 years, due mainly to antibody-mediated rejection (ABMR), where recipient donor-specific antibodies (DSA) are thought to drive tissue injury. Unfortunately, predicting ABMR onset is challenging, as 30-60% of DSA$^+$ transplant patients do not develop ABMR. We aim to identify factors that regulate kidney protein expression in DSA$^+$ kidney transplant recipients with and without ABMR.

Methods: Glomeruli and tubulointerstitium isolated from DSA$^+$ABMR (n=24) and DSA$^+$ no ABMR (NA; n=21) kidney biopsies using laser capture microdissection were digested to peptides and analyzed by liquid chromatography mass spectrometry. MaxQuant and Perseus software were used to assess protein identification and differential expression. Significantly differentially expressed proteins (t-test, $p<0.05$) were then mapped to signaling pathways using the pathDIP database (FDR with Benjamini Hochberg adjustment, $q<0.05$).

Results: 120 glomerular and 246 tubulointerstitial proteins were significantly differentially expressed between DSA$^+$ABMR and DSA$^+$NA patients, with 55% of these

proteins upregulated in ABMR (Figure 1). pathDIP analysis showed that upregulated proteins mapped significantly to pathways involving the immune system (glomeruli, q=7.6e-8; tubulointerstitium, q=3.8e-11), antigen processing (glomeruli, q=5.6e-11) and integrin activity (tubulointerstitium, q=1.0e-8), while downregulated proteins mapped to tight junction regulation (glomeruli, q= 1.0e-3) and cellular metabolism (tubulointerstitium, q=1.8e-9).

Conclusions: Our preliminary results suggest that ABMR in DSA$^+$ patients is strongly linked to dysregulated immune and cellular responses in multiple kidney tissues. These findings will ultimately help us identify novel targets for the development of therapeutics for kidney transplant recipients.

Funding: Government Support - Non-U.S.

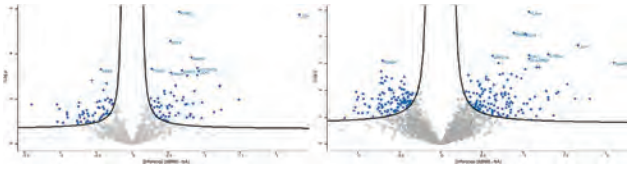


Fig1. Differentially expressed ($p<0.05$) proteins in the glomeruli (*left*) and tubulointerstitium (*right*) of DSA$^+$ kidney transplant recipients with vs without ABMR.

FR-PO728

Role of Urine Exosomal Proteome for Identifying Potential Biomarkers to Predict Renal Allograft Survival

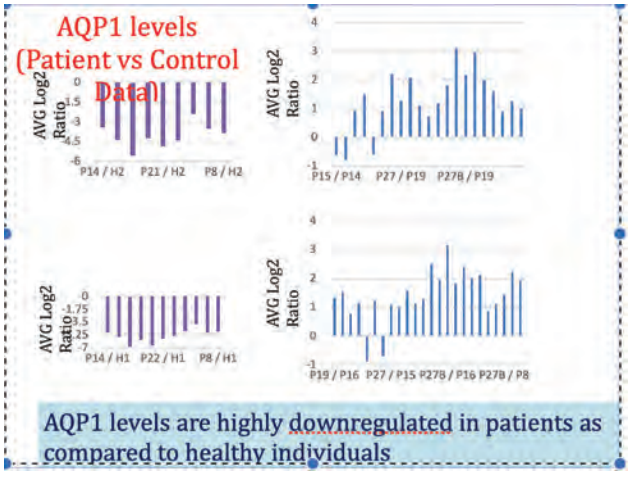
Vinant Bhargava, Anil Bhalla, Ashwani Gupta, Manish Malik, Anurag Gupta, Vaibhav Tiwari, Shiv Chadha. *Sir Gangaram Hospital, New Delhi, India.*

Background: Urine contains proteins bound to extracellular vesicles (exosomes) which are secreted by the cells into the urine as a result of renal insult. We propose to identify exosomal protein markers in urine to predict allograft survival. Molecule-bearing urinary exosome is altered in various kidney diseases. Exosomal molecules such as Aquaporins (AQPs) can be used as potential biomarkers.

Methods: Post renal transplant patient urine samples at 6/7th day were collected using standard protocol. Isolation of exosomes from urine samples was done using standardized protocol. Urine samples were collected at 3, 6, 12 months or/and at the time of graft dysfunction. Further, characterization of exosomal proteins was done through Flow cytometry, Western blotting and NTA (Nano-particle tracking analysis). Exosomal proteome was analysed through LC-MS.

Results: Samples were collected from13 renal allograft patients and 14 healthy controls. There was decreased abundance of urinary exosomal aquaporin-1 observed in allograft renal transplant recipients in the immidiate post transplant and in those with allograft dysfunction (6/13 patients) as compared to healthy individuals. All the 6 patients underwent biopsy and demonstrated rejection (ABMR :2, Tcellrejection: 1), CNI toxicity (n= 2), BKVN (n=1). 24 months followup is underway.

Conclusions: The preliminary analysis of Mass Spectrometry data shows that AQP1 levels are highly downregulated in allograft patients in the immidiate post transplant period and those with allograft dysfunction. This suggests that the excretion of Urinary exosomes UE-AQP1 is altered under the conditions of renal insult. Segregating and co-relating the differential proteome data with clinical parameters and demographic features will help us to define biomarkers specific to a particular cause of allograft dysfunction in our ongoing analysis



Preliminary analysis of mass spectrometry data

FR-PO729

GADD45A and GADD45B as Novel Biomarkers Associated with Chromatin Regulators in Renal Ischemia-Reperfusion Injury and Their Correlation with Immune Cells

Ming Xie,[1] Ruiyan Xie,[2] Yat Hin Desmond Yap,[2] Peng Wu.[1] *[1]Southern Medical University Nanfang Hospital, Guangzhou, China; [2]Queen Mary Hospital, Hong Kong, Hong Kong.*

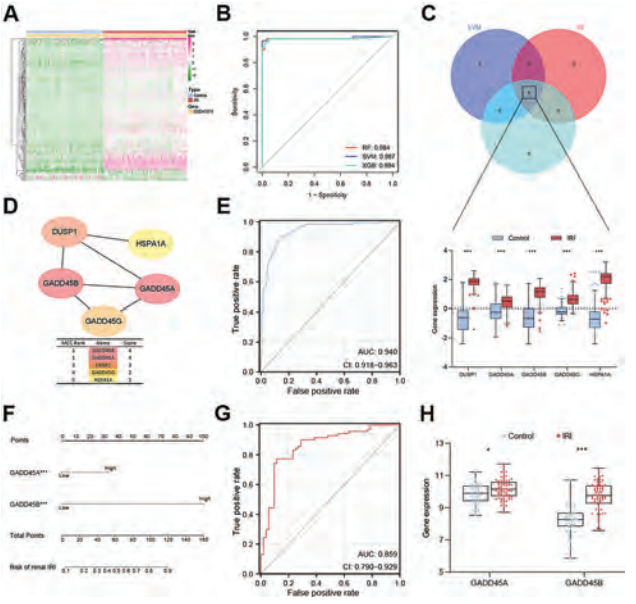
Background: The role of chromatin regulators (CRs) in the pathogenesis of renal ischemia-reperfusion injury (IRI) remains unclear.

Methods: We performed a bioinformatic analysis on the differentially expressed genes of CRs in renal IRI patients using machine learning methods. The hub CRs identified were used to develop a risk prediction model for renal IRI, and their expressions were validated using a murine renal IRI model. We also examined the relationships between hub CRs and infiltrating immune cells in renal IRI.

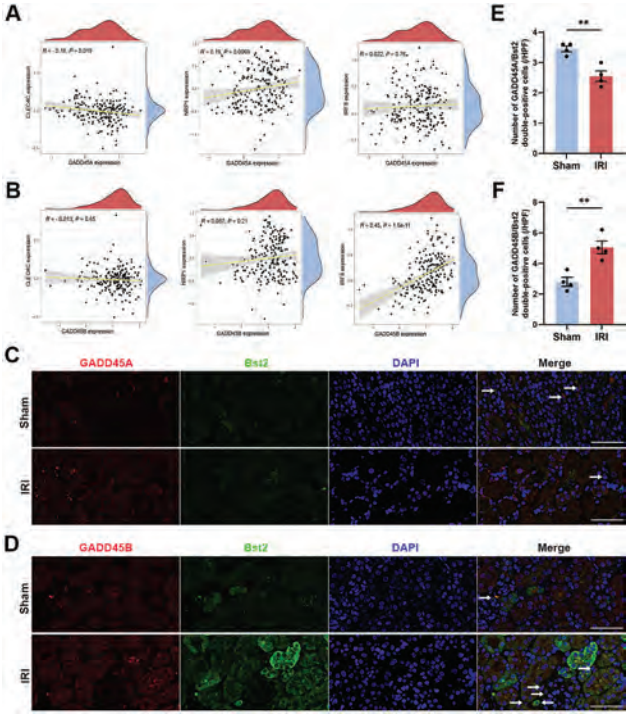
Results: GADD45A and GADD45B were upregulated in renal IRI. GADD45A and GADD45B were chosen to develop a renal IRI risk prediction model and showed good performance. GADD45A and GADD45B showed correlations with plasmacytoid dendritic cells (pDCs) in infiltrating immune cells analysis.

Conclusions: Dysregulation of GADD45A and GADD45B is related to renal IRI and the infiltration of pDCs.

Funding: Government Support - Non-U.S.



Identification of CRs-associated differentially expressed genes in renal ischemia-reperfusion injury using machine learning models, construction and validation of a CRs-associated predictive nomogram.



Correlation analysis of GADD45A and GADD45B expression with cell surface markers of pDCs in renal IRI.

FR-PO730

Renal Denervation Is Protective Against the Development of CKD in a Rat Model of Tacrolimus Nephrotoxicity

Alexander R. Dayton, Mariana Ruiz Lauar, Jaryd Ross, Louise C. Evans, John Osborn. *University of Minnesota Twin Cities, Minneapolis, MN.*

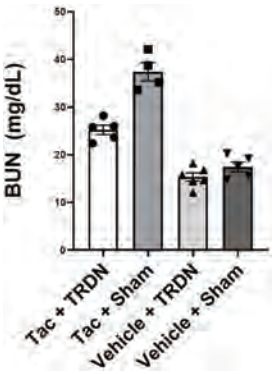
Background: Tacrolimus is the most widely used immune suppressant medication after solid-organ transplant, however it is associated with significant morbidity due to nephrotoxicity and the development of chronic kidney disease. It has recently been appreciated that recipients of transplanted kidneys, which lack intact renal nerves, have a lower incidence of tacrolimus-induced nephrotoxicity. Here we present data demonstrating that denervated kidneys are protected from the development of tacrolimus nephrotoxicity in rats.

Methods: Male and female Sprague-Dawley rats (n=6) underwent either total renal denervation (TRDN) or sham denervation and were subsequently treated with either 2 mg/kg tacrolimus for 14 days or the equivalent dose of vehicle. At the end of treatment BUN was assessed as a marker of renal function. Histology was performed to assess renal fibrosis and glomerulosclerosis. RNA was extracted from the cortex and medulla, and then transcriptome was assessed.

Results: BUN was significantly lower in TRDN animals compared to sham(26 vs 38 mg/dl, $p < 0.01$). Additionally, medullary fibrosis was decreased in denervated rats. RNA-sequencing studies to further investigate the mechanism behind this protection are ongoing.

Conclusions: These findings present an exciting new avenue for the use of renal denervation – if confirmed these would provide the foundation for prophylactic renal denervation in non-renal transplant patients requiring tacrolimus.

Funding: Other NIH Support - R01 HL 116476, T32 HL 144472



Tacrolimus treatment for 14 days induces substantial renal dysfunction. Total renal denervation (TRDN) decreases BUN significantly compared to sham denervation.

FR-PO731

Angiotensin-Converting Enzyme 2 in Delayed Graft Function After Kidney Transplantation

Cosimo L. Cianfarini, Jan Wysocki, Jiao-Jing Wang, Minghao Ye, Zheng J. Zhang, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

Background: Delayed graft function (DGF) is a severe form of acute kidney injury occurring post kidney transplantation. There is clinical evidence that the renin angiotensin system (RAS) is overactive in DGF. Angiotensin converting enzyme 2 (ACE2) is a RAS enzyme abundantly present in the kidney and localized in the apical brush border of the proximal tubule where it metabolizes Angiotensin II (Ang II) to form Angiotensin 1-7 thereby protecting from undesirable Ang II accumulation. Here we studied the expression and distribution of ACE2 in a mouse model of DGF.

Methods: Syngeneic kidney transplantation was performed between male C57BL/6 mice using donor kidneys exposed to 3hrs of cold ischemia. The transplanted kidneys (n=9) were harvested 48hrs after surgery and stained for ACE2 by immunohistochemistry (IHC). ACE2 protein was assessed by Western Blot and enzymatic activity using a fluorogenic substrate. Molecular markers for kidney damage and inflammation were assessed by Real-Time PCR. Kidney Angiotensin II levels were measured by ELISA.

Results: In mice with DGF, BUN was increased above 100mg/dl and NGAL and KIM-1 were increased in the kidney cortex. Markers of inflammation and immune cell invasion (IL-6, MCP-1, CD68, CD11b) were increased as well. Kidney Ang II levels were increased 2-fold (1.6±0.2 vs 0.7±0.06 pg/mg total protein, p=0.001) and ACE2 staining by IHC revealed profound alterations in the distribution of apical tubular ACE2 as compared to the healthy contralateral kidney. Tubules were widened and filled with ACE2 positive material, particularly in the corticomedullary region. The medulla showed luminal deposition of ACE2 positive material whereas staining was totally absent in the healthy contralateral kidney. These alterations were associated with decreased kidney ACE2 protein (57±13 vs 100±13 ACE2/GAPDH, p=0.03) and decreased ACE2 enzymatic activity (7.4±0.5 vs 9.3±0.6 RFU/µg total protein/h, p=0.03).

Conclusions: In mice with DGF post kidney transplantation there is a striking maldistribution of tubular ACE2 with loss of apical membrane bound full-length ACE2 into the tubular lumen. This loss results in decreased kidney ACE2 protein, enzymatic activity and increased kidney Ang II. The deficiency of this protective enzyme suggests that its replenishment could have an important therapeutic implication for DGF.

Funding: Other NIH Support - NIAID, Private Foundation Support

FR-PO732

Cellular Responses to BK Polyomavirus Infection in Transplanted Kidneys

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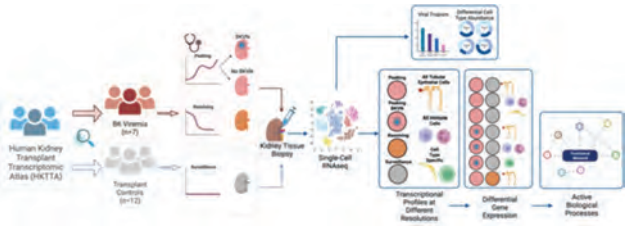
Background: BK virus (BKV) infection remains problematic following kidney transplantation. Despite delineation of tubular responses in cell culture, the effect of an immune system on the cell-specific response *in vivo* to BKV is less well-understood.

Methods: Single-cell RNA sequencing of kidney biopsies (12 surveillance, 5 peak viremia, and 9 resolving viremia) from the Michigan Human Kidney Transplant Transcriptomic Atlas study were analyzed for cell type-specific transcriptomic responses to viremia and viral nephropathy and compared with healthy surveillance biopsies and BKV infected cells in culture.

Results: BKV transcripts were found in tubular cells and immune cells, confirmed in lymphoid clusters by VP1 immunohistochemistry. Cytokine signaling, cell-cycle regulation, translation, and wound healing were activated in BKV-infected tubular cells but not in tubules of viremic patients without nephropathy where stress-signaling and immune response predominated. During peak viremia there was an expansion of adaptive but not innate immune response. BKV-infected tubules showed increased cytokine, interferon γ, and tumor necrosis factor (TNF) signaling in humans. In contrast, TNF signaling was reduced in cell cultures.

Conclusions: Differential transcriptional responses to BKV infection *in vivo* and *in vitro* highlight the complex cellular and immune crosstalk not captured in 2D models. These findings also point towards exploration of anti-TNF therapies for BKV.

Funding: NIDDK Support



FR-PO733

Cyclosporine Distinctly Damages Proximal Tubules, Tacrolimus the Filtration Barrier in Calcineurin Inhibitor Nephrotoxicity

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Background: Calcineurin inhibitors (CNI) are the backbone for immunosuppression after solid organ transplantation. Although succesful in preventing kidney transplant rejection, their nephrotoxic side affects notoriously contribute to allograft injury despite attempts to optimize their application, often with additional medications. Complex renal parenchymal damage occurs for cyclosporine A (CsA) as well as for the currently favoured tacrolimus (Tac). We asked whether CsA and Tac exert distinct damage patterns during onset stages CNI nephropathy. We combined mulitomics analysis with histopatholgy from rat kidney exposed to continuous CNI delivery.

Methods: CsA and Tac were administered chronically in wild type Wistar rats using osmotic minipumps (total n=112) over 4 weeks. Physiological parameters were controlled. Animals were prepared for high-end morphological analysis, elective immunostaining, and multiomics analysis. Large scale electron microscopy, confocal stimulated emission-depletion (STED) and 3D-structured illumination microscopy were used for pathology. Standart biochemistry, RNAseq, proteomic, and phosphoproteomic technology was performed to identify molecular alterations.

Results: Damage forms varied strikingly. Both drugs caused significant albeit differential damage in vasculature and nephron. The glomerular filtration barrier was more affected by Tac than CsA, showing prominent deteriorations in pore endothelium and podocytes along with impaired VEGF/VEGFR2 signalling and podocyte-specific gene expression. By contrast, proximal tubule epithelia were more severely affected by CsA than by Tac, revealing lysosomal dysfuction and enhanced apoptosis and necrosis along with impaired proteostais and oxidative stress.

Conclusions: We conclude that pathogenic alterations in renal microenvironments are specific for either treatment. Should this translate to the clinical setting, CNI choice should reflect individual risk factor for renal vasculature and tubular epithelia. As a step in this direction, we share products identified from multiomics for differential pathonomonic biomarkers.

Funding: Government Support - Non-U.S.

FR-PO734

Human Kidneys House Tissue-Resident B Cells with a Distinct Anatomical Location and Phenotype that Changes with Age

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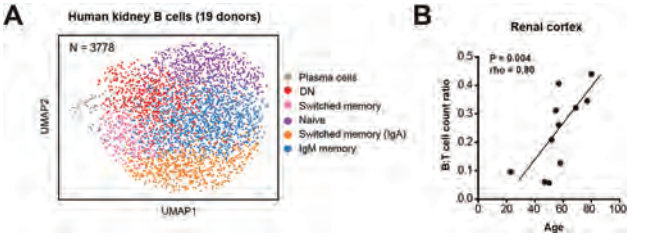
Background: B cells play a central role in humoral immunity but have also antibody-independent functions, important for generating local immune responses and tolerance. Kidneys are the most commonly transplanted solid organ worldwide but whether they harbor B cells in homeostasis and how they change with donor age has received little attention.

Methods: We examined the number, phenotype and clonality of B cells in human kidneys that were perfused to remove circulating cells, and in matched splenic tissue obtained from the same transplant donor (N=19, median age 56 years (range: 18–80). Suspensions from homogenized organs were analyzed using a 35-marker mass cytometry panel and single-cell RNA sequencing (Figure A). B cells were also sorted for bulk BCR-sequencing.

Results: The frequency of B cells within kidney CD45$^+$ cells was lower than in spleen (8.8% vs. 26%, P<0.005). The renal cortex harbored ten times more B cells per gram of tissue than medulla. In contrast to spleen, B cell count and B:T cell ratio in renal cortex significantly increased with age (Figure B). Kidney B cells were enriched for non-naïve (CD27$^+$IgD$^-$ and double-negative) subsets with innate-like characteristics when compared to spleen or younger donors. BCR analysis showed CDR3 repertoire differences between kidney and spleen, suggesting a specific antigenic exposure, but also clonotypes sharing between matched organs and across donors.

Conclusions: Our study shows that under homeostatic conditions, human kidneys harbor both antigen-experienced and innate-like B cells, mirroring studies of murine tissue-resident T cells. These cells expanded with age and showed a specific anatomical location to the outer part of the kidney, an area specialized for filtration of blood. These kidney B cells may play a role in local immune defense or contribute to immunopathology (autoimmunity, organ rejection), and further studies on diseased tissues and murine models are underway.



FR-PO735

Cell-Specific Expression of Class II HLA Genes in Rejecting Kidney Transplant Biopsies by Single-Cell RNAseq

Andrew F. Malone, Aidan Leckie-Harre, Venkatrao Nunna, Benjamin D. Humphreys, Chang Liu. *Washington University in St Louis School of Medicine, St Louis, MO.*

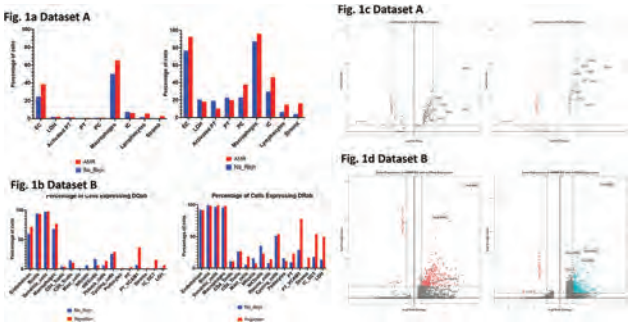
Background: Antibody-mediated rejection (AMR) remains one of the major causes of allograft failure. Anti-HLA antibody binding to endothelial cells is thought to be a central event driving AMR. Expression of both alpha and beta chains encoded by class II HLA genes is required for complete HLA class II protein expression on the cell surface.

Methods: We determined the expression of HLA-DR and HLA-DQ genes from single cells from two datasets of human kidney transplant biopsies. The proportion of cells expressing both alpha and beta chains for HLA-DR (DRA/DRB1, or DRab hereafter) and for HLA-DQ (DQA1/DQB1 or DQab hereafter) was determined across all rejection phenotypes. The gene expression pattern in endothelial cells with DRab or DQab was compared to that of endothelial cells not expressing DRab or DQab.

Results: We analyzed two datasets for this study: A) 81139 cells from 5 biopsies (AMR or no-rejection) published previously, and B) new data of 31,203 cells from 11 biopsies (no-rejection, AMR, TCMR or mixed). In dataset A, DQab expression was restricted to endothelial cells (EC) and immune cells with little expression in other cells of the kidney. DRab was widely expressed in all cell types. Similar profiles were found in dataset B (fig1a+b). In EC, *PLA1A*, a molecular marker for AMR, showed a significantly increased expression in EC positive for DQab or DRab when compared to EC negative for DQab/DRab (fig1c+d).

Conclusions: Cell specific class II HLA gene expression can be determined from single-cell RNAseq data. Expression of DQab/DRab in ECs is associated with molecular markers for AMR, which may provide diagnostic and mechanistic insight for AMR.

Funding: NIDDK Support



FR-PO736

Kidney Storage at Subzero Temperature Is Safe for Porcine Auto-Transplantation: A World First In Vivo Study

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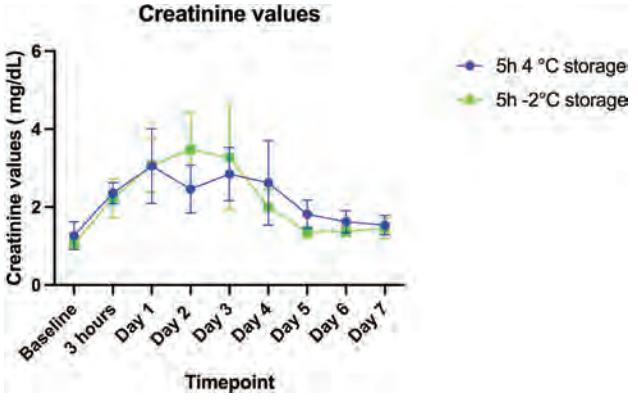
Background: Static cold storage (SCS) at 4°C remains the method of choice for kidney preservation prior to transplantation, but the rapid decline of graft quality at 4°C limits prolonged SCS and graft exchange over larger distances. Kidney storage below 0°C could prolong graft viability and offer new opportunities for kidney graft exchange over larger distances, or controlled scheduling of kidney transplant. The aim of this study was to determine the feasibility of sub-zero storage followed by auto-transplantation of porcine kidneys.

Methods: Kidneys were retrieved from Yorkshire pigs and either stored at 4°C for five hours (n=4) or flushed and stored using a novel preservation solution (CrS SC 0.3 EQ, Cryostasis Inc®) at –2°C (n=4). After storage, kidneys were auto-transplanted.

Results: All kidneys were successfully transplanted and immediately produced urine. Results were compared between the two groups, and assesed using T-test or ANOVA. Creatinine values at days 1, 3 and 7 for the -2°C and 4°C groups were 3.07 vs. 3.05 mg/dL, 3.28 vs. 2.84 mg/dL, and 1.4 vs.1.54 mg/dL, respectively (p>0.05). 24-hour urine output was 1700 ml (562.5 - 3250 ml) vs. 1700 ml (1450- 2650 ml) for -2°C and 4°C groups. Lactate values at 1, 3 and 7 days were 0.9 vs. 1.1, 0.75 vs. 0.56, and 0.95 vs. 0.88 mmol/L (p= 0.34). AST levels at 1, 3 and 7 days were: 152.3 vs.101.6, 33.3 vs. 27.8 and 25 vs. 22.8 U/L (p>0.05). Potassium levels were 4.8 vs. 4.2, 4.3 vs. 3.8 and 4.2 vs. 4.4 mmol/L at days 1, 3 and 7 (p=0.05).

Conclusions: Sub-zero short storage of porcine kidneys is feasible and results are comparable to ideal heartbeating-donor kidneys briefly stored at 4 °C. Histological, celular and molecular analyses are underway to better understand sub-zero protective mechanisms, and its extents will be further studied by prolonging storage times.

Funding: Commercial Support - Cryostasis Incorporated



FR-PO737

Sirolimus Toxicity Manifested with Fanconi Syndrome in a Kidney Transplant Patient

Christopher F. Middleman, Megha R. Joshi. *Walter Reed National Military Medical Center, Bethesda, MD.*

Introduction: Sirolimus, a mechanistic target of rapamycin (mTOR) inhibitor, decreases antigen and cytokine stimulated T-lymphocyte activation and proliferation, and inhibits antibody production. It has been shown to prolong kidney allograft survival, and reverse acute rejection. In transplant patients with recurrent basal and squamous cell carcinomas, sirolimus is frequently used to prevent or reduce recurrence of these malignancies. This case highlights a rare but important to recognize side effect of the drug and how it can be managed.

Case Description: A 75-year-old female, with end stage kidney disease due to hypertension, received a living related kidney transplant in 2017. Over the next 5 years her course was complicated by recurrent non-melanomatous skin cancers requiring multiple Mohs surgeries. Immunosuppressive therapy was changed from tacrolimus to sirolimus to reduce skin cancer recurrence while preventing rejection. The sirolimus trough goal was 4-6 ng/mL. Her baseline serum creatinine (sCr) was 0.8-0.9 mg/dL without proteinuria. Within two months of transitioning to sirolimus, she developed lower extremity edema, loss of appetite and generalized fatigue. She was found to have proteinuric acute kidney injury with 1.6 gm protein/gm Cr, sCr 1.1mg/dL, hypokalemia (2.8 mmol/L) and hypophosphatemia (2.3 mg/dL). Sirolimus trough level was 12.9 ng/mL. Further urine testing revealed elevated fractional excretions of potassium, phosphorus, and uric acid. The sirolimus dose was reduced, with subsequent normalization of serum creatinine, electrolytes, and complete resolution of proteinuria. The patient's symptoms also resolved.

Discussion: Long-term use of sirolimus may be associated with proteinuria and sCr increases in kidney transplant patients, however this is the first case to our knowledge where a supratherapeutic level of sirolimus induced a generalized proximal tubular dysfunction (i.e., Fanconi's syndrome), which completely resolved with dose reduction to therapeutic range. As sirolimus is increasingly used in the setting of non-melanomatous skin cancers after kidney transplant, improving awareness and early diagnosis and treatment of associated Fanconi syndrome is critical for allograft survival. *Disclaimer: The views expressed in this abstract are those of the authors and do not reflect the official policy of the Department of Defense, or the United States government.*

FR-PO738

Transplant Renal Artery Embolization: An Alternative to Transplant Nephrectomy in Patients with Graft Intolerance Syndrome

Imran Chaudhri, Martha Pavlakis. *Beth Israel Deaconess Medical Center, Boston, MA.*

Introduction: A subset of patients with failing renal allografts can develop what is known as graft intolerance syndrome (GIS); characterized by fever, malaise, hematuria, and graft tenderness. Traditionally, this was treated by surgical removal of the allograft, but embolization of the transplant renal artery is a potential alternative. Here, we describe a case of GIS with rapid resolution using non-surgical management.

Case Description: A 61-year-old man with history of type 2 diabetes, hypertension, hyperlipidemia, and end stage kidney disease (ESKD) presented in August 2022 with acute onset right lower quadrant (RLQ) abdominal pain. He had a deceased donor kidney transplant in December 2018 and his post-transplant course had been complicated by multiple episodes of acute antibody- and cell-mediated rejection. During this time, his immunosuppression was adjusted multiple times and in June 2022, he was admitted for volume overload and hyperkalemia and was initiated on hemodialysis. On that discharge, he was instructed to continue on a prednisone taper and mycophenolate. Despite these instructions, the patient stopped taking his immunosuppression on his own and subsequently presented with abdominal pain in August 2022. On exam, he was hypertensive to 190/76 and had tenderness to palpation over his allograft. Computerized tomography (CT) of his abdomen showed that his allograft kidney was enlarged at 14 cm by length. A diagnosis of GIS was made. A multidisciplinary discussion between transplant surgery, transplant nephrology, and interventional radiology (IR) occurred and in the end, percutaneous renal artery embolization was pursued by IR. His symptoms resolved, and he was discharged 2 days after the procedure.

Discussion: Traditionally, when GIS is treated with transplant nephrectomy, reported complications include infection, bleeding, human leukocyte antigen sensitization, and death. Transplant renal artery embolization is less invasive, associated with shorter length of stay and, in some studies, with reduced mortality and morbidity. Our patient obtained almost immediate relief with a much less invasive approach and continues to be symptom free. In summary, this case illustrates that renal artery embolization of the allograft can be an effective and safe alternative to transplant nephrectomy in patients with GIS.

FR-PO739

Rare Case of Renal Vein Thrombosis in a Transplanted Kidney with Successful Endovascular Thrombectomy

Hywel Soney, Victor E. Serrano-Santiago, Kosunarty Fa, Roberto L. Collazo-Maldonado. *Methodist Dallas Medical Center, Dallas, TX.*

Introduction: Transplant-associated renal vein thrombosis (RVT) is a rare complication in kidney transplant recipients, with high risk of allograft loss and further complications. Here, we present a case of RVT managed by endovascular thrombectomy.

Case Description: A 75-year-old African American female with a history of ESRD due to T2DM, underwent deceased donor renal allograft implantation with Thymoglobulin induction, maintenance with mycophenolate, tacrolimus, and prednisone, and was discharged without complications and stable Creatinine (Cr) 1.0 mg/dL. She was readmitted 4 weeks after transplant for diminished urine output, hypotension, and elevated Cr (2.8 mg/dL). Urinalysis on admission demonstrated >100 red blood cells along with 5-10 white blood cells. Doppler ultrasound demonstrated elevated intrarenal resistive indices, reversed diastolic flow in the renal artery, deep vein thrombosis from the right common femoral vein through the popliteal vein, and with a nonocclusive thrombus in the iliac vein straddling the anastomosis. With high suspicion for RVT, the patient underwent a successful endovascular thrombectomy. Follow-up renal ultrasound demonstrated normalized transplant renal flow dynamics and correction of the reversed diastolic flow in the iliac arteries. Allograft biopsy was performed with findings of acute tubular necrosis and no evidence of rejection. During this time, the patient's Cr peaked at 6.9 mg/dL with intermittent need for vasopressors and continuous renal replacement

therapy. Within the following two weeks, the patient's urine output and Cr recovered to baseline status and she was continued on anticoagulation thereafter.

Discussion: RVT in new transplants has a high risk of poor outcomes. Events usually occur within the first two weeks and can present with worsening renal function, oliguria, hematuria, and/or abdominal pain. Early detection with Doppler ultrasound is key to evaluating for potential RVT and initiating further diagnostic actions or interventions to prevent complications. Interventions may include direct surgical thrombectomy, endovascular thrombectomy or thrombolytic therapy, although studies are lacking in identifying an optimal first-line intervention. Having a high suspicion for RVT and acting quickly is vital in avoiding critical complications in new allografts.

FR-PO740

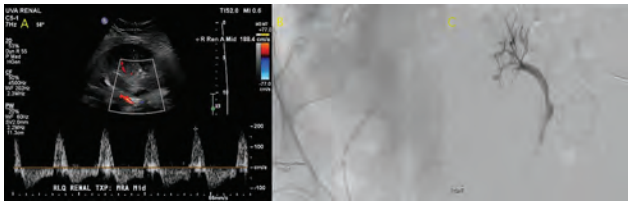
Transplant Renal Vein Thrombosis

Monarch Shah, Swati Rao, Angie G. Nishio Lucar. *University of Virginia, Charlottesville, VA.*

Introduction: Transplant renal vein thrombosis (TRVT) is a dire complication of kidney transplantation and can lead to graft failure. This case highlights the importance of awareness of this infrequent complication and the importance of reviewing donor anatomy to assist in timely diagnosis.

Case Description: A 40-year-old male with ESKD due to IgAN diagnosed at 17 was on peritoneal dialysis since age 36 and underwent a deceased donor kidney transplant (KT). The KDPI was 12%, calculated PRA were 0%, and EPTS was 13%. The donor renal artery was anastomosed to the recipient's external iliac artery. As the right renal vein (RV) is shorter an IVC extension graft is utilized for anastomosis. Despite the atypical incision on the donor IVC, the surgeon achieved a good extension for anastomosis to the recipient's external iliac vein. The kidney perfused well with immediate graft function. Immunosuppression induction was with anti-thymocyte globulin and steroids and maintenance with MMF and tacrolimus. Creatinine improved to 1.8 mg/dl by POD4 (9.4 mg/dl preoperatively). He was re-admitted on POD 8 with hematuria, abdominal pain & reduced urine output. Creatinine was 2.4 mg/dl. CT scan showed a hypoattenuating KT. Ultrasound (fig A) showed diastolic reversal of arterial flow and absence of RV doppler signal. Venography showed thrombosis of the transplant RV up to the anastomosis. Rheolytic thrombectomy of the transplanted RV, balloon angioplasty (Fig B), and stent placement of the juxta-anastomotic stenosis was done with fast outflow (Fig C) seen from the allograft. The allograft was salvaged & urine output is > 1L/day, but he is dialysis dependent. The venous stent thrombosed 2 months post-transplant requiring thrombectomy and balloon angioplasty. Currently, the allograft outcome remains guarded.

Discussion: AKI in transplant patients has a broad differential, and there should be a high suspicion index for TRVT. Knowing donor anatomy and the operative course aids in rapid diagnosis. Despite prompt therapy, TRVT causes profound ischemic damage leading to allograft loss and nephrectomy.



A: Diastolic reversal of arterial flow, B: Balloon angioplasty of the juxta-anastomotic segmental stenosis, C: Fast outflow from the allograft

FR-PO741

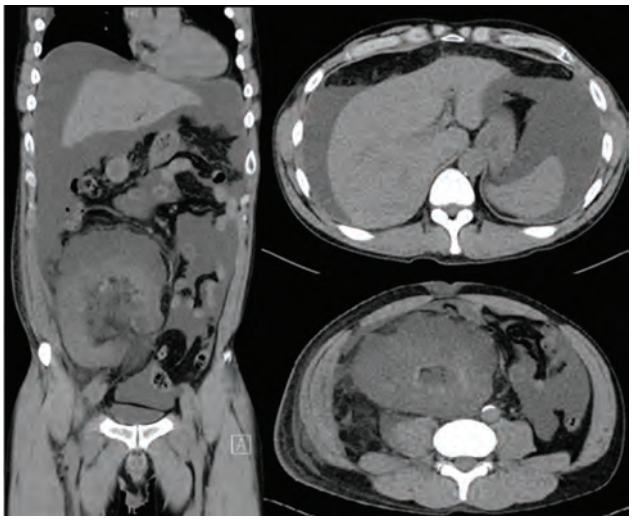
Renal Allograft Lymphangiectasia After Kidney Transplantation

Eun jeong Ko, Byung ha Chung, Chul Woo Yang. *The Catholic University of Korea, Seoul, Republic of Korea.*

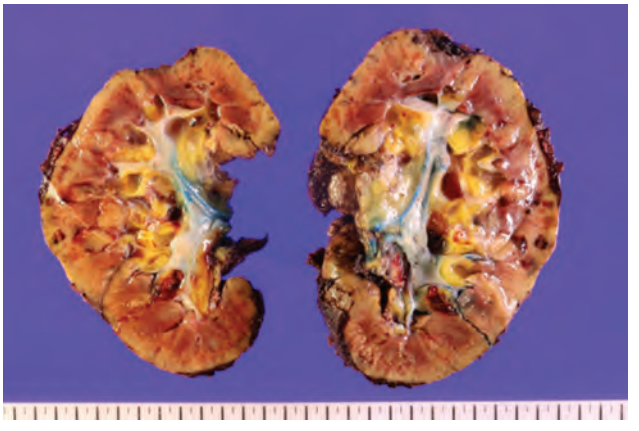
Introduction: Renal lymphangiectasia is a rarein the setting of transplant kidney. We report a case of renal lymphangiectasia after kidney transplantation

Case Description: A 43-year-old man received living donor kidney transplantation due to IgA nephropathy. 14 years after transplantation, he presented with abdominal distension, and dyspnea. Serum creatinine level was elevated to 1.6mg/dL from 1.1mg/dL. Computed tomography (CT) showed multi-septated cystic lesions around the graft kidney with a large amount of ascites. Ascites profile showed transudative, non-chylous, suggesting lymphatic fluid. There was no evidence for infectious or malignant disease. At first, tacrolimus was switched to sirolimus for anti-lymphangiogenic effect, consequently the amount of ascites was significantly reduced. However, 3 weeks after, large amount of ascites were recurred. Surgical approach with explore laparotomy, argon coagulation and helixor injection through Hemo-vac drain were performed. Also, lymphatics embolization was performed using lipiodol. Nevertheless, massive ascites recurred just after 1 week from procedures, therefore, allograft nephrectomy was inevitable

Discussion: Post-transplant renal lymphangiectasia is a rare but critical complication of allografts, still poorly understood. However, once it happens, active treatment is required.



Abominal computed Tomography



Gross pathology of transplant nephrectomy

FR-PO742

Unrecognized Ureteral Injury After Attempted Hysterectomy in Transplant Patients

Amber Anwar, Saed Shawar, Kareem Eid. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Although frequently overlooked, ureteral injuries are well-documented complications following gynecologic surgeries, potentially causing acute kidney injury and failure. To mitigate these undesirable outcomes, involvement of a multidisciplinary team, including transplant surgeons, is highly recommended in complex patients. We present a unique case of a simultaneous pancreas-kidney transplant patient with an unrecognized ureteral during an attempted hysterectomy.

Case Description: A 42-year-old woman with End-Stage Renal Disease due to Type 1 Diabetes Mellitus and status post simultaneous kidney and pancreas transplant in 05/2021. Induced with Alemtuzumab and Solumedrol and maintained on Tacrolimus, Mycophenolate Mofetil, and Prednisone, with creatinine range 0.8-1mg/dl, alongside normal amylase and lipase levels. In 07/2022, the patient attempted a laparoscopic hysterectomy at a local hospital for unresolved menorrhagia. However, the surgery was abandoned due to extensive intraabdominal adhesions, with partial adhesiolysis performed before closure. Following discharge on the same day, she presented with acute abdominal pain, anuria and rise in creatinine 11mg/dl from 0.93mg/dl. CT scan revealed an edematous transplant kidney with hydroureteronephrosis and intra-abdominal and pelvic ascites. The Transferred to Vanderbilt University Medical Center, where ultrasound confirmed hydroureteronephrosis and a discontinuity of the ureter with the bladder. In addition, CT cystogram showed lack of opacification of the reimplanted ureter, concerning for ureteral injury. An urgent laparotomy was performed by a multidisciplinary team of urologists and renal transplant surgeons, resulting in drainage of three liters of urine from the abdominal cavity and the identification of a transected ureter above the urinary bladder. Assisted cystourethroscopy was utilized to repair and reimplant the ureter to the urinary bladder, resulting in the resumption of urine output and a rapid decrease in creatinine levels to baseline.

Discussion: For complex intra-abdominal or pelvic surgeries, involvement of transplant surgeons is paramount. Negligence can lead to significant postoperative complications, such as acute kidney injury, increasing morbidity and mortality. Prompt interventions, like ureteral repair and reimplantation conducted in this case, can lead to a remarkable recovery from severe complications.

FR-PO743

Infection: A Potential Trigger of Recurrent C3 Glomerulonephritis in a Kidney Transplant Recipient

Amber Anwar, Sarah Abu Kar, Laura Binari, Yihan Wang, Saed Shawar. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: C3 Glomerulonephritis (C3GN) is a rare kidney disease caused by dysregulation of the alternative complement pathway through genetic or acquired alteration in regulatory protein. 67- 84% of kidney transplant recipients have recurrence within median time of 14-28 months and graft loss at 18 months after diagnosis. Therapy for recurrent C3GN can include immunosuppression, plasmapheresis, and complement targeting agents like Eculizumab. We present a case of recurrent C3GN in a kidney transplant recipient.

Case Description: A 57-year-old male with end-stage kidney disease secondary to C3GN on monthly Eculizumab underwent a living unrelated kidney transplant with Alemtuzumab and Solumedrol for induction. He had immediate graft function with nadir creatinine (Cr) of 1.05 mg/dL and urine protein of 0.1g/g, and maintenance immunosuppression was Tacrolimus, Mycophenolate Mofetil (MMF) and Prednisone. Two months post-transplant, he was admitted with periodontitis treated with Augmentin. Also had neutropenia which improved with 3 doses of filgrastim and transient discontinuation of MMF, Bactrim and Valcyte. He was maintained on Tacrolimus and Prednisone 10mg. At 1 week follow up, Cr was 1.9 mg/dl attributed to CNI toxicity and Tacrolimus dose was adjusted. However, he soon after developed hypertension, hematuria, proteinuria (0.75g/g), thrombocytopenia and AKI with Cr 2.7 mg/dl. An allograft biopsy was performed, showed C3GN recurrence with mesangial proliferative GN with C3-dominant and monotypic IgG4 dominant deposits. Functional complement panel showed high C3 nephritic factor (34unit/ml). He was treated with 7 plasmapheresis sessions and reinduction with Eculizumab 900mg IV weekly for 4 weeks and then 1200mg every 2 weeks. A repeat C3 nephritic factor level was undetectable. At 3 months, the Cr stabilized at 2mg/dl and proteinuria resolved.

Discussion: We speculate that C3GN recurrence was triggered by infection and reduction in immunosuppression. Prompt control of disease activity can be achieved with removal of offending proteins via plasmapheresis and stabilization of complement activity with Eculizumab. Close surveillance is deemed necessary for control of disease progression.

FR-PO744

Hypercholesterolemia Is Associated with Cardiovascular Morbidity and Mortality Among Kidney Transplant Recipients

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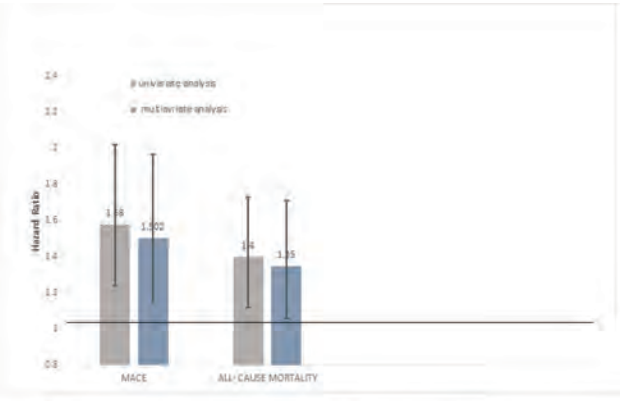
Background: Hypercholesterolemia is highly prevalent among kidney transplant recipients (KTR). Unlike the general population, the correlation between hypercholesterolemia and cardiovascular disease in KTR has not been well established. Therefore, we investigated the association between abnormal cholesterol profiles and cardiovascular morbidity and mortality in this unique population

Methods: We conducted a single-center retrospective cohort study that included all adult KTR who had a functioning graft for at least 12 months after transplantation, between January 2005 and April 2014. The primary outcome was a Major Adverse Cardiovascular Event (MACE) defined as non-fatal myocardial infarction, non-fatal CVA, coronary revascularization, hospitalization for acute coronary syndrome and cardiovascular mortality. The secondary outcome was all-cause mortality. To calculate exposure to abnormal cholesterol levels, we used a time-weighted average (TWA) calculation, for LDL-C and HDL-C. MACE risk was analyzed using a multivariate and univariate time-varying Cox model.

Results: The study included 737 KTR, with a median follow-up of 2920 days. The TWA level of LDL-C decreased from 91.6±22.8 mg/dL during the first year to 89.5±20.7 during the 7th year (p=0.021). The TWA level of HDL-C increased from 49.2±12.7 mg/dl to 50.5±13 (p=0.012). A total of 126 patients (17.6%) experienced a MACE event. A correlation was found between high LDL-C levels and MACE risk by multivariate analysis (HR 1.008 per mg/dL, 95%CI 1.001 – 1.016), while low HDL-C levels were not significantly associated with MACE (HR 0.992 per mg/dl, 95%CI 0.976 – 1.009). Higher LDL-C/HDL-C ratios were significantly associated with an increased risk of MACE in both univariate and multivariate analyses (HR 1.502, per unit, 95%CI 1.147-1.968), as well as all-cause mortality (HR 1.35 per unit, 95%CI 1.06 – 1.71).

Conclusions: Exposure to high LDL-C /HDL-C ratio among KTR is associated with an increased risk of cardiovascular morbidity and mortality



LDL/HDL ratio is associated with MACE and all-cause mortality by multivariate analysis.

FR-PO745

Hemophagocytic Lymphohistiocytosis in Adult Renal Transplant Patients: A Case Series of Three Patients

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Introduction: Hemophagocytic lymphohistiocytosis (HLH) is a rare, life-threatening disease that presents with non-specific symptoms, leading to a delay in diagnosis and early initiation of treatment. We present 3 cases of HLH in renal transplant patients at our institution.

Case Description: 1) 40-year-old female with end stage renal disease (ESRD) on hemodialysis (HD), diabetes mellitus (DM), and hypertension (HTN) who underwent simultaneous kidney-pancreas transplant (SPK) with Thymoglobulin induction on 9/2021, admitted with neutropenia 2 months later. She developed fever, mental status changes, and cholestatic jaundice. CT abdomen showed mild hepatosplenomegaly. Labs showed WBC 0, plt 32, Hgb 6.6, ferritin 11k, CMV 1852, EBV 346, elevated soluble interleukin-2 (sIL-2). Bone marrow biopsy (BMB) revealed hemophagocytic cells. The probability of HLH was 54%-70% based on H score. She was treated with dexamethasone and Etoposide without response. She expired 2 months post presentation. 2) 34-year-old male with chronic kidney disease stage 5, DM, HTN who underwent SPK with thymo induction on 1/2022 admitted with fever and fatigue one month post-transplant. Labs showed WBC 0, plt 27, hgb5.4, ferritin 68k, CMV 1741, EBV 28600, transaminitis, and elevated sIL-2. The probability of HLH was 54-70% based on H score. BMB showed hypocellular marrow (5-10%) with many histiocytes and markedly decreased trilineage hematopoiesis. He received dexamethasone, eltrombopag and cyclosporine without response and expired 6 weeks post presentation. 3) 62-year-old male with DM, HTN, ESRD on HD, who underwent deceased donor kidney transplant with thymo induction on 9/2022, admitted with fever, malaise, and vomiting 4 months post-transplant. Labs showed hgb 6.7, ferritin >100k, elevated triglyceride and sIL-2. CT scan revealed splenomegaly, and BMB showed HLH secondary to histoplasmosis. He received Amphotericin with good response and was discharged 3 weeks after presentation.

Discussion: Idiopathic HLH carries a poor prognosis with high mortality, but HLH secondary to infection has better prognosis if the infection is treated successfully. Early identification and treatment are crucial to optimize outcomes.

FR-PO746

Hemophagocytic Lymphohistiocytosis After Kidney Transplantation

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Introduction: Hemophagocytic Lymphohistiocytosis (HLH) is an immunological disorder resulting in blood cell phagocytosis. In kidney transplant (KT) recipients (KTR), HLH is usually secondary to infectious or neoplastic processes. Typical findings of HLH are fever, hepatosplenomegaly, cytopenia, hypertriglyceridemia, coagulopathy-related hypofibrinogenemia, liver dysfunction, and elevated ferritin. Early diagnosis with appropriate treatment is recommended.

Case Description: An 18-year-old man with ESRD due to Focal Segmental Glomerulosclerosis (FSGS) received a deceased donor kidney transplant (DDKT). Immunosuppression regimens were anti-thymocyte globulin for induction, and tacrolimus, mycophenolate, and prednisone for maintenance. On postoperative day (POD) 4, he developed a high-grade fever and acute kidney dysfunction with increased serum creatinine, proteinuria (507 mg/gm), and edema. Allograft biopsy showed isolated glomerulitis. Pertinent laboratory data included 6.8 103 /uL WBC, 1367/947 iu/L AST/ALT, and 2,329 iu/L LDH. Workup for infection revealed positive serum HSV PCR treated with IV acyclovir. Hemodialysis was initiated on POD 10 for anuria and hyperammonemia. The patient eventually met 5 out of 8 required HLH-1994 diagnostic

criteria including high SIL-2R level (3171.5 pg/mL), low NK cell (25 cells/uL), and hyperferritinemia (14,397 ng/mL). Etoposide was administered on POD 17 per the HLH-94 protocol along with cyclosporine and dexamethasone. The patient attained renal recovery around POD 50 after completing 9 doses of Etoposide. His hematologic and serum inflammatory markers have since normalized.

Discussion: HLH is a rare syndrome, with extremely high mortality due to an excessive immune activation triggered by events such as infections and immunosuppression that disrupt immune homeostasis. Rapid diagnosis and prompt treatment post-transplant are key to favorable outcomes. In this case, the most likely cause of secondary HLH was HSV infection aggravated by immunosuppressive medications. Current therapy protocols are almost exclusively validated in pediatric patients and for primary HLH. Our case demonstrates the safe and successful application of this treatment protocol in a young adult patient presenting with HLH after a KT.

FR-PO747

Progressive Multifocal Leukoencephalopathy (PML): A Dreaded Complication of Immunosuppression

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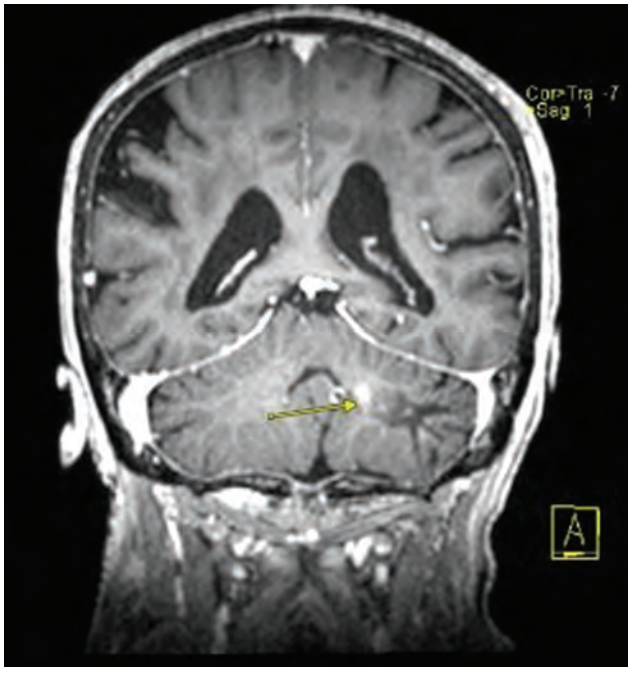
Introduction: JC virus (JCV) can cause progressive multifocal leukoencephalopathy (PML), a demyelinating disorder, in immunosuppressed patients. This infection may present with a variety of neurologic symptoms, ranging in severity and duration, usually identified by the area of white matter lesion. We share a case of a patient who presented with neurological weakness & was found to have PML in the cerebellar region yet no signs of cerebellar dysfunction.

Case Description: A 77-year-old lady, PMH of ESKD due to RPGN received a live donor KT in 2021, on MMF, prednisone & belatacept, presented with lower extremity motor weakness for 2 months without sensory deficits. No cause was identified on clinical exam & lab work. Allograft function was intact. A brain MRI showed a left cerebellar peduncle lesion and surrounding enhancement which did not explain her weakness. This prompted a biopsy that showed features of PML. CSF later resulted positive for JCV by PCR. To reduce her immunosuppression(IS) and belatacept effect, a plasmapheresis session was performed followed by administration of one dose of IVIG 25g. Unfortunately, the next day she had worsening headaches prompting a CT which revealed a large bleed in posterior fossa originating from the biopsy site. Given poor neurological prognosis, decision was made to transition to hospice care, and she died shortly after.

Discussion: PML is catastrophic in patients on chronic IS. It's insidious presentation makes it challenging for an accurate & timely diagnosis. While the site of white matter involvement is associated with signs & symptoms, one must be mindful that lack of classical findings should not rule out a diagnosis of PML. Lack of targeted treatment for JCV infection leaves (IS) withdrawal as the only option which becomes challenging in patients on novel agents with more prolonged half-lives.



FR-PO748

The Importance of Enzyme Replacement Therapy After Kidney Transplantation in Fabry Disease

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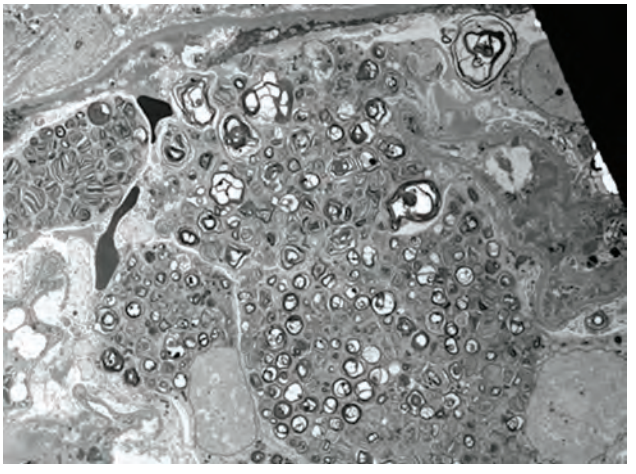
Introduction: Fabry disease(FD) is an X-linked disease caused by an enzyme alpha-galactosidase defect due to GLA gene mutations. It can lead to multi-organ involvement including kidneys, heart and nervous system. We present a case of Fabry disease in a patient who received a kidney transplant was initially unable to afford and continue enzyme replacement therapy(ERT) and developed extra-renal complications of FD

Case Description: A 51-year-old woman with a history of Fabry disease was referred to us with progressive kidney disease. The patient was diagnosed with Fabry disease at the age of 32 and subsequently received ERT. However, her therapy ceased due to medical insurance issues. She had progressive kidney disease and development of dilated cardiomyopathy. Genetic testing revealed a novel heterozygous mutation variant c.820G>C (p.Gly274Arg) in the GLA gene that was deemed of unknown significance. A native kidney biopsy revealed glomerular inclusions with diffuse renal parenchymal scarring, Figure 1. The patient was eventually prescribed agalsidase beta due to non-amenability to chaperone therapy with migalastat. However, she progressed to ESRD and subsequently received a kidney transplant with excellent function. She was prescribed agalisidase maintenance therapy. She was admitted 3 months posttransplant with chest pain and found to have increased septal hypertrophy and progression of aortic stenosis. The patient reported that she had been off agalsidase for over 9 months due to a recurrence of medical insurance issues.

Discussion: ERT and migalastat are currently the only approved specific therapies for Fabry disease. In patients with ESRD due to Fabry nephropathy, kidney transplantation is recommended. ERT is safe after kidney transplantation and recommended to be continued posttransplant for extrarenal manifestations, with observational studies demonstrating a slower increase in left ventricular mass index in transplanted patients who continued ERT.



FR-PO749

Combined Liver and Kidney Transplantation from Living Donors in a Young Patient with Primary Hyperoxaluria Type 1: A Case Report

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Introduction: Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inherited disease, caused by mutations in AGXT gene. Combined liver kidney transplant (CLKT) is the preferred transplant option for most patients with PH1 since orthotopic liver transplantation replaces the deficient enzyme, thus restoring normal metabolic oxalate production.

Case Description: We present a case of a 27-year-old male with end-stage kidney disease (ESKD). The patient had a right nephrectomy due to recurrent renal stones and chronic pyelonephritis. Histological analysis of the right kidney revealed calcium oxalate deposition within tubules, and genetic testing confirmed the diagnosis of PH1 with a mutation in the AGXT gene. He was maintained on hemodialysis since 2020. Preoperatively, he patient received daily high flux hemodiafiltration (HDF) sessions for ten days. The CLKT was performed using living donors, with his mother donating a kidney and an unrelated person as a liver donor. Perioperative period was uneventful, with both grafts functioning well. His serum creatinine level returned to normal after three days, and his plasma oxalate level decreased from 65 to 22 μmol/L (normal ≤ 30 μmol/L) after 20 days postoperatively. The patient was maintained on immunosuppressive therapy consisting of prednisolone, mycophenolate mofetil, and tacrolimus after the surgery. The patient maintained stable graft function with no complications during the follow-up period. However, his 24-hour urinary oxalate level remained persistently high despite the normalization of his plasma oxalate level, necessitating the addition of pyridoxine and magnesium citrate to his medication regimen in addition to hyperhydration.

Discussion: This case report highlights the successful role of CLKT from living donors in a patient with PH1 with good outcome. Also, preoperative HDF dialysis intensification reduced the oxalate burden, and may reduce incidence of oxalate deposition postoperatively. Crystallization inhibitors may be used postoperatively for a long time to prevent urinary oxalate deposition.

FR-PO750

Primary Hyperoxaluria Type 3 Diagnosed After Kidney Transplant

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Introduction: Primary hyperoxaluria (PH) is a group of genetic disorders that lead to increased hepatic production of oxalate. PH type 3 (PH3), the most recently identified subtype results from mutations in the mitochondrial 4-hydroxy-2-oxoglutarate aldolase gene (HOGA1). To date, there have been 3 cases of kidney failure reported in PH3 patients. Here we report a case of a man with recurrent kidney stones in his childhood who was diagnosed with PH3 late in life after receiving a kidney transplant.

Case Description: A 74-year-old Norwegian man with a history of recurrent kidney stones since infancy leading to left nephrectomy at the age of 12 presented with proteinuric chronic kidney disease (CKD). His eGFR based on serum Cr of 2.6 mg/dL was 23 ml/min/1.73m^2. His urine protein-creatinine ratio was around 2 gm/gm. An ultrasound showed a 13.8 cm right kidney with 2 non-obstructing stones. His CKD was presumably due to secondary focal segmental glomerulosclerosis from adaptive hyperfiltration. Fifteen months later, he received a pre-emptive deceased donor kidney transplant out-of-state with an excellent allograft function. Due to the unclear diagnosis of his kidney disease, he completed a genetic testing panel which was positive for homozygous HOGA1 mutation. His 24-hr urine collection showed a mildly elevated oxalate level at 40 mg/day. This may have reflected his habitual dietary oxalate restriction since childhood. The differential diagnosis may have included oxalate nephropathy in his native kidney.

Discussion: Our case signifies the necessity of metabolic workup and genetic testing in patients with kidney stones, particularly in recurrent cases. PH3 was described as a less severe form of PH. Our case is unique in that despite his severe disease early in life, he did not progress into end-stage renal disease until 5 decades after his nephrectomy. Not until the recently FDA-approved Oxlumo (lumasiran), an RNA interference agent, as a medical therapy for PH type 1, the only curative treatment for PH had been a liver transplant or a combined liver/kidney transplant. While our patient may have missed the opportunity to receive a combined liver/kidney transplant, the impact of PH3 on his metabolic profile is mild and medically manageable. The RNA interference agents for PH type 2 and type 3 are being investigated but are not yet FDA-approved. Our patient may be a candidate for such therapy in the future.

FR-PO751

Opening New Frontiers: Nedosiran Enables Kidney-Only Transplantation for Primary Hyperoxaluria Type 1: A Case Report

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Introduction: Primary hyperoxaluria type 1 (PH1) is a genetic disorder caused by deficient activity of the liver enzyme alanine-glyoxylate aminotransferase (AGT) encoded by AGXT. PH1 is associated with overproduction of oxalate that is excreted into the urine, increasing the risk for formation of calcium oxalate crystals, nephrocalcinosis, urinary stones, and kidney failure. Recent short-term placebo-controlled trials have shown the efficacy of two new siRNA-based therapies, lumasiran and nedosiran, in reducing plasma oxalate concentrations and hyperoxaluria. While combined liver-kidney transplantation has been the preferred approach for PH1 patients with kidney failure, kidney-only transplantation may be a safe alternative for those who have responded well to siRNA-based therapy. Here we describe a successful kidney-only transplant in a PH1 patient treated with nedosiran.

Case Description: This adult male had recurrent (calcium oxalate) kidney stones from 2 years of age and was diagnosed with PH1 based on reduced AGT enzyme on liver biopsy; subsequently, AGXT mutations (c.508G>A, p.G170R, and C.744_delC) were confirmed. Although partially responsive to pyridoxine, he progressed to CKD. In early 2021, he was enrolled in a phase III study to receive nedosiran monthly. Due to an acute on chronic kidney injury, he began hemodialysis in July 2021. He received a living donor kidney transplant at age 29 in early 2023 while remaining on nedosiran. Immediately post-transplant, serum creatinine level plateaued at ~150 µmol/L. A transplant biopsy revealed minimal oxalate crystal deposition. Thus, daily hemodialysis was resumed on post-transplant day 6 for two weeks. Serum creatinine remained stable, and plasma oxalate remained low at 4-8 µmol/L, as did the urine oxalate/creatinine ratio <80µmol/mmol at three months post-transplant.

Discussion: We present a patient with PH1 who underwent a successful kidney-only transplant while receiving nedosiran to reduce hepatic oxalate production. To our knowledge, this is the first reported case of kidney-only transplant after initiating this agent. If long-term safety and efficacy are confirmed, a siRNA-based approach will change the care of PH1 patients with kidney failure since kidney-only transplantation is safer than combined liver-kidney transplantation.

FR-PO752

Megalocytic Interstitial Nephritis in a Renal Transplant Patient

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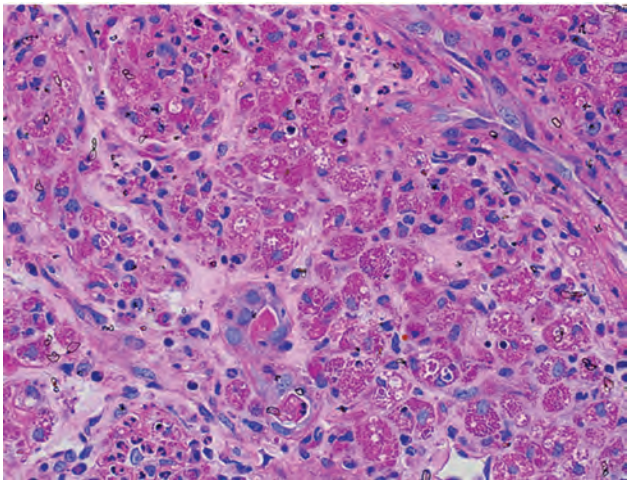
Introduction: Megalocytic interstitial nephritis is a rare form of interstitial nephritis first describe by Zollinger in 1945. The exact mechanism of the pathology is unknown but is presumed to be secondary to impairment of bacterial clearance by neutrophils and macrophages, especially in immune-deficient patients. It is clinically identical to the ineffective inflammatory process called malakoplakia. Here we present a unique case of megalocytic interstitial nephritis in a renal transplant patient.

Case Description: A 68-year-old male with medical history of end stage renal disease who underwent a transplant allograft biopsy, 15 months prior, presented with volume overload and acute kidney injury. He was diagnosed with cirrhosis after his transplant and clinical course was complicated by recurrent ascites requiring paracentesis, upper gastrointestinal bleeding requiring variceal banding. His exam was significant for bilateral leg swelling, tense abdomen. Labs on presentation were significant for creatinine of 4.26 mg/dL which was up from his baseline of 1 mg/dL. He underwent paracentesis on admission and the peritoneal fluid analysis was consistent with spontaneous bacterial peritonitis. He was started on antibiotics. His kidney function did not improve and biopsy was performed which showed megalocytic infiltration. He remained dialysis dependent despite antibiotics.

Discussion: Our patient developed megalocytic interstitial nephritis in the setting of spontaneous bacterial peritonitis, likely as a consequence of seeding to the graft, in the setting of kidney transplant immunosuppression. It is a rare disorder and can only be diagnosed by histological examination. A high index of suspicion is required in immunosuppressed patients with slow renal recovery in setting of infection. Treatment of this disease includes antibiotics to control the infection and high dose steroids.



FR-PO753

Adenine Phosphoribosyl Transferase (APRT) Deficiency as an Under-recognized Cause of Kidney Graft Failure: A Case Report

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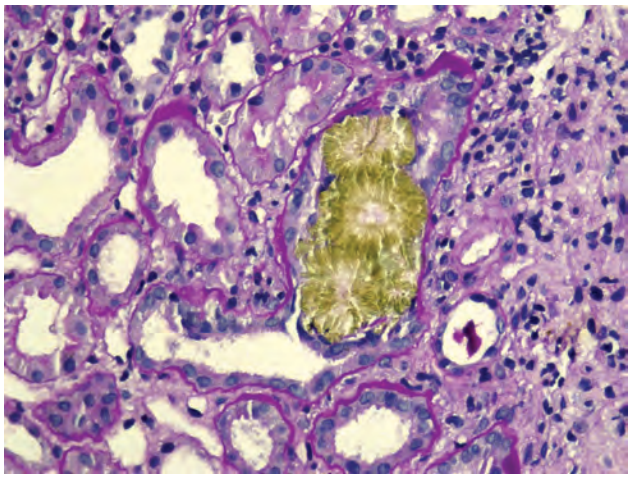
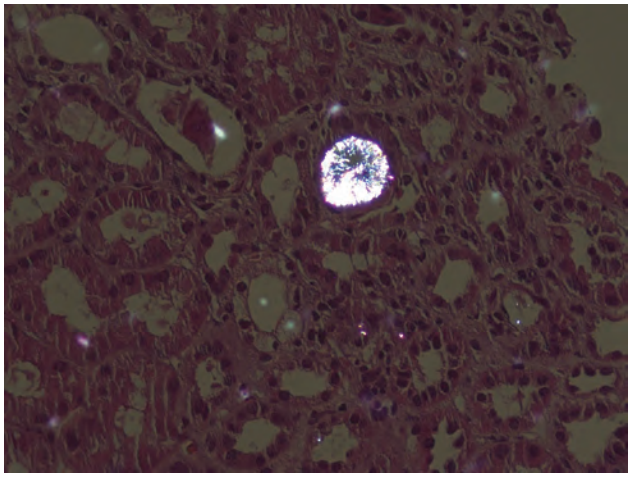
Introduction: APRT deficiency is a rare and treatable cause of End-stage Kidney Disease (ESKD) that often goes unrecognized. The recurrence of the disease in the allograft may have dire repercussions. Diagnosis and treatment may prevent graft failure.

Case Description: A 32-year-old male with ESKD previously diagnosed as secondary to chronic interstitial nephritis was referred for a pre-transplant evaluation. Due to a history of kidney stones, he and his family were screened for hyperoxaluria, and the results were negative. He underwent a deceased donor transplant in January 2023 and presented with delayed graft function. A graft biopsy was performed and showed a prominent crystalline nephropathy. The biopsy did not distinguish oxalate from 2,8-dihydroxyadenine (2,8-DHA) crystals. Therefore, a genetic test was ordered, and it was positive for a recessive mutation in the APTR gene. Treatment with allopurinol was started, and kidney function remained stable.

Discussion: APRT is the enzyme responsible for adenosine metabolism. APRT deficiency leads to the conversion of adenine into 2,8-DHA by xanthine dehydrogenase. This insoluble compound precipitates in the urine, resulting in the formation of kidney stones and crystal nephropathy. Diagnosis is often challenging and usually made after allograft failure. Genetic testing should be widely available as Allopurinol is an effective treatment.





FR-PO754

A Unique Case of Prolonged Bile Cast Nephropathy (BCN) Status After Orthoptic Liver Transplant

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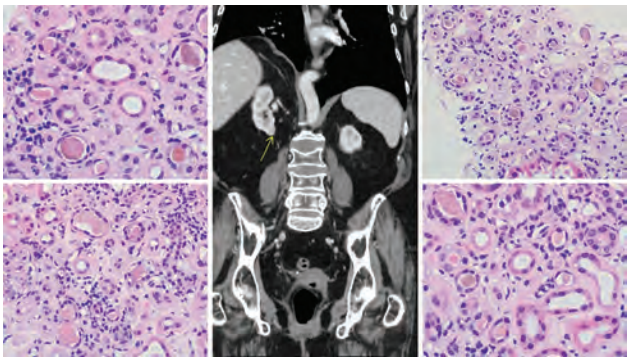
Introduction: BCN or Cholemic Nephropathy refers to AKI in the setting of Decompensated liver injury with elevated bilirubin levels. Even though it was first described in 1899 by Quicke while studying cadaveric kidneys, it is still not well investigated, contributing to its limited appearance in current medical literature. It is a multidimensional entity resulting in tubular and interstitial inflammation, tubular obstruction, direct bile salt-induced tubular toxicity, and altered renal hemodynamics.

Case Description: Our patient is a 56-year-old female with history of ESLD due to EtOH s/p Orthoptic liver transplant 3 years ago and ESRD due to ESLD s/p DDKT 1.5years ago. Post transplant course significant for biopsy proven TCMR with suspicion for AMR, treated with IV steroids, PLEX x4 rounds and IVIG. She was also started on everolimus during this admission and was on quadruple therapy. The patient had MRI Abdomen done for abdominal pain with incidental finding of Exophytic enhancing mass off the lower pole of Native right kidney measuring up to 1.5 cm. Ct guided biopsy was performed, which missed the mass however sampled the native kidney. Pathology of native kidney revealed Many bile casts. At this point of time the patient was more than 2.5 Years post liver transplant and had normal LFTs with a normal bilirubin level.

Discussion: In patients with decompensated liver cirrhosis, renal biopsy is usually not performed due to abnormal coagulation profile, hence BCN is underdiagnosed. There is paucity of literature to demonstrate relationship between Total Bilirubin levels and degree or the timing of renal dysfunction. Biliary salt is known to have low solubility in water, and it is not well known the duration that biliary casts persist or the clinical significance of such casts. Our patient is unique with persistence of Biliary casts more than 2.5 years post Liver transplant, thereby pointing to the unknown mechanism as well as much lesser-known chronology of BCN.



Native kidney Biopsy Light Microscopy showing Many Bile casts.

FR-PO755

A Case of Self-Limited Thrombotic Microangiopathy (TMA) After an ABO Incompatible (ABOi) Kidney Transplant (KT)

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Introduction: TMA is a potentially fatal complication that occurs after solid organ transplant. Post transplant TMA development most commonly triggered with antibody mediated rejection (AMR) and calcineurin inhibitors (CNI).

Case Description: A 44 year old male with CKD secondary to congenital anomalies of kidney and urinary tract who underwent a preemptive living donor ABOi KT (blood type A to O). Anti-A titers prior to transplant were 1:4, and had no donor specific antibodies. Was started on mycophenolate prior to transplant, did not need any further desensitization therapies. Intraop course was uncomplicated with immediate graft function. Induction regimen included thymoglobulin 6 mg/kg, received rituximab and was started on tacrolimus on POD 1. He had worsening anemia and thrombocytopenia on POD 2 with high LDH level and low haptoglobin concerning for TMA. He underwent one session of plasmapheresis on POD 4. His kidney function continued to improve since transplant. Hemolysis improved on POD 5, so further pheresis sessions were held. An allograft biopsy on POD 7 showed acute endothelial injury, diffusely enlarged endothelial cell with mitotic figures and entrapped RBC fragments but no fibrin thrombi. There was no concern for AMR with absence of glomerulitis and peritubular capillaritis. C4d was positive as excepted in ABOi KT.

Discussion: TMA is encountered twice as much in ABOi KT compared to other KT. The rapid clinical improvement with minimal therapy and while remaining on tacrolimus, and the absence of pathological evidence makes AMR and CNI use as less likely triggers of TMA. Evidence of early onset TMA, with injury isolated to endothelial cell, likely from an immune mediated injury triggered by isohemaglutinins against endothelial cells bearing blood group A antigens. The self-limited nature of this insult is possibly similar to the accommodation phenomena which is seen in ABOi KT.

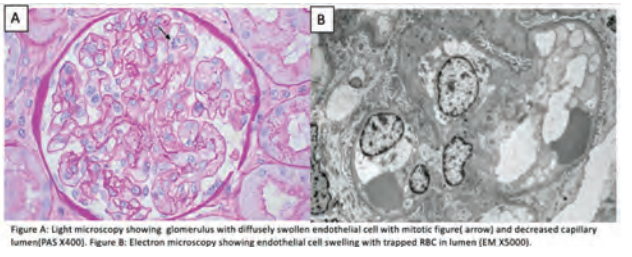


Figure A: Light microscopy showing glomerulus with diffusely swollen endothelial cell with mitotic figure(arrow) and decreased capillary lumen(PAS X400). Figure B: Electron microscopy showing endothelial cell swelling with trapped RBC in lumen (EM X5000).

FR-PO756

Non-ADAMTS13-Mediated Hemolytic Uremic Syndrome (HUS) in a Kidney Transplant Recipient due to SARS-CoV-2 Infection and Its Response to PLEX: A Case Report

David A. Momand, Surakshya Regmi, Lakshmi Ganesan, Rafael Villicana, Aamir Raza, Sami M. Akram. *Loma Linda University Medical Center, Loma Linda, CA.*

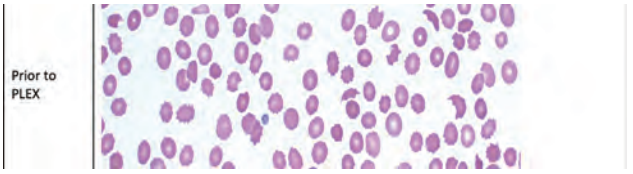
Introduction: During the COVID-19 pandemic many new complications in kidney transplant recipients have arisen. One such entity is Hemolytic Uremic Syndrome characterized by Thrombotic Microangiopathy. Here, we report a rare case of non-ADAMTS-13 and non-complement mediated TMA in a kidney transplant recipient with mild COVID-19 disease.

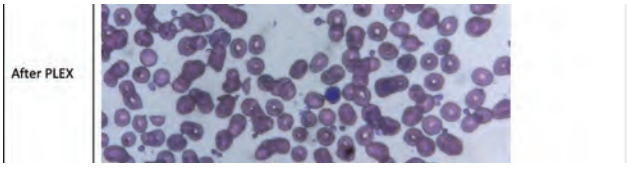
Case Description: 27 y/o F with a history of GN-mediated ESRD, status post DDKTx in April 2016, thymo induction, on tacrolimus, mycophenolate mofetil and prednisone, presented with a two-day history of fevers and diffuse myalgias. Lab work-up positive for COVID19 and AKI with Cr 4.6 mg/dL and oliguria (baseline Cr 0.8 mg/dL). On day 3, platelets decreased to 68K cells/mm^3. Peripheral smear performed showing many schistocytes with low haptoglobin and elevated LDH. C3 and C4 were normal. Alternate

complement pathway function (Mayo laboratory) was normal. Negative for Shiga toxin in stool and the ADAMTS13 activity 73%. Von Willebrand Factor distribution normal. PLEX initiated with high dose steroids with resolution of schistocyte index and AKI.

Discussion: HUS after COVID19 has been reported. The virus can cause HUS directly or indirectly by reducing ADAMTS13. The distribution of vWF multimers can be altered by the virus. A case of Dengue virus causing non-ADAMTS13 HUS has been reported before. Another mechanism of HUS/TMA is dysfunction of alternative complement pathway (inherited or acquired). Also, complement inhibitors such as Eculizumab may not be helpful. Empiric therapy with PLEX was helpful as illustrated by schistocyte response. To the best of our knowledge this is the first case report showing a schistocyte response with two sessions of PLEX in a SARS-CoV-2 mediated HUS.

Differential Diagnosis	Typical HUS	Complement-mediated atypical HUS	Atypical HUS due to COVID19	TTP
Background	No gastroenteritis	No prior C3GN/aHUS	Recent SARS-CoV-2 infection	No history
Testing/Diagnosis	Shiga toxin negative	Complements normal. Alternate complement function S test normal.	UNKNOWN MECHANISM	ADAMTS13 is 73% (normal). vWF distribution normal
Pathophysiology	Shiga toxin mediated endothelial injury	Alternate complement pathway dysregulation (congenital or acquired)	Non-complement mediated endothelial injury	ADAMTS13 deficiency
Therapy	Supportive care	PLEX + Eculizumab	PLEX + Steroids	PLEX + Steroids





FR-PO757

Post-Transplant Thrombotic Microangiopathy as a Manifestation of Atypical Haemolytic Uraemic Syndrome of Primary Origin

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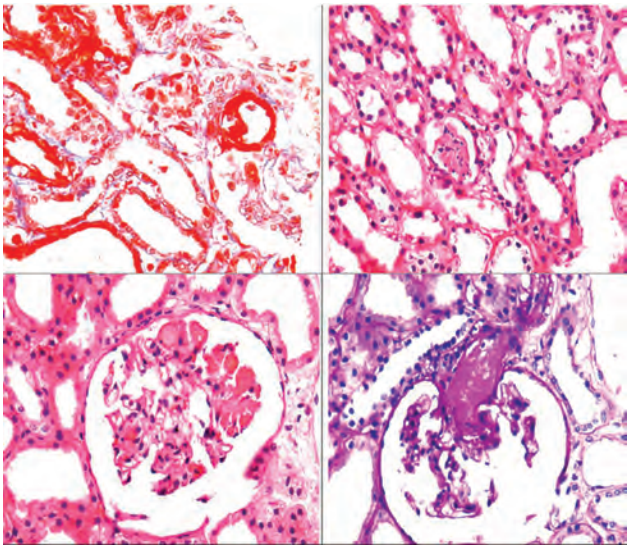
Introduction: Several conditions could trigger endothelial injury that leads to Thrombotic Microangiopathy (MAT) which can have primary and secondary etiology. If transplant associated, early diagnosis and aggressive treatment should be done in order to preserve allograft function.

Case Description: 42 year old woman with history of CKD and kidney allograft rejection eighteen years ago. She underwent second kidney transplant from deceased donor, induction immunosuppression included methylprednisolone and thymoglobulin. On day five post-op she developed abrupt onset anuria, delayed graft function and laboratory showed anemia, thrombocytopenia elevated LDH, schistocytes on peripheral smear and normal ADAMST-13 activity, autoimmune screen and coagulation parameters. She also developed surgery associated complications that derived in surgical reintervention. Kidney allograft biopsy was performed and it showed swollen endothelial cells, fibrin-platelet thrombi within glomerular capillaries and negative C4d stain (Fig 1), genetic testing revealed a variant on DGKe gene. Therapeutic plasma exchange was done, soon after patient kidney function improved and started treatment with anti-C5 monoclonal antibody, renal function is successful and stable.

Discussion: In this case we faced a patient who developed what it appears to be an Atypical Haemolytic Uraemic Syndrome (aHUS). Ischemia-reperfusion injury and antibody mediated rejection, secondary causes as well as infections were ruled out. Based on genetic testing aHUS is presumed to be of primary origin.



FR-PO758

Tacrolimus-Induced Thrombotic Microangiopathy After Kidney Transplant

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Introduction: Thrombotic microangiopathy (TMA) can present with hemolytic anemia, thrombocytopenia, and organ damage. Risks associated with post-transplant TMA include immunosuppressive drugs, viral infections, antibody-mediated rejection, and ischemia-reperfusion injury. We report a case of tacrolimus (TAC) induced TMA early after a kidney transplant (KT).

Case Description: A 73-year-old white woman with ESRD due to acute kidney injury (AKI) from high output ostomy, ulcerative colitis, proctocolectomy and ileostomy, and Hepatitis C was admitted for a deceased donor KT. Induction immunosuppression was with Basiliximab and maintenance was with Prednisone, Cellcept, and TAC, initiated within 24 hours post-KT. On postoperative day (POD) 4, hemoglobin (Hb) and platelets (PLT) dropped to 8.2 g/dL and 37,000/μL respectively. Haptoglobin was <30 mg/dL, lactate dehydrogenase was 1640 IU/L, and peripheral smear revealed schistocytes. Hematology was consulted for concern for TAC-induced TMA. ADAMTS13 activity was 72%, and the Coombs test was negative. She developed AKI requiring hemodialysis (HD) on POD 5. Allograft biopsy revealed severe TMA with coagulative necrosis (Figure 1). TAC was held, and Belatacept was initiated on POD 6. Hematology started Eculizumab on POD 7. PLT improved to 145,000/μL and the patient was discharged on dialysis on POD 12. Genetic susceptibility testing for atypical hemolytic uremic syndrome (aHUS) came back negative. She achieved renal recovery with the last HD on POD 31 and maintained a baseline creatinine of 2.2. Eculizumab was discontinued on POD 48 after 4 doses.

Discussion: Drug-induced TMA (DITMA) due to TAC can present early after KT. DITMA could be idiosyncratic or dose-related. Timely diagnosis and discontinuation of the offending agent are key to management. Eculizumab can be used as rescue therapy in severe cases.

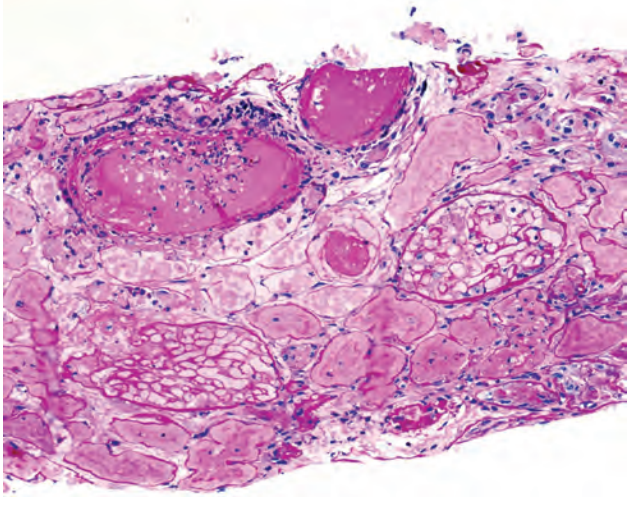

Figure 1 Arterial fibrin thrombi and cortical necrosis (PAS, 200x)

FR-PO759

Ocular Toxoplasmosis After Kidney Transplant

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Introduction: Toxoplasmosis (TOXO) is a zoonotic infection where the parasite persists dormant within tissue cysts and can result in a life-threatening infection in immunocompromised patients. Acute retinal necrosis (ARN) is a vision-threatening necrotizing retinitis with the most common cause being due to the herpes virus family. We describe a case of ocular TOXO after a kidney transplant (KT).

Case Description: A 58-year-old woman with a history of ESRD due to diabetes and hypertension received a deceased donor KT and was directed to the ER by ophthalmology for severe vision loss (counting finger vision) 2 months post-transplant (PT). At transplant, both recipient and donor were positive for Toxoplasma, CMV, and EBV IgG antibodies and induction was with alemtuzumab followed by triple tacrolimus-mycophenolate-prednisone regimen. Her PT course was complicated by slow graft function, persistent hyperkalemia and neutropenia necessitating switching of TMP/SMZ to pentamidine and BK viremia requiring immunosuppression reduction at the 1st and 2nd months PT, respectively. Based on a funduscopic exam, the ophthalmologist diagnosed her with ARN (Figure 1). She was empirically started on intravitreal ganciclovir and IV followed by PO acyclovir, which was changed to Valtrex. Subsequently, her aqueous sample, which was negative for CMV, VZV, and HSV, tested positive for TOXO PCR. She was started on induction dose Bactrim DS PO BID for 6 weeks followed by lifelong Bactrim prophylaxis. Her steroids were increased to reduce ocular inflammation and tissue damage. On follow-up, her ocular pain improved but significant vision impairment in the left eye (20/200) remains.

Discussion: A high index of suspicion for toxoplasma disease should be maintained when prophylaxis without coverage for toxoplasma is used in kidney transplants where donor and/or recipient has positive toxoplasma serology.

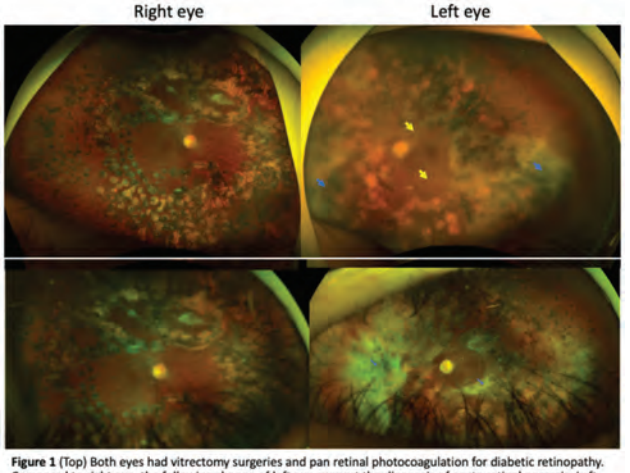

Figure 1 (Top) Both eyes had vitrectomy surgeries and pan retinal photocoagulation for diabetic retinopathy. Compared to right eye, the following change of left eye support the diagnosis of acute retinal necrosis: Left eye has blurred view due to vitritis and Left eye has tortuous and sclerosed blood vessels (yellow arrow) and whitening of periphery retina (blue arrow)

(Bottom) After treatment left eye vitritis resolved. There is fibrotic membrane at nasal retina and at posterior retina around optic nerve and macula (blue arrows)

FR-PO760

Post-Transplant Thrombotic Microangiopathy: A Miraculous Outcome with Eculizumab and Belatacept

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Introduction: Post-transplant TMA is a rare but devastating complication, often resulting in graft loss. Calcineurin-inhibitors, antibody-mediated rejection and complement pathway mutations are commonly implicated but the diagnosis is often challenging. We present a case of TMA highlighting these diagnostic challenges.

Case Description: A 57-year-old woman with ESKD from reflux nephropathy underwent her 3rd deceased donor kidney transplant (prior grafts failed from chronic AMR, cPRA 100%, KDPI 1%, rATG for induction and tacro/MMF/pred maintenance), complicated by delayed graft function. On post-op day 6, she developed microangiopathic hemolytic anemia, thrombocytopenia, and a kidney biopsy with focal TMA, 10% cortical necrosis, and negative C4d. HLA testing revealed persistent preformed low-level B44 and new Bw4 DSAs (MFI 3537). Plasmapheresis x 5, IVIG and rituximab were employed for AMR and tacrolimus was switched to cyclosporine. A repeat biopsy on day 14 for persistent DGF revealed diffuse TMA with 50% cortical necrosis and negative C4d/SV40. DSAs were at lower levels. Eculizumab was started and cyclosporine switched to sirolimus. MMF was switched to azathioprine for severe diarrhea, but this caused severe pancytopenia. Antimetabolites were stopped and she started belatacept 5 weeks post-transplant. She made urine shortly thereafter and came off dialysis by week 6. An aHUS panel returned with CFH mutation. She continues belatacept, eculizumab and prednisone (5mg daily) with creatinine 1.2 (eGFR 50), now 100 days post-transplant.

Discussion: We present a challenging case with multiple causes of TMA acting in combination on a background of CFH gene mutation. While eculizumab is commonly used for complement-related TMA, experience with belatacept is limited. The treatment of calcineurin-inhibitor induced TMA is withdrawal of the offending agent but there may be refractory cases like ours. A regimen of belatacept and the mTOR inhibitor, sirolimus, resulted in rapid improvement in graft function in our patient. While AMR was probably contributing to the TMA, treatment with lowering of DSA levels did not immediately improve graft function. Testing for complement pathway mutation is not readily available and has a long turnaround time. But this should not deter physicians from sending this as it is a valuable guide for continued use of eculizumab.

FR-PO761

Successful Kidney Transplant in a Patient with Overlap C3 Glomerulonephritis and Thrombotic Microangiopathy Treated with Ravulizumab

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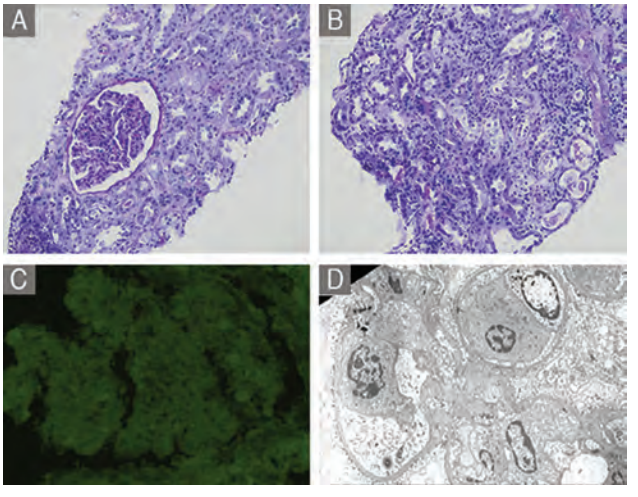
Introduction: Overlap of C3 glomerulopathy (C3G) and thrombotic microangiopathy (TMA) has recently been acknowledged as one of the possible manifestations of a dysregulation of the alternative complement pathway. C3G of genetic cause has high risk of recurrence after kidney transplant (KT). Data of KT in patients with overlap C3G and TMA is scarce.

Case Description: A 30-y/o woman with kidney failure secondary to overlap C3G/TMA received a deceased-donor KT 6 years ago with primary graft failure secondary to early recurrence of C3G and TMA. Genetic study showed two pathogenic variants in complement-factor H. Post-KT PRA was 100%. While on dialysis she received immunoglobulin for desensitization. She then received a second deceased-donor KT. Flow cytometry (FC) crossmatch (XM) was negative. Ravulizumab, thymoglobulin and steroids were used for induction and five sessions of plasma exchange were performed (one pre-KT). She developed DGF requiring dialysis for 3-4 weeks after KT. Graft biopsy one-week post-KT revealed signs of ATN without signs of TMA or antibody-mediated rejection (Fig. 1), with negative C4d. DSA anti-HLA antibodies class I and II were positive and FC XM was positive (T and B). She was discharged on dialysis with tacrolimus, mycophenolate and prednisone. Four weeks after KT creatinine dropped to 2.9 mg/dL, leading to interruption of dialysis. Since then, allograft function has improved to creatinine of 1 mg/dL at month 3 post-KT.

Discussion: Overlap C3G and TMA is an infrequent condition with a high risk of recurrence. While C3G component secondary to a genetic cause has no treatment available, TMA can be successfully treated with complement inhibitors. This case shows a successful KT in a patient with overlap of C3G and TMA secondary to genetic cause and could therefore serve as guidance to the management of KT in these patients.



FR-PO762

A Case of Collapsing Focal Segmental Glomerulonephritis (cFSGS) After Kidney Transplant (KT): Association with SARS-CoV-2 Infection

Lalida Kunaprayoon, William F. Glass, Joseph T. Leeds, Swati Rao, Jeanne Kamal. *University of Virginia, Charlottesville, VA.*

Introduction: cFSGS is manifested by high grade proteinuria and rapid decline in kidney function leading to end stage kidney disease (ESKD). Viral infections including HIV, cytomegalovirus, BK and SARS-CoV-2 can trigger cFSGS in KT. High-risk APOL1 genotype in donors is linked with higher risk of cFSGS and poor allograft outcomes.

Case Description: This is the case of a 70-year-old white man with history of renal cell carcinoma requiring unilateral nephrectomy and eventually ESKD. He received a successful deceased donor KT. After 1.5 years from KT, he developed nephrotic syndrome (creatinine (Cr) 2.2 from 1.1, proteinuria 18-23 g/24h). He had mild COVID infection 2 months prior. On biopsy, glomeruli showed podocyte hyperplasia and hypertrophy consistent with cFSGS. He had diffuse glomerulitis and peritubular capillaritis (ptc)

suspicious of antibody mediated rejection. C4d ptc stain was negative with no evidence of donor specific antibodies. In addition to proteinuria management with RASS blockage, SGLT2i and spironolactone, he completed 13 sessions of plasmapheresis, 2g/kg of IVIG and 2 doses of rituximab. Follow-up biopsy (5 months later) showed progressive glomerular injury (cg2), but improvement of cFSGS. Follow-up Cr is 1.5 and proteinuria is 5 g/g. The donor reported race is white, and APOL1 genotype was negative for high-risk alleles.

Discussion: This is a case of COVID-related de novo cFSGS after KT in APOL1-negative donor and recipient. It is unique as cFSGS manifested 2 months after COVID resolution. Though, case series have shown a link of APOL1 high-risk genotype with COVID19-related cFSGS, cFSGS in KT recipient from APOL1-negative donors has been reported. It is important to rule out a concomitant or recent history of rejection or viral infection in KT recipients with cFSGS. Aggressive treatment is warranted to salvage the kidney allograft.

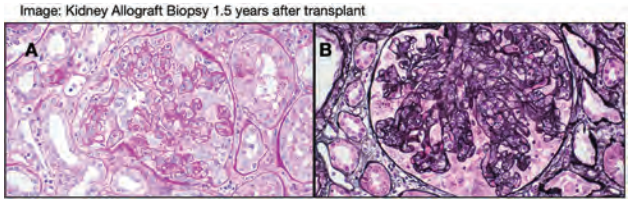


Figure A: Light microscopy (LM)-glomerulus with variably collapsed capillaries, extracapillary hypercellularity with prominent podocyte protein reabsorption droplets & segmental glomerulitis (PASx200) **Figure B:** LM-glomerular capillary collapse & extracapillary hypercellularity (Silverx200)

FR-PO763

An Unusual Regional Cellular FSGS Secondary to Artery Stenosis in a Renal Allograft

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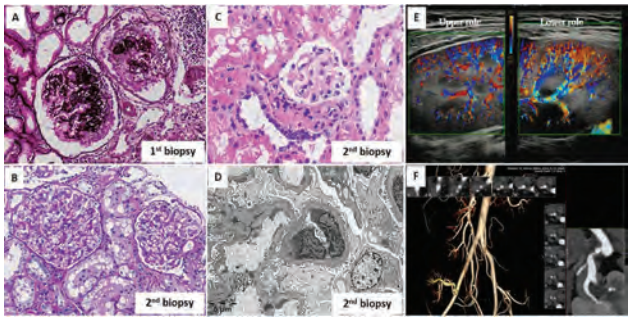
Introduction: Focal segmental glomerulosclerosis (FSGS) in renal allograft derived from various etiology shares similar morphology regardless of recurrent or de novo onset. Here, we reported a recipient presented with moderated proteinuria whose consecutive renal biopsies showed drastic discrepancy due to different regional hemodynamics.

Case Description: A 20-year-old female with end stage IgA nephropathy received a successful renal transplantation 3 years ago. Two years later she developed hypertension and serum creatinine (Scr) increased from 60 to 177 umol/L. Computer tomography angiography (CTA) showed renal artery stenosis. After a percutaneous transluminal angioplasty, her Scr recovered and urine protein remained negative. Six months later she developed moderate proteinuria (2.5g/d) for unknown reason. Renal biopsy showed diffuse (10 out of 16 glomeruli) cellular FSGS lesion without IgA deposition. Ultrastructure change of podocytes was not available due to absence of glomeruli in EM. De novo FSGS was diagnosed with uncertain etiology. Corticosteroid impulse therapy was applied and meanwhile a second biopsy was performed because of unmatched pathology and symptoms. No FSGS among 37 glomeruli but mild ischemic change and remarkable enlarged juxtaglomerular apparatus (JGA) was found. CTA and ultrasound revealed two different hemodynamic areas, which the hypo-infused upper role was fed by the stenotic main artery and the hyper-infused lower pole by an accessary artery. The two biopsies happened to be sampled from opposite poles. Therefore the cellular FSGS was speculated as secondary to hyperperfusion. Corticosteroid impulse therapy was stopped. Her urinary protein turned negative and Scr decreased to 80umol/L 3 days after an endovascular stent angioplasty.

Discussion: Adaptive FSGS caused by hyperperfusion usually shows perihilar pattern. This allograft kidney perfectly simulated unilateral renal artery stenosis of native kidneys, i.e. the hypoperfused area underwent ischemia and proliferation of JGA, while the hyperperfused developed secondary FSGS which could be reversed by improved hemodynamics.



FR-PO764

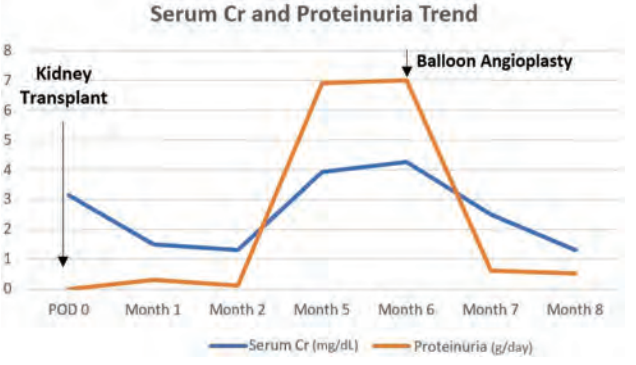
An Unusual Cause of Reversible Nephrotic Syndrome in a Kidney Transplant Recipient

David M. Brooker, Sheahahn V. Soundranayagam, Kalathil K. Sureshkumar, Reem Daloul. *Allegheny Health Network, Pittsburgh, PA.*

Introduction: New onset proteinuria in kidney transplant recipients (KTRs) could be related to recurrent/de novo glomerular diseases or more commonly to chronic antibody mediated rejection. We present a KTR who had a very uncommon cause of nephrotic syndrome.

Case Description: A 73-year old female with diabetic nephropathy underwent deceased donor kidney transplantation using Thymoglobulin induction and tacrolimus/mycophenolate mofetil maintenance along with infection prophylaxis using valgancyclovir and trimethoprim-sulfamethoxzole. There was prompt allograft function with a nadir serum creatinine of 1.3 mg/dl. Serum creatinine started increasing 4 months post-transplant and patient developed significant edema along with worsening hypertension. Further evaluation revealed new nephrotic range proteinuria, hypoalbuminemia, no DSA, along with negative infectious and monoclonal gammopathy work up. Kidney allograft biopsy showed no rejection, negative immunofluorescence, with segmental foot process effacement without transplant glomerulopathy or immune deposits on electron microscopy. Repeat allograft biopsy 2 weeks later showed similar findings. Allograft Doppler ultrasound revealed increased peak systolic velocity of 240 cm/sec in the renal artery which increased to 289 cm/sec on repeat Doppler study 2 weeks later. Based on the Doppler finding, persistent allograft dysfunction and hypertension, patient underwent CO2 angiogram that revealed severe stenosis of the transplant renal artery near the anastomosis with external iliac artery. Stenosis was successfully treated with balloon angioplasty. Within next several weeks, there was improvement in serum creatinine to 1.29 mg/dl and proteinuria to 0.5 g/d.

Discussion: Nephrotic range proteinuria is an uncommon presentation of renal artery stenosis (RAS) that has previously been reported in native kidneys. Our case shows that similar presentation can occur in allograft kidneys. Transplant RAS should be considered as a potential cause for nephrotic syndrome in KTRs.



FR-PO765

Diffuse Proliferative Glomerulonephritis After Allogenic Hematopoietic Stem Cell Transplantation: A Rare Manifestation of Chronic Graft vs. Host Disease

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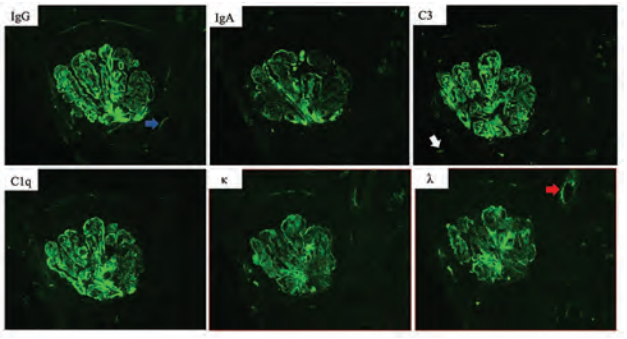
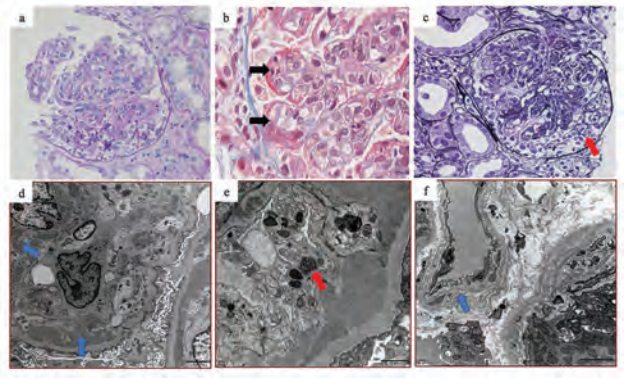
Introduction: Renal involvement is rare in chronic graft-versus-host disease (GVHD), of which membranous nephropathy (MN) and minimal change disease (MCD) were the most common renal pathological manifestations. In addition to glomerular diseases, thrombotic microangiopathy and tubulointerstitial diseases had also been detected in this entity.

Case Description: This paper presents a case report of a rare manifestation of chronic graft-versus-host disease (GVHD) in an 18-year-old male patient who underwent hematopoietic stem cell transplantation 3 years ago. This patient was clinically manifested as rapidly progressive glomerulonephritis with various autoantibodies detected in the serum and kidney, which was lupus-like manifestations. The renal pathology of this patient was immune complex-mediated diffuse proliferative glomerulonephritis with partial crescent formation, which was a rare manifestation of chronic GVHD. The patient initially received intensive immunosuppressive therapy and achieved partial remission.

Discussion: Immune-complex mediated diffuse proliferative glomerulonephritis was a rare manifestation of chronic GVHD after HSCT, which response well to immunosuppressive therapy. Our findings suggest that a combination of methylprednisolone pulse and cyclophosphamide followed by mycophenolate mofetil and prednisone was effective in managing the condition. We emphasize the need to consider the possibility of different renal manifestations in GVHD and to give it adequate attention.





FR-PO766

ANCA-Associated Vasculitis Recurrence After Kidney Transplantation

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Introduction: ANCA-associated vasculitis (AAV) is a well-recognized cause of End Stage Kidney Disease (ESKD). It is a necrotizing vasculitis that affects small vessels without immune complex deposition. About 20-25% of patients will progress to ESKD in a few years after diagnosis. AAV may recur in about 5-10% of cases after kidney transplantation despite standard immunosuppression. Here we present a case of AAV recurrence in a kidney transplant recipient.

Case Description: A 49-year-old white female with a past medical history of HTN and ESKD secondary to p-ANCA positive, pauci-immune glomerulonephritis received DDKT 3 years ago with post-transplant course complicated by cryptococcus meningitis and mycobacterium avium infection. She was maintained on cyclosporine and prednisone. Her creatinine rose from baseline of 0.9 to 2.3 along with new onset of microscopic hematuria and proteinuria and UPCR of 2.6 g/g. Her p-ANCA titer is 1:640. Cyclosporine levels ranged from 100-144 ng/ml. Kidney biopsy showed focal crescentic and necrotizing glomerulonephritis, borderline acute TCMR, and diffuse acute tubular injury. Of 22 glomeruli, 3 glomeruli contain cellular, 3 glomeruli contain fibrocellular, 2 glomeruli contain fibrous crescents and 2 glomeruli with cellular crescents also have fibrinoid necrosis. A focal segmental granular mesangial and loop staining is seen with IGG (trace), IGM (1+), C3 (1+), C1q (1+), kappa (trace), and lambda (trace). There is 1+ arteriolar and 2+ focal segmental tubular basement membrane staining with C3. Tubular casts are equally positive with IGA, kappa, and lambda. Electron microscopy with no deposits in any locations. The patient received a 3-days of pulse methylprednisolone, one dose of rituximab and is scheduled to receive a second dose of rituximab in two weeks. The patient was discharged on prednisone with plans for gradual taper over 4-6 months.

Discussion: The diagnosis of AAV flare post transplantation is difficult as relapses may mimic infections and other complications of immunosuppression. Disease recurrence of AAV should be considered in the differential diagnosis of sudden worsening of kidney function and must be confirmed by biopsy. Rituximab is the therapy of choice both in ESKD and kidney transplant patients. It is recommended to maintain continuous vigilance in all AAV transplant recipients for early detection of relapses.

FR-PO767

When Rare Things Return: A Case of Late, Indolent, Post-Transplant Recurrent Collagenofibrotic Glomerulopathy

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Introduction: Collagenofibrotic glomerulopathy (CG), also known as Collagen Type III glomerulopathy, is an extremely rare disorder caused by abnormal glomerular deposition of type III collagen. Etiology and prognosis are poorly understood, and its implication in kidney transplantation is unclear.

Case Description: A 44-year-old female with a history of diabetes mellitus developed kidney dysfunction and nephrotic range proteinuria. A biopsy revealed mesangial expansion and nodularity suggestive of diabetic glomerulopathy, however, electron microscopy revealed extensive subendothelial deposition of type III collagen fibrils, consistent with CG. She progressed to ESKD and received a living donor kidney transplant. She experienced a straightforward transplant course with excellent graft function for more than a decade. 12 years post-transplant, she developed sub-nephrotic range proteinuria (UPCR 1.0) with otherwise stable graft function (serum creatinine 1.2 mg/dl). Biopsy revealed features of recurrent CG with notable curved, banded subendothelial aggregates (Figure 1). Diagnosis of recurrent collagenofibrotic glomerulopathy was made and supported by tandem mass spectrometry which confirmed composition of the aggregates as type III collagen.

Discussion: CG is a rare disorder characterized by abnormal glomerular deposition of type III collagen. Its cause and pathogenesis are unclear and lack definitive treatment. There is a paucity of cases describing recurrence post-transplant and its implication on long-term graft outcomes is unknown. Here, we describe a case of late recurrent CG, presenting with sub-nephrotic proteinuria and stable allograft function.

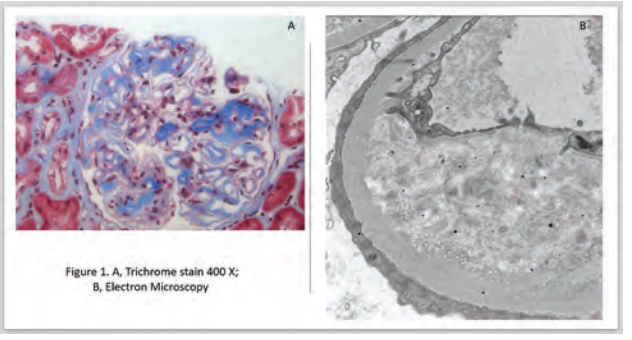

Figure 1. A, Trichrome stain 400 X; B, Electron Microscopy

FR-PO768

Outcome of Renal Allograft with Preexisting Lupus Nephritis

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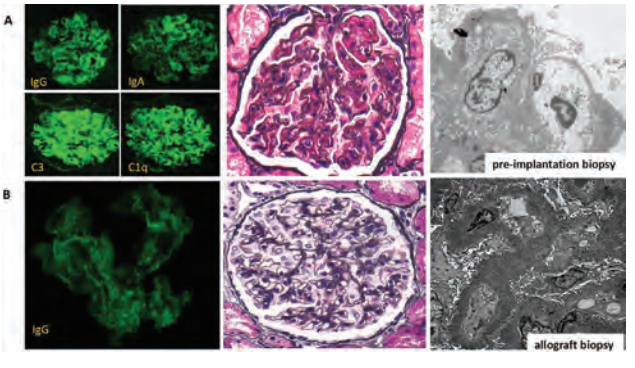
Introduction: Preexsisting gomelular nephritis(GN) was not a contraindication for kidney donation. The outcome of renal allograft with pre-exsisting GN was not clearly demonstrated. Here, we presented a case of renal allograft with pre-exsisting proliferative lupus nephritis(LN).

Case Description: A 31-year-old female with diffuse sclerotic GN accepted deceased donor kidney transplantation(KT) at 2020. The 32-year-old female donor died of frontal lobe encephalorrhagia, with a medical history of systemic lupus erythematosus. At the time of death, the donor had proteinuria(urine ALB: 3.72g/L), increased serum creatinine(Scr)(180 umol/L), positive ANA(18.4U/ml) and dsDNA(>300.00IU/ml). Pre-implantation histological examination of the kidneys showed "full-house" deposition in immunofluoroscence(IF), diffuse mesangial and endothlial proliferation with immune complex(IC)deposition under light microscope(LM), suggestive of RPS IV(A)+V,Remuzzi scoring=1. After KT, the recipient's Scr decreased while nephrotic range urine protein was notified. At 10th day post-KT, her Scr dropped to 100 umol/L and remained stable afterward, while her urine ALB was 4.34g/L and descended slowly. 3 months later, she undertook allograft renal biopsy with persistent proteinuria(urine ALB:111.5mg/L). The IC deposition persisted in glomerular base membrane with decreased intensity in IF, resembling membranous nephropathy(MN) in LM and electronic microscope. No hypercellularity or rejection was identified. Her urine protein turned negative 4 months after KT. Only slight transient ANA elevation was noted within the first 2 weeks (15-22 U/L), while dsDNA remained negative all throughout.

Discussion: Glomerular IC deposition is common in donor kidney biopsies, which would eventually "wash-out" over time. In our case, the allograft still presented with proteinuria and MN-like change 3 months after KT, indicating that IC clearance was slower than disappearance of hypercellularity. Hence allograft with pre-exsisting GN should undergo careful surveillance before radical clearance of IC to avoid possible complication caused by GN.



FR-PO769

Curious Case of De Novo Lupus Nephritis in Geriatric Patient After Kidney Transplant

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Introduction: Glomerular nephritis after transplant can develop De novo or as a recurrence of primary GN. Glomerulonephritis (GN) after a kidney transplant significantly contributes to long-term graft loss. We present a rare de novo lupus nephritis (Membranous GN) case after a kidney transplant.

Case Description: A 73 -year-old African American Male with a history of ESRD presumed secondary to long-standing HTN and DM. He had a Diseased Donor Kidney Transplant (DDKTx) 10 years ago, complicated by graft failure after five years of the transplant secondary to chronic allograft nephropathy diagnosed on kidney biopsy. He was restarted on hemodialysis and subsequently underwent a second DDKTx, Donor 38 AAF, KPDI 61%, CPRA 98%, CMV +/+, EBV +/+, Cold time 13 hours, induction therapy with Anti Thymoglobulin, bortezomib and Solumedrol and maintenance with Tacrolimus, Mycophenolate Mofetil, and prednisone. The post-transplant course is complicated by delayed Graft Function (DGF), 2nd-degree AV block type 1 Wenckebach, and paroxysmal atrial fibrillation. He has maintained the patient on dialysis for DGF. Laboratory studies revealed hemoglobin of 9.5 g/dL, platelets 200 x100 /µL, Leukopenia of 3.200, Creatinine 8 mg/dL, Urine with >500 protein, and 24 protein excretion is 4 grams. Urine Microscopy was bland. Work up for proteinuria; HIV, Hepatitis B, and C are negative, Low C3, and normal C4, Normal PT/INR and APTT. A kidney Biopsy was done in the second week of the transplant and showed Membranous GN, focal glomerulonephritis, and extraglomerular immune complex deposit, EXT2 positive favor autoimmune etiology. Then subsequently, Lupus work up positive for dsDNA. The patient continued on the immunosuppression with Tacrolimus dose adjusted to achieve a level of 8-10, Mycophenolate Mofetil 360 twice a day, and 40 mg of prednisone slowly tapered. In 4 weeks after discharge, the patient off dialysis Kidney functions improved Cr 1.7. Proteinuria resolved, and his three-month protocol kidney biopsy showed similar changes to the previous biopsy result.

Discussion: .De Novo GN after transplant are underdiagnosed because of chronic immune suppression state. Lupus nephritis can occur at any age and may reflect alloimmunization from a previous kidney transplant or an underlying autoimmune condition gets triggered during the transplant.

FR-PO770

Late-Onset Recurrent Lupus Nephritis (rLN) in a Kidney Transplant Recipient

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Introduction: Despite advances in early allograft survival, long-term graft survival has continued to be a challenge. Recurrence of glomerular disease along with acute/chronic rejection is the most common cause of allograft failure. We present a treatable case of graft failure 27 years post-transplant.

Case Description: A 53-year-old Latino male with history of Class IV Lupus nephritis (LN) 27 years post living related kidney transplantation, maintained on azathioprine and prednisone with good medical adherence presented for a follow-up. He was noted to have a rise in creatinine of 1.51mg/dL (baseline of 1.1-1.3mg/dL) and a urine protein creatinine ratio of 500mg/g. Work-up was significant for suppressed complements, an elevated Anti-DS DNA (16IU/ml), with positive Anti-cardiolipin and Anti-B2 Glycoprotein antibodies. Renal allograft biopsy showed 1/14 glomeruli sclerosed and 2 glomeruli showing endocapillary hypercellularity with hyaline deposits and vascular intimal thickening. There was an old chronic anti-allograft lesion and C4D staining of peritubular capillaries, which is deceivingly noted in LN. There was full house immunofluorescence staining of the glomerular capillary walls and mesangium in 5 glomeruli. Electron microscopy revealed prominent electron-dense deposits in the subendothelium, mesangium, peritubular capillaries and basement membranes. Overall suggestive of rLN Class IV with mild activity and chronicity. The patient was switched to Mycophenolic acid and prednisone 10 mg daily which resulted in complete remission in the next six months that persists three years post-biopsy.

Discussion: rLN is common cause of transplant failure describing upto 93% incidence of graft failure and 43% allograft rejections in the first 10 years of transplant. We demonstrate rLN 27 years post-transplant. Although rLN is reported upto 15 years, it is uncommon, underdiagnosed and adds a potentially treatable cause of graft failure to the evergrowing kidney waitlist. Also, our patient is a perfect outlier for traditional risk factors for rLN such as African ancestry, female gender, age 30-40 yrs, pre-transplant dialysis, and receiving a deceased donor transplant. Therefore, this report conveys the importance of keeping high suspicion for prompt diagnosis and management of rLN to improve the long-term survival of the allograft.

FR-PO771

IgG4-Related Disease Tubulointerstitial Nephritis: Successful Treatment of Post-Transplant Relapse

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Introduction: IgG4-related disease (RD) is a heterogenous condition with renal manifestations. We report a case of IgG4-RD tubulointerstitial nephritis (TIN) with relapse post-transplant.

Case Description: A 66 yo male with a history of chronic kidney disease (CKD) 3b presents with acute renal failure. He underwent a renal biopsy demonstrating interstitial infiltrate with IgG4+ plasma cells consistent with TIN and was diagnosed with IgG4-RD. He underwent preemptive live donor kidney transplant without complication and was started on tacrolimus and mycophenolate (MMF). Two years post-transplant creatinine increased from 1.0 to 1.5. Allograft biopsy showed IgG4+ plasma cells consistent with TIN from recurrence of IgG4-RD. He started on prednisone and rituximab with improvement of his creatinine to 1.2. Steroids were tapered over months. Creatinine returned to 1.1. Ten months after rituximab repeat allograft biopsy showed improvement of TIN. He required no further doses of rituximab and remains on prednisone, tacrolimus and MMF. 11-years after transplantation his creatinine remains 1.1.

Discussion: IgG4-RD is characterized by autoimmune dysregulation of IgG4+ plasmacytes impacting many organs in an inflammatory to fibrotic process. T_h cells stimulate B cells to produce IgG4 and collectively release inflammatory cytokines. Fibroblasts replace the inflammatory milieu with stromal tissue. IgG4 antibodies play an unknown role. Renal involvement can be intrinsic or secondary to retroperitoneal fibrosis. Intrinsic disease typically manifests as TIN. Laboratory findings of TIN include pyuria, variable proteinuria, hypocomplementemia and elevated IgG4 subclass. Histologic evaluation demonstrates IgG4+ plasmacyte infiltrate, storiform fibrosis, and obliterative phlebitis. Progression to renal failure is uncommon and kidney transplant occurs rarely. Treatment of IgG4-RD includes glucocorticoids tapered over 6 months. Rituximab is used with 90-100% remission rate even if refractory to treatment and relapse. Recurrent IgG4-RD TIN post-transplant has only been reported once prior in literature. This is the first reported case without concurrent rejection and the first case demonstrating successful treatment of recurrent IgG4-RD post-transplant. Our case suggests effective use of rituximab, glucocorticoids, and MMF for recurrent IgG4-RD TIN in a post-transplant patient.

FR-PO772

Revealing the Invisible: Invasive Mucormycosis in a Kidney Transplant Recipient

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Introduction: Mucormycosis is a rare, life-threatening fungal infection; prompt diagnosis and intervention are critical for survival. We present a case where initial sinus CT imaging demonstrated minimal changes despite a severe invasive fungal infection. Further investigation underlined the necessity of nasal endoscopic biopsy to diagnose high-risk patients exhibiting progressive sinus symptoms.

Case Description: A 38-year-old male with ESRD secondary to Alport Syndrome had two kidney transplants, the most recent being a deceased-donor kidney transplant in 2/2022. He was induced with alemtuzumab and maintained on tacrolimus, mycophenolate mofetil, and prednisone. His post-transplant course was complicated by antibody-mediated and cellular rejection in 12/2022, which were treated with PLEX, IVIG, rituximab, and thymoglobulin. His condition was stable until 3/2023 when he started having left-sided facial pain and congestion. A sinus CT scan showed mild mucosal thickening of the left maxillary sinus ethmoid cells. Levofloxacin was given for presumed bacterial sinusitis and a same-day ENT appointment was scheduled, but he was lost to follow-up. Three weeks later, he presented with aggravated facial pain and left-sided numbness, with no other neurological or pulmonary symptoms. A follow-up sinus CT scan suggested progressive chronic sinusitis without aggressive features. However, given the concern for fungal infection, ENT was consulted and did a nasal endoscopy which revealed black and necrotic inferior and middle left turbinates, suggesting invasive fungal sinusitis. The patient underwent surgical debridement and pathological examination confirmed invasive mucormycosis. Amphotericin therapy was initiated. A chest CT revealed a mass-like consolidation in the right middle lobe indicative of fungal pulmonary involvement. Following weekly debridements and amphotericin therapy, the patient improved and transitioned to isavuconazole therapy, further alleviating his symptoms.

Discussion: Invasive mucormycosis can manifest subtly in kidney transplant patients, with early CT scans often minimally indicative despite severe tissue damage. This emphasizes the importance of a high index of suspicion for invasive fungal sinusitis in patients presenting with severe progressive sinusitis and of prompt endoscopic evaluation and early treatment to enhance patient survival.

FR-PO773

Symptomatic Cytomegalovirus (CMV) Infection and Antibody-Mediated Rejection (ABMR) of Kidney Allograft

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Introduction: CMV infection is a common complication after transplantation, occurring in up to 30% of kidney transplant recipients. The main risk factor for CMV viremia is serological mismatch between the donor and the recipient. Infection can lead to direct virus-induced cytopathic effect on host cells in various systems, such as pneumonia,

gastrointestinal disease, hepatitis, and even invasion of the transplanted organ. However, mechanisms of allograft injury are not limited to direct viral cytotoxicity only, as CMV infection has been shown to promote immune-mediated transplant rejection. We present a patient with symptomatic CMV infection leading to antibody-mediated allograft rejection requiring dialysis, with complete renal recovery after antiviral treatment.

Case Description: A 59 year-old male CMV D+/R- kidney transplant recipient presented seven months after transplantation with fever, chills, fatigue and acute kidney injury. Within four days, creatinine worsened to 4.6 from a baseline of 1.3. He was found to have CMV viremia with a peak of 8350 copies/mL and was started on intravenous ganciclovir. He had previously been on valganciclovir as prophylaxis. Kidney allograft biopsy demonstrated features of antibody mediated rejection, albeit with anti HLA antibodies only against third party antigens. Despite intravenous methylprednisolone and five sessions of plasmapheresis, renal function continued to deteriorate to a creatinine of 11.3, along with signs and symptoms of uremia and volume overload prompting initiation of dialysis two weeks after the initial presentation The patient continued to receive intravenous ganciclovir throughout hospitalization and CMV viral load decreased to 104 copies/mL by the time of dialysis initiation. After 1 week of dialysis, kidney recovery ensued and CMV viral load was undetectable. Repeat allograft biopsy three weeks after initiation of antiviral treatment showed signs of resolving ABMR. Patient has been off dialysis and showed complete recovery of function, with creatinine levels back at baseline two months after initial presentation

Discussion: The immune nature of antibody-mediated allograft rejection may mislead clinicians into overlooking viral infections as a potential underlying etiology. This case highlights the importance of identifying CMV viremia as a trigger of ABMR in kidney transplant recipients, as adequate treatment can lead to complete allograft recovery

FR-PO774

Donor-Derived Disseminated Bartonella Infection After Renal Transplant

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Introduction: Bacillary angiomatosis is a manifestation of the rare infection caused by *Bartonella quintana*, with disseminated or chronic relapsing infection occurring most often in the immunocompromised. This organism is usually transmitted between hosts via the human body louse. Donor related infection is rare and screening is not routine. Those infected commonly complain of fever, headache, joint pain or weakness. Diagnosis is challenging as typical serologic testing may be negative in the immunocompromised.

Case Description: A 59 year-old male with CKD secondary to biopsy proven lambda light chain AL amyloidosis underwent a deceased donor renal transplant. He received induction immunosuppression with Basiliximab and continued on standard immunosuppression, achieving good graft function, with creatinine 1800mg/dL. The patient did not encounter clinical rejection. His background medical history was significant for amyloidosis, with disease quiescence confirmed on bone marrow aspirate and trephine biopsy pre-transplant. He had travelled extensively, had secure housing and owned a dog and chickens with no other animal exposures. Over the next several months, the patient presented with recurrent episodes of profound fatigue, weakness, headaches and occasional fever with a septic appearance on clinical examination and associated leukocytosis. Broad microbiological work-up was negative. This included serology for Bartonella species. Six months after his original presentation, the patient described small cherry red lesions on his thigh, arm and buccal mucosa. Biopsy identified bacillary angiomatosis. Warthin-Starry stains were negative, but *B. quintana* was confirmed on PCR. Serology later returned a positive result. He was treated for disseminated infection with doxycycline 100mg BID. Rifampicin was not used due to interaction with immunosuppressants. Subsequent testing of donor serum confirmed the presence of *B. quintana* antibodies. On follow-up, the patient demonstrated improvement with resolving symptoms and lesions.

Discussion: This case highlights the challenges inherent in atypical donor derived infections. Patient serology was uninformative, being initially negative after several months of symptoms and became positive much later. Given the prolonged period of infection and the inherent difficulties in diagnosis, reviewing risk factors for infection in the donor may have been useful.

FR-PO775

Concern for Donor-Derived Candidiasis Causing a Mycotic Aneurysm in the Transplanted Renal Artery

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Introduction: Donor-derived infections can be associated with dire consequences in transplant recipients. Although extremely rare, fungal infections in renal allografts can result in renal arteritis, urinoma, graft site abscess, and surgical site infection. We present a clinical case of a mycotic aneurysm secondary to Candida krusei infection in a kidney transplant recipient.

Case Description: A 75 year old male with end stage kidney disease secondary to presumed diabetic nephropathy underwent a deceased donor kidney transplantation. At the time of transplantation the donor was noted to have untreated candida species isolated from both urine and sputum. His post-operative course was complicated by delayed graft function and post-operative myopathy. On POD 11 he was found unresponsive and pulseless in his hospital bed. Chest compressions were emergently initiated with return of spontaneous circulation. Labs were notable for new lactic acidosis, acute anemia, and hyperkalemia. CT scans of his abdomen and pelvis were obtained and notable for a large pelvic hematoma with active extravasation. He underwent emergent re-exploration of his kidney transplant and was found to have a 23 cm hematoma, and a necrotic posterior wall of his main renal artery with concern for a ruptured mycotic aneurysm (Figure 1). Both fungal and surgical cultures were positive for Candida krusei. He was initiated on Micafungin and then transitioned to Voriconazole with subsequent clearance of his fungemia after 6 weeks of therapy. Following this event he has had prolonged delayed graft function.

Discussion: Allograft artery mycotic aneurysm is an extremely rare and life-threatening complication that can develop following kidney transplantation. A high index of suspicion is needed to make the correct diagnosis of Candida associated mycotic aneurysms due to its insiduous presentation.

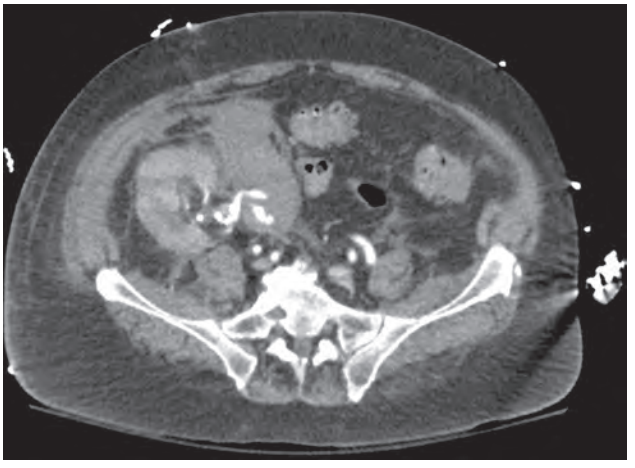

Figure 1: CT Abdomen with extravasation from transplanted renal artery

FR-PO776

A Rare Cause of Early Graft Failure: Mycotic Aneurysm

Adnan Faruqui, Asif A. Sharfuddin, Oluwafisayo O. Adebiyi, Muhammad S. Yaqub, Muhammad Y. Jan. *Indiana University School of Medicine, Indianapolis, IN.*

Introduction: Pseudoaneurysm of the kidney artery is a rare complication, seen in <1% of transplant recipients, generally secondary to infectious causes and at the anastomotic site(1). Kidney allograft artery thrombosis is also a rare complication similarly seen in <1% of transplant recipients. Mycotic pseudoaneurysms can present variably from being asymptomatic to fever, abdominal pain, pulsatile expansile mass, and hemorrhagic shock from rupture (2, 3). We present a case of acute allograft dysfunction in a kidney transplant patient caused by mycotic pseudo-aneurysm of the transplanted renal artery(TRA) complicated by thrombosis leading to allograft nephrectomy.

Case Description: A 40-year-old male with a history of ESKD status post deceased donor kidney transplant presented for allograft biopsy for AKI and worsening proteinuria (2.27 g/g from 0.67 g/g). Pre-Biopsy kidney ultrasound showed a new pseudoaneurysm of TRA. He underwent urgent surgical exploration and a cadaveric iliac bypass to the renal artery was done. Subsequently, to reduce the chances of pseudoaneurysm rupture given its friability, interventional radiology was consulted for a covered stent in the aneurysm. Pre-procedure angiogram showed thrombosed transplant renal artery graft, occlusion of the right external iliac and bypass, and transplant nephrectomy was performed. The infected pseudoaneurysm led to disruption of flow to the TRA leading to thrombosis Surgical pathology of the allograft kidney showed organizing thrombi in the main renal artery and segmental branch, acute tubular damage. Clinically the patient remained afebrile, infectious disease workup including blood and urine cultures were negative, Culture of the thrombosed pseudoaneurysm grew Staphylococcus hominis which was treated with IV antibiotics.

Discussion: Renal artery thrombosis and renal artery pseudoaneurysm are themselves rare complications seen in kidney transplant recipients, here we highlight a rare case of pseudoaneurysm contributing to thrombosis, which may further demonstrate urgency in the treatment of pseudoaneurysm.

FR-PO777

Cardiac Tamponade Secondary to Campylobacter Fetus Infection in a Kidney Transplant Recipient

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Introduction: Campylobacter fetus (C.fetus) is known to cause diarrhea as well as bacteremia, meningitis, osteomyelitis, mycotic aneurysms, and pericarditis. Immunocompromised patients are at high risk of developing systemic symptoms. We present the first case of cardiac tamponade secondary to C.fetus in a kidney transplant patient and review the outcome of C. fetus infection in organ-transplanted patients.

Case Description: A 61-year-old man with a history of ABO-compatible living-donor kidney transplantation presented to the Emergency Department with altered mental status and fever. Four months before the presentation, he complained of fatigue with mildly

elevated C-reactive protein. Although CT chest with contrast showed a small amount of pericardial effusion, he was carefully monitored without further workup. A week ago, he gradually felt weak and developed a fever. On the presentation day, he was unable to move and call an ambulance. On arrival, he was confused and hypotensive. A physical exam showed elevated jugular venous distension with a muffled heart sound. Transthoracic ultrasound demonstrated pericardial effusion with the diastolic collapse of the right ventricular. Pericardiocentesis was performed, draining 200 mL of purulent fluid. He was diagnosed with bacterial pericarditis and started on meropenem and teicoplanin. The culture returned positive for C.fetus. Then antibiotics were switched to ampicillin according to the susceptibility. He was discharged on 31 hospital-day to a nursing home for rehabilitation.

Discussion: We experienced the first case of cardiac tamponade due to C.fetus infection in a patient with a kidney transplant. C.fetus is known to colonize cattle and sheep and can be transmitted to humans via undercooked meat. Of note, this patient stated that he ate raw cattle liver and meat at a restaurant several months before the presentation. We also reviewed the five cases of C.fetus infection in patients with organ transplants. Four out of five cases responded to antibiotics, whereas one died due to sepsis. The presentations varied from bacteremia, meningitis to splenic abscesses. Interestingly, none of the five cases reported any history of exposure to cattle or sheep or raw meat intake. Nevertheless, this case reminds us of the need for guidance regarding raw meat consumption in patients who take immunosuppressive medications.

FR-PO778

Trichodysplasia Spinulosa: A Rare, Widespread Eruption in a Kidney Transplant Patient

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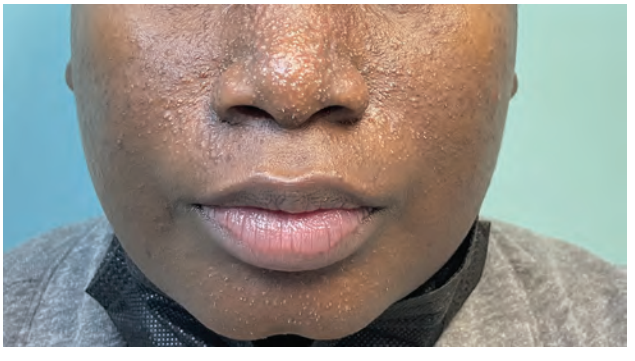
Introduction: Trichodysplasia Spinulosa (TS) is a rare dermatologic condition that occurs primarily in immunocompromised populations carrying the trichodysplasia spinulosa-associated polyomavirus (TSPyV), though its pathophysiology remains incompletely understood. Lesions are commonly described as flesh-colored or erythematous folliculocentric papules with protruding keratin spines and may be pruritic as well as cosmetically disfiguring if left untreated.

Case Description: A 37-year-old female with a history of deceased-donor kidney transplantation 7 months prior was referred to the dermatology clinic for a 1-month history of a pruritic, follicular rash on the face, arms, and back following the discontinuation of prophylactic valganciclovir. She was initially prescribed azelaic acid for suspected acneiform eruption on the face and triamcinolone for pruritic papules on the body. She returned 9 months later with progression of the rash and spread to her lower extremities. A punch biopsy of the patient's cheek eventually confirmed the diagnosis of TS after 13 months. The patient was prescribed cidofovir cream and tretinoin and referred to the Transplant Infectious Disease clinic.

Discussion: Due to its scarcity in medical literature, patients with TS are often misdiagnosed, leading to treatment delays and disease progression. With no standardized treatment guidelines for TS, patients can undergo several ineffective treatment trials. While the condition typically regresses after resolution of the immunosuppressive state, this can prove to be challenging in some transplant recipients, particularly those who are highly sensitized or had prior transplant rejection. Several other treatment options have been trialed with varying levels of success, the most efficacious reportedly being topical cidofovir and oral valganciclovir. Increased awareness of this condition along with close, multi-specialty interprofessional collaboration is required to expedite diagnosis, solidify a treatment plan, and ultimately improve the quality of life of solid-organ transplant patients.



FR-PO779

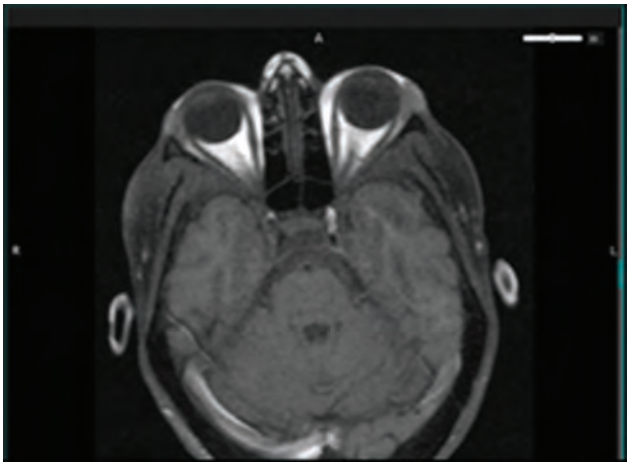
Neuro-Ophthalmic Manifestation of Cryptococcus Meningitis in a Kidney Transplant Patient

Karla G. Carias Martinez, Olwen C. Murphy, Sam Kant. *Johns Hopkins University, Baltimore, MD.*

Introduction: Cryptococcosis is the third most common cause of invasive fungal infection in solid organ transplant recipients- cryptococcal meningitis is the main clinical presentation. Vision loss in cryptococcal meningitis can be due to papilledema or optic nerve sheath infiltration

Case Description: 37-year-old female with atypical HUS (aHUS) on chronic ravulizumab, LRKT in 2019 and 3 prioe failed kidney transplants, maintained on tacrolimus and prednisone for immunosuppression regimen was admitted with progressive left vision loss consistent with optic neuritis. She was initially given pulse steroids followed with a taper with no improvement in symptoms. Subsequent work-up showed cryptococcus fungemia and meningitis with high fungal load on CSF. MRI orbit with contrast (Figure 1) showed marked perineural enhancement of the left optic nerve. There was no history of recent travel or constitutional symptoms. Mycophenolate was held and prompt treatment was started with Amphotericin and flucytosine induction for 2 weeks and then transitioned to maintenance fluconazole.

Discussion: Based on the clinical presentation and orbit MRI results that showed marked perineural enhancement of the optic nerve (a surrogate of meningeal inflammation) and the temporal association with her diagnosis of cryptococcal meningitis, this was deemed to be the most likely etiology of her vision loss. This is an unusual and rare presentation of cryptococcal meningitis but has been described in the literature. With her long-term use of CNIs, tacrolimus induced optic neuropathy was considered. This rare side effect, however, usually affects both optic nerves and orbital MRI reveal optic disc or nerve inflammation in the form of contrast enhancement. The common clinical practice is to switch tacrolimus to another immunosuppressive agent but as her clinical presentation was not consistent with this and her immunosuppression regimen was not altered.



FR-PO780

A Case of Hemorrhagic Cystitis Leading to Disseminated Disease from Adenovirus in a Renal Transplant Patient

Neetha Mathew, Sonalis Fernandez, Zahidul H. Mondal, Sonika Puri, Amar M. Bhagat, Chioma Madu. Rutgers Robert Wood Johnson University Hospital Dept of Nephrology. *Robert Wood Johnson University Hospital, New Brunswick, NJ.*

Introduction: Adenovirus can cause many infections in immunocompromised hosts including nephritis and hemorrhagic cystitis. It commonly occurs in immunocompromised patients from reactivation of latent infection or primary infection. It is especially concerning in patients with renal transplants. The diagnosis requires the use of multiple diagnostic specimens to detect viral shedding. Diagnosis is also made in the context of clinical manifestations, as in our patient who developed adenovirus infection with hemorrhagic cystitis.

Case Description: This is a 63-year-old woman with a history of ESRD secondary to hypertensive nephrosclerosis status-post DDRT on 9/13/2016. Her post-transplant course was uneventful and she was discharged with a creatinine of 0.7 mg/dl. She presented to the hospital six years post-transplant with dysuria, urinary urgency, urinary frequency and lower abdominal pain with urination. Her creatinine at this time was 0.6 mg/dL. Her urinalysis showed 37 white blood cells and > 182 red blood cells. She was started on Zosyn for possible pyelonephritis. Her urine culture had no growth and she was discharged on levofloxacin. She was readmitted about one week later with recurrence of urinary symptoms and hematuria. Her urinalysis showed > 182 red blood cells and her creatinine was 1.6 mg/dL. A CT urogram was done and was unremarkable. Due to her AKI, a renal biopsy was performed which was unable to be analyzed due to an inefficient tissue sample. She was found to be positive for adenovirus PCR DNA and was started on cidofovir and probenecid. Her creatinine normalized to her baseline. She was continued on her immunosuppression regimen of Myfortic, Envarsus and prednisone. She completed treatment for her adenovirus infection after two months with resolution of her symptoms and notable clearance of adenovirus DNA in the serum.

Discussion: Most adenovirus infections are self-limited and treatment is usually supportive. However, adenovirus can be fatal in immunocompromised hosts with high morbidity and mortality. Disseminated adenovirus disease may be preceded by a period of asymptomatic viremia. Thus, the diagnosis can be missed leading to poor outcomes. The early identification of the disease by monitoring viremia has been shown to be beneficial, as we see for CMV infections in immunocompromised patients.

FR-PO781

Donor-Derived Human Herpes Virus-8 (HHV8)-Related Kaposi Sarcoma (KS) in Renal Allograft Following a Hepatitis C Virus (HCV)-Positive Kidney Transplantation

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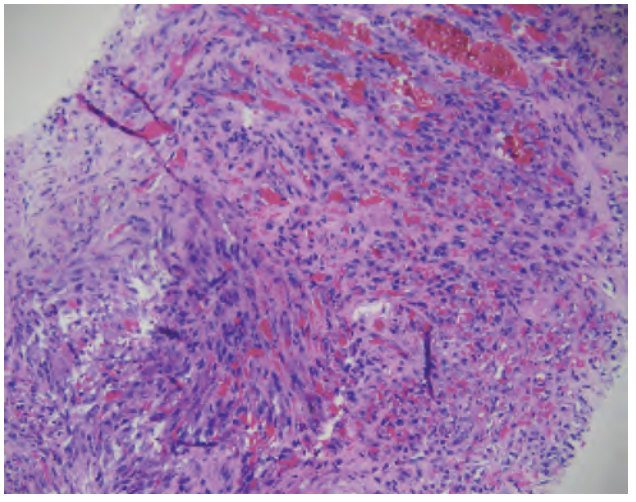
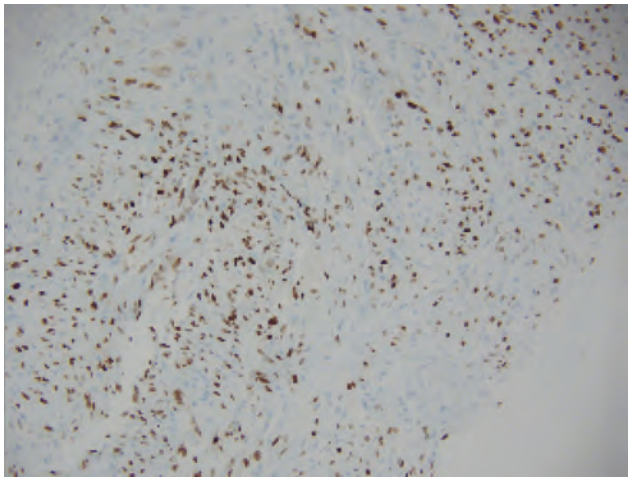
Introduction: KS post Kidney transplantation can develop due to reactivation of recipient latent HHV8 infection, or donor acquired HHV8 infection. We describe a rare case of Donor derived HHV8 related KS involving the allograft, presenting as Acute kidney Injury.

Case Description: 54-year-old female underwent kidney transplant from HCV positive deceased donor. Immunosuppression(IS) included Thymoglobulin followed by tacrolimus and mycophenolate (MMF). She was successfully treated for Donor-derived HCV infection with Sofosbuvir/Velpatasvir. Baseline serum creatinine was 1.4 mg/dl. She developed CMV Viremia that responded well to reduced IS and valganciclovir. However, creatinine increased to 2.3mg/dl, and transplant biopsy was done to rule out rejection. It showed foci of vascular proliferation, prominent mitoses, atypical cells with enlarged nuclei (Fig 1) and positive Immunostain for HHV8 (Fig2) indicating KS. Her MMF was switched to Everolimus. She had no cutaneous lesions on exam and has been referred to Oncology.

Discussion: Increasing proportion of PHS high risk organ recipients are at risk for HHV8 infection and KS. To our knowledge only 8 cases of KS involving renal allograft have been described, with only 2 derived from HCV positive donors. With limited pre transplant testing of donors for HHV 8 infection, close monitoring of recipients with PHS high risk organs for KS is suggested.





FR-PO782

Kaposi Sarcoma Involving the Renal Allograft: Report of Two Cases

Khaled Murshed, Mostafa Elshirbeny, Mohamad M. Alkadi, Awais Nauman. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: The use of immunosuppressive agents for prevention of allograft rejection increases the risk of malignancy. The magnitude of the higher risk is dependent on cancer types, with the greatest risk in viral-related and immune driven cancers such as post-transplant lymphoproliferative disease (PTLD) and Kaposi sarcoma (KS). Involvement of the renal allograft by KS is extremely rare. Here, we present two cases of KS involving the renal allograft

Case Description: Case 1: Sudanese gentleman who was diagnosed to have ESRD. He had live unrelated kidney transplant in June 2014. His course was unremarkable till 7/2015 when he presented with acute graft dysfunction and MRI abdomen revealed: bulky transplanted kidney with multiple liver, splenic and vertebral lesions. Anti-human herpes virus 8 (HHV-8) antibody was positive and transplanted kidney and liver biopsies revealed KS. Immunosuppression was reduced and patient experienced improving general condition later. Case 2: 46 years old Mozambican gentleman, known case of ESRD. Underwent living unrelated renal transplant then 10 months after transplant, patient was admitted with rising serum creatinine and pancytopenia. Transplanted kidney biopsy revealed: extensive infiltration by Kaposi sarcoma with negative C4d and SV-40. HHV8 was positive in the nuclei of most of the tumor cells. Then patient decided to return back to his home country.

Discussion: Kaposi sarcoma (KS) was first reported in 1872 by Moritz Kaposi, a Hungarian physician. Several reports have documented an endemic form of KS mostly encountered in Africa**.** Indeed, the incidence of KS is now known to reflect differences in the prevalence of Kaposi Sarcoma Virus (KSHV). This virus is also called Human Herpes Virus8 (HHV8). Patient 1 was from Sudan which generally not considered a Sub-Saharan country but it nevertheless has high incidence of KS. Patient 2 was from Mozambique, a country in Sub Saharan known to have high incidence of KS. Involvement of the renal allograft by KS however is extremely rare with only eight cases reported in the literature. The patient's age ranged from 28 to 71 year and in all cases, KS was diagnosed within 12 months after transplantation. Reduction of immunosuppression resulted in regression of the tumor in most cases. In conclusion we present 2 cases of KS in the renal allograft which brings the number of cases to 10.

FR-PO783

"Goose Bumps" Trichodysplasia spinulosa Viremia in a Patient with Kidney Allograft

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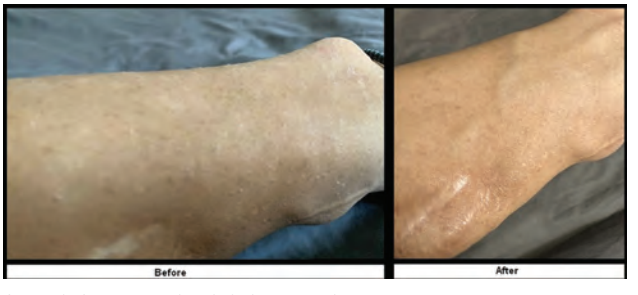
Introduction: Trichodysplasia Spinulosa (TSPyV) is a DNA virus in the polyomavirdae family first identified 1995 and genotyped 2010. This virus is ubiquitous in immune competent humans and immunosuppressed patients rarely have clinical manifestations of viremia.

Case Description: 35-year-old man with h/o ESKD due to an unknown etiology s/p (DDKT) in June of 2021, HTN, Crohn's, asthma, and anaphylaxis to peanuts was seen in transplant clinic for maintenance of immune suppression on tacrolimus (Tac), mycophenolate (MMF), and prednisone. The patient developed a rash involving his gluteus, face, nose, and extremities 7 months post-transplant. (See image) He described it as "bumps with feathers growing out of them." A shave biopsy revealed hyperkeratotic and parakeratotic debris in the hair shaft consistent with TSPyV. Treatment advised was a reduced Tac goal and reduced MMF dose as well as initiation of topical cidofovir. The patient went on a 6-month trekking trip where lesions worsened and was not available for follow up. At this time, he self-discontinued prednisone due to GI upset and stopped cidofovir after 1-2 weeks of use due to skin breakdown. He was switched from MMF to everolimus, but he stopped this due to cystic acne which he attributed to everolimus. After 13 months of adjustments the patient showed improvement of skin lesions and continues Tac with goal of (4-5) and MMF 500mg BID off prednisone Cidofovir and everolimus.

Discussion: TSPyV viremia may have significant dermatologic manifestations and there are allograft threatening implications in the management which typically includes topical antivirals, clinical monitoring, and reduction of immune suppression with lower Tac goals in the 4-5 range. It is important for clinicians to counsel patients on the importance of medication adherence and follow up regarding complications of immune suppression. **Viremia not confirmed. Diagnosis made by clinical presentation and histopathological appearance.*



Before and after TSPyV viremia lesions on patient's arm.

FR-PO784

Donor-Derived West Nile Virus Infection After Renal Transplant Treated with Plasmapheresis

Syeda S. Bukhari,[1] Adrianne F. Basa,[2] Omar N. Elhawary,[1] Sandeep R. Sasidharan,[1] Moro O. Salifu,[1] Subodh J. Saggi.[1] *[1]SUNY Downstate Health Sciences University, New York City, NY; [2]NYU Langone Health, New York, NY.*

Introduction: West Nile Virus is a single-stranded RNA Flavivirus usually transmitted through mosquito bites. The clinical presentation usually varies from asymptomatic, mild gastrointestinal symptoms and fever to <1% developing Neuroinvasive disease. The literature showed that organ derived WNV infection is associated with 70% of neurological sequelae and 30% of severe morbidity and mortality. The onset of symptomatic WNV infection post-organ transplant is usually around 13 days however the range varies from 5-37 days.

Case Description: A 50 Y/O male who presented for a Deceased Donor kidney transplant. His previous history included ESRD on Peritoneal dialysis, Focal segmental Glomerulosclerosis, and Hypertension. He denies any sick contacts and recent travel. His review of systems and physical examination were normal. He developed fever, altered sensorium and seizures almost 16 days post-transplant. On neurological examination, he was found to be minimally responsive. Initial work including CSF fluid analysis and a CT scan of the Brain was inconclusive. His MRI showed linear symmetric restricted diffusion in both cerebellar hemispheres and his post-transplant Ct scan showed a colonic mass. The patient was given two sessions of plasmapheresis based on the pertinent MRI findings and suspicion of paraneoplastic syndrome. His lab reported later showed negative paraneoplastic panel. The primary team sent the WNV panel to the Department of Health and it came back positive for WNV IgM. His serum and urine PCR also came back positive for WNV antigen. Plasmapheresis was stopped and IVIG was started based on some previous case reports. Additional two sessions of plasmapheresis were given post-IVIG, and his blood and urine turned negative for WNV IgM after 14 days of treatment. Repeated MRI also showed stable restriction diffusion defects.

Discussion: The treatment for WNV is usually supportive, reduction of immunosuppressants and IVIG. Some case reports show additional benefits of plasmapheresis especially in neuroinvasive disease. So far only IVIG has been used and showed benefits in West Nile Virus Infection after solid organ transplant. This was the first-time plasmapheresis was done and showed a significant response. WNV screening should be considered a routine workup for potential organ donors living in endemic areas.

FR-PO785

Concurrent Epstein-Barr Virus (EBV) Viremia, Non-Tuberculosis (TB) Mycobacterial Infection, and Acute T Cell-Mediated Rejection (TCMR) in Kidney Transplant (KT) Recipient

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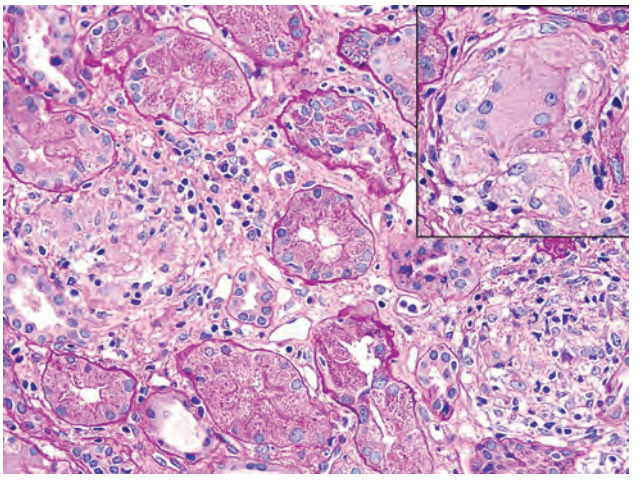
Introduction: Managing concurrent rejection and infection after KT is a therapeutic challenge. M. genavense is a rare, difficult-to-identify mycobacterial infection. We present a case of simultaneous EBV viremia, disseminated M. genavense infection, TCMR.

Case Description: A 54yo man with ESKD due to HTN underwent deceased donor KT with thymoglobulin induction followed by tacrolimus dosed for goal trough 9-12 and mycophenolate mofetil (MMF) 1g BID. EBV IgG detectable in donor but not recipient. Initial post-KT course was uncomplicated (nadir Cr 1.19) until developing EBV viremia (1,992 cop/ml) and night sweats 6 months post-KT. MMF was stopped. PET-CT revealed 1.8cm FDG-avid posterior mediastinal node, diffuse increased marrow activity, and possible old granulomatous lung disease. Lymph node biopsy showed non-necrotizing granulomas with AFB. Quantiferon gold was negative. Low-grade EBV viremia, night sweats, chills, and fever continued with labs at 9 months post-KT showing elevated LFTs (Alk Phos 544, TB 3.9, AST 69, ALT 46). Empiric treatment initiated with azithromycin, rifabutin, moxifloxacin, and ethambutol. Liver biopsy revealed non-caseating granulomas consistent with disseminated mycobacterial infection, finally speciated 4 months later as M. genavense. 14 months post-KT, Cr rose from 1.29 to 2.34 with Banff grade 1B TCMR and interstitial non-caseating granulomas on allograft biopsy (Figure). IVIG 2g/kg every other month was initiated and Cr decreased to 1.34. 8 months later, he was asymptomatic and repeat renal biopsy showed no rejection. Antibiotics were discontinued after 12 months of treatment. On follow up 2 years post-KT, remains asymptomatic with Cr 1.34, undetectable EBV, and normalized LFTs.

Discussion: Combination antibiotic treatment for 1 year, high-dose IVIG, and immunosuppression reduction effectively treated concurrent EBV viremia, disseminated M. genavense infection, and TCMR.



FR-PO786

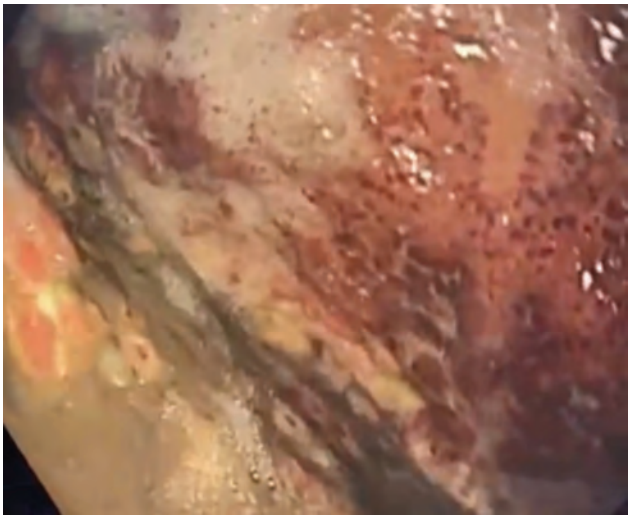
Phlegmonous Gastritis After Renal Transplantation First Case Reported in the Literature

Alejandro R. Montaño, Axel Corona-Deschamps, Lucero Salgado-Ambrosio, Cesar Adolfo Nieves Perez. Equipo Nefrología-Trasplante Ángeles Pedregal. *Hospital Angeles del Pedregal, Mexico City, Mexico.*

Introduction: Phlegmonous gastritis (PG) is a rare condition. Approximately one case per year has been reported in the literature, with a total of around 500 reported cases. We present the first case of phlegmonous gastritis following kidney transplantation, to the best of our knowledge based on the literature available.

Case Description: This is about a 36-year-old man with a history of type 2 diabetes, systemic arterial hypertension, chronic kidney disease, who underwent a living-related kidney transplant in 2022, with a PRA-SA of 0/0%. He received induction with basiliximab and methylprednisolone, and maintenance immunosuppression with tacrolimus, mycophenolic acid, and prednisone. With baseline creatinine of 1.0 mg/dL. Two months after the transplant, he developed, fever, oral intolerance. He was hospitalized, and a fever of 40 °C was documented, mild epigastric tenderness was noted on abdominal examination. Laboratory tests revealed leukocytosis, elevated C-reactive protein, creatinine (2.5 mg/dL). Abdominal computed tomography confirmed pneumobilia, pneumoperitoneum, gastric wall thickening. Tacrolimus and mycophenolic acid were discontinued, and steroid therapy was continued. Meropenem was initiated. An endoscopy performed within 12 hours of symptom onset revealed multiple areas of diffuse gastric necrosis and purulent material. Linezolid was added to the treatment regimen, and a nasojejunal tube was placed for total enteral nutrition. Pseudomonas aeruginosa putida and Candida glabrata were isolated from the gastric tissue. He was discharged on day 27 with a baseline creatinine level of 0.9 mg/dL, and on cyclosporine and prednisone.

Discussion: PG is a condition with high mortality. It is important to suspect it in immunosuppressed patients with sepsis, as early diagnosis can save the patient's life and prevent serious complications.



FR-PO787

Progressive Dysphagia in Kidney Transplant Recipient: An Unusual Cause

Robert Ryhal, Reem Daloul, Khaled Nashar, Kalathil K. Sureshkumar. *Allegheny Health Network, Pittsburgh, PA.*

Introduction: Upper gastrointestinal (GI) symptoms such as dysphagia and odynophagia in immunocompromised hosts are generally caused by viral or fungal infections. We present a kidney transplant recipient who developed progressive dysphagia and odynophagia caused by mycophenolate mofetil (MMF) that improved after discontinuation of MMF and serial endoscopic esophageal dilatation.

Case Description: A 49-year old male (CMV IgG-,EBV IgG+) received kidney transplantation from sister (CMV IgG+, EBV IgG+) with Thymoglobulin induction, tacrolimus/MMF maintenance and infection prophylaxis using valgancyclovir, trimethoprim-sulfamethoxazole and nystain. There was immediate allograft function with discharge serum creatinine of 1.5 mg/dl. One month later, patient presented with progressive dysphagia and odynophagia with reduced appetite and weight loss. MMF was discontinued and replaced with azathioprine. Upper endoscopy showed benign appearing intrinsic severe distal esophageal stenosis (Figure 1A). The stricture was dilated to 7 mm and biopsy showed focal acute inflammation (Figure 1B). PAS staining for fungal elements and immunohistochemistry for CMV and HSV type1/2 were negative. Patient required 9 more stricture dilatations over the next 3 months to a final diameter of 18 mm. His dysphagia gradually resolved with improvement in dietary intake and weight gain over next few months.

Discussion: MMF has several GI side effects and more commonly involve lower GI tract. MMF-related esophageal stricture is extremely rare. The mechanism is not clear but may involve MMF-induced blockade of guanosine nucleotide synthesis thus disrupting GI epithelial barrier. MMF-metabolites may also cause autoimmunity and hypersensitivity-like reactions. Our case highlights MMF as an uncommon cause of esophageal stricture and should be considered as a potential etiology of dysphagia in a transplant recipient.

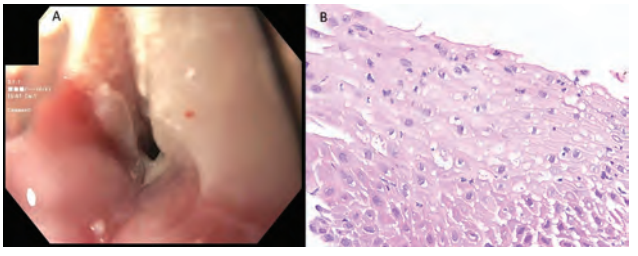


Figure 1: (A) Upper endoscopy showing benign appearing intrinsic severe distal esophageal stenosis that was 5 cm long and 4 mm in diameter. **(B)** H&E staining of stricture area biopsy showing benign squamous mucosa with reactive changes and focal acute inflammation.

FR-PO788

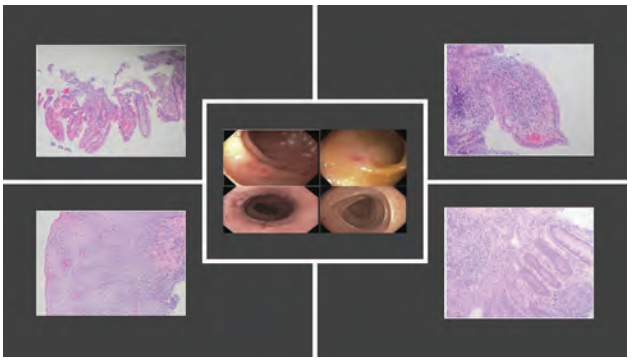
Eosinophilic Gastroenteritis due to Belatacept: Novel Side Effect of a Novel Agent

Aisha Batool, Vineet Veitla, Ehab R. Saad. *Medical College of Wisconsin, Milwaukee, WI.*

Introduction: Belatacept is a novel fusion protein composed of the Fc fragment of human IgG1 linked to the extracellular domain of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), selectively inhibits T-cell activation through costimulation blockade. Eosinophilic Gastrointestinal Disease (EGID) is a rare disorder characterized by focal or diffuse eosinophilic infiltration of the bowel wall with various gastrointestinal manifestations.

Case Description: Our Patient is a 24-year-old Caucasian Male with ESRD s/p LRKT 10 years ago. The patient was induced with Simulect(Basiliximab), thereafter he was started on immunosuppression regimen with Belatacept 750mg intravenous injection, Cellcept 750mg twice daily and tapering doses of Prednisone and has had a smooth post transplant course. About two years after the transplant, he started complaining of epigastric pain, worse on 'bending forward'. Laboratory data revealed peripheral eosinophilia 9% and iron deficiency anemia. Endoscopy revealed mucosal edema with extensive ulcerations and nodularity of esophagus, duodenum, and terminal ileum. Histopathology revealed extensive ulcerations of esophagus, duodenum, and terminal ileum with diffuse eosinophilic infiltration. Belatacept was stopped resulting in complete resolution of clinical symptoms, peripheral eosinophilia, Anemia and also complete resolution of the esophageal and duodenal ulcerations with resolution of eosinophilic infiltration.

Discussion: Drug induced EGIDs are very rare and there are only few case reports of drug induced EGIDs. Diagnosis is usually lead by High index of suspicion paired with exclusion of other causes of peripheral eosinophilia. Final diagnosis is made with biopsy proven eosinophilic infiltration of bowel wall. T cell co-stimulation through CD28 and B7–2 plays an important role in allergic responses and administration of a CTLA-4 immunoglobulin blocks this interaction. Thus, we may surmise that costimulation blockade with Belatacept could trigger allergic conditions such as EGIDs.



FR-PO789

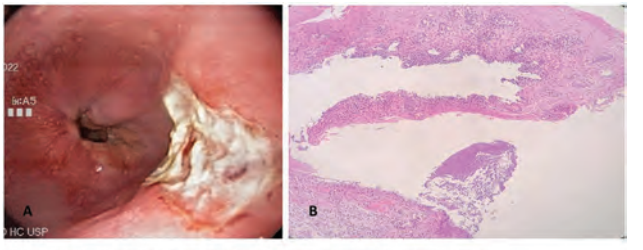
An Uncommon Presentation of Esophageal Actinomycosis in a Patient with Recent Kidney Transplant

Joao P. Ferreira,[1] Liliana M. Kassar,[1] Felipe Carvalho Barros Sousa,[1] Raquel M. Moreira.[2] *[1]Universidade de Sao Paulo Hospital das Clinicas, Sao Paulo, Brazil; [2]Universidade de Sao Paulo, Sao Paulo, Brazil.*

Introduction: Actinomycosis is a rare granulomatous disease, caused by a gram positive anaerobic bacterium, which inhabits the gastrointestinal tract and oral cavity in a commensal manner, but can cause an infectious process by invading injured tissue. *Actinomyces israelii* is the main human pathogen. The most common site of involvement is cervicofacial region with formation of abscesses and granulomas, followed by abdominal and thoracic involvement.

Case Description: A 33-years-old male, three months after kidney transplant from deceased donor, zero HLA mismatches, non-sensitized, started with fever and oral ulcers three days prior admission to the hospital. The patient's immunossupression was tacrolimus and mycophenolate. He had been on treatment with Valganciclocir for 20 days due to asymptomatic cytomegaly with positive antigenemia. The patient was hospitalized and started on empirical IV Ganciclovir due to possible cytomegalovirus (CMV) disease. Despite the treatment, he maintained fever episodes and experienced worsening of oral ulcers, and onset of odynophagia, with the presence of esophageal ulcers in the upper digestive endoscopy. Biopsy of esophageal ulcers was performed with the presence of gram-positive colonies and *Actinomyces spp*. The patient was treated with IV ceftriaxone, and then oral amoxicillin for 4 months with clinical improvement.

Discussion: The case reported above is a rare presentation of Actinomycosis, a disease with low prevalence and difficult diagnosis. The occurrence of oral and esophageal ulcers is uncommon with few cases reported. Main clinical forms comprise cervicofacial features with the occurrence of chronic cutaneous nodules and emergence of gastrointestinal tumors, usually in the ileocecal region, presenting with abdominal pain, weight-loss and weakness. In this case, the diagnosis was challenging due to a large number of possible infections such as herpes simplex, CMV, oral moniliasis, among others, especially in the first 6 months after kidney transplant.



A – Patient's esophageal ulcer. B – Esophageal mucosa with *Actinomyces spp* (optical mycroscopy).

FR-PO790

Distinct Mutation Patterns in BK Polyomavirus Genome-Integrated Urothelial Carcinomas and Urothelial Carcinomas with Mutational Signature of Aristolochic Acid

Ya-chung Tian. *Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

Background: Urothelial carcinoma (UC) is highly prevalent among kidney transplant recipients in certain regions and may be linked to the integration of BK polyomavirus (BKPyV) genome into the human genome. In Taiwan, a high prevalence of aristolochic acid (AA) mutational signatures in UC was exhibited in general population. To better understand these etiologies in UC oncogenesis in kidney transplant patients, whole-genome sequencing (WGS) was employed to determine the integration of BK polyomavirus (BKPyV) genome into the human genome and AA mutational signatures in UC.

Methods: Twenty UC specimens underwent WGS analysis to evaluate BKPyV genome integration and AA mutational signatures, with Sanger sequencing used for confirmation of BKPyV genome integration.

Results: Twenty UC specimens underwent WGS analysis to evaluate BKPyV genome integration and AA mutational signatures, with Sanger sequencing used for confirmation in UC specimens with BKPyV genome integration. Results: BKPyV genome integration was found in 7 out of 20 UC specimens (37%), while 16 out of 20 UC specimens (80%) contained the AA mutation signature. Three specimens (15%) had both characteristics. A total of 106 integration sites in UC specimens with BKPyV genome integration were identified. Most of the integration sites were located in introns and intergenic regions, with only two sites in exons. Notably, a specific integration site with a breakpoint at TAg4289 of the BKPyV genome and at the intron of the human eukaryotic translation initiation factor 2B subunit alpha (EIF2B1) was observed in three distinct UC specimens, and this finding was confirmed via Sanger sequencing. The WGS results also revealed a high prevalence (80%) of the AA mutational signature in these UC specimens. A high percentage of UC cases exhibited mutations in genes related to chromatin modification (KMT2C, 70%), the cell-cycle pathway (TP53, 55%), and the RTK-PI3K pathway (ERBB2, 25%). Interestingly, UC cases with BKPyV genome integration had significantly lower total mutation burden and fewer mutations in these genes compared to those with the AA mutational signature, suggesting distinct mechanisms of carcinogenesis in UC.

Conclusions: In conclusion, our findings provide compelling evidence for different mechanisms underlying the development of UC in Taiwanese kidney transplant recipients.

FR-PO791

Health Equity Gaps in Access to Kidney Transplant

Chiao Wen Lan,[1] Deidra C. Crews,[3] Sumit Mohan,[2] Sherri Morgan-Johnson,[4] Melissa Murphy.[4] *[1]Health Services Advisory Group Inc, Phoenix, AZ; [2]Columbia University, New York, NY; [3]Johns Hopkins Medicine, Baltimore, MD; [4]Centers for Medicare and Medicaid Services (CMS), Baltimore, MD.*

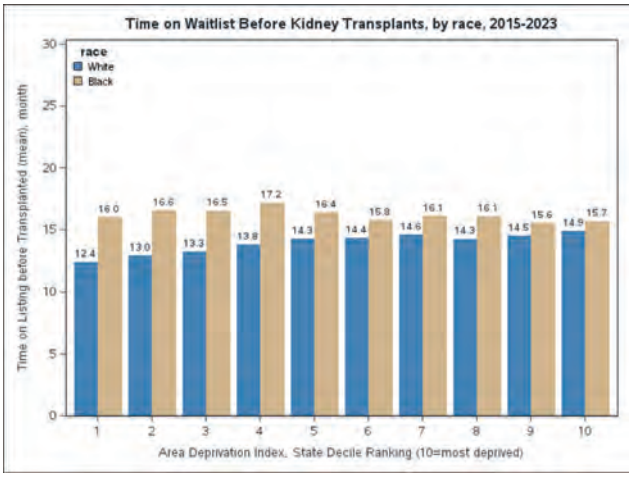
Background: Research has documented cascading barriers to care, while accessing kidney transplant across neighborhood characteristics have not been fully examined.

Methods: ESRD Quality Reporting System (EQRS) data between 1/1/2015-5/20/2023 were analyzed. Access to transplants is examined, including calculating time on dialysis to listing and time on list before transplanted. Data were linked to the Area Deprivation Index (ADI), a neighborhood-level metric that combined 17 specific indicators (e.g., poverty, housing).

Results: 9.5% of patients added to the waitlist were from the most disadvantaged neighborhoods, while 14.6% of ESRD patients residing there. Among patients who received transplants, waitlist time was consistently longer for Black patients compared to White patients ($p<0.001$), and the difference has narrowed over the years, yet the gap remains. Neighborhood characteristics are associated with health disparities, where patients from more disadvantaged neighborhoods waited longer on the list before getting transplanted than those from the least disadvantaged areas (15.3 vs. 13.4 months, $p<0.0001$). Racial disparities exist across neighborhood socioeconomic level. White ESRD patients in the most disadvantaged neighborhoods were added to the waitlist faster than Black patients in the least disadvantaged neighborhoods (38.6 vs. 43.2 months, $p<0.01$). The time on the list before transplantation among White patients in the most disadvantaged neighborhood was shorter than Black patients in the least disadvantaged neighborhoods (14.9 vs. 16.1 months, $p<0.0001$).

Conclusions: The results show significant disparities in access to care among ESRD patients in disadvantaged neighborhoods and that Black patients have reduced access to the transplant waitlist regardless of neighborhood characteristics. These results emphasize the need for policies and strategies that overcome structural racism barriers in addition to improving access for socioeconomically disadvantaged patients.

Funding: Other U.S. Government Support



FR-PO792

Outcome of Organ Procurement and Transplantation Network (OPTN) Policy Allowing for Waiting Time Modification for Candidates Affected by Race-Inclusive eGFR Calculations: Early Impact from a Single Center

Debra Wekesa, Scott G. Westphal, Clifford D. Miles. *University of Nebraska Medical Center, Omaha, NE.*

Background: Black patients have a high burden of kidney disease yet experience lower rates of waitlisting and kidney transplantation. There is a myriad of reasons for these disparities, including the historic race modifier used for GFR estimation, which ascribes a higher GFR at a given serum creatinine level in black individuals. Since eGFR ≤ 20 ml/min is required for waiting time accrual, the eGFR race modifier could delay listing for some black patients. In January 2023, the OPTN implemented a policy whereby registered black transplant candidates could receive waiting time adjustment if a prior race-inclusive eGFR calculation yielded values such that "non-African American" eGFR was ≤ 20 ml/min, but the "African American modified eGFR was >20 ml/min.

Methods: Upon enactment of this policy, our transplant program identified potential candidates, and through internal EMR review, communication with patients, their nephrologists, and PCPs, eligible candidates were identified for waiting time modification. Here, we report the impact of this policy change at a single center one month after submission for waiting time modification for eligible candidates.

Results: 37 adult patients on our waitlist had self-identified as Black or African American. In 19 (51.4%) patients, historic race-inclusive GFR estimates were found that allowed for waiting time modification. In these patients, a mean 753 ± 788 and median 407 (327, 901) additional days of waiting time was added. The maximum time added for a single patient was 3,323 days (9.1 years). 4 of the 19 (21%) candidates received a deceased donor kidney transplant within 1 month of waiting time modification.

Conclusions: At a single center, >50% of patients were eligible for waiting time addition, with an average of >2 years of waiting time added per eligible candidate. Importantly, this modification yielded near immediate impact, with >20% of patients receiving a transplant within the first month of the modification. While the number of black patients on our waiting list is small relative to many centers, this early assessment of the policy impact demonstrates the potential of its intended effects. Centers with large numbers of black patients will require a coordinated effort to ensure timely identification and implementation of appropriate waiting time addition.

FR-PO793

Bridging the Literacy Gap in Living Kidney Donation Information by ChatGPT

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Background: Improving diversity and equity in living kidney donation requires ensuring that information on the topic is accessible to people with different levels of literacy. The average American adult reads at an eighth-grade level, highlighting the need to modify complex medical information for easier comprehension. ChatGPT, an AI language model, has the potential to modify medical information to improve readability. This study aimed to assess the effectiveness of ChatGPT in modifying living kidney donation information to an eighth-grade reading level.

Methods: We collected 27 questions and their answers from a widely accessible FAQs website (Donate Life America) related to living kidney donation. ChatGPT (03/23 Version) modified the text of the answers to make them easier to comprehend for those who read at or below an eighth-grade level. Original and modified information were assessed for readability using the well-validated Flesch-Kincaid formula. The grade level of each answer was compared before and after modification, and a paired t-test was used to evaluate the significance of any reduction in grade level.

Results: The average grade level of the original answers was 9.6±1.9, while the average grade level of the modified answers was 7.7±1.8, indicating a significant reduction in grade level ($p<0.001$). ChatGPT was able to modify the information to an eighth-grade reading level or below in 16 out of 27 cases (59%). The grade level of the modified answers ranged from 3.4 to 11.3.

Conclusions: Our study demonstrates that ChatGPT can be a useful tool in improving the grade level readability of information on living kidney donation for individuals with lower literacy levels. Although ChatGPT was not able to modify all the information to below an eighth-grade reading level, it significantly reduced the grade level readability of the modified information compared to the original information. This suggests that ChatGPT may potentially play a role in promoting diversity and equity in living kidney donation by making information more accessible to a wider range of individuals. While our study shows that ChatGPT can significantly reduce the grade level readability of modified information, there is still room for improvement.

FR-PO794

Strategies to Increase Deceased Organ Donation: A Single-Center Experience from an Inner-City Hospital in the Bronx

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Background: Kidney transplantation is the treatment of choice for end-stage kidney disease as it improves the quality of life and reduces the mortality risk. However, the average wait time ranges from 4 months to > 6 years, with 1 out of 20 (5%) patients dying each year while waiting. According to a 2022 report by the New York Organ Donor Network, the Bronx has the lowest organ donation rate at 11.3% vs. 18.1% in New York City. The Bronx had the highest number of people on the waiting list, with 1,500 people. Several factors, including SDOH contribute to the Bronx's low organ donation rate. Centers for Medicare & Medicaid Services (CMS) introduced the End Stage Renal Disease Treatment Choices Learning Collaborative (ETCLC) in August 2021 with the goal to accomplish one of the goals of the Advancing American Kidney Health by increasing kidney transplants.

Methods: From June 2020 to March 2022. We excluded patients under 18 years old and those who died upon arrival. Electronic medical records were reviewed, and statistical analysis was performed using StataBE17.

Results: There were a total of 375 patient deaths. Of these, 212 were male (56.53%), and 163 were female (43.47%). The mean age was 68.9 years. Thirty-three patients (8.8%) were diagnosed with brain death. Of these, 14 patients (42%) became organ donors. Acute kidney injury (AKI) was present in 42% of patients with brain death. The breakdown of AKI severity was as follows: KDIGO I: 28% KDIGO II: 50% KDIGO III: 22% Timely referral to the OPO was made in 65% of the cases. Nephrology was contacted for 12% of these patients and all 12% required kidney replacement therapy

Conclusions: Identifying the missed opportunities for deceased organ donations is the first step in improving the process. We have implemented processes such as ongoing education of the stake holders and we are committed to working with our partners at the New York Organ Donor Network to ensure that every eligible patient has the opportunity to receive a life-saving organ transplant.

June 2021 - March 2022 Observations (%)

Deceased Patients	375 total			
Sex	Male	212 (56.53%)	Female	163 (43.47%)
Age	Mean 68.9 years			
Brain death (BD)	33 (8.8%) of 375	Harvest Organs 14 (42%) of 33		
AKI in BD	19 (57%)	KDIGO I 4 (12%)	KDIGO II 7 (21%)	KDIGO III 3 (9%)
KRT in BD	4 (12%)	KRT in Harvest Organ patient 1 (3%)		
Nephrology consulted BD	4 (12%)			

Brain dead (BD), Kidney replacement therapy (KRT), Acute KIdney Injury (AKI)

FR-PO795

Perceived Barriers to Transplantation in the Hispanic Community

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Background: Hispanics have a higher prevalence of kidney disease but a lower rate of kidney transplantation (KT). Multiple barriers have been proposed, but patient reported barriers have not been assessed. We interviewed Hispanic patients with kidney failure to assess first-hand reports of patient perceived barriers to KT.

Methods: We interviewed patients from dialysis units and clinics between June and October 2022. The inclusion criteria were age 18-65, eGFR of ≤ 20 ml/min, and Spanish as the primary language. Interviews were conducted in Spanish, audio recorded, transcribed to English, and uploaded to a qualitative data analysis software DEDOOSE. The interviews were then analyzed and coded into *a priori* twenty-three communication-based categories created by a communications framework.

Results: Most patients felt willing and able to undergo KT. Patients lacked knowledge about the KT process and could not make a well-informed decision. Living donation (LD) was discussed with very few; in general, patients lacked knowledge about LD. Some viewed LD as a significant health risk to the donor. Misconceptions were evident, with a few patients reporting discussions on emigration to their native countries increasing their chances of KT. Lack of insurance or cost of KT were common concerns. Patients reported infrequent counseling, with most interactions with individuals other than a nephrologist. Often, the initial communication regarding KT occurred in the emergency room or when initiating dialysis. Use of translators and Spanish-speaking providers was common. Discussions were limited when a Spanish interpreter was absent. Occasionally, the translation was inadequate or difficult to understand.

Conclusions: Multiple patient perceived barriers to KT were noted during our interviews. These included access to nephrologists, barriers in communication despite interpreters, and infrequent counseling. Additional resources and efforts are needed to improve KT rates in the Hispanic population.

Patient characteristics N=20	
Age (years)	57 ± 11
Female Sex	10 (50)
Marital status	
Single	3 (15)
Married	11 (55)
Separated	3 (15)
Other	3 (15)
Education	
<7 years	15 (75)
7-12 years	4 (20)
>12 years	1 (5)
Employment	
Employed	1 (5)
Unemployed	17 (65)
Retired	2 (10)
Social Support*	4.6 ± 0.9
Comfort with English*	2.5 ± 1.2
Comfort with written English*	2.0 ± 1.1
Annual income	
<$50, 000	14 (70)
No response	6 (30)
Country of Origin	
Mexico	16 (80)
Guatemala	3 (15)
Venezuela	1 (5)
Years in the US	23 ± 11

Continuous variables are presented in mean ± standard deviation and categorial variables are presented in number (%)
*Comfort with English and social support were reported on a Likert scale of 1-5 with a score of 1 indicating no support/comfort and 5 indicating excellent support/ comfort.

FR-PO796

Promoting Transplant Equity: Characterizing Deceased Organ Donation by Noncitizens in the United States

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Background: There are no citizenship restrictions to receiving or donating a kidney transplant per the United Network for Organ Sharing and the Organ Procurement Transplantation Network. However, the major barrier to transplant for most undocumented immigrants are insurance barriers as undocumented immigrants are barred from receiving federal insurance. Non-citizens are aware of the double standard allowing them to donate organs despite the restrictions to receiving them. Restricting access to organ transplant pool while being able to contribute to it is inequitable. However, the degree of contribution to the organ pool by non-citizens has not been recently assessed. The aim of this study is to illustrate the degree to which non-citizens contribute to the organ pool in the US between 2015 and 2020.

Methods: We utilized UNOS data examining decreased organ donors in the US between 2015 and 2020. To summarize recipient and donor characteristics, median and interquartile range (IQR) were used for continuous variables and counts and percents were used for categorical variables. Characteristics were stratified by reported citizenship status. To test for differences across groups, ANOVA (for normally distributed) or Kruskal-Wallis (non-normally distributed) tests were used for continuous variables after testing for normality via the Shapiro-Wilk test and Chi-square tests were used for categorical variables.

Results: Non-US Citizen/US Residents (NCR) accounted for 2.8% and Non-US Citizens/Non-US Residents (NCNR) accounted for 0.4% of the donor population. Compared with US citizens, non-citizen residents were more likely to be older, male, O blood type and have diabetes. Regarding citizenship status of donors and recipients, 91% of NCR and 90% of NCNR organs (n=5581) were received by US citizens. 5.8% of organs (n=9172) donated by US citizens were received by NCR or NCNR recipients.

Conclusions: There are no citizenship restrictions on organ donation from deceased individuals, however, restrictions on federal insurance is a barrier to transplant for non-citizens. We illustrate that non-citizens donate healthy, viable organs to the US organ pool, the majority of which are received by US citizens. Any system that uses these gifts from individuals who would themselves not be considered eligible for an organ transplant is unjust.

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FR-PO797

Renal Transplant Outcomes Among Pediatric Non-English Language Preference Patients

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Background: Non-English language preference (NELP) is associated with disparities in health care access and quality and worse clinical outcomes in children. To our knowledge, no studies characterize the role of NELP in the renal transplant process. The primary aim of this study is to compare pediatric renal transplant outcomes among NELP and English Language Preference (ELP) populations.

Methods: This retrospective single-center study included pediatric patients between the ages of 0 to 21 who received renal transplants between January 2014 and September 2022. The determination of NELP was made based on interpreter use, language spoken at home, or explicit documentation of NELP in the electronic medical record. Proportions were compared using Mann-Whitney, Chi-squared tests, and unpaired t-test. Two-tailed p values of <0.05 were considered significant.

Results: 45 renal transplant recipients were included. 26% (12) of these patients were identified as NELP. The average age at transplant for NELP patients was 12.3 (± 5.3) and ELP was 10.7 (± 5.4). Those identified as NELP were significantly less likely to have a

living donor transplant (p<0.01). Worsened eGFR was seen in the NELP cohort at 7.43 compared to ELP at 5.91 (p=0.12). Rejection and graft failure were more likely in the NELP cohort (50% vs 33%, p=0.30 and 17% vs 3%, p=0.10, respectively). There was no statistical difference in viral activity.

Conclusions: NELP patients were less likely to receive living donor grafts, demonstrating an ongoing disparity. Although not statistically significant, NELP rejection and graft failures appear to be clinically significant for long-term outcomes. Our results suggest NELP is a risk factor for poor transplant outcomes in children. Our single-center study is limited given small sample size. Larger multi-centered studies are needed to identify interventions for bridging the gap among NELP patients.

Table 1. Demographics and Transplant Outcomes

	NELP (n=12)	ELP (n=33)	p-value
Age at transplant (years)	12.3	10.7	0.28
Ethnicity, n (%)			0.28
African American	0 (0)	11(33)	
Hispanic	11 (92)	1 (3)	
Caucasian	0 (0)	18 (54)	
Other	1 (8)	4 (12)	
Cause of ESRD, n (%)			
Glomerular Disease	8 (67)	19 (58)	0.83
Non-glomerular Disease	4 (33)	14 (42)	0.83
DDRT, n (%)	6 (50)	15 (45)	0.79
LDRT, n (%)	6 (50)	18 (55)	< 0.01*
eGFR pre-transplant, ml/min/1.73m2 (mean)	7.43	5.91	0.12
1 year post-transplant Outcomes			
CMV Seroreactivity Status, n (%)	1 (8)	7 (21)	0.57
BK Virus Seroreactivity Status, n (%)	4 (33)	12 (36)	0.86
eGFR 1 year post-transplant, ml/min/1.73m2 (mean)	0.96	1.07	0.84
Post-transplant DSA-1 year post-transplant, n (%)	3 (25)	7 (21)	0.89
Rejection, n (%)	3 (25)	2 (6)	0.21
Number of hospital stays-1 year post transplant, days	3.64	4.19	0.23
Long-term Outcomes			
CMV Seroreactivity Status, n (%)	1 (8)	4 (12)	0.13
BK Seroreactivity Status, n (%)	4 (33)	9 (27)	0.16
eGFR 5 year post-transplant, ml/min/1.73m2 (mean)	0.99	1.21	0.83
Rejection, n (%)	6 (50)	11 (33)	0.30
Graft Failure, n (%)	2 (17)	1(3)	0.10

* Suggests statistical significance, p value < 0.05, ESRD: End Stage Renal Disease, CMV: Cytomegalovirus, DDRT: Deceased Donor Renal Transplant, LDRT: Living Donor Renal Transplant, DSA: Donor Specific Antigens

FR-PO798

Transplantation, Waitlist Status, and County Indices of Economic Health in West Virginia

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Background: Kidney transplantation is the optimal treatment for patients with end stage kidney disease. Many patients are never waitlisted for transplant. West Virginia (WV) has a high poverty rate (PR) (17.1 vs 12.85% for the US) with 33 of its 55 counties recognized as economically distressed or thereby at risk. We searched for a potential association between transplant waitlisting and the receipt of a transplant with indices of economic health.

Methods: Data on initiation of kidney replacement therapy with dialysis or transplant, waitlist for kidney transplant and death between 1965 and 2020 for WV patients were collected from USRDS. Data on county PR and economic distress including composite index (CI) for national economic status were collected from the Appalachian Regional Commission.

Results: Of the 23,055 WV patients identified in USRDS data, 2,999 (13%) were transplanted compared to 514,050 (15.3%) for the rest of the US (p< 0.001). Patients who never received a kidney transplant were from counties with higher PRs (18%) compared to transplanted patients (17.5%); p<0.001. Overall, waitlisted patients (2,375) came from counties with lower PRs than those who were never waitlisted (17.6 vs 18%; p<0.001). Waitlisted patients were less likely to be from distressed or at-risk counties (32 vs 34.3%; p=0.05) or counties with lower CI (141.9 vs 145.2; p<0.001) than patients who were never waitlisted. Among those who were never transplanted, waitlisted patients (792) came from counties with lower PRs (17.1 vs 18%; p<0.001), less distressed or economically at-risk counties (28.9 vs 34.5%; p=0.003) and counties with a lower CI (139 vs 145.5; p<0.001) than those who were never waitlisted (20,479). In multivariable logistic regression, county PR remained an independent predictor of lower odds of being transplanted (OR 0.91, 95% CI: 0.85-0.97; p=0.005) or waitlisted (OR 0.9, 95% CI: 0.84-0.96; p=0.001) per 5% increase in poverty rate after adjusting for age, sex, BMI, tobacco use, functional status, comorbid medical conditions and drug dependence.

Conclusions: Waitlisted patients and transplant recipients from WV were more likely to hail from counties with lower PRs and those in better economic health.

FR-PO799

Assessment of Disparities in Access to Valganciclovir Cytomegalovirus Prophylaxis in High-Risk African American Kidney Transplant Patients

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Background: While access and outcomes disparities in African American (AA) kidney transplant recipients are well-known, there are limited studies assessing medication access disparities in transplant medicine. Cytomegalovirus (CMV) is a common viral infection that can cause serious complications in transplant recipients, with potential excess burden in AA communities. The high out-of-pocket costs associated with valganciclovir prophylactic therapy likely affect its use, so research is needed to fully understand differences in access to antiviral CMV prophylaxis and its impacts on CMV infection in AA transplant recipients.

Methods: This was a single-center, retrospective longitudinal cohort study in high-risk (CMV serostatus D+/R-) adult kidney recipients transplanted between 6/1/2010 and 5/31/2020, representing a 10-year cohort. Data was collected through electronic and manual medical record abstraction. Standard univariate comparative statistics were utilized in conjunction with binary logistic regression for multivariable modeling.

Results: 418 kidney transplant recipients were included, of which 179 (42.8%) were AA and 239 were non-AA. Baseline demographics were significantly different in mean age in years (46.5 ± 12.9 AA vs. 50.9 ± 13.9 non-AA, p=0.001) and private and Medicaid insurance status (p<0.001). AAs experienced higher rates of death-censored graft loss (10.6% AA vs. 5.0% non-AA, p=0.031). There was no difference in CMV infection rate, opportunistic infection rate, leukopenia incidence, or death between AA and non-AA patients. AA patients were 42% less likely to receive valganciclovir assistance in covering out-of-pocket costs (assistance programs and/or fundraising/savings use) compared to non-AA patients (OR 0.58, 95% CI [0.379-0.892], p=0.013). In a multivariable model including age, Medicaid status, and donor marginality variables, the impact of AA race on use of these assistance programs was no longer statistically significant (OR 0.70, 95% CI [0.448-1.094], p=0.118).

Conclusions: In univariate analyses AAs were significantly less likely to utilize assistance programs or fundraising/savings to access valganciclovir, which was somewhat explained by age, insurance status, and donor type. Despite this, CMV infection rates did not differ significantly between the AA and non-AA cohorts.

FR-PO800

Structural Racism and Access to Kidney Transplantation: Examining Residential and Transplant Center Segregation

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Background: Disparities in kidney transplantation (KT) access exist for systematically disadvantaged communities. Racial/ethnic segregation, a marker of structural racism, in a candidate's residential neighborhood and their transplant center's neighborhood may drive KT disparities.

Methods: We identified 158,506 Black and White KT candidates (age≥18) first listed between 1995-2021 using SRTR. Segregation scores were calculated based on Thiel's H method. These scores were subsequently categorized into tertiles. We used proportional hazards models, adjusting for individual- and neighborhood-level factors, to quantify the likelihood of deceased donor KT (DDKT) and live-donor KT (LDKT). We also assessed the differential impact of segregation on KT access for Black candidates, using an interaction term of segregation tertiles and candidate race.

Results: Black candidates were more likely to reside in high-segregation neighborhoods (70.1% vs. 30.9%; P <0.001) and be listed at transplant centers located in these neighborhoods (63.9% vs. 38.2%; P<0.001). Candidates living in a high-segregation neighborhood were less likely to receive LDKT but not DDKT; furthermore, residence in a high-segregated neighborhood was associated with lower access to LDKT for Black candidates (aHR=0.88, 95%CI: 0.82-0.95) but not White candidates ($P_{interaction}$<0.001). Candidates listed in centers in a high-segregation neighborhood had lower access to DDKT, independent of race. However, LDKT access was lower for Black candidates listed at centers in a high-segregation neighborhood (aHR=0.90, 95%CI: 0.84-0.97; $P_{interaction}$=0.042).

Conclusions: Access to LDKT was significantly lower for Black candidates who resided in or were listed in centers in segregated neighborhoods, and access to DDKT was lower for all candidates whose centers were in high-segregation neighborhoods. Targeted efforts should address the impacts of racial/ethnic segregation on equitable access to KT.

Funding: NIDDK Support, Other NIH Support - National Institute on Aging, National Institute of Allergy and Infectious Diseases

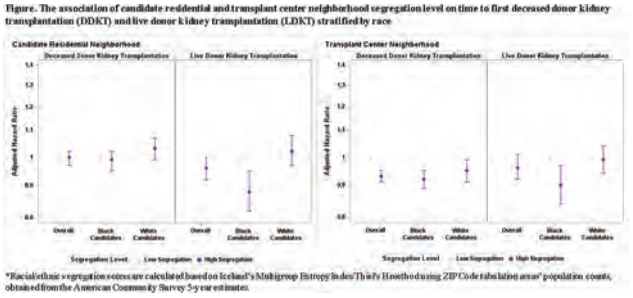

Figure. The association of candidate residential and transplant center neighborhood segregation level on time to first deceased donor kidney transplantation (DDKT) and live donor kidney transplantation (LDKT) stratified by race

*Racial/ethnic segregation scores are calculated based on Iceland's Multigroup Entropy Index (Theil's H score) using ZIP Code tabulation areas' population counts, obtained from the American Community Survey 5-year estimates.

FR-PO801

Impact of Race on Estimated Post-Transplant Survival Score in Patients with ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) affects individuals of every race equally. Access to kidney transplant (Tx) and post-Tx outcomes may vary by race. Estimated Post Transplant Survival (EPTS) scores are used to allocate high-longevity kidneys to patients who are expected to receive the most years of graft function. We examined EPTS scores in ADPKD by race, and compared these results to Tx recipients with other kidney diseases.

Methods: ADPKD and non-ADPKD patients age>30 years who received Tx 1/2000-3/2021 were selected from OPTN/UNOS data when ethnicity was unambiguously identified as White, African American, Hispanic, or Asian with available EPTS scores. Using the current EPTS table, EPTS percentages were categorized as ≤20%, >20-80%, and >80%. The four components of EPTS (age, diabetes, prior Tx, and years of dialysis) were analyzed by race for both groups.

Results: Overall, ADPKD patients were more likely (43.5%) to have EPTS≤20% compared to other kidney disorders (26.1%). Although African American, Hispanic and Asian ADPKD patients were more likely to have EPTS≤20% than other kidney disorders, differences in EPTS≤20% were greater across race in ADPKD individuals than in those with other kidney disorders. In ADPKD patients, White patients had significantly lower duration of dialysis and EPTS was predominantly determined by dialysis duration. In non-ADPKD patients, diabetes and prior transplantation were more often determinants.

Conclusions: Overall, transplanted ADPKD patients had significantly lower EPTS scores than other transplant recipients. However, increased dialysis time among non-white ADPKD patients leads to less favorable EPTS scores reducing allocation of best-quality kidneys to minority patients with ADPKD.

Expected Post Transplant Survival Scores, by diagnosis and race

ADPKD EPTS %	White n=22,932	African American n=3,087	Hispanic n=2,679	Asian n=871	ALL N=29,569
≤20	45.4	33.4	41.5	36.1	43.5
>20	54.6	66.6	58.5	63.9	56.5
Age, years	54 (48, 61)	54 (47, 60)	52 (45, 59)	55 (47, 62)	54 (47, 61)
DM, %	5.0	7.7	6.5	8.2	5.5
Prior Tx, %	3.1	3.1	2.2	2.8	3.0
Dialysis years	0.6 (0.0, 2.5)	3.0 (0.8, 5.5)	2.6 (0.4, 5.2)	1.9 (0.1, 4.1)	0.9 (0.0, 3.1)
NON-ADPKD EPTS %	White n=154,027	African American n=80,643	Hispanic n=44,900	Asian n=17,633	ALL N=279,203
≤20	25.0	26.5	27.7	29.7	26.1
>20	75.0	73.5	72.3	70.3	73.9
Age, years	54 (44, 63)	52 (43, 60)	51 (41, 60)	54 (44, 63)	53 (43, 62)
DM, %	42.4	40.7	48.3	37.1	42.5
Prior Tx, %	17.4	9.8	9.8	8.6	13.7
Dialysis years	1.1 (0.0, 2.9)	3.6 (1.5, 6.0)	3.0 (1.0, 5.6)	2.7 (0.8, 5.1)	2.0 (0.4, 4.4)

Expected post transplant survival scores, by diagnosis and race.

FR-PO802

Impact of Race on Kidney Transplant Outcomes in Patients with ADPKD

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is equally present in all ethnicities. Disparities in access to transplant (Tx) exist for African American (AA) and Hispanic (H) ADPKD patients. We examined outcomes among ADPKD patients who received kidney Tx, by self-reported race.

Methods: OPTN/UNOS files were used to identified ADPKD patients age>30 receiving Tx 2000-2021, and ethnicity was White (W), AA, H, or Asian (A). A Cox model provided hazard ratios for death and a subdistribution hazards model for graft failure accounted for death as a competing outcome. Adjustments for age, gender, BMI, HLA/DR mismatch, dialysis years, diabetes, immunosuppression, CMV, cold ischemia, center distance, PRA, private insurance, donor KDPI, delayed graft function, and living/pre-emptive Tx were included with W as the reference.

Results: Among 32,611 ADPKD recipients, W, AA, H, and A were 76.4, 10.7, 9.8, and 3.1% respectively (Table 1). Compared to W, all others had more dialysis years and more mismatches, but less private insurance and fewer living and preemptive Tx. There was more delayed graft function, despite more lymphocyte depleting induction and corticosteroids.

Conclusions: Tx recipient survival did not differ between W and AA ADPKD patients, but was superior in H and A patients. Decreased allograft survival in African American ADPKD patients persisted after adjustment, suggesting that additional biological or social/economic factors remain to be identified.

	White (n=24,926)	African Am (n=3,491)	Hispanic (n=3,180)	Asian (n=1,014)	ALL (n=32,611)
Age, mean (std)	54.3 (9.6)	53.8 (9.6)	52.0 (9.5)	55.0 (9.9)	54.1 (9.6)
Female sex, %	45.6	51.7	45.4	44.2	46.2
Living donor, %	48.8	18.7	31.6	30.3	43.3
KDPI ≤20%, deceased	14.5	17.5	17.5	13.5	15.1
KDPI 21-85%, deceased	33.9	58.5	46.8	50.5	38.3
KDPI>85%, deceased	2.8	5.3	4.1	5.7	3.3
Preemptive Tx, %	39.1	16.6	20.7	22.9	34.4
Dialysis Yrs,(non-preemptive)	2.1 (0.9, 3.8)	4.0 (2.2, 6.4)	3.7 (1.8, 6.2)	3.1 (1.5, 5.5)	2.5 (1.1, 4.5)
Private Insurance, %	58.5	34.0	38.8	47.9	53.6
HLA mis match, % 0-2	19.8	7.6	15.6	9.6	17.7
3-4	42.6	38.7	40.0	38.0	41.8
5-6	37.6	53.8	44.4	52.4	40.5
DR mismatch, % 0	20.0	11.9	17.0	11.7	18.6
1	46.2	47.6	46.5	45.0	46.3
2	33.8	40.5	36.5	43.3	35.1
CMV pairing,% D+/R- %	25.0	13.5	12.9	5.5	21.9
D+or D-/R+	53.0	78.6	79.9	90.3	59.7
D-/R-	21.0	7.9	7.2	4.2	18.4
Delayed Graft Function, %	10.5	22.8	19.3	17.7	12.9
Lymphocyte depletion, %	58.2	67.0	62.7	60.9	59.7
Steroids maintenance, %	70.4	76.4	72.9	74.3	71.4

Patient Characteristics by Race

RACE (Reference: white)	Unadjusted Hazard Ratio (95% CI)	P	Adjusted Hazard Ratio (95% CI)	P
Death				
African American	1.34 (1.25, 1.44)	<0.001	0.95 (0.88, 1.03)	0.2
Hispanic	0.89 (0.82, 0.98)	0.01	0.75 (0.68, 0.82)	<0.001
Asian	0.88 (0.75, 1.03)	0.1	0.70 (0.60, 0.82)	<0.001
Death-Censored Graft Failure				
African American	2.07 (1.89, 2.26)	<0.001	1.50 (1.36, 1.67)	<0.001
Hispanic	1.29 (1.16, 1.45)	<0.001	1.04 (0.93, 1.17)	0.5
Asian	1.06 (0.86, 1.31)	0.6	0.95 (0.77, 1.17)	0.6

Patient and Allograft Survival

FR-PO803

The Association of Altered Sense of Smell with Nutritional Status in Patients with Advanced CKD

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Background: Anorexia is common in patients with advanced CKD and could lead to protein energy wasting (PEW). Altered sense of smell, a reflection of olfactory dysfunction, is a potential mechanism that exacerbates the impact of anorexia on PEW. In this study, we examined the extent of altered sense of smell and its association with PEW in patients with moderate to advanced CKD.

Methods: We studied 139 participants (34 healthy subjects, 50 patients with stage 3-4 CKD, 55 patients on maintenance hemodialysis (MHD)) using the odor identification test (Sniffin' Sticks odor screening test containing 12 different smells). Odor identification test were scored as correct or incorrect, and a total odor score was calculated for each participant. Malnutrition Inflammation Score was used to assess PEW.

Results: CKD patients had elevated levels of C-reactive protein and reduced eGFR and serum albumin concentrations compared to controls (Table1). There was a gradual decrease in the total odor score between groups, controls with highest and MHD patients with lowest scores. A similar gradual worsening was observed in MIS scores with MHD patients displaying worst nutritional score ($p \leq 0.001$) (Table 1). The number of participants with severe olfactory dysfunction (≤ 6 correct answers) was statistically significantly higher in the CKD and MHD groups compared to the control group ($p \leq 0.01$) There was a statistically significant inverse correlation between total odor score of the participants and MIS score for the entire population ($r = -0.3$, $p \leq 0.001$) (Figure 1), more prominently observed in the CKD and MHD groups.

Conclusions: This cross-sectional study suggests that olfactory dysfunction, as assessed by an odor identification test, is altered in patients with advanced CKD, most notably in ones on MHD. In CKD patients, the severity of the loss of sense of smell is directly associated with worse protein-energy wasting. Further studies are needed to examine the casual relationship between odor sensation and development of PEW in patients with CKD.

Variable Median (IQR)	Control	CKD	MHD	Compare: All Groups
eGFR	106.6 (96.9–112.4)	40.2 (30.3–47.8)	6.4 (5.3–9.1)	p ≤ 0.001
C-Reactive Protein	1.5 (1.0–2.3)	2.6 (1.9–4.4)	6.6 (3.5–13.4)	p ≤ 0.001
Albumin	4.30 (4.00–4.30)	4.50 (4.30–4.77)	4.05 (3.84–4.39)	p ≤ 0.001
Total Odor Score	9 (7–10)	8 (6–9)	7 (6–9)	p = 0.001
MIS Score	0 (0–0)	2 (1–3)	7 (5–10)	p ≤ 0.001

Table 1

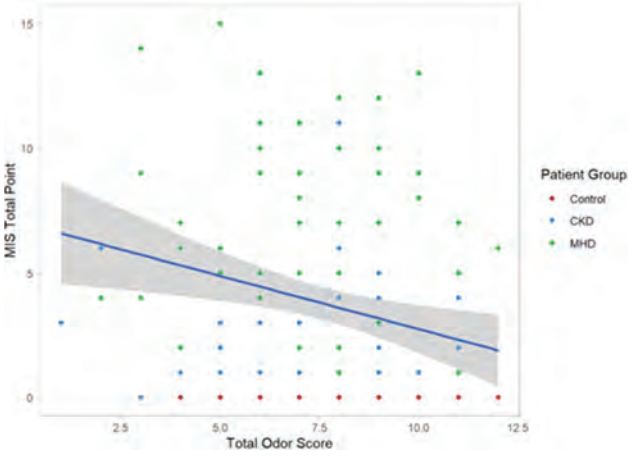

Figure 1

FR-PO804

Effect of Kidney Transplant (KT) on the Sense of Taste and Its Association with Nutritional Status in Patients with ESRD Who Receive Kidney Transplantation

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Background: Taste alteration of bitter, sour, sweet, salty and umami test are common, identification of patients with altered taste perception could reach to implement strategies and to prevent or improve malnutrition. There is not information regarding the change of taste perception after renal transplantation, and the association of taste change with nutritional status.

Methods: Prospective cohort in receptors of 1st transplant (Jan-Oct 2022). Subjects with dental prostheses, oral alterations, and active infection were excluded. The sample was 47 patients, and only 21 have completed the evaluation after the transplant. Subjective global assessment, pica questionnaire, current medications, and taste perception test. Anthropometric measurements were taken.

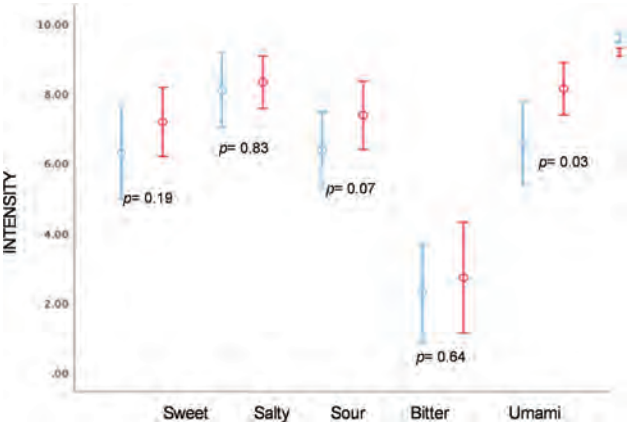
Results: Forty seven patients were inlcuded, 38.8 years old (mean); 70% were male, 51% had unknown cause of ESRD, 51% had hemodialysis, 43% peritoneal dialysis and 6% early trasplant.

Conclusions: There is a beneficial effect of kidney transplant on the sense of taste and nutritional status. Patients with indicators of adiposity have an alteration of taste before the KT. The umami taste significantly increases the perception of intensity, and the sour taste presents a not significant trend, this after renal transplantation, despite that almost all taste intensities increases. Patients who present BMI 25-30 kg/m2 before the transplant decrease significantly after the transplant and muscle mass indicators (AMA) present a trend.

Funding: Government Support - Non-U.S.

Comparison of nutritional status according to taste alteration

Variable N=47	No taste alteration N=9	Taste alteration N=38	p value
Dry weight	58.3 (54.6-66.8)	68.9 (57.1-80.6)	0.04
Body mass index	21.4 (19.8-24.6)	26.1 (23.0-30.1)	0.004
Subscapular skinfold	12.0 (10.0-16.0)	18.5 (11.7-26.2)	0.04
Triceps skinfold	10.0 (6.5-17.0)	13.5 (9.0-19.2)	0.27
Mean arm circumference	25.6 (21.8-26.7)	27.7 (24.8-31.1)	0.03
Arm muscle area	27.8 (20.4-36.2)	33.8 (28.2-43.1)	0.06



FR-PO805

Association Between Physical Activity and Cardiovascular Events, Tumors, and All-Cause Mortality in Patients with Maintenance Hemodialysis with Different Nutritional Status

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Background: The current research focuses on the effects of nutritional supplementation and exercise on dialysis patients, but Whether exercise can improve outcomes in patients with different nutritional status is not clear.

Methods: The MHD patients were recruited from April 2021 to April 2022. The information of PA was obtained from the IPAQ and followed up once in 3 months. The outcomes were cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor, and all-cause death. We used COX proportional risk model to estimate the association between PA and the outcomes of MHD patients. Patients are classified into two groups based on Geriatric Nutritional Risk Index (GNRI) and classified by age, and we used COX proportional risk model to estimatehe association of PA and outcomes in subgroups. ISM was used to estimate the effects of replacing LPA with MPA or VPA on risk of cardiovascular events, tumors, and all-cause death in different subgroups. The association between PA and outcomes was estimated with COX proportional risk model in different subgroups stratified according to baseline characteristics. The effects of PA on ankle-brachial index and body fat content were analyzed in different IPAQ groups.

Results: A total of 241 maintenance hemodialysis patients were included, 105 peoples developed cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor or all-cause death(43.6%). The median follow-up time was 12 months. MPA reduced the risk of outocme in MHD patients or high GNRI patients (40%vs39%). In MHD patients who was under 65 years with high GNRI, MPA reduced cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumoror all-cause death by 55%. PA reduced the risk of cardiovascular event by 65%, but did not reduce the risk of tumor and all-cause death. Replacing LPA with VPA did not improve clinical outcomes. It actually increases the risk of heart failure 0.4%.

Conclusions: MPA reduced the risk of cardiovascular death, myocardial infarction, stroke, heart failure, atrial fibrillation, tumor, or all-cause death in MHD patients under 65 years, while VPA had no health benefit.

FR-PO806

Prevalence and Risk Factors of Sarcopenia in ESRD Patients

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Background: Sarcopenia is a progressive skeletal muscle disorder involving the accelerated loss of muscle mass and strength, associated with increased adverse outcomes like falls, poor quality of life, frailty, and mortality. Prevalence of sarcopenia in the dialysis population varies from 4% to 63%. However, the prevalence and risk factors in the Indian dialysis population remains uncertain.

Methods: The aim was to study the prevalence of sarcopenia, to identify associated risk factors and to assess the effect of dietary counselling on sarcopenia. It was a prospective observational study, in which, 70 adult patients on maintenance hemodialysis were enrolled and monitored for 6 months. All patients were given dietary counselling at baseline, 1, 3 and 6 months. Bio-impedance spectroscopy, a hand grip dynamometer, and a 4-meter walk test were employed to evaluate muscle mass, strength, and function, respectively. Asian Working Group for Sarcopenia criteria were used for defining sarcopenia. Univariate and multivariate analysis was done for the factors affecting sarcopenia.

Results: Seventy dialysis patients were evaluated. Age of the cohort was 55.3 ± 13.74 years old. The prevalence of probable sarcopenia, sarcopenia, and severe sarcopenia was

11.43%, 25.71%, and 7.1% respectively. Increasing age and diabetes were potential risk factors for sarcopenia ($p < 0.0001$ and $P< 0.0093$ respectively). Sarcopenia was associated with lower BMI (p=0.0006), and lower normalised protein catabolic rate nPCR (p=0.026). Hemoglobin, albumin, calcium, phosphorus, and high sensitivity C reactive protein (hsCRP) did not show any association with sarcopenia. Prevalence of sarcopenia at the end of 6 months was reduced to 17.46% from 25.71%. There was a significant improvement in hand grip strength. nPCR at 6 months was significantly increased in all patients as compared to baseline ($p<0.05$) which implies improvement in protein consumption.

Conclusions: High prevalence of sarcopenia in dialysis patients in this study emphasizes the importance of increasing clinical awareness about sarcopenia and nutritional status assessment in this group of patients. Several variables like age, BMI, diabetes mellitus and nPCR were significantly associated with sarcopenia. Detailed dietary recall and nutritional intervention can improve sarcopenia and must be actively pursued.

FR-PO807

Associations Between Submaximal Indices of Physical Function and VO2 Peak in Patients on Hemodialysis

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Background: Cardiopulmonary exercise testing (CPET) is well-recognized as the gold standard tool for quantifying cardiovascular functional capacity (as assessed by peak oxygen uptake, VO_2Peak during exercise). VO_2Peak is a strong predictor of survival in patients with chronic kidney disease (CKD). It is currently unknown whether basic submaximal tests can reliably predict VO_2Peak in patients with advanced CKD. Herein, we sought to compare the association between various submaximal assessments of physical function with VO_2Peak in patients on hemodialysis.

Methods: We analyzed data from the ongoing, "Effects of long interdialytic intervals on Cardiovascular Functional Capacity (ECON)" study, a randomized crossover trial of patients on hemodialysis. All participants underwent CPET and a battery of submaximal tests of physical function and mobility on a non-dialysis day. Multivariable step regression analysis was used to assess the association between the submaximal tests and VO_2Peak.

Results: A total of 30 patients were stratified based on the median VO_2Peak value of 11.2 mL/kg/min into a High group (n=15, 11 [73%] men, age=54 [11]; VO_2Peak=14.4 [2.5] mL/kg/min) and a Low group (n=15, 8 [53%] men, age=56 [12]]; VO_2Peak=9.8 [1.3] mL/kg/min). The High group had a lower BMI (26.7 [5.9] kg/m^2) compared to the Low group (33.6 [7.4] kg/m^2; p=0.008). No group differences were observed in age, sex, race/ethnicity, dialysis vintage, hypertension, or diabetes (all p's>0.05). The High group had a higher balance score (p=0.003), faster usual gait speed (p<0.001), faster time to complete 5 sit-to-stands (STS-5; p=0.013), longer distance walked during the 6-min walk test (p=0.003), and higher scores in the SF36-PFS (p=0.012) and PROMIS Mobility (p=0.004) questionnaires. After adjusting for age, sex, BMI, and diabetes, only STS-5 (ß [SE]=-0.51 [0.20]; p=0.022) remained significantly associated with VO_2Peak.

Conclusions: Our results indicate that the STS-5, a simple submaximal test that can be completed in less than 1 minute, is superior to the 6-min walk test, usual gait speed, and SF36-PFS and PROMIS Mobility questionnaires for predicting VO_2Peak in dialysis patients.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

FR-PO808

Aerobic Exercise Capacity and Kidney Function Decline in Heart Failure with Preserved Ejection Fraction Patients

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Background: Chronic kidney disease (CKD) is a complication frequently found in HFpEF patients and results in poor prognosis. However, factors related with increased risk of kidney function decline in HFpEF are not well known.

Methods: Among a total of 424 HFpEF patients with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2, aerobic exercise function was assessed by the peak O2 consumption (VO_{2peak}) values obtained through cardiopulmonary exercise test. Primary outcome was development of incident CKD, defined as two consecutive eGFR of <60 ml/min/1.73 m^2 separated by ≥90 days.

Results: The mean age of patients was 64.2 ± 10.6 years and 33.5% were male. Cardiac ejection fraction and eGFR at baseline were 67.0 ± 6.8 % and 87.5 ± 12.2 mL/min/1.73 m^2, respectively. During 1082.8 person-years of follow-up, CKD incidence rate gradually increased in patients with lower VO_{2peak} levels. Multivariable Cox analyses revealed that 1-standard deviation increase in the VO_{2peak} level was associated with a 33% lower risk of CKD development. The adjusted HR (95% CI) of the lowest VO_{2peak} tertile group was 3.07 (1.51-6.24) when compared to the highest tertile group.

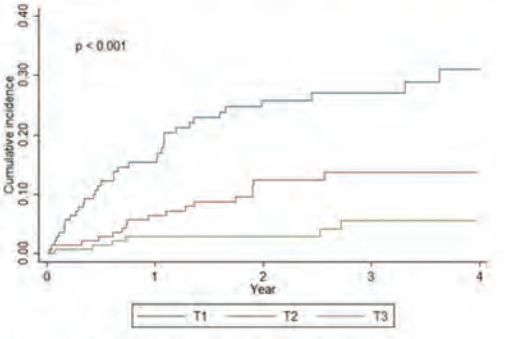
Conclusions: Poor aerobic exercise capacity, represented by reduced VO_{2peak} levels, is closely related with a higher risk of CKD development among HFpEF patients.

Table 1. Baseline characteristics among tertile groups stratified by the level of VO_{2peak}.

	Total (N=424)	Tertile groups stratified by the level of VO_{2peak}			P
		T1 (N=140)	T2 (N=142)	T3 (N=142)	
Demographic data					
Age (year)	64.2 ± 10.6	68.8 ± 10.1	64.1 ± 10.0	59.6 ± 9.9	<0.001
Male	142 (33.5)	44 (31.4)	36 (25.4)	62 (43.7)	0.004
BMI (kg/m^2)	24.8 ± 3.5	25.3 ± 3.5	24.5 ± 3.6	24.5 ± 3.2	0.09
Comorbidities					
Hypertension	366 (86.3)	128 (91.4)	121 (85.2)	117 (82.4)	0.08
Diabetes	100 (23.6)	42 (30.0)	38 (26.8)	20 (14.1)	0.004
Dyslipidemia	263 (62.0)	87 (62.1)	91 (64.1)	85 (59.9)	0.76
Atrial fibrillation	42 (9.9)	18 (12.9)	14 (9.9)	10 (7.0)	0.26
Stroke	46 (10.8)	22 (15.7)	15 (10.6)	9 (6.3)	0.04
Laboratory parameters					
eGFR (mL/min/1.73m^2)	87.5 ± 12.2	84.2 ± 11.7	87.4 ± 11.7	90.8 ± 12.3	<0.001
Proteinuria	56 (18.7)	20 (18.7)	24 (21.4)	12 (11.5)	0.15
Hemoglobin (g/dL)	13.4 ± 1.4	13.1 ± 1.3	13.3 ± 1.3	13.9 ± 1.4	<0.001
NT-proBNP (pg/mL)	87.0 [44.0-196.5]	138.0 [67.5-345.5]	93.0 [45.0-220.0]	52.5 [30.0-107.0]	<0.001
Medications					
RAS inhibitors	210 (49.5)	70 (50.0)	79 (55.6)	61 (43.0)	0.10
Diuretics	197 (46.5)	86 (61.4)	67 (47.2)	44 (31.0)	<0.001
Beta blockers	140 (33.0)	58 (41.4)	47 (33.1)	35 (24.6)	0.01
Other anti-hypertensives	140 (33.0)	48 (34.3)	47 (33.1)	45 (31.7)	0.90
Statins	166 (39.2)	60 (42.9)	51 (35.9)	55 (38.7)	0.49
Echocardiography					
Ejection fraction (%)	67.0 ± 6.8	66.5 ± 7.1	67.1 ± 6.9	67.2 ± 6.4	0.64
LVMI (g/m^2)	94.7 ± 21.2	96.4 ± 24.0	94.5 ± 20.5	93.4 ± 19.0	0.48
LAVI (ml/m^2)	32.6 ± 10.9	34.5 ± 12.6	32.1 ± 9.6	31.2 ± 10.2	0.03
E/E' ratio	11.8 ± 3.5	13.0 ± 3.7	11.9 ± 3.8	10.6 ± 2.5	<0.001
CPET parameters					
VO_{2peak} (mL/kg/min)	23.9 ± 5.6	18.1 ± 2.3	23.4 ± 1.4	30.1 ± 3.7	<0.001
Baseline SBP (mmHg)	123.0 ± 16.2	121.2 ± 17.7	124.5 ± 15.5	123.2 ± 15.1	0.21
Peak SBP (mmHg)	187.9 ± 30.7	176.4 ± 30.5	190.2 ± 31.6	196.7 ± 26.4	<0.001
Base HR (bpm)	72.1 ± 12.8	73.2 ± 14.5	72.7 ± 12.0	70.4 ± 11.7	0.15
Peak HR (bpm)	147.8 ± 22.7	131.9 ± 22.3	148.2 ± 19.7	162.0 ± 14.5	<0.001
RER	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1	<0.001
VE/VCO_2 slope	31.0 ± 6.0	35.5 ± 6.8	30.4 ± 5.5	29.1 ± 4.8	<0.001
LT time (sec)	485.4 ± 282.8	323.8 ± 242.5	520.0 ± 233.8	610.3 ± 227.4	<0.001
VD/VT	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.3 ± 0.0	0.48
$PetCO_2$ (mmHg)	36.9 ± 5.1	35.5 ± 5.6	37.4 ± 4.7	37.6 ± 4.8	<0.001
Chronotropic incompetence	95 (22.4)	66 (47.1)	24 (16.9)	5 (3.5)	<0.001
Abnormal HRR	58 (13.7)	40 (28.6)	13 (9.2)	5 (3.5)	<0.001
HFA-PEFF scores					<0.001
Intermediate	315 (74.3)	85 (60.7)	103 (72.5)	127 (89.4)	
High	109 (25.7)	55 (39.3)	39 (27.5)	15 (10.6)	

Note: Data are presented as mean ± SD, median [interquartile range], or n (%).
Abbreviations: BMI, body mass index; CPET, cardiopulmonary exercise testing; E, early diastolic mitral inflow velocity; E', early diastolic septal tissue doppler velocity; eGFR, estimated glomerular filtration ratio; HR, heart rate; HRR, heart rate recovery; LAVI, left atrial volume index; LT, lactate threshold; LVMI, left ventricular volume index; NT-proBNP, N-terminal pro B-type natriuretic peptide; $PetCO_2$, end tidal carbon dioxide; RAS, renin-angiotensin system; RER, respiratory exchange ratio; SBP, systolic blood pressure; VD/VT, dead space/tidal volume ratio; VE/VCO_2 slope, minute ventilation-carbon dioxide output relationship; VO_{2peak}, peak oxygen consumption.

Figure 1. Kaplan-Meier curves for the cumulative incidence of incident chronic kidney disease based on the VO_{2peak} categories.



Notes: Statistical analysis was performed using the log-rank test.
Abbreviations: VO_{2peak}, peak oxygen consumption.

FR-PO809

Measurement Properties of the Most Common Performance-Based Measures of Physical Function in CKD: A Systematic Review

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Background: There is wide heterogeneity in physical function tests for clinical and research use in chronic kidney disease (CKD). The aim of this review was to identify and evaluate the most frequent physical function measures in terms of clinimetric properties.

Methods: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, CINAHL, Scopus, and Web of Science were searched from inception to March 2022, identifying studies which evaluated a clinimetric property (validity, reliability, measurement error, responsiveness) of an objectively

measured performance-based physical function outcome. All ages and any stage of CKD were included. The most common tests (defined as having 4 or more studies) are described in terms of reliability and validity.

Results: 50 studies with 21,315 participants were included, the majority were HD. Clinimetric properties were reported for 22 physical function tests; the following were most common: Hand grip strength (HGS), six minute walk test (6MWT), V02 peak, short physical performance battery (SPPB), gait speed, Sit to stand test-60 (STS-60), timed up and go (TUG), STS-5 and incremental shuttle walk test (ISWT). Very few studies reported properties of criterion (ISWT) and responsiveness (V02 peak and 6MWT).

Conclusions: The SPPB demonstrates high GRADE evidence for construct validity, reliability and measurement error. The next best tests include: 6MWT and TUG with high GRADE for reliability and measurement error. This review is an important step towards standardizing a core outcome set of tools to measure physical function in research and clinical settings for CKD.

Physical function tests GRADE evidence

Physical function test (number of studies)	Construct Validity	Reliability	Measurement Error
HGS (13)	Low	Low	Moderate
6MWT (11)	Low	High	High
SPPB (10)	High	High	High
Gait speed (8)	Moderate	Moderate	Very Low
STS-5 (8)	High	Moderate	Low
V02 peak (8)	Low	Low	Low
TUG (7)	Moderate	High	High
STS-60 (6)	Moderate	High	Moderate
STS-30(4)	Low	High	Moderate
ISWT (4)	Moderate	Low	Low

FR-PO810

Association of Myosteatosis with Poor Physical Function and Mortality in Hemodialysis Patients

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Background: Skeletal muscle area, which is measured by computed tomography (CT), can be divided into normal attenuation muscle area with little fat infiltration and low-attenuation muscle area with high fat infiltration. Herein, we aimed to investigate the differential effects of normal and low-attenuation muscles at the L3 vertebra and myosteatosis on physical function and mortality in patients undergoing hemodialysis.

Methods: All patients underwent non-enhanced abdominal CT. The skeletal muscle index (SMI), normal attenuation SMI (NSMI), low attenuation SMI (LSMI), and fatty muscle fraction (FMF) at the L3 vertebra were determined (as shown in figure 1). Physical function was measured using handgrip strength, gait speed, sit-to-stand in 60 s (STS-60) test, and instrumental activities of the daily living scale.

Results: There were 101 patients on maintenance hemodialysis (mean age 52.73, 39.6% women), and 19 patients died during a median follow-up time of 26.2 months. The NSMI was moderately positively correlated with handgrip strength, gait speed, and STS-60 score (rho:0.363 to 0.542;$P < 0.001$); In contrast, the LSMI was negatively correlated with all physical function measures (rho: – 0.439 to -0.317;$P < 0.001$). In multivariate regression analyses, larger NSMI, lower LSMI, and lower FMF than SMI were significant predictors of better physical performance. Moreover, according to the Kaplan–Meier curve and Cox regression analysis, high FMF (aHR 4.09, 95% CI [1.36, 12.32]) and LSMI (aHR 4.28 [1.42,12.89]) were significantly associated with high mortality.

Conclusions: This study demonstrated distinct effects of normal and low-attenuation muscles on physical function. Moreover, it highlights the importance of myosteatosis in determining poor physical performance and predicting mortality in patients undergoing hemodialysis.

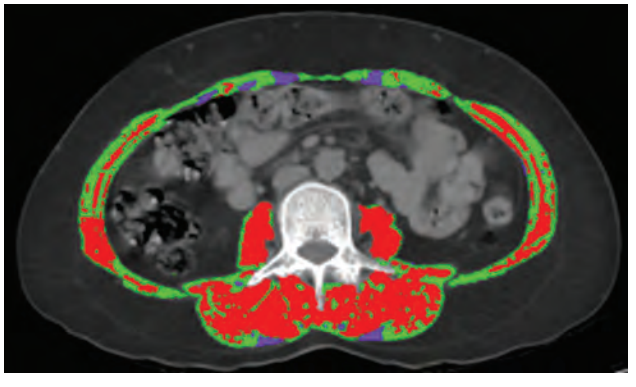

Figure 1. Muscle quality map at L3 derived from abdominal CT using region growing mode. The axial CT images at L3 were segmented into NAMA (red), LAMA (green), and IMAT (purple).

FR-PO811

Dialysis Malnutrition Score and Handgrip Strength with Quality of Life Among Patients on Maintenance Hemodialysis in Cebu City, Philippines

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Background: Malnutrition is common in hemodialysis patients and is a powerful predictor of morbidity and mortality. End stage renal disease (ESRD) has been shown to negatively affect the Quality of Life (QoL) of patients. Among Chronic Kidney Disease (CKD) patients on maintenance hemodialysis, there is a considerable effect on the functional state and QoL. Malnutrition in CKD patients is one of the factors that afflicts QoL.

Methods: One hundred eight (108) patients on maintenance hemodialysis in a tertiary hospital were assessed nutritionally by DMS and HGS while the overall perception QoL and health was assessed using World Health Organization Quality of Life - BREF (WHOQoL-BREF) questionnaire. Kendall's tau was used to determine whether there is a correlation between DMS and HGS with quality of life scores. A p-value of <0.05 will be considered as statistically significant.

Results: Based on DMS, 87% of patients had mild to moderate malnutrition and 64.8% had renal cachexia based on HGS. Those with poor nutritional status in DMS showed significant decrease in overall perception of their quality of life p = 0.003, quality of health p = 0.026, physical p = 0.013 and environmental domains p = 0.044 of WHOQoL. Handgrip score however did not have any correlation with the overall QoL, perception of general health and on the four domains.

Conclusions: DMS and HGS are simple and accessible nutritional assessment tools to detect malnutrition among hemodialysis patients. DMS correlates with QoL with higher DMS reflecting malnutrition and the overall quality of life decreases. Early detection of malnutrition can prevent further health deterioration with nutritional interventions and therefore improve QoL in the aspects they are most affected.

Table 1. DMS and HGS on Quality of Life ($n = 108$)

Variables		DMS	p-value	HGS	p-value
Overall Quality of Life		-0.265	0.003	-0.001	0.994
General perception of health		-0.219	0.026	0.098	0.311
4 Domains of QoL	Physical Domain	-0.098	0.013	0.182	0.060
	Psychological Domain	-0.219	0.262	0.162	0.094
	Social Domain	-0.209	0.298	0.176	0.068
	Environmental Domain	0.094	0.044	-0.018	0.857

Table 1. DMS and HGS on Quality of Life

FR-PO812

Effect of Leucine Supplementation and Resistance Exercise for Prevention of Sarcopenia in Patients on Maintenance Hemodialysis

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Background: Sarcopenia frequently occurs in hemodialysis patients up to 40%. We examined the effects of supplementation of leucine amino acid combined with resistance exercise on preventing sarcopenia in patients on maintenance hemodialysis (MHD).

Methods: This was a single center, prospective, single-arm pilot study. 22 non-sarcopenic patients on MHD at our hospital were enrolled. During the intervention period (first 12 weeks), participants were provided with daily 6g of leucine (3g in capsule and 3g via beverage) and a protocol for daily resistance exercise. Both interventions were stopped during following 12 weeks. Bioimpedance analysis (BIA), handgrip strength (HGS), short physical performance battery (SPPB), serum chemistry, immunophenotype of peripheral blood mononuclear cells were examined at baseline, 12 week and 24 week. Participants who expressed 5% or more improvement in each parameter were defined as responders.

Results: Among 22 patients, mean age was 55±11.8 years and hemodialysis vintage was 4.7±3.5 years. 7 patients (31.8%) were female. 21 patients (95.4%) showed improvement in at least one or more parameters. At 12 week, the number of responders were 14(63.5%) for skeletal muscle index and 7(31.8%) for grip strength. Baseline low grip strength (<35.0kg) was the strongest predictor of improvement in grip strength (AUC 0.933). Increase in grip strength was significant in females (7.6±8.2 vs -1.6±7.2%, p=0.03), in age over 60 (5.3±6.2 vs. -1.4±9.1%, p=0.04), and with higher exercise adherence (6.8±7.7 vs -3.2±6.4%, p=0.004). The number of responders were 13 patients (59.1%) for gait speed and 14(63.5%) for sit-to-stand time. Baseline low hemoglobin(<10.5 g/dL) and low hematocrit lower(<30.8%) were predictors of improvement in sit-to-stand time (AUC

0.862 and 0.848, respectively). Immunophenotypic analysis found that the intervention tended to increase naïve/memory $CD8^+$ T cell ratio (from 1.2±0.8 to 1.4±1.1, p=0.07).

Conclusions: Supplementation of leucine amino acid combined with resistance exercise contributed to improvement of muscle mass, muscle strength, and physical performance in certain group of non-sarcopenic hemodialysis patients. This intervention may have effect on prevention of sarcopenia in old-age, anemic, female patients on MHD with lower HGS.

Funding: Government Support - Non-U.S.

FR-PO813

Electric Acupuncture Mimics Exercise to Ameliorate Muscle Wasting by Promoting Angiogenesis and Neurogenesis in CKD

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Background: Our previous study demonstrated that acupuncture with low frequency electrical stimulation (Acu/LFES) attenuates skeletal muscle atrophy by improving muscle progenitor cells regeneration. The present study examines whether Acu/LFES improves revascularization, innervation, and protein anabolism in muscle of chronic kidney disease (CKD) mice.

Methods: CKD was induced by the 5/6 nephrectomy. Acu/LFES was applied in hindlimbs of CKD mice. Acu/LFES points were selected by WHO Standard Acupuncture classification. Proteins from hindlimb (gastrocnemius), forelimb (triceps brachii) and back (longissimus) muscles were isolated at 0.5, 6, 24, 48 and 72 hours after Acu-LFES therapy. Protein synthesis was measured by the surface-sensing of translation (SUnSET) assay. Exosomes were isolated using serial centrifugation and subjected to microRNA deep sequencing. NanoSight was used to measure exocomes concentration. The microRNA library was validated using a High Sensitivity DNA chip.

Results: Protein synthesis was enhanced in the Acu/LFES-treated gastrocnemius; however, in non-Acu/LFES treated muscles, triceps brachii and longissimus, protein synthesis was also significantly increased after treatment. These increases were accompanied with increased phosphorylation of mTORC1 and 4EBP-1. Myogenesis markers, Pax7, myoD and myogenin were significantly upregulated. The mRNA expression of PDGF and ENO2 were enhanced by Acu/LFES. The protein amount of Igf-1, Igf-1 receptor, VEGF (a protein that stimulates the formation of blood vessels), and peripherin (expressed mainly in the nervous system) were also increased by Acu/LFES. Deep sequencing revealed that miR-5107-5p and miR-30-5p were sharply decreased in serum exosomes of Acu/LFES mice. Using a luciferase reporter assay, we demonstrated that miR-5107-5p directly inhibits VEGF, and miR-30-5p inhibits ENO2, which suggests a mechanism in which downregulation of these two miRNAs results in expanding VEGF and ENO2 leading to accelerate revascularization and innervation.

Conclusions: Acu/LFES treatment increases myogenesis, angiogenesis and neurogenesis, as well as protein synthesis. Acu/LFES inhibits miR-5107 and miR-30, resulting in increased VEGF and ENO2 contributing to these processes. Our study provides strong mechanistic insights for Acu/LFES treatment of muscle atrophy in CKD.

Funding: Private Foundation Support

FR-PO814

The Practices and Views of US and Canadian Nephrologists, Nurses, and Allied Health Professionals Regarding Exercise and Physical Activity for People Receiving Peritoneal Dialysis

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Background: In the US and Canada people receiving peritoneal dialysis (PD) are frequently sedentary and experience poor physical function. This creates clinical challenges because basic physical function is required to maintain independence for this home-based therapy. The aim of this study was to explore exercise-related practices and perceptions of nephrologists, PD nurses and allied health clinicians across the US and Canada.

Methods: Secondary analysis of an international cross-sectional 13-item web-based survey of PD health professionals, exploring perspectives and practices regarding exercise for people receiving PD. Recruitment in the US and Canada was done through professional nephrology networks including the American Society of Nephrology, the Canadian Society of Nephrology, the American Nephrology Nurses' Association and the Canadian Association of Nephrology Nurses and Technicians.

Results: 211 clinicians (88 nephrologists, 87 nurses and 36 allied health professionals) responded from the US (49%) and Canada (51%) with most (72%) reporting greater than 2 years PD experience. Most respondents (89%) believed PD patients could perform more exercise than they currently do. Most respondents (86%) agreed that structured exercise programs would be beneficial for people receiving PD. Eighty-six percent stated that PD patients would benefit from exercise professionals, however, only 27% of Canadian and 4% of US clinics had exercise professionals involved in programs. Sixty-one percent agreed and 34% were unsure whether people receiving PD could perform abdominal strengthening exercises safely. Seventy-three percent of PD programs had formal guidelines for swimming, 78% for lifting, 63% for falls, and 78% for physical activity resumption following PD catheter insertion.

Conclusions: US and Canadian PD health professionals recognize the importance of exercise in people receiving PD and most programs have exercise-related policies. Even though there are few dedicated PD exercise programs in the US and Canada, most clinicians believed that exercise professionals and structured exercise programs would benefit people receiving PD.

FR-PO815

Exercise Has Mode-Specific Effects on Musculoskeletal Health in a Rat Model of CKD-MBD

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Background: Chronic kidney disease (CKD) progression is associated with deterioration of musculoskeletal health. We hypothesized that voluntary wheel running as compared to forced treadmill would preferentially impact musculoskeletal health in CKD.

Methods: We used a progressive, naturally occurring, CKD rat model (Cy/+ rat) (n=10-12/gr): 1) normal littermates (NL), 2) Cy/+ (CKD) rats, 3) CKD-treadmill (CKD-TM) 4) CKD-wheel (CKD-W). For 10 weeks treadmill rats ran 40 minutes/day, 4 days/week, for 0° grade, wheel rats had 24/7 free access; training volumes similar between the modes. Termination, and blood and tissue collection occurred at 33 weeks. Outcome measures were maximal muscle torque and fatigue, maximal running endurance, and tibia cortical bone morphology. Data analysis included one-way ANOVA with Tukey's multiple comparisons test.

Results: Overall CKD versus NL impaired cortical bone with increased porosity (mean 0.18±0.12 NL, 2.03±1.8 CKD; $p<0.05$), and reduced area (mean 6.64±0.43 NL, 5.77±0.58 CKD; $p<0.01$) and thickness (mean 0.48±0.30 NL, 0.34±0.11 CKD; $p<0.001$). Skeletal muscle function worsened in CKD (vs NL) with reduced maximal torque (mean 57.3±7.7 NL, 47.6±9.3 CKD; $p<0.05$) and increased fatigue (mean 42.8±9.9 NL, 56.5±8.7 CKD; $p<0.01$). Running endurance was significantly reduced in CKD (mean 24.2±3.3 NL, 20.8±4.5 CKD; $p<0.05$). Treadmill running increased maximal torque (mean 47.6±9.3 CKD, 57.1±8.8 CKD-TM; $p<0.05$) and running endurance (mean 20.8±4.5 CKD, 25.9±3.9 CKD-TM; $p<0.05$) when compared to CKD. Wheel running significantly improved maximal running endurance (mean 20.8±4.5 CKD, 24.7.03±2.9 CKD-W; $p<0.05$), but did not impact maximal muscle torque, muscle fatigue or cortical bone parameters.

Conclusions: CKD deteriorates the musculoskeletal system through cortical bone loss, and reduced muscle strength and greater muscle fatigue. To determine optimal delivery of exercise we compared treadmill to wheel running. Both methods improved maximal running endurance after 10 weeks; however, only treadmill running improved maximal muscle strength. These marginal improvements mimic what is seen in clinical meta-analyses and emphasizes the need for novel approaches to exercise prescription and/or the need for pharmaceutical or nutraceutical treatments to improve musculoskeletal health in advanced CKD.

Funding: NIDDK Support

FR-PO816

Progressive Individualized Exercise Intervention Impacted the Cecal Microbiota Composition in a Rat Model of CKD

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Background: Exercise interventions are recommended to improve the musculoskeletal and cardiopulmonary health in chronic kidney disease (CKD). Exercise has been shown to impact the gut microbiome, but data in CKD is limited. We have previously shown that bone health and serum biochemistry was improved following 10 weeks of wheel running and this study hypothesized that treadmill running will improve gut microbiome in the Cy/+ rat model of CKD.

Methods: We examined the following groups (n=6-8/group): 1) Normal littermates (NL); 2) CKD rats; 3) CKD + treadmill exercise (CKD+EX). The exercise intervention was performed for at a 5° grade, 50 minutes/day, 4 days/week for 10 weeks. The running speed was progressively increased if the rat was in the upper 1/3 of the belt in the final 10 minutes; maintained if in middle; and reduced if in lower 1/3. Treatments began at 22 weeks until 32 weeks of age (moderate to severe CKD, respectively). Cecal digesta was collected at euthanasia at 32 weeks of age and the V4 region of the 16S rRNA gene was sequenced and analyzed via QIIME2.

Results: Richness of the microbiota (alpha-diversity) was not impacted by CKD phenotype or exercise. The overall microbial community (beta-diversity) was not different between NL and CKD; however, CKD+EX was different from NL and CKD (PERMANOVA corrected $p<0.04$). There was a higher relative abundance of *Bacteroides, Ruminococcus,* unclassified Desulfovibrionaceae, unclassified Peptostreptococcaceae, and *Prevotella* (corrected $p<0.05$) with exercise. Taxa whose relative abundance was lowered by the exercise intervention included *Lactobacillus, Akkermansia,* and *Blautia.*

Conclusions: A personalized progressive treadmill intervention impacted the cecal microbiota. Future studies should aim at examining the impact of exercise on microbially-derived uremic toxins and outcomes in CKD.

Funding: NIDDK Support

FR-PO817

Differences in Subjective Global Assessment Score and Mortality Risk Across Race and Ethnicity in a Prospective Hemodialysis Cohort

Ji Hoon Yoon,[1] Yoko Narasaki,[1] Seungsook You,[1] Masaki Okazaki,[1] Adnan M. Ismail,[1] Diana Tran,[1] Man Kit Michael Siu,[1] Sara S. Kalantar,[1] Parth Kumar,[1] Silvina Torres Rivera,[1] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh,[2] Connie Rhee.[1] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Harbor-UCLA Medical Center, Torrance, CA.*

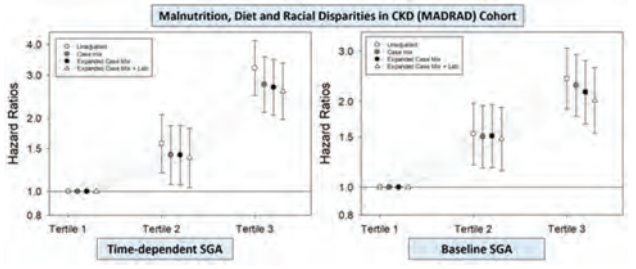
Background: Protein-energy wasting is a major predictor of mortality in advanced CKD patients, and clinical guidelines endorse use of the Subjective Global Assessment (SGA) survey as a validated measure of nutritional status in HD patients. We examined the relationship between SGA score and survival in a diverse HD cohort and how associations differ across race/ethnicity.

Methods: We evaluated 1018 HD patients from the prospective NIH MADRAD Study recruited across 18 dialysis clinics who underwent protocolized SGA surveys over 10/2011-12/2021. Using Cox models adjusted for expanded case-mix+laboratory covariates, we examined associations of time-dependent and baseline SGA score categorized as tertiles with all-cause mortality risk. We then examined differential SGA score—mortality associations across race/ethnicity using interaction tests.

Results: The mean±SD age of the cohort was 55±14 years, among whom 44% were female; and 53%, 27%, 10%, and 9% were Hispanic, Non-Hispanic (NH) Black, Asian, and NH White. In analyses of time-dependent SGA score, incrementally higher (worse) tertiles were associated with higher mortality (ref: Tertile 1): HRs (95%CIs) 1.41 (1.07, 1.87) and 2.68 (2.06, 3.48), respectively, for Tertiles 2 and 3, respectively (Fig). Similar findings were observed in baseline SGA analyses. Subgroup analyses showed that Tertile 3 of time-dependent SGA scores were associated with higher mortality in all racial/ethnic groups, with the strongest point estimates observed in Hispanic and NH White patients: HRs (95%CIs) 1.91 (1.59, 2.30), 1.47 (1.19, 1.82), 1.50 (1.01, 2.24), and 2.07 (1.29, 3.32) for Hispanic, NH Black, Asian, and NH White patients, respectively (p-interaction <0.001).

Conclusions: In a multicenter prospective HD cohort, higher (worse) SGA scores were associated with worse survival in all racial/ethnic groups. Further studies are needed to determine personalized approaches to optimizing nutritional status in diverse HD populations.

Funding: NIDDK Support



FR-PO818

Goal Attainment Scale as an Outcome Measure in a Randomized Controlled Trial of Lifestyle Interventions

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Background: Goal attainment scale (GAS) is a validated patient-reported outcome measure (PROM) that can be used to quantitate achievement of individualised patient goals. GAS has not been assessed as a PROM in lifestyle intervention trials. We report the GAS findings of a predefined sub-analysis of the U-DECIDE study, which assessed the feasibility of digital health-assisted lifestyle interventions (DHALI) in people with kidney and liver disease.

Methods: Adults with kidney or liver disease and metabolic syndrome were randomized to either usual care (UC) or DHALI+UC. All participants received goal setting support, a wearable activity monitor, and individualized dietitian counselling. The DHALI+UC group could opt-in to receive exercise and/or dietetic video consultations; had access to nutrition and exercise applications; and text-message education. Pre-randomization, participants were assisted by a clinician to generate up to 2 SMART (specific, measurable, attainable, realistic and timely) lifestyle goals. Possible outcomes ('much better than expected', 'better than expected', 'as expected', 'worse than expected', 'much worse than expected') for each goal were predetermined and quantified by the participants. The ΔGAS score was calculated for each participant at the end of the trial by using a validated formula which incorporated the importance, difficulty and outcome scores of each goal.

Results: 67 participants were randomized, 46 (70%) with kidney disease. Mean age was 51 ± 13 years, 56% were men. Participants set weight loss (46%), followed by fitness (29%), dietary (15%) and body composition (5%) goals. 66 (99%) participants completed both goal setting (at baseline) and outcome review (at 26 weeks) sessions, each taking <10 minutes per patient. Though underpowered for this outcome, there was no significant difference in ΔGAS between UC and DHALI+UC groups (7 vs 6, p = 0.578) over time.

Conclusions: Participants commonly selected weight loss and fitness goals. GAS is a feasible, convenient and inexpensive PROM that can be used to quantitate change in patient determined lifestyle goals.

FR-PO819

Performance and Self-Perceived Restless Leg Syndrome Associated with Use of High-Flux Dialyzers: Results from the eMPORA III Trial

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Background: The eMPORA III study was a prospective, multicenter, crossover trial with 4-week randomized treatment sequences comparing the performance and hemocompatibility of dialyzers (FX CorAL 600 vs two comparators) in post-dilution online hemodiafiltration (HDF). Primary outcome was beta-2 microglobulin (B2M) removal and self-perceived restless leg syndrome (RLS) was also assessed using the International RLS Study Group Rating Scale survey.

Methods: Medically stable adult HDF patients with a functioning fistula/graft were recruited from 8 centers in Germany, Czechia, Hungary (NCT04714281). B2M removal rate (B2M RR) pre-HDF vs 240 min was measured in week 3 of each 4-week treatment period. RLS survey was administered at baseline and the end of periods. Survey captures the severity and impact of symptoms in the prior week on a 0 (no RLS) to 40 (very severe RLS) point scale, and has 2 subscales. Global RLS scores >10 points imply moderate-to-very severe RLS symptoms. Effect of dialyzers were estimated using a linear mixed model adjusted for center and patient in the intention-to-treat (ITT) group.

Results: Study enrolled 82 subjects (76 ITT group, mean age=67.0±15.6 years, 26.3% female, 34.2% diabetes). FX CorAL 600 showed a +0.60±0.39% and +1.82±0.38% higher B2M RR vs FX CorDiax 600 (non-inferiority p<0.0001; superiority p=0.0606) and xevonta Hi 15 (non-inferiority p<0.0001; superiority p<0.0001). Mean global RLS score was 3.2±6.24 (**Figure 1**). FX CorAL 600 showed a +0.24±0.54 and +0.33±0.54 point change in global RLS scores vs FX CorDiax 600 (p=0.65) and xevonta Hi 15 (p=0.54); consistent findings were found for subscale scores.

Conclusions: FX CorAL 600 provided a higher B2M RR than comparator dialyzers. RLS symptoms were consistent between dialyzer types. Average scores indicate mild-to-no RLS among trial participants, yet some patients reported severe symptoms. Higher middle molecule clearance may not affect RLS symptoms, but more investigations are needed with longer follow-up and should consider patients with moderate-to-severe symptoms.

Funding: Commercial Support - Fresenius Medical Care

Figure 1: International Restless Legs Syndrome Study Group Rating Scale by Dialyzer

Dialyzer		FX CorAL 600	FX CorDiax 600	xevonta Hi 15	Overall
Patient n		74	71	76	82
Observation n		71	71	76	218
Global RLS	Mean±SD	3.4±6.66	3.2±5.89	2.9±6.24	3.2±6.24
	Min, Median, Max	0.0, 0.0, 28.0	0.0, 0.0, 19.0	0.0, 0.0, 25.0	0.0, 0.0, 28.0
Severity	Mean±SD	2.2±4.23	2.1±3.81	1.9±4.14	2.1±4.05
	Min, Median, Max	0.0, 0.0, 18.0	0.0, 0.0, 12.0	0.0, 0.0, 19.0	0.0, 0.0, 19.0
Impact on daily living	Mean±SD	0.7±1.65	0.6±1.29	0.6±1.38	0.6±1.44
	Min, Median, Max	0.0, 0.0, 7.0	0.0, 0.0, 5.0	0.0, 0.0, 6.0	0.0, 0.0, 7.0

Max, maximum; min, minimum; N, number of patients; RLS, Restless Legs Syndrome; SD, standard deviation.

FR-PO820

Exploring Health-Related Decision-Making in Advancing CKD

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Background: Patients with chronic kidney disease (CKD) often rely on family caregivers to help cope with illness and make health-related decisions. While many patients desire detailed information about their disease and prognosis, clinicians often report not sharing prognostic information to maintain hope. These decision-making trends leave patients and caregivers under-informed, potentially resulting in missed opportunities for them to take greater ownership of their disease management. Given the scarcity of literature describing health-related decision-making before initiating renal replacement therapy, we undertook a study to describe the needs, challenges, and experiences of patients with CKD and their family caregivers when making health-related decisions.

Methods: A qualitative descriptive study was conducted with individuals with Stage 3 or higher CKD, including end-stage and their family caregivers. Recruitment occurred from April 2022 to December 2022 at two outpatient nephrology clinics within an urban academic medical center. Data was collected via one-on-one, semi-structured interviews. A community advisory group of CKD patients and clinicians developed the guide. Data were analyzed using thematic analysis.

Results: Patient and caregiver participants (*N*=30) were older (over 60; *n*=20), and the majority were female (*n*=21). Black (*n*=14) and White (*n*=16) individuals were represented almost evenly. Three themes describing the decision-making experience were identified: 1) decisions triggered by declining health and broad in scope, 2) challenges to decision-making, and 3) factors influencing decision-making. Participants' experiences demonstrated that decisions were triggered when health declined. Yet, decisions that

impact disease progression were being made as early as stage 3. Decision-making was made difficult due to poor resource utilization and lack of information. Yet, the structure and nature of the medical appointment and resources served to remove challenges by assisting with enhanced communication and greater self-advocacy.

Conclusions: This study's findings demonstrate the need for decision-support interventions upstream of advanced illness that train patients and caregivers to be empowered participants in answer-seeking behaviors that enhance their ability to make informed patient-centered decisions.

Funding: Private Foundation Support

FR-PO821

Association Between the Fibrosis-4 (FIB-4) Score and ≥20% Decline in the Estimated Glomerular Filtration Rate in the General Population with Abdominal Adiposity

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Background: The prevalence of chronic kidney disease is increasing in patients with non-alcoholic fatty liver disease (NAFLD), and obesity is a known risk factor for both conditions. The fibrosis index based on four factors (FIB-4) score, a non-invasive indicator, is strongly associated with liver injury and fibrosis in patients with NAFLD. The association between the FIB-4 score and the estimated glomerular filtration rate (eGFR) slope remains unclear. In this study, we investigated whether the FIB-4 score is associated with eGFR decline in the general population.

Methods: This retrospective observational cohort study included individuals who underwent health check-ups across Japanese companies between 2009 and 2014. Participants who consumed ≥30 g of alcohol/day were excluded. An FIB-4 score of ≥1.30, which indicates moderate-to-severe liver fibrosis, was set as the cut-off value. Propensity score matching based on FIB-4 scores (<1.30, ≥1.30) was performed to eliminate biases associated with covariances across participants' backgrounds.

Results: We recruited 11,296 participants at baseline; however, 5943 participants were excluded, and data of 464 participants were analyzed after propensity score matching. Participants' mean age was 50 years, mean eGFR was 74.7 mL/min/1.73 m^2, and the mean waist circumference (WC) was 81.8 cm. FIB-4 scores ≥1.30 were significantly associated with ≥20% decline in the eGFR over 5-year follow-up (odds ratio [OR] 3.94, 95% confidence interval [CI] 1.29–12.06). Subgroup analysis showed that an FIB-4 score ≥1.30 was significantly associated with ≥20% decline in eGFR 5 years later in participants with WC ≥85 cm (OR 8.78, 95% CI 1.05–73.53) but not in those with WC <85 cm (OR 2.70, 95% CI 0.70–10.38).

Conclusions: Our findings show that an FIB-4 score ≥1.30 was associated with ≥20% decline in the eGFR 5 years later. Abdominal adiposity accompanied by an FIB-4 score ≥1.30 was a particularly important risk factor for eGFR decline.

FR-PO822

Subcutaneous Fat Area Can Predict Two-Year Survival in ESRD Patients Initiating Dialysis

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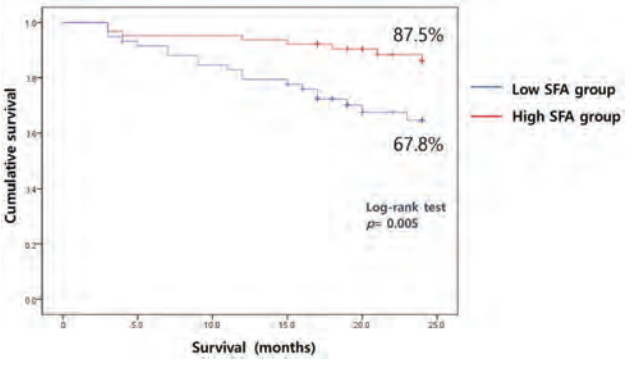
Background: Obesity is a risk factor for increased cardiovascular disease and diabetes in general population. However, the "obesity paradox" is observed in chronic disease such as ESRD patients. BMI does not discriminate between subcutaneous fat, visceral fat or muscle. Either overhydration or PEW state in the initial dialysis patient makes it difficult to properly assess BMI and muscle mass, the initial measurement of this modality difficult to assess the patient's prognosis. Fat tissue can be assessed relatively accurate than muscle even in patients starting dialysis. However, the association of fat tissue or the distribution of fat and mortality in ESRD patient not established yet. The aim of this study was to investigate the association subcutaneous fat and all-cause mortality in initial dialysis patient.

Methods: total 123 patient newly initiated maintenance hemodialysis who underwent abdominal CT were enrolled between January 2018 and June 2021. Patient with age ≥18year were include. Subcutaneous fat area (SFA) were determined using abdominal CT. The analysis was conducted using open-source software to identify SFA in CT images for body composition analysis.

Results: During the 2-year follow-up period, the Kaplan–Meier survival rates were 67.8%, 87.5% in low SFA group (group 1) and high SFA group (group 2) (log rank p=0.005), respectively (Figure1). In Cox proportional hazards analysis, adjusting for (Model 1)+ CONUT, PNI as nutritional risk evaluation, low SFA group showed high risk for all-cause mortality (HR 2.979, 95% CI 1.137-7.808, p= 0.026) (Table 1).

Conclusions: In conclusion, low SFA increases the risk of 2-year all-cause mortality, suggesting that early SFA analysis may be predictive of mortality in patient risk analysis in initial dialysis populations.



K-M survival curve between SFA groups

	Hazard ratio (95% CI)	p value
Crude	3.105 (1.356-7.113)	0.005
Model 1	3.596 (1.391-9.292)	0.008
Model 2	2.979 (1.137-7.808)	0.026

- **Model 1**: age, sex, SFA grade, visceral fat, DM, HTN, Hb, BUN, Cr, eGFR, total protein, albumin, glucose, Tchol, TG, CRP, BMI
- **Model 2**: Model 1 + CONUT, PNI (nutrition score)

Cox regression for SFA groups

FR-PO823

Association of Weight-Adjusted Waist Index with Abdominal Aorta Calcification and Mortality in Hemodialysis Patients

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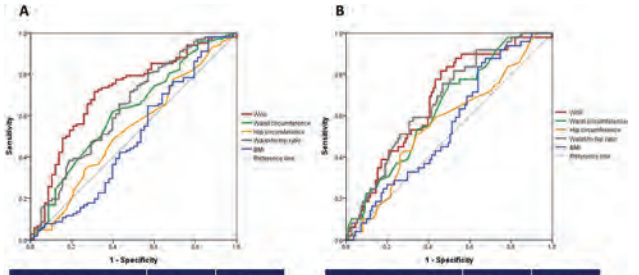
Background: Weight-adjusted-waist index (WWI) is a novel indicator of central obesity, and is associated with abdominal aortic calcification (AAC) and mortality in the general population. However, obesity paradox has been described in patients with kidney disease. The association of WWI with AAC and mortality remains uncertain in hemodialysis (HD) patients.

Methods: This study included 161 patients on maintenance HD >3 months. WWI was determined as waist circumference divided by the square root of weight. Severity of AAC was quantified by the AAC score measured from lateral lumber radiography. The association between WWI and moderate or severe AAC was examined using logistic regression analysis. Cox regression analysis was performed to investigate the association of WWI with all-cause mortality. The area under the receiver operating characteristic curve (AUC) was used to compare the ability of WWI and other obesity indices to predict AAC and mortality.

Results: We found 103 HD patients had moderate or severe AAC. During a median follow-up of 5.0 years, 50 deaths occurred. In multiple logistic regression, the highest WWI category (3rd tertile >11.40 cm/√kg) (OR=4.38, 95% CI: 1.39–13.78, *p*=0.012) was associated with moderate or severe AAC. Compared to the lowest WWI category, 2nd tertile WWI (10.76–11.39 cm/√kg) (HR=3.25, 95% CI: 1.18–8.93, *p*=0.022) was significantly associated with increased risk of all-cause mortality in multivariate-adjusted Cox analysis. Furthermore, WWI had the greatest AUC for predicting moderate or severe AAC (AUC=0.713) and all-cause mortality (AUC=0.667) when compared with body mass index, waist circumference, hip circumference, and waist-to-hip ratio.

Conclusions: These findings indicated that WWI may serve a valuable indicator for identifying moderate or severe AAC and predicting mortality among maintenance HD patients.



Anthropometric indices	AUC	95% CI
WWI	0.713	0.629–0.798
Waist circumference	0.617	0.526–0.709
Hip circumference	0.532	0.437–0.626
Waist-to-hip ratio	0.641	0.550–0.732
BMI	0.489	0.390–0.587

Anthropometric indices	AUC	95% CI
WWI	0.677	0.590–0.763
Waist circumference	0.639	0.550–0.727
Hip circumference	0.561	0.465–0.657
Waist-to-hip ratio	0.673	0.588–0.759
BMI	0.552	0.461–0.644

Area under ROC curves of different obesity indices for predicting (A) moderate or severe AAC and (B) all-cause mortality

FR-PO824

Successful Bariatric Laparoscopic Sleeve Gastrectomy in a Home Hemodialysis Patient Led to Reduced Hemodialysis Frequency

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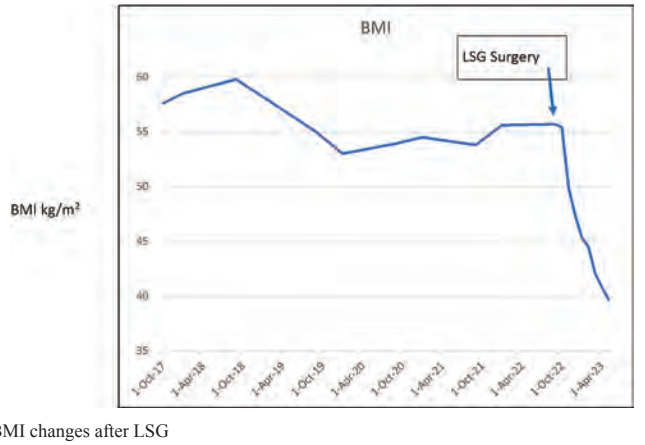
Introduction: Bariatric surgery (BS) is an established treatment for achieving weight loss. Patients with kidney disease and not on dialysis had a reduction in mortality compared to matched controls with vertical laparoscopic sleeve gastrectomy (LSG) being the safer option compared to Roux-en-Y gastric bypass. Use of BS in dialysis patients is not common due to fears of complications including high post-operative mortality and myocardial infarction. Furthermore, observational studies suggest a protective association of elevated BMI versus death in HD patients, although this has not been consistently observed in peritoneal dialysis patients. Our patient demonstrated that BS while on HHD is a desirable option to achieve target weight loss.

Case Description: A 36-year-old female started HHD for anuric hypertensive end stage renal disease 5.5 years before LSG. Before LSG, she did HHD 5 times a week to maintain adequacy. The renal and bariatric teams worked closely to provide a unified approach to her diet pre- and post-surgery, which included fluid diets and progression to solids. Medications and supplements were also adjusted to meet both dialysis and bariatric guidelines. Since LSG, she has exhibited progressive weight loss of 26% over 6 months (Figure), while maintaining her nutritional status. We reduced HHD frequency from five to four times weekly to mitigate intradialytic hypotension, and still maintained HD adequacy. She is more active, more energetic, takes longer walks, twice daily, and now works in her garden.

Discussion: Our HHD patient had successful bariatric surgery with 26% weight loss in 6 months and can now be listed for kidney transplant. Despite a paucity of literature on intentional approaches to weight loss in ESRD, LSG is increasingly used for patients with kidney failure and severe obesity. More research is needed to assess long-term cardiovascular and kidney transplant outcomes following BS.



BMI changes after LSG

FR-PO825

Poor Vitamin K Status and Inflammation in Patients with CKD

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Background: Vitamin K is vital to cardiovascular and bone health and can mitigate inflammation. Vitamin K inhibits the activation of NF-κB, which seems related to vitamin K-dependent proteins, inhibiting the production of IL-6 by macrophages. Patients with CKD frequently present a deficiency of vitamin K. Considering the high mortality rate linked to cardiovascular disease (CVD), reduced quality of life and poor outcomes related to inflammation, it is essential to understand the relationship between vitamin K deficiency and inflammation, raising the possibility of new therapeutic targets in treating CKD-induced CVD. This study aimed to evaluate the correlation between vitamin K status and inflammation in patients with CKD (non-dialysis and hemodialysis - HD).

Methods: 108 patients undergoing HD (51 male, 52 yrs) and 23 non-dialysis patients (7 male, 58 yrs) were evaluated. Plasma desphospho-uncarboxylated matrix Gla-protein (dp-ucMGP), a functional vitamin K deficiency biomarker, was analysed using the IVD CE-marked chemiluminescent InaKtif MGP assay on the IDS-iSYS system. IL-6 plasma levels were evaluated by ELISA. The results were adjusted for age, sex and BMI.

Results: HD patients had significantly higher values of dp-ucMGP [728 (IQR=724) pmol/L] than non-dialysis patients [563 (IQR=296) pmol/L] (p=0.05), indicating vitamin K deficiency. Furthermore, a significant positive correlation was observed between dp-ucMGP and IL-6 levels in HD patients, which reflects elevated levels of IL-6 in patients with vitamin K deficiency (**Fig. 1**).

Conclusions: The results reveal a positive correlation between vitamin K deficiency and the pro-inflammatory biomarker IL-6 in patients with CKD. Vitamin K supplementation may be a strategy to mitigate inflammation in these patients.

Funding: Government Support - Non-U.S.

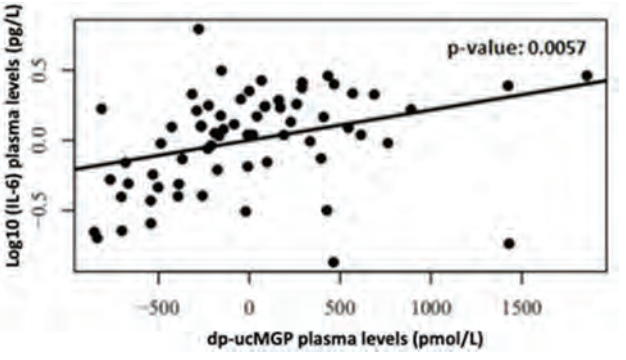

Fig 1. Correlation between dp-ucMGP and IL-6 plasma levels of HD patients. Pearson correlations were performed with residuals of linear fixed effects models, including confounders (Age, Sex, BMI, and time on dialysis).

FR-PO826

Depressive Symptoms Are Associated with Increased Hospitalization Rate in CKD Patients: A Systematic Review and Meta-Analysis of Cohort Studies

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Background: Depressive symptoms are relatively common in patients with chronic kidney disease (CKD). Recent studies showed that depressive disorders are associated with increased mortality risk in patients with CKD. However, evidence regarding the impact of depression on the risk of hospitalization in the CKD population is still limited. Therefore, we performed a systematic review and meta-analysis to explore the association between depressive symptoms and the risk of hospitalization in CKD patients.

Methods: We comprehensively searched MEDLINE, EMBASE and Cochrane Library from inception to October 2022. Included studies were cohort studies assessing the association of depressive symptoms on hospitalization rate among CKD patients, using the random-effects to calculate risk ratios (RR) and 95% confidence intervals (CIs).

Results: Six cohort studies were included in the analysis with a total of 11,258 CKD patients (7,404 patients with depressive symptoms and 4,122 patients without depressive symptoms). Subjects with depressive symptoms had an increased risk of hospitalization (pooled RR 1.139, 95% CI: 1.055–1.229, p = 0.001, I2 = 51.1%) compared to those without depressive symptoms. In subgroup analysis, depressive symptoms were associated with an increased risk of hospitalization in both CKD patients who were not receiving dialysis (pooled RR 1.432, 95% CI: 1.204-1.704, P = <0.001, I2 = 0.0%) and CKD patients who were receiving dialysis (pooled RR 1.088, 95% CI: 1.057-1.119, P = <0.001, I2 = 0.0%).

Conclusions: Our meta-analysis demonstrated that depressive symptoms were associated with an increased risk of hospitalization. This possible association is essential given the implication of depression screening to improve the quality of life in CKD patients.

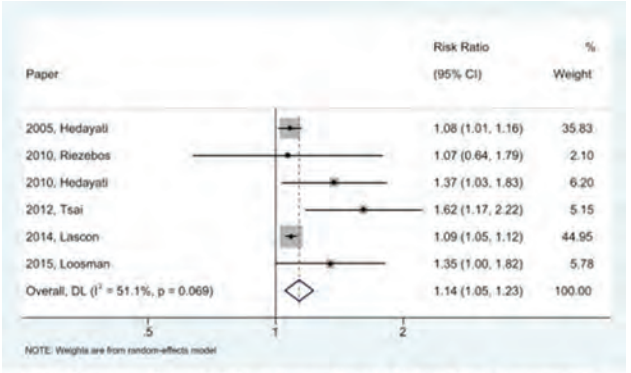

Figure 1: Forest plot of the included studies comparing risk of hospitalization between patients with depressive symptoms vs patients without depressive symptoms (p = 0.001)

FR-PO827

Hypothyroidism (HT) Rate and Testing Among Incident CKD Patients Who Transitioned to Dialysis Within Kaiser Permanente Southern California (KPSC)

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Background: HT and CKD are highly prevalent conditions with a bidirectional relationship. Among a large diverse real world CKD cohort who transitioned to dialysis, we sought to determine the rate of HT, factors associated with HT, and the overall screening rates for HT

Methods: We conducted a cross-sectional study within KPSC during 2007-2017. Patients aged ≥ 18 years with incident CKD (defined by at least 2 consecutive eGFR less than or equal to 45 at least 90 days apart) who initiated outpatient dialysis (hemodialysis or peritoneal dialysis) were identified. HT was defined as TSH > 4 mIU/L and or use of thyroid replacement medication. The rate of HT and HT screening with TSH measurements were determined. HT rate ratio (RR) and its 95% confidence interval were estimated using multivariable Poisson regressions with Robust error

Results: Among 6,812 CKD patients who transitioned to dialysis 927 (14%) had HT. 50% of incident CKD who initiated outpatient dialysis were screened with a TSH measurement in the 1 year prior to ESKD. Adjusted HT RR (95% CI) were 1.66 (1.19,2.33), 1.73 (1.53,1.95), 1.20 (1.03,1.39), and 1.54 (1.27,1.87) for age ≥ 70 years, females, atrial fibrillation, and weighted Charlson comorbidity index ≥5, respectively. Adjusted HT RR (95% CI) were 1.22(1.05,1.42), 0.62 (0.51,0.75) and 0.75 (0.61,0.93) for non-Hispanic whites, non-Hispanic blacks and Asians, respectively. Heart failure was not associated with HT (Table 2)

Conclusions: Our study observed that 14% of CKD patients who transitioned to dialysis had HT which is higher than the ~5% described among the general population. We observed that only half of CKD patients were screened for HT prior to initiation of dialysis suggesting a potential care gap. Further studies may provide insights into understanding whether greater screening and identification of HT among CKD patients initiating dialysis will lead to improved CKD dialysis related outcomes.

Table 1. Characteristics of Incident CKD Patients who initiated outpatient dialysis by hypothyroidism status

	No Hypothyroidism	Hypothyroidism	Total
N	5,885	927	6,812
Age at index date, n (%)			
18 - 39	441 (12.1)	38 (7.9)	479 (11.6)
40 - 54	1267 (34.8)	121 (25.1)	1388 (33.7)
55 - 69	2439 (67.1)	356 (73.9)	2795 (67.8)
70+	1718 (46.7)	412 (85.5)	2130 (51.7)
Gender, n (%)			
Male	3869 (65.7)	468 (50.5)	4104 (60.2)
Female	2330 (39.6)	459 (49.5)	2689 (39.5)
Race/Ethnicity, n (%)			
Non-Hispanic White	1276 (21.7)	286 (30.8)	1562 (22.9)
Non-Hispanic Black	1245 (21.2)	127 (13.7)	1372 (20.1)
Hispanic	2459 (41.8)	388 (41.9)	2847 (41.8)
Asian	771 (13.1)	91 (9.8)	862 (12.7)
Other/Unknown	134 (2.3)	15 (1.6)	149 (2.2)
Prevalent HF Status, n (%)			
Yes	2068 (35.1)	446 (48.1)	2514 (36.9)
No	3817 (64.9)	481 (51.9)	4298 (63.1)
Comorbidities, n (%)			
Diabetes	4534 (77.0)	719 (77.6)	5253 (77.1)
Atrial Fibrillation	825 (14.0)	114 (12.3)	939 (13.8)
CAD	1235 (21.0)	226 (24.4)	1461 (21.4)
Weighted Charlson, n (%)			
<5	2006 (34.1)	173 (18.7)	2179 (32.0)
5+	3879 (65.9)	754 (81.3)	4633 (68.0)
Thyroid medication use at outpatient dialysis initiation, n (%)			
Yes	0 (0.0)	581 (62.7)	581 (8.5)
No	5885 (100.0)	346 (37.3)	6231 (91.5)
TSH (lab, uIU/mL)			
N	2,587	857	3,444
Mean (SD)	1.9 (0.9)	6.3 (11.0)	3.1 (5.9)
Median (IQR)	1.9 (1.3, 2.6)	4.5 (2.6, 6.2)	2.1 (1.3, 3.3)

Table 2. Factors associated with hypothyroidism among incident CKD patients who initiated outpatient dialysis

	Full cohort analysis (N = 6,812)
	Multivariate RR* (95% CI)
Heart Failure Status	
No HF	Ref
18 - 39	Ref
40 - 54	0.97 (0.68, 1.38)
55 - 69	1.23 (0.88, 1.72)
70+	1.66 (1.19, 2.33)
Gender	
Male	Ref
Female	1.73 (1.53, 1.95)
Race/Ethnicity	
Hispanic	Ref
Non-Hispanic White	1.22 (1.05, 1.42)
Non-Hispanic Black	0.62 (0.51, 0.75)
Asian	0.75 (0.61, 0.93)
Dialysis Modality	
HD	Ref
PD	1.06 (0.89, 1.25)
Diabetes	1.08 (0.90, 1.29)
Hypertension	0.89 (0.55, 1.46)
Atrial Fibrillation	1.20 (1.03, 1.39)
Weighted Charlson Comorbidity	
<5	Ref
5+	1.54 (1.27, 1.87)
Medicaid	1.10 (0.89, 1.36)
Neighborhood Education	
0% - 50%	Ref
51% - 75%	1.07 (0.84, 1.36)
76% - 100%	1.06 (0.84, 1.34)

*Adjusted for all variables in table above.

FR-PO828

Poor Life Prognosis of Patients with Rapid Progression of Peripheral Artery Disease

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Background: Peripheral artery disease (PAD) is one of the major complications in patients undergoing hemodialysis (HD), leading to a higher mortality risk. As skin reperfusion pressure (SRPP) measurement is a useful screening tool for PAD, early detection and prevention of progression using this tool would be important. However, only a few studies have focused on the speed of PAD progression, and its effects on life prognosis and associated factors have not been fully examined yet. We aimed to evaluate the impact of rapid progression of PAD on life prognosis and identify the factors associated with PAD prognosis.

Methods: We included patients undergoing HD with more than two SRPP measurements at our facility between January, 2013 and August, 2022. Patients were followed up until August, 2022. Medical data were collected at the time of the first SRPP measurement, and the associations between survival and patient backgrounds were analyzed.

Results: The study included 142 patients (71.0±9.1 years old; 59.2% men; median dialysis vintage, 58.5 months). The median observation period was 1,142.5 days (interquartile range: 680.8–1,709.8 days), and 76 patients died during the observation time. Among the participants, 17 patients underwent lower limb amputation. The patients were divided into four groups, according to the SRPP reduction rate (Q1–4). Log-rank test analysis showed that patients with SRPP reduction rate Q4 had a poor prognosis ($p<0.001$). Multivariable Cox proportional hazards analysis demonstrated that SRPP reduction rate Q4 (hazard ratio, 2.51; 95% confidence interval [CI]: 1.46–4.30; $p<0.001$) was significantly associated with survival. Multivariable logistic regression analysis revealed that body mass index (BMI) (odds ratio [OR]: 1.13, 95% CI: 1.00–1.28, p=0.048) and serum creatinine level (OR: 0.77, 95% CI: 0.61–0.96, p=0.02) were associated with SRPP reduction rate Q4.

Conclusions: Patients with a large SRPP reduction rate had a poor life prognosis. BMI and serum creatinine levels were associated with a large SRPP reduction rate. As serum creatinine levels in patients undergoing HD can reflect their skeletal muscle mass, sarcopenic obesity, indicated by excessive BMI and low creatinine levels, may be a risk factor for the rapid progression of PAD in our participants. Maintaining adequate body weight and muscle mass is critical in preventing PAD progression.

FR-PO829

Readmission After Gastrointestinal Bleeding Hospitalization Type in Dialysis Patients

Yue Jiao,[1] Belen Alejos,[2] Melanie Wolf,[2] John W. Larkin,[1] Anke Winter,[2] Sheetal Chaudhuri,[1] Manuela Stauss-Grabo,[2] Len A. Usvyat,[1] Jeffrey L. Hymes,[1] Franklin W. Maddux,[6] David C. Wheeler,[3] Peter Stenvinkel,[4] Jürgen Floege.[5] On Behalf of the INSPIRE Core Group. *[1]Fresenius Medical Care, Waltham, MA; [2]Fresenius Medical Care, Bad Homburg, Germany; [3]University College London, London, United Kingdom; [4]Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [5]University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany; [6]Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany.*

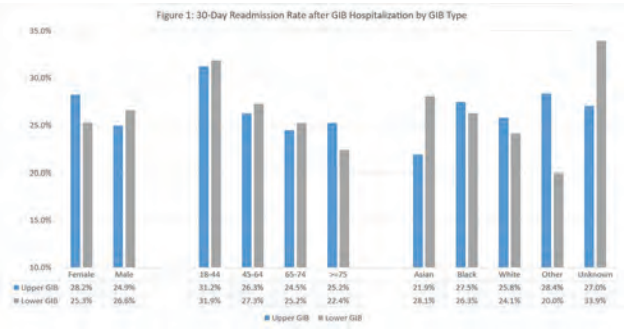
Background: The incidence of gastrointestinal bleeding (GIB) is high in the dialysis population. GIB episodes frequently lead to hospitalization, yet associated outcomes have not been defined and may differ by GIB type. The INSPIRE group aimed to define the all-cause hospital readmission rates after an index GIB hospitalization considering the type of GIB (upper or lower).

Methods: We used data on adult chronic dialysis patients who were hospitalized for a GIB in the United States during Jan-2018 to Mar-2021. GIB hospitalizations were identified from ICD discharge diagnosis codes (Zhao et al., AHRQ 2006). All-cause readmission rate considered events within 30 days from an index GIB hospitalization by GIB type. Index GIB hospitalizations with an unspecified location for the GIB were not included in the analysis of GIB types.

Results: In a population of 405,530 patients, 19,663 GIB hospitalizations occurred. Overall, there was a 26.4% all-cause 30-day readmission rate after an index GIB hospitalization. Readmission rate was consistent by GIB types at 26.4% for upper and 26.0% for lower GIB hospitalizations. Readmission rates after a GIB hospitalization were highest among patients 18-44 years old for all GI bleed types (**Figure 1**). Readmission rates after an upper GIB were higher for females, patients ≥75 years old, and those with a black and other race. Readmission after a lower GIB was most common among patients with an Asian and unknown race.

Conclusions: All-cause readmission rate after a GIB hospitalization was about 26% for all GIB types. Readmission rates were higher (>30%) among younger patients for upper and lower GIBs. Sex-dependent differences in readmission rates were observed after an upper-GIB hospitalization, as well as differences by age and race in readmission rates after an upper- and lower-GIB hospitalization. Further adjusted analyses are needed to confirm these findings and understand the disparities in outcomes.

Funding: Commercial Support - Fresenius Medical Care



FR-PO830

Gastrointestinal Bleeding Types and Associated Mortality Rates in Dialysis Patients

Belen Alejos,[1] Yue Jiao,[2] Melanie Wolf,[1] John W. Larkin,[2] Anke Winter,[1] Sheetal Chaudhuri,[1] Manuela Stauss-Grabo,[1] Len A. Usvyat,[2] Jeffrey L. Hymes,[2] Franklin W. Maddux,[3] David C. Wheeler,[4] Peter Stenvinkel,[5] Jürgen Floege.[6] On Behalf of the INSPIRE Core Group. *[1]Fresenius Medical Care, Bad Homburg, Germany; [2]Fresenius Medical Care, Waltham, MA; [3]Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany; [4]University College London, London, United Kingdom; [5]Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [6]University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany.*

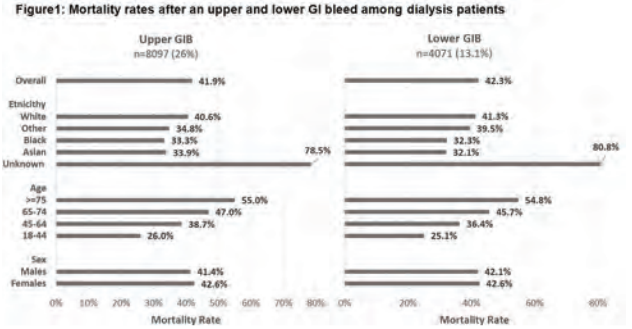
Background: The incidence of gastrointestinal bleeding (GIB) is ~7-fold higher in the dialysis vs general population. The INSPIRE collaborative group has aimed to describe mortality after a GIB episode by the type of bleed among chronic dialysis patients treated at a national provider in the United States (US).

Methods: We used data from adult dialysis patients who had ≥1 GIB episode between Jan-2018 to Mar-2021. GIB episodes were defined from ICD codes for comorbidities, or hospital discharge. We calculated crude mortality rates any time after the first GIB by type (upper or lower; Zhao et al., AHRQ 2006). GIB episodes with an unspecified location were not included in the analysis of GIB types.

Results: The incidence of a patient having ≥1 GIB episode was 7.7% (31,084/405,530). Overall, GIB was most common in patients between ages of 45-64 years (38.9%) & 65-75 years (28.7%), males (56.0%), and those of a white race (54.5%). GIB location was specified for 39.1% of the first GIB episodes. Demographics for patients with and without a specified GIB location did not differ. Crude mortality rate after the first GIB was 41.9% (n=3,392) for upper GIB and 42.3% (n=1,722) for lower GIB. Mortality rate for both GIB types was positively associated with age, and was the highest for patients with missing data on race (10.4% of cohort), followed by white race (**Figure 1**).

Conclusions: Mortality rate after the first GIB episode in a dialysis patient was >40%, regardless of the location of bleeding. Age and race specific differences were consistent for upper and lower GIBs. Most GIB episodes were classified as an unspecified type, suggesting the need for improvements in evaluation/coding. Further adjusted analyses are needed to confirm these results and understand the differences by dialysis modalities, risk factors, and causes of mortality.

Funding: Commercial Support - Fresenius Medical Care



FR-PO831

Cigarette Smoking and Prevalent Kidney Stone: The National Health and Nutrition Examination Survey 2011-2018

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Background: Cigarette smoking (CS) may affect the risk of kidney stone (KS) disease because it has been linked to an increased bone loss. In addition, major trace elements found in cigarette can also promote KS formation. Here, we aimed to examine the independent association between CS and prevalent KS disease defined as self-reports of any previous episode of kidney stone.

Methods: We examined The Third National Health and Nutrition Examination Survey (NHANES) 2011-2018, a large US population-based cross-sectional study, and used logistic regression analyses to determine the independent association between CS and prevalent KS disease.

Results: 19,405 participants were included for analysis, 1,895 had KS disease. 19% of stone formers (SF) versus 18% of non-stone formers (NSF) were active smokers (p<0.001), and average daily cigarettes smoked were 14 among SF vs. 12 among NSF (p= 0.02). Mean serum cotinine (a major metabolite of nicotine) concentration (SCC) was 64 ng/ml among SF vs. 54 ng/ml among NSF (p=0.01). Active CS associated strongly with an increased odds of KS disease in regression analysis after adjustment for demographics, BMI, histories of hypertension, diabetes, dyslipidemia and cardiovascular disease, alcohol intake, and dietary sodium, potassium and water intakes, odds ratio (OR)=1.30, 95% confidence interval (CI)=1.05-1.50, p=0.02 (Table 1). Higher SCC also associated significantly with an increased odds of KS disease when SCC was modeled as a continuous variable (OR=1.0007, 95% CI: 1.00-1.01, p=0.003), or when comparing highest tertile of SCC to lowest tertile (OR =1.30, 95% CI: 1.10–1.50, p=0.001)(Table 1). No major interactions were found in the final regression analyses.

Conclusions: Our study showed CS had a strong independent association with an increased risk of KS disease. Future prospective studies are needed to clarify the causal relationship between CS and KS formation.

Funding: Private Foundation Support

Table 1. OR of prevalent kidney stone according to the smoking status in the multivariate regression model

		OR (95% CI)	P value
Status of smoking per history			
Active vs. nonactive	Never	REF	
	Past	1.10 (0.89-1.30)	0.46
	Active	1.30 (1.05-1.50)	0.02
Laboratory cotinine measurement			
Continuous variable		1.0007 (1.00-1.01)	0.003
Categorial variable	Tertile. 1	REF	
	Tertile 2	1.10 (0.80-1.50)	0.61
	Tertile 3	1.30 (1.10-1.50)	0.001

FR-PO832

Dietary Magnesium Intake and Kidney Stones: The National Health and Nutrition Examination Survey 2011-2018

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Background: The association between dietary magnesium intake (DMI) and kidney stone disease (KSD) is not clear.

Methods: We examined The National Health and Nutrition Examination Survey (NHANES) 2011-2018 and used logistic regression analyses adjusting for age, sex, race, BMI, histories of hypertension, diabetes, thiazide use, cigarette smoking, alcohol drinking, dietary intake of calories, protein, sodium, calcium, and, supplemental calcium and vitamin D to determine the independent associations between DMI and prevalent KSD.

Results: A total of 19271 participants were eligible for the final analysis which included 1878 people who self-reported a history of the stone. The mean DMI was 295.4mg in stone formers and 309.6 mg in non-stone formers, p=0.02 (Table 1). Stone formers tended to be older, more likely to be male and Caucasian, and had a higher BMI. In univariate analysis, lower DMI was strongly associated with increased odds of prevalent KSD when DMI was modeled as a continuous variable (OR 0.94, 95% CI: 0.89-0.99, p=0.02) or when comparing the highest quartile of DMI to the lowest quartile (OR=0.74, 95% CI: 0.60-0.92, p=0.007). As shown in Table 2, after regression analysis, when DMI was modeled as a continuous variable odds of prevalent KSD were 0.92, with 95% CI: 0.84-1.01, p=0.07 but was strongly associated when comparing the highest quartile of DMI to the lowest quartile (OR=0.70, 95% CI: 0.52-0.93, p=0.01).

Conclusions: Our study suggests that higher DMI is associated with a reduced risk of kidney stone disease. Future prospective studies are needed to clarify the causal relationship.

Baseline characteristics of the study population

			Stone former	Non-stone former	P value
Total number, unweighted			1878	17393	
Age (years)			53.7 ±0.46	47.1 ± 0.34	<0.001
Sex (male %)			53.8	47.7	0.006
Race (Non-Hispanic White %)			74.9	63.6	<0.001
BMI (mg/m2)			30.8 ± 0.25	29.1 ± 0.12	<0.001
History of hypertension (%)			47.7	32.3	<0.001
History of diabetes (%)			19.4	9.4	<0.001
Thiazide use (%)			12.1	7.7	<0.001
Smoking (%)	Everyday/some day		19	18.7	<0.001
	Past smoker		30.8	24.1	
	Not at all		50.2	57.2	
Alcohol (%)	Heavy		2.5	4.4	0.02
	Light		19	21.4	
	None		78.6	74.3	
DMI (mg)	Mean		295.4 ± 6.2±	309.6 ± 2.2	0.02
	Quartiles	0-204	27.8	25.2	0.01
		205-280	25.1	24.6	
		281-378	26.1	24.6	
		>378	20.9	25.5	

Values are expressed as means ± SE or %. Abbreviations: DMI= dietary magnesium intake.

Odds ratio of prevalent kidney stone according to dietary magnesium intake in the multivariable regression model

		OR (95% CI)	P value
Dietary magnesium intake			
Continuous variable		0.92(0.84-1.01)	0.07
Categorial variable	Quartile 1	REF	
	Quartile 2	0.91 (0.77-1.08)	0.26
	Quartile 3	0.91 (0.75-1.10)	0.34
	Quartile 4	0.70 (0.52-0.93)	0.01

FR-PO833

Diet-Induced Oxalate Nephropathy: Eating Too Much "Healthy" Food

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Introduction: Oxalate nephropathy is an intrinsic kidney disease characterized by kidney tubular injury via the deposition of calcium oxalate crystals with initial acute tubular injury that can progress to scarring and eventually to end-stage kidney disease. This condition may be caused by primary hyperoxaluria (genetic), enteric hyperoxaluria (in the setting of fat malabsorption), and ingestions (foods high in oxalate, ethylene glycol toxicity). We present a case of "healthy" diet-induced oxalate nephropathy.

Case Description: A 57-year-old man with type II diabetes mellitus, hypertension, urinary retention requiring indwelling urinary catheterization, and psychiatric comorbidities including obsessive compulsive disorder presented to nephrology clinic with acute kidney injury. He reported a diet consisting of obsessive compulsive eating behavior. He reported heavy ingestion of foods presumed to be healthy, including oranges, assorted nuts, turkey, and up to 5 protein bars at a time. Vital signs and physical exam were unremarkable. Serum creatinine was 2.1 mg/dL (baseline 1.2 mg/dL) with a bland urinalysis without hematuria or proteinuria. Serologic work-up was unremarkable. A kidney biopsy revealed numerous calcium oxalate crystals associated with diffuse acute tubular injury, diagnostic of oxalate nephropathy.

Discussion: Oxalate nephropathy is an intrinsic kidney disease characterized by deposition of calcium oxalate crystals in the kidney tubules. Excessive consumption of foods high in oxalate or its precursors can cause acute or chronic kidney disease. In this case, the ingestion of oranges, nuts, turkey slices, and protein bars may have led to oxalate nephropathy. Vitamin C (ascorbic acid) found in citrus fruits is a precursor to oxalate. However, vitamin C supplementation is more commonly reported as a cause because it is more bioavailable. Nuts are also a high oxalate food, with almonds, Brazil nuts, and pine nuts holding the highest oxalate content. Finally, high protein intake may increase oxalate excretion in the urine. Patients with acute oxalate nephropathy typically recover kidney function and have a better prognosis than those with chronic disease. In this case, the patient reduced his intake of high oxalate foods and increased fluid intake to 2 liters of water daily. Thereafter he had progressive improvement of kidney function back to baseline.

FR-PO834

Coexposure of Melamine and Di-2-Ethylhexylphthalate Changes Mitochondrial Dynamics and Accelerates Kidney Injury in Adenine Diet-Induced CKD Mice

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Background: Environmental chemical exposures have shown to be risk factors for chronic kidney disease (CKD). Even though the 2008 event of melamine-added formula milk was over, environmental melamine exposure still occurs due to the contamination in daily food products and widely uses of melamine-made tableware. Our previous study found that environmental melamine increased oxidative stress and early kidney injury in adults. Bis-2-ethylhexylphthalate (DEHP) is presented widely in plastic products and has been suggested that it could cause kidney fibrosis. Melamine and DEHP are common environmental pollutants and their interactive toxicity remains unclear. The aims of this study are to clarify the nephrotoxicity of melamine and DEHP coexposure and to investigate the role of mitochondrial oxidative stress in the pathological mechanisms using a mouse model based on the US-FDA suggested human tolerable daily intake (TDI) levels of melamine and DEHP.

Methods: An adenine-rich-diet induced CKD model was conducted in male and female ICR mice with the coexposure of TDI levels of melamine and DEHP for 4 weeks. Urine albumin-creatinine ratio (uACR) was used to monitor kidney function. Kidney injury molecule (KIM-1) immunohistochemistry, Sirius-Red staining and TUNEL assay were applied to observe kidney injury, fibrosis, and apoptosis. We used Western blotting to detect target proteins, real-time PCR to measure mitochondrial DNA (mtDNA) and MitoSOX staining to detect mitochondrial ROS.

Results: Our results showed that melamine and/or DEHP exposure increased uACR, indicating a decline of kidney function. Fibrosis, apoptotic cells and KIM-1 were increased in the kidney sections of CKD mice exposed to melamine and/or DEHP. Biomarkers of oxidative stress (MDA, 4-HNE), inflammation (NF-kB) and fibrosis (TGF-b, collagen IV) were also elevated. Melamine and DEHP increased mitochondrial ROS and changed mtDNA and mitochondrial dynamic proteins (Pink1, Parkin, Mfn2, Drp1, Fis1) in the kidney of CKD mice.

Conclusions: Our findings suggest that melamine and/or DEHP exposure accelerates a progression of kidney injury in CKD, which may be mediated by changes in mitochondrial dynamics. Avoiding exposure of environmental melamine and DEHP should be advised in patients with CKD.

Funding: Government Support - Non-U.S.

FR-PO835

The Vitamin D Metabolite Ratio and Incident Cardiovascular Disease: The Multi-Ethnic Study of Atherosclerosis

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Background: Vitamin D deficiency has been linked to cardiovascular disease (CVD) with mixed results. The vitamin D metabolite ratio (VMR), the ratio of $24,25(OH)_2D$ to 25(OH)D, has shown stronger associations with bone health and mortality than 25(OH)D alone. Our study assessed the association between the VMR and CVD outcomes.

Methods: We evaluated 6,313 Multi-Ethnic Study of Atherosclerosis (MESA) participants without CVD using Cox regression to test the associations of both VMR and 25(OH)D with incident CVD (including myocardial infarction, resuscitated cardiac arrest, stroke, coronary heart disease death, and stroke death), heart failure (HF), and cardiovascular mortality. We adjusted models for age, gender, race, physical activity, BMI, smoking, diabetes, blood pressure condition and medication use, C-reactive protein, cholesterol levels and medication use, triglycerides, kidney function, parathyroid hormone, fibroblast growth factor 23, calcium, and phosphate.

Results: The study participants had a mean age of 62, with 53% of them being female. The cohort was 38% White, 28% Black, 22% Hispanic, and 12% Chinese. The mean (SD) 25(OH)D level was 22.7 (11.0) ng/mL, and the mean VMR was 15.2 (5.0). In fully adjusted models, a two-fold increase in VMR was associated with a 24% reduction in incident CVD (HR: 0.76, 95% CI: 0.65-0.88). However, there was no association between the VMR and HF (0.98, 0.78-1.24), or cardiovascular mortality (0.96, 0.77-1.21). 25(OH)D was not significantly associated with any CVD outcome.

Conclusions: In a multi-ethnic cohort, VMR was significantly associated with reduced incident CVD, but not HF or cardiovascular mortality over 15 years of follow-up. The results suggest that VMR may provide greater insight into vitamin D metabolism compared with 25(OH)D levels alone.

Funding: NIDDK Support, Veterans Affairs Support

Association of VMR and 25(OH)D with Cardiovascular Outcomes: Fully Adjusted Model

Outcome	HR (95% CI)	N Events / N at Risk	Mean Follow Up Time (Years)	p-value
VMR*				
CVD	0.76 (0.65, 0.88)	800 / 6,303	14.5	<0.001
HF	0.98 (0.78, 1.24)	398 / 6,301	14.7	0.891
Cardiovascular Mortality	0.96 (0.77, 1.21)	413 / 6,310	16.0	0.754
25(OH)D*				
CVD	0.95 (0.85, 1.06)	801 / 6,306	14.5	0.395
HF	1.03 (0.88, 1.2)	398 / 6,304	14.7	0.748
Cardiovascular Mortality	0.91 (0.78, 1.06)	414 / 6,313	16.0	0.237

*Per two-fold increase

FR-PO836

Paradoxical Association of Vitamin D Supplementation with Elevated Blood Pressure in Individuals Without Vitamin D Deficiency

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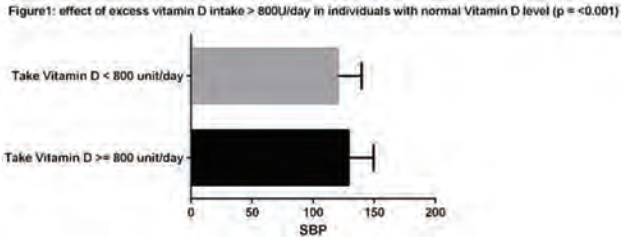
Background: While vitamin D(Vit D) deficiency(def) is associated with high blood pressure(BP), potential effects of supplemental Vit D intake on BP in individuals without Vit D def is unknown. This study aims to examine the association of the amount of Vit D intake with BP in individuals with and without Vit D def.

Methods: This cross-sectional study utilized data from the 2017-2018 Continuous NHANES. Participants' average daily Vit D intake over a 30-day period and their BP were collected through questionnaires and examinations. The study included individuals with more or less Vit D intake(>800 or <800IU/day). Difference in systolic and diastolic BP (SBP and DBP) between two groups stratified by presence and absence of Vit D def defined by Vit D level <30 and ≥30nmol/L, respectively was evaluated by an independent sample t-test.

Results: Among participants without Vit D def, 1068 had more and 837 had less Vit D intake. SBP in the former group were greater than those of the latter group ($SBP_{more\ vs\ less}$ 128.95±20.46 vs. 120.37±19.22mmHg; $mean_{difference}$ 8.59mmHg, P <0.001). Similarly, DBP was higher in the more Vit D intake group ($DBP_{more\ vs\ less}$ 70.02±15.09 vs. 67.66±16.35mmHg; $mean_{difference}$ 2.36mmHg, P <0.001). Of 90 participants with Vit D def (34 and 56 with more and less Vit D intake), both SBP and DBP remained higher in the more Vit D intake group but there was no statistical significance ($SBP_{more\ vs\ less}$ 125.71±21.47 vs. 122.82±19.38mmHg; $mean_{difference}$ 2.88mmHg, P 0.513 and $DBP_{more\ vs\ less}$ 70.71±10.17 vs. 69.68±10.79mmHg; $mean_{difference}$ 1.027mmHg, P 0.651)

Conclusions: Although Vit D supplementation is associated with lowering BP in individuals with Vit D def, supplemental Vit D intake greater than 800IU/day is paradoxically associated with higher BP in individuals without Vit D def compared to lesser Vit D takers. In the absence of Vit D def, whether Vit D supplementation causes an imbalance of mineral and bone metabolism related to vascular calcification leading to elevated BP requires further studies.



FR-PO837

A Randomized Controlled Trial Comparing Between Fixed Dose and Serum Level-Based Titration Regimen of Vitamin D Supplementation on Sarcopenia Outcomes Among Dialysis Patients

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Background: Low vitamin D status is associated with either low muscle mass or impaired muscle function in dialysis patients. However, there is no consensus on how best to correct vitamin D deficiency in patients with end-stage kidney disease (ESKD). We investigated the effect of different vitamin D supplementation regimens on sarcopenia outcomes in ESKD patients.

Methods: This was a randomized controlled trial (ClinicalTrial.gov NCT05434377). ESKD patients treated with maintenance hemodialysis or peritoneal dialysis with low vitamin D status, defined as serum 25-hydroxyvitamin D (25-OH D) level <30 ng/mL were 1:1 randomized to either receive oral ergocalciferol using a fixed dose regimen of 20,000 IU/week or utilizing serum 25-OH D level-based titration of dosage adjustment as a control group. The change of muscle mass measured by bioimpedance spectroscopy (BIS), muscle strength using a hand grip dynamometer, and physical performance measured by gait speed were determined. Baseline data after 6 months of supplementation were compared between groups.

Results: A total of 76 dialysis patients were enrolled (HD=43%). Baseline characteristics including age, diabetes mellitus, muscle parameters, and dialysis vintage were similar. After supplementation, the average serum 25-OH D levels in the fixed dose and titration groups were significantly elevated from 14.9±6.4 to 28.8±11.5 ng/mL, p<0.001 and from 15.0±7.2 to 26.9±13.2 ng/mL, p<0.001, respectively, but did not differ between groups at 6 months (p=0.52). Despite comparable energy and protein intake, the mean BIS-derived total-body muscle mass normalized to height squared was significantly increased at 6 months in the fixed dose group (14.4±3.4 to 15.3±3.0 kg/m^2, p<0.03) compared with the titration group (13.6±2.7 to 13.7±3.0 kg/m^2, p=0.58). However, muscle strength and gait speed were not different between two groups (p>0.05). Neither hypercalcemia nor hyperphosphatemia was found throughout the study.

Conclusions: A fixed dose supplementation of ergocalciferol demonstrates better improvement in muscle mass among patients receiving maintenance dialysis. Vitamin D supplementation appears to be a promising treatment of sarcopenia among dialysis population.

Funding: Government Support - Non-U.S.

FR-PO838

Effects of Two-Month Low-Sodium (Na+) Diet on Muscle Na+, Fat, and Function in Hemodialysis (HD) Patients

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Background: Higher muscle sodium concentration ([Na^+]) in HD patients is linked with muscle metabolic disturbances. We aimed to test if a 2-month low-Na^+ diet would reduce muscle [Na^+], thereby improving muscle structure or function in HD patients.

Methods: Eleven HD patients (56±11 y) received 2 and 1 low-Na^+ meal(s)/day during the first and second months of intervention, respectively, along with dietary counseling. The [Na^+] and fat fraction (FF) in muscles were measured by 3T ^{23}Na- and ^{1}H-MRI at pre- and post-intervention in 6 muscles: tibialis anterior (TA), extensor digitorum longus (EDL), peronei (PER), soleus (SOL), and lateral (LG) and medial (MG) gastrocnemius. Lower-limb muscle function was assessed using the 30s sit-to-stand (STS) test after MRI. Data were analyzed using the paired t test and Pearson's or Spearman's correlation.

Results: At baseline, muscle [Na^+] was inversely correlated with STS score in all muscles except SOL (**Fig.1**) and tended to positively correlate with FF in MG (r=0.60, P=0.05). There were no significant changes in muscle [Na^+] or FF post-intervention in each muscle studied (all P>0.05), with no improvement seen in STS score (P=0.34). An increase in muscle [Na^+] from pre- to post-intervention was associated with a decrease in STS score in all muscles except SOL (**Fig. 2**). There was no correlation between pre- to post-intervention changes in muscle FF and changes in STS score for each muscle (all P>0.05).

Conclusions: Two-months of a low-Na^+ diet did not reduce muscle [Na^+] in HD patients. However, the inverse correlations between baseline muscle [Na^+] and STS score and the changes in muscle [Na^+] and STS score, may serve as a rationale for developing new interventions to mitigate muscle dysfunction in HD patients by controlling muscle [Na^+].

Funding: Private Foundation Support

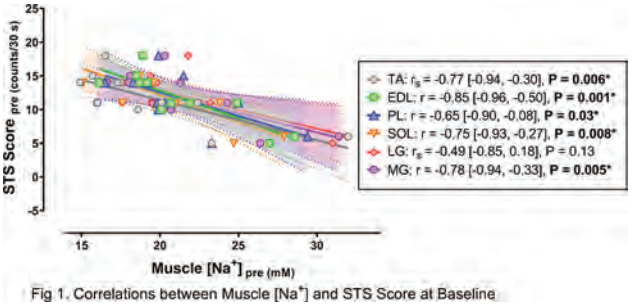

Fig 1. Correlations between Muscle [Na^+] and STS Score at Baseline

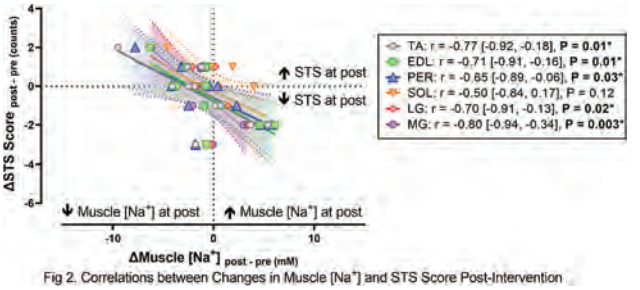

Fig 2. Correlations between Changes in Muscle [Na^+] and STS Score Post-Intervention

FR-PO839

The Effect of Controlled Ovarian Stimulation (COS) on Kidney Health Outcomes: A Protocol

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Background: The prevalence of chronic kidney disease (CKD) in females is >12% and prevention of CKD is a patient-identified research priority. Females face unique risks to their kidney health, and exogenous hormone use (hormone replacement therapy and contraceptives) has been implicated in kidney risk. However, there is a paucity of data on how exogenous hormone use in controlled ovarian stimulation (COS), commonly utilized in fertility treatment and preservation, affects kidney health. This prospective study will examine the effect of COS on kidney health outcomes, including 1) filtration fraction (FF), 2) glomerular filtration rate (GFR), and 3) kidney plasma flow (KPF).

Methods: Healthy females treated with COS will be recruited from the fertility clinic in Calgary, Canada to participate in 2 study days in the research laboratory. Study Day #1 will be a baseline visit immediately prior to initiation of COS treatment and Study Day #2 will be completed at the peak of the hormone administration phase of COS. On each study day, serum hormone levels will be measured. Using standardized protocols, participants will receive intravenously-administrated iohexol and para-aminohippurate and subsequent plasma monitoring to determine GFR and KPF, respectively. FF will be calculated as follows: GFR/KPF.

Results: Using a paired non-paramtric student t-test such as the Wilcoxon signed rank test, changes in GFR, KPF and FF will be compared between between Study Day #1 and Study Day #2.

Conclusions: The prevalence of CKD in females is increasing rapidly, highlighting the urgency of preventative interventions. COS treatment is common, and this research will elucidate the relationship between COS and kidney health, inform future studies, and empower females and their care providers in their reproductive choices.

Funding: Government Support - Non-U.S.

FR-PO840

Involvement of Type I Interferon-Responsive Myeloid Cells in Renal Inflammation in a Lupus Mouse Model

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Background: Systemic Lupus Erythematosus (SLE) is an autoimmune disease that damages multiple organs, including the kidneys in Lupus Nephritis (LN). Current treatments for SLE/LN are limited to conventional disease-modifying anti-rheumatic drugs and corticosteroid therapy. A more targeted therapy is necessary to address the underlying disease pathogenesis. Type I interferon (IFN-I) and its receptor (IFNAR) are known to play a significant role in the progression of SLE/LN, making them a major focus of research and therapy.

Methods: 3 female mice strains were used to investigate whether deficiency of IFNAR on myeloid cells will drive or reduce disease progression of SLE/LN. The study mice were LysM cre/cre, IFNAR flx/flx B6.Nba2 (n=16) with knockout of IFNAR on myeloid cells (cKO). We also used B6.Nba2 (WT) mice that develop lupus-like disease (n=18) and B6 (C57Bl/6) healthy mice (n=4). The tests performed include flow cytometry on 9 month (9mo) kidney cells, spleen multi-cytokine array of pro-inflammatory cytokines and chemokines, and ELISA of urine biomarkers S100a8, VCAM-1, and PF4.

Results: Kidney 9mo flow data revealed elevated neutrophil and decreased monocytic infiltration in the WT, but normalized levels in cKO, as well as specifically reduced levels of B cells in cKO. CD4+ T cells were specifically reduced, CD8+ T cells were specifically elevated, and Double positive (DP) T cells were normalized in 9mo cKO kidneys. Furthermore, we found that urinary biomarkers S100a8 and PF4 were decreased in 9mo cKO compared to the WT. 9mo spleen IL-21, IL-10, IL-6, IL-4, IFN-γ, and TNF-α were reduced in cKO, and cKO mice developed accelerated Splenomegaly at 2 months, followed by Nephromegaly at 9mo.

Conclusions: In essence, we observed reduced levels of neutrophilic cells, B cells, CD4+ T cells and DP T cells associated with reduced levels of urine biomarkers and that lack of type I interferon expression on myeloid cells affects the trafficking pattern of both monocytic and neutrophilic cells. Thus, our hypothesis for LN development follows: IFNAR facilitates the infiltration of neutrophilic cells, leading to the release of chemokines and the recruitment of inflammatory lymphocytes, and ultimately resulting in renal cell damage and the development of LN. Future directions include further analyses of renal infiltrates and additional urinary biomarkers.

FR-PO841

Healthy Women Have Higher Systemic Uromodulin Levels: Identification of Uromodulin as an Estrogen Responsive Gene

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Background: Urinary and serum uromodulin (gene: UMOD), secreted by the kidney, gained attention as potential biomarkers for kidney function in the context of acute and chronic kidney diseases and as an overall marker of health. However, there are few analyses focusing on a large number of healthy subjects, and the ranges and physiological regulation of serum uromodulin have not been well established.

Methods: Using ELISA, we measured serum uromodulin levels of healthy human subjects (n = 380) available from the Indiana University Biobank. To identify predictors of levels, we performed automated linear modeling in SPSS using relevant predictor variables extracted from deidentified patient charts (age, sex, body mass index, race, serum creatinine, eGFR, prescription drug usage). We also measured serum uromodulin in mice using ELISA. To identify a potential mechanism for increased serum uromodulin levels in females, mouse kidney thick ascending limb (MKTAL) cells were treated with 17β-estradiol, and uromodulin mRNA and protein expression were evaluated by RT-qPCR and Western blotting, respectively.

Results: Healthy subjects showed a wide range of serum uromodulin levels. Automated linear modeling in SPSS identified sex and body mass index (BMI) as significant ($p < 0.05$) predictors of serum uromodulin level. Serum uromodulin levels are higher in healthy females than healthy males. To identify a potential mechanism for increased serum uromodulin levels in females, we analyzed the UMOD locus in *H. sapiens* and *M. musculus*. We found two non-canonical estrogen response elements (ERE) and 29 canonical half-EREs in the *H. sapiens* sequence and 45 canonical half-EREs in the *M. musculus* sequence. Consistent with this, serum uromodulin levels normalized to weight are higher in female mice. Additionally, treatment with 10 pM – 1 nM of 17β-estradiol increases uromodulin expression at the mRNA and protein levels in MKTAL cells.

Conclusions: Healthy females have higher serum uromodulin levels, likely due to the estrogen responsiveness of the UMOD gene. Since uromodulin has an immunomodulatory role and is protective against acute kidney injury, estrogen-responsive increases in serum uromodulin might partially explain sex-specific susceptibility to infection and kidney injury.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

FR-PO842

Sex-Based Differences in Proximal Tubule Recovery of Filtered Proteins

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Background: The proximal tubule (PT) efficiently reclaims albumin and other proteins that escape the glomerular filtration barrier to maintain protein free urine. The recovery of filtered proteins occurs via receptor-mediated endocytosis facilitated by the multiligand receptors megalin and cubilin. PT health is impacted by excess albumin uptake that occurs when the glomerular barrier is breached and by nephrotoxic drugs that enter cells in a megalin/cubilin dependent manner. Transcriptomic and proteomic studies in male rodents have demonstrated differences in the expression of megalin and cubilin across the S1, S2, and S3 sub-segments that comprise the PT. Based on this, we previously developed an axial model of protein uptake in mice which predicts that most uptake under normal conditions occurs in S1, with S2 providing excess uptake capacity under nephrotic conditions. Multiple studies have shown that females are more protected from renal injury than males, however, the mechanisms underlying this difference in protection from renal injury are unknown.

Methods: To determine if there are sex-based differences in baseline PT recovery of filtered proteins, urine and kidneys were collected from five male and five female 13-week-old C57BL/6 mice. Urinary albumin was quantified by ELISA. Kidneys were processed for Western blotting and immunofluorescence staining. We used imaging-based approaches to quantify the expression and distribution of megalin and cubilin in SGLT2-positive S1 and SGLT2-negative S2 segments.

Results: Compared to males, female mice had lower levels of urinary albumin excretion when normalized to creatinine at baseline. Female mice had greater expression of total megalin and cubilin and decreased expression of NHE3 in the kidney cortex. Male and female mice had similar levels of megalin expression and surface localization in S1, however, female mice had greater expression and surface localization of megalin in S2. A greater fraction of total cubilin localized to the apical surface compared to megalin along the length of PT.

Conclusions: Our data suggest differences in the capacity of the PT to recover filtered proteins between male and female mice which could be especially relevant under nephrotic conditions. Current studies are focused on incorporating these sex-based differences into a mathematical model of protein uptake along the length of the PT.

Funding: NIDDK Support

FR-PO843

Sex Differences in Regional Distribution of Key Steroidogenic Enzymes in the Rat Kidney

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Background: Extragonadal estrogen (E_2) synthesis has been demonstrated in tissues such as brain, bone, and adipose tissue. We recently demonstrated preliminary evidence for an intrarenal E_2 synthesis machinery in the outer medulla (OM) of Sprague Dawley rats. Measurement of renal E_2 showed higher E_2 levels in female inner medulla (IM) compared to male rats. Thus, we aimed to investigate regional sex differences in renal E_2-synthesizing enzymes that impact sex differences in E_2 abundance.

Methods: Kidneys from male and female Sprague Dawley rats (n=8/group) were flushed, dissected into cortex (CTX), OM, and IM regions, and assessed for mRNA expression or protein abundance of enzymes in the E_2 biosynthesis pathway.

Results: mRNA expression of 3-hydroxy-3methylglutaryl CoA reductase (HMGCR), the key enzyme in cholesterol synthesis (the first substrate in steroidogenesis), was higher in female OM compared to males (100.0 ± 14.4 *vs* 254.4 ± 50.5 relative expression, p=0.0148), while no sex difference in HMGCR mRNA was observed in CTX or IM. Cytochrome P450 (CYP) 17a1, which synthesizes weak androgens, showed greater mRNA expression in female CTX and OM, while males expressed higher levels in IM (CTX: 100.0 ± 34.7 *vs* 204.0 ± 71.1, p=0.0120; OM: 100.0 ± 41.0 *vs* 228.9 ± 78.0, p=0.0017; IM: 100.0 ± 37.5 *vs* 36.3 ± 15.2, p=0.0010). We also assessed mRNA expression of 17b-hydroxysteroid dehydrogenase (HSD17b) 1, 2, and 3 which interconvert androgens and estrogens. HSD17b1 was higher in male CTX and OM (CTX: 100.0 ± 46.5 *vs* 7.6 ± 1.3, p=0.0003; OM: 100.0 ± 52.6 vs 10.1 ± 2.4, p=0.0005), while HSD17b2 and 3 were higher in female CTX and OM (CTX: 100.0 ± 43.8 *vs* : 454.8 ± 271.1, p=0.0042, 100.0 ± 49.9 *vs* 199.5 ± 119.8, p=0.0790, respectively; OM: 100.0 ± 40.5 *vs* 619.6 ± 311.8, p=0.0006, 100.0 ± 25.8 *vs* 164.8 ± 33.2, p=0.0011, respectively). Protein expression of aromatase (estrogen synthase) was detected in CTX, OM, and IM without sex differences.

Conclusions: Our data indicate sex- and region-specific differential expression of the intrarenal E_2 biosynthesis pathway within the rat kidney. HMGCR, CYP17A1, and HSD17b2 and 3 were upregulated within the female rat renal CTX and/or OM, but not IM, compared to males. Region-specific upregulation of these enzymes in females may contribute to renoprotective effects.

Funding: Other NIH Support - ASN Carl Gottschalk Research Scholar Grant to EYG; Vanderbilt Short Term Research Training Program for Medical Students (NIH grant DK007383)

FR-PO844

Multiple Pregnancy Can Induce Preeclampsia-Like Changes in Complement Factor H Point Mutation Mice

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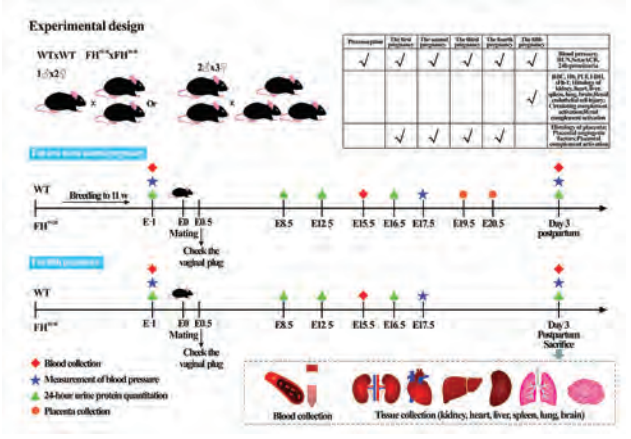
Background: Preeclampsia is a severe placenta-related pregnancy disorder, its pathogenesis has still not been fully elucidated. Studies suggested a link between complement activation and preeclampsia. In view of that normal pregnancy can induce appropriate activation of the complement system, we assumed that patients with preeclampsia may have increasing genetic susceptibility to overactivation of complement system, and under the burden of pregnancy, overactivation of the complement system occurs, in turn leading to the occurrence of preeclampsia.

Methods: We mated the female and male mice with heterozygous mutations in complement factor H through five times and assessed clinicopathological indicators of preeclampsia.

Results: Along with complement activation, multiple pregnant heterozygous complement H mutation mice recapitulated the key features of human preeclampsia: hypertension, proteinuria, elevated blood urea nitrogen, lactic dehydrogenase, reduced placental weight, restricted fetal growth, typical histology change in placenta and kidney of preeclampsia, placental imbalance of angiogenesis and renal endothelial cell injury.

Conclusions: This study provided direct evidence that pregnant status can induce overactivation of complement system in mice with mutation in complement regulator gene, which could lead to the development of preeclampsia. This model provided a new option for the investigation of the pathogenesis of preeclampsia.



FR-PO845

Screening Fabry Disease in Women Combining Enzyme Activity with Lyso-GL3: Results of a Brazilian Study

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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disease that can affect multiple organs, including the kidneys. The main objective of this study was to evaluate the effectiveness of a combination of α-GAL enzyme activity and plasma levels of lyso-GL3 for screening FD in women with chronic kidney disease (CKD).

Methods: Women with CKD, stages 3 to 5, in regular nephrological follow-up were selected from renal centers in all regions of Brazil. Exclusion criteria: under 18 years old and known diagnosis of FD. Patients underwent biochemical analysis of α-GAL enzyme activity and plasma levels of lyso-GL3. GLA gene sequencing was performed if α-GAL enzyme activity was below and/or lyso-GL3 levels were above the reference range. Sensitivity and specificity analyzes were performed to evaluate the performance of the combined biochemical approach for the diagnosis of FD.

Results: From October 2020 to December 2022 1,647 collections were carried out. Low α-GAL activity was found in 44 (2.6%) of the cases and increased lyso-GL3 was found in 101 (6.1%) of the cases. The mean age was 53 [42 – 64] years. All cases of low α-GAL and/or increased lyso-GL3 were submitted to genetic analysis, and 6 positive cases were found. As for genetic variants, four patients have R118C, one A143T and other with T430G, all considered variants of uncertain significance (VUS). The sensitivity and specificity of α-GAL reduction for the detection of FD was 83.3% and 97.6%, respectively. As for the increase in lyso-GL3, the values were 16.6% and 93.9%, respectively. There were no cases that presented a concomitant increase in lyso-GL3 and a reduction in enzymatic activity.

Conclusions: Preliminary results suggest that the combination of α-GAL enzymatic activity with lyso-GL3 measurement may be a good alternative for screening FD in women with CKD. A thorough medical evaluation is required to determine the pathogenicity of variants in these patients.

Funding: Commercial Support - Sanofi-Genzyme

FR-PO846

Sexual Function, Activity, and Satisfaction Among Young Females with CKD

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Background: Up to 80% of women with chronic kidney disease (CKD) experience sexual dysfunction, though its link with sexual activity and sexual satisfaction is not known. Recent literature demonstrates that among older women with kidney failure treated with dialysis, the majority report sexual inactivity, few describe sexual dysfunction and most report high sexual satisfaction. Whether this applies to young females with CKD has not been described. Our objectives were to determine the incidence of sexual activity, sexual dysfunction and sexual satisfaction among young females with CKD.

Methods: Females < 51 years old with CKD were recruited from nephrology clinics in Calgary, Alberta, Canada. Participants completed a modified version of the Female Sexual Function Index, a validated tool to assess sexual function.

Results: Thirty-six females with CKD (61% hemodialysis, 14% peritoneal dialysis, 14% stage G3-5 CKD, 11% transplant) participated. The median age was 37 years old (IQR 32, 43) and all participants identified as cis-gender. Eighteen participants (51%) reported sexual activity, and 82% of these individuals met criteria for sexual dysfunction. Among all participants, only 23% reported satisfaction with their sex life, while 57% reported moderate to severe dissatisfaction. Sexual dissatisfaction was more common among women experiencing sexual dysfunction ($p = 0.003$).

Conclusions: Young females with CKD are sexually active and experience a high incidence of both sexual dysfunction and dissatisfaction. These findings emphasize the importance of screening for sexual dysfunction and providing effective treatment options.

FR-PO847

Albuminuria and Vascular Health in Females with CKD

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Background: Cardiovascular (CV) disease is the leading cause of death in chronic kidney disease (CKD), and elevated CV risk occurs earlier in the CKD disease course in females compared to males. Albuminuria, a marker of CKD severity, has been independently associated with CV disease in females, however the mechanism of this association is not yet understood. This study aimed to determine the association between albuminuria and markers of vascular health, including mean arterial pressure (MAP) and arterial stiffness, as measured by aortic augmentation index (AIx) and pulse-wave velocity (PWV), in females with CKD.

Methods: An exploratory cross-sectional study recruited 54 females with CKD from nephrology clinics in Calgary, Alberta. Albuminuria was quantified by collection of a midstream urine and measurement of urine albumin-to-creatine ratio (ACR). Using standardized protocols, blood pressure and arterial stiffness were measured. Multiple linear regression analysis was used to estimate the association between urine ACR and each marker of vascular health.

Results: Albuminuria was significantly associated with MAP ($R^2 = 0.20$; $p = 0.001$) and AIx ($R^2 = 0.21$; $p = 0.006$), but was not associated with PWV ($R^2 = 0.11$; $p = 0.127$).

Conclusions: Disruptions in vascular health, specifically related to elevated blood pressure and increased peripheral wave reflection, may represent the pathophysiologic mechanism by which albuminuria is associated with increased CV risk in females with CKD. These risk factors may represent modifiable risk factors that serve as treatment targets for CV risk reduction in this important population.

Funding: Government Support - Non-U.S.

FR-PO848

To Assess Serum Prolactin Levels in Female Patients of CKD on Maintenance Haemodialysis

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Background: Kidneys play an important role in endocrine regulation, not only producing hormones such as erythropoietin and renin but also acting on the metabolism of others such as insulin, cortisol and prolactin. Therefore, CKD patients have numerous endocrine dysfunctions, with changes in feedback loops, reduced transport of protein-bound hormones, and reduced metabolism and hormone elimination. Hyperprolactinemia occurs by several mechanisms of which reduction in metabolism is one of the main mechanism. The other is increased prolactin secretion by lactotrophs in the uremic state – reduced availability of dopamine in the brain directly stimulates prolactin secretion as also increased autonomic production state. As a result of hyperprolactinemia, normal cyclic GnRH secretion decreases, resulting in the loss of pulsatile LH and FSH release. The high elevated level of circulating prolactin in ESRD represents biologically active hormone and is thought to contribute to the high prevalence of hypogonadism, anovulation and sexual dysfunction in patients on dialysis (due to prolactin inhibition of gonadotropin secretion). It is unknown whether higher serum prolactin concentration observed in patients with ESRD are associated with symptoms other than those directly related to relative gonadal deficiency. Thus, hyperprolactinemia in these patients becomes very prevalent, ranging from 30% in CKD early stages to 65% in those on haemodialysis.

Methods: Observational prospective study with a sample size of 30 patients in the age group of 15 to 45 years

Results: In our study of 30 patients, prolactin was high in 16 patients (53%) of end stage renal disease on dialysis.

Conclusions: To summarise, serum prolactin concentrations were high in a large majority of patients with ESRD. Even with a greatly increased prevalence in CKD, the clinical diagnosis of hyperprolactinemia in this population is difficult. Signs and symptoms of hyperprolactinemia are confused with some manifestations of CKD itself such as oligomenorrhoea, amenorrhoea, decreased libido, erectile dysfunction, infertility and osteoporosis.

FR-PO849

Bilateral Ureteral Obstruction: Cause of AKI in Pregnancy

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Introduction: Pregnancy-related acute kidney injury (PR-AKI) has an incidence of about 2% (1). The incidence has decreased significantly over the past years in developed countries and this is attributed to improved antenatal care (2). A rare cause of PR-AKI is bilateral ureteral obstruction, which has been reported in only a few studies. We report the case of obstructive AKI in a pregnant woman at term who had complete reversal of AKI post delivery.

Case Description: A 27-year-old G1P1 female with no known medical history was admitted for induction of labour at 39 weeks. On the night of her admission, she experienced decreased urine output and a foley catheter was inserted. On the second day, she was anuric and repeat labs showed elevated creatinine. She received one litre bolus of IV fluids and one dose of IV Lasix (20 mg). However, her creatinine levels continued to rise and she developed metabolic acidosis. Her creatinine level on admission was 0.61 mg/dL, but it increased to as high as 3.11 mg/dL with a BUN of 29 mg/dL and an HCO3 of 19 mmol/L. Her electrolyte levels were normal, but her uric acid level showed 5.8 mg/dL. Her UA on admission was benign, and she was asymptomatic. Nephrology was consulted for acute kidney injury, and renal ultrasonography showed bilateral mild hydronephrosis of the kidneys. Vitals: blood pressure of 125/77 mmHg, heart rate of 80 BPM, respiratory rate of 18, oxygen saturation of 100% on room air, and temperature of 98.4°F. Nephrology recommended immediate delivery. Immediately after surgery, the patient had good renal recovery with normal creatinine levels of 0.8 mg/dL and very good urine output.

Discussion: AKI is one of the complications that has high feto-maternal mortality and morbidity. Post renal cause of AKI secondary to ureteral obstruction is rare only 18 cases have been reported. Risk factors for AKI in pregnancy are polyhydramnios, twin pregnancy and obstruction of solitary kidney. (3) In normal pregnancy there is progesterone induced smooth muscle relaxation causing ureteral dilation and hydronephrosis. In our case ureteral dilation and hydronephrosis resulted from gravid uterus causing obstruction and possibly high levels of progesterone. The risk is usually greater in primigravida due to higher levels of progesterone.(4) AKI is rapidly reversible when the obstruction is relieved, with return of renal function to baseline.

FR-PO850

Rare Case of Recurrent Hypokalemia in Pregnancy: Broaden Your Differentials

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Introduction: Geller's syndrome is in the differential diagnosis when a pregnant woman presents with hypertension and severe hypokalemia. Here, we present a case of a patient with severe hypokalemia and hypertension in recurrent pregnancies. Careful history taking, in this case however, revealed a unique cause of her symptoms.

Case Description: A 30 year old, G5P3013 presented at 39 weeks 5 days gestation in labor and found to have severe hypokalemia and HTN. Labs notable for K <2.0 mg/dl, Mg 1.6 mg/dl, calcium 9.1 mg/dl (corrected), phosphorus 4.2 mg/dl and Cr 0.67 mg/dl. EKG noted U-waves. She required aggressive replacement of potassium (IV and PO for 2 days). She had history of severe hypokalemia requiring aggressive potassium repletion in last two pregnancies except first and prior history of preeclampsia. Further workup revealed normal TSH and cortisol levels, with a renin level of 0.39 ng/mL/hr (0.167-5.380 ng/mL/hr) and suppressed aldosterone level (below 1 ng/dL). Urine K < 5 mEq/L at the same time when serum K was 2.6 mg/dl, which was negative for renal potassium wasting. The remaining labs and imaging studies were unremarkable. Within 72 hours following delivery, potassium levels improved and remained normal postpartum. Hypertension was again in setting of pre-eclampsia (had proteinuria with Urine protein/creatinine ratio of 625), with improvement in BP post-delivery. Genetic testing was negative for mutation in mineralocorticoid receptor which ruled out Geller syndrome. On further inquiry, she mentioned that she had been taking calabash, a type of chalk/clay multiple times a day, to ameliorate third trimester symptoms during pregnancy. Clay ingestion was identified as the cause of recurrent hypokalemia. Hypertension was due to recurrent pre-eclampsia and not related to the development of hypokalemia in this case.

Discussion: Clay ingestion is a culturally imbedded common practice based on indigenous knowledge among certain cultures. It is important to be aware of its association with potential pregnancy complications. As in our patient who had normal potassium levels in her first pregnancy, when she did not eat clay, but her three subsequent pregnancies were complicated by severe hypokalemia when she consumed significant amounts of clay. Clay binds to potassium in the gut and leads to increased intestinal excretion of potassium, resulting in hypokalemia.

FR-PO851

Successful Treatment of Nephrotic Syndrome due to Preeclampsia Diagnosed by Renal Biopsy

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Introduction: Preeclampsia (PE) is the most frequent renal complication of pregnancy and is characterized by hypertension and proteinuria after 20 weeks of gestation. However, some patients with PE do not show hypertension. If the patients left untreated, PE could lead to serious complications for both the mother and baby, such as kidney function impairment, or fetal growth restriction. Thus, PE is no longer considered to be a transitory kidney disease that is cured when the baby is delivered. Moreover, the rate of pre-existing renal disease in preeclamptic women is about 70%. Focal segmental glomerulosclerosis (FSGS) is the common cause of nephrotic range proteinuria in pregnancy. It is difficult to distinguish between PE and glomerulonephritis during late pregnancy.

Case Description: A 32-year-old woman was referred for hypertension (180/108 mmHg) and massive proteinuria (13.7 g/gCr) at 34 weeks gestation. Even after delivery, massive proteinuria (7.3 g/gCr) was detected, despite well controlled blood pressure. Then, renal biopsy was performed for definitive diagnosis. Histological findings showed focal endotheliosis of the glomeruli and double contour. Immunofluorescent study showed no remarkable glomerular deposition. Reticulation of endothelial cell and duplication of GBM were detected by electron microscopy. Histological interpretation lead to definitive diagnosis as PE and to appropriate treatment, resulted in diminish of proteinuria.

Discussion: High levels of proteinuria after delivery is important index for intervention of treatment. Patients after PE has 4 times risk of hypertension, and twice risk of type 2 diabetes and dyslipidemia. Management of lifestyle-related disease after delivery is also important. In present case, histological implication lead to appropriate treatment. Therefore, histological diagnosis is important in PE patient for postpartum management.

FR-PO852

Hey Baby, the Kidney Allograft Is Not a Pillow: A Complex Case of Pregnancy in a Kidney Transplant Recipient

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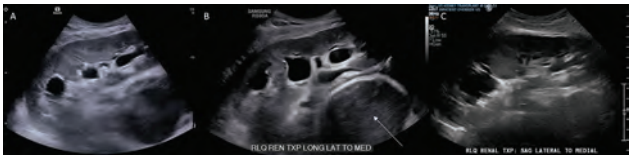
Introduction: Pregnancy in kidney transplant recipients (KTR) have favorable patient, allograft, and fetal outcomes. However, these pregnancies are high-risk for pre-eclampsia (25%), preterm (50%), and C-section (50%). While rates of rejections are low (1-2%), there are high rates of urinary tract infection (UTI) and multifactorial acute kidney injury (40%). We report a case of pregnancy in KTR with a successful outcome despite multiple complications.

Case Description: A 35-year-old with ESKD due to sickle cell disease with kidney transplant 3 years ago had her first planned pregnancy. The first two trimesters were complicated by recurrent UTIs (rUTIs) managed with suppressive antibiotics. At 24 weeks, mild hydronephrosis of the allograft was seen on ultrasound, which progressed to moderate hydronephrosis by week 36 due to the fetal head compressing the renal hilum (Fig 1A/B). Pre-eclampsia developed at 28 weeks; initial hypertension was followed by proteinuria at 34 weeks. Delivery was performed by C-section due to fetal distress at 37 weeks. Meticulous surgical technique ensured the safety of the transplanted ureter. Two days after delivery, hydronephrosis was improved (Fig 1C). She did not have a sickle cell crisis during pregnancy, with the use of erythropoietin stimulating agents and 1 unit of blood transfusion during C-section.

Discussion: Fertility and sexual health are important quality-of-life metrics in KTR, and our patient was determined to pursue pregnancy. Her case is an example of multidisciplinary care by transplant nephrology, maternal-fetal medicine, hematology, and transplant surgery supporting a complex case of pregnancy in KTR. Prior to conception, her allograft function, immunosuppressive regimen, and comorbidities were optimized. Despite multiple insults to the allograft (rUTIs, pre-eclampsia, and hydronephrosis), creatinine remained stable (0.8mg/dL). Postpartum, blood pressure and hydronephrosis are rapidly improving. Proteinuria persists but we expect improvement in the next few weeks as VEGF signaling normalizes and endothelial-podocyte homeostasis recovers.



Ultrasound of transplanted kidney at 24 weeks (A), 36 weeks (B) with fetal head compressing renal hilum (white arrow), and 2 days postpartum (C).

FR-PO853

Renal Artery Stenosis in Early High-Risk Pregnancy

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Introduction: Renovascular hypertension is an uncommon cause of hypertension in pregnancy.[1] Renovascular hypertension management is complicated by contraindication in pregnancy to established first line treatment of ACE-I and ARBs due to teratogenicity. The potential teratogenic risks of radiological intervention using fluoroscopy limits diagnostic options.[2] Previous cases of pregnant patients presenting with new onset or superimposed preeclampsia secondary to renovascular hypertension have been rarely reported.[2] We present a case report of renovascular hypertension in a pregnant patient who was at 17 weeks gestation at the time of diagnosis.

Case Description: 38-year-old pregnant female presenting for routine prenatal care. Preexisting diagnoses of insulin-dependent T2DM complicated by diabetic neuropathy, combined systolic/diastolic heart failure, history of methamphetamine use in remission, prior stroke x2 with residual left-sided deficits (2020), and poorly controlled hypertension. Confirmatory 24 -hour urine protein: 7,410 mg/24H 24h BP monitor: average reading of 185/87 Aldosterone/renin activity ratio: normal Regularly scheduled visits with her obstetrician soon revealed difficulties with hypertension control, resulting in an increase of her labetalol dose to 300 mg twice daily. At 17 weeks gestation, duplex ultrasound of the renal arteries confirmed high-grade stenosis at the origin of high renal artery, greater than 70%. Patient was promptly admitted for renal revascularization with renal artery stenting.

Discussion: Diagnosis of RAS can be done through duplex ultrasound imaging, CTA scan, or MRA. A catheter angiogram, which requires contrast to be injected via a catheter threaded through the renal artery is considered the gold standard diagnostic tool. However, it is not widely used during pregnancy due to radiation effects.[7] While extra-abdominal radiologic examinations render insignificant exposures to the pregnant uterus, high quality tools such as, fluoroscopically- or CT-guided interventional procedures (such as renal artery angioplasty) should be carefully considered during pregnancy.[8] The management of hypertension in early pregnancy should involve screening for RAS, especially in the setting of resistance to antihypertensive medications. [7] The benefits of early diagnosis of renal artery stenosis in pregnancy must be balanced with the risks of diagnostic imaging, interventional procedures, and its teratogenic risks.

FR-PO854

Neither Infantile nor Idiopathic: A Challenging Case of Hypercalcemia During Pregnancy

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Introduction: Idiopathic Infantile Hypercalcemia (IIH) Type 1 is a rare cause of hypercalcemia presents both in infancy and in adulthood. Autosomal recessive mutations in the *CYP24A1* gene, which encodes for the 24-hydroxylase enzyme, were recently identified in patients diagnosed with IIH Type 1. A deficiency or loss of function in this enzyme leads to reduced metabolism of activated vitamin D. Here we present a case of a patient presenting with hypercalcemia, hypertension, and nephrocalcinosis during pregnancy.

Case Description: A 34 year old woman G3P0303 with a history of three pregnancies complicated by hypercalcemia and pre-eclampsia with severe features was referred to Nephrology for evaluation of persistent post-partum hypercalcemia. During her most recent pregnancy, she was hypertensive with a total serum calcium ranged from 9.9 - 12.7 mg/dL. Post-partum, she was initiated on nifedipine, hydralazine, and enalapril. Initial labs were consistent with PTH-independent hypercalcemia with an inappropriately normal serum 1,25 dihydroxy vitamin D. Work up for a granulomatous disease process was negative. Imaging revealed bilateral medullary calcinosis. 24 hour stone analysis showed an increased risk for formation of calcium phosphate stones. A 25 Hydroxyvitamin D:24,25 Dihydroxy-vitamin D ratio could not be calculated as 24,25-Dihydroxy-vitamin D was below the limit of quantification. Genetic testing confirmed the presence of compound heterozygous mutations in the *CYP24A1* gene.

Discussion: A deficiency in the 24-hydroxylase enzyme can manifest in adulthood as hypercalcemia, hypertension, and nephrocalcinosis, often in the setting of pregnancy. Given the rarity of this genetic disease, diagnosis is often delayed. Initial laboratory work up often reveals hypercalcemia, suppressed parathyroid hormone, and normal to mildly elevated 1,25 dihydroxy-vitamin D. Diagnosis requires either genetic testing or an elevated 25 Hydroxyvitamin D:24,25 Dihydroxy-vitamin D ratio, often greater than 80. In our case, the patient developed recurrent gestational hypercalcemia and hypertension. As a result of a delayed diagnosis, measures had not been taken to avoid excess vitamin D and calcium supplementation. This case highlights the importance of pursuing the diagnosis of 24 hydroxylase deficiency in patients that present with hypercalcemia and hypertension in the setting of pregnancy.

FR-PO855

Observational Cohort with Embedded Randomised Controlled Trials to Study Pregnancy-Associated Progression of Renal Disease (ORCHARD)

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Background: 46% of women with moderate-severe chronic kidney disease (CKD) will require dialysis or lose at least 25% of kidney function within six months of delivery with no development of preventative treatments.

Methods: Biological samples, longitudinal and outcome data will be collected in a prospective cohort and eligible women identified to participate in ORCHARD-BEET randomised controlled feasibility trial. Inclusion criteria: singleton pregnancies; 24^{+6} weeks or less; CKD (pre-pregnancy eGFR<90mls/min/m^2 or pregnancy Cr>70µmol/l). Randomisation: 1 to 1. Standard care or daily beetroot juice supplement (nitrate 400mg). Primary outcome: recruitment rate; secondary outcomes: tolerability, acceptability, eGFR change at 6 months postpartum.

Results: 118 women consented to participate in the cohort and 104 were randomised to ORCHARD-BEET trial. 65% of eligible participants approached consented to be enrolled in the trial. Cohort maternal baseline characteristics are presented in Table 1. Trial results will be reported in 2024 once follow up complete.

Conclusions: To our knowledge this is the largest prospective cohort study with embedded pragmatic feasibility trial with concurrent biobanking of pregnant participants which is representative of women with moderate and severe CKD. Findings will be used to inform future intervention trials to prevent pregnancy associated progression of kidney disease. ISRCTN 91211980

Funding: Private Foundation Support

Table 1. Baseline Characteristics

Baseline Characteristic	Cohort(n=118) Mean (SD)/Median (IQR)/N(%)
Age, yrs	34.9(5.3)
Smoker	6(5.1%)
Nulliparous	58(49.2%)
Non-White ethnicity	51(42.2%)
Gestation weeks at recruitment	17(13,21)
BMI	27.8(5.2)
High Deprivation*	53(44.9%)
Systolic Blood Pressure	121(12.6)
Diastolic Blood Pressure	74(9.9)
Pre-pregnancy eGFR (ml/min/1.73m2)	56.7(18.6)
Pre-pregnancy uACR (mg/mmol)	12.5(2.0,61.4)
Primary cause of renal disease	--
Polycystic Kidney Disease	10(8.5%)
Glomerular disease	32(27.1%)
Reflux nephropathy	13(11.0%)
Diabetic nephropathy	4(3.4%)
Congenital/inherited	3(2.5%)
Renal transplant	13(11.0%)
Unknown cause/other	43(36.5%)
Diabetes	13(11%)
Chronic hypertension	62(52.5%)

* Index of Multiple Deprivation UK 2019

FR-PO856

Maternal Outcomes Following Nephrology Review in Pregnancy

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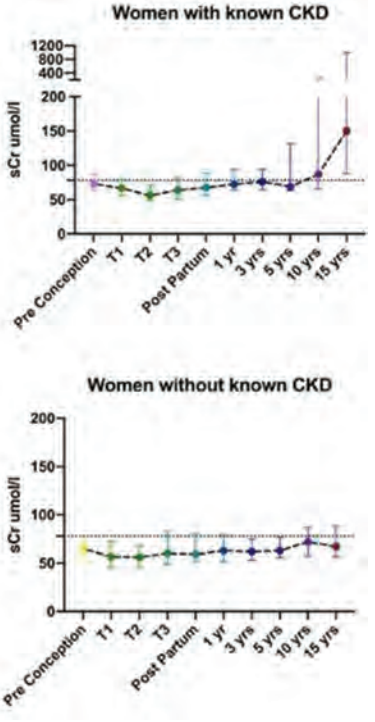
Background: Chronic kidney disease [CKD] is estimated to affect 3% of pregnant women. Dialysis-requiring pregnancy-associated acute kidney injury [PRAKI] is increasing in incidence, however accurate definitions for non-dialysis requiring PRAKI are lacking.

Methods: We conducted a retrospective cohort study of women who were reviewed by our Obstetric Nephrology Service from January 1st 2007 to March 31st 2023. Maternal and fetal outcomes were collected. Ethical approval was provided by the institution's ethics committee. Statistical analysis was performed with GraphPad version 7 and R.

Results: 459 women met inclusion criteria. We report the interim analysis of 154 pregnancies in 128 women. Mean maternal age at conception was 32.9 ± 5.3 years. 30% of mothers were nulliparous and 25% had hypertension pre-pregnancy. Indication

for review was pre-existing CKD (57%), acute kidney injury and/or new proteinuria/ hematuria (20%) and newly diagnosed CKD in the index pregnancy (9%). CKD was attributed to urological causes in 44%, glomerulonephritis in 29% and polycystic kidney disease in 15% of the cohort. In women with newly detected CKD in pregnancy, 26% underwent subsequent kidney biopsy. In women with CKD, serum creatinine [sCr] preconception was 73 µmol/L (63-138) and in trimester 2 during pregnancy was 56umol/L. Follow-up sCr at 1 yr was 73 µmol/L (65-94), 3 yrs was 76 µmol/L (65-94), 10 yrs was 87 µmol/L(66-250) and at 15 years was 150 µmol/L (88-850umol/). 3% of all women developed ESKD during follow up.

Conclusions: Results from this single-center study provide longitudinal kidney and maternal outcomes from a large cohort of women who received obstetric nephrology care.



Serial serum creatinine measurements (µmol/L) from pre-conception to 15 years of follow up.

FR-PO857

Adverse Maternal-Fetal Outcomes in Pregnant Women with CKD on Hemodialysis: A Single-Center Experience

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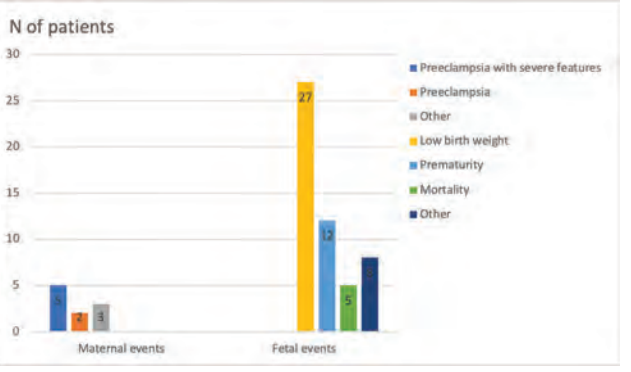
Background: Chronic kidney disease (CKD) pregnant women are at high risk of adverse maternal and fetal outcomes (AMAFO). 4% of women of childbearing age suffer from CKD, an independent risk factor for prematurity, low birth weight, neonatal death, and preeclampsia. **Objective:** To determine the incidence of AMAFO in pregnant women with CKD in hemodialysis (HD).

Methods: Observational retrospective study of 30 patients with CKD in HD and pregnancy from Aug 2017 to Dec 2021. Sociodemographic data, comorbidities, and AMAFO were recorded and analyzed.

Results: The incidence of adverse maternal events was 33%, the most frequent was preeclampsia with severe features (17%), followed by preeclampsia (7 %), HELLP syndrome (3%), gestational diabetes (3%), and placental abruption (3%). Neither patient died during the follow-up. 90% of the newborns present with adverse fetal outcomes, 90% with low birth weight, 40% with prematurity, 13 % with transient tachypnea of the newborn, 7% with premature rupture of the membranes, 7% with fetal distress, and 17% died.

Conclusions: There was a 33% incidence of adverse maternal events and 90% of adverse fetal outcomes in pregnant women with CKD in HD, with only 10% of pregnancies without AMAFO.

	N= 30
Age (years)	28.87 ± 4.1
Preeclampsia in previous pregnancies n (%)	6 (20%)
Chronic hypertension n (%)	23 (77%)
Diabetes n (%)	3 (10%)
CKD diagnosis before pregnancy n (%)	25 (83%)
GFR n (ml/min/1.73m2)	18.127; 5.7-55.8
24-hour urinary creatine clearance (ml/min/1.73m2)	14.1954 ± 7.2
Start of hemodialysis	
First trimester	5 (17%)
Second trimester	17 (57%)
Third trimester	8 (26%)



FR-PO858

Characteristics and Outcomes of Patients with Pregnancy-Related ESKD

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Background: The incidence of pregnancy-related AKI is increasing and associated with morbidity including progression to ESKD. We aimed to examine characteristics and clinical outcomes of patients with a pregnancy-related primary cause of ESKD(PR-ESKD).

Methods: We studied 183,640 reproductive-aged females with incident ESKD, 341 with PR-ESKD, from Jan 2000-Nov 2020 in USRDS. We compared baseline characteristics of those with PR-ESKD to the US birthing population using CDC natality data. We built multivariable Cox/competing risk models to examine 1) mortality, 2) access to kidney transplant(KT), and 3) time to KT after joining the waitlist between those with PR-ESKD and reproductive-age women with other causes of ESKD.

Results: Versus the general US birthing population, Black patients were overrepresented in PR-ESKD(31.9% vs. 16.7%). PR-ESKD had similar/lower hazards of mortality but significantly less acess to KT vs other causes of ESKD(Figure); this persisted in adjusted analyses(Table). Those with PR-ESKD were less likely to have nephrology care prior to ESKD-onset (aRR=0.47,95% CI:0.40-0.56).

Conclusions: Black patients are disproportionately affected by pregnancy-related ESKD. Our finding of reduced access to KT and pre-ESKD care highlight the need for improved postpartum and long-term support.

Figure: Mortality Among Those with Pregnancy-Related ESKD Compared to Those with Other Causes, (a) All Ages, (b) Pregnancy-Related ESKD Compared to an Age-Matched Cohort, and Time from (c) ESKD Onset to Access to Kidney Transplant (Joining the Deceased Donor Waitlist or Receiving a Kidney from a Live Donor), and (d) Among Those Who Were Waitlisted, Joining the Waitlist To Kidney Transplant

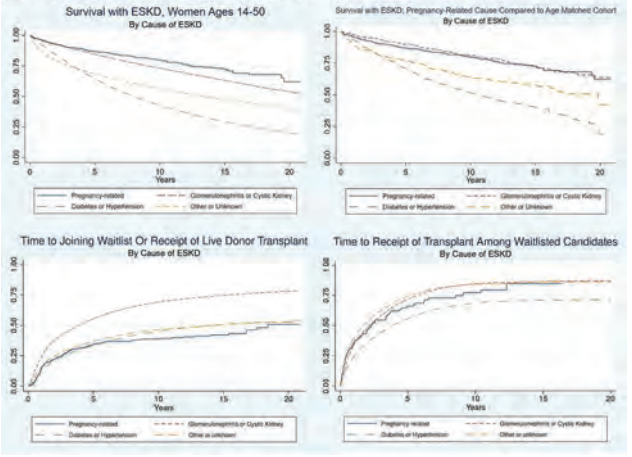

Table: (a) Multivariable Cox Proportional Hazards Model: Time to Death, and Multivariable Competing Risk Models** for (b) Time to Access to Transplant (Joining Kidney Transplant Waitlistor Receipt of Live Donor Transplant), (c) Time to Transplant After Joining Waitlist, Among Reproductive Age Females with End-Stage Kidney Disease, by Primary Cause of Kidney Failure**

(a) Death	HR (95% CI)*	p-value
Pregnancy-related vs	1.00	
Glomerulonephritis/cystic kidney	0.97 (0.78-1.29)	0.8
Diabetes/hypertension	0.49 (0.39-0.61)	<0.001
Other/unknown	0.61 (0.49-0.76)	<0.001
(b) Access to Transplant	**SHR (95% CI)**	**p-value**
Pregnancy-related vs	1.00	
Glomerulonephritis/cystic kidney	0.47 (0.38-0.56)	<0.001
Diabetes/hypertension	0.67 (0.56-0.81)	<0.001
Other/unknown	0.68 (0.57-0.83)	<0.001
(c) Time to Transplant After Joining Waitlist	**SHR (95% CI)**	**p-value**
Pregnancy-related vs	1.00	
Glomerulonephritis/cystic kidney	0.87 (0.68-1.10)	0.2
Diabetes/hypertension	1.08 (0.85-1.37)	0.5
Other/unknown	0.86 (0.67-1.09)	0.2

HR = hazard ratio, SHR = subhazard ratio
**Inverse hazard ratios shown for cause of renal failure, so should be interpreted as the hazard for patients with pregnancy-related ESKD compared to each of the other causes **Model adjusted for potential confounders including race, Hispanic Ethnicity, insurance type,current employment, and comorbidities including congestive heart failure, COPD, cerebrovascular disease, alcohol dependence, hypertension, inability to ambulate, current smoker*

FR-PO859

Acute Starvation Ketoacidosis in Pregnancy: Too Fast, Too Furious

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Introduction: Starvation ketoacidosis in pregnancy is rare and potentially lethal. Maternal mortality rates up to 35% and fetal mortality rates up to 85% have been reported. Moreover, maternal acidosis is associated with detrimental fetal neural development. Majority of previously reported cases were in setting of pre-existing diabetes mellitus and required emergent caesarean section. This case demonstrates a distinctive presentation characterized by severe ketoacidosis in the context of acute starvation, absence of diabetes, and positive fetomaternal outcomes.

Case Description: 26-year-old female G4P2103 at 35 weeks of gestation with history of anemia presented to labor unit with intractable vomiting for around 24 hours. Further history was significant for acetaminophen use for a month. Vitals were significant for pulse 115/min, respiratory rate 20/min, BP 106/63 mm Hg. Blood chemistry showed CO2 9 mmol/L, glucose 61 mg/dL, and anion gap 19. Urinalysis showed specific gravity > 1.030, protein > 300 mg/dL, ketones > 160 mg/dL. On arterial blood gas, pH was 7.184, PCO2 31 mm Hg, and a base deficit –16 mmol/L. Blood lactate, ethanol, methanol, and acetaminophen levels were normal. Beta hydroxy butyrate was 52.29 mg/dL. Diabetic ketoacidosis was ruled out based on glucose 61 mg/dL and hemoglobin A1c 4.8%. Diagnosis of starvation ketoacidosis was made. She was treated with intravenous sodium bicarbonate and dextrose infusion for around 24 hours, with improvement in metabolic acidosis. No fetomaternal complications occurred.

Discussion: In healthy individuals, it takes a minimum of 14 days for starvation to reach its peak severity, characterized by a pH value typically above 7.3 while in pregnancy, starvation ketosis can develop within a few days. In pregnancy, heightened levels of estrogen, progesterone, and human placental lactogen cause insulin resistance, hindering cellular glucose uptake. Consequently, increased lipolysis and free fatty acids lead to ketosis. Management primarily includes bicarbonate and dextrose infusion along with fetal monitoring. Insulin does not play a role in starvation ketoacidosis as opposed to diabetic ketoacidosis.

FR-PO860

Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) as a Marker of Disease Activity and Pregnancy-Related Adverse Outcomes in Pregnant Women with Inflammatory Bowel Disease

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Background: Control of disease activity in pregnant women with inflammatory bowel disease (IBD) is crucial as an uncontrolled disease is associated with higher risks of adverse pregnancy outcomes for both the mother and newborn. Human neutrophil gelatinase-associated lipocalin (NGAL) is an acceptable biomarker in some pathological conditions such as acute and chronic kidney injuries and high levels of NGAL were observed in the colon, serum, and stool of patients with IBD. In pregnancy, first-trimester NGAL was found to be an early marker of late-onset preeclampsia. However, no data exists on urinary NGAL in pregnant women with IBD.

Methods: The study recruited women with (IBD) who attended the IBDMOM clinic for antenatal and postnatal follow-up. The correlation of urinary NGAL levels with baseline clinical characteristics and its predictive capacity for pregnancy-related adverse outcomes such as preterm birth, preeclampsia, stillbirth, low-birth weight, and IBD flares were assessed by univariate and multivariate stepwise regression analyses.

Results: The median age of patients was 28 years and the median duration of IBD at the time of conception was 6 years. A total of 252 urine samples (172 samples from patients with Crohn's disease, 77 with ulcerative colitis, and 3 with unclassified IBD) were examined. Urinary NGAL measurements were obtained from 192 pregnancies, throughout the different gestational periods (1st trimester n = 90; 2nd trimester n = 111; 3rd trimester n = 92). Urinary NGAL levels were not significantly higher in patients with active IBD compared with inactive IBD (median 47.7 ± 4.7 ng/mL vs. 52.8 ± 3.98 ng/mL, p = 0.242). Forty-nine patients reached secondary outcomes (27, 8 and 14 had preterm deliveries, abortions, and either preeclampsia, IUGR, and stillbirth, respectively). There was no statically significant correlation between urinary NGAL levels and obstetric adverse outcomes. However, the incidence of cesarean sections, treatment regimen changes and hospital admissions during pregnancy were significantly higher in patients with active IBD (p = 0.001).

Conclusions: Our data suggest limited predictive capacity of urinary NGAL levels for predicting disease flares or obstetric adverse outcomes in pregnant women with IBD. However, the role of serum NGAL in this patients population remains to be elucidated.

Funding: Private Foundation Support

FR-PO861

Maternal and Foetal Outcomes in ANCA Vasculitis: A Review of the Literature

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Background: Limited data exists on the effects of ANCA-associated vasculitis (AAV) on maternal and foetal outcomes. Although historically rare in pregnancy and primarily affecting individuals >65 yrs, the incidence of AAV in younger women is increasing. This highlights the significant impact of AAV on fertility and the need for increased healthcare provision and interdisciplinary approach to management. There is however a lack of literature guiding healthcare professionals in managing AAV patients throughout the pre-conception, prenatal and postnatal periods. This review examines maternal and foetal outcomes associated with AAV, compares outcomes with the general population and explores the effectiveness of AAV treatments during pregnancy.

Methods: A literature search using PubMed, Cochrane and WoS was conducted, to identify all published studies that included pregnant women with a diagnosis of AAV. Two reviewers screened the papers and studies were assessed for quality.

Results: Five papers were included with a total of 60 women and 84 pregnancies. Results showed an increased risk of pre-eclampsia, pre-term delivery, low birth weight and high rates of caesarean delivery compared to the general population (Fig.1). Risks varied according to organ involvement with patients who had multi-system involvement at highest risk of adverse outcomes. The majority of patients received prednisolone and or azathioprine treatment during their pregnancy and >30% received no treatment at all. Pregnancies in women with disease remission had favourable outcomes.

Conclusions: Data on pregnancy outcomes in AAV is limited and there is a lack of guidance regarding patient management in the pre-conception, prenatal and postnatal periods. The literature suggests adverse outcomes in pregnant patients with AAV, emphasizing the need for additional support and further research looking at maternal health risks, the impact of disease relapse and the role of data registries.

Study outcomes and patients included (n)	AAV patients (n,%)	Incidence in the general population (developed countries)
Pre-eclampsia (n= 83)	8 (9.6%)	0.4%
Pre-term births (n= 84)	12 (14.3%)	4.3 - 8.7%
Foetal loss (n = 45)	6 (13.3%)	10.0 - 25.0%
Premature rupture of membrane (n = 32)	2 (6.3%)	8.0 - 10.0%
Low birth weight (n = 80)	16 (20.0%)	7.0%
Caesareans (n = 67)	16 (23.9%)	6.0%
Emergency	9 (13.4%)	2.7%
Elective	7 (10.4%)	2.3 %
Deterioration of maternal renal function during pregnancy (n = 35)	5 (14.3%)	-
Disease flare (n= 84)		-
During pregnancy	21 (25.0%)	
Postpartum	15 (17.9%)	
Increase in serum creatinine (n = 25)	10 (40%)	-

Maternal and foetal outcomes in AAV compared to the health population averages

FR-PO862

The Effect of Pregnancy and Delivery on Renal Prognosis in Patients with Autosomal Dominant Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a frequent inherited renal disease, which is caused by PKD1 and PKD2 gene abnormalities and results in the progressive development and enlargement of numerous cysts in the bilateral kidneys, leading to progressive deterioration of renal function and end-stage renal failure. It has been reported that the pregnancy and delivery rates of women with ADPKD are similar to those without it in terms of fertility, miscarriage, stillbirth, and fetal complications. On the other hand, it has also been reported that the hypertensive disorders of pregnancy (HDP) are higher and the risk of renal failure is higher in women with ADPKD. This result may lead ADPKD women who wish to have a baby to hesitate in pregnancy and delivery. This study aims to determine whether the development of HDP affects renal function after delivery in women with ADPKD.

Methods: We performed a questionnaire on pregnancy and delivery to obtain clinical data and circumstances around women with ADPKD. The primary outcome was renal failure, with or without induction of dialysis. Survival analysis was performed to evaluate whether the primary endpoint is HDP with Cox proportional hazards analysis. Factors associated with the risk of the primary outcome will be evaluated using univariate and multivariate logistic analysis.

Results: One hundred eighty-three ADPKD women (including 100 patients on hemodialysis) were enrolled in this study. The median age was 58.6 years. The mean age at first delivery was 26.9 years. The average number of births was 2.5. the mean duration from the first delivery to dialysis is 31.7 years. The age of induction of dialysis was 54.4 years. Eighteen percent of the patients developed HDP at the time of first delivery, and 71.4% of the women with a history of HDP developed HDP at the time of second delivery. Although the incidence of HDP was higher than that of the general population in Japan, there was no difference in cumulative renal survival between patients with HDP (n=28) and those without (n=148). (p=0.27, Log-rank test). Multivariate analysis also showed that the presence or absence of HDP was not a risk for poor renal prognosis.

Conclusions: In female patients with ADPKD, the presence of HDP does not affect renal prognosis and accelerate renal failure.

FR-PO863

Native Renal Biopsy D4 Postpartum

Alexa E. Golbus, Natalie T. Freidin. *Medical University of South Carolina, Charleston, SC.*

Introduction: aHUS is a thrombotic microangiopathy caused by overactivation of the alternative pathway of complement activation. aHUS can be diagnosed on renal biopsy, and treatment with eculizumab should begin as soon as possible in order to prevent progression to ESRD. However, evidence regarding appropriate timing of renal biopsy in pregnancy and the immediate period postpartum is not clear.

Case Description: Following vaginal delivery complicated by postpartum hemorrhage and subsequent dilation and curettage with an estimated blood loss of 1.5 L, a 33-year-old female developed atypical hemolytic uremic syndrome and AKI with serum creatinine to 9.4 mg/dl (baseline 0.6). PLEX was initiated and CT-guided renal biopsy 4 days postpartum demonstrated aHUS with cortical necrosis, which was subsequently treated with eculizumab. In the days following renal biopsy, our patient had abdominal and flank pain and a renal subcapsular hematoma was found on CT, measuring 5.9 x 4.4 cm, but self-resolved without further complication. 18 months later Cr recovered to 1.1 mg/dl.

Discussion: In patients with p-aHUS not treated with eculizumab, 62% reach ESRD within a month, and over 75% ultimately reach ESRD. Eculizumab, a complement C5 inhibitor, significantly reduces the risk of progression to ESRD and need for kidney transplantation. Therefore, early identification in cases of aHUS is important. While pregnancy and the postpartum period are thought to increase risk of complications in renal biopsy including bleeding and hematoma, due to increased blood flow through the kidneys, there is not a consensus regarding appropriate timing of biopsy. A systematic review of renal biopsy in pregnancy and postpartum demonstrated a 7% incidence of complications in pregnant patients, with the majority of serious adverse events occurring in weeks 23-26. Notably, postpartum patients had no severe adverse events, and complications, which occurred in 1% of cases, were mild and included microhematuria and hematoma. While there remain no clear guidelines on timing and specific indication for biopsy in this patient population, timely biopsy in our patient allowed for early initiation of treatment with eculizumab. Renal biopsy in pregnant and postpartum patients is an area lacking research and clear guidance and is likely underperformed due to the perceived risk, whether real or overstated.

FR-PO864

The Positive Association of Black Race with Kidney Diseases Among a Cohort of Pregnant Women May Be Related to a Higher Rate of Prior Nonsteroidal Anti-Inflammatory (NSAID) Use

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Background: Chronic kidney disease (CKD) portends adverse outcomes for women of reproductive age. Black women have greater CKD prevalence and worse pregnancy outcomes compared to their counterparts. However, key contributors to these racial disparities in CKD and pregnancy outcomes are poorly described.

Methods: We conducted a retrospective cohort study of 21,603 pregnant women who were hospitalized in a large New York City health system in Bronx, NY, between January 1, 2016 and December 31, 2020 and identified 1,289 (5.9%) pregnant patients with preexisting CKD (as defined by eGFR<60 or proteinuria/albuminuria>200mg within 5 years prior to hospitalization). Data was extracted on socio-demographic variables, comorbidities, prior prescriptions for NSAIDS and smoking. We describe socio-demographic and behavioral characteristics (e.g., SES, marital status, smoking status), prior comorbid conditions (e.g. SLE, sickle cell, HTN), and prior NSAID prescription use among those with and without CKD. We quantified the association between preexisting CKD and race/ethnicity using logistic regression, adjusting for age, comorbidities, SES, prior NSAID use and smoking.

Results: Pregnant women with kidney disease (versus without) had higher prevalence of chronic HTN, prior preeclampsia, diabetes, antiphospholipid syndrome, sickle cell disease, systemic lupus and heart failure (p<0.001) and higher prior NSAIDs prescriptions (65.32% vs 41.74%, p<0.001). The majority of prescriptions were written for high dose ibuprofen (600-800mg), naproxen (500 mg) and indomethacin (500mg). After adjusting for age, BMI comorbidity, insurance type and SES, Black women had a 1.46 greater odds of CKD prevalence (p=0.03). After further adjustment for prior NSAID prescriptions, the association between Black race and CKD prevalence was no longer statistically significant (OR 1.37; p=0.08).

Conclusions: Black pregnant women have a higher rate of pre-existing CKD than their counterparts. Further investigation of racial disparities in NSAID use and their contribution to disparities in CKD prevalence among pregnant women is needed.

FR-PO865

Women with Preexisting CKD and a History of Preeclampsia Have a High Rate of Subsequent Pregnancy Complications but Are Seldom Linked to Adequate Care

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Background: Pregnancy provides a unique opportunity to identify patients with undiagnosed CKD, which includes ongoing proteinuria from previous pre-eclampsia episode, and integrate them with healthcare resources. Pregnant women with pre-existing CKD and a history of pre-eclampsia have a high incidence of adverse outcomes but whether these outcomes occur despite adequate linkage to care is not known.

Methods: We evaluated a retrospective cohort of pregnant women with preexisting CKD (as defined by eGFR<60 or proteinuria >200mg within 6 months and 5 years prior to admission) and a previous history of preeclampsia who were hospitalized in a large New York City health system in Bronx, NY, between January 1, 2016 and December 31, 2019. Data on socio-demographic variables, comorbidities, pregnancy complications, and follow up within 2 years post-discharge was extracted from Looking Glass©, a combined clinical and claims database. Descriptive analyses showed proportion with at least one visit to primary care or nephrology and an instance of proteinuria checked within 2 years in those with preeclampsia and CKD.

Results: We identified 296 hospitalized pregnant women with a history of pre-eclampsia and CKD of which 2.9% were White, 40.5% were Black, and 46.9% were Hispanic. Median eGFR among those with CKD defined by eGFR only was 42.5 (IQR 38-50), while mean proteinuria for all was 469 mg (IQR 325-862). Median age was 30 yrs (IQR 26-34), and mean BMI 34.0 (SD 7.1). Coexisting comorbidities included hypertension in 49.3 %, diabetes in 5.1%, heart failure in 1.0%, and lupus in 1.7% of patients. Overall, 87.5% of patients had at least one pregnancy complication. The most common complications were preeclampsia during current pregnancy (86.4%), followed by oligohydramnios (5.8%) and preterm labor (3.8%). Of this group, 65 (22.0%) had a clinic visit with primary care/nephrology post discharge, and 149 (50.3%) had proteinuria checked within 2 years. Mean time to first clinic visit was 29.2 days (SD 15.9).

Conclusions: Pregnant patients with prior CKD and pre-eclampsia are at high risk of pregnancy complications, yet only a small proportion are linked to care. There is a dire need for patient centered medical care among pregnant women with CKD, to improve clinical outcomes.

FR-PO866

Temporal Trends in Pregnant CKD Patients

Priscilla Koirala, Vesna D. Garovic, Andrea G. Kattah. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Chronic kidney disease (CKD) during pregnancy significantly increases both maternal and perinatal morbidity and mortality and the incidence of CKD is increasing in persons of childbearing age. In this study, we aimed to identify changes in demographics and comorbidities over time in people with CKD and pregnancy in our tertiary care practice.

Methods: We identified pregnancies delivered at Mayo Clinic in Rochester, MN from 2010 to 2022 and screened the population for ICD-9/10 codes for CKD present prior to the date of delivery. If more than 1 pregnancy occurred in the study period, we evaluated the first pregnancy with pre-existing CKD. We abstracted data on demographics, comorbidities, body-mass index, etiology and stage of CKD. Maternal and perinatal outcomes were evaluated. We compared characteristics by era –2010 to 2016 vs. 2016 to 2022 – using Fischer's exact test for categorical variables and Kruskal-Wallis test for continuous variables. Correlations were evaluated by Spearman's correlations.

Results: We identified 67 deliveries in patients with pre-existing CKD. Median (interquartile range (IQR)) pre-pregnancy BMI was lower prior to 2016 than after (24 (22-31) vs. 30.5 (24-34.5), p=0.048). There was also a significant trend toward increasing BMI by year of delivery ($\rho = 0.27$, $p = 0.04$). Consistent with this trend was the increasing incidence of CKD due to diabetes (14.8% to to 27.3%, before vs. after 2016), though this was not statistically significant. Six patients had biopsies during pregnancy, between 11 and 24 weeks gestation, that established the cause of CKD and had no complications. There was no increase in the incidence of preeclampsia, preterm delivery or maternal ICU stays by era. The eGFR at baseline was significantly associated with gestational age at delivery ($\rho = 0.32$, $p= 0.01$) and birth weight ($\rho = 0.30$, $p = 0.02$).

Conclusions: We found that pre-pregnancy BMI has been increasing over time in patients with CKD. Additionally, worse baseline kidney function was associated with earlier gestational age at delivery and lower birth weight in infants. Given that obesity impacts both pregnancy and CKD health and that there are more obesity treatments available, more investigations should be done to understand whether treatment of obesity prior to conception could impact outcomes of pregnancy in patients with CKD.

FR-PO867

Uric Acid and Risk of Preeclampsia: A Mendelian Randomization Study

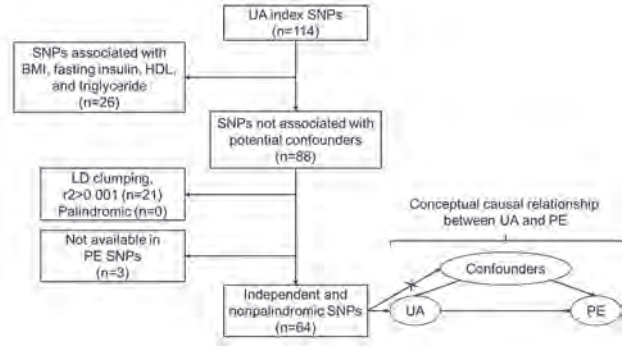
Yitao Lin, Yixin Ma, Lubin Xu, Limeng Chen. *Peking Union Medical College Hospital, Dongcheng-qu, China.*

Background: Maternal serum uric acid (UA) is observationally associated with preeclampsia. However, whether elevated uric acid is a marker of the disease or a causal factor remains unknown. We conducted a two-sample Mendelian randomization (MR) analysis to explore the potential causal effect of UA on preeclampsia.

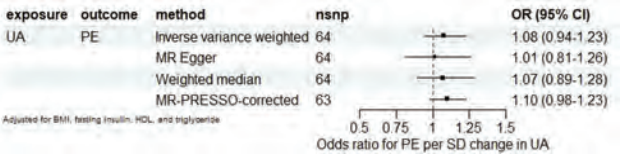
Methods: Summary statistics for UA were from a meta-analysis of genome-wide association studies involving 288,649 individuals of European ancestry, while summary statistics for preeclampsia or eclampsia (PE) were from the FinnGen consortium with 6,436 cases and 176,113 controls. Independent SNPs strongly associated with UA were selected as instrumental variables in causal inference, removing the confounders influencing PE, such as BMI, fasting insulin, HDL, and triglyceride. We applied the inverse variance weighted (IVW) method as the primary analysis and applied MR Egger, weighted median, and MR-PRESSO to evaluate the results. We calculated F statistics to detect weak instrument bias and calculated the power of the MR analysis.

Results: The four MR methods did not reveal the significant causal effect of UA on PE (IVW: OR, 1.08; 95% CI, 0.94-1.23; MR Egger: OR, 1.01; 95% CI, 0.81-1.26; weighted median: OR, 1.07; 95% CI, 0.90-1.27; MR-PRESSO: OR, 1.10; 95% CI, 0.98-1.26). F statistics for individual SNP and overall SNPs were all greater than 10, indicating that weak instrument bias was low. The MR analysis had 48.7% power to detect an OR of 1.1.

Conclusions: This MR study did not support the causal effect of UA on PE.



Selection of instrumental variables.



MR analyses of the causal effect of UA on PE.

FR-PO868

Kidney Hyperfiltration Is Associated with Pregnancy Outcome in Patients with CKD

Shinji Kitajima, Yasunori Iwata, Tadashi Toyama, Akinori Hara, Norihiko Sakai, Miho Shimizu, Takashi Wada. *Kanazawa Daigaku Fuzoku Byoin, Kanazawa, Japan.*

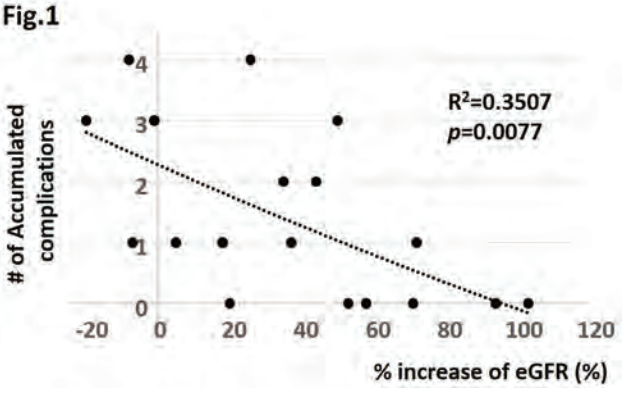
Background: While major population of chronic kidney disease (CKD) is older patients, some population of younger patients are also suffered from CKD. The increased risks of adverse pregnant outcomes were reported in CKD patients. In fact, the frequency of adverse pregnancy outcome is increased in accordance with the severity of kidney dysfunction. In healthy kidney, hemodynamics shifts to hyper-dynamic state during pregnancy. However, details of hemodynamics during pregnancy and its effects for pregnancy outcome are not clear in CKD patients. Therefore, we explored the association between kidney function and pregnancy outcome in CKD patients in this study.

Methods: We retrospectively enrolled 21 CKD patients with pregnancy. The patients visited or were admitted to the Department of Nephrology and Laboratory Medicine and/or Department of Obstetrics in Kanazawa University between 2004 and 2018. The association between kidney function, especially hyperfiltration during pregnancy and adverse pregnancy outcome was evaluated.

Results: The patients without adverse pregnancy complication showed higher eGFR than those with complication during pregnancy period. The increase of estimated glomerular filtration rate (eGFR) during pregnancy is associated with good pregnancy outcome in CKD patients(Fig.1). Even in patients with high eGFR in pre-pregnancy, the absence of increase of eGFR during pregnancy is associated with adverse pregnancy events.

Conclusions: The increase of eGFR during pregnancy was associated with good outcome in CKD patients. Further studies may raise the possibility that assessment of kidney function during pregnancy may be useful marker for the prediction of the pregnancy outcome in CKD patients.

Fig.1



The % increase of eGFR inversely correlated with the numbers of accumulated complications.

FR-PO869

Measurement of Kidney Function and Adverse Pregnancy Outcomes

Anika Lucas, Yixuan Feng, Christina M. Wyatt, Benjamin A. Goldstein. *Duke University School of Medicine, Durham, NC.*

Background: Although it is estimated that 3% of women of childbearing age have kidney disease, there are no guidelines for routinely testing patients for kidney disease in the United States. Our objectives included identifying patients who received 1st and 2nd trimester serum creatinine measurements and evaluating rates of adverse pregnancy outcomes by level of kidney function.

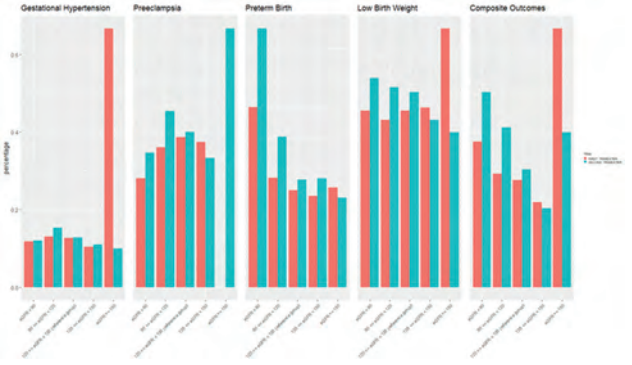
Methods: Pregnant patients with serum creatinine measurements in the 1st and 2nd trimesters of pregnancy were identified in the electronic health record from 2014 to 2019. The 2021 Chronic Kidney Disease Epidemiology Collaboration Equation was used to calculate estimated glomerular filtration rate. Patients were divided into eGFR strata based on previously established eGFR cutoffs. Adverse pregnancy outcomes of interest included low birth weight, preterm birth, gestational hypertension, preeclampsia and a composite outcome.

Results: We identified 6460 patients who had creatinine measurements in the 1st trimester, representing 27% of patients receiving care during the 1st trimester. We further

identified 5268 patients with a 2nd trimester creatinine, only 22% of patients receiving care in the 2nd trimester. Patients who received 1st trimester creatinine measurements were more likely to be <35 years old, Black and from disadvantaged areas. Patients with eGFR <90 ml/min/1.73 m² in the 1st and 2nd trimesters of pregnancy had the highest rates of preterm birth. Patients with eGFR>150 ml/min/1.73 m² had the highest rates of adverse outcomes, though a very small portion of the population.

Conclusions: Less than 1 in 3 patients had serum creatinine measurements available during the 1st and 2nd trimesters of pregnancy. More data is needed to evaluate the utility of creatinine measurements in pregnancy.

Funding: Private Foundation Support



Baseline Characteristics	First Trimester Creatinine	No First Trimester Creatinine Labs	Second Trimester Creatinine labs	No Second Trimester Creatinine
Maternal Age				
<35 y/o	4964 (76.8%)	13451 (77.0%)	4048 (76.8%)	14367 (77.0%)
>35y/o	1496 (23.2%)	4010 (23.0%)	1220 (23.2%)	4286 (23.0%)
Race/ethnicity				
Non-Hispanic Asian	266 (4.1%)	1296 (7.4%)	206 (3.9%)	1356 (7.3%)
Hispanic	870 (13.5%)	2001 (11.5%)	808 (15.3%)	2063 (11.1%
Non-Hispanic Black	3060 (47.4%)	5451 (31.2%)	2482 (47.1%)	6029 (32.3%)
Non-Hispanic White	2076 (32.1%)	8109 (46.4%)	1611 (30.6%)	8574 (46.0%)
Other	188 (2.9%)	604 (3.5%)	161 (3.1%)	631 (3.4%)
Area Deprivation Index (Neighborhood Census Track)				
Mean (SD)	56.0 (23.1)	49.0 (22.8)	57.7 (23.1)	49.0 (22.7)
Median (Min, Max)	56.0 [1.00, 100.0]	48.0 [1.00, 100]	58.0 [5.00, 100]	48.0 [1.00, 99.0]
Missing	596 (9.2%)	1776 (10.2%)	569 (10.8%)	1803 (9.7%)
Medical comorbidities				
Hypertension	837 (13.0%)	594 (3.4%)	585 (11.1%)	846 (4.5%)
Diabetes	477 (7.4%)	256 (1.5%)	316 (6.0%)	417 (2.2%)
CKD or ESKD	63 (1.0%)	22 (0.1%)	56 (1.1%)	29 (0.2%)
Cardiovascular disease	631 (9.8%)	718 (4.1%)	522 (9.9%)	827 (4.4%)
Autoimmune Diseases	100 (1.5%)	28 (0.2)	94 (1.8%)	34 (0.2%)
HIV	27 (0.2%)	17 (0.1%)	16 (0.3%)	28 (0.2%)
Liver Disease	157 (2.4%)	132 (0.8)	131 (2.5%)	158 (0.8%)
Lung Disease	1011 (15.7%)	1525 (8.7%)	779 (14.8%)	1757 (9.4%)
Cancer history	344 (5.3%)	826 (4.7%)	248 (4.7%)	922 (4.9%)

FR-PO870

Maternal Exposure to Tetrahydrocannabinol (THC) During Pregnancy Increases Kidney Damage in Mouse Offspring

Sahar Emami Naeini, Evila Salles, Bidhan Bhandari, Karim M. Saad, Sholeh Rezaee, Ahmed A. Elmarakby, Jack C. Yu, Lei Wang, Babak Baban. *Augusta University, Augusta, GA.*

Background: Maternal use of cannabis during pregnancy has been associated with adverse effects on fetal development. However, little is known about the impact of maternal cannabis use on kidney development in offspring. In this study, we investigated the effects of maternal exposure to placebo, CBD, and THC inhalers on kidney damage in mouse offspring.

Methods: Pregnant mice were randomly assigned to receive either a placebo, CBD, or THC inhaler throughout pregnancy. Offspring kidneys were collected at birth and evaluated for kidney damage using the Kim-1 antibody. The percentage of Kim-1 was measured using flow cytometry.

Results: Kim-1 expression higher in THC treated group compared to the placebo and CBD groups, suggesting more kidney injuries in THC treated animals.

Conclusions: Our findings suggest that maternal exposure to THC during pregnancy may increase the risk of kidney damage in offspring. These results highlight the need for further research on the potential long-term effects of cannabis use during pregnancy.

FR-PO871

Practice Patterns of Nephrologists Who Care for Pregnant Patients with CKD

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Background: Chronic kidney disease (CKD) increases adverse pregnancy events such as pre-eclampsia, preterm delivery, and progression of maternal CKD. While live birth rates among pregnant people with kidney disease have increased, these pregnancies remain a high risk, emphasizing the critical need for advanced understanding and management strategies. Data on Canadian nephrologist practice patterns and center-specific strategies to improve outcomes for pregnant people with CKD are limited. This study used survey methodology to assess practice patterns and policies in this area.

Methods: We conducted a national, cross-sectional survey to assess the practice patterns of Canadian nephrologists caring for pregnant people with CKD. Following literature review, we developed a list of items covering key aspects of CKD management in people who are pregnant, including pre-conception counseling, multispecialty team collaboration and post-transplant care. Items were refined and deduplicated through iterative review by team members. The survey was distributed through professional networks. The responses were analyzed descriptively and key findings were presented as percentages. Additionally, the results for each aspect of the questionnaire were evaluated in light of existing recommendations.

Results: The survey response rate was 71% (25/35). Of the responding nephrologists, 76% identified as women, and 52% had been in practice between 10 and 19 years. Regarding multispecialty care, 36% reported having a full team, 40% had some team elements, and 24% had no team. Individualization of patient care was the most common practice, as opposed to a conventional or standardized approach. This preference for individualization extended to offering pre-natal genetic counselling, antenatal kidney biopsy and antibiotic prophylaxis, and post-partum ACE inhibitor re-initiation.

Conclusions: Our study is the first to assess the practice patterns and policies of Canadian nephrologists caring for pregnant people with CKD. We found important variations in obstetric nephrology care, and that the majority of programs did not have a full multispecialty team. These results emphasize an opportunity to improve care through the creation of formal multidisciplinary teams and the consistent adoption of evidence-based policies.

FR-PO872

Can ChatGPT Keep up with Obstetric and Gynecologic Nephrology? Assessing Its Proficiency in Key Concepts

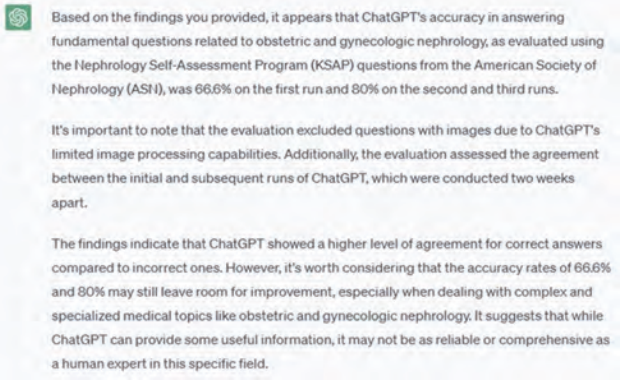
Maria Lourdes Gonzalez Suarez, Vesna D. Garovic, Andrea G. Kattah, Iasmina Craici, Charat Thongprayoon, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: ChatGPT is a language model known for its ability to generate responses similar to those of humans across a variety of tasks. Despite ongoing discussions about the potential of ChatGPT to replace clinicians in clinical contexts, its ability to address essential concepts in a multidisciplinary field, such as obstetric and gynecologic nephrology, has not been thoroughly evaluated. The purpose of this study is to evaluate ChatGPT's proficiency in addressing fundamental questions related to the diagnosis, treatment, and management of hypertension in pregnancy.

Methods: Using the Nephrology Self-Assessment Program (NephSAP) issues V15N2 and V21N4 (questions 25-30), we conducted a study of ChatGPT's accuracy in answering fundamental questions related to obstetric and gynecologic nephrology. Questions with images were excluded. Analysis included 30 questions. Each question set was run 3 times using ChatGPT (version Mar 14, OpenAI), and we evaluated the agreement between the initial and subsequent runs, which were conducted 2 weeks apart.

Results: ChatGPT had accuracies of 66.6% on the 1st, 80% on the 2nd and 3rd runs for the NephSAP questions. We found that ChatGPT demonstrated a higher level of agreement for correct answers than for incorrect ones. However, it is important to note that the accuracy rates of 66.6% and 80% may still have room for improvement, particularly when dealing with complex and specialized medical topics like obstetric and gynecologic nephrology. ChatGPT itself acknowledged these results (**Figure 1**).

Conclusions: ChatGPT's proficiency in addressing fundamental queries related to obstetric and gynecologic nephrology management is below the minimum passing threshold of 75% set by the ASN for nephrologists in its 1st attempt, with an accuracy rate of 66.6%. While ChatGPT can provide some useful information, it may not be as reliable or comprehensive as a human expert in this specific field.


Based on the findings you provided, it appears that ChatGPT's accuracy in answering fundamental questions related to obstetric and gynecologic nephrology, as evaluated using the Nephrology Self-Assessment Program (KSAP) questions from the American Society of Nephrology (ASN), was 66.6% on the first run and 80% on the second and third runs.

It's important to note that the evaluation excluded questions with images due to ChatGPT's limited image processing capabilities. Additionally, the evaluation assessed the agreement between the initial and subsequent runs of ChatGPT, which were conducted two weeks apart.

The findings indicate that ChatGPT showed a higher level of agreement for correct answers compared to incorrect ones. However, it's worth considering that the accuracy rates of 66.6% and 80% may still leave room for improvement, especially when dealing with complex and specialized medical topics like obstetric and gynecologic nephrology. It suggests that while ChatGPT can provide some useful information, it may not be as reliable or comprehensive as a human expert in this specific field.

ChatGPT response on its performance

FR-PO873

Terminal Complement Activation and Regulation in Placentas of Women with Kidney Transplantation and CKD

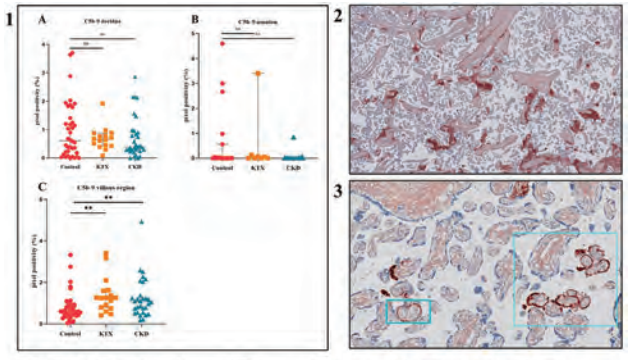
Gesa Tiller,[1] Firas F. Alkaff,[1,2] G. G. Talen,[1] Hanna M. Komdeur,[1] Jelmer Prins,[1] Margriet de Jong,[1] Mirthe H. Schoots,[1] Jacob Van Den Born,[1] Stefan P. Berger.[1] *[1]Universitair Medisch Centrum Groningen, Groningen, Netherlands; [2]Universitas Airlangga Fakultas Kedokteran, Surabaya, Indonesia.*

Background: Women with chronic kidney disease (CKD) or kidney transplant (KTX) are at increased risk of adverse pregnancy outcomes, including pre-eclampsia, intrauterine growth restriction and premature birth. The role of the complement and its relation to placental histopathology has not been studied in this group. We evaluated terminal complement activation and regulation in KTX, CKD and control placentas.

Methods: We retrospectively included 92 placentas, with 33 placentas from CKD, 18 from KTX women, and 42 placentas from healthy pregnancies. Histopathological reports were systematically re-evaluated for lesions scores. Immunohistochemical analysis for terminal complement C5b-9 and its corresponding regulator CD59 were performed in consecutive tissue slides.

Results: C5b-9 expression was pronounced in the villi area of CKD and KTX placentas ($p<0.01$) (1C), with localization of C5b-9 in areas of villous fibrinoids (2). In eight placentas, we noted a unique expression of C5b-9 along the syncytiotrophoblastic layer (3). All of these eight placentas were derived from KTX/CKD women, who were more often treated with tacrolimus during pregnancy ($p<0.05$), and had higher overall expression of C5b-9 in the villous region ($p<0.05$). CD59 expression was higher in the CKD group in the decidual ($p<0.01$), and linked to low birth weight ($p=0.03$) and prematurity ($p=0.049$). Local C5b-9, CD59, and CD59/C5b9 ratio were not linked to lesion scores.

Conclusions: Terminal complement activation in the placental villi of women with KTX or CKD is increased, without corresponding alternations in complement regulation. Altered decidual complement regulation might potentially interfere with placentation, possibly accounting for low birth weight and intrauterine growth restriction. Syncytiotrophoblastic C5b-9 in a subgroup of KTX and CKD women might be of clinical relevance and needs further investigation in a larger cohort.



(1) C5b-9 in KTX, CKD and control placentas in decidua, annuco and villi region, quantified as percentage of pixels. (2) Fibrinoid deposition of C5b-9 as dark red staining (3)Villi with syntiotrophpiblastic positivity are indicated by blue squares. All of these 8 placentas with a syncyitiotrophoblastic staining pattern were amongst the KTX/CKD group.*, significant with p<0.05; ** significant with p<0.01; ns, not significant.

Terminal Complement in KTX, CKD and control placentas

FR-PO874

Multi-Omics of Sex-Based Differences in Nephrotoxic Serum Nephritis

Valerie Garcia,[1] Matthew Wright,[1] Esther Liu,[1] Andra Campbell,[1] Andrew O. Kearney,[1] Jennie Lin.[1,2] *[1]Northwestern University Feinberg School of Medicine, Chicago, IL; [2]Jesse Brown VA Chicago Healthcare System, Chicago, IL.*

Background: Sex-based differences have been observed in the incidence and clinical course of acute kidney injury as well as chronic kidney disease. Compared to males, female patients are more protected from kidney injury and disease progression. Prior studies have identified sexual dimorphism in kidney development and ischemic response, but the mechanisms by which inflammatory stimuli contribute to kidney sex-based differences have not been fully elucidated.

Methods: To examine these differences, we induced nephrotoxic serum (NTS) nephritis in female and male C57BL/6 mice of either 8-12 weeks or 18 months of age. Changes in urine and serum markers were measured, and differences in fibrosis were quantified by Sirius Red staining in kidneys harvested on Day 10. Multi-omics data from matched single nucleus RNA-seq (snRNA-seq) and single nucleus ATAC-seq (snATAC-seq) were generated from those kidneys, with 66,430 nuclei examined.

Results: On Days 4, 7, and 10 after NTS injection, young male mice had significantly higher urinary albumin to creatinine ratio than young females ($p<0.01$), while no differences in albuminuria were seen in aged males vs. females. Although no significant sex-based differences in serum creatinine or renal fibrosis were observed, on a molecular level snRNA-seq revealed major NTS-induced differences in metabolic programs in young male vs. female proximal tubule segments and endothelial cells, and surprisingly few transcriptomic changes in immune cells. Most differentially accessible chromatin regions (DARs) were found in the S3 segment of the proximal tubule with notable motif enrichment for Hnf4a, while DARs in endothelial cells were enriched for Stat3/5 binding motifs. Overall correlation between DARs and differential gene expression across cell populations was 0.54. Despite loss of female renoprotection in aged females, differentially accessible chromatin regions in young females were not enriched in motifs containing estrogen responsive elements, suggesting that cis-regulation by ESR1 is not the direct driver of sex-based differences in NTS nephritis.

Conclusions: Sexual dimorphism in NTS nephritis is characterized by more severe albuminuria in young male mice, likely due to sex-based differences in metabolic pathways in different cell populations rather than direct cis-regulatory function of estrogen receptor binding activity.

Funding: NIDDK Support

FR-PO875

Targeting Interleukin-6/Glycoprotein130 Signaling Ameliorates Renal Injury in Polycystic Ovary Syndrome

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Background: Polycystic ovary syndrome (PCOS) usually presents with hyperandrogenism, chronic low-grade systemic inflammation, and renal injury. The inflammatory cytokine Interleukin-6 (IL-6) is involved in the pathogenesis of several renal injury models by activating its soluble receptor (sIL-6R) and a membrane-bound glycoprotein130 (gp130); however, its role in PCOS-mediated renal damage is unknown. We aimed to test the hypothesis that the increases in systemic and renal IL-6 levels, mediate renal injury in PCOS via IL-6/gp130 signaling activation.

Methods: PCOS was induced in three-week-old female mice using dihydrotestosterone (DHT)-filled Silastic tubes (8 mg, SC) or vehicle for 12 weeks. Eight weeks post-induction, the animals were treated with the IL-6/gp130 signaling inhibitor SC144 (10 mg/kg, SC, 3x/week) or its vehicle for 4 weeks. Body weight, fat mass (EchoMRI), kidney weight, the glomerular filtration rate (GFR, transcutaneous fluorescence), as well as the renal injury markers urinary albumin to creatinine ratio (UACR, clinical chemistry analyzer) and NGAL (ELISA) were assessed. Renal gp130 protein and IL-6 mRNA expression were quantified by Western blot and RT-qPCR, respectively. H&E stained renal sections were used for histopathological analysis, whereas Masson trichrome staining was used to assess renal fibrosis.

Results: DHT significantly ($p<0.05$) increased body weight (26.2±0.9 vs. 22.23±0.4 g), fat mass (3.2±0.4 vs. 1.9±0.4 g), kidney weight (1.4-fold), UACR (1,227±420 vs. 404±169 µg albumin/mg creatinine), urinary NGAL (2-fold), and serum IL-6 levels (2.2-fold). DHT also increased the expression of renal gp130 and IL-6 (1.5-fold). The disturbance in the aforementioned parameters was associated with decreased GFR and a worsen renal histological structure with congested glomeruli, exfoliation of luminal epithelial lining, interstitial hemorrhage, and fibrotic changes. SC144 therapy had no significant effects on kidney weight, GFR, or NGAL, but it attenuated DHT-induced increases in fat mass and UACR while decreasing both glomerular and tubular injury and renal fibrosis.

Conclusions: IL-6/gp130 activation plays a significant role in renal outcomes in PCOS and could be targeted as a novel therapeutic approach to ameliorate renal injury in PCOS.

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FR-PO876

Recovered Parental AKI Results in Dysfunctional Pregnancy and Offspring Programming

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Background: Rhabdomolysis-induced acute kidney injury (RIAKI) follows muscular trauma and is observed in people of childbearing age. Although apparent recovery is common, prior AKI increases the risk of renal and reproductive disease. We hypothesized that recovered AKI induces pregnancy complications and developmentally programs offspring disease.

Methods: Procedures were approved by institutional IACUC. Rhabdomyolysis in 8-12 week old C57BL/6J mice was induced via intramuscular injection of 50% glycerol (8 mL/kg); shams were untreated. AKI was assessed 24 hours later via glomerular filtration rate (GFR; uL/min/100g body weight) and repeated 2 weeks post-recovery to establish functional recovery, followed by 1) timed sham/sham and RIAKI/RIAKI matings for pregnancy (gestational day (GD) 16.5) and 2) adult offspring (12 weeks, 6 months) effects. Urine was collected 24 hours before GFR and tissue harvest for later analysis. Statistics were assessed by t-test for 2 group analyses, and 2-way ANOVA with posthoc tests for analyses by sex.

Results: 1) Despite normal GFR pre-pregnancy, recovered RIAKI dams had lower GFR than shams at GD 16.5 ($p<0.01$). Fetoplacental ratio was lower in RIAKI offspring ($p<0.01$) with no difference in litter size but 3x more perinatal death. Albuminuria ($p<0.01$) was observed in RIAKI dams. RIAKI dams had less megalin ($p<0.05$) and more angiotensin II (AngII) in the proximal tubule brush border than shams, with evidence of subcapsular fibrosis. 2) Offspring of recovered RIAKI parents have sexually dimorphic responses related to renal function. GFR was reduced in offspring of both sexes by 6 months (males: $p<0.05$, females: $p<0.01$). Circulating AngII levels were decreased in

plasma from only female RIAKI offspring compared to shams ($p<0.05$); however, adult males from RIAKI pairings gained more weight than sham males between young and middle adulthood ($p<0.05$).

Conclusions: RIAKI poses reproductive risk long after initial apparent recovery, likely due to new proximal tubule dysfunction in the setting of pregnancy after RIAKI. Renal function in pregnancy, particularly essential function of the proximal tubule via megalin and AngII, is altered by prior RIAKI and developmentally programs offspring with adult-onset reduced GFR, and older male offspring with increased weight gain.

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FR-PO877

Prevalence of CKD in Older Adults by Different Filtration Markers in eGFR Equations

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Background: The prevalence of chronic kidney disease (CKD) is known to increase with age, but few studies investigate age specific prevalence and progression of CKD in populations over 65. Glomerular filtration rate (GFR) can be estimated using different filtration markers that have not been thoroughly studied in older populations, opening the door for research on how these markers may differentially characterize the prevalence and progression of CKD in older age.

Methods: The study population included a community-based sample of 6,393 White and Black participants aged 65-100 stratified into 5-year age categories from Visit 5 of the Atherosclerosis Risk in Communities Study (ARIC). GFR was estimated using CKD-EPI (2021) and Inker et al (2021) equations, and by the following combinations of filtration markers: creatinine (eGFRcr), cystatin C (eGFRcys), both (eGFRcr-cys), and combined with beta-2-microglobulin (eGFRcr-cys-b2m). We calculated the proportion of participants with eGFR <60 ml/min/1.73 m^2 by each marker equation across age strata at Visit 5 (2011-2013), 6 (2016-2017), and 7 (2018-2019), and calculated the proportion of participants with a 30% decline in eGFR at ARIC Visit 6 or 7, across age strata.

Results: Average age at Visit 5 was 75.8 years (SD, 5.3). Mean eGFRcr, eGFRcys, eGFRcr-cys, and eGFRcr-cys-b2m were 71, 61, 68, and 65 ml/min/1.73 m^2, respectively. The proportion with eGFR <60 was lowest with eGFRcr and highest with eGFRcys for all age groups at all visits, and prevalence increased with age for all markers (Figure 1). More people with eGFRcr ≥60 were reclassified to <60 when using eGFRcys (33%) compared with eGFRcr-cys (12%) or eGFRcr-cys-b2m (18%). The proportion with 30% eGFR decline was lowest with eGFRcr and highest with eGFRcys, with greater incidence in older age groups for all markers.

Conclusions: The prevalence and progression of CKD increases with age but varies depending on filtration marker used. Creatinine underestimates CKD compared to other filtration markers.

Funding: NIDDK Support, Other NIH Support - NHLBI

	ARIC Visit 5 (2011-2013)					ARIC Visit 6 (2016-2017)					ARIC Visit 7 (2018-2019)				
Age	N	eGFRcr	eGFRcys	eGFRcr-cys	eGFRcr-cys-b2m	N	eGFRcr	eGFRcys	eGFRcr-cys	eGFRcr-cys-b2m	N	eGFRcr	eGFRcys	eGFRcr-cys	eGFRcr-cys-b2m
65-69	666	15%	26%	17%	21%										
70-74	2317	19%	39%	24%	29%	524	21%	39%	25%	28%	90	15%	42%	22%	24%
75-79	2794	26%	51%	33%	38%	1493	25%	49%	32%	37%	1355	28%	57%	36%	41%
80-84	1152	37%	65%	47%	53%	963	33%	62%	44%	49%	1051	34%	62%	45%	50%
85-89	459	46%	82%	60%	68%	504	38%	74%	50%	57%	532	42%	78%	56%	64%
90-94						223	50%	90%	72%	76%	263	57%	93%	75%	80%

FR-PO878

Estimated Glomerular Filtration Rate Thresholds Associated with Poor Long-Term Outcomes in the Elderly with Diabetes

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Background: Age-adapted estimated glomerular filtration rate (eGFR)-based chronic kidney disease (CKD) criteria was recently proposed, which has been supported by the fact that mortality risks start to increase at GFR <45 mL/min/1.73m^2 in the elderly. However, the eGFR threshold for mortality and kidney outcomes in elderly with diabetes was less understood. We aimed to evaluate eGFR categories that raise the risk of mortality and end-stage kidney disease (ESKD) by age group, using an 8-year follow-up cohort of elderly diabetic patients.

Methods: Elderly patients (≥65 years) with type 2 diabetes who visited our outpatient diabetes center during 2009 were identified and followed up until 2017. Patients were categorized into four groups per their CKD-EPI equation-based eGFR: ≥60, 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73m^2. Cox proportional hazard model for all-cause mortality and competing-risk analysis for ESKD (with a competing event of pre-ESKD death) were performed.

Results: Among 3,065 subjects, 19%, 8%, and 2% patients had eGFR 45 to 59, 30 to 44, and 15 to 29 mL/min/1.73m^2 at baseline, respectively. After adjusting multiple clinical covariates, including blood pressure, diabetes duration, urine albumin/creatinine ratio, HbA1c, serum cholesterol levels, and comorbidity index, patients with eGFR 30 to 44 and 15 to 29 mL/min/1.73m^2 had 1.51-fold (95% CI 1.17–1.95, P <.001) and 2.66-fold (1.87–3.79, P <.001) greater risks of death, respectively, whereas patients with eGFR 45 to 59 mL/min/1.73m^2 had a comparable risk (1.18, 0.96–1.45, P = 0.127) to those with eGFR ≥60 mL/min/1.73m^2. Substitution hazard ratios for ESKD were 2.29 (1.41–3.71, P = 0.001), 5.25 (3.27–8.41, P <.001), and 16.74 (9.73–28.80, P <.001) in patients with eGFR 45 to 59, 30 to 44, 15 to 29 mL/min/1.73m^2, respectively. In a subgroup of patients 75 or older (n=800), patients with eGFR 45 to 59 mL/min/1.73m^2 showed comparable risks for both ESKD and mortality, and ESKD risk started to increase from eGFR <45 mL/min/1.73m^2.

Conclusions: Reduced eGFR <60 mL/min/1.73m^2 predicted an increased risk of ESKD in elderly diabetic patients, suggesting that the current traditional eGFR threshold appears feasible. However, in patients ≥75 years, eGFR ranging from 45 to 59 mL/min/1.73m^2 had little effect on long-term outcomes for both mortality and ESKD.

FR-PO879

Large Discordances Between Creatinine (Cr) and Cystatin C-Based Estimated Glomerular Filtration Rates (eGFR) Are Associated with Adverse Outcomes in a Nationally Representative Cohort of Older Adults

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Background: Creatinine based eGFR may be overestimated in adults with sarcopenia. While the combined equation CKD-EPI eGFR-CRE-CYS may be more accurate on a population level, patients whose eGFR-CYS is significantly lower than eGFR-CRE (eGFR discordance) may be at high risk for adverse outcomes.

Methods: In a longitudinal cohort study of adults 65+ yrs, from the Health and Retirement Study 2016 Venous Blood Study, we calculated eGFR-CRE and eGFR-CYS with current CKD-EPI. Outcomes included fall, hip fracture, hospitalization, and death 2 years from baseline assessment. We plotted the relationship between eGFR discordance and likelihood of outcomes in each ventile using a loess plot with span 75%. We fit separate multivariable logistic regression to determine the association between large eGFR discordances (i.e. >30%) and each outcome, adjusted for confounders.

Results: There were 5574 participants with a mean age of 75 ±7.2 yrs, 58% women, 80% white, and 10% Hispanic. 35% had chronic kidney disease (CKD) (eGFR-CRE-CYS <60 ml/min/1.73m^2). 30% had eGFR-CYS >30% lower than eGFR-CRE. We found increasing rates of falls, hospitalizations, and death at higher eGFR discordances **[Figure 1]**. In adjusted analyses, large eGFR discordance was associated with a significantly greater odd of fall, hospitalization, and death **[Figure 2]**.

Conclusions: Older adults with a large eGFR discordances have a greater risk of adverse outcomes, possibly due to misdosing of renally cleared medications, occult CKD or sarcopenia.

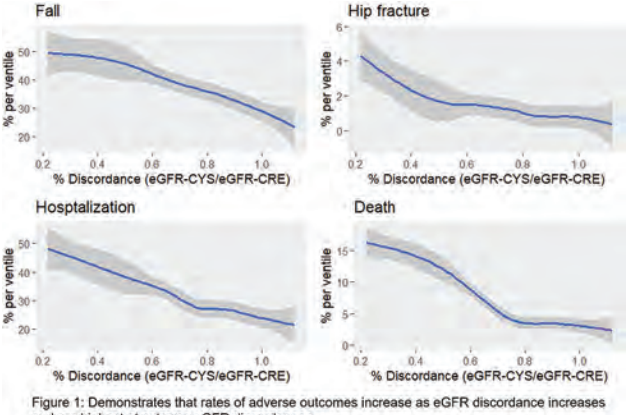
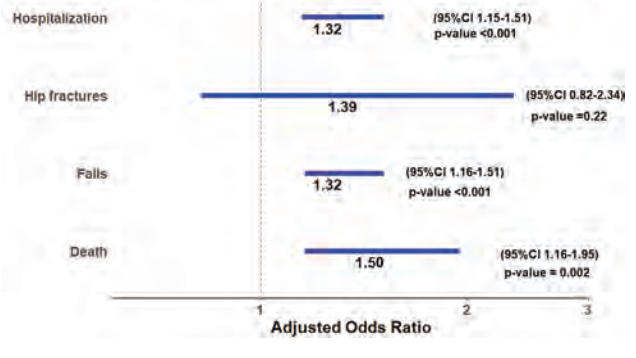


Figure 1: Demonstrates that rates of adverse outcomes increase as eGFR discordance increases and are highest at extreme eGFR discordances.

Figure 2: Adjusted odds ratio for adverse outcomes in participants with eGFR discordance > 30%



FR-PO880

Serum and Urine Metabolites and Kidney Function in an Older Community-Based Population

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Background: Metabolites represent a cellular read-out of ongoing processes underlying states of health and disease.

Methods: We evaluated cross-sectional and longitudinal associations between 1254 serum and 1398 urine metabolites (untargeted, Metabolon HD4, 713 present in both biofluids) and kidney function in 1613 participants of the Atherosclerosis Risk in Communities (ARIC) Study (visit 5; mean age 76 years, 56.1% women, mean eGFR and urine albumin-to-creatinine levels (ACR) of 62 mL/min/1.73m^2 and 4 mg/g, respectively). All analyses were comprehensively adjusted including for baseline eGFR and ACR.

Results: In cross-sectional analysis, 674 serum and 542 urine metabolites were associated with eGFR (p<4E-5), including 245 in both biofluids. Fewer metabolites (75 serum and 92 urine metabolites, including 7 shared across both biofluids) were associated with ACR. Five metabolites, including 2 unnamed metabolites, were significantly associated with both eGFR and albuminuria (Table 1). In longitudinal analysis, higher levels of N2,N2-dimethylguanosine and X-25422 were associated with greater risk of eGFR decline (defined as 40% decrease over a mean follow-up of 6.6 years) and increase in albuminuria (defined as doubling of UACR levels) in both serum and urine (p<0.05). Next, we estimated the relative fractional excretion (rFE) of metabolites shared in both biofluids (713). The rFE of 482 metabolites had negative associations with eGFR, whereas 5 metabolites had positive associations (p<7E-5). The most negative associations with eGFR were for 5-methylthioribose and 5-oxoproline and the most positive was for gamma-glutamylglutamine. Thirty-eight rFE of metabolites were associated with eGFR decline (p<0.05), including guanine, S-methylcysteine sulfoxide, and hypoxanthine which were protective for eGFR decline, but none met Bonferroni significance (p<5E-5).

Conclusions: In summary, untargeted metabolomic profiling can identify metabolites of interest in kidney disease. Notably, the metabolomic coverage was markedly increased by the inclusion of both matrices.

Funding: NIDDK Support

Metabolite	β_{eGFR} (serum) [95% CI]	β_{eGFR} (urine) [95% CI]	β_{ACR} (serum) [95% CI]	β_{ACR} (urine) [95% CI]
Guanidinosuccinate	-0.039 [-0.042, -0.037]	-0.018 [-0.021, -0.016]	0.071 [0.42, 0.10]	0.049 [0.027, 0.071]
N2,N2-dimethylguanosine	-0.017 [-0.017, -0.016]	-0.004 [-0.005, -0.003]	0.022 [0.013, 0.031]	0.020 [-0.028, -0.012]
Hydroxy-N6,N6,N6-trimethyllysine	-0.024 [-0.025, -0.023]	-0.007 [-0.009, -0.006]	0.030 [0.018, 0.042]	-0.030 [-0.044, -0.016]
X-13844	-0.040 [-0.045, -0.036]	-0.020 [-0.024, -0.016]	0.13 [0.088, 0.18]	0.082 [0.045, 0.12]
X-25422	-0.035 [-0.037, -0.032]	-0.017 [-0.019, -0.015]	0.079 [0.058, 0.10]	0.049 [0.029, 0.069]

Table 1: Metabolites associated with both eGFR and albuminuria.

FR-PO881

Perceptions of Shared Decision-Making and Preferences for Engagement Among Older Adults with CKD: A Mixed-Methods Study

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Background: Older adults with advanced chronic kidney disease (CKD) face preference-sensitive decisions regarding dialysis initiation. Although shared decision-making (SDM) is recommended, clinicians are unsure how to best facilitate SDM and few CKD patients report experiencing SDM. This study characterizes clinician perspectives on SDM and patient preferences for engagement.

Methods: A mixed-method, longitudinal analysis of surveys and semi-structured interviews was conducted with English-speaking adults 70 years or older with CKD stages 4-5 in Boston, Chicago, San Diego, or Portland (ME) as part of the Decision Aid for Renal Therapy (DART) Trial. Patients' preferences for engagement were measured using the validated Control Preferences Scale (CPS), which categorizes patients as preferring active, collaborative, or passive engagement. Semi-structured interviews were conducted with a subset of purposively sampled patients and clinicians at these four sites. We used descriptive statistical analysis to examine quantitative data, and thematic and narrative analyses to examine qualitative data.

Results: Among 363 patient-participants at baseline, 42% were female, 13% identified as Black, and 21% had high school education or less. Overall, 92% preferred to play an active or collaborative role in decision-making. CPS preferences were stable throughout; at the individual level, only 4.6% demonstrated a major change (active to passive or passive to active) between baseline and first follow-up. A subset of 75 participants (44 patients and 31 clinicians) completed qualitative interviews, contributing to four qualitative themes: 1) active and collaborative control preferences tied to patient engagement; 2) clinicians constrain information flow; 3) patients with collaborative and active preferences want free-flowing information; and 4) clinician responsiveness to control preference tied to patient satisfaction.

Conclusions: Older adults with advanced CKD overwhelmingly preferred collaborative or active roles, with more prognostic information earlier in the process. Utilizing the single-item CPS may be a simple and effective way for clinicians to assess patients' preferred level of engagement and determine the flow of information.

Funding: Private Foundation Support

FR-PO882

Patient and Clinician Perspectives on an Advance Care Planning Decision Aid for Older Patients with CKD: Decision Aid for Renal Therapy (DART)-Advance Care Planning (ACP)

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Background: Among Medicare beneficiaries 65 and older with chronic kidney disease (CKD), adjusted mortality is over twice as high compared to age-matched non-CKD counterparts. However, few older adults with CKD complete advance care plans (ACP), which can align care with patient preferences. We assessed the accessibility and feasibility of a decision aid tailored to ACP for other populations have been shown to increase knowledge of ACP and readiness for end-of-life conversations.

Methods: Qualitative study using semi-structured interviews (March 2022-March 2023) with purposively sampled patients (CKD stage 4-5 patients, age ≥50) and clinicians (nephrologists). Participants viewed DART-ACP modules prior to interviews. Patient participants were approached in participating nephrology clinics in Greater Boston. Audio recordings were transcribed verbatim, and content and thematic analysis were conducted.

Results: 61 participants (29 clinicians; 33 patients) completed interviewed. Among clinicians, 38% were women and 41% were from the Northeast. Among patients, 36% were women, 39% identified as Black, and mean age was 70 ± 9 years. Four themes emerged during thematic analysis: 1) acceptability of DART-ACP among patients and clinicians; 2) difficulty in understanding granularity and impact of end-of-life decisions; 3) demand for information on palliative care; and 4) empowering patients to document wishes. DART-ACP was described as clear, approachable, and informative for patients across demographic categories and among most clinicians. DART-ACP was acceptable even among patients who reported being hesitant about ACP. Suggestions for improvement included incorporating lived experiences, integrating ACP documents into the modules, and including information for carepartners.

Conclusions: Patients and clinicians found DART-ACP accessible and useful in the context of dialysis decision-making, especially information about palliative care. Participant feedback will inform tailoring DART-ACP for clinical use.

Funding: Private Foundation Support

FR-PO883

Understanding Patient Engagement in Advance Care Planning

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Background: Approaches enabling shared decision-making for serious illness and end-of-life care with kidney patients are variable with significant challenges. There is no systematic approach to introduce these conversations and data understanding patient engagement is limited.

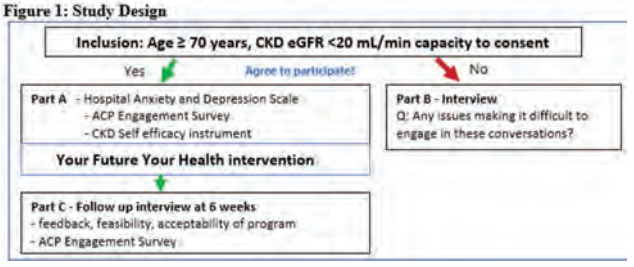
Methods: An interventional mixed methods study aimed to understand patient perspectives of advance care planning (ACP) at a single kidney care centre in Australia (Figure 1). A 1-hour conversation between kidney clinicians (nurse or doctor) and patients provided information regarding kidney health, and ACP concepts were introduced. Descriptive statistics and paired t-tests estimated the effect of the intervention and qualitative data were analysed thematically.

Results: Between December 2022 and April 2023, 47 kidney patients were consented: 40 in Part A and 7 in Part B. The average age was 80 years, 57% male, 57% Australian-born, 81% English speaking, 37% CKD, 47% satellite dialysis, 14% home dialysis. Participants' perceived kidney disease related self-efficacy was high, with few symptoms of depression or anxiety. Median time between interview and follow up feedback was 6 weeks [IQR 4,9]. During this period 64% of people reported having an ACP conversation with family or caregivers. The intervention showed an improvement in mean "readiness to formally ask someone to be a medical decision maker" (3.2[1.9] to 3.8[1.6], p=0.04). No improvement on other dimensions of ACP engagement was found. Preliminary analysis of qualitative data highlighted disabling patient factors that hindered ACP engagement, including: 1. Perceived cultural and physical barriers to communication. 2. Coping strategies focused on living in the present. 3. Differing perceptions of the utility of end-of-life discussions. 4. Distress and fear at the prospect of serious illness or death.

Conclusions: These findings suggest that the intervention facilitated conversations between patients and their of medical decision makers. This study also highlights the social and psychological factors which impact patient engagement in future treatment planning.

Funding: Other NIH Support - Eastern Health Foundation Grant

Figure 1: Study Design



FR-PO884

The Current Status of Advance Care Plan and Dialysis Withdrawal in Elderly Hemodialysis Patients in South Korea

Jangwook Lee,[1] Woo Yeong Park,[2,3] Jang-Hee Cho,[4,5] Byung chul Yu,[6] Miyeun Han,[7] Sang Heon Song,[8] Jae Won Yang,[9,10] Sungjin Chung,[11,12] Yu Ah Hong,[13,14] Young Youl Hyun,[15,16] Eunjin Bae,[17] In O Sun,[18] Hyunsuk Kim,[19,20] Won Min Hwang,[21] Soon hyo Kwon,[22] Kyung Don Yoo,[23,24] Jiyun Jung,[1] Jae Yoon Park,[1] Sung Joon Shin.[1] Korean Society of Geriatric Nephrology (KSGN). *[1]Dongguk University Ilsan Hospital, Goyang, Gyeonggi-do, Republic of Korea; [2]Keimyung University Dongsan Medical Center, Daegu, Republic of Korea; [3]Keimyung University School of Medicine, Daegu, Republic of Korea; [4]Kyungpook National University Hospital, Daegu, Republic of Korea; [5]Kyungpook National University School of Medicine, Daegu, Republic of Korea; [6]Soonchunhyang University Hospital Bucheon, Bucheon, Gyeonggi-do, Republic of Korea; [7]National Medical Center, Seoul, Republic of Korea; [8]Pusan National University School of Medicine, Yangsan, Republic of Korea; [9]Wonju Severance Christian Hospital, Wonju, Gangwon-do, Republic of Korea; [10]Yonsei University Wonju College of Medicine, Wonju, Republic of Korea; [11]Catholic University of Korea Yeouido Saint Mary's Hospital, Seoul, Republic of Korea; [12]The Catholic University of Korea School of Medicine, Seoul, Republic of Korea; [13]Catholic University of Korea Daejeon St Mary's Hospital, Daejeon, Daejeon, Republic of Korea; [14]The Catholic University of Korea School of Medicine, Seoul, Seoul, Republic of Korea; [15]Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea; [16]Sungkyunkwan University School of Medicine, Suwon, Republic of Korea; [17]Gyeongsang National University Changwon Hospital, Changwon, Gyeongsangnam-do, Republic of Korea; [18]Presbyterian Medical Center, Jeonju, Jeollabuk-do, Republic of Korea; [19]Chuncheon Sacred Heart Hospital, Chuncheon, Gangwon-do, Republic of Korea; [20]Hallym University College of Medicine, Chuncheon, Gangwon, Republic of Korea; [21]Konyang University Hospital, Daejeon, Republic of Korea; [22]Soonchunhyang University Hospital, Seoul, Republic of Korea; [23]Ulsan University Hospital, Ulsan, Republic of Korea; [24]University of Ulsan College of Medicine, Ulsan, Republic of Korea.*

Background: Only a few studies have investigated end of life care or experiences of elderly hemodialysis patients. We aimed to explore advance care plan and dialysis withdrawal in elderly hemodialysis patients at the end of life in South Korea.

Methods: We analyzed medical data of elderly dialysis patients (≥70 years old) who died between January 1, 2010 and December 31, 2017, at 10 university hospitals in the Korean Society of Geriatric Nephrology (KSGN). We examined causes of death, the presence of advance care plan, and clinical variables related to dialysis and life-sustaining treatments.

Results: Of 404 deaths, 57.7% were male and the mean age was 77 years. Dialysis was maintained for an average of 792 days. The most common causes of death in elderly dialysis patients were infection, cardiovascular disease and malignancy accounting for 48.8%, 20% and 8.7% of cases, respectively. The overall rate of advance care planning including Do-Not-Resuscitate orders in these patients reached to 70%. Despite of the explicit expressions against life-sustaining treatment, ventilator care was provided in 45.3% and cardiopulmonary resuscitation was performed in 33.4% of the patients. Moreover, more than half (63.9%) continued to receive hemodialysis until three days before death (91.2% until two weeks prior to death).

Conclusions: Our findings imply the importance to respect patients' preferences and advance care plan when it comes to end of life care in elderly dialysis patients. Shared decision making could play a key role in that regard to resolve the discrepancy between advance care plan and actual provision of life-sustaining treatments at the end of life.

Funding: Other NIH Support - Cooperative Research Grant 2019 from the Korean Society of Nephrology.

FR-PO885

Acceptability of a Palliative Care Intervention for Older Adults Facing Dialysis Decisions: A Qualitative Study of Patients, Caregivers, and Their Nephrologists

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Background: Older adults in the US often receive kidney therapy (KT) that doesn't align with their goals. Palliative care specialists are experts in decision-making, but few palliative care decision-support interventions exist for older adults with advanced chronic kidney disease.

Methods: A trained research coordinator interviewed patients and nephrologists participating in the CKD-EDU study. Three coders analyzed the data using a thematic analysis approach to identify salient themes around the acceptability of the intervention and nephrologists' views on palliative care.

Results: The study included 20 patients with a mean age of 80.5 ± 4.9 years, of whom 10 (52%) were women, 16 (76%) were White, and 17 (81%) had an education level of ≥12th grade or higher. The study also included 24 nephrologists with a mean age of 43 ± 9.5 years, of whom 15 (63%) were men, 14 (58%) were White, and 12 (50%) had 0-5 years of experience in nephrology. Patients and caregivers found the intervention valuable due to personalized care, assistance with making decisions, and help with understanding prognostic information. Nephrologists appreciated support for their patients in making therapy decisions, assistance with symptom management, and help with a conservative kidney management pathway.

Conclusions: Both patients/caregivers and nephrologists found the intervention for kidney therapy decision-making to be acceptable and useful. Future studies assessing the effectiveness and implementation of palliative care services in routine clinical care are needed.

Funding: NIDDK Support, Other NIH Support - University of Rochester KL2 program, Private Foundation Support

FR-PO886

Concurrent Hospice in a Veterans Affairs Dialysis Unit: A Single-Center Experience

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Background: Patients with end stage kidney disease experience significant underutilization of hospice services. The Centers of Medicare and Medicare Services allows for enrollment in concurrent hospice and dialysis. We sought to share our experience with this program.

Methods: We analyzed all deaths among dialysis patients at our institution (n=49) between 2019 and 2022. Of these, 27 (55%) were enrolled in concurrent hospice. Data collected included: demographics, comorbidities, health care utilization, code status, and location of passing. Descriptive statistics were used for continuous data. Associations between variables of interest and concurrent hospice were assessed using $\chi 2$, Fisher's exact, or Wilcoxon Rank Sum tests. All analyses were performed using SAS 9.4.

Results: Among patients receiving concurrent hospice services and hemodialysis, the median time on hospice was 26 days (IQR: 9.0, 62.0). There were no differences between the two cohorts for year of passing, age and common comorbid conditions. During the last 12 months of life, there were no differences in emergency department visits, hospitalizations, invasive procedures, or blood cultures drawn. A higher proportion of patients on concurrent hospice, had "do not resuscitate" orders at the time of passing (96.3% vs. 22.7%; $p < 0.0001$). Patients on hospice were less likely to pass in the hospital setting (22.2% vs. 63.6%, $p = 0.004$), but more likely to pass at home or in a skilled nursing facility (77.8% vs. 31.8%, $p = 0.002$).

Conclusions: Our data suggests that among the hemodialysis population, enrollment in concurrent hospice services was not associated with increased healthcare resource utilization. This information may help increase enrollment in hospice among dialysis patients and promote optimal end of life care.

Hospice Enrollment Status	Enrolled	Not Enrolled	p-value
N	27	22	
Age	71 (66, 76)	67 (54, 74)	0.07
Days on dialysis	1381 (488, 1813)	935.5 (477, 1670)	0.55
ED visits	6.0 (2.0, 8.0)	3.5 (1.0, 7.0)	0.33
Hospitalizations	2.0 (1.0, 4.0)	2.0 (2.0, 4.0)	0.96
IR visits	1.0 (0.0, 3.0)	1.0 (0.0, 2.0)	0.53
Blood cultures	1.0 (0.0, 5.0)	1.0 (0.0, 3.0)	0.49
DNR at time of death	26 (96.3%)	5 (22.7%)	< 0.0001
Passed in hospital setting	6 (22.2%)	14 (63.6%)	0.0042
Passed at home or SNF	21 (77.8%)	7 (31.8%)	0.0022

FR-PO887

Nephrology Providers' Experiences with Discussing the Option of Forgoing Kidney Replacement Therapy with Patients

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Background: Understanding how nephrology providers discuss therapeutic alternatives to kidney replacement therapy (KRT) for advanced kidney disease is paramount to supporting efforts to improve shared decision-making with patients.

Methods: We conducted a cross-sectional survey study of national sample of nephrology providers recruited through US professional societies between March-July 2022 about their experiences caring for patients who forgo KRT. We invited a random sample of survey respondents to complete follow-up qualitative interviews between August-October 2022 about their experiences discussing this option with patients.

Results: Overall, 203 nephrology providers (age 47±12 years, 66.0% female, 53.2% white), of which 49.8% were nephrologists and 50.2% were advanced practice providers completed the survey. The terms "active medical management without dialysis" (44.4%) and "conservative kidney management" (12.0%) were rated "overall best" in conveying the approach to care for patients who forgo KRT. From interviews with 21 (age 54±13 years, 81.0% female, 57.1% white) survey respondents, 3 dominant themes reflecting experiences with discussing this option with patients emerged: 1) Terminology used: there was inconsistency in the terms used to describe this option across different providers, the terms used by the same provider with different audiences, and the meaning of the same term to different providers; 2) Interpreting patients' expressed preferences: when patients communicated a desire not to receive KRT, providers were unsure whether patients truly meant to never pursue KRT and whether patients were likely to change their minds; and, 3) Sharing decision-making: providers spoke to challenges with negotiating respect for patients' autonomy, perceived best interests for the patient, and influences from family members when counseling patients about decisions to forgo KRT.

Conclusions: There is substantial inconsistency and ambiguity in providers' discussions with patients about care for patients who forgo KRT. Our findings highlight a need to build professional consensus on language used to discuss this option and for additional tools to assist providers with navigating these discussions.

Funding: Private Foundation Support

FR-PO888

Promoting Goals of Care Conversations in Older Veterans Referred for Dialysis Education: A Quality Improvement Study

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Background: Elderly patients that progress to end stage kidney disease (ESKD) have multi-morbidity and higher mortality rates than others of similar age. The Veterans Affairs Life Sustaining Treatment Initiative (LSTI) promotes goals of care conversations in high-risk veterans to identify preferences for life sustaining treatments (LSTs). Life-sustaining treatment preferences are then documented in a LST note.

Methods: This quality improvement project created a palliative care (PC) consult trigger process for all ESKD Veterans 70 and older who were referred for dialysis modality education between 9/2022 –4/2023. The goal was to increase rates of LST note completion prior to dialysis initiation.

Results: Twenty Veterans were referred for dialysis education in the six-month period. Sixteen of the 20 Veterans met age criteria for a PC trigger consult, characteristics are shown in table 1. Thirteen veterans attended the PC consult, one did not attend, and two declined. Only three veterans had LST notes completed prior to their referral for dialysis education. All Veterans who met with PC completed LST notes. One of 16 veterans opted for conservative treatment, and three initiated dialysis. Outcomes are shown in Table 2.

Conclusions: Trigger PC consultation at time of dialysis education in older patients led to 100 percent LST note completion rate. Including PC prior to dialysis initiation clarifies and documents preferences for LSTs. Future studies should examine the impact of PC consultation on the clinical course and quality of life in older ESKD Veterans.

Characteristics	Total cohort (N=16)
Age (years), mean	78
Gender, n (%)	
Male	16 (100)
Female	0 (0)
DM , n (%)	13 (80)
HTN, n (%)	16 (100)
Amputation, n (%)	1 (6)
Dementia, n (%)	1 (6)
Hx of cancer, n (%)	4 (25)
Albumin level (g/dl), mean	3.9
eGFR (mL/min/1.73 m^2), mean	15

Table 1

Outcomes	Total cohort (N=16)
Attend PC, n (%)	13 (80)
LSTI at referral, n (%)	3 (20)
LSTI after PC consult, n (%)	13 (80)
Dialysis modality chosen	
HD, n (%)	10 (60)
PD, n (%)	4 (25)
Conservative Rx, n (%)	1 (6)
Dialysis initiated, n (%)	3 (19)

Table 2

FR-PO889

Commitment to Practice Change Through Case-Based Learning to Improve Palliative Care for Older Patients with Kidney Failure

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Background: Patients with advanced chronic kidney disease (CKD) and kidney failure have many unmet palliative care needs. Nephrologist buy-in to implement primary palliative care has been cited as a major barrier. Interventions are needed to increase nephrologist awareness of and commitment to palliative care for their patients.

Methods: In a New York City-based CKD and dialysis program, we held a year-long series of monthly Project ECHO-style webinars. CKD and dialysis center staff screened patients for appropriateness for palliative care referral, agreed on pertinent patient issues, and presented their cases to an interdisciplinary expert faculty with backgrounds in nephrology, palliative medicine, and psychology. Participants evaluated webinars for practice relevance, whether they motivated them for practice change, and if so, in what way. Faculty categorized the major issue raised by each case. The online registration tool recorded the number and disciplines of participants.

Results: By discipline, 65 clinicians participated one or more times including nephrologists. nurses, social workers, a psychologist, and palliative medicine physicians. On a scale from 1-5 (low to high relevance), participants rated information from webinars that could be applied to practice a mean of 4.9. Based on webinar content, 95% reported they were planning to make one or more changes to their practice, most commonly involving other team members in decision process (53%) and changing how often they raise palliative care topics (48%). Major issues raised by cases included whether to start frail nonagenarians with comorbidities on dialysis and how to manage the following issues in in-center hemodialysis patients: failing to thrive, dementia-related aberrant behavior, and substance use disorder. Knowledge exchange between nephrology and palliative medicine clinicians was reciprocal and fostered referral relationships.

Conclusions: Project ECHO format with case- and evidence-based experiential learning addressing practical, relevant patient care issues engaged nephrology clinicians and motivated them to implement primary palliative care skills into their practices. These preliminary findings suggest a potentially fruitful approach to gain nephrology clinician buy-in to primary palliative care and warrant further study and collaboration.

Funding: Private Foundation Support

FR-PO890

Optimizing Veteran Video Connect: Engaging Veterans with Advanced Kidney Disease in Goals of Care Conversations

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Background: Chronic kidney disease (CKD) prevalence and its associated morbidity and mortality is higher among Veterans than in the general population. As such, goals of care conversations (GOCC) are indicated. Little is known regarding the use of tele-palliative consultation for GOCC in older adult Veterans with CKD. This pilot study examined the acceptability, facilitators, and barriers of engaging this population in GOCCs via telehealth.

Methods: This study used prospective observational design and semi-structured interviews. Eligibility criteria included geriatric patients ≥70 with CKD 4 or 5 without documented life-sustaining treatment (LST) preferences in the past 90 days. Patients were referred to palliative care (PC) clinic for GOCCs.

Results: 62 patients were identified and 40 were enrolled. Most patients preferred in-person and telephone PC visits (70%). Only 30% preferred telehealth. There were no clinical or demographic differences among patients based on visit modality preference, including in LST preferences. In patients who preferred an in-person visit, 42% cited discomfort with technology and 25% cited functional deficits.

Conclusions: Life sustaining treatment preferences and note completion rates among older Veterans with advanced CKD did not vary based on GOCC visit modality. Discomfort with technology was the most common barrier to telehealth. Future studies should focus on how to reduce technology barriers for older Veterans.

Funding: Veterans Affairs Support

LST completion rate and preferences by modality of GOCC (n=38)[a]				
		In-person or telephone PC visit (n=28)	VVC or CVT PC visit (n=10)	P-value[b]
		n (%)		
LST completed during PC visit		22 (78.6)	8 (80.0)	1.000
LST preferences selected during completed PC visit				
	DNR	0 (0)	1 (12.5)	0.434
	DNR without limits to LSTs	12 (54.5)	4 (50.0)	
	Full code	6 (27.3)	1 (12.5)	
	Full code without limits to LSTs	4 (18.2)	2 (25.0)	

[a]Two patients died before scheduled visit date and two patients who initially preferred VVC completed their visit by telephone.

[b]Fisher exact test was conducted when expected cell value was less than 5; Wilcoxon rank-sum (Mann-Whitney) test for non-normally distributed variables and t-test for age.

FR-PO891

Using Population Health Management Program to Promote Patient Choice for Medical Management Without Dialysis

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Background: Patients with advanced chronic kidney disease (CKD) often start on dialysis as the default treatment option, without a shared decision making discussion (SDM) in which they and their care partners actively choose a renal replacement therapy option that best aligns with their values and wishes. We describe a program to promote SDM and characteristics of patients who chose medical management without dialysis (MMWD).

Methods: As part of the ongoing CKD population health management program at UPMC, high-risk CKD patients not seeing a nephrologist are identified through electronic health record and co-managed with their primary care provider. Patients age>85 years with eGFR <30 ml/min, or those with surprise question ("will you be surprised if this patient dies in next 12 months") "no" are automatically referred to discuss treatment options with a kidney palliative care advanced practice provider (APP) via telemedicine. Among people who received care in an APP-led decision-making session, we (1) assessed the frequency of selecting MMWD, and (2) compared demographic and clinical characteristics of those who chose MMWD to those who did not.

Results: Of 150 patients who met with an APP, 74 elected MMWD (49%), while 76 (51%) chose to pursue dialysis as a future treatment option. Patients who chose MMWD did not differ by age (mean 88y vs 86y, p = 0.072), gender (59.5% vs. 61.8% female, p=0.77), or eGFR (mean 29.5 vs 32.2, p=0.085) compared to patients who chose dialysis. Additionally, patients who chose MMWD did not have a significantly higher burden of comorbidities compared to those who chose dialysis, including coronary artery disease (59.5% vs. 56.6%, p=0.72), cancer (40.5% vs 38.2%, p=0.77), chronic heart failure (50% vs 46.1%, p=0.63), chronic obstructive pulmonary disease (28.4% vs 21.1%, p=0.30), depression (28.4% vs 35.5%, p=0.35), and diabetes (50.0% vs 50.0%, p=1.00).

Conclusions: CKD population health management program with automated referrals to palliative care-led decision making session is an innovative method to identify and provide patients with CKD increased access to opportunities to discuss treatment options. Our results demonstrate the need for SDM process to promote patient choice in older patients with CKD.

FR-PO892

Impact of Conservative Management vs. Dialysis on Hospitalization Outcomes in US Veterans with Advanced CKD

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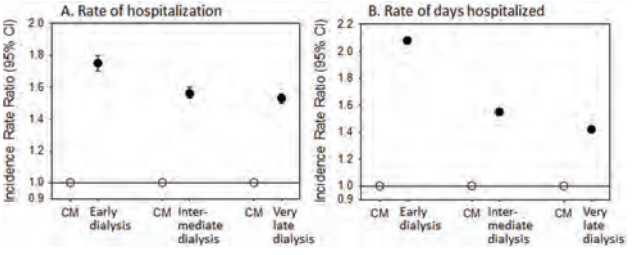
Background: Given high early mortality rates, healthcare utilization, and withdrawal in incident dialysis subgroups, particularly those of older age or multi-morbidity, there is interest in conservative management (CM) as an alternative treatment strategy for advanced CKD. We examined the impact of CM vs. dialysis transition on hospitalization outcomes in Veterans with advanced CKD.

Methods: We examined Veterans with advanced CKD (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25). Patients in the dialysis group were categorized according to timing of dialysis transition, defined as earlier dialysis (ED) vs. intermediate dialysis (ID) vs. very-late dialysis (VLD) (eGFRs ≥15, 10-<15, vs. <10 at dialysis transition). We compared rates of hospitalization (primary outcome) and days hospitalized (secondary outcome) in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio to address confounding using Poisson regression.

Results: In PS-matched models, compared with CM, each dialysis group was associated with higher rates of hospitalization, with incrementally higher rates observed with earlier dialysis transitions: IRRs (95%CIs) 1.53 (1.50-1.56), 1.56 (1.53-1.60), and 1.75 (1.70-1.80) for VLD, ID, and ED, respectively (Fig A). Similarly, each dialysis group was associated with higher rates of days hospitalized, with incrementally higher rates observed with earlier dialysis transitions (ref: CM): IRRs (95%CIs) 1.42 (1.41-1.44), 1.55 (1.54-1.56), and 2.08 (2.06-2.10) for VLD, ID, and ED, respectively (Fig B). Similar findings were observed in sensitivity analyses doubly-adjusted for PS covariates.

Conclusions: Compared with CM, increasingly earlier dialysis transitions were associated with higher rates of hospitalization and days hospitalized. Further studies are needed to examine the comparative effectiveness of CM vs. dialysis transition on other hard endpoints and patient-centered outcomes in US Veterans.

Funding: NIDDK Support



FR-PO893

Dialysis as Destination Therapy vs. Medical Management in a National Cohort of Older Adults with Kidney Failure: A Target Trial Emulation Study

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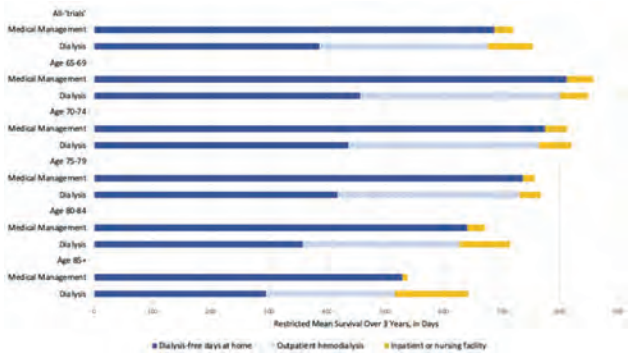
Background: For older adults who are not candidates for kidney transplantation, medical management is an alternative to lifelong dialysis, but little evidence is available to inform treatment decisions.

Methods: We emulated a target trial in which patients were randomized to dialysis versus medical management using electronic health record data between 2010 and 2018 from the U.S. Department of Veterans Affairs. We included adults aged 65 years or older with chronic kidney failure and an estimated glomerular filtration rate <12 ml/min/1.73m^2 who were not candidates for kidney transplantation. We used causal inference methods to estimate restricted mean survival time difference using a weighted flexible parametric model and difference in home-time using weighted fractional regression at one and three years.

Results: We emulated a series of 99 trials using data from 16,363 adults with a mean age of 77 ± 9 and mean eGFR of 10 ± 2 who were predominantly male (2%) and white (64%). In intention to treat analyses, compared to medical management, dialysis was associated with an increase in one-year survival of 4 days (95% CI 2.0, 6.1), offset by 8 fewer days at home (95% CI -10, -7). At 3-years, compared to medical management, dialysis was associated with an increase in survival of 35 days (95% CI 23, 47), offset by 11 fewer days at home (95% CI -16, -4). Subgroup analyses showed that the survival benefit of dialysis was larger at older ages and at lower eGFR, and largely explained by an increase in survival in institutional settings (**Figure**).

Conclusions: Among older adults ineligible for transplantation, we found evidence of a modest survival benefit of dialysis compared to medical management, at the expense of fewer days at home. The findings suggest that medical management should be more widely considered as a patient-centered alternative to dialysis treatment and underscore the importance of engaging patients in shared decision-making.

Funding: Veterans Affairs Support



FR-PO894

Results from GUIDAGE-CKD: Guideline-Compliant Care of Patients Aged 70+ with CKD

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Background: Currently, few data exist on guideline-based care for older patients with CKD. The GUIDAGE-CKD project develops quality indicators (QI) for outpatient care of pts 70+ years with CKD and tests them in Berlin Initiative Study (BIS) and claims data. We investigate trends over time after introduction of KDIGO guidelines in 2012.

Methods: Using a Delphi process, a set of 7 QIs was consented for use in claims data (Module 1). QIs were validated in BIS data with comprehensive claims data (Module 2). Prevalences of QIs were described in age- and sex-stratified random samples in claims data (n=62,200 indiv. 70+) for the years 2012, 2014, 2016, and 2018 and standardized to the German 70+ population. Trends over time were examined with Cochran-Armitage trend test (Module 3). Initial results using claims data were reported for 5 QIs.

Results: Prevalence of CKD increased from 17.9% (95% confidence interval [CI] 15.0–21.4) in 2012 to 25.9% (CI 22.3–30.0) in 2018 (Table). Incidence of CKD increased from 6.3% (CI 4.5–8.8) in 2012 to 7.5% (CI 5.5–10.5) in 2018. The proportion of incident CKD cases with urinary albumin creatinine ratio (ACR) measurement (QI 8) increased from 10.9% (CI 10.0–12.0) in 2012 to 12.6% (CI 11.5–13.7) in 2018. The proportion of confirmed CKD G4-5 caseswith perscribed NSAIDs (QI 12, contraindicated) decreased from 3.8% (CI 2.9–4.9) in 2012 to 2.3% (CI 1.8–3.0) in 2018. The proportion of cases with CKD receiving combined prescriptions of ACE inhibitors (ACEi) and ARBs (angiotensin II receptor blockers) (QI 23, contraindicated) decreased from 3.0% (CI 2.6–3.3) in 2012 to 0.6% (CI 0.5–0.7) in 2018.

Conclusions: From 2012-2018, the prevalence and incidence of CKD increased constantly, while the proportion of contraindicated NSAID medications in stage 4-5 CKD and combined prescriptions of ACEi and ARBs decreased. These trends suggest improvements in CKD diagnosis, guideline adherence, and quality of care.

Table – Sociodemographics and results for quality indicators (QI) for chronic kidney disease (CKD) in persons aged 70+ years over 4 single-year periods

	2012	2014	2016	2018	Trend *	
					β	p
Sociodemographics						
Sample size [1], n	62,200	62,200	62,200	62,200		
Age (years), mean (SD)	81.0 (7.4)	81.1 (7.3)	81.1 (7.3)	81.1 (7.4)		
Women, n (%)	31,100 (50.0)	31,100 (50.0)	31,100 (50.0)	31,100 (50.0)		
Prevalence: proportion of patients ≥70 years with diagnosed or coded CKD [3]						
Eligible persons, n (%) [4]	62,200 (100)	62,200 (100)	62,200 (100)	62,200 (100)		
% (CI) [5]	17.9% (15.0–21.4)	20.7% (17.5–24.4)	23.9% (20.2–27.6)	25.9% (22.3–30.0)	+8.0%	<0.0001 *
Incidence: Proportion of patients ≥70 years with CKD [3] and without CKD one year before first diagnosis						
Eligible persons: n (%) [4]	50,040 (80.5)	48,382 (77.8)	46,736 (75.1)	44,911 (72.2)		
% (CI) [5]	6.3% (4.5–8.8)	7.3% (5.4–10.1)	9.2% (6.1–11.1)	7.5% (5.5–10.5)	+1.2%	<0.0001 *
QI 8: Proportion of patients ≥70 years with initial diagnosis of CKD [3] (incidence indicator) who had a urinary albumin-creatinine ratio determined.						
Eligible persons, n (%) [4]	3,837 (6.2)	4,011 (6.4)	4,046 (6.5)	3,465 (5.6)		
% (CI) [5]	10.9% (10.0–12.0)	12.2% (11.3–13.3)	12.6% (11.6–13.9)	12.6% (11.5–13.7)	+1.7%	0.0145
QI 12: Proportion of patients ≥70 years with CKD and eGFR <30 ml/min/1.73m² [3] for whom NSAIDs (nonsteroidal anti-inflammatory drugs) were prescribed.						
Eligible persons, n (%) [4]	1,397 (2.2)	1,824 (2.9)	2,127 (3.4)	2,426 (3.9)		
% (CI) [5]	3.8% (2.9–4.9)	4.2% (3.4–5.2)	3.2% (2.5–4.0)	2.3% (1.8–3.0)	-1.5%	0.0013 *
QI 23: Proportion of patients ≥70 years with CKD [3] who had multiple (≥2) combined prescriptions of ACE inhibitors and angiotensin II receptor blockers over at least 2 quarters within 3 quarters after the quarter with the first simultaneous prescription.						
Eligible persons, n (%) [4]	8,639 (13.9)	9,968 (16.0)	11,303 (18.2)	12,555 (20.2)		
% (CI) [5]	3.0% (2.6–3.3)	1.7% (1.4–2.0)	0.8% (0.5–0.7)	0.6% (0.5–0.7)	-2.4%	<0.0001 *

SD = standard deviation. CI = 95% confidence interval calculated using the Wilson method (1927). * statistically significant for p < 0.0083 (after Bonferroni-correction).
[1] Sampling strategy: after an a priori defined case number estimation, an equally distributed random sampling was performed for each year according to following age and sex strata: 50% women and 20% each in the age group 70-74, 75-79, 80-84, 85-89, and ≥90 years.
[2] For CKD, the following diagnoses were used: ICD-10-GM N18.3, N18.4, N18.5, N18.8, N18.9, N19, within 1 year at least 1 outpatient diagnosis with diagnostic certainty "confirmed" or 1 "must" or "secondary" inpatient diagnosis.
[3] For CKD with eGFR <30 ml/min/1.73m², the following diagnoses were used: ICD-10-GM N18.4, N18.5, within 1 year at least 1 outpatient diagnosis with diagnostic certainty "confirmed" or 1 "must" or "secondary" inpatient diagnosis.
[4] The number of eligible persons indicates how many persons were eligible for testing of the respective QI (denominator). E.g., for incidence: only persons who did not have a CKD diagnosis in the respective previous year.
[5] The prevalences of the QIs were standardized using nationwide demographic age and sex distributions (Destatis).
[6] Time trends were tested using the Cochran-Armitage test with Bonferroni correction.

FR-PO895

Baseline Characteristics of the First Geriatric Nephrology Clinic in Mexico City

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Background: Older adults with advanced CKD have a high burden of geriatric syndromes (GS). A Geriatric Assessment is fundamental to optimize care and help with shared decisions. In 2022 an integrated Geriatric Nephrology Clinic was opened at our Institution. Patients ≥70 years with eGFR ≤20 mL/min are referred for evaluation, interventions, and planning by a Geriatric Nephrology team. We present baseline characteristics of this population.

Methods: We included patients (pts) referred to the GNC between Jan. 2022 and Mar. 2023. Charts were reviewed and data regarding GS captured and analyzed.

Results: During this time, 71 pts were referred to clinic; 59 had non-dialysis dependent (NDD) CKD and 12 were on dialysis. Average age was 80 ±7.6 years, 50% were female, and the main cause for CKD was diabetes (49%). Dialysis pts were younger (75.8±8.8 vs. 81.6±7.1, p<0.05), more likely to have healthcare coverage (66.7% vs. 32.2%, p=0.03) and had lower comorbidity (CCI 6.5±1.3 vs. 8.14±3.2, p<0.05). Dialysis vintage was 2 years (IQR 1,4). NDD pts had an average eGFR of 14.2 mL/min, 79% had ≥A2 albuminuria. Risk of progression to CKD was high (2-year KFRE >20%) in 61%. Dialysis pts had better physical performance (SPPB 9.5±1.8 vs. 6.8±2.4 points, p<0.001). No other differences were found. Burden of GS was high, with an average of 6.7±2.2 out of 14 possible. Prevalence of individual GS was: 1) frailty 62%, 2) ADL disability 46%, 3) IADL disability 61%, 4) impaired mobility 56%, 5) falls 51%, 6) low physical performance 78% 7) slow gait 46%, 8) visual deficit 42%, 9) auditory deficit 40%, 10) malnutrition 11%, 11) positive depression screening 16%, 12) altered sleep 21%, 13) abnormal cognitive screening 49%, 14) polypharmacy 91%. After the first visit, 13% of NDD pts opted for dialysis, 24% were undecided, 49% opted for conservative or palliative care and 14% did not answer. One dialysis pt asked for assistance with dialysis discontinuation.

Conclusions: The Geriatric Nephrology Clinic has been fundamental to identify and intervene in geriatric syndromes for our older patients with CKD. Patients referred to our clinic have high comorbidity, high geriatric syndrome burden and are mostly managed conservatively.

FR-PO896

Clinical Characteristics and Outcomes of Hemodialysis Therapy Focusing on Older Patients in Korea from the 2023 Korean Renal Data System

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Background: As the aging population increases worldwide, the prevalence of older patients with end-stage kidney disease (ESKD) is rapidly increasing. Understanding the characteristics of elderly ESKD patients is essential for establishing suitable dialysis policies and plans, but information on this population is currently unclear in Korea.

Methods: This study investigated the characteristics and outcomes of elderly hemodialysis patients using Korean Renal Data System. Of a total of 173,216 patients, 40,972 hemodialysis patients were included in the final analysis after excluding patients with missing values, who started dialysis before 2001, or who were younger than 18 years old.

Results: Of the enrolled patients, 39.3% were under the age of ≥ 65 years, 26.6% were 65-74 years, and 34.1% were ≥ 75 years (p<0.001). The incidence of ESKD is increasing but the prevalence is decreasing in patients aged ≥ 75 years from 2017 to 2022. The proportion of patients with cardiac disease increased with age: 16% (<65 years), 19.6% (65-74 years), and 21.8% (≥75 years) (p<0.001). The levels of body mass index, hemoglobin, albumin, calcium, phosphorus, and intact parathyroid hormone significantly decreased with increasing age (p<0.001 for each parameter). The proportions of arteriovenous fistula creation and left forearm placement reduced with increasing age (p<0.001, and p<0.001, respectively). Although low surface area (1.0-1.5 m2) dialyzers utilization was increased with age at 41.4% (<65 years), 49.5% (65-74 years), and 58.5% (≥75 years), the urea reduction ratio and Kt/V increased with age, achieving the dialysis adequacy target in all elderly population. Mortality rates had increased in patients aged ≥ 75 years compared to other age groups over the past 20 years and the proportion of deaths due to cardiovascular disease decreased and deaths due to infectious diseases increased with age in older hemodialysis patients (p=0.002, and p=0.025, respectively).

Conclusions: The incidence of elderly hemodialysis patients has increased over time, and especially very older adults aged ≥ 75 years has a higher risk of mortality compared to other age groups in Korea. To improve outcomes for older ESKD patients, appropriate guidelines for ESKD management should be developed based on age-appropriate, individualized strategies.

FR-PO897

A Pragmatic Randomized Clinical Trial: Twice-Weekly vs. Thrice-Weekly Incident Hemodialysis in Elderly Patients (PRIDE): Study Protocol

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Background: The optimal frequency for hemodialysis in older adults with end-stage kidney disease (ESKD) has not been established. This study aims to investigate whether a twice-weekly dialysis schedule using an incremental approach can reduce hospitalization rates in older adults with incident dialysis, compared with conventional thrice-weekly dialysis in South Korea.

Methods: We have designed a pragmatic randomized controlled trial to compare the effects of twice-weekly versus thrice-weekly hemodialysis in 428 ESKD (drop-out rate 20%) individuals aged 60 years or older with residual kidney function (urine output > 500 mL/day). The trial will be conducted across 18 referral hospital-based dialysis centers in Korea. Individual participants will be randomized to either the twice-weekly (with incremental approach) or thrice-weekly dialysis group and will be followed up for 24

months. The primary outcome of the study is the difference in all-cause hospitalization rates, while secondary outcomes include dialysis-specific hospitalization rates, mortality, quality of life, frailty, and cost-effectiveness. Participants have the flexibility to transfer to other dialysis centers as needed. The decision to increase dialysis frequency will be made by the treating physicians.

Results: The study is ongoing and will be completed in May 2026.

Conclusions: This study will provide valuable insights into the benefits and risks of twice-weekly dialysis with an incremental approach in older adults with residual kidney function compared to conventional dialysis treatment.

Funding: Government Support - Non-U.S.

FR-PO898

Association of Polypharmacy and Incident Frailty Differs Between Older Adults with and Without CKD

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Background: Older adults with chronic kidney disease (CKD) have a high prevalence of comorbidities and are prone to polypharmacy. We aim to analyze if CKD modifies the association of polypharmacy and incident frailty.

Methods: Data from the Berlin Initiative (cohort) study were used, in which older adults (≥70 yrs.) were interviewed biennially using a standardized face-to-face questionnaire. Non-frail individuals were followed-up for 2 years and incident frailty according to Fried phenotype was assessed. Polypharmacy was defined as the intake of five or more regularly prescribed drugs and CKD as $eGFR_{BIS2}$ <60 mL/min/1.73m^2 or ACR ≥30 mg/g. Logistic regressions were used to analyze the association of polypharmacy and incident frailty to estimate crude and adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) in individuals with and without CKD.

Results: Individuals with CKD were older (84 vs. 81 years) and had more often hypertension (85 vs. 68%) or diabetes (25 vs. 13%) compared to individuals without CKD. After 2 years, fewer individuals without CKD became frail (7.5%) compared to individuals with CKD (19.7%), independent of their polypharmacy status. Individuals with CKD and polypharmacy became frail more frequently (26.7%) compared to individuals with CKD without polypharmacy (14.2%) (Table). In individuals without CKD, there was no difference in frailty incidence between those with (8.3%) and without (7.1%) polypharmacy. In individuals with CKD, those with polypharmacy had 2.1 times the odds (95% CI 1.23–3.59) of becoming frail compared to those without. In old adults without CKD, we found no association between polypharmacy and incident frailty.

Conclusions: CKD modifies the effect of polypharmacy on frailty. In older adults with CKD, care providers should be aware of this interaction with polypharmacy and should consider initiating frailty prevention interventions early.

Funding: Private Foundation Support, Government Support - Non-U.S.

Table: CKD modifies the association of polypharmacy and incident frailty

	Total	Number of Events (%)	Crude model OR (95% CI)	Adjusted Model* OR (95% CI)
CKD				
No Polypharmacy	261	37 (14.2%)	Reference	Reference
Polypharmacy	206	55 (26.7%)	2.21 (1.39 – 3.51)	2.10 (1.23 – 3.59)
No CKD				
No Polypharmacy	126	9 (7.1%)	Reference	Reference
Polypharmacy	48	4 (8.3%)	1.18 (0.35 – 4.03)	0.97 (0.23 – 4.11)

*Adjusted for gender, age, smoking, physical activity, Charlson Comorbidity Index (CCI), and Body-Mass-Index (BMI)

CKD modifies the association of polypharmacy and incident frailty

FR-PO899

Physical Function Before and After a Health Stressor in Older Veterans with Advanced CKD

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Background: Health stressors (HS), defined as acute health events that require an ED visit or hospitalization, are common among older adults with chronic kidney disease (CKD) and associated with functional decline. Describing the trajectory of function before and after a HS may be vital to predicting future functional status and developing strategies to improve functional recovery after health events.

Methods: The Physical Resilience Prediction in Advanced Renal Disease (PREPARED) is a national, prospective cohort study of Veterans ≥ 70 years old (*n*=412) with advanced CKD (eGFR <30 ml/min/1.73m^2 (excluding dialysis or transplant)) who were tracked longitudinally to detect the occurrence of a HS in near real-time. Participants completed scheduled phone surveys of physical function every 8 weeks. For enrolled participants, if a HS was detected in the VA electronic health record during follow-up, additional phone surveys were conducted immediately following the HS, at 8-, and 16-weeks post-HS. This approach provided data on function approximately 16- and 8-weeks before and 8- and 16-weeks after a HS. Physical function was assessed at each timepoint using the Life-Space Assessment (LSA) score (0-120, higher scores reflect greater community mobility). Linear mixed models were used to assess the trajectory of function in relationship to the HS.

Results: A total of 272 PREPARED participants (77.9 ± 6.4 years old, 98% male, 25% Black) had a HS. On average, LSA score was highest (54.0 ±26.2) at baseline (16-weeks prior to a HS). LSA scores declined 8-weeks prior to a HS (52.2 ±28.6). The lowest LSA score was immediately following the HS (45.3 ±28.6). LSA scores rebounded at 8-weeks (51.0 ±27.7) and 16-weeks post-HS (50.0 ±26.4) but did not return to pre-HS levels. Compared to baseline, statistically significant differences in LSA scores were seen immediately following the HS, and at 8- and 16-weeks post-HS (all p<0.01).

Conclusions: Among older Veterans with advanced CKD declines in physical function occurred leading up to and following a HS. Though physical function improved in the weeks following the HS, participants did not fully regain baseline physical function status even after 4 months. These data demonstrate the importance of developing strategies to bolster older adults' ability to recover following an acute health event.

Funding: Veterans Affairs Support

FR-PO900

Kidney Transplantation in Older People (KTOP): The Frail Experience

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Background: Older people with kidney failure are vulnerable to frailty. Understanding their experiences is integral to kidney transplantation(KT) decision making.

Methods: The KTOP:impact of frailty on outcomes study assessed frailty, quality of life(QoL), and clinical outcomes in people >60, on the waitlist(WL) and after KT. Mixed-effect analysis identified trends and frailty variations.

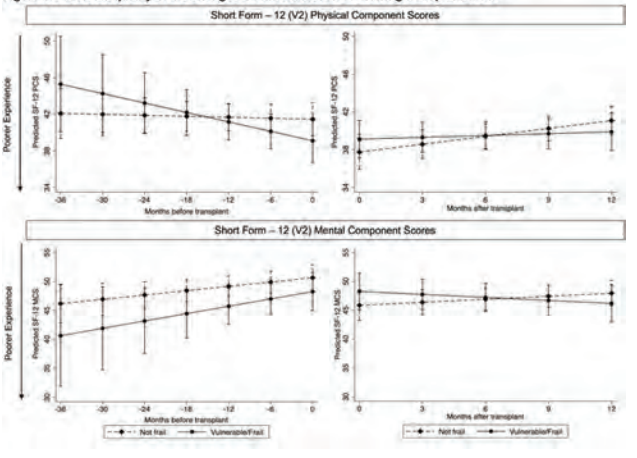
Results: 210 patients were recruited;118 were transplanted. At recruitment 63.4%(118) were not frail, 19.4%(36) vulnerable, and 17.2%(32) frail. The study was powered only for QOL changes, but on the WL vulnerable/frail candidates were more likely to have major infections and spend longer suspended. After KT vulnerable/frail recipients were more likely to be hospitalised, have longer admissions, and possibly higher graft loss and mortality(table). On the WL, QoL trends showed stable physical component scores(PCS) in not frail candidates and declining scores in vulnerable/frail. Post-KT not frail candidates PCS declined before slowly recovering, whilst PCS stabilised in vulnerable/frail. WL mental component scores (MCS) improved in both groups. MCS after KT declined then improved in not frail candidates, and worsened in vulnerable/frail(figure 1).

Conclusions: Frail/vulnerable older people had worse WL and KT clinical outcomes. KT did not change QoL hugely for either group, but trends varied by frailty. Achieving a holistic understanding will enable better assessment, counselling, and support for older people considering KT.

Clinical outcomes by frailty

Outcome	Not Frail	Vulnerable/Frail	p Value
WL mortality	10 (22.2%)	14 (31.1%)	0.340
WL major infection episode	11 (24.4%)	27 (60%)	0.001
WL total time suspended (days) (mean, ±SD)	307 (244)	434 (295)	0.0246
KT mortality	5 (7%)	8 (18.2%)	0.0774
All cause graft loss	7 (9.9%)	10 (29.4%)	0.0588
KT major infection episode	39 (54.9%)	29 (69%)	0.138
Hospitalised in 1sy year after KT	37 (52%)	32 (73%)	0.028
Total Length of stay in 1st year after KT (days) (mean, ±SD)	20.5 (24.8)	36.6 (32.7)	0.0238

Figure 1. Predicted quality of life changes on the waitlist and following transplantation.



FR-PO901

The Association Between Oral Frailty and Physical Performance in Patients with CKD

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Background: Chronic kidney disease (CKD) is one of the major causes and exacerbating factors for sarcopenia. Patients with CKD frequently experience dry mouth due to water restriction and decreased appetite due to uremic toxins, which leads to malnutrition, protein-energy wasting, and increased mortality. The association between

oral function and the sarcopenia index in CKD remains unclear. The purpose of this study was to evaluate the oral function and its correlation with the sarcopenia index in patients with CKD.

Methods: The participants were non-dialysis CKD patients (stage 3~5) who visited an outpatient clinic in a single center. Oral frailty was evaluated by the Oral Frailty Index-8 and physical examinations assessing the number of teeth, tongue-lip motor function, and tongue coating index. The sarcopenia index and the Frail Questionnaire were assessed.

Results: Among the 72 patients (49 males, 23 females; mean age 67.0±11.8 years; mean serum creatinine level 3.83±2.65 mg/dl), 55.6% of participants had oral frailty, defined as an Oral Frailty Index-8 score of 4 points or more. Male participants had higher serum creatinine levels than the female group (4.24±2.94 mg/dl vs. 2.96±1.67 mg/dl, respectively). Muscle strength measured by handgrip strength in the male group with oral frailty was lower than that without oral frailty (26.9±6.11 vs. 32.6±7.10kg, respectively, P=0.003), whereas there was a decreasing trend in the female group (15.1±4.72 vs. 19.5±5.77kg, respectively, P=0.06). Patients who have oral frailty showed decreased physical performance (with oral frailty 12.9±5.45s, vs. without oral frailty 8.89±3.05s, P<0.001). Oral frailty was linked with lower physical performance, according to the logistic regression analysis (OR 1.30, CI 1.097-1.546, P=0.003). In simple linear regression, the level of serum creatinine and the oral frailty score were associated (r=0.26, P=0.03).

Conclusions: Oral frailty is present in more than half of outpatients with non-dialysis CKD. This suggests the significance of managing physical performance early for CKD patients to avoid oral frailty. Additionally, muscle-strengthening exercises should be more crucial to prevent oral frailty as CKD progresses.

FR-PO902

Gait Speed and Mortality in Older Adults with CKD: The Chronic Renal Insufficiency Cohort

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Background: Current models to predict mortality in older persons with CKD use only demographic, kidney, and medical history data. Yet prior work shows impaired physical function independently and strongly predicts death in older adults. We assessed if a measure of physical function, gait (walking) speed, improves mortality prediction for older adults with CKD.

Methods: We included Chronic Renal Insufficiency Cohort participants who were ≥65 years with eGFR <60 mL/min/1.73m², not receiving kidney replacement therapy, non-missing UACR, and with at least 1 gait speed assessment. Gait speed at usual pace on a 4.57 meter course was timed and then categorized (≥ 0.84 meters/second, 0.83 to 0.65, 0.64 to 0.47, ≤ 0.46, or unable to do). We designated the visit with gait speed measurement as baseline. Our primary outcome was time to all-cause death. We used a flexible parametric modeling approach with kidney replacement therapy as a competing risk, adjusting for age, sex, race, eGFR, UACR, smoking, diabetes, heart failure and stroke. C statistics were used to compare models with and without gait speed as a predictor.

Results: Among 2,345 persons, mean age was 70.0±4.4 years; 43% were female and 41% Black. Mean eGFR was 43.3±12.5 mL/min/1.73m² and median UACR was 33.8 (IQR 9.3-283.4). At baseline, 80% had a gait speed ≤ 0.83 m/s. Over 5 years, 393 persons died, and 164 had kidney failure. For those that died, median survival time was 2.6 years. In time-to-event analyses, slower gait speeds correlated with greater mortality (Figure). After adjustment, the inclusion of gait speed as a predictor improved model performance with the c statistic improving from 0.625 (95% CI 0.624-0.627) to 0.736 (95% CI 0.735-0.737).

Conclusions: In older adults with CKD, we found that gait speed improves mortality prediction. Clinicians should consider assessing gait speed when discussing life expectancy and goals of care with older adults with CKD.

Funding: NIDDK Support, Other NIH Support - K23AG057813; Chronic Renal Insufficiency Cohort Opportunity Pool Award, Veterans Affairs Support

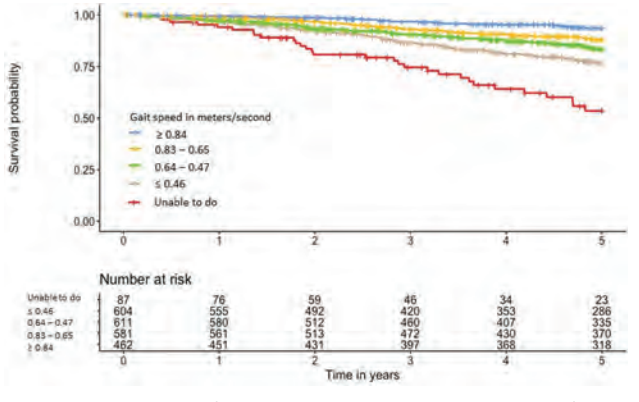

Figure: Kaplan Meier curve of gait speed and all-cause mortality, censoring for kidney failure

FR-PO903

Ultrasound Evaluation of Rectus Femoris Muscle Thickness as a Diagnostic Tool for Sarcopenia in Peritoneal Dialysis Patients

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Background: Sarcopenia is a frequent cause of morbidity and mortality among patients with chronic kidney disease (CKD), combining loss of both muscle strength and mass. Handgrip strength is a reliable surrogate for measures of arm and leg strength. Several tools have been developed for muscle mass evaluation, such as bioelectrical impedance analysis (BIA). Ultrasound evaluation has been increasing recently, taking advantage of its feasibility in daily clinical setting. The aim of this study was to evaluate the rectus femoris muscle thickness (RFMT) by ultrasound in peritoneal dialysis (PD) patients and its association with muscle strength and BIA parameters.

Methods: Single-centre cross-sectional study including patients on PD for > 3 months and aged > 18 years. Patients with acute infection, amputated limbs and implantable cardiac devices were excluded. Demographic and clinical data were collected from the electronic records. Parameters evaluated included serum biomarkers, BIA and dialysis adequacy. Muscle strength was measured by handgrip strength using a dynamometer. RFMT was evaluated using ultrasound at bedside.

Results: A total of 32 patients (19 male) were included with a mean age of 59±15 years. PD vintage was 17 months (10,5-29,8) with a weekly Kt/V of 1,98 (1,68-2,55). Most were on continuous ambulatory peritoneal dialysis (CAPD; 68,8%), either as high or medium-high transporters (65,6%). Hypertension was reported in 28 patients (87,5%), accompanied by diabetes mellitus (DM; 31,3%), peripheral artery disease (31,3%) and obesity (28,1%). Age (r=-0,442; p=0,013), Clinical Frailty Score (r=-0,481; p=0,006) and NT-proBNP (r=-0,54; p=0,003) were negatively associated with RFMT. Lean tissue index (r=0,357; p=0,049), phase angle (r=0,567; p=0,001) and handgrip strength (r=0,49; p=0,006) were positively associated with RFMT. In a multivariate analysis, phase angle (adjusted R^2=0,261; p=0,026) was positively associated with RFMT, adjusting to age, time on PD, DM and serum albumin.

Conclusions: Ultrasound evaluation of RFMT is feasible in daily practice in the outpatient setting. It may be useful as an additional tool to BIA for diagnosis of sarcopenia, particularly in elderly, fragile and malnourished patients. Further prospective studies are warranted in order to validate this tool for PD patients.

FR-PO904

Relationship Between Frailty, Sodium, and Blood Pressure in Elderly People

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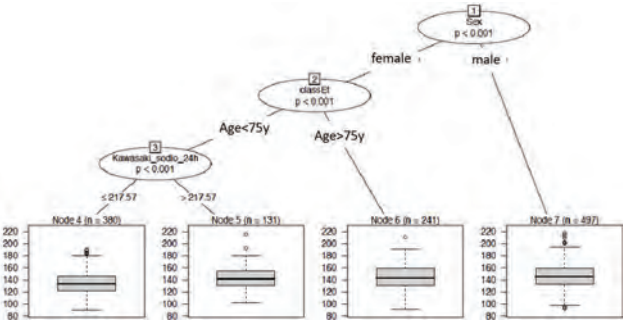
Background: The objective of the FRASNET project is to investigate the correlation between frailty, natriuresis, and blood pressure (BP) in the elderly population to identify subgroups useful for diagnostic and therapeutic algorithms.

Methods: The FRASNET geriatric population (1204 subjects) is an Italian observational cohort that includes frail (35%), pre-frail (37.3%) and robust (27.7%) subjects. They have been characterized for BP, renal function, sodium intake (Kawasaki formula), cognitive status, quality of life (QoL), anamnestic factors, health and socio-economic status. ANOVA and conditional inference tree analysis have been carried out.

Results: 745 participants out of 1203 (60%) were under anti-hypertensive treatment but 71.4% had a suboptimal control of BP. The significant elements are the male gender (p=0.002), waist circumference (p=0.01), visceral fat index (p<0.01), and fewer medications taken (p<0.01). An inferential analysis (Fig 1) evidenced a first dissection between males and females, a second one age-related (75 y) and a third with natriuresis (217 mEq Na). Non-frail subjects had the highest values for both systolic and diastolic BP; the frail group had the lowest values, below the 140 mmHg threshold. BPs negatively correlate with frailty status (systolic p=0.048, diastolic p <0.001, Fig 2).

Conclusions: The more severe the frailty, the lower the BP is supposed to be. The evidence of this inverse tendency is supported by physiological explanations and by therapeutic implications. Frail patients are usually more prone to injury; therefore, they are more likely to be prescribed more drugs and the most aggressive therapies to decrease risks. Ultimately, this correlation suggests that both conditions grant a relative decrease in risk with respect to the other one, at least when considering elder individuals.



	Optimal BP control (n= 213, 28.6%)	Suboptimal BP control (n= 532, 71.4%)	P value (ANOVA)
Waist measurement (cm)	93.75	96.16	**0.014**
BMI (kg/m^2)	27.29	27.79	0.148
Visceral fat index	11.17	12.6	**<0.01**
eGFR (ml/min/1.73m^2)	68.1	69.97	0.2
ACR (mg/g)	49.5	42.0	0.51
Sodiuria (Kawasaki formula) mmol/24h	191.7	201.7	0.1
Age (Y)	74.69	74.39	0.47
Total medications	4.77	4.01	**<0.01**
Male n (%)	73 (34.3%)	247 (46.4%)	X^2, **p<0.01**

FR-PO905

White Matter Alternation at Corpus Callosum and Stria Terminalis Contributes to the Cognitive Impairment in ESRD via Dysregulating Homeostasis of Calcium

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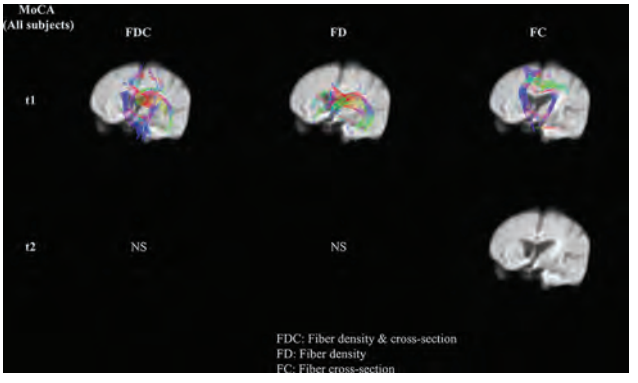
Background: Cognitive impairment is common in patients with end stage kidney disease (ESRD). White matter alternation is important pathologic change in cognitive impairment, and fixel-based analysis quantifies the fiber loss. The study is to elucidate the white matter alternation in uremic cognitive impairment patients.

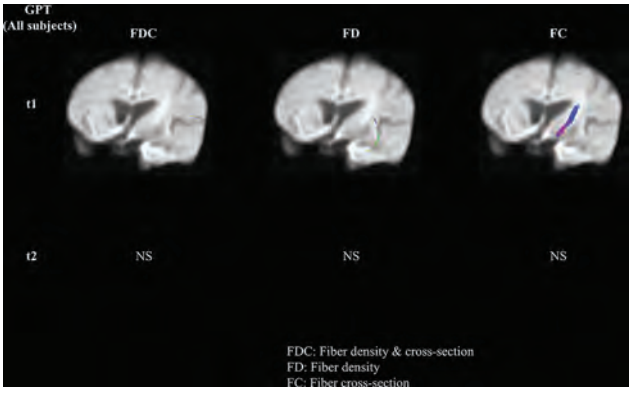
Methods: The study period was from August 2019 to December2020. The participants were divided into three groups according to the MMSE score and the status with end stage renal disease or not: (1) control (n=16): MMSE>24 without end stage renal disease; (2) group 2 (n=17): end stage renal disease with MMSE 25~30; (3) group 3 (n=14): end stage renal disease with MMSE10~24. All participants received magnetic resonance imaging and hematologic and biochemical parameters. Fixel-based analysis was performed to assess the fiber density.

Results: The fiber density, the fiber cross section and the summation of the fiber density and cross section were lower in the ESRD patients. The decrease in corpus callosum and fornix/stria terminalis was associated with the decrease in Montreal Cognitive Assessment($p<0.05$). The concentration of calcium(8.80± 0.79mg, vs 9.27± 0.29mg for control group, $p<0.05$) was lower in ESRD patients. The serum concentration of calcium was positive associated with the fiber density in the corpus callosum and fornix/stria terminalis($p<0.05$).

Conclusions: The white mater density decreased in the ESRD patients, and the decrease was associated with cognitive impairment. Serum calcium positively correlated with the fiber density in corpus callosum and fornix terminalis.



The association between imparied fibers and MoCA.



The fibers influenced by calcium concentration.

FR-PO906

Association of Dementia Diagnosis at Dialysis Initiation with Mortality in the Elderly ESKD Population in South Korea

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Background: Dementia is highly prevalent among patients with end-stage kidney disease (ESKD), with a 2–7 fold increase compared to the general population. However, the clinical implications of dementia have not been sufficiently studied in elderly ESKD patients. Therefore, the aim of this study was to identify elderly ESKD patients with newly started hemodialysis and determine whether the comorbidity with dementia increases mortality.

Methods: The Korean Society of Geriatric Nephrology retrospective cohort includes 2,736 elderly ESKD patients (≥70 years old) who started hemodialysis between 2010 and 2017. Kaplan-Meier survival and Cox regression analyses examined all-cause mortality between patients with and without dementia.

Results: Of the 2406 patients, patients with dementia at the initiation of dialysis were 8.3% (n = 200, Fig. 1), older (79.6±6.0 years old) than patients without dementia (77.7±5.5 years old), and included more women (male:female = 89:111). Pre-ESKD diagnosis of dementia was associated with an increased risk of post-ESKD mortality (HR 1.503; 95% CI, 1.263–1.788; P<0.0001, Fig. 2), and this association remained consistent after multivariate adjustment (HR 1.270; 95% CI, 1.062–1.519; P = 0.009). In the subgroup analysis, prevalent dementia was more closely related to mortality following dialysis initiation in female participants, patients aged 75 to 85, patients with no history of CVA or severe behavior disorder, no nursing home residence, no hospitalization, or short-term hospitalization.

Conclusions: A pre-ESKD diagnosis of dementia was associated with mortality following dialysis initiation in the Korean elderly population. Cognitive assessment at the initiation of dialysis is necessary in the elderly with ESKD, and further studies are needed to compare the prognosis of different treatment options for ESKD in the elderly with dementia.

Figure 1.

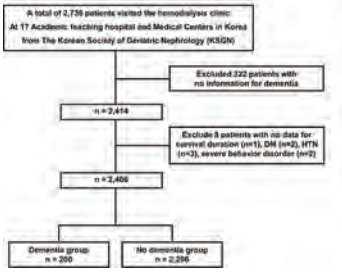
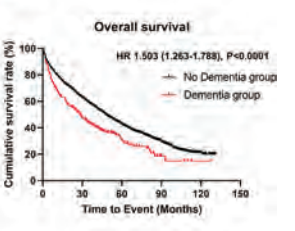


Figure 2.



FR-PO907

The Effect of Dementia Screening Tests on Subsequent Kidney Function in the Elderly

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Background: Previous cross-sectional and longitudinal studies have demonstrated that chronic kidney disease is associated with an increased risk for cognitive impairment at baseline and cognitive decline over time in older adults. However, it is unknown whether older people with subjective cognitive decline would be more likely to subsequently develop kidney dysfunction.

Methods: From the Korean National Health Insurance Service-National Elderly cohort database, this study included 111,846 subjects older than 60 years who completed the Korean Dementia Screening Questionnaire-Prescreening (KDSQ-P) or –Cognition (KDSQ-C) between 2007 and 2015. The association between subject cognitive decline and the incidence of kidney dysfunction was investigated during the follow-up.

Results: After adjusting for potential confounding factors, the risk of kidney dysfunction, defined as a decline of more than 30% in estimated glomerular filtration

rate, was significantly lower in elderly without subjective cognitive decline based on both KDSQ-P results (HR=0.892, 95% CI 0.852-0.935, p <0.001) and KDSQ-C (HR=0.934, 95% CI 0.877-0.996, p=0.048) compared to those with subjective cognitive decline. The number of outpatient visits and admission as well as newly diagnosed cardio-metabolic disorders significantly increased in subjects with subjective cognitive decline after taking the dementia screening tests, indicating that a positive answer on the responses to KDSQ-P or KDSQ-C would have led to an increase in healthcare service utilization.

Conclusions: Subjects aged 60 years and older diagnosed as having suspicious cognitive dysfunction from dementia screening programs tend to have more preserved renal function probably through improvements in appropriate medical care with increased health concerns.

FR-PO908

Association Between Family Longevity and Kidney Function in Ashkenazi Jewish Older Adults

Laith Alzyood,[1] Garry A. Graham,[1,3] Sandra Aleksic,[1,2] Tina Gao,[1,2] Sofiya Milman,[1,2] Wei Chen.[1,2] LonGenity. *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Montefiore Health System, Bronx, NY; [3]Columbia University, New York, NY.*

Background: Familial longevity is associated with protection against age-related diseases; thus, studying familial longevity may provide insights into the mechanisms that protect against age-related decline in kidney function, which are not fully understood. LonGenity is a longitudinal cohort study of community dwelling Ashkenazi Jewish adults aged 65-94 years that aims to identify genetic determinants of familial longevity. Using this cohort, we hypothesized that offspring of parents with exceptional longevity (OPEL) had better kidney function than offspring of parents with usual survival (OPUS).

Methods: In this cross-sectional study, we used multiple linear regression to compare eGFR between OPEL (n=442, defined as having at least 1 parent living past the age of 95 years) and OPUS (n=455, defined as having neither parent who survived to 95 years). eGFR was calculated based on serum creatinine, age and sex using the CKD-EPI equation.

Results: Compared to OPUS, OPEL were younger (74 vs. 77 years), more likely to be female (59% vs. 51%), and less likely to have diabetes mellitus (7% vs. 11%), hypertension (37% vs. 50%) and cardiovascular disease (11% vs. 19%). OPEL had higher mean eGFR than OPUS (73±16 vs. 70±18 ml/min/1.73m^2, p=0.001; Table). This association remained significant after adjusting for body mass index, socioeconomic status, diabetes and cardiovascular disease (p=0.03), but became non-significant after further adjusting for hypertension.

Conclusions: Using this unique cohort, we found familial propensity for longevity was associated with better kidney function independent of diabetes and cardiovascular disease, but this became nonsignificant after adjusting for hypertension. Whether hypertension mediates the relationship between familial longevity and kidney function needs further investigation.

Funding: NIDDK Support, Other NIH Support - NIA

Multiple linear regression of eGFR with familial longevity (OPEL vs. OPUS)

	β (95% confidence interval)	p
Unadjusted	3.85 (1.62, 6.08)	0.001
Model 1: body mass index, socioeconomic status	3.17 (0.90, 5.44)	0.006
Model 2: 1 plus diabetes mellitus, cardiovascular disease	2.51 (0.26, 4.77)	0.03
Model 3: 2 plus hypertension	1.76 (-0.55, 4.07)	0.14

FR-PO909

Familial Longevity Modifies the Association Between Hypertension and Kidney Function in Ashkenazi Jewish Older Adults

Wei Chen,[1,2] Laith Alzyood,[1,2] Sanish Sathyan,[1] Sandra Aleksic,[1,2] Tina Gao,[1] Sofiya Milman.[1,2] LonGenity. *[1]Albert Einstein College of Medicine, Bronx, NY; [2]Montefiore Medical Center, New York, NY.*

Background: Familial longevity is associated with protection against age-related diseases. Prior studies suggest that hypertension worsens age-related decline in kidney function. We hypothesized that familial longevity modified the association between hypertension and kidney function in older adults, and sought to identify its associated proteomic profile.

Methods: LonGenity is a cohort study of community dwelling Ashkenazi Jewish adults aged 65-94 years that aims to identify genetic determinants of familial longevity by comparing offspring of parents with exceptional longevity (OPEL) with offspring of parents with usual survival (OPUS). Exceptional longevity was defined as living past the age of 95 years. GFR was estimated using serum creatinine and CKD-EPI equation. In multiple linear regression, stratified by OPEL (n=422) vs. OPUS (n=455), we examined the cross-sectional association between hypertension and eGFR. Plasma proteins (n=4,265) were measured using SomaScan. Top differentially expressed proteins in OPEL vs. OPUS were identified after adjusting for age and sex using a p-value cut-off of 0.001, and then tested for effect modification with hypertension using first-order interaction terms.

Results: Mean age was 76±7 years; 55% were female; 44% had hypertension; mean eGFR was 71±17 ml/min/1.73m^2. After adjusting for demographics, marital status, waist circumference, diabetes, and cardiovascular disease, the presence of hypertension was associated with 3.3 ml/min/1.73m^2 lower eGFR in OPEL (95% CI: -6.4, -0.1; p=0.04) and 4.7 ml/min/1.73m^2 lower eGFR in OPUS (95% CI: -8.0, -1.5; p=0.004). Among the top 14 differentially expressed proteins identified, protein-tyrosine sulfotransferase 2 (TPST2) and hepatoma-derived growth factor related protein-2 (HDGR2) significantly modified the association between hypertension and eGFR with a p-value for interaction of 0.04 and 0.003, respectively.

Conclusions: In this unique cohort, we found that the status of familial longevity and proteins associated with familial longevity modified the association between hypertension and eGFR. While further studies are needed to validate these findings, our study could have clinical implications on personalized medicine for the management of hypertension in older adults.

Funding: NIDDK Support, Other NIH Support - NIA

FR-PO910

Correlation Between Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios and Progression of CKD in Elderly Patients

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Background: The systemic inflammation associated with chronic kidney disease (CKD) increases acute-phase protein and inflammatory mediators, which has been associated with higher mortality. Neutrophil-to-lymphocyte (NLR) ratio and platelet-to-lymphocyte ratios (PLR) have been widely studied as inflammatory markers in malignancies, hypertension, heart diseases, and vascular diseases. NLR predicts CKD progression and PLR predicts mortality among hemodialysis patients. The role of NLR and PLR in predicting CKD progression, death or dialysis initiation in elderly is unknown.

Methods: We assessed the composite outcome of death/dialysis initiation and CKD progression in 139 patients with stages 4 or 5 CKD, aged 70 years or more, participants of an ongoing trial (Aging Nephropathy Study -AGNES). NLR and PLR ratios were measured at the study entry. Fast progression was defined as > 5 mL/minute/year loss of estimated glomerular filtration rate (eGFR).

Results: Average age was 83±7 years, eGFR 19.8±7.0ml/min/1.73m2, 56% men, 53% with diabetes. NLR was 2.9±1.4 and PLR was 131.6. Over time, the decline in eGFR was 2.4 (1.1, 6.2) ml/min/yr. NLR but not PLR was higher in fast progressors (p=0.021 and 0.238, respectively). NLR (p-0.028) but not PLR (p=0.077) was higher in patients who died/started dialysis (N=55, 39.6%). Logistic regression/Cox regression revealed NLR as an independent risk factor for CKD progression and death/dialysis initiation, respectively, in fully adjusted models. ROC curve defined 3.77 as the best cut-off value of NLR to predict death/dialysis initiation (specificity 88.1%).

Conclusions: NLR seems to be a good marker for mortality/dialysis initiation and also CKD progression in older patients with advanced CKD, in a higher value than that described for the general population. NLR, a non-expensive tool, should be widely used in this population to identify patients at risk.

FR-PO911

Relationship Between High-Density Lipoprotein Cholesterol and Mortality in Elderly Hemodialysis Patients: Data from the Korean Society of Geriatric Nephrology Retrospective Cohort

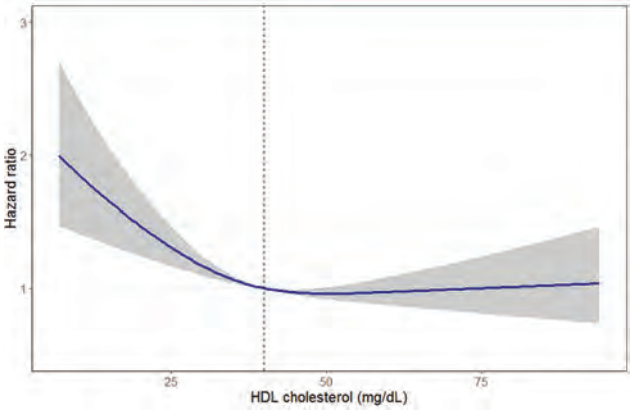
Seung Hye Chu,[1,2] Soyeon Kim,[1,2] Kootae Park,[1,2] Haekyung Lee,[1,2] Soon hyo Kwon,[1,2] Hyunjin Noh,[1,2] Hyoungnae Kim.[1,2] *[1]Soonchunhyang University Hospital, Yongsan-gu, Seoul, Republic of Korea; [2]Soonchunhyang University Hospital Kidney Center, Yongsan-gu, Seoul, Republic of Korea.*

Background: The association between high-density lipoprotein (HDL) cholesterol and mortality in elderly hemodialysis patients has not been well-established. This study aimed to investigate this association in a Korean elderly hemodialysis patients.

Methods: We recruited 1860 incident hemodialysis patients over the age of 70 from the retrospective cohort of Korean Society of Geriatric Nephrology. The primary outcome was all-cause mortality.

Results: The mean age was 77.8 years and 1049 (56.4%) patients were men. When we grouped patients into HDL cholesterol tertiles, T1 group (HDL level <30 mg/dL in men, <33 mg/dL in women) had a higher proportion of patients with end-stage kidney disease due to diabetic nephropathy. During the median follow-up period of 3.1 years, 1109 (59.7%) deaths occurred. In a multivariable Cox regression model, the T1 group had significantly higher risk of mortality (hazard ratio [HR], 1.29; 95% confidence interval [CI], 1.10-1.50; p=0.002) compared to the T3 group. A non-linear analysis using restrictive spline curve showed that low HDL cholesterol levels were associated with increased HR when HDL cholesterol levels were below 40 mg/dL, but there was no association between HDL cholesterol and mortality when levels above 40 mg/dL. Triglyceride/HDL ratio was not significantly associated with risk of mortality (HR per 1 log increase, 1.08; 95% CI, 0.99-1.18; p=0.075).

Conclusions: Low HDL cholesterol was associated with increased risk of mortality in elderly patients with hemodialysis. However, there was no significant relationship between HDL cholesterol levels and mortality when levels were within the normal range. Therefore, HDL cholesterol lower than normal may be a useful risk factor for predicting mortality in elderly hemodialysis patients.



FR-PO912

Clinical Characteristics of Anti-Nephrin Autoantibody-Positive Minimal Change Disease in Adults: A Case Series in Elderly Japanese

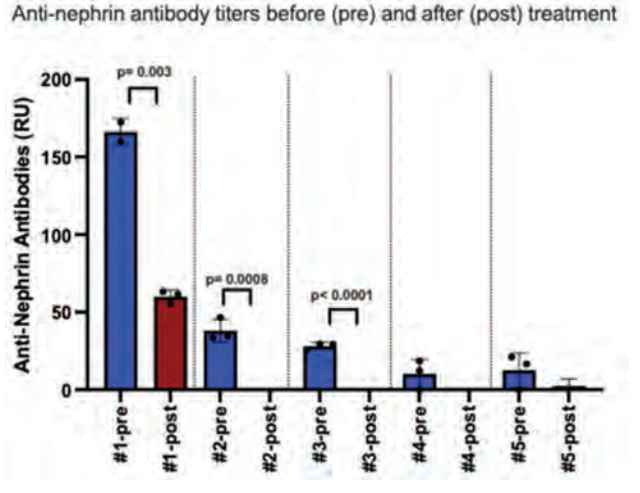
Yoko Fujita,[1,5] Andrew J. Watts,[2,3] Daisuke Ichikawa,[1] Yugo Shibagaki,[1] Tomo Suzuki,[4] Keith H. Keller,[2] Astrid Weins,[2,3] Naoka Murakami.[2,3]
[1]St. Marianna University School of Medicine, Kawasaki, Japan; [2]Brigham and Women's Hospital, Boston, MA; [3]Harvard Medical School, Boston, MA; [4]Kameda Medical Center, Kamogawa, Japan; [5]Yokohama General Hospital, Yokohama City, Japan.

Background: Minimal change disease (MCD) is a leading cause of nephrotic syndrome in adults and is more common in the Japanese population. Recently, nephrin autoantibodies were reported in a North American Cohort of adults and children with MCD supporting an autoantibody mediated etiology. However, the clinical characteristics of nephrin autoantibody positive MCD in elderly Japanese patients have scarcely been studied.

Methods: In this single-center case series in Japan, we included 8 consecutive adult cases of biopsy-proven MCD presented to our center in 2021. We evaluated serum, obtained at presentation and following treatment, for circulating nephrin autoantibodies by indirect ELISA. The renal biopsies were evaluated for punctate IgG deposition and co-localization with nephrin by immunofluorescence confocal microscopy imaging.

Results: The median age was 75 years (range 56-84), 43% male, median creatinine and median urine protein/creatinine ratio at diagnosis were 0.92 mg/dL (range 0.47-4.5) and 10.9 g/g (range 7.7-14.0 g/gCr) respectively. Five out of eight cases (63%) had circulating anti-nephrin autoantibodies at presentation and this correlated completely with "punctate IgG" that colocalized with nephrin in the renal biopsies of all positive patients. All 8 patients achieved complete remission after therapy and those with serum anti-nephrin antibodies had reduction in antibody titer with clinical response (Figure). Anti-nephrin antibody positive group had shorter relapse-free time (median 16.5 months), compared to negative group (no relapse).

Conclusions: In our cohort of anti-nephrin antibody-positive adult Japanese MCD cases in elderly Japanese patients, we observed the correlation of anti-nephrin antibody titer with disease activity and shorter relapse-free time. Larger studies are needed to further characterize anti-nephrin antibody positive MCD cases in adults.



FR-PO913

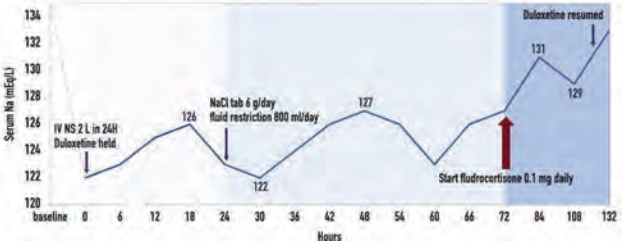
Fludrocortisone-Responsive Hyponatremia in the Elderly

Noppawit Aiumtrakul,[1,3] Chinnawat Arayangkool,[1,3] Manasawee Tanariyakul,[1,3] Thiratest Leesutipornchai,[1,3] Roland C. Ng.[1,2] *[1]University of Hawai'i at Manoa John A Burns School of Medicine, Honolulu, HI; [2]Kuakini Medical Center, Honolulu, HI; [3]Hawaii Residency Programs Inc, Honolulu, HI.*

Introduction: Case studies report a rare manifestation of hyponatremia responsive to fludrocortisone, presenting as SIADH or salt-wasting syndrome (SWS), which fails to correct with both fluid restriction and Na replacement.

Case Description: A 79-year-old Japanese woman with T2DM and depression on duloxetine was found to have asymptomatic hyponatremia with Na level of 122 mEq/L. She reported eating 3 meals and drinking water 2 L/day. Vital signs were hemodynamically stable without presence of dehydration. Initial work-up showed serum osmolality at 256 mOsm/kg, urine Na at 94 mEq/L, urine osmolality at 292 mOsm/kg, serum creatinine at 0.4 mg/dL and BUN at 10 mg/dL, with normal serum glucose, AM cortisol and TSH. CT brain without contrast was unremarkable. Duloxetine was initially held. The patient received 2 L of IV normal saline, followed by NaCl tabs 6 g/day. Fluid intake was restricted to <800 ml/day. The serum Na remained low between 122-126 mEq/L for the next 48 hrs. After initiating fludrocortisone acetate 0.1 mg daily, the serum Na increased to 133 mEq/L within 60 hours, without falling after resuming duloxetine. Her urine output was 1-2 L/day. Her pre- and post-admission weights were 35 and 32.9 kg. Her hematocrit was stable at 34%.

Discussion: Reports in the literature list 10 non-neurosurgical patients with hyponatremia responsive to fludrocortisone, 5 with cerebral salt-wasting, 3 with SIADH, and 2 did not have a clear diagnosis. All of them were Japanese elderly patients. 3 of 10 cases had a prior history of traumatic brain injury. The clinical response of SIADH or SWS to fludrocortisone is rarely discussed as a treatment of hyponatremia in medical patients. This is another case of fludrocortisone-responsive hyponatremia. Common characteristics include Japanese race, female, elderly, hypo osmolality, hypertonic urine and high urine Na. Volume status can be either hypo or euvolemic. In 1987, Ishikawa et al. proposed the concept of mineralocorticoid-responsive hyponatremia of the elderly (MRHE). MRHE is thought to be caused by a decline in the response to the RAAS and in the kidneys' ability to retain sodium.



FR-PO914

Kappa Light Chain Myeloma Presenting as Acute Renal Failure

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Introduction: Multiple Myeloma is a plasma cell dyscrasia commonly affecting the elderly. Acute renal failure carries a particularly poor prognosis. Here we present a 95-year-old woman who came with fatigue, polyuria and new onset renal failure. Work up showed multiple myeloma with kidney biopsy showing diffuse tubular necrosis and bone marrow biopsy showing kappa light chain myeloma. She was started on chemotherapy within 13 days of admission. Despite prompt initiation of chemotherapy, kidney function did not improve, and she deteriorated in a month's time.

Case Description: The patient was a 95-year-old woman with a history of HTN/HLD and a remote history of PE on warfarin. She was fully functional and independent at baseline; she was compliant with medication and labs 6 months prior were normal. She was referred to the ED for bradycardia, had been having polyuria and fatigue one week prior. In the ED, vitals were normal, physical exam showed chronic bilateral hearing loss, labs were notable for a Hgb of 6.5, MCV of 104, a BUN of 150 and a Cr of 12 with a potassium of >7.5, her corrected calcium was 9.5; a stool occult test was positive, and her INR was 7.9. She was admitted to the ICU for CVVHD, concern for acute GI bleed with severe pre-renal AKI, however her hemoglobin normalized and was unable to wean off HD. Workup for RPGN, vasculitis and multiple myeloma was done which showed significantly elevated kappa/lambda ratio, kidney biopsy showed diffuse acute tubular necrosis without glomerulonephritis and bone marrow biopsy and serum studies showed kappa light chain myeloma. Chemotherapy was started 13 days after diagnosis; however, her kidney function did not improve, and she deteriorated within a month from episodes of fluid overload while on dialysis and vascular access site infections.

Discussion: Renal impairment in multiple myeloma has a life expenctancy of less than a year, and is an independent negative prognostic factor when noted in the first 6 months of diagnosis. The biggest indicator of overall prognosis is renal response to treatment including dialysis and chemotherapy. Our patient's case showed a rare case of kappa light chain myeloma presenting with acute renal failure from ATN which unfortunately did not improve with treatment. More research into modalities such as high output dialysis or plasmapheresis in this population would be useful to reduce light chain burden and resulting ATN.

FR-PO915

Association of Serum Magnesium Concentration with Renal Prognosis in Patients with CKD

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Background: Magnesium plays a crucial role in various physiological processes, and disruptions in its balance have been linked to adverse health effects. By investigating the impact of magnesium levels on renal outcomes, this study aims to contribute to our understanding of managing magnesium levels in CKD patients. The findings may provide valuable insights for clinical practice and future intervention studies in this population.

Methods: This study utilized the J-CKD-DB-Ex database, comprising CKD patients enrolled between 2014 and 2020. Only patients with at least two measurements of magnesium and eGFR were included. The index date was established as the time of the initial magnesium measurement, and individuals with an eGFR greater than 15 and less than 60 ml/min/1.73 m^2 at the index date were selected. The study categorized participants into three groups based on their magnesium levels: low, normal, and high magnesium. Patients who had a single clinic visit or a history of hospitalization were excluded from the analysis. The primary outcome was defined as the progression to ESKD, determined by an eGFR below 15 mL/min/1.73m^2 or a decline of 30% or more in eGFR from baseline.

Results: A cohort of 9,996 patients without prior hospitalization was analyzed. Hypomagnesemia was present in 6% of patients, while hypermagnesemia was observed in 4% of patients. Initial Kaplan-Meier survival curve analysis, without adjustment, showed a significantly worse renal prognosis in the hypomagnesemia group. However, to address potential confounding factors, multiple imputation and Cox regression analysis were conducted, with the normal magnesium group as the reference. After adjusting for covariates, the hypomagnesemia group had a hazard ratio of 1.26 (95% confidence interval: 1.08-1.46), indicating an increased risk of adverse renal outcomes compared to the normal magnesium group. Adjusted restricted cubic spline analysis also supported this trend, demonstrating that lower magnesium levels were associated with poorer renal prognosis.

Conclusions: The study findings suggest that the renal prognosis of patients is influenced by their serum magnesium concentration, with poorer outcomes observed in individuals with hypomagnesemia.

Funding: Private Foundation Support

FR-PO916

Ionized and Total Magnesium Levels and Cardiovascular Risk in Patients with CKD

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Background: We sought to determine whether serum ionized (iMg) and total (tMg) Mg levels are associated with major adverse cardiovascular events (MACE) in patients with CKD.

Methods: CKD-REIN is a prospective cohort of CKD outpatients (not on dialysis). Baseline iMg and tMg serum concentrations were respectively centrally measured using the NOVA BIOMEDICAL Stat Profile PRIME ES and with Atellica® CH SIEMENS analyzers. Adjusted cause-specific Cox proportional hazard models were used to estimate hazard ratios (HRs) for first MACE (CV death, myocardial infarction, stroke or hospitalization for heart failure).

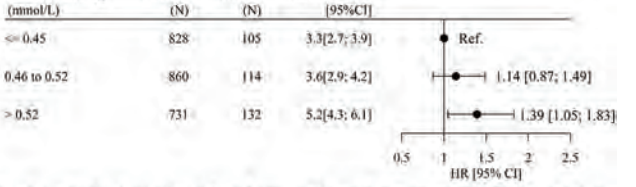
Results: Of the 2419 included patients (median [IQR] age: 68[60-76]; mean (SD) eGFR 33.5(13.5) mL/min/1.73 m^2), 52% had a history of CV disease. Correlation between iMg and tMg was very high (r=0.88; p<0.001). Over a median follow-up of 4.4 years [IQR,2.3-5.0], 351 experienced a first MACE event, leading to an incidence rate [95%CI] of 3.9[3.5;4.3] per 100 person-years (**figure**). After multiple adjustments, patients in Tertile 3 (T3) of iMg had a higher risk of MACE compared to patients in Tertile 1 (T1), HR [95% CI], 1.39[1.05;1.83]. No difference was noted for patients in Tertile 2 (T2) compared to patients in T1. Regarding tMg, patients in T3 of total Mg had a higher risk of MACE compared to patients in T1 (HR=1.40[1.07;1.83]). A nonsignificant lower risk of MACE was noted for patients in T2 compared to patients in T1, revealing a potential U shape relation between MACE risk and tMg level.

Conclusions: This study suggests that high serum iMg and tMg levels are associated to cardiovascular outcomes in patients with moderate to advanced CKD. Further research is needed to explore the shape of the relationships and the mechanisms.

Funding: Government Support - Non-U.S.

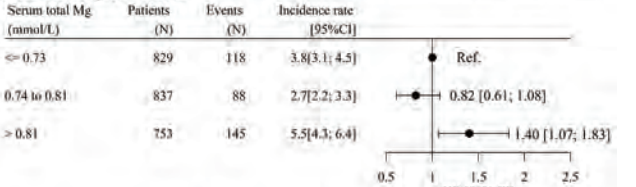
A. Adjusted hazard ratios for major adverse cardiovascular events according to the baseline serum ionized magnesium level

Serum ionized Mg (mmol/L)	Patients (N)	Events (N)	Incidence rate [95%CI]
<= 0.45	828	105	3.3[2.7; 3.9]
0.46 to 0.52	860	114	3.6[2.9; 4.2]
> 0.52	731	132	5.2[4.3; 6.1]



B. Adjusted hazard ratios for major adverse cardiovascular events according to the baseline serum total magnesium level

Serum total Mg (mmol/L)	Patients (N)	Events (N)	Incidence rate [95%CI]
<= 0.73	829	118	3.8[3.1; 4.5]
0.74 to 0.81	837	88	2.7[2.2; 3.3]
> 0.81	753	145	5.5[4.3; 6.4]



HR are adjusted for age at baseline, sex, body mass index, baseline estimated glomerular filtration rate, baseline serum urea, sodium, calcium, bicarbonates, serum albumin, pulse pressure, diabetes, dyslipidemia, baseline prescription of proton pump inhibitor, agents acting on the renin-angiotensin system, diuretic, ciclosporin and drugs for constipation.

Figure: Adjusted HRs for major adverse cardiovascular events, according to the baseline serum magnesium levels.

FR-PO917

Epidemiology and Outcomes of Hyperphosphatemia in Non-Dialysis CKD Patients in China

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Background: Information on epidemiology and outcomes of hyperphosphatemia (HP) in non-dialysis CKD (ND-CKD) patients is still lacking.

Methods: Hospitalized patients aged ≥18 years with a diagnosis of CKD between 2013 and 2020 in the China Renal Data System (CRDS) were included. The prevalence of HP (defined as a serum phosphate concentration > 1.45 mmol/L when first detected during hospitalization) was analyzed. Secondary endpoints were use of phosphorus-lowering medications, all-cause mortality, cardiovascular mortality and progression of kidney disease. This is the interim report of the study.

Results: A total of 210,806 ND-CKD patients from 19 hospitals were screened, of whom 157,987 (74.94%) had serum phosphate testing during the first hospitalization. The overall prevalence of HP was 14.83% in these patients (CKD G1 8.26%, G2 6.17%, G3a 7.32%, G3b 12.43%, G4 26.74%, G5 65.85%). The utilization rates of phosphorus-lowering medications (including calcium acetate, calcium carbonate, lanthanum carbonate, and sevelamer carbonate) in ND-CKD G3-5 were 9.62% (G3a), 11.29% (G3b), 14.84% (G4), and 23.92% (G5), respectively. Among 64,662 patients with a median follow-up of 3.3 year on death, patients with HP (n=8856) had a 13% increased risk of all-cause mortality (HR 1.13, 95% CI 1.06-1.22) and a 28% increased risk of cardiovascular mortality (HR 1.28, 95% CI 1.04-1.56), compared with those with normal serum phosphate concentration at baseline with confounders adjusted for age, sex, region, CKD stage, co-morbidity. Among the patients with HP the risk of all-cause mortality and cardiovascular mortality were reduced by 12% and 16%, respectively, in patients with phosphorus-lowering medications compared to those without phosphorus-lowering medications. Among 47,581 patients with a median follow-up of 1.8 years on kidney function, patients with HP (n=3622) had a 9% increased risk of kidney disease progression than those with normal serum phosphate concentration at baseline (HR 1.08, 95% CI 1.00-1.17).

Conclusions: HP is common in ND-CKD in China and is an independent risk factor for mortality and kidney disease progression. The use of phosphorus-lowering medications was associated with the decreased risk of all-cause mortality and cardiovascular mortality in patients with CKD G3-5.

Funding: Commercial Support - Sanofi

FR-PO918

Intensity of Serum Phosphate Lowering Is Related to the Risk of RRT in Non-Dialysis Dependent (NDD)-CKD Patients with Hyperphosphatemia

Sheng Nie,[1] Qi Gao,[1] Shiyu Zhou,[1] Lichen Hao,[2] Yan Zhang,[3] Muhan Yuan.[3] *[1]Southern Medical University Nanfang Hospital, Guangzhou, China; [2]Sanofi, Bridgewater, NJ; [3]Sanofi, Beijing, China.*

Background: Few studies have explored the association between intensity of serum phosphate lowering and risk of renal replacement therapy (RRT) in patients with non-dialysis dependent chronic kidney disease (NDD-CKD).

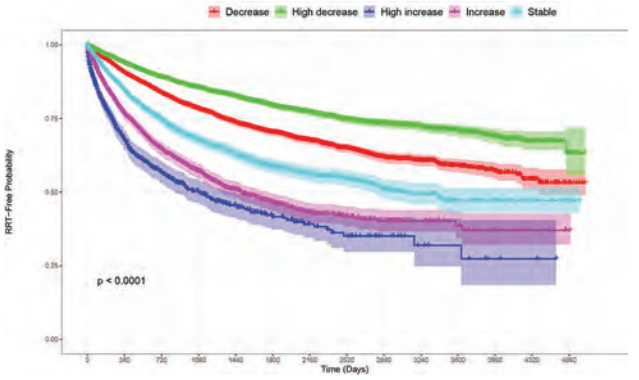
Methods: Data was extracted from the Optum Humedica EHR database. The study period started from July 1, 2007, to June 30, 2021. We enrolled NDD-CKD adult patients with two consecutive results of elevated serum phosphorus (defined as non-same day but ≤180 days apart, >4.5 mg/dL on both occasions). The study exposure was defined as the

change in serum phosphorus concentration at 360 days after the enrollment. 360 days after the enrollment was defined as the index date. Study outcome was the initiation of RRT.

Results: A total of 28,165 patients were analyzed, of whom 45% were male, the mean age was 60 years, and 43% were in CKD stage 5. Based on the changes in serum phosphorus concentration at 360 days, 11,599 (41.2%), 10,135 (36.0%), 3,165 (11.2%), 2,293 (8.1%) and 975 (3.5%) were categorized into the high decrease group (decrease of ≥25%), decrease group (decrease of 5% to 25%), stable group (decrease of <5% to increase of <5%), increase group (increase of 5% to <25%), and high increase group (increase ≥25%), respectively. The high decrease group and decrease group were associated with lower risk of RRT compared with the stable (high decrease: adjusted hazard ratio (aHR)=0.51, 95% confidence interval (CI): 0.47-0.56; decrease: aHR=0.75, 95% CI: 0.69-0.81). Meanwhile, the high increase group and increase group were associated with higher risk of RRT compared with the stable (high increase: aHR=1.34, 95% CI: 1.19-1.51; increase: aHR=1.24, 95% CI: 1.13-1.36).

Conclusions: The level of serum phosphate change was associated with the risk of RRT in patients with NDD-CKD and hyperphosphatemia. Our findings suggest that intensive lowering of serum phosphate might help to delay the time to RRT in patients with NDD-CKD.

Funding: Commercial Support - Sanofi



The Kaplan-Meier curves of RRT-free probability in different groups.

FR-PO919

Metabolic Acidosis and CKD Progression

Carmine Zoccali,[1,2] Graziella D'Arrigo,[3] Mercedes Gori,[3] Giovanni Tripepi,[3] Francesca Mallamaci.[3,4] On Behalf of MAURO Study Group. *[1]Renal Research Institute, New York, NY; [2]BIOGEN, Ariano Irpino, Italy; [3]IFC-CNR, Reggio Calabria, Italy; [4]Nephrology, Dialysis, and Transplantation, Reggio Calabria, Italy.*

Background: An inverse relationship between venous bicarbonate and CKD progression has been reported in several observational studies, but only sparse longitudinal observations testing this relationship exist. Bicarbonate supplementation trials have been conflictual, with limited power and a high risk of bias. Longitudinal studies may provide circumstantial new evidence for implicating metabolic acidosis in the risk of adverse kidney outcomes.

Methods: We performed a longitudinal study in 528 patients with at least 3 longitudinal measurements of bicarbonate over 32 months (IQR: 30-36). The association between bicarbonate trajectories over time and the incidence of renal events (>30% eGFR reduction, dialysis or transplantation) were investigated by a two stages analysis: 1) in the first stage, we identified distinctive group-based bicarbonate trajectories analysis (GBTM); 2) in the second stage we assessed the association between bicarbonate trajectories groups and the risk of renal events by Cox model.

Results: Overall, 126 patients had renal events. Four trajectories of bicarbonate were identified and labelled as low trajectory [bicarbonate: 19.07± 2.5 mEq/L], moderate [21.2± 2.3 mEq/L], moderate-high [25.1± 2.2 mEq/L] and high [27.9± 2.8 mEq/L]. In crude and adjusted analyses (age, gender, systolic BP, haemoglobin, albumin, phosphate, PTH, 24h proteinuria, and eGFR), the hazard rate (HR) of renal events decreased in a dose-dependent fashion from the lowest bicarbonate trajectory (reference category, HR 1) [moderate (HR:0.82, 95%CI 0.50-1.35, p=0.443), high moderate (HR:0.59, 95%CI 0.34-1.00, p=0.050), and high bicarbonate category (HR: 0.37, 95%CI 0.15-0.95, p=0.039), p for trend p=0.010]. (P for trend=0.005). Thus, for patients in the high bicarbonate category (27.9± 2.8 mEq/L), there is an 63% risk reduction for a renal composite endpoint.

Conclusions: In a longitudinal analysis of a cohort of CKD patients, high bicarbonate levels are associated with a substantially reduced risk of renal events. These findings represent a strong call for well-designed, adequately powered randomised trials testing the effect of bicarbonate supplements or pharmacologic interventions that increase serum bicarbonate on renal outcomes. Given the substantial risk reduction in patients in the highest bicarbonate trajectory, these trials are an absolute clinical research priority.

FR-PO920

Serum Uric Acid Trajectories and CKD Progression in the African American Study of Kidney Disease in Hypertension (AASK)

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Background: Serum uric acid levels increase with progressive kidney disease, due to retention of uric acid resulting from a reduced glomerular filtration rate (eGFR). Chronic elevations in circulating and tissue levels of uric acid may contribute to progression of chronic kidney disease, although this remains controversial.

Methods: We used data from the African American Study of Kidney Disease in Hypertension (AASK) to examine the hypothesis that subjects whose serum urate levels declined during the study period would manifest less composite end-stage kidney disease (ESKD) event. The composite ESKD outcome was defined as 50% decline from baseline eGFR, eGFR ≤15 mL/min/1.73 m2, self-reported initiation of chronic dialysis, or kidney transplantation. To estimate the trajectory, the group-based trajectory modeling of the uric acid level change was done. We classified into 5 groups ; high-stable group, the high-increasing group, the extreme high-stable group, normo-increasing group, and high-decreasing group. Cox proportional hazards model was used to estimate whether the different group membership would predict the composite ESKD outcomes.

Results: We found that compared with subjects in the normal-increasing uric acid group (*i.e.,* those who had the lowest overall serum uric acid levels), three groups had higher incidence of the composite ESKD event: the high-stable uric acid group, HR = 2.28, $p = 0.012$, the high-increasing uric acid group, HR = 1.95, $p = 0.042$, and the extremely high-stable uric acid group, HR = 3.21, $p < 0.001$. Further, the extremely high-stable group had a higher composite ESKD incidence, compared with the high-decreasing group, HR = 1.98, $p = 0.046$.

Conclusions: Uric acid trajectories are associated with ESKD incidence. In particular, subjects whose uric acid levels decreased over time had a better composite ESKD event than other groups.

Funding: Government Support - Non-U.S.

FR-PO921

Projected Benefits of Gout Control on the Health and Economic Burden of CKD Patients with Uncontrolled Gout

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Background: Gout affects 1 in 4 patients with stage 3-5 CKD and is an independent risk factor for CKD progression. Since oral urate lowering therapies (ULTs) cannot adequately manage gout in some CKD patients, this study examines potential benefits of pegloticase treatment in CKD patients with refractory gout.

Methods: A validated microsimulation model was used to project gout burden in a virtual US CKD population. In the baseline scenario, individuals were assigned an eGFR, albuminuria status, and serum urate (SU) level. Those with gout were assigned complication risks for stroke, diabetes, and hypertension, direct and indirect costs, oral ULT use/efficacy probability (use: 29.9-41.9% [based on eGFR], efficacy: 48.3%) and utility weight. In the intervention scenario, patients with uncontrolled gout (SU>6 mg/dL despite oral ULT, and ≥2 gout flares/year or ≥1 tophi) were "treated" with pegloticase, assuming a 71% SU-lowering efficacy rate (SU<6mg/dL) through simulation end. Health/economic benefits were projected through 2035.

Results: Prevalence of comorbid gout and CKD was projected to rise from 8.2M in 2023 to 10.5M in 2035, with 28% having uncontrolled gout. Annual costs of gout in CKD patients were projected to rise from $39.1B in 2023 to $50.4B in 2035. Pegloticase use in all CKD patients with uncontrolled gout resulted in 301,000 fewer uncontrolled gout cases, 208,000 quality-adjusted life years gained, and 53,000 complications avoided by 2035 (**Figure**). Compared to the baseline (non-treatment) scenario, intervention scenario costs were $23.4B lower in 2035.

Conclusions: Gout prevalence in CKD patients is projected to markedly increase over the next 12 years. This microsimulation suggests that intervention could result in health and quality of life improvements in CKD patients with uncontrolled gout, with associated cost reductions.

Funding: Commercial Support - Horizon Therapeutics plc

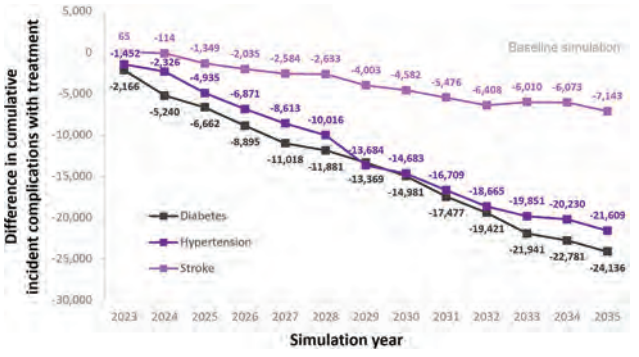


Figure. Difference in incident complications in CKD pts between treated (intervention) and untreated (baseline) uncontrolled gout scenarios.

FR-PO922

Factors of Poor Prognosis Associated with CKD by Stage in Ambulatory Patients: A Cross-Sectional Study

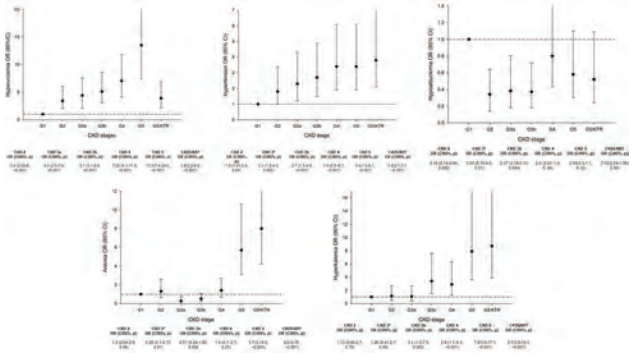
L. M. Perez-Navarro, Rafael Valdez-Ortiz. *Hospital General de Mexico Dr Eduardo Liceaga, Ciudad de Mexico, Mexico.*

Background: Mexico has a high prevalence of chronic kidney disease (CKD) but limited information about the early stages of CKD and their clusters of poor prognosis factors (PPF) such as hyperuricemia, electrolyte abnormalities or comorbidities. Objective. To assess the prevalence of PPF by CKD stages in ambulatory patients.

Methods: A cross-sectional study with 1772 adult patients with CKD that attended the Nephrology Outpatient Clinic. PPF data is reported as adjusted OR (95% confidence interval) (CI).

Results: Mean age was 56.2 ± 15.8 years. Kidney Replacement Therapy (KRT) was reported in 12% of the patients. Type 2 diabetes mellitus (T2DM), age >50 years and male gender were the PPF associated with all CKD stages. The PPF in CKD 2 and 3a hyperuricemia OR 3.4 (2.02,6.0) and 4.4 (2.5,7.6), and hypertension OR 1.8 (1.01,3.4) and 2.3 (1.2,4.3) respectively. In CKD 3b were hyperuricemia OR 5.1 (3.1,8.6), hypertension OR 2.7 (1.5,4.9) and hyperkalemia OR 3.4 (1.5,7.6). For CKD 4, 5 without KRT and 5 were hyperuricemia OR 7.02 (4.1,11.8), 13.5 (7.4,24.6), 3.9 (2.2–6.9), hypertension OR 3.4 (1.9,6.1), 3.4 (1.9,6.1), 3.8 (2.1,7.1), and hyperkalemia 2.9 (1.3,6.3), 7.9 (3.6,17.3), 8.7 (3.9,19.3), respectively. Anemia was important for CKD 5 without KRT and 5 with OR of 5.7 (3.09,10.6) and 8 (4.2,15), respectively.

Conclusions: This is the largest study of Mexican patients with CKD; most of them without KRT. Patients had multiple modifiable PPF. Early and comprehensive management of PPF could prevent or delay progression to KRT. Treatment of associated PPF should be a priority, as it could make a significant difference both for CKD progression and its subsequent cardiovascular risk.



FR-PO923

Hyperuricemia and Polygenic Risk Score for CKD: Evaluating Its Impact Beyond Genetic Predisposition for CKD

Yaerim Kim,[1] Jin hyuk Paek,[1] Kyubok Jin,[1] Seungyeup Han,[1] Jung Pyo Lee,[2] Dong Ki Kim,[3] Chun Soo Lim,[2] Jeonghwan Lee.[2] *[1]Keimyung University School of Medicine, Daegu, Republic of Korea; [2]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Dongjak-gu, Seoul, Republic of Korea; [3]Seoul National University Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: The bidirectional effect of hyperuricemia on chronic kidney disease (CKD) underscores the importance of hyperuricemia as a risk factor for CKD. We evaluated the effect of hyperuricemia on the presence and development of CKD after considering genetic background by calculating polygenic risk scores (PRSs).

Methods: We employed genome-wide association study summary statistics—excluding the United Kingdom Biobank (UKB) datasets among published CKD Gen Consortium papers—to calculate the PRSs for CKD in white background subjects. To validate PRS performance, we divided the UKB into two datasets to validate and test the data. We used logistic regression analysis to evaluate the association between hyperuricemia and CKD, and performed Cox proportional hazard analysis exclusively for subjects with available follow-up data.

Results: In total, 438,253 clinical data points and 4,307,940 single nucleotide polymorphisms from 459,155 samples were included. We observed a significant positive association between PRS and CKD and the presence and development of CKD. Hyperuricemia significantly increased CKD risk (adjusted odds ratio 1.54, 95% confidence interval 1.49–1.58). The impact of hyperuricemia on CKD was maintained irrespective of PRS range but was more pronounced in subjects with low PRS (1st tertile range). Survival analysis indicates that the presence of hyperuricemia significantly increased the risk of CKD development.

Conclusions: The PRS for CKD thoroughly reflects the risk of CKD development. Hyperuricemia is a significant indicator of CKD risk, even after incorporating the genetic risk score for CKD. Irrespective of genetic risk, patients with a prospective risk of developing CKD require uric acid monitoring and management.

FR-PO924

Polygenic Risk Affects the Penetrance of Monogenic Kidney Disease

Atlas Khan,[1] Ning Shang,[1] Jordan G. Nestor,[1] Chunhua Weng,[1] George Hripcsak,[1] Peter C. Harris,[2] Ali G. Gharavi,[1] Krzysztof Kiryluk.[1] Kiryluk Group. *[1]Columbia University, New York, NY; [2]Mayo Foundation for Medical Education and Research, Rochester, MN.*

Background: Chronic kidney disease (CKD) is a genetically complex disease determined by an interplay of monogenic, polygenic, and environmental risks. Most forms of monogenic kidney diseases have incomplete penetrance and variable expressivity. It is presently unknown if some of the variability in penetrance can be attributed to polygenic factors.

Methods: Using the UK Biobank (N=469,835) and the All of Us (N=98,622) datasets, we examined the two most common forms of monogenic kidney disorders, autosomal dominant polycystic kidney disease (ADPKD) caused by deleterious variants in the *PKD1* or *PKD2*, and COL4A-associated nephropathy (COL4A-AN caused by deleterious variants in *COL4A3*, *COL4A4*, or *COL4A5*). We used the eMERGE-III electronic CKD phenotype to define cases (estimated glomerular filtration rate (eGFR) <60 or kidney failure) and controls (eGFR >90). The effects of the genome-wide polygenic score for CKD were tested in monogenic variant carriers and non-carriers using logistic regression controlling covariates.

Results: As expected, the carriers of known pathogenic and rare predicted loss-of-function variants in *PKD1* or *PKD2* had a high risk of CKD (OR_{meta}=17.1, 95% CI: 11.1-26.4, P=1.8E-37). The GPS was comparably predictive of CKD in both ADPKD variant carriers (OR_{meta}=2.28 per SD, 95%CI: 1.55-3.37, P=2.6E-05) and non-carriers (OR_{meta}=1.72 per SD, 95% CI=1.69-1.76, P< E-300) independent of age, sex, diabetes, and genetic ancestry. Compared to the middle tertile of the GPS distribution for non-carriers, ADPKD variant carriers in the top tertile had a 54-fold increased risk of CKD. In contrast, ADPKD variant carriers in the bottom tertile had only a 3-fold increased risk of CKD. Similarly, the GPS was predictive of CKD in both COL4-AN variant carriers (OR_{meta}=1.78, 95% CI=1.22-2.58, P=2.38E-03) and non-carriers (OR_{meta}=1.70, 95%CI: 1.68-1.73 P<E-300). The carriers in the top tertile of the GPS had a 2.5-fold higher risk of CKD, while the risk for carriers in the bottom tertile was similar to the middle tertile of non-carriers.

Conclusions: Variable penetrance of kidney disease in ADPKD and COL4-AN is partially explained by differences in polygenic risk profiles. Accounting for polygenic factors has the potential to improve risk stratification in monogenic kidney disease and may have implications for genetic counseling.

Funding: NIDDK Support, Other NIH Support - NHGRI

FR-PO925

Association Between Dyslipidemia and the Risk of Incident CKD Affected by Genetic Susceptibility: Polygenic Risk Score Analysis

Boram Weon,[1,2] Wencheng Jin,[1,3] Ara Ko,[2] Jeonghwan Lee,[1,3] Jung Pyo Lee.[1,3] *[1]Seoul National University Seoul Metropolitan Government Boramae Medical Center, Seoul, Republic of Korea; [2]Seoul National University Hospital Department of Internal Medicine, Seoul, Republic of Korea; [3]Seoul National University College of Medicine Department of Internal Medicine, Seoul, Republic of Korea.*

Background: Polygenic risk of dyslipidemia on kidney disease outcomes has been inconclusive, and it requires further clarification. Therefore, we aimed to investigate the effects of genetic factors on the association between dyslipidemia and the risk of chronic kidney disease (CKD) using polygenic risk score (PRS). score (PRS) provides information of the overall contribution of numerous genetic variants on disease outcomes. The effect

Methods: We analyzed data from 373,523 participants of UK biobank aged 40 to 69 and without history of chronic kidney disease. The PRS for incident CKD was constructed using GWAS summary statistics of CKDGen overall European ancestry (n=480,697). The impacts of lipids and PRS on incident CKD were assessed using Cox proportional hazard model. To investigate the interaction between lipids and genetic factor on incident CKD,

we introduced multiplicative interaction terms between them to multivariable analysis model and performed subgroup analysis stratified by PRS tertiles.

Results: A total of 4,424 participants developed CKD. In multivariate analysis, the PRS was significantly predictive of the risk of incident CKD (continuous variable; HR, 1.075; 95% CI, 1.043-1.109). 1-SD lower levels of total cholesterol (HR, 0.898; 95% CI, 0.867-0.931), LDL-C (HR 0.899, 95% CI; 0.931), HDL-C (HR, 0.877; 95% CI, 0.841-0.914), and higher triglyceride (HR, 1.078; 95% CI, 1.048-1.109) were significantly associated with the risk of incident CKD. The interactions between triglyceride and intermediate (HR, 1.122; 95% CI, 1.026-1.228) and high PRS (HR, 0.932; 95% CI 0.872-0.995) were significant, and the interactions were inversely associated with the risk of incident CKD. Similar relationship between triglyceride and PRS were observed in subgroup analysis stratified by PRS tertiles.

Conclusions: The PRS for incident CKD presented significant predictive power for incident CKD. Higher triglyceride, lower total cholesterol, lower LDL-C, and lower HDL-C increased the risk of incident CKD. There were interactions between triglyceride and genetic factor, and the individuals in the low-PRS group had a higher risk of triglyceride-related incident CKD.

FR-PO926

Discovery and Prioritization of Genetic Determinants of Kidney Function in Approximately 310,000 Individuals from ESKD-Prevalent Taiwan and Japan

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Background: Limited ancestral diversity in genome-wide association studies (GWASs) on kidney function confines their generalizability to regions with a high incidence of end-stage kidney disease (ESKD).

Methods: We conducted a meta-analysis of GWASs (n=244952) of estimated glomerular filtration rate (eGFR) and a replication dataset (n=27058) from Taiwan and Japan. Additionally, polygenic risk scores (PRSs) for chronic kidney disease (CKD) substantially differentiated the CKD risk in independent cohorts from Taiwan (n=30433) and the United Kingdom (n=260245). (**Fig. 1**)

Results: Our analysis identified 238 independent signals in 97 loci that were associated with eGFR. Functional analyses revealed that variants associated with *F12* expression and *ABCG2* missense mutation link inflammation, coagulation, and urate metabolism to a high risk of decreased kidney function. The median time to 10% CKD incidence in PRS_{CKD} risk groups (above, in-between, and below two standard deviations of mean) was 64, 66, and 71 years after birth, respectively. (**Fig. 2**) The 7-year difference between high– and low–genetic risk groups can be observed from the age of 50.

Conclusions: Our findings suggest that PRS_{CKD} has the potential to be used for early kidney disease prevention, particularly in countries with a high incidence of ESKD.

Funding: Government Support - Non-U.S.

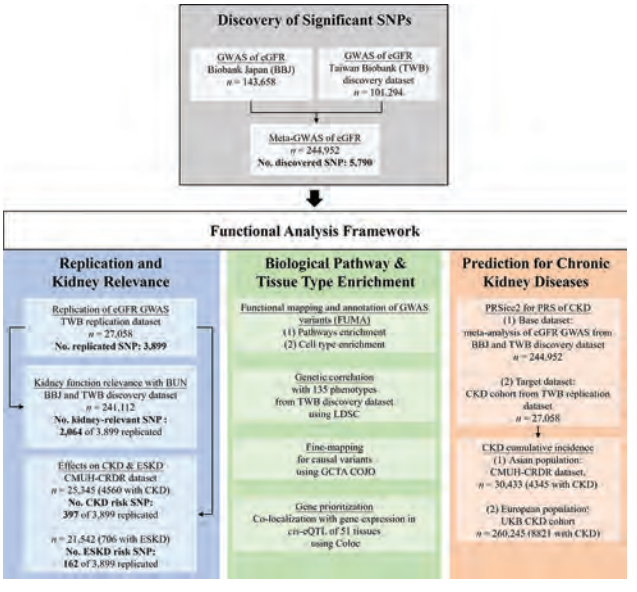


Figure 1. Study design flowchart

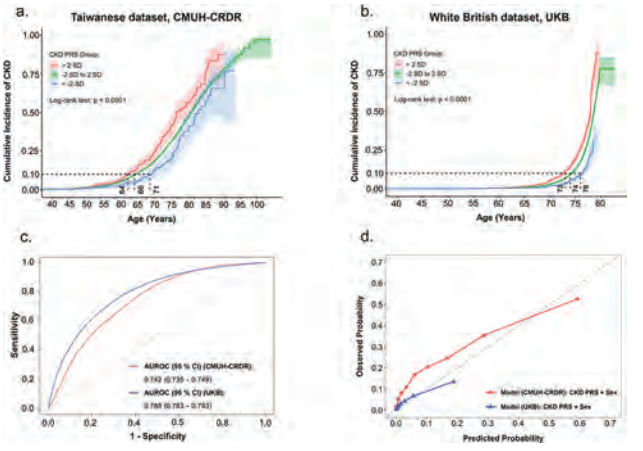


Figure 2. Cumulative incidence of CKD based on PRS stratification

FR-PO927

Abstract Withdrawn

FR-PO928

Common Genetically Predicted Skipping of COL4A4 Exon 27 Is Associated with Hematuria and Albuminuria

Moumita Barua,[1] Frida Lona Durazo,[2] Kohei Omachi,[3] Damian Fermin,[4] Felix H. Eichinger,[4] Jonathan P. Troost,[5] Jeffrey H. Miner,[3] Andrew Paterson,[6] Sarah A. Gagliano Taliun.[2] *[1]Toronto General Hospital, Toronto, ON, Canada; [2]Universite de Montreal Faculte de Medecine, Montreal, QC, Canada; [3]Washington University in St Louis School of Medicine, St Louis, MO; [4]University of Michigan Division of Nephrology, Ann Arbor, MI; [5]Michigan Institute for Clinical and Health Research, Ann Arbor, MI; [6]SickKids Research Institute, Toronto, ON, Canada.*

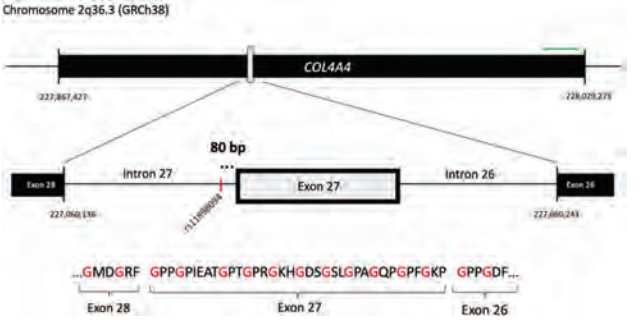
Background: Hematuria is an established sign of glomerular disease and can be associated with kidney failure, but there has been limited scientific study of this trait.

Methods: Here, we combined genetic data from the UK Biobank with predicted gene expression and splicing from GTEx kidney cortex samples (n = 65) in a transcriptome-wide association study (TWAS) to identify additional biological mechanisms influencing hematuria.

Results: Our TWAS using kidney cortex identified significant associations for 5 genes in terms of expression and 3 significant splicing events. Notably, we identified an association between hematuria and the skipping of *COL4A4* exon 27, which is genetically predicted by intronic rs11898094 (minor allele frequency 13%). The association was also found with urinary albumin excretion. We found independent evidence supporting the existence of this skipping event in glomeruli-derived mRNA transcriptomics data (n = 245) from the NEPTUNE dataset. The functional significance of loss of exon 27 was demonstrated using the split NanoLuc-based type IV collagen α3α4α5(IV) heterotrimer assay, in which heterotrimer formation was quantified by luminescence.

Conclusions: Altogether, our results highlight the value of investigating the role of non-coding sequence, an underexplored region, by integrating multiple data types to shed light on kidney traits and their underlying disease mechanisms.

Funding: NIDDK Support



Genomic overview of the exon 27 skipping event of *COL4A4*.

FR-PO929

Circulating Proteins Associated with Mortality in Patients with CKD

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Background: Proteomics could provide pathophysiologic insight into the increased risk of mortality in patients with chronic kidney disease (CKD). This study aimed to investigate associations between the circulating proteome and all-cause mortality among patients with CKD.

Methods: In this observational cohort study, we quantified the associations of 6790 circulating proteins with the outcome of all-cause mortality among 703 participants in the African American Study of Kidney Disease (AASK) Study. Proteins with significant associations were further evaluated among Atherosclerosis Risk in Communities (ARIC) Study participants with chronic kidney disease (Visit 5; N = 1628).

Results: In the AASK cohort, mean age was 54.5 years, 271 (38.5%) were women and mean measured GFR was 46 ml/min per 1.73m^2. Median follow up was 9.6 years and 7 distinct proteins (Lamin-B2, Spondin-1, Somatostatin receptor type 1, N-terminal pro-BNP, DDRGK domain-containing protein 1, Beta-2-microglobulin, and N6-adenosine-methyltransferase 70kDa subunit) were associated with all-cause mortality at Bonferroni-level threshold (p<0.05/6790) after adjustment for demographics and clinical factors, including baseline measured eGFR and proteinuria. In ARIC visit 5 cohort, mean age was 77.2 years, 903 (55.5%) were women, mean estimated GFR was 54 ml/min per 1.73m^2 and median follow up was 6.9 years. Of the seven proteins found in AASK, three (Beta-2-microglobulin, Spondin-1, and N-terminal pro-BNP) were available in the ARIC data, with all three significantly associated with death in ARIC.

Conclusions: Using large-scale proteomic analysis, known and novel proteins were reproducibly associated with mortality in two cohorts of participants with CKD.

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FR-PO930

Characterization of the Urine Proteome in 769 Patients with Early-Stage CKD

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Background: Analyses of urinary proteins aim to identify new biomarkers for early disease detection, prognosis and therapeutic response in patients with chronic kidney disease (CKD). Hence, we used the antibody-based Olink Explore 3072 platform to quantify 2925 proteins in urine samples from 769 participants of the German Chronic Kidney Disease (GCKD) study and present a comprehensive characterization of the urine proteome at unprecedented scale.

Methods: Proteins were quantified in urine samples from persons with eGFR >45 and ≤60 mL/min/1.73 m^2 and UACR <300 mg/g. Protein detectability was computed as percentage of samples with Normalized Protein Expression above protein-specific limits of detection. Urine dilution was corrected before association and correlation analyses. Plasma detectability of 1463 corresponding proteins (Olink 1536 panel) and comparisons to urine were based on >52,000 participants of the UK Biobank.

Results: In total, 1926 of 2925 (65.8%) proteins had detectability >10% in urine. Of these, 593 (20.3%) were highly detectable (>80%), showing a strong overrepresentation for proteins from extracellular exosomes and extracellular regions. Highly detectable urine proteins were enriched for specific expression in liver, placenta, lung, and kidney, and for molecular functions as proteolytic enzymes or cell adhesion proteins. We found significant associations with participant characteristics for 342 urine proteins, including sex (268 proteins, e.g., prostate-specific MSMB and KLK3 were higher in men), age (20 proteins, e.g. RGMA, CILP) and BMI (54 proteins, e.g. IL1RN, IL1A). Correlation analyses revealed multiple clusters of co-regulated proteins (e.g. AZU1, PRTN3, MPO, all components of azurophilic granules in neutrophils). Compared to plasma, 16 of 1463 proteins (1.1%) had significantly higher detectability in urine, 105 (7.2%) were equally detectable, and 1342 (91.7%) had lower detectability.

Conclusions: The Olink Explore 3072 technology is suitable for urine proteomics with large sample sizes, and yields biologically plausible correlations and associations. The obtained information about detectability, composition and phenotypic associations of the urine proteome represents a basis for biomarker discovery, and facilitates future, more targeted studies in CKD and other diseases.

Funding: Government Support - Non-U.S.

FR-PO931

The Transcriptomic Landscape of microRNAs Encapsulated in Circulating Extracellular Vesicles and CKD Progression in Japanese Adults

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Background: The global economic burden of chronic kidney disease (CKD) and end-stage-kidney disease (ESKD) is still increasing. However, non-invasive techniques to predict CKD progression have yet to be established. This study aimed to determine circulating small extracellular vesicle (cEV)-encapsulated miRNAs predictive of kidney outcome in patients with CKD.

Methods: We enrolled 36 Japanese adults with non-dialysis-dependent CKD patients from the previously published cohort studies. We performed miRNA transcriptomic analyses using cEVs extracted from the serum of the participants. The patients were followed up until death, transfer, or ESKD requiring dialysis. The correlation between miRNA expressions and baseline eGFR was examined with the linear regression model. A stratified Cox regression model was used to assess the risk of a kidney composite outcome including ESKD or 30% eGFR reduction. We also performed the logistic regression analysis to examine the risk of rapid eGFR decline, which was defined as eGFR reduction <-5 mL/min/1.73 m^2/year or dialysis initiation within a follow-up of six months. All analyses were adjusted for potential confounders including age, sex, diabetes mellitus, and cardiovascular disease.

Results: The median age of the participants was 71 years (interquartile range, 61-79), 25% was female, and the median baseline eGFR was 31 (21-53) mL/min/1.73 m^2. After a median follow-up period of 636 days, the kidney composite outcome and rapid eGFR decline occurred in 16 and 16 patients, respectively. Among 2578 miRNAs identified, all three criteria including the negative association between miRNA expression levels and baseline eGFR ($P < 0.1$), increased hazards ratios for a risk of the kidney composite outcome (HR ≥ 1.5; $P < 0.05$), and increased odds ratios (ORs) for a risk of rapid eGFR decline (OR ≥ 1.5; $P < 0.1$) were met for three miRNAs. The KEGG molecular pathways associated with miRNA target molecules found ubiquitin-mediated proteolysis, Hippo signaling pathway, protein processing in endoplasmic reticulum, and MAPK signaling pathway.

Conclusions: This study uncovered miRNA signature encapsulated in cEVs that is strongly associated with a risk of CKD progression in adults.

Funding: Private Foundation Support

FR-PO932

Evaluation of Novel Candidate Filtration Markers from a Global Metabolomics Discovery for Glomerular Filtration Rate Estimation

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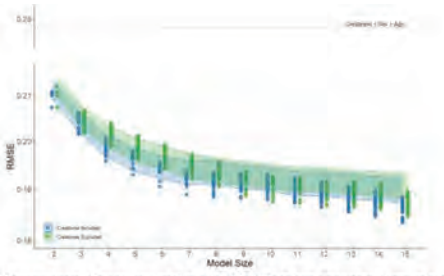
Background: Creatinine and cystatin-C are recommended for estimating glomerular filtration rate (eGFR) but accuracy is suboptimal. Using untargeted metabolomics data, we sought to identify candidate filtration markers using a novel approach based on their maximal joint association with measured GFR (mGFR) and with flexibility to consider their biological and chemical properties.

Methods: We analyzed metabolites measured in seven diverse studies of 2,851 participants on the Metabolon H4 platform that had Pearson correlations with log mGFR. We used a stepwise approach to develop models to estimate mGFR including two to 15 metabolites with and without inclusion of creatinine and demographics. We then selected candidate filtration markers from those metabolites found >20% in models that did not demonstrate substantial overfitting in cross-validation and with small (<0.1 in absolute value) coefficients for demographics.

Results: In total, 456 named metabolites were present in all studies, and 36 had correlations < -0.5 with mGFR. We developed 2,225 models including these metabolites; all had lower root mean square errors (RMSE) and smaller coefficients for demographic variables compared to estimates using untargeted creatinine. Cross-validated RMSEs (0.187-0.213) were similar to original RMSEs for models with ≤ 10 metabolites (Figure). Our criteria identified 17 metabolites, including 12 new candidate filtration markers.

Conclusions: We identified candidate metabolites with maximal joint association with mGFR and minimal association with demographic variables across varied clinical settings. Next, we will assess the selected metabolite biological and chemical characteristics to develop a panel eGFR that is more accurate and less reliant on demographic variables than current eGFR.

Funding: NIDDK Support



Comparison of near-optimal model RMSEs when untargeted creatinine is included as a candidate versus when untargeted creatinine is excluded.
The colored bands show the range of cross-validated (CV) RMSEs. Points are non-CV model errors. Models are fit with study terms but not demographic variables.

FR-PO933

Association Between Serum Kynurenine Levels and Cardiovascular Outcomes and Overall Mortality in CKD

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Background: Kynurenine is a protein-bound uremic toxin. Its circulating levels are increased in chronic kidney disease (CKD). Experimental studies showed that it exerted deleterious cardiovascular effects. We sought to evaluate the association between serum kynurenine levels and adverse fatal or nonfatal cardiovascular events and all-cause mortality before kidney replacement therapy (KRT) in patients with CKD.

Methods: The CKD-REIN study is a prospective cohort of CKD patients before KRT (estimated glomerular filtration rate (eGFR) < 60ml/min/1.73m^2) followed-up over five years. Baseline frozen samples of total and free fractions of kynurenine and tryptophan were measured using a validated liquid chromatography tandem mass spectrometry technique. Cause-specific Cox models were used to estimate hazard ratios (HRs) for each outcome.

Results: Of the 2,406 included patients (median age: 68 years; median eGFR: 24.7 ml/min/1.73 m^2), 52% had a history of cardiovascular disease. A 1.5-fold increase in serum free kynurenine levels was associated with a 12%-increased hazard of cardiovascular events (466 events, HR[95% CI]: 1.12 [1.02,1.23]), independently of eGFR, serum free tryptophan level, and traditional cardiovascular risk factors. The association of serum free kynurenine with cardiovascular mortality was also independently significant (87 events; adjusted HR [95%CI]: 1.39[1.07, 1.70]). However, the association of serum free kynurenine with all-cause mortality vanished after adjustment on serum free tryptophan (311 events, HR[95%CI]: 1.06[0.94, 1.21]).

Conclusions: Our findings imply that serum free kynurenine, independently of other cardiovascular risk factors (including eGFR), is associated with fatal or nonfatal cardiovascular outcomes, particularly non-atheromatous cardiovascular events, in patients with CKD. Strategies to reduce serum kynurenine levels should be evaluated in further studies.

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FR-PO934

Associations of Plasma Trimethylamine N-Oxide-Related Metabolites with the Development and Progression of Albuminuria

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Background: Trimethylamine N-oxide (TMAO) is a gut-microbiota generated metabolite of dietary choline and carnitine. In animal models, TMAO increases albuminuria, an early, sensitive marker of kidney damage. Yet, little is known about TMAO and albuminuria in humans. We investigated prospective associations of plasma TMAO and its two microbiome-derived intermediates, crotonobetaine and γ-butyrobetaine, with the development and progression of albuminuria.

Methods: We included 6,101 US adults with normal (<30mg/g) baseline urine albumin to creatinine ratio (ACR) from the Multi-ethnic Study of Atherosclerosis, a community-based cohort. TMAO-related metabolites were measured using mass spectrometry at baseline and year 5. ACR levels were measured up to 4 times during follow-up. Time-varying Cox models related serial TMAO measures to elevated albuminuria, defined as the first occurrence of ACR ≥ 30 mg/g, adjusting for sociodemographic, lifestyle, diet, and CVD risk factors. Linear mixed models related serial TMAO measures to annualized ACR changes in 6,319 participants with at least one follow-up ACR measure (no exclusions for baseline ACR levels), adjusting for baseline ACR and other covariates.

Results: During a median follow-up of 16 years, 995 participants developed elevated albuminuria. Higher levels of TMAO and crotonobetaine, but not γ-butyrobetaine, associated with higher risk of elevated albuminuria (Figure). All three metabolites positively associated with annualized ACR increase (5th vs. 1st quintile [95%CI] =3.54 [1.10, 5.98], 4.28 [1.89, 6.67], and 4.49 [1.36, 7.61] mg/g per year, respectively).

Conclusions: In a multi-ethnic, community-based cohort of US adults, higher levels of gut microbiota-generated TMAO-related metabolites were associated with elevated albuminuria and its progression.

Funding: Private Foundation Support

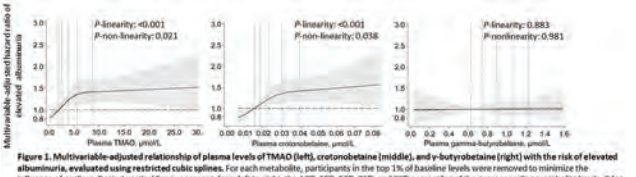

Figure 1. Multivariable-adjusted relationship of plasma levels of TMAO (left), crotonobetaine (middle), and γ-butyrobetaine (right) with the risk of elevated albuminuria, evaluated using restricted cubic splines. For each metabolite, participants in the top 1% of baseline levels were removed to minimize the influence of outliers. Dotted vertical lines represent, from left to right, the 10th, 25th, 50th, 75th, and 90th percentiles of the corresponding metabolite levels. P for linearity was the P value for a given metabolite in a model with the metabolite analyzed as a linear term. P for non-linearity was obtained by a likelihood ratio test comparing the model with linear metabolite vs. the model with all spline terms of the metabolite. Multivariable adjustments included baseline age, sex, race/ethnicity (White, Black, Chinese American, and Hispanic), study site (6 sites), education (<high school, high school, some college, bachelor's degree, graduate school), household income (<$20,000, $20,000 – < $50,000, $50,000 – < $100,000, ≥ $100 000), alternate healthy eating index, total energy intake (kcal/day), and time-varying health status (poor, fair, good, very good, excellent), smoking status (never, former, and current), alcohol intake (drinks/week), physical activity (MET-MIN per week), antibiotic use in the past two weeks, BMI, waist circumference, systolic blood pressure, diastolic blood pressure, LDL-C, HDL-C, triglycerides, CRP, diabetes, anti-hypertensive medication, and lipid-lowering mediation, each updated at the same time as the serial TMAO measures using the most recent measures.

Multivariable-adjusted relationship of plasma levels of TMAO (left), crotonobetaine (middle), and γ-butyrobetaine (right) with the risk of elevated albuminuria

FR-PO935

On the Accuracy of the Kidney Failure Risk Equation

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Background: The accuracy of Kidney Failure Risk Equation (KFRE) is based on the Receiver Operating Characteristic (ROC) curve, Area Under the ROC Curve (AUC), and Harrell's C-statistic. We examined the predictive power of the 4-variable KFRE described in [1] and considered the limitations of ROC curves and C-statistics.

Methods: We used data from the UK's NURTuRE CKD cohort with outcomes for 2426 CKD patients. 149 patients had reached ESKD at follow up. Model performance was assessed by: * Harrell's C-statistic * AUC * Average precision * Average negative predictive value

Results: The C-statistic was 0.89 and AUC for 2-year discrimination 0.91, both corroborating [1]. The C-statistic on the subset of patients with known time to ESKD was 0.64. Average negative predictive value was 0.99. Average precision was 0.32. Excluding patients above age 40, average precision was 0.42.

Conclusions: The C-statistic is computed by counting patient pairs that the model orders correctly for time to ESKD. Most pairs include a patient who reached ESKD before follow-up and one who did not. Therefore, the C-statistic overestimates the KFREs ability to order patients for time to ESKD. For the subset of patients whose time to ESKD was known, the C-statistic was only 0.64. In other words, the KFRE cannot be used reliably to sort NURTuRE patients by time to ESKD. The AUC is the probability that a randomly chosen positive patient would be assigned a larger risk score than a randomly chosen negative patient. Since most such pairs can be easily sorted for time to ESKD, this metric turns out well. In contrast, precision measures the probability that a patient will reach ESKD given that (s)he is predicted to by the KFRE. A precision of 0.32 in this case means that only 32% of patients predicted to reach ESKD within 2 years will do so. Interestingly we see an increase in precision in younger patients, which we believe is due to a higher correlation between eGFR and time to kidney failure in lower age brackets. In summary: With a negative predictive value of 0.99, the KFRE can rule out near term kidney failure with high probability but cannot confirm it. Therefore, while its application for referrals is appropriate, the KFRE should not be used as a basis for costly or risky medical intervention. **References:** 1. Tangri, Navdeep, et al. *JAMA* 305.15 (2011): 1553-1559.

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FR-PO936

Kidney Failure Risk Equation Prediction in a Real-World Population with CKD

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Background: Risk prediction helps to identify patients with chronic kidney disease (CKD) who may benefit from awareness, detection, and intervention to preserve kidney function. The purpose of this study was to externally validate the Kidney Failure Risk Equation (KFRE) using the 4-variable (4-KFRE) and 6-variable (6-KFRE) equations to predict end stage renal disease (ESRD; eGFR <15 mL/min/1.73 m^2) over 2- and 5-year periods in a real-world population with moderate-to-severe CKD.

Methods: Patients with CKD stages 3 and 4 (N=20,947) were selected from electronic health records data in the CURE-CKD Registry from the UCLA (N=3,599) and Providence (N=17,348) Health systems. Patient demographics (age and sex), estimated glomerular filtration rate (eGFR), and log-normalized urine albumin/creatinine ratio were used for the 4-KFRE. The 6-KFRE was applied to patients who also had diabetes and hypertension.

Results: The prevalence of ESRD was 7% for the 2-year period and 11% for the 5-year period. The performance of the 6-KFRE and the 4-KFRE models was similar (4-KFRE is shown in **Table 1**). Specificity (0.994) reflects the model's ability to predict non-ESRD patients, while sensitivity (0.135) signifies the ability to predict ESRD patients. The area under the precision-recall curve (PR-AUC) was 0.466, and the area under the receiver operating curve (AUC ROC) was 0.853, suggesting accurate KFRE predictions. The model performance improved with lower eGFR.

Conclusions: The KFRE equations depicted high performance when applied to a real-world population with moderate-to-severe CKD. While highly specific for ESRD, it lacked sensitivity, but improved for more advanced CKD stages.

Results from the Four Variable KFRE (UCLA + Providence)

	2-Year Risk of ESRD	5-Year Risk of ESRD
Precision/PPV	0.770	0.696
PR AUC	0.447	0.486
Average Precision	0.447	0.486
Sensitivity	0.070	0.200
Specificity	0.999	0.990
AUC ROC	0.864	0.842
Brier Score	0.052	0.076

KFRE: Kidney Failure Risk Equation; ESRD: end stage renal disease; PPV: positive predictive value; PR AUC: precision recall area under the receiver operating curve

FR-PO937

Colombian Validation of the Kidney Failure Risk Equation with Four Variables

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Background: Chronic Kidney Disease (CKD) programs need to identify patients at risk of progression. Our objective is to evaluate the performance of this 4 variables model in the Colombian population where this risk model has not yet been validated.

Methods: Historical cohort of patients with stage 3, 4 and 5 CKD, adults, with no history of dialysis or kidney transplantation and with a two-year follow-up, belonging to the Renal Care Services Baxter Colombia clinic network. The performance model was evaluated using concordance index and the area under the time-dependent ROC curve, with the nearest neighbor method, as well as the sensitivity and specificity. The degree of agreement between the observed outcome and the probabilities predicted by the model using the Hosmer-Lemeshow statistic.

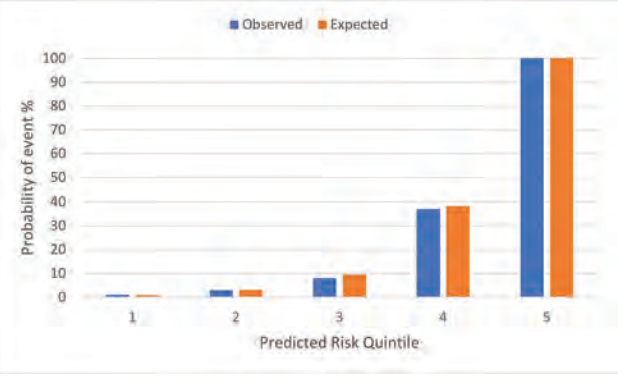
Results: A total of 5477 patients were included, the mean age was 72 years, and the mean baseline eGFR was 36 ml/min/1.73 m2. The rate of admission to dialysis therapy was 3 events per-100 patient years. See **Figure 1.** Sensitivity 0.938 and specificity 0.757, with the area under the ROC curve 0.92. Harrell C statistic was 0.88 per total population and >65 year was 0.93. The validation of the model showed a good calibration, see **Figure 2.**

Conclusions: In this Colombian cohort, the kidney failure risk equation with 4 variables has excellent calibration and discrimination, therefore its use is recommended in the routine follow-up of these CKD prevention programs.

Funding: Commercial Support - Baxter Renal Care Services

Characteristics	Pre-dialysis program N= 5477
Demographics	
Age, mean (SD), years	72.0 (13.4)
< 65 years	1323 (24.2)
>= 65 years	4154 (75.8)
Sex, n (%)	
Male	2840 (51.8)
Female	2637 (48.2)
Ethnicity, n (%)	
Others	5439 (99.3)
Afro- American	38 (0.7)
Comorbid conditions	
Diabetes, Yes	1993 (36.4)
Major Cardio-vascular disease [a]	799 (14.6)
Laboratory data	
GFR, mL/min/1.73 m2 Baseline, mean (SD)	36.1 (13.6)
30-59	3523 (64.3)
15-29	1659 (30.3)
< 15	295 (5.4)
Serum creatinine, mean (SD), mg/dL	1.9 (0.8)
Urine albumin-to-creatinine ratio, mg/g, median (IQR)	112 (30,496)
< 30	1325 (24.2)
30-299	2331 (42.6)
>= 300	1821 (33.2)
Outcomes	
Observation time, days *mean (SD)*	683 (132.5)
Kidney failure events, n	
Hemodialysis	101
Peritoneal Dialysis	211
Kidney Transplant	4
KRT rate, per 100 person-year	3.0 [2.9 – 3.6]

GFR, glomerular filtration rate; IQR, interquartile range; SD, Standard Deviation. [a] Cardio-vascular disease is defined as presence of coronary artery disease or peripheral vascular disease. KRT: Kidney Replacement therapy



FR-PO938

Validation of a Multimarker eGFR Equation in Preserved and Reduced eGFR Using the GENOA Cohort

Maria Clarissa Tio,[1] Xiaoqian Zhu,[1] Andrew D. Rule,[2] Seth Lirette,[1] Yoshitsugu Obi,[1] Timothy E. Yen,[1] Michael Hall,[1] Neville R. Dossabhoy,[1] Tariq Shafi.[3] *[1]University of Mississippi Medical Center, Jackson, MS; [2]Mayo Clinic Minnesota, Rochester, MN; [3]Houston Methodist, Houston, TX.*

Background: Performance of the race-free CKD-EPI 2021 equation varies with severity of kidney disease. We sought to examine the performance of a novel multimarker eGFR panel (panel-eGFR) among Black and White persons stratified by eGFR categories using the biracial Genetic Epidemiology Network of Arteriopathy (GENOA) cohort.

Methods: We included 224 sex, race/ethnicity, and measured GFR (mGFR)-category-matched persons. GFR was measured using urinary clearance of iothalamate. Panel-eGFR was calculated using serum creatinine, valine, myo-inositol, cystatin C, age, and sex. All GFR's are presented as mL/min/1.73 m^2. We compared panel-eGFR's reliability to the 2021 CKD-EPI creatinine and cystatin C (eGFR-Cr-CysC) equation using bias, precision, and accuracy metrics between race (Black vs. White participants) and eGFR (eGFR-Cr-CysC≥60 or preserved eGFR vs. <60 or reduced eGFR) subgroups.

Results: In the overall cohort, 49% were Black individuals and 79% had eGFR-Cr-CysC≥60. Among those with preserved eGFR, eGFR-Cr-CysC was lower than mGFR by 5.6 and 6.6 among Black and White participants, respectively. In contrast, panel eGFR was unbiased among Black (bias: -0.5; 95% CI: -2.8, 2.9) and White participants (bias: -0.4; 95% CI: -5.6, 4.5) with preserved eGFR. Among those with reduced eGFR, eGFR-Cr-CysC was unbiased among Black and White participants. Conversely, panel-eGFR was higher than mGFR in both Black (bias: -9.8; 95% CI: -11.8, -3.1) and White (bias: -6.3; 95% CI: -9.0, -3.7) participants with reduced eGFR. P30 for panel-eGFR among Black participants with reduced eGFR was 70%. Otherwise, P30 metric was acceptable (>80%) for both equations across race and eGFR subgroups.

Conclusions: A novel panel-eGFR performs better than the current eGFR-Cr-CysC equation among persons with preserved eGFR, and this is consistent between Black and White persons.

Funding: Other U.S. Government Support

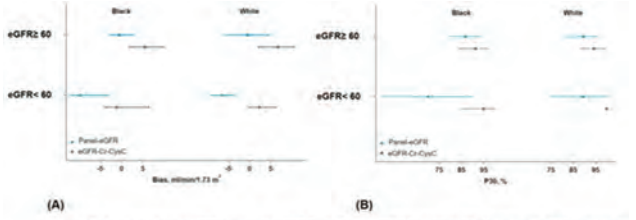


Figure 1: Performance of panel-eGFR compared to eGFR-Cr-CysC in the GENOA cohort stratified by race and eGFR (calculated using the CKD EPI 2021 creatinine and cystatin C equation). (A) Median bias is defined as the median of the differences between mGFR and eGFR, in units of ml/min/1.73m². (B) P30 is defined as the proportion of eGFR within 30% of mGFR.

FR-PO939

Predicting All-Cause Mortality in Patients with Advanced CKD

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Background: Patients with advanced CKD are at high risk of mortality, kidney failure and cardiovascular events. Accurately identifying patients that are at a higher risk for mortality may aid in clinical decision making and preventing unnecessary dialysis therapies that may cause more harm. We developed and externally validated a risk prediction tool using commonly collected clinical measurements to predict all-cause mortality among patients with advanced CKD.

Methods: We developed a prediction model using demographic, clinical and laboratory data in adult patients (≥ 18 years) with advanced CKD (eGFR <30 mL/min/1.73m²) from Manitoba, Canada, between January 2012, and September 2020, with external validation from Ontario, Canada. Our primary outcome was time to all-cause mortality. If dialysis was initiated in follow-up, we ascertained all-cause mortality within 1 year of dialysis initiation. We assessed model discrimination using the area under the receiver operating characteristic curve (AUC) and calibration using plots of observed and predicted risks.

Results: The development cohort included 397 patients (mean age 65.4 ± 13.9) with 121 events. The final model included age, sex, estimated GFR, hemoglobin, serum albumin and congestive heart failure and achieved a 2-year and 5-year AUC of 74.3 (CI: 68.4 – 80.1) and 80.2 (CI: 75.3 – 85.1), respectfully. Discrimination and calibration were adequate in the external validation data set with 2-year and 5-year AUC scores of 71.4 (CI: 70.8 – 72.0) and 73.0 (CI: 72.5 – 73.5).

Conclusions: We developed a simple prediction model that included commonly measured variables that can accurately predict all-cause mortality in patients with advanced CKD. This equation may aid as a support tool for nephrologists in dialysis decision making, especially in patients who are at high risk of mortality.

FR-PO940

CKD Progression Model (CKD-PM): Development and Validation

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Background: Patients with CKD are at risk of disease progression and related complications. Existing CKD models are limited to the risk of end stage kidney disease (ESKD) and selected cardiovascular disease (CVD) outcomes. Our aim was to develop a CKD-PM, that uses evolving risk factors to project risk of a broad range of CKD related complications.

Methods: Development of the CKD-PM was informed by systematic and targeted literature reviews of relevant models and risk factors for CKD progression and risk of complications. The result was a patient-level state transition model with KDIGO categories as health states. Evolving risk factors project CKD progression and occurrence of complications, with submodules for: CVD, infections, anemia, diabetes, hypertension, acidosis, hyperkalemia, mineral and bone disorders, hospitalisations, acute kidney injury, cancer and ESKD. Internal and external model validation was performed by comparing predicted outcomes with those observed in cohort studies, utilizing source study patient characteristics and follow up time. An ordinary least squares (OLS) linear regression line (LRL) was fitted to the data, and the slope was used to categorize the quality of the prediction. Deviation <25% from the perfect prediction (LRL slope =1) was considered accurate (mild deviation), 25-50% deviation was considered moderate, and severe beyond 50%.

Results: Core inputs (mortality, CVD and evolution of risk factors including eGFR and uACR) were sourced primarily from two research groups: Chronic Renal Insufficiency Cohort [CRIC] and Chronic Kidney Disease Prognosis Consortium [CKD-PC]). Seven large CKD cohorts studies were used to validate the CKD-PM predictions. Both internal and external validation results demonstrated robust modeling properties. All-cause mortality (ACM) was accurately projected, with mild under-prediction, either through direct prediction (hazard ratio by eGFR and uACR levels) or as a composite of CVD mortality, renal and other deaths. CVD mortality was mildly under-predicted in internal validation, and mildly over-predicted in external validation. Projected mean change of eGFR or uACR values and ESKD rates were within an acceptable range compared to external values.

Conclusions: CKD-PM is a comprehensive tool with robust modeling properties demonstrated through internal and external validation.

Funding: Commercial Support - Boehringer Ingelheim International GmbH

FR-PO941

IMPACT CKD: Projecting the Growing Environmental Burden of CKD in the United States

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Background: Chronic kidney disease (CKD) is a significant source of morbidity and mortality with substantial costs associated with renal replacement therapy (RRT) (including dialysis and transplantation). However, it is imperative to understand the wider impact of CKD, including its societal and environmental consequences, to inform healthcare planning and policy development. This study aims to comprehensively quantify the burden of CKD in the United States (US).

Methods: A patient-level simulation model, IMPACT CKD, was developed to simulate the natural history of CKD progression while incorporating the impact of acute kidney injury, cardiovascular events and comorbidities. CKD status was assigned using estimated glomerular filtration rate (eGFR) and albuminuria levels, and clinical progression was predicted by annual eGFR decline rate. The model was used to forecast the 10-year impact of CKD on environment in the US in addition to clinical, economic, and societal outcomes. The model was validated and calibrated for the US setting.

Results: While CKD prevalence is predicted to remain steady from 2022 to 2032 (17%), the number of patients increases from 57 to 60 million. The projected distribution of CKD stages includes 38% in stage 1, 19% in stage 2, 34% in stage 3, 5% in stage 4, and 4% in stage 5 (including RRT) in 2032. Substantial increases are observed in stage 3 to pre-RRT stage 5 (14.5%) and the number of patients receiving RRT is expected to rise by 48% (882,026 to 1,303,141). Alongside the escalating clinical burden, CKD and RRT are poised to exert detrimental environmental impacts. Freshwater consumption, fossil fuel depletion, and CO_2 emissions associated with CKD and RRT are estimated to rise by 26%, 26%, and 37% respectively, from 2022 to 2032. RRT accounts for the most substantial environmental burden, with projected contributions of 1.9 billion m^3 of freshwater consumption, 26.9 billion kg of fossil fuel depletion, and 64.9 billion kg of CO_2 emissions over the next decade.

Conclusions: The IMPACT CKD model highlights the enduring burden of CKD in the US. With projected high prevalence and environmental burdens, improved management strategies mitigating the substantial environmental impact of CKD and RRT are vital for a healthier future.

Funding: Commercial Support - AstraZeneca

FR-PO942

Modest Reductions in Kidney Function and Adverse Outcomes in Young Adults

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Background: Whether modest declines in estimated glomerular filtration rate (eGFR below age-expected values) in younger adults are associated with adverse outcomes is unknown. We aim to estimate the association of an early eGFR decline with adverse outcomes by age group (18-39, 40-49, 50-65 years).

Methods: We included 8.7 million adults (aged 18-65) with ≥1 eGFR value using linked healthcare datasets in Ontario from January 2008-March 2020. The association of eGFR categories from <60 to >120 mL/min/1.73m² and adverse outcomes (death, cardiovascular outcomes, end-stage kidney disease) was examined using adjusted Cox models. Comparisons were relative to age normalized measured GFR categories (100-110 mL/min for 18-39, 90-100 mL/min for 40-49, 80-90 mL/min for 50-65).

Results: The mean age, eGFR and median follow up were 41 years, 104 mL/min and 9.2 years, respectively. 17.3%, 18.9%, and 17.7% had an eGFR below normal for ages 18-39, 40-49, and 50-65, respectively. The risk of an adverse event increased in a stepwise manner with eGFR values below the referent and occurred at higher eGFR values in those 18 to 39 [eGFR 70-80, age 18-39: incidence 4.37 events per 1000 person-years [p-y], HR 1.54(1.46-1.61); age 40-49: incidence 9.78 per 1000p-y, HR 1.18(1.15-1.21); age 50-65: incidence 24.0 per 1000p-y, HR 1.11(1.10-1.12)] (see **Figure**). Results persisted for each outcome individually, and after using repeated eGFR, using a common referent, and adjusting for multiple covariates.

Conclusions: Young adults (18-39) with an early eGFR decline were at a higher risk of adverse events and this occurred at higher eGFR levels relative to middle-aged and older adults.

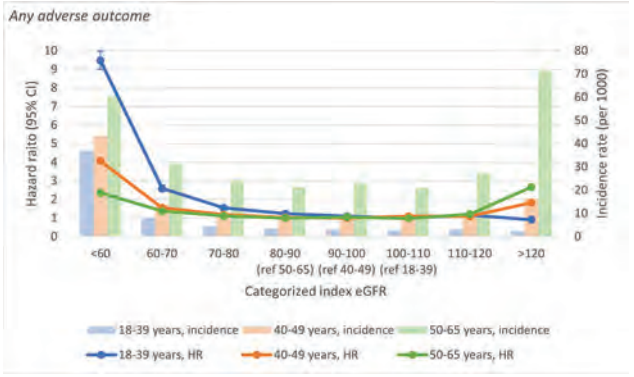

Figure: Incidence rates (events per 1000 person-years) and adjusted hazard ratios (HRs, 95% CI) for any adverse outcome (first of all-cause mortality, cardiovascular outcomes, end-stage kidney disease) relative to age-specific eGFR reference ranges, by age-group.

FR-PO943

Risk Analysis of Healthy Life Expectancy Based on Kidney Function Using the Long-Term Care and Medical Database

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Background: The world's population is rapidly aging, with the aging rate expected to reach 17.8% by 2060. Healthy life expectancy is known to be shortened by unhealthy diet, hypertension, smoking, obesity and diabetes. Kidney dysfunction is also expected to shorten healthy life expectancy due to its effects on physical inactivity, malnutrition, and atherosclerosis. This study aims to clarify the relationship between kidney function and healthy life expectancy.

Methods: This was a community-based historical cohort study of adults living from 2012 to 2022 in Hakui City, Ishikawa Prefecture, Japan. Participants were divided into five groups (<45, ≥45 to <60, ≥60 to <75, ≥75 to <89, and ≥90 mL/min/1.73 m2). The primary composite outcome was the event of unhealthy status (care level ≥2 or death). Care level 2 was a level of social support for those who have difficulty performing basic activities of daily living independently and require some form of nursing care in Japan's long-term care system. Baseline risk factors included age, sex, body mass index, current smoking status, diabetes mellitus, systolic blood pressure, and social support level. Multivariable Cox proportional hazards model adjusted for baseline risk factors was used to estimate the risk of the primary outcome by eGFR group. Total annual healthcare cost, the sum of annual medical and long-term care cost, were examined as a secondary outcome.

Results: The number of participants was 5,592, the mean age was 67 years, the mean eGFR was 70.9 mL/min/1.73 m^2, and the mean follow-up was 6.5 years. During the observation period, 8.2% of the participants reached the primary outcome. For the primary outcome, using eGFR ≥60 to <75 as the reference, the hazard ratios (HRs) for eGFR ≥45 to <60 and eGFR <45 were 1.35 (95% CI 1.05, 1.75) and 1.93 (95% CI 1.41, 2.66), respectively. The HRs for the eGFR ≥75 to <90 and eGFR ≥90 groups were 1.48 (95% CI 1.14, 1.93) and 1.61 (95% CI 1.14, 2.28), respectively. The mean total healthcare cost for those who achieved the primary outcome was approximately 1,760,000 yen per year. The lower eGFR group had higher annual costs.

Conclusions: Both lower and higher eGFR were risk factors for becoming unhealthy, need for long-term care or death. Annual total healthcare costs were higher in people who became unhealthy.

Funding: Government Support - Non-U.S.

FR-PO944

Long-Term Outcomes in Persons with Stage 3 CKD Recruited from Primary Care

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Background: The majority of persons with chronic kidney disease (CKD) are elderly, have moderately reduced glomerular filtration rate (GFR) and are cared for in primary care in the UK. There are few long term studies to describe the risks of adverse outcomes in this under-studied population.

Methods: Participants with CKD stage 3 were recruited from primary care in 2008-10. Clinical assessment and investigations were performed at baseline, 1 and 5 years. In 2019-20, electronic records were reviewed to obtain data on deaths and latest available outpatient estimated GFR (eGFR) and urine albumin to creatinine ratio (UACR). CKD progression was defined as a decline in eGFR of ≥25% and progression to a more advanced stage.

Results: Participants: 1741 with median (IQR) age 74 (67-79) years, eGFR 53.8 (45.3-61.7) ml/min/1.73m^2, UACR 0.3 (0.001-1.5) mg/mmol; 16.9% diabetes at baseline. Outcomes: 680 deaths (39.1%); CKD progression in 430 of 1402 (30.7%) participants after a median 9.8 (9.2-10.0) years; only 24 of 1741 (1.4%) reached CKD stage 5. UACR increased from 0.3 (0.001-1.26) to 1.4 (0.3-5.90) mg/mmol (p<0.001) in 1188 participants with repeat measurements. Changes in KDIGO GFR category are presented in the table. CKD category improved in 161 (11.5%), progressed in 695 (49.6%) and did not change in 546 (38.9%). Logistic regression analysis identified male sex, diabetes status and lower baseline eGFR, higher baseline UACR and systolic blood pressure (SBP) as independent predictors of CKD progression. Cox Proportional Hazards models identified age, male sex, diabetes status, past or current smoking, lower baseline eGFR and higher baseline UACR as independent risk factors for all-cause mortality.

Conclusions: CKD progression was observed in a minority of participants and < 2% reached CKD stage 5. The risk of CKD progression was exceeded by the competing risk of death. Our observations confirm that in primary care, persons with CKD require monitoring and interventions to minimise risk of adverse outcomes but few progress to kidney failure.

Funding: Commercial Support - Roche, Private Foundation Support

Baseline CKD Category	Year 10 CKD Category					
	1 (n=8; 0.6%)	2 (n=281; 20%)	3a (n=492; 35%)	3b (n=424; 30%)	4 (n=173; 12%)	5 (n=24; 2%)
1 (n=1; 0.1%)	0	1	0	0	0	0
2 (n=475; 34%)	7	176	198	83	11	0
3a (n=632; 45%)	1	93	251	227	56	4
3b (n=275; 20%)	0	10	43	108	95	19
4 (n=19; 1.4%)	0	1	0	6	11	1

FR-PO945

A Distribution-Based Approach to Age Associations Between Continuous Kidney Function and Adverse Events in the General Population

Manish M. Sood,[1] Junayd Hussain,[1] Mark Canney,[1] Meghan J. Elliott,[2] Gregory L. Hundemer,[1] Navdeep Tangri.[3] *[1]University of Ottawa School of Epidemiology and Public Health, Ottawa, ON, Canada; [2]University of Calgary Cumming School of Medicine, Calgary, AB, Canada; [3]University of Manitoba Max Rady College of Medicine, Winnipeg, MB, Canada.*

Background: Whether having a low eGFR value relative to age-based medians is associated with a higher risk of an adverse event is yet to be explored. We aim to derive continuous age-specific associations between percentiles (1st, 2.5th, 5th, 10th) of eGFR and any adverse outcome (first of death, cardiovascular events, end-stage kidney disease), and obtain corresponding eGFR values.

Methods: We included 8.7 million adults (aged 18-65) with ≥1 eGFR value during January 2008-March 2020 in Ontario. Adjusted Cox models were used to estimate the association of a lower eGFR percentile (1st, 2.5th, 5th, 10th) and an adverse event by age from 18 to 65 relative to the age based median.

Results: Overall eGFR values declined with age and the risk of an adverse event was higher with an eGFR in the 10th percentile of lower across all age groups (see **Figure**). In younger individuals, lower percentiles of eGFR occurred at higher eGFR cutoffs relative to older individuals and were associated with an elevated risk of an adverse event. For example, an eGFR in the lowest 5th percentile would occur < 93 ml/min at age 20, < 80 ml/min at age 40, and below 65 ml/min at age 60 with corresponding adjusted HRs for an adverse event of 1.42, 1.28 and 1.32, respectively.

Conclusions: An age distribution-based approach to identifying lower eGFR values and their associated risk of an adverse event may improve care.

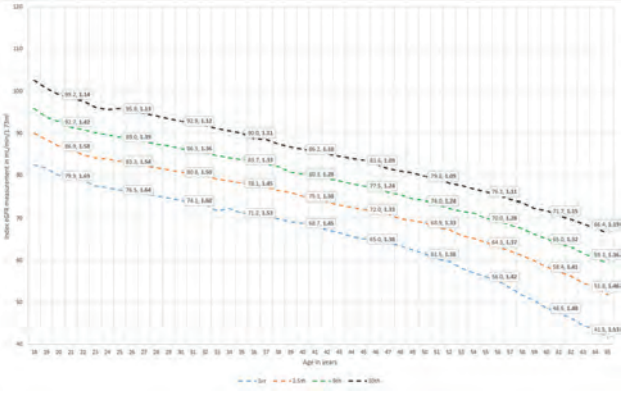

Figure: Trends in index estimated glomerular filtration rate (eGFR, in mL/min/1.73m^2) and associated adjusted HRs of any adverse outcome (first of death, cardiovascular events, end-stage kidney disease) by continuous age

FR-PO946

Kidney Function and Mortality in the Mexico City Prospective Study

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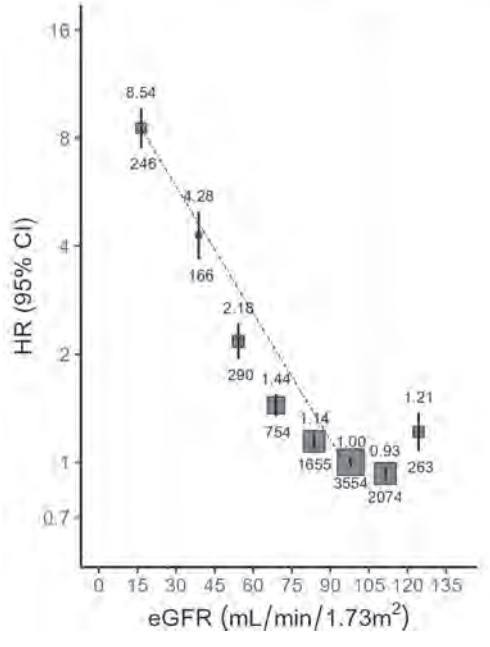
Background: Prospective studies in the US, Europe, Asia, and Australia have shown decreased kidney function is a strong predictor of mortality. There is limited data from Latin America where chronic kidney disease (CKD) is a major cause of morbidity and mortality.

Methods: In 1998-2004, 150,000 adults (aged ≥35 years) were recruited into the Mexico City Prospective Study, and followed for median 19 years. About 120,000 participants currently have nuclear magnetic resonance (NMR) spectroscopy-measured biomarkers in plasma, including creatinine. Cox regression was used to relate a single measurement of baseline eGFR (CKD-EPI equation) to mortality. Analyses were adjusted for age at risk, sex, district, education, smoking, alcohol, physical activity, height, weight, waist and hip circumference, and diabetes. They excluded those who at recruitment had incomplete data or prior chronic disease (except diabetes or CKD).

Results: Among the 33,423 men and 68,133 women aged 35-74 years with complete data, median (IQR) eGFR was 101 (90-109) mL/min/1.73 m^2, mean (SD) BMI was 29.1 (4.9) kg/m^2, 1% had self-reported CKD, 12% had previously-diagnosed diabetes, and 9,002 died at ages 35-74 years. Despite the inaccuracy of a single eGFR baseline measurement, eGFR <30 mL/min/1.73m^2 was associated with eight-fold higher all-cause mortality than eGFR 90-105 (HR 8.5 [95% CI, 9.8-7.5]). Below 90-105, every 15 mL/min/1.73m^2 lower eGFR was associated with 40% higher all-cause mortality (HR 1.40 [1.36–1.42] overall, and 1.37 [1.34-1.40] in those without self-reported CKD). eGFR was most strongly associated with renal deaths (HR 29.9 [24.4-36.9] for eGFR <30 vs 90-105) and vascular occlusive deaths (HR 6.2 [4.4-8.7]). Baseline assessments of blood pressure, lipids, and inflammation explained about a third of the association of eGFR with premature mortality.

Conclusions: In this study in Mexico, lower kidney function was strongly associated with increased premature mortality, with the association about twice as strong as previously reported in high-income countries.

Figure. Relevance of eGFR to ALL-CAUSE mortality at ages 35 to <75 years in the Mexico City Prospective Study.



FR-PO947

Prevalence and Significance of Family History of Kidney Disorders in the EHR in Three Large US Health Care Systems

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Background: Chronic kidney disease (CKD) affects 1 in 7 adults and has a strong genetic component with prior studies reporting ~15% of White patients and nearly 25% of Black patients with end-stage kidney disease (ESKD) having family history of ESKD. Little is known about the prevalence of family history of CKD and ESKD in electronic health records (EHRs).

Methods: We examined the prevalence of family history of CKD and ESKD among patients 18+ years of age receiving primary care in 3 large health systems (Geisinger [n=454,740], Utah [n=215,432], New York University [NYU; n=284,890]). In additional analyses using Geisinger data, we used logistic regression, adjusted for age, sex, race, and ethnicity, to examine the association of family history of CKD and ESKD with having a diagnosis of CKD and ESKD.

Results: In a sample of 955,062 adults receiving primary care in 3 health systems, prevalence of family history of CKD was fairly similar across health systems (Geisinger 4.6%, Utah 4.0%, NYU 5.1%), as was family history of ESKD (Geisinger 0.8%, Utah 0.6%, NYU 0.9%). By comparison, 36.8% of patients at Geisinger had family history of diabetes. Individuals with a family history of CKD were at increased risks of having CKD (OR 1.86, 95% CI: 1.78, 1.94) and ESKD (OR 5.63, 95% CI: 5.12, 6.20). Similar risks were observed for family history of ESKD with having CKD (OR 2.27, 95% CI: 2.07, 2.48) and ESKD (7.68, 95% CI: 6.55, 9.00). Among individuals with ESKD at Geisinger, Black patients were more likely than non-Black patients to have family history of kidney problems (27.1% vs. 19.5%; p=0.008) though not specifically family history of ESKD (6.9% vs. 6.4%; p=0.9).

Conclusions: EHR-reported family history of CKD is strongly associated with risks of CKD and ESKD and infrequently reported across 3 large health systems. Future research is needed on how to improve capture of this important CKD risk factor.

FR-PO948

Greater Variability in eGFR Is Associated with CKD Progression: A Retrospective Japanese Nationwide Database Study

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Background: Variability in renal function is a phenomenon frequently observed in routine clinical practice. This variability may be indicative of pathophysiological factors, including the impaired autoregulation of renal blood flow and the effective circulating volume. With this study, our aim was to assess the relationship between the variability in eGFR and the risk of CKD progression.

Methods: We utilized the Japanese Chronic Kidney Disease Database (J-CKD-DB-Ex), a comprehensive, nationwide, multicenter longitudinal CKD registry, and included individuals with stage 3 and 4 CKD from 2014 to 2020 for the current analysis. We defined the variability of eGFR over a year using the coefficient of variation (eGFR-CV), standard deviation adjusted for the number of measurements (eGFR-adjSD), and average real variability (eGFR-ARV). The primary endpoint included the progression of CKD, defined as either a 40% decline in eGFR or the development of end-stage renal disease (ESRD).

Results: Of 24,986 participants, with an average age of 71.1 ± 11.8 years and 56.5% were male, the mean eGFR was calculated as 49.6 ± 7.8 ml/min/1.73m^2, and the median coefficient of variation for eGFR (eGFR-CV) was 7.6% [IQR 5.2 – 11.7]. Over a follow-up period of 3.3 years, 1,324 (5.3%) participants experienced a 40% decline in eGFR and 647 (2.6%) developed ESRD. Higher eGFR variability was associated with an increased risk of CKD progression in all patients after adjusting for eGFR slope over a year, and eGFR and other covariates at baseline (Table). These results were similar when other variability indices (eGFR-SD, eGFR-adjSD, and eGFR-ARV) were used instead of eGFR-CV. Furthermore, incorporating eGFR-CV into a predictive model that already included proteinuria and eGFR slope improved the prediction of outcomes, as evidenced by an increase in Harrell's c-index by 0.040 (95%CI 0.030 - 0.049, P<0.001).

Conclusions: eGFR variability is an independent predictor for CKD progression.

Funding: Government Support - Non-U.S.

Table. Hazard ratio of CKD progression by eGFR-CV

	Crude		Model1		Model2		Model3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
eGFR-CV per 1% increase	1.035 (1.031 - 1.039)	<0.001	1.029 (1.024 - 1.034)	<0.001	1.029 (1.024 - 1.033)	<0.001	1.012 (1.006 - 1.018)	<0.001
eGFR-CV Q1 (~5.173)	ref		ref		ref		ref	
eGFR-CV Q2 (5.173 - 7.649)	1.488 (1.247 - 1.777)	<0.001	1.438 (1.196 - 1.704)	<0.001	1.441 (1.208 - 1.723)	<0.001	0.931 (0.709 - 1.222)	0.608
eGFR-CV Q3 (7.649 - 11.657)	2.206 (1.864 - 2.611)	<0.001	1.954 (1.675 - 2.351)	<0.001	2.016 (1.702 - 2.391)	<0.001	1.395 (1.093 - 1.781)	0.008
eGFR-CV Q4 (11.657~)	4.855 (3.435 - 4.720)	<0.001	3.278 (2.370 - 3.866)	<0.001	3.318 (2.811 - 3.914)	<0.001	1.565 (1.552 - 2.487)	<0.001

Crude: %CV
Model 1: eGFR of index day + eGFR slope
Model 2: model 2 + Sex, Age
Model 3: model 3 + proteinuria, Hb, Alb, TCH, UA, CRP

FR-PO949

Association Between Changes in Urinary Albumin and Protein Excretion and Risk of Kidney Failure in Patients with CKD: The CKD-JAC Study

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Background: There has been progress in studying albuminuria as a surrogate endpoint for kidney failure with replacement therapy (KFRT) in patients with chronic kidney disease (CKD). However, the relationship between changes in proteinuria and KFRT has not been well studied.

Methods: The Chronic Kidney Disease - Japan Cohort (CKD-JAC) is a prospective observational study of patients with CKD in Japan. This study used the CKD-JAC cohort to examine the associations between a twofold increase in albuminuria (urine albumin-creatinine ratio) within the first two years of follow-up and the subsequent development of KFRT. In addition, in the subgroup with available proteinuria during follow-up, the relationship between the doubling of proteinuria (urine protein-creatinine ratio) in the first and second year and KFRT was examined in a similar way. A multivariable Cox proportional hazards model was used for analyses.

Results: The study analyzed 1,753 patients with an average age of 60 years, a mean eGFR of 30 mL/min/1.73 m^2, and a mean albuminuria of 419 mg/gCr. During the observation period, 618 patients (35.2%) initiated kidney replacement therapy. The hazard ratio (HR) and 95% confidence interval of KFRT for a doubling of albuminuria within 2 years was 1.57 (1.46, 1.70). Further analysis of the subgroup with proteinuria demonstrated that a doubling of proteinuria was associated with KFRT at the 2-year change (HR 1.41 [1.25, 1.59]). A similar association was found for the 1-year change of proteinuria as well (HR 1.30 [1.15, 1.47]).

Conclusions: In subjects with CKD, a doubling of albuminuria within the first two years of follow-up could potentially serve as a surrogate endpoint for KFRT. Similarly, proteinuria could also be a surrogate endpoint for KFRT.

Funding: Commercial Support - Kyowa Kirin Co.,Ltd.

FR-PO950

Risk Factors for Progression to Kidney Failure in Patients with CKD Stages 3B and 4 in a Singaporean Cohort

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Background: The prevalence of chronic kidney disease (CKD) is increasing globally and the burden of kidney failure is also increasing. We aim to examine the risk factors for progression to kidney failure in patients with CKD stages 3B and 4 and develop a risk prediction model for predicting kidney failure in our local multi-ethnic population.

Methods: Demographics, clinical and laboratory data of patients with CKD stages 3B and 4 referred from polyclinics to Tan Tock Seng Hospital(TTSH) Renal Medicine between April 2017 to February 2022 were collected. The primary outcome was kidney failure defined as an estimated glomerular filtration rate (eGFR)<15ml/min/1.73m^2. The secondary outcome was that of a composite of kidney failure, death, doubling of serum creatinine and eGFR decline by 40%. Multivariate cox proportional hazard regression analyses were used to evaluate risk factors for the primary outcome. A risk prediction model for predicting kidney failure was developed and performance was evaluated by C-statistic.

Results: There were 2033 patients with CKD 3B and 4 referred from polyclinics to TTSH between 2017 to February 2022. 848 patients with less than 1 year of follow up was excluded(except if they developed kidney failure in less than 1 year, n=8). There were 1193 patients included in the analysis of which 66.3% had CKD 3B and 33.7% had CKD 4. The median age of these patients was 70.8(31.3-83.6) years old. 56.9% were males and the median eGFR was 33(IQR:15-44)ml/min/1.73m^2. 73.1% of the cohort had diabetes mellitus and 93.8% had hypertension. 80.6% of patients were on an ACE inhibitor or ARB. Mean duration of follow up was 36.8 months. 6.2% of patients died and 12% developed the primary outcome. 19.6% of patients developed the secondary outcome. Higher proteinuria (HR 1.15,95%C.I 1.02-1.30) higher serum creatinine (HR 1.04, 95%C.I 1.03-1.05), higher annual rate of decline of eGFR, Malay ethnicity (HR2.13 95% C.I 1.05-4.33), higher diastolic blood pressure(HR 1.05 95%CI 1.01-1.08) and female gender were risk factors for kidney failure. The Harrell C-statistic for the final model was 0.93.

Conclusions: Our model for predicting kidney failure in patients with CKD stage 3B and 4 including the variables ethnicity, annual eGFR decline, baseline proteinuria and serum creatinine had a C-statistic of 0.93 and should be validated in a larger population of patients.

FR-PO951

Early-Stage Characteristics and Potential Predictors of CKD Among US Veterans

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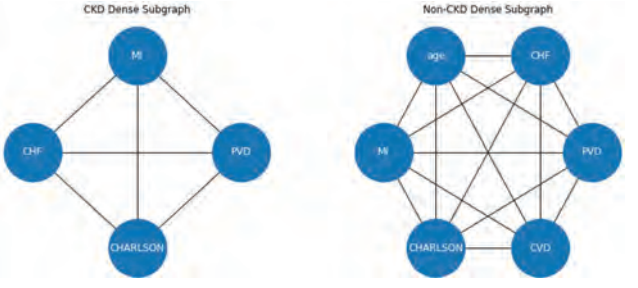
Background: Chronic Kidney Disease (CKD) is prevalent but under-diagnosed across the world. Its prediction remains a formidable challenge, even when complete clinical and demographic information is available. We studied a large patient cohort from the US Department of Veterans Affairs (VA) in an effort to identify predictive characteristics common to those afflicted with CKD before the disease becomes clinically evident.

Methods: From a cohort of 692,942 veterans with stable eGFR >60 ml/min/1.73m^2, we identified 174,627 patients who developed CKD within up to eight years following enrollment and compared them to patients who remained CKD free. Over these two patient subgroups, we calculated Pearson correlation coefficients for all baseline variable pairs and, for each such pair, we examined those that were differentially correlated as defined by an absolute difference of at least 0.15 between the CKD and non-CKD cohorts. Using a graph theoretic approach, we created finite, simple, undirected graphs, with variables of interest represented by vertices and edges weighted by correlation then thresholded. From these graphs we extracted dense subgraphs indicative of latent variable relationships to account for complex correlations.

Results: Age and a variety of specific comorbidities were correlated higher within the non-CKD subgroup than within the CKD subgroup. From graph theoretical analysis, we found that the Charlson index, congestive heart failure (CHF), myocardial infarctions (MI), and peripheral vascular disease (PVD) formed a dense subgraph indicative of highly interconnected disease relationships (Figure). Age and cardiovascular disease (CVD) only entered this putative network among non-CKD patients.

Conclusions: These results suggest that kidney disease belongs to a constellation of comorbidities that may help to act as predictors of incipient CKD. Chronological age may not play a prominent role in the development of comorbidities in patients with CKD, which may be explained by premature ageing seen in CKD.

Funding: Veterans Affairs Support



FR-PO952

Physical Activity Is an Independent Predictor of CKD Development Among Healthy Individuals

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Background: The cardiovascular and metabolic benefits of physical activity has been discussed in length, however, the association between physical fitness and progression to kidney disease is lacking. We aimed to identify the association between cardiorespiratory fitness and development of chronic kidney disease (CKD) among healthy population.

Methods: We investigated 11,579 healthy self-referred subjects who underwent annual medical screening. All subjects had an eGFR above 60 ml/min/1.73m2, no known kidney disease, hematuria or proteinuria, and were free of diabetes or cardiovascular disease at baseline. All participants completed a maximal exercise test, and were categorized into low and high cardiorespiratory fitness groups based on age- and gender-specific quintiles. The primary end point was the development of CKD defined as eGFR below 45 ml/min/1.73m2 during follow-up.

Results: Median follow-up was 7.6 years, and the median participants' age was 50±8years. Baseline creatinine and eGFR were 1.02 mg/dl and 81 ml/min/1.73m2, respectively. During follow-up, 81 (0.6%) participants developed CKD, the cumulative probability significantly higher among the low fitness group (HR=2.41, p=0.001). The effect of physical fitness on the risk to develop CKD remained significant after adjusting for age, gender, baseline creatinine and other cardiovascular risk factors.

Conclusions: Cardiorespiratory fitness is an independently risk factor inversely associated with development of significant CKD.

FR-PO953

Association Between Physical Activity and Renal Outcomes in Patients with CKD G3b-5: A Result from a Japanese Cohort Study, the REACH-J

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Background: Association between physical activity and renal outcome in patients with chronic kidney disease (CKD) has remained largely unexamined.

Methods: We recruited 2,249 advanced CKD patients (eGFR<45 ml/min/1.73m²) receiving nephrologist care from a national sample of 31 facilities throughout Japan, randomly selected with stratification by region and facility size, aligned with the international CKD Outcomes and Practice Patterns Study (CKDopps). Association between baseline physical activity levels (active or inactive, from Rapid Assessment of Physical Activity (RAPA) surveys) and 5-year renal outcomes (40% eGFR decline, end-stage kidney disease, or death) were analyzed.

Results: Of 1808 eligible CKD patients with RAPA assessment, 407 patients with diabetic kidney disease (DKD) and 1401 patients without diabetes (non-DKD) were enrolled. Of them, 1237 patient (68% of total, 66% of DKD and 69% of non-DKD) were categorized "active" (often active or very active by RAPA score), and others were categorized "inactive". The mean ages and eGFRs in "active" and "inactive" patients were 68.5±12.5 and 70.8±11.7 years, and 24.1±10.4 and 22.1±10.4 mL/min/1.73m², respectively. Crude rates for CKD progression per 100 person-years in "active" and "inactive" patients were 19.4 and 22.1 events in DKD, and 12.1 and 13.7 events in non-DKD, respectively. In addition, crude rates for mortality in those patients were 3.9 and 4.8 events in DKD, and 1.8 and 3.8 events in non-DKD, respectively. Composite CKD progression and mortality were considerably lower at higher physical activity in both DKD and non-DKD patients, with hazard ratios of 0.84 (0.66, 1.08) and 0.80 (0.69, 0.93), respectively.

Conclusions: This multicenter study suggested the association between higher physical activity and lower CKD progression and better survival in both DKD and non-DKD patients. These findings may support future studies understanding impact of physical activity for better renal outcomes in patients with CKD stage G3b-5.

FR-PO954

Longitudinal Impacts of Bariatric Surgery on Renal Function in CKD

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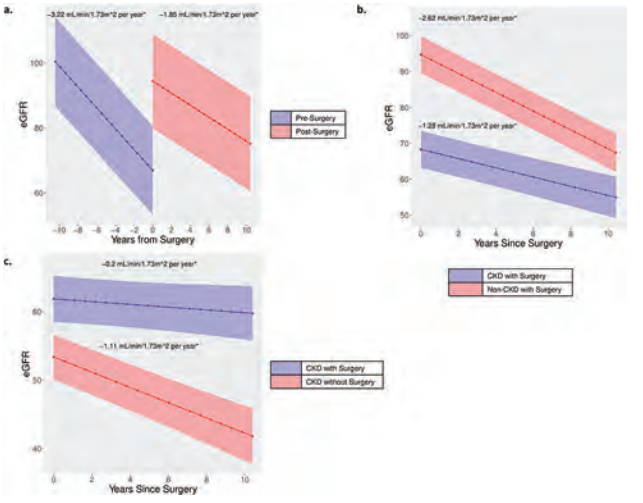
Background: Prior studies of obesity show improved renal function after bariatric surgery. This study examines renal function over 10 years pre- and post-bariatric surgery among patients with a reduced baseline eGFR, including patients with CKD.

Methods: Retrospective cohorts of patients with CKD and/or who underwent bariatric surgery prior to 11/30/22 were identified from the Michigan Medicine EHR using ICD-10 and CPT codes. Multivariable piecewise linear mixed models were fit on eGFR (2021 CKD-EPI), adjusting for age, gender, race, ethnicity, BMI, hypertension, diabetes, and surgery type or CKD stage. Pre- and post-surgery eGFR trajectories were compared in patients with a baseline eGFR<90. eGFR trajectories were then compared between CKD patients post-surgery and either propensity score-matched non-CKD patients post-surgery or CKD patients who did not undergo surgery.

Results: Patients with baseline eGFR<90 (n=688) had a slower annual rate of eGFR decline [95% CI] post vs. pre-surgery (-1.85 [-1.97,-1.72] vs. -3.22 [-3.41,-3.02] mL/min/1.73m²; p<0.001). Following surgery, CKD patients (n=139) had a slower annual rate of eGFR decline compared to 278 matched non-CKD patients (-1.28 [-1.87,-0.69] vs. -2.62 [-2.83,-2.41] mL/min/1.73m²; p<0.001). Annual eGFR decline was also slower among CKD patients who underwent surgery compared to 278 matched CKD patients who did not (-0.20 [-0.83,0.43] vs. -1.11 [-1.37,-0.85] mL/min/1.73m²; p<0.001).

Conclusions: Bariatric surgery is associated with a slower rate of eGFR decline in patients with a reduced baseline eGFR, including CKD patients. Future modeling of proteinuria may support these findings and identify if the faster eGFR decline in healthy patients correlates to a decrease in glomerular hyperfiltration after surgery.

Funding: Other NIH Support - NIH T35 Short Term Training Program (Grant 5T35HL007690-38)



Predicted values of eGFR (95% CI) from adjusted linear mixed models of (a) patients with baseline eGFR<90, (b) bariatric surgery patients with/without CKD, and (c) CKD patients with/without bariatric surgery

FR-PO955

Association Between Weight Change from 20 Years of Age and the Risk of All-Cause and Cardiovascular Mortality in Patients with CKD

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Background: Weight changes from a young age have been reported as being linked to poor life outcomes in the general population. However, little is known concerning the association between weight changes from a young age and life expectancy in patients with chronic kidney disease (CKD).

Methods: The data of 2,806 non-dialysis CKD patients who participated in the Fukuoka Kidney disease Registry (FKR) Study, a multi-center observational study, were analyzed. All-cause mortality was the primary outcome, while cardiovascular mortality was a secondary outcome. The covariate of interest was weight change, defined as the difference between body weight at study enrolment and that at 20 years of age. We estimated the risks of mortality for participants with weight changes of ≥5 or <5 kg using Cox proportional hazards models, as compared to those with stable weights.

Results: In total, 243 participants (8.7% of the total) died from all-cause, and 62 participants died from cardiovascular disease within the 5-year observation period. The risk of all-cause mortality was significantly higher in the weight loss group than in the stable weight group (multivariable-adjusted hazard ratio [95% confidence interval], 2.11 [1.52–2.93]). In addition, the risk of cardiovascular mortality was significantly higher in the weight loss group than in the stable weight group (multivariable-adjusted hazard ratio [95% confidence interval], 2.48 [1.32–4.64]). No significant associations were found between weight gain and the risks of all-cause and cardiovascular mortality.

Conclusions: Weight loss since 20 years of age is associated with increased risks of all-cause and cardiovascular mortality in non-dialysis CKD patients.

FR-PO956

Appraisal of a Simplified Protein Energy Wasting Score in CKD Patients at a Single University-Based Hospital: A Five-Year Retrospective Cohort Study

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Background: Undernutrition poses a significant complication of chronic kidney disease (CKD), leading to devastating effects on quality of life, morbidity, hospitalization, and mortality. We developed a novel Protein Energy Wasting (PEW) score, utilizing the nomenclature proposed by the International Society of Renal Nutrition and Metabolism in 2008.

Methods: We enrolled participants aged 18 years or older, with CKD stages G3 to G5ND between January 2016 and December 2020. These were utilized for diagnosing PEW using the simplified PEW score (sPEW). The sPEW was defined by the following criteria (**Figure 1**), and the Lean Body Mass Index (LBMI = LBM/height2) was subsequently determined.

Results: In total, 224 patients were identified (64% male, 36% female; mean age 77 years), with the majority classified as stages 3a, 3b, and 4 CKD (41%, 38%, and 18%, respectively). The prevalence, according to the sPEW score, showed 85 (38%) with mild PEW, 26 (12%) with moderate PEW, and four (2%) with severe PEW. LBMI was 17.3 ± 22.4, 15.7 ± 1.9, 15.5 ± 2.1, and 13.5 ± 0.5 kg/m2 in the none, mild, moderate, and severe sPEW groups, respectively (P<0.001). The multiple linear regression analysis indicated that changes in lean body mass index negatively correlated with changes in the sPEW score and gender (P<0.001) (**Figure 2**).

Conclusions: These studies suggest that the sPEW, when used in CKD patients, appears to reflect the LBMI in these populations. Further research is required to determine the validity of the sPEW as a nutritional marker and to explore its predictive value for other clinical outcomes in CKD patients.

Simplified Protein Energy Wasting Score (sPEW)

Definition of the Simplified Protein–Energy Wasting Score		Score Point
Serum albumin (g/dL)	≤3.8	1
Body mass index (kg/m2)	≤23	1
nPNA (g/kg/day)	≤0.8	1

No PEW = 0; Mild PEW = 1; Moderate PEW = 2; Severe PEW = 3

Figure1

Prevalence and association of simplified PEW score and risk factors with lean body mass index in chronic kidney disease population

	Prevalence	Lean body mass index (kg/m²) regression coefficient (95% CI)	
		Univariate analysis	Multivariate analysis *
sPEW:			
- mild	38%	-1.60 (-2.36; -0.85)	-1.53 (-2.27; -0.79)
- moderate	12%	-1.86 (-2.97; -0.74)	-1.50 (-2.64; -0.36)
- severe	2%	-3.834 (-6.92; -0.75)	-2.70 (-5.71; 0.31)
Gender (female)	36%	-2.75 (-3.42; -2.14)	-2.77 (-3.39; -2.15)
Low serum albumin (<3.8 g/dl)	14%	-0.73 (-1.79; 0.33)	-1.12 (-1.20; 0.96)
Low body mass index (<23 kg/m²)	37%	-2.02 (-2.72; -1.32)	-1.198 (-2.88; -1.29)
Low dietary protein intake (<0.80 g/kg/d)	16%	-0.37 (-1.42; 0.68)	-0.22 (-1.24; 0.79)
Low dietary energy intake (<25 kcal/kg/d)	25%	1.11 (0.23; 1.98)	1.28 (0.43; 2.13)

*Each cell represents a separate model adjusted for age, diabetes, hypertension, any tumor (including leukemia and lymphoma) and metastatic cancer.

Figure2

FR-PO957

Food Insecurity and High Blood Pressure Among Individuals with CKD in West Africa

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Background: Based on the Diet, CKD, and ApolipoproteinL1 (DCA) study data, this cross-sectional study examines the relationship of food insecurity with estimated glomerular filtration rate (eGFR) and systolic and diastolic blood pressure (SBP and DBP). Very few studies have yet studied these associations in sub-Saharan African populations. Understanding the impact of food insecurity is crucial to guide care for patients with CKD.

Methods: We recruited 570 participants with CKD (eGFR < 60mL/min/1.73m², or albuminuria > 30 mg/g) from 7 centers in the H3Africa Kidney Disease study. We measured food insecurity using a standardized question, "Did you cut meals size/skip meals because there was insufficient money during the past year?" We used mixed-effect linear regression models with clinical centers as random intercepts. Outcomes were eGFR (CKD-EPI 2009 equation), SBP, and DBP. We analyzed factors associated with food insecurity using logistic regression with a random intercept for the clinical center.

Results: The mean age for our population was 48.7 (SD = 17.5), and 47% were female. The prevalence of food insecurity in the DCA cohort was 28%, with the highest in Southeast Nigeria (69%, p<0.0001). Individuals with CKD stages 3-5 had the lowest prevalence of food insecurity (25%). The overall study population had no significant association of food insecurity with eGFR, SBP, or DBP (Table 1). Higher BMI (OR: 0.90–0.98, p<0.01), higher education (OR: 0.25–1, p=0.05), and higher income (OR: 0.003–0.38, p=0.01) were all associated with lower odds of food insecurity.

Conclusions: Our study shows a higher prevalence of food insecurity in Southeast Nigeria and a lower prevalence of food insecurity in patients with more advanced CKD. Investigating the true effect of food security on kidney function or cardiovascular disease in sub-Saharan Africa merits further study.

Funding: NIDDK Support

Associations between Food Insecurity, eGFR and Blood Pressure

	Unadjusted Model		Fully Adjusted Model*	
Outcome	Beta Coefficient (95% CI)	p-value	Beta Coefficient (95% CI)	p-value
eGFR	8.26 (0.37 to 16.23)	0.04	5.51 (-1.09 to 12.00)	0.11
Systolic BP	0.45 (-4.07 to 4.82)	0.84	1.88 (-2.53 to 6.13)	0.40
Diastolic BP	1.76 (-1.26 to 4.82)	0.26	2.31 (-0.79 to 5.45)	0.15

*Adjusted for age, sex, education, income, smoking, diabetes, obesity, and SBP (for eGFR), Clinical Center as Random Effect

FR-PO958

Economic Burden of CKD in the United States: A Systematic Literature Review

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Background: With nearly 37 million cases of CKD in the US, the economic impact is substantial. To fully understand the economic burden of CKD to payers and health systems, as well as drivers of burden, a comprehensive assessment of the recent evidence base is needed. This review aimed to characterize direct medical costs of those diagnosed with CKD in the US, overall and by CKD stage, insurance type, and presence of diabetes mellitus (DM), cardiovascular disease (CVD), and obesity.

Methods: A systematic literature review was conducted using MEDLINE and Embase, supplemented by a grey literature search, to identify studies reporting direct medical costs for CKD in the US, published between 01/01/2017 and 07/27/2022. Conference proceedings from 2020 to 2022 that were identified in the search were also considered for inclusion. Two reviewers independently performed study selection and data extraction according to PRISMA guidelines. Patient characteristics and cost estimates were summarized; mean annual cost estimates were converted to 2022 USD and reported.

Results: From 3,424 abstracts, 52 citations representing 39 distinct studies were included. Sample sizes ranged from 52 to 7,091,324; mean age ranged from 45 to 79 years and the percentage of males from 33% to 98%. Direct medical costs ranged from $6,592 to $280,727 per patient. In studies of CKD-only patients reporting costs by stage (n=3), costs ranged from $6,592 (stage 3) to $143,745 (end stage kidney disease [ESKD]). Of studies evaluating comorbidities (n=14), patients with DM had costs as high as $280,727 (new onset ESKD & DM), while those with CVD had costs as high as $70,742 (CKD & heart failure). No studies investigated costs among those with comorbid obesity. In studies reporting components of medical costs for CKD-only (n=7), inpatient costs tended to be the largest component ranging from $2,331 to $116,309. No trend was observed in costs by payer type.

Conclusions: The review found that direct medical costs among patients with CKD continues to be high, primarily driven by inpatient costs. Other contributory factors included advanced CKD stages and presence of cardiometabolic comorbidities.

Funding: Commercial Support - This study was funded by Boehringer Ingelheim.

FR-PO959

Improving Compliance with CKD Screening and Monitoring in a Resident Continuity Clinic

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Background: Chronic kidney disease (CKD) is a significant burden on the adult population, affecting up to 1 in 10 individuals. Early identification and intervention in early-stage CKD are crucial for preventing cardiovascular morbidity and mortality, specially with the availability of advanced treatment options. Guidelines recommend annual measurement of estimated glomerular filtration rate (eGFR) and proteinuria quantification in individuals at risk of CKD or with early-stage CKD. As only one third of primary care providers (PCPs) are completely confident in how to screen, diagnose, and manage CKD, we hypothesized that compliance with CKD monitoring and screening would be suboptimal in our Resident Continuity Clinic (RCC).

Methods: We conducted a quality improvement project in our RCC, comprising 34 internal medicine resident physicians serving as PCPs. We focused on patients seen in the RCC between July 1, 2020 and February 28, 2023. We assessed CKD monitoring by determining the percentage of patients with CKD, diabetes, or hypertension who underwent at least one measurement of eGFR and urine protein/creatinine or urine albumin/creatinine ratio (ACR) during the study timeframe. Patients were considered to have diabetes, hypertension, or CKD if the disease specific ICD-10 code was present on their chart.

Results: 59% of the 1,811 patients seen in the RCC during the evaluation period had CKD, diabetes, or hypertension. While eGFR was measured in 90% of these patients, only 24% had eGFR and proteinuria measured. To address this gap, we implemented Plan-Do-Study-Act cycles to include resident education, introduction of an order set in the electronic medical record (EMR) to facilitate appropriate laboratory testing, and an

EMR update to prompt PCPs to order yearly urine ACR for patients with diabetes. Post-intervention data will be collected quarterly, with initial results available July 2023.

Conclusions: Despite satisfactory adherence to eGFR measurements, proteinuria evaluation was underutilized. Proteinuria is an independent predictor of cardiovascular morbidity and mortality and CKD progression and has therapeutic implications. Our findings highlight the need for healthcare system interventions to ensure proper proteinuria evaluation in patients at risk for CKD.

FR-PO960

Investigating Barriers to Implementation of Functional Status Assessments in CKD Care: A Mixed Methods Study Among Stakeholders

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Background: Chronic kidney disease (CKD) clinical practice guidelines (CPG) recommend regular functional status assessments at all stages of CKD to identify those at high risk for poor functional decline. However, functional status tests are not routinely incorporated into CKD care, and the reasons for this gap have not been explored.

Methods: We used the Consolidated Framework for Implementation Research (CFIR) to guide survey and interview questions to identify barriers to implementing CPG recommended functional status assessments in CKD care. Online survey invitations were sent to stakeholders in CKD care, including staff providing direct care and administrators with decision-making roles in a large health system in southeastern Pennsylvania. Volunteers among survey respondents participated in phone interviews with a qualitative researcher. Interviews were transcribed verbatim and de-identified. Transcripts were analyzed with inductive coding as well as deductive coding using CFIR domains, and codes were grouped into themes.

Results: Thirty-nine stakeholders in CKD care responded to surveys: 28 were nephrologists, 9 were other care staff, and 2 were administrators; 62% were women, 59% White, 31% Asian, and 5% Black. Only 36% were aware of CPG recommendations for functional testing in CKD care and 22% reported that testing was currently performed. Two-thirds of respondents agreed that functional testing should be performed in CKD care (66%) and that these tests could be conducted effectively in their clinics (69%). In the survey, the three most commonly selected barriers to performing functional testing were: clinical burden, lack of familiarity with tools, and lack of space and/or equipment. Seven respondents volunteered to be interviewed (3 nephrologists, 4 advanced practitioners). Themes identified as barriers to CPG implementation included: limited awareness/knowledge, limited resources (time, space), lack of competence/confidence in conducting tests and interpreting results, and lack of a standard operating procedure for testing.

Conclusions: Identified barriers, including limited awareness/knowledge, resources (time, space, equipment), and a standard procedure will inform strategies to improve the implementation of CPG recommended functional testing in CKD care.

Funding: Private Foundation Support

FR-PO961

Implementation of the Kidney Failure Risk Equation in a US Nephrology Clinic

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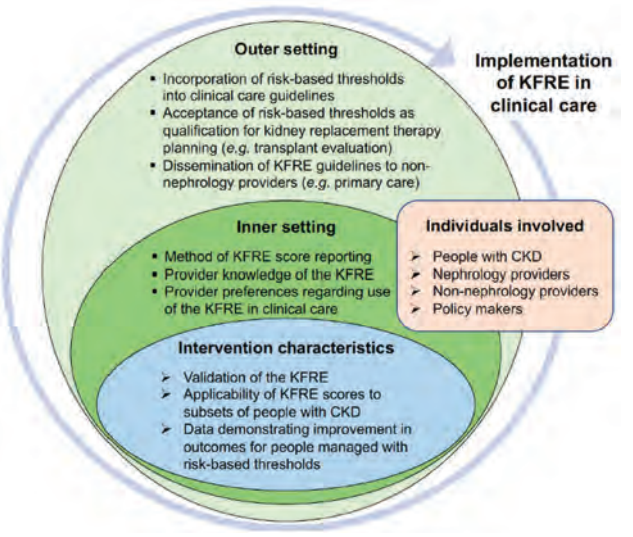
Background: The kidney failure risk equation (KFRE) estimates a person's risk of kidney failure. We explored implementation of the KFRE in a U.S. nephrology clinic.

Methods: We integrated KFRE scores into the electronic health record (EHR) for patients with CKD being seen in Johns Hopkins nephrology clinics. We quantified documentation of KFRE scores in clinic notes and conducted surveys and focus groups of nephrology providers to assess provider perspectives on its use. Focus groups were audio-recorded and transcripts were coded using thematic analysis.

Results: Documentation of KFRE scores increased over time, reaching 25% of all eligible outpatient nephrology clinic notes after 11 months. Of 44 nephrology providers, 3 documented KFRE scores in > 75% of notes, whereas 25 documented scores in < 10% of notes. Survey respondents (n=25) reported variability in use of KFRE scores for decisions such as maintaining nephrology care, referring for transplant evaluation, or providing dialysis modality education. Provider perspectivess, assessed by qualitative analysis of focus groups transcripts, included three common themes: 1) KFRE scores may be most impactful in care of specific subsets of people with CKD; 2) there is uncertainty surrounding KFRE risk-based thresholds to guide clinical care, and 3) education of patients, nephrology providers, and non-nephrology providers on appropriate interpretations of KFRE scores may help maximize their utility. Based upon these findings, we propose key components of KFRE implementation as a roadmap for future efforts to increase its use in clinical care (Figure).

Conclusions: KFRE score documentation increased over time, with variability in adoption by providers. Further knowledge surrounding utilization of the KFRE in clinical decisions may enhance its implementation.

Funding: NIDDK Support



Roadmap for KFRE implementation.

FR-PO962

A Quality Improvement Initiative to Bridge Gaps in Treatment and Interprofessional Care of CKD

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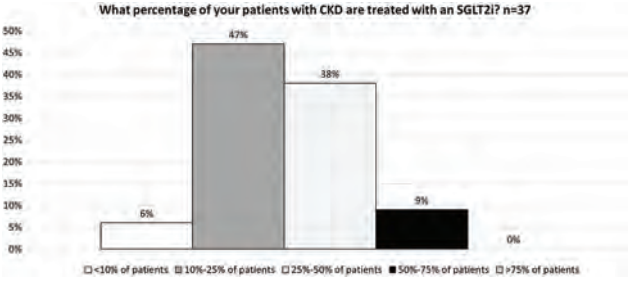
Background: Diagnosing, treating, and coordinating care for patients with chronic kidney disease (CKD) can be challenging, contributing to gaps in the quality of care in CKD. Uncovering the needs of nephrology care teams treating patients with CKD can help to close these gaps and improve patient outcomes.

Methods: A quality improvement (QI) initiative within 5 nephrology clinics was conducted to assess current practice patterns through surveys administered to nephrology care team members (n=83). Each center then participated in an interactive audit-feedback educational session with a national CKD expert and developed action plans to address system-specific barriers to treatment.

Results: Provider surveys identified gaps in patients meeting clinical targets and receiving guideline-directed care. Notably, 37% of providers reported less than half of their CKD patients were meeting blood pressure targets and 67% of providers reported that less than half of their CKD patients were meeting HbA1C targets. When CKD care team members were asked how many of their patients with CKD were prescribed an SGLT2 inhibitor, 53% of respondents reported that less than 25% of their patients were receiving an SGLT2 inhibitor as part of their treatment plan (Fig. 1). Following the intervention, CKD care team members prioritized the following areas for improvement to support patients and align clinical practice with current guideline recommendations: 1) patient education to improve lifestyle modification (41%), 2) developing individualized treatment plans based on patient specific factors (22%), and 3) improving co-management of patients with primary care physicians and other specialists (22%).

Conclusions: The surveys identified real-world challenges inhibiting patients from achieving clinical targets and contributing to discordances with guideline-directed treatment recommendations. Overall, QI programs for interprofessional CKD care teams are critical tools for understanding and addressing system-specific barriers to effective treatment of CKD.

Funding: Commercial Support - Boehringer Ingelheim Pharmaceuticals



FR-PO963

The Role of Patients' Education in Improving Quality Outcomes in CKD

Rula A. Abdulrahman, Sandeep K. Mallipattu. *Stony Brook University, Stony Brook, NY.*

Background: CKD prevalence in US is ~ 14%. The measures to delay CKD progression are well known to providers but not to most patients with CKD, specifically minorities and patients in the lower socioeconomic class. Providing intense CKD education can improve quality outcome in this population and delays dialysis requirement. Home dialysis (HoD) therapies have been associated with improved quality of life and reduced costs, in US HoD percentage is ~13%. Currently most patients start dialysis with central venous catheter (CVC) ~ 83%in US, our goal is to increase HoD, efficiency of arteriovenous fistula (AVF) or arteriovenous graft (AVG) placement, and to increase referrals and listing for kidney transplantations (KT), as suggested in ESRD treatment choice model.

Methods: We initiated a CKD education clinic (CKDEC) with 3 aims: delay the progression of CKD and onset of dialysis, increase the number of HoD, improve access and timely referral to KT. Individuals who attend the clinic will be educated to avoid the factors and behaviors that can expedite CKD progression and dialysis initiation. Patients will be provided with guidance about controlling underlying medical diseases and introduced to ESRD treatment modalities. We also facilitate their access to obtain permanent access in a timely manner. We are educating the patients about KT and facilitate the appointments & encourage follow up.

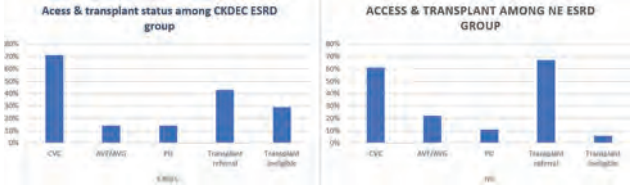
Results: 209 patients that are CKD IV and V at our outpatient facility & 25 dialysis. Of those, who chose HoD after CKDEC are 14.3%. This is higher than the national rate of 13%. CKDEC improved referral rate to KT and vascular access (Table 1). Many of our patients who started dialysis in 2021-2022 used CVC (71%) after CKDEC, this is lower than the national CVC rate (83%) image 1

Conclusions: CKD education improves HoD rate, referrals to KT and dialysis access among CKD but not ESRD group. we need to continue earlier access to CKD education clinic to continue to improve our outcome measures.

Table 1

	CKDEC transplant referral	CKDEC access referral	NE transplant referral	NE access referral
CKD IV	42.8%	23.8%	2.8%	2.2%
CKD V	71.4%	92.8%	61.3%	67.7%

CKDEC: chronic kidney disease education clinic. NE: did not attend CKDEC



FR-PO964

Optimizing Palliative Care Referrals for Veterans with Kidney Disease in the Iowa City VA Health Care System

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Background: The kidney clinic at Iowa City VA (ICVA) sees 20-40 patients weekly, with an estimated 5-15% benefiting from palliative care referrals. Hospice aims to enhance end-of-life quality and enable death at home. However, the lack of quality metrics in the industry hinders care assessment. National median length of stay (LOS) in hospice was 18 days in 2018. In ICVA, only 1.8% of palliative care referrals were for kidney disease patients, with a median LOS of 14 days, highlighting the need for improvement.

Methods: We aimed to evaluate delays in kidney disease referrals to palliative care and enhance appropriate referral percentage. Mixed methods were used, reviewing referral data and examining qualitative barriers. Three iterative Plan-Do-Study-Act (PDSA) cycles were implemented. The first focused on educating the kidney team to consider the patient holistically. The question, "Would death within six months not be unexpected?" was introduced. The second involved a multidisciplinary conference, broadening education. The third proactively reviewed charts of returning patients to identify referral candidates.

Results: Analysis using a Statistical Process Control (SPC) p-chart showed consistent low referrals (<10% of eligible Veterans), indicating the need for improvement. Barriers identified included concerns about time required for discussions and referrals.

Conclusions: Our project has not entered the sustainability phase, as there has been no significant improvement in referrals for eligible patients. Further iterative PDSA cycles are necessary to integrate palliative care effectively. Future efforts will focus on reducing rural disparities in accessing palliative care through virtual visits. We aim to align resources in the kidney clinic, increase efficiency, and consider implementing an opt-out process for Veterans on dialysis or with significant kidney disease. By addressing these challenges, we aim to improve appropriate palliative care referrals, enhance end-of-life care for kidney disease patients at ICVA, and provide early access to specialized person-centered care, ultimately improving their quality of life.

Funding: Private Foundation Support

FR-PO965

Impact of Conservative Management vs. Dialysis Transition on Survival in a National Advanced CKD Cohort

Connie Rhee,[1] Ji Hoon Yoon,[1] Seungsook You,[1] Yoko Narasaki,[1] Csaba P. Kovesdy,[2] Dana B. Mukamel,[1] Susan T. Crowley,[3] Silvina Torres Rivera,[1] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh.[4] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]Yale University, New Haven, CT; [4]Harbor-UCLA Medical Center, Torrance, CA.*

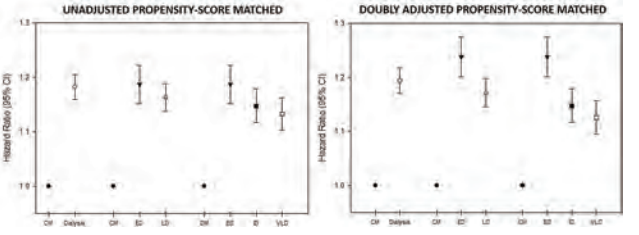
Background: While dialysis has been the dominant treatment paradigm in advanced CKD patients progressing to ESKD, this approach may lead to impaired physical function, independence, and quality of life among certain subpopulations. We compared the impact of non-dialytic conservative management (CM) vs. dialysis on survival in a national advanced CKD cohort.

Methods: We compared survival in advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25) over 1/1/07-6/30/20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. In secondary analyses, we examined finer gradations of dialysis timing, defined as earlier dialysis (ED) vs. later dialysis (LD) (eGFRs ≥15 vs. <15 at dialysis transition), and in tertiary analyses we compared ED, intermediate dialysis (ID), vs. very-late dialysis (VLD) (eGFRs ≥15, 10-<15, vs. <10 at dialysis). We compared survival in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio to address confounding by indication using Cox models.

Results: In 28,829 CM patients PS-matched to 28,829 dialysis patients, dialysis transition was associated with higher mortality vs. CM: HR (95%CIs) 1.18 (1.16, 1.21). In secondary analyses, both ED and LD were each associated with higher mortality vs. CM: HRs (95%CIs) 1.21 (1.17, 1.25) and 1.17 (1.14, 1.20), respectively. In tertiary analyses, increasingly earlier dialysis transition was associated with worse survival vs. CM. Similar findings were observed in sensitivity analyses doubly-adjusted for PS covariates.

Conclusions: Patients treated with CM as an alternative patient-centered treatment strategy had lower mortality risk compared to dialysis, irrespective of dialysis transition timing. Further studies are needed to examine the comparative effectiveness of CM vs. dialysis on CKD outcomes.

Funding: NIDDK Support



FR-PO966

Ambulatory Palliative Care (PC) in Advanced CKD

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Background: Under 10% of patients on dialysis discuss goals, values, and preferences with their nephrologist; nearly 90% want to. PC can enhance patient quality of life, improve illness understanding and alter decisions at end of life. Global ambulatory renal PC clinics have been successful but are rare in the US. We tested the feasibility of integrating ambulatory PC for patients with CKD via manual EMR screening.

Methods: Renal and PC developed screening criteria: 1. Age >70 w/ stage 5 CKD 2. Age >70 w/ stage 4 CKD and cardiovascular disease or diabetes 3. Age >80 w/ stage 4 CKD For 11 weeks, study staff used the EMR to screen patients scheduled in renal clinic. A list of patients who met criteria were emailed to renal providers. If deemed appropriate, renal introduced PC to the patient. If the patient agreed, a PC referral was placed. PC saw referred patients before or after their renal clinic visit in the same room.

Results: See Fig 1. Renal agreed 33% of patients who met criteria were PC appropriate. Of patients who met criteria, 19% were seen by PC (Fig 2). PC saw significantly more patients in the 3 months after the intervention (n= 22), compared to before the intervention (n = 3), [$X^2 = 14.3$; $p < 0.001$].

Conclusions: Our study showed the feasibility of using screening criteria to integrate PC into renal clinic for advanced CKD patients. The higher volume seen by PC suggests the process helped renal providers identify patients appropriate for PC. Manual screening was resource intensive. An automated EMR screen would be more sustainable. The continued increase in PC visits after the study suggests a change in practice and improved access to PC. Our model for an integrated renal PC clinic promotes patient centered quality care for patients with advanced CKD.

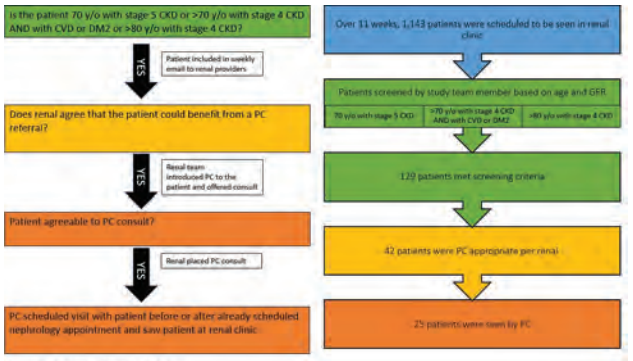
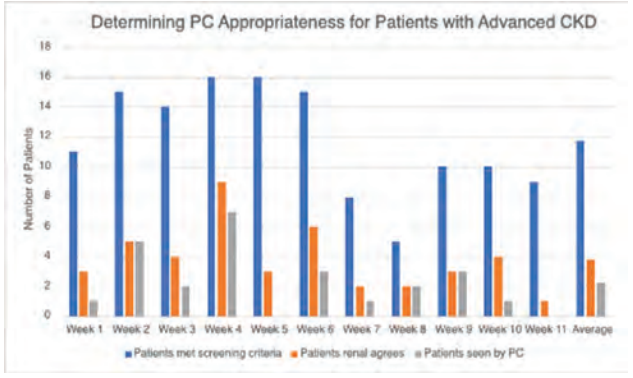


Figure 1: Process Flow and Results



FR-PO967

Effect of Social Support on Response to Treatment of Depression in Patients with CKD

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Background: The Chronic Kidney Disease Antidepressant Sertraline Trial (CAST) was a randomized, double-blind, placebo-controlled trial of sertraline vs. placebo in patients with nondialysis CKD, which did not reveal a statistically significant improvement in depressive symptoms. Using the validated Kidney Disease Quality of Life Questionnaire (KDQOL) and Quick Inventory of Depressive Symptomatology-Clinician Rated scale (QIDS-C), we investigated whether higher baseline social support would affect adherence to study drug by pill count and improve response to antidepressant treatment.

Methods: Two-hundred-and-one patients with stages 3b-5 non–dialysis CKD were enrolled. The primary outcome was improvement in depressive symptoms from baseline to 12 weeks by QIDS-C (higher score, more depression), stratified by baseline social function tertiles (higher tertile, higher social function). The interaction of treatment group (sertraline vs. placebo) by social function was also tested.

Results: Mean age was 58.2±13.2 years. Those in the highest tertile of social function were more likely to be older (p=0.0002), male (p=0.01), live alone (p=0.04), and be less educated (p=0.009) than the lowest tertile. Baseline CKD stage or eGFR did not differ between tertiles. Participants with the highest level of social function at baseline had the largest decrease in QIDS-C score if treated with placebo (-6.13), but participants with the lowest level of social functionhad the largest decrease in QIDS-C if treated with sertraline (-5.87), interaction p=0.03. There was a stepwise increase in percent of drug taken (88%, 95%, and 97%) for lowest, middle and highest tertiles of social function in the sertraline group (p=0.008) which was not observed in the placebo group. In addition, there was a significant interaction such that participants assigned to sertraline took a higher percent of their study drug if their social function was better at baseline, but this was not true of placebo, interaction p=0.01.

Conclusions: Sertraline may be more effective than placebo for improving depression in those with non-dialysis CKD with worse social functioning at baseline, even though participants with lower social function may be less adherent to antidepressant medications.

FR-PO968

Unexpected Improvement of CKD After Removal of Over-the-Counter Agent

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Introduction: Prescription and over-the-counter (OTC) nonsteroidal anti-inflammatory drugs (NSAIDs) represent an important component in the treatment of acute and chronic pain. Products containing salicylates are one of the most widely used medications. They can be found in topical ointments, lotions, solutions used in hot steam, and oral and topical analgesia. Approximately 10-30% of salicylates are excreted via the kidneys as free salicylic acid but it is unknown whether the efficacy may be due to direct local absorption or the result of systemic absorption and distribution throughout the vasculature. Here we present a worsening of chronic kidney disease with OTC topical analgesic.

Case Description: Case of a 65-year-old male with a past medical history of CHF, DM2 and CKD who presented with shortness of breath. Patient with bilateral lung crackles and peripheral edema, who was admitted due to decompensated CHF. Medication regimen included apixaban, atorvastatin, metoprolol succinate, lisinopril, spironolactone and empagliflozin, and NSAIDs use was denied. Laboratory remarkable for worsening renal function. Patient's nephrotoxic medications were placed on hold and his creatinine level started to improve after careful IV diuresis. Upon achieving euvolemia, the diuretic was transitioned to oral. All of a sudden his renal function started to decline. Renal ultrasound resulted with no obstructive uropathy but with cortical thinning and increased echotexture. Urinalysis was remarkable for few epithelial cells. FEUrea resulted in 41.7% suggestive of intrinsic damage. Upon further questioning, the patient had been using a topical methyl-salicylate every 4 hours for articular and muscle pain without disclosing it for 48-72 hours. Once topical NSAIDs were removed, and IV hydration was implemented the serum creatinine gradually returned to baseline in the following days.

Discussion: Topical NSAIDs has been less associated with renal impairment than the oral route. Around 9.3% of patients with salicylate poisoning develop AKI and increased risk of organ failure, in-hospital mortality, longer length of hospital stay, and higher cost of hospitalization. This case highlights the importance of a careful review of patients' medication history including OTC medication and raises concern of potential role and impact on renal function not well known by topical NSAIDs.

FR-PO969

Association Between Laxative Use and Serum Phosphate Levels in Patients with CKD: A Large Nationwide Observational Study of US Veterans

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[1]The University of Tennessee Health Science Center, Memphis, TN; [2]University of California Irvine, Irvine, CA; [3]VA Memphis Medical Center, Memphis, TN.

Background: Reducing intestinal phosphate (P) absorption is key to maintain normal P balance in patients with CKD. Laxative use may enhance fecal P excretion and help reduce serum P levels; however, little is known about the association of laxative use with serum P levels.

Methods: In a nationwide cohort of 513,653 US veterans receiving care from the VA healthcare system from 2004-2006 and with ≥1 outpatient serum P measurements during the follow-up through 2019, we examined the association of time-varying non-P containing laxative use with serum P levels across CKD stages, using generalized estimating equations with adjustment for demographics, smoking status, BMI, comorbidities, and time-varying use of relevant drugs, number of different types of laxatives, serum calcium, and eGFR. Serum P levels at each P measurement were treated as a repeated multinomial outcome (i.e., <2.5 [low-P], 2.5-≤3.5 [normal-P: reference], and >3.5 mEq/L [high-P]).

Results: Patients were 66.5±11.9 years old; 94.3% were male; 20.9% were African American; and 39.4% were diabetic. Their baseline eGFR was 76.8±23.3 mL/min/1.73m^2. There was no significant interaction between laxative use and eGFR (p=0.85). After multivariable adjustment, the use (vs. non-use) of laxatives was significantly associated with greater risk of low-P (adjusted OR [95% CI], 1.10 [1.04-1.16]) and high-P (1.07 [1.03-1.11]) in patients with CKD stages G1-2 (Table). The greater risk of low-P associated with laxative use was more pronounced in patients with more advanced CKD stages; while the laxative use-related risk of high-P was not evident in those with CKD stages G3-5 (Table).

Conclusions: The use of non-P containing laxatives was independently associated with greater likelihood of lower serum P levels in patients with CKD, particularly in those with more advanced CKD stages. Our findings suggest potentially distinct pharmacological contribution of laxatives to P homeostasis across CKD stages.

Funding: Veterans Affairs Support

Adjusted odds ratios (95% CI) for low and high serum phosphate levels associated with the use (vs. non-use) of time-varying non-P containing laxatives (n=513,653)

	Time-varying serum phosphate concentration (mEq/L)		
	<2.5 (low-P)	2.5 to =3.5 (normal-P)	>3.5 (high-P)
% of all repeated values	6.9 %	53.7 %	39.4 %
CKD stages† (n)			
G1-2 (394,280)	1.10 (1.04-1.16)	1 [reference]	1.07 (1.03-1.11)
G3a (68,475)	1.20 (1.04-1.38)	1 [reference]	0.98 (0.90-1.07)
G3b (34,017)	1.23 (1.01-1.50)	1 [reference]	1.04 (0.92-1.16)
G4-5 (16,881)	1.27 (0.96-1.70)	1 [reference]	0.94 (0.80-1.11)

†Model was adjusted for demographics, smoking status, BMI, comorbidities, and time-varying use of relevant medications, number of different types of laxatives, serum calcium, and eGFR

FR-PO970

Effects of Lactobacillus rhamnosus GG on Gut-Derived Uremic Toxins and Gut Microbiome in Non-Dialysis CKD Patients

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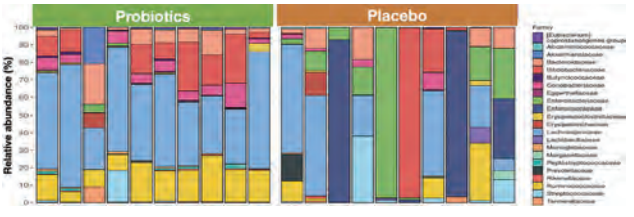
Background: Accumulation of uremic toxins in chronic kidney disease (CKD) is linked to progression to kidney failure via multiple mechanisms, including gut dysbiosis and gut-derived uremic toxins (GDUT) production. We explored the effects of *Lactobacillus rhamnosus* GG (GG), a probiotic, on GDUT and gut microbiome in CKD patients.

Methods: We conducted a randomized, double-blinded, controlled trial. After 2-week run-in, non-dialysis CKD stage 3-5 patients were assigned to receive LGG or placebo for 8 weeks and additional 12-week follow-up. Primary outcomes were changes in serum GDUTs (Indoxyl sulfate;IS, P-cresol sulfate;PCS) at end of treatment. Secondary outcomes included fecal microbiome analysis, serum inflammatory markers, eGFR, proteinuria, and adverse effects. In parallel, *in vitro* effects of *E.coli* lysate (ECL) with/without LGG-conditioned media (LCM) were explored in Caco-2 enterocytes and THP-1 macrophages.

Results: Among 60 participants (aged 70.15±12 years; 57% male; eGFR 38.17 ml/min/1.73m^2), 30 each group, baseline characteristics were comparable. At the end of treatment, median changes in serum IS and PCS from baseline were lower in probiotic group (-0.89 vs +0.15 μmol/L, P<0.01) and (+0.1vs +1.0 μmol/L, P=0.01), respectively. Serum inflammatory markers were lower in probiotic group (endotoxin 0.29 vs 1.19 U/mL; P=0.02, IL-6 1.25 vs 2.52 pg/mL; P<0.01, and TNF-a 0.04 vs 0.36 pg/mL; P=0.02). The eGFR, proteinuria, and adverse effects were comparable. Fecal microbiome analysis in probiotic group showed decreased diversity and reduction in pathogenic *Proteobacteria* (Fig 1). *In vitro*, there were higher pro-inflammatory gene expression in Caco-2 and THP-1 cells with ECL, and lower enterocyte integrity. These effects were attenuated with LCM, indicating protective effects on enterocyte inflammation and integrity.

Conclusions: LGG improved gut dysbiosis, attenuated GDUT production, and reduced inflammatory responses linked to CKD progression. Probiotics may have a role in retarding CKD progression. Larger RCT is warranted.



Fecal microbiome analysis at end of treatment

FR-PO971

Lubiprostone Inhibits Progression of Renal Failure via Intestinal Microbiome

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Background: The gut microbiota and chronic kidney disease (CKD) are believed to be closely interrelated. We previously reported that the administration of the chronic constipation treatment drug lubiprostone (Lubi) in a mouse model of renal failure suppressed the accumulation of uremic toxins in the body during renal failure and demonstrated a renal protective effect. Based on these findings, we hypothesized that Lubi could be a potential novel treatment for kidney diseases.

Methods: The objective of this study was to investigate the effects of Lubi on the suppression of uremic toxin accumulation and disease progression in patients with renal failure. The trial design was randomized, double-blind, placebo-controlled, multicenter collaborative, and exploratory physician-initiated. A total of 118 patients with CKD Stage 3b were assigned to the placebo group (33 patients), 8 μg group (35 patients), or 16 μg group (50 patients), and the trial was conducted at eight domestic facilities from 2017 to 2020. The primary outcome was the change in plasma indoxyl sulfate (IS) levels from baseline to 24 weeks after the start of the trial. The secondary outcomes included changes in uremic toxins (phenyl sulfate, p-cresyl sulfate, trimethylamine N-oxide) and eGFR. Statistical analysis involved conducting ANCOVA analysis with the eGFR value at allocation and the baseline values of each evaluation item as covariates, followed by post hoc testing using Dunnett's method.

Results: The change in IS levels was as follows: placebo group: 0.13±0.15 μg/ml, 8 μg group: 0.091±0.15 μg/ml, 16 μg group: 0.13±0.13 μg/ml (least squares mean ± standard error), and no significant differences were observed. However, the change in eGFR was as follows: placebo group: -1.55±0.65 ml/min/1.73m^2, 8 μg group: -0.34±0.66 ml/min/1.73m^2, 16 μg group: 0.37±0.54 ml/min/1.73m^2, with a significant difference observed between the placebo and 16 μg groups (p-value = 0.0457).

Conclusions: While Lubi 16 μg did not improve uremic toxin levels, it improved eGFR, thereby generating new evidence for the treatment of CKD. In the future, we plan to analyze metabolites and the gut microbiota from the samples obtained in this trial to explore the mechanism of the inhibitory effect of Lubi on the progression of renal failure and search for new targets for renal failure treatment.

FR-PO972

Extended-Release Calcifediol: A Data Journey from Phase 3 Studies to Real-World Evidence Highlights the Importance of Early Treatment of Secondary Hyperparathyroidism (SHPT)

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Background: Early secondary hyperparathyroidism (SHPT) diagnosis and treatment are crucial to delay the progression of SHPT and related complications, in particular, cardiovascular events and bone fractures. Extended-release calcifediol (ERC) has been developed for the treatment of SHPT in patients with stage 3 or 4 chronic kidney disease (CKD) and vitamin D insufficiency (VDI).

Methods: In this descriptive analysis, laboratory parameters of SHPT-CKD stage 3–4 subjects randomised to ERC in two phase 3 clinical studies (NCT01651000 [N=141] and NCT01704079 [N=144]) were compared with those treated with ERC in a RWE study (MBD-AWARE study; N=174]).

Results: The main baseline laboratory parameters showed consistency between the phase 3 studies and the RWE study, except for baseline parathyroid hormone (PTH). Mean±standard deviation baseline PTH levels were 147±56 pg/mL and 148±64 pg/mL in the intent-to-treat populations on ERC in NCT01651000 and NCT01704079, respectively, and 181±98 pg/mL in the RWE study. Moreover, in the RWE study, 53% of subjects receiving ERC had CKD stage 4 with an even higher baseline PTH level versus stage 3 CKD subjects. ERC treatment significantly reduced PTH levels and increased 25-hydroxyvitamin D [25(OH)D], regardless of CKD stage, in all 3 studies. In the phase 3 per-protocol populations, 74% of subjects treated with ERC were up-titrated to 60 μg daily after 12 weeks at 30 μg daily, 97% attained 25(OH)D levels ≥30 ng/mL, and 40% achieved ≥30% reductions in PTH. In contrast, based on an apparent 'wait longer approach' to test key markers of SHPT, only 2% of subjects in the RWE study were up-titrated. Nevertheless, 70% of subjects achieved 25(OH)D levels ≥30 ng/mL, and 40% had a ≥30% reduction in PTH, consistent with the phase 3 results.

Conclusions: These data suggest a 'continuum' of clinical evidence of ERC effectiveness for treating SHPT, irrespective of CKD stage. A clinically relevant response was observed with ERC in the RWE study, consistent with the phase 3 studies, despite higher baseline PTH levels and lower ERC dose. In summary, these data support early treatment initiation with ERC, following diagnosis of SHPT, VDI and stage 3 CKD, to delay the progression of SHPT.

Funding: Commercial Support - CSL Vifor

FR-PO973

Effects of Three Months of Ergocalciferol Supplementation in Patients with Stages 3 and 4 CKD: Results from a Randomized Clinical Trial

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Background: Patients with chronic kidney disease (CKD) have higher prevalence of vitamin D deficiency. This is associated with albuminuria but clinical studies have shown mixed results. This randomized, placebo-controlled, double-blind clinical trial hypothesized that supplementation with ergocalciferol would decrease albuminuria in participants with CKD stages 3 and 4.

Methods: 74 participants were assigned to either oral ergocalciferol 50,000 IU or placebo weekly for 8 to 12 weeks depending on baseline 25 hydroxyvitamin D (25OHD) levels. The primary outcome was change in albuminuria. Secondary outcomes included change in laboratory values serum 25 hydroxy vitamin D (25-OH-D), 1,25-dihydroxy vitamin D (1,25OH2D), calcium, phosphate, intact PTH (iPTH), fibroblast growth factor 23 (FGF-23), estimated GFR levels, emergency department (ED) visits and hospitalizations.

Results: Mean age of participants was 58 years (standard deviation (SD): 13 years). The participants were 43% female, 48% Hispanic, 38% non-Hispanic Black.

68% had CKD stage 3 at enrollment. There was no significant difference in the change in albuminuria between the groups (Placebo group: 437 mg/gm [IQR 158-1256] at baseline, 580 mg/gm [IQR 175-1160] at 12 weeks; Ergocalciferol group: 829 mg/gm [IQR 244-1942] at baseline, 850 mg/gm [IQR 137-1405] at 12 weeks; p value= 0.13). Analysis of secondary outcomes showed significant differences in 25(OH)D levels at 12 weeks placebo 16.6 ng/mL (SD 7.8) versus ergocalciferol group 29.4 ng/mL (SD 13.4) (p<0.001) and mean eGFR (Placebo: 36.7 (SD 13.4) at baseline and 37.6 (SD 16.2) at 12 weeks; Ergocalciferol group: 37.7 (SD 14.3) at baseline and 30.5 (SD 12.3) at 12 weeks; p=0.001). There was no difference in 1,25OH2D, calcium, phosphate, intact PTH or FGF-23 between the groups. Participants in the ergocalciferol group had fewer hospitalizations and ED visits (seventeen) versus the participants treated with placebo (twenty-seven).

Conclusions: Among non-Hispanic Black and Hispanic adults with CKD stage 3 or 4, supplementation with ergocalciferol resulted in no significant difference in albuminuria levels and mineral metabolism markers. However, eGFR significantly decreased at 12 weeks after treatment with ergocalciferol.

Funding: NIDDK Support

FR-PO974

Effect of Cholecalciferol Supplementation on Immune Modulation, Inflammation, and Vascular Function in CKD

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Background: Vitamin D deficiency is common in chronic kidney disease (CKD) and short term studies have shown beneficial effect of vitamin D supplementation on vascular function in CKD. In this study we investigated the effect of cholecalciferol supplementation on vascular and immune functions in non-diabetic patients with early stage CKD.

Methods: In this pre-post study, non-diabetic CKD with eGFR 15-60 ml/min/1.73m^2 and 25(OH)D levels <20 ng/ml were enrolled. Participants receive 300000 IU of cholecalciferol at enrolment and 8 weeks. Change in circulating T cell subsets, flow mediated dilatation (FMD), serum levels of pro and anti-inflammatory cytokines and mRNA expression of Cathelicidin, VDR, Cyp27b1, IL-10 were analysed at 16 weeks.

Results: Out of these 69 participants enrolled, 62 participants completed follow up. 25(OH)D levels increased at 16 weeks (14.4 ± 8.6 ng/ml vs 39.8 ± 19.1 ng/ml, P<0.001). A significant increase in Th2 cell and Th17 population was noted whereas no change was observed in Th1 and Treg cell populations (Table 1). FMD showed a significant increase at 16 weeks (10.54± 6.30 % vs 13.82±8.62 %, P=0.02). Increased mRNA expression of Cathelicidin, IL-10, VDR and Cyp27b1 by 2 to12 fold (Fig.1A) and significant changes in levels of various pro-inflammatory and anti-inflammatory cytokines (Fig.1B) were observed at follow-up.

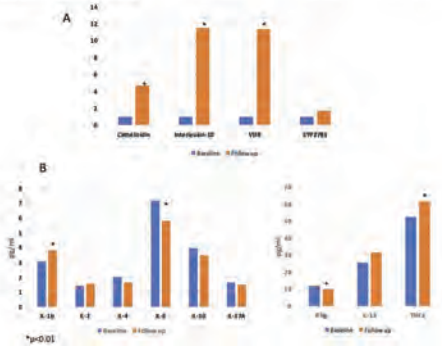
Conclusions: Cholecalciferol supplementation in vitamin D deficient patients with non-diabetic CKD significantly improved the immune and vascular function, inflammatory responses and enhanced the expression of vitamin D responsive.

Funding: Government Support - Non-U.S.

Table 1: Levels of various T cell subpopulation

T cell subpopulation	T cell marker	Baseline (%cells)	Follow up (%cells)	P value
TH1 cells	CD3+CD4+CXCR3+	40 ± 19.27	30.08 ± 15.37	0.736
	CD3+CD4+Tbet+	13.63 ± 13.75	15.41 ± 13.34	0.183
	CD3+CD4+IFNg+	19.32 ± 14.29	23.20 ± 16.75	0.229
TH2 cells	CD3+CD4+IL4+	11.33 ± 9.51	19.72 ± 17.45	0.006
	CD3+CD4+STAT6+	13.63 ± 14.16	13.58 ± 10	0.503
	CD3+CD4+GATA3+	22.09 ± 13.93	21.17 ± 12.26	0.828
TH17 cells	CD3+CD4+IL17+	6.33 ± 6.20	13.22 ± 16.54	0.004
	CD3+CD4+RORgt+	14.19 ± 11.14	15.48 ± 16.20	0.909
Treg cells	CD3+CD4+CD25+	16.42 ± 10.01	17.09 ± 14.34	0.981
	CD3+CD4+CD25+CD127-FOXP3+	3.67 ± 3.55	3.79 ± 2.34	0.270

Figure 1: A) mRNA expression various Vitamin D responsive genes and **B)** levels of pro-inflammatory and anti-inflammatory cytokines at baseline and 16 weeks follow up



FR-PO975

Comparison of the Effect of Benidipine and Amlodipine on Clinical and Biochemical Parameters in CKD with Hypertension and Proteinuria

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Background: Amlodipine targets L-type calcium channels on glomerular afferent arterioles resulting in their dilation, and leading to an increase in intraglomerular pressure and proteinuria. Benidipine blocks L-, N-, and T- type calcium channels which lower efferent arteriolar resistance and intraglomerular pressure, thereby reducing glomerular hypertension and proteinuria. We compared the effect of benidipine and amlodipine on proteinuria, blood pressure and estimated glomerular filtration rate (eGFR).

Methods: Sixty CKD patients with hypertension on maximum tolerated renin-angiotensin blockage whose UPCR (Urine protein creatinine ratio) >150 mg/gm were included in this study. Out of sixty patients, thirty patients were randomly assigned to either amlodipine (n=30) or benidipine (n=30). Blood pressure, serum creatinine, eGFR, UPCR, and serum albumin were monitored at baseline, 3rd month and 6th month. Continuous variables between the study drugs were compared by independent t-test (normal distribution) or Mann–Whitney U test (skewed distribution). Within-group comparisons at each follow-up for both drugs were done by Paired t-test (normal distribution) or Wilcoxon sign rank test (skewed distribution).

Results: Blood pressure decreased in both groups in the 3rd and 6th months. Systolic blood pressure (SBP) has decreased significantly in the benidipine group as compared to the amlodipine group (p-0.0014). UPCR values in benidipine and amlodipine groups changed from 2.89±2.17 to 1.42±1.34 and 2.27±1.46 to 2.47±1.55 after 6 months respectively (p-0.07). Despite not attaining the target systolic blood pressure (SBP<120 mm of Hg), it was observed that there was a significant decrease in UPCR at follow-up visits in the benidipine group. There was no significant change in eGFR in both groups at the end of the study. There was a significant improvement in serum albumin in benidipine-treated patients (p-0.001).

Conclusions: Benidipine is more effective than amlodipine in reducing proteinuria and blood pressure in chronic kidney patients with hypertension

FR-PO976

Impact of Oral Spherical Carbon Adsorbent in Predialysis CKD on Cardiovascular Outcomes and Mineral-Bone Disorder After Dialysis Therapy

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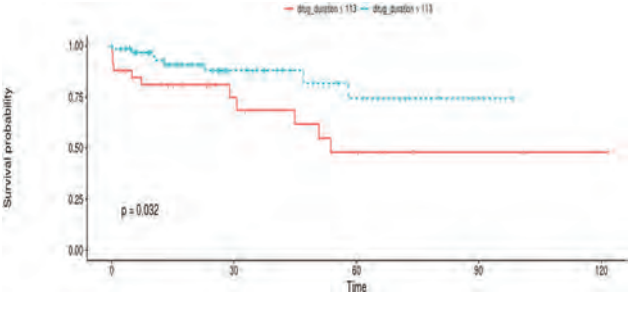
Background: Oral spherical carbon adsorbents (OSCA) are known to slow the progression of chronic kidney disease (CKD) by inhibiting the absorption of uremic toxins produced in the intestine. In this study, we evaluated the impact of using OSCA in pre-dialysis CKD patients on cardiovascular outcomes and mineral-bone disorder after dialysis therapy.

Methods: This study was a retrospective cohort study that enrolled patients who started dialysis therapy including hemodialysis and peritoneal dialysis at Kangdong Sacred Heart Hospital. A total of 294 patients were included in this study, including 98 CKD patients who were administered OSCA before dialysis therapy (OSCA group) and 196 patients who were not administered OSCA with 1:2 matching by age and sex (control group).

Results: The mean age was 62.2 ± 12.7 years, with 60.2% male, and the most common cause of CKD was diabetes (67.0%). The ejection fraction in the echocardiogram was significantly higher in the OSCA group (58.1 ± 9.1 % vs. 55.5 ± 9.9 %, P = 0.033). The cardiovascular events in the control group were higher than those in the OSCA group, however, there were statistically not significant (26.0% vs. 19.4%, P = 0.266). However, the patients who were administered OSCA for more than 113 days showed significantly fewer cardiovascular events after dialysis therapy than those less than 113 days (P = 0.032 by log-rank test), which remained significant in multivariate cox regression analysis (HR 1.48, 95% CI 1.05-2.08, P = 0.025). There was no difference in bone mineral density, pulse wave velocity, bone-specific alkaline phosphatase, parathyroid hormone, and 25(OH) vitamin D levels. In the subgroup analysis of diabetes, all-cause mortality was significantly lower in the OSCA group (27.1% vs. 12.7%, P = 0.029).

Conclusions: The administration of OSCA in CKD patients before dialysis tended to reduce the incidence of cardiovascular events after the start of dialysis therapy, and the longer the period of administration of OSCA, the more significant difference was shown.

Funding: Commercial Support - Daewon Pharmaceutical Co., Ltd.



FR-PO977

Effect of Sodium Bicarbonate Treatment on Cognitive Function in CKD

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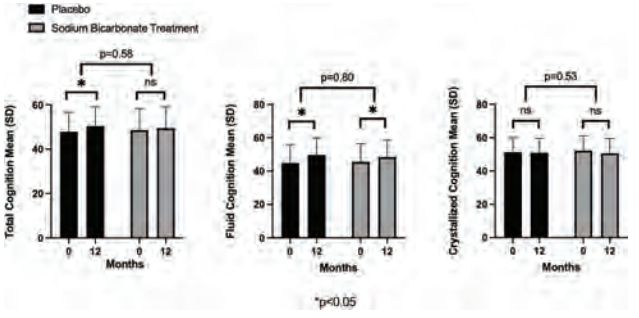
Background: Cognitive impairment, prevalent in adults with chronic kidney disease (CKD), contributes to mortality, functional decline, depression, frailty, and diminished quality of life. Lower serum bicarbonate levels, even within normal parameters, associate with cognitive impairment in CKD. However, the effect of sodium bicarbonate ($NaHCO_3$) supplementation on cognitive function in CKD is not known. We examined the effect of $NaHCO_3$ therapy on cognitive function in patients with CKD stage 3B-4.

Methods: We performed an ancillary study using participants in the Bicarbonate Administration in CKD Trial, which was a randomized prospective, double-blind, placebo-controlled trial of 109 participants with CKD stage 3B-4 (eGFR 15-44 ml/min/1.73m^2) with serum bicarbonate levels 22-27 mEq/L. Participants were randomly assigned to receive either $NaHCO_3$ or placebo at a dose of 0.5 mEq/LBW-kg/day for 12 months. Cognitive function was measured at baseline and 12 months using the National Institutes of Health Toolbox® (NIH-TB) cognitive battery, which assesses fluid cognition (e.g., executive and memory function) and crystallized cognition (e.g., language skills).

Results: 90 patients (50.4% female) with a mean (SD) age of 61.7 ± 11.6 years and eGFR of 35.9 ± 9.8 ml/min/1.73m^2 completed the study. The mean (SD) serum bicarbonate level at baseline was 23.4 ± 2.2 mEq/L. After 12 months, serum bicarbonate levels increased, on average, 1.35 mEq/L (95% CI: 0.34-2.36, p=0.003) in the $NaHCO_3$ group compared to placebo. Both the $NaHCO_3$ and placebo groups had a significant increase in fluid cognition scores after 12 months, but there was no significant difference between the groups (Figure). $NaHCO_3$ therapy did not result in a significant improvement in crystallized or total cognition. $NaHCO_3$ therapy was safe and well-tolerated with no significant changes in blood pressure, anti-hypertensive medication, weight, calcium or potassium levels.

Conclusions: Twelve months of $NaHCO_3$ therapy in patients with moderate to advanced CKD and normal serum bicarbonate levels did not improve cognitive function.

Funding: Other NIH Support - NHLBI



FR-PO978

Observations from the LiFT Study: Lokelma for Maximization of RAASi in Patients with CKD and Heart Failure, Ongoing Trial

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Background: The management of patients with chronic kidney disease (CKD) and heart failure (HF) - CKD-HF poses a clinical challenge. The use of renin-angiotensin-aldosterone inhibitors (RAASi) reduces hospital admissions due to fluid overload and has mortality benefit; however, this is limited by hyperkalaemia, and concerns of worsening renal function. The purpose of this trial is to evaluate the role of sodium zirconium cyclosilicate (SZC) in maximizing of RAASi in CKD-HF. We present preliminary data regarding uptitration of RAASi achieved as part of the study

Methods: This is a double blind, placebo-controlled, phase III randomised control trial. The primary outcome is to compare SZC and Placebo with respect to enabling patients to achieve the maximum tolerated RAASi dose while keeping [K+] < 5.6mmol/L. Secondary outcomes include the number and maximum doses of ACEi/ARBs (angiotensin converting enzyme inhibitors/angiotensin receptor blockers) and MRA (mineralocorticoid receptor blockers) achieved during the study period

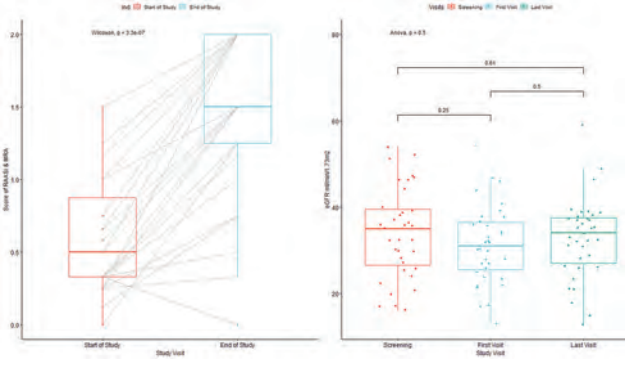
Results: We present preliminary data regarding up-titration of RAASi achieved for 35 patients who have completed the trial so far, having started with none or sub-optimal RAASi. The mean age of participants is 74 years. Of the 35 participants, 34 achieved uptitration to maximum tolerated doses in the treatment duration of 2 to 12 weeks. There was no significant change in the eGFR at end of treatment compared to start

Conclusions: While the study is ongoing preliminary data suggests that rapid maximization of RAASi in this frail, comorbid group can be achieved without detriment to renal function

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

Table 1: Baseline Characteristics at the start and end of treatment duration

	n = 35
Age at enrolment (yrs) (mean (SD))	74.29 (11.22)
Sex (M/F) = M (%)	29 (82.9)
Ethnicity (%)	
Non-Caucasian	11 (31.4)
Caucasian	24 (68.6)
BMI (mean (SD))	27.03 (3.60)
eGFR screening visit (mean (SD))	33.94 (10.39)
eGFR first visit (mean (SD))	31.26 (9.00)
eGFR last visit (mean (SD))	32.74 (9.26)
BNP screening visit (mean (SD))	4258.74 (6759.01)
BNP first visit (mean (SD))	3952.94 (5922.46)
BNP last visit (mean (SD))	4322.97 (7095.21)
RAASi first visit (%)	
Candesartan4 mg OD	1 (2.9)
Candesartan16 mg OD	1 (2.9)
Eplerenone12.5 mg OD	1 (2.9)
Eplerenone25 mg OD	2 (5.9)
Ramipril2.5 mg OD	3 (8.8)
Ramipril10 mg OD	2 (5.9)
Ramipril5 mg ODSpironolactone12.5 mg OD	1 (2.9)
Ramipril7.5 mg OD Eplerenone12.5 mg OD	1 (2.9)
Ramipril10 mg ODSpironolactone25 mg OD	1 (2.9)
Sacubitril/valsartan24/26 mg BD	11 (32.4)
Sacubitril/valsartan49/51 mg BD	4 (11.8)
Sacubitril/valsartan97/103 mg BD	3 (8.8)
Sacubitril/valsartan24/26 mg BDSpironolactone12.5 mg OD	1 (2.9)
Sacubitril/valsartan49/51 mg BDEplerenone25 mg OD	1 (2.9)
Sacubitril/valsartan97/103 mg BDEplerenone12.5 mg OD	1 (2.9)
RAASi last visit (%)	
Candesartan16 mg BDSpironolactone12.5mg OD	1 (2.9)
Candesartan32 mg ODSpironolactone25mg OD	1 (2.9)
Ramipril10 mg ODEplerenone50mg OD	1 (2.9)
Ramipril5 mg ODSpironolactone12.5mg OD	1 (2.9)
Ramipril10 mg ODSpironolactone25mg OD	2 (5.9)
Ramipril10 mg ODSpironolactone50mg OD	2 (5.9)
Sacubitril/valsartan24/26 mg BD	1 (2.9)
Sacubitril/valsartan49/51 mg BD	1 (2.9)
Sacubitril/valsartan49/51 mg BDEplerenone25mg OD	1 (2.9)
Sacubitril/valsartan97/103 mg BD	1 (2.9)
Sacubitril/valsartan97/103 mg BDEplerenone12.5mg OD	3 (8.8)
Sacubitril/valsartan97/103 mg BDEplerenone25mg OD	9 (26.5)
Sacubitril/valsartan97/103 mg BDEplerenone50mg OD	8 (23.5)
Sacubitril/valsartan97/103 mg BDSpironolactone25mg OD	2 (5.9)



FR-PO979

A Phase IIb Randomized, Double-Blind, Placebo-Controlled, Multi-Centre, Dose Ranging Study of Atuliflapon in Participants with Proteinuric CKD

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Background: 5-lipoxygenase activating protein (FLAP) is a key component in the synthetic pathway for leukotrienes and thought to contribute to inflammation and CKD progression. We assessed the albuminuria lowering effect of Atuliflapon (AZD5718), a reversible FLAP inhibitor.

Methods: Participants with proteinuric CKD: eGFR 20 -75 mL/min/1.73m^2; uACR 200-500 mg/g were randomised to three doses of Atuliflapon or placebo. Treatment period 1 of 12 weeks on existing standard of care (SOC), which included SGLT2i in 25% of the DKD patients, was followed by treatment period 2 where all participants initiated 8 weeks treatment with 10 mg dapagliflozin on top of existing SOC.

Results: A total of 613 participants were randomised. Following the results of an interim analysis the Sponsor decided to terminate the study early based on no significant reduction in uACR compared to placebo after 20 weeks of treatment (Table), at which point 438 had completed treatment period 1 and 318 had completed treatment period 2. Median age was 66 years (range 27-87); 65.8% male; Type 2 DM 76.5%; Median eGFR 40 mL/min/1.73m^2. The target of 80% suppression of urinary and plasma leukotriene B4 was achieved. The expected reductions in uACR and eGFR on commencing SGLT2i treatment were seen after the addition of dapagliflozin in the second treatment period. There were no significant safety issues.

Conclusions: Atuliflapon did not significantly reduce uACR in any of the treatment groups compared to placebo.

Funding: Commercial Support - AstraZeneca

Table

Dose Atuliflapon	uACR baseline (mg/g; Geometric mean)	Difference vs placebo after 20 weeks of treatment (% change; 95% CI)	p-value
Placebo	735		
Low	615	-5.49% (-21.37, 13.60)	0.55
Medium	744	-3.58% (-19.74, 15.82)	0.70
High	708	-8.07% (-23.24, 10.10)	0.36

FR-PO980

Design and Baseline Characteristics of the FIND-CKD Trial: Efficacy of Finerenone on Kidney Disease Progression in People with Non-Diabetic CKD

Hiddo J. Heerspink,[1] Rajiv Agarwal,[2] George L. Bakris,[3] David Cherney,[4] Carolyn S.P. Lam,[5] Brendon L. Neuen,[6] Katherine R. Tuttle,[7] Christoph Wanner,[8] Meike Daniela Brinker,[9] Sara Dizayee,[10] Peter Kolkhof,[11] Patrick Schloemer,[12] Paula H. Vesterinen,[13] Vlado Perkovic.[6] On Behalf of the FIND-CKD Steering Committee and Investigators. *[1]University Medical Center Groningen, Groningen, Netherlands; [2]Indiana University School of Medicine, Indianapolis, IN; [3]The University of Chicago Medicine, Chicago, IL; [4]University Health Network, Toronto, ON, Canada; [5]National Heart Centre Singapore and Duke-National University of Singapore, Singapore, Singapore; [6]The George Institute for Global Health, Sydney, NSW, Australia; [7]Providence Washington, Seattle, WA; [8]Universitatsklinikum Wurzburg, Wurzburg, Germany; [9]Cardiology and Nephrology Clinical Development, Bayer AG, Wuppertal, Germany; [10]Regulatory Strategy Cardiology and Nephrology, Bayer AG, Wuppertal, Germany; [11]Preclinical Research Cardiovascular, Research and Development, Bayer AG, Wuppertal, Germany; [12]Statistics & Data Insights, Bayer AG, Berlin, Germany; [13]Cardiology and Nephrology Clinical Development, Bayer AG, Espoo, Finland.*

Background: Finerenone, a selective, nonsteroidal mineralocorticoid receptor antagonist, improved kidney and cardiovascular (CV) outcomes in people with CKD and type 2 diabetes (T2D) in two phase 3 outcome trials. However, CKD is due to non-diabetic etiologies in most people across many parts of the world. The effects of finerenone on kidney outcomes in people with CKD without diabetes are being investigated in the FIND-CKD trial (NCT05047263 and EudraCT: 2021-000421-27).

Methods: FIND-CKD is a randomized, double-blind, and placebo-controlled phase 3 trial for people with CKD of non-diabetic etiology. People with a urine albumin-to-creatinine ratio of ≥200–≤3500 mg/g and estimated glomerular filtration rate (eGFR) ≥25–<90 ml/min/1.73 m^2 at screening are randomized 1:1 to once daily 10 or 20 mg finerenone or placebo on top of optimized renin-angiotensin system blockade. The primary efficacy outcome is total eGFR slope, defined as the mean annual rate of change in eGFR from baseline to month 32. Secondary efficacy outcomes include a combined cardiorenal composite outcome comprising time to kidney failure, sustained ≥57% decrease in eGFR, hospitalization for heart failure or CV death, as well as separate kidney and CV composite outcomes. Adverse events are recorded to assess tolerability and safety.

Results: The FIND-CKD trial will study the efficacy and safety of finerenone in people with non-diabetic causes of CKD at high risk of disease progression. The first patient was enrolled in September 2021 and patient enrolment completed in May 2023. Baseline clinical characteristics and demographics will be presented.

Conclusions: FIND-CKD is the first phase 3 trial of finerenone in people with CKD of non-diabetic etiology. This trial will determine the potential expanded role for finerenone for the treatment of CKD beyond T2D.

Funding: Commercial Support - The study and this analysis were funded by Bayer AG, Wuppertal, Germany. Medical writing and/or editorial assistance was provided by Charlotte Simpson, PhD, and Melissa Ward, BA, both of Scion, London, UK. This assistance was funded by Bayer AG, Wuppertal Germany according to Good Publication Practice guidelines.

FR-PO981

Effects of Empagliflozin on Weight and Blood Pressure in CKD: Analyses from the EMPA-KIDNEY Trial

Kaitlin J. Mayne.[1,2] The EMPA-KIDNEY Collaborative Group. *[1]University of Oxford Nuffield Department of Population Health, Oxford, United Kingdom; [2]University of Glasgow College of Medical Veterinary and Life Sciences, Glasgow, United Kingdom.*

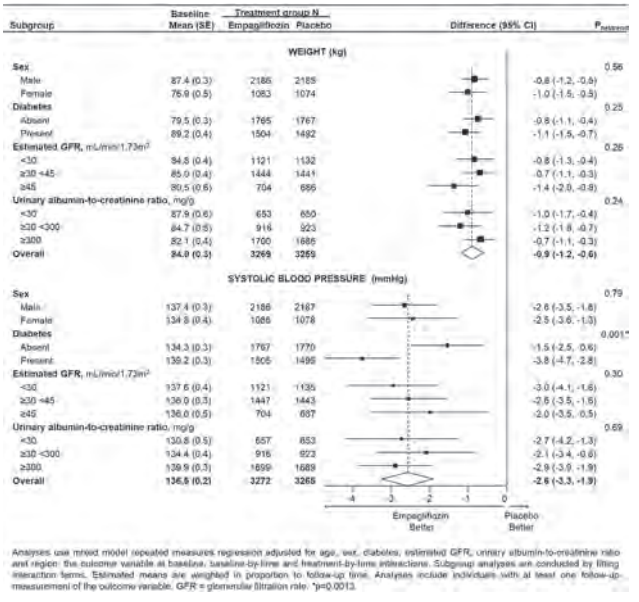
Background: Sodium-glucose co-transporter-2 (SGLT2) inhibitors slow kidney disease progression and reduce cardiovascular risk in patients with CKD. SGLT2 inhibitors have additionally been shown to reduce weight and blood pressure (BP). We aimed to assess whether diabetes status or kidney function modify the effects of empagliflozin on weight and BP.

Methods: EMPA-KIDNEY compared empagliflozin 10 mg once daily with placebo among 6609 patients with CKD (Clinicaltrials.gov: NCT03594110). Eligible patients had an eGFR of 20 to <45; or 45 to <90 ml/min/1.73m^2 with a urinary albumin-to-creatinine ratio (uACR) ≥200 mg/g. Changes in weight and blood pressure from baseline were pre-specified analyses using mixed model repeated measures regression. Results were assessed overall and in important subgroups and put in the context of a bioimpedance substudy of 660 participants which is reported separately.

Results: At baseline, mean±SD eGFR was 37.3±14.5 mL/min/1.73m^2 with mean weight of 84.1±21.4 kg, and mean systolic and diastolic BP were 136.5±18.3 and 78.1±11.8 mmHg, respectively. The study-average between-group difference in weight was -0.9 (95% CI -1.2, -0.6) kg with similar-sized effects in all subgroups (Figure). Effects on weight persisted over time and bioimpedance analyses in a 660-participant substudy demonstrated that it reflected reductions in intracellular and extracellular water with no significant effect on adiposity. The study-average between-group differences (95% CI) in systolic and diastolic BP were -2.6 (-3.3, -1.9) and -0.5 (-0.9, -0.1) mmHg, respectively, with similar difference by baseline eGFR and uACR, but somewhat larger effects in patients with diabetes.

Conclusions: In a broad range of patients with CKD, empagliflozin reduces weight and BP, even at low eGFR, low uACR and in the absence of diabetes.

Funding: Commercial Support - Boehringer Ingelheim & Eli Lilly



Analyses use mixed model repeated measures regression adjusted for age, sex, diabetes, (estimated) GFR, urinary albumin-to-creatinine ratio and region; the outcome variable at baseline, baseline-by-time and treatment-by-time interactions. Subgroup analyses are conducted by fitting interaction terms. Estimated means are weighted in proportion to follow-up time. Analyses include individuals with at least one follow-up measurement of the outcome variable. GFR = glomerular filtration rate. *p=0.0013.

FR-PO982

Albuminuria-Lowering Effect of Sodium-Glucose Cotransporter 2 Inhibitors, Finerenone, and Their Combination in Patients with CKD

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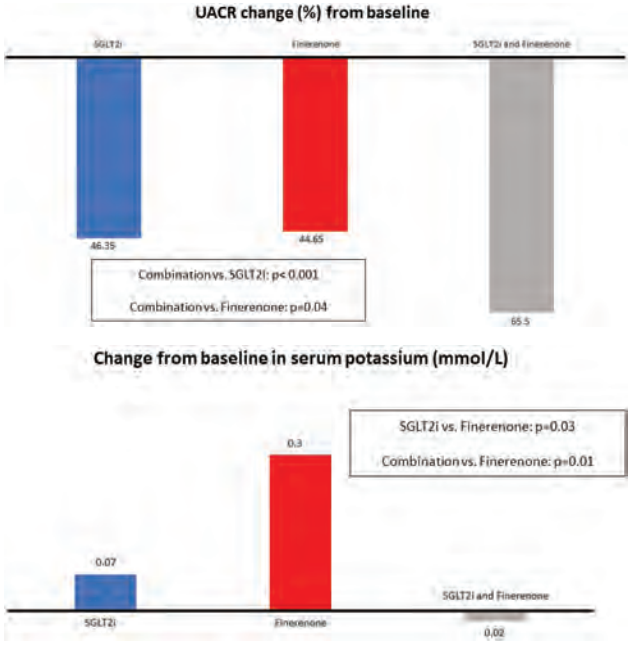
Background: Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2is) and Finerenone reduce urine albumin-to-creatinine ratio (UACR) and confer kidney and cardiovascular protection in patients with Chronic Kidney Disease (CKD).

Methods: We conducted a retrospective study in patients seen in a community nephrology practice with eGFR 25-90 ml/min per 1.73 m2 and UACR ≥30 mg/g Cr. Patients were stratified into 3 groups: 8 months treatment period with SGLT2is, 4 months treatment period with Finerenone, and 8 months with combination therapy (SGLT2i for 4 months followed by SGLT2i and Finerenone for additional 4 months). The outcome was the percent change in UACR from baseline.

Results: Of 402 patients screened between 1/2022 and 9/2023, 85 were included with mean eGFR, 51.5 ml/min per 1.73 m2, and median UACR 594 mg/g. 47 patients received SGLT2i (dapagliflozin 10 mg/day or empagliflozin 10 mg/day), 19 received Finerenone

(20 mg/d for eGFR > 60 or 10 mg/d for eGFR 25-60, and 19 were on combination therapy. The mean percentage change from baseline in UACR in the SGLT2is group and Finereone group was -46.35% (95% CI, -53.39 to -39.31) and -44.65% (95% CI, -68.67, -20.64), respectively. SGLT2i-Finerenone combination therapy decreased UACR by -65.5% (95% CI, -71.82, -59.17; P<0.001 vs SGLT2i; P=0.04 vs Finerenone) (Fig 1). Compared with the Finerenone group, the mean change in serum potassium level (mmol/L) was significantly lower in the combination group (+ 0.3 vs -0.02, P=0.01). (Fig 2)

Conclusions: Combining dapagliflozin or empagliflozin with Finerenone resulted in a significantly additive UACR-lowering effect with a significant decrease in the risk of hyperkalemia.



FR-PO983

Dapagliflozin Suppresses Urinary Biomarkers of Kidney Damage Regardless of Proteinuric Levels in CKD

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Soonchunhyang University Hospital, Seoul, Republic of Korea.

Background: Sodium glucose cotransporter 2 inhibitor (SGLT2i) reduce the risk of chronic kidney disease (CKD) progression in individuals with or without diabetes mellitus (DM). However, the beneficial effect of SGL2i on CKD patients with low levels of proteinuria has not been established. The objective of this study was to compare the effect of dapagliflozin on biomarkers of kidney injury in CKD patients stratified by albuminuria level.

Methods: We prospectively enrolled healthy volunteers (HVs) (n=20) and CKD patients (n=43) with or without DM. The CKD group received dapagliflozin (10mg). Urine and serum samples were collected before treatment and 3 and 6 months after administration of dapagliflozin. We measured kidney injury molecule-1 (KIM-1), interleukin-1β (IL-1β) and mitochondrial DNA nicotinamide adenine dinucleotide dehydrogenase subunit-1 (mtND1) copy number in the urine.

Results: Age did not differ between HV and CKD patients (52.05 ± 8.13 vs 53.90 ± 14.96 years, p=0.774). The estimated glomerular filtration rate (eGFR) level of CKD patients was lower than that of HV (62.55 ± 24.22 vs 94.95 ± 11.21 mL/min, p < 0.001). Among the CKD patients, 11 % (n=5) had diabetes. The median urinary albumin/creatinine ratio (uACR) in CKD patients was 339.80 mg/g (IQR 80.0-647.0 mg/g). Kidney injury markers were significantly elevated in the CKD patients compared to the HVs. Dapagliflozin reduced urinary KIM-1, IL-1 β and mtND-1 in CKD at 6 months after treatment (p < 0.001, p < 0.001 and p = 0.021, respectively). Futhermore, when CKD patients were divided into two groups according to uACR level (< 300 mg/g, ≥ 300 mg/g), dapagliflozin decreased urinary KIM-1 and IL-1β at 3 months after treatment in the high albuminuria group (n=22) (p=0.034 and p=0.047, respectively). In the low albuminuria group (n=20), uKIM-1 and IL-1β decreased after 6 months of dapagliflozin treatment (p=0.004 and p=0.0021). However, dapagliflozin did not change uACR and eGFR during the study period.

Conclusions: CKD patients with high albuminuria showed an earlier response to dapagliflozin compared to those with low albuminuria. Nevertheless, dapagliflozin demonstrated a reduction in urinary kidney injury biomarkers in CKD patients regardless of proteinuria levels. These findings suggest that SGLT2i may attenuate the progression of low proteinuric CKD.

Funding: Government Support - Non-U.S.

FR-PO984

A Novel Titratable Pig Model of Mild, Moderate, and Severe CKD

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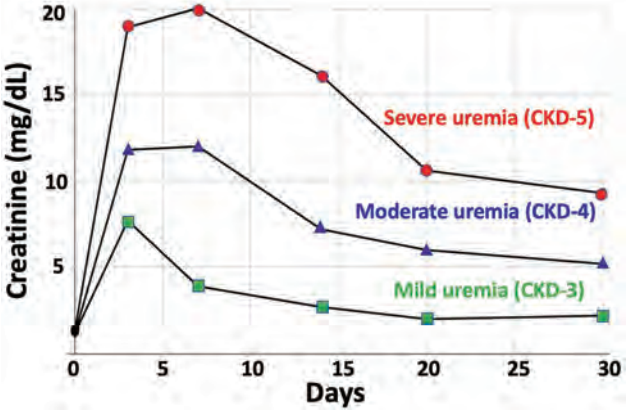
Background: Patients with CKD stages 3-5/ESKD have a very significant cardiovascular (CV) and peripheral vascular morbidity and mortality characterized by a "reverse epidemiology". Despite the magnitude of the clinical problem there has been minimal investigation into the impact of different levels of uremia on vascular complications (cardiovascular *and* vascular access) in CKD/ESKD patients. In order to address this unmet translational science need we aimed to surgically induce differing levels of uremia corresponding to CKD stages 3-5 in a pig model.

Methods: Yorkshire Cross pigs underwent a unilateral nephrectomy followed by selective ligation of the arterial tree of the contralateral kidney in order to leave 30% (mild CKD), 15% (moderate CKD) or 7.5% (severe CKD) only of the contralateral kidney with viable perfusion.

Results: Fig 1 describes the initial rise in creatinine followed by a stable creatinine (days 20-30) in the three groups above. Initial data also documents increased levels of known uremic vascular toxins such as indoxyl sulphate and para cresol in the uremic pigs. Importantly, the pigs remained responsive at high creatinine levels (upto 20mg/dL) and did not have significant hyperkalemia.

Conclusions: The described titratable uremic pig model will allow us to (a) describe the concentrations of known uremic vascular toxins such as indoxyl sulphate at different levels of CKD severity (b) perform "omic" analyses on vascular tissue at different levels of CKD severity both prior to and following vascular injury and (c) identify uremia specific pathways of vascular injury that could result in the identification of novel biomarkers and druggable targets for CV risk stratification and future CV therapeutic intervention respectively in CKD patients.

Funding: Veterans Affairs Support



FR-PO985

A Novel Mouse Model: Authentic Reproduction of Human CKD

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Background: Animal models are vital for understanding chronic kidney disease (CKD) pathogenesis and developing effective treatments. However, existing models fail to accurately replicate typical changes in human CKD. We present a novel mouse model faithfully recapitulating key aspects of human chronic kidney diseases.

Methods: We employed the *Pax8*-rtTA transgenic mouse model with high expression of the reverse tetracycline-dependent transactivator (rtTA) in kidney tubules under the control of the *Pax8* promoter. Through crossing *Pax8*-rtTA mice with tetracycline-responsive Jun mice, an inducible CKD-JUN model was established, resulting in *Jun* overexpression specifically in kidney tubules upon doxycycline administration. Control mice were generated without doxycycline or *Jun* expression. Ten-week-old mice received continuous doxycycline (0.5 mg/ml) in their drinking water for 2 or 12 weeks. Body weight and kidney size were measured. Blood urea nitrogen (BUN) and serum creatinine were determined. Kidney tissue was subjected to H&E, PAS, and Trichrome staining to evaluate histological changes. Renal inflammation was evaluated through Luminex analysis of cytokine secretion in serum and kidney tissue supernatants, along with assessment of immune cell infiltration.

Results: Following a 2-week induction, histological analysis confirmed acute tubular necrosis in CKD-JUN mice, validating early tubular injury due to Jun induction. After a 12-week induction, both male and female CKD-JUN mice exhibited stable kidney impairment, with males showing a higher propensity for chronic kidney injury and faster CKD progression. CKD-JUN mice displayed decreased body weight, reduced kidney size, elevated BUN and creatinine levels indicative of renal function failure, increased pro-fibrotic inflammatory cytokines in serum and kidney tissue supernatants, and histological signs of glomerular hypertrophy, tubular dilation, interstitial fibrosis, and inflammatory cell infiltration. Other organs in CKD-JUN and Control mice showed no significant

differences, confirming the kidney-specific nature of this model. These findings closely resemble characteristic renal abnormalities observed in human CKD.

Conclusions: Our CKD-JUN mouse model faithfully recapitulates essential clinical and histological characteristics of human CKD, making it a reliable and invaluable tool for studying CKD mechanisms and evaluating therapeutic interventions.

FR-PO986

Transcriptome-Wide Association Study Identified USP24 as a Kidney Disease Risk Gene

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Background: Established transcriptome- wide association study (TWAS) have shown lower USP24 expression in kidneys associated with higher eGFR. USP24 has been shown to deubiquitinates proteins associated with apoptosis, DNA repair, and inflammation in tumor cells. However, the role of USP24 on kidney diseases is not well described. We believe the elucidation of the function of USP24 on kidneys help to achieve the future precision medicine.

Methods: LocusZoom was used to visualize single nucleotide polymorphisms (SNPs). Correlated gene expression and pathway analysis was examined using the database of around 400 human kidneys. An established single-cell database was used to annotate cell types expressing USP24. Immunostaining of USP24 with renal tubule markers was examined in kidneys from humans and various mice models CRISPR-CAS9 system was used to generate tubule-specific USP24 deletion mice. Immunoprecipitation analysis was attempted for exploring protein-protein interaction.

Results: The SNPs highly associated with eGFR and USP24 expression in kidneys were located near the promotor regions, and these SNPs had strong linkage disequilibrium ($r>0.8$). The alternative allele of top SNP (rs17413465) showed a positive Z-score for eGFR GWAS, and negative beta value with USP24 expression in kidney eQTL, indicating higher USP24 expression associated with lower eGFR. Kidney single-cell data showed higher USP24 expression in renal tubule cells compared to non-tubule cells. Double immunofluorescent staining of USP24 with tubule marker, KSP validated the expression of USP24 in renal tubules. Gene correlation analysis in a large scale of human kidney samples showed enrichment of genes correlated with USP24 expression in biological pathways related to chromatin modification, and DNA repair, consistent with the previous reports. Successful insertion of the floxed allele next to USP24 with the CRISPR-CAS9 system was confirmed by genotyping PCR. The cloning of USP24 from cultured mice renal tubules and insertion of HaloTag to the C-terminal of USP24 was confirmed by subsequent DNA sequence.

Conclusions: Multi-omics analysis and experimental analysis suggested lower expression of USP24 in renal tubules might protect from kidney dysfunction by modulating chromatin status and DNA repair.

FR-PO987

Mitochondrial Aldehyde Dehydrogenase rs671 Single Nucleotide Polymorphism Increases the Susceptibility of Kidney Injury in Adenine-Induced CKD Mice

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Background: In Taiwan, chronic kidney disease (CKD) and end stage kidney disease are major public health issues. Genetic factors increase the susceptibility and severity of kidney diseases. Genome-wide association studies have discovered hundreds of genomic loci associated with CKD. However, which genes are critical contributors to CKD remain unclear. ALDH2 is a mitochondrial enzyme and plays a central role in the liver to metabolize acetaldehyde produced from ethanol into acetate. In addition to liver, ALDH2 is also highly expressed in the kidney, especially in kidney tubular cells. ALDH2 gene has a variant ALDH2*2 allele (rs671) that appears to be the most prevalent in Han Chinese and Taiwanese as higher than 40% in population. Individuals who carry ALDH2*2 allele have lower ALDH2 enzyme activity. Thus far, limited studies investigate genetic polymorphisms of ALDH2 on chronic kidney disease. In this study, we investigated whether ALDH2*2 variants could increase susceptibility to kidney injury.

Methods: We conducted an animal model that male C57BL/6 mice and ALDH2*2 knock-in mice were treated with 100 mg/kg body weight/day of adenine in drinking water to induce early stage CKD. Transdermal GFR measuring system and urine albumin-creatinine ratio (uACR) were used to monitor kidney function. We applied Periodic Acid-Schiff (PAS) staining, Masson trichrome staining, TUNEL assay, MitoSOX staining, real-time PCR and Western blotting to observe kidney injury, fibrosis, apoptosis, mitochondrial ROS, mitochondrial DNA (mtDNA) copy number and related protein expression, respectively.

Results: We found that declined kidney function, tubular damage, tubulointerstitial fibrosis and apoptosis were enhanced in the ALDH2*2 knock-in mice, compared to the wild-type mice. The biomarkers of oxidative stress (MDA, 4-HNE), inflammasome (NLRP3) and fibrosis (Collagen I) were significantly elevated in the kidney of ALDH2*2 knock-in mice. We also observed increased mitochondrial ROS, decreased mtDNA copy number and differential expressed mitochondrial dynamic proteins (Pink1, Parkin, Mfn2, Opa1, Drp1, Fis1) in the kidney of ALDH2*2 knock-in mice.

Conclusions: Our findings suggest that the carrier of ALDH2*2 variant may be more susceptible to kidney injury due to mitochondrial dysfunction.

Funding: Government Support - Non-U.S.

FR-PO988

Shared and Distinct Renal Transcriptome Signatures in Three Standard Mouse Models of CKD

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Background: Various mouse models with differing disease etiologies are available in preclinical chronic kidney disease (CKD) research. Characterizing these models according to their renal transcriptomics enables better selection of the optimal model for preclinical drug discovery studies. We therefore characterized the kidney transcriptome signature of three well-established models of CKD, i.e. unilateral ureter obstruction (UUO), unilateral ischemic reperfusion injury (uIRI) and adenine-supplemented diet feeding (ADI).

Methods: Male C57BL/6J mice were used in all studies. Mice underwent UUO or uIRI surgery and were terminated two- and six-weeks post-surgery, respectively. Sham-operated mice served as controls. For ADI, mice received an adenine-supplemented diet or control diet for six weeks. Endpoints included plasma biochemistry, kidney histology and RNA sequencing.

Results: All three models displayed increased macrophage infiltration (F4/80) and fibrosis (Col1a1). An excessive number of renal differentially expressed genes (≥11,000) was observed in all three models, with a notable overlap in their transcriptome signatures. Gene expression markers of inflammation, fibrogenesis and kidney injury supported histological findings in the models. A subset of genes showed model-specific changes, including genes representing current drug targets for CKD (e.g., Ednrb, Nr3c2, Glp1r, Flt1 and Ptch1), emphasizing the applicability of the three CKD models in preclinical target and drug discovery.

Conclusions: While the UUO, uIRI and ADI mouse models of CKD demonstrate notable commonalities in renal transcriptome signatures, model-specific transcriptional changes in genes encoding current drug targets emphasize that the three models have different utility in preclinical drug discovery.

Funding: Commercial Support - Gubra A/S

FR-PO989

Characterising Human Kidney Disease Using Single-Cell Resolution Spatial Transcriptomics

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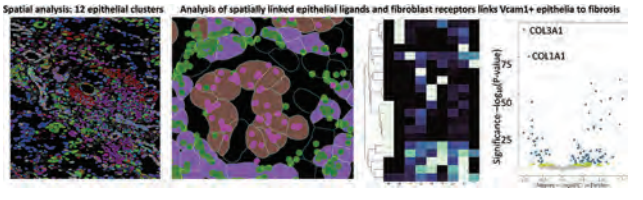
Background: There is accumulating evidence of the role played by subsets of transcriptionally altered epithelia in the progression of experimental chronic kidney disease (CKD) (Muto et al 2021, Mylonas et al 2021). Whilst bulk and single cell RNA-seq analysis has increased our understanding of kidney biology – the lack of spatial context has limited efforts to identify pathways by which inflammatory Vcam1+ epithelia, leukocytes and fibroblasts interact within the human kidney. Advances in spatial sequencing now provide single cell resolution analysis in formalin fixed, paraffin embedded renal biopsies. We hypothesized that spatial analysis of cell-cell signalling in human kidneys would uncover signalling pathways relevant to progressive chronic kidney disease

Methods: We used the NanoString CosMx spatial molecular imager to analyse ~1000 RNA transcripts in 13 human renal biopsies spanning benign (minimal change disease, MCD) non progressive IgAN and progressive IgAN CKD (defined as >30% eGFR loss over study period).

Results: Interrogating our spatial dataset, we identified 19 transcriptionally distinct cell types – including previously published and novel Vcam1+ epithelia from proximal tubules and loop of Henle. Analysis was undertaken on Vcam1+ epithelia in patient biopsies of MCD and IgAN. Assessment of ligand receptor signalling pathways between Vcam1+ epithelia, leukocytes and fibroblasts within 50microns revealed multiple spatially linked ligand/receptor pathways (see Figure below). One example was the spatial link between reduced Vcam1+ epithelia<>fibroblast distance and increased fibroblast Col1a1 and Col3a1 production (n=10,935 total fibroblasts, all $p<0.0001$ vs spatially distant SC/fibroblast pairings, with reduced mean distance in progressive IgAN vs MCD).

Conclusions: Our data demonstrates the ability of spatial transcriptomic analysis to identify and map multiple transcipts and ligand/receptor pairings. The addition of spatial information adds additional information about putative signalling pathways in disease progression

Funding: Commercial Support - Research Grant awarded by NanoString, Government Support - Non-U.S.



FR-PO990

A Novel Method to Identify and Visualize Senescent Cells In Vivo with High Sensitivity

Ryo Yamada,[1] Takuya Morinishi,[1] Yohei Iwashige,[1] Koji Muro,[1] Shigenori Yamamoto,[1] Toshio Kitamura,[2] Motoko Yanagita.[1] Cell Cycle Group. *[1]Kyoto Daigaku Daigakuin Igaku Kenkyuka Igakubu, Kyoto, Japan; [2]Koeki Zaidan Hojin Kobe Iryo Sangyo Toshi Suishin Kiko, Kobe, Japan.*

Background: Cellular senescence occurs in response to repeated passages, persistent DNA damage, and oxidative stress and is characterized by permanent growth arrest. Recently, it has been noticed that senescent cells accumulate *in vivo* and correlate with organ dysfunction, but a highly sensitive method to identify senescent cells *in vivo* has not yet been established.

Methods: The cell cycle of proximal tubular cells was evaluated in mice expressing the proximal tubule-specific G0 marker (*Ndrg1CreER^{T2}:R26-mVenus-p27K^{-}*). The G0 marker is mVenus-p27K^{-}, a fusion protein that combines the fluorescent protein mVenus with CDK inhibitor p27^{Kip1} mutant p27K^{-} (p27 protein without CDK inhibitory function), and is usually used to identify cells in quiescent phase (G0 phase). Using this mouse line, we analyzed cell cycle of proximal tubular cells after DNA damage caused by aristolochic acid and cisplatin nephropathy models. We also performed spatial transcriptomics of G0 marker-positive cells using photo-isolation chemistry (PIC)-based system.

Results: In G0 marker mice, almost all proximal tubular cells remained in the G0 phase under physiological conditions. In the chronic phase of kidney injury, most proximal tubular cells were G0 marker-positive, but some G0 marker-positive cells exhibited nuclear abnormalities, such as nuclear enlargement. Surprisingly, immunohistochemical analysis revealed the G0 marker-positive cells with nuclear abnormalities expressed high levels of cyclin D1 along with the G0 marker (G0^{+}CycD1^{high}), which was inconsistent with normal cell cycle. The PIC-based RNAseq study showed that G0^{+}CycD1^{high} cells exhibited the characteristic features of “Injured PTC” and “Senescence” compared with G0^{+} cells in the vehicle group. We also isolated primary proximal tubular cells from G0 marker mice and induced senescence. Time-lapse imaging assays revealed that these senescent cells continuously expressed G0 marker. Furthermore, most of the senescent cells with G0 marker expressed Cyclin D1 and had enlarged nuclei.

Conclusions: Our data suggest that G0 marker mice can be a useful tool for identifying senescent proximal tubular cells both *in vivo* and *in vitro*, in combination with cyclin D1 expression. This system can be used to identify new markers of cellular senescence *in vivo* and evaluate the efficacy of senolytic treatments.

FR-PO991

Multiplexed Imaging of Senescent Chromatin States in Single Cells in Kidney

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Background: The gradual loss of kidney function with age and disease can be linked to changes in physiology and single cell epigenetics. As cells become stressed or damaged from these conditions, they undergo the process of becoming senescent, a state of permanent cell cycle arrest associated with massive chromatin rearrangement, as a way to mitigate further damage. The order of events and extent of epigenetic changes within single cells and their correlation to physiological alterations as the kidney ages or becomes diseased and senescence forms are not fully understood.

Methods: Super-resolution optical microscopy techniques were used with advanced chemical labeling methods to concurrently study epigenetic states and nanoscale physiology in mouse kidney slices. We used multiplexed imaging to simultaneously study histone marks, gene loci, and tissue morphology at the single cell level.

Results: The use of optical super-resolution techniques allows for ~70 nm spatial resolution. Multiple histone modifications have been detected and quantified at locations of repetitive DNA sequences (telomeres, major and minor satellites) and genes of interest (e.g. *Nphs2*, *CDKN1a/2a, PAI-1*) in single cells with a high degree of accuracy. In the same sample, these single cell epigenetic signatures were correlated with nanoscale features within glomeruli. The quantification of these nanoscale features includes the glomerular basement membrane thickness, width of individual podocyte foot processes, and the size of endothelial fenestrations. Multiplexed imaging has allowed for the use of 6-8 unique stains in one sample, with the potential for more.

Conclusions: The combination of these advanced labeling methods and super-resolution optical microscopy techniques allow for an unprecedented view and correlation of single cell epigenetic states and nanoscale physiology in kidney tissue at many age points. Our approach has implications for identifying specific epigenetic changes in the kidney that precede the development of senescence and related diseases and their physiological markers. Understanding the sequence of events may assist in predicting disease formation along with studying the effectiveness of various treatments.

Funding: NIDDK Support, Other NIH Support - NIGMS T32GM008268

FR-PO992

Aging Alters Microenvironmental Cues for Gli1+ Myofibroblast Progenitors to Promote Tissue Remodeling in the Kidneys

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Background: Aging is associated with decreased renal function as well as tissue alteration including interstitial fibrosis. We previously identified Gli1+ myofibroblast progenitors that contribute to tissue fibrosis in the kidney and other organs. However, the role of this cell type in aging-induced alteration in the kidney remains elucidated.

Methods: We genetically labeled Gli1+ cells in Gli1-CreERt2; R26-tdTomato mice by pulsing with tamoxifen at 8 weeks of age and chasing them until 12 weeks (young) or 2 years of age (old). We sorted tdTomato+ cells and performed bulk RNA-seq. We also performed single nucleus transcriptomic analysis (snRNA-seq) on these mouse kidneys (n=3 pairs: 12 weeks vs 2 years of age) using 10x Genomics platform.

Results: We identified tdTomato+ cells in 2-year-old mouse kidneys labeled at 8 weeks of age. Bulk RNA-seq on sorted tdTomato+ cells from aged kidneys showed a tissue-remodeling gene expression signature with increased *Ccn2*, *Serpina1b*, *Mmp3* expressions. We performed snRNA-seq on these mouse kidneys and identified all major cell types (35,592 nuclei from n=3 young and old kidneys; 19 cell types). We observed a large cluster of immune cells as well as emergence of *Vcam1*+ failed-repair proximal tubular cells (FR-PTC) with pro-inflammatory and pro-fibrotic gene expression signature in aged kidneys. Immunofluorescence analysis validated Vcam1+ atrophic tubules in 2-year-old mouse kidneys. Intercellular communication inference based on snRNA-seq data indicated interactions between FR-PTC and fibroblast/pericyte cluster through molecules modifying tissue fibrosis (*Tgfb2, Spp, Pdgfd, Bmp6*). Endothelin expressed in FR-PTC was also predicted to target fibroblast/pericytes in 2-year-old mice. In situ hybridization validated high level of *Edn1* expression in *Vcam1*+ tubular cells, suggesting a potential role of endothelin to mediate interaction between FR-PTC and Gli1+ myofibroblast progenitors to promote interstitial fibrosis in elderly population.

Conclusions: By combining long-term lineage tracing and snRNA-seq we elucidated a molecular interaction between Gli1+ myofibroblast progenitor and FR-PTC. Targeting this interaction may mitigate age-related renal fibrosis.

Funding: NIDDK Support

FR-PO993

Lineage-Tracing Experiments of Senescent Cell Marker p16INK4a-Positive Cells Show that Kidney Aging Proceeds on a Nephron-by-Nephron Basis

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Background: Senescent cells in *in vitro* experiments are the cells that have permanently arrested the cell cycle and acquired senescence-associated secretory phenotypes. p16^{INK4a} is a known marker for senescent cells. However, the lack of good antibodies has made it difficult to identify p16^{INK4a}-positive cells *in vivo* and to elucidate their distribution and dynamics in tissues.

Methods: We lineage-traced senescent cells using p16Cre^{ERT2}:R26-tdTomato mice, where tdTomato (tdT) was induced by tamoxifen in the cells with p16^{INK4a} activity. We analyzed the localization of tdT+ cells in aged mice and young mice with kidney injury models, specifically focusing on the proximal tubules (PTs). Using the novel photo-isolation chemistry (PIC) technology, which allows us to obtain RNA from a single cell in tissue sections, we compared PIC-RNAseq in three groups: tdT+ proximal tubular cells (PTCs), tdT- PTCs located in PTs with or without tdT+ PTCs.

Results: Among the other segments, the PTs had the highest number of tdT+ cells. Interestingly, the number of tdT+ PTCs was significantly higher in old female mice than that in young female mice, whereas there was no difference between young and old male mice. Furthermore, tdT+ PTCs were significantly increased in female mice with ovariectomy as well as in male mice that received irradiation. Tissue clearing and three-dimensional imaging of the kidneys of aged female mice revealed a unique localization of tdT+ PTC, which clustered and contiguous within the same nephron. PIC-RNAseq showed shared gene expression patterns between tdT+ PTCs and tdT- PTCs located in the same PTs, and genes involved in ER stress, stress response and post-translational modifications were heterogeneously enhanced in these cell groups compared with tdT- PTCs in PTs without tdT+ PTCs. These results were further confirmed by immunostaining.

Conclusions: We found that senescent cells clustered in the same proximal tubules in aged kidneys and that senescent cells and non-senescent cells that reside in the same tubule shared common characteristics. These results indicated that kidney aging occurs at the nephron level, which is important for future therapeutic strategies.

FR-PO994

Skeletal Muscle Mitochondrial Dysfunction in Patients with CKD and Heart Failure (HF)

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Background: Skeletal muscle dysfunction is a well-known cause of decreased physical performance and quality of life in patients with CKD and HF. While muscle mitochondrial dysfunction has been proposed as a possible mechanism in patients with either CKD or HF. The incremental effect of co-existing HF and CKD is not studied in detail. We hypothesized that the presence of HF and CKD is associated with worse mitochondrial function and physical performance compared to CKD alone.

Methods: In this cross-sectional study, we examined 24 patients, 6 with CKD Stage 3-5 with a clinical diagnosis of HF, and 18 with CKD Stage 3-5 without HF. Patients on dialysis were excluded. ^{31}Phosphorus magnetic resonance spectroscopy (^{31}P-MRS) was

used to measure PCr recovery time after exercise. A longer PCr recovery results in a greater time constant tau (τ), which indicates worsening mitochondrial function. Physical performance was measured with the six-minute walk test (6MWT) and repeated chair stand test.

Results: Groups were similar in terms of age, gender, race, and eGFR. Patients with co-existing CKD and HF presented a prolonged time constant compared to patients with CKD alone [CKD/HF: 77.825 (71.2, 82.515) *vs.* CKD alone: 48.41 (41.13, 49.175), p<0.001, **Figure 1A**] Patients with co-existing CKD and HF walked a shorter distance than patients with CKD alone [CKD/HF: 372 (294, 395) *vs.* CKD alone: 491 (417, 519.5) meters, median (IQR), p=0.003, **Figure 1B**].

Conclusions: Our results suggest that presence of HF worsens mitochondrial dysfunction in patients with moderate to advanced CKD. Similar adverse impact of HF is observed in physical performance measures. Future studies should evaluate the mechanisms leading to muscle dysfunction in these two chronic diseases to provide new insights into novel therapeutic targets.

Funding: NIDDK Support, Other NIH Support - National Center for Research Resources grant 1UL-1RR024975

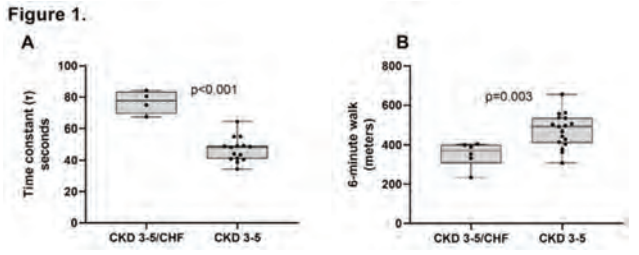

Figure 1

	Median (Interquartile Range)		
Characteristic	*CKD without HF (n=18)*	*CKD with HF (n=6)*	*p-value (1)*
Age (years)	68 (65,69)	69.50 (65, 71.5)	0.28
Male, n (%)	10 (55.5)	5 (83.3)	0.24 (2)
African American origin, n (%)	5 (27.7)	1 (16.6)	0.25 (2)
Body Mass Index (kg/m^2)	29.7 (24.9, 34.6)	30.0 (24.15, 35,75)	0.87
GFR (ml/min/1.73m^2)	47 (36,51)	28 (13,40)	0.49
SBP (mmHg)	130 (127, 139)	146 (137,158.5)	0.415
DBP(mmHg)	73 (67.5, 78)	69.5 (63,76)	0.378
History of diabetes, n (%)	3 (16.6)	2 (33.3)	0.37 (2)
Six minute walk test (meters)	491 (417, 519.5)	372 (294, 395)	**0.003**
Time Constant Tau	48.41 (41.13 , 49.175)	77.825 (71.2, 82.515)	**0.001**

(1) Mann-Whitney U test; (2) Chi-Square test; GFR:Glomerular Filtration Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood pressure

Demographic Table

FR-PO995

Interplay Between Skeletal Muscle Catabolism and Remodeling of Arteriovenous Fistulae via YAP1 Signaling

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Background: Arteriovenous fistulae (AVFs) are the preferred dialysis access choice, but they are prone to complications and have a high incidence of failure. The aim of this study is to understand the crosstalk of skeletal muscle catabolism and AVF maturation failure, and the role of myostatin and YAP1 signaling pathway in regulating AVF maturation.

Methods: AVFs were created in mice with chronic kidney disease (CKD). The skeletal muscle metabolism and AVF maturation were evaluated in mice that were treated with myostatin or its antagonist antibody. The role of YAP1 in transdifferentiation of adventitial mesenchymal stem cells (MSC) into neointima cells was investigated. Finally, "red light"-controlled verteporfin nanoparticles were used to block YAP1 activation in AVFs.

Results: PDGFRA reporter mice showed that positive MSCs were found both in muscle interstitial and vascular adventitial. These MSCs were activated in response to myostatin, that was increased in atrophied muscle fibers in CKD mice and was associated with vascular stiffness. Increased trichrome signals and stenosis were observed in AVFs from mice that were treated with myostatin. In contrast, blocking myostatin function by anti-myostatin peptibody not only improved body weight and muscle size in CKD mice, but also decreased neointima formation in AVFs. These responses were paralleled with decreased accumulation of PDGFRA$^+$ cells in AVFs. In cultured MSCs, YAP1 signaling mediated activation and differentiation of MSCs when MSCs were treated with myostatin or seeded on hard surface. "Red light"-controlled release of verteporfin nanoparticles, YAP1 inhibitor, alleviated MSC activation. Local application of verteporfin nanoparticles significantly suppressed accumulation of neointima cells in AVFs in irradiation group vs non-irradiated groups.

Conclusions: There were increased muscle atrophy and myostatin production in CKD mice, the latter stimulates MSCs activation and vascular fibrosis that are linked to AVF stenosis. YAP1 signaling was activated in this process. Blocking myostatin or inhibiting YAP1 activation suppressed neointimal formation with improved AVF function.

Funding: NIDDK Support

FR-PO996

Therapeutic Targeting of Vascular Calcification by KL1 in a CKD-MBD Rat Model

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Background: Vascular calcification is a common complication in patients with CKD that causes arterial stiffening, which can lead to hypertension and adverse cardiac remodeling. Klotho-deficient animal models exhibit a similar vascular calcification phenotype seen in patients with CKD, which can be ameliorated with exogenous administration of full-length Klotho. The KL1 domain of Klotho can be cleaved from full-length Klotho removing its FGF23-binding domain. Studies have shown that KL1 is biologically active, however it is unknown whether KL1 can directly exert anti-calcific effects similar to full-length Klotho.

Methods: Cy/+ male rats were fed a casein-based diet starting at 22 weeks old, and then treated daily with intraperitoneal injections of 50 μg/kg human recombinant KL1 (Cat. No. 100-53, PeproTech; *n*=6) or vehicle (0.1% bovine serum albumin in 0.9% saline; CKD, *n*=12) for 5-7 weeks starting at 27 weeks old. Rats were euthanized for tissue collection at 32-34 weeks old. Normal littermates (NL, *n*=8) were used as a control. Tissue calcification assessment, histology and protein analysis of the aorta were performed.

Results: CKD rats, compared to NL rats, developed elevated BUN (mean±SD: 46.13±9.41 mg/dL vs. 19.44±3.57 mg/dL; *P*<0.001), creatinine (1.53±0.61 mg/dL vs. 0.44±0.053 mg/dL; *P*<0.001), plasma phosphate (12.67±4.71 mg/dL vs. 6.17±1.12 mg/dL; *P*<0.001), decreased eGFR (671.61±463.83 μL/min vs. 2912.01±213.51 μL/min; *P*<0.001) and increased total kidney weight normalized to body weight (TKW/BW, 13.46±3.36 mg/g vs. 6.69±0.23 mg/g; *P*<0.001). CKD rats developed significant aortic calcification (62.88±31.22 mg/dL) compared to NL rats (27.69±14.27 mg/dL; *P*<0.005). Moreover, CKD rats treated with KL1 exhibited significantly reduced aortic calcification (32.5±15.53 mg/dL; *P*<0.018) and BUN (37.76±1.95 mg/dL; *P*<0.02) compared to vehicle treated CKD rats. Phosphate (10.99±1.38 mg/dL, *P*>0.27), creatinine (1.57±0.35mg/dL; *P*>0.86), eGFR (599.84±190.48 μL/min; *P*>0.65), and TKW/BW (13.31±2.44 mg/g; *P*>0.91) in KL1 treated rats did not significantly differ from vehicle treated CKD rats.

Conclusions: KL1 reduces aorta vascular calcification in a rat CKD-MBD model. This suggests that the KL1 domain of Klotho can directly exert cardiovascular protective effects. Further studies are warranted to elucidate the underlying molecular mechanisms.

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FR-PO997

Homocysteine Is Associated with Kidney Injury and Increased Arterial Stiffness

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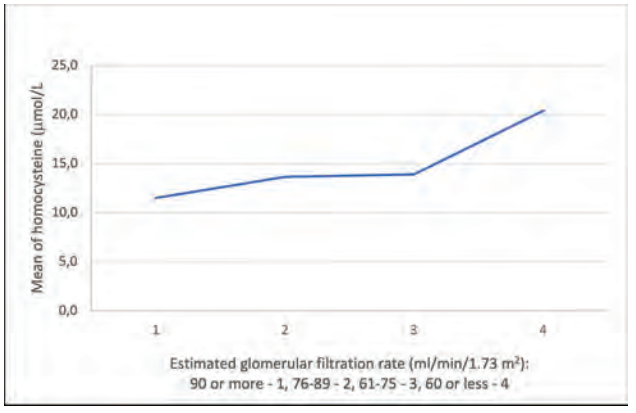
Background: Homocysteine (Hcy) promotes atherogenesis and is elevated in chronic kidney disease (CKD). Few studies addressed the association between Hcy, different markers of kidney injury and arterial stiffness (AS).

Methods: 127 patients (70.9% male, mean age 65.0±9.2 years, 78.7% hypertensive, and 20.5% diabetics) were admitted due to elective coronarography. The immunoassay method was used to measure serum Hcy (mmol/L) and cystatin C (CysC, mg/L). Hyperhomocysteinemia was defined by Hcy≥15 (Group 1, n=37), and patients with Hcy<15 were included in Group 2 (n=90). Albuminuria was expressed as UACR (mg/g). The glomerular filtration rate was estimated (eGFR) by the CKD-EPI 2009 equation (ml/min/1.73 m^2). Carotid-femoral pulse wave velocity (cfPWV, m/s) was used as a marker of AS (SphygmoCor®, Atcor, Australia). SPSS® (version 22) was used for statistical analysis.

Results: Mean Hcy was 14.1±5.7, eGFR 75.5±17.2, CysC 1.1±0.7, UACR 25.9±35.7 and cfPWV 10.3±2.7. Spearman's test showed a significant correlation between Hcy and CysC (r_s=0.608, p<0.001), UACR (r_s=0.264, p=0.004), eGFR (r_s=-0.485, p<0.001) and between Hcy and cfPWV (r_s=0.328, p<0.001). Group 1 had lower eGFR (62.4±21.5 vs 80.3±12.2, p<0.001), higher cysC (1.5±1.2 vs 0.9±0.2, p<0.001), higher UACR (49.6±57.5 vs 16.5±13.7, p<0.001), and higher cfPWV (11.5±3.3 vs 9.6±2.1, p<0.001). No difference was observed in comorbidities or medications. Multiple regression analysis (independent variables gender, age, diabetes, hypertension) confirmed a correlation between Hcy and eGFR (β=-0.535, p<0.001), UACR (β=0.331, p<0.001) and cysC (β=0.561, p<0.001). Hcy was higher in patients with lower eGFR (Figure 1). An independent correlation was also found between Hcy and cfPWV (β=0.238, p=0.005) and age and cfPWV (β=0.407, p<0.001). No association was found between cfPWV/Hcy and coronary artery disease (CAD).

Conclusions: Serum Hcy is associated with decreased eGFR, increased UACR, increased cysC and increased AS, but not CAD.



FR-PO998

The Nonsteroidal Mineralocorticoid Receptor Antagonist Finerenone Improves Left Ventricular Function in Preclinical CKD

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Background: The mineralocorticoid receptor (MR) plays an important role in the development of CKD and associated cardiovascular complications. Antagonizing the overactivation of the MR with MR antagonists (MRA) is a therapeutic option. Finerenone is a novel non-steroidal MRA that has been recently studied in two large clinical trials showing the beneficial effects in stage 1 to 4 CKD patients with type 2 diabetes (T2D) in the FIDELIO-DKD and FIGARO-DKD trials. **Aim:** To test whether finerenone improves renal/cardiac functions in preclinical non-diabetic CKD.

Methods: CKD was induced by 5/6 nephrectomy in 6 weeks old Sprague Dawley rats. Finerenone (10 mg/kg/day) was administered as curative treatment (1 month after 5/6 nephrectomy). Left Ventricle (LV) function/hemodynamics, LV tissue perfusion and GFR were assessed in vivo at the age of 24 weeks. Cardiac fibrosis was estimated by Sirius red staining and activation of eNOS (peNOS ser 1177) in the heart was estimated by western-blot analysis.

Results: 12 weeks after 5/6 nephrectomy, the rats showed classical signs of CKD: reduced GFR and increased kidney weight; associated with LV diastolic dysfunction: increased in LV end-diastolic pressure (LVEDP), LV relaxation constant (Tau) and LV end-diastolic pressure volume-relation (LVEDPVR), while LV perfusion was reduced. Changes associated with increased cardiac fibrosis and reduced peNOS ser 1177. Curative treatment with finerenone reduced significantly both LVEDPVR and Tau; and increased LV tissue perfusion, associated with a reduction in cardiac fibrosis and increased eNOS phosphorylation. Finerenone treatment did not impact GFR but reduced renal hypertrophy.

Conclusions: Curative treatment with finerenone improves non-diabetic CKD related LV diastolic function, associated with a reduction of cardiac fibrosis, and increased cardiac eNOS activating phosphorylation (ser 1177) independently from changes in kidney function.

Funding: Commercial Support - Bayer-AG, Government Support - Non-U.S.

	LVESP	LVESPVR (mmHg/relative volume unit)	LVEDP (mmHg)	Tau (msec)	LVEDPVR (mmHg/relative volume unit)	Perfusion (ml/min/g)	LV Weight	Heart fibrosis (%)	eNOS activation (peNOS s1177, relative expression)	GFR (ml/min/100g body weight)	Kidney weight (g)
Sham	135.7 ± 5.2	27.4 ± 1.2	5.12 ± 0.38	9.4 ± 0.08	1.13 ± 1.4	0.26 ± 0.22	1.06 ± 0.06	2.5 ± 0.1	1 ± 0.26	3.07 ± 0.08	1.81 ± 0.05
CKD	144.7 ± 8	26.2 ± 1	7.99* ± 0.84	10.4* ± 1.0.46	4.2* ± 0.31	7.99* ± 0.72	1.42 ± 0.06	4.9* ± 0.3	0.62* ± 0.04	0.86* ± 0.07	2.6* ± 0.21
CKD+Fine post	141.2 ± 6.2	29.4 ± 1.1	5.92 ± 0.4	9.28* ± 0.57	1.69* ± 0.19	9.08* ± 0.81	1.05 ± 0.03	2.9* ± 0.2	2.84* ± 0.33	2.56 ± 0.08	1.88* ± 0.06

*p<0.05 vs Sham
†p<0.05 vs CKD

FR-PO999

CKD, Heart Failure, Cytokines, and NF-κB: Is There a Connection?

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Background: Nuclear factor kappa (NF-κB) is a master transcription factor of inflammatory signaling and its prolonged activation is cytotoxic and may promote heart failure (HF). We developed a translational swine model of chronic kidney disease (CKD) that displays early-stage HF and cardiac activation of NF-κB. However, the mechanisms underpinning cardiac NF-kB activation in CKD remain unclear. We hypothesize that inflammatory cytokines released from the kidney and retained in the heart contribute to cardiac NF-κB activation and cardiac injury in CKD.

Methods: Normal and CKD pigs (n=6 each) were studied after 14 weeks; their systemic inflammatory cytokine profile was characterized (pig Luminex multi-panel assay) and their renal (renal vein - systemic) and cardiac (coronary sinus - systemic) gradients calculated. *In vitro* NF-kB expression (qPCR) and activation (immunofluorescence) was studied in pig heart slices and cardiomyocytes exposed to normal plasma, and CKD plasma with or without cytokine neutralizing antibodies (NA).

Results: Out of 13 cytokines, we found that tumor necrosis factor (TNF)-α and interleukin (IL)-6 showed the most significant increase in CKD, paired with positive renal and negative cardiac gradients, suggesting TNF-α/IL-6 renal release and cardiac retention. *In vitro* NF-kB expression and activation were higher in heart slices and cardiomyocytes exposed to CKD plasma but decreased in those treated with TNF-α and IL-6 NA (Figure).

Conclusions: These observations shed light into targeted mechanisms of cardiac NF-kB activation and may support future development of novel modulatory strategies to offset cardiac injury in CKD.

Funding: NIDDK Support, Other NIH Support - NHLBI

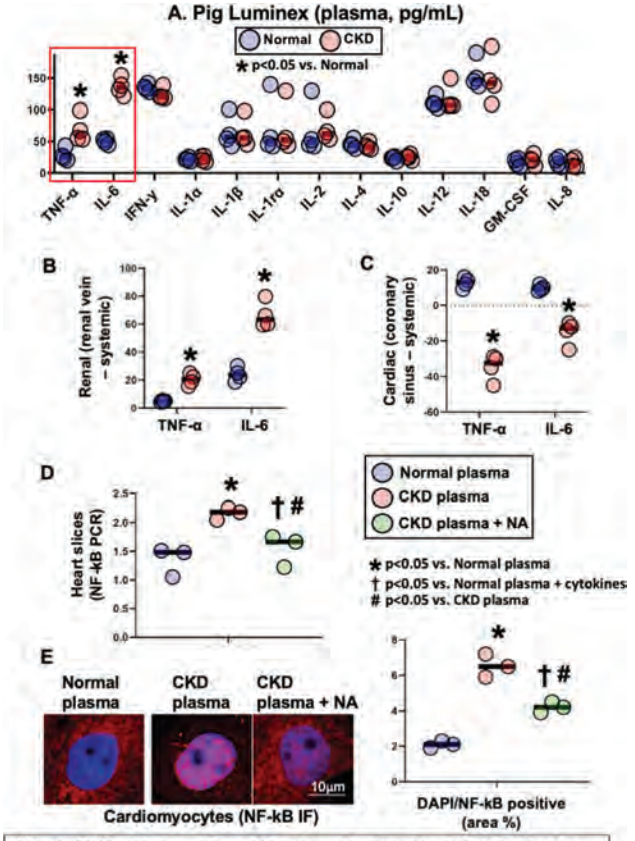

Figure: Unbiased pig multi-panel Luminex showing elevated systemic plasma levels of TNF-α and IL-6 in CKD **(A)**, paired with positive renal **(B)** and negative cardiac **(C)** gradients, suggesting renal release and cardiac retention. NF-kB cardiomyocyte expression (PCR, heart slices, **D)** and activation (IF, nuclear expression, **E)** increases after exposure to CKD plasma and decreases after treatment with NA.

FR-PO1000

Novel Role of ST2+ Tubular Cells in Shaping Immune Microenvironment

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Background: IL-33 is an 'alarmin' cytokine that regulates the immune response during injury. After release, IL-33 acts in an autocrine/paracrine manner on its membrane receptor (ST2 aka interleukin 1 receptor-like 1, IL1RL1), triggering innate and adaptive immune responses. ST2 expression is induced in tubular cells during chronic inflammation in various kidney diseases. However, the role of ST2^{+} tubular cells and their implication in chronic kidney injury (CKI) is poorly understood.

Methods: *ST2*$^{fl/fl}$ mice were crossed with *PEPCK*^{Cre} mice for proximal tubular cell (PTC)-specific ST2 deletion. Bilateral ischemia-reperfusion (IR) induced acute injury (AKI) and mice were euthanized 24hrs later. Unilateral ischemia-reperfusion injury simulated chronic injury, with contralateral nephrectomy performed on day 13 post-IRI. Kidney structure and function were analyzed using flow cytometry, histology, immunohistochemistry, gene expression, and biochemical analysis. In vitro, ST2-deficient and ST2-sufficient primary mouse PTC were subjected to ischemic conditions and assessed for metabolic fitness using Seahorse metabolic flux analyzer and cytokine production.

Results: ST2's potential involvement in immune cell activation and mobilization to injury sites was investigated. Selective ST2 deletion in PTC, in acute and chronic injury models, resulted in reduced renal injury. In the chronic injury model, the absence of IL33/ST2 signaling in tubular cells led to decreased immune cell infiltration, reduced inflammatory cytokine production, and lower fibrosis. Interestingly, *in vitro* treatment of TKPTS, PTC cell-line with recombinant IL-33 increased metabolic fitness, indicated by higher oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) in a dose-dependent manner. Additionally, IL-33 treatment paradoxically enhanced the expression of autophagy and mitochondria-related genes LC3, Beclin, and Rubicon in TKPTS cells. These findings underscore the intricate role of IL-33/ST2 biology in PTC.

Conclusions: $ST2^+$ tubular cells play a crucial role in leukocyte trafficking to the injured kidneys. Our data provide novel information to suggest epithelial-immune cell crosstalk mediated through the IL-33/ST2 axis and identification of novel therapeutic targets.

Funding: NIDDK Support

FR-PO1001

Magnesium Protects Against CKD Progression by Reducing DNA Damage

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Background: DNA damage accelerates the the progression of chronic kidney disease (CKD) and kidney aging. Emerging evidence suggests that magnesium (Mg) has the ability to suppress DNA damage by promoting chromatin aggregation. In this study, we aimed to investigate the potential of Mg administration in reducing DNA damage and mitigating the progression of CKD.

Methods: Male C57BL/6 mice (8 weeks old) were treated with a dosage of 600 mg/kg of Mg or deionized distilled water (DDW) and were subjected to renal irradiation with 8 Gy of radiation. As another model, male C57BL/6 mice (8 weeks old) underwent unilateral ischemia/reperfusion (I/R) injury with renal pedicle clamping for 35 minutes. These mice received Mg or DDW every 12 hours after I/R. Then, mice were sacrificed one- or three-week after I/R. *In vitro* experiments were also conducted using rat renal tubular (NRK52E) and rat kidney fibroblast (NRK49F) cells, which were irradiated with 1 Gy of radiation at different Mg concentrations (0.8mM, 3.2mM, 6.4mM) in the medium.

Results: Western blotting analysis revealed that the effects of radiation injury were confirmed by an increase of γH2AX, a marker of DNA double-strand breaks. Mice were treated with 600 mg/kg of Mg and subjected to renal irradiation with 8 Gy of radiation. Remarkably, the Mg-treated group exhibited reduced levels of γH2AX in the kidneys compared to the non-treated group. Furthermore, NRK52E and NRK49F cells irradiated with 1 Gy of radiation showed a reduction in γH2AX levels as the Mg concentration in the medium increased (0.8 mM, 3.2 mM, 6.4 mM). In the one-week I/R model, Western blotting analysis revealed that Mg administration resulted in a reduction of DNA damage markers (γH2AX and rad51), markers of aging (p16 and p21) and the inflammation marker (cGAS-Sting). Immunostaining demonstrated that Mg administration resulted in a reduction of markers of aging (p16 and p21) and the inflammation marker (F4/80). Furthermore, real-time PCR analysis indicated that Mg administration led to a decrease in markers of inflammation (IL-6 and IL-1β). In the three-week I/R model, Western blotting and immunostaining revealed that fibrotic markers (αSMA and collagen I) were also reduced in the Mg-treated group.

Conclusions: Administration of Magnesium reduces DNA damage and mitigates renal I/R injury, including aging, inflammation and fibrosis.

FR-PO1002

A Novel, Small Molecule Inhibitor of Gut Microbial Choline Trimethylamine Lyase (CutC) Slows the Loss of Kidney Function in a Rat Model of CKD

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Background: Trimethylamine *N*-oxide (TMAO), a gut microbiota-dependent uremic toxin, is both a cause and driver of chronic kidney disease (CKD). Choline trimethylamine (TMA) lyase (CutC) is a microbial enzyme that plays a key role in the formation of TMA, a precursor of TMAO, in the gut. Here we describe the pharmacological effects of a novel, small molecule CutC inhibitor on serum TMAO level and kidney function in an adenine-induced rat model of CKD.

Methods: CKD was induced in rats by adding 0.75% adenine to a standard chow diet for 2 weeks (induction phase) and maintained by adding 0.25% adenine to the diet supplemented with 1% choline in the drinking water for 4 weeks (maintenance phase). The small molecule CutC inhibitor, ZTx101, was administered via ileal-cecal catheter directly into the colon at doses of 15, 50, and 150 mg/kg of body weight, twice a day, during the maintenance phase. Serum TMAO was quantified using LC-MS/MS. Kidney function was assessed by serum levels of creatinine and blood urea nitrogen (BUN). Renal fibrosis was assessed by biomarker analysis and histology.

Results: Serum levels of TMAO, creatinine, and BUN were elevated in rats with adenine-induced CKD supplemented with choline. Administration of ZTx101 at all three doses resulted in rapid and sustained reduction of serum TMAO to the normal range (<5 μM) during the maintenance phase of the study. At the end of study, ZTx101 significantly reduced serum levels of creatinine (1.5 mg/dL in 150 mg/kg ZTx101 vs. 3.1 mg/dL in untreated; $P<0.0001$) and BUN (102.6 mg/dL in 150 mg/kg ZTx101 vs. 140.0 mg/dL in untreated; $P<0.05$). ZTx101 also significantly reduced TGF-β level in the kidney (36.6 pg/mg tissue in 150 mg/kg ZTx101 vs. 70.2 pg/mg tissue in untreated; $P<0.0001$), a biomarker of renal fibrosis. In addition, neutrophilic tubulitis and tubulointerstitial nephritis were reduced in animals treated with ZTx101, compared to untreated controls.

Conclusions: The small molecule CutC inhibitor ZTx101 is effective in reducing and normalizing elevated levels of uremic toxin TMAO and slowing the loss of kidney function in a rat model of CKD. Reduction of serum TMAO level by the CutC inhibitor ZTx101 may provide a potential new approach to slow disease progression in persons with CKD.

Funding: Commercial Support - Zehna Therapeutics Inc., Private Foundation Support

FR-PO1003

Protective Effects of Lrp2 Knockout Are Independent of Sex-Specific Renal Injury in Mice on Western Diet

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Background: Megalin (*Lrp2*) is a multiligand receptor that plays a crucial role in maintaining endocytic flux in the kidney proximal tubule (PT). Knockout (KO) or disabled function of megalin is protective against nephrotoxicity, though the mechanism(s) are unknown. We previously found that KO of *Lrp2* in opossum kidney cells and mice reduces transcription of sodium-glucose cotransporter-2 (*Sglt2*). Because *Sglt2* inhibition attenuates hyperglycemia in diabetic patients and protects against kidney disease in non-diabetic patients, we compared metabolic and renal function in male and female wild type (WT) and *Lrp2* KO mice fed regular chow (RC) or Western diets (WD).

Methods: Sixteen-week-old WT or *Lrp2* KO mice on RC were administered glucose tolerance tests (GTT) and then placed in metabolic cages for 48 h. The mice were tested again after 6 weeks on WD. Spot urine samples were also collected. Urine, tissue, and blood samples were collected at sacrifice for analysis.

Results: Male and female *Lrp2* KO mice on RC and WD had increased glucose tolerance compared to WT mice. *Lrp2* KO mice also consumed more water and had increased activity. Respiratory exchange ratio (RER) data suggests a difference in fatty acid oxidation between genotypes. These features persist in male and female *Lrp2* KO mice fed WD, and both gained far less fat mass than their WT counterparts. Strikingly, whereas female *Lrp2* KO mice had normal blood electrolyte, BUN, and creatinine levels, these values suggested kidney injury in male *Lrp2* KO mice on WD. Histology and qPCR analyses confirmed that *Lrp2* KO male mice exhibited significant kidney injury.

Conclusions: *Lrp2* KO mice had increased glucose tolerance, water consumption, and RER compared to WT mice. This phenotype is similar to those of *Sglt2* KO mice or WT mice treated with Sglt2 inhibitors. Remarkably, these features persist following WD in both female and male *Lrp2* KO mice, despite male mice exhibiting significant kidney disease. These results suggest that the protective effects of *Lrp2* KO are independent of kidney injury. Further studies are underway to understand how megalin regulates PT function in a high-fat environment.

Funding: NIDDK Support

FR-PO1004

Farnesoid X Receptor Agonism Prevents Neutrophil Extracellular Traps via Reduced Sphingosine-1-Phosphate in CKD

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Background: Activation of the farnesoid X receptor (FXR) reduces renal inflammation, but the underlying mechanisms remain elusive. Neutrophil extracellular traps (NETs) are webs of DNA formed when neutrophils undergo specialized programmed cell death (NETosis). Sphingosine-1-phosphate (S1P) is a signaling lipid that stimulates NETosis via its receptor on neutrophils. Here, we identify FXR as a negative regulator of kidney NETosis via repressing S1P signaling in male but not female mice.

Methods: We determined the effects of the FXR agonist obeticholic acid (OCA) in mouse models of adenosine phosphoribosyltransferase deficiency and Alport syndrome. We assessed renal NETosis by immunofluorescence in these models and in biopsies from patients with Alport syndrome (6 male, 9 female). We also inhibited de novo sphingosine production in Alport mice to show a causal relationship between S1P signaling and renal NETosis.

Results: Renal FXR activity is greatly reduced in both models, and OCA prevents kidney fibrosis, inflammation, and lipotoxicity. OCA reduces renal neutrophilic inflammation and NETosis in male adenine and Alport mice, but not in female adenine mice. Extensive NETosis was also identified in human Alport kidney biopsies. Kidney sphingosine kinase 1 (Sphk1) expression is increased in mice with kidney disease and reduced by OCA in male but not female mice. Also, Sphk1 expression correlates with NETosis in male but not female mice. Short-term inhibition of sphingosine synthesis reduces neutrophilic inflammation and NETosis.

Conclusions: FXR agonism represses kidney Sphk1 expression in male but not female mice. This inhibits renal S1P signaling, thereby reducing neutrophilic inflammation and NETosis in a sex-dependent manner.

Funding: NIDDK Support

FR-PO1005

Lactobacillus acidophilus KBL409 Protects Against Kidney Injury via Improving Mitochondrial Function with CKD

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Background: Recent advances have led to greater recognition of the role of mitochondrial dysfunction in the pathogenesis of chronic kidney disease (CKD). There has been evidence that CKD is also associated with dysbiosis. Animal studies have shown that dysregulated gut microbiota can alter mitochondria metabolism of intestinal mucosa cells, leading to mitochondrial dysfunction. Here, we aimed to evaluate whether probiotic supplements can have protective effects against kidney injury via improving mitochondrial function.

Methods: KBL409 was selected because this strain was proved to maintain intestinal integrity and reduce p-cresyl sulfate level *in vitro* in prior experiments. An animal model of CKD was induced by feeding C57BL/6 mice a diet containing 0.2% adenine. KBL409, a strain of *Lactobacillus acidophilus*, was administered via oral gavage at a dose of 1×10^9 CFU daily. We isolated primary mouse TECs and treated them with TGF-β (10 ng/ml) or p-cresyl sulfate (0.5mM) and sodium butyrate (10μM), a short-chain fatty acid that is considered the end products of commensal bacteria.

Results: There were prominent structural alterations in CKD mice and KBL409 administration significantly attenuated renal fibrosis. Transcript and protein expression levels of PGC-1α, a key regulator of mitochondrial biogenesis, were significantly decreased in CKD mice, which were restored by KBL409. There were concomitant changes in mitochondrial content and mitochondrial dynamic-related proteins in response to KBL409. In addition, mice with KBL administration showed improvement in fatty acid oxidation defect and mitochondrial structure compared with CKD mice. *In vitro*, TGF-β or p-cresyl sulfate treatment in TECs recapitulated the findings of *in vivo* study and these alterations were reversed by butyrate administration. Mitochondrial function assay showed that butyrate significantly improved mitochondrial respiration, fatty acid oxidation defect, oxidative phosphorylation, and ATP production in TGF-β- or p-cresyl sulfate-treated TECs.

Conclusions: This study demonstrates that administration of the probiotic *Lactobacillus acidophilus* KBL409 protects against kidney injury via improving mitochondrial function.

FR-PO1006

N-Acetylcysteine Ameliorates Hematuria-Associated Tubulointerstitial Injury in 5/6 Nephrectomy Mice

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Background: Chronic kidney disease (CKD) is characterized by increased interstitial fibrosis and tubular atrophy (IFTA) in the kidney. Chronic hematuria is a hallmark of several human kidney diseases and often is seen in patients on anticoagulation therapy. We had previously demonstrated that chronic hematuria associated with warfarin increases IFTA in 5/6 nephrectomy (5/6NE) rats, and such treatment increases reactive oxygen species (ROS) in the kidney. The goal of this study was to evaluate the effects of the antioxidant N-acetylcysteine (NAC) on the progression of IFTA in 5/6NE mice.

Methods: 5/6NE C57BL/6 and 5/6NE 129S1/SvImJ mice were treated with warfarin alone or with warfarin and NAC for 23 weeks. Serum creatinine SCr), hematuria, blood pressure (BP), and ROSs in the kidney were measured; kidney morphology was also evaluated. Warfarin doses were titrated to achieve prothrombin time (PT) increase to the levels seen with therapeutic human doses.

Results: Warfarin treatment resulted in an increased SCr, systolic BP, hematuria (Figure 1), and ROS in the kidney in both mouse strains. IFTA was increased as compared with control 5/6NE mice, and this increase in IFTA was more prominent in 129S1/SvImJ than in C57BL/6 mice. NAC ameliorated the warfarin-associated increase in SCr and BP but not hematuria. IFTA and ROS in the kidney were reduced in mice treated with NAC and warfarin as compared to mice treated with warfarin alone.

Conclusions: NAC mitigates the increase in SCr and IFTA in mice with chronic hematuria by reducing oxidative stress in the kidney. This data open novel possibilities for treatments in CKD patients.

Funding: NIDDK Support

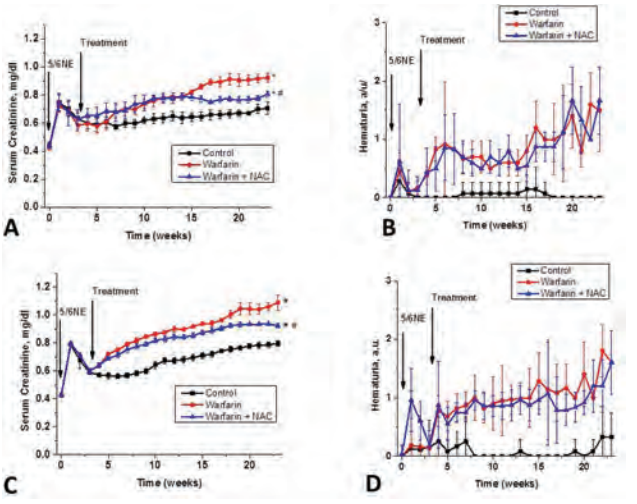

Figure 1. Changes in serum creatinine and hematuria in mice treated with NAC and warfarin.

FR-PO1007

Glucagon Agonism Protects the Kidney from Obesity by Restoring Peroxisomal Catalase and Fatty Acid Oxidation Capacity

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Background: Obesity challenges the nephron through fatty acid overload, leading to impaired energy metabolism and impaired renal filtration. Glucagon agonism elicits well described enhancement of fatty acid oxidation and mitochondrial rejuvenation in the liver and other organs, and was hypothesised here to protect the kidney from obesity-related pathology.

Methods: Sprague Dawley rats fed HFHS (DIO) or chow diet for 10 weeks were administered 10nmol/kg lipidated glucagon receptor agonist g1437 daily for seven days. IF was used to visualise the distribution and morphology of peroxisomes and mitochondria across the kidney, alongside the organelle content of key metabolic and ROS handling enzymes. Primary human PTECs transfected with either MitoTimer or with a novel peroxisomal ROS sensor were cultured with and without linoleic/oleic acid for 72 hours alongside 100 nM g1437 or vehicle. To interrogate the underlying signalling mechanism of glucagon, cortex and medulla from mice acutely administered 10nmol/kg g1437 were analysed by phosphoproteomics.

Results: Kidneys of DIO rats demonstrated peroxisomal proliferation and altered mitochondrial morphology. Glucagon agonism also induced mitochondrial and peroxisomal morphological changes. Peroxisomal catalase and FAO enzyme content was perturbed in kidneys of DIO relative to chow fed rats. Concomitantly with weight loss, renal peroxisomal and mitochondrial FAO enzyme content was partially restored in g1437 administered rats. Primary human PTECs cultured with 150 μM linoleic/oleic acid mixture for 72 hours demonstrated greater mitochondrial and peroxisomal reactive oxygen species generation than controls. Phosphoproteomics determined that catalase was 1.48-fold more phosphorylated in kidney cortex of mice acutely administered g1437, a phosphorylation shown to enhance catalase activity. Peroxisomal fatty acid oxidation biogenesis were pathways significantly phosphorylated as part of the glucagon signalling cascade.

Conclusions: Obesity and fatty acid overload led to fission of renal mitochondria and peroxisomes, alongside increased capacity for ROS production and FAO. Glucagon agonism did not reverse changes in organelle morphology, yet enhanced FAO capacity and lowered ROS production capacity, possibly through catalase phosphorylation.

Funding: Commercial Support - AstraZeneca

FR-PO1008

Proximal Tubular FHL2 Mediates Obesity-Induced Renal Tubulointerstitial Inflammation via Regulating FoxO1 Activity

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Background: Lipid accumulation caused by fatty acid β-oxidation deficiency in renal proximal tubular cells (PTCs) is a major factor triggering obesity-related chronic kidney disease (OR-CKD), and the low activity of forkhead box class O1 (FoxO1) is a key mediator between metabolic abnormalities and cellular damage. It was reported that four and a half LIM domain-only protein 2 (FHL2) could inhibit FoxO1 activity in prostate cancer cells. However, the potential effect of FHL2 on FoxO1 activity and lipid toxicity injury in PTCs during OR-CKD remains to be elucidated.

Methods: Mice with PTCs-specific deletion of FHL2 were generated by mating FHL2-floxed mice with Ggt1-Cre transgenic mice. The expression and function of FHL2 were examined in palmitate acid (PA)-stimulated NRK-52E cells (rat PTCs) and in the kidneys from mice with obesity induced by high-fat diet, respectively.

Results: PA induced FHL2 expression in a time- or dose-dependent manner in cultured NRK-52E cells. Knockdown of FHL2 via small interfering RNA largely suppressed PA-induced mRNA expression of several inflammatory factors including interleukin-6, monocyte chemoattractant protein-1, and tumor necrosis factor α (TNFα). *In vivo*, FHL2 was induced in renal PTCs in the obesity mice at 16 weeks after feeding on high-fat diet. Compared with wild-type littermates, the kidneys from mice with PTCs-specific ablation of FHL2 exhibited less interstitial inflammation, lower levels of urinary neutropil gelatinase-associated lipocalin, and lower urinary albumin-creatinine ratio. *In vitro*, PA induced FHL2 physically interact with FoxO1 in the nuclei. Treatment with PA resulted in a decrease in FoxO1 activity, which was evidenced by an increase in the phosphorylation (Ser256) of FoxO1 and a decrease in the abundance of FoxO1 in the nuclei. Knockdown of FHL2 inhibited the phosphorylation (Ser256) of FoxO1 in cells treated with PA, whereas ectopic expression of FHL2 promoted the phosphorylation (Ser256) of FoxO1. In addition, ChIP assay revealed that TNFα-induced protein 1 (TNFAIP1), an inhibitor of NF-κB signaling, was a putative downstream target gene of FoxO1.

Conclusions: Our results suggest that FHL2, via regulating FoxO1 activity, plays a crucial role in mediating PA-induced inflammatory reaction in PTCs and contributes to tubulointerstitial inflammation and kidney damage resulted from obesity.

Funding: Government Support - Non-U.S.

FR-PO1009

Renal Microvascular Inflammation in Human Obesity Detected by Urinary Extracellular Vesicles

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Background: Obesity is characterized by systemic inflammation and activation of the inflammatory marker monocyte chemoattractant protein (MCP)-1, but the involvement of inflammation in early renal injury is unclear. Plasmalemmal vesicle-associated protein (PLVAP), a marker of renal peritubular capillaries, is upregulated in diabetes. We hypothesized that human obesity induces renal microvascular inflammation detectable by elevated levels of PLVAP+/MCP-1+ urinary extracellular vesicles (uEVs).

Methods: Obese patients (OB, n=6) and healthy volunteers (HV, n=7) were prospectively enrolled. Blood and urine were collected, and uEVs were isolated (Total Exosome). uEVs were quantified (Nanoparticle Tracking Analysis) and characterized (Flow cytometry) for CD31, PLVAP, CD144 (expressed on glomerular endothelium), and MCP-1, and their relationship with body mass index (BMI) and serum glucose levels was evaluated.

Results: OB had significantly higher BMI than HV, but both groups showed preserved renal function and glucose levels (Table-1), and a similar number and size of uEV. However, the fraction of CD31-/PLVAP+/CD144-/MCP-1+ was higher in OB and directly correlated with both glucose levels and BMI in OB but not in HV (Figure-1).

Conclusions: Non-diabetic obese patients show elevated numbers of PLVAP+/MCP-1+ uEVs that correlate with BMI and glucose levels. These early markers of renal microvascular inflammation that herald the development of pre-diabetes might be useful in the management of patients with obesity.

Funding: NIDDK Support, Other NIH Support - DK120292 (NIDDK) and HL158691 (National Heart, Lung, and Blood Institute)

Demographics (mean± standard deviation (SD) or median(min,max))

Parameter	HV	OB
Age, Yrs.	46 ± 12	45 ± 10
Sex, M/F	1/6	0/6
BMI, Kg/m^2	26.3 ± 2.5	46.4 ± 8.2*
Serum Creatinine, mg/dl	0.84 ± 0.13	0.67 ± 0.15
eGFR, ml/min/1.73m^2	90 (90,81)	89 (85,90)
Serum Glucose, mg/dl	100 ± 7.7	101 ± 19

*P<0.05 vs. HV

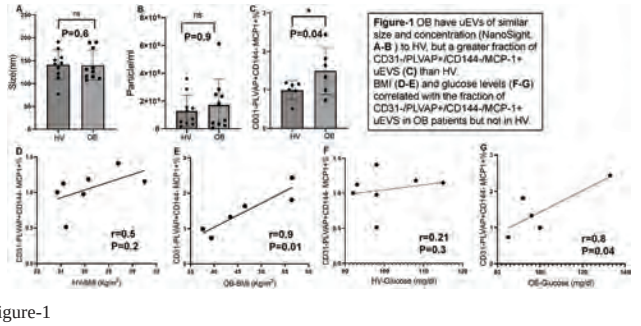

Figure-1

FR-PO1010

Insulin Resistance and Intermuscular Adipose Tissue (IMAT) in Patients with CKD

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Background: Insulin resistance (IR) is commonly observed in CKD and plays a critical role in protein energy wasting (PEW). We have found that patients with moderate to advanced CKD have increased IMAT accumulation. In this study, we hypothesized that the extent of IMAT is associated with homeostatic model assessment of insulin resistance (HOMA-IR), a measure of insulin resistance and systemic inflammation

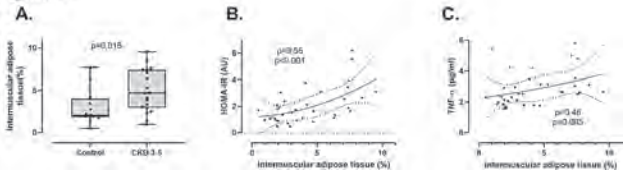
Methods: In this cross-sectional study, we included 46 patients (21 control, 25 with CKD stage 3-5). Anthropometry, inflammatory biomarkers, and HOMA-IR) were measured in all participants. Quadriceps IMAT was analyzed with magnetic resonance imaging (MRI) of the thigh.

Results: The control and CKD groups were matched by gender and body mass index. There was no difference in HOMA-IR, glucose, or insulin levels between the groups. Quadriceps IMAT accumulation was higher in patients with Stage 3-5 CKD compared to the control group (**Figure 1A**). Higher insulin resistance was associated with greater IMAT accumulation (rho=0.55, p<0.001, **Figure 1B**). Greater IMAT accumulation was associated with increased levels of tumor necrosis factor-alpha (TNFα) (rho=0.16, p=0.005, **Figure 1C**).

Conclusions: In patients with stage 3-5 CKD, there is greater accumulation of IMAT that associates with insulin resistance and increased TNFα levels compared to controls. IMAT accumulation may contribute to skeletal muscle insulin resistance by promoting a local inflammatory milieu. Further studies should evaluate if IMAT reduction may improve insulin sensitivity in CKD.

Funding: NIDDK Support, Other NIH Support - NCRR

Figure 1.



FR-PO1011

High-Fat Diet Changes Lipid Profiles and Induces Podocyte Injury in Unilateral Kidney Model: Targeted Lipidomic and Kidney Podocyte-Specific Analysis

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Background: We investigated that high fat diet changes lipidomic profiles and dysregulated lipid metabolism induces podocyte injury in unilateral nephrectomized mouse model using targeted lipidomics analysis and podocyte specific analysis.

Methods: Mice were randomized to undergo unilateral nephrectomy and fed standard or high-fat diets for 13 weeks. There were four groups; normal diet (ND), high-fat diet (HD), normal diet and received uninephrectomy (NDU), and high-fat diet and received uninephrectomy (HDU). After 13 weeks, lipidomics analysis was performed in podocytes isolated from the kidney. In vitro, CIHP-1 cells were treated with cholesterol ester for 24 hours.

Results: A high-fat diet accompanied by unilateral kidneys accelerated the increase in podocyte lipid droplets, glomerular size and tubular cell vacuole formation, resulting in deterioration of renal function. HDU showed different lipidomics profiles compared to other groups. Specifically cholesterol ester (CE), the CE20:4, increased significantly in HDU. Expressions of nuclear receptors, ABCA1, and CPT1A related to lipid metabolism decreased in the HDU and CIHP-1 cells treated with CE 20:4. Transmission electron microscopy confirmed loss of mitochondrial cristae, morphological changes and increased autophagosome formation in the HDU. In addition, reduction of NRF1/2 and increase of DRP1 were confirmed in HDU. In CIHP-1 cells stimulated with CE20:4, proteins related to mitochondrial, such as NRF1/2, PGC1-α, and PDK4 decreased, and mitochondrial fission was increased. Expressions of Beclin-1 and P62 were significantly increased in the HDU and CIHP-1 cells treated with CE 20:4. Kidney injury by such abnormal lipid metabolism induced renal fibrosis in the HDU.

Conclusions: High-fat diet increases lipid accumulation and lipid toxicity in podocytes induced renal structural and functional damage in the unilateral kidney model. In addition, lipotoxicity reduces mitochondria biogenesis, increases fission of mitochondria and increases incomplete action of autophagy.

Funding: Government Support - Non-U.S.

FR-PO1012

Bariatric Surgery: Benefits that May Harm, a Cause of Rapid Deterioration of Kidney Function

Enrique F. Morales Lopez, Juan D. Diaz Garcia, Ydris Z. Rosillo-Salgado, Martin B. Yama Estrella, Francisco J. Hernandez Copca, Francisco Velasco Garcia Lascurain, Jose L. Ortega, Victor M. Ulloa Galvan, Mario Alamilla-Sanchez, Guillermo E. Ramírez Garcia, Irving G. Ramirez. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Introduction: Secondary hyperoxaluria in post-bariatric surgery patients is well documented. The en y de roux and gastric band bypass techniques are the most closely related. A frequent complication is renal lithiasis with progressive loss of renal function.

Case Description: 63-year-old female, history of gastric bypass due to morbid obesity (150 to 90 kg), DM 2 difficult to control. He was admitted to nephrology due to rapidly progressive deterioration of function, basal creatinine 1.12 mg/dl, on admission with 4.5 mg/dl, C3 49 mg/dl, C4 17 mg/dl (low) ANA 1:80. Renal biopsy: with 2 silver + acellular nodules, interstitium with patches of fibrosis and tubular atrophy, infiltrate of lymphocytes, polymorphonuclear cells, and eosinophils. Birefringent intratubular calcifications, loss of brush border. negative IFI

Discussion: Lithogenicity from bariatric surgery is multifactorial with mechanisms: (1) calcium saponification as a result of fat malabsorption reduces calcium-oxalate binding. (2) Increased bile salts in the colon (as a result of their decreased absorption in proximal portions of the intestine) increased mucosal permeability to oxalate (3) reduced colonization by oxalobacter formigenes, especially with the use of beta-lactams. **Conclusions:** serum and urinary metabolic screening of patients after bariatric surgery would allow an increase in the early detection of patients at high risk of enteric hyperoxaluria. once the lithiasic disease is detected, dietary adjustments and avoiding the indiscriminate use of antibiotics are essential to prevent the progressive deterioration of renal function.

FR-PO1013

Endoplasmic Reticulum (ER) and Mitochondrial Stress Markers of Heavy Metals Exposure in the CRIC Study

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Background: Chronic kidney disease (CKD) is a progressive disease that affects ~13% of the population. Heavy metal (HM) exposure contributes to the rapid progression of kidney disease due to persistent stress stimuli that lead to dysregulation of inflammatory and oxidative stress pathways. Our hypothesis is that cumulative exposure to metals increases progression of CKD via inflammation and oxidative stress.

Methods: We obtained matching nail samples (n=40) from 20 participants of the Chronic Renal Insufficiency Cohort (CRIC) at baseline (n=20) and 24-month follow-up (n=20). An equal number of subjects had fast progressing disease (n=10) and stable disease (n=10). Samples were a random pick of all available samples and were sent anonymized prior to analysis. We quantified twenty-five metalloids in the nail samples using Inductively Coupled Plasma Mass Spectrometry (ICP/MS). Mercury was measured on a Flow Injector Mercury System (FIMS), and boron with ICP/Optical Emission Spectroscopy (ICP/OES). Biochemical markers were measured at the CRIC Scientific and Data Coordinating Center (SDCC) using commercial kits.

Results: Marker concentrations at baseline and follow-up are shown for the fast progressing and stable progression cohorts.

Conclusions: Although not significant, in the fast-progressing disease cohort, ATF, VAR6, and PERK were all increased while GRP78, Caspase 12, and mitofilin were all decreased at follow-up. In the stable cohort, all markers were increased at follow-up with the exceptions of mitofilin (decreased) and PERK (unchanged). Increased ER and mitochondrial stress markers showed a trend towards higher metal burden.

Funding: NIDDK Support

Marker	Pathway	Fast Progression		Stable Progression	
		Baseline	Follow-up	Baseline	Follow-up
GRP78	ER Stress	0.245 ± 0.133 ng/mL	0.159 ± 0.140 ng/mL	0.174 ± 0.108 ng/mL	0.411 ± 0.581 ng/mL
ATF6	ER Stress	0.089 ± 0.148 ng/mL	0.330 ± 0.676 ng/mL	0.130 ± 0.187 ng/mL	0.250 ± 0.252 ng/mL
caspase 12	ER Stress	607 ± 244 pg/mL	453 ± 271 pg/mL	453 ± 201 pg/mL	523 ± 426 pg/mL
VAR6	ER Stress	3.34 ± 2.14	4.90 ± 4.97	4.88 ± 6.00	5.43 ± 5.36
PERK	ER Stress	648 ± 261 pg/mL	711 ± 507 pg/mL	646 ± 341 pg/mL	645 ± 303 pg/mL
mitofilin	Mitochondrial Stress	1.354 ± 0.595 ng/mL	4.731 ± 7.992 ng/mL	3.302 ± 4.514 ng/mL	2.611 ±3.725 ng/mL

FR-PO1014

Heavy Metals Quantification in Nail Samples from the CRIC Study

Robert M. Taylor,[1] Justin T. Baca,[1] V. Shane Pankratz,[1] Wei Yang,[2] Xue Wang,[2] Mark L. Unruh,[1] Vallabh O. Shah.[1] *[1]University of New Mexico Health Sciences Center, Albuquerque, NM; [2]University of Pennsylvania, Philadelphia, PA.*

Background: Chronic kidney disease (CKD) affects >37 million American adults who experience high rates of cardiovascular events, kidney failure, and premature mortality. Recent reports suggest that environmental heavy metal (HM) exposure contributes to the rapid progression of kidney disease. Our overall hypothesis is that cumulative exposure to trace metals increases progression of CKD and higher metal burden will correlate with CKD risk.

Methods: We obtained matching nail samples (n=40) from 20 participants of the Chronic Renal Insufficiency Cohort (CRIC) at baseline (n=20) and 24-month follow-up (n=20). An equal number of subjects had fast progressing disease (EGRF CRIC difference between baseline and follow-up of -1 to 1) (n=10) and stable disease (EGFR CRIC difference between baseline and follow-up <= -10) (n=10). Metal concentrations were analyzed using Inductively Coupled Plasma Mass Spectrometry (ICP/MS). Mercury was measured on a Flow Injector Mercury System (FIMS), and boron was measured using ICP/Optical Emission Spectroscopy (ICP/OES).

Results: We successfully quantified 25 metalloids in all nail samples. Most metalloids had concentrations < 5 μg metalloid / g sample. Aluminum, boron, copper, iron, and zinc had concentrations between 5-80 μg/g. A trend was seen of lower concentrations in the 24-month, compared with the baseline samples. Chromium concentrations in the fast-progressing group were significantly lower at follow up (0.59 ± 0.45 μg/g) versus baseline (2.01 ± 1.64 μg/g) (p=0.036). Average total metal burden (sum of all metal concentrations) across all participants was 520 ± 72 μg/g and 327 ± 40 μg/g for the baseline and 24-month visits, respectively. At baseline, metal burden was 659 ±1006 μg/g and 382 ± 345 μg/g for subjects with fast and slow progressing CKD, respectively. At 2-year follow-up, metal burdens were 313 ± 327 μg/g and 340 ± 415 μg/g, respectively.

Conclusions: All metals we examined were above the limit of detection. Although not significant with a Wilcoxon Rank Sum Test, a trend of higher total metal burden was observed in the rapid progressing cohort, compared with stable progressing cohort.

Funding: NIDDK Support

FR-PO1015

Cosmic Kidney Disease: A Pan-Omic Investigation of the Health Consequence of a Trip to Mars and Back

Keith Siew, Stephen B. Walsh. London Tubular Centre. *University College London, London, United Kingdom*.

Background: Missions into Deep Space are planned this decade. Yet the health consequences of exposure to microgravity and galactic cosmic radiation (GCR) over years-long missions on indispensable visceral organs such as the kidney are largely unexplored.

Methods: We performed biomolecular (epigenomic, transcriptomic, proteomic, epiproteomic, metabolomic, metagenomic), clinical chemistry (electrolytes, endocrinology, biochemistry) and morphometry (histology, 3D imaging, miRNA-ISH, tissue weights) analyses using samples and datasets available from 11 spaceflight-exposed mouse and 5 human, 1 simulated microgravity rat and 4 simulated GCR-exposed mouse missions.

Results: We found that spaceflight induces: 1) renal transporter dephosphorylation which may indicate astronauts' increased risk of nephrolithiasis is in part a primary renal phenomenon rather than solely a secondary consequence of bone loss; 2) remodelling of the nephron that results in expansion of distal convoluted tubule size but loss of overall tubule density; 3) renal damage and dysfunction when exposed to a Mars roundtrip dose-equivalent of simulated GCR.

Conclusions: This study is the largest to ever look at the effect of spaceflight on kidney function. We have demonstrated that there is renal structural and functional remodelling likely caused by microgravity, probably synergistically with GCR. We have shown that this remodelling is a potential driver of kidney stone formation and many of the changes in the urinary biochemistry of humans and animals experienced by those exposed to spaceflight. We have also shown that acute exposure to simulated GCR causes both acute and chronic tubular epithelial and vascular damage that appears both progressive and irreversible

Funding: Government Support - Non-U.S.

FR-PO1016

Therapeutic Potential of Oxalobacter formigenes in CKD Development and Progression

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Background: Cardiovascular events are the leading cause of death in chronic kidney disease (CKD) patients, but the mechanisms are poorly understood. Oxalate retention has been shown to induce systemic fibrosis and inflammation, contributing to CKD progression and cardiovascular complications in renal failure. Hydroxyproline is a common component of meats and a precursor of oxalate. Oxalobacter Formigenes (OxF) is a specialist oxalate degrader in the human intestines. We hypothesize that OxF colonization in CKD mice reduces oxalate levels and attenuates CKD progression and cardiovascular damage.

Methods: Twenty 5/6 nephrectomy (CKD) mice and 20 Sham-operated mice received a 1% hydroxyproline-supplemented diet for five months. 10 CKD and 10 Sham mice received one dose of OxF (1x109 CFU), and the other mice received culture medium as control. Mouse urine and blood were collected at different time points for measuring oxalate and creatine. All mice were sacrificed after five months, and their kidneys and hearts were harvested.

Results: Hydroxyproline supplementation induced kidney damage. Plasma oxalate and creatine level were increased in all mice. OxF treatment reduced plasma oxalate and creatine in both Sham and CKD groups. CKD mice had more severe inflammation and

fibrosis in the kidney than Sham mice. OxF treatment ameliorated inflammation and fibrosis in both Sham and CKD mice. Perivascular fibrosis was found in the heart of CKD mice, but OxF-treated CKD mice displayed less perivascular fibrosis. RNA-seq of heart tissue revealed that the top altered genes and pathways in CKD compared to control mice were related to increased inflammation and fibrosis, decreased lipid metabolism, and increased lipid accumulation. However, OxF treatment reversed those pathways and genes altered in CKD control mice.

Conclusions: Hydroxyproline promoted CKD development and progression, likely through increased oxalate levels. OxF treatment attenuated CKD progression and ameliorated cardiovascular damage.

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FR-PO1017

Spatiotemporal Landscape of Kidney Tubular Responses to Glomerular Proteinuria

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Background: Large increases in glomerular protein filtration induce major changes in kidney function and body homeostasis, and increase the risk of cardiovascular disease. We investigated how elevated protein exposure modifies the landscape of tubular function along the entire nephron, to better understand the cellular changes that mediate these important clinical phenomena.

Methods: We conducted single nuclei RNA sequencing, functional intravital imaging, and antibody staining to spatially map transport processes along the mouse kidney tubule. We then delineated how these are altered in a transgenic mouse model of inducible glomerular proteinuria (POD-ATTAC) at 7 and 28 days. Results were compared to an ischemic model of tubular injury.

Results: Glomerular proteinuria activates large-scale and pleotropic changes in tubular cell gene expression in all major nephron sections, the majority of which are functional in nature. Extension of protein uptake from the early to late part of the proximal tubule results in a substantial shift in the balance of reabsorptive and secretory processes, and associated metabolic pathways, including lipid metabolism. Meanwhile, overflow of luminal proteins to the distal tubule causes transcriptional convergence between specialized regions and generalized dedifferentiation.

Conclusions: Proteinuria is a potent modulator of cell signaling in tubular epithelia and triggers extensive remodeling, in a segment specific manner. Thus, luminal protein concentration is a critical micro-environmental factor that links glomerular and tubular function in vivo. These findings could explain some of the well-recognized clinical complications that arise in proteinuric kidney disease, and may also be important for understanding nephron patterning in organ development.

FR-PO1018

Urinary Phosphate Contributes to Kidney Injury, Cyst Formation, and Inflammation

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Background: High dietary phosphate intake increases urinary phosphate excretion and has been associated with an increased risk for chronic kidney disease (CKD) progression. We hypothesize that high dietary phosphate hastens CKD progression by stimulating tubular nanocrystal formation, epithelial cell injury, microcyst formation, and inflammation when concentrations of phosphate exceed supersaturation in tubular fluid; however, the mechanisms driving this relationship remain poorly defined.

Methods: First, a mouse model of cystic kidney disease, the *Pkd1*$^{RC/RC}$ mouse, was fed a high versus low phosphate diet and analyzed for changes in kidney cyst growth, mineral deposition, tubular injury, inflammation, and fibrosis. Second, NaPi2a$^{-/-}$ mice, a model of primary urinary phosphate wasting, was evaluated to determine the direct effect of urinary phosphate excretion on mechanisms of kidney injury and inflammation.

Results: *Pkd1*$^{RC/RC}$ mice fed a high phosphate diet exhibited more rapid cyst growth and increased deposition of phosphate-based crystals in their kidneys compared to mice fed a low phosphate diet. Mineral deposits in these kidneys were spatially colocalized with macrophages and osteopontin, a matricellular protein that is critical for maintaining urinary phosphate solubility. Moreover, gene expression for markers of kidney injury, inflammation, and fibrosis were increased in *Pkd1*$^{RC/RC}$ mice on a high phosphate diet. In separate studies utilizing NaPi2a$^{-/-}$ mice, phosphaturic mutants exhibited extensive kidney crystal deposition, reduced kidney function, as well as increased gene expression for markers of kidney injury, inflammation, and fibrosis compared to wild-type controls. Separate analysis of electron microscopy in wild type mice on a high phosphate diet showed interaction of phagocytic cells with kidney mineral deposits.

Conclusions: Increased urinary phosphate excretion directly contributes to tubular injury, kidney cyst growth, inflammation, and fibrosis in CKD. Current evidence suggests a direct interaction between phosphate-based nanocrystals and local inflammatory cells may be a primary contributor to this relationship.

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FR-PO1019

Gut-Derived Uremic Toxins Correlate with Anxiety and Decreased Locomotor Activity in CKD Mice

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Background: The altered gut microbiome in chronic kidney disease (CKD) is a source of circulating uremic toxins including p-cresyl sulfate (pCS), indoxyl sulfate (IS), and trimethylamine N-oxide (TMAO). Microbe-derived uremic toxins have been correlated with depression and cognitive impairment in CKD patients. In the current study, continuous subcutaneous infusion of gut-derived toxins was done to evaluate the impact of gut-derived uremic toxins on behavior outcomes in CKD mice.

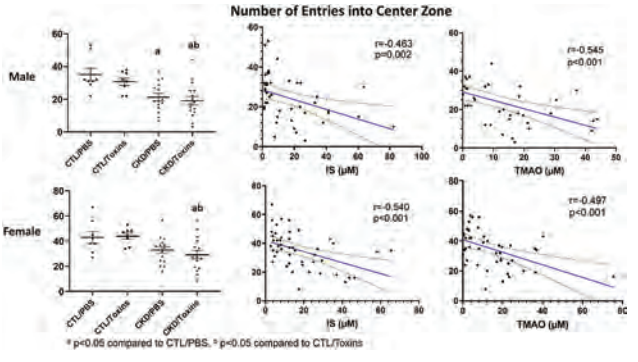
Methods: Male and female C57Bl/6J mice were randomly assigned to control or CKD groups. Tubulointerstitial nephritis CKD was induced by 0.2% adenine diet. Alzet pumps containing placebo (PBS) or uremic toxins (a mix of pCS, IS and TMAO) were implanted which delivered continuous subcutaneous dosing for 4 weeks. Prior to termination, spontaneous locomotion and anxiety (open field test) and recognition memory (novel object recognition test) were assessed. Serum levels of creatinine and gut-derived uremic toxins were measured. Group means were compared using ANOVA, and correlation analyses were done using Spearman's coefficient (r).

Results: Serum creatinine, pCS, IS, and TMAO were significantly elevated in CKD vs control mice (Table). Toxin infusion in CKD animals (CKD/Toxins) further increased serum pCS and IS compared to CKD/PBS mice in both sexes. Male and female CKD animals demonstrated decreased exploratory behavior (increased anxiety). Higher levels of creatinine, IS and TMAO were significantly associated with anxiety behavior. Infusion of gut-derived toxins did not further increase anxiety behavior compared to PBS (Figure). Recognition memory was not altered in CKD mice.

Conclusions: Gut-derived uremic toxins were significantly correlated with anxiety behavior in CKD mice. However, infusion of toxins did not further worsen behavior scores beyond control vs CKD status.

Funding: Other NIH Support - NIH R01

	Male				Female			
	CTL/PBS (n=7)	CTL/Toxins (n=8)	CKD/PBS (n=15)	CKD/Toxins (n=16)	CTL/PBS (n=8)	CTL/Toxins (n=8)	CKD/PBS (n=15)	CKD/Toxins (n=16)
Cr (mg/dL)	0.047±0.001	0.051±0.001	0.216±0.013[ab]	0.209±0.016[ab]	0.062±0.004	0.059±0.005	0.158±0.014[ab]	0.170±0.013[ab]
pCS (μM)	1.10±0.20	6.33±0.73	0.98±0.11	80.82±12.33[ab]	1.07±0.31	4.79±0.64	1.46±0.37	37.33±7.15[ab]
IS (μM)	2.03±0.31	3.06±0.39	12.01±2.30	33.86±5.65[ab]	4.06±0.42	6.39±1.04	14.89±1.78	30.39±4.09[ab]
TMAO (μM)	Not detected	0.97±0.28	11.64±2.91	20.86±3.20[ab]	2.10±1.15	1.86±0.35	14.69±2.11	23.92±4.56[ab]



FR-PO1020

CKD Induces Endotoxin-Related Activation of the Innate Immune System and Is Associated with Overall Mortality

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Background: Chronic inflammation is associated with poor outcome. The gut-kidney axis is considered an important contributor via the leaky gut. Lipopolysaccharide (LPS) is a pyrogen found in the exterior cell membrane of most gram-negative bacteria. When absorbed through the intestinal epithelium, LPS induces inflammation by activating macrophages and monocytes. Due to short half-life direct quantification of LPS is a poor marker of innate immune system activation. Lipoprotein binding protein (LBP) is an essential component of the innate immune response to LPS. Circulating LBP significantly enhances the sensitivity of CD14+ cells (mostly monocytes and macrophages) to stimulation by LPS. Levels of LBP peak in serum shortly after endotoxemia, and remain increased up to 72 hours later. We hypothesized that CKD increases levels of LBP and is associated with an increased risk of mortality.

Methods: We analyzed plasma LBP (species-specific ELISA, HycultBiotech, The Netherlands) in the Leuven mild-to-moderate CKD cohort (NCT00441623). To study causality, we used animal models of experimentally induced CKD. To exclude model-related bias, two different rat models of CKD, i.e. 5/6th nephrectomy and 0.25% w/w adenine supplementation, were used. We analysed the association between LBP and overall mortality using Cox proportional hazards analysis.

Results: In a cohort of 460 patients with CKD, LBP is significantly inversely correlated with eGFR (p <0,0001; Spearman r: -0,2209). In two different rat models, induction of CKD resulted in a significant increase of LBP. In these animals, we observed a significant inverse association between eGFR (and measured creatinine clearance) and LBP concentrations (P<0.0001). In univariate Cox proportional hazard analysis, plasma LBP was significantly associated with mortality (p <0.01). This association remained significant in multivariate models adjusted for the systematic coronary risk evaluation (score) model.

Conclusions: Patients with CKD have higher levels of LBP. Experimental CKD leads to elevation of LBP, indicative of a causal relationship. Higher LBP associates with increased risk of overall mortality. Combined with functional data on increased gut permeability our data strengthen the hypothesis of the gut-kidney axis as a source of chronic inflammation.

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FR-PO1021

Omega-3 Fatty Acid Modifies the Mitochondrial Membrane Fatty Acid and the Erythrocyte Membrane Fatty Acid in Uremic Rats

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Background: The kidney has the second highest mitochondrial content in the human body. Fatty acids (FAs) are one of the important energy sources and main constituents of cell membranes. Higher erythrocyte membrane oleic acid contents are related to acute coronary syndrome and omega-3 FA can reduce oleic acid contents. We investigated whether omega-3 FA modifies not only erythrocyte membrane FA but also mitochondrial membrane FA of kidney in adenine-induced uremic rats.

Methods: Male Sprague-Dawley rats were fed diets containing 0.75% adenine and 2.5% protein for three weeks. Rats were randomly divided into six groups that were fed diets containing 2.5% protein and saline with cholecalciferol (3000 IU/kg/week) or omega-3 FAs (300 mg/kg/day) with cholecalciferol, and supplemented by gastric gavage for four weeks: normal control, adenine control sacrified at 3 weeks, adenine control sacrified at 5 weeks, adenine control sacrified at 7 weeks, omega-3 FAs group sacrified at 5 weeks, and omega-3 FAs group sacrified at 7 weeks. The mitochondrial isolation membrane was used for renal mitochondrial extraction. The mitochondrial and erythrocyte membrane FA contents were measured by gas chromatography.

Results: Compared to the normal controls, serum creatinine levels in adenine controls were significantly increased and improved in omega-3 FA group. Compared to the adenine controls, erythrocyte and mitochondrial membrane monounsaturated FA contents including oleic acid and arachidonic acid (AA) levels were significantly decreased in omega-3 FA group. FA compositions were similar between erythrocytes and mitochondrial membranes in each group. Monounsaturated FA contents including oleic acid, and eicosapentaenoic acid (EPA) were higher and saturated FA was lower in the mitochondrial membrane than erythrocyte membrane in adenine controls.

Conclusions: Omega-3 FA affects not only erythrocyte membrane FA but also mitochondrial membrane FA in uremic rats. Erythrocyte membrane FA contents can reflect mitochondrial membrane FA contents of the kidney.

FR-PO1022

Mendelian Randomization of Hypothyroidism and Kidney Function in Veterans

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Background: Hypothyroidism and chronic kidney disease (CKD) are highly prevalent conditions with a potential mechanistic link. A previous study in women from the WGHS (N 3336) demonstrated an association of hypothyroidism and CKD. We studied the association of genetically predicted hypothyroidism in MVP, a large cohort composed of 93% men (exposure), and kidney function (outcome). The outcomes were creatinine-based GFR and cystatin-based GFR (both log-transformed) from CKDGen. We replicated our findings using two additional genetic datasets for the exposure.

Methods: Two-sample MR was conducted to study the associations between hypothyroidism and kidney function. The primary genetic instrument of the exposure for MR was derived from GWAS of hypothyroidism using data from MVP in 289,307 European American individuals (18,740 cases, 270,567 controls). We repeated the analysis in the FinnGen study (26,064 cases, 59,912 controls) and in UKBB (16,376 cases, 320,783 controls). In MVP and UKBB, the definition of hypothyroidism was based on diagnosis codes, and in FinnGen, on levothyroxine prescription purchases. The outcome was evaluated using summary statistics from GWAS for eGFR from CKDGen for eGFR creatinine (N 133,413) and eGFR-cystatin (N 32,834).

Results: Genetically predicted hypothyroidism demonstrated a causal relation with the risk of lower kidney function. In our primary analysis Cohorts: MVP/CKDGen (beta (SE): -0.009 (0.002), p 0.001). Results were consistent in sensitivity and replication analyses, as shown in **Table 1.** There was no evidence of horizontal pleiotropy.

Conclusions: Our study findings support that hypothyroidism is causally associated with lower kidney function. The mendelian randomization methodology supports a causal relationship and is less susceptible to confounding and reverse causation biases.

Funding: Veterans Affairs Support

Exposure hypothyroidism; Outcome GFR

	MVP	UKBB	Finn	MVP	UKBB	Finn
Hypothyroidism #Cases/Control	63629/384460	16376/320783	26064/59912	63629/384460	16376/320783	26064/59912
	GFR-creatinine			GFR-cystatin C		
Sample Size	133413	133413	133413	32834	32834	32834
n_SNP	68	59	20	156	58	20
IVW (beta)	-0.0092	-0.1191	-0.009	-0.0053	-0.1983	-0.0133
p-value	0.0012	0.0004	0.0062	0.0073	0.0072	0.0544
W_Median (beta)	-0.0089	-0.1242	-0.009	0.002	-0.2087	-0.0004
p-value	0.0007	0.003	0.0002	0.1572	0.0204	0.9352
MR_Egger (beta)	-0.0126	-0.1818	-0.014	-0.0019	-0.3552	-0.018
p-value	0.0226	0.02	0.1596	0.653	0.0431	0.3653

FR-PO1023

Action of 3-Hydroxymethylglutaryl CoA Reductase Inhibitors on ABCA-1 Protein (ATP-Binding Cassette Transporter-1) in Endothelial Cells Stimulated with Uremic Serum

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Background: High incidence of cardiovascular events in chronic kidney disease (CKD) presents an epidemic character, including patients on predialysis, hemodialysis and post-transplant patients covering about 50% of deaths, with a mortality rate around 9% per year. The statins have been used primarily in the treatment of dyslipidemia and have pleiotropic effects not fully elucidated, as well as, there is no evidence to support its use for attenuation of the cardiovascular outcome and its potential action on ABCA-1 transporter modulation in DRC. Thus, our aim was to verify the effect of statins on ABCA-1 modulation in cells culture of human umbilical vein (HUVEC) incubated with uremic serum from CKD patients.

Methods: Human umbilical cord vein endothelial cells (HUVEC) were pretreated with simvastatin and incubated with uremic serum. All groups were incubated for 24 hours at 37ºC, under ideal conditions of humidity and CO_2 concentration. Expression of LxR α, LxRβ, RxR-α, and ABCA-1 was performed by real-time PCR, the levels of Interleukin 10 and TNF-α in the cell supernatant were measured by enzyme immunoassay, using the ELISA kit. Transfection of HUVEC cells was performed for analysis of promoter activation mediated by LxR and RxR-reporter gene and the expression of LxRβ, RxRα and ABCA1 evaluated by Western Blott.

Results: We demonstrate that statins act on the inflammatory response of HUVEC cells exposed to the uremic environment by decreasing TNF-α secretion when compared to basal secretion. Our results suggest that the uremic environment reduces the expression of LxR-β and RxR-α leading to a consequent decrease in ABCA-1 expression in HUVEC. Pretreatement of endothlial cellwith simvastatin showed increased expression of ABCA-1, LxR-β and RxR-α, as well as the transcription of ABCA-1, LXR-β and RxR-α was significantly increased.

Conclusions: Our results suggests that statins may exert positive modulation on the LxR-β and RxR-α receptors for ABCA-1 transcription activation.

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FR-PO1024

AQP7 as a Novel Marker of p-Cresol-Induced Renal Cell Damage: Beneficial Effects of Hydroxytyrosol and a Polyphenolic Enriched Complex Derived from Olive Oil Mill Wastewater

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Background: *p*-cresol, a gut microbiota-derived uremic toxin, is related to renal injury and Chronic Kidney Disease (CKD). Nevertheless, the molecular mechanisms causing renal damage are still far from being clarified. Here, the actions of *p*-cresol and the beneficial effects of a polyphenolic enriched complex (Momast®) and hydroxytyrosol were evaluated.

Methods: Human proximal tubular kidney cells (HK-2) were used as an experimental cell model. Several cell stress biomarkers were assayed, including Reactive Oxygen Species (ROS) generation and Oil Red O lipid droplets formation. Gene and protein expression was tested by Real Time PCR and Western Blotting.

Results: Exposure of HK-2 cells to *p*-cresol (100 μM for 24 hours) caused a significant increase in ROS content and polymerization of the actin cytoskeleton. Moreover, a significant accumulation in lipid droplets was found as well. Interestingly, Real Time PCR and Western Blotting analysis revealed that *p*-cresol significantly upregulates the expression of the aquaglyceroporin AQP7. Notably, selective inhibition of AQP7 using Z433927330 prevented the *p*-cresol-induced lipid droplets storage. Of interest, the harmful actions induced by *p*-cresol were reversed by treating cells with Momast®, a natural complex derived from olive oil mill wastewater enriched with hydroxytyrosol (HT), which is filtered by the kidney and recovered in the urine. Preliminary data revealed that HT itself also prevents the *p*-cresol-induced AQP7 increase.

Conclusions: Altogether these findings propose for the first time AQP7 as a novel target related to *p*-cresol exposure. Selective inhibition of AQP7 significantly decreased lipid droplets accumulation, which is known to be correlated with renal cell injury. Additionally, treatment with Momast® prevented the effects induced by *p*-cresol. Moreover, obtained data indicate HT as a possible natural coadjuvant to counteract renal cellular injuries induced by *p*-cresol.

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FR-PO1025

Exaggerated Angiotensin II-Induced NF-kB p65 Signaling and Oxidative Stress in GSTM1-Deficient Kidney Primary Tubular Epithelial Cells Is Ameliorated by Hydrogen Sulfide

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Background: Glutathione S-transferase μ-1 (GSTM1) belongs to the superfamily of GSTs that are phase II antioxidant enzymes regulated by nuclear factor erythroid 2-related factor 2 (Nrf2). In humans, homozygous carriers of the common *GSTM1(0)* null allele are deficient of the enzyme and have increased risks of chronic kidney disease (CKD) progression. Global *Gstm1* knockout (KO) mice have increased renal levels of reactive oxygen species (ROS), inflammation, and kidney injury in angiotensin II (Ang II)-induced hypertension. We previously reported that deletion of *Gstm1* augments Ang II activation of proinflammatory NF-kB p65 signaling pathway in primary tubular epithelial cells (PTECs). Recently, we discovered that GSTM1 modulates the transsulfuration (TSP)-hydrogen sulfide (H_2S) pathway; loss of GSTM1 downregulates H_2S production. GYY4137, an H_2S donor, has been shown to prevent multi-organ damage in disease models. We hypothesize that GYY4137 would ameliorate AngII-induced NF-kB activation and ROS production in *Gstm1* KO PTECs.

Methods: PTECs were isolated from *Gstm1* KO and wild-type (WT) kidneys. Cells were starved for 4 hr, then treated with Ang II (100 nM) and with or without GYY4137 (100 mM) for 24 hr. Cells were stained with anti-NF-kB p65 antibody and assayed for ROS production using ab113851 kit (Abcam). NF-kB p65 nuclear staining was quantified as % of p65 nuclei-positively stained cells to the total cells, with 5 random fields counted (n = 6 mice in each group).

Results: After Ang II treatment, compared to WT, KO PTECs had significantly increased nuclear p65 staining (% p65+ cells: WT 9.8 ± 1, KO 23.8. ± 2.5; p = 0.001), and ROS (1.48 x higher than WT; p = 0.002). Compared to Ang II only, Ang II + GYY4137 significantly decreased p65 nuclear translocation by 4.2% in WT (p = 0.02) and 11.4 % in KO (p=0.003), and ROS generation in both WT(55%, p = 0.002) and KO PTEC (68%, p = 0.001).

Conclusions: Deletion of *Gstm1* augments Ang II induced ROS production and activation of NF-kB in PTECs in an H_2S dependent manner. Targeting the TSP-H2S pathway may be a novel therapeutic approach for CKD in those genetically susceptible.

Funding: NIDDK Support

FR-PO1026

Antisense Oligonucleotide-Mediated Terminal Intron Retention of Endoglin to Reduce Extracellular Matrix Production in Chronic Allograft Dysfunction

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Background: Chronic allograft dysfunction (CAD) is a chronic, progressive, and irreversible process associated with progressive interstitial fibrosis and tubular atrophy. Transforming growth factor-beta (TGF-β) is considered an important cytokine in the development of interstitial fibrosis. The TGF-β co-receptor endoglin *(ENG)* tends to be upregulated in several human organs when chronic damage and fibrosis is present, including the kidney. *ENG* has two membrane bound isoforms occurring by alternative splicing. The long endoglin isoform (l-*ENG)* was previously shown to enhance the extent of renal fibrosis in an UUO mouse model, while the short endoglin isoform (s-*ENG*) inhibited renal fibrosis in this model.

Methods: We isolated mRNA from kidney biopsy material of patients with CAD (n=12) to investigate expression of *ENG* and short endoglin (s-*ENG*). As a control, kidneys that were excluded for transplantation were used (n=6). Furthermore, we designed antisense oligonucleotides (ASOs) to achieve higher levels of s-*ENG* by terminal intron retention of the *ENG* pre-mRNA and transfected these in the human kidney fibroblast cell line TK173.

Results: *ENG* mRNA is 2.3 fold ($p<0.05$) upregulated in the interstitium of patients with CAD compared to mRNA from controls. Interestingly, mRNA levels of s-*ENG* were not upregulated. Therefore, the fraction of s-*ENG* from the total *ENG* mRNA was significantly lower in CAD patients compared to controls (2.4% vs 4.3%; $p<0.05$). We showed that ASOs enhanced the splicing to the short endoglin isoform (2 fold; $p<0.05$). Combining multiple ASOs did not amplify this enhancement. After transfection with various ASOs, the ASO covering the exonic splicing enhancer decreased *CCN2*, *COL1A1* and *FN1* mRNA expression after TGF-β1 stimulation (respectively 20%, 30%, 20%; $p<0.05$).

Conclusions: *ENG* mRNA levels are upregulated in CAD, but s-*ENG* which is suggested to inhibit renal fibrosis, does not increase accordingly. With ASOs targeting *ENG* splicing we were able to alter the *ENG* isoform ratio towards s-*ENG* and reduce TGF-β1 downstream signaling. These results open the way to explore the potential of *ENG* ASOs as a therapy to reduce interstitial fibrosis and thereby slowing down the progression to end stage kidney disease.

FR-PO1027

p300/CBP-Associated Factor (PCAF) Modulates HIF-1 Activity at Multiple Steps

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Background: Hypoxia-inducible factor (HIF) is a transcription factor that mediates the cellular response to hypoxia. The activity of HIF may be inadequate relative to the degree of hypoxia in patients with chronic kidney disease (CKD), resulting in impaired cellular adaptation to hypoxia. p300/CBP-associated factor (PCAF) is a transcriptional coactivator and has acetyltransferase activity. Recent studies have suggested that PCAF expression is downregulated in patients with end-stage kidney disease (ESKD). We aimed to elucidate the relationship between PCAF and HIF-1 in the kidney.

Methods: We subjected human kidney-2 (HK-2) cells, a human proximal tubular cell line, to hypoxia and examined the association between PCAF and HIF-1 by qPCR, western blotting, microarray analysis, hypoxia-responsive element-luciferase (HRE-luc) reporter assay, and Gal4 responsive element-luciferase (GRE-luc) reporter assay. GRE-luc assay employed a vector encoding Gal4 DNA binding domain (DBD)-HIF-1α transactivation domain (TAD) fusion protein and a GRE-driven luciferase reporter vector.

Results: Knockdown (KD) of PCAF resulted in decreased expression levels of HIF-1α protein and *VEGF* mRNA, one of the major HIF-1 target genes. The HRE-luc assay revealed that PCAF KD reduced HIF-1 transcriptional activity. The GRE-luc assay showed the inhibition of HIF-1α TAD activity by PCAF KD. Overexpression of full-length PCAF upregulated GRE-luc activity, whereas a mutant PCAF lacking the histone acetyltransferase (HAT) domain failed to increase GRE-luc activity, indicating that the HAT domain was necessary for the regulation of HIF-1α TAD activity. Additionally, PCAF KD led to decreased mRNA and protein levels of ARNT, a binding partner of HIF-1α, and inhibited the interaction between HIF-1α and ARNT. Transcriptome analysis using microarray revealed that PCAF KD globally downregulated the expression of hypoxia-inducible genes.

Conclusions: Our findings demonstrate that PCAF modulates HIF-1 activity at multiple steps and serves as a global positive regulator for HIF-1.

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FR-PO1028

Pathophysiology of Hyperoxaluria in SAMP1/YitFc Mice

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Background: Enteric hyperoxaluria (EH) is postulated to arise from increased oxalate (Ox) bioavailability in the gastrointestinal (GI) tract secondary to fat malabsorption. This could lead to chronic kidney disease progression or recurrent kidney stones. Crohn's disease (CD) is one of the most prevalent conditions causing EH. The SAMP1/YitFc (SAMP1) mouse model develops spontaneous ileal inflammation mimicking human CD pathology. In this ileitis mouse model, we aim to confirm the development of the EH phenotype and explore the different factors underlying EH pathophysiology.

Methods: We compared adult SAMP1 mice and their closest genetic control (AKR mice) on three different fat-containing diets (10%, 45%, and 60%), all supplemented with 1% Ox. Urine (U), plasma (P), and fecal samples were collected during the study and GI segments were harvested at sacrifice at week 5. We measured Ox and creatinine (Cr) levels in the blood and urine. We performed lipidomics assessments of fecal fats to assess malabsorption. Tight junction proteins are important determinants of gut permeability. Occludin and ZO1 were assessed in the ileum using qPCR and Western Blots (WB), respectively.

Results: UOx increased with the percentage of dietary fat, an increase marked in the SAMP1 mice compared with AKR. At sacrifice comparing SAMP1 to AKR, UOx/UCr was 0.40±0.01 vs 0.28±0.01 μmol/mg on 45% fat and 0.45±0.04 vs 0.28±0.02 μmol/mg on 60% fat (both $p<0.0001$). At sacrifice, POx and PCr were higher in SAMP1 mice compared to AKR. The SAMP1 mice had a higher abundance of lipid species in the feces. Specifically, increased amounts of diacylglycerols and free fatty acids in SAMP1 stool samples suggest fat malabsorption. ZO1 and Occludin levels were lower in SAMP1 as compared to AKR mice.

Conclusions: After confirming the EH phenotype, we were able to characterize important factors underlying EH in this model. Decreased TJ in SAMP1's ileum, suggesting increased gut permeability, and a higher bioavailability of Ox arising from fat malabsorption contribute to increased passive Ox reabsorption. Next steps will include exploring the microbiome of these mouse models and characterizing the determinants of kidney injury in these models.

Funding: NIDDK Support

FR-PO1029

Glutathione Synthesis Contributes to the Formation of Tertiary Lymphoid Tissues in the Kidney

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Background: Tertiary lymphoid tissue (TLT) is an ectopic lymphoid tissue that is induced in non-lymphoid organs by several stimuli such as autoimmunity, aging, and chronic inflammation. TLTs serve as local sites for adaptive immune responses, in which vigorous lymphocyte proliferation and inflammatory cytokine production occur. Unlike the systemic activation of secondary lymphoid tissues, de novo formation of TLTs in local organs may require significant metabolic remodeling to meet the increased demand for metabolic resources both in parenchymal cells and immune cells. However, how renal parenchymal cells and locally recruited immune cells undergo metabolic alterations that support TLT formation remains to be elucidated.

Methods: We employed imaging mass spectrometry and metabolome analysis to investigate the key metabolic pathways that characterize renal TLTs. We also performed in situ hybridization combined with immunofluorescence to investigate the key molecules that govern the metabolic microenvironment of TLTs. Furthermore, we analyzed urine samples from both humans and mice to explore the metabolites that predict the presence of renal TLTs.

Results: Compared to other organs, the kidney contained more cysteine/cystine, a glutathione substrate. Kidneys with TLTs exhibited a significantly higher concentration of glutathione than normal kidneys, and high-level enrichment of glutathione was observed specifically in renal TLTs, highlighting the altered redox homeostasis within TLTs. DCs and fibroblasts within TLTs co-expressed xCT and MRP1, which are essential for external cystine intake and intercellular glutathione transport, respectively. Pharmacological inhibition of xCT prevented renal TLT formation, highlighting the importance of glutathione synthesis in renal TLT formation. Furthermore, enhanced glutathione synthesis in TLTs was reflected in the urinary glutathione concentrations in both mice and humans, indicating that urinary glutathione levels could effectively predict the presence or absence of renal TLTs.

Conclusions: We demonstrated that enhanced glutathione synthesis facilitates TLT formation in the kidney and that urinary glutathione can serve as a biomarker to detect renal TLTs. Immunometabolic interventions may provide new therapeutic strategies for kidney diseases.

Funding: Government Support - Non-U.S.

FR-PO1030

DNA Double-Strand Breaks in Proximal Tubular Epithelial Cells Induce a Systemic Lipodystrophy-Like Phenotype

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Background: We have recently reported that podocyte DNA double strand breaks (DSBs) induce alteration in DNA methylation of CD8 memory T cells which exacerbates severe podocyte injuries (Cell Rep 2023). We next investigated the pathophysical significance of DNA DSBs in PTECs.

Methods: To investigate the significance of DNA double-strand breaks (DSBs) in PTECs, we generated PTEC-specific I-PpoI-expressing mice (I-PpoI mice) which express homing endonuclease I-PpoI inducing non-mutagenic DNA DSBs.

Results: I-PpoI mice showed only mild elevation of tubular markers, but presented weight loss, increased liver free fatty acid content, decreased epidermal fat mass and impaired glucose tolerance at 16 weeks of age, which was consistent with the phenotype of systemic lipodystrophy. Metabolomic analysis showed mitochondrial dysfunction with impaired fatty acid metabolism in kidney cortex and liver. Single-cell RNA seq analysis revealed a marked expansion of inflammatory $Ly6C^{hi}$ monocytes and $Ccr2^{hi}$ $CD11c^{+}$ macrophages in renal cortex of I-PpoI mice, which is reported to play an important role on metabolic derangement in adipocytes and insulin resistance. In vitro analysis of cultured PTECs overexpressing I-PpoI showed mitochondrial dysfunction as observed in I-PpoI mice measured by Seahorse Extracellular Flux Analyzer. In addition, culture medium of PTECs overexpressing I-PpoI caused an activation of macrophages. Next, methylated DNA Immunoprecipitation (MeDIP)-Sequencing of peripheral blood cells in wild type and I-PpoI mice was performed. Interestingly, the motif analysis showed hypomethylated regions in binding sites of KLF9, which is reported to be associated with diabetic complications in humans (Nat Metab 2020). It was also confirmed that downstream genes of KLF9 was hypomethylated, including PFKFB3, which is reported to promote the proliferation and infiltration of inflammatory $Ly6C^{hi}$ monocytes into tissues and its differentiation into macrophages.

Conclusions: DNA damage in PTECs activated a different population of immune cells and caused quite different phenotypes from that in podocytes. PTEC DNA damage causes systemic metabolic alterations, associated with altered DNA methylation in peripheral blood cells.

FR-PO1031

Detection of Cellular Respiration Pattern of Platelets and Peripheral Blood Mononuclear Cells in CKD

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Background: Reduced cellular respiration of platelets and increased respiration of peripheral blood mononuclear cells (PBMCs) were reported to be associated with more severe chronic heart diseases. This cellular phenotype remains to be established for patients with chronic kidney disease (CKD).

Methods: The analysis included stage 4 or 5 CKD patients and healthy controls with normal kidney function. The investigation was performed using Oroboros O2K-respirometer on intact and digitonin permeabilized cells. Cellular respiration was measured with a high resolution respirometry. Demographic and medical characteristics of participants including the cellular respiration of platelets and PBMCs were compared using Wilcoxon Rank Sum or Chi-square test.

Results: There were 27 CKD participants and 15 controls; median age (y) was 61 and 56, respectively. Two-third CKD subjects were African Americans and half of them were diabetic. The median GFR was 18 in the CKD group and 90 in the control group. There were no differences in white blood cell count or platelet count between the two groups. There was reduced respiration in the intact CKD platelets and in the permeabilized CKD platelets via Complex I & II of the electron transport chain (ETC). There was increased respiration in the intact CKD PBMCs as well as in the permeabilized CKD PBMCs via complex I & II of ETC.

Conclusions: Cellular respiration is reduced in CKD platelets and is increased in CKD PBMCs. Future studies should explore whether these cellular phenotypes result in a pro-inflammatory CKD state that is associated with worse cardiorenal outcomes.

Funding: Private Foundation Support

FR-PO1032

Alterations in Frequency and Function Exhausted Memory B Cells in Lupus Nephritis and Systemic Lupus Erythematosus

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Background: Various B cell abnormalities have been implicated in the pathogenesis of LN, and our previous studies have demonstrated that memory B cells assume pathogenic relevance in disease relapse. Exhausted B cell is a B lymphocyte aberration initially reported in HIV infection, and was also observed in autoimmune disorders. The pathogenic roles of exhausted B cells in LN and disease relapse remains unclear.

Methods: Classical memory (CD19+CD21+CD27+) and exhausted B cells (CD19+CD21–CD27–) were measured in LN patients with multiple relapses (MR) (n=12) or no relapse (NR) (n=12) during disease remission. B cell-related cytokines, homing and inhibitory receptors, proliferation and calcium mobilization in classical and exhausted memory B cells were also assessed. Using single-cell RNA sequencing data from NIH and GEO, we also performed bioinformatics analysis to identify genes and pathways relevant to memory and exhausted B cells in SLE, LN and healthy controls.

Results: The MR group exhibited higher proportion of circulating exhausted B cells compared to NR (16.7 ± 9.5% vs 10.5 ± 5.7%, $p < 0.05$). Blood levels of IL-6, BAFF and IL-21 in MR patients were higher than the NR group (75.1 ± 37.2 vs 33.6 ± 14.2 pg/ml; 1491.1 ± 680.9 vs 1120.1 ± 384.1 pg/ml and 23.5 ± 23.0 vs 5.1 ± 3.1 pg/ml respectively; $p<0.05$, for all). The MR had higher blood levels of Siglec-6, CXCR3 and CD62L than the NR group (2.6 ± 0.8 vs 1.3 ± 0.6 ng/ml; 2.3 ± 1.4 vs 1.6 ± 0.8 ng/ml; 3240.9 ± 1002.0 vs 2497.0 ± 671.8 ng/ml respectively, $p<0.05$ for all). Expression of inhibitory receptors CD22, CD85j, CD183 and FCRL4 in exhausted B cells were increased in the MR group compared to the NR group. Exhausted B cells from MR patients also showed decreased proliferation compared to NR patients (1.9 ± 1.1% vs 3.8 ± 1.3%, $p<0.05$) and impaired calcium mobilization in response to B-cell receptor triggering. STAT1, XAF1, MX1, IFI44L, EPSTI1, LCP1, OAS1, NEAT1, IFI16, IFI44 in exhausted B cells and XAF1, MX1, IFI44L in memory B cells play a pathogenic role in LN patients. SLE patient also show increased proportion of exhausted B cells compared to healthy control and the expression of STAT1, XAF1, MX1, IFI44L correlate positively with the proportion of exhausted B cells.

Conclusions: Our results suggested that altered numbers and function of exhausted B cells may have pathogenic significance in SLE and LN.

Funding: Government Support - Non-U.S.

FR-PO1033

Leukocyte Chemotactic Factor 2 Amyloidosis in an Egyptian Immigrant

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Introduction: Amyloidosis results from the accumulation of misfolded protein in one or more organs. Over 30 amyloid proteins have been discovered[1]. Identification of the pathogenic amyloid protein is crucial for the management of amyloidosis. Here we present a case of an unexpected cause of amyloidosis.

Case Description: A 69-year-old Egyptian man was referred for evaluation for chronic kidney disease. His history included well-controlled diabetes and hypertension. His creatinine was 1.7 mg/dL, having increased steadily from 0.96 mg/dL five years prior. Urinalysis was bland and urine protein to creatinine ratio was 0.1 g/g. Serologic evaluation was unremarkable except for a monoclonal spike seen on urine protein

electrophoresis. He underwent a kidney biopsy to evaluate for monoclonal gammopathy of renal significance. It showed abundant amyloid deposition in the interstitium; amyloid was also seen in the mesangium and glomerular capillary walls. Mass spectrometry analysis at the Mayo Clinic Laboratories identified the amyloid protein not as an immunoglobulin but as leukocyte chemotactic factor 2 (LECT-2). He does not appear to have LECT-2 amyloidosis (ALECT-2) involvement of other organs. He continues to be managed supportively with an ACE-inhibitor and a SGLT-2 inhibitor. Despite these measures, his creatinine continues to increase by 0.2-0.3mg/dL per year.

Discussion: ALECT-2 was first described in 2008 in an individual with nephrotic syndrome[2]. Nephrotic syndrome has only been found in a minority of cases of ALECT-2 in subsequent series – individuals typically have a bland urine sediment and minimal proteinuria. ALECT-2 commonly affects the kidneys and liver; cardiac involvement appears rare. Its prevalence appears to vary significantly among ethnic groups. In the United States, it has been found most commonly in Hispanic populations, particularly in those of Mexican descent[2]. ALECT-2 is also common in Egypt; in an Egyptian case series, it was the second most common type of renal amyloidosis, accounting for 31% of cases[3]. It is unclear why it is more common in certain populations, although a single nucleotide polymorphism of the LECT2 gene has been found in individuals of Mexican ancestry. Currently, there is no specific treatment for ALECT-2. ALECT-2 is likely underdiagnosed due to the frequent lack of proteinuria. An individual's ancestry may provide a clue toward the diagnosis.

FR-PO1034

Unveiling the Masquerade: Misdiagnosis of CKD in the Shadow of HIV Treatment

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Introduction: HIV is associated with acute and chronic kidney disease (CKD). The co-existence of CKD with HIV is associated with poor outcomes and limits therapeutic interventions, particularly those that require renal-dose adjustment. Specific antiretroviral therapies (ART) are directly nephrotoxic, leading to low GFR (Glomerular Filtration Rate) and elevated serum creatinine. However, some ART can increase serum creatinine by inhibiting the tubular secretion of creatinine, leading to elevated serum creatinine, erroneous estimation of GFR by eGFR, and a misdiagnosis of CKD. These drugs include non-nucleoside reverse transcriptase inhibitors (NNRTI) such as rilpivirine, HIV integrase inhibitors such as dolutegravir, and pharmacokinetic boosters such as cobicistat. We present a case of mislabeled CKD in the setting of cobicistat use.

Case Description: A 44-year-old man with a history of hypertension, non-insulin-dependent type 2 diabetes, and HIV was referred for evaluation of "CKD," diagnosed due to persistent elevation of serum creatinine. The patient's HIV was well controlled on Genvoya®, ART containing elvitegravir, cobicistat, emtricitabine, and tenofovir. Previous creatinine levels were 1.2, 1.4, and 1.6 mg/dL, in the last 12 months. Recent pre-clinic labs showed a creatinine of 1.48 mg/dL with an eGFR of 59 mL/min/1.73 m2 without albuminuria or hematuria. Renal ultrasound showed preserved renal size and normal anatomy. To obtain an accurate assessment of GFR, we directly measured GFR (mGFR) using plasma clearance of iohexol, a non-radiolabeled contrast agent. The mGFR of 72 mL/min/1.73 m2. Thus, the eGFR calculation was incorrect and mislabeled him as CKD. Cobicistat reduces serum creatinine secretion by reducing proximal tubular creatinine efflux by the SLC47A1 cation transporter.

Discussion: Evolving combination HIV therapies have improved compliance, tolerance, and sustained viral suppression. However, clinicians must be mindful of the impact of ART on the kidney. Our case highlights the false elevation of serum creatinine induced by ART like Genvoya® and the importance of directly measured GFR. Modern methods to measure GFR are simple and easy to implement in outpatient practice. It is essential that nephrologists learn these techniques and use them in clinical practice to prevent misdiagnosis of CKD and avoid further invasive tests, including kidney biopsy.

FR-PO1035

Finerenone Added to Renin-Angiotensin System (RAS)/SGLT2 Blockade for Non-Diabetic CKD: Results of a Preclinical Randomized Controlled Trial

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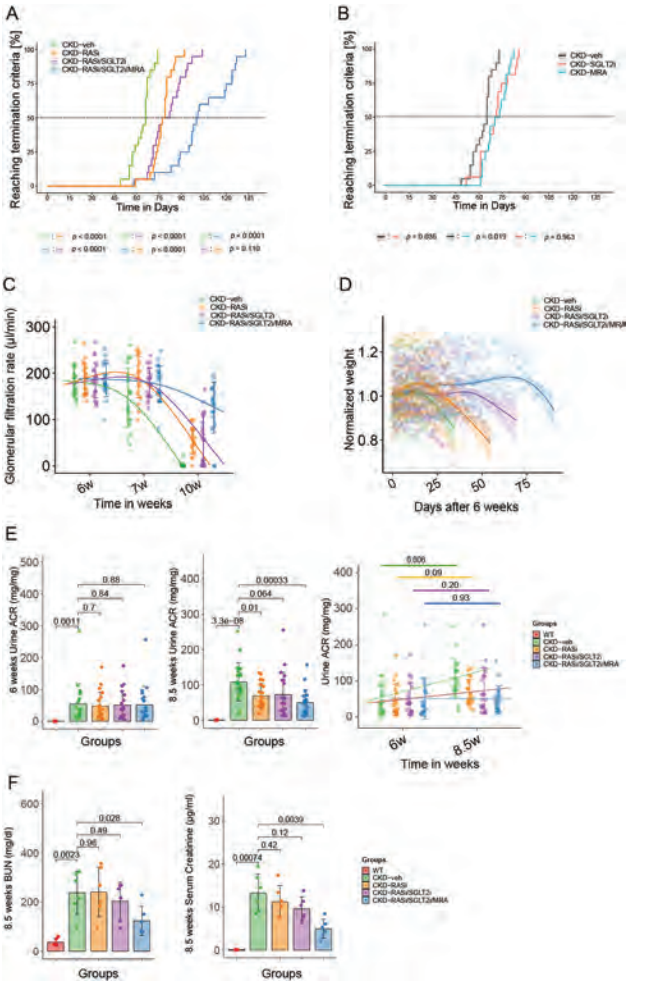
Background: Dual inhibition of RAS plus SGLT2 or plus MR demonstrated additive renoprotective effects in large clinical trials. We hypothesized that triple therapy with a combination of RAS/SGLT2/MR inhibitors would be superior to dual RAS/SGLT2 blockade in prolonging kidney lifespan.

Methods: We performed a preclinical randomized controlled trial (PCTE0000266) in *Col4a3*-/- Alport mice. Treatment was initiated late (6 weeks of age) in mice with elevated serum creatinine and albuminuria and in presence of glomerulosclerosis, interstitial fibrosis and tubular atrophy. We randomized male and female mice to either nil (vehicle) or late onset food admixes of either monotherapy, ramipril (10 mg/kg) plus empagliflozin (30 mg/kg) or ramipril plus empagliflozin plus finerenone (10 mg/kg). Other control mice received empagliflozin or finerenone monotherapy.

Results: Mean lifespan was 63.7 ± 10.0 days (vehicle), 77.3 ± 5.3 days (ramipril), 70.4 ± 9.2 days (empagliflozin), 71.1 ± 7.1 days (finerenone), 80.3 ± 11.0 days (dual), and 103.1 ± 20.3 days (triple), respectively. Sex did not affect outcome. Histopathology, pathomics, and RNA sequencing revealed significant add-on anti-inflammatory and anti-fibrotic effects on the tubulointerstitial compartment when adding finerenone to dual RAS/SGLT2 inhibition.

Conclusions: This pRCT suggests that triple RAS/SGLT2/MR blockade may significantly prolong uremia-free lifespan significantly in patients with Alport syndrome and possibly other progressive chronic kidney disorders for its synergistic protective effects on the glomerular and tubulointerstitial compartment, respectively.

Funding: Government Support - Non-U.S.



Overall survival and other markers of excretory kidney function; Albuminuria and other markers of kidney barrier function.

FR-PO1036

Protective Effect of Resveratrol on Glycocalyx Loss due to Endothelial Cell Dysfunction in Renal Aging

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Background: Aging had an effect on diminished endothelial glycocalyx caused by various mechanisms, and sirtuin1 (SIRT1) pathway was one of the crucial components of them. As aging process, there was decline in SIRT1 activity with consequent increase in oxidative stress and inflammation, which were known causes of aging. Resveratrol, an SIRT1 activator, may prevent these undesired events by activating SIRT1 pathway. We examined whether resveratrol could improve renal function and prevent from diminishing endothelial glycocalyx caused by aging, and consequently with changes of oxidative stress.

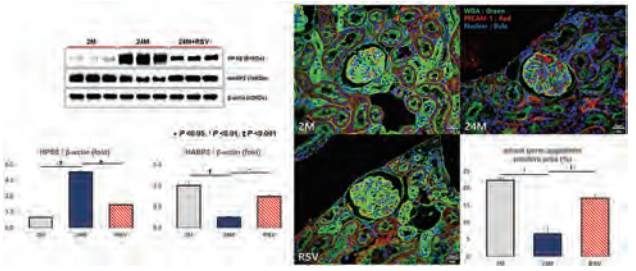
Methods: Male 2-month-old and 18-month-old C57BL/6 mice were divided into three groups: 2-month-old young group, 18-month-old aged control group and 18-month-old aged treatment group. Resveratrol (40 mg/kg) was administered to aged treatment group for 6 months. Renal function, histologic changes and aging-related protein expression, especially with oxidative stress and SIRT1 pathway, were measured. Endothelial glycocalyx was also examined by immunofluorescence staining with WGA.

Results: Compared to young group, aged group showed decreased renal function, increased oxidative stress, progressed renal fibrosis, decreased expression of SIRT1, eNOS and increased expression of iNOS, NF-κB, heparanase which is consistent with

aging process. On the contrary, aged treatment group showed improvement of creatinine clearance and albuminuria which represent renal function. Histologic changes of mesangial proliferation and tubulointerstitial fibrosis were also improved. Expression of SIRT1 protein and eNOS was also increased and expression of iNOS, NF-κB, and heparanase was decreased, which could explain that activation of SIRT1 pathway ameliorate oxidative stress. Endothelial glycocalyx of treatment group was also markedly observed, whereas which of aged group sparsely observed.

Conclusions: These results suggest that the activation of SIRT1 had protective effect against aging-related oxidative stress in mice via SIRT1 pathway and consequently gave a stability in endothelial glycocalyx.

Funding: Government Support - Non-U.S.



FR-PO1037

The Effect of Ischemia-Reperfusion Injury on Mitochondrial Reduced Glutathione Levels in Kidney Cortex and Medulla from Aging Female Lewis Rats

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Background: The purpose of the study was to determine the effect of ischemia-reperfusion injury (IRI) on changes in the mitochondrial reduced glutathione (GSH) levels in kidney cortex and medulla from old rats. GSH is the major antioxidant inside cells, and a decrease in GSH levels would result in oxidative stress and damage due to increased generation of free radicals in IRI.

Methods: Anesthetized female Lewis rats (22 months of age) were used. Both renal pedicles were clamped for 60 min, followed by 60 min of reperfusion in the Experimantal Group (n =5). The kidneys were then harvested, separated into cortex and medulla, and homogenized. Kidneys in the Control Sham Group (n=5) were not subjected to IRI before being harvested. The mitochondrial fractions were isolated by differential centrifugation, and GSH levels were measured using a spectrophometric assay. The water contents of the cortex and medulla were determined to allow GSH levels to be expressed as nmol/g kidney dry weight. A Student's T Test was used to compare groups, and statistical significance was determined at $p< 0.05$. All data reported as X ± SEM.

Results: There was a significant 58% decrease in mitochondrial GSH levels in the kidney cortex, from 388 ± 19 nmol/g kidney dry wt in the Control Group to 163 ± 6 nmol/g kidney dry wt in the Experimental Group. There was also a significant 40 % decrease in mitochondrial GSH levels in the kidney medulla, from 531 ± 32 nmol/kidney dry wt in the Control Group to 318 ± 22 nmol/ g kidney dry wt in the Experimental Group.

Conclusions: Mitochondrial GSH levels in rat kidney cortex and medulla did not return to normal levels after one hour of reperfusion following 60 minutes of ischemia. This finding suggests that mitochondria in both the kidney cortex and medulla are experiencing major oxidative stress, and this may be contributing to the renal dysfunction seen in IRI.

FR-PO1038

Age-Related CKD: Roles of Advanced Glycation End Products and Insulin-Like Growth Factor Binding Protein-3

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Background: CKD is more prevalent in US adults aged 65 years or older. Advanced glycation end products (AGEs) are highly associated with diabetic nephropathy, and its levels are elevated in individuals with advancing age. A pro-apoptotic effect of insulin-like growth factor binding protein-3 (IGFBP-3) was found in diabetic nephropathy. Blood IGFBP-3 levels increase in CKD patients that is negatively correlated with eGFR. Roles of AGEs and IGFBP-3 in renal senescence and dysfunction during aging process remains unclear that's what we want to investigate.

Methods: A commercial tissue microarray for human normal kidneys from subjects with various ages was used to test the expression of Nε-(1-Carboxymethyl)-L-lysine (CML; an AGEs) and IGFBP-3. Male C57BL/6 mice with the age of 6, 19, 70 and 107 weeks were used. To determine the roles of AGEs and IGFBP-3 in aging kidney, aged mice (70-week-old) were orally administered with aminoguanidine, an inhibitor of AGEs, or injectedly administered with a neutralizing IGFBP-3 antibody.

Results: Both CML and IGFBP-3 protein expression levels in the human kidneys were significantly higher in the elderly (≥ 50 years) than in the young ($p<0.05$, n=24). In naturally aged mice (70- and 107-week-old), the blood renal function markers examination, Periodic acid-Schiff stain, and Masson's trichrome stain showed that there were renal dysfunction, histological changes, and collagen deposition, respectively ($p<0.05$, n=8). The depositions of CML/AGEs and IGFBP-3 were obviously increased in the kidneys of aged mice compared to the young controls ($p<0.05$, n=8). Moreover, the protein expression levels of markers for senescence and fibrosis increased in the kidneys of aged mice ($p<0.05$, n=8). The pathological features, increased CML and IGFBP-3 protein expression, and increased senescence and fibrosis-related markers protein expression in the kidneys of aged mice could be effectively antagonized by AGE inhibitor aminoguanidine treatment ($p<0.05$, n=8). The neutralizing IGFBP-3 antibody treatment could also alleviate the pathological features and fibrosis in the kidneys of aged mice ($p<0.05$, n=8).

Conclusions: These findings demonstrated that both AGEs and IGFBP-3 played the roles in age-related CKD. An AGEs-regulated IGFBP-3 signaling pathway may contribute to the renal dysfunction and injury during natural aging process.

Funding: Government Support - Non-U.S.

FR-PO1039

Aldehyde Dehydrogenase 2 Interacts with PHB2 to Alleviate Renal Fibrosis and Ferroptosis in a Mitochondria-Dependent Manner

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Background: We recently proved the protective role of acetaldehyde dehydrogenase 2 (ALDH2) in acute kidney injury (AKI). In this study, we aimed to investigate the impact of ALDH2 on renal fibrosis in regulating ferroptosis in a mitochondria-dependent manner.

Methods: Renal fibrosis model was established by unilateral ureteral obstruction (UUO) in C57BLmice, followed by injection of Alda-1 (an ALDH2 agonist) on the first postoperative day and continued for 14 days until mice were sacrificed. We assessed renal fibrosis, ferroptosis, and mitochondrial function in vivo and in vitro using RSL-3 (a ferroptosis-inducing agent) in human renal proximal tubular epithelial (HK-2) cells, with or without Alda-1 (20μm). Furthermore, we identified the potential targets of ALDH2 in regulating ferroptosis and mitochondrial dysfunction by mass spectrometry screening and co-immunoprecipitation assays, then explored the role of ALDH2 on different cell types by single-cell RNA sequencing.

Results: ALDH2 protein was reduced by 64% in UUO mice accompanied by renal interstitial fibrosis. ALDH2 agonist Alda-1 alleviated renal interstitial fibrosis, as confirmed by Masson staining and the decreased expression of α-SMA and collagen 1. Ferroptosis was initiated during UUO-induced renal fibrosis, while Alda-1 inhibited ferroptosis, indicated by reduced malonaldehyde (MDA) (1.60±0.10 versus 0.66±0.08 nmol/mg, $P<0.001$) and elevated GSH/GSSH ratio (1.42±0.32 versus 6.80±0.84, $P<0.05$). In addition, decreased mitochondrial-related proteins (PGC-1α and ATP5a1) were observed in UUO mice but reversed by Alda-1 treatment. In HK-2 cells, ALDH2 improved RSL-3-induced ferroptosis, fibrosis, and mitochondrial dysfunction. Mechanistically, mass spectrometry screening and co-immunoprecipitation assays revealed the interaction of ALDH2 with prohibitin 2 (PHB2), a crucial mitophagy receptor and ferroptosis inhibition target. Immunofluorescence staining revealed the co-localization of ALDH2 and PHB2, and Alda-1 facilitated PHB2 recruitment into mitochondria from the cytoplasm.

Conclusions: ALDH2 might be a promising therapeutic target in alleviating renal fibrosis and ferroptosis by interacting with PHB2 to facilitate their mitochondrial translocation.

FR-PO1040

Acyloxyacyl Hydrolase Protects Against Kidney Injury via Inhibition of Tubular CD74-Macrophage Cross-Talk

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Background: Renal tubulointerstitial fibrosis is the final common pathway in the progression of chronic kidney disease (CKD) to end-stage renal disease (ESRD). Acyloxyacyl hydrolase (AOAH) is expressed in renal tubular epithelial cells and other immune cells. Research shows that AOAH plays a critical role in infections and chronic inflammatory diseases. However, its role in kidney injury and fibrosis is unknown.

Methods: AOAH expression was examined in human and mouse kidneys. Single cell RNA sequencing (scRNA-seq) was performed for kidneys from FA-treated wild type (WT) and *Aoah*$^{-/-}$ mice. *Aoah*$^{-/-}$ mice and *Aoah*$^{-/-}$ mice with overexpression of *Aoah* in kidney were used to determine its role in kidney injury induced by folic acid (FA), unilateral ureteral obstruction (UUO), and lipopolysaccharide (LPS).

Results: AOAH expression was positively correlated with estimated glomerular filtration rate (eGFR) while negatively correlated with the degree of renal fibrosis in human kidney biopsy tissue. AOAH deletion led to exacerbated kidney injury and fibrosis after FA administration, which was reversed by overexpression of *Aoah* in kidney. scRNA-seq analysis revealed that *Aoah*$^{-/-}$ mice exhibited increased subpopulation of proximal tubular epithelial cells (PTECs) expressing CD74, even though total PTECs were decreased compared to WT mice after FA treatment. Finally, exacerbated renal inflammation and fibrosis seen in *Aoah*$^{-/-}$ mice after kidney injury was attenuated via administration of ISO-1, an inhibitor of macrophage inhibition factor (MIF) and CD74 binding.

Conclusions: AOAH plays a protective role in renal inflammation and fibrosis by inhibiting renal tubular epithelial cells CD74 signaling pathways, which involves tubule-macrophage crosstalk. Targeting kidney AOAH represents a promising strategy to prevent renal fibrosis progression.

FR-PO1041

Protective Role of Tubular Interferon Regulatory Factor 5 (IRF5) Against Renal Tubulointerstitial Fibrosis

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Background: Tubulointerstitial fibrosis (TIF) is the inevitable outcome of chronic kidney diseases, regardless of etiology. Interferon regulatory factor 5 (IRF5) is a key transcription factor involved in regulating the expression of proinflammatory cytokine and responses to infection in immune cells, but its role in renal epithelial cells and renal TIF remain unknown.

Methods: Renal biopsies of CKD patients and kidney of unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion (UIR) mice were used to evaluate the expression pattern of IRF5 in fibrotic kidneys. Then, the function of IRF5 was explored in UUO mice via high-throughput tail vein delivery of IRF5 over-expression plasmids or IRF5 targeting CRISPR/Cas9 plasmids. The TIF was histologically detected by Masson staining; pro-fibrosis gene expressions were evaluated via Western blotting and qRT-PCR techniques. *In vitro*, mouse proximal tubular epithelial cells (mPTCs) were transfected with IRF5 over-expression plasmids and then stimulated with TGF-β1 for phenotype evaluation. IRF5 over-expression mPTCs were also co-cultured with renal interstitial fibroblasts (NRK-49Fs) and macrophage cells (RAW 264.7). Finally, IRF5 overexpressing mPTCs were treated with Smad3 selective inhibitor SIS3 to explore whether the anti-fibrotic effect of IRF5 is Smad3 dependent.

Results: IRF5 was consistently up-regulated in fibrotic kidneys of CKD patients and mice models, dominantly in the tubules. Overexpression of IRF5 markedly alleviated renal TIF, and knocking down of IRF5 significantly aggravated the degree of fibrosis in UUO mice. *In vitro*, overexpression of IRF5 inhibited TGF-β1 induced partial epithelial-mesenchymal transition (p-EMT) of mPTCs. IRF5 over-expression in TGF-β1 induced mPTCs also suppressed the activation of co-cultured NRK-49Fs and RAW 264.7 cells. Mechanic research revealed that IRF5 suppressed fibrotic response possibly by antagonizing TGF-β1/Smad3 signaling.

Conclusions: These findings demonstrated that up-regulation of IRF5 may inhibit p-EMT of tubular epithelial cells via antagonizing TGF-β1/Smad3 signaling. In turn, protected tubular epithelial cells attenuated the activation of interstitial fibroblasts and macrophages and thus attenuate kidney fibrosis. Targeted activation of IRF5 may serve as a potential intervention strategy in retarding CKD progression.

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FR-PO1042

TP53RK in Fibroblasts Drives the Progression of CKD by Phosphorylating Birc5

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Background: Renal fibrosis is a common characteristic of various chronic kidney diseases (CKDs) driving the loss of renal function. During this pathological process, proliferation and activation of interstitial fibroblasts chiefly determine the extent of renal fibrosis. TP53RK is an atypical protein kinase and an important component of the EKC/KEOPS complex. Recently, TP53RK was identified as novel monogenetic cause of Galloway–Mowat syndrome. However, no experimental evidence confirmed the role of TP53RK in CKDs.

Methods: Expression and localization of TP53RK was evaluated in kidneys of CKD patients and mice with unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion (UIR). Then, the specific function of fibroblast TP53RK in CKD was determined with fibroblast specific TP53RK knockout mice with UUO or UIR and TGF-β1-treated renal interstitial fibroblasts (NRK-49F). Furthermore, co-immunoprecipitation and immunofluorescent staining were applied to determine the co-localization and interaction between TP53RK and Birc5. UUO mice with global Birc5 knockdown were employed to specify the role and downstream mechanism of Birc5 in renal fibrosis. Finally, TP53RK inhibitor fusidic acid and Birc5 specific inhibitor YM-155 were tested in UUO mice to evaluate the translational potential of pharmacological blockade in treating CKD.

Results: P53RK was upregulated in fibrotic human and animal kidneys with a positive correlation to kidney dysfunction and fibrotic markers. Specifically, TP53RK was up-regulated in interstitial fibroblasts of fibrotic kidneys. Fibroblasts specific deletion of TP53RK could mitigate renal fibrosis in UUO and UIR mice models. *In vitro*, knocking down of TP53RK attenuated activation and proliferation of NRK-49F. Mechanistic investigations revealed that TP53RK phosphorylated Birc5 and facilitated its nuclear translocation, which displayed a pro-fibrotic effect possibly via activating PI3K/Akt and MAPK pathways. Moreover, pharmacologically inhibiting TP53RK and Birc5 using fusidic acid and YM-155 respectively both ameliorated kidney fibrosis in UUO mice.

Conclusions: These findings demonstrate that activated TP53RK/Birc5 signaling promotes the proliferation and activation of renal interstitial fibroblasts, thus driving CKD progression. A genetic or pharmacological blockade of this axis serves as a potential strategy for retarding fibrosis in CKD.

Funding: Government Support - Non-U.S.

FR-PO1043

Activation of GPER1 in macrophage ameliorates Unilateral Ureteral Obstruction (UUO)-Induced Renal Fibrosis

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Background: Numerous studies have established the fundamental role of macrophages in the process of renal fibrosis. Interestingly, emerging data suggested that G protein-coupled estrogen receptor 1 (GPER1), a novel estrogen receptor, plays a ubiquitous role in regulating macrophage activities and proinflammatory pathways. However, the precise role of GPER1 in macrophage-mediated renal fibrosis remains unknown.

Methods: First, we pretreated ovariectomized (OVX) female and male mice with G-1 (GPER1 agonist) and subjected them to UUO (Ureteral Unilateral Obstruction) surgeries. And renal fibrosis and M1 and M2 macrophage infiltration were analyzed. Next, using CRISPR/Cas9 gene editing technique, we also generated global knockout Gper1 mice. We performed UUO modeling on the male Gper1-/- mice and measured the degree of renal fibrosis and inflammation. In in vitro study, bone marrow-derived macrophages were treated with G-1 in response to LPS/Interferon γ or Interleukin 4 and cocultured with PTECs (primary tubular epithelial cells) or fibroblasts.

Results: Compared to vehicle-treated OVX female and male mice subjected to UUO, both G-1-treated OVX female and male UUO mice exhibited fewer renal fibrotic lesions and less M1 and M2 macrophage infiltration in the kidney tissues, respectively. On the other hand, Gper1 deletion accelerated renal fibrosis and enhanced chemokines and proinflammatory cytokines expression. In vitro study demonstrated that GPER1 activation prevented M0 macrophages from polarizing towards the M1 and M2 phenotypes. The Gene Ontology analysis of differentially expressed genes in macrophages treated with or without G-1 indicated that GPER1 activation was primarily involved in the inactivation of MAPK pathways, which was further validated by immunoblotting. In addition, PTECs cocultured with G1-pretreated M1 macrophages exhibited fewer injuries and immune activation, and fibroblasts cocultured with G1-pretreated M2 macrophages showed downregulated extracellular matrix expression.

Conclusions: Overall, our study is the first study to demonstrate the effect of GPER1 on macrophage-mediated renal fibrosis via inhibition of M1 and M2 macrophage polarization. These results indicate that GPER1 may serve as a promising therapeutic target for the treatment of renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO1044

GPER1 Plays a Protective Role Against AKI to CKD Transition

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Background: Male patients have a higher prevalence of CKD and increased rates of ESRD than those observed in female patients. Many factors are believed to be involved in this phenomenon. GPER1, a de novo estrogen receptor, has been shown to play an important role in the renal fibrosis process. Whether GPER1 is protective against AKI to CKD transition and its main mechanism remains unclear.

Methods: Using CRISPR/Cas9 gene-editing technique, we generated Gper1 global knockout mice. We subjected the mice to Aristolochic acid(AA) and Folic acid(FA) injections to mimic AKI to CKD transition. We treated AA-injected and FA-injected mice with a GPER1 agonist(G-1). We also cultured primary tubular epithelial cells(TECs) from wild-type and *Gper1*$^{-/-}$ mice and treated the primary cells and NRK-49F cell lines with TGFβ1 and oleic acid with or without G-1 administration.

Results: In both AA and FA injection models, Gper1 knockout mice exhibited more severe renal fibrosis, increased inflammation infiltration, decreased fatty acid oxidation, and activated PI3K/AKT pathway compared to wild-type mice. GPER1 agonist attenuated renal fibrosis and improved fatty acid oxidation in AA-injected and FA-injected mice models, respectively. In vitro study, TGFβ1-treated Gper1-/- TECs showed a reduction in fatty acid oxidation and ATP synthesis. GPER1 activation restored fatty acid oxidation and ATP synthesis, which were suppressed by TGFβ1 and oleic acid in primary PTECs and NRK-49F.

Conclusions: These results suggest that GPER1 may play a protective role against AKI to CKD transition through the fatty acid oxidation pathway. Activation of GPER1 expression may provide a new therapeutic target for AKI to CKD transition.

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FR-PO1045

Inhibition of ATP-Citrate Lyase Improves CKD Through Multiple Mechanisms

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Background: ATP-citrate lyase (ACLY), upregulated in chronic kidney disease (CKD), catalyzes the synthesis of acetyl-coA from citrate. Acetyl-CoA is a vital precursor for lipid synthesis and histone acetylation that regulates gene expression. In kidney cells, ACLY regulates fibrogenic, lipogenic and inflammatory gene expression; its inhibition reduced fibrosis in the unilateral ureteral obstruction (UUO) model. The ACLY metabolic by-product malonyl-coA, however, is also an important inhibitor of fatty acid oxidation (FAO), and defective FAO in proximal tubular epithelial cells (PTEC) is now established as a major contributor to fibrosis. Here we tested the efficacy of a novel ACLY inhibitor (ACLYi) on reducing fibrosis and its potential role in improving FAO in UUO.

Methods: 8-week-old male C57BL/6J mice underwent UUO surgery and were treated orally with an ACLY inhibitor (Espervita Therapeutics) for 10 days. Kidneys were assessed by immunohistochemistry, immunoblotting and RNAseq. Effects of ACLYi were tested on the HK2 PTEC cell line and primary renal fibroblast responses to TGFβ1 (5ng/ml, 48h), a cytokine known to promote fibrosis and reduce FAO. Lipid accumulation was assessed by Oil Red O staining and LC/MS analysis.

Results: ACLYi significantly and dose-dependently decreased fibrosis in the UUO model determined by trichrome, PSR, fibronectin and α-smooth muscle actin (SMA) expression. ACLYi decreased macrophage (F4/80) infiltration including that of the profibrotic M2 phenoype marked by CD206. RNAseq analysis showed upregulation of FAO-related hallmark pathways and reduction in inflammation pathways with ACLYi. Defective FAO is known to result in PTEC apoptosis and lipid accumulation. ACLYi reduced both apoptosis, as assessed by the presence of cleaved caspase 3, as well as lipid accumulation, with a particular decrease in cholesteryl esters. In HK2 cells and renal fibroblasts, TGFβ1-induced fibrotic protein expression was inhibited by ACLYi, and lipid accumulation was reduced in PTEC.

Conclusions: ACLYi reduced renal fibrosis, apoptosis and lipid accumulation in UUO mice. ACLYi also prevented profibrotic responses to TGFβ1 in PTEC and fibroblasts. Current studies are ongoing to confirm beneficial effects on restoring FAO.

Funding: Commercial Support - Espervita Therapeutics, Government Support - Non-U.S.

FR-PO1046

Immunomodulatory and Metabolic Adaptation in Transcriptional Signature After Knockdown of Proliferating Lymphatic Vessels in Mice with Renal Fibrosis

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Background: Our previous study has reported that renal lymphangiogenesis accelerates the progression of chronic kidney disease (CKD). However, it is not clear which immune cell types drive renal outcome.

Methods: We established the selective proliferating lymphatic vessel knockout mice for unilateral ureteral obstruction (UUO)-induced fibrosis. Bulk RNA sequencing and single-cell RNA sequencing were used to characterize changes in the transcriptional profiles of renal parenchymal and immune cell following the knocking down of lymphatic vessels (LVs).

Results: The fibrosis were alleviated following knockdown of LVs. Bulk RNA sequencing showed that the impaired secretion of cytokines and chemokines, and impaired energy metabolism were improved. Single-cell RNA sequencing confirmed that the decreased proportion of epithelial cells was restored, and the immune cells aggregation (especially NK cells and T lymphocytes) was dissipated. Three subpopulations of NK cells were identified: NK1, characterized as $CD27^{+}CD11b^{+}$ NK cells that primarily facilitate the migration of myeloid immune cells, was enhanced; NK2, characterized as $CD27^{+}CD11b^{-}$ NK cells that mainly stimulate the differentiation of lymphoid immune cells, was increased; and NK3, characterized as $CD27^{-}CD11b+$ NK cells that function as pro-inflammatory cells, was significantly decreased. Ten subpopulations of T lymphocytes were identified: the proportion of CD8+T, CD4+ T, γδT, NKT, IFN-related T, effector memory T, and Tregs were increased, serving mainly to promote immunity cell activation, while the proportion of proliferative T, Th17, and naïve CD8+T, that mainly promoting the migration of immune cells, were significantly decreased. Subsequently, stromal cells and their extra-cellular matrix (ECM) production capacity decreased following LV knockdown. Additionally, the LVs knockdown caused an attenuation of G2/M arrest and programmed death in injured tubular epithelial cells (TECs) while restoring fatty acid oxidation and gluconeogenesis.

Conclusions: Knocking down of proliferating LVs improve the inflammatory immune microenvironment via the regulation of NK and T cells, and then inhibit stromal cells to produce ECM and restore the energy metabolism of TECs, which suggest proliferating LVs is a potential therapeutic target for renal fibrosis.

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FR-PO1047

1,3-Butanediol Decreases Unilateral Ureteral Obstruction (UUO)-Induced Tubulointerstitial Inflammation and Fibrosis by Regulating the mTORC1 Signaling Pathway

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Background: Chronic kidney disease (CKD) has long been considered a prominent contributor to global mortality due to its extensive prevalence and profound negative consequences. Given the widespread prevalence and severe adverse impact of CKD, it is imperative to develop new strategies for the prevention and treatment. Acetoacetate, β-hydroxybutyrate (BHB), and acetone can be called "endogenous ketone bodies." It has been suggested that renal ketogenesis, specifically BHB contributes to cell metabolism under conditions of energy deprivation, including fasting and exercise. This study evaluated the effect of exogenous BHB in UUO-injured renal inflammation and fibrosis mice.

Methods: Seven to eight-week-old male C57BL/6 mice were divided into four groups randomly and assessed whether unilateral ureteral obstruction operated or sham-operated in this experiment. The mice were administered with whether 20% 1,3-butanediol (1,3-BD) solution or vehicle served as a daily drink seven days before UUO surgery and continued for 14 days after surgery. We evaluated renal histology, immunohistochemistry, and immunofluorescent staining for renal tubulointerstitial inflammation and fibrosis. We also assessed proinflammatory cytokines and chemokines by qRT-PCR and western blotting.

Results: 1,3-BD is an exogenous ketone body chemical that can be administered orally. 1,3-BD treatment mitigates UUO-induced renal tubular injury, inflammatory cell infiltration, and fibrosis. The inflammatory response was induced with the recruitment of inflammatory cells and tissue regeneration, and treatment of BHB in UUO-injured mice decreased proinflammatory cytokines and cell adhesion molecules expression. There was an increased phosphorylation/activation of mTORC1 signaling in the veh-treated UUO group, and it was attenuated after the administration of 1,3-BD.

Conclusions: Administration of 1,3-BD decreases the UUO-induced renal tubulointerstitial injury, inflammation, and fibrosis by suppressing the activation of the mTORC1 signaling pathway. Suppression of mTORC1 signaling might have a protective effect on UUO-induced tubular injury, fibrosis, and inflammation.

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FR-PO1048

Dicarboxylic Acids Protect Against CKD

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Background: Chronic kidney disease (CKD) affects 30 million people in the US and over 800 million people worldwide. Treatment for end-stage renal failure is largely limited to renal transplant or lifelong dialysis, creating an urgent need for new therapies. We have shown that dicarboxylic acids are protective against acute kidney injury (AKI) in the proximal tubule via hypersuccinylation of mitochondrial and peroxisomal proteins, thereby bolstering peroxisomal fatty acid oxidation over mitochondrial FAO. In this study we aimed to determine whether this mechanism could be leveraged to protect against fibrotic damage due to chronic kidney injury, which we model using Unilateral Ureteral Obstruction (UUO) surgery.

Methods: Wild-type male B6/129 mice were procured from Jackson Laboratories and the experimental group fed with an 10% 8-chain dicarboxylic acid (DC_8, suberic acid) diet. Both the experimental and the control groups underwent UUO surgery, whereby the ureter of one kidney was obstructed for three days before both kidneys were harvested. Each kidney was split into four pieces as follows – 1. histological and immunohistochemical staining; 2. fatty acid oxidation analysis; 3. succinylome analysis using targeted mass spec; 4. snap-frozen for validation and downstream analysis of fibrosis, as well as peroxisomal and mitochondrial signaling.

Results: As previously shown, there was hypersuccinylation in the DC_8 treated animals compared to control fed animals. This was accompanied with corresponding upregulation of peroxisomal FAO specifically in the collecting ducts, which was confirmed by targeted mass spec. Supplementation of DC_8 showed marked protection in the collecting ducts, with decreased dilation and tubular epithelial shedding compared to controls. There was also a decrease in the dilation of the renal pelvis in DC_8 treated animals. Further to this immunohistochemical staining showed a decrease in fibrotic markers in the kidneys of DC_8-fed animals.

Conclusions: Taken together this suggests that DC_8 is protective against collecting duct damage and fibrotic changes that occur in CKD. This expands the utilization of DC8 therapy beyond the acute setting and into fibrosis and chronic kidney disease.

FR-PO1049

Dose-Dependent Nephroprotective Effects of an ALK5 Inhibitor in the Unilateral Ureteral Obstruction (UUO) Mouse Model of Kidney Fibrosis

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Background: Development of renal fibrosis is a hallmark of chronic kidney disease (CKD) and an essential factor for progressive loss of kidney function and development of end-stage kidney disease. The unilateral ureteral obstruction (UUO) mouse is a widely used surgery-induced model of CKD with rapid induction of renal inflammation and fibrosis. Here, we characterized the effect of an anti-fibrotic TGF-β type 1 receptor kinase inhibitor (ALK5 inhibitor, ALK5i) on renal outcomes in the UUO mouse.

Methods: Male C57BL/6J mice (9 weeks old) were randomised into study groups based on body weight and were either sham-operated or underwent UUO surgery. UUO mice received vehicle or ALK5i (3, 10 or 30 mg/kg, PO, BID) for 8 days. Vehicle-dosed sham-operated mice served as controls. At termination, both kidneys were weighed, and the obstructed left kidney was processed for quantitative histological assessment of macrophage infiltration (F4/80), fibrosis (Col1a1, Col3a1), myofibroblast activation (α-SMA) and tubular injury (KIM-1). Plasma was sampled for measurement of KIM-1 levels.

Results: UUO mice displayed marked kidney tubular injury, macrophage infiltration, myofibroblast activation, and fibrosis as compared to sham-operated animals. ALK5i dose-dependently improved kidney histology and plasma KIM-1 levels.

Conclusions: ALK5i exerted dose-dependent nephroprotective effects in the UUO mouse. Given the rapid induction of fibrosis and inflammation, the UUO mouse is optimal for screening of compounds with potential anti-inflammatory and anti-fibrotic effects.

Funding: Commercial Support - Gubra

FR-PO1050

Cellular Prion Protein Attenuates Renal Fibrosis by Interaction with Epithelial Growth Factor Receptor

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Background: Cellular prion protein (Prp^c) coded by the *Prnp* gene, is a kind of cell-surface copper-binding protein, anchoring on cell membrane lipid rafts through glycosyl phosphatidyl inositol anchor (GPI), and plays an important role in cell information transmission. Prp^c is expressed in the kidney. However, the role of Prp^c in regulating fibrotic maladaptive repair of the injured kidney remains largely unknown.

Methods: Wild-type FVB mice, $Prnp^{-/-}$ mice were used for in vivo studies. Renal I/R injury model was induced by bilateral renal pedicle clamping for 35 minutes. Renal fibrosis models were induced by unilateral renal pedicle clamping for 30 minutes (UIR) and by unilateral ureteral obstruction (UUO). HK-2 cells were used for in vitro studies. HK-2 cells were treated with TGF-β induce EMT.

Results: Prp^c is overexpressed in the kidney biopsies from patients with CKD. This is supported by our experimental data showing that Prp^c is gradually upregulated in the kidney following I/R, UIR and UUO insult and Prp^c deletion by knocking out *Prnp* promoted AKI and facilitated fibrosis at later stages. Proteomics analysis indicated that the expression of key protein in DDR, including replication protein A (RPA), minichromosome maintenance protein 2/4/6 (MCM2/4/6) and cyclin-dependent kinases 1/2 (CDK1/2), as well as epidermal growth factor receptor (EGFR) drastically upregulate in the I/R kidney, while in $Prnp^{-/-}$ mice, EGFR rises even further with DDR-associated protein slumping. Furthermore, we uncover a critical role of Prp^c in the control of EGFR signaling by promoting internalization of EGFR in renal tubular epithelia cells, which in turn influences DNA replication followed injury and renal fibrosis.

Conclusions: In summary, our study provides experimental evidence showing that Prp^c plays an adaptive nephroprotective role by modulating activation of EGFR pathway and promoting cell cycle progression.

Funding: Government Support - Non-U.S.

FR-PO1051

Piperazine Ferulate Regulates Renal Fibrosis by Alleviating Oxidative Stress in Renal Tubular Epithelial Cells

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Background: Chronic kidney disease (CKD) is one of the greatest public health hazards worldwide with a high mortality rate, poor quality of survival. Oxidative stress in CKD could aggravate tubular injury to renal fibrosis. The treatment of oxidative damage to renal tubular epithelial cells still needs extensive research and development of drugs. This study was conducted to explore the effect of piperazine ferulate on renal fibrosis and the antioxidant mechanism of renal tubular epithelium and to provide a theoretical basis for the application of piperazine ferulate in CKD.

Methods: 36 male C57 mice at 6-8 weeks were randomly divided into six groups (n=6): sham group (saline 0.2 mL), UUO group (saline 0.2 mL), piperazine ferulate low-dose intervention in UUO group (piperazine ferulate 50 mg/kg, 0.2 mL), piperazine ferulate medium-dose in UUO group (piperazine ferulate 100mg/kg, 0.2 mL), piperazine ferulate high dose in UUO group (piperazine ferulate 200mg/kg, 0.2 mL), and piperazine ferulate alone (piperazine ferulate 200mg/kg, 0.2 mL). The mice were then anesthetized and executed on the 7th day after surgery, and the relevant samples were collected and stained with HE, PAS and Masson to observe the tubular shape, atrophy, necrosis and the degree of interstitial fibrosis, and the fibrosis-related indexes FN, collagen-1, αSMA and p-Smd3 were observed by immunohistochemistry or protein blotting. The safe concentration range of piperazine ferulate in HK2 cells was screened by CCK8 in vitro and IC50 was calculated to select a safe concentration for intervention in TGF β-treated HK2 cells, subsequently protein blotting was used to detect FN, collagen-1, p-Smad3, KIM-1, HO-1 and dichlorofluorescein (DCF) was revealed in HK2 cells after intervention. of renal tubular epithelial cells were detected by protein blotting.

Results: Pathological staining showed that the fibrosis, renal tubular epithelial injury and oxidative stress significantly ameliorated in UUO mice after piperazine ferulate treatment at a dosage dependent manner, compared to that of sham-operated group. We also observed the same phenomenon in the HK2 cells with piperazine ferulate treatments upon TGF β stimulation.

Conclusions: Piperazine ferulate could significantly alleviate oxidative stress injury in renal tubular epithelial cells against renal fibrosis.

Funding: Government Support - Non-U.S.

FR-PO1052

Apabetalone Reduces Fibrotic Inflammatory and Calcific Factors in Renal Cells and Patient Plasma

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Background: The BET protein inhibitor apabetalone downregulates the expression of genes involved in fibrosis, inflammation and calcification, processes that drive cardiovascular disease and kidney dysfunction. In the phase 3 BETonMACE trial, apabetalone reduced the risk of major acute cardiac event (MACE) by 50% in the subpopulation with CKD (eGFR<60) implying favorable effects on the kidney-heart axis. Here we examine effects of apabetalone on processes of nephropathy in human renal mesangial cells (MCs) and assess plasma proteomics in CKD subjects or controls.

Methods: MCs were stimulated with TGF-β1, a pro-fibrotic cytokine, ± 1 to 25μM apabetalone. Gene expression was measured by real-time PCR, protein secretion by ELISA, smooth muscle actin (α-SMA) by immunofluorescence, collagen with picrosirius red, cell contraction in collagen gels and tissue non-specific alkaline phosphatase (TNAP) activity in biochemical assays. Plasma proteomics (Somascan 1.3) were evaluated in 8 CKD subjects (eGFR <30) and 8 controls after a 100mg dose of apabetalone. Ingenuity Pathway Analysis (IPA) analyzed upstream regulators.

Results: In MCs, apabetalone downregulated TGF-β1 stimulated α-SMA gene expression up to 89% and abolished α-SMA stress fiber formation and cell contraction. Collagen deposition was reduced to unstimulated levels. mRNA and enzyme activity levels for TNAP, involved in calcification, were reduced up to 96%. Apabetalone countered TGF-β1 induced gene expression and protein secretion of key drivers of fibrosis and inflammation including thrombospondin, fibronectin, periostin, osteonectin and IL-6 ($p<0.001$ for all MC results). Plasma levels of these factors were reduced 12h after taking apabetalone specifically in CKD subjects. IPA predicted TGF-β1 pathway activation in CKD vs controls, and its inhibition after the dose of apabetalone.

Conclusions: Through epigenetic regulation of transcription in MCs, apabetalone suppresses fibrotic, inflammatory and calcific factors associated with CKD. Plasma levels of fibrotic and inflammatory proteins were reduced specifically in CKD subjects. This may, in part, explain reduced MACE risk in the CKD subpopulation receiving apabetalone in BETonMACE, which will be further evaluated in future phase 3 trials.

Funding: Commercial Support - Resverlogix Corp.

FR-PO1053

Deletion of EZH2 from Renal Tubular Cells and Stroma-Derived Interstitial Cells Protects Mice from Kidney Fibrosis by Inhibition of Notch Signaling and Preservation of Klotho and BMP7 Expression

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Background: Although histone methyltransferase enhancer of zeste homolog 2 (EZH2) was denovo expressed in multiple cell types in the injured kidney, the contribution of EZH2 in specific cell type to renal fibrosis and the underlying mechanism remains poorly defined.

Methods: Mice with deletion of EZH2 from renal interstitial fibroblasts or renal tubular cells were generated and subjected to unilateral ureteral obstruction (UUO) to investigate renal fibrotic changes and signaling mechanisms and in comparison with the effect of EZH2 inhibitors. Chromatin immunoprecipitation was performed to analyze the association of EZH2 and H3K37 with Notch1 and Notch 3 as well as klotho and BMP7 promoters, respectively.

Results: Compared with wild type, mice with conditional deletion of EZH2 in renal interstitial cells or in renal tubular cells developed less renal fibrosis following UUO injury. Tubule-specific deletion of EZH2 was associated reduced expression of vimentin and Snail and preserved expression of E-cadherin. Genetic depletion of EZH2 in either cell type or pharmacological inhibition of EZH2 reduced injury –induced expression of Notch1 and Notch3, active form of Notch1 and their signaling components Jagged-1, Hes1 and Hes2. In wild-type mice, pharmacological inhibition of EZH2 with GA or GSK126 also improved tubulo-interstitial damage and antagonized activation of Notch

signaling. In cultured renal epithelial cells, TGFb1 exposure promoted the interaction of EZH2 with Notch1 or Notch3, and expression of Jagged-1, Hes1 and Hes2, and EZH inhibition abrogated these responses. Finally, chromatin immunoprecipitation indicates that kidney injury enhanced EZH2 and H3K27me3 at the promoter regions of the Notch1 and Notch3 promoter, and treatment with EZH2 inhibitor abolished this response.

Conclusions: Our data indicate that overexpression of EZH2 in renal tubular cells and fibroblasts contributes to renal fibrosis by a mechanism associated with the activation of Notch signaling and suppression of Klotho and BMP7.

Funding: Government Support - Non-U.S.

FR-PO1054

Protective Effect of Heparan Sulphate Derivative Against Glycocalyx Damage-Induced Renal Fibrosis in Aging Mice

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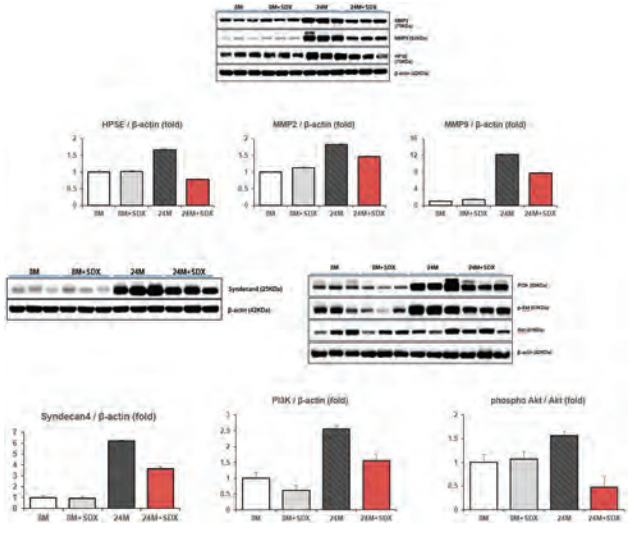
Background: Aging-related glycocalyx loss causes renal fibrosis in aging kidneys. Heparan sulphate (HS) derivative was anticipated overcoming diabetic nephropathy model. Sulodexide is a well-known HS derivative. We investigated the effects of SDX on the PI3K/Akt pathway as a renoprotective pathway in a mouse model of aging.

Methods: C57BL/6 mice were divided into four groups according to age and SDX administration for six months: the eight-month-old mice with vehicle (YM group, n= 10), the eight-month-old mice with SDX (YM+SDX group, n=8), the twenty four-month-old mice with vehicle (AM group, n= 10), the twenty four-month-old mice with SDX (AM+SDX group, n=8). SDX was administered to 10 mg/kg per oral daily for six months. We compared the following parameters between the groups: renal function, blood pressure, renal pathology, activities of the PI3K-Akt-MMP2 and MMP9-Syndecan4 in renal tissue.

Results: Renal function was improved based on serum creatinine and 24 hours albuminuria in AM+SDX group compared with the AM group ($p<0.05$ for all), but it was not different between the YM group and the YM+SDX group. Areas of renal fibrosis and expressions of protein related to fibrosis significantly reduced in the AM+SDX group compared with the AM group ($p<0.05$), but the YM+SDX group was similar with the YM group. In protein related with PI3k-Akt pathway, the AM+SDX group showed significantly lower expression of PI3K, phosphorylated Akt, MMP2, MMP9 and syndecan4 than the AM group ($P<0.05$ for both), but the YM+SDX group was not different compared with the YM group.

Conclusions: SDX, which is a HS derivative, alleviated the protein expression associated with PI3k-Akt pathway in kidneys of aging mice, but those changes were not observed in that of young mice. SDX may provide renoprotective effects via PI3k-Akt pathway in aging kidneys.

Funding: Government Support - Non-U.S.



FR-PO1055

Rubus coreanus Extract Attenuates Kidney Fibrosis Through TGF-β/Smad Pathway Inhibition

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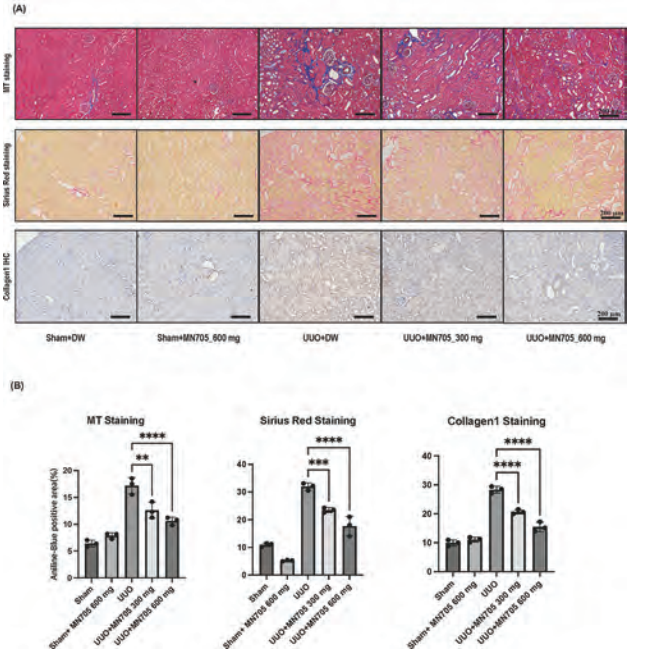
Background: Rubus coreanus, a wild berry belonging to the Rosaceae genus, has been found to have various health benefits, including anti-oxidative effects.

Methods: Male C57BL/6 mice (7 weeks old, n = 30) were randomly assigned to the sham/vehicle (distilled water), sham/MN705 (600 mg/kg/day), UUO/vehicle, UUO/MN705-low dose (300 mg/kg/day), and UUO/MN705-high dose (600 mg/kg/day) groups in the same numbers (n = 6 in each group). MN705 and distilled water were administered orally using a stainless feeding needle. After 7 days of pre-treatment, sham or UUO operation was performed, and treatment drugs were administered at the same dose for 7 days. In addition, HK-2 cells were cultured and challenged with TGF-β (2 ng/ml) with or without an extract of Rubus coreanus (0.05-0.2 mg/ml).

Results: In the histopathologic specimen of Masson's trichrome stain, areas of kidney interstitial fibrosis were attenuated in the treatment group (3.6 ± 0.9 % area vs. 8.7 ± 3.0 % area, $P < 0.01$).). In the Western blot analysis, protein abundance of collagen-1 (50.6% of control, $P = 0.04$) significantly decreased in the treatment group. In the *in vitro* experiment, HK-2 cells treated with TGF-β and MN705 showed a dose-dependent significant decrease in the protein expression of fibronectin (64.7% of control in 0.1 mg/ml dose, 22.3% of control in 0.2 mg/ml dose, $P = 0.01$). and phospho-smad2/3 (87% ± 22% of control in 0.2 mg/ml dose, $P < 0.01$)

Conclusions: The extract of Rubus coreanus attenuates kidney fibrosis in the UUO mouse model and TGF-β-treated human kidney proximal tubular cells. TGF-β-related Smad and Smurf signaling pathways involved in the development of fibrosis in both *in vivo* and *in vitro* models are effectively inhibited through extract of Rubus coreanus and can be a potential target for treatment of kidney fibrosis**.**

Figure 4



FR-PO1056

HSP90 Inhibitor 17-DMAG Downregulated METTL3 and Attenuates Renal Fibrosis in AKI to CKD Model

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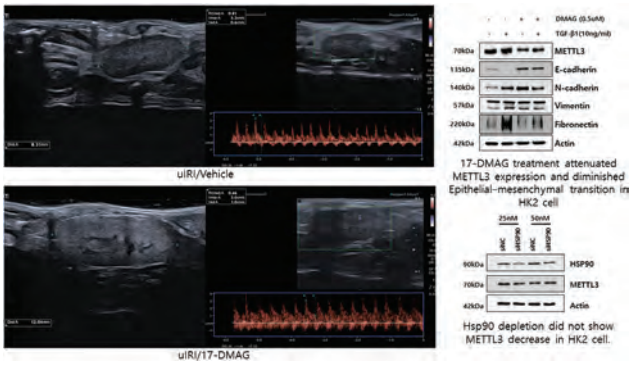
Background: N6-methyladenosine (m6A) RNA methylation has been reported to participate in post-transcriptional gene expression regulation and development of kidney fibrosis.

Methods: AKI to CKD transition was induced by unilateral ischemic-reperfusion (uIRI) method (transient clamping followed by de-clamping of renal artery) in C57BL/6 mice. HSP90 Inhibitor 17-DMAG was injected intraperitoneally with 20 mg/kg dose. Renal fibrosis is evaluated using both imaging and molecular parameters. As imaging parameters, size, resistive index (RI), vascular index (VI; colored pixels / all pixels on microvascular imaging), and shear wave parameters were compared. Histology-based fibrosis score was also evaluated. And we evaluated the expression of fibrosis and inflammatory marker proteins such as TGF-β, α-SMA, Collagen 1 and E-Cadherin in uIRI model. Furthermore, we incubated human proximal tubular epithelial (HK2) cells under TGF-β (10 ng/ml) treatment as an in vitro model of kidney fibrosis.

Results: Imaging biomarkers of uIRI/17-DMAG showed better results than that of uIRI/vehicle (Size, 7.3±3.3mm vs. 10.7±0.86mm; RI, 0.79±0.09 vs. 0.68±0.05; VI, 9.4±6.0% vs. 18.0±4.1%, all $p<0.05$). Shear wave elastography did not show significant difference between uIRI/17-DMAG and uIRI/vehicle mice. 17-DMAG treatment attenuated the degrees of kidney fibrosis in vivo mice uIRI model (Histology-based fibrosis score 7.5±1.2 in uIRI/vehicle vs. 4.6±1.7 in uIRI/17-DMAG, $P = 0.016$). Expression of α-SMA and Collagen 1 proteins were lesser in uIRI/17-DMAG compared to uIRI/vehicle. In HK2 cell, 17-DMAG attenuated METTL3 expression regardless of TGFβ treatment. 17-DMAG treatment also downregulated epithelial marker (E-cadherin), and upregulated interstitial markers (N-cadherin, Vimentin, NET1). However, Hsp90 depletion using siHsp90RNA did not show METTL3 decrease in HK2 cell.

Conclusions: 17-DMAG treatment attenuated renal fibrosis both in vitro TGFβ-challenged HK2 cell model and in vivo AKI to CKD mice model. METTL3 expression was diminished by 17-DMAG treatment.



FR-PO1057

Omega 3 Fatty Acids Attenuated AKI to CKD Transition and Renal Fibrosis: Identification of Anti-Fibrotic Metabolites

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Background: Renal fibrosis, recognized as a histological hallmark of CKD, has become an object of interest as a prospective therapeutic target. Recent meta-analyses showed that the patients with AKI are at high risk of developing CKD, and the concept of AKI to CKD was established. ω3 fatty acids (ω3PUFA) were reported to exhibit renal protective effects. However, their renal protective mechanism has remained unclear. In this study, we aimed to investigate the effect of ω3PUFA on AKI to CKD and to identify the active fatty acid metabolites against renal fibrosis.

Methods: Mice were fed a normal diet or an ω3PUFA diet. After 4 weeks of feeding, bilateral renal ischemia-reperfusion (IR) was performed. The activity of fatty acid metabolites was assessed by using human monocyte-derived cell lines (THP-1 cells) and human tubular epithelial cell lines (HK-2 cells) and rat renal fibroblasts cell lines (NRK49F cells).

Results: The normal or ω3PUFA diet was fed for 4 weeks, and IR (35 min) was performed to induce severe AKI. ω3PUFA diet improved the survival after AKI as compared to the normal diet. Next, AKI to CKD model (IR: 30 min) was subjected to evaluate the effect of ω3PUFA. ω3PUFA group exhibited the suppression of tubular damage and fibrosis at day 14 after renal IR. Renal fatty acid metabolites were measured, and multivariate analysis showed a significant increase in eicosapentaenoic acid (EPA) and its metabolites (18-HEPE, 17,18-EpETE, 17,18-diHETE) in the ω3PUFA group. When THP-1 cells were stimulated with LPS and the supernatant was added to HK-2 cells, an increase in IL-6 expression was observed, whereas when THP-1 cells were co-treated with EPA's metabolites, IL-6 expression was suppressed. In NRK-49F cells, TGF-β1-stimulated upregulation of α-SMA expression was suppressed by the presence of EPA and its metabolites.

Conclusions: Feeding ω3PUFA improved the survival after severe AKI and reduced tubular damage and renal fibrosis in AKI to CKD. The anti-inflammatory and anti-fibrotic effects of EPA and its metabolites were shown.

FR-PO1058

Inhibition of HDAC11 Attenuates Renal Fibrosis Through Blocking Partial Epithelial-Mesenchymal Transition

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Background: HDAC11 is the only member of the class IV histone deacetylases (HDACs) and is highly expressed in brain, heart, kidney et al and participates in diverse pathophysiological processes, such as tumor growth, immune regulation, oxidant stress injury et.al. However, it remains unclear whether HDAC11 involves in renal fibrosis.

Methods: In this study, we assess the role of HDAC11 in the development of renal fibrosis in Unilateral Ureteral Obstruction (UUO) mouse model. To examine the efficacy of HDAC11 in renal fibrosis after UUO injury, FT895 at 5mg/kg in 50 uL DMSO was given intraperitoneally after ureteral ligation and then administered daily for 7 days. The mice were euthanized kidney was collected on day 7.

Results: Masson trichrome staining results showed collagen fibrils were extensively deposited within the interstitial space in the kidney after UUO injury. Immunoblot analysis of kidney tissue lysate demonstrated increased expression of αSMA, collagen I, and fibronectin in the kidney after UUO injury. However, administration of FT895 significantly reduced ECM deposition and significantly decreased the expression levels of αSMA, collagen I, and fibronectin. To determine the effect of HDAC11 inhibition on the arrest of epithelial cells at G2/M and partial epithelial-mesenchymal transition (EMT), we examined the expression of pH3Ser10, a hallmark of cells arrested at G2/M and Snail and Twist, key transcription factors that drive EMT development in the obstructed kidney. Immunoblot analysis results showed that administration of FT895 significantly reduced the expression of pH3Ser10, Snail and Twist. In addition, we further visualize the immune cell infiltration by immunohistochemistry analysis of F4/80, a macrophage marker. FT895 treatment decreased infiltration of F4/80 macrophages in the interstitial areas of the obstructed kidneys.

Conclusions: These data provide strong evidence that inhibition of HDAC11 attenuates development of renal fibrosis in vivo through suppression of several events associated with partial EMT development. Therefore, inhibition of HDAC11 would be a promising therapeutic strategy for the treatment of renal fibrosis.

FR-PO1059

Neuropilin-1, the Co-Receptor of TGF-β and TNF-α, Is a Novel Therapeutic Target for Renal Injury and Renal Fibrosis

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Background: Renal fibrosis is the ultimate common pathway of a variety of progressive kidney diseases, in which TGF-β plays an important role. However, current strategies targeting TGF-β showed poor clinical efficacy. One of the reasons for its futility is the co-receptor surrogacy. Neuropilin-1 (NRP1) is a transmembrane glycoprotein acting as a co-receptor of TGF-β and TNF-α, which is recently identified as a potential therapeutic target for pulmonary fibrosis. However, its role in kidney injury and renal fibrosis is unclear.

Methods: Kidney samples from patients with transplanted renal insufficiency and ischemia-reperfusion mice was analyzed. NRP1-KSP mice were generated to deplete NRP1 in renal tubular epithelial cells (TECs). The molecular mechanisms of NRP1 in kidney injury and renal fibrosis were explored via multi-omics analysis of single cell sequencing, transcriptomics and proteomics.

Results: NRP1 expression is upregulated in TECs in transplanted renal insufficiency patients and mice with IR induced AKI, which is co-expressed with receptors of TGF-β or TNF-α. Knockdown of NRP1 in TECs reduced IR-induced kidney injury and fibrosis in mice. NRP1+ distal tubular cells secreted collagen and cytokines, and communicated with myofibroblasts, exacerbating renal fibrosis by activating the SMAD pathway in TECs in a TGF-β receptor dependent manner. Meanwhile, in TGF-β receptor negative distal TECs, NRP1 upregulated TNF-α and its target gene NFKB1 via TNR1A (TNF-α receptor), thereby inhibiting ETV6-related crotonylase expression, which led to downregulation of lysine crotonylation on key glucose metabolic enzymes, exacerbating renal injury, inflammation and fibrosis.

Conclusions: NRP1 is a key molecule promoting kidney injury and fibrosis via activation of SMAD3, TECs-myofibroblasts crosstalk and inhibiting crotonylation of key glucose metabolic enzymes, which promotes the pro-fibrotic and pro-inflammatory effects in both TGF-β receptor negative and positive TECs. Therefore, NRP1 is a novel therapeutic target for kidney disease.

Funding: Government Support - Non-U.S.

FR-PO1060

Therapeutic Strategies Targeting RAGE Prevent Kidney Injury and Renal Fibrosis in Systemic Lupus Erythematosus

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Background: Lupus nephritis (LN) occurs in up to 60% of patients with systemic lupus erythematosus (SLE). Despite of current development of immunosuppressant agents, LN still impairs the survival and quality of life in SLE patients. Receptor for advanced glycation endproducts (RAGE) is a multi-ligand receptor is associated with innate immune system. In the present study, we examined whether RAGE is involved in the development of LN. Further, we explored the therapeutic impact of DNA-aptamer directed against RAGE (RAGE-apt) on lupus-related kidney injury.

Methods: [Protocol 1] RAGE expression in kidneys and urinary RAGE excretion (uRAGE) were determined at several time points by real-time PCR and ELISA, respectively in MRL/lpr, SLE-prone mice. [Protocol 2] LN was induced by peritoneally injecting pristane in wild type and RAGE globally knockout mice. [Protocol 3] MRL/lpr mice were subcutaneously administrated with RAGE-apt or Control-aptamer (Ctrl-apt) for 10weeks. [Protocol 4] Isolated proximal tubules from wild type and RAGE knockouts were treated with CpG-ODN for 7 days in the presence or absence of chroloquine.

Results: [Protocol 1] uRAGE was increased since 8-week-old MRL/lpr mice, and was positively correlated with urinary NAG, a tubular injury marker. RAGE was upregulated in distal tubules in early stage, meanwhile RAGE started to be extensively expressed in nephron at later time point. In proximal tubules (PTC), RAGE was co-localized with cathepsine D, a lysosomal aspartyl protease, and Rab7, a marker of late endocytosis, suggesting that PTC RAGE is involved in endosome pathway. [Protocol 2] Pristane-induced kidney injury and renal fibrosis were attenuated in RAGE knockouts with reduction in systolic blood pressure. [Protocol 3] Administration of RAGE-apt reduced systolic blood pressure and attenuated renal dysfunction. Expression levels of IL-6, TNF-a, and MCP-1 were inhibited by RAGE-apt, but not Ctrl-apt, in MRL/lpr mice. [Protocol 4] α-SMA was upregulated in wild type primary PTC, but not RAGE KO primary PTC, which was prevented by chroloquine, suggesting that the protective effect of RAGE inhibition is possibly through endosome-lysosome pathway.

Conclusions: RAGE could be involved in the pathogenesis of LN, and RAGE-apt can be potential to become a promising therapeutic option for preventing the development of LN.

FR-PO1061

Daphnepedunin A, a Natural Small Molecule, Targets Cdc42-Mediated GSK-3β/β-Catenin Signaling to Combat Renal Fibrosis

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Background: Renal fibrosis is a common fate in various chronic kidney diseases (CKD), eventually leading to renal dysfunction. So far there is no effective treatment for this pathological process. *Wikstroemia chamaedaphne*, a shrub endemic in China, is a medicinal plant that have been used in folk medicines to treat edema, but its application and mechanism in kidney-related diseases are unknown.

Methods: The inhibitory effects of ethanolic extracts of *Wikstroemia chamaedaphne* on the activation of renal fibroblasts were detected in the *in vitro* model of rat renal fibroblast cell line stimulated by transforming growth factor-β1. A phenotypic screening was conducted to identify the most potent diterpenoid isolated from *Wikstroemia chamaedaphne* on the *in vitro* model of renal fibroblast activation. Unilateral uretera obstruction mouse model of renal fibrosis was utilized to confirm the anti-renal fibrotic activity of the diterpenoid. The drug efficacy of the diterpenoid was compared with pirfenidone, the anti-renal fibrotic drug undergoing clinical phase 2 trial. RNA-sequencing was employed to explore the underlying pharmacological mechanism. By incorporating cellular thermal shift assay with quantitative mass spectrometry (MS-CETSA), the direct target of the diterpenoid was identified. Surface plasmon resonance and active GTP-binding cdc42 pull-down experiments was performed to verify the target protein. Small interfering RNA was used to knock down the target protein in NRK-49F cells and the drug efficacy of the diterpenoid was testified.

Results: In our bioassay-guided chemical investigation on the medicinal plant *Wikstroemia chamaedaphne*, the daphne diterpenoid daphnepedunin A (**15**) was identified as a promising anti-renal fibrotic lead. **15** showed significant anti-renal fibrosis effects both *in vitro* and *in vivo*, much more potent than the clinical trial drug pirfenidone. Leveraging MS-CETSA, we identified cell division cycle 42 (cdc42), a GTPase, as the direct target of **15**. Mechanistically, **15** inhibited the activity of cdc42, disrupting cdc42-dependent glycogen synthase kinase-3β (GSK-3β) serine 9 phosphorylation, which in turn activates GSK-3β and downregulates downstream β-catenin profibrotic signaling.

Conclusions: Our findings suggest that cdc42 is a potential therapeutic target for renal fibrosis, and **15** has great potential as a cdc42 inhibitor for the treatment of CKD.

Funding: Government Support - Non-U.S.

FR-PO1062

The Renal Damage Induced by an Experimental Model of Early CKD Is Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Dependent

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Background: In chronic kidney disease (CKD), the progressive decline in renal function is accompanied by inflammatory and fibrotic processes. These processes can contribute to the increasing levels of proteinuria, which is recognized as a risk factor in patients and associated to the CKD progression. Neutrophil gelatinase-associated lipocalin (NGAL) is an accepted biomarker for assessing renal damage in CKD patients and experimental animals. However, it is still uncertain whether NGAL actively promotes proteinuria in the context of early CKD, and whether this phenomenon is related to the renal pro-inflammatory/fibrotic status. **Objective:** To determine whether the 5/6 nephrectomy ($Nx_{5/6}$) at 5 days in mice is associated to renal dysfunction and to the pro-inflammatory/fibrotic damage, and whether this is NGAL-dependent.

Methods: Male C57BL/6 Wild type (WT) and knock-out for NGAL (NGAL-KO) mice (8-12 weeks), underwent a model of $Nx_{5/6}$ for 5-days (n=4-6), to evaluate function and kidney damage.

Results: The $Nx_{5/6}$ model at 5 days in WT and NGAL-KO mice resulted in a significant reduction in glomerular filtration rate, with 56.1% and 58.2%, respectively. Notably, the increase in blood urea levels was significantly higher in WT mice compared to NGAL-KO (43.07±2.15 *vs.* 29.58±13.08mg/dl). Also, the ratio protein/creatinine in urine exhibited NGAL-dependency (10.29±3.90 vs. 2.09±0.62 arbitrary units in NGAL-KO). Concerning the renal damage, the early CKD model induced tubular lumen dilation in WT mice (13.6±0.9 *vs.* 8.0±0.3mm in Sham), which was prevented by the NGAL absence ($P<0.01$). Additionally, the normalized fibrosis area in remanent kidney was significantly 2.3 times lower in the NGAL-KO mice with respect to WT animals, which correlated with the mRNA abundance of interleukin-6 ($P<0.01$). Finally, we found an increased protein production of macrophage (Mf) monocyte chemoattractant (CCL2) in kidneys of WT mice due to $Nx_{5/6}$ model, which was not observed NGAL-KO mice ($P<0.05$).

Conclusions: Our results show that renal overexpression of IL-6 and CCL2 after 5-days of $Nx_{5/6}$ are NGAL-dependent. This pro-inflammatory phenotype correlates with the tubular remodeling, fibrosis, and the proteinuria, suggesting a possible role of NGAL for the CKD progression from the early stages.

Funding: Government Support - Non-U.S.

FR-PO1063

Identification of Surrogate Biomarkers Reflecting Tubular Failed Repair in CKD

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Background: Interstitial fibrosis, tubular atrophy and inflammation (IFTA) are common final pathways to end-stage kidney disease (ESKD), contributing to progressive nephron loss and functional decline in most chronic kidney diseases (CKD), including those typically glomerular in origin. Disease-associated failed repair proximal tubule cells (FR-PTs) have been described in rodent models and are characterized by a proinflammatory and profibrotic phenotype that contributes to IFTA severity. We have recently demonstrated that accumulation of FR-PTs in humans predicts reduced event-free survival in multiple CKD etiologies. Here we used multi-omics analysis of patient-matched kidney biopsies and biofluids from the NURTuRE CKD cohort to discover biomarkers associated with an accumulation of FR-PTs to non-invasively identify patients at risk for progression.

Methods: Serum (n = 99) and urine samples (n = 22) from multiple etiologies from the NURTuRE biobank were assayed using Olink and SomaScan proteomics platforms, respectively. Patient-matched kidney biopsies for each of the samples were analyzed via RNA-Seq and scored for a gene signature reflecting FR-PTs. Correlation analysis of biofluid protein abundance with kidney mRNA expression and FR-PTs signature scores suggested candidate non-invasive biomarkers for further validation ($r \geq 0.4$ and $p \leq 0.05$).

Results: Proteomic analysis identified 78 serum and 79 urine proteins significantly correlated with the kidney biopsy FR-PT score in CKD patients. Strong positive correlation of 14/78 serum and 9/79 urine proteins with kidney mRNA expression suggests these proteins originate from the kidney or share a common regulatory mechanism. Importantly, expression of the respective genes was negatively correlated with eGFR and enriched in FR-PTs and immune cells, likely reflecting the kidney inflammatory and fibrotic microenvironment.

Conclusions: This study identified potential surrogate biomarkers associated with the accumulation of FR-PTs in subjects with different CKD etiologies from the NURTuRE cohort. These may aid in identifying patients with a disease-relevant phenotype and at risk for progression and will complement our target identification and validation focused on maladaptive tubular repair.

Funding: Commercial Support - Chinook Therapeutics, Evotec SE

FR-PO1064

Single-Cell Sequencing Identifies Novel Activated Fibroblast Marker, Distal Spatial Tubular Injury Pattern, and Functionally Significant Nephrogenic Program Reactivation in Adult AKI-to-CKD Transition

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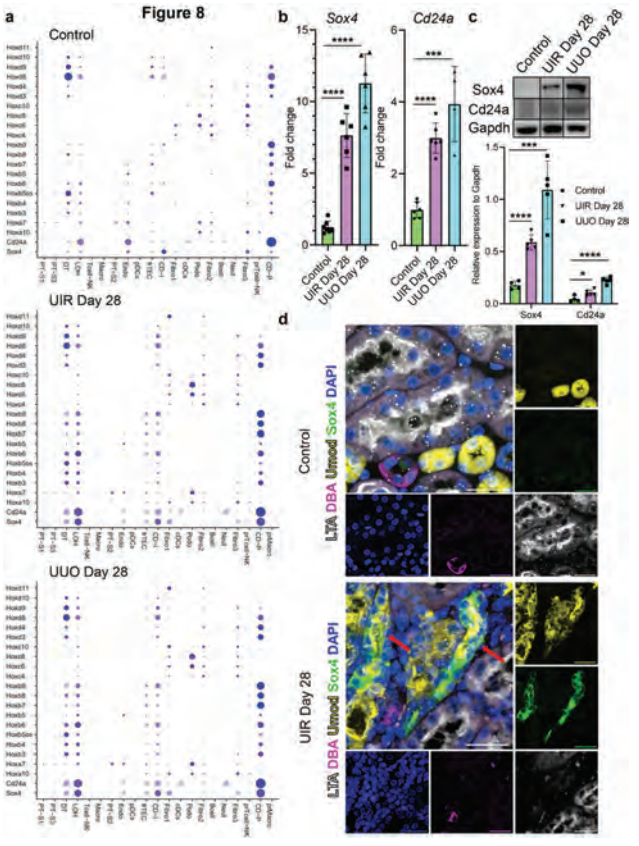
Background: Examining kidney fibrosis is crucial for mechanistic understanding and developing targeted strategies against chronic kidney disease (CKD). Enduring fibroblast activation and tubular epithelial cell (TEC) injury and dedifferenriation are key CKD contributors. However, specific activated kidney fibroblast markers and mechanistic targets of renal parenchymal remodeling remain elusive.

Methods: scRNA-seq, thorough molecular analysis and TEC specific transgenic model were used to mechanistically dissect AKI-to-CKD progression in two clinically relevant UIR and UUO murine models.

Results: Advanced kidney injuries elicited three separate "secretory", "contractile" and "vascular" fibroblast clusters. Gucy1a1 was validated as a novel marker selectively labelling three fibroblast populations. Also, we found robust and previously unrecognized distal nephron tubular segment (DNTS) injury in both models, while the surviving proximal tubules (PTs) showed restored transcriptional signature. Both models elicited failed repair TECs (frTECs) exhibiting decline of mature epithelial markers and elevation of stromal and injury genes, which shared transcriptional identity with DNTSs of the embryonic kidney. We also found a persistent nephrogenic signature, including *Sox4* elevation previously reported by us in AKI, in the UIR and UUO DNTSs. *Sox4* targeting using *KspCre^{ERT2}* transgenic model revealed renoprotective effects of *Sox4* DNTS specific ablation in the kidney fibrosis.

Conclusions: We identified Gucy1a1 as a novel kidney fibroblast specific marker and targeting *Sox4* in DNTSs as a promising strategy to halt AKI-to-CKD progression. Our findings might advance understanding of and targeted intervention in fibrotic kidney disease.

Funding: NIDDK Support, Other NIH Support - RO1 HL13395 and P50 DK096418 to PD, R01DK120842 to SP.



FR-PO1065

BRCA1 Potentiates Maladaptive Repair and Fibrosis Through Induction of Proximal Tubule G2/M Arrest and Senescence

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Background: DNA damage is a major contributing factor in the progression of fibrotic renal disease. Proximal tubular (PT) epithelial cells are particularly vulnerable to toxic, ischemic, and obstructive injury in the kidney, leading to replication fork arrest and DNA double-strand breaks (DSBs), triggering the DNA damage response. Subsequent to DSBs, ATM-mediated phosphorylation of BRCA1^{Ser1524} initiates the DDR, a protective adaptation in many pathologies, notably in the prevention of carcinogenesis. Until recently, the role of BRCA1 in renal fibrosis has been largely unexplored. We hypothesized that the effect of BRCA1 on arresting the cell cycle would exacerbate maladaptive repair through the initiation of G2/M cell cycle arrest.

Methods: *Slc34a1-Cre* mice were crossed with *Brca1*$^{flox/flox}$ mice yielding mice with PT *Brca1 exon 11* gene deletion. Mice were subjected to bilateral ischemia/reperfusion (BIRI) or aristolochic acid (AA)-induced injury. Markers of DNA damage, cell cycle arrest, senescence and fibrosis were evaluated by immunofluorescence staining and western blot analysis of tissue sections and patient-derived PTCs subjected to AA or cisplatin. HKC8 cells were transfected with shRNA and treated with either cisplatin or AA to investigate the role of BRCA1 in injury-associated apoptosis, growth arrest and senescence.

Results: BRCA1 protein expression was increased in human CKD kidneys. The expression of *Brca1 exon 11* was increased following BIRI or AA. PT *Brca1* deletion protected mice from fibrosis, as shown by Sirius red staining, fibronectin, collagen 1, and a-smooth muscle actin (a-SMA) following BIRI or AA. PT-*Brca1* depleted mice had fewer pH3+ cells, a G2/M cell cycle phase marker and reduced S-β-Gal, a senescence marker. Primary PTCs displayed increased p-BRCA1^{Ser1524} after 48h AA or cisplatin treatment, with increased activation of growth arrest genes p53 and p21. shRNA-induced reduction of BRCA1 in HKC8s decreased the percentage of cells in the G2/M cell cycle phase and significantly reduced cell viability.

Conclusions: BRCA1 induces fibrosis after tubular injury. Loss of BRCA1 from PTs reduces G2/M cell cycle arrest, cellular senescence, and secretion of profibrotic mediators *in vivo* and *in vitro*. Thus, transient inhibition of BRCA1 can be beneficial for preventing AKI-CKD transition.

Funding: NIDDK Support, Other NIH Support - American Heart Association

FR-PO1066

Elucidating the Function of a Novel Arg-1+/Clec4d+ Scar-Associated Monocyte-Derived Macrophage Population in Driving Fibrosis in Kidney Disease Models

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Background: Fibrosis is the final common pathway in all progressive kidney disease. Macrophages are a major myeloid cell component of the renal mononuclear phagocyte system, with roles in defence against infection, renal injury, and repair. Using single-cell RNA sequencing, we identified a novel myeloid cell subset exclusively present in acute injury of the unilateral ureteric obstruction (UUO) model of kidney fibrosis. This population transcriptomically aligns to monocytes but is enriched for both *Arginase-1* (*Arg1*) and the *C-type lectin 4d* (*Clec4d)* and a large number of pro-inflammatory and pro-fibrotic genes. We hypothesise that this novel *Arg1*$^{+}$*/Clec4d*$^{+}$ population contributes to fibrosis deposition in progressive kidney disease.

Methods: The presence of the *Arg1*$^{+}$*/Clec4d*$^{+}$ cells was validated in the UUO, unilateral ischaemic reperfusion injury (uIRI) and subtotal nephrectomy models of kidney injury.

Results: Analysis of intra-renal inflammation revealed CD45^{+}CD11b^{+}Arg1^{+} cells persisted and increased in number across 7 days in our injury models. Post-injury, Arg1^{+} cells were confirmed to be Clec4d^{hi}. As time progressed post-injury, consistent with a monocyte to macrophage transition, there was a decrease in Ly6C but increase in F4/80, MHCII and CD206 expression in this subset. To confirm that Arg1^{+}/Clec4d^{+} cells were derived from monocytes (Ccr2^{+}), we administered tamoxifen to Ccr2Cre^{ERT2}-TdTomato mice under a single or multiple-dose regimen following UUO surgery. At day 7 post-injury, ~50% and ~90% of the Arg1^{+} cells were TdTomato^{+} following a single or multiple doses of tamoxifen, respectively, suggesting that these cells are primarily monocyte derived. Moreover, the Arg1^{+}/Clec4d^{+} cells were found to localise to areas of scarring. To investigate the therapeutic potential of targeting Clec4d^{+} expressed on the Arg1^{+}/Clec4d^{+} macrophages, mice underwent UUO surgery and were given multiple doses of a Clec4d-neutralising antibody. A decrease in *Arg1* and fibrosis-related gene expression was evident by day 7 post-injury.

Conclusions: Further investigation into targeting this population in kidney disease has the potential to aid the development of novel therapeutics to limit fibrosis and halt progression of disease.

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FR-PO1067

The Adenine-Induced Mouse Model of CKD Shows Rapid Development of Impaired Kidney Function, Renal Fibrosis, Muscle Wasting, and Anemia

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Background: Translational rodent models are essential to identify more efficacious treatment options for patients with chronic kidney disease (CKD). However, most preclinical CKD models do not demonstrate impaired kidney function as determined by decreased glomerular filtration rate (GFR). Here, we characterize an adenine diet-induced (ADI) mouse model of CKD that enables clinical translational studies of CKD.

Methods: Male C57BL/6j mice (11 weeks old) were randomized into study groups (n=8-10 per group) based on body weight. ADI mice received a control diet from study day -2 and a CKD-inducing diet containing 0.2% adenine from study day 1, while control mice received a control diet from day -2 and continued with it throughout the study period. All groups received oral vehicle dosing once daily starting from day 1 until termination. Transdermal GFR (tGFR), urine creatinine-to-albumin ratio, and plasma cystatin C(pCyC) were evaluated at week 3 and 5. Blood was collected for glycated haemoglobin analysis, and gastrocnemius muscle and kidney tissue were sampled and weighed. Kidneys were collected for RNA sequencing or processed for histological evaluation of markers of macrophage infiltration (F4/80) and fibrosis (Col1a1).

Results: Compared to controls, ADI mice showed a significant tGFR decline correlating with an increased pCyC and marked albuminuria at 3 and 5 weeks after diet-induction. At termination, ADI mice showed significantly decreased glycated haemoglobin (14.7 vs 17.6 g/dL) and gastrocnemius muscle weight compared to mice receiving the control diet (0.12 vs 0.15 g). Furthermore, Quantitative kidney histomorphometric analysis demonstrated an increase in kidney fibrosis (Col1a1) and macrophage infiltration (F4/80) in ADI mice. Consistent with tGFR decline and kidney histology, the renal transcriptome signature in ADI mice indicated upregulation of gene expression markers of fibrosis (e.g. *Col1a1, Grem1)*, inflammation (e.g. *Il6, Il1b)*, and angiogenesis (e.g. *Ednra, Agt)*.

Conclusions: ADI mice rapidly develop functional, biochemical and histological hallmarks of CKD complicated by anaemia and muscle wasting. Consequently, ADI mice are highly relevant in preclinical target and drug discovery for CKD.

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FR-PO1068

Annexin A2 Promotes Tubular Epithelial Trans-Differentiation and Kidney Fibrosis

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Background: Annexin A2 is a Ca^{2+}- and phospholipid-binding protein widely expressed in various cells and tissues. It acts as a cell surface receptor for tissue plasminogen activator (tPA) and plasminogen, regulating the homeostasis of blood coagulation, fibrinolysis and matrix degradation. However, its role in kidney fibrosis remains largely unknown. Our previous *in vitro* work has shown that annexin A2 mediates NF-κB activation and promotes macrophage M2 to M1 phenotypic change, suggesting a critical role of annexin A2 in kidney fibrogenesis.

Methods: Unilateral ureteral obstruction (UUO) was induced in a novel annexin A2 knockout mice and their wildtype counterparts. Renal histology was evaluated. Kidney fibrosis, renal annexin A2 level, and epithelial transdifferentiation were examined in these mice.

Results: Annexin A2 was dramatically induced in the obstruction-induced fibrotic kidneys in a time-dependent manner, and its induction correlated with the extent of fibrotic injury as indicated by fibronectin deposition. Intriguingly, double immune staining analysis found that annexin A2 was dramatically induced in the interstitial F4/80-positive macrophages. It was further found that, after obstructive injury, annexin A2 knockout mice displayed significantly reduced tubular epithelial damage and dramatically decreased deposition of matrix components such as collagen and fibronectin than that of their control littermates. Additionally, obstruction-induced epithelial transdifferentiation was significantly reduced in annexin A2 knockout mice as indicated by increase of Ecadherin and decrease of de novo induction of αSMA.

Conclusions: Thus, it is clear that annexin A2 promotes epithelial transdifferentiation and kidney fibrosis after obstructive injury. Additionally, our results indicate a role of macrophages in annexin A2-mediated epithelial damage and transdifferentiation.

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FR-PO1069

Alveolar Type II Cell-Specific Mitofusins Modulate Kidney Fibrosis and Associated Lung Injury

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Background: Chronic kidney disease (CKD)-associated lung injury and implications of deleterious lung-kidney crosstalk on the progression of kidney fibrosis are under-recognized. Mitochondrial fusion proteins, mitofusin (MFN)1 and MFN2, play critical roles in regulating mitochondrial physiological function, which is essential for kidney homeostasis. We studied the effects of type II alveolar epithelial cell (AEC II)-specific loss of *Mfn1* or *Mfn2* on kidney fibrosis and associated lung injury during CKD.

Methods: AEC II (*Spc-Cre*$^{+/-}$)-specific *Mfn1* (*Mfn1*$^{fl/fl}$) or *Mfn2* (*Mfn2*$^{fl/fl}$) knockout (KO) and control (*Spc-Cre*$^{+/-}$) mice were subjected to unilateral ureteral obstruction (UUO) or sham surgery (7-days) or fed with adenine (AD) or control diet (28-days). Kidneys, lungs, blood, and bronchoalveolar lavage (BAL) fluid were analyzed by western blot, Masson's trichrome staining, and flow cytometry. Serum creatinine (Scr) and blood urea nitrogen (BUN) were measured.

Results: MFN1 and MFN2 in AEC II (EpCAM+ CD45-), lungs, and kidneys decreased while pro-inflammatory monocytes (CCR2+ Ly6C+ CD11b+) in blood, kidneys, lungs, and BAL fluid increased after UUO or AD. AEC II-specific *Mfn1* or *Mfn2* KO mice displayed higher expression of fibronectin, arginase-I, galectin-3, IL-1β, and TGF-β1, and collagen deposition in the kidneys and lungs after UUO than control mice. *Mfn1* or *Mfn2* loss in AEC II resulted in increased kidney macrophages (KM, CD11b+ F4/80+ CD45+) in obstructed kidneys and increased alveolar macrophages (AM, siglecf F+ CD11C+ CD45+) in the lungs and BAL fluid after UUO. KM and AM from AEC II-specific *Mfn1* or *Mfn2* KO mice exhibited higher mitochondrial-specific reactive oxygen species and galectin-3 after UUO than control mice. Moreover, AEC II-specific *Mfn2* KO mice displayed a lower number of proximal tubular cells (megalin+ CD45-) in obstructed kidneys, and higher BUN and Scr levels than control mice after UUO.

Conclusions: In 2 models of kidney fibrosis, we show downregulation of MFN1/2 in both the lungs and kidneys. AEC II-specific loss of *Mfn(s)* augmented inflammatory and fibrotic responses in KM and AM during CKD, suggesting the role of macrophages in inter-organ crosstalk. Mitochondrial-derived damage-associated molecular patterns from AM and injured AEC II may be involved in deleterious lung-kidney crosstalk and aggravate kidney fibrosis.

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FR-PO1070

The Uremic Toxin Indoxyl Sulfate Contributes to Renal Fibrosis via mTORC1 Signaling Pathway

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Background: Activation of mTORC1 in renal tissue has been reported in chronic kidney disease (CKD)-induced renal fibrosis. This suggests that the regulation of renal mTORC1 activity represents a potential therapeutic target for the treatment of renal fibrosis. However, the molecular mechanisms responsible for activating mTORC1 in CKD pathology are not well understood. The purpose of this study was to identify the uremic toxin involved in mTORC1-induced renal fibrosis.

Methods: Human renal proximal tubule epithelial cells (HK-2 cells), rat renal interstitial fibroblast (NRK-49F cells), and human monocytes (THP-1 cells) were used in *in vitro* studies. Adenine-induced CKD mice were used in *in vivo* studies.

Results: Among the seven protein-bound uremic toxins, only indoxyl sulfate (IS), an indole-containing compound, caused significant activation of mTORC1 in HK-2 cells. This IS-induced mTORC1 activation was inhibited in the presence of an organic anion transporter inhibitor, a NADPH oxidase inhibitor, and an antioxidant. IS also induced epithelial-mesenchymal transition of tubular epithelial cells, differentiation of fibroblasts into myofibroblasts, and inflammatory response of macrophages, which are associated with renal fibrosis, and these effects were inhibited in the presence of rapamycin (mTORC1 inhibitor). In *in vivo* experiments, IS-overload was found to activate mTORC1 in the mouse kidney. The administration of AST-120 or rapamycin targeted to IS or mTORC1 ameliorated renal fibrosis in CKD mice.

Conclusions: The findings reported herein indicate that IS activates mTORC1, which then contributes to renal fibrosis. Therapeutic interventions targeting IS and mTORC1 could be effective against renal fibrosis in CKD.

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FR-PO1071

The Role of SRY-box Transcription Factor 4 in Renal Fibrosis

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Background: Chronic kidney disease (CKD) is a widely prevalent disorder around the world, which affects over 10% adults. The pathological feature of CKD is renal fibrosis, characterized by the excessive production and deposition of extracellular matrix (ECM). The production and accumulation of ECM is partly due to tubular epithelial cell (TEC) dedifferentiation. However, the molecular mechanisms underlying TEC dedifferentiation are not fully understood. In this study, we investigated the role of SRY-box transcription factor 4 (SOX4) in regulating TEC dedifferentiation during the development of CKD.

Methods: We generated SOX4 conditional knockout mice by crossing SOX4 floxed mice with tamoxifen-inducible CAG-CreER mice. CAG-Cre$^{+/-}$SOX4$^{f/f}$ mice were given tamoxifen to induce SOX4 deletion (SOX4^{GKO}). CAG-Cre$^{-/-}$SOX4$^{f/f}$ mice received the same dose of tamoxifen and used as controls (SOX4^{CON}). Both SOX4^{CON} and SOX4^{GKO} mice were subjected to unilateral ureteral obstruction (UUO). Kidneys were harvested at 10 days after UUO injury. Kidney sections were prepared and stained for histological and immunological analysis. Western blot analysis and immunostaining were performed to detect the levels of signaling molecules, fibronectin, collagen type I, and alpha-SMA in the kidneys. Sirius red staining was performed to detect total collagen deposition in the kidney. Cultured TECs were employed to examine the role and molecular mechanisms of SOX4 in the regulation of TEC dedifferentiation *in vitro*.

Results: The expression of SOX4 was increased in TEC after UUO injury. In response to obstructive injury, SOX4^{CON} mice exhibited TEC dedifferentiation with senescence and G2/M arrest, fibroblast activation and developed substantial total collagen deposition and ECM protein production in the kidney. Global SOX4 deficiency significantly alleviated TEC dedifferentiation, suppressed fibroblast activation, and reduced total collagen deposition and ECM protein production in the kidney with UUO injury. Furthermore, knockdown SOX4 by shRNA inhibited TEC dedifferentiation in cultured TEC in response to TGF-β1. Mechanically, SOX4 facilitated TGF-β1-Smad3 signaling to promote TEC dedifferentiation.

Conclusions: Our results demonstrate that SOX4 plays an essential role in the development of renal fibrosis by regulating TEC dedifferentiation and fibroblast activation. Therefore, SOX4 may serve as a novel therapeutic target for CKD.

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FR-PO1072

Cell-Specific Iron Metabolism in Kidney Fibrosis

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Background: Chronic kidney disease (CKD) affects 10-15% of the adult U.S. population. Our recent data indicate that in CKD, most kidney macrophages (KMφ) have pathologically depleted cellular labile iron pool, which induces their pro-fibrotic responses. However, the mechanism of intracellular iron deficiency of KMφ and iron metabolism in other cell types that participate in fibrosis, particularly in tubular epithelial cells (TEC) have not been elucidated in CKD.

Methods: We used two models of kidney fibrosis, adenine diet and unilateral ureteral obstruction (UUO). We analyzed expression of iron-related genes (*Tfrc*: iron importer, transferrin receptor 1 [TfR1], a marker of cellular iron deficiency or overload; *Fth1* and *Ftl*: ferritin heavy and light chains; *Slc40a1*: iron exporter, ferroportin [FPT]; and *Ncoa4*, a marker of ferritinophagy) and respective proteins in whole kidney tissue, as well as in sorted KMφ and TEC (isolated using CD11b and CD133 magnetic microbeads). We also analyzed expression of these genes in publicly available single cell/nucleus transcriptomic mouse and human kidney fibrosis datasets.

Results: In contrast to KMφ, *Tfrc* gene was suppressed in whole kidney tissue and in the proximal TEC of UUO kidneys, suggesting iron excess in some (e.g., proximal tubules) and labile iron deficiency in other (e.g., KMφ) cell types during kidney fibrosis. Interestingly, LIP depletion in KMφ was observed despite suppression of FPT in CD11b-positive KMφ, while both *Slc40a1* gene and FPT protein were induced in whole kidney tissue during fibrosis. This suggests that regulation of FPT is independent of systemic

hepcidin in most kidney cells (but not in KMφ) during fibrosis. *Fth1* and *Ftl* genes were suppressed while FtH and FtL proteins were induced in whole kidney tissue, KMφ, and in TEC during fibrosis. Taken together with TfR1/*Tfrc* data, this suggests excessive expression of FtH in KMφ and insufficient in TEC during fibrosis. Cell-specific ferritin dysregulation in kidney fibrosis may owe to disrupted ferritinophagy. Indeed, NCOA4 expression was drastically reduced in KMφ and had only a trend toward reduction in TEC during fibrosis.

Conclusions: Cellular iron status varies among different cell types participating in kidney fibrosis, which likely differentially modulates fibrotic responses of these cells and may inform novel cell-specific therapeutic targets.

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FR-PO1073

IRhom2 Promotes Kidney Fibrosis Through Activation of EGFR in Fibroblasts

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Background: In the kidney, tubulointerstitial fibrosis can result from incomplete recovery from acute kidney injury (AKI). Activation of the epidermal growth factor receptor (EGFR) has been implicated as a potential mediator of interstitial fibrosis. **iRhom2**, an inactive member of the Rhomboid intramembrane proteinase family, can regulate EGFR signaling pathway via activation of ADAM17 (TACE) and secretion of EGFR ligands, including amphiregulin and HB-EGF as well as secretion of TNF-α. The current studies were designed to investigate the potential role of iRhom2 in the development of kidney fibrosis.

Methods: iRhom2 knockout (iRhom2-/-) and WT mice (C56/Bl6, male, 8-12 weeks old) were used for all experiments. Models of kidney injury included ischemia/reperfusion (IRI) and unilateral ureteral obstruction (UUO). Kidney myeloid cells and fibroblasts/myofibroblasts were isolated with corresponding microbeads.

Results: In the UUO model, iRhom2 mRNA expression increased in total kidney, isolated myeloid cells, and isolated kidney fibroblasts/myofibroblasts. Immunofluorescent staining confirmed iRhom2 expression in renal macrophages (F4/80+ iRhom2+ cells) and myofibroblasts (α-SMA+ iRhom2+ cells). Although the numbers of α-SMA+ cells and p-EGFR+ α-SMA+ cells were minimal under normal condition, they markedly increased after UUO for 8 days. In iRhom2-/- mice, both the numbers of α-SMA+ myofibroblasts and p-EGFR+ (indication of EGFR activation) α-SMA+ myofibroblasts decreased, with the percentage of p-EGFR expressing myofibroblasts decreasing from 43% to 17%. Quantitative Picrosirius red staining clearly showed less kidney interstitial fibrosis in iRhom2-/- mice. Four weeks after ischemic injury, iRhom2-/- mice also developed less fibrosis, as indicated by reduction in kidney profibrotic and fibrotic gene and protein expression as well as quantitative Picrosirius red staining. In addition, iRhom2-/- mice had preserved kidney function, as indicated by higher glomerular filtration rate 4 weeks after ischemic injury.

Conclusions: These studies provided evidence for a potential role of iRhom2 in development of kidney fibrosis in response to kidney injury, due at least in part by stimulating EGFR activation in fibroblasts/myofibroblasts. Targeting iRhom2 may provide a new strategy for prevention of kidney interstitial fibrosis.

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FR-PO1074

IGFBP-5/TGF-β1-Induced Cell Cross-Talk Between Endothelia and Tubular Epithelia Promotes Renal Fibrosis

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Background: Renal fibrosis is a common pathophysiological characteristic of chronic kidney disease (CKD) for which there is no effective treatment. The mechanism of renal fibrosis is complicated and remains unclear. Our previous study revealed that Insulin-like growth factor binding protein 5 (IGFBP-5) induces glycolytic activation in ECs and ultimately aggravates renal inflammation in diabetic kidney disease (DKD).

Methods: HK-2 and HUVEC cells were included in this study. UUO and ANN model were obstructed by Wild-type, *IGFBP-5*$^{-/-}$ and IGFBP-5$^{flox/flox}$, cre mice. IGFBP-5, TGF-β and fibrosis makers were detected to explore the mechanism of IGFBP-5 in fibrosis.

Results: We found that the serum IGFBP-5 levels were significantly increased in CKD, that IGFBP-5 was dominantly localized in vascular endothelial cells (ECs) of kidney tissue, and that IGFBP-5 deficiency relieved renal fibrosis in CKD model mice. In vitro experiments indicated that IGFBP-5 exacerbated the fibrosis phenotypic alteration of tubular epithelial cells (TECs) by the TGF-β1/p-Smad3 signaling pathway. In turn, TGF-β1 could facilitate the synthesis of IGFBP-5 in ECs. The crosstalk between TECs and ECs mediated by IGFBP-5 and TGF-β1 was confirmed in a coculture system and endothelial-specific IGFBP-5-deficient mice.

Conclusions: Renal fibrosis is exacerbated by TEC-EC cellular crosstalk through the feedback loop consisting of IGFBP-5 and TGF-β1. These findings suggest that IGFBP-5 may be a new pathogenic factor in renal fibrosis and a potential new therapeutic target in CKD.

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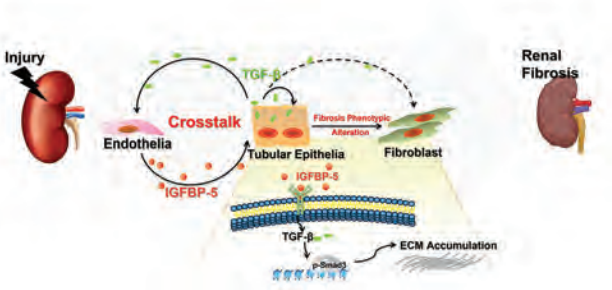

Mechanism of the involvement of IGFBP-5 in renal fibrosis

FR-PO1075

Lcn2 Plays a Key Role in Dot1l-HDAC2-ET1-Mediated Kidney Fibrosis

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Background: Kidney fibrosis is a hallmark of chronic kidney disease. The genetic and epigenetic factors regulating kidney fibrosis are largely unknown. Kidney injury marker Lipocalin 2 (Lcn2) is involved in kidney fibrosis. We reported that *Aqp2Cre* mice express Cre specifically in Aqp2^{+} progenitor cells, which generates at least 5 types of cells forming distal convoluted tubule 2 (DCT2), connecting tubule (CNT) and collecting duct (CD). Our recent studies also indicated that disruption of histone H3 K79 methyltransferase *Dot1l* in Aqp2^{+} progenitor cells led to upregulation of endothelin 1 (ET1) and kidney fibrosis through histone deacetylase 2 (HDAC2) during normal aging. Here, we hypothesize that Lcn2 is a new component of this process and upregulates HDAC2, which in turn increases ET1 and facilitates kidney fibrosis.

Methods: Using the *Aqp2Cre* driver, we developed three conditional knockout mice: 1) DCT2/CNT/CD-specific *Dot1l* conditional knockout mice (*Dot1l*$^{f/f}$ *Aqp2Cre* or *Dot1l*^{AC}); 2) DCT2/CNT/CD-specific *Dot1l* and *Edn1* double conditional knockout mice (*Dot1l*$^{f/f}$ *Edn1*$^{f/f}$ *Aqp2Cre* or *DE*^{AC}*);* 3) DCT2/CNT/CD-specific *Dot1l* conditional knockout plus Lcn2 global knockout mice (*Dot1l*$^{f/f}$ *Aqp2Cre Lcn2*$^{-/-}$ or *DL*$^{-/-}$). WT and the three knockout mice were analyzed at the age of 14 months. A variety of approaches including immunofluorescence staining coupled by high-resolution confocal microscopy, metabolic assays, real-time RT-qPCR, and Western blotting were used to assess kidney fibrosis, kidney function, and/or expression of HDAC2, Lcn2, and ET1 in mice, in IMCD3 cells overexpressing Lcn2, or in IMCD3 cells treated with various doses of recombinant Lcn2.

Results: Like *DE*^{AC} vs. *Dot1*^{AC} mice, *DL*$^{-/-}$ vs. *Dot1*^{AC} mice displayed less pronounced kidney fibrosis and improved kidney function. While high Lcn2 expression remained in *DE*^{AC} vs. *Dot1*^{AC} mice, significantly reduced HDAC2 and ET1 levels were observed in *DL*$^{-/-}$ vs. *Dot1*^{AC}. In IMCD3 cells, silencing *Dot1l* in IMCD3 cells led to upregulation of Lcn2, and addition of recombinant Lcn2 or overexpression of Lcn2 increased expression of HDAC2 and ET1.

Conclusions: Dot1l-Lcn2-HDAC2-ET1-kidney fibrosis may be considered as a new fibrogenesis pathway. That is, disruption of *Dot1l* in Aqp2^{+} progenitor cells not only directly upregulates ET1, but also indirectly through Lcn2, which positively regulates HDAC2, further facilitating ET1-mediated kidney fibrosis.

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FR-PO1076

Stimulator of Interferon Genes (STING) Mediates Endoplasmic Reticulum Stress Activation Causing Renal Fibroinflammation

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Background: Endoplasmic reticulum (ER) stress plays a pivotal role in kidney disease pathogenesis, yet the mechanisms leading to ER stress are largely unexplored. Viruses are known to manipulate ER-related processes, potentially aiding their replication or pathogenesis. The adaptor molecule STING, known for detecting double-strand DNA in pathogenic infections. In light of these insights, we investigated the relationship between STING, ER stress, and the development of kidney disease.

Methods: We utilized STING N153S mice, exhibiting constitutive STING activation, and mice with a conditional deletion of STING from kidney tubules. We performed in vitro experiments, including the silencing of STING or ER stress pathways, and analyzed molecular events through immunofluorescence, qPCR, western blot, and immunoprecipitation techniques. Gene expression data was scrutinized through RNA sequencing from human control and diseased samples, as well as mouse kidney disease models.

Results: In both the cisplatin and UUO models, we identified a consistent activation of STING and the ER stress–activated eIF2α kinase (PERK) pathway. Interestingly, STING was found to physically interact with and activate PERK, leading to ER stress and, subsequently, renal fibroinflammation. On the contrary, deletion of STING or PERK inhibition showed a protective effect against disease development. Further, transcriptomic

analysis of human CKD patients and mouse kidney injury models bolstered the association between renal dysfunction and ER stress pathway activation.

Conclusions: Our findings unveil a novel mechanism wherein STING activation triggers ER stress via the PERK pathway, leading to kidney tubule injury and fibrosis. This breakthrough research offers promising avenues for devising strategies to modulate ER stress and develop potent therapies for treating fibroinflammatory kidney diseases.

Funding: NIDDK Support

FR-PO1077

Hyaluronan Synthase Contributes to Tubulointerstitial Fibrosis in a Murine Model of CKD

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Background: Chronic kidney disease (CKD) is characterized by progressive tubulointerstitial fibrosis and tubular atrophy, leading to kidney failure. There is currently no effective treatment for CKD. Understanding the mechanisms that mediate tubulointerstitial fibrosis is prerequisite for the development of novel treatment options. Hyaluronan (HA) is a ubiquitous component of the extracellular matrix and has pleiotropic functions depending on its molecular weight. High molecular weight HA is generated by HA synthase (HAS) I and II and possesses anti-inflammatory and anti-fibrotic properties, whereas low molecular weight HA is synthesized by HAS III and contributes to inflammatory and fibrotic processes. We investigated the role of HAS I, II and III in tubulointerstitial inflammation and fibrosis in CKD.

Methods: CKD was induced in wild-type (WT) and HAS I, III or I/III-knockout (KO) mice by feeding with 0.2% adenine in casein-based chow for 8 weeks after which time, mice were sacrificed and kidneys harvested and assessed for histopathological changes. Twenty-four hour urine was collected to determine proteinuria. WT and KO mice fed with casein-based chow served as non-CKD controls.

Results: Tubulointerstitial HA expression was increased in WT CKD mice compared with non-CKD WT controls and this was accompanied by development of proteinuria, tubular atrophy, infiltration of immune cells, and increased collagen and α-smooth muscle actin expression. HAS I, III and I/III KO mice with CKD showed less severe histopathological abnormalities with decreased expression of mediators of fibrosis and reduced immune cell infiltration, the latter being more pronounced in HAS I KO mice, compared to WT CKD mice. Moreover, HAS I and HAS III KO, but not HAS I/III KO mice with CKD showed a significant reduction in proteinuria compared to WT CKD mice ($P<0.05$, for both).

Conclusions: Our data suggest that HAS I, II and III have distinct contribution to kidney function deterioration and tubulointerstitial inflammation and fibrosis in murine adenine-induced CKD.

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FR-PO1078

Excessive Mitochondrial Copper Load Driven by Upregulated Copper Transporter 1 Contributes to Mitochondrial Dysfunction and Renal Fibrosis

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Background: Copper is an essential trace element in living organisms and serves as a crucial cofactor for various enzymes. Our previous research has revealed that intracellular copper overload promotes renal fibrosis. However, the underlying mechanisms remain largely unknown. In this study, we found that copper ions mainly accumulate in mitochondria, leading to oligomerization of the DLAT protein involved in the tricarboxylic acid cycle, mitochondrial dysfunction, cellular apoptosis and renal fibrosis. Additionally, copper transporter 1 (CTR1), responsible for transporting copper ions into cells, was significantly upregulated in the renal fibrosis models. Therefore, we propose that CTR1 may drive mitochondrial copper overload, resulting in mitochondrial dysfunction and renal fibrosis.

Methods: We assessed the expression levels of CTR1 in fibrotic renal biopsy samples, 28-day fibrosis model of ischemia-reperfusion injury, and NRK-52E cell treated with TGF-β1. We used lentiviral vectors to overexpress and downregulate of CTR1 in NRK-52E and used CTR1 knockdown transgenic mice. Molecular dynamics simulations were conducted to explore the effect of copper ions on the lipoylated DLAT protein. ICP-MS was used to study the regulatory role of CTR1 on mitochondrial copper content. Non-reducing gel electrophoresis was performed to detect DLAT oligomer level. DLAT enzyme activity was evaluated. We used mitoSOX staining and electron microscopy to investigate mitochondrial function. We also use WB, QPCR and Masson to explore the role of CTR1 in renal fibrosis.

Results: Compared to the sham-operated group, mitochondrial copper was overload in IRI 28d fibrotic model and led to mitochondrial swelling and mitochondrial dysfunction. Furthermore, mitochondrial copper overload targeted lipoylated modification sites of DLAT, leading to DLAT oligomerization, enzyme activity inhibition and increased mitochondrial reactive oxygen species. Additionally, CTR1 was increased in fibrotic renal biopsy samples, IRI 28d fibrosis model and TGF-β1 treated cells. Downregulation of CTR1 decreased mitochondrial copper level and improved mitochondrial function.

Conclusions: In renal fibrosis, high expression of CTR1 drives mitochondrial copper overload, leading to abnormal aggregation of lipoylated DLAT protein, enzyme activity inhibition, mitochondrial dysfunction and renal fibrosis.

FR-PO1079

TSPO Mediates Tubulointerstitial Fibrosis and Kidney Inflammation After Unilateral Ureteral Obstruction

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Background: Tubulointerstitial fibrosis is a hallmark of chronic kidney disease (CKD) and predicts progression to kidney failure. A better understanding of its pathogenetic mechanisms is required for designing novel and effective treatments for this irreversible pathological process. Translocator protein (TSPO), located on the outer mitochondrial membrane, is associated with renal tubular cell death and regeneration in acute kidney injury. However, the role of TSPO in progressive CKD remains unknown.

Methods: Unilateral ureteral obstruction (UUO) or sham operation were performed on C57BL/6J mice to establish progressive tubulointerstitial fibrosis. TSPO antagonist PK11195 or vehicle was administrated daily to UUO mice for 7 days starting on the day of surgery. Kidneys were harvested for histology, inflammation and fibrosis.

Results: Histopathologically, tubular damage induced by UUO was reversed by PK11195 treatment. Induction of TNF-α, CCL-2 and IL-1β mRNA in the UUO kidney was reduced in PK11195 group compared to vehicle control. UUO-induced collagen deposition, as demonstrated by Masson's Trichrome and Picrosirius Red staining, was decreased after PK11195 treatment, and immunohistochemical analysis further confirmed significant reduction of Col-1 and Col-3 expression. Furthermore, PK11195 treatment downregulated UUO-induced fibronectin, α-SMA, vimentin and TGF-β levels by Western blotting.

Conclusions: We provided novel data to show that blockade of TSPO activity could alleviate kidney fibrosis and inflammation in murine UUO, suggesting that TSPO could play an important role in regulating progressive kidney disease. **Funding:** Health and Medical Research Fund (HMRF) of Hong Kong (grant no. 09202356); Hong Kong Society of Nephrology Research Grant 2022

Funding: Government Support - Non-U.S.

FR-PO1080

Tryptophan Metabolite Accumulation in CKD: Unraveling the Link Between Kidney Dysfunction and Brain Injury

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Background: The prevalence of cognitive impairment increases dramatically with the progression of Chronic Kidney Disease (CKD). The underlying pathophysiology of cognitive decline with advanced CKD remains to be established. We performed targeted metabolomics in plasma from patients with CKD stages 3 to 5 and kidney and brain samples from a mouse model of rapid kidney failure.

Methods: Clinical plasma samples were analyzed via mass spectrometry for essential amino acid tryptophan and its metabolites. A mouse kidney failure model was established by MDM2 deletion in proximal tubules in a doxycycline-inducible mouse model. Six days post-doxycycline administration, control and MDM2-conditional knock-out (cKO) mice were sacrificed, and kidneys and brains were harvested for cryosectioning, protein, and RNA extractions. Metabolomics analysis was performed via a Thermo-Orbitrap QExactive HFX) and microfluidic platform (ZipChip, 908 Devices). Data and pathway analysis were performed using MetaboAnalyst 5.0.

Results: Neurotoxic tryptophan metabolite 3-hydroxykynurenine (3-HK) was significantly ($p<0.01$) elevated in patients with CKD stage 5 (n=8) not-on-dialysis compared to CKD stages 3B and 4 (n=18). Mice lacking MDM2 in the renal tubules (n=4) exhibited aggressive renal tubular loss with increased systemic inflammation based on a significant increase in neutrophils to lymphocytes ratio ($p<0.05$) and plasma IL-6 levels ($p<0.01$), compared to control mice (n=4). Metabolomics analysis in plasma samples of MDM2cKO vs. control mice highlighted an accelerated tryptophan degradation via the kynurenine pathway with resultant accumulation of 3-HK levels ($p<0.01$). 3-HK plasma concentration correlated with plasma creatinine ($r=0.82$; $p<0.01$). Interestingly, brain tissue analysis showed increased 3-HK levels ($p<0.01$). Assessment of the brain cortex of the MDM2cKO mice via TUNEL assay identified a significant increase in apoptotic cells.

Conclusions: Our study indicates that advanced CKD is associated with accelerated tryptophan degradation and increased levels of circulating 3-HK, which can readily cross the blood-brain barrier. Accumulation of 3-HK potentially causes brain cell toxicity and cognitive dysfunction in CKD.

Funding: Other NIH Support - NIH/NCATS TL1 TR002647, Veterans Affairs Support

FR-PO1081

Uremic Toxin Indoxyl Sulfate Impairs Hydrogen Sulfide Formation in Nephrectomy Rats

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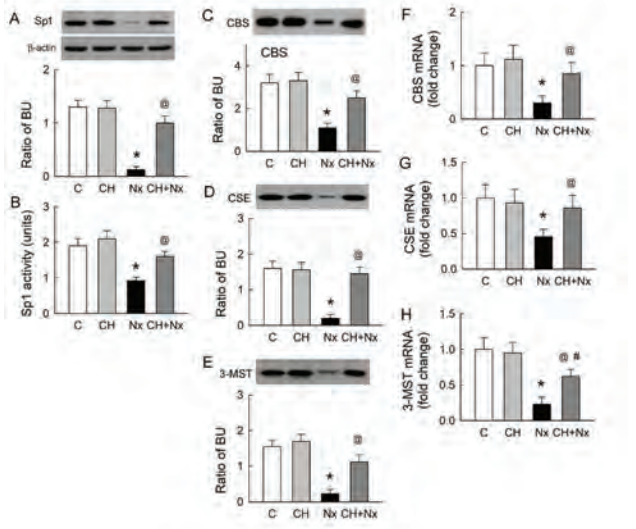
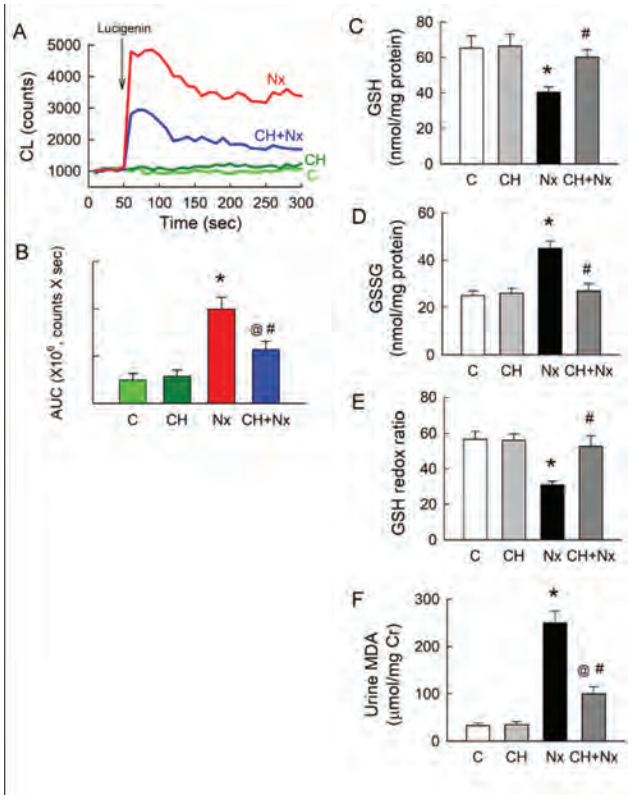
Background: Hydrogen sulfide (H2S) has antioxidant properties but is reduced in CKD, making the cells more vulnerable to oxidative damage. The interaction between Indoxyl Sulfate (IS) and H2S in CKD needs further exploration.

Methods: Male Wistar rats had nephrectomy and received CH-223191, an AhR antagonist. Blood and urine samples were collected post-treatment for H2S level measurement. Kidney tissue was evaluated for H2S-producing enzyme and Sp1 protein activity, and reduced GSH and oxidized GSSG levels.

Results: Administering CH-223191 to rats after nephrectomy prevented the harmful effects of IS on the kidneys. CH-223191 restored H2S levels, reduced IS accumulation, and reversed the changes in H2S-producing enzymes and the transcription factor Sp1 (Fig1). It also decreased oxidative stress and lipid peroxidation in the nephrectomy rats (Fig2). These findings indicate that CH-223191 protects against kidney damage by mitigating IS-induced effects, preserving H2S generation, and reducing oxidative stress.

Conclusions: Impaired H_2S generation caused by IS renders the kidney susceptible to oxidative stress damage, representing one of the mechanisms underlying IS-mediated kidney function loss.





FR-PO1082

The Pathogenic Role of C5a/C5aR Axis in AKI-to-CKD Transition

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Background: Activation of complement C5a/C5aR axis contributes to the pathogenesis of acute kidney injury (AKI). However, whether it plays a role in the transition to chronic kidney disease (CKD) after AKI remains unclear. In this study, we investigated the chronic effects of bilateral ischemia-reperfusion injury on C5aR deficient mice and dissected C5aR-dependent mechanisms during AKI-to-CKD transition.

Methods: Wild type $C5aR^{+/+}$ and knockout $C5aR^{-/-}$ mice were subjected to bilateral ischemia and sacrificed at day 3 and 7 after reperfusion. Kidney damage was assessed by evaluating kidney function, histopathological changes and expression levels of pro-inflammatory, fibrotic, oxidative and injury markers.

Results: Compared to the $C5aR^{+/+}$ controls, $C5aR^{-/-}$ mice showed significant decrease in serum creatinine and reduced expressions of Kim1 and Ngal in both the 3-day and 7-day BIRI models. The improvement in kidney injury in BIRI $C5aR^{-/-}$ mice was further confirmed by PAS staining. The expression levels of MCP-1, TNF-α, IL-6 and IL-1b were significantly decreased in $C5aR^{-/-}$ mice after BIRI. In particular, there was decreased infiltration of M1 macrophages with an increase in M2 macrophage number in $C5aR^{-/-}$ mice on day 7 after reperfusion. Sirius red and Masson Trichrome staining demonstrated a progressive development of interstitial fibrosis in $C5aR^{+/+}$ mice after BIRI, which were suppressed in $C5aR^{-/-}$ mice with less deposition of collagen 1 and collagen 3 in the post-ischemic kidneys. Moreover, the oxidative stress markers NOX2 and 8-OHdG were significantly reduced in $C5aR^{-/-}$ mice after BIRI.

Conclusions: C5aR deficiency protected mice from kidney inflammation and fibrosis by reducing oxidative stress during AKI-to-CKD transition. **Funding:** Research Grants Council of Hong Kong (General Research Fund, grant no. 17108222), Hong Kong Society of Nephrology Research Grant (2021)

FR-PO1083

Establishment and Application a Novel Reversible Unilateral Ureteral Obstruction (RUUO) Mouse Model and in Mechanism Study of AKI to CKD

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Background: Acute kidney injury (AKI) is a worldwide health problem. About 35-71% of AKI progress to chronic kidney disease (CKD) due to renal repair failure. Studies on the progression of AKI to CKD are focused on animal models of prerenal and renal AKI. It is necessary to establish an animal model to investigate the progression of postrenal AKI to CKD.

Methods: We established a RUUO mouse model. In brief, we ligated the left ureter to create a ureteric obstruction in mice. After 5 or 10 days, ureteral obstruction was removed by the coincidation of the ureter and bladder. Three days later, we performed the right nephrectomy and then monitor renal function and molecular mechanisms on the left kidney with IF and IHC staining, scanning electron microscopy and flow cytometry analysis.

Results: We observed adaptive and maladaptive repairs in 5 and 10 days RUUO kidneys. During the complete recovery of AKI in 5 days RUUO kidneys, 1) the infiltration of M2 macrophages marked by F4/80 + CD206 and CD11b + $ly6C^{int}$ was increased; 2) the expression of inflammatory factors (TNF-α, IL-1β, IL-6 and IL-4, IL-10), autophagy components (Beclin-1, Bcl-2, BNIP3, LAMP2, LC3BII/I and P62), and HIF-1α and HIF-2α, and the population of peritubular capillaries (PTC) (VEGF and CD31) were normalized to baseline; and 3) the activation of pericytes into myofibroblasts was blocked and alleviated as examined by PDGFRβ+α-SMA staining. In the process of AKI to CKD in 10 days RUUO kidneys, 1) M1 macrophages marked by F4/80+iNOS and CD11b+$Ly6C^{high}$ were dominant at the beginning, and then gradually transformed into pro-fibrotic CD11b+$Ly6C^{low}$ cells; 2) the expression of pro-inflammatory factors was high, but the expression of antiinflammatory factors was low; 3) the expression of the components of autophagy was decreased and would not be recovered; 4) the population of PTC maintained at low level; 5) pericytes were constantly be activated into myofibroblasts to form fibrosis, and 6) the expression of HIF-1α and HIF-2α was initially increased, then decreased to baseline (normal) level but increased again in the late stage.

Conclusions: With our new RUUO mouse model, we confirm that renal adaptive repair occurs in 5-days-RUUO kidneys to simulate the complete recovery of AKI, whereas renal maladaptive repair occurs in 10-days-RUUO kidneys to simulate the progression from AKI to CKD.

FR-PO1084

Clinical Characteristics and Renal Outcome of Patients with Thrombotic Thrombocytopenic Purpura from a Large Multicenter Cohort (USTMA Registry)

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Background: Thrombotic thrombocytopenic purpura (TTP) is a rare hematological disease caused by autoimmune deficiency of ADAMTS13 and responds to urgent plasma exchange. Renal dysfunction is typically mild and several clinical scores have incorporated creatinine (Cr) level < 2.0 mg/dL to differentiate TTP from other thrombotic microangiopathies. However, renal dysfunction and outcomes are not well studied in TTP. Therefore, we used the United States Thrombotic Microangiopathies (USTMA) TTP registry, the largest US TTP registry, to evaluate clinical characteristics of patients with severe renal dysfunction at presentation and estimate loss of kidney function over time.

Methods: The USTMA TTP registry contains data on TTP episodes between 1985 to 2019 from 14 centers across the US. We compared the clinical characteristics

upon presentation between patients presenting with mild (Cr ≤ 2 mg/dl) versus severe (Cr >2 mg/dl) renal dysfunction. To model eGFR loss over time with TTP episodes, we used longitudinal linear mixed-effects models.

Results: Between 1985-2019, there were 1257 TTP episodes (771 patients) and the majority of episodes had mild renal dysfunction (n=1115, 88.7%). Compared to mild renal dysfunction, patients with severe renal dysfunction had more severe symptoms, lower platelets and higher lactate dehydrogenase (LDH). There were 285 unique patients with multiple TTP episodes to evaluate for eGFR loss over time. Overall, we found a mean slope of eGFR per year of -0.70 (95% CI –0.84, –0.56). There were no differences in eGFR slopes according to the number of TTP episodes a patient experienced. LDH level was associated with eGFR loss between episodes, with a modestly sized effect (change in eGFR per year slope 0.020 (95% CI 0.008-0.032) per 2-fold increase in LDH).

Conclusions: Severe renal dysfunction is uncommon in TTP but it is more likely to be present in patients with multi-organ dysfunction. Hence, existing clinical prediction scores are likely less accurate in more severe TTP episodes. Loss of eGFR over time is consistent with previous estimates of age-related eGFR, hence we conclude that subsequent TTP episodes do not significantly affect eGFR loss and likely confirms previous findings that most patients with TTP recover normal renal function with modern treatment.

FR-PO1085

Chromatin Remodeling Factor, INO80, Inhibits PMAIP1 in Renal Tubular Cells Through Exchange of Histone Variant H2A.Z for H2A

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Background: Epigenetic modifications such as histone modifications and chromatin structures in the kidney contribute towards the progression of chronic kidney disease (CKD). In this study, the role of chromatin remodeling factor, inositol requiring 80 (INO80) was investigated because INO80 has been reported to be associated with renal function in a genome-wide analysis. Although INO80 regulates transcription by altering the chromatin structure at the nucleosome level, its role in the kidney remains unknown. Our aim of this study is to clarify the pathophysiological role of INO80 in the kidney.

Methods: We evaluated the expression level of *INO80* using UUO (unilateral urethral obstruction) model rats. We also investigated INO80 mRNA expression in a proximal tubular cell line (HK2) under hypoxia. To identify the downstream target genes of INO80, we performed RNA-seq using siRNA of INO80. We examined the effects of INO80 on apoptosis of tubular cells.

Results: The mRNA level of INO80 extracted from UUO group (n = 6) was significantly reduced compared to the contralateral kidney group. INO80 knockdown promoted apoptosis, suggesting that INO80 plays a role in inhibiting tubular cell apoptosis. The expression levels of INO80 in HK2 cells under 1% hypoxic condition significantly decreased than those under normoxia. We identified 32 down-regulated genes and three up-regulated genes. These genes were suspected to be INO80 downstream target candidates. As a result of gene ontology (GO) apoptosis-related genes such as *TP53* (tumor protein p53), *E2F1* (E2F transcription factor 1), and *PMAIP1* (phobol-12-myristate-13-acetate-induced protein 1 were significantly associated with INO80 functions. *PMAIP1* is a member of pro-apoptotic subfamily of the BCL-2 protein family and is a known target of p53. Chromatin immunoprecipitation was performed on HK-2 cells with *INO80* knockdown using the H2A.Z. antibody, because INO80 has been reported to remove the H2A.Z. variant and exchange it for the H2A variant. INO80 knockdown significantly increased H2A.Z. in the promoter region of *PMAIP1*, while H2A expression significantly decreased in the promoter region of *PMAIP1*.

Conclusions: INO80 plays an important role in exchanging H2A.Z. for H2A in the promoter region of *PMAIP1* in tubular cells to inhibit apoptosis during CKD progression.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO1086

Subclinical Acidosis Assessed by a New Urine Acid-Base Score Is an Independent Risk Factor for CKD Progression

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Background: Acidosis is reported to exacerbate the gradual loss of kidney function in patients with chronic kidney disease (CKD). Current guidelines advise assessing acid-base (AB) status of CKD patients by plasma bicarbonate, although covert acidosis may be present before it is reflected in this. Indeed, others have found a correlation between subclinical acidosis (SA), evidenced by low urinary NH_4^+ excretion, and progression of kidney disease. However, low NH_4^+ excretion may also be present in physiological states with low demand for acid elimination. To identify a sensitive and specific marker of SA, we analyzed several AB markers in urine samples from CKD patients. We hypothesized that a measure incorporating both pH_u and $[NH_4^+]_u$ would reflect the demand and capacity for sufficient renal acid excretion in CKD patients, and that this would be associated with CKD progression.

Methods: We included biobanked urine samples from CKD patients from two clinical studies (RENVAS, development cohort, 81 CKD patients and 25 healthy controls and PUMA, validation cohort, 65 CKD patients). Outcomes included mGFR at 18 months and composite outcome of 50% eGFR reduction or kidney failure defined by initiation of dialysis or kidney transplantation. AB-score was calculated from $[NH_4^+]_u$ and pH_u. Patients were stratified as SA if their AB score was below the 2.5th percentile of the control group or non-SA if their score was above.

Results: In the development cohort (mean eGFR 34.1mL/min, age 61.7y) 62% had SA. A higher baseline AB score was associated with a slower decrease in mGFR (p=0.002) and patients with SA had a greater mGFR decline after 18 months (p=0.039). Renal events were more frequent in patients with SA (p<0.001, mean follow-up 5.1y). When adjusted for covariates, including tCO2 and eGFR, the hazard ratio (HR) of reaching the composite outcome was 0.41(95%CI 0.21-0.79, p=0.009) per SD higher AB score and in patients with SA 5.3 (95%CI 1.2-24.2, p=0.039). In the validation cohort (mean eGFR 36.8mL/min, age 68.0y, mean follow-up 3.4y) 65% had SA. Adjusted HR was 0.27 (95%CI 0.1-0.76, p=0.013) per SD higher AB score and in patients with SA 15.5 (95%CI 1.9-129.4, p=0.011).

Conclusions: SA associates with greater mGFR decrease after 18 months and an increased risk of kidney failure or a >50% reduction of eGFR.

Funding: Private Foundation Support, Government Support - Non-U.S.

FR-PO1087

Kidney Medullary Oxygen Availability Is Higher in CKD: Truth or Fallacy?

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Background: Chronic hypoxia hypothesis (CHH) suggests kidneys with progressive CKD are hypoxic. Currently Blood Oxygenation Level Dependent (BOLD) MRI is the only known technique to afford evaluation of kidney oxygen status in humans. Results to-date show higher R2* (i.e. lower O2 availability) in cortex but lower R2* in medulla (suggesting higher O2 availability) in CKD compared to controls. Whether the lower R2* in medulla in CKD an anomaly remains untested. Hypothesizing that reduced fractional blood volume (fBV) within tissue is the cause for this anomaly [PMID: 29571450], we measured fBV in CKD using ferumoxytol, an intravascular MRI contrast agent.

Methods: Data was available in 9 each in controls and individuals with CKD. After baseline R2* maps were acquired, ferumoxytol (5mg/kg) was administered and R2* measurement repeated. fBV, and oxygen saturation of hemoglobin (StO2) were calculated using equations described previously for brain MRI [31482602].

Results: Table 1 summarizes the R2*, fBV, StO2 and bloodPO2 for cortex and medulla. Consistent with prior reports, R2* in medulla is significantly lower in CKD implying higher O2 availability in CKD. However, when including the fact that fBV is lower in CKD, estimated StO2 and bloodPO2 are significantly lower in medulla.

Conclusions: Our data for the first time demonstrate that fBV is significantly lower in CKD in both cortex and medulla. When including this lower fBV, cortex and medulla are both moderately hypoxemic in CKD while in controls, cortex was normoxemic and medulla mildly hypoxemic. The blood pO2 estimates are consistent with the only report to-date in rat kidneys [16357065].

Funding: NIDDK Support, Commercial Support - Covis Pharma (providing drug)

Table 1: Group comparison of BOLD MRI parameters between the two groups of participants, individuals with CKD and healthy controls.

		N	Mean	Std. Dev.	Significance
R2*_cortex s^{-1}	Control	9	17.74	0.94	0.489
	CKD	9	18.69	2.43	
R2*_medulla s^{-1}	Control	9	28.21	3.77	0.024
	CKD	9	23.61	3.22	
fBV_cortex (%)	Control	9	0.32	0.08	<<0.01
	CKD	9	0.10	0.03	
fBV_medulla (%)	Control	9	0.45	0.13	<<0.01
	CKD	9	0.27	0.03	
StO2_cortex (%)	Control	9	0.90	0.03	<<0.01
	CKD	9	0.76	0.08	
StO2_medulla (%)	Control	9	0.84	0.06	0.031
	CKD	9	0.77	0.07	
bloodPO2_cortex mmHg	Control	9	63.29	8.74	<<0.01
	CKD	9	42.43	6.59	
bloodPO2_medulla mmHg	Control	9	51.88	8.26	0.024
	CKD	9	43.19	6.69	

Significance by Mann Whitney U Test

FR-PO1088

Eicosanoids and Related Metabolites Associated with ESKD in a Community-Based Cohort

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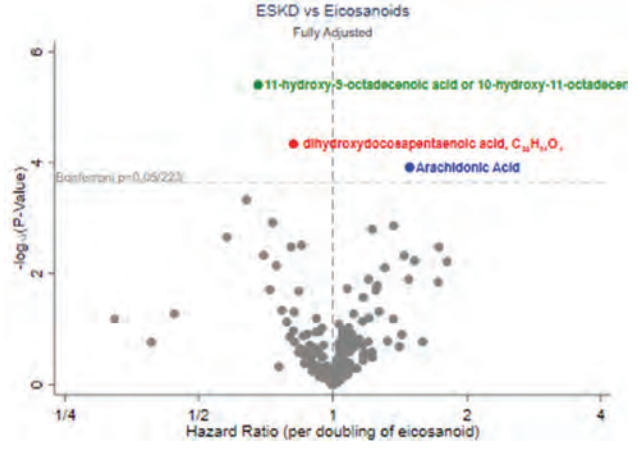
Background: Eicosanoids are derivatives of polyunsaturated fatty acids and participate in the inflammatory response and endothelial function maintenance. Specific eicosanoids have been linked to various diseases, including hypertension and asthma, and may reduce renal blood flow. A systematic investigation of eicosanoid-related metabolites and adverse kidney outcomes could identify key mediators of kidney disease and inform work in drug development.

Methods: Profiling of eicosanoid-related metabolites was performed in 9,650 participants in the Atherosclerosis Risk in Communities Study (visit 2; mean age, 57 years). The associations between metabolite levels and the development of ESKD was investigated using Cox proportional hazards regression (N= 256 events; median follow-up, 25.5 years). Metabolites with statistically significant associations with ESKD were evaluated for a potential causal role using Mendelian randomization techniques, linking genetic instruments for eicosanoid levels to genome-wide association study summary statistics of estimated GFR.

Results: The 223 eicosanoid-related metabolites that passed QC were generally uncorrelated with eGFR in cross-sectional analyses (median Spearman correlation, -0.03; IQR -0.05 to 0.002). In models adjusted for multiple covariates, including baseline eGFR, three metabolites had statistically significant associations with ESKD (p-value <0.05/223). These included a hydroxyoctadecenoic acid, a dihydroxydocosapentaenoic acid which were protective and an arachidonic acid, detrimental. Mendelian randomization suggested a causal role for the hydroxyoctadecenoic acid in determining eGFR.

Conclusions: High throughput eicosanoid profiling can identify metabolites that may play a protective role in the development of kidney disease.

Funding: Other NIH Support - NIH/NIDDK R01DK108803, R01DK124399, and NIH/NHLBI K24HL155861.



FR-PO1089

Glomerular Hyperfiltration and Th17 Responses Precede Glomerulosclerosis Following Nephron Loss

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Background: Chronic kidney disease (CKD) affects 37 million Americans resulting in $87 billion healthcare cost annually. Impaired renal autoregulation in obesity, diabetes and hypertension causes elevated glomerular capillary pressure and glomerular hyperfiltration (GHF), ultimately leading to glomerulosclerosis (GS) and CKD. Increased renal perfusion pressure directly drives T cell infiltration and T helper (Th) 17 cells promote renal fibrosis in hypertension and kidney ischemia-reperfusion injury, but their roles in GS are poorly understood.

Methods: We investigated the roles of GHF and Th17 responses in GS in a mouse CKD model induced by reduced kidney mass (RKM), which involved uninephrectomy and partial renal artery ligation in the remaining kidney such that the functional renal mass is reduced by ~ 3/4. Male 129/S6 mice received sham or RKM surgery at 8 weeks of age, and blood pressure (BP, by radiotelemetry), glomerular filtration rate (GFR, by transcutaneous FITC-sinistrin) and serum/urine CKD markers were assessed at baseline (BL), and day (D) 0, 3, 7, 14, 21, 28, 56, and 84 post-surgery.

Results: BP and GFR of RKM mice were identical to sham controls at BL (n=4-6). Immediately after RKM, GFR dropped to 22% of BL, consistent with the extent of renal mass ablation. BP increased by 29 mmHg by D5 post RKM (144 ± 8 vs 112 ± 2 mmHg, p<0.05, 2-way ANOVA), and serum creatinine, blood urea nitrogen and urinary albumin were significantly elevated by D14. BP and CKD markers were significantly elevated through D84 in RKM mice, but remained at BL levels in sham controls. The GFR of RKM mice gradually increased to 38% of BL at D3, 57% at D7 and 68% at D14, and plateaued at ~70% at D21-28, suggesting that the early rise in BP and impaired autoregulation may have caused GHF following initial nephron loss. The adaptive increase in GFR post-RKM was associated with marked renal Th17 cell infiltration at D14, preceding glomerular hypertrophy and mesangial expansion at D28 and subsequent recruitment of myeloid cells, monocyte/macrophages and T regulatory cells. Importantly, GFR declined to 42% of BL at D56 post-RKM, with concomitant GS and interstitial fibrosis as evidenced by Periodic Acid Schiff and Picro Sirius Red staining.

Conclusions: Together, our data suggest that both GHF and Th17 responses promote CKD progression and further loss of nephrons through glomerular fibrosis.

Funding: NIDDK Support, Other NIH Support - JW is supported by University of Rochester Pilot Awards (Prime Sponsors: NIAID P01AI102851 and NIEHS P30ES001247)

FR-PO1090

Regenerative Capacity Decline and Progressive Tubular Cell Polyploidization as Adaptive Kidney Tubule Response to Aging

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Background: Kidney function declines progressively with age, leading to chronic kidney disease (CKD) in the elderly. CKD is a major global health problem, explaining why there is the need to understand the age-related mechanisms in CKD development. Most adult organs contain a pool of stem cells, whose function decline leads to tissue ageing. To what extent do resident stem cells or differentiated cells contribute to organ ageing remain to be clarified. Recently, we revealed two response programs in the kidney tubule to recover kidney function and a structural integrity upon AKI. On the one hand, a population of resident renal progenitors (RPC) self-renew and differentiate to replace lost tubular cells. On the other, tubular cells (TC) undergo endoreplication to become polyploid. We aimed to study how these two mechanisms affected the kidney ageing.

Methods: To study RPC, we used the inducible Pax2/Confetti mice, in which RPC (Pax2+cells) are randomly labelled by one of the four fluorescent reporter genes. To identify polyploid TC, we used two inducible mouse models: the heterozygous Pax8/Confetti mice and Pax8/FUCCI2aR mice. In the former model, all TC are labelled randomly by one of the four fluorescent reporter genes. Polyploid TC appear as bi-coloured due to recombination of two fluorochromes in the same cell. In the second model, polyploid TC are identified by expression of cell cycle fluorescent proteins (FUCCI2aR technology) in combination with DNA content analysis. Mice were analyzed at 2, 6, 12 and 18 months of age.

Results: Pax2/Confetti mice revealed that Pax2+RPC of proximal tubule declined during ageing and their clonogenic capacity is impaired. By contrast, Pax8/Confetti mice showed an increase of polyploid TC during ageing. Analysis of aged Pax8/FUCCI2aR mice revealed that polyploid TC increased furtherly their DNA content by going through additional cell cycles and that this was associated with fibrosis, senescence and kidney function decline. Thus, while the pool of RPC is progressively lost during ageing, impairing the kidney tubule regenerative capacity, TC enter the cell cycle to become polyploid. These accumulate in aged kidneys and trigger fibrosis and senescence, leading to CKD.

Conclusions: These results suggest a previously unknown role for RPC and polyploid TC in kidney tubule response to ageing.

FR-PO1091

In Vivo Single Cell Analysis of Senescence in Aging Kidney Disease and CKD

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Background: It remains largely unknown how senescent cells affect kidney aging and chronic kidney diseases (CKD) in vivo. Previously, we generated a p16-CreERT2-tdTomato mouse model (p16-tdTomato mice hereafter) in which cells with high p16 expression, a prototypical senescent marker, were labeled with tdTomato through the administration of tamoxifen. In this study, we aimed to reveal the pathophysiological role of senescent cells in the kidney using p16-tdTomato mice.

Methods: We investigated three different kidney conditions; normal aging kidneys, adenine-induced kidney diseases, and rhabdomyolysis-induced kidney diseases model. Male 6-24-month-old p16-tdTomato mice and 2-3-month-old p16-tdTomato mice were used for the normal aging process and disease models, respectively. The adenine diet was administered for three weeks, while 50% glycerol was injected into each leg to induce rhabdomyolysis thrice weekly. All the mice were sacrificed after the five times of tamoxifen injections. For further analysis of single senescent cells, the kidneys were directly digested, and flow cytometry (FACS) separately sorted tdTomato-positive senescent or tdTomato-negative cells.

Results: In the normal aging process, 20-24-month-old mice showed an accumulation in tdTomato-positive senescent cells compared to young mice. In both CKD models, the serum analysis demonstrated kidney dysfunction with increased BUN and Cr. Histopathological examinations showed tubular damage, interstitial fibrosis, and infiltration of immune cells, resembling CKD progression. Notably, the tdTomato-positive senescent cells increased following CKD; mainly, tdTomato-positive senescent PTECs were significantly detected. RNA-sequence analysis revealed that tdTomato-positive senescent PTECs collected from the CKD model by FACS showed high inflammatory signaling pathways, including hallmark TNFα signaling through NFkB, IL6 JAK-STAT, and TGFβ signaling. These inflammatory cascades are all related to senescence-associated secretory phenotype (SASP).

Conclusions: These data suggest that CKD progression might cause premature kidney aging. In particular, tdTomato-positive PTECs might contribute to an inflammatory environment in CKD by producing SASP. These tdTomato-positive PTECs might be a therapeutic target to prevent CKD progression and rejuvenate premature kidney aging.

Funding: Government Support - Non-U.S.

FR-PO1092

Possible Involvement of Renal Tubular NFAT5 in Aging-Associated Renal Phenotypes and Dysfunction

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Background: The number of patients with chronic kidney disease (CKD) and hypertension is increased with age; however, it is not clearly defined why and how aging causes renal dysfunction and hypertension. Nuclear factor of activated T-cells 5 (NFAT5) is a transcription factor that is activated upon hypertonic conditions as observed in the renal medulla. We have already shown that the renal tubular cell-specific NFAT5 conditional knockout (KO) mice exhibit salt-sensitive hypertension, while the mice exhibit impaired urine concentrating ability and are susceptible to renal fibrosis. These phenotypes resemble aging-associated renal dysfunction, i.e., urine concentrating disorder, salt-sensitive hypertension, and renal fibrosis. We therefore investigated the possible involvement of NFAT5 in aging-related changes of the kidney.

Methods: The mRNA expressions of NFAT5 and its downstream genes including AQP2, urea transporter A-1 (UTA-1), and aldose reductase (AR) were examined by real-time PCR in the whole kidney tissue of wild type (WT) mice at 3, 6, 12, and 18 months old. To investigate the involvement of NFAT5 in aging-related phenotypes of the kidney, kidneys collected from NFAT5 KO mice (3 and 18 months old) were characterized and compared with WT mice. Senescence-associated beta-galactosidase (SA-β-Gal) activity was examined by fluorescence study in the whole kidney slices. Gene expressions of senescence-associated secretory phenotype (SASP)-related factors (TGF-β1, COL1A1, ICAM1, PAI-1, and MMP3) were examined by real-time PCR. Renal fibrosis was evaluated by AZAN staining.

Results: While the expression of NFAT5 was increased with age, the mRNA expressions of AQP2, UTA-1 and AR were decreased significantly at 6 and 12 months old compared to 3 months old. SA-β-Gal activity was increased in the corticomedullary region in KO mice at 3 months. Gene expressions of SASP-related factors were significantly increased in KO mice. At 18 months old, KO mice exhibited renal atrophy and fibrosis in the medulla, which phenotypes were significantly accelerated than WT mice.

Conclusions: These results indicate that the expression of genes downstream of NFAT5 could be decreased with aging kidney, suggesting that the decreased activity of NFAT5 may be involved in aging-related renal dysfunction.

FR-PO1093

Single-Nucleus RNA Sequencing Reveals Cellular Heterogeneity and Cell-Cell Interactions Contributing to Tertiary Lymphoid Tissue Development in the Aged Injured Kidney

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Background: Tertiary lymphoid tissues (TLTs) are ectopic lymphoid structures that develop in non-lymphoid organs with chronic inflammation. TLTs can develop in kidney diseases such as IgA nephropathy and transplanted kidneys and are associated with poor renal prognosis. However, how TLTs affect renal tissues and expand remains unclear.

Methods: Single-nucleus RNA-sequencing (snRNA-seq) was performed on three aged mouse kidneys with TLTs after ischemia–reperfusion injury or an aged kidney after sham surgery. The results were validated using immunostaining, *in situ* hybridization (ISH) of murine and human kidneys, and *in vitro* experiments.

Results: snRNA-seq identified 15,986 and 7,485 nuclei in the injured kidneys and the sham-treated kidney, respectively. In the injured kidneys, proinflammatory and profibrotic *Vcam1*$^+$ injured proximal tubules (PTs) with activation of NFκB and interferon (IFN)-inducible transcription factors were detected. Importantly, VCAM1$^+$ PTs were preferentially localized around TLTs and suggested to drive inflammation and fibrosis via the expression of multiple chemokines or cytokines. snRNA-seq analysis and ISH revealed that *Tnf* and *Ifng* were highly expressed by lymphocytes within TLTs, and these inflammatory cytokines synergistically upregulated *VCAM1* and chemokine expression in cultured PT cells. In addition, snRNA-seq and immunostaining identified proinflammatory and profibrotic fibroblasts, which resided within and outside TLTs, respectively. Proinflammatory fibroblasts with STAT1 activation expressed various chemokines or cytokines, including *Cxcl9/Cxcl10* and *Tnfsf13b* (encoding B cell-activating factor), suggesting their contribution to lymphocyte recruitment and survival. IFNγ upregulated the expression of these molecules in cultured fibroblasts in a STAT1-dependent manner, indicating potential bidirectional interactions between proinflammatory fibroblasts and IFNγ-producing CXCR3$^+$ T cells within TLTs. These cellular and molecular components were confirmed in human transplanted kidneys with TLTs.

Conclusions: TLTs develop via intense interactions between proinflammatory renal parenchymal and immune cells. These interactions may serve as novel therapeutic targets in kidney diseases with TLT formation.

Funding: Government Support - Non-U.S.

FR-PO1094

Single-Nucleus Transcriptome Revealed Differential Cell Fate of Human Proximal Tubular Cells with Aging

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Background: Proximal tubular cell (PTC) is a high energy-requiring cell-type in the kidneys. But how this cell type ages remains incompletely understood throughout life course.

Methods: We explored transcriptional profiles through life time using the public dataset, Kidney Precision Medicine Project. We extracted the nuclei annotated as PTC from normal kidneys and discarded potential doublets that expressed other cell-type markers, which retained 18,765 nuclei.

Results: We found transcriptionally distinct 7 subclusters reannotated as healthy PT-1, healthy PT-2, stressed PT, scattered PT, injured PT-1, injured PT-2, and proliferating PT. Healthy PT-2 distinctively expressed PLIN2, a lipid dropet marker, and stressed PT showed enhanced expressions of ALDOB, PCK1, and GPX3. Scattered PT and injured PT-2 commonly expressed VIM, CD24, and S100A6, and injury PT population only expressed VCAM1. We found that healthy PT-2 showed the highest gene expression implicated in lipid metabolism, such as HMGCS2, ACSL1, and CPT1, and its PPAR-α signaling is upregulated than Healthy PT-1. In addition, scatter cells were enriched with lysosomal genes and has upregulation in glycolysis, oxidative phosphorylation, and actin cytoskeleon regulation compared to Healthy PT-1. In the trajectory analysis, healthy PT has two disintact pathes, one of which flow toward scattered PT through stressed PT and the other of which direct to injured PT. Each path had differential metabolic fate represented by enhanced and impaired fatty acid oxidation along the former and latter pathes.

Conclusions: PTC undergoes differential cell fate with aging on the view of gene expression and metabolism.

FR-PO1095

Higher Serum IL-6 and IFN-γ Are Associated with Increased Seroconversion Rate Against SARS-CoV-2 Spike Protein Either After Vaccination or SARS-CoV-2 Infection

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Background: Maintenance immunosuppressives lead to a decreased immunogenic response to SARS-CoV-2 infection and vaccination in renal transplant recipients (RTRs) than in healthy populations. However, healthy people with SARS-CoV-2 infection often develop neutralizing antibodies and secrete high quantities of cytokines leading to virus clearance and sometimes more severe COVID-19. Associations of cytokines with seroconversion rate in immunocompromised RTRs are not well studied, particularly in living donor scenarios.

Methods: In this study, we included 210 living-related RTRs, who acquired SARS-CoV-2 infection or were vaccinated with two doses of either COVISHIELD or COVAXIN; and 35 healthy controls who were neither vaccinated nor had anti-SARS-CoV-2 spike IgG as controls. Cytokines IL-6, IFN-γ, TGF-β, and IL-10 were measured using the ELISA, and SARS-CoV-2 spike protein-specific IgG titre by chemiluminescent microparticle immunoassay methods.

Results: We found a seroconversion rate of 115/132 (87.12%), with a median antibody titer of 706.40 au/ml (IQR, 215.45-1844.42) in the infection group and 63/78 (80.76%) with a median titer 1454.20 (IQR, 80.52-3838.75) au/ml in vaccination group. The IL-6, IFN-γ, TGF-β, and IL-10 levels were significantly higher in both the infection and vaccination groups than in the healthy control. In the infection group, IL-6 (55.41±24.30 vs 31.64±16.98 pg/ml; p<0.001); IFN-γ (91.21±33.09 vs 61.69±33.28 pg/ml; p=0.001), were significantly higher in the seroconverter group as compared to non-seroconverter. TGF-β (730.48±400.47 vs 765.47±366.39 pg/ml; p=0.92) and IL-10 (91.31±48.54 vs 96.73±59.53 pg/ml; p=0.88) were similar between seroconverter and non-seroconverter. Similarly, in the vaccination group, IL-6 (50.31±25.67 vs 30.00±11.19 pg/ml; p=0.002) and IFN-γ (65.70±39.78 vs 32.14±17.48 pg/ml; p=0.001) were significantly higher in seroconverter post-vaccination compared to non-seroconverter. In contrast, TGF-β (820.96±415.78 vs 1045.57±204.66; p=0.046) was elevated in non-seroconverter, and although IL-10 (93.18±35.45 vs 112.90±59.61 pg/ml; p=0.11) was similar between seroconverter and non-converter.

Conclusions: Inflammatory cytokines IL-6 and IFN-γ are significantly associated with higher seroconversion rates in RTRs after SARS-CoV-2 infection and vaccination.

FR-PO1096

Usefulness of Multiplex Immunodot Method for COVID-19 Vaccination Monitoring in Dialysis Patients: Results of the COVIDIAL Study

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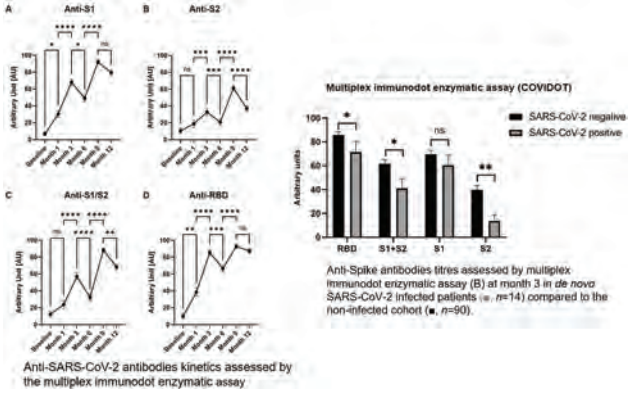
Background: COVID-19 vaccine was demonstrated to be effective in dialysis patients, but boosters are mandatory due to a rapid waning of anti-spike antibodies. A vaccination strategy based on efficient immunologic response monitoring might be useful to maintain a favourable risk-benefit balance in this vulnerable population.

Methods: CoviDial is an observational prospective study enrolling 121 dialysis patients to receive a 3-dose mRNA-1273 vaccine according to a uniform schedule. At baseline, months 1, 3, 6, 9, and 12, anti-spike antibodies against four epitopes (S1, S2, ECD-S1+S2, RBD) were monitored with a multiplex immunodot enzymatic assay. Potential correlation between initial serologic response and subsequent COVID-19 infection was then assessed.

Results: Overall, 96.2% and 96.8% of patients developed anti-RBD antibodies at 3 and 12 months, respectively. All antibodies titres significantly decreased at month 6 compared to month 3. Booster vaccine induced a robust serologic response at month 9, but with a waning three months later, particularly for anti-S2 (37.2 ± 3.3 vs. 61.3 ± 3.0, p<0.0001) and anti-S1+S2 antibodies (68.4 ± 3.3 vs. 88.4 ± 2.3, p<0.01). Fifteen patients were later tested positive for SARS-CoV-2. At month 3, mean titres of anti-RBD, anti-S1+S2 and anti-S2 antibodies were lower in the subsequent SARS-CoV-2 infected cohort (71.57±9.01 *vs.* 85.79±2.61, $p<0.05$; 41.07±7.96 *vs.* 61.68±3.56, $p<0.05$; 13.79±5.03 *vs.* 39.70±3.86, $p<0.01$; respectively).

Conclusions: Three doses of mRNA-1273 vaccine induce a robust but time-limited immunologic response in dialysis patients. Lower anti-spike antibodies titres after initial vaccination are associated with a higher risk to subsequently contract SARS-CoV-2, even beyond six months.

Funding: Private Foundation Support



FR-PO1097

Barriers to COVID-19 Vaccination in Dialysis Populations: A Patient Perspective

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Background: ESKD patients are at risk for serious illnesses and death related to COVID-19. It is challenging for ESKD patients to stay updated with recommended COVID vaccination. We aim to study the perceived barriers to complete COVID vaccination in our dialysis population.

Methods: 205 ESKD patients consented to complete our questionnaires. Descriptive statistics including proportions, median, and interquartile range were calculated for categorical and continuous variables to describe the study population, and to report the patient perceived barriers to vaccination. Comparisons by age, race/ethnicity, sex, level of education and income were conducted to evaluate differences between those vaccinated vs unvaccinated.

Results: 205 patients participated in the study. 88.3%(n=181) received at least one COVID vaccine. 80.5%(n=165) completed primary series. 54.6%(n=112) received the bivalent booster. 7%(n=8) of males and 17.5% of females (n=16) were unvaccinated. Majority of unvaccinated patients were unemployed/retired/disabled, have income ≤ $30,000, and with at least a high school education. Among vaccinated group, 96.6% reported it was easy to get vaccines, while 56.2% were concerned to be vaccinated. 25.3% of patients received the vaccine because it was required by transplant program, and 28% felt pressure to be vaccinated. Of 24 unvaccinated patients, 62.5% were concerned with potential long term complications. 66.7% were unsure of the efficacy. 52.4% of patients felt that the vaccine was safe, and 78.3% were aware it was free. 12.5% thought they had medical reason not to be vaccinated. Only 22.7% of patients believed that vaccination decreased death or ICU admissions. 20.8% of patients felt social media influenced on their decision.

Conclusions: Most ESKD patients reported having received vaccines and did not feel that physical limitation, transportation, or accessibility were barriers to vaccination. Uncertainty of long term complications and efficacy of vaccinnation appeared to be the major barriers.

Funding: Commercial Support - Northeast Ohio Renal Research Innovation Award, Centers for Dialysis Care

Selective Responses From 24 Unvaccinated ESKD Patients					
N = 24	Yes (%)	No (%)			
Reasons for not getting COVID-19 vaccine:					
- Do not think the vaccine is safe	62.5%	37.5%			
- Unsure about long term complications	37.5%	62.5%			
- Unsure about the efficacy	66.7%	33.3%			
Aware vaccine is free	78.3%	21.7%			
No difficulties to get COVID-19 vaccine	50%	50%			
Feel that social media sites have influenced their decision	79.2%	20.8%			
	Not at all	Little	Mod	Very	
Concerned getting COVID disease	25%	45.8%	12.5%	16.7%	
Is COVID vaccine safe for you	47.6%	28.6%	14.3%	9.5%	
	Strongly Disagree	Disagree	Neither	Agree	Strongly Agree
Believe vaccine decreases chances of dying or ICU admission	4.5%	13.6%	59.1%	18.2%	4.5%
Felt pressured to get vaccine	62.5%	12.5%	8.3%	0%	16.7%

FR-PO1098

Malnutrition Is a Risk Factor for Lower Humoral Immune Response After Anti-SARS-CoV-2 Vaccination in Patients on Hemodialysis: A Multi-Center Clinical Study

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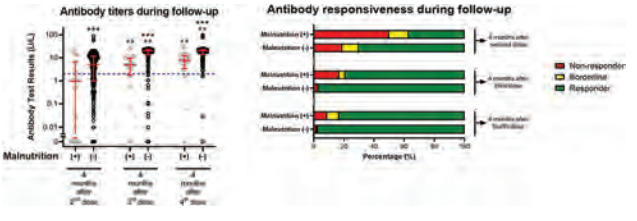
Background: Malnutrition is frequent in patients with end-stage renal disease (ESRD). This condition is an independent risk factor for developing adverse events, including severe infections and infection-related deaths. Previous studies have shown that patients with malnutrition, both in the general population and ESRD patients, have an impaired immune response. Currently, there is little data on malnutrition's effects on the induction of the immune response to anti-SARS-CoV-2 vaccination. Therefore, our objective was to evaluate the impact of malnutrition on the humoral immune response after anti-SARS-CoV-2 vaccination in ESRD patients on hemodialysis.

Methods: Prospective cohort of ESRD patients on chronic hemodialysis who received a three-dose anti-SARS-CoV-2 immunization schedule between 2021 and 2022. We measured the plasma levels of anti-SARS-CoV-2 IgG antibodies before vaccination, four months after doses 2, 3 and 4. Based on anthropometric parameters and subjective global assessment (SGA), we stratified patients according to their baseline nutritional status. In addition, we evaluated potential predictors of humoral response using multivariate analysis.

Results: 214 patients were evaluated in four hemodialysis centers. Age: 63.7 ± 16.3 years, men: 116 (54.2%). 41 patients (19.1%) were diagnosed with malnutrition. Malnourished patients had a lower humoral response after anti-SARS-CoV-2 vaccination compared to those without malnutrition (4 months after the second dose: 61.3% vs. 79.4%, p<0.01; 4 months after the third dose: 78.3% vs 93.1%, p<0.01. Figures 1 and 2). Multivariate analysis indicated that malnutrition is an independent risk factor for a decreased humoral immune response after vaccination (OR: 3.1, [1.5-9.9], p=0.01).

Conclusions: Our results suggest malnutrition is a risk factor for a lower humoral response after anti-SARS-CoV-2 vaccination in ESRD patients on hemodialysis. These data suggest that improving nutritional status can improve the post-vaccination immune response, which should be evaluated in future studies. Study supported by FONDECYT Regular 1221571.

Funding: Government Support - Non-U.S.



FR-PO1099

High Fibroblast Growth Factor 23 Levels Increase Risk of SARS-CoV-2 Infection and Mortality in End-Stage CKD on Hemodialysis: A Three-Year Follow-Up Prospective Cohort

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Background: End-stage renal disease (ESRD) patients are a population with high rates of COVID-19 and mortality. Fibroblast Growth Factor 23 (FGF23) is a protein hormone associated with impaired immune response in experimental murine models.

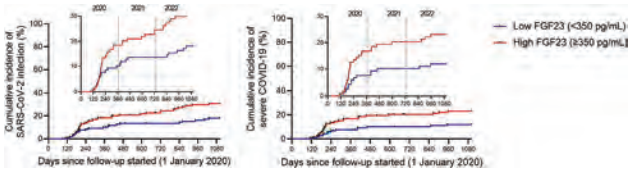
ESRD patients have high plasma levels of FGF23, and recent studies suggest that patients with high FGF23 levels have increased rates of severe infections and infection-related mortality. Therefore, our objective was to evaluate the association between FGF23 levels and the development of SARS-CoV-2 infection in ESRD patients on hemodialysis.

Methods: A prospective cohort of ESRD patients on hemodialysis who had plasma intact FGF23 (iFGF23) measurements in 2019. We evaluated rates of SARS-CoV-2 infection and severe COVID-19 (COVID-related hospitalization or death) between January 2020 and December 2022 (3-year follow-up). In addition, we evaluated potential predictors of outcomes using multivariate analyses.

Results: 243 patients were evaluated. Age: 60.4±10.8 years. Women: 120 (49.3%), diabetes: 110 (45.2%). 57 patients developed COVID-19 (23.4%), 41 were hospitalized, and 46 died (mortality rate: 18.9%). Patients with high iFGF23 (equal to or greater than 350 pg/mL) had a higher rate of SARS-CoV-2 infection (30.8% vs. 18.1%; Hazard ratio: 1.81 [1.08–3.04], p=0.024) and severe COVID-19 (23.1% vs. 11.9%; Hazard ratio: 2.02 [1.09–3.73], p=0.031) compared to those with lower levels (Figures 1 and 2). Multivariate analysis showed that elevated iFGF23 plasma levels were an independent risk factor for SARS-CoV-2 infection and severe COVID-19.

Conclusions: Our data suggest that increased iFGF23 levels are a risk factor for developing COVID-19 in ESRD patients on hemodialysis. In addition, these data support the potential immunosuppressive effect of FGF23, which may contribute to the increased risk of adverse clinical outcomes in renal patients. Study supported by FONDECYT Regular 1221571.

Funding: Government Support - Non-U.S.



FR-PO1100

The Comparison of Humoral Response Between Third and Fourth Doses of COVID-19 Vaccines in ESRD on Hemodialysis (HD)

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Background: The humoral response of coronavirus disease 2019 (COVID-19) vaccine in hemodialysis (HD) patients decrease substantillay overtime compare to the general population. Currently, experts recommend to recieve additional boosting vaccines against these high risk patients. However, the effects between additional third and fourth boosting vaccine in HD patients are not yet clear.

Methods: Total 86 HD patients from two hospitals (Gangdong Kyung Hee University Hospital and Kyung Hee Medical Center) were enrolled in this study. Patients were classifed into 4 groups according to the total dose of vaccines and whether they were infected with COVID-19. Serum IgG to receptor-binding domain (RBD) of the S1 subunit of the spike protein of SARS-CoV-2 was measured at 1 month after the first dose (T1), 2 months (T2) and 4 months after the second dose (T3), 4 months after third dose and (T4), 4-7 month after fourth dose of vaccine or 11 month after third dose (T5) for all groups. Neutralizing antibody also measured at T3 and T4 by plaque reduction neutralization test.

Results: Anti-RBD IgG after the second dose (T3) of vaccine was rapidly decreased (median [interquartile range] 1255.7[642.0, 2337.1] AU/ml), but it was significantly elevated after third dose (T4) in COVID19 naïve HD patients 3979.1[1966.1, 17098.1] AU/ml. The level of anti-RBD IgG was markedly higher in the COVID19 naïve patients with 4th doses than in them with 3rd doses (14075.3[4527.1, 30460.0], 2492.5[851.2, 17086.3] AU/ml, P < 0.001). However, the difference of anti-RBD IgG levels between 3rd and 4th vaccine was not observed in the COVID19 infected HD patients. Anti-RBD antibody titers were well correlated with neutralizing antibodies against omicron and delta at T3 and T4 (P < 0.001). Of the total 34 COVID-19 infected patients, 6 patients had high severity(4 hospital admission, 2 death), and their anti-RBD IgG showed a lower trend than those with COVID-19 naïve 1255.7[642.0, 2337.1] AU/ml and low severity COVID-19 infected patients 1486.4[677.6, 3044.1]. In particular, two death HD patientsed showed significantly lower anti-RBD IgG(342, 317 AU/ml).

Conclusions: Humoral response was better after 4th dose compared with 3rd doses in COVID-19 naïve HD patients.

FR-PO1101

Vaccination, Prior Infection, and the Risk of COVID-19 Reinfection Across the Spectrum of CKD

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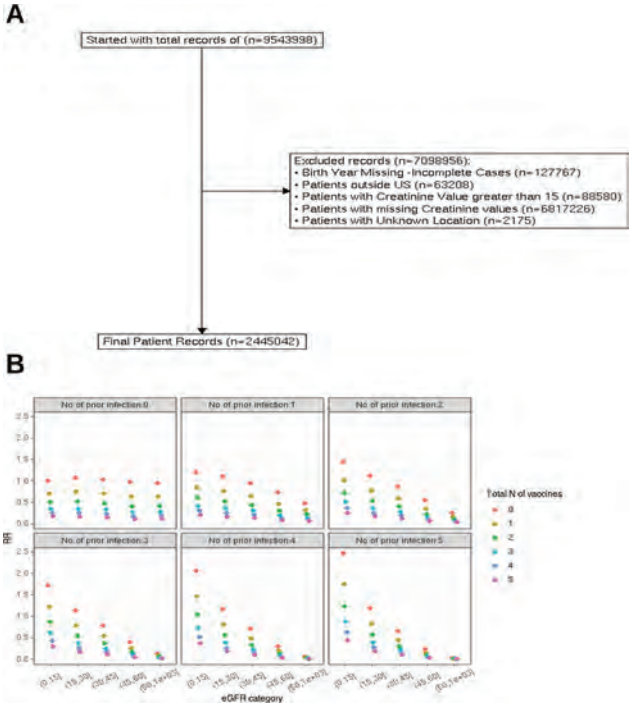
Background: Patients with CKD have a higher burden of sequelae due to COVID19 (C19), but little is known about the impact of prior vaccination (vax) & infection (inf) on the risk of reinfection (reinf) across the spectrum of CKD.

Methods: We analyzed C19 inf (ICD10 B97.29, U07.1, U07.2, J12.82, B34.2) & vax data from the TRINETX Health Research Network of electronic medical records from 59 healthcare organizations from inception until June, 1st 2022. eGFR was assessed with the CKDEpi 2021 formula using the most recent creatinine to the first inf or C19 vax. Repeated C19 episodes were analyzed with proportional hazards models using cluster variance methods. Interactions between eGFR & time updated prior number of infections(NI) or vaccinations (NV) were used to answer the primary question. Patients who tested negative for C19 served as controls.

Results: 9.5M pts were identified, but 2.4M were eligible for analyses (most pts were excluded due to missing eGFR [Fig]A. Mean age was 56, 42.4% were male, 9.7% were Hispanic & African Americans were 19.2%. 90.7% of pts were unvaxxed, 2.1%, 4.13% & 2.4% had received 1,2,3 vax. 10.3% of pts had a single C19 inf, 3.2% 2 & <0.1% more than 3 inf. In models adjusting for demographics, region, age, eGFR, and secular trends, there was a statistical significant interaction between CKD stage and NI and NV [Fig]B. While a prior C19 inf reduced the risk of a subsequent reinf for eGFR>30, it increased the risk for those with eGFR≤30. Cumulative NV was protective across all eGFR levels.

Conclusions: Prior C19 inf increases subsequent risk for inf for pts with eGFR <30, even after adjusting for number of vax. Pts with CKD stages 4-5 should strongly consider adhering to nonpharmaceutical interventions & stay up to date with C19 vax to reduce their risk of C19 disease.



FR-PO1102

Immune Response After the Fourth COVID-19 Vaccine Dose in Hemodialysis Patients

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Background: Hemodialysis (HD) patients have shown a suboptimal immune response to COVID-19 vaccines, and it remains unclear whether current vaccination schemes are suitable for these patients. We assessed humoral and cellular responses after the administration of the 4th dose of mRNA-based COVID-19 vaccine in HD patients.

Methods: We included HD patients from a NephroCare clinic in Spain who were vaccinated with three doses of an mRNA-based COVID-19 vaccine and scheduled to receive the 4th dose. Humoral response was assessed at T0 (max. 4 weeks before 4th dose) and T1 (1 month post 4th dose) using a Bioplex IgG antibody panel. IFN-g released by S1 protein stimulated T-cells was used to assess cellular response in a subsample of 5 patients.

Results: Twenty patients (80% males and median age 76.3 (IQR: 65.2; 84.2) years) were analyzed. Immune response was measured at T0 in a median period of 158 days after the 3rd dose and 100% patients maintained Anti-RBD and Anti-Spike 1 IgGs above the protective level. At T1, all humoral response markers significantly increased and cellular response was positive in 80% (4/5) patients. Anti-Nucleocapsid IgG, detecting contact with the virus, were positive in 3 (15%) patients at T0 and 4 (20%) at T1 but no COVID-19 infection was reported in the study period (figure 1).

Conclusions: Our study suggests that HD patients maintain a reasonable immune protection after three doses of an mRNA COVID-19 vaccine that further increases after the 4th dose. The first and second authors contributed equally to this work.

Funding: Commercial Support - Fresenius Medical Care

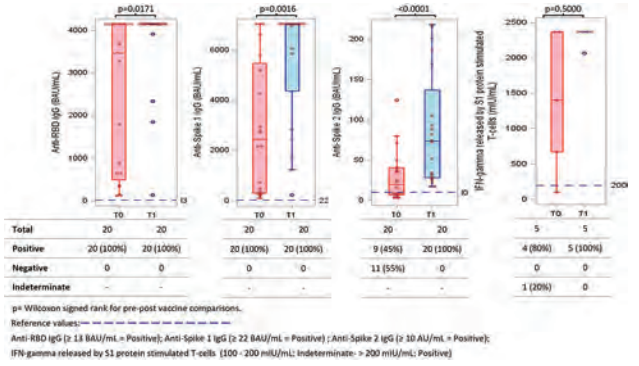

Figure 1: Humoral and cellular immune levels before and after the fourth COVID-19 vaccine dose in HD patients.

FR-PO1103

Longitudinal SARS-CoV-2 Antibody and T-Cell Immune Responses in Patients on Hemodialysis During the Omicron Era

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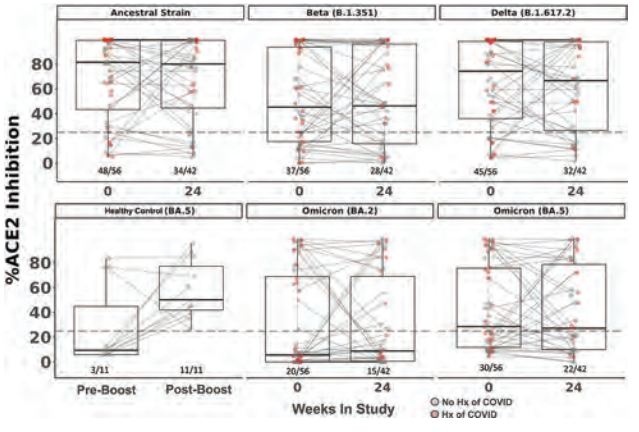
Background: Individuals receiving renal replacement therapy via hemodialysis (HD) are at high risk for severe outcomes from COVID-19, have attenuated responses to the original COVID-19 vaccine series, and are at increased risk for contracting SARS-CoV-2 due to frequent healthcare exposures. How immunity to SARS-CoV-2, and risk for severe disease, evolve with episodes of infection and additional booster vaccinations in this vulnerable population has not been described.

Methods: An observational multicenter cohort of 55 HD patients (>90% received at least two doses of mRNA COVID-19 vaccine, 56% female, 47% with diabetic kidney disease, age [med, IQR] 67, 58-74 years) were followed for 24 weeks between Dec 2021 and Nov 2022 and provided blood samples at enrollment (week 0), 8 weeks, and 24 weeks. Plasma was tested for anti-SARS-CoV-2 IgG and ACE2 inhibition (surrogate neutralization; 0-100% with >25% consistent with neutralizing antibody) against ancestral, Beta, Delta, and Omicron subvariants using the MSD platform. T cell responses to SARS-CoV-2 spike and nucleocapsid were assessed via ELISpot. Changes in antibody and T cell responses were assessed by paired Wilcoxon rank-sum testing. Additionally, responses were compared to boosted healthy controls (HC) (n=11).

Results: Antibody responses against ancestral virus remained relatively constant in the HD cohort (p = 0.9). Neutralization of BA.5 remained low throughout with 48% of participants below the 25% threshold associated with live-virus neutralization. While ACE2 inhibition was similar to HCs (Figure), the proportion of HD participants above the 25% threshold for BA.5 was significantly lower than HCs (p = 0.004). Neutralizing capacity of BA.5 among HD patients with a history of COVID-19 was not greater than those with no history of COVID-19. Spike specific T cell responses increased in HD patients over time.

Conclusions: Original vaccine formulations are insufficient to induce reliable Omicron subvariant neutralization in HD patients.

Funding: Commercial Support - This work was supported by Fresenius Medical Care



FR-PO1104

Symptoms After COVID-19 Vaccination Are Associated with Anti-SARS-CoV-2 Antibody Response in Kidney Transplant Recipients

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Background: SARS-CoV-2 messenger RNA (mRNA) vaccines, BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna), have been associated with local and systemic symptoms. We investigated the association of self-reported post-vaccination symptoms with anti-SARS-CoV-2 antibody response among kidney transplant recipients.

Methods: This study included data collected from 251 kidney transplant recipients at Yochomachi Clinic from 2021 to 2022. All participants were administered an mRNA vaccine (BNT162b2 or mRNA-1273), as indicated. Serum samples from each patient were subsequently collected before the first and second vaccination and at 1, 3, and 6 months after the second vaccination. For the assessment of antibody titers, S-IgG and N-IgG levels were measured (Elecsys®, Roche). As post-vaccination symptoms, local (injection site pain, rash, heat sensation, swelling, itchiness) and systemic (headache, fever, moderate to severe fatigue) symptoms were recorded from the 1st day of vaccination to the 10th day, for both the first and second vaccination.

Results: Major symptoms after the second vaccination included injection site pain (80%), itchiness (43%), moderate to severe fatigue (27%), and headache (19%). Itchiness and headache were significantly less common in the group of patients <1 year post-transplant (p=0.049, 0.03). Based on vaccine type, itchiness and fatigue were significantly more common with the mRNA1273 vaccine (p<0.01). S-IgG titers at 3 and 6 months after the second shot were significantly higher in patients who reported fatigue or headache (p<0.05). Logistic regression analysis revealed that headaches were associated with acquisition of anti-SARS-CoV-2 antibodies 3 months after the second shot, independent of age and sex. (Table1)

Conclusions: Systemic symptoms after vaccination for COVID-19 might be related to acquisition of anti-SARS-CoV-2 antibodies.

Funding: Government Support - Non-U.S.

Table1. Result of the logistic regression analyses for acquisition of anti–SARS-CoV-2 antibody at 3 months after 2nd vaccination

	univariate		multivariate	
Variables	OR (95% CI)	p	OR (95% CI)	p
Age at vaccination	0.97 (0.95--0.99)	<.01	0.98 (0.96--0.999)	.046
Male (ref. female)	1.14 (0.66--1.98)	.63	1.28 (0.66--2.30)	.52
Interval from transplantation to vaccination <1 year	0.08 (0.03--0.25)	<.01	0.11 (0.04--0.36)	<.01
mRNA1273 vaccine	3.25 (1.30--8.15)	<.01	2.91 (1.08--6.88)	.04
use of rituximab at transplantation	0.40 (0.22--0.72)	<.01	0.43 (0.22--0.81)	<.01
local symptoms after 2nd vaccination				
injection site pain	1.73 (0.89--3.37)	.11		
rash	1.05 (0.31--3.61)	.93		
heat sensation	2.77 (1.22--6.27)	.01		
swelling	6.14 (0.78--48.4)	.09		
itchiness	1.82 (1.05--3.14)	.03		
systemic symptoms after 2nd vaccination				
headache	3.07 (1.36--6.93)	<.01	2.61(1.09--6.27)	.03
moderate to severe fatigue	1.94 (1.02--3.68)	.04		

FR-PO1105

COVID-19 Vaccine Immune Response in Hemodialysis Patients

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Background: COVID-19 infection is associated with increased morbidity and mortality in chronic kidney disease patients, especially those on maintenance hemodialysis. The comparison of immunogenicity of different COVID vaccines in the dialysis populations is lacking especially in the middle east region.

Methods: We conducted a retrospective observational study, that includes 164 hemodialysis patients (HD) and 54 health workers (HW), who received 2 doses of either Pfizer-BioNTech or Sinopharm vaccine. The primary endpoint was to report the rate of seroconversion and the factors affecting it.

Results: HD patients have a significantly low seroconversion rate than HW (HD vs HW: 76.54% and 100%, p=<0.05), also S1 IgG antibody level was significantly low in HD patients (HD vs HW: 183.5 and 400 BAU/ml, p=<0.05). The type of vaccine and hypo-response to the HBV vaccine were two statistically significant factors affecting the seropositivity rate in HD patients. As compared to Sinopharm, Pfizer-BioNTech vaccinated HD patients exhibit not only higher seroconversion rate (Pfizer-BioNTech vs Sinopharm: 90.80% and 60%, p=<0.05) but also express high S1 antibody titer (Pfizer-BioNTech vs Sinopharm: 425 and 162 BAU/ml (p=<0.05), however, there is no significant difference in post-vaccine COVID infection rate among the two vaccines (Pfizer-BioNTech vs Sinopharm: 39.24% and 42.22% (p= 0.176).

Conclusions: Lower Immune response to the COVID vaccine is observed in HD patients as compared to HW participants, also Pfizer-BioNTech vaccinated HD patients exhibit better seroconversion rates and higher antibody titer than Sinopharm vaccine in HD patients, so alternative vaccine strategies should be designed in dialysis patients

Table no: 1. Baseline charracterstics of Health workers (HW) & Hemodialysis patients (HD).			
	HD patients(n=162)	Health workers(n=52)	p value
Ethnicity			0.83
Arab	148(91.36)	4(7.69)	
Age in years, median (IQR)	58 (45.25-69)	50(38.75-55)	<0.05
Gender			<0.05
Male	100(61.72)	10(19.23)	
Vaccine			
Pfizer	87(53.70)	48(92.30)	
Sinopharm	75(46.29)	4(7.69)	
Immune response			<0.05
Seronegative	38(23.46)	0(0.0)	
Seropositive	124(76.54)	52(100)	
COVID Ab, median (IQR)	183.5(44-993.3)	400(167-723)	<0.05
co-morbid			
Diabetes mellitus	98(60.49)	18(34.61)	<0.05
Hypertension	129(79.62)	8(15.38)	<0.05
Albumin median	4(3.60-4.15)	4.5(4.2-4.6)	<0.05
<3.4	16(9.87)	0(00)	
≥ 3.4	146(90.12)	52(100)	

Table No:2. Comparison of Characterstics of seropositive & seronegative HD patients.			
	Seropositive (n=124,76.54%)	**Seronegative (n=38, 33.46%)**	
Ethnicity			0.275923
Arab	110(88.70)	36(94.73)	
Age in years, mean (SD)	56.23±15.93	58.97± 14.59	0.34606
Gender			
Male	77(62.09)	23(60.52)	0.861663
Vaccine			<0.05
Pfizer	79(63.70)	8(21.05)	
Sinopharm	45(36.29)	30(78.94)	
co-morbid			
Diabetes mellitus	75(60.48)	23(60.52)	0.996264
Hypertension	98(79.03)	31(81.57)	0.733086
Albumin median (IQR) (n=152)	3.90(3.6-4.15)	3.95(3.7-4.10)	0.469837
<3.4	16(12.90)	3(7.89)	
≥ 3.4	108(87.09)	35(92.11)	
Hyporesponse to HBV vaccine			<0.05
Yes	24(19.35)	15(39.47)	
No	120(80.65)	23(60.53)	

FR-PO1106

Omicron BA.1, BA.5, BQ.1.1, and XBB.1.5 Neutralizing Antibodies Following BNT162b2 BA.4/5 vs. mRNA-1273 BA.1 Bivalent Vaccination in Hemodialysis Patients and Kidney Transplant Recipients

Kevin Yau,[1,2] Darren A. Yuen,[1,3] Jeffrey Perl,[1,3] Christopher T. Chan,[1,4] Adeera Levin,[5] Matthew J. Oliver,[1,2] Michelle A. Hladunewich.[1,2] *[1]University of Toronto Temerty Faculty of Medicine, Toronto, ON, Canada; [2]Sunnybrook Health Sciences Centre, Toronto, ON, Canada; [3]St Michael's Hospital, Toronto, ON, Canada; [4]Toronto General Hospital, Toronto, ON, Canada; [5]BC Provincial Renal Agency, Vancouver, BC, Canada.*

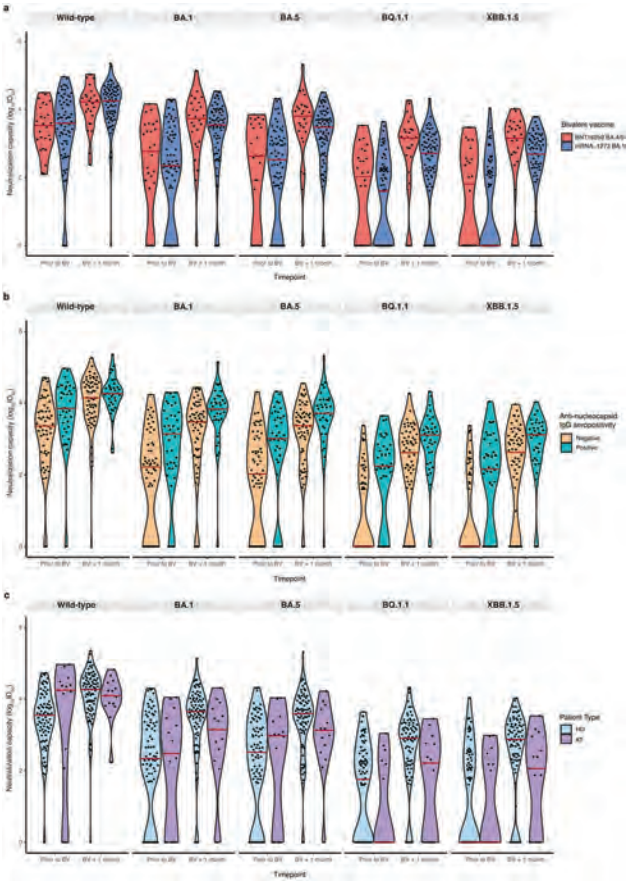
Background: Bivalent COVID-19 vaccines are recommended, however differences in neutralization of emerging Omicron subvariants by vaccine type have not been evaluated in patients with kidney disease.

Methods: This was a prospective observational cohort study at three centres in Toronto, Canada from July 25, 2022 to November 30, 2022 in 98 patients receiving hemodialysis or with a kidney transplant. Participants received either the BNT162b2 (original and Omicron BA.4/BA.5) or mRNA-1273 (original and Omicron BA.1) COVID-19 vaccine. Neutralizing antibodies against wild-type, Omicron BA.1, BA.5, BQ.1.1, XBB.1.5 subvariants were measured prior to and one month following the receipt of a bivalent vaccine.

Results: Neutralizing antibodies against BA.1, BA.5, BQ.1.1, and XBB.1.5 increased 8-fold one month following bivalent vaccination. In comparison to wild-type, neutralizing antibodies against Omicron-specific variants were 7.3-fold lower against BA.1, 8.3-fold lower against BA.5, 45.8-fold lower against BQ.1.1, and 48.2-fold lower against XBB.1.5. Viral neutralization did not differ by bivalent vaccine type: wild-type (p=0.48), BA.1 (p=0.21), BA.5 (p=0.07), BQ.1.1 (p=0.10), XBB.1.5 (p=0.10).

Conclusions: The BNT162b2 and mRNA-1273 bivalent vaccines induced similar neutralization against all Omicron subvariants in hemodialysis and kidney transplant recipients, suggesting that bivalent vaccines confer protection against emerging Omicron subvariants even if they are antigenically different from the circulating variant.

Funding: Government Support - Non-U.S.



Neutralizing antibody levels stratified by a) bivalent vaccine type b) anti-nucleocapsid IgG seropositivity c) and hemodialysis versus kidney transplant recipients.

FR-PO1107

Safety and Efficacy of One and Two Booster Doses of SARS-CoV-2 mRNA Vaccines in Kidney Transplant Recipients: A Randomized Clinical Trial

Petr Drenko,[1] Martin Kacer,[1] Lukas Kielberger,[1] Tomas Vlas,[2] Radek Kucera,[3] Tomas Reischig.[1] *[1]Department of Internal Medicine I, Faculty of Medicine in Pilsen, Charles University, and University Hospital, Pilsen, Czechia; [2]Department of Immunology and Allergology, Faculty of Medicine in Pilsen, Charles University, and University Hospital, Pilsen, Czechia; [3]Department of Immunochemistry Diagnostics, Faculty of Medicine in Pilsen, Charles University, and University Hospital, Pilsen, Czechia.*

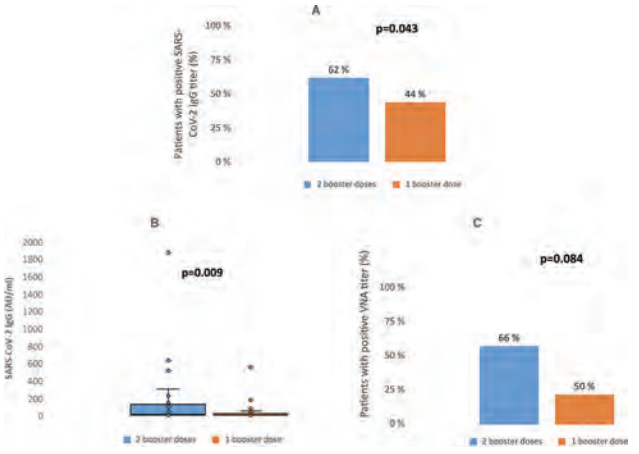
Background: Kidney transplant recipients are at risk for a severe course of COVID-19 with a high mortality rate. Although an adequate humoral response to COVID-19 vaccination is therefore essential, a considerable number of patients remains without a satisfactory serological response after the baseline and adjuvant SARS-CoV-2 vaccination schedule.

Methods: In this prospective, randomized study, we evaluated the efficacy and safety of one and two booster doses of mRNA vaccines (either mRNA-1273 or BNT162b2) in 125 COVID-19 naive, adult kidney transplant recipients who showed an insufficient humoral response (SARS-CoV-2 IgG <10 AU/ml) to the previous 2-dose vaccination schedule. The primary outcome was the occurrence of a positive antibody response between one and two booster doses at one month after the final booster dose.

Results: A positive humoral response was observed in 36 (62%) patients who received two booster doses and in 28 (44%) patients who received one booster dose (p=.043). Moreover, median SARS-CoV-2 IgG levels were higher with two booster doses (p=.009). The number of patients with positive virus neutralizing antibody levels was numerically higher in the two booster doses compared to the single booster dose, but without statistical significant (66% vs. 50%, p=.084). There was no significant difference in the rate of positive seroconversion and antibody levels between mRNA-1273 and BNT162b2 vaccines.

Conclusions: A higher number of kidney transplant recipients achieved a positive antibody response after two booster doses compared to one booster dose.

Funding: Other NIH Support - Charles University Cooperatio Program; "Fighting INfectious diseases" (FIND) project; Faculty Hospital in Pilsen; BBMRI-CZ: Biobank network



FR-PO1108

SARS-CoV-2 Vaccination Reduces the Frequency of Acute Kidney Disease in COVID-19 Patients: A Prospective Multicenter Multinational Study

Raul Lombardi,[1] Alejandro Ferreiro,[1] Joanna Y. Venegas justiniano,[2] Mariana B. Pereira,[3] Maria C. Carlino,[4] Rolando Claure-Del Granado,[5] Daniela Ponce,[6] Maria A. Zinoveev.[1] *[1]Universidad de la Republica Facultad de Medicina, Montevideo, Uruguay; [2]Corporacion Arzobispo Loayza SAC, Lima, Peru; [3]Universidade de Sao Paulo, Sao Paulo, Brazil; [4]Circulo Medico de Rosario, Santa Fe, Argentina; [5]Universidad Mayor de San Simon, Cochabamba, Bolivia, Plurinational State of; [6]Universidade Estadual Paulista Julio de Mesquita Filho, Sao Paulo, Brazil.*

Background: The development of renal alterations in SARS-CoV-2 infection is frequent and is associated with poor outcome. Objectives. To evaluate AKD (proteinuria, hematuria, AKI) and the impact of immunization with vaccine for the acquisition of kidney complications of the disease.

Methods: Observational, prospective, multicenter, multinational, longitudinal study. Inclusion criteria: patients ≥ 18 years with COVID-19 by RT-PCR who required hospital admission between march 2021 and may 2022. Patients receiving KRT, or CKD stage 4 - 5 were excluded. Data collected in electronic web form. Approved by the Ethics Committee. H_0 was rejected with a p value <0.05.

Results: 360 patients from 5 countries: Peru (45%), Brazil (22.5%), Bolivia (14.7%), Argentina (11.1%), Uruguay (6.7%). 57.7% male. Age 62 (48-75) years. Comorbidities: hypertension (49.7%), diabetes (31.8%) obesity (26.3%). 73.8% were hospitalized in a conventional ward, 15.6% in the ICU and 10.6% in the emergency room. At admission: Scr 0.86 (0.68-1.07) mg/dl, proteinuria 225 patients (62.5%); (27,4% developed at evolution). 36,4% developed AKI, most of them KDIGO stage 3 (47.9%) KRT (37.4%). Diuresis preserved in 71.4%. Complete recovery 40.2%, partial 12.4% and 47.4% had no recovery. 50.9% were admitted to the ICU and 163 (45.3%) received mechanical ventilation. 56.2% developed sepsis. In-hospital mortality was 30.2%. Mortality was analyzed according 4 groups: 1) without proteinuria or AKD (5,8%); 2) proteinuria without AKI (24,1%) ; 3) AKI withot proteinuria or hematuria (36,4%) ; 4) proteinuria and AKI (55,5%) (p< 0.0001). Patients who received at least one dose of SARS CoV-2 vaccine had lower frequency of proteinuria (52 vs 71.8% p<0.001), hematuria (24.4 vs 44.4%, p<0.01), AKI (42 vs 47.1%, p<0.05) and mortality adjusted for comorbid factors (25 vs 44.5%, p<0.001).

Conclusions: The epidemiological profile of COVID associated AKD in Latin America was similar to previous reports. Isolated proteinuria was the most frequent manifestation of AKD. Mortality of AKD was maximal in AKI associated with proteinuria. Vaccination against SARS CoV-2 decreased the frequency of AKD, and was associated with a decrease in mortality.

FR-PO1109

Despite Vaccination, Risk of COVID-19 Outcomes Is Elevated in Patients with ESRD: Initial Results from INFORM Retrospective Study in England using National Health Service Datasets

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Background: Patients (pts) with end-stage renal disease (ESRD) are considered immunocompromised. However, pre-exposure prophylaxis (PrEP) is not always recommended in this population. We report initial results from the INFORM retrospective study on severe COVID-19 outcomes in fully vaccinated (≥3 doses) pts with ESRD or dialysis (ESRD or D) and ESRD with dialysis (ESRD+D).

Methods: COVID-19–related hospitalizations and deaths in pts aged ≥12 years in England were identified from a random sample of 25% of pts in National Health Services datasets (Jan 1, 2022–Dec 31, 2022). Incidence rates (IRs) per 100 person years (PY) were determined in pts with ESRD or D and with ESRD+D. Incidence rate ratios (IRRs) per 100 PY (crude and adjusted for age and sex) were calculated for pts with ESRD or D and ESRD+D versus those without.

Results: Pts with ESRD or D or with ESRD+D had higher IRs for COVID-19–related hospitalizations or deaths than those without. Adjusted IRRs for hospitalization and mortality were higher in pts with ESRD or D and ESRD+D than those without. Hospitalization adjusted IRRs for pts with ESRD or D and ESRD+D were 5.59 (95% CI 5.07–6.16) and 9.91 (95% CI 8.69–11.30), respectively (Table). Mortality adjusted IRRs for pts with ESRD or D and ESRD+D were 5.04 (95% CI 4.11–6.16) and 8.68 (95% CI 6.41–11.77), respectively (Table).

Conclusions: Despite full COVID-19 vaccination, including boosters, pts with ESRD or D and ESRD+D are at greater risk of severe COVID-19 outcomes than those without. Therefore, vaccinated pts with ESRD may benefit from PrEP to reduce the risk of severe COVID-19.

Funding: Commercial Support - AstraZeneca

Table. COVID-19 hospitalizations and deaths in 2022 in patients with ESRD or dialysis and patients with ESRD and dialysis who are fully vaccinated (≥3 doses)

	N* (%)	COVID-19-related hospitalizations: Total number of hospitalizations,*#	Pts with (1 hospitalization, n (%))	Incidence rate per 100 person-years	Crude IRR (95% CI)	Age and sex adjusted IRR (95% CI)	COVID-19-related mortality: Deaths, n (%)	Death rate per 100 person-years	Crude IRR (95% CI)	Age and sex adjusted IRR (95% CI)
Fully vaccinated (≥3 doses) pts with ESRD or dialysis^	99 450 (0.3)	680	470 (3.4)	2.47 (2.26–2.69)	10.17 (9.02–11.21)	5.59 (5.07–6.16)	105 (0.5)	0.38 (0.32–0.76)	10.15 (8.79–13.19)	5.04 (4.11–6.16)
Fully vaccinated (≥3 doses) pts with ESRD/dialysis^	8290 (0.1)	265	200 (2.1)	3.26 (2.89–3.61)	12.88 (11.29–14.82)	9.91 (8.69–11.30)	46 (0.5)	0.61 (0.45–0.79)	10.68 (7.89–14.46)	8.68 (6.41–11.77)

*The table consists of a random sample of 25% of patients in ESRD datasets;
#any hospital admissions (<24 hours) with COVID-19 recorded as the primary diagnosis;
^Pts are compared to population without ESRD or dialysis.
CI, confidence interval; ESRD, end-stage renal disease; IRR, incidence rate ratio; pts, patients.

FR-PO1110

Risk Factors for COVID-19-Related Hospitalization After Reinfection in Maintenance Dialysis Patients

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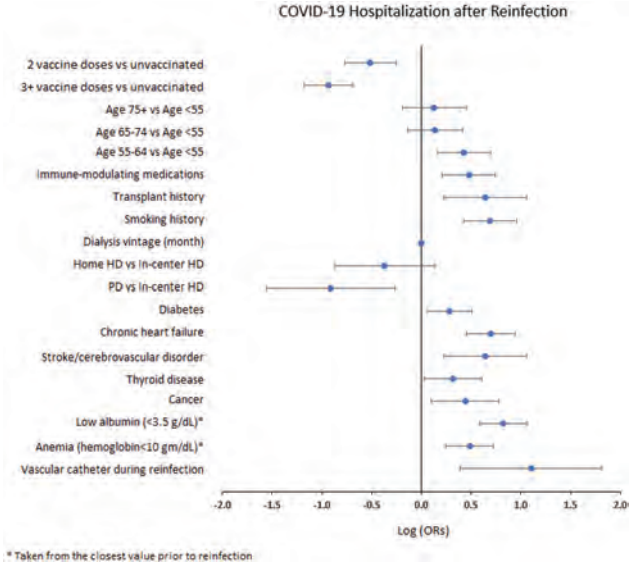
Background: SARS-CoV-2 reinfection is a common occurrence. However, risk factors for COVID-19-related hospitalization with COVID-19 recurrences among maintenance dialysis patients are uncertain.

Methods: All adult maintenance dialysis patients at Dialysis Clinic, Inc. with 1) at least two COVID-19 diagnoses between 2/1/2020 and 1/31/2023 and 2) the second diagnosis was after 2/1/2021 (when vaccine became available) were included. SARS-CoV-2 reinfection was defined by a positive test >90 days after the first positive test. SARS-CoV-2-related hospitalization (within 30 days) of a recurrent infection were defined by a documented primary diagnosis for the episode of care of COVID-19. Stepwise logistic regression models were used to identify risk factors for COVID-19 hospitalization after reinfection. Exposure time accounting for time since last vaccination and prior COVID-19 infection was weighted for all models.

Results: Of 610 patients with ≥2 COVID-19 infections included in the analysis, 99 (16.2%) patients were hospitalized after COVID-19 reinfection. 410 were not hospitalized, 165 were hospitalized once, and 35 were hospitalized twice. Unvaccinated status, older age, usage of immune-modulating medications, transplant history, smoking history, comorbidities, low serum albumin, anemia, and vascular catheter usage were associated with increased risk for COVID-19 hospitalization after reinfection. There was a dose-response relation between higher vaccine number and lower risk of hospitalization (p for trend=0.02).

Conclusions: Hospitalization risk for COVID-19 reinfection remained high (16.2%). Despite prior infection, unvaccinated patients had higher risk. Traditional risk factors such as age, diabetes, low serum albumin, and catheter usage remained significant.



COVID-19 Hospitalization after Reinfection

FR-PO1111

Outcomes of Patients with CKD and ESRD Hospitalized with COVID-19: A Retrospective Cohort Study in Michigan

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Background: A large patient cohort, multivariate regression models, and inverse probability of treatment weights (IPTWs) to determine the effect of kidney disease on mortality in hospitalized CoVID-19 patients.

Methods: 6,737 hospitalized, SARS-CoV-2 positive patients from the South East Michigan CoVID Consortium dataset were analyzed for common dimensions of risk factors for increased mortality. Univariate, multivariate logistic regression, and IPTW propensity scoring models were used to reflect the effect of each variable on outcomes. IPTW models required patient population trimming to include patients only within the region of common support, thus less patients were analyzed in the fully adjusted (N=6,117) and IPTW (N=4131) models.

Results: Unadjusted models show significant increases in all outcomes in any level of renal disease. No association with increased mortality as a result of renal disease after adjusting for covariates. IPTW model finds that renal dysfunction infers longer duration of hospitalization, and average higher SOFA scores. In CKD patients, SOFA scores were 1.34 times higher (p<0.001) versus control patients. ESRD patients were hospitalized longer (IRR=1.19;p<0.001), and had higher SOFA scores (IRR=1.98;p<0.001) than control patients.

Conclusions: Here, we show that renal disease in of itself does not directly lead to increased mortality in CoVID-19 patients. Initial findings of increased mortality in CKD and ESRD patients may more likely be a result of chronic disease burden as shown by sequela comorbidities seen in CKD and ESRD patients.

Association between CKD/ESRD and Binary CoVID-19 Outcomes

Model	N	Overall p-value	CKD vs Control		ESRD vs Control		ESRD vs CKD	
			RR (95% CI)	p-value	RR (95% CI)	p-value	RR (95% CI)	p-value
In-Hospital Death								
Unadjusted	6737	<0.001	1.72 (1.45-2.05)	<0.001	1.43 (1.02-2.00)	0.038	0.83 (0.57-1.19)	0.32
IPTW	4131	0.59	1.06 (0.85-1.33)	0.61	0.79 (0.44-1.42)	0.44	0.75 (0.4-1.39)	0.35
In-Hospital Death or Expected Death (Transfer to Hospice)								
Unadjusted	6737	<0.001	1.76 (1.52-2.03)	<0.001	1.23 (0.9-1.68)	0.19	0.70 (0.50-0.98)	0.036
IPTW	4131	0.95	1.01 (0.84-1.23)	0.90	0.92 (0.52-1.66)	0.79	0.92 (0.5-1.67)	0.77
Admission to ICU								
Unadjusted	6737	<0.001	1.31 (1.15-1.49)	<0.001	1.88 (1.58-2.25)	<0.001	1.43 (1.16-1.75)	0.001
IPTW	4131	0.42	1.90 (0.76-1.07)	0.25	1.10 (0.78-1.54)	0.59	1.22 (0.83-1.75)	0.31
Total Duration of Hospitalization (days)								
Unadjusted	6737	<0.001	1.22 (1.15-1.29)	<0.001	1.53 (1.39-1.70)	<0.001	1.27 (1.12-1.41)	<0.001
IPTW	4131	<0.001	1.03 (0.98-1.08)	0.28	1.19 (1.12-1.27)	<0.001	1.16 (1.08-1.25)	<0.001
Highest SOFA score recorded across inpatient stay								
Unadjusted	5842	<0.001	1.65 (1.52-1.79)	<0.001	2.53 (2.20-2.91)	<0.001	1.54 (1.32-1.79)	<0.001
IPTW	3682	<0.001	1.34 (1.25-1.44)	<0.001	1.98 (1.80-2.18)	<0.001	1.47 (1.33-1.64)	<0.001

FR-PO1112

COVID-19 Omicron Infections in a Chinese Peritoneal Dialysis Center

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Background: In December 2022, an outbreak of the COVID-19 Omicron variant occurred in China, resulting in widespread population transmission. Peritoneal dialysis (PD) patients, as a predisposed group, faced significant risks. The aim of this study was to investigate the outcomes and risk factors in peritoneal dialysis (PD) patients infected with COVID-19.

Methods: Demographic and clinical characteristics of 341 PD patients were recorded at admission. Both binary logistic regression analysis and Cox proportional hazard regression analysis were used to evaluate potential risk factors for infection and mortality.

Results: COVID-19 was confirmed in 260 (76.2%) patients. Among infected patients, 57 (16.7%) were hospitalized and 11 (4.2%) patients died. Old age (odds ratio [OR] 1.042, 95% confidence interval [95% CI] 1.010-1.075, p=.01), dyspnea (OR 6.113, 95% CI 2.268-16.475, p<.001), use of systemic glucocorticoids (OR 5.830, 95% CI 1.164-29.201, p= .03), baseline hyponatremia (OR 3.096, 95% CI 1.125-8.517, p=.03), and baseline high-sensitivity C-reactive protein (hsCRP) (OR 1.089, 95% CI 1.011-1.173, p=.02) were associated with hospitalization. Patients with a higher Charlson comorbidity index score (OR 2.143, 95% CI 1.094-4.198, p=.03), weight loss (OR 9.168, 95% CI 1.604-52.399, p= .01), and baseline hyponatremia (OR 19.345, 95% CI 2.229-167.862, p=.007) were more likely to die compared to survivors.

Conclusions: Older PD patients with dyspnea, in receipt of glucocorticoid therapy, and baseline hyponatremia had a higher risk of hospitalization. Charlson comorbidity index score, weight loss, and baseline hyponatremia were associated with mortality.

FR-PO1113

Encapsulating Peritoneal Sclerosis Related to SARS-CoV-2 Infection

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Introduction: Encapsulating peritoneal sclerosis (EPS) is an extremely rare complication of long-term PD, associated with high morbidity and mortality (50%). The reported incidence is 0.7 and 13.6 per 1,000 pts-year. PD duration is the key risk factor, higher dialysate glucose exposure, peritonitis rate, younger age, abdominal surgery, icodextrin (ICO), UF failure, and higher peritoneal solute transport rate as well. Diagnosis is based upon a combination CT findings and intermittent subacute bowel obstruction. Only a fibrous cocoon wrapped around the bowel is diagnostic.

Case Description: 41-year-old female, history of diabetes and hypertension. CKD of unknown etiology since 2020, she began APD since 1 yr, 2.5% PD solution + ICO. 3 episodes of peritonitis in 2021. History of umbilical hernia repair and 2 cesareans. 9 days before admission with a + Covid-19 test, 3 days before she had abdominal pain and clinical data of intestinal oclussion (IO). She was admited with BP 60/40 mmHg, IV resuscitated and treated w/MTZ and CRO. PD count (PDC) showed 1,842 leu, concluding IO and peritonitis. An exploratory laparotomy (EL) was performed with removal and replacement of catheter. After 5 days a PDC showed refractory peritonitis, transferred to HD and antibiotics were escalated (VCM and CTZ). 7 days after EL, PD catheter was removed. She persisted with IO, a CT scan corroborate it; A new EL was done with finding of fibrous cocoon wrapped around the bowel and peritoneal biopsy with fibrosis and chronic inflammation.

Discussion: The patient has risk factors for EPS: PD with ICO, and 2.5% PD solutions, however the main reported risk factor is time in PD, in her case it was considered low. Covid-19 infection has been associated with a possible effect of the virus on the peritoneal mesothelial cells (MCs). Although there is no in vivo direct evidence so far of MCs infection by the virus, despite this, MCs have been found to express SARS-CoV-2 specific receptors/co-receptors ACE2. In this case we consider a strong association between Covid-19 and EPS. To our knowledge there are not previous reported cases and this represents and area for future research.

FR-PO1114

Comparing Infectious Diagnoses in ESKD Before and After the COVID Era

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Background: Undoubtedly, the 2020 worldwide COVID-19 pandemic had a major impact on healthcare. This study aims to compare infections among inpatients with end stage kidney disease (ESKD) before and after the onset of the pandemic in the USA.

Methods: All adult hospitalizations from the 2016-2020 National Inpatient Sample (NIS) database with a principal diagnosis of infection and a secondary diagnosis of ESKD were analyzed. We compared data between the pre-COVID era (2016-2019) with those from the COVID era (2020).

Results: 990,550 hospitalizations between 2016-2020 had both an infection and ESKD. Of those, 752,640 were from the pre-COVID era and 237,910 were from the COVID era (figure 1). Those from the COVID era had less females, higher inpatient charges, and higher adjusted in-hospital mortality (14.4% vs 10.2%; p<0.001) (figure 1). In 2020, COVID-19 became the second most frequent infection seen in ESKD inpatients (figure 2). Various types of sepsis remained frequent in both groups, along with pneumonia, line infection, peritoneal dialysis catheter infection, and urinary tract infection.

Conclusions: ESKD patients with an infection experienced a higher adjusted in-hospital mortality in 2020. COVID became the second most common infection in ESKD patients in 2020. Nine of the top ten infections remained identical between the groups. Sepsis remained the predominant infection in the post-COVID era. This information should alert nephrologists to the frequency of COVID in ESKD inpatients.

Figure 1: Descriptive Characteristics of Endstage Kidney Disease Patients Hospitalized Primarily for an Infection Before and After 2019 (n=990,550)

Descriptive Characteristics	Infections in ESKD 2016-2019 (n=752,640)	Infections in ESKD in 2020 (n=237,910)	P-value
Age, median (IQR)	65 (54-74)	65 (54-74)	0.819
Female (%)	46.2%	44.4%	<0.001
Race/Ethnicity (%)			
White	43.1%	39.6%	<0.001
African American	29.9%	30.9%	0.228
Hispanic	16.1%	18.3%	0.002
Asian or PI	4.3%	4.5%	0.721
Native American	1.4%	1.6%	0.278
Other	2.9%	3.2%	0.089
Length of Stay, median (IQR)	6 (3-10)	6 (3-12)	<0.001
Total Charges, median (IQR)	$56,704 (29,775-115,409)	$68,680 (35,947-140,831)	<0.001
In-hospital Mortality (%)	10.2%	14.4%	<0.001*

*p-value adjusted for age, Charlson comorbidity index, gender, and race

Figure 1

Top 10 Infections 2016-2019	Top 10 Infections in 2020
1. Sepsis, ICD-10 A41.9	1. Sepsis, ICD-10 A41.9
2. Pneumonia, unspecified organism, ICD-10 J18.9	2. COVID-19, ICD-10 U07.1
3. Line Infection, ICD-10 T80.211A	3. Pneumonia unspecified organism, ICD-10 J18.9
4. Urinary tract infection, ICD-10 N39.0	4. Other Sepsis, ICD-10 A41.89
5. Infection of PD Catheter, ICD-10 T85.71XA	5. Line Infection, ICD-10 T80.211A
6. Sepsis E. coli, ICD-10 A41.51	6. Infection PD Catheter, ICD-10 T85.71XA
7. Sepsis MRSA, ICD-10 A41.02	7. Urinary tract infection, ICD-10 N39.0
8. Sepsis MSSA, ICD-10 A41.01	8. Sepsis MSSA, ICD-10 A41.01
9. Other Sepsis, ICD-10 A41.89	9. Sepsis E. coli, ICD-10 A41.51
10. Procedure Infection, ICD-10 T81.4XXA	10. Sepsis MRSA, ICD-10 A41.02

Legend: E. coli= Escherichia coli; MRSA= methicillin resistant Staph aureus, MSSA= methicillin sensitive Staph aureus, PD =peritoneal dialysis;

Figure 2

FR-PO1115

The Effect of ESKD on COVID-19 In-Hospital Mortality

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Background: Significant morbidity resulted when the COVID-19 infection became a pandemic in the United States. This study aimed to study the effect of end stage kidney disease (ESKD) on mortality on those with COVID.

Methods: We performed a retrospective analysis of all adult hospitalizations with a principal diagnosis of COVID from the 2020 National Inpatient Sample (NIS) database. They were subdivided in those with and without ESKD. Variables with a p value ≤0.2 in the univariable screen were included in a multivariable analysis for in-hospital death.

Results: There were 27,668,666 adult hospitalizations in the 2020 NIS database. Of those, 1,011,340 had COVID without ESKD and 38,705 had COVID with ESKD (figure 1). Among COVID inpatients, univariable analysis showed an association for death for the following variables: age, CCI, male gender, White, African American, Hispanic, Native Americans, ESKD, Income Q1, and Income Q3. Multivariable analysis showed higher odds for death for the following variables: Age (OR 1.04; p<0.001), CCI (OR 1.18; p<0.001), Male (OR 1.39; p<0.001), Hispanics (OR 1.09; p= 0.019), Native American (OR 1.57; p<0.001), ESKD (OR 1.25; p<0.001), and Income Q1 (OR 1.12; p<0.001) (figure 2).

Conclusions: Age, CCI, male gender, Hispanic race, Native American ethnicity, ESKD, and a lower income were associated with higher odds of death among those hospitalized with COVID. This information can alert clinicians of the negative effects of ESKD on COVID mortality. Further studies on COVID mortality must account for ESKD.

Variable	COVID without ESKD (n=1,011,340)	COVID with ESKD(n=38,705)	P-value
Age, median (IQR)	66 (54-77)	65 (55-74)	< 0.001
Male, n (%)	532,710 (52.6%)	21,740 (56.2%)	<0.001
Race (%)			
White	51.9%	28.7%	<0.001
African American	17.3%	33.6%	<0.001
Hispanic	19.7%	25.3%	<0.001
Asian or PI	3.1%	3.9%	<0.001
Native American	1.0%	2.2%	<0.001
Other	4.0%	3.9%	0.783
Length of Stay, median (IQR)	5 (3-9)	7 (4-12)	<0.001
Total Charges, median (IQR)	$41,094 (23,012-76,726)	$61,494 (32,805-122,701	<0.001
Household Income Q1(%)	33.4%	41.6%	<0.001
Household Income Q2(%)	27.3%	26.0%	0.024
Household Income Q3(%)	21.7%	18.9%	<0.001
Household Income Q4(%)	16.1%	11.5%	<0.001
CCI, median (IQR)	1 (0-3)	5 (4-6)	<0.001
In-hospital Mortality, n (%)	110,095 (10.9%)	7,145 (18.5%)	<0.001

Legend: CCI =Charlson comorbidity index; ESKD= Endstage Kidney Disease; IQR=interquartile range; n=number; PI= Pacific Islander; Q=quartile

Figure 1

Variable	Univariable Analysis			Multivariable Analysis		
	Odds Ratio	P value	95% C.I.	Odds Ratio	P value	95% C.I.
Age	1.05	<0.001	1.045-1.047	1.04	<0.001	1.042-1.045
CCI	1.27	<0.001	1.258-1.275	1.18	<0.001	1.168-1.187
Male	1.28	<0.001	1.243-1.315	1.39	<0.001	1.346-1.427
White	1.12	<0.001	1.078-1.165	0.77	<0.001	0.727-0.822
African American	0.85	<0.001	0.810-0.892	0.80	<0.001	0.746-0.858
Hispanic	0.93	0.004	0.879-0.975	1.09	0.019	1.014-1.167
Asian/PI	0.95	0.384	0.859-1.060			
Native Americans	1.39	<0.001	1.188-1.624	1.57	<0.001	1.316-1.880
Other Race	1.04	0.362	0.951-1.148			
ESKD	1.85	<0.001	1.746-1.969	1.25	<0.001	1.168-1.336
Income Q1	1.08	<0.001	1.041-1.127	1.12	<0.001	1.075-1.170
Income Q2	0.99	0.565	0.952-1.028			
Income Q3	0.93	<0.001	0.893-0.968	0.97	0.099	0.926-1.007
Income Q4	0.97	0.237	0.918-1.021			

Legend: CCI =charlson comorbidity index; C.I.=Confidence interval; ESKD= Endstage Kidney Disease; PI= Pacific Islander; Q=quartile

Figure 2

FR-PO1116

COVID-19's Impact on Dialysis Waste: A Greek Dialysis Group's Experience

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Background: The COVID-19 pandemic has increased the generation of biomedical waste and put enormous strain on waste collection thus damaging the environment. Our dialysis group operates 9 dialysis clinics in Greece treating approximately 1000 patients. We are continuously implementing national regulations-protocols and extra measures protecting patients from COVID-19. We investigated the effect of COVID-19 pandemic on the generation of hazardous and infectious waste amounts and waste production rate in our dialysis clinics.

Methods: We performed routine weighing of all dialysis clinics' infectious and hazardous waste including: 1.Personal protective equipment(PPE): gloves, gowns, tapes, coveralls, goggles, masks, caps, shoe covers. 2.The SARS-CoV-2 rapid antigen test (RAT) components 3.dialyzer filters, circuits, connections. 4.Contaminated single-use material, drapes, gauzes, compresses, bandages, and single-use care kits. We compared all amounts of waste produced before the pandemic, year 2019, and during the pandemic, years 2020, 2021 and 2022: per waste category, as total categories' aggregates, per dialysis session, per dialysis clinic and for all dialysis clinics.

Results: Aggregated hazardous and infectious waste increased during the pandemic in all our dialysis clinics. Indicatively: Total kilograms of waste discarded were 142361.04, 152978.25, 149448.92 and 166640.5 in the years 2019, 2020, 2021 and 2022 respectively. 2022 presented a 4% increase compared to 2019. Per dialysis session Kilograms of waste increased from 0.997191409 in 2019 to 1.018591946 in 2020 and 1.034520114 in 2022. PPE and RATs were the main attributes of increase. In one dialysis clinic RATs weighted 0, 4.860, 34.956 and 98.217 kilograms in 2019, 2020, 2021 and 2022 respectively.

Conclusions: Dialysis waste management is of paramount importance. In the years following the pandemic, our dialysis clinics' waste generation increased, making efficient waste management even more critical. Our group's dialysis clinics are currently implementing new, more efficient and environment friendly practices and we trust that their beneficial effects will be soon documented.

FR-PO1117

Nationwide In-Hospital Morbidity and Mortality Analysis of COVID-19 Infection in Advanced CKD (aCKD), Dialysis Patients, and Kidney Transplant (KT) Recipients

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Background: Individuals with kidney disease, including aCKD, end-stage kidney disease (ESKD), and KT have an increased risk for COVID-19 infection, hospitalization, and mortality compared to those without CKD (CKD-free). The comparative morbidity and mortality among hospitalized COVID-19 patients with aCKD, ESKD, KT, and CKD-free remain uncertain.

Methods: We queried the 2020 Nationwide Inpatient Sample (NIS) database for non-elective adult COVID-19 hospitalizations. Patients were classified into four kidney disease categories: aCKD (stage 3-5, non-dialysis), ESKD (dialysis), KT, and CKD-free. The primary outcome was in-hospital mortality; secondary outcomes included morbidity (septic shock, acute respiratory failure, acute respiratory distress syndrome (ARDS), mechanical ventilation, pressor requirement) and resource utilization (length of hospital stay (LOS), total charges). Outcomes were analyzed with either multivariable logistic or linear regression and adjusted for demographic and comorbidity confounders.

Results: A total of 1,018,915 adults hospitalized for COVID-19 in 2020 were included. Of these, 5.9% had aCKD, 3.9% had ESKD, 0.4% were KT recipients, and 85.0% had no pre-existing CKD. The all-cause in-hospital mortality was 9.7% for CKD-free, 20.5% for aCKD, 19.7% for ESKD, and 12.4% for KT. Results were shown in Figures.

Conclusions: Our study found hospitalized COVID-19 patients with aCKD and ESKD exhibited more comorbidities and higher mortality than those without renal disease. Notably, mortality in KT patients was comparable to the CKD-free group. Thus, managing comorbidities and promoting vaccination is critical in aCKD and ESRD patients.

Figure 1. Outcomes of adult patients hospitalized for COVID-19

		Total	CKD-free	aCKD	ESKD	KT	P-value
Mortality	All cause in hospital mortality N %	113,180 (11.1%)	83,495 (9.7%)	12,300 (20.5%)	7,730 (19.7%)	550 (12.4%)	<0.001
Morbidity							
	Septic shock N %	34,365 (3.4%)	25,895 (3.0%)	2,895 (4.6%)	3,180 (8.1%)	205 (4.6%)	<0.001
	Acute respiratory failure N %	575,370 56.5%	490,430 56.7%	33,490 56.1%	21,670 54.8%	2,065 46.4%	<0.001
	ARDS N %	53,560 (5.3%)	44,140 (5.1%)	3,785 (6.2%)	2,545 (6.5%)	275 (6.2%)	<0.001
	Mechanical ventilation N %	87,295 (8.6%)	69,375 (8.0%)	6830 (11.4%)	5,059 (12.9%)	355 (8.0%)	<0.001
	Vasopressor N %	18,475 (1.8%)	14,100 (1.6%)	1,500 (2.5%)	1,610 (4.1%)	80 (1.8%)	<0.001
Resource Utilization							
	Mean LOS (days)	7.48 ± 0.03	7.22 ± 0.03	8.94 ± 0.09	10.35 ± 0.15	7.03 ± 0.25	<0.001
	Mean total hospitalization charges (USD)	79,101	75,907	87,060	127,728	81,760	<0.001

Figure 2. Associations between CKD-free, advanced CKD, ESKD, KT and outcomes of adult patients hospitalized for COVID-19.
Significant values (p < 0.05) are shown in bold.

		CKD-free	aCKD	ESKD	KT
In hospital mortality	OR (95% CI)	1.00	2.41 (2.29-2.53)	2.29 (2.15-2.43)	1.32 (1.07-1.63)
	aOR (95% CI)	1.00	**1.19 (1.12-1.27)**	**1.58 (1.47-1.71)**	1.24 (1.0-1.55)
	P value		**<0.001**	**<0.001**	0.053
Septic shock	OR (95% CI)	1.00	1.57 (1.43-1.74)	2.87 (2.62-3.14)	1.57 (1.13-2.16)
	aOR (95% CI)	1.00	**1.21 (1.08-1.35)**	**2.05 (1.83-2.30)**	1.27 (0.91-1.78)
	P value		**0.001**	**<0.001**	0.163
Acute respiratory failure	OR (95% CI)	1.00	0.98 (0.94-1.02)	0.93 (0.88-0.97)	0.66 (0.58-0.76)
	aOR (95% CI)	1.00	0.96 (0.92-1.00)	0.98 (0.93-1.04)	**0.77 (0.67-0.89)**
	P value		0.088	0.480	**<0.001**
ARDS	OR (95% CI)	1.00	1.23 (1.14-1.34)	1.28 (1.16-1.42)	1.23 (0.93-1.62)
	aOR (95% CI)	1.00	**1.11 (1.01-1.22)**	1.06 (0.94-1.18)	1.10 (0.83-1.47)
	P value		**0.026**	0.346	0.512
Mechanical ventilation	OR (95% CI)	1.00	1.47 (1.38-1.56)	1.70 (1.59-1.83)	1.00 (0.78-1.26)
	aOR (95% CI)	1.00	0.99 (0.92-1.07)	**1.18 (1.08-1.28)**	0.88 (0.69-1.13)
	P value		0.842	**<0.001**	0.318
Vasopressor	OR (95% CI)	1.00	1.53 (1.36-1.72)	2.60 (2.28-2.94)	1.11 (0.68-1.79)
	aOR (95% CI)	1.00	1.11 (0.97-1.27)	**1.79 (1.53-2.08)**	0.85 (0.52-1.39)
	P value		0.122	**<0.001**	0.517
LOS	β (95% CI)	Ref	1.72 (1.54-1.89)	3.13 (2.84-3.41)	-0.19 (-0.69-0.30)
	Adjusted β (95% CI)	Ref	**0.34 (0.15-0.53)**	**1.79 (1.49-2.10)**	**-0.97 (-1.49--0.45)**
	P value		**<0.001**	**<0.001**	**<0.001**
Total hospitalization charges	β (95% CI)	Ref	11152.46 (8396.65-13908.28)	51820.09 (46525.76-57114.41)	5852.64 (-2892.66-14597.94)
	Adjusted β (95% CI)	Ref	-661.79 (-3693.68-2376.09)	**32307.58 (26937.61-37677.54)**	-5845.07 (-14730.49-3040.35)
	P Value		0.669	**<0.001**	0.197

FR-PO1118

Circulating FGF23 Is Associated with AKI and Predicts Survival in COVID-19

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Background: 20-40% of severely ill COVID-19 patients develop acute kidney injury (AKI). AKI is now considered to be a negative prognostic factor for survival in COVID-19 patients. FGF23 is a bone-derived phosphatonin that is elevated in AKI. To-date, no study has investigated the associations between FGF23 and AKI in the COVID-19 population. Herein, we performed a study evaluating FGF23 levels in a cohort of COVID-19 patients and its association with AKI status and survival.

Methods: We conducted a prospective cohort study in 111 patients hospitalized with COVID-19. Total FGF23 levels were measured using an ELISA assay (Quidel). AKI status and FGF23 levels were determined concurrently. The primary outcome was death and secondary endpoint was AKI status. The median follow-up to death was 22.6 months. Associations between FGF23 levels and AKI status and survival were assessed by logistic regression and cox proportional hazards models, respectively.

Results: Of the 111 patients, 77 had no AKI (eGFR=91.0 [69.2,101.3] ml/min/1.73m^2), 17 had AKI (eGFR=39.7 [28.7,57.8] ml/min/1.73m^2), and 17 had end-stage kidney disease (ESKD, p<0.001). Patients did not significantly differ in sex (p=0.6) or age (p=0.9) but differed in BMI (p=0.023). Median FGF23 levels were higher in patients with AKI (305.6 [134.6, 350.8] RU/mL) and ESKD (3,607.7 [440.5, 7,452.7] RU/mL) compared to those with no AKI (120.7 [64.3, 249.7] RU/mL]; p<0.001). After adjusting for patient age, patients with high FGF23 showed increased odds of having AKI (p=0.004). Survival at 24 months was higher among non-AKI patients (71%) compared to AKI (65%) and ESKD (35%) patients (p=0.02). Finally, controlling for patient age and group-specific death hazards among non-AKI, AKI and ESKD groups, FGF23 was significantly associated with an increased risk of death (p<0.001).

Conclusions: Elevated FGF23 levels are associated with AKI and were predictive of survival in a cohort of COVID-19 patients. These findings indicate that FGF-23 levels may help with risk stratification and management of AKI in patients with COVID-19.

Funding: Other NIH Support - National Institutes of Health, National Center for Advancing Translational Sciences, Clinical and Translational Sciences Award

FR-PO1119

Kidney Injury Molecule-1 Is an Independent Receptor from ACE2 for SARS-CoV-2 in Lung and Kidney

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Background: Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2 continues to contribute to a world-wide pandemic. SARS-CoV-2-associated respiratory failure and acute kidney injury are major complications of infection. KIM-1 is a scavenger receptor expressed by renal epithelial cells and has been reported to be a receptor for several viruses. We hypothesized that KIM-1 is a receptor for SARS-CoV-2 and may play an essential role in COVID-19 lung and kidney injury.

Methods: Human lung and kidney autopsy samples were immunostained and analyzed. Uptake of "virosomes", liposomal nanoparticles displaying the SARS-CoV-2 spike protein, by A549 lung epithelial cells, mouse primary lung epithelial cells, and human kidney tubular organoids was evaluated in the presence or absence of anti-KIM-1 antibody or TW-37, a KIM-1-mediated endocytosis inhibitor. Protein-protein interaction characteristics between purified SARS-CoV-2 spike protein and purified KIM-1 were determined using flow cytometry-based immunoprecipitation. HEK293 cells expressing human KIM-1 but not functional angiotensin-converting enzyme 2 (ACE2), a known receptor, were infected with live SARS-CoV-2. ACE2 complete knockout HEK293 cells were produced and exposed to the SARS-CoV-2 spike protein.

Results: KIM-1 was expressed in lung and kidney epithelial cells in COVID-19 patient samples. Human and mouse lung and kidney epithelial cells expressed KIM-1 and endocytosed spike-virosomes. Both anti-KIM-1 antibodies and TW-37 inhibited uptake. Enhanced KIM-1 expression in human kidney tubular organoids increased virosome uptake. Purified SARS-CoV-2 spike protein and KIM-1 bound to each other and TW-37 inhibited the binding. KIM-1-expressing HEK293 cells without functional ACE2 expression had increased susceptibility to infection by live SARS-CoV-2 when compared with control cells. KIM-1-expressing ACE2 knockout HEK293 cells internalized SARS-CoV-2 spike protein.

Conclusions: KIM-1 is an independent receptor from ACE2 for SARS-CoV-2 in the lung and kidney based on ACE2 knockout cell condition. TW-37 can be potential therapeutic agent and/or prophylactic agent for COVID-19.

Funding: NIDDK Support, Commercial Support - Bayer Yakuhin Ltd., Private Foundation Support, Government Support - Non-U.S.

FR-PO1120

JAK Inhibitor Exaggerates Kidney Injury in the Early Phase of SARS-CoV-2 Infection in a Murine COVID-19 Model

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Background: COVID-19 is a respiratory illness caused by SARS-CoV-2 infection, and its clinical manifestations range from mild respiratory illness to severe progressive pneumonia and multiple organ failure. The serious cases of COVID-19 are treated with blockade of IL-6/JAK signaling, such as anti-IL-6 receptor antibody (anti-IL-6R mAb) and JAK inhibitor Baricitinib. Kidney injury is one of the complications of COVID-19; however, the mechanisms by which SARS-CoV-2 infection results in kidney injury and the effects of current therapies against COVID-19 on kidneys are not fully understood.

Methods: Male Balb/c mice (6-10-week old) were nasally infected with mouse-adapted SARS-CoV-2 (MA10). PCR was performed with specific primers for the detection of MA10 to examine for viral entry into the lungs and kidneys. MA10 infection-induced lung injury was evaluated with H&E staining and the expression of inflammatory cytokines. Measurements of serum creatinine (sCr) level, urinary albumin/creatinine ratio

(ACR), and urinary Ngal/Cr ratio, and histological analyses were performed to evaluate kidney injury day 4 after MA10 infection. MA10-infected mice were treated with anti-IL-6R mAb (1.4 mg/head, i.p.) or Baricitinib (10 mg/kg, p.o.) at day 1 or day1-3, respectively.

Results: MA10 infection caused about 20% body weight loss in mice day 4 after infection. H&E staining and quantitative PCR revealed that inflammation was induced in the lungs of MA10-infected mice. sCr level, ACR, and Ngal/Cr ratio was increased, and tubular damage was observed in the kidneys day 4 after MA10 infection, suggesting that kidney injury was evoked in the murine COVID-19 model. However, PCR analysis revealed that MA10 was not detected in the kidneys, whereas in the lungs. As we hypothesized that cytokine storm induced kidney injury in COVID-19, MA10-infected mice were treated with anti-IL-6R mAb or Baricitinib. Unexpectedly, ACR and Ngal/Cr ratio tended to be increased in anti-IL-6R mAb group. Upon Baricitinib treatment, ACR and Ngal/Cr ratio was significantly increased.

Conclusions: Blockade of IL-6/JAK signaling in the early phase of SARS-CoV-2 infection exaggerates kidney injury, providing a novel insight into the pathogenesis of COVID-19-related kidney injury.

FR-PO1121

Ferroptosis of Kidney After SARS-CoV-2 Infection

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Background: Although kidney involvement have been evaluated for human Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) infection, none have fully evaluated the ferroptosis in the kidney after SARS-CoV-2 infection. Here, we evaluate the ferroptotic renal injury in the transgenic mice expressing the human ACE2 receptor driven by the cytokeratin-18 gene promoter (K18-hACE2) after SARS-CoV-2 infection.

Methods: To investigate the effect of SARS-CoV-2 on renal ferroptosis, we administered 2.5 x 10^4 p.f.u. SARS-CoV-2 via intranasal to K18-hACE2 mice. After 7 days SARS-CoV-2 infection, kidney tissues were harvested. SARS-CoV-2 infection and ferroptosis were evaluated by immunohistochemistry. Next, ferroptosis-related markers, glutathione peroxidase 4(*Gpx4*), prostaglandin-endoperoxide synthase 2(*Ptgs2*), Acyl-CoA synthetase long chain family member 4(*Acsl4*), nuclear factor erythroid-2-related factor 2(*Nrf2*), heme oxygenase-1(*Ho-1*), transferrin receptor 1(*Tfr1*), ferritin heavy chain 1(*Fth1*) and nuclear receptor coactivator 4(*Ncoa4*) were evaluated by quantitative PCR.

Results: SARS-CoV-2 infection significantly increase the expression of SARS-CoV-2 spike protein in the tubular epithelial cells of the renal cortex and medulla. Protein expression of GPX4 was significantly decreased in the renal medulla. In the kidney of SARS-CoV-2-infected mice, the ferritin-related markers ferritin heavy chain 1(FTH1) and transferrin receptor 1(TFR1) and lipid peroxidation marker, dihydroethidium (DHE) were also increased in histological experiments. Next, the mRNA levels of *Ptgs2*, *Acsl4*, *Nrf2*, *Ho-1*, *Fth1* and *Ncoa4* were increased in the kidneys of SARS-CoV-2 infected mice compared to non-infected mice.

Conclusions: All of our data suggest that SARS-CoV-2 infection shares many features of ferroptosis in the kidney and can be used to define the ferroptosis of kidney injury and antiviral-based countermeasures in COVID-19 infection.

Funding: Government Support - Non-U.S.

FR-PO1122

University of California (UC) Kidney COVID-19 Study AKI Cohort

Hiba Hamdan, Brian M. Paciotti, Blythe Durbin-Johnson, Juan P. Moreno-Ortiz, Brian Y. Young, Baback Roshanravan. *UC Davis Health, Sacramento, CA.*

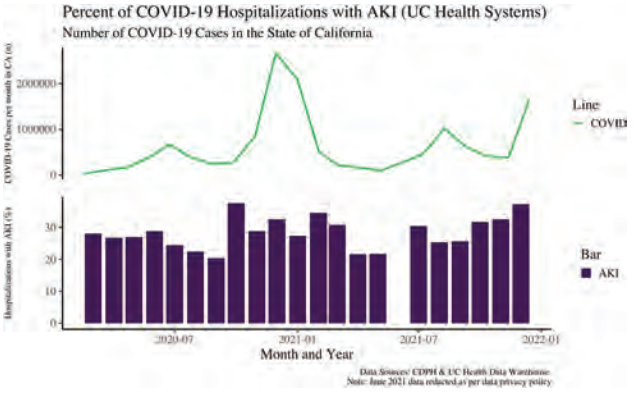
Background: A wide range of rates of AKI associated with COVID-19 have been reported, often specific to select timeframes and associated SARS-CoV-2 variants of the pandemic. The aim of our study is to comprehensively describe the rates of AKI in people hospitalized with COVID-19 over the course of the first two years of the pandemic and identify risk factor for AKI in that population.

Methods: We conducted a retrospective cohort study of adults receiving care within the 5 major University of California (UC) Health Systems. The cohort included people who underwent PCR testing and were positive for SARS-CoV-2 between March 1, 2020, and December 31, 2021, and required hospitalization within 10 days of testing. The cohort was further restricted to those without ESKD, without documented pregnancy, and length of stay ≥1 day. To examine risk factors associated with AKI, we used a logistic model including age, gender, race, Area Deprivation Index (ADI), UC site of care, DM, HTN, heart failure, CKD, smoking status, BMI, use of NSAIDS at time of admission, use of ACEIs/ARBS at time of admission, ARDS, sepsis, mechanical ventilation, and month of COVID-19 diagnosis.

Results: The cohort included 5451 people with COVID-19. Patients had an average age of 59 years, 59% were male and 45% were Hispanic. From March 2020 to December 2021 the rates of AKI ranged from 20-38% and varied over the course of the pandemic (Figure 1). The factors associated with the highest odds (OR,95% CI) of AKI were: Black race (2.2,1.0-1.5), mechanical ventilation (5.1,4.2-6.2), sepsis (2.9,2.4-3.6), HTN (1.7,1.4-2.1) and CKD (1.5,1.1-2.0).

Conclusions: In a large cohort of people hospitalized with COVID-19, in one of the largest healthcare systems in California, AKI rates generally exceeded 25%. Black race, HTN, CKD, and in hospital sepsis and mechanical ventilation were associated with higher odds of AKI.

Funding: Other NIH Support - UC Davis School of Medicine



FR-PO1123

University of California (UC) Kidney COVID-19 Study Outpatient Cohort

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Background: The long-term kidney effects of COVID-19 infection are unknown, especially among non-hospitalized patients where changes may be less noticeable. Among five major University of California (UC) Health Systems, we compared changes in kidney function between non-hospitalized COVID-19 patients to those without COVID-19.

Methods: We conducted a retrospective cohort study that included all adults who had SARS-CoV-2 PCR testing between 3/1/20-12/31/21 and were not hospitalized within 10 days of testing. Individuals were classified with or without COVID-19 based on index SARS-CoV-2 PCR. Inclusion required kidney function measurement within 12 months prior and at least one outpatient creatinine 30 days after index SARS-CoV-2 PCR. Follow up was until December 31, 2022. The cohort excluded patients with ESKD or pregnancy. We also excluded from controls any patients with a subsequent positive SARS-CoV-2 PCR test during the study period. Thus, none of the controls were ever COVID-19 positive. The primary outcome was the difference in the rate of change in eGFR at least 30-days after index SARS-CoV-2 PCR. Three linear mixed models were fitted, as detailed in the figure below.

Results: The cohort included 10915 and 152620 people with and without COVID-19. COVID 19. Patients were more likely to be Hispanic, have higher BMI and DM, and reside in areas with higher ADI (Area deprivation index). Results of the three liner mixed effects models are shown in figure below.

Conclusions: In a cohort from the largest academic health system in California, in adjusted models we didn't observe a statistically significant difference in the rate of eGFR loss in non-hospitalized COVID-19 patients compared to controls over an average follow up period of two years. This study has one of the longest follow up times of kidney function post SARS-CoV-2 infection.

Funding: Other NIH Support - UC Davis School of Medicine

Estimates of Annual eGFR Change in Outpatients from Linear Mixed Effects Models

Variable	Estimate	95% CI Lower Bound	95% CI Upper Bound	P-Value
Model 1				
Annual eGFR Change in Non-COVID	-0.411	-0.471	-0.350	< 1e-05
Annual eGFR Change in COVID	-0.807	-1.062	-0.551	< 1e-05
Difference	-0.396	-0.659	-0.134	0.0013136
Model 2				
Annual eGFR Change in Non-COVID	-0.417	-0.475	-0.358	< 1e-05
Annual eGFR Change in COVID	-0.654	-0.896	-0.411	< 1e-05
Difference	-0.237	-0.487	0.013	0.066897
Model 3				
Annual eGFR Change in Non-COVID	-0.548	-0.626	-0.471	< 1e-05
Annual eGFR Change in COVID	-0.772	-1.020	-0.524	< 1e-05
Difference	-0.224	-0.475	0.027	0.091447

Model 1-unadjusted. Model-2 adjusted for age, race, gender, ADI, UC site of care and BMI. Model-3 adjusted for all variables in Model 2 and Baseline eGFR, Diabetes, hypertension, CHF, smoking status, and COVID month of testing.

LME models-Outpatients

FR-PO1124

Association Between Urine Sediment Examination and Adverse Outcomes in Hospitalized Patients with AKI and Severe COVID-19

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Background: COVID-19 and Acute kidney injury (AKI) are associated with increased mortality and worse kidney outcomes. Although several factors including age, sex, and comorbidities are associated with increased morbimortality, to our

knowledge, no study has dwelled into the evaluation of urine sediment and prognosis in patients who developed AKI during Covid-19.

Methods: Retrospective cohort study that included clinical and biochemical data of 288 hospitalized patients with COVID-19 who developed AKI at any stage. Univariate and Cox regression analyses were used to evaluate the role of urine sediment and progression in AKI with Covid-9. Mayor Adverse Kidney Events (MAKE) was a composite of AKI stage 3, mortality, and need for renal replacement therapy. The Perazella score was used to evaluate the number of cellular renal tubular epithelial cells (CRTEC) and granular casts.

Results: The mean age of the patients was 57 ± 14 years, 69% were women, the mean body mass index (BMI) was 27.9±5.6 kg/m2, and median time in hospital was 11 (6-19) days. Overall, 47.3% had diabetes and 33.8% hypertension. The rate of AKI 3, MAKE, and mortality was 32.3%, 46.3% and 32.6%, respectively. After adjusting for demographics and comorbidities the Cox model regression, a Perazella score 2 and 3 was associated with increased risk for AKI 3 (HR= 2.664 [1.174-6.645] and HR= 3.273 [1.172-9.139]; respectively), MAKE (HR= 3.162 [1.486-6.727] and HR= 4.644 [1.815-11.886]; respectively), and mortality (HR= 3.322 [1.375-8.251] and HR= 4.743 [1.594-14.112]; respectively).

Conclusions: The examination of the urine sediment could predict worse outcomes in patients with AKI and severe Covid-19.

FR-PO1125

The Association Between COVID-19 Medications and AKI: Analysis of the United States Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) and Bulk Kidney RNA-seq Data

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Background: The FDA has approved three medications: Tocilizumab, Remdesivir, and Baricitinib, and issued several existing emergency use authorizations (EUAs) medications such as Paxlovid, REGEN_COV antibody et al., for the treatment of COVID-19. However, it has been observed that these medications may pose a risk factor for acute kidney injury (AKI). This study aims to investigate the potential association between the usage of these medications and the occurrence of AKI, as well as to elucidate the molecular mechanism underlying AKI induced by COVID-19 medications.

Methods: The risk of AKI was compared among the COVID-19 patients receiving different medications. Pharmacovigilance data obtained from the FAERS was analyzed. Furthermore, we investigated whether the risk of AKI was influenced by factors such as sex, dosage, and potential drug-drug interactions among the medications used in COVID-19 patients. Additionally, we sought to identify genes and pathways associated with AKI that are regulated by COVID-19 medications, by comparing gene expression of kidneys from mice treated with COVID-19 medications to those from control mice. Whole kidney RNA-seq data was generated and analyzed.

Results: We found that COVID-19 patients treated with remdesivir demonstrated a significantly higher risk of AKI compared to patients treated with other medications. Specifically, patients aged 50-70 or over 70 years were twice as likely to report AKI, compared to the <50 age demographic. Male patients prescribed remdesivir had a two-fold higher likelihood of reporting AKI compared to females. Additionally, patients who took vancomycin alongside remdesivir exhibited a 3.87-fold increased likelihood of reporting AKI as an adverse event (P<0.0001) when compared to patients prescribed vancomycin or remdesivir alone. Furthermore, RNA-seq revealed that genes up-regulated by remdesivir included Edar, Per1, Gadd45g, Wnt7b, Wnt16, Agt, and Dusp15. The corresponding regulated pathways include Stress-activated MAPK cascade and JNK cascade.

Conclusions: COVID-19 patients treated with remdesivir exhibited a higher risk of reporting AKI as an adverse event than patients prescribed other approved treatments for COVID-19 infection. This increased occurrence of AKI may be attributed to the activation of MAPK/JNK signaling pathway.

Funding: NIDDK Support, Private Foundation Support

FR-PO1126

Impact of AKI in Critical Patients Hospitalized with COVID-19: A Cohort Study in the Western Amazon

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Background: The coronavirus pandemic had a significant impact on areas of the Western Amazon. Intensive care units (COVID ICU) were developed specifically for infected patients in response to this demand. Considering the renal impairment caused by COVID-19, the objective of this study was to analyze the development of acute kidney injury (AKI) and its association with the outcome of critically ill patients.

Methods: A retrospective, multicentric cohort, carried out in two hospitals in a region of the Western Amazon from March 2020 to March 2022. Patients (aged ≥18 years) hospitalized with COVID-19, with a length of stay longer than 48 hours in a COVID ICU, and who did not have previous kidney disease. The exposure was the development of LRA (using the KDIGO classification to define it). The outcome analyzed was in-hospital death.

Results: Of the 385 patients evaluated, 75.1% had previous comorbidities, with a predominance of males (60%), a mean age of 59.3 (18–96) years, and a mean length of stay of 13.5 (2–75) days. Based on the total number of patients in the study, 54.5% of patients developed some degree of AKI (Stage 1: 39.5%, Stage 2: 14.2%, Stage 3: 7.6%, and Stage 3D: 38.7%). Compared with patients who did not have AKI, the number of deaths was higher in patients with AKI (61% vs. 17%; absolute risk difference was 44% [95% CI, 41–46]). The degree of acute kidney injury was directly proportional to the death rate (39.7% AKI 1, 60% AKI 2, 68.7% AKI 3, and 81.4% AKI 3D). Finally, taking those without AKI as the reference group, we observed higher risks of in-hospital death for patients with AKI 1-3D (HR 3.5 [95% CI, 2.6–4.1]).

Conclusions: The occurrence of AKI and the need for renal replacement therapy (AKI 3D) were common in critically ill patients with COVID-19. Advanced stages of AKI are associated with extremely high mortality in these patients. However, it was observed that the development of some degree of kidney injury is already associated with a significant risk of death.

FR-PO1127

Long-Term Outcomes After AKI in Hospitalized Patients with COVID-19

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Background: Acute kidney injury (AKI) is frequent in hospitalized patients with COVID-19 and contributes to adverse short and long-term outcomes. We aimed to evaluate the association of AKI and long-term outcomes in a cohort of survivors of a hospitalization for COVID-19.

Methods: Single-centre and retrospective study of hospitalized patients admitted to a Dedicated Unit for COVID-19 at Centro Hospitalar Universitário Lisboa Norte, Portugal, between March 2020 and October 2020. AKI was defined and classified according to the Kidney Disease: Improving Global Outcomes (KDIGO) classification, using SCr criteria. The analysed outcomes were development of major adverse kidney events (MAKE), major adverse renal cardiovascular events (MARCE), and mortality over a two-year follow-up period. MAKE was defined as a composite of death from any cause, renal replacement therapy dependence or worsened kidney function (decrease in eGFR to <25% of baseline and/or eGFR<60 mL/min/1.73m2). MARCE was defined as major adverse kidney event (death, RRT dependence or worsened renal function) and/or major adverse cardiovascular event (myocardial infarction, stroke, and heart failure).

Results: From the included 409 patients, AKI occurred in 60.4% (n=247). Within two years after discharge, 31.8% (n=130) of patients had an eGFR<60mL/min/1.73m2 and/or a 25% decrease on eGFR and 1.7% (n=7) of patients required RRT, 5.6% (n=23) of patients had CV events and 27.9% (n=114) of patients died. The incidence of MAKE was 60.9% (n=249), and MARCE was 36.6% (n=155). On a multivariate analysis, older age (adjusted HR 1.02 (95% CI: 1.01-1.04), p=0.008), cardiovascular disease (adjusted HR 2.22 (95% CI: 1.24-3.95), p=0.007), chronic kidney disease (adjusted HR 5.15 (95% CI: 2.22-11.93), p<0.001), and AKI (adjusted HR 1.76 (95% CI: 1.12-2.78), p=0.015) were independent predictors of MAKE. Older age (adjusted HR 1.06 (95% CI: 1.04-1.08), p<0.001) and neoplasia (adjusted HR 4.88 (95% CI: 2.37-10.04), p<0.001) were independent predictors of mortality.

Conclusions: AKI was independently associated with the risk of long-term need for dialysis and/or renal function decline and/or mortality after hospital discharge for COVID-19. Given the long-term impact of AKI, early detection of high-risk patients is essential to improve the outcomes of COVID-19 patients.

FR-PO1128

Association of Body Mass Index with Multiple Organ Failure in Hospitalized Adults with COVID-19

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Background: Patients with severe coronavirus disease 2019 (COVID-19) experience an excessive cytokine release syndrome, which promotes an increased risk of acute organ dysfunction and death. The aim of our study was to examine whether excessive adipose tissue, as measured by body mass index (BMI), is associated with higher systemic markers of inflammation and higher risk of severe acute organ failure or in-hospital death among hospitalized patients with COVID-19.

Methods: 1370 hospitalized adults (18 years or older) with COVID-19 during the first wave of the pandemic in Massachusetts (March 1, 2020, to July 31, 2020) met inclusion criteria. Our primary outcome was the composite of severe acute kidney injury (AKI), as defined by acute dialysis requirement, severe acute lung injury (ALI), as defined by use of high-flow nasal canula, non-invasive ventilation, or mechanical ventilation, or in-hospital death. Secondary endpoints of interest included the association of BMI with serum peak CRP level, a systemic marker of inflammation.

Results: After adjustment for age, gender, race, Charlson Comorbidity Index (CCI), baseline eGFR, and the NIH clinical spectrum of SARS-CoV-2 infection, the highest BMI stratum of > 40 kg/m^2 (compared to the BMI <25 kg/m^2 reference group) was associated with higher odds for the composite of severe AKI, severe ALI, or in-hospital death (adjusted odds ratio [OR_{adj}] 1.69; 95% CI 1.03, 2.78), and the composite of severe ALI or in-hospital death (OR_{adj} 1.69; 95% CI 1.03, 2.77). As a continuous variable, BMI (per 5-kg/m^2 increase) remained independently associated with these outcomes. Interestingly, this association was no longer significant after adjustment for peak CRP level.

Conclusions: Among hospitalized adult with COVID-19, higher BMI associates with higher risk of severe organ failure or death, which dissipates after adjustment for CRP level. This supports the hypothesis that inflammation is a downstream mediator of the adipose tissue on acute organ dysfunction, possibly through dysregulated immune responses. More research is needed to understand this association in COVID-19.

Funding: Other NIH Support - National Institutes of Health, Grant No. UL1 TR000073 and UL1 TR001064

FR-PO1129

Prolonged Myoglobinuric AKI in Young Female in the Era of the COVID-19 Pandemic

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Introduction: We present a 26-year-old female with no pertinent medical history who presented to the nephrologist with persistently elevated creatinine (Cr) and urinalysis significant for microscopic hematuria without red blood cells.

Case Description: The patient reported being ill 2 months prior to presentation with symptoms of fatigue, myalgias, pharyngitis and general malaise. During her illness, she ran a marathon, treated her myalgias with NSAIDs and discontinued spironolactone for acne vulgaris. On assessment, she described ongoing symptoms of fatigue, myalgias and decreased appetite. Lab work indicated Cr of 2.15mg/dL (baseline <1 mg/dL), mild metabolic acidosis, urinalysis and urine chemistry indicated +1 myoglobulin (88.26 ng/mL, normal <21 ng/mL), and creatine phosphokinase 44 IU/L. Further studies revealed normal ANA, complements, ANCA, myositis panel and other autoimmune workup. She was diagnosed with myoglobinuric acute kidney injury (AKI) in the setting of recent viral illness, remote NSAID and spironolactone use, however the extent and persistence of her AKI was not completely understood. COVID antibody screen was positive for antinucleocapsid antibody and antispike glycoprotein antibody titer >250 units/mL. She was closely monitored with biweekly labs, encouraged to drink electrolyte rich fluids, and treated with oral sodium bicarbonate. Her Cr peaked at 2.3 mg/dL and urine myoglobin at 278.9 ng/mL, however both normalized by the fourth month. We concluded the patient likely had COVID-19 infection in November and was experiencing "long COVID" renal disease.

Discussion: COVID-19 infection can directly injure kidneys through endothelial destruction, complement activation, coagulopathy and indirectly through multiorgan damage. Large-scale studies exploring COVID-19 and AKI focus on severely ill, unvaccinated, older patients, with multiple comorbidities. There are also a handful of small case reports that have examined COVID-19 induced rhabdomyolysis requiring hemodialysis. However, there remains limited understanding of why healthy, vaccinated, young patients may develop persistent AKI and what this means for their future kidney function, even in cases where creatinine levels return to normal. This case demonstrates the importance of considering COVID-19 induced AKI, even in patients who are not at high risk of developing severe infection related illness.

FR-PO1130

Predictors of Mortality in COVID-19 Patients Diagnosed with AKI: A Case-Control Study

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Background: COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a multi-systemic infection with various manifestations, including acute kidney injury (AKI). This study aimed to identify factors associated with mortality in COVID-19 patients diagnosed with AKI during hospitalization at Clínica de la Costa in Barranquilla, Colombia from 2020 to 2022.

Methods: A case-control study. COVID-19 patients with acute kidney injury (AKI) were enrolled. Cases included fatal outcomes, while controls survived. AKI was defined using The Kidney Disease: Improving Global Outcomes criteria. A range of independent variables, including sociodemographic characteristics, comorbidities, initial laboratory parameters, and clinical features, were examined. Inferential analysis was performed using Chi-square, t-test, and Mann-Whitney U tests ($p < 0.05$). Associations were further evaluated using logistic regression, and odds ratios (ORs) with 95% confidence intervals were calculated.

Results: The study sample included 159 cases (deceased) and 74 controls (survivors). The average age in the deceased group was 66 ± 14 years, significantly higher than the average age of 59 ± 17 years in the survivor group (p-value = 0.005). No statistically significant differences were observed in terms of gender (p-value = 0.278) and municipality of residence (p-value = 0.078) between the study groups. The final adjusted model revealed several significant risk factors for mortality, including admission to the intensive care unit (OR = 4.8; 95% CI 1.5-15.6), invasive mechanical ventilation (OR = 51.1; 95% CI 10.9-240.7), renal replacement therapy (OR = 11.7; 95% CI 1.1-123.0), and Acute Kidney Injury Network (AKIN) II classification (OR = 8.8; 95% CI 2.5-30.5).

Conclusions: It is crucial for healthcare providers to maintain heightened surveillance in Covid-19 patients with AKI who require ICU admission, IMV, and RRT, as these factors are associated with higher mortality rates.

Funding: Clinical Revenue Support

Table 1. Clinical characteristics and outcomes of proliferative and non-proliferative lupus nephritis patients

	Parameter at onset	LN Class		*P* value
		Proliferative LN (n=506)	Non-proliferative LN (n=73)	
	Age, yrs (Mean ± SD)	44,9 ± 14,4	40,6 ± 12,9	*0,02*
	Female, (%)	442 (87)	63 (86)	*0,94*
	Male, (%)	64 (13)	10 (14)	
Disease Severity	Mean Proteinuria (g/day)	3,76 ± 3,6	2,8 ± 3,5	*0,02*
	Hematuria, n, (%)	217 (43)	31 (42)	*0,79*
	Mean Serum Creatinine (mg/dl)	3,6 ± 2,9	2,6 ± 2,4	*0,008*
	Activity_Index	7,1 ± 3,8	5,8 ± 3,2	*0,008*
	Chronicity_Index	3,9 ± 2,7	3,8 ± 2,8	*0,92*
	eFGR <60 ml/min/m2, n, (%)	344 (68)	59 (80)	*0,03*
	Low C3 (<80 UI), n, (%)	263 (52)	37 (51)	*0,37*
	Low C4 (<15 UI), n, (%)	108 (21)	11 (15)	*0,53*
Outcomes	Complete Remission,n, (%)	115 (23)	17 (23)	*0,45*
	Partial Remission,n, (%)	108 (21)	9 (12)	*0,39*
	No Remission,n, (%)	210 (41)	29 (40)	*0,23*
	Death,n	4	1	*0,53*

LN: Lupus Nephritis; yr: Years; C3: C3 Complement; C4: C4 Complement; eFGR: estimated glomerular filtration rate. *P < 0.05 Chi-square test and Mann–Whitney U test.

FR-PO1131

Proteinuria and Clinical Outcomes in Hospitalized COVID-19 Patients: Bolivia Experience

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Background: Kidney involvement is frequent among patients with coronavirus disease 2019 (COVID-19), and occurrence of AKI is associated with higher mortality in this population. The objective of this study was to describe incidence of proteinuria and its influence on AKI in COVID-19 patients.

Methods: We conducted a single-center prospective study among patients who were admitted with COVID-19 in a tertiary care center in Bolivia. Urine dipstick was performed, and spot urine protein/creatinine ratio was quantified within 24 hours of admission. AKI at hospital admission was excluded from analysis. Subsequent development of AKI was diagnosed using KDIGO criteria over 7 days follow-up. Secondary outcome was initiation of renal replacement therapy and death.

Results: Among 57 patients, de novo proteinuria at admission was present in 44 patients (77.1%). Mean urine protein/creatinine ratio was 896±1420 mg/g; with 4 patients (9%) presenting nephrotic range proteinuria. Patients with de novo proteinuria had higher leukocyte count (6395±1580/mm3 vs. 5212±870/mm3; p = 0.0127). De novo proteinuria was not different in patients with diabetes, hypertension or CKD. Of patients with de novo proteinuria, 34% (15/44) patients developed subsequent AKI. Majority of AKI cases (80%) were mild (stage 1 KDIGO). Urine protein-creatinine ratio ≥150 mg/g was associated with AKI (odds ratio (OR), 17.4; 95% CI, 0.97 to 31; p = 0.05). None of patients required kidney replacement therapy. Total proteinuria was associated with mortality in unadjusted and adjusted models.

Conclusions: We observed higher prevalence of proteinuria among patients admitted for COVID-19. Patient will proteinuria also had a higher risk of developing AKI and a poor prognosis for survival. Future studies should focus on proteinuria for risk stratification and prognosis.

FR-PO1132

Liver and Kidney Cross-Talk in Korean COVID-19 Patients

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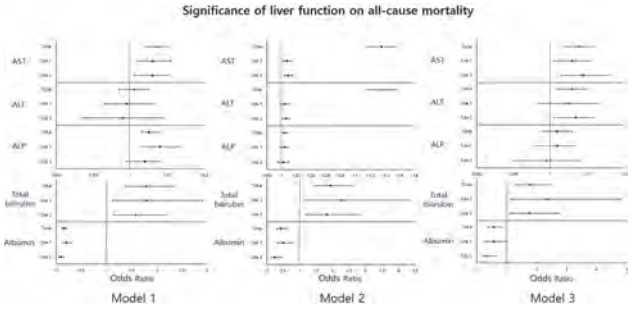
Background: Previous studies suggested that liver function tests (LFTs) could serve as a prognostic tool in assessing the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections. However there have been no published large-scale studies conducted for Koreans with similar topics.

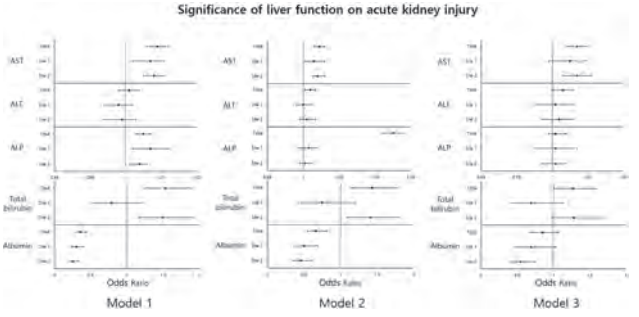
Methods: This research was conducted using the data from two hospitals in Korea. Data from 4,367 adults out of 4,423 patients without missing values, end-stage renal disease, a history of kidney transplant, or use of immunosuppressants were analyzed. We used LFTs measured on the day of hospitalization for SARS-CoV-2 infection. The main outcomes of interest were two things: all-cause mortality and the incidence of acute kidney injury (AKI). Statistical analysis was performed with logistic regression.

Results: Analysis of data for 4,367 people (mean age 54.5±18.3 years, 54.3% female) suggests that high bilirubin is associated with high mortality (adjusted hazard ratio [aHR], 1.794; 95% confidence interval [CI], 1.292 to 2.492; P<0.001) and risk of AKI (aHR, 1.263; 95% CI, 1.005 to 1.588; P=0.045). Also low albumin level is associated with high mortality (aHR, 0.574; 95% CI, 0.378 to 0.873; P<0.001). However no significant impact of alanine transferase and alkaline phosphatase on mortality and the incidence of AKI is identified.

Conclusions: Abnormal LFTs, especially in aspartate transaminase, total bilirubin and albumin level, is relevant to higher mortality and risk of AKI in Koreans with COVID-19. Therefore LFTs should be performed early in hospitalization as a screening tool for risk stratification in Korean COVID-19 patients.



Significance of liver function on all-cause mortality



Significance of liver function on the incidence of AKI

FR-PO1133

Long-Term Renal Outcome and Mortality in Hospitalized Patients with COVID-19 Infection and AKI at UCLA

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Background: Acute kidney injury (AKI) is a common complication in patients with COVID-19 infection and has been associated with poor outcomes. At the ASN 2022 Kidney Week, we presented data from RECOVID study evaluating the need for renal replacement therapy (RRT) and early mortality among patients with COVID-19 infection and AKI in both vaccinated and unvaccinated populations. Here we present updated long term mortality follow-up data from RECOVID cohort.

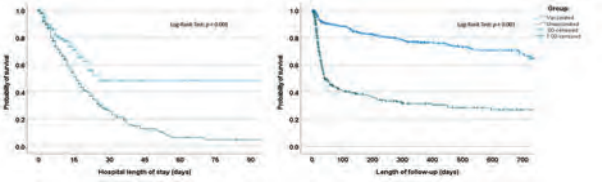
Methods: In this retrospective, observational cohort study, we explored long term mortality data for the RECOVID cohort, which evaluated patients admitted for COVID-19 infection who developed an AKI at UCLA from March 2020. These patients were followed until February 2023.

Results: Among the 3527 hospitalized patients with COVID-19, 878 patients met criteria for inclusion in the study. Of the 878 patients with AKI 46.8% did not receive the COVID-19 vaccine and 53.2% were vaccinated. When evaluating long term follow-up among AKI patients, vaccinated patients continued to have significantly less mortality with a mean survival of 715 days (95% CI, 667-762) as compared to unvaccinated patients with a mean survival of 316 days (95% CI, 262-369). Association of unvaccinated status with shorter overall survival remained significant after multivariate analysis (HR, 5.11 [3.87- 6.76]; $P < .001$).

Conclusions: Vaccinated patients with COVID-19 infection and AKI had improved long-term survival and were less likely to be dialysis-dependent.

Characteristic/Outcome	Vaccinated (n=467)	Unvaccinated (n=411)	*p*-value
Female – no. (%)	180 (38.5%)	152 (37.0%)	0.634
Age at diagnosis (yr) – median (SD)	67.4 (17.3)	67.0 (19.7)	0.740
BMI – mean (SD)	28.0 (7.4)	28.3 (7.1)	0.563
Smoking – no. (%)	175 (39.7%)	122 (39.9%)	0.959
Black – no. (%)	46 (9.9%)	56 (13.6%)	0.082
Asian – no. (%)	29 (6.2%)	30 (7.3%)	0.520
Hispanic – no. (%)	153 (32.8%)	136 (33.1%)	0.918
White – no. (%)	254 (54.4%)	182 (44.3%)	0.003
American Indian or Alaska Native – no. (%)	0 (0.0%)	1 (0.2%)	0.286
Native Hawaiian or Other Pacific Islander – no. (%)	1 (0.2%)	3 (0.7%)	0.257
AKI Stage at Admission – no. (%)			0.513
0	276 (59.1%)	250 (61.1%)	
1	175 (37.5%)	150 (36.7%)	
3	16 (3.4%)	9 (2.2%)	
AKI Stage 30 Days Post-Admission – no. (%)			0.959
0	383 (82.0%)	338 (82.6%)	
1	15 (3.2%)	12 (2.9%)	
3	69 (14.8%)	59 (14.4%)	
AKI Stage 60 Days Post-Admission – no. (%)			0.938
0	381 (81.6%)	331 (80.9%)	
1	12 (2.6%)	12 (2.9%)	
3	74 (15.8%)	66 (16.1%)	
Discharged on dialysis – no. (%)	57 (12.2%)	74 (18.0%)	0.016
Hospital Stay Duration – mean (SD)	11.8 (13.3)	16.8 (16.3)	<0.001
Deceased – no. (%)	92 (19.7%)	195 (47.4%)	<0.001

Table 1. Patient Characteristics and Outcomes



FR-PO1134

Patient Outcomes in De Novo Kidney Replacement Therapy Requiring AKI Following COVID-19 Infection

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Background: Among patients infected with COVID-19, AKI affects >20% of hospitalized patients and >50% of patients admitted to the ICU. While kidney function recovery in COVID-19 patients at discharge and for a short duration of follow up after discharge has been studied, little is known about longer-term outcomes and kidney function recovery in patients who go on to require dialysis during the acute hospitalization for COVID. The aim of the study was to look at the factors associated with dialysis requiring AKI, the impact on survival, the factors associated with continued need for dialysis in patients who start KRT during hospitalization for COVID-19 pneumonia and rate of kidney function recovery following the initiation of KRT.

Methods: A retrospective observational cohort study was conducted at the Mayo Clinic Hospital system in the United States. The study included hospitalized patients aged 18 years or older who were admitted between January 1, 2020, and December 31, 2022, and had a diagnosis of both SARS-CoV-2 infection and new onset Acute Kidney Injury (AKI) requiring Kidney Replacement Therapy (KRT). The primary outcome was mortality and the secondary outcomes included incidence of the composite outcome of death, requirement for KRT and kidney function decline of ≥25% from baseline at 60 days and 365 days (MAKE60 and MAKE365).

Results: A total of 145 patients required Kidney Replacement Therapy (KRT). Among them, 64 patients (44.1%) survived to discharge and 21 patients (14.5%) remained dependent on dialysis at discharge. At 60 days, major adverse kidney event (MAKE60) was 17.2%. Among the patients discharged on dialysis, the MAKE 365 incidence was 52.4%.

Conclusions: COVID-19-associated AKI was associated with high mortality, was associated with worse long-term post-AKI kidney function recovery and MAKE outcomes.

	Not survived to ho	Survived to hosp	p-value	Need of RRT at d	No need of RRT a	p-value
Age, median(IQR)	61(45-70)	55(48-66)	0.3	54(48-65)	59(47.5-67)	0.5
BMI, median(IQR)	**29.95(26.8-35.7)**	**33.1(29.31**	**0.03**	32.5(29.6-35.9)	34.8(28.7-40.62)	0.8
Gender, male(n%)	57(70.4)		0.68	16(76.2)	30(69.8)	0.5
Race						
White	62(76.5)	67(73.4)		15(71.4)	31(72.1)	
African American	6(7.4)	5(7.8)		1(4.8)	4(9.3)	
American Indian	3(3.7)	5(7.8)	0.8	2(9.5)	4(9.3)	0.6
Co-morbidities						
Coronary artery disease	19(23.5)	7(10.9)	0.05	2(.5)	5(11.6)	0.8
Hypertension	47(58)	35(54.7)	0.68	13(61.9)	21(48.8)	0.3
Cardiac arrhythmia	9(11.1)	7(10.9)	0.974	2(9.5)	5(11.6)	0.8
CHF	9(11.1)	7(10.9)	0.974	3(14.3)	3(7.0)	0.3
Valvular Heart Disease	**20(24.7)**	**7(10.9)**	**0.03**	**0(0)**	**8(18.6)**	0.03
CKD	27(33.33)	25(39.1)	0.47	10(47.6)	14(32.6)	0.2
Chronic Dialysis	7(8.6)	12(8.8)	0.47	6(28.6)	6(14)	0.1
Diabetes	29(35.8)	24(37.5)	0.833	8(38.1)	16(37.2)	0.9
Malnutrition	3(3.7)	8(12.5)	0.04	2(9.5)	6(14.0)	0.61
Invasive Mechanical Ventil	**23(28.4)**	**29(45.3)**	**0.03**	**7(33.3)**	**22(51.2)**	0.1
NIPPV at ventilation	16(19.8)	11)17.2)	0.69	4(19)	8(18.6)	0.9
Lab Values at admission						
Baseline Creatinine, media	1.66(0.94-2.5)	1.07(0.8-1.5)	0.65	**2.36(1.4-3.7)**	**0.98(0.86-1.3)**	**<0.001**
CRP at admission, median(I	163(73-235)	132(82-205)	0.28	190(117-270)	126(79-174)	0.19
Lactate , median(IQR)	2(1.5-3.1)	1.9(1.5-2.5)	0.05	1.1(0.78-1.9)	1.6(1.4-1.9)	0.44
Ph, median(IQR)	7.36(7.31-7.44)	7.35(7.26-7.42)	0.13	7.31(7.2-7.3)	7.3(7.26-7.4)	0.03
Bicarbonate , median(IQR)	21(17-23)	21.5(17-25)	0.41	19(16-23)	22(18.5-25)	0.036
BUN , median(IQR)	33(19-50)	36.2(22-67)	0.27	**59(42-88)**	**26(20-47)**	**0.001**
AST , median(IQR)	63(39-107)	52.5(38-91)	0.63	40(32.5-52.5)	58(44.5-90)	0.01
ALT, median(IQR)	36(19.5-57.5)	33.5(23-50)	0.72	23(18-37.5)	38(24.5-53.5)	0.09

FR-PO1135

Association of Renal Function with Mortality Among Hospitalized Patients Treated with Remdesivir for COVID-19

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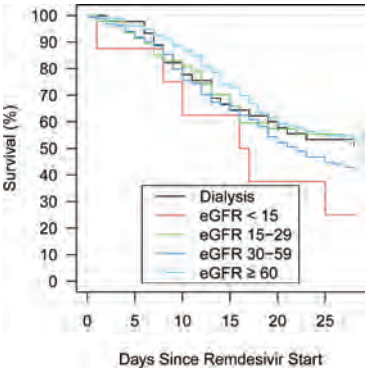
Background: Renal dysfunction is associated with poor outcomes in patients with coronavirus disease 2019 (COVID-19). In an effort to improve outcomes, intravenous remdesivir has been broadly used off label for the treatment of COVID-19 in patients with low estimated glomerular filtration rate (eGFR). Our study assessed the outcomes of patients with low eGFR after treatment with remdesivir for COVID-19.

Methods: We conducted an observational, retrospective, cohort study of adults hospitalized with COVID-19 treated with at least one dose of remdesivir between 11/6/2020, and 11/5/2021. Electronic medical records were reviewed to obtain patient characteristics, laboratory data, and outcomes. Primary endpoint was all-cause mortality by day 28. Multivariable logistic regression was used to evaluate association among groups.

Results: We studied 3024 patients hospitalized with COVID-19 and treated with remdesivir. Median age was 67 [IQR 55, 77] years; 42.7% were women, 88.6% were white. Median eGFR was 76.6 mL/min/1.73 m^2 [IQR 52.5, 95.2]; 67.2% of patients had eGFR ≥ 60, while 9% had eGFR <30. All-cause mortality by day 28 was 8.7%. All-cause mortality rates were significantly higher among patients with impaired renal function (Odds Ratio [OR] 1.94 for patients with eGFR 30-59; OR 1.94 for eGFR 15-29; OR 3.62 for eGFR <15 and OR 9.08 for patients on dialysis) compared to patients with eGFR ≥60 (all p<0.01) (Figure 1).

Conclusions: Lower eGFR is an independent risk factor for mortality in COVID-19 despite treatment with remdesivir. These observations suggest that, even with the availability of effective antiviral treatment, prevention of COVID-19 remains a major goal especially among those with impaired renal function.

Funding: Commercial Support - Gilead



Overall survival according to eGFR

FR-PO1136

Decision Tree Analysis to Study the Short- and Long-Term Renal Outcomes in Patients Hospitalized During the First Year of the COVID-19 Pandemic

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Background: COVID-19 has been associated with AKI in hospitalized patients and GFR decline after discharge. However, analysis of risk factors associated with renal outcomes has been limited to traditional machine learning models. Additionally, length of hospitalization (LOH) or days on the ventilator (DOV) have not been typically used for risk prediction.

Methods: In this retrospective single center study, we applied a Classification and Regression Trees algorithm (CART decision trees) to study renal outcomes in patients hospitalized in the United States during the COVID-19 pandemic in 2020 (pre-vaccination era). Outcomes: Moderate/severe AKI (Stage 2 & 3) in the hospital and eGFR decline during a 24-month follow-up (until February 2023. To address the effect of confounding demographics in ICU vs. non-ICU and COVID-19 positive vs. negative patients, propensity score matching (PSM) was applied. Influential variables were selected based on feature importance in Random Forest plots.

Results: In our initial cohort of adult 6.933 patients (without baseline end-stage kidney disease), 10.4 % (719) were diagnosed with AKI-2/3. CART decision tree analysis on the primary cohort and the ICU and COVID-19 status PSM cohorts showed DOV, sepsis, age and vasopressor use as key factors for AKI-2/3 risk categorization. In the follow-up study hospital survivors (n = 1,747), those originally admitted to the ICU and those with COVID-19 had a greater mean GFR decline compared to control groups. CART analysis (Figure 1) showed LOH, age, AKI-2/3, body mass index, vasopressor use, and baseline CKD as the main features that risk categorized patients for rate of GFR decline.

Conclusions: To our knowledge, this is one of the first studies to report renal outcomes in patients with and without COVID-19 using CART decision tree analysis. Besides traditional risk factors, days in the hospital and on the ventilator were noted as key features that stratified patients' risk for renal outcomes.

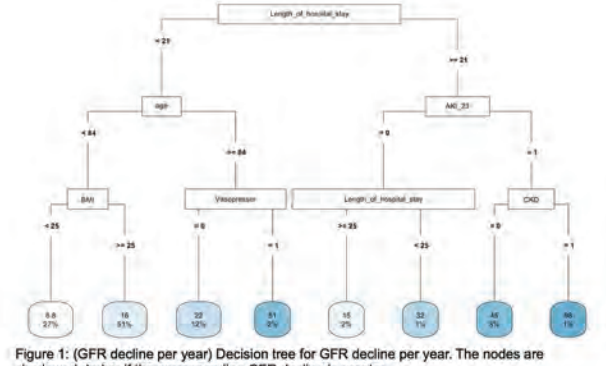

Figure 1: (GFR decline per year) Decision tree for GFR decline per year. The nodes are shadowed darker if the corresponding GFR decline is greater.

FR-PO1137

Long-Term Kidney Function of Hospitalized COVID-19 Survivors Who Did or Did Not Develop AKI

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Background: COVID-19 increases acute kidney injury (AKI) risk; however, it is unclear its long-term effect in high CKD prevalence settings. Aim: To assess evolution, at least 6 months after discharge, of kidney function in hospitalized COVID-19 survivors who did or did not develop AKI.

Methods: Prospective cohort of confirmed COVID-19 patients (03/20-10/21) From inpatient registry, survivors were contacted; those who agreed to participate had a clinical interview and eGFR and albumin/creatinine ratio evaluation.

Results: Of 585 COVID-19 patients discharged alive, 121 (21%) developed AKI; 166 without AKI and 34 with AKI were included and evaluations performed at 20.0±0.3 months. Comparisons between groups are shown in Table 1 and Table 2. Overall mean time survival was 26.1±0.5 months; comparison according to AKI development is shown in Figure.

Conclusions: A fifth of surviving patients hospitalized for COVID-19 developed AKI, 73% of them recovered kidney function upon discharge. Patients with AKI had lower kidney function throughout the study and higher ACR at end of follow-up compared to those without AKI; however, the latter displayed slight eGFR decrease at the end of the study compared to baseline. Survival was significantly lower in patients with AKI and seemed to be worse in those with higher stages.

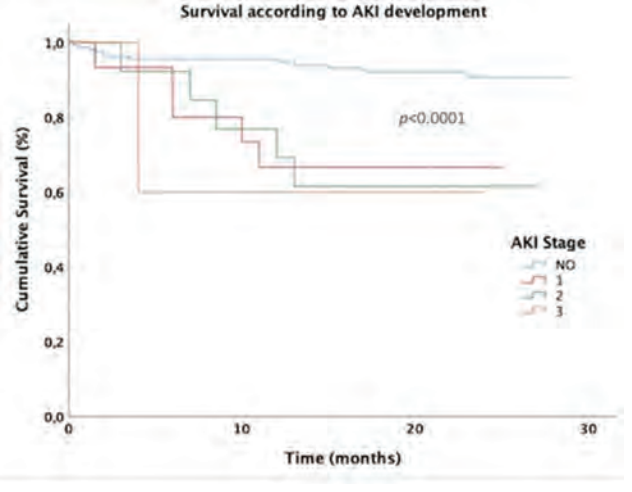
Table 2. Comparison of kidney function recovery and treatment according to KDIGO classification

Variable	AKI 1 (n 15)	AKI 2 (n 13)	AKI 3 (n 6)	p
Kidney function recovery, n (%)				
Treatment, n (%)	10 (67)	11 (85)	4 (67)	
Conservative	14 (93)	12 (92)	4 (67)	0.51
Hemodialysis	1 (7)	1 (8)	1 (17)	0.23
Peritoneal dialysis	0	0	1 (17)	

Table 1. Comparisons of sociodemographic and kidney function between groups.

Variable	No AKI (n 166)	AKI (n 34)	p
Age (years)	54.9 + 14.2	59.6 + 13.9	0.08
Male gender, n (%)	94 (57)	23 (68)	0.46
Body mass index (Kg/m²)	30.3 + 6.8	30.6 + 5.1	0.81
Diabetes mellitus, n (%)	64 (39)	16 (48)	0.33
Hypertension, n (%)	63 (38)	22 (67)	0.002
Cardiovascular disease, n (%)	8 (5)	6 (18)	0.01
Chronic kidney disease	3 (2)	6 (18)	0.001
eGFR ml/min/1.73m²			
Baseline	103.0 (93-116)	70.0 (40-108)	<0.0001
Maximal Decrease	97.1 (87-108)*	46.0 (31-76)*	
Discharge	103.8 (94-113)/	69.5 (48-101)/	<0.0001
End of follow-up	94.6 (82-106)*/†	69.6 (45-91)	<0.0001
ACR at end of follow-up (mg/g)	10.1 (6.6-23.9)	17.5 (9.5-106.6)	0.04

*p<0.05 vs baseline in the same group. / p<0.05 vs maximal decrease in the same group.
† p<0.05 vs discharge in the same group.



FR-PO1138

Identification of COVID-19 Disease and Impact on Kidney Function Using Urine Raman Spectroscopy and Chemometrics

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Background: COVID19 can have a deleterious effect on renal function. Timely prediction of renal dysfunction is not achievable with available laboratory armamentarium, and scores currently used for severity of illness are highly provider dependent and subjective in nature.

Methods: We developed a Raman spectroscopic technology (Rametrix® molecular urinalysis) to detect COVID19 systemic/renal effects by analysis of patient urine. It is based on chemometric analysis of the Raman spectrum of urine and detects metabolomic differences. The technology is not designed to detect virus/viral components. We hypothesized that COVID19 disease would alter urine composition and that Rametrix® analysis could detect renal dysfunction via urine molecular 'fingerprinting'. We applied Rametrix® analysis on 85 urine specimens from 64 patients hospitalized for COVID19 disease (Omicron variant prevalent). Patients were 30-92 years of age (median age 67), and ca. 50%/50% M/F. Collections were done at admission (n=66), discharge (n=7), and follow-up (n=12). Medical record and laboratory data were correlated with Rametrix® results; 66 patients had GFR values at both admission and discharge. Disease severity scores were collected repeatedly during hospitalization. Using chemometric analysis, we compared hospitalized patient COVID19 urine spectra with urine spectra from healthy controls (pre-COVID19), patients with CKD (pre-COVID), asymptomatic-mildly symptomatic outpatients (2020/mid-2021 variants), bladder cancer patients (pre-COVID19) and Lyme disease patients (pre-COVID19).

Results: Rametrix® molecular urinalysis distinguished COVID19-associated changes in urine composition with predictive metrics (accuracy, sensitivity, specificity, PPV, and NPV) ranging between 93-96.5%. A correlation between changes in urine Raman spectra and physician assessment of disease severity was also found through computational analysis. Spectra from patient urine collected at admission and stratified based on eGFR, demonstrated molecular 'fingerprints' predictive of future renal dysfunction in 91.7% of high-risk patients.

Conclusions: Raman molecular urinalysis can be a useful tool in detecting and predicting future renal dysfunction in patients hospitalized with COVID19 disease.

Funding: Clinical Revenue Support

FR-PO1139

Postdischarge All-Cause Mortality in COVID-19-Recovered Patients: The Impact of CKD

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Background: In Brazil, the COVID-19 burden was substantial, and risk factors associated with higher in-hospital mortality rates have been extensively studied. However, information on short-term all-cause mortality and factors associated with death in patients who survived the hospitalization period of acute SARS-CoV-2 infection is less abundant. We analyzed the 6-mo post-hospitalization mortality rate and possible risk factors of COVID-19 patients admitted from Mar/20 to Dec/20 in a single center in Brazil.

Methods: Retrospective cohort study focused on a 6-mo follow-up. Exclusion criteria were: death during hospitalization, transference to another hospital, and age under 18. We collected data from the charts of all hospitalized patients from Mar/20 to Dec/20 with positive RT-PCR test for SARS-CoV-2, a time when vaccination against the infection was not available and no variant other than the wild one had been identified in Brazil. The main outcome was death after hospitalization. Comorbidities and demographics were evaluated as risk factors.

Results: We studied 106 patients. The crude post-hospitalization death rate was 16.0%. The first 30 days of follow-up had the highest mortality rate. In a Cox regression model for post-hospitalization mortality, previous CKD (HR, 4.06, 95%CI 1.46 – 11.30) and longer hospital length of stay (HR 1.01, 95%CI 1.00 - 1.02) were the only factors statistically associated with death.

Conclusions: Substantial 6-mo all-cause mortality was observed. Within the 6-mo follow-up, a higher risk of death was observed for patients who had prior CKD and longer hospital length of stay. These findings highlight the importance of more intensive medical surveillance during this period.

General characteristics of the studied population at entrance (data are shown as number and percent unless specified)

	Overall (N = 106)	Death w/ 6 mo. (N = 17)	Alive at 6 mo. (N = 89)
Male sex	57 (52.8)	9 (52.9)	47 (52.8)
Age [a] (years)	58 ± 16	63 ± 9	58 ± 17
Diabetes	31 (29.2)	4 (23.5)	27 (30.3)
Hypertension	71 (67.0)	14 (82.4)	57 (64.0)
Obesity	19 (17.9)	0(0.0)	19 (21.3)
Neoplasia [b]	40 (37.7)	8 (47.1)	32 (36.0)
Asthma/COPD	19 (17.9)	1 (5.9)	18 (20.2)
Immunosuppression [b]	25 (23.6)	4 (23.5)	21 (23.6)
CKD	15 (14.2)	6 (35.3)	9 (10.1)
Stroke	6 (5.7)	2 (11.8)	4 (4.5)
ICU Admission	40 (37.7)	5 (29.4)	35 (39.3)
Orotracheal intubation	18 (17.0)	3 (17.6)	15 (16.9)
Hemodialysis (AKI)	12 (11.3)	2 (11.8)	10 (11.2)
IV catecholamines	15 (14.2)	4 (23.5)	11 (12.4)
Number of failed organs (0 / ≥1)	81 (76.4) / 25 (23.6)	13 (76.5) / 4 (23.5)	68 (76.4) / 21 (23.6)
Hospital LOS [a] (days)	29 ± 34	46 ± 47	24 ± 26

[a]Mean ± SD; [b]Current or past; [c]Current or within the past 3 months; *AKI* Acute Kidney Injury; *COPD* Chronic Pulmonary Obstructive Disease; *ICU* Intensive Care Unit; *LOS* Length of Stay.

SA-PO001

Microphysiological Model of Human Kidney Collecting Duct

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Background: Understanding kidney physiology is indispensable for maintaining human health, developing effective treatment strategies, implementing therapeutic interventions, and advancing personalized medicine approaches. However, much of our current knowledge of kidney physiology relies on non-human models, which do not accurately reflect human cell and system responses. To overcome this challenge, human stem cell-derived cells can be employed within a physiological microenvironment to achieve advanced physiological functions.

Methods: We developed a physiologically relevant human kidney collecting (CD) duct model using human stem cell-derived CD cells on the Epithelial Microphysiological Analysis Platform (Epi-MAP). scRNA-Seq analysis identifies the ureteric bud organoids as highly enriched in inner medullary CD principal epithelial cells We designed physiological media with compositions resembling intraluminal and basolateral conditions *in vivo* and used physiologically relevant tubular flow rates. Moreover, our Epi-MAP is integrated with proximal surface electrodes for in-situ real-time monitoring of physiological dynamics, enabling simultaneous tracking of optical microscopy and electrophysiological records.

Results: Compared to stationary cultures without flow, our Epi-MAP culture conditions significantly enhanced various aspects of the CD physiology. This includes improved epithelial morphology and enhanced mRNA expression of genes related to ion transport, tight junctions, water and urea transport, and receptor signaling. Our electrophysiological monitoring shows that CD-specific functions of vectorial transport and epithelial tight junction are further advanced in the physiological Epi-MAP culture. We also observed the conversion of CD principal cells to intercalated cells, resulting in a more physiological model. With our high-precision, continuous electrophysiological characterization, we also comprehensively studied the CD responses to vasopressin and aldosterone signaling, particularly on ion and water flux and tight junction integrity.

Conclusions: This human cell-derived, physiologically relevant model represents a powerful model *in vitro* for understanding human kidney biology, increasing drug modeling precision, understanding disease processes, and potentially serving to help create an important functional component of a biohybrid artificial kidney.

Funding: NIDDK Support, Other NIH Support - NCAT

SA-PO002

A High-Throughput Kidney-on-a-Chip Platform for CKD Therapy Discovery

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Background: Glomerular and/or proximal tubule (PT) dysfunction often culminates in the onset of chronic kidney disease (CKD). Existing therapies address symptoms rather than the underlying causes, resulting in significant side effects. More targeted therapies with increased specificity to the glomerulus or PT are needed, but their development is greatly hindered by the lack of relevant human model systems. To address this, we developed a three-dimensional *in vitro* kidney-on-a-chip mimicking glomerular and PT function in a high-throughput platform: the NephroPlate.

Methods: The NephroPlate was established in MIMETAS' OrganoPlate, a 40-assay format allowing culture with inner tissue flow in a standard microtiter plate. The glomerular unit was prepared using primary human podocytes and glomerular endothelial cells. The PT unit was prepared using renal PT epithelial cells (RPTEC) and human umbilical vein endothelial cells (HUVEC). Barriers were assessed using transepithelial electric resistance via Organo(TEER). To assess glomerular filtration (GF), FITC-albumin was added to cultures mimicking either healthy or Membranous Nephropathy (MN) conditions. Expression was confirmed by immunostaining and media were collected for evaluation of secreted factors.

Results: Cultures within the NephroPlate maintained cell phenotypes in a three-dimensional format, facilitating the de novo production of glomerular basement membrane (GBM) components and mimicking GF. While all donor-derived cultures recapitulated healthy functions, treatment with serum from patients with MN resulted in a donor-dependent loss of GF and TEER. In CKD models, treatment with α-melanocyte-stimulating hormone rescued the MN serum-mediated loss of GF as demonstrated by albumin retention, while TEER did not recover within the experimental timeframe. Upon transfer of CKD glomerular filtrate to the PT, elevated KIM-1, a marker of PT injury, was observed.

Conclusions: The NephroPlate captures many aspects of the kidney microenvironment, including complex composition as well as GF function and its dynamic response to mimic CKD. The high-throughput capabilities of our system allow for up to 40 conditions to be assessed simultaneously, enhancing our ability to screen existing and novel drugs as well as identifying better, more targeted therapies for CKD.

Funding: NIDDK Support, Other NIH Support - NCATS Support

SA-PO003

Tubuloids on Primary Human Renal Tubular Epithelial Cells (hRTECs) Recapitulates Cisplatin-Induced Kidney Injury

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Background: Kidney organoids derived from human pluripotent stem cells has been an attracting pathophysiological model recapitulating a response of human kidney to drugs in recent years. Here, we have developed an alternative way to make more homogeneous epithelial-like structures called tubuloids based on primary human renal tubular epithelial cells (hRTECs) and tested their efficacy by administering cisplatin.

Methods: hRTECs were obtained from the non-tumor kidney tissue removed from patients with renal or ureteric malignancies. Renal cortex was diced and digested with collagenase. Tubules were seeded on plates with serum-free media containing epidermal growth factor. After passage, cells were cultured on ultra-low attachment plates for several days and transferred into media containing matrigel, epithelial growth factor, hepatocyte growth factor, fibroblast growth factor-2 and 5% fetal bovine serum. After tubuloids were completed, cisplatin was administered at a concentration of 0.2 – 20.0 μg/ml.

Results: Tubuloids expressed LTL and Megalin, indicating that they were highly differentiated structures composed of proximal tubular epithelial cells. Treatment of tubuloids with cisplatin increased γH2AX, a marker for DNA damage, in a dose-dependent manner. KIM-1, a marker of kidney injury, and cleaved caspase-3, a marker for apoptotic signals were expressed as well. Vimentin, an intermediate filament, was also upregulated by cisplatin treatment, suggesting that tubular epithelial cells were in the process of epithelial-mesenchymal transition. Enhancement of the NF-κB and IL-1β was also observed. These findings may recapitulate the events of post-acute kidney injury, which, after an acute phase response, acquires senescence-associated secretory phenotype (SASP) and induces inflammation and fibrosis.

Conclusions: We succeeded in establishing a model of cisplatin-induced kidney injury based on tubuloids using hRTECs. Tubuloids can be utilized to simulate the response of epithelial cells to toxins and therapeutic agents. This alternative way is potentially an excellent tool not only as cisplatin-induced kidney injury, but also as a pathological model for various renal diseases including chronic kidney disease.

Funding: Commercial Support - Bayer Yakuhin, Ltd., Private Foundation Support, Government Support - Non-U.S.

SA-PO004

In the Same Vein: Developing a Novel In Vitro Flow Model for Endothelium Using 3D-Printed, Patient-Specific Arteriovenous Fistulas

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Background: Endothelial cell dysfunction is a feature of several medical conditions including chronic kidney disease (CKD). The global prevalence of advanced CKD (Stage 3-5) is approximately 8%, affecting an estimated 850 million people worldwide. For patients with end stage kidney disease treated with hemodialysis, easy vascular access is best achieved using a surgically-created arteriovenous fistula (AVF). Why some AVFs fail to mature while others develop high blood flow is unclear. Standard cell culture provides valuable insight into the role of endothelial cells in this process, but the flat surface neglects the complex physiology of disturbed blood flow through intricate vessel geometries. The use of animal models is limited by the ethical implications of the required interventions, the necessary surgical skill, an inability to simulate relevant comorbidities, differences in vessel size, breed genetic diversity, and limited commercially available reagents. The aim of this study was to use 3D-printing to create patient-specific models of arteriovenous fistulas for use in vascular research.

Methods: Patient AVFs were imaged using a modified ultrasound device. Specialised segmentation software generated AVF geometries which were 3D-printed using a water-soluble filament. Prints were cast in silicone and dissolved away leaving an AVF-shaped cavity. Human dermal microvascular endothelial cells (HMEC-1) were cultured on the internal surface of these models. Closed circuit hemodialysis tubing was then used to expose the endothelial cells to varying magnitudes of continuous flow.

Results: Fabrication of patient-specific models was accurate and reproducible. Immunofluorescence with DAPI and Phalloidin confirmed an HMEC-1 monolayer on the luminal surface. The endothelial cell monolayer was maintained after exposure to continuous flow over a 24-hour period. HMEC-1 cells exposed to flow polarized in the direction of flow as judged by alignment of the actin cytoskeleton.

Conclusions: Our 3D in vitro model overcomes limitations of current cell culture techniques whilst maintaining the 3D geometry only seen in humans and animal models. This will allow rapid investigation of endothelial cell signalling in true AVF geometries.

SA-PO005

Using Organ-on-a-Chip Co-Culture Technology to Explore the Pathophysiology of Tubulopathies: A Paradigm Shift in Kidney Disease Research

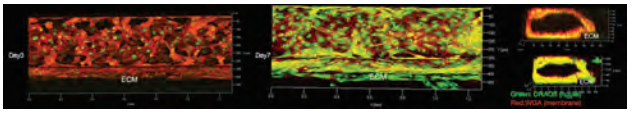
Chutong Zhong, Alessandra Grillo, Keith Siew, Stephen B. Walsh. London Tubular Centre. *University College London, London, United Kingdom.*

Background: Tubulopathies are a group of renal disorders that significantly impact patient morbidity and mortality, with limited current treatment options. The complex pathophysiology of these diseases hampers our understanding, resulting in a pressing need for advanced, physiologically relevant models. This research harnesses Organ-On-a-Chip (OOaC) technology to simulate human tubular physiology, thus elucidating the pathogenesis of tubulopathies and potentially facilitating development of novel therapeutic strategies.

Methods: Urine-derived renal tubular epithelial cells (uRTEC) and blood outgrowth endothelial cells (BOEC) were isolated from urine and blood samples collected from healthy volunteers and patients from tubular clinic by methods previously described (Ormiston et al., 2015; Ikeda et al., 2020). uRTEC and BOEC cells were applied adjacently in a three-lane microfluidic chip platform OrganoPlate following manufacture's protocol with modifications on the constitution of the extracellular matrix gel.

Results: Patient-derived renal tubules and blood vessel endothelium formed in the OrganoPlate channel on an average of 7-10 days of culture. Barrier integrity assay in the OrganoPlate using fluorescent probes confirmed tight junctions between cells. qPCR of the cell lysate showed these tubules expressed the distal convoluted tubule specific marker NCC (*SLC12A3*).

Conclusions: These preliminary data demonstrate that patient-derived uRTEC and BOEC were able to form tubule/blood vessel-like structures in the OrganoPlate. Given these samples are primary cells from patients, we propose this OOaC model will dynamically reflect *in vivo* human renal physiology with tubule-capillary interaction. We highlight the potential of OOaC culture systems combined with patient-derived cells to uncover tubulopathy. Furthermore, this innovative methodology can be employed to screen a panel of drugs, revealing varying drug efficacies and toxicity profiles individually with continuous monitoring of disease progression, ultimately bringing personalised medicine to tubular diseases.



The 3D confocal imaging of the immortalised uRTEC cells in the OOaC on Day 3 and Day 7, showing a gradual completion of the tubule in the plate.

SA-PO006

Proteomic Profiling of a Novel Immortalised Human Distal Convoluted Tubule Cell Line

Chutong Zhong, Keith Siew, Stephen B. Walsh. London Tubular Centre. *University College London, London, United Kingdom.*

Background: Tubulopathies are renal disorders with complex and inadequately understood pathophysiology, creating an urgent need for improved *in vitro* models to facilitate research. The development of a novel immortalised human distal convoluted tubule cell (hDCT) line represents a breakthrough in this field, offering a promising model for investigating the pathogenesis of tubular diseases. This research focuses on the proteomic characterisation of this cell line, a critical step towards understanding its utility for research into distal tubulopathies.

Methods: Four immortalised hDCT cell lines, primarily isolated from healthy volunteer's urine, were gifted from Dr Kusaba and were cultured as previously described (Ikeda et al., 2020). Cells were treated in 8M urea and 0.1% SDS in the presence of phosphatase and protease inhibitors for protein extraction and cell lysates were analysed through Liquid Chromatography and tandem Mass Spectrometry (LCMS). Western blot analysis was performed for DCT-specific marker NCC (*SLC12A3*).

Results: WNK1, SPAK, CAB39, CUL3, OxSR1 and PMCA1 (*AT2B1*) have been identified by LCMS from four hDCT cell lines at a high level, of which hDCT3 has an additionally abundant detection for WNK4 and KCC4 (*SLC12A7*). NCC was detected from all four hDCT cell lysates in the western blot.

Conclusions: The proteomic analysis of the novel immortalised hDCT cell line has unveiled the presence of key proteins of the DCT region. Notably, the identification of regulator proteins such as WNK1 and SPAK and ion channel corroborates the promising potential of this cell line as a representative model for studying DCT physiology. These findings serve as a preliminary validation of the hDCT cell line's suitability for tubular modeling, enriching our toolset for investigating renal disorders. In future research, we aim to focus on functional experiments for a more comprehensive characterisation of the cell line, solidifying its utility in unraveling the physiology of tubulopathies and potentially guiding targeted therapeutic developments.

SA-PO007

Quantifying Composition Changes in Serum Biomarkers of Vascular Calcification in CKD

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Background: Vascular calcification (VC) is a strong predictor of cardiovascular morbidity and mortality for chronic kidney disease (CKD). Cardiovascular disease (CVD) is the leading cause of death for patients with CKD worldwide. Despite its importance in CVD/CKD, there are no tools to noninvasively diagnose VC, monitor progression, or prognosticate outcomes. Calciprotein particles (CPPs) are circulating biological nanoparticles composed of minerals, lipids, and proteins, and represent a novel biomarker of CVD. When CKD disrupts serum mineral and protein balance, CPPs mature into pathogenic secondary CPPs, which initiate tissue calcification. Here, we present the development of a new technology to assess VC risk: Raman Trapping Analysis (RTA), a quantitative label-free optical technique, is used to quantify composition of healthy and uremic patient derived serum.

Methods: Serum collected from healthy and uremic patients was processed to isolate CPPs and initiator components. Size exclusion was used to separate soluble CPP constituents and incubation in FBS supplemented with Ca and PO_4 was used to generate mature CPPs. The gel-filtration method using OsteoSence reporter was used to quantify CPP levels, and dynamic light scattering (DLS) and transmission electron microscopy (TEM) to assess particle size and morphology. RTA of CPPs was acquired during maturation (24 hr) and after incubation (72 hr). Particle spectra were analyzed to investigate compositional differences between disease groups and time points.

Results: Analysis validated the formation of secondary CPPs. DLS/TEM confirmed particle maturation, and the OsteoSense assay indicated increased CPP levels between uremic vs healthy samples. RTA obtained particle spectra from CPPs comprising Ca-PO_4 mineral, lipid, and protein signatures. A spectral model of chemical constituents was developed, and signatures were extracted for further statistical analysis.

Conclusions: RTA is capable of noninvasive label-free chemical characterization of CPPs derived from patient serum and provides novel information regarding dynamic changes in the composition and heterogeneity of these biomarkers. Precise evaluation of these signatures may provide new insights into serum biomarkers that can differentiate innate mineralization propensity and prognosticate patient risk for VC.

Funding: NIDDK Support

SA-PO008

New Translational Screening Assay with Phenotypic and Transcriptomic Readouts Using Induced Pluripotent Stem Cell (iPSC)-Derived Cells and Organoids from a Nephrotic Syndrome Patient

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Background: Professor Nishinakamura's group previously generated pluripotent stem cell (iPSC)-derived kidney organoids from a patient suffering from a congenital nephrotic syndrome caused by the mutations in the nephrin gene (c.G1379A, c.2515delC in NPHS1). We further developed this system into a robust, reproducible, and high-throughput organoid assay useful for the progression of drug discovery programs.

Methods: To enable readouts in 384w, we scaled up the production of iPSC-podocytes and iPSC-kidney organoids. We also developed and applied a 3D whole mount immunostaining readout to quantify the phenotypic signature of iPSC-derived podocytes and kidney organoids. Bulk ScreenSeq™ and single-nucleus sequencing was applied to characterize the transcriptomic profiles of both systems.

Results: A specific lack of nephrin phosphorylation was confirmed via automated western blotting. Besides, our kidney organoids completely lacked nephrin signals in synaptopodin-positive regions of glomerular structures. We further quantified the general nephrin deficit with a new script-based whole mount imaging analysis. Finally, by comparing transcriptomic disease signatures, we showed the translational relevance of these organoids for drug discovery in the field of podocytopathies.

Conclusions: We successfully developed and characterized a patient-derived kidney organoid assay and made it available in a high-throughput format. This translational system will prove useful in the identification and validation of candidate targets and for the progression of new kidney therapeutics.

SA-PO009

Design of Kidney-Targeted Nanoparticles for Delivery of Gene Therapies

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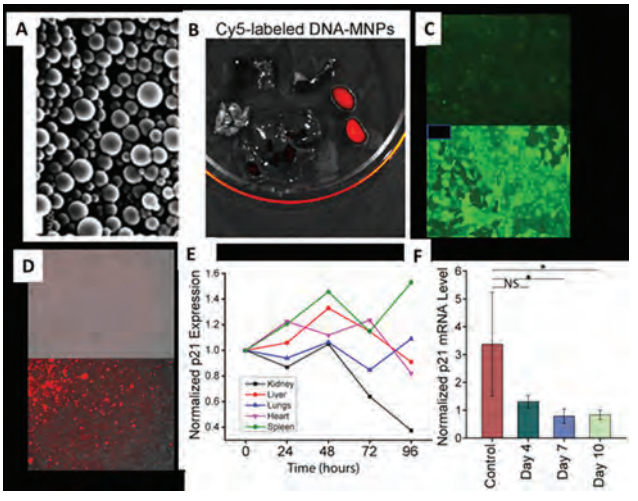
Background: Therapeutic gene and drug delivery to organ sites outside of the liver remains elusive with few strategies to do so for renal diseases. In prior studies, we found that polymeric mesoscale nanoparticles (MNPs) localize to the kidneys up to 26-fold greater than any other organ, specifically to the renal proximal tubular epithelium.

Methods: Here, we investigated the potential to adapt this MNP platform to specifically deliver various RNA-based gene therapies to the renal proximal tubules. We formulated MNPs loaded with either reporter or gene-specific siRNA, mRNA, or CRISPR gRNA/Cas9 that conformed to the 300-400 nm diameter size range which demonstrates tubular localization. We then conducted in vitro studies using renal proximal tubular epithelial cells, as well as in vivo studies with healthy mice, to confirm their function and renal-specific delivery.

Results: Our results demonstrated successful modification of polymeric MNPs such that they maintained kidney targeting while encapsulating RNA therapeutics. mCherry mRNA-loaded MNPs exhibit rapid and bright protein translation in vitro with no cytotoxicity. GFP-targeted CRISPR gRNA/Cas9 MNPs turned off expression of GFP in a stably-transfected cell line. In vivo, we found that kidney-targeted MNPs specifically target the kidneys and achieve gene-specific knockdown.

Conclusions: In ongoing studies, we are using this modified MNP design to deliver gene therapies that modulate inflammation and oxidative stress in salt-sensitive hypertension models of chronic kidney disease.

Funding: Other NIH Support - CA132378



a) Images of mesoscale nanoparticles. b) Kidney-specific delivery of fluorescently-labeled nucleic acids. c) GFP expression in vitro (bottom) is deleted by delivery of GFP CRISPR gRNA-Cas9 d) Renal cell lines (top) express mCherry fluorescent protein upon addition of mRNA-loaded MNPs. e) MNPs reduce gene expression specifically in the kidneys. f) Knockdown persists for up to 10 days.

SA-PO010

Integrative Systems Analysis of Calcineurin Inhibitor Action on Podocytes and Proximal Tubular Epithelial Cells

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Background: Calcineurin inhibitors (CNI), including Cyclosporin A (CSA), Tacrolimus (TAC) and Voclosporin (VCS) are used to treat proteinuric kidney disease. The mechanisms driving differential podocyte and tubular cell responses upon clinical exposure are poorly understood. Here, we tested the in vitro cellular response of these three most commonly used CNIs using a combination of integrated systems biology methods.

Methods: We used high content image analysis to assess the changes in cytoskeletal and focal adhesion architecture; isobaric-tagged LC-MS/MS to assess altered proteomic response; image-based and colorimetric assays to assess viability and metabolic response. For all above assays, immortalized human podocytes and proximal tubular epithelial cells were treated with increasing doses of CSA, TAC and VCS. Respective drug dose responses were mapped back to the translational plasma concentrations as measured in the associated clinical trial.

Results: All CNIs were well tolerated by immortalized human podocytes with minimal change in viability. Immortalized human tubular epithelial cells also showed little change in cell viability with high levels of cell death only in the highest doses of TAC. Morphometric changes were similar in CNIs, with increased focal adhesion area and aspect ratio. Levels of remodeling for all CNIs mirrored their respective calcineurin IC50 values with VCS showing a more robust dose response for both altered focal complex signaling and cell spreading. Quantitative proteomics at the physiologically relevant drug doses recapitulated the altered focal adhesion complex signatures for all CNIs. While network analyses of the differentially abundant podocyte adhesome showed a core CNI proteomic signature, this was supplemented by differing peripheral drug-specific networks that showed different neighborhoods for each CNI.

Conclusions: While integrated viability, proteomic and high-content morphometric analyses show a common CNI-induced signature within human proximal tubular epithelial cells and podocytes, differences were observed among CSA, TAC and VCS for both differentially abundant proteins and drug dose responses. Consistent adhesome and cytoskeletal changes may point to a conserved biophysical role of calcineurin in podocytes with differences in off-target effects.

Funding: Commercial Support - Aurinia

SA-PO011

Development of a Glomerulus-on-a-Chip Model: An Innovative Model to Study Paracrine Pathways to Unravel Glomerular Disorders

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Background: Crosstalk between glomerular endothelial cells (GEnC) and glomerular epithelial cells (podocytes) is increasingly becoming apparent as a crucial mechanism to maintain the glomerular filtration barrier (GFB) integrity. However, *in vitro* studies directly investigating the effect of this crosstalk are scarce because of the lack of suitable models. Therefore, we developed a custom-made glomerulus-on-a-chip model recapitulating the GFB, in which we investigated the effects of co-culture of GEnC and podocytes on barrier function and cellular phenotype.

Methods: The custom-made glomerulus-on-a-chip model was designed using soft lithography. The chip consisted of two parallel microfluidic channels separated by a semi-permeable polycarbonate membrane. iPSC derived podocytes and conditionally immortalized GEnC and podocytes were differentiated in the chip. Shear stress induced by laminar flow was applied on endothelial cells. Cellular morphology and glycocalyx was visualized by fluorescent staining. The barrier integrity of the model was determined by measuring the transport rate of labelled dextran from top to bottom channel. The effect of crosstalk on the transcriptome of GEnC and podocytes was investigated via RNA-sequencing.

Results: GEnC and podocytes were successfully cultured on opposite sides of the membrane in our glomerulus-on-a-chip. Barrier integrity of the chip was significantly improved when GEnC were co-cultured with podocytes compared to monocultures. Co-culture enlarged podocyte foot process surface area and increased glycocalyx thickness. RNA-sequencing analysis revealed the regulation of cellular pathways involved in cellular differentiation and cellular adhesion as a result of the interaction between GEnC and podocytes.

Conclusions: We present a novel custom-made glomerulus-on-a-chip and demonstrated that co-culture in the device affects the morphology and transcriptional phenotype of GEnC and podocytes. Moreover, we showed that co-culture improves barrier function as a relevant functional readout for clinical translation. This model can be used in future studies to investigate specific glomerular paracrine pathways and unravel the role of glomerular crosstalk in glomerular (patho) physiology.

SA-PO012

Isolation and Purification of Mesangial Cells for Bioengineered Kidneys

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Background: With over 85,000 patients waiting for a kidney transplant, bioengineered kidneys (BEKs) offer a way to address this large clinical need. BEKs are created from isolated native cell types from donor kidneys not accepted for transplant. Of these isolated cell types, mesangials help maintain the glomerular filtration barrier of the kidney. Here, an isolation and purification process are presented to isolate mesangial populations that can be used for glomerular recapitulation of the BEK.

Methods: Using enzymatic digestion, whole glomeruli were isolated from human kidneys and then plated on tissue culture flasks for 14 days. Mesangials were purified from the outgrowths using CD140b/PDGFRβ positive magnetic bead sorting. Purification of the bound mesangial cell population was confirmed using flow cytometry. Post sort, mesangials were expanded, then cryo-banked at passage 2. Cryopreserved cells were thawed and expanded to passage 5, where the mesangials were seeded into a BEK along with other native glomerular cell types.

Results: The bound mesangial population isolated from 6 kidney donors had 89.2% ± 13.4% CD140b positive cells. To assess the potential of isolated mesangials for cryo-banking and expansion, mesangials were cryopreserved, and expanded in 2D up through passage 5. The mesangials remained viable through 2D culture (95.3% ± 2.9% at passage 5, n=7), and were seeded and cultured in 3D in a BEK (n=1) along with other glomerular cell types (podocytes). This BEK demonstrated improved protein and RBC filtration in comparison to BEKs seeded only with podocytes and parietal epithelial cells, after 60 minutes of whole porcine blood perfusion.

Conclusions: Mesangial cells are a necessary cell type known for their structural support as well as their contractile properties to aid in ultrafiltration. This study demonstrates a process in which the mesangial population can be isolated from human donor kidneys, purified, cryo-banked, and expanded for making BEKs. Furthermore, when seeded into a BEK, the mesangials demonstrated improved BEK filtration function. Cryo-banked populations of mesangial cells, as well as other cell types, will allow for BEK creation on demand, thus helping to reduce the number of patients waiting for a kidney transplant.

Funding: Commercial Support - Miromatrix Medical Inc.

SA-PO013

Case Series of Novel PTEC Isolations from Human Kidney Biopsy: Optimized Protocols and Systematic Characterisation

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Background: Human kidneys provide water, electrolyte, and acid-base homeostasis while enabling endo- and exogenous compound metabolism and excretion. Various causes, such as medications (especially in polypharmacy), can quickly disrupt this delicate balance, and currently used methods for nephrotoxicity assays limit the prediction of human response. Our work aimed to develop novel and optimised protocols for isolating proximal tubular epithelial cells (PTEC) from human kidney biopsy.

Methods: We performed nine diagnostic kidney biopsies (informed consent was obtained from the patients) with parts of tissue used to isolate and characterise PTEC. We used two protocols, using five and four biopsy specimens, respectively. The first employed enzymatic dissociation with 0.25% trypsin/EDTA and culture with Advanced DMEM supplemented with 5% fetal bovine serum. In comparison, the second used 0.2% collagenase type 1 and was cultured in selective serum-free culture media (Advanced DMEM/F12 with added insulin, transferrin, selenite, epidermal growth factor, and hydrocortisone). Light microscopy was used for morphologic characterisation, while several markers characteristic of PTEC were chosen for phenotypic characterisation.

Results: Following the protocols resulted in isolating cells that formed first colonies after seven days (range 1-13 days) and three days (range 1-5 days), respectively. Based on light microscopy, the cells exhibited a cobblestone appearance and reached confluence after approximately three weeks following the first protocol and ten days following the second protocol. Population doubling time (PDT) for the best isolate in the first and the second protocol was 29.7 hours and 23.6 hours, respectively. The isolated cells were positive among others for sodium-glucose cotransporter 2 (SGLT2), multidrug-resistant protein 4 (MRP4), organic anionic transporter 1 and 3 (OAT1 and OAT3), organic cationic transporter 2 (OCT2), p-glycoprotein (p-gp), multidrug and toxin extrusion protein 1 (MATE1), and N-cadherin.

Conclusions: In this study, we developed two protocols for isolating and cultivating primary human PTEC from biopsy samples. To the best of our knowledge, we have performed the most extensive systematic characterisation following the isolation of PTEC from the diagnostic kidney biopsy reported.

SA-PO014

Investigating Use of the Biodesix Microsampling Device for Longitudinal Biomarker Studies in Glomerulonephritis (GN) and Renal Transplantation

Kashif J. Anwari, Alan D. Salama. *University College London, London, United Kingdom.*

Background: There has been an increase in the availability of devices allowing home testing of urine, blood and most recently NP aspirates. Biodesix is a lateral flow microsampling device that has been validated in the performance of proteomics, and potentially could be used by patients at home to collect blood and urine, then sent by post for subsequent analysis. We studied whether this device could be used to identify changes in patients with a) GN flares using urine (normalized CD-163) and blood (PR3 antibody and serum-PR3 antigen levels) and b) renal transplant dysfunction (DSA), by comparing with conventional methods of isolating serum and urine.

Methods: Following ethical approval and informed consent, blood/urine samples were obtained from patients with GN (during disease flare and remission) and from renal transplant patients with positive anti-HLA antibodies and CRF >90%. 250uL of sample was placed on a biodesix paper and incubated at room temperature for 5-10 days. The plasma component of the biodesix paper was treated in a standardized manner, reconstituted with 500uL PBS, vortexed for 5 minutes and then centrifuged in 0.45um spin filters for 3 minutes. Samples were analyzed using commercially available ELISA kits and via Luminex (DSA). Biodesix samples were compared with centrifuged blood/urine.

Results: All patients with active GN (n=7) demonstrated raised normalized-CD163 levels with the biodesix device that were comparable with standard urine isolation (p=0.17). Serum and biodesix samples showed concordance with PR3-antibody levels (n=3, p=0.40) and serum-PR3 antigen levels (n=4, p=0.49), and similar results were noted between biodesix samples processed at various time points after blood collection (3, 10 or 90 days). Luminex revealed near identical HLA profiles for biodesix samples vs whole blood in transplant patients (n=4), but MFI values were significantly lower for former.

Conclusions: We have demonstrated that the biodesix device can provide comparable data to standard urine/blood analysis, and potentially be used to identify GN flares and development of de novo DSAs. These devices provide potential benefits including patient convenience, ability to perform more frequent monitoring with earlier detection, and access to a wider patient cohort for biobanking. Further work to validate the biodesix device in these cohorts is required.

SA-PO015

Rapid Loss of Proximal-Tubule-Specific Gene Expression in Primary Culture Associates with HNF4a Downregulation

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Background: Cell culture models are used widely to study the functions of proximal tubule epithelial cells on the implicit assumption that in vitro cell behavior represents in vivo cell function. The advent of tools for transcriptome-wide analysis in culture models has revealed that immortalized cell lines poorly mimic the native proximal tubule. While the dedifferentiation of proximal tubules induced by cell culture has long been appreciated, the dynamics of genome-wide transcription changes accompanying this process have not been described in detail yet are critical to interpret findings in bioengineered and standard cell culture models.

Methods: We isolated proximal tubules from 6-week-old female C57B6 mice by enzymatic and mechanical dissociation followed by gradient centrifugation yielding > 90% proximal tubules. We cultured cells on standard non-porous tissue culture plastic in a standard incubator (37 °C, 5% CO2) in DMEM/F-12 with standard glucose (3.8 g/L) supplemented with low serum (0.5%) and epidermal growth factor (EGF) as representative conditions among the myriad of reported techniques. At various timepoints, RNA was harvested and subjected to bulk RNA sequencing. Cells also were characterized by immunofluorescence staining.

Results: Proximal-tubule-specific genes with more than 15 transcripts per million detected decreased from 77% to 18% after only 4 d. This fraction did not increase with culture duration despite the formation of morphologically mature epithelial structures including typical cuboidal morphology, apical Zo-1 staining, and basolateral sodium potassium ATPase identified by confocal microscopy. Gene set enrichment against the Molecular Signatures Database Hallmark gene sets indicated cultured cells permanently downregulate genes associated with oxidative and fatty acid metabolism within the first 24 h of culture. The transcriptional networks inferred by these changes using ChEA3 point to a central role of decreased HNF4a activity, which itself is silenced by 1 week of culture.

Conclusions: Our results indicate that cultured proximal tubules irreversibly silence most proximal tubule specific genes within just a few days of culture. These findings highlight the need for optimized culture conditions from the moment of isolation.

Funding: NIDDK Support

SA-PO016

AMP-Activated Protein Kinase (AMPK) and TGF-β Alter Cell Size and Morphology in Renal Tubule Epithelial Cells

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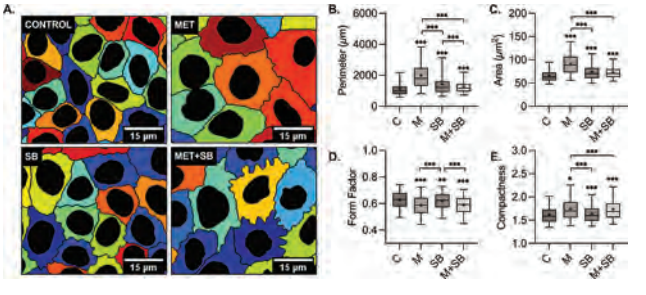
Background: Epithelial barrier function is regulated by tight junction protein complexes (TJ) between adjacent cell membranes. TJ may develop non-linear ruffled or spiked architectures which in turn alter cell morphology. Here we observe that AMP-activated protein kinase (AMPK) and Transforming Growth Factor-β (TGF-β) alter renal tubule epithelial cell (RTEC) morphology and induce a ruffled appearance when administered together.

Methods: Primary human RTEC were obtained from Innovative Biotherapies (Ann Arbor, MI). Cells were maintained in DMEM/F12 and seeded onto polycarbonate cell culture inserts at 100,000 cells/cm^2. After two weeks, cells were apically supplemented with AMPK activator Metformin (200μM, MET), TGF-β receptor I inhibitor SB431542 (10μM, SB), or both. After four weeks, cells were stained for DAPI and ZO-1, and imaged using conventional methods. CellProfiler (Broad Institute) was used to threshold and segment nuclei and cell perimeters. Form factor (FF) was calculated as 4*pi*area/perimeter^2. Compactness index (CI) was calculated as the mean^2 distance between the objects pixels from the centroid divided by area. Statistical significance was assessed by performing 2-way ANOVA using Prism 9 (GraphPad).

Results: In comparison to controls, all treatments increased cell perimeter and cell area. MET increased cell perimeter and cell area, in comparison to SB and combination treatments. All treatments significantly reduced FF and increased CI, respectively.

Conclusions: All treatments increase cell perimeter and area, suggesting cell swelling. All treatments reduce FF, suggesting reduced circularity. All treatments increase CI, which suggests increased irregularity of shape, such as increased cell interdigitation or plasma membrane ruffling.



SA-PO017

Smad4 Knockout Increases NHE3 Expression in Renal Tubule Epithelial Cells In Vitro

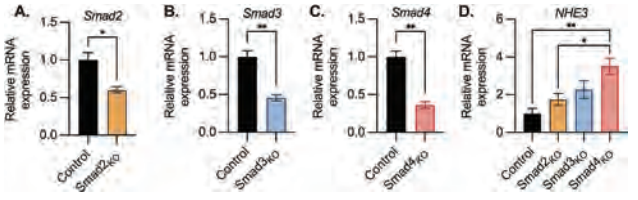
Kuniko Hunter,[1] Harold D. Love,[1] Shuvo Roy,[2] William H. Fissell.[1] The Kidney Project. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]University of California San Francisco, San Francisco, CA.*

Background: Sodium-hydrogen antiporter 3 (NHE3) is a critical indicator of terminal renal proximal tubule epithelial cell (RPTEC) differentiation and accounts for 80% of tubular water reabsorption in vivo. In vitro, RPTEC have reduced NHE3 expression, which limits their functional fidelity. Transforming Growth Factor-β (TGF-β) is a pleiotropic cell signaling pathway, involved in the regulation of epithelial cell fate and plasticity. Canonical TGF-β signaling is mediated by the Smad proteins, Smad2/3/4. Here we observe that knockout of Smad4 increases NHE3 transcription in vitro.

Methods: HEK293 (ATCC, Manassas, VA) were plated at a density of $5x10^5$ in 35mm plates to achieve 60% confluence the following day. Cells were co-transfected with CRISPR sgRNA with PiggyBac (Pb) hygromycin resistance and eGFP vectors and the m7pB hyperactive Pb transposase at a 3:1 ratio using Lipofectamine LTX Plus (Thermo Fisher). For control transfection, cells were transfected with a scramble sequence. 48 hours post-transfection, cells were supplemented with 200μg/mL hygromycin for one week. Cells were passaged once then harvested for RT-PCR analysis.

Results: Smad2, Smad3, and Smad4 knockouts significantly reduced expression of Smad2, Smad3, and Smad4, respectively. NHE3 expression significantly increased with only Smad4 knockout.

Conclusions: Smad4 modulates NHE3 expression in renal tubule epithelial cells.



SA-PO018

Advancing Urine-Based Cell Studies: Introducing the Cell Catcher Device

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Background: Urine-derived cells have gained prominence as a valuable tool for biomedical research and clinical applications due to their non-invasive and repeatable acquisition from patients, in contrast to invasive biopsies. However, the full potential of urine-derived cells remains untapped, due to lack of standardised protocols and reliance on lab-based centrifugation within 4 hours. This study aims to address these limitations by evaluating a novel filtration-based Cell Catcher device, and comparing its efficiency to centrifugation.

Methods: We obtained urine from 18 adults attending a tubulopathy clinic and directly compared the effectiveness of viable cell isolation using either Cell Catcher or centrifugation by using paired analysis.

Results: The results demonstrate that the Cell Catcher device significantly improves the chances of obtaining viable cells, with a 28% increase compared to centrifugation. Furthermore, the device enhances the yield of primary renal cells capable of attachment and proliferation, with a twofold increase compared to conventional methods. The cultured cells showed heterogeneity in terms of cell morphology and expression of renal markers. In all samples, we detected expression of *WT1* and *ENPEP* suggestive of podocyte and proximal tubule cells. Some samples were also positive for *NPHS2*, but not *NPHS1*, *AQP3*, *UMOD* or *UPK3A.*

Conclusions: This innovation in urine processing methods has the potential to revolutionize urine-based cell studies and unlock the vast potential of urine as a non-invasive source of patient-specific cells. Further refinements and investigations are warranted to explore the device's compatibility with different cell types and its potential applications in nephrology, regenerative medicine, and urological cancers.

Funding: Other NIH Support - Kidney Research UK, Commercial Support - Encelo Laboratories Limited

SA-PO019

A Microfluidic Approach for Cardiovascular Risk Stratification in CKD and ESKD Patients

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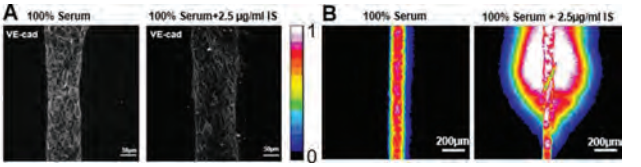
Background: Cardiovascular (CV) complications are responsible for over 50% of the overall morbidity and mortality in CKD and ESKD patients. Surprisingly, conventional cardiovascular risk factors such as hyperlipidemia and obesity are not as predictive of CV complications in the CKD/ESKD population as compared to the general population and statins in particular do not reduce CV events in hemodialysis patients. This so called "reverse epidemiology" is thought to reflect a primacy of uremia induced vascular dysfunction in the pathogenesis of CV complications in this unique patient population. In order to develop novel, real world and holistic markers of uremia induced inflammation, oxidative stress and endothelial dysfunction, we herein report a 3D microfluidic device to quantify the negative effects of uremic serum on endothelial cells.

Methods: HUVECs were seeded in cylindrical channels in collagen I hydrogels to form microvessels (Fig. 1). After 48 h, perfusion media was exchanged from cell culture media to 100% human serum for 24 hours. To mimic the uremic environment, we added pathophysiological levels of indoxyl sulfate (IS) to serum from healthy donors (Fig 1A-B).

Results: Microvessels perfused with serum from healthy donors exhibited distinct, pericellular VE-cadherin staining, while microvessels perfused with serum containing IS displayed diffuse VE-cadherin indicating immature or dysfunctional adherens junction integrity (**Fig. 1A**). Consistent with these observations, microvessels perfused with serum containing IS exhibited marked increase in solute permeability compared to microvessels perfused with healthy serum (**Fig. 1B**).

Conclusions: These results demonstrate a humanized microfluidic device that can be used to assess endothelial dysfunction in response to uremic toxins. We demonstrate high sensitivity of the assay, as IS at concentrations similar to those for CKD-3 patients resulted in significant cytoskeletal and permeability defects, suggesting that this platform could be used to screen for CV risk in CKD/ESKD patients.



SA-PO020

Pulsed Ultrasound of the Splenic Nerve Increases the Splenic Resistive Index in Humans

Faeq Husain-Syed,[1,2] William Nash,[1] Igor Shumilin,[1] Jennie Z. Ma,[1,3] John Hossack,[4] Mark D. Okusa.[1] *[1]University of Virginia Division of Nephrology, Center for Immunity, Inflammation and Regenerative Medicine, Charlottesville, VA; [2]Justus Liebig Universität Giessen Department of Internal Medicine II, Giessen, Germany; [3]University of Virginia Department of Public Health Sciences, Charlottesville, VA; [4]University of Virginia Department of Biomedical Engineering, Charlottesville, VA.*

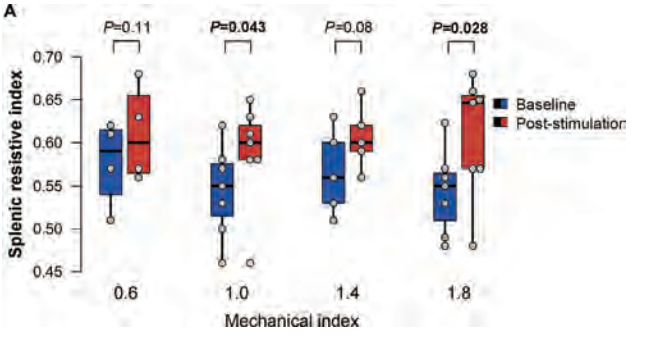
Background: Splenic pulsed ultrasound (pUS) attenuates ischemia-reperfusion injury-induced systemic inflammation and AKI in mice by activating the cholinergic anti-inflammatory reflex pathway (CAP). We aimed to translate the preclinical discoveries to human inflammation and identify clinical parameters for evaluating the efficacy of pUS. Given the dense splenic innervation by sympathetic neurons (SNs) and norepinephrine (NE) release by sympathetic nerve terminals following CAP activation, we hypothesized that NE release post-pUS increases vascular resistance and, hence, the resistive index (RI).

Methods: We analyzed data from an ongoing human pilot study that tests whether pUS within FDA-approved limits of diagnostic medical sonography attenuates inflammation and alters immune cell composition (clinicaltrials.gov; NCT05685108). Healthy adults were exposed to pUS targeting the splenic nerve with varying ultrasound intensities as defined by burst mechanical index (MI). Spectral Doppler ultrasonography was performed before, immediately after, and 24 h after pUS to determine any functional effects.

Results: 23 pUS procedures were performed in 12 subjects (median age, 28 [IQR, 26 to 36] years; median BMI 24 [22 to 27] kg/m^2; 50% male). We observed a significant increase in splenic RI (+0.05 [0.01 to 0.08]; $P<0.001$) and decrease in splenic volume (-8.4 [-23.1 to -1.1] cm^3; $P=0.008$) immediately after pUS, but not in renal RI nor renal volume. The splenic RI increase was accompanied by an increase in the ratio of systolic-to-diastolic flow velocity, and seemed to depend on the magnitude of applied MI (Figure). 24 h post-pUS, the observed splenic changes were no longer detectable (data not shown).

Conclusions: Our preliminary results in humans demonstrate that pUS transiently increases the splenic RI. This novel physiological effect of pUS provides proof of concept that pUS activates SNs. The increase in vascular resistance may serve as a functional clinical measure of pUS and may contribute to the anti-inflammatory effect of CAP activation.

Funding: Other NIH Support - Research reported in this publication was supported by the National Institute of Diabetes and Digestive and Kidney Diseases of the NIH (R01 DK105133 to Mark D. Okusa).



SA-PO021

Fluid Shifts in Septic Shock During Early Hospitalization: A Bioelectrical Impedance Analysis (BIA) Study

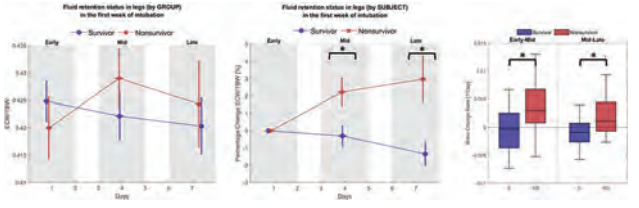
Susie Cha,[1] Jesse E. Diaz Correa,[2] Harold M. Szerlip.[3,4] *[1]InBody, Cerritos, CA; [2]Grupo Renal del Este, Caguas, Puerto Rico; [3]Medical University of South Carolina, Charleston, SC; [4]Baylor College of Medicine, Dallas, TX.*

Background: In the early management of septic shock, aggressive fluid resuscitation is crucial but carries the risk of fluid overload, potentially increasing mortality rates. However, our understanding of fluid distribution and dynamics in the body during this phase is limited. To address this, bioelectrical impedance analysis (BIA) has emerged as an effective tool for monitoring fluid status and guiding treatment decisions in the ICU.

Methods: An observational study was conducted in a university hospital ICU from Feb 2020 to Jul 2021 to assess fluid status in adult septic shock patients. Enrolled patients required mechanical ventilation for respiratory failure. Assessments using the InBody S10, a multifrequency BIA device, were performed at three time points: within 24 hrs of admission, and on days 3 and 7 of ICU stay. Parameters evaluated included extracellular water (ECW) ratio, ECW, intracellular water, and total body water. Fluid status changes were calculated by comparing subsequent measurements to the baseline (day 1). Survival data at 60 days were collected, with 11 survivors and 8 non-survivors.

Results: The study found that most ICU patients had persistent overhydration. Survivors showed a progressive decrease in fluid status, while non-survivors had a temporary increase on day 3, followed by a decrease on day 7, but still elevated compared to the baseline. These fluid fluctuations were mainly driven by changes in ECW, particularly in the legs and trunks. The relative change in fluid status highlighted divergent trends between the groups. Survivors had a sustained decrease of -0.3% and -1.4% on days 3 and 7, respectively, while non-survivors had a sustained increase of 2.2% and 3.0% on days 3 and 7, respectively, with significant differences observed between the groups at those time points. No significant weight change was observed.

Conclusions: Assessing individual changes was crucial due to patient variability. The findings offer insights into fluid shifts and the prognostic implications of BIA parameters in sepsis management, demonstrating its practicality for personalized measurements and informed treatment decisions.



Daily Fluid Change Comparing Survivors and Non-survivors

SA-PO022

A 3D Organ-on-Chip Model of the Collecting Duct for the Study of Electrolyte Disorders

Alessandra Grillo, Chutong Zhong, Keith Siew, Stephen B. Walsh. London Tubular Centre. *University College London Research Department of Renal Medicine, London, United Kingdom.*

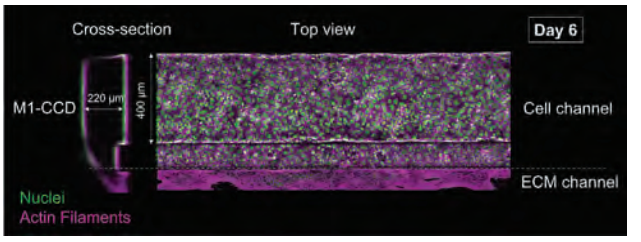
Background: Kidney basement membrane components play a crucial role in the function of different segments of the nephron. For example hensin is an ECM protein that promote transition between α and β intercalated cells, stimulating different mechanisms of action in the collecting duct (CD). Current models using organ-on-chip systems mainly use collagen I, without considering segment-specific compositions. Additionally, most kidney models reproduce proximal tubule systems, with no current 3D model of the collecting duct to study physiological mechanisms *in vitro*. Therefore, the aim of the study is to develop a 3D model of the collecting duct using organ-on-chip system by integrating more biomimetic ECM components and physiological cues.

Methods: M1-CCD cells from collecting duct were cultured on the top channel of a three-lane organ-on-chip systems (OrganoPlate, Mimetas) to produce tubular structures, where the middle channel was filled with a permeable ECM formed by collagen I. Different combinations of collagen I, collagen IV and laminin I were used as ECM scaffold. Human umbilical vein endothelial cells (HUVEC) were seeded on the bottom channel to mimic the renal vascular system in contact with the CD.

Results: M1-CCD showed intrinsic ability to form 3D structures when seeded on low-attachment plates. M1-CCD were then cultured on the OrganoPlate system including different combinations of basement membrane proteins, such as collagen IV and laminin, in addition to collagen I, to create a biomimetic environment for collecting duct epithelial cells. M1-CCD cells successfully formed a tubular structure as shown in Figure. The bottom channel was cultured with endothelial cells and transport of small ions was evaluated between the two channels.

Conclusions: We successfully developed and characterised a 3D *in vitro* model of the collecting duct using the organ-on-chip technology. Further steps include the incorporation of patient urine-derived epithelial and blood-derived endothelial cells to create a more accurate and personalised platform for disease modelling and drug testing.

Funding: Other NIH Support - Kidney Research UK



Tubule of M1-CCD at day 6 on collagen I (Syto16 - nuclei, Phalloidin - actin filaments).

SA-PO023

An Immunoprotective Multi-Channel Kidney Bioreactor for Implantable Renal Replacement

Alonso Torres,[1] Edward Porock,[1] Charles Blaha,[1,2] Nathan Wright,[1] Thomas Sorrentino,[1] Eun jung Kim,[1] Caressa Chen,[1] Tariq M. Haniff,[1] Benjamin W. Chui,[1] Jarrett Moyer,[1] Paul R. Brakeman,[1] H. David Humes,[3] William H. Fissell,[4] Shuvo Roy.[1,2] *[1]University of California San Francisco, San Francisco, CA; [2]Silicon Kidney, San Francisco, CA; [3]University of Michigan, Ann Arbor, MI; [4]Vanderbilt University Medical Center, Nashville, TN.*

Background: Clinical renal replacement therapy for end-stage renal disease should replace the kidney's filtration function and vital endocrine role. Our group engineered single-channel macroencapsulation devices housing silicon nanopore membranes (SNM) to act as renal proximal tubule epithelial cell (RPTEC) bioreactors and implanted these subclinical-scale devices in swine. To approach clinical efficacy, we are developing a scalable multi-channel design of blood-interfacing SNM bioreactors to house increased renal cell mass.

Methods: SNM with an average pore size of 7 nm and total surface area of 21 cm^2 covered with thin Al_2O_3 coatings were plasma bonded in alternating four-channel stack pattern. The stacks were incorporated into polycarbonate housings. Cell inserts were machined from acrylic, epoxied to porous transwell membranes, seeded with 500,000 human RPTEC/cm^2, and inserted into ultrafiltrate chambers of the SNM stack on the opposite side of the blood flow path. Bioreactors (n=3) were anastomosed to iliac vessels and implanted into the retroperitoneum of Yucatan minipigs. No immunosuppression or therapeutic anticoagulation was administered. Vascular angiograms using contrast were performed after a week prior to explant. Live/dead imaging of RPTEC as well as ammonia and calcitriol concentrations were measured from the ultrafiltrate chambers and pig plasma via enzyme-linked immunosorbent assays.

Results: There were no technical complications from the implants and devices were patent at explant. Angiograms showed rapid transit of contrast through the multi-channel bioreactors 7 days after implant. Live/dead imaging showed comparable cell viability in the bioreactor compared to *in-vitro* controls (61.0±5.70% vs 56.0±9.10%). Ammonia concentrations were similar in the pig plasma and bioreactor ultrafiltrate (0.35±0.01E-2 vs 0.36±1.00E-3 mM). Levels of calcitriol were decreased compared to pig plasma (48.0E2±93.0 vs 172.0±21.0 pg/mL).

Conclusions: We demonstrated successful implantation of multi-channel bioreactors with RPTEC for 7 days despite no immunosuppression or anticoagulation. Future directions include improving RPTEC viability and function, conducting a longer temporal study, and scaling up to larger multi-channel devices.

Funding: Other NIH Support - NIH NIGMS IMSD (#R25GM056847-23), Private Foundation Support

SA-PO024

Exposure of Mesenchymal Stromal Cells (MSCs) to INF-γ Boosts the Therapeutic Potency of Their Exosomes (Exos) in the Rescue Therapy of Severe AKI in Rats

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Background: Preclinical and clinical studies have shown MSCs and their Exos to be effective for prevention of AKI. Yet when MSCs are given 48 hrs post-insult, a time when most patients with severe AKI are diagnosed, show them to be ineffective or even detrimental due to the compromised microvasculature. MSCs' are renoprotective by their paracrine release of anti-inflammatory, trophic cytokines and their Exos. Exos signal, post uptake, through the lateral transfer of mRNAs, miRNAs, DNA, proteins, and lipids. We tested here whether priming of human MSCs with INFγ would result in the release of a more potent Exos-based biotherapy in rats with severe IRI AKI.

Methods: (1) 12 sets of hMSCs were culture expanded, then changed to SFM. 6 were exposed ON to 10ng/ml INFγ (*Expt*), and the other 6 to vehicle (*Control*). All Exos sizes and numbers (NanoSite), mRNAs and miRNAs were determined (rtPCR, Rosalind). **(2)** 3 groups of anesthetized adult female Fisher rats (n=6) were subjected to I/R AKI (55 min bilateral renal pedicle clamp) and infused via left carotid artery at 48 hrs post reflow with **(a)** vehicle (1 ml PBS, *Control*), **(b)** Exos harvested from ~2x10e6 hMSCs (Exos), **(c)** Exos harvested from ~2x10e6 INF-g exposed MSCs (*ExptExos*). Each Exos treatment was the equivalent of ~400 mg protein or ~ 2x10e9 particles. Post injury, SCreatinine, and Uprotein/creatinine were assessed at baseline, days 1-10, then monthly x 3.

Results: (1) Exos numbers were comparable in *Expt* and *Control* groups. *ExptExos* were slightly larger than *Controls. ExptExos*' cargo contained both significantly increased immune modulatory mRNAs (IDO-1, CCL8, CXCL9, CXCL10, PD-L1) and 4 anti-inflammatory, angiogenic and anti-apoptotic miRNAs (MiR-548-3P; MiR-548N; MiR-148-3P; MiR-877-5P). **(2)** *In vivo*, Exos therapy with both unexposed and INFg-treated MSCs reduced SCr short and long term vs. control. Only Exos from the INFg group significantly reduced both SCr and UProtein/Creatinine at 3 mos.

Conclusions: Programming of MSCs with INFγ results in the release of Exos that deliver significantly greater renoprotective activities in the compromised microvasculature of severe AKI. We posit, these data have significant clinical promise as rescue therapy in AKI.

Funding: Commercial Support - SymbioCellTech

SA-PO025

Application Myo-Inositol Oxygenase Fluorescent Renal Proximal Tubular-Specific Mitochondrial AKT1 Transgenic Mice in Kidney Disease Research

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Background: Renal tubular AKT1 is activated and translocated into mitochondria upon renal injuries. To determine whether tubular mitochondrial AKT1 (mito-AKT) plays a protective role, we generated a novel transgenic mouse strain harboring inducible mitochondria-targeting constitutively active AKT1 (mcaAKT) driven by the renal proximal tubule-specific promoter.

Methods: The manufacturing process used a bacterial artificial chromosome clone containing mouse *Miox* as the transgene backbone and inserted the IRES-CreERT2-polyA and promoter CAGGS-loxP-GFP-polyA-loxP-MTS-AKT1(308T>D; 437S>D)-3XFLAG-polyA cassettes into the exon 5 and 3' downstream of *Miox,* respectively, using Red/ET DNA recombination technology. The CreERT2 is tamoxifen-inducible Cre recombinase, the GFP is a green fluorescent protein, and the MTS is the mitochondria-targeting sequence. The modified transgenic construct was injected into mouse pronuclei and transferred into a surrogate mother to generate the transgenic mice.

Results: The GFP was expressed ubiquitously and observed by epifluorescence in transgenic mice carrying the transgene. The expression of mcaAKT protein was only detected in the kidneys of tamoxifen (TAM)-injected KMioCAKT but not in corn oil-KMioCAKT mice or TAM-wildtype (WT) mice. The mcaAKT was exclusively expressed in kidneys but not in other organs in TAM-KMioCAKT. Moreover, we confirmed mcaAKT co-localized with mitochondria in the renal tubules with tissue staining. To measure the mitochondrial respiratory capacity, we used the Seahorse XF Analyzer and found significant differences in basal respiration, spare respiration, and ATP-dependent respiration ($p<0.05$) between TAM-KMioCAKT and corn oil-KmioCAKT.

Conclusions: These findings suggest that mitochondrial AKT1 is a renal tube bioenergy regulator. We will continue to explore whether it plays a protective role in renal tubules. These findings shed new light on the application in nephrology research. They may be used to screen for new drugs and develop new strategies for preventing and treating kidney diseases.

Funding: Government Support - Non-U.S.

SA-PO026

Optimizing Free Radical Scavenger-Loaded Kidney-Targeted Polymeric Nanoparticles for Increased Therapeutic Efficacy in CKD

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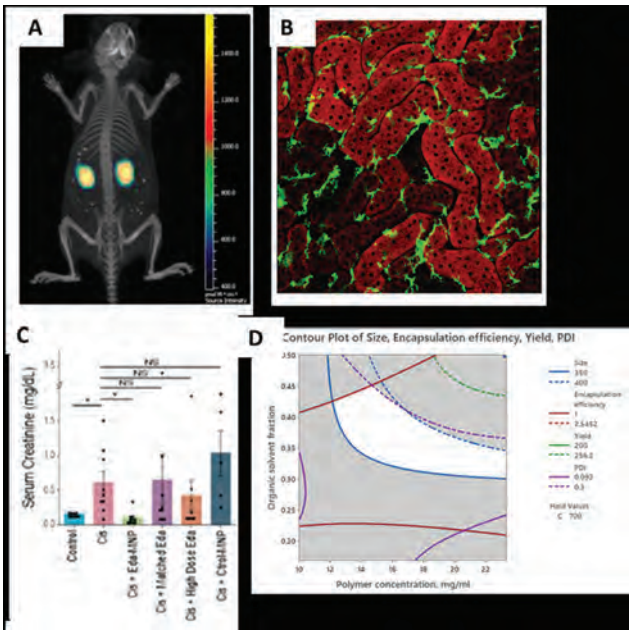
Background: Therapeutic development for renal diseases has been hampered by a lack of poor pharmacological properties by many investigational drugs. To alleviate this bottleneck, our prior studies discovered a polymeric mesoscale nanoparticle (MNP) system capable of targeting the kidneys, specifically the renal proximal tubules. Here, we sought to define MNP formulation characteristics such that the system is robust to delivery of a small molecule cargo while maintaining the appropriate surface chemistry and size necessary for renal targeting.

Methods: We used a quantitative statistical modelling approach based on the Design of Experiments (DoE) to define which drug and particle formulation characteristics allow for MNP renal targeting. We formulated MNPs with the FDA-approved ROS scavenger edaravone and a biocompatible, FDA-approved polymer made of poly(lactic-co-glycolic acid) coated with polyethylene glycol (PLGA-PEG).

Results: We found that MNP formulation parameters control the ability to target the renal proximal tubules and modifications allow for robust production of MNPs with varying therapeutic cargoes. Specifically, polymer concentration and solvent ratios allow mesoscale formulation and optimization of drug cargo loading for therapeutic drug delivery to the kidney.

Conclusions: Ongoing studies are aimed at using these formulation parameters to incorporate increased therapeutic cargo and their ability to ameliorate hypertensive chronic kidney disease.

Funding: Other NIH Support - CA132378



a) MNP localization to the kidneys in mice. b) MNPs (red) in mouse kidneys. C) Edaravone-loaded MNPs successfully ameliorate cisplatin-induced acute kidney injury. d) Contour plot from DoE indicating the appropriate formulation parameters to obtain kidney-targeted MNPS (in white).

SA-PO027

Racial and Ethnic Differences in Incident CKD in US Veterans

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Background: Despite a well-documented higher incidence of end-stage kidney disease among racial and ethnic minorities compared to White adults, less is known about the incidence of earlier-stage chronic kidney disease (CKD) by race and ethnicity. We examined risks of incident CKD among veterans of various racial and ethnic groups in the US Veterans Health Administration (VHA).

Methods: The cohort included 1,883,779 veterans with the first occurrence (index date) of the estimated glomerular filtration rate (eGFR) between 60 and 100 mL/min/1.73m^2 (based on the 2021 CKD-EPI equation) during 2003-2015, followed through May 2018. Veterans who had a prior eGFR <60 mL/min/1.73m^2 or were in VHA for <2 years prior to the index date were excluded. The outcome was incident CKD (CKD stage G3 or higher) defined as the first time when follow-up eGFRs decreased to <60 mL/min/1.73m^2 for >3 months. We examined hazard ratios (HR) of incident CKD, censoring for death, by racial and ethnic groups compared to the non-Hispanic White group.

Results: At the index date, the average age was 56 years overall, with Black veterans being the youngest (51 years) and White veterans the oldest (58 years). Average eGFR was 85 mL/min/1.73m^2 for Black veterans and 87-89 mL/min/1.73m^2 for other groups. Overall, after adjusting for age, sex, index year, and baseline eGFR, compared to Whites, the adjusted risk of incident CKD was 53% greater for Blacks and 3-9% greater for other race groups (Table). For subgroups of baseline eGFR 90-100 and 60-89 mL/min/1.73m^2 and those with available data on urine albumin-to-creatinine ratio (UACR) ≥30 mg/g, Black veterans exhibited consistently greater risks of CKD (29% to 81% greater) while other groups varied depending on the subgroup.

Conclusions: Racial and ethnic minority veterans had a greater risk of CKD, as defined by eGFR, compared to their White peers. Enhanced screening programs for racial and ethnic minority adults to detect early stages of CKD is warranted.

Funding: NIDDK Support

Adjusted HRs (95% CIs and p values) of incident CKD by racial and ethnic groups compared to Whites

Race and ethnicity (N in the overall cohort)	Overall cohort (n=1,883,779)		Subgroup of baseline eGFR 90-100 (n=925,980)		Subgroup of baseline eGFR 60-89 (n=957,799)		Subgroup of baseline UACR ≥30 mg/g (n=39,192)	
American Indian/Alaska Native (n=13,521)	1.07 (1.00-1.14)	0.059	0.91 (0.80-1.05)	0.20	1.12 (1.04-1.22)	0.003	0.85 (0.69-1.07)	0.16
Asian, Native Hawaiian/Pacific Islander (n=28,267)	1.03 (0.98-1.08)	0.19	0.98 (0.89-1.08)	0.69	1.04 (0.99-1.10)	0.094	1.07 (0.92-1.24)	0.41
Black (n=343,571)	1.53 (1.51-1.55)	<0.0001	1.81 (1.76-1.86)	<0.0001	1.46 (1.44-1.48)	<0.0001	1.29 (1.21-1.36)	<0.0001
Hispanic (n=117,279)	1.07 (1.05-1.10)	<0.0001	1.02 (0.97-1.07)	0.45	1.10 (1.06-1.13)	<0.0001	1.04 (0.96-1.12)	0.36
Multiple or other races (n=32,474)	1.09 (1.04-1.13)	0.0002	1.13 (1.05-1.23)	0.002	1.07 (1.01-1.12)	0.012	0.96 (0.79-1.16)	0.65
White (n=1,348,667)	Reference		Reference		Reference		Reference	

SA-PO028

Facility-Level Variation in Care of Veterans with Urinary Stone Disease

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Background: Urologic care after kidney stone procedure presents an opportunity to implement stone prevention measures, but the frequency of urologic follow up and stone prevention measures are not known. We studied variation in urology visits and stone prevention measures within 6 months after a urinary stone procedure.

Methods: We used data from the Veterans Health Administration (VHA) to identify patients from 97 facilities who had a stone procedure between 2016 and 2018. We constructed multilevel regression models to estimate Median Odds Ratio (MOR) for facility-level variation for urology follow up visits and stone prevention measures. The base model was a random intercept for facility. The 2nd model was adjusted for patient covariates (age, sex, race, driving distance to nearest VA, comorbidities). The 3rd model was adjusted for patient and facility characteristics (geographic region, complexity). We used MOR to quantify facility-level variation and variance partition coefficient (VPC) to quantify the sources of unexplained variation.

Results: Our cohort included 24,057 Veterans who were predominantly white (78.7%) and male (93.8%), with a mean age of 63.8 years. Within 6 months of stone procedure, 93.8% had urology follow-up, 7.4% completed 24-hour urine testing, 7.8% had serum PTH measurement, and 26.2% received stone-related medications. The fully adjusted MOR for urology follow-up, 24-hour urine testing, PTH measurement, and medication prescriptions was 1.59, 1.98, 1.40 and 1.20 respectively. The fully adjusted VPC was 0.19, 0.33, 0.11 and 0.03 respectively.

Conclusions: Sizable variation exists in stone disease care across VHA facilities. Variation due to between-facility differences was higher for 24-hour urine testing (33%) and urology follow-up (18.6%) and lower for PTH measurement (10.8%) and prescription of stone-related medications (3%). Variation across facilities was 1.6-fold in rates of urology follow-up, 2-fold in rates of 24-hour urine testing, 1.4-fold in obtaining PTH levels, and 1.2-fold in stone-related medication prescriptions. There is a need for standardization of urinary stone disease care across facilities. More work is needed to establish clear guidelines for stone prevention and the factors underlying variation in stone prevention care in the VHA and civilian healthcare systems.

Funding: Veterans Affairs Support

SA-PO029

Risk of ESKD and Death Among Homeless Veterans with Incident CKD

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Background: Chronic kidney disease (CKD) requires comprehensive management to limit disease progression, a particular challenge among the homeless. We evaluated the risk of end-stage kidney disease (ESKD), defined by transplant or dialysis requirement, and death among homeless veterans with incident CKD in the US Veterans Health Administration (VHA).

Methods: Incident CKD was defined as the first time estimated glomerular filtration rate (eGFR) decreased to <60 mL/min/1.73 m^2 for >3 months. We excluded veterans with <2 years of VHA care prior to diagnosis of incident CKD or those with pre-existing ESKD. Homelessness was defined using VHA specific codes and/or ICD diagnosis codes for homelessness recorded ≥1 time during the 2 years prior to incident CKD. Cox proportional hazards models examined the association between homeless status and risk for ESKD and death.

Results: An incident CKD cohort of 836,361 veterans were identified from 2005-2017, with follow-up through 2018. A total of 46,561 veterans (6%) were identified as homeless. In a model adjusted for age, sex, race, incident CKD year and eGFR, homelessness was significantly associated with a 6% increased risk of ESKD and a 46% increased risk of death. Further adjustment for variables that may be both a cause and consequence of homelessness (body mass index, comorbidities, use of renin-angiotensin-aldosterone system antagonists and statins, behavioral factors) attenuated findings for both outcomes. Therefore, the abovementioned factors may in part explain the observed associations between homelessness and ESKD and death.

Conclusions: The hazard for ESKD or death is significantly higher among homeless veterans compared to thosenot experiencing homelessness, and the increased risk is partly driven by modifiable factors. These findings emphasize the importance of housing and comprehensive health care in addressing the difficulties in CKD management among homeless veterans.

Funding: Other NIH Support - WY, AKC, KN and GY are partially funded by NIH 1R01DK112008., Veterans Affairs Support, Other U.S. Government Support

Hazard Ratios and 95% Confidence Intervals for the Association Between Homeless Status and ESKD or Death Among Adult Veterans

	Model 1	Model 2	Model 3
Kidney failure	1.91 (1.83-1.99)	1.15 (1.10-1.20)	1.06 (1.02-1.11)
Death	1.01 (1.00-1.03)	1.48 (1.46-1.50)	1.46 (1.44-1.48)

Model 1: unadjusted; Model 2 adjusts for age, sex, race, incident year; Model 3 additionally adjusts for eGFR;

SA-PO030

Implementing a Successful Tele-Nephrology Program for Rural Veterans

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Background: Rural Veterans experience increased morbidity and mortality as a result of chronic kidney disease (CKD) and refractory hypertension. Nephrologists usually practice in urban, acute-care facilities and decreased access to specialist care likely contributes to poorer outcomes in rural Vaterans.

Methods: We established a Tele-Nephrology Hub & Spoke Network (TNN) to provide care to rural facilities. Hub nephrologists reviewed the medical record and provided video-based visits to spoke sites in Maine, New Hampshire, Indianapolis, Oklahoma, Montana, and Colorado. Where possible, hub staff trained a local advanced practice provider (APP) to triage consults and manage emergencies. To understand barriers and facilitators to TNN implementation, we conducted semi-structured interviews with clinicians at five spoke sites. We used the Reach, Effectiveness, Adoption, Implementation and Maintenance (RE-AIM) framework to develop our interview guide. Interviews were conducted using Microsoft Teams and qualitative data was analyzed using open thematic analysis. Results are presented according to each major RE-AIM dimension.

Results: Reach: Rural and highly rural Veterans were seen at all spoke sites. Veterans were given the option of seeing a local and/or tele-provider. Adoption: Adoption was more successful when facilities had a local APP. Local APPs were quickly able to triage consults and address emergencies independently. Where APP were not available, more reliance was placed on hub providers. Implementation: The TNN was successfully implemented at each facility, with >50% of consults being addressed through telenephrology. Maintenance: A telenephrology champion organized the program. Across nearly every interview, the telenephrology champion was mentioned as a critical reason for program success. We anticipated finding that sites had challenges with technology or that Veterans were uncomfortable with remote care but neither of these issues emerged during interviews. We found that the Covid-19 pandemic served as an excellent introduction to telehealth and so there was little anxiety about receiving care from remote nephrologists.

Conclusions: In conclusion, establishing a TNN improved access to specialist care for rural veterans. A telenephrology champion and local APPs with renal training facilitate program adoption and expansion.

Funding: Veterans Affairs Support

SA-PO031

Interaction of Race and Treatment with GLP1-RA, SGLT2i, and Insulin on Mortality in Veterans with Type 2 Diabetes Mellitus (T2DM) and CKD

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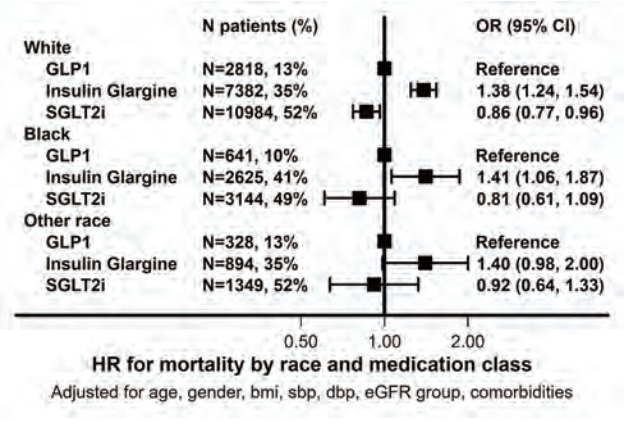
Background: Racial disparities in the use of anti-glycemic medications have been reported but it is unclear whether there is an interaction between diabetic medications and race on mortality.

Methods: In an active comparator, new user design study of veterans (N = 30165) with T2D with CKD (eGFR < 60) on metformin who then initiated on IG or SGLT2i or GLP1-RA for the first time between 01/01/2018 to 12/31/2021, we 1. examined racial disparities in initiation of these agents and 2. the mortality associations of each of these agents with Black, White and Other races.

Results: Mean age was 71 years, mean baseline eGFR 49.5 ml/min/1.73m2. Compared to White veterans, Black veterans were less likely to be prescribed GLP1-RA's (OR 0.69, CI 0.63-0.77), were more likely to be prescribed insulin glargine (OR 1.11, CI 1.04-1.19), and were similarly prescribed SGLT2i's (OR 1.05, CI 0.99-1.12). There were 4,660 deaths over 80,043 patient-years in the entire cohort. Compared to GLP1RA, insulin glargine was associated with increased mortality in both Blacks and Whites (Figure)

Conclusions: Even though there are racial disparities in prescription of insulin glargine, race does not appear to modify the increased mortality associated with insulin glargine compared to GLP1RA.

Funding: Veterans Affairs Support



SA-PO032

Factors Influencing SGLT2i Utilization in an Inner-City Public Hospital

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Background: Sodium-glucose cotransporter-2 inhibitors (SGLT2i's) remained underutilized in chronic kidney disease (CKD) patients despite their renoprotective benefits. We present the factors associated with SGLT2i prescription in a public hospital in New York City.

Methods: Cross-sectional analysis of adult primary care patients at Jacobi Medical Center, Bronx, NY was done from Jan 2022 to Dec 2022. The sample included patients with CKD and Type 2 Diabetes Mellitus (T2DM). Exclusion criteria were no medication list and eGFR<20 mL/min/1.73 m^2. Descriptive statistics and logistic regression analysis were performed using STATA 18 (StataCorp).

Results: Among 2307 eligible patients, SGLT2i prescription rate was 14%. After controlling for gender, age, and subspecialty follow-up, no significant association was found between the prescription of SGLT2i and the patient's race, language, or coexisting comorbidities/complications. Please see Table 1 for the odds ratios of different significant variables.

Conclusions: Women were found to be prescribed less SGLT2i than men, perhaps due to side effects that affect women not identified in this study. Patients without insurance or with public insurance were more likely to be prescribed. As the drug can be dispensed in our hospital pharmacy for the uninsured as opposed to the need for an onerous prior authorization process for those with insurance; public insurances usually do not require prior authorization. Subspecialized services and hospital physicians increased the likelihood of SGLT2i prescription, perhaps reflecting the higher level of evidence-based application in a teaching hospital. By understanding these factors, we can strategize to enhance the utilization of this class of medications.

Table 1. Logistic Regression

	OR	SE	z	p-value	95% CI
Gender					
Male (Ref.)					
Female	0.68	0.09	-2.78	0.00	0.52-0.89
Primary Care Provider					
No PCP (Ref.)					
Advanced Practitioner	1.96	0.76	1.74	0.08	0.91-4.21
Hospital Resident	2.46	0.85	2.60	0.00	1.24-4.87
Outside Provider	1.29	0.62	0.54	0.59	0.50-3.34
Hospital Attending	2.54	0.89	2.67	0.00	1.28-5.05
Insurance Type					
Private (Ref.)					
Public	1.37	0.20	2.18	0.02	1.03-1.83
Non on File	2.01	0.55	2.53	0.01	1.16-3.45
Nephrology Follow up					
No (Ref.)					
Yes	2.33	0.35	5.61	0.00	1.73-3.13
Cardiology Follow up					
No (Ref.)					
Yes	3.61	0.47	9.77	0.00	2.79-4.67

Prob > Chi^2= 0.000
Pseudo R2= 0.086
n= 2,307

PCP= Primary Care Provider Ref.=Reference OR=Odds Ratio SE= Standard Error z= Z-Score

Table 1. Logistic Regression SGLT2i Prescription

SA-PO033

High Prevalence of Diabetes and Kidney Disease in Areas of Chicago Historically Subjected to Housing Discrimination Laws (Redlining)

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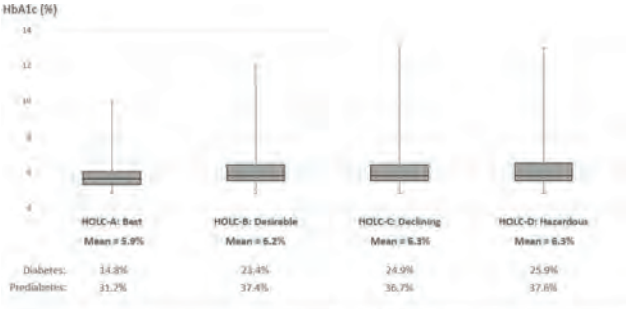
Background: In 1940, Home Owners' Loan Corporation (HOLC) produced a map of Chicago, IL as a safety investment guide for mortgage lenders. The areas labeled "hazardous" reinforced racial residential segregation with lasting patterns of inequality continuing today. We hypothesize that individuals residing in these "less desirable" neighborhoods continue to face numerous challenges contributing to the development and progression of kidney disease, including a higher prevalence of diabetes.

Methods: Using 2022 Labcorp data from ~400K laboratory tests from individuals residing in previously mapped HOLC districts, we spatially joined results to each category (A: Best, B: Desirable, C: Declining, and D: Hazardous). We examined results for both kidney disease indicators (eGFR <60 ml/min/1.73m^2 and urine albumin to creating ratio >30 mg/g), as well as HbA1c to examine potential diabetes (HbA1c ≥6.5%) and prediabetes (HbA1c of 5.7%-6.4%). The odds of kidney disease, diabetes, and prediabetes by HOLC grade were assessed by logistic regression, adjusting for age and sex.

Results: Individuals who live in HOLC-A neighborhoods (<1%) were older with a higher proportion of males than the other HOLC categories, which were more similar in demographic characteristics (53 years vs. 48 years and 42.3% vs. 40.8% male). Mean HbA1c was higher in HOLC grades B-D vs A, with correspondingly higher rates of potential diabetes and prediabetes. After adjusting for differences in age and sex, the odds of all three outcomes were significantly higher in HOLC grades B-D, compared to HOLC-A (p<0.0001).

Conclusions: Significant associations were seen between historically redlined areas and the odds of diabetes, prediabetes, and kidney disease. It is imperative to both understand the mechanisms underlying these observations and to develop place/person-centered intervention programs to mitigate the effects of these disparities.

Funding: Other U.S. Government Support



Outcome	Adjusted OR (95% CI)			
	HOLC-A	HOLC-B	HOLC-C	HOLC-D
Diabetes	1.00 (ref)	2.27 (1.88-2.73)	2.75 (2.29-3.30)	2.58 (2.15-3.10)
Prediabetes	1.00 (ref)	1.36 (1.18-1.56)	1.37 (1.20-1.58)	1.36 (1.18-1.56)
Kidney Disease	1.00 (ref)	1.43 (1.24-1.66)	1.40 (1.21-1.61)	1.49 (1.29-1.73)

* Adjusted for age & sex, all p<0.0001

SA-PO034

Individual vs. Neighborhood-Level Social Determinants of Health and ESKD Mortality

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Background: Social determinants of health (SDOH) have a substantial impact on disease morbidity and mortality. Neighborhood-level SDOH indices are increasingly being used for clinical risk prediction and resource allocation to improve health equity. However, whether neighborhood-level SDOH are independently associated with mortality among incident end-stage kidney disease (ESKD) patients is unknown.

Methods: We identified patients with incident ESKD admitted to the Rogosin Institute, a New York City-based non-profit dialysis organization, and excluded patients with missing Social Vulnerability Index (SVI) and acute kidney injury requiring dialysis. We used Cox regression to generate four nested prediction models for mortality. Model 1 adjusted for age, sex, and race and ethnicity. Model 2 additionally adjusted for primary cause of ESKD and 31 Elixhauser comorbidities. Model 3 additionally adjusted for individual SDOH (marital status and employment). Model 4 additionally adjusted for census tract-level SVI, which incorporates Census variables of socioeconomic status, household composition and disability, minority status and language, and housing type and transportation.

Results: Of 3,585 patients with incident ESKD, the median age was 62 (IQR 50 – 73). A total of 56% were male, 37% non-Hispanic Black, 24% non-Hispanic White, 15% Hispanic, and 14% were Asian. The mortality prediction model containing age, sex, and race and ethnicity had a Harrell's C-statistic of 0.7028. Adding cause of ESKD and comorbidities improved prediction performance (Harrell's C 0.7585, likelihood ratio

[LR] test p<0.001). Individual SDOH also improved prediction performance (Harrell's C 0.7652, LR test p<0.001). Census tract-level SVI and SVI themes did not improve mortality prediction (Harrell's C 0.7653, LR test p = 0.645).

Conclusions: Neighborhood-level SVI did not improve mortality prediction in a diverse cohort of incident ESKD patients in New York City, independent of demographics, comorbidities, and individual-level SDOH. Neighborhood-level SDOH indices may have limited utility to predict clinical outcomes in the ESKD population.

SA-PO035

Health Inequalities in Kidney Disease: Meeting the Urgent Need to Identify Early Disease in High-Risk Communities (HIDDEN-CKD): A Feasibility Study

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Background: There is a global epidemic of chronic kidney disease (CKD) and people of ethnic minority groups and those living with socioeconomic deprivation are disproportionately affected. Peer educators (PEs) are members of target demographic groups and provide culturally congruous education and support. HIDDEN-CKD explored the feasibility of using PE led kidney health screening events in South East London to increase the reach, equity and acceptability of routine healthcare interventions to identify early disease in African and Caribbean communities.

Methods: Stage 1: Public engagement to co-develop culturally appropriate CKD materials **Stage 2:** PE recruitment and accredited training; engagement with local faith and non-faith community leaders **Stage 3:** Events were held in African and Caribbean faith and non-faith based community settings; following an educational session people were invited to consent to the study and demographic and medical details, blood pressure, body mass index and urinary albumin creatinine ratio (uACR), (measured by smart-phone analysis) were collected. Culturally tailored information and peer support were available throughout and after testing. **Stage 4**: All participants individually followed up by phone and supported to seek medical attention where appropriate. **Stage 5:** Quantitative analysis of uACR results.

Results: We have trained 30 PEs, who have performed 305 uACR semi quantitive tests in community settings to date. The majority of participants were black African or black Caribbean (n= 228, 75%; n = 29, 10% respectively), female (n = 163, 53%) and had no known medical history (n=128, 49%). 164 (54%) tests were ACR >3mg/mmol and 24 (8%) >30mg/mmol.

Conclusions: People from African and Caribbean communities appear to be willing to participate in PE led community CKD screening, and high rates of albuminuria are detected. Further qualitative and longitudinal work is underway to assess acceptability and to confirm CKD diagnosis. This approach may provide a new opportunity to reduce health inequalities.

SA-PO036

Social Deprivation Index and Kidney Failure Replacement Therapy (KFRT) Risk Among 2.5 Million Patients

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Background: Neighborhood-level social determinants of health (SDOH) are known to influence kidney disease risk. However, limited SDOH data are available from large, multi-ethnic, national samples with measured risk factors. We aimed to determine the extent to which place-based measures of SDOH relate to KFRT risk, and whether the associations vary by race/ethnicity.

Methods: We studied 2,536,627 patients in the Optum Labs Data Warehouse. Social deprivation index (SDI, deciles 1 to 10 as a composite measure of poverty, education, employment, home rental & crowding, single-parent households and no car ownership, with 10 representing the most deprived status) was geocoded at the zip code level. Cox models quantified the adjusted relative hazard of incident KFRT defined using hospitalization billing codes overall, and stratified by race/ethnicity (as coded in the electronic health record).

Results: Patients were a mean age of 52 years, 57% were female, 9.8% were Black and 4.3% were Hispanic persons; most were insured (76% commercial, 16% Medicare, 2.6% Medicaid, 2.4% uninsured and 0.8% other type). Median SDI differed by race/ethnicity, with Black and Hispanic patients having markedly higher social deprivation. SDI was associated with risk of KFRT in all models overall and across race/ethnicity groups.

Conclusions: Social deprivation is consistently associated with KFRT risk even after adjustment for established risk factors. The unequal distribution of SDI by race/ethnicity likely reflects both present and past influences, including structural racism.

Funding: NIDDK Support, Private Foundation Support

Table. Hazard ratios (95% CI)* of kidney failure replacement therapy (KFRT) in relation to social deprivation index (SDI) per 5 deciles, overall and by race/ethnicity

	All Patients*	White Patients	Black Patients	Hispanic Patients	Asian Patients	Other/ Unknown Patient Race
Events N Patients (%)	6334 2,536,627 (100%)	4106 2,006,085 (79%)	1524 248,341 (9.8%)	404 108,865 (4.3%)	107 60,722 (2.4%)	193 112,614 (4.4%)
SDI, median (IQR)	4 (2-7)	4 (2-6)	8 (5-10)	6 (3-9)	3 (2-6)	4 (2-7)
Adjustment variables:						
Age, sex	**1.70 (1.55, 1.87)**	**1.37 (1.26, 1.49)**	**1.27 (1.15, 1.41)**	**1.38 (1.11, 1.17)**	1.80 (0.85, 3.79)	**2.47 (1.80, 3.39)**
Age, sex, eGFR, ACR**	**1.21 (1.12, 1.31)**	**1.17 (1.07, 1.27)**	1.16 (0.98, 1.36)	**1.28 (1.02, 1.61)**	1.70 (0.69, 4.18)	**1.54 (1.10, 2.16)**

*Bold indicates p<0.05

** 2021 CKD-EPI eGFR modeled with splines at 60 and 90 and ACR modeled on the log scale so this model includes a re-fit Kidney Failure Risk Equation (KFRE) to this population

SA-PO037

Population Impact of Social Determinants of Health on Premature Death Among US Adults with CKD

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Background: Social determinants of health (SDOH) are important underlying components of population health and are associated with adverse outcomes among patients with chronic kidney disease (CKD). However, the US population-level impact of SDOH on premature death among adults with CKD is unknown.

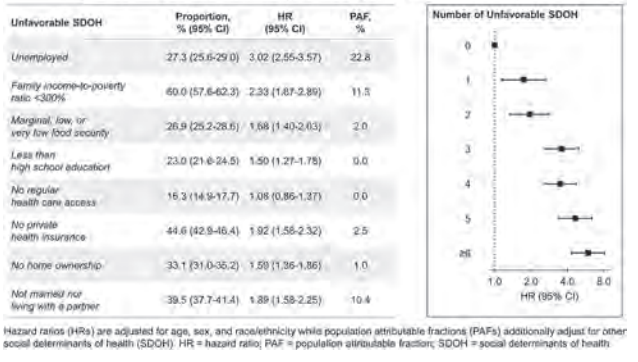
Methods: A nationally representative sample of individuals aged 20-74 from the US National Health and Nutrition Examination Survey (NHANES) 1999-2018 were included. We selected those with CKD defined as estimated glomerular filtrate rate <60 ml/min/1.73 m^2 and/or urinary albumin-creatine ratio ≥30 mg/g. Self-reported SDOH were collected in each survey cycle (Figure). Deaths were ascertained from linkage to the National Death Index through 2019. Multivariable Cox proportional hazards regression and average population attributable fractions were used to investigate the contributions of SDOH to population-level premature all-cause mortality. All analyses accounted for the complex survey design.

Results: A total of 8422 individuals aged 20-74 years with CKD were included (11.0% weighted population prevalence). Mean survey-weighted age was 52.6 years and 55.3% were women. During a mean 8.6-year follow-up, 1252 deaths were recorded. After adjustment for age, sex, and race/ethnicity, all SDOH were significantly and independently associated with higher all-cause mortality and accounted for substantial portions of the US population mortality burden (Figure). Furthermore, dose-response associations were observed between the cumulative number of unfavorable SDOH and premature death, with having six or more unfavorable SDOH increasing mortality 6-fold.

Conclusions: SDOH were strongly and independently associated with premature death among US adults with CKD, and accounted for 50% of premature deaths in this population. Innovative structural policy interventions are urgently needed to prevent adverse events associated with SDOH among patients with CKD.

Funding: Other NIH Support - National Institute of General Medical Sciences (P20GM109036)

Figure. SDOH and premature all-cause mortality in US adults aged 20-74 years with chronic kidney disease.



Hazard ratios (HRs) are adjusted for age, sex, and race/ethnicity while population attributable fractions (PAFs) additionally adjust for other social determinants of health (SDOH). HR = hazard ratio; PAF = population attributable fraction; SDOH = social determinants of health

SA-PO038

Impact of Race-Free Estimated Glomerular Filtration Rate (eGFR) on Racial Disparity in Receiving Timely Outpatient Nephrology Care

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Background: In 2021, an international taskforce of kidney experts recommended implementation of a revised formula for estimated glomerular filtration rate (eGFR) that removes the race variable. Differences in eGFR and chronic kidney disease (CKD) stage

have been reported for Black patients following implementation of the new CKD-EPI 2021 formula. However, the impact of the new equation on care and referral disparities is not well understood.

Methods: We conducted a retrospective cohort study of all adult patients referred to Indiana University Health outpatient nephrology clinics during a two-year period surrounding the change in eGFR formula. To analyze the impact of the new formula, we performed a multivariate linear regression with eGFR as the dependent variable, and sex, self-reported race, age, timeframe, BMI, and an interaction term between race and timeframe as covariates.

Results: 812 patients met our criteria for analysis. Multivariate linear regression revealed that mean eGFR was statistically influenced by sex, race, age, and implementation of the new formula. Mean eGFR increased by 5.9 mL/min/1.73m2 (95% CI: 0.3, 11.4) for all patients after implementation of the new formula. However, the analysis revealed no evidence that the racial disparity in mean eGFR at the time of the first visit with nephrology was significantly influenced by the formula change (-3.7, 95% CI: -10.1, 2.7). Mean eGFR at the first visit was 6.7 mL/min/1.73m2 (95% CI: 2.4, 10.9) lower for Black patients compared to non-Black patients across the entire study period.

Conclusions: A general trend of increased mean eGFR across all patients after the equation change indicates earlier overall referrals to nephrology. Despite this improvement, our analysis did not reveal a significant change in the existing disparity in timely referral to nephrology observed between Black and non-Black patients. Black patients still had a lower mean eGFR at the initial visit to nephrology when compared to non-Black patients after implementation of the new eGFR formula, suggesting a persistent delay in referral to nephrology for Black patients.

SA-PO039

Combatting CKD: Kidney Health Screenings Through the Kidney Disease Screening and Awareness Program at the University of Virginia

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Background: The Kidney Disease Screening and Awareness Program (KDSAP) was initially founded with the goal to increase awareness about chronic kidney disease (CKD) in the community through education and free kidney health screenings. The KDSAP chapter at the University of Virginia (UVA) was founded in 2021 to bring these initiatives to members of the Charlottesville area.

Methods: The Diversity, Equity, Inclusion, and Community Health Grant funds KDSAP at UVA through the UVA Department of Medicine. In the spring of 2023, KDSAP at UVA hosted its first kidney health screening at Mt Zion First African Baptist Church. The screening is run by volunteers, organized by undergraduate students, and supported by medical students, residents, fellows, and physicians. Participants proceeded through 8 stations within 30 minutes: registration, form filling, urinalysis, BMI, blood glucose, blood pressure, physician consultation, and exit survey. We performed a descriptive analysis amongst screened membersself-reproted racial representation. Descriptive data is reported as numbers (n). The reported race/ethnicity was: White/Non-Hispanic White, Black, Asian, Hispanic or Latin(o), and not reported.

Results: 34 community members were screened during the inaugural KDSAP at UVA kidney health screening. 15 participants were referred to follow-up with nephrology due to abnormal results from: urinalysis, blood pressure, or blood glucose. With regards to racial representation amongst folks screened are outlined in the table.

Conclusions: KDSAP at UVA is the first organization to be led by undergraduate students in collaboration with the UVA Department of Medicine for kidney health-related community outreach to underserved populations. We screened 58.8% African americans, 26% Asians, 2% hispanic or latin(o), 8% white population. Continued efforts to host more kidney health screenings in different locations in Charlottesville, targeting at-risk communities, will forge a future of increased kidney disease awareness and early detection.

Race	Male	Female
African American	11	9
Asian	6	3
Hispanic/Latino	1	0
White	2	1
Not Reported	0	1

SA-PO040

A Trauma-Informed Approach to Address Systemic Racism in Outpatient Clinics

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Background: The primary objective of this project is to mitigate perceptions of racism noted among Black Veterans with kidney disease at the Crescenz VA Medical Center (Philadelphia). Understanding that racism can be traumatic, we hypothesized that a trauma-informed care intervention to address systemic racism would reduce perceptions of racism, improve trust in our healthcare system, and lead to improvements in overall health (*e.g.*, reduction in no-show visits).

Methods: Informed by the Center for Health Care Strategies, we developed a multi-level intervention: provider training, environmental scan (health equity walkthrough), developing a patient advisory board, and creating a referral pathway for racial trauma. We provided two 60-minute workshops to clinicians. We provided a framework to define interpersonal discrimination from structural racism and tools to help center Black Veterans and their experience with systemic racism. The training provided guidance to create an inclusive environment during clinical encounters. Clinicians were surveyed to evaluate the acceptability and feasibility of the surveys. We conducted a "walkthrough" of the Renal clinic to assess how the clinic infrastructure could be redesigned to be more inclusive for all Veterans. A health equity researcher, led the walkthrough and invited Veterans and clinicians to conduct their own walkthroughs of the clinic. Findings were compiled to generate action items to improve the clinic infrastructure.

Results: Eight clinicians (42%) attended the 2 workshops conducted in November 2022. The clinicians included 5 advanced practice providers and staff, 2 MDs, and 1 social worker. Five participants completed the surveys, all of whom ranked the workshop quality as "high" (on a scale from "very low" to "very high") and noted they would recommend the training to others. Participants "completely agreed" that the workshop was appropriate to education, experience, and skill level. All "agreed" or "completely agreed" to use the information and skills provided by the workshop during clinical encounters with their patients.

Conclusions: Our pilot demonstrates that 1) it is feasible and acceptable to deliver trauma-informed care training to clinicians to help address perceptions of systemic racism in clinics and 2) health equity walkthroughs can generate action items to expand inclusivity in healthcare settings.

Funding: Veterans Affairs Support

SA-PO041

Advancing Excellence in Diversity, Equity, and Inclusion: A Concept Map for Development of a DEI Chief Fellowship in Nephrology

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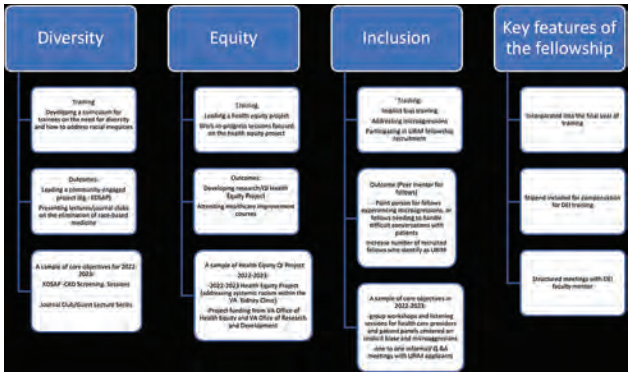
Background: Despite decades of attempts to recruit and retain a diverse physician workforce that better represents the patients we serve, inequities in medicine persist. In keeping with the 2021 Executive Order to advance racial equity, the University of Pennsylvania's Renal-Electrolyte & Hypertension Division developed the DEI Chief Fellowship program to provide training and a leadership role to fellows interested in advancing excellence in DEI. This abstract describes a concept map of the core components of the DEI chief fellowship.

Methods: Through stakeholder feedback and a review of the AAMC DEI competencies, we developed a concept map outlining the core trainings and objectives of the DEI fellowship.

Results: See attached image

Conclusions: The DEI Chief Fellowship is a structured year-long position designed to help trainees become leaders in responsibly advancing excellence in DEI through 1) furthering the inclusion of those underrepresented in medicine, 2) identifying and reducing healthcare disparities, 3) expanding equity into quality improvement and research, and ultimately 4) to improve patient outcomes. It encompasses work-in-progress sessions, leadership experience (*e.g.*, leading community engagement projects, facilitating fellowship recruitment), and core lectures (*e.g.*, addressing implicit biases and microaggressions, incorporating health equity into learning health system). The Renal DEI Chief Fellowship position helped establish similar DEI tracks in Endocrinology and Pulmonary/Critical Care Division within the University of Pennsylvania. We hope Nephrology Divisions across the country will use this concept map to build a pipeline of leaders who graduate fellowship with a strong foundation of excellence in DEI.



SA-PO042

Beck Depression Index-II Scores and Survival in a Multi-Center Prospective Hemodialysis Cohort

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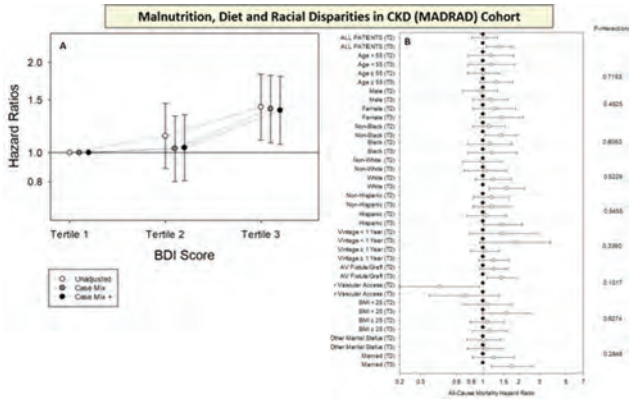
Background: Population-based studies have uncovered a high burden of depression among advanced CKD patients, including those receiving dialysis. We examined the relationship between self-reported depression and mortality among a diverse multi-center prospective cohort of HD patients.

Methods: We evaluated 956 HD patients from the prospective NIH MADRAD Study recruited across 18 dialysis clinics across Southern California who underwent protocolized Beck Depression Index-II (BDI-II) surveys over 2011-2021. Using multivariable Cox models adjusted for expanded case-mix covariates, we examined associations of time-dependent BDI-II score categorized as tertiles with all-cause mortality risk. We then examined differential BDI-II score—mortality associations across race/ethnicity using interaction tests.

Results: The mean±SD age of the cohort was 55±14 years, among whom 45% were female; 29% were Black; and 55% were Hispanic. In analyses of time-dependent BDI-II score, the highest (worse) Tertile 3 was associated with higher death risk (ref: Tertile 1): HR (95%CI) 1.40 (1.08, 1.81) (Fig A). Subgroup analyses showed that point estimates for the highest Tertile 3 of BDI-II scores was associated with higher mortality in Black vs. Non-Black patients (HRs [95%CIs] 1.30 [0.81, 2.08] and 1.18 [0.87, 1.61]) and in Hispanic vs. Non-Hispanic patients (HRs [95%CIs] 1.18 [0.83, 1.68] and 1.25 [0.86, 1.82]), with non-significant p-interaction values suggesting equivalent risk across race/ethnicity (Fig B).

Conclusions: In a multicenter prospective HD cohort, higher (worse) BDI-II scores were associated with worse survival in all racial/ethnic groups. Further studies are needed to identify multi-modal strategies that effectively treat depression in diverse HD populations.

Funding: NIDDK Support



SA-PO043

Association of Food Insecurity and Treatment Nonadherence or Hospitalization Among Adults on Hemodialysis

Kathryn Taylor,[1] Marlena Fisher,[1] Sydney Santos,[2] Yuling Chen,[1] Owen W. Smith,[1] Nancy A. Perrin,[1] Deidra C. Crews.[3] *[1]Johns Hopkins University School of Nursing, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [3]The Johns Hopkins University School of Medicine, Baltimore, MD.*

Background: Food insecurity is associated with hospitalization among children on hemodialysis, but existing research has not tested associations among adults.

Methods: We conducted a prospective cohort study to test associations between food insecurity and missed treatments or hospitalizations. We enrolled a convenience sample of adults (>=18 years) on hemodialysis (>=3 months) from 17 facilities in Maryland, Washington, D.C., or Virginia from February through November 2021. Participants completed demographics and the US Adult Food Security Survey Module at baseline and remained in the study for 6 months. We collected missed treatment counts and hospital admission and discharge dates (all-cause and fluid or electrolyte-related) from facility records. We created negative binomial regression and Cox models to test associations between food insecurity and missed treatments or hospitalizations, respectively. We repeated hospitalization analyses stratifying by age (<55 or >=55 years) to account for confounding.

Results: We analyzed data from 288 out of 322 participants (89%) who completed surveys. Mean age was 60 years (range 27 – 86 years), 58% of the sample were male, 73% self-identified race as Black. At baseline, 61 participants (21%) reported food insecurity. During follow-up, 138 participants (48%) missed at least one hemodialysis treatment (range 0 – 29 treatments) and 91 participants (32%) were hospitalized (range 0 – 5 hospitalizations). Twenty participants (7%) were hospitalized due to fluid overload or hyperkalemia. Participants reporting food insecurity missed more dialysis treatments (**Table 1**). Food insecurity was not associated with all-cause hospitalization, but the association differed by age group (*food insecurity x age group* interaction term p = 0.14). In bivariate analyses, food insecurity increased relative hazard of fluid or electrolyte-related hospitalization.

Conclusions: This is the first report of associations between food insecurity and outcomes among adults on hemodialysis. Food insecurity was associated with missed treatments and fluid or electrolyte-related hospitalizations.

Funding: Other NIH Support - National Institute of Nursing Research

Table 1. Missed Treatments and Hospitalizations by Level of Food Security

	Missed Treatments[a]	All-cause Hospitalization[b]			Fluid-related Hospitalization[b]
	Uncensored Sample, aIRR	Full Sample, HR	Age < 55, HR	Age >= 55, HR	Full Sample, HR
Food Security					
High or Marginal *(n=215)*	(ref)	(ref)	(ref)	(ref)	(ref)
Low or Very Low *(n=61)*	1.77 (1.01 – 3.12) p = 0.05	0.98 (0.6 – 1.61) p = 0.94	1.56 (0.76 – 3.21) p = 0.23	0.72 (0.34 – 1.52) p = 0.72	2.58 (1.04 – 6.4) p = 0.04

[a]Negative binomial regression model, adjusted for age and educational attainment; subset of participants uncensored before end of study period

[b]Cox regression model, censored at first hospitalization, death, transplant, change in modality, transfer to new facility

SA-PO044

Multilevel Challenges Faced in Renal Replacement Therapy of Morbid Obesity

Lina Frauenfeld, Sheena Pramod. *University of Florida College of Medicine, Gainesville, FL.*

Introduction: We discuss the challenges faced in treatment options in a morbidly obese patient with advanced CKD Methods: Dialysis modalities have significantly improved over the years with several options. Home dialysis increases patient autonomy, portability and compliance, but remains low due to multiple challenges.

Case Description: 57 year old male is referred to with advanced CKD. PMHx includes morbid obesity, gastric bypass in 2003, anemia and proteinuria. Previously, patient weighed 700 lbs, before gastric bypass, and went down to 300 lbs. He is 598 lbs at the time of evaluation. Since 2018, he has been bedridden due to back issues and has not been able to leave his home until his visit in a modified stretcher. Labs reveal: Serum Creatinine of 4.1 mg/dl, EGFR (CKD-EPI) of 16 mL/min/1.73m2, microalbumin/Creatinine ratio 938 mg/g creatinine and urine protein creatinine ration 2,272 mg/g creatinine suggestive of secondary FSGS. On follow up visit, he reports mild uremic symptoms, resulting in a discussion regarding his RRT options. In-center HD was not an option given his physical condition and inability to sit in HD chair or weight bear. Home HD was considered, but 6 week home training was not feasible because of wife's work needs, bariatric stretcher unable to fit through doorways, and out of pocket costs of transportation for training. We considered PD as a last option. He would need a pre-sternal PD catheter placed given his large pannus. Surgeon though agreeable to place pre-sternal PD catheter, if cleared by anesthesia, sadly, his bariatric stretcher was too large to fit the local dialysis home units, prohibiting his training and an option to perform PD training at home was limited. The only future alternative is him presenting to emergency room for inpatient hemodialysis knowing that he may not receive OP placement. He was referred for home palliative care simultaneously.

Discussion: This case highlights the challenges faced by our morbidly obese population which are growing in numbers despite the advancements that have been made in home hemodialysis. Dialysis and insurance companies should incentivize and support units to provide training at patient's homes, alleviating some of the hurdles faced in improving the shift to home therapy. The ability to train younger patients such as ours in their own homes may alter their clinical trajectory.

SA-PO045

Sex, Gender, and Quality of Life in Hemodialysis

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Background: Women with kidney failure treated with hemodialysis (HD) report lower quality of life (QoL) compared to men. Decreasing HD frequency is a potential strategy to improve QoL but may result in undertreatment of females compared to males due to biological differences in body water distribution.

Methods: Individuals initiating HD in Alberta, Canada were recruited. Sex assigned at birth (SAAB) and gender identity were self-reported and gender score, a measure of social expectations and norms typically associated to a given gender, was calculated using the GENESIS-PRAXY scale. The primary outcomes were the change in Kidney Disease Quality of Life 36 physical (PCS) and mental component scores (MCS) at 3 months, validated markers of mortality, stratified by HD dose (3 vs 2 sessions/week). The associations between SAAB, gender score and change in PCS and MCS by HD dose were measured using non-parametric test and multiple linear regression, respectively.

Results: There were 33 participants on 3x/wk HD (14 female, 19 male) and 27 on 2x/wk (12 female, 15 male). PCS increased with 3x/wk (p=0.010) but not 2x/wk (p=0.521) in females, but no differences were observed in MCS. No changes were observed in PCS or MCS in males, irrespective of HD dose. Gender score was positively associated with change MCS on 2x/wk HD (p=0.049) but not 3x/wk HD (p=0.102). While gender score was not associated with change in PCS, HD dose modified the relationship (p=0.035).

Conclusions: Higher HD dose was associated with improved physical health in females, but lower HD dose was associated with improved mental health in participants with roles traditionally ascribed to women.

SA-PO046

Race and Ethnicity Do Not Influence the Performance of Fistula Failure Machine Learning Model

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Background: Risk stratification models are important decision support aids in medicine yet can inadvertently introduce bias if social factors, such as race and ethnicity, are included in models that predict biological outcomes. (Obermeyer et al., Science 2019). The inclusion of social factors in model development may not have a significant impact on model performance. In the development of a model to predict an arteriovenous fistula (AVF) failure event in a hemodialysis (HD) patient, we investigated the effect of inclusion/exclusion of race and ethnicity as predictor variables on model performance.

Methods: AVF failure was defined by the change from active to unusable status within 30 days. We built two machine learning (ML) algorithms (XGBoost) using HD patient data from Jan to Dec 2018 at large integrated kidney disease healthcare provider. Models were trained using demographics, treatment, laboratory, comorbidity, clinical notes, hospitalization data. Model A included race and ethnicity and Model B did not. Both models considered approximately 2,400 predictor variables. Dataset was randomly split into 60% training, 20% validation 20% testing data. Unseen testing data was used to evaluate the model's performance.

Results: Models were developed using data on approximately 67000 patients (approximately 14000 patients had events). Model A & B showed an area under the curve (AUC) of 0.76 vs 0.75, sensitivity of 0.53 vs 0.53, and specificity of 0.84 vs 0.84 respectively (**Figure 1**).

Conclusions: ML model performance was not affected by race or ethnicity data, suggesting they should be excluded from models of biological outcomes to minimize biases that could disproportionally classify risk and lead to disparities in care. Patient factors that may affect biology are critical to consider and validate during model development, and should span beyond race and ethnicity.

Funding: Commercial Support - Fresenius Medical Care

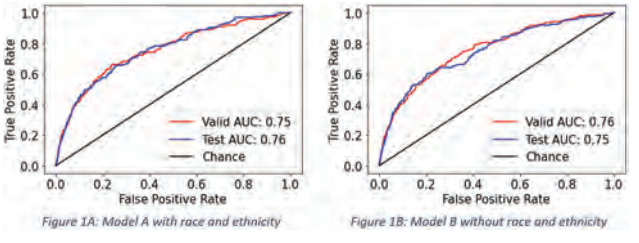


Figure 1: AUROC of AVF failure model with and without race and ethnicity data

SA-PO047

Racial and Ethnic Differences in Arteriovenous Access (AVA) Use One Year After Hemodialysis (HD) Initiation with a Central Venous Catheter (CVC)

Melandrea L. Worsley, Jingbo Niu, Kevin F. Erickson, Wolfgang C. Winkelmayer, L Parker Gregg. *Baylor College of Medicine, Houston, TX.*

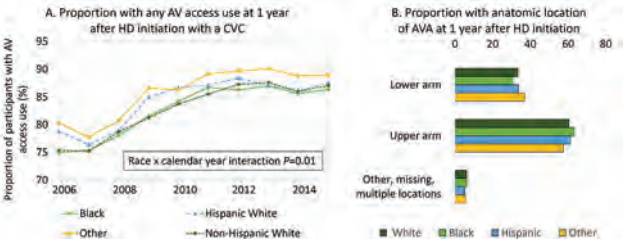
Background: Racial and ethnic differences exist in AVA use, which includes AV fistulas and grafts, at HD initiation. We evaluated temporal trends in racial/ethnic differences in AVA use and anatomic location 1 year after HD initiation among those who had initiated HD with a CVC.

Methods: Using data from a large dialysis organization (LDO), we identified patients who initiated HD with a CVC between 2006 and 2016 and who remained on HD with same LDO for 1 year. Race/ethnicity (hereafter referred to as race) was categorized as Black, Hispanic, White, & Other. The use of an AVA within 1 year after HD initiation was plotted by calendar year, Annual racial differences in proportions with AVA were assessed using logistic regression, adjusted for demographics and comorbidities, and changes over time were assessed using a race x calendar year interaction term. Anatomic locations of AVA were defined as lower arm, upper arm, or other/missing/multiple locations.

Results: Of 198,186 participants, 67,315 (34%) were Black, 31,711 (16%) Hispanic, 86,117 (43%) White, and 13,043 (7%) were of other races/ethnicities. Compared to White patients, Black, Hispanic, and Other patients were younger and less likely to have heart failure or peripheral arterial disease, whereas the Hispanic and Other groups were more likely to have diabetes than Black and White patients. From 2006 to 2016, use of an AVA within 1 year increased in all racial/ethnic groups (P<0.001), with race x calendar year interaction at P=0.01 (**Figure 1A**). Compared to White patients, Black patients had similar odds of using an AVA within 1 year, while those of Other race were consistently more likely and the Hispanic group was at times more likely than Whites. However, Black patients were less likely to use an AVA placed in the preferred location in the lower arm than the other groups (**Figure 1B**).

Conclusions: Although there has been an improvement in AVA use at 1 year after initiation of HD with a CVC in all racial groups, differences in AVA use and location remain and warrant further investigation.

Funding: NIDDK Support



SA-PO048

Sociodemographic Characteristics of Hemodialysis Patients Prescribed Sucroferric Oxyhydroxide and Other Phosphate Binders

Meijiao Zhou, Joanna Willetts, Linda Ficociello, Nwamaka D. Eneanya, Len A. Usvyat. *Fresenius Medical Care Global Medical Office, Waltham, MA.*

Background: Promoting health equity in the treatment of hemodialysis (HD) patients (pts) includes ensuring ready access to effective medications, regardless of an individual's sociodemographic characteristics (SDC). One such medication is sucroferric oxyhydroxide (SO), a brand-name phosphate binder (PB) that has demonstrated effectiveness in managing serum phosphorus with a lower pill burden. However, the cost of brand-name medication may limit its availability to certain pt populations. To address this issue, Velphoro Access Solution (VAS) was created as a program to explore available resources that make SO more accessible and affordable through the benefit investigation (BI) process. In 2022, > 56,000 BIs were submitted to VAS for Fresenius Kidney Care (FKC) pts. This study examines the SDC of HD pts prescribed SO and other PBs, to identify any disparities in SO access that may exist.

Methods: Adult HD pts from FKC with active prescription (Rx) of PBs (SO, ferric citrate, lanthanum carbonate, sevelamer, and calcium acetate) during 7/1/2022-12/31/2022 were included. Pts were divided into 2 groups: SO Rx (n=30,513) and other PB Rx (n=121,357). We described SDC such as age, gender, race, ethnicity, and insurance status.

Results: 20% of pts were prescribed SO. The average age of pts with SO Rx was 60, 4 years younger than those with other PB Rx. There was a 4% higher proportion of male (61% vs 57%) and African American (40% vs 36%) and 4% lower White (54% vs 58%) pts among those prescribed SO. The ethnic composition was similar in SO group and other PB group (Hispanic 18% vs 19%). A higher % of pts with commercial insurance (17% vs 14%) and Medicaid (47% vs 44%) but with lower % Medicare (34% vs 38%) were observed in those with SO compared to pts with other PB Rx.

Conclusions: In our analysis of FKC HD pts, we found a higher % of pts prescribed SO who were younger, male, African American, and insured by Medicaid or commercial coverage. Programs such as VAS may improve access and affordability of medications that are crucial for dialysis care.

Funding: Commercial Support - Fresenius Medical Care

Sociodemographic Characteristics*	5D Prescription (n=30,513; 20%)	Other PB Prescription (n=121,357; 80%)
Age, mean± standard deviation	60.1 ±13.7	64.3 ±13.9
Gender, n (%)		
Female	11,885 (39.0)	52,044 (42.9)
Male	18,628 (61.0)	69,313 (57.1)
Race, n (%)		
White	16,028 (53.8)	67,763 (57.7)
African American	11,790 (39.6)	41,899 (35.7)
Asian	1,205 (4.0)	4,720 (4.0)
American Indian or Alaska Native	266 (0.9)	1,114 (0.9)
Native Hawaiian/other Pacific Islander	517 (1.7)	2,015 (1.7)
Ethnicity, n (%)		
Hispanic	5,280 (17.7)	22,335 (19.0)
Non-Hispanic	24,503 (82.3)	94,985 (81.0)
Combined Insurance, n (%)		
Any commercial	5,086 (16.7)	16,876 (13.9)
Any Medicaid	14,229 (46.6)	52,926 (43.6)
Medicare	10,358 (33.9)	45,599 (37.6)
Other	840 (2.8)	5,956 (4.9)

*All comparisons were statistically significant (p<.0001)

SA-PO049

Applying Sequence Analysis Techniques to Describe ESKD Patients' Treatment Histories

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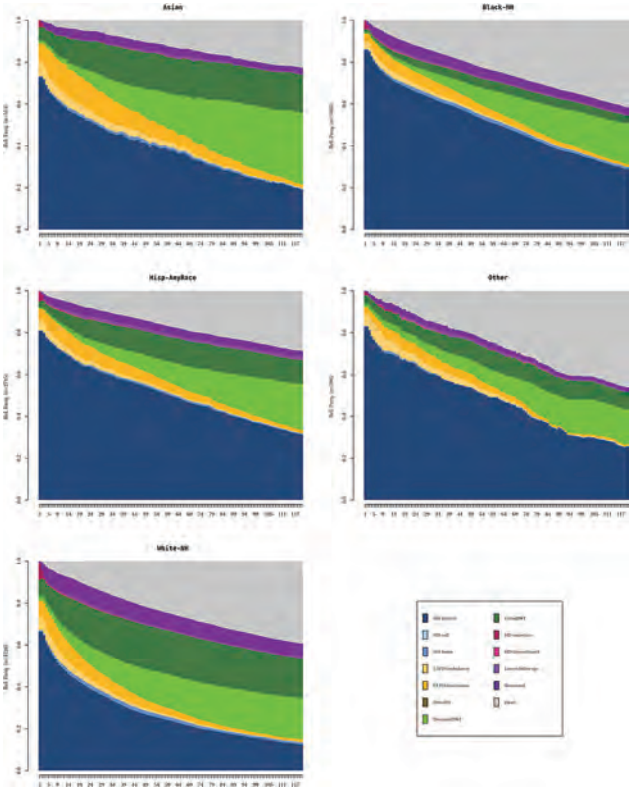
Background: Although outcomes for particular treatments for ESKD have been studied, characterizing full treatment sequences (including timing, order, and duration) for different racial/ethnic groups may offer deeper insights into patient experiences and outcomes.

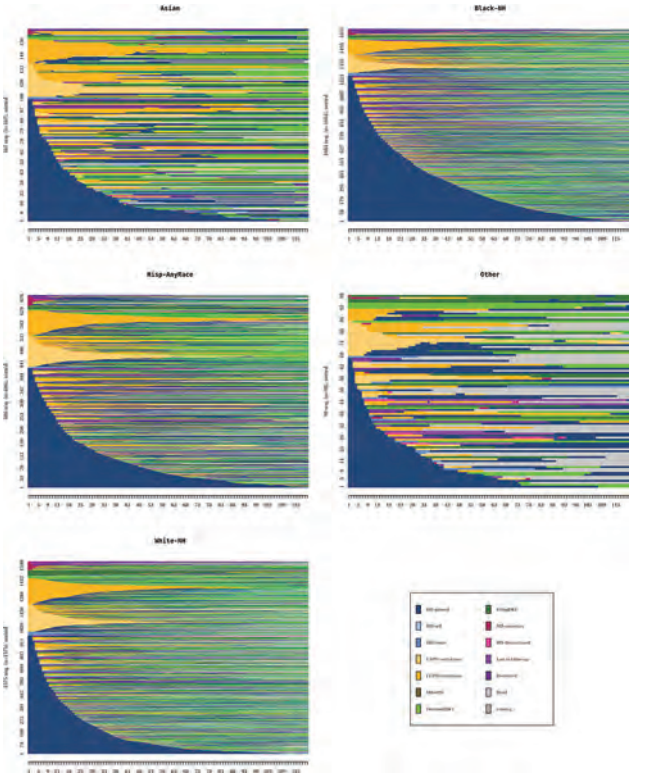
Methods: We study 10-year treatment sequences of the 2009 incident ESKD cohort age 18-44 in the USRDS. The state plot characterizes the distribution of treatments over time; the index plot traces individual patients' treatment sequences with one line per unique sequence.

Results: *State plot*: White and Asian groups exhibit higher rates of hemodialysis (especially CAPD and CCPD for Asians) and transplant. *Index plot*: More sequences for non-White patients involve uninterrupted hemodialysis than for White patients. More sequences for Black patients involve early loss to follow-up. White patients have more preemptive LDKTs than other groups. Significant shares of sequences for White, Hispanic, and Asian patients begin with CCPD/CCAD before transitioning to other treatments, but this is a smaller share of sequences for Black patients.

Conclusions: Sequence analysis techniques hold potential to more fully describe ESKD patient treatment histories and offer a new insight into racial/ethnic disparities.

Funding: NIDDK Support





SA-PO050

Switchers from Medicare Fee-for-Service Program to Medicare Advantage Early 2021 Among ESKD Patients

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Background: Before 2021, Medicare beneficiaries with end-stage kidney disease (ESKD) were not permitted to switch from traditional Medicare (Medicare fee-for-service, MFFS) to Medicare Advantage (MA). However, starting in January 2021, beneficiaries were eligible to switch to MA, thanks to the 21st Century Cures Act. Using the United States Renal Data System, we examined differences between beneficiaries who continued with MFFS and those who switched to MA.

Methods: Adults (aged≥18 years) on dialysis or with a kidney transplant (ktx), with MFFS as primary payor, as of December 2020 were assessed for their Medicare coverage in January 2021.

Results: In total, 412,769 patients (pts) were included; 315,015 receiving dialysis and 97,754 with a ktx. Among dialysis pts, 11.5% switched from MFFS to MA (9.6% among home dialysis pts, 11.8% among in-center dialysis pts); 5.4% among Ktx pts. Those who switched were younger (median age for dialysis pts, switcher vs non-switcher: 61.3 vs 65.6 years; for those with a ktx, 62.4 vs 63.6). Pts who switched were also more likely to be non-Hispanic (NP)-Black or Hispanic (dialysis pts, NP-Black: 47.9% vs 32.7%; Hispanic, 17.8% vs 15.3%; ktx recipients, NP-Black, 37.3% vs 21.6%, Hispanic, 15.8% vs14.1%); and more likely to have dual Medicare and Medicaid coverage (dialysis, 51.7% vs 43.8%; ktx, 35.7% vs 29.1%). Those who switched were also more likely to have diabetes or hypertension as their cause of ESKD (Table).

Conclusions: In 2021, more than one tenth of pts with ESKD switched from MFFS to MA; switching was associated with age, race/ethnicity, and Medicaid enrollment. This shift alters the generalizability of the MFFS population with ESKD, and heightens the need for monitoring of outcomes among patients enrolled in MA.

Funding: NIDDK Support

Table. Characteristics of end-stage renal disease patients who switched from Medicare fee-for-service to Medicare advantage vs those who did not, by treatment modality

	Dialysis		Kidney Transplant	
	MFFS* to MA†	Stayed in MFFS*	MFFS* to MA†	Stayed in MFFS*
N	36,378	278,637	5,267	92,487
Age, Median (IQR)	61.3 (53.0, 68.4)	65.6 (54.8, 74.1)	62.4 (53.1, 68.6)	63.6 (51.7, 70.8)
Age Group				
18-44	10.2	11.1	10.9	15.3
45-55	20.1	14.4	18.8	15.6
55-64	33.3	22.7	29.5	22.4
65-74	25.6	29.2	33.5	35.0
75-84	9.0	17.4	6.9	10.8
>=85	1.8	5.3	0.6	0.9
Sex				
Female	41.9	41.9	39.6	40.3
Male	58.1	58.1	60.4	59.7
Race				
NH¶-White	29.6	43.9	39.3	53.8
NH¶-Black	47.9	32.7	37.3	21.6
Hispanic	17.8	15.3	15.8	14.1
Asian	2.5	4.8	3.6	5.3
Other	2.2	3.4	4.1	5.2
MM Dual Eligible				
No	48.3	56.2	64.3	70.9
Yes	51.7	43.8	35.7	29.1
Cause of ESKD‡				
Diabetes	46.5	44.7	30.8	25.6
Hypertension	33.5	30.3	26.4	21.5
Glomerulonephritis	8.8	10.2	19.1	23.4
Other	11.3	14.9	23.8	29.6

* Medicare fee-for-service; † Medicare Advantage; ‡ End-stage kidney disease; ¶ Non-Hispanic

SA-PO051

Characteristics of Migrant and Non-Migrant ESRD Patients in Nepal

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Background: Thousands of young Nepali migrant workers have died and many developed ESRD while working abroad. Although the etiology of kidney disease is yet to be established, exposure to recurrent heat stress is identified as a potential risk factor.

Methods: Cross-sectional study was conducted in 2 dialysis centers. Patients 18-80 yrs of age getting incenter hemodialysis were sampled. Questionnaire with migration and occupational history was administered.

Results: A total of 354 patients were included (mean age 46.5 ±13.9 yrs; 36% female). 31% were returnee migrant workers (88% male; 83% worked in the Gulf States, Malaysia, & India). The median duration of work abroad was 14 yrs (IQR 9-18) & >50% returned due to health problems. 50% of returnee migrant workers were <40 yrs old, compared to 30% of non-returnee migrant workers (P<0.001). A lower prevalence of diabetes (12% vs 24%; P=0.009) & immunologic diseases (5% vs 14%; P=0.022) were observed among returning migrants. Returnee migrants experienced extreme workloads (36%), no breaks (37%), & exhaustion (68%). Among those who reported heat exposure at work, 70% were exposed daily.

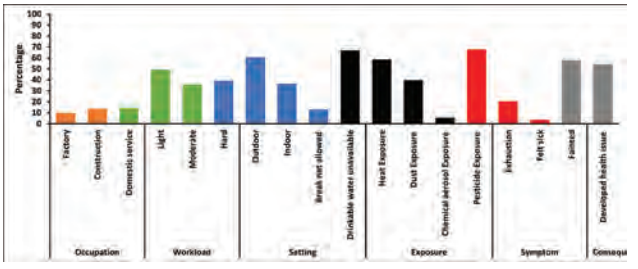
Conclusions: The findings provide meaningful information on potential risk factors for CKDnT. These results underscore the importance of conducting further studies to better understand & address the specific risks & challenges they face.

Funding: Private Foundation Support

Table 1: Participants characteristics

	All	Returnee Migrant Workers	Non-Returnee Migrant Workers	P-value
Age, mean (SD)	46.5(13.9)	43.1 (11.2)	47.9 (14.6)	0.003
Age < 40, n (%)	128 (36.2%)	54 (49.5%)	74 (30.2%)	<0.001
Female, n (%)	127 (35.9%)	13 (11.9%)	114 (46.5%)	<0.001
Years of education, median (IQR)	8 (2-10)	9 (4-10)	8 (0-11)	0.29
Family history of CKD, n (%)	21 (5.9%)	7 (6.4%)	14 (5.7%)	0.79
Current smoking, n (%)	6 (1.7%)	2 (1.8%)	4 (1.6%)	0.89
Alcohol use, n (%)	11 (3.1%)	6 (5.5%)	5 (2.0%)	0.083
Hypertension, n (%)	326 (92.1%)	100 (91.7%)	226 (92.2%)	0.87
Diabetes, n (%)	72 (20.3%)	13 (11.9%)	59 (24.1%)	0.009
Gout, n (%)	57 (16.1%)	20 (18.3%)	37 (15.1%)	0.44
Nephrolithiasis, n (%)	49 (13.8%)	15 (13.8%)	34 (13.9%)	0.98
Immunologic diseases, n (%)	40 (11.3%)	6 (5.5%)	34 (13.9%)	0.022
Regular use of NSAIDs, n (%)	95 (29.9%)	27 (27.0%)	68 (31.2%)	0.45
Frequent use of antibiotics, n (%)	87 (27.4%)	29 (29.0%)	58 (26.6%)	0.66

Characteristics of Participants



Occupational and environmental risk factors among returnee migrant workers (n=109)

SA-PO052

Assessment of Dialysis Operations in Conflict-Affected Areas: Insights from Survey Results from Northwest Syria

Sami Alasfar,[1] Hani S. Alashawi,[4] Lina Murad,[3] Gilbert M. Burnham.[2] *[1]Mayo Clinic Arizona, Scottsdale, AZ; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD; [3]Metropolitan Access Center, Bretnwood, MD; [4]The Health Cluster, Gaziantep, Turkey.*

Background: In areas affected by armed conflict, the opertions of hemodilayis (HD) are hindered by the lack of required infrastructure. Despite the growing prevalence of kidney disease, humanitarian agencies have given little attention to HD in such situations. Northwest (NW) Syria is an example of such a conflict-affected region where approximately 800 patients rely on HD provided by non-governmental agencies (NGOs).

Methods: We conducted a survey conisting of 346 questions to assess HD operations in NW Syria. Onsite visits were made to interview HD facilities managers and technicians, and the data was collected during these visits. The survey covered various areas related to HD operations, including current infection and prevention and control practices, medical protocols, built environment, health care worker competencies, equipment maintenance, dialysis unit management and leadership, and record keeping.

Results: Answers to selected questions of the survey are in tables 1&2.

Conclusions: In regions affected by conflict, there are significant deviations from the standards of HD operations, highlighting the need for an action plan that involves NGOs responsible for administering HD, in order to implement and maintain minimal standards for HD.

Table 1: Answers to selected survey questions about Infection Prevention and Control (IPC) practices

Item		Result
Presence of IPC Protocol		
IPC Protocol present		7/14 (50%)
Presence of IPC Advisor		5/14 (36%)
Key Components of IPC		
Hepatitis B and C testing		6/7 (85%)
Effective cleaning & disinfection of equipment		6/7 (85%)
IPC Training		
IPC Training in the last 12 months		8/14 (43%)
Training on accessing dialysis access		6/8 (75%)
IPC Surveillance		
Process to review surveillance results		4/7 (57%)
Frequency of screening for Hepatitis B and C	Every 3 months Every 6 months	2/14 (14%) 11/14 (79%)
IPC Implementation		
Hepatitis B patients undergo hemodialysis in isolation		8/14 (57%)
Staff who are not vaccinated for Hepatitis B are allowed to administer dialysis to patients with Hepatitis B		2/14 (14%)
Staff caring for hepatitis B positive patients are allowed to care for hepatitis B negative patients at the same time		12/14 (86%)
IPC Monitoring		
Regular assessment of prevalence of infections		8/14 (57%)
Written procedures to examine infection control practice once a patient is found to have hepatitis B or C or if there in an infection outbreak		2/14 (14%)
Built Environment and Supplies		
The design of the unit follows a national or international guideline for dialysis units		3/14 (21%)
IPC records		
IPC Training Records	Yes No No training received	4/14 (29%) 4/14 (29%) 6/14 (43%)
Records of patients' hepatitis B vaccination		3/14 (21%)

Table 2: Answers to selected survey questions about Medical Quality practices

Medical Protocols					
Medical Protocols present		7/14 (50%)			
Individualized dialysis prescription		9/14 (64%)			
Comprehensive assessments by a nephrologist		5/14 (36%)			
Medical records for each dialysis visit		12/14 (86%)			
Record of patients' death		3/14 (21%)			
Equipment and Maintenance					
Frequency of dialysis machines maintenance per year	0 1 2 3 4	2/12 (16%) 3/12 (25%) 4/12 (33%) 4/12 (33%) 1/12 (8%)			
Dialysis maintenance follows the manufacturer check list		2/12 (16%)			
Regular maintenance for water treatment system		2/14 (14%)			
Water quality assessment done in the last 12 months		5/14 (36%)			
Access to laboratory testing					
How easy is it to get laboratory testing?		Easy	Moderate	Difficult	Not possible
Hemoglobin/Hematocrit		12 (86%)	2 (14%)	0 (0%)	0 (0%)
Calcium and Phosphorus		7 (50%)	5 (36%)	1 (7%)	1 (7%)
Potassium		4 (29%)	3 (21%)	2 (14%)	5 (36%)
PTH		4 (29%)	1 (7%)	1 (7%)	8 (57%)
Iron studies		7 (50%)	1 (7%)	1 (7%)	5 (36%)
Hepatitis B and C serology		10 (71%)	1 (7%)	1 (7%)	2 (14%)

SA-PO053

Primary Caregiver Burden in a Mexican Hemodialysis Facility: Prevalence and Risk Factors

Edgar Solis, Sergio Hernández-Estrada. Medica Santa Carmen. *Médica Santa Carmen, Guanajuato, Mexico.*

Background: Caregiver burden is a subjective interpretation of resources, abilities and impact of caregiving process. A validated Zarit survey has been recommended among caregivers in patients with HD.

Methods: Primary HD caregivers from a single facilitie in Mexico responded a validated Zarit survey. Incident patient and caregivers (< 3 months) were excluded. Social and demographic caregiver data also included. Descriptive, linear regression and coef. correlation analysis was done.

Results: 86 primary caregivers answered: Most females with a mean age of 47. Housewives 43% was the main occupation. Couples take care of patients in 42%. Median monthly income 220 dlls. We identified burden in 54%: slight 32% and severe 68%. Female sex and unemployees predicts higher scores. A non-significative negative correlation was found between income and score.

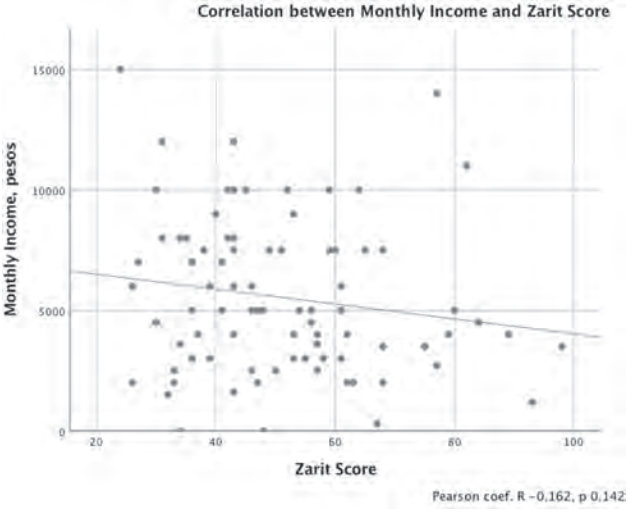
Conclusions: Caregiver burden is prevalent. Economic difficulties exacerbate complexity and caregiver burden. Results should be added to public health burden of ESRD in Mexico.

Caregiver factors and Zarit Score - Linear regression analysis

Variable	Coef	IC (95%)	p value
Female sex	11.01	(1.51 - 20.52)	0.02
Unemployee	27.64	(10.44 - 44.84)	0.002
Caregiver age	-0.33	(-0.61, -0.04)	0.02
Monthly income	-0.001	(-0.003 - 0-000)	0.01

Adjusted by caregiver age, illness, sleeping hours, life spent caring, patient-caregiver relation, meals a day, social security.

General Characteristics	n = 86
Age, mean (SD)	47 ± 15
Female, n (%)	66 (77)
Sleep hours	6.5 ± 1.6
Monthly Income, median (dlls)	220 (132 - 453)
Marital Status	
Married	66 (77)
Single	11 (13)
Education level	
Primary School	38 (44)
Middle School	24 (28)
Occupation	
Homemaker	37 (43)
Employee	25 (29)
Patient's relation	
Couple	36 (42)
Parent	23 (27)
Other cargiver's dependents	
None	30 (35)
1 to 3	47 (56)
>3	7 (8)
Zarit Cargiver burden	
Zarit Score	51 ± 16
None, (<46)	39 (45)
Slight (45 - 55)	15 (17)
Severe (>56)	32 (37)



SA-PO054

Increasing Home Dialysis Among Spanish-Speaking Mexican American Patients: Challenges and Opportunities

Karen-Marie Eaton,[1] Steven M. Brunelli,[1] Danelle Radney,[2] Unini Odama,[2] Francesca Tentori.[1] *[1]Davita Clinical Research, Minneapolis, MN; [2]DaVita Inc, Denver, CO.*

Background: Home dialysis offers patients another treatment option for kidney failure. Since home dialysis use is lower in Mexican American patients, in this study we sought to understand experiences and uncover influencing factors and barriers that patients and care partners face.

Methods: A total of 28 participants (Mexican American patients at a dialysis provider, both in-center and home, and their care partners) were recruited to join in-person focus groups held in December 2022. Focus groups were audio and video recorded and transcribed verbatim. Groups were held in Spanish language, translated in real time by a certified interpreter, and transcribed in English. Responses were analyzed using inductive thematic analysis.

Results: Patients reported that physicians did not make a clear connection between poor management of underlying health conditions and kidney failure; this led to difficulty accepting a kidney failure diagnosis and need for dialysis. Patients and caregivers want improved education in English and Spanish to help make the initial modality decision. Physician guidance was cited as the most important factor in the initial modality decision for Mexican American patients and care partners. Trust in physician recommendation is largely unquestioned, influenced by factors such as respect for physician authority, limited literacy, and language barriers. While most patients and care partners acknowledge the benefits of home dialysis, significant barriers included the fear of being solely responsible for a complex procedure and loss of social interaction and/or support from other dialysis patients and center staff. Unsurprisingly, care partners are a critical part of the decision to choose home dialysis. Faith plays a significant role for many respondents; many speak about their experience of disease in faith-based terms, such as trusting God.

Conclusions: Opportunities exist to build on the strong patient preference for physician led health information, and to focus on decreasing literacy and language barriers in the Mexican American population.

SA-PO055

Disparities in Home Dialysis for Latinx People with Kidney Disease: A National Qualitative Study of Dialysis Social Workers

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Background: Latinx people have a 2.1 fold higher incidence rate of kidney failure compared to non-Latinx White individuals, yet are less likely to use home dialysis. This discrepancy has not been completely explained by medical, socioeconomic, or demographic variables. Improving access to home dialysis is a priority of the Advancing American Kidney Health Initiative, a 2019 executive order to transform kidney disease care for individuals in the US. Dialysis social workers play a crucial role in home dialysis assessment and education. In this study, we utilized qualitative interviews with dialysis social workers across the US to better understand the facilitators and barriers to home dialysis for Latinx patients with kidney failure.

Methods: We conducted a qualitative study with adult (age >18) dialysis social workers in the US with experience working with Latinx populations. The semi structured interview guide included open ended questions exploring dialysis modality education, dialysis decision making, and home dialysis uptake and maintenance. Interviews were audio-recorded, transcribed verbatim, de-identified and transcripts were analyzed independently by two members utilizing thematic analysis.

Results: We interviewed 20 dialysis social workers from ten different states, with a median age range of 30-40 (35%), 100% female, 14 (70%) identified as White and 5 (25%) of participants spoke Spanish. Participants described five themes affecting home modality access for Latinx people: 1) Variation in modality education 2) Evaluating candidacy for home dialysis 3) Role of language and communication 4) Facilitators to home dialysis and 5) Barriers to home dialysis (Table).

Conclusions: Our study illustrates early language and culture concordant education is critical for home modality uptake amongst Latinx people with kidney disease. Involving the social worker early in the home dialysis is critical for evaluating for important issues that may affect home dialysis treatment.

Funding: NIDDK Support

Theme	Sub themes	Illustrative quote
Variation in home modality education	-Standardized modality classes -Forms of educational materials -Role of the social worker -Early and frequent education	- As a social worker get very frustrating when you try to advocate for change and try to get things that are systemic fixed and it's just barrier after barrier, after barrier. - I think it's being able to see it like the pictures help more and not just talking about it.
Evaluating candidacy for home dialysis	-Assessment of barriers to home -Overcoming structural barriers -Housing and space -Insurance and financial barriers	- When I talk to them in Spanish, I tend to find out that they are here undocumented, that they are working under the table, that they're getting paid in cash, that, you know, they share a room with ten other people or whatever it is to be here. - I wish it was more equitable, accessible to everyone despite where they come from.
Language and communication	-Experience with interpreters -Clinician-patient communication barriers -Language concordant staff -Working with illiterate patients -Gender differences in communication	- I am bilingual. So, I think that helps, because even though I am Caucasian speaking Spanish, I think it just gives you that added layer of rapport and trust. - I think the men are definitely more guarded. That's normally who has the trust issues with providers and the medical system as a whole. But if they are younger and they lose their job and their wife is the primary breadwinner at that point, you can definitely see depression and just feeling the loss of worth.
Facilitators to home dialysis	-Family support -Culture concordant care -Importance of trusting relationships - Supportive clinic environment -Patient activation - Motivation for autonomy	- I think it speaks about a lot of our families, right there. Is there a grandparent in the home, they come living with their children and grandchildren, like a lot of our Hispanic families are multi-generational. - The community outreach is really important, in certain areas, certain neighborhoods rather, there's more of population of Latinx, and the community being able to reach out to their neighbors if they know someone who also has kidney disease requiring them to have dialysis, then there's some camaraderie there, I have found that to be the case.
Barriers to home dialysis	-Responsibility is overwhelming -Health literacy and language incongruency -Fear and isolation -Burden on family -Misinformation amongst Latinx community -Transition from in-center	- Fear around being responsible for this treatment has been one really big one. Not wanting people in their house. You know, wanting to be more private about their living situation has been another really big one. - One of the experiences I've had is that a lot of times they talk to each other, it's a small community tight-knit, so if one person has a bad experience, it gets spread to everybody else that it has been poor for that patient.

SA-PO056

Racial and Socioeconomic Differences in Success on Home Dialysis

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Background: Home dialysis offers several advantages to patients and health care systems including improved patient-centered outcomes, lower cost, and equal if not better clinical outcomes. Despite this, utilization of home dialysis remains low. Although home dialysis is not always the ideal modality for patients with End Stage Renal Disease (ESRD), most dialysis patients are viable candidates for this modality. Variance in home dialysis underutilization falls along both racial and socioeconomic lines, with lower home dialysis utilization by racial and ethnic minorities and higher rates among black individuals of transfer to in-center dialysis. Provider fear of adverse outcomes and home dialysis failure remains a barrier to home therapy referral. We investigated whether markers for sociodemographic stress would predict success on home therapy.

Methods: We performed a retrospective cohort study of adult incident ESRD patients from January 1 2015 through December 31 2021 admitted to providers within the University of Rochester division of nephrology (N= 898, including 794 in-center hemodialysis, 39 home-hemodialysis and 65 Peritoneal dialysis) with observation period ending December 31, 2021. Using cox proportional hazards model, we compared race to social deprivation index (derived through Census Tract) as predictors for home dialysis failure (defined by conversion to in-center dialysis or death).

Results: Black and African American patients were more heavily represented amongst subjects starting in-center HD (31% vs 16.3%). There was no significant difference between mean social deprivation index (SDI) or Charlson co-morbidity index (CCI) scores in subjects starting in-center compared to at home. Over the observation period, 128 subjects performed home dialysis for a mean of 45 months. None of the variables evaluated were predictors of success on home therapy (age, sex, race, SDI or CCI).

Conclusions: Despite similar markers of medical co-morbidity and sociodemographic stress, fewer non-white patients started dialysis on a home modality compared to in-center. Neither social deprivation nor race predicted success on home therapy. This highlights a disparity in the initial referral process to home therapy which is not supported by commonly cited predictors of adverse outcome.

SA-PO057

Disparities in Home Dialysis Utilization Among Dual Eligible Medicare Fee-for-Service (FFS) Beneficiaries

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Background: Since the 2019 Advancing American Kidney Health (AAKH) initiative, the federal government has focused on enhancing prevention and treatment of kidney disease, including introducing new incentives for home dialysis use for patients who require renal replacement therapy. Access to optimal kidney care services influences greater mortality and morbidity rates. We hypothesized that patients with lower socioeconomic status may have lower use of home dialysis due to the nature of what is required to access this dialysis modality (e.g., health literacy, caregiver support, proper home infrastructure).

Methods: We used 100% Medicare Fee-For-Service (FFS) claims data to identify patients with End Stage Renal Disease (ESRD) who received renal replacement therapy (peritoneal dialysis and hemodialysis) excluding beneficiaries who have received a kidney transplant between January 2019 to June 2022. We stratified beneficiaries by Medicaid dual eligibility status.

Results: Between Q1 2019 – Q2 2022, the rate of home dialysis utilization grew from 12.3% to 15.9% across all Medicare FFS beneficiaries. In Q2 2022, 12.0% of 113,226 dual-eligible beneficiaries utilized home dialysis compared to 19.7% of 115,497 non-dual eligible beneficiaries utilizing home dialysis ($p<0.01$). This difference in utilization

was consistent across the period of analysis; the rate of non-dual eligibles utilizing home dialysis was 7.7 percentage points higher than dual eligible beneficiaries in Q1 2019 and 7.4 percentage points higher in Q1 2022.

Conclusions: The AAKH initiative – compounded by the COVID-19 pandemic – served as a catalyst to advancing home dialysis. However, these findings indicate that access to care is still greatly influenced by socioeconomic status, even with policy changes that intentionally aim to close disparity gaps. Future research and policy should seek to identify how disparities in socioeconomic status and associated challenges can be addressed to allow for equitable access to all treatment modalities for ESRD.

Rates of Unique Medicare FFS Patients with a Home Dialysis Service in the Given Quarter

Strata	Q1 2019	Q2 2019	Q3 2019	Q4 2019	Q1 2020	Q2 2020	Q3 2020	Q4 2020	Q1 2021	Q2 2021	Q3 2021	Q4 2021	Q1 2022	Q2 2022
All FFS Beneficiaries	12.3%	12.5%	12.7%	13.0%	13.4%	13.4%	13.9%	14.1%	14.7%	14.8%	15.2%	15.4%	15.9%	15.9%
Not Dual Eligible	16.4%	16.5%	16.8%	17.2%	17.6%	17.5%	18.0%	18.2%	18.8%	18.8%	19.1%	19.3%	19.9%	19.7%
Medicaid Full/Partial Dual in Any Month of Quarter	9.0%	9.2%	9.4%	9.6%	9.9%	10.1%	10.5%	10.6%	11.0%	11.2%	11.4%	11.6%	11.9%	12.0%

SA-PO058

Social Determinants of Health and AKI During Hospitalization

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Background: AKI is highly prevalent in hospitalized patients. Social determinants of health (SDOH) have been understudied as AKI risk factors. Our goal was to determine whether SDOH impacts AKI risk and AKI recovery during hospitalization.

Methods: Retrospective cohort study of patients aged ≥18 years without end-stage kidney disease admitted to the hospital from 10/2014 to 9/2017. Outcome measures were (1) Incident AKI defined by the KDIGO SCr-criteria and (2) AKI recovery defined as last SCr before discharge <25% or <0.3 mg/dL from baseline and not receiving dialysis within 72 h of discharge in patients who survived the hospitalization. We linked geocoded patient addresses at the index hospitalization to the corresponding U.S. Census tracts and block groups and the following SDOH measures: (1) neighborhood socioeconomic status measured with Area Deprivation Index (ADI) scores, (2) food access measured with Low Income Low access (LILA) scores, (3) rurality measured with Rural Urban Commuting Area (RUCA) scores, and (4) residential segregation measured with dissimilarity and isolation scores. Multivariable logistic regression was used to quantify the association between SDOH measures, each independently, and AKI development and recovery.

Results: Out of 26,769 patients, 6,976 (26%) developed AKI during hospitalization. Compared to those who did not develop AKI, patients who developed AKI were older (60 [47,71] vs 57 [47,68] years), more likely to be men (55 vs 50%), and more likely to be Black (38 vs 33%). Patients who lived in the highest tertile for ADI (most disadvantaged) were more likely to develop AKI during hospitalization even after adjustment (Table). In the fully adjusted model, Patients who lived in the highest tertile of ADI and in a LILA tract were less likely to have AKI recovery at the time of discharge (OR 0.85 [0.72,0.99] and OR 0.86 [0.74,0.99]). Rurality and residential segregation were not associated with incident AKI or AKI recovery.

Conclusions: Patients in the highest tertile of neighborhood disadvantage were more likely to develop AKI and less likely to recover.

Funding: NIDDK Support

Table: Association of SDOH measures with incident AKI in hospitalized patients

	Model 1	Model 2	Model 3
Area Deprivation Index at state level (highest tertile is the most disadvantaged): *A measure of socioeconomic status and housing for individuals*			
Low [1, 3]	ref	ref	ref
Medium [3, 7]	1.08 [1.00, 1.16]	1.10 [1.03, 1.19]	1.10 [1.01, 1.19]
High [7, 10]	1.21 [1.13, 1.30]	1.16 [1.08, 1.24]	1.16 [1.07, 1.25]
Low-income and low-access tract measured at 1 mile-urban and 10 miles-rural (yes vs. no): *A measure of food access*	1.13 [1.06, 1.21]	1.04 [0.97, 1.11]	1.03 [0.96, 1.11]
Rural Urban Commuting Area (urban vs. not)	1.09 [1.03, 1.16]	0.98 [0.92, 1.03]	0.96 [0.92, 1.01]
Measure of segregation:			
Index of dissimilarity (highest tertile has the highest vulnerability):			
Low (0.005, 0.42)	ref	ref	ref
Medium (0.52, 0.60)	1.02 [0.95, 1.09]	0.98 [0.91, 1.05]	0.95 [0.89, 1.03]
High (0.69, 1)	0.97 [0.92, 1.05]	0.99 [0.93, 1.07]	0.99 [0.92, 1.06]
Social Isolation (highest tertile has the highest vulnerability):			
Low (0.01, 0.32)	ref	ref	ref
Medium (0.32, 0.70)	1.07 [0.99, 1.16]	1.04 [0.97, 1.11]	1.03 [0.96, 1.11]
High (0.70, 1)	1.19 [1.11, 1.27]	1.00 [0.92, 1.09]	0.99 [0.91, 1.08]

Model 1: unadjusted; Model 2: age, sex, race, diabetes, obesity, baseline estimated glomerular filtration rate, systolic blood pressure

Model 3: Model 2 + delirium comorbidity score (total measure of comorbidities)

SA-PO059

Health-Related Social Needs During the COVID-19 Pandemic in the Chronic Renal Insufficiency Cohort (CRIC) Study

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Background: Health-related social needs, such as housing and food insecurity, are associated with risk factor control and care engagement among people with CKD. Social needs were exacerbated for many during the COVID-19 pandemic.

Methods: Questionnaires on social needs (housing insecurity, food insecurity, and transportation and utility issues) were administered to participants from three sites of the CRIC study from 2020 to 2023. We examined the prevalence of social needs, and used multivariable logistic regression to identify correlates of social needs.

Results: Among 600 participants, 122 (20%) experienced ≥1 social need, and 29 (5%), 61 (10%), 67 (11%), and 22 (4%) reported housing insecurity, food insecurity, transportation and utility issues, respectively. Compared to participants without social needs, those reporting ≥1 social need were more likely to be female (63% vs 43%) and Hispanic/Latino/a/x (27% versus 23%), and less likely to have a college education (21% versus 42%) (Table).

Conclusions: Among CRIC study participants, Black and Hispanic/Latino/a/x individuals and females were more likely to experience health-related social needs during the COVID-19 pandemic. Associated long-term outcomes are worthy of investigation.

Funding: NIDDK Support

Table. Odds ratios associated with reporting ≥1 social need and each individual need

	Odds Ratio for ≥1 Social Need n = 122 (20%)	Odds Ratio for Housing Insecurity n = 29 (5%)	Odds Ratio for Food Insecurity n = 61 (10%)	Odds Ratio for Transportation Issues n = 67 (11%)	Odds ratio for Utility Issues n = 22 (4%)
Age, per 10 years	0.82	0.80*	0.74	0.82	0.90
Gender					
Female	1.97*	0.66	2.49*	3.20*	2.09
Male	Ref	Ref	Ref	Ref	Ref
Race/ethnicity					
Nonhispanic white	Ref	Ref	Ref	Ref	Ref
Nonhispanic Black	2.28*	2.61	3.40*	1.78	4.86
Hispanic	3.40*	3.24	7.04*	1.73	9.31*
Other	3.58	NA	NA	5.16	NA
Education level					
Less than high school	Ref	Ref	Ref	Ref	Ref
High school graduate	0.52	0.47	0.45	0.57	0.31
Some college	0.65	0.57	0.67	0.94	1.27
College graduate	0.49*	0.46	0.87	0.57	na
Current smoker	1.52	2.35	2.18	0.62	0.83
Blood pressure ≥130/80 mmHg	1.36	1.81	1.76	1.76*	1.33
Hemoglobin A1C, per 1%	1.04	1.05	0.90	1.03	1.11
eGFR, per 10 ml/min/1.73m^2	1.00	0.90	1.00	0.90	0.82

*Statistically significant findings.

Note: variables were tested in combination with all other variables.

Abbreviations: na – not applicable (there were not enough individuals within this category); eGFR – estimated glomerular filtration rate

SA-PO060

Food Security in Jamaicans with CKD Following the COVID-19 Pandemic: A Pilot Observational Study

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Background: Limited data exists on food security amongst persons with chronic kidney disease (CKD) in the Caribbean, especially since the onset of the COVID-19 pandemic. We describe the prevalence of food-insecurity in persons living with CKD from a single centre in Jamaica.

Methods: A cross-sectional survey was conducted between December 1,2022 and March 31, 2023 among 18 and 74 year old patients attending the University Hospital of the West Indies renal clinic prior to the onset of the pandemic (March 2020) and who were not on dialysis. Informed consent was obtained from patients who agreed to share their contact information with the study team prior to enrolment. A telephone administered questionnaire that included details on demographics, food security and health care utilization was administered by trained interviewers. Data on cause of CKD, creatinine values at each clinic visit, and hospital and emergency room visits were abstracted from hospital records. Self-reported food insecurity was based on responses to a standard Centers for Disease Control questionnaire. Means and standard deviations were used to describe continuous variables, whilst proportions were used to describe categorical data.

Results: 43 participants [51.4±14.8 (mean ±SD) years, 72% female] were included. The majority (32%) had CKD Stage 3 disease, with 11% with CKD Stage 4 and 2% with CKD Stage 5. CKD was attributed to diabetes/hypertension in 30% of persons, lupus in 25%, and sickle cell disease in 28%. The majority (84%) had at least high school education and 35% were either retired or unemployed. Food insecurity was reported by 42 (95% CI=28-59)% of participants before the pandemic and 52(36-68)% during the pandemic. Less than half (46%) of patients had one or more hospitalizations or emergency room visit during the covid pandemic. There was no difference in mean age between food secure and insecure(52.1 versus 48.2 years, p=0.238) but a higher proportion of women reported food insecurity (61 versus 27%, p=0.05) during the pandemic. There was no statistically significant association between hospitalization or emergency room visits and food insecurity (p=0.169).

Conclusions: There was a high prevalence of food insecurity in the patients with CKD evaluated. Larger studies are needed to examine how this impacts health care outcomes and utilization in the region.

Funding: Government Support - Non-U.S.

SA-PO061

Area Deprivation Index and Spanish Language Are Barriers to Equitable Nephrology Care in a Hispanic Pediatric Subspecialty Cohort

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Background: Hispanics are the largest population of Chicago youth and they have an increased risk and rate of chronic kidney disease progression. Addressing healthcare disparities in Hispanic patients is important to improve health outcomes. This study aims to understand the impact of language and socioeconomic disadvantage on access to care in Hispanic patients seen in pediatric nephrology clinics.

Methods: All patients that identified as Hispanic seen in Lurie Children's Hospital nephrology clinic between January and June 2021 received the validated tool "Barriers

to Care Questionnaire" to assess healthcare access. Parents or patients older than 18 completed the survey in their preferred language. A score of 100 equates no barriers to care, and a score < 75 equates a failed score due to high barriers. We also collected sociodemographic data and the Area Deprivation Index (ADI), a metric of socioeconomic disadvantage that incorporates 17 socioeconomic measures. The national ADI score ranges from 1 (most advantaged) to 100 (most disadvantaged). We created linear regression models to describe the association between barriers and ADI scores and tested for interactions based on language.

Results: In 109 surveys (49% Spanish, 51% English), we identified high skills and pragmatic barriers to care, with mean (+/-standard deviation) scores of 74 (+/-26) and 75 (+/-21), respectively. The mean ADI score was 55 (+/-20). Spanish-speaking families had higher skills barriers (p<0.001); no difference in pragmatic barriers (p=0.40*)* and mean ADI score (p=0.38). A higher ADI score correlated with higher total barriers (p=0.006*)* and significant interaction effect by language (p=0.04).

Conclusions: Hispanic youth in Chicago face significant barriers to accessing nephrology care. Spanish-speaking patients with higher socioeconomic disadvantages struggle to navigate the healthcare system. Findings indicate the need for a diverse and multicultural team to support Spanish-speaking families. Prospective studies are necessary to advocate for programs and policy changes to address these barriers and reduce racial and ethnic disparities in pediatric nephrology care.

SA-PO062

Impact of Social Determinants of Health on the Prevalence of CKD in Jalisco, Mexico

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Background: Social determinants of health have been linked with disparities on the incidence and prevalence of CKD. In Mexico, CKD has become an important public health problem; current guidelines recommend routine CKD testing in patients at increased risk. We report the impact of social determinants of health on the prevalence of chronic kidney disease in Jalisco.

Methods: Between 2006-2019 we screened people at risk for the presence of CKD using mobile units that traveled to rural and urban communities of Jalisco. Trained personnel collected demographic and clinical data and obtained blood and urine for serum chemistry and dipstick urinalysis. Individuals who were aware they had kidney disease were not assessed; all others were eligible to participate. GFR was estimated with the EPI-CKD formula. CKD was defined as an eGFR < 60 ml/min/1.73 m2.

Results: Between 2016-2019, 63,918 individuals were evaluated. Findings in individuals with CKD and without it were compared. CKD was more prevalent among individuals without schooling (p=< 0.001), homelessness (p=0.003), unemployed (p< 0.001) and lacking health care insurance (p<0.001) (Table 1). By multivariate analysis, illiteracy (OR 1.10, 95% CI 1.01-1.21, p=0.04) and lack of health care insurance (OR 1.12, 95% CI 1.04-1.19, p 0.001) independently increased the risk of CKD.

Conclusions: Social determinants of health were associated with a greater prevalence of CKD in our population. Our findings suggest that interventions addressing the social determinant factors are needed in individuals with CKD.

Table 1.- Demographics characteristics of the participants.

	CKD n = 5,868 n (%)	no-CKD n = 58,050 n (%)	p
Age (years)	65.9 ±13.4	48.6 ±14.4	<0.001
Female gender	4,340 (74.0%)	36,914 (63.6%)	<0.001
DM	1,868 (31.8%)	10,232 (17.6%)	<0.001
HTA	3,146 (53.6%)	14,645 (25.2%)	<0.001
eGFR (ml/min/1.73m2)	48.9 (11.2)	88.0 (16.0)	<0.001
Illiterate	792 (13.5%)	2,689(4.6%)	<0.001
Homeless	105 (1.8%)	763 (1.3%)	0.003
Unemployed	3,075 (52.4%)	19,695 (33.9%)	<0.001
Uninsured	1,684 (28.7%)	13,663 (23.5%)	<0.001

SA-PO063

Mesoamerican Nephropathy: Opening New Horizons

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Introduction: Mesoamerican nephropathy is a chronic kidney disease of significant importance in Central America. It mainly affects young men in the agricultural field from the Pacific Coast of Nicaragua, and a prevalence of up to 42% has been described in this population. The precise etiology of Mesoamerican Nephropathy (MeN) still remains a mystery.

Case Description: A 37-year-old male from an urban area, who works in construction, with no personal history of hypertension, diabetes, or autoimmune diseases, presents with edema and fatigue. Creatinine levels of 16.5 mg/dL and BUN of 78 mg/dL were observed. Physical examination revealed normal blood pressure and hyporeflexia. Significant laboratory findings included uric acid: 10.6, potassium:3.1 mmol/l, sodium: 134 mmol/l, urinalysis showing proteinuria lower than 0.7 g/dL, and urate crystals. Imaging findings were consistent with CKD. Considering his place of origin and occupation, which expose him to thermal stress and repetitive episodes of dehydration, and in the absence of other causes that could explain the CKD, the first differential to be considered is MeN. Histopathological studies are not feasible for diagnostic confirmation. According to case definitions, this patient can be classified as a probable case of MeN. The patient initiated renal replacement therapy with hemodialysis in a 3-session-per-week schedule, resulting in significant improvement of the clinical condition.

Discussion: The high risk of CKD in agricultural workers in warm areas of Central America has been previously described. However, a high prevalence (12.1%) has also been reported in other occupation with high temperature expose. MeN diagnosis still remains a challenge due to the lack of access to histopathological diagnosis confirmation in the healthcare system. This clinical case allows us to consider other occupation and geographical locations as possible risk factors for the occurrence of MeN. Priority and urgent actions to contain the advancement of this disease should be focused on early diagnosis and prevention in high-risk areas and occupations. It is important to expand the study of MeN to other occupations that share exposure to high temperatures. The economic and health impact of MeN should be mitigated with diagnostic and treatment strategies, as well as expanded research funding for other occupations.

SA-PO064

Geographic Disparities in the Rate of Major Adverse Kidney Events Among Patients with CKD in Alberta

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Background: Individuals in rural communities in Alberta disproportionately experience adverse health outcomes. Characterizing temporal trends in the incidence of major adverse kidney events (MAKE) by geographic characteristics could identify inequities in the management of CKD that can guide policy action.

Methods: We quantified the annual incidence of MAKE in Alberta from 2003-2019, overall and by geographic characteristics of patients' residential zip codes, using routine healthcare data available in the Alberta Kidney Disease Network (AKDN) database. CKD status for cohort eligibility was ascertained based on outpatient eGFR and defined as 2 eGFR values <60 ml/min/1.73m^2 at least 60 days apart; patients entered the cohort on the date of the second qualifying eGFR measurement. MAKE was defined as all-cause death or kidney failure (i.e., chronic dialysis, transplant or sustained eGFR <15 ml/min/1.73m^2) and assessed as the annual proportion of patients with the event from April 1 to March 31. Temporal trends in the rate of change of MAKE were estimated using linear regression.

Results: Among 262,392 patients (median age 75 years; 56% female), the overall incidence rate of MAKE decreased from 7.3% between 2003 and 2004 to 6.5% between 2018 and 2019; and the corresponding rate of change in the annual incidence of MAKE was -0.08 (95% confidence interval -0.10 to -0.06). There was an excess incidence rate of MAKE in rural vs urban locations between 2003 and 2004 (8.7% vs 7.4%); however, this excess rate was attenuated between 2018 and 2019 (6.7% vs 6.5%). Likewise, the excess incidence rate of MAKE in residential locations >100 km vs ≤50 km from the nearest nephrology center between 2003 and 2004 (9.3% vs 6.8%) was substantially reduced between 2018 and 2019 (6.5% vs 6.4%).

Conclusions: Disparities in incident MAKE by geographic characteristics of patients in Alberta have improved over the last 2 decades. Future studies exploring factors (e.g., CKD care indicators, population mix) that might have contributed to these noticeable improvements are needed for development of policy interventions to optimize CKD outcomes equitably for all patients.

Funding: Government Support - Non-U.S.

SA-PO065

Searching for Significance in Oceania: A Voyage of Recurrent FSGS in a Patient from the Marshall Islands with Variants of Uncertain Significance

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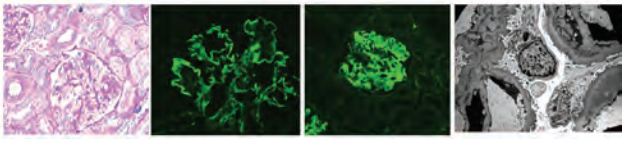
Introduction: The success of next generation exome sequence analysis has dependency on clinical and pathologic phenotypic correlation. There is a gap in knowledge of genetic variants in glomerulopathy unique to those referred to the Pacific Basin's single adult organ transplantation program. The effects of the U.S. Nuclear Weapons Testing Program (USNWTP) in the Bikini Atoll between 1946-1958 with aggregate detonation of "7,200 Hiroshima atomic bombs" are unknown for the relocated inhabitants. We present a case of recurrent FSGS with unusual mesangial IgM predominant deposits and associated variants of uncertain significance.

Case Description: The patient is a 21 year old female from the Marshall Islands with history of deceased donor renal transplant 3 years prior who presents with increased proteinuria. Renal biopsy showed no evidence of rejection but segmental sclerosis with IgM positivity in a membranoproliferative pattern along with diffuse mesangial C4d positivity with electron dense deposits (Figure 1). Review of history showed she was diagnosed with FSGS on biopsy in the Philippines at age 16 then relocated to Honolulu, Hawaii where she was evaluated by pediatric nephrology. Results from KidneySeq^{tm}v3.0 (Figure 2) revealed heterozygous variants of uncertain significance. Two were in XPO5 (exportin-5), variants of which have been associated with autosomal recessive FSGS, one in NPHS2 (podocin), and a variant in CUBN, a receptor on intestinal mucosa with high affinity binding to APOA1/HDL and intrinsic factor-vitamin B12.

Discussion: We demonstrate the possibility of a recurrent glomerulopathy due to circulating factor rather than donor related disease. VUS analysis must be made alongside biopsy phenotype correlation for greatest benefit. Patients most in need of equity in health and technology must also be included in gene variant databases.



From left to right, light microscopy, IgM, C4d, electron microscopy

Gene	Chromosome		Path Prediction
ANLN	chr7	NM_018685;C752g>a, p.Ser251Asn	4/6
CUBN	chr10	NM_001081;c.6089G>A, p.Arg2030Gln	0/6
ITGA3	chr17	NM_002204;c.2362G>A, p.Val788Met	3/6
NPHP4	chr1	NM_015102, c.4145G>A, p.Gly1382Glu	1/5
NPHS2	chr1	NM_014625, c.1064A>G, p.Asn355Ser	2/6
XPO5	chr6	NM_020750;C.2117G>C,p.Cys706Ser	1/6
XPO5	chr6	NM_020750;c.1655T>C,p.Val552Ala	5/6

SA-PO066

Climate Change and Sustainability in Kidney Care in Canada: A Knowledge, Attitudes, and Practices (KAP) Survey by the Canadian Society of Nephrology's Sustainable Nephrology Action Planning Committee

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Background: Climate change impacts kidney health while threatening the stability of kidney care delivery systems, while health care itself has a significant environmental impact. Knowledge and attitude of Canadian kidney care providers toward climate change is unknown, and there are limited published data on environmental sustainability measures in kidney care in Canada. This study aimed to (1) assess knowledge and attitude about climate change among Canadian kidney care providers; (2) establish the current state of kidney care sustainability activities in Canada.

Methods: An electronic KAP survey, created by the Canadian Society of Nephrology – Sustainable Nephrology Action Planning (CSN-SNAP) committee, was distributed to kidney care providers across Canada.

Results: A total of 386 individuals completed the survey, while an additional 130 incomplete answers were provided. Most respondents (79%) identified as women and 26%, 31% and 26% were aged 30-39, 40-49 and 50-59 years, respectively. Consultant nephrologists and kidney nurses comprised 23% and 44% of respondents, respectively. Most respondents were either extremely (25%), very (46%) or moderately (23%) concerned about climate change; and similarly extremely (23%), very (39%) or moderately (28%) concerned about the amount of waste generated in their kidney care program. Respondents deemed reducing the carbon footprint important in both their personal lives (very 39%; important 35%; fairly 17%), and in the kidney care services they provide (very 34%; important 37%; fairly 18%). The sustainable strategies most frequently incorporated into kidney care were reduced use of office consumables and equipment, water saving taps, waste management (mostly bins, including recycling), clinical care consumables' use prioritized by expiry dates, virtual care options to minimize unnecessary transportation, and medication stewardship strategies.

Conclusions: Most Canadian kidney care providers are highly concerned about climate change and think it is important to reduce the environmental impact in both their personal lives, as well as in the kidney care services they provide. Few sustainable strategies are incorporated into kidney care services across the country.

SA-PO067

Assessment of Equity, Inclusiveness, and Quality of Life for French-Speaking Male and Female Nephrologists: A Survey by the FEMKY Group

Bénédicte Sautenet,[1,2] Sabine Karam,[3] Laurence Vrigneaud,[5] Cecile M. Vigneau,[6] Valerie Chatelet Pouliquen.[4] Group FEMKY from SFNDT. *[1]Universite de Tours, Tours, France; [2]Centre Hospitalier Regional Universitaire de Tours, Tours, France; [3]University of Minnesota Twin Cities School of Medicine, Minneapolis, MN; [4]Normandie Universite, Caen, France; [5]Hopital Prive La Louviere, Lille, France; [6]Universite de Rennes, Rennes, France.*

Background: Recent surveys report a high rate of burnout for nephrologists. The quality of life at work and in personal life as well as the perception of gender discrimination at work are insufficiently defined.

Methods: The FEMKY group (FEMmes KYdney) conducted a cross-sectional 'descriptive observational study by sending an online survey to French-speaking nephrologists members of the Francophone Society of Nephrology, Dialysis and Transplantation (SFNDT) and of the young nephrologists club in France (CJN), from November 2022 to January 2023. We assessed 6 domains: demographic characteristics, working conditions, quality of life at work and in personal life, gender discrimination and history of workplace harassment.

Results: 257 female and 128 male nephrologists responded. 76% of women and 66% of men were under 45 years old and 53% and 51% respectively worked in a university hospital. Quality of life at work was similar for both genders but significantly lower for women at the personal level ($p=0.03$). Feeling of fatigue ($p=0.01$) and dissatisfaction with leisure time were significantly higher in women ($p<0.001$). The opinions of the two genders were significantly different regarding whether the fact of being a woman closes doors at work ($p=0.02$), that women are less trusted ($p<0.001$), and that pregnancies and children education are an obstacle for a woman career ($p=0.001$). Harassment and humiliation at work were described by 37% and 46% of women and 26% and 36% of men ($p=0.03$ and $p=0.06$ respectively).

Conclusions: The quality of life at work was similar between the two genders despite a more important and concerning rate of feeling of discrimination, harassment, and humiliation at work for women and a lower quality of personal life.

SA-PO068

Fellow Attitudes and Perceptions of Health Equity Care and Training in Nephrology

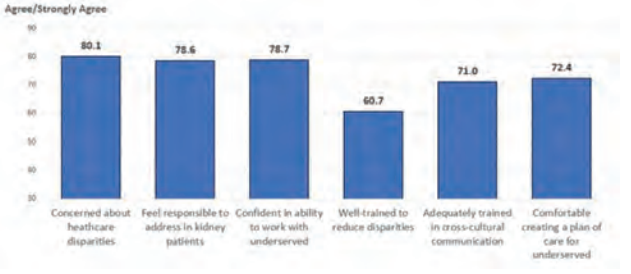
Areeba Jawed, Jennifer L. Bragg-Gresham, Michael Heung, Laura H. Mariani, Panduranga S. Rao, Julie A. Wright Nunes. *University of Michigan Michigan Medicine, Ann Arbor, MI.*

Background: Little is known about the current state of Health Equity care and training within Nephrology Fellowship. We developed a survey to assess fellow attitudes about caring for diverse and underserved patient populations and perceptions on fellow training to prepare them to do so.

Methods: Via a survey administered to all U.S nephrology trainees through the ASN inservice training exam (ITE) Spring 2022 we assessed fellow attitudes and perceptions. The survey included 13 questions: 5 demographics and 8 assessing attitude in caring for underserved patients and perceptions of how well training prepared them to do so.

Results: Of the 816 trainees taking the ITE survey, 706 provided informed consent to use their responses, and 689 responses were analyzed due to missing data, for a response rate of 84.4%. The survey reliability factor was 0.7-0.8. Respondents were on average 34 years old, 57% Male, and 11% Hispanic. Predominant races were White (34.2%) and South Asian (27.7%) and most were international (26.3%) or US (24.3%) medical graduates, with 72.3% reporting working with underserved populations often/always. In multivariate analysis Hispanic and African American fellows and graduates of US medical schools were more likely to have worked with underserved patients and show concern for disparities within nephrology. Women and fellows who were further out in training scored lower when it came to confidence and perceptions regarding adequate training to reduce health care disparities.

Conclusions: Although fellows stressed the importance of caring for underserved patients a high proportion did not feel fellowship prepared them adequately for this. Effort needs to be made to better equip trainees with the skills they need to care for all patients, with opportunity to address needs in women.



SA-PO069

Trends in Race/Ethnicity of ASN Kidney Week Faculty (Speakers, Moderators, and Program Chairs): 2018-2022

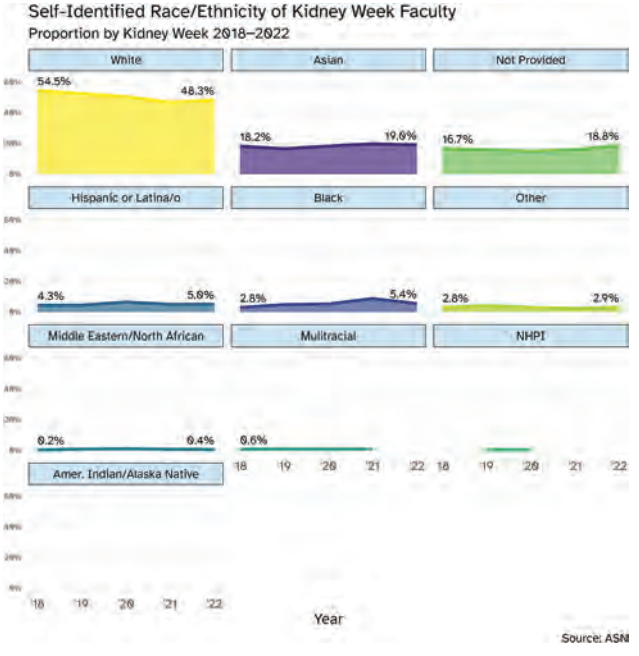
Tushar Chopra,[1] Kurtis A. Pivert,[2] Rasheed A. Balogun,[1] Suzanne Boyle,[3] Jason Cobb,[4] Sana Waheed,[4] Hassan Gorji,[5] Rakesh Malhotra.[5] *[1]University of Virginia, Charlottesville, VA; [2]American Society of Nephrology, Washington, DC; [3]Lewis Katz School of Medicine at Temple University, Philadelphia, PA; [4]Emory University School of Medicine, Atlanta, GA; [5]University of San Diego, San Diego, CA.*

Background: ASN Kidney Week (KW) is the world's premier nephrology meeting. As one of ASN's key goals is to promote diversity, equity, and inclusion (DEI) to advance kidney health, we analyzed self-reported racial/ethnicity amongst KW faculty.

Methods: We conducted a retrospective analysis of trends in race/ethnicity of U.S. KW faculty 2018–2022. Self-reported race/ethnicity for KW faculty (speakers, moderators, and program chairs) was obtained from ASN's database. We performed a descriptive analysis amongst KW faculty cohort racial proportions over time. Descriptive data is reported as relative percentage frequency. The reported race/ethnicity was: White/Non-Hispanic White, Black, Asian, Hispanic or Latin(o), American Indian or Alaska Native, Native Hawaiian or Pacific Islander, and Mixed. We also added a category of others/unknowns who did not report race.

Results: 23% (mean n=12,132) of ASN members and 16% (mean n=508) of faculty did not self-report race/ethnicity during KW 2018–2022. White (33-35%) was the most common self-reported race among ASN members, followed by Asian (24%). Blacks were 4.3-4.6%, and Hispanics or Latin(o) were 5.4-6% among ASN members. Over the five years, white faculty declined from 54.5% to 48.3%. At the same time, we found improving trends of Blacks in KW faculty representation from 2.7 to 5.4%. Hispanic or Latin(o) representation remains stable at 5.4-6% among KW faculty.

Conclusions: We found that Asian, Black and Hispanics KW faculty were underrepresented as KW faculty. However, these findings may also be reflection of their lower representation as ASN members. Prioritizing DEI to close this gap is key to fostering the innovation and creativity needed to advance kidney health.



Trends in Race/Ethnicity of KW Faculty

SA-PO070

Validation of ISN 0by25 Acute Kidney Injury Risk Score for Low- and Low Middle-Income Countries

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Background: Incidence of Acute Kidney Injury (AKI) is increasing in low-resource countries and is associated with morbidity and mortality. Early identification of patients at increased risk for AKI is the first step to implement preventive and treatment strategies. Multiple risk scores to predict AKI have been developed in higher-income countries and are specific for particular risk settings. Here, we validated new symptoms-based ISN 0by25 AKI risk score that can be easily implementable in resource-constrained environments.

Methods: Forty-seven hospitalized patients from Clinica "Los Olivos" in Cochabamba, Bolivia were enrolled in this ongoing study. Data for predictor variables was extracted from patient's medical charts at the time of admission. The ISN 0by25 risk score was calculated at admission and patients with a risk score of ≥ 3 points were included. Patient information was recorded from the time of diagnosis and renal function (serum creatinine[sCr]) was followed up daily up to 7 days. AKI was defined using KDIGO sCr criteria.

Results: A total of 29 patients (61.7%) developed AKI and 77% were female. The main risk factors for AKI were age ≥65 years (64%), DM (60%) and congestive heart failure (40%). The 3 main causes of AKI were nephrotoxins exposure (93.6%), dehydration (87.2%), and hypotension (38.2%). Positive and negative predictive values for the optimal cutoff value of ≥ 6 points in the cohort were 87.5% and 65.2% respectively with an odds ratio (OR) of 13.1 (95% CI 3.0-57.8; p=0.0007). The risk score has a good performance in predicting AKI with a ROC-AUC of 0.85 (95% CI 0.75 - 0.96; p = 0.0001). None of the patients who developed AKI required dialysis.

Conclusions: We validated the performance of the ISN 0by25 risk score in predicting hospital-acquired AKI, which showed good performance. This risk assessment tool could help clinicians stratify patients for primary prevention, surveillance and early therapeutic interventions to improve the care and outcomes of high-risk patients in low-resource settings.

SA-PO071

Assessing Ambient Heat Exposure and AKI Using Alternate Case Definitions

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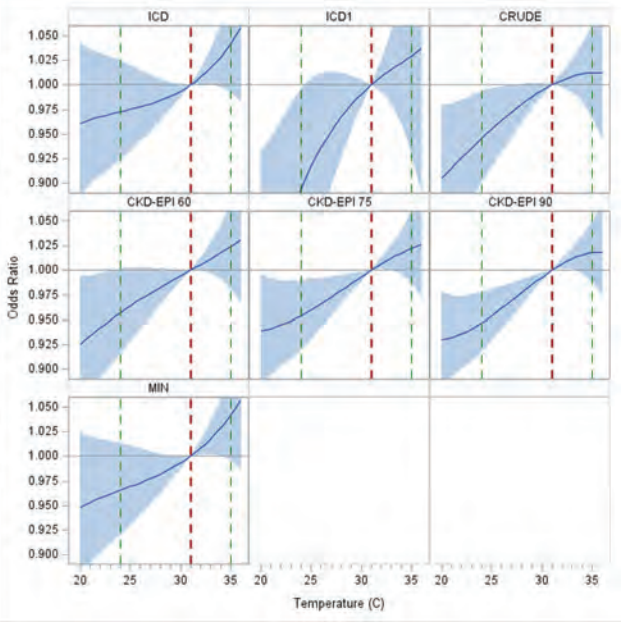
Background: Ambient heat exposure is an established risk factor for the development of acute kidney injury (AKI). However, prior work using International Classification of Disease (ICD)-coded data has important limitations in evaluating heat-AKI. We hypothesized that Kidney Disease: Improving Global Outcomes (KDIGO)-based AKI definitions would improve the accuracy of heat-AKI effect estimates compared to ICD-coded data by improving AKI case sensitivity.

Methods: We conducted a case-crossover study comparing AKI-related emergency department (ED) visits with same-day maximum temperatures in Atlanta, Georgia during 6 consecutive warm seasons. We created 7 case definitions for AKI using ICD-coded data and KDIGO-derived equations. KDIGO definitions compared an individual's serum creatinine measurements to surrogate values for baseline renal function.

Results: We analyzed 368,682 total ED visits between 2014 and 2019. Cases of AKI ranged from 5,868 to 64,269 across the 7 definitions. Higher temperatures were associated with AKI-related ED visits in all 7 definitions (Figure 1). When we stratified individuals by the presence of an ICD-coded AKI diagosis, we detected a persistent heat-AKI effect among individuals *without* a coded AKI diagnosis under the "CKD-EPI 75" (OR 1.06, 95% CI 1.02-1.12) and "CKD-EPI 90" (OR 1.07, 95% CI 1.03–1.11) definitions.

Conclusions: Our results support KDIGO-based definitions as an improved tool to evaluate the heat-AKI relationship. This method may enable reseachers to capture additional AKI cases otherwise missed by code-classified data, for whom a significant heat-AKI effect exists.



Exposure response functions by case definition for the risk of AKI across daily maximum temperature (Odds ratios provided with 95% CI).

SA-PO072

Worldwide Incidence and Associated Mortality of AKI in Neonates: A Systematic Review and Meta-Analysis

Jahnavi Phanidhar Kocharlakota,[1] Jitendra Meena,[1] Joginder Kumar Yadav,[2] Amit Kumar,[1] Aditi Sinha,[1] Pankaj Hari,[1] Arvind Bagga.[1] *[1]All India Institute of Medical Sciences, New Delhi, India; [2]Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

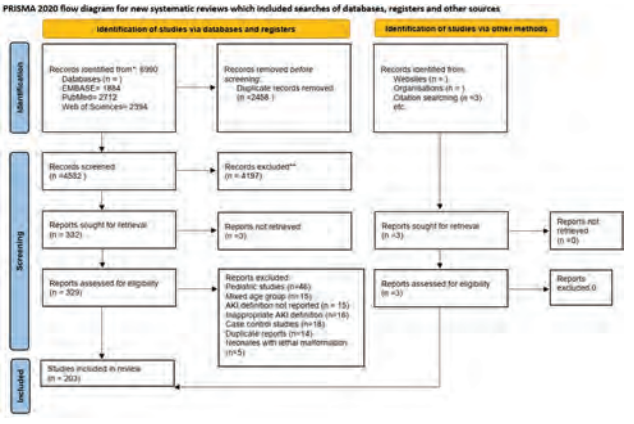
Background: There is limited literature on the global incidence of acute kidney injury (AKI) and associated mortality in neonates. We aim to systematically assess the worldwide incidence of AKI in neonates to increase awareness and inform policymakers.

Methods: We searched three databases (PubMed, Embase, Web of Sciences) from 2004 to December 2022 without language or geographical restrictions. Cohort and Cross-sectional studies reporting the incidence of AKI in neonates were included in this systematic review. Eligible studies had at least 10 participants and used AKIN, RIFLE, and KDIGO or their equivalent criteria to define AKI. Two authors independently extracted data about the study and patients' characteristics and outcomes (incidence and AKI-associated mortality) and assessed the risk of bias. We used a random-effects meta-analysis to generate pooled estimates.

Results: From the initial 6990 records, we included 201 studies (98470 neonates) from 51 countries. The pooled incidence of any stage AKI was 34% (95% confidence interval: 31-37), and that of severe AKI was 15% (14-17). The incidence of AKI was lower in high-income 31% (27-35), low-middle-income 40% (32-48), and low-income 47% (6-97) countries. Pooled mortality was higher (OR 3.2; 95% CI 2.9-3.5) in neonates with AKI (29%; 95% CI 25-34) compared to those without AKI (8%; 95% CI 8-10). Mortality was lower in high-income 25% (20-30), low-middle-income 30% (20-42), and low-income 37% (20-56) countries.

Conclusions: AKI was observed in almost one-third of hospitalized neonates and is associated with increased mortality risk. Incidence and mortality associated with AKI were higher in low-middle-income countries than in high-income countries.

Funding: Government Support - Non-U.S.



PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

SA-PO073

Epidemiology of Perioperative AKI in Neonates Undergoing Noncardiac Surgeries

Morgan E. Beebe,[1] Brett Klamer,[2,1] Jonathan L. Slaughter,[1] Tahagod Mohamed.[1] *[1]Nationwide Children's Hospital, Columbus, OH; [2]The Ohio State University, Columbus, OH.*

Background: The epidemiology of AKI in neonates requiring cardiac surgeries exists; however, the incidence of AKI in neonates undergoing noncardiac surgeries is not fully characterized. Our study aims to evaluate the epidemiology and outcomes of perioperative AKI (POAKI) in neonates undergoing noncardiac surgeries in the first 28 days of life at our institution. We hypothesized that noncardiac surgeries can be a risk factor for AKI, and infants who develop POAKI have worse short-term outcomes.

Methods: This is a retrospective review of neonates admitted to a single, level IV neonatal intensive care unit from Nov '14-Jan '22. Neonates aged 0-28 days who required a noncardiac surgery in the first 28 days of life were included for analysis. Neonates requiring a cardiac surgery, ECMO, had a lethal chromosomal abnormality, or with significant underlying kidney disease were excluded. Data were evaluated for the development of AKI in the 72 hours following surgery according to the neonatal modification of Kidney Disease: Improving Global Outcomes (KDIGO) criteria. We evaluated the distribution of fluid balance in the postoperative period. Descriptive statistics were used to summarize patient characteristics. Fisher's exact test, Pearson's Chi-squared test, and the Wilcoxon rank sum test were used to analyze the relationship between AKI status with other variables. Statistical significance was assessed at an alpha level of 0.05.

Results: A total of 873 neonates were included. Of those, 705 neonates had creatinine measurements available and 42% were females. The median gestational age, birthweight and age at surgery were 37 weeks, 2760 g and 4 days respectively. Abdominal, ENT, and Neuro- surgeries were most common. The rate of POAKI was 5%. With POAKI, the 1 min Apgar scores were significantly lower, postoperative day 1 fluid balance was significantly higher (11 vs 4%) and hospital mortality rates significantly higher (25 vs 4%).

Conclusions: In this single-center retrospective analysis, POAKI occurred in 5% of neonates requiring non-cardiac surgeries in the first 28 days of life. Low Apgar scores, fluid overload, and hospital mortality were more frequent in neonates who developed POAKI. Future work should focus on monitoring kidney health in neonates undergoing non-cardiac procedures to prevent AKI and implement effective therapies for management of fluid overload.

SA-PO074

A Case of Fulminant Leptospirosis

Sakshi Yadav, Hanni Menn-Josephy. *Boston Medical Center, Boston, MA.*

Introduction: Leptospirosis, the most prevalent zoonosis worldwide, is a disease that has historically had low reported cases in the United States. However, recent discussions have focused on the re-emergence of Leptospirosis in this region.

Case Description: We present the case of a 69-year-old Hispanic male who presented with acute onset abdominal pain, fever, and muscle cramps persisting for three days. The patient was found to have acute kidney injury(with a creatinine of 3.3 mg/dL) and promptly initiated on intravenous fluids and empiric antibiotics. Urinalysis revealed mild proteinuria and hematuria, with microscopic examination of the urine sediment showing a few red and white blood cells, few granular casts, and rare white blood cell casts cellular casts. A 24-hour urine protein collection yielded a result of 452 mg. Despite antibiotic therapy, the patient continued to experience daily fevers, excessive night sweats, and severe myalgias and continued to deteriorate with worsening nonoliguric kidney injury (creatinine level peaked at 5mg/dL). He developed thrombocytopenia (platelet count nadir of 45) and hyperbilirubinemia (total bilirubin 6mg/dL with direct bilirubin 4mg/dL), despite otherwise normal liver function. The patient had markedly elevated inflammatory markers with an erythrocyte sedimentation rate (ESR) of 104 mm/hour, C-reactive protein (CRP) of 226 mg/dL, and a fibrinogen level of >800 mg/dL. Complement (C3 and C4) levels, creatine kinase, were within the reference range, and serological/autoimmune workup was negative. Subsequent renal biopsy revealed predominant acute interstitial nephritis and some focal acute tubular injury. An infectious workup confirmed the presence of Leptospira DNA. The patient was initiated on doxycycline therapy, leading to symptom resolution and improvement of multiorgan failure.

Discussion: Leptospirosis, previously regarded as a rural disease primarily affecting tropical regions, is now increasingly reported in urban areas and temperate climates. Factors such as weather changes, population growth, and habitat encroachment have heightened the risk of human exposure to Leptospirosis and its carriers. Therefore, in cases of fulminant multiorgan failure with presumed infectious etiology, clinicians should consider Leptospirosis as a potential cause. Timely initiation of treatment can prevent the progression of chronic kidney disease and, ultimately, end-stage kidney disease.

SA-PO075

Persistent AKI Following Orthotopic Liver Transplant: Prevalence, Risk Factors, and Long-Term Renal Outcomes

Noemi Del Toro-Cisneros, Luis Á. Rivas Sánchez, Karina C. Felix Bauer, Adela U. Pérez, Olynka Vega. *Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Background: This study investigated the pre- and postoperative factors associated with the development of persistent AKI (AKI >72 hours of duration) post-transplant and its impact on renal function during a 5-year follow-up.

Methods: Retrospective study that included all patients who underwent OLT from January 2008 to December 2018. Demographic data, data inherent to the surgical procedure and post-operative factors associated with AKI. Subsequently, we performed logistic analysis with variables to predict persistent AKI. Finally, we analyzed the renal trajectory between the two groups: those with persistent AKI and those without it.

Results: 305 patients were included, 23% developed persistent AKI post-OLH. Demographic characteristics, comorbidities, and perioperative variables are shown in **Table 1**. In the multivariate analysis, the significant variables are shown in **Table 2**. Mortality at hospital discharge was not different between the groups. In the analysis of the renal trajectories, the patients who presented persistent AKI had a lower eGFR with a median difference at 5 years of follow-up of 10ml/min/1.73m2.

Conclusions: In the present study, the factors associated with AKI development were: male gender, ascites drainage during surgery, diuresis <500ml in the first 24 hours post-OLT, use of antifungals, and anhepatic time >50 minutes. Long-term renal function in patients who developed persistent AKI deteriorated more compared to those who did not.

Table 1: Clinical characteristics of patients included in this study.

	Persistent AKI (n=70)	No AKI (235)	p-Value
Demographics			
Age, years	54 (45-61)	51 (40-59)	0.08
Male, n (%)	**48 (69)**	**100 (43)**	**0.000**
Hepatocellular carcinoma, n (%)	8 (11)	54 (23)	0.05
Indice de Charlsen, n (%)	4 (3-5)	4 (3-5)	0.84
MELD score	18 (14-22)	17 (14-21)	0.54
Kidney function			
Baseline SCr, mg/dL	**0.8 (0.7-1.0)**	**0.7 (0.6-0.9)**	**0.000**
SCr at OLT, mg/dL	**0.9 (0.8-1.3)**	**0.8 (0.6-0.9)**	**0.000**
SCr at hospital discharge, mg/dL	**1.0 (0.8-1.3)**	**0.7 (0.5-0.9)**	**0.000**
OLT			
Surgery time, hours	7 (5-8)	6 (5-8)	0.07
Surgery bleeding, liters	**3 (1.6-6)**	**2 (1.2-3)**	**0.000**
Anhepatic time, minutes	57 (52-66)	55 (49-60)	0.08
Norepinephrine >0.25mcg/kg/min, n (%)	49 (70)	133 (57)	0.07
Ascites drainage in OLT, n (%)	**35 (50)**	**85 (36)**	**0.006**
Post OLT in ICU			
Antibiotics, n (%)	**54 (77)**	**145 (62)**	**0.007**
Antifungals, n (%)	**41 (59)**	**85 (36)**	**0.001**
ICU transfusion, n (%)	**22 (31)**	**39 (17)**	**0.007**
Norepinephrine >0.25mcg/kg/min, n (%)	**23 (33)**	**25 (11)**	**0.000**
Reoperation, n (%)	**12 (17)**	**10 (4)**	**0.001**
Diuresis <500ml in the first 24h	**18 (26)**	**31 (13)**	**0.014**
Death, n (%)	10 (14)	19 (8)	0.07

Note. Continuous variables are expressed as median (interquartile range).
Abbreviations. MELD, Model for End stage Liver Disease; OLT, orthotopic liver transplant; AKI, acute kidney injury; SCr, serum creatinine; ICU, intensive care unit.

Table 2. Multivariate logistic regression analysis for factors associated with persistent AKI post-OLT.

	Multivariate		
Characteristic	**OR**	**95%CI**	**p-Value**
Age, per year	1.033	0.998-1.069	0.066
Male, vs female	**4.190**	**1.726-10.174**	**0.002**
Ascites drainage in OLT, Vs no	**2.277**	**0.997-5.198**	**0.051**
Reoperation, Vs no	3.780	0.741-19.281	0.110
Diuresis <500ml in the first 24h, Vs no	**2.485**	**1.026-6.016**	**0.044**
Antifungals, Vs no	**3.055**	**1.245-7.497**	**0.015**
Anhepatic time >50 min, Vs no	**3.585**	**1.029-12.485**	**0.045**

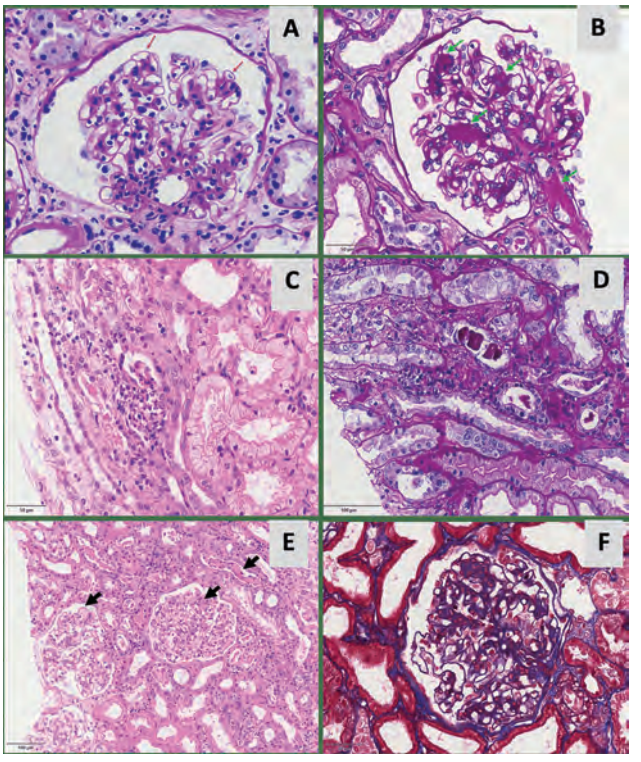
SA-PO076

AKI due to Acute Tubulo-Interstitial Nephritis and Diabetic Nephropathy in a Patient with Pulmonary Aspergillosis

Clementina Elizabeth Calderon Garcia, Guillermo Navarro Blackaller, Eric J. Zavala López, Jonathan Chavez. *Hospital Civil de Guadalajara Unidad Hospitalaria Fray Antonio Alcalde, Guadalajara, Mexico.*

Case Description: A 45-year-old woman with diabetes mellitus, 8 years of evolution in poor control, asthma, and chronic smoking. Admited with hyperglycemic crisis due to pneumonia: procalcitonin 0.3, Hb 16g/dl, WBC 16, albumin 3.74g/dl, SCr 0.79mg/dl, urea 25mg/dl, glucose 933mg/dl, HbA1c 14%. Patient presents cough, fever, hemoptysis, a chest tomography with pulmonary infiltrates and cavitated nodules. Bronchoscopy reported Aspergillus. Management with liposomal amphotericin, presented acute kidney injury, SCr 4 mg/dl, proteinuria 1g/24hrs, urinary sediment: leukocytosis, erythrocytes without acanthocytes. Renal biopsy reports: Acute tubulointerstitial nephritis (aTIN), presence of a mixed lymphoplasmacytic infiltrate of lymphocytes and eosinophils suggestive of aTIN due to drugs and a concomitant diabetic nephropathy (Thickening of glomerular capillaries, diffuse glomerulosclerosis, with mesangial expansion and Kimmelstiel-Wilson nodules). Management with pulsed methylprednisolone 250mg and prednisone 0.5mg/kg per day for 6 weeks.

Discussion: aTIN is a form of glomerular-sparing non-oliguric renal disease that results from an allergic or immunologic reaction to intrarenal antigens and leads to tubular damage. The drugs normally associated are NSAIDs, antibiotics, and proton pump. Our patient was exposed to liposomal amphotericin. In the case series of renal biopsies in patients with DM2 (4876 patients), the prevalence of glomerulopathy not associated with DN was up to 35% and mixed forms 45%. Conclusion In the case that we present a patient living with chronic and poorly controlled diabetes who presented AKI, DN, the AKI approach must be considered regardless of comorbidities where the use of drugs is not innocuous.



SA-PO077

Parenchymal and Nontraditional Etiologies of AKI in Patients with End-Stage Liver Disease

Vipin Varghese, Akanksh Ramanand, Lauren Cohen, Dustin R. Chalmers, Juan Carlos Q. Velez. *Ochsner Health, New Orleans, LA.*

Background: In the context of acute kidney injury (AKI) and end-stage liver disease (ESLD), AKI is frequently attributed to either hepatorenal syndrome type 1 (HRS-1), ischemic acute tubular injury (ATI), or pre-renal azotemia (PRA). We hypothesized that other parenchymal causes of AKI including toxic ATI, acute glomerulonephritis (AGN) and acute interstitial nephritis (AIN) may account for a small but not negligible proportion of cases of AKI in patients with ESLD.

Methods: We established prospective data collection in patients with ESLD with AKI stage ≥ 2 (AKIN) over 5-years who were seen by the nephrology consultation service. Demographic and clinical data were collected. Etiology of AKI was adjudicated based on history, clinical assessment, laboratory results, urine microscopy findings, and kidney biopsy data.

Results: We included 234 patients with AKI and ESLD. The median age was 57 (20-88), 37% were female, 76% were white, and 15% were black. CKD was a pre-existing comorbidity in 26%. PRA was the cause of AKI in 12 (5%) (low rate likely explained by resolution without consultation to nephrology), HRS-1 in 76 (32%), cardiorenal syndrome type 1 (CRS-1) in 6 (3%) abdominal compartment syndrome (ACS) in 2 (1%) and obstructive uropathy (OU) in 3 (1%). Parenchymal etiologies of AKI were noted in 137 (59%) of patients. Among parenchymal etiologies of AKI, ischemic ATI was the primary diagnosis in 78 (58%), toxic ATI in 26 (19%), ischemic/toxic ATI in 22 (16%), AIN in 2 (1%), and AGN in 7 (5%). Among those with toxic ATI, 3 were due to vancomycin, 2 to ciprofloxacin, 1 to uric acid, 1 to contrast, 15 to cholemic tubulopathy, and 4 due to other drugs. Both cases of AIN were associated with ciprofloxacin use. Among those with AGN, 4 were biopsy-proven (3 IgA nephropathy, 1 immune complex-GN) and 3 were clinical diagnoses (2 IgA nephropathy, 1 SLE-GN).

Conclusions: Combining toxic ATI (drug-induced, endogenous toxins), AIN, and AGN, non-traditional parenchymal causes of AKI accounted for 15% of the cases in these cohort of patients with ESLD and AKI. When added to CRS-1, ACS and OU, a total of 19% of the cases were not within the traditional 3-way split (PRA, HRS-1, ischemic ATI). Comprehensive diagnostic assessment is recommended in this clinical setting.

SA-PO078

Rare Case of Mycobacterium avium Complex (MAC)-Associated Immune Reconstitution Inflammatory Syndrome (IRIS) Presenting as Acute Interstitial Nephritis

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Introduction: With the advent of antiretroviral therapy (ART), HIV associated comorbidities have declined significantly. However, new conditions related to HIV treatment, rather than progression of the disease itself, have emerged. One such condition

is immune reconstitution inflammatory syndrome (IRIS). ART can lead to a rapid decline in circulating HIV RNA within 1-2 weeks after initiating therapy, which then results in the reemergence of both memory and naïve CD4 T cells, which can sometimes lead to unmasking of opportunistic infections (OIs) by an exaggerated immune response. One of the earliest OIs unmasked after ART therapy is Mycobacterium avium Complex (MAC). MAC- related IRIS occurs in 3.5% of the patients, and usually occurs when the CD4+ count is below 100 cells/mL prior to ART initiation. Common manifestations include lymphadenitis, pulmonary-thoracic disease, and intra-abdominal disease, with less commonly affected organs like skin, bone. We present here a rare case of MAC-associated IRIS presenting as acute interstitial nephritis (AIN).

Case Description: The patient is a 54-year-old male who had been started on Biktarvy after being diagnosed with advanced HIV (initial CD4 count 8, VL 119k). At the time of HIV diagnosis, he had signs and symptoms that included the following: left cervical lymphadenopathy with a predominant node measuring 5cm, fevers, night sweats, fatigue, and significant weight loss. A biopsy of the enlarged left cervical lymph node 1 month after ART initiation revealed the presence of MAC infection. He was subsequently initiated on MAC therapy with azithromycin+ethambutol. Prior to the initiation of these antimicrobials, he was noted to have AKI with Cr 2.7 (baseline 0.8-1). His urine microscopy showed numerous RTE casts without notable WBCs or WBC cast. Kidney biopsy was performed showing AIN with an infiltrate consisting of predominantly CD8+ T cells and histiocytes. He was then started on slow prednisone taper over months while continuing ART with eventually improving kidney function.

Discussion: MAC-associated IRIS is a rare cause of AKI in patients with HIV/AIDs. It presents after initiation of ART, making it sometimes difficult to differentiate from medication associated kidney injury. The injury pattern on kidney biopsy is AIN, which may not be apparent based on urine microscopy as in the case we described here.

SA-PO079

Late-Onset Shiga Toxin-Related Hemolytic Uremic Syndrome

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Introduction: HUS may occur after improvement of gastrointestinal tract symptoms, andl we should carefully monitor for the onset of HUS, even if the patient has few symptoms.

Case Description: A 34-year-old male transferred to the University Medical Center New Orleans for evaluation of nephrotic range proteinuria and edema. He presented to his local hospital ED with edema and bloody diarrhea that started in November and resolved in April after a course of antibiotics for acute pancreatitis. He reported weakness and fatigue, an 11-pound weight loss, nose bleeds, and shortness of breath for about 5 days prior to admission. His initial treatment consisted of 5 UPRBC, and diuresis. He developed an AKI, and a renal biopsy was performed that was consistent with Post-Infectious Glomerulonephritis. WBC 17.0 10’3/uL, Hgb 7.5 gm/dl, Hct 23.4 %, Plt 667 10’3/uL, Schistocytes 3+, Retic Count 7.5%, C3 Compliment 172 mg/dL, C4 Compliment 35 mg/dL, LDH 433, ADAMTS 13 Activity 73.9%, Urine PH 5.0, SG >1.030 Glucose >500 mg/dL, Bld 0.03 mg/dL, RBC 3-5, Protein 100 mg/dL, Prt/Cr ratio 1,100, Hep B, Hep C, HIV all negative, Na 139 mmol/L, K 3.9 mmol/L, Cl 106 mmol/L, CO2 mmol/L, BUN mg/dL, Cr 1.24 mg/dL, ANA neg, haptoglobin <30 mg/dL.

Discussion: Shiga toxin-related hemolytic uremic syndrome (HUS) is a thrombotic microangiopathy that typically begins days after clinical gastroenteritis caused by Shiga toxin–producing Escherichia coli and is characterized by a triad of thrombocytopenia, microangiopathic hemolytic anemia, and acute kidney injury. The patient in this case report presented with few subjective symptoms, and the onset of HUS may not have been noticed if the patient was not hospitalized. In conclusion, this abstract describes a patient with late onset HUS that was preceded by the appearance of minimal gastrointestinal and HUS symptoms, who was successfully treated with IV fluid therapy and corticosteroids alone. In adults with an EHEC infection, HUS may occur after improvement of gastrointestinal symptoms. Careful monitoring of HUS symptoms and changes in chemistry, hematology and urinalysis findings is recommended, regardless of the severity of gastrointestinal symptoms.

SA-PO080

Associations Between Blood Pressure Variability and Renal Recovery and Mortality During Continuous Renal Replacement Therapy

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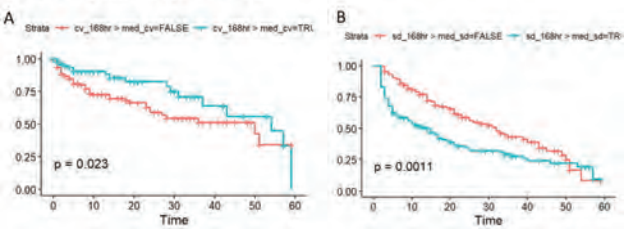
Background: Acute kidney injury (AKI) requiring dialysis is frequently occurred in critically ill patients, leading to chronic kidney disease progression and dialysis dependency. Blood pressure variability (BPV) has been known to contribute the development of AKI by impairing kidney perfusion. However, the association between short-term and long-term BPV and AKI recovery and mortality remains uncertain.

Methods: We enrolled the patients aged ≥18 years who underwent continuous renal replacement therapy (CRRT) due to AKI for ≥24 hours at Inha University Hospital from January 1, 2018 to December 31, 2020. Patients with end-stage kidney disease were excluded. We extracted 1-hour-interval blood pressure records during CRRT and calculated several BPV parameters including standard deviation (SD), coefficient of variation (CV), average real variability (ARV), and variation independent of mean (VIM). Outcomes are in-hospital mortality and dialysis dependence at the time of discharge. Multivariable logistic regression and Cox proportional hazard analysis were poerformed.

Results: A total of 243 patients were included in the main analysis. Mean age was 69.7 years and male was 56.8%, and 52.2% were sepsis-associated AKI. Median duration of CRRT was 4 days. Multivariable logistic regression showed a significant association between four BPV parameters and dialysis dependence at discharge (SD, OR 1.94 (95% CI 1.07-3.59); CV, OR 2.69 (95% CI 1.47-5.06); VIM, OR 1.92 (95% CI 1.06-3.54), ARV, OR 1.90 (95% CI 1.03-3.54)). These parameters also showed close associations with in-hospital mortality in cox-proportional hazard analysis (SD, HR 1.74 (95% CI 1.25-2.43); CV, HR 2.17 (95% CI 1.55-3.03); VIM, HR 1.77 (95% CI 1.27-2.47), ARV, HR 1.65 (95% CI 1.17-2.32)).

Conclusions: BPV during CRRT was found to be an independent predictor of dialysis dependence at discharge and in-hospital mortality in AKI patients who underwent CRRT. Minimizing BPV during CRRT might be an important factor for recovery to dialysis independence and patient survival.

Figure 1. Kaplan-Meier curves of coefficient of variation for (A) dialysis independence at discharge (B) in-hospital mortality.



SA-PO081

Hope in Hardship: AKI in Haiti

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Background: AKI is a significant global issue, especially in low-resource areas with limited healthcare. Worldwide estimates suggest 13 million AKI occurrences/year with 1.7 million deaths, 85% in developing nations. In this study, we describe the presentation of AKI to a single healthcare center in Haiti and how collaboration can improve health care delivery for AKI.

Methods: The Hôpital Universitaire de Mirebalais (HUM), a 300 bed Partners in Health facility in rural Mirebalais has six residency programs. A partnership was formed between Beth Israel Deaconess Medical Center (BIDMC), Dartmouth Health and HUM focusing on educating internal medicine residents and staff through online presentations and short visits to Boston or Hanover for training in nephrology, urinalysis, HD, kidney biopsy, and bedside renal ultrasound. We planned that trainees would advance the ISN goal of eliminating preventable or treatable deaths from AKI by 2025.

Results: This program has enhanced the knowledge of medical residents and students in AKI diagnosis, management, electrolyte physiology, and HD, improving patient care and clinical outcomes at HUM. Between July 2021 to October 2022, 194 patients presented with AKI (11 cases/wk). Their mean age was 48 and main causes were heart failure (43%), glomerulopathy (26%), sepsis (12%) eclampsia (5%), other infectious diseases (e.g., leptospirosis, COVID, 2%), and volume depletion (2%). Due to lack of dialysis nurses, all HUM medical residents receive training in hemodialysis, and if the patient meets criteria for HD, a resident will initiate the procedure, performed without cost, as the majority of Haitians cannot afford dialysis. Of these 194 AKI patients, 19% had received HD of which 83% survived. The overall survival was 78%. Despite shortages of HD supplies and other medical equipment and inability to bring visiting professors to teach in Haiti due to multiple lockdowns and unrest, we have found alternative ways to receive shipments and to train our residents online. These residents become our future teachers, as with only 10 nephrologists for 11 million Haitians, the internists and general practitioners provide care for a large proportion of patients with AKI.

Conclusions: HUM, through education and training, in cooperation with BIDMC and Dartmouth, has provided care for patients with AKI, small victories that offer hope in managing hardship in Haiti.

SA-PO082

AKI in Hospitalizations with Sickle Cell Disease in Jamaica

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Background: Renal disease is amongst the leading causes of mortality in persons living with sickle cell disease (SCD). We describe the epidemiology and associations of acute kidney injury (AKI) in Jamaicans hospitalized with SCD.

Methods: A retrospective cohort study of admissions with coded diagnoses of SCD between January 1, 2016 to December 31, 2019 at the University Hospital of the West Indies was performed. Exclusion criteria were age < 1 month or if less than two creatinines were available. AKI was defined using Kidney Disease improving global outcomes (KDIGO) as either an increase of at least 1.5 times baseline creatinine if known. If baseline creatinine was unavailable this was defined as an increase of 1.5 times the maximum creatinine to the lowest creatinine in the admission. The index admission for each case was analysed. Data were described using summary statistics. Differences between AKI and non-AKI groups were performed using chi-square or t-tests were appropriate. Multivariable logistic regression was used to determine associated factors with AKI.

Results: Of 144 participants, mean age 27.0 ±15.4 years, 62.2% were female and 84.5% Hemoglobin-SS genotype. One third (n=48) of participants were children (age<18 years). AKI occurred in 19.4% (n=28). The main admitting diagnoses were vaso-occulsive crises in 61.1%, Acute chest syndrome 27.8%, Lower Respiratory Tract Infection 17.4%, hepatic sequestration 13.2%. Baseline CKD was reported in 6.3%, hydroxyurea use in 4.9% and NSAID use 20.1%. Three participants were admitted to the intensive care unit. There were no in-hospital deaths. Mean duration of hospitalization was 8.8±8.3 days(range:1-59 days). A quarter of patients (26.4%) had red blood cell (RBC) transfusion, exchange transfusion was performed in 2 children. Compared to no AKI, AKI participants were older (mean age 32.1 ±14.9 versus 25.8 ±15.4 years, p=0.05), with a higher proportion receiving RBC transfusion (46% versus 21.6%, p=0.007). Based on a logistic regression model adjusting for age and sex, RBC transfusion was associated with AKI in adults (OR 3.1 95% CI: 1.1-8.6, p=0.003), but not children (OR: 0.5 95%CI 0.04-6.5, p=0.612). There was no difference in length of hospital stay in AKI and non AKI groups.

Conclusions: AKI frequently complicates admissions with sickle cell disease. Further studies determining long-term outcomes following AKI events are needed.

SA-PO083

Black Patients at Higher Risk of Hospital-Acquired AKI but Lower Risk of Community-Acquired AKI

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Background: Previous studies showed higher incidence of acute kidney injury (AKI) among Black patients compared to Whites but failed to adequately characterize this difference. Further detail on racial/ethnic risk of defined types of AKI could inform preventive interventions.

Methods: We describe a cohort of hospitalizations of pediatric and adult patients without prior kidney failure in Montefiore Health System, Bronx, NY, between October 1, 2015 and December 31, 2018. We defined community-acquired AKI(CAAKI) as criteria met by KDIGO in first 48 hours of admission and hospital-acquired AKI(HAAKI) as a 48-hour window rise in creatinine defined by KDIGO occurring after 48 hours of admission and before discharge. We examined unadjusted logistic regression with HAAKI and CAAKI as outcomes, race as exposure, and sequentially adjusted variables accounting for comorbidities and in-hospital risk of mortality. We stratified multivariable adjusted models by in-hospital events according to: 1-severe illness: exacerbation of heart or liver failure, sepsis/shock, cardiac arrest and mechanical ventilation, 2-exposure to nephrotoxic agents: contrast, NSAIDS, diuretics and nephrotoxic chemotherapy, and 3-surgery: occurrence of cardiopulmonary, vascular, orthopedic or neurosurgery; to understand association of race with risk of HAAKI in each scenario.

Results: Of a total 286,383 hospitalizations, 42% were male, 11% were White, 29% were Black, and mean age was 48 years(SD:27). White patients [mean age 63 years(SD: 23)] were older than Black [51 years(SD:25)]. AKI occurred in 56,731 (20%) instances, of which 23,524 (41%) were CAAKI and 33,207 (59%) were HAAKI. In adjusting for age and sex, Black patients were at higher risk for HAAKI [OR 1.21, (CI 1.17-1.27)] and lower risk for CAAKI [0.92, (CI 0.88-0.96)]. Risk for HAAKI attenuated with addition of prior comorbidities, BMI and APR score, but remained significant [OR 1.13, CI (1.08-1.17)]. Black patients had higher odds of HAAKI than White patients when hospitalized with severe illness and underwent major surgery. There was no difference in HAAKI by race with nephrotoxic agent exposure.

Conclusions: Black patients are at higher risk of HAAKI when hospitalizations involve severe illness or major surgery, and at lower risk of CAAKI. Drivers of higher HAAKI risk among severely ill Black patients should be identified.

SA-PO084

Association of Black Race, Diabetes, and Obesity with AKI During Hospitalization in a Large Multicenter US Cohort

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Background: AKI is a common complication during hospitalization that is associated with morbidity and mortality. Whereas multiple studies have identified risk factors for the development of AKI in hospitalized patients, few have examined risk factors for the severity of AKI, including non-recovery of AKI.

Methods: Multicenter retrospective cohort study of patients ≥18 years old without ESKD or kidney transplant who were admitted to the hospital from 10/2014 to 9/2017. Data were extracted from electronic health records of 3 large academic medical centers. Study outcomes included (1) incidence and severity of AKI and (2) non-recovery from AKI in those who survived the hospitalization. AKI was defined by KDIGO SCr-criteria, using all inpatient SCr data available and the lowest value of the first three inpatient measurements as the baseline. Non-AKI recovery was defined in hospital survivors as persistent AKI stage ≥1 using the last SCr during the hospitalization or if the patient received dialysis within 72h of hospital discharge. We used multivariable logistic regression models to evaluate the association of black race, diabetes and obesity (BMI ≥30 vs. <30 kg/m^2) with the outcomes, and each of the models was adjusted for 2 other of these main factors, and covariates such as study site, age, sex, baseline eGFR, and Elixhauser comorbidity score.

Results: Among 56,056 patients included in the study, 12,954 (23%) developed AKI during hospitalization. In adjusted models, black race (OR 1.26, 95%CI 1.20-1.32), diabetes (OR 1.14, 95%CI 1.08-1.19) and obesity (OR 1.14, 95%CI 1.10-1.20) were all associated with incident AKI, though only obesity was associated with AKI stage 2 or 3. Only obesity was associated with non-recovery from AKI at hospital discharge (OR 1.27, 95%CI 1.17-1.39).

Conclusions: Black race, diabetes and obesity were associated with incident hospitalized AKI, but only obesity was associated with moderate to severe AKI and non-recovery from AKI at hospital discharge. Obesity may help identify individuals at highest risk for severe AKI and those survivors requiring close follow-up after discharge.

Table: Association of race, diabetes, and obesity with incident AKI and non-recovery from AKI in a multicenter cohort of adult hospitalized patients

	Black vs. non-Black race OR (95%CI)	Diabetes vs. no-Diabetes OR (95%CI)	BMI ≥ vs. < 30 kg/m2 OR (95%CI)
Incident AKI (n = 56,056)	**1.26 (1.20, 1.32)**	**1.14 (1.08, 1.19)**	**1.14 (1.10, 1.20)**
AKI Stage 1	**1.27 (1.21, 1.34)**	**1.16 (1.11, 1.22)**	**1.10 (1.06, 1.16)**
AKI Stage 2	1.09 (0.88, 1.35)	0.79 (0.63, 1.00)	**1.58 (1.31, 1.90)**
AKI Stage 3	1.00 (0.82, 1.21)	1.00 (0.81, 1.23)	**1.92 (1.61, 2.28)**
Non-recovery from AKI in survivors (n = 11,672)	0.85 (0.77, 0.93)	1.02 (0.93, 1.12)	**1.27 (1.17, 1.39)**

SA-PO085

Nephrology Follow-Up After Community-Acquired AKI Among US Veterans

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Background: Community-acquired acute kidney injury (CA-AKI) is a common condition developed outside of the hospital that increases the risk of future hospitalization and death. Little is known about care patterns following CA-AKI, so we evaluated post-AKI nephrology care after an episode of advanced CA-AKI.

Methods: We constructed a retrospective cohort using national VA administrative and lab data to assess the cumulative CA-AKI incidence among active VA primary care users in 2013-2017 with a recorded outpatient serum creatinine (SCr). Veterans with a history of severe kidney disease (≥ Stage 5 or kidney transplant) were excluded. Stage 2 and 3 CA-AKI were defined as ≥ 2.0-2.9-fold or ≥ 3 fold relative increase, respectively, in outpatient SCr or inpatient SCr (≤ 24 hours from admission), from a reference value defined as the preceding outpatient SCr ≤ 12 months prior. A Cox model was used to estimate the association between baseline socio-demographics, comorbidities, care patterns, and CA-AKI event characteristics (stage, setting).

Results: Of the 43,473 veterans with Stage 2 (73%) or Stage 3 (27%) CA-AKI between 2013-2017, mean age was 66.7 years; 5.6% were female, 21.3% Black race, and 6.6% Hispanic ethnicity. Mean eGFR was 70.9 ml/min/1.73m^2 and 16.1% had documented CKD. The majority (62.6%) had a history of primary care visit ≤ 90 days prior to the CA-AKI event but few (1%) had a nephrology visit before CA-AKI. Overall, 3.5% of veterans were seen by nephrology ≤ 90 days after their CA-AKI event (3.3% Stage 2, 4.0% Stage 3, 3.8% outpatient CA-AKI, 3.0% inpatient CA-AKI); half (47.7%) of these visits included a diagnosis code for AKI. Veterans with inpatient CA-AKI (HR 0.64 [95% CI 0.57, 0.72]), advancing age (HR 0.88 [0.86, 0.91] per 5 years), and female gender (0.73 [0.56, 0.95]), were less likely to see nephrology within ≤ 90 days after CA-AKI. Those with a CKD (1.58 [1.38, 1.80]), Stage 3 CA-AKI (1.60 [1.43, 1.80]), lower eGFR (1.13 [1.12, 1.15] per 5 unit decrease) or prior nephrology visit ≤ 90 days (3.40 [2.74, 4.22]) had higher likelihood of a follow-up nephrology visit.

Conclusions: Few veterans with Stage 2 or 3 CA-AKI were seen by nephrology in the 90 days after a CA-AKI event. Post-AKI care models prioritizing recognition and nephrology care may improve the adverse outcomes associated with CA-AKI.

Funding: NIDDK Support

SA-PO086

Contrast-Related Risk of Progressing to ESRD in Patients Undergoing Percutaneous Coronary Intervention: Iohexol vs. Iodixanol

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Background: Our study aims to determine the differential risk of accelerated progression to end-stage renal disease (ESRD) associated with the contrast agents Iohexol and Iodixanol in patients undergoing percutaneous coronary intervention (PCI). This research is particularly important for addressing concerns about the use of PCI in individuals with chronic kidney disease (CKD).

Methods: This matched cohort study identified patients undergoing PCI of China Medical University Hospital between 2003 and 2017. For each patient administered with Iohexol, we identified a corresponding patient who was administered Iodixanol, ensuring that they were matched in terms of age, sex, baseline serum creatinine, and the year of the procedure. We employed multivariable Cox proportional hazard models to evaluate the risk of ESRD in the Iohexol group in comparison to the Iodixanol group. Subgroup analyses were further conducted specifically for patients with and without CKD.

Results: Among a total of 5,335 patients who used Iohexol and an equal number of control patients who used Iodixanol, we noted ESRD incidence rates of 3.47% and 3.26%, respectively. In the subcategory of patients with CKD, the incidence rates were 17.4% and 17.3% respectively for the Iohexol and Iodixanol groups. After adjusting for factors such as hypertension, diabetes, heart failure, medication use, electrolyte levels, and hemoglobin, we found that Iodixanol significantly associated with lower risk of

ESRD with an adjusted hazard ratio (aHR) of 0.65 (95% CI, 0.47–0.90; p-value: 0.01), compared with the Iohexol group. In the subgroup analysis, the protective effect was only observed among patients with CKD with an adjusted hazard ratio (aHR) of 0.70 (95% CI, 0.49–0.99; p-value: 0.04).

Conclusions: Our study suggests that Iodixanol is significantly associated with a reduced risk of progression to ESRD following PCI compared to Iohexol in real-world practice. Therefore, when considering contrast agents for these procedures, particularly in CKD patients, Iodixanol emerges as a preferable choice to mitigate the risk of ESRD.

Funding: Government Support - Non-U.S.

Table 2. Hazard ratios (95% confidence interval) for risk of progression to ESRD between Omnipaque and Visipaque users and for risk by CKD stage.

CKD stage	Contrast	n	ESRD	PYs	Rate	Crude model HR (95% CI) N = 10670	p-value	Model 1 HR (95% CI) N = 10670	p-value	Model 2 HR (95% CI) N = 9488	p-value
Overall	Omnipaque	5335	86	24805	3.47	ref		ref		ref	
	Visipaque	5335	77	23623	3.26	0.90 (0.67-1.23)	0.52	0.73 (0.54-0.99)	0.04	0.65 (0.47-0.90)	0.01
Non-CKD	Omnipaque	4283	11	20494	0.54	ref		ref		ref	
	Visipaque	4253	7	19570	0.36	0.71 (0.28-1.81)	0.53	0.67 (0.26-1.71)	0.71	0.67 (0.23-1.89)	0.45
CKD	Omnipaque	1052	75	4311	17.4	ref		ref		ref	
	Visipaque	1082	70	4053	17.3	0.86 (0.61-1.21)	0.73	0.76 (0.54-1.06)	0.11	0.70 (0.49-0.99)	0.04

Rate: ESRD incidence, per 1000 person-year.

Table 2. Hazard ratios for risk of progression to ESRD

SA-PO087

Imaging Evidence of Contrast-Induced Nephropathy: A Case Report

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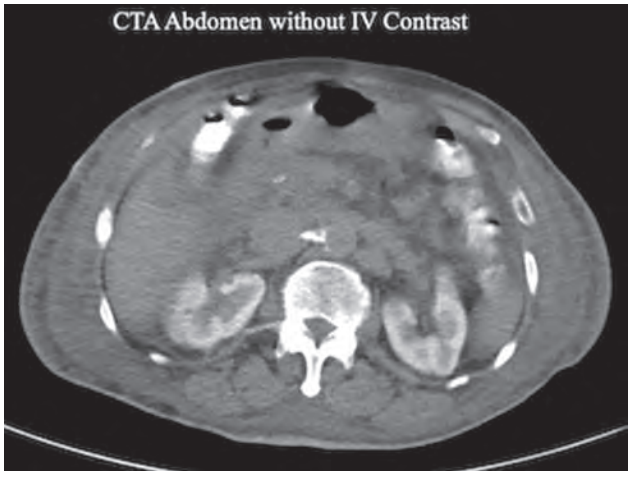
Introduction: AKI after IV contrast media (CM) exposure has been reported since 1950. CKD and DM are two major risk factors associated with contrast-induced nephropathy (CIN). One of the mechanisms is that the hyperosmotic property of CM increases tubular fluid viscosity which leads to renal CM retention and eventually tubular and medullary injuries. We report a case of CIN with a CT scan visualizing the prolonged CM renal retention.

Case Description: An 85-year-old man with HTN, DM II, CAD, and BPH was admitted for syncope with poor oral intake while taking furosemide. His initial serum BUN and serum creatinine (sCr) were 32mg/dL and 1.6mg/dL (baseline 1.3mg/dL). He received IV fluids (IVF) and furosemide was continued. sCr was 2.3mg/dL on day 2 when furosemide was stopped. sCr improved to 1.9mg/dL and he had CTA of chest to rule out pulmonary embolism with Omnipaque 95 ml. His sCr rose to 3.5md/dL within 48 hours. After addition of Valsartan he became oliguric. Renal service recommended IVF, post void bladder scan and discontinuation of Valsartan, with differential diagnoses including CIN, pre-, and post-renal etiology. Urinary obstruction was ruled out. However his sCr continue to rise 3 days after IV contrast. A non-contrast CT of abdomen to evaluate lymphadenopathy revealed renal parenchyma significantly enhanced by contrast administered 5 days ago. His sCr worsened to 6.7mg/dL on day 10, with improved urine output and normal electrolytes. He had a cardiac arrest and passed away before planned RRT.

Discussion: We hypothesized that this patient developed CIN with risk factors of DM, AKI on CKD, dehydration, use of ARB and urinary retention, with CT scan 5 days after IV contrast still showing contrast in the renal parenchyma. This prolonged exposure to CM proved by imaging may have contributed to his severe renal injury. This case report provides imaging evidence and highlights the risk factors that are strongly associated with CIN.



SA-PO088

Atorvastatin and Renoprotective Effects for Contrast-Induced NephropAthy Prevention (ARENA): A Pilot Feasibility Randomized Controlled Trial

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Background: Contrast-induced acute kidney injury (CI-AKI) can complicate coronary angiography (CAG) that can lead to increased morbidity and mortality. Previous studies have shown the protective effects of high-dose statin pretreatment in various scenarios. However, the role of statins in preventing subclinical AKI is still under investigation.

Methods: We conducted a randomized controlled trial including 50 patients at stage G3-4, who were randomly assigned to receive either 80 mg of atorvastatin or placebo once daily for 2 days prior to undergoing CAG. The primary outcome was the change in urine NGAL concentration 6 hours after CAG compared to baseline. Secondary outcomes included the incidence of AKI based on serum creatinine criteria, changes in estimated glomerular filtration rate (eGFR) from baseline to 7 days after the procedure, and the occurrence of adverse events such as hepatitis and myositis. Additionally, an in-vitro study was conducted to explore the effect of radiocontrast on NGAL assay.

Results: The mean baseline eGFR was 53.4 ± 17.8 ml/min/1.73m^2, and 22 patients (44%) had not previously used statins. Percutaneous coronary intervention was performed in 19.1% of patients, and all participants received iso-osmolar contrast with a median volume of 37.5 [30-80] ml. There were no significant differences observed in urine NGAL concentrations 6 hours after CAG between the atorvastatin and placebo groups (median [IQR] 4.4 [2.8-18.1] vs 6.6 [2.4-13.0], p = 0.9). The analysis also revealed no significant interaction with prior statin use, and no cases of CI-AKI were identified based on serum creatinine criteria. No adverse events were reported, and there were no significant increases in transaminase and creatine phosphokinase enzymes. The additional in-vitro study demonstrated no assay interference of radiocontrast in measuring urine NGAL.

Conclusions: The administration of high-dose atorvastatin as pretreatment of CAG was well tolerated in this study involving patients with early CKD and low-volume iso-osmolar contrast. However, the study did not demonstrate a renoprotective effect in this population, indicating a limited benefit for atorvastatin in this low-risk setting.

Funding: Government Support - Non-U.S.

SA-PO089

Spilling the Tea ON AKI

Gabrielle V. Carroll,[1] Gabriella Primera,[2] Connie Chen,[2] Parth Patel,[2] Kathryn Jobbins,[2] Daniel L. Landry.[2] *[1]University of Massachusetts Chan Medical School, Worcester, MA; [2]Baystate Medical Center, Springfield, MA.*

Introduction: Oxalate nephropathy (ON) is characterized by oxalate crystal deposition in the tubulointerstitium leading to acute kidney injury (AKI) and possible chronic kidney disease (CKD).[1] We present two cases of ON from excessive black tea consumption with full recovery.

Case Description: Case 1: A 52-year-old diabetic male was admitted after two weeks of poor solid food intake complicated by three days of acute left-sided vision loss and creatinine 8.5 mg/dl (baseline 1.6 mg/dl). Urinalysis showed benign sediment without proteinuria. Renal ultrasound revealed no hydronephrosis. MRI orbit showed bilateral increased optic nerve enhancement. Renal biopsy demonstrated acute tubular injury with calcium oxalate deposits and underlying diabetic nephropathy (DN). He later reported consumption of 5.5 liters of black tea a day for several weeks. He had full recovery of his renal function 2 months later after complete cessation of black tea intake. He never regained left eye vision, which was likely due to acute oxalate vasculopathy. Case 2: A 70-year-old diabetic male was admitted for abnormal creatinine of 5.9 mg/dL (baseline 1.2 mg/dl) in the setting of one week of diarrhea. He denied toxic ingestion but had consumed large volumes of black tea for months to lose weight. He had a benign urinary sediment and enlarged kidneys on ultrasound (13 cm). Renal biopsy revealed DN changes with acute ON.[2] Avoidance of black tea led to full renal recovery within 4 months.

Discussion: Hyperoxaluria is defined as a urine oxalate level greater than 40-45 mg/day.[2] US diets contain approximately 150 mg/day of oxalate with intake over 1000 mg/day associated with toxicity.[3] A recent 2020 study described 4.1% of biopsies in the New York City metro area containing oxalate deposits, contributing to CKD progression in 3.6% of cases.[4] Causes of hyperoxaluria include primary hyperoxaluria type1 and 2, and secondary hyperoxaluria from nutritional deficiencies, increased intestinal absorption, impaired excretion, or excessive intake of oxalate-rich foods or precursors.[2] Black tea contains 50-100 mg of oxalates per 100ml.[5] Treatment of ON includes supportive care and calcium supplementation to bind intestinal oxalate. Over-ingestion of black tea is an underrecognized cause of acute ON. While acute ON can lead to residual CKD, our cases are notable for full renal recovery after timely cessation of the offending agent.

SA-PO090

Outcomes of Intravenous Contrast Media on Patients with CKD: Systematic Review and Meta-Analysis

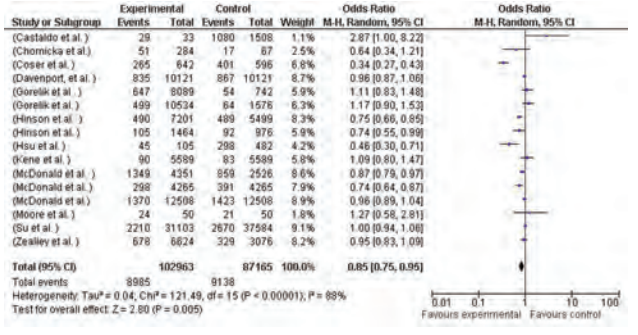
Ibrahim Tawhari. King Khalid University College of Medicine. *King Khalid University, Abha, Saudi Arabia.*

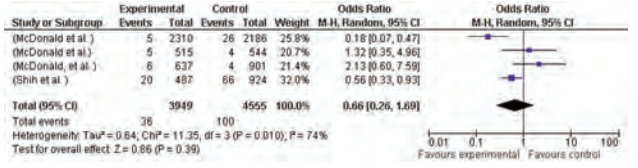
Background: Intravenous contrast media is frequently used in diagnostic and interventional procedures. Contrast-associated acute kidney injury (AKI) had been described as a complication associated with intravenous contrast media, which can lead to acute kidney injury and adverse clinical outcomes, especially in patients with underlying chronic kidney disease (CKD). However, this complication has been a subject of debate. The goal of this analysis is to evaluate the outcomes of intravenous contrast media use in patients with CKD.

Methods: A systematic search was conducted in PubMed, Scopus, ScienceDirect and Google Scholar for articles published from 2013 to March 2023. The reference lists of the included studies were also searched to retrieve possible additional studies.

Results: The meta-analysis included a total of 24 studies with a combined sample size of 278,908 participants. The pooled incidence of acute kidney injury in the OR was 0.85 (95% confidence interval [CI]: 0.75-0.95, P=0.005). In the association of dialysis and contrast media, had OR of 0.66(95%CI: 0.26-1.69), p=0.39.

Conclusions: These findings suggest that contrast media use is not associated with a higher risk of acute kidney injury and dialysis needs in patients with chronic kidney diseases. More research is needed to fully understand the potential risks of contrast media used in this patient population.





SA-PO091

Return of the MAC: Granulomatous Interstitial Nephritis Secondary to Disseminated Mycobacterium Avium Complex (MAC) Infection

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Introduction: Mycobacterium Avium Complex (MAC) is a group of non-tuberculous mycobacteria with the potential to cause severe infection in the immunocompromised, notably with HIV and AIDS. MAC is mostly known as a respiratory pathogen, however can disseminate in the bloodstream and has been seen in nearly all organ systems.

Case Description: A 27-year-old male with a history of HIV on antiretroviral therapy (ART) presented with 2 weeks of painful swelling of his left jaw. He was diagnosed with HIV 5 months prior and discharged on ART. After discharge, the patient's blood cultures became positive for MAC but he was never informed or treated. Vital signs were stable, and physical exam showed a tender subcutaneous mandibular mass. CT of the face showed a 3.8 cm abscess adjacent to the mandible. A chest radiograph showed no acute findings. Labs showed BUN of 78 mg/dL, serum Creatinine of 12.2 mg/dL, and an estimated 24-hour proteinuria of 1g/day. Kidney function was previously normal. Ultrasound showed enlarged kidneys without hydronephrosis. HIV PCR was undetectable, and CD4 testing could not be calculated due to severe lymphopenia The abscess was drained, and cultures were positive for MRSA and MAC. The patient was started on cefazolin, ethambutol, and azithromycin, and symptoms improved rapidly. Testing for other opportunistic infections was negative. ART was held until definitive diagnosis for AKI was made on biopsy, which showed granulomatous tubulointerstitial nephritis and crystalline nephropathy. Renal function stabilized, ART was resumed, and outpatient follow-up was arranged.

Discussion: Given the positive MAC culture found in subcutaneous abscess drainage and severe granulomatous inflammation seen on kidney biopsy disseminated MAC infection was the likely underlying etiology of the patient's AKI. MAC is less commonly known to affect the skin, though several case descriptions can be found in the literature. Granulomatous interstitial nephritis is a rare finding, occurring in less than 1% of all biopsies. Other considered etiologies of AKI included HIV associated nephropathy, sarcoidosis, and granulomatosis with polyangiitis. Clinicians should be aware of extrapulmonary manifestations of MAC and ensure prompt outpatient follow-up at the time of HIV diagnosis in order to prevent adverse outcomes.

SA-PO092

Preadmission Veterans Aging Cohort Study Index Is Associated with AKI in Hospitalized People with HIV

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Background: People with HIV (PWH) are at increased risk for acute kidney injury (AKI) and its sequelae. Numerous biomarkers have been shown to predict AKI but most are not routinely measured in practice. The Veterans Aging Cohort Study (VACS) index is a score based on age, CD4 count, HIV viral load, hemoglobin, eGFR, hepatitis C virus (HCV) antibody, platelets, AST and ALT. The VACS index predicts a number of outcomes and is highly correlated with markers of inflammation, including TNF alpha and IL-6 which have been shown to be predictive of AKI. We therefore hypothesized that preadmission VACS index would be associated with AKI.

Methods: We performed a cohort study of 1,186 PWH hospitalized in a New York City health system between 2010-2019. Outpatient laboratory values prior and closest to admission (7-365 days) were used to create the VACS index. The VACS index was divided into quartiles (≤22, >22 to 34, >34 to 55, >55). AKI was defined by KDIGO criteria. Multivariable Cox regression adjusting for sociodemographics, diabetes and intensive care unit admission was used to determine the association between VACS quartile and risk of AKI, treating the competing risks of death and discharge as censoring events.

Results: Median age was 53 years (IQR 43, 60), 516 (43.5%) were women, 500 (42.2%) were Hispanic, 522 (44%) were non-Hispanic Black and 195 (23.1%) were coinfected with HCV. Median CD4 count was 465 cells/mm^3 (IQR 201, 714) and 65% were virally suppressed (<200 copies/mL). The unadjusted AKI incidence was higher with increasing VACS quartile: 39 (10.7%) in Q1, 41 (18.6%) in Q2, 61 (28.1%) in Q3 and 107 (60.7%) in Q4. Compared to those in the lowest VACS quartile, the adjusted relative hazard (aHR) of AKI was 1.50 times higher (95% CI 0.96, 2.33; p=0.07) in Q2, 1.93 times higher (95% CI 1.28, 2.91) p=0.002) in Q3 and 3.23 times higher (95% CI 2.21, 4.74; p<0.0001) in Q4.

Conclusions: Preadmission VACS index is independently associated with AKI. The VACS index may allow for timely identification of PWH at risk for AKI and initiation of preventative strategies including intravenous fluids, avoidance of nephrotoxic medications and careful drug dosing. Our findings should be replicated in a larger cohort and future studies should evaluate its ability to predict severe AKI and nonrecovery from AKI.

Funding: Other NIH Support - NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant #UL1TR001073

SA-PO093

Unique Presentation of Hydronephrosis of a Transplanted Kidney from an Inguinal Hernia

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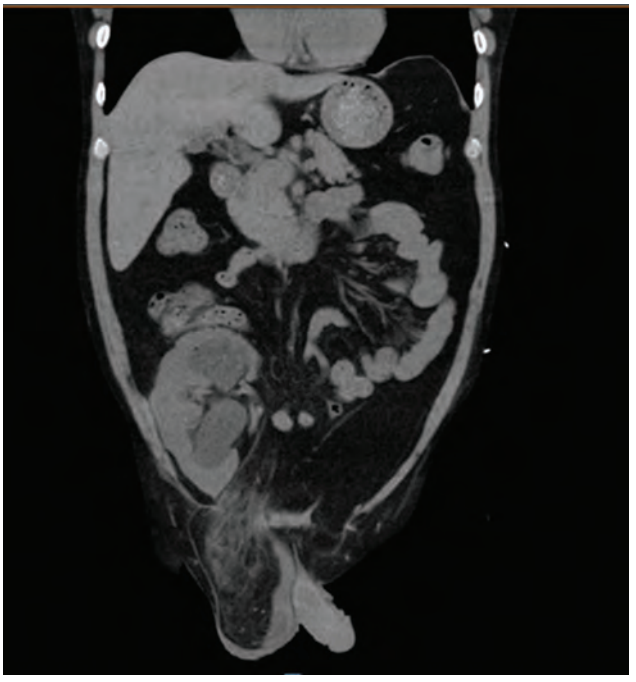
Introduction: End stage renal disease (ESRD) increases morbidity and worsens quality of life. Kidney transplants improve clinical outcomes in ESRD. This is a unique case of a post-renal acute kidney injury in a transplanted kidney secondary to a complicated right inguinal hernia.

Case Description: A 56-year-old male with history of right inguinal hernia and right kidney transplant on immunosuppression presented to the ED with a tender inguinal hernia for two days and inability to completely void. Prior attempts to reduce the hernia had been successful and notably improved his urinary symptoms. However, he could not longer reduce the hernia. On arrival, the patient was found to have a creatinine of 1.81 (baseline 1.1) and BUN of 32. A CT abdomen and pelvis showed a right inguinal hernia containing the distal ureter of the transplanted kidney and portions of the bladder. (Figure 1). General surgery was able to reduce the hernia. Once reduced, the patient began producing normal range urine output, and creatinine improved. He was transferred to a transplant facility for surgical evaluation. He underwent open inguinal hernia and incisional repair with mesh, which revealed bladder sidewall protruding through the hernia. Post-operatively, the patient continued to clinically improve, and his creatinine was near baseline.

Discussion: Kidney transplants provide an avenue without dialysis dependency and can increase life expectancy. We present a unique case of an AKI of a transplanted kidney due to complications from an inguinal hernia. Renal transplant recipients have unique changes to their anatomy, which can generate uncommon presentations of ordinary medical cases. We hope to raise awareness among physicians to diversify their differentials when encountering a transplant patient.



SA-PO094

Kidney Failure Requiring Dialysis due to Renal Metastatic Spread from a Laryngeal Squamous Cell Carcinoma

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Introduction: Renal metastatic spread from laryngeal squamous cell carcinoma (SCC) is particularly rare. We here report the unique case of a patient with acute dialysis requiring renal failure due to diffuse metastatic spread of a laryngeal SCC.

Case Description: A 59-year-old man presented with progressive dyspnea, and anuria. His past medical history was remarkable for right sided supraglottic laryngeal cancer cT3cN2bcM0 diagnosed two and a half years earlier. The histopathological work-up had revealed a squamous cell carcinoma (SCC). A radiochemotherapy had been effectuated and the patient had since then been in remission. The initial diagnostic workup revealed acute kidney failure AKIN-3. Initially, a prerenal cause was assumed. Bedside sonography did not show urinary retention. Due to uremia symptoms intermittent hemodialysis was initiated. Since renal function did not improve, a percutaneous kidney biopsy was obtained. The histopathological work-up revealed squamous cell carcinoma infiltrates consistent with renal metastasis from the supraglottic laryngeal carcinoma (Figure 1). The neighboring healthy renal parenchyma showed only few vital glomeruli, without any signs of glomerular damage. We hence concluded that the origin of the kidney failure was a diffuse renal metastatic spread from the primary cancer. Due to persistent anuria, a tunneled dialysis catheter was placed and the patient was started on intermittent hemodialysis thrice a week.

Discussion: To the best of our knowledge, only 3 previous cases of renal metastasis from laryngeal SCC have been described in the literature (Paul, Harden et al. 1999, Lecoeuvre, Degardin et al. 2003, Erbag et al. 2013). In contrast to these previous reports dealing with unilateral renal metastasis, our patient case is unique in the way that both kidneys were diffusely infiltrated by metastasis, that led to end-stage kidney disease. This case report highlights that one should always consider renal metastasis as a cause of acute kidney failure in tumor patients.

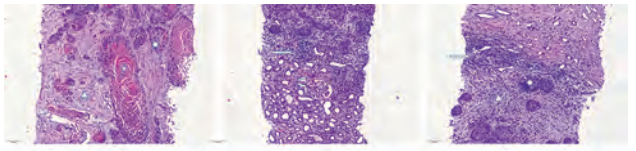

Figure 1: Squamous cell carcinoma infiltrating kidney tissue
Left – typical 'nested' morphology of moderately differentiated squamous cell carcinoma (○) with keratinization (☆) and prominent desmoplastic stroma reaction (△).
Center and right – kidney tissue with tumor-associated acute inflammation (▭) next to vital glomeruli (◎).
Image acquisition was done using a PreciPoint scanning microscope (using objective ×40/0.65 NA) and MicroPoint software (v.2016-02-05; PreciPoint, Freising, Germany).

SA-PO095

Recurrent AKI for a Patient with Mutation in the MCP/CD46 Gene and Plasminogen Deficiency

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Introduction: Complement-mediated thrombotic microangiopathy (CM-TMA) is a systemic disease characterized by hemolytic anemia, thrombocytopenia, and organ damage including acute kidney injury (AKI). Some causes of CM-TMA occur from dysregulation of complement proteins leading to loss of function in regulators and gain of function in effectors. Pathogenic gene variants of plasminogen, a component of the coagulation cascade, are thought to play role for CM-TMA. We present a case report of a patient with plasminogen deficiency and mutation in MCP/CD46 gene presenting with recurrent AKI.

Case Description: 64 years old female patient with history of asthma, alopecia universalis and gout presented for evaluation of recurrent episodes of AKI. She reports around five episodes of AKI over 5 years. She required dialysis and steroids in two occasions with complete kidney recovery. Her symptoms start with nausea, vomiting and flank pain followed by gross hematuria. Past work up was notable for thrombocytopenia, elevated D-dimer and AKI. Kidney biopsies obtained in 2016 and 2019 revealed acute tubular injury without signs of thrombotic microangiopathy (TMA). During her most recent episode, she presented with similar symptoms. Labs showed Hgb 10.9 g/dl, platelet 78.1 K/uL (150 - 400), D dimer >35,200 ng/ml (< 500), creatinine of 4.9 mg/dl (0.6 - 1), LDH of 3417 U/L (135 - 214), haptoglobin < 10mg/dl (31 - 238), plasminogen Assay 52% (69 - 137), plasminogen antigen 6.2 mg/dl (7.5 -15.5), schistocytes on peripheral smear, norma ADAMT-13 and unrevealing bone marrow. Genetic testing showed a variant in MCP/CD46 gene and a variant in plasminogen. She was treated with steroids, fresh frozen plasma and IVIG for 3 days, and discharged on tapered dose steroids for a month. On subsequent follow up, her kidney recovered within a month.

Discussion: The exact interplay between individual coagulation factors and complement system is not well understood. Plasmin has been shown to have some inhibitory role on complement mediated hemolysis. Pathogenic variants of the coagulation proteins such as plasminogen is found to play a role in CM-TMA such as atypical hemolytic uremic syndrome. In this case, plasminogen deficiency is likely contributing to TMA from MCP/CD46 mutation warranting further studies for better understating.

SA-PO096

Renal Function Recovery After Urinary Stone Removal Is Diverse for Patients with Urinary Stones in Different Locations

Wen Wen. *Beijing Tsinghua Changgung Hospital, Beijing, China.*

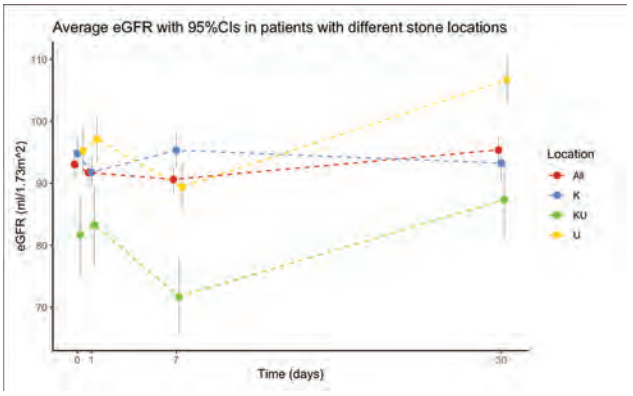
Background: The impact on renal function might be diverse in urolithiasis in different locations. We conducted a retrospective cohort study to analyze the trend of estimated glomerular filtration rate (eGFR) variation for urolithiasis in different locations after stone removal.

Methods: Clinical and laboratory characteristics of urolithiasis patients hospitalized in Beijing Tsinghua Changgung Hospital from March 2015 to September 2017 were screened according to our eligibility criteria. Creatinine values on 4 different time points (before surgery, 1 day after surgery, 7 days after surgery, and 1 month after surgery) were collected. Multi-level random effect models were constructed and the variations of eGFR were compared among patients with different stone locations. Subgroup analyses were done in patients with impaired renal function at baseline (eGFR < 60ml/min*1.73m^2).

Results: Among the 760 urolithiasis patients included (mean age: 50.8 ± 21.6 years, males: 62.8%), 483 had kidney stones, 168 were with ureter stones, and 109 had stones in both kidney and ureter. Coronary artery disease, urinary tract infection, hemoglobin, and serum albumin were unevenly distributed factors (P<0.001). The greatest improvement in eGFR and the most significant proportion of eGFR improvement was seen in patients with ureter stones. In contrast, the worst eGFR recovery was noted in patients with kidney stones (P<0.001). In multi-level models adjusted for related factors or not, a decrease of eGFR was noted at day 7 and an increase of it was observed at day 30 compared to baseline (P<0.05). Similar trends were noted in patients with ureter stones and those with kidney&ureter stones. However, the eGFRs kidney stone patients were not improved at day 30 (P>0.05).

Conclusions: Patients with stones only located in kidney may have the worst outcome in renal recovery after surgery. Large prospective studies are warranted to further establish the relationship between stone location and renal recovery.

Funding: Private Foundation Support



eGFR variations in patients with different stone locations

SA-PO097

Clinical Characteristics and Outcomes of Urolithiasis

Sungyeon Kim,[1] Young Eun Choi,[1] Yookyung Jang,[1] Suk Min Chung,[1] Ko Yoon Sook,[1] Lee Hee Young,[1] Jihyun Yang,[2] Tai yeon Koo,[1] Sewon Oh,[1] Myung-Gyu Kim,[1] Sang-Kyung Jo.[1] *[1]Korea University, Seongbuk-gu, Republic of Korea; [2]Kangbuk Samsung Hospital, Jongno-gu, Seoul, Republic of Korea.*

Background: Recent studies have showed the incidence of urolithiasis is increasing and known to be associated with chronic kidney disease (CKD)/end stage kidney disease (ESKD). Although kidney and ureter stones are heterogenous in composition, it is usually considered as single entity. The aim of this study was to compare the different clinical characteristics and outcomes of kidney/ureter stone diseases according to compositions.

Methods: We performed a single center retrospective study of symptomatic stone formers with known stone compositions (n=758). Baseline characteristics, blood and urinary excretory profiles, prevalence of diverse comorbid conditions as well as acute kidney injury (AKI) and long-term outcomes including ESKD and death were compared.

Results: Mean age was 58.6 yrs with male predominance (64.5%). Calcium oxalate stone was the most common type (68%) followed by struvite stone (15.5%), uric acid stone (13%) and mixed stones. Uric acid stone formers were significantly older (68yrs) with male predominance (76.5%) and showed higher prevalence of diabetes mellitus, hypertension, ischemic heart disease/heart failure, dementia and cancer. Calcium oxalate stone formers excrete significantly higher levels of glucose and calcium while uric acid stone formers showed low urinary pH. Incidence of AKI was 36.3% and older age, hypertension, low total CO2, and uric acid stone were found to be independent risk factors of AKI. During the mean follow-up of 456 days, 33 (4.3%) progressed to ESKD and 35 (4.6%) died. AKI was found to be an independent risk factor for both ESKD and mortality regardless of stone composition.

Conclusions: Kidney stone disease is thought to be a heterogenous condition with different clinical characteristics and longterm outcomes. Occurrence of AKI regardless of stone composition is an important predictor for adverse longterm outcomes. Better understanding of epidemiology, risk factors and pathogenesis of this heterogenous conditions are needed.

SA-PO098

The Clinical and Pathologic Characteristics of Patients with Oxalate Nephropathy

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Background: Oxalate nephropathy (ON) is characterized by deposition of calcium oxalate crystals in the kidney and is commonly underrecognized. Causes of ON include primary hyperoxaluria, enteric hyperoxaluria and ingestion of excess oxalate or its precursors.

Methods: We report the clinical and pathological characteristics of the largest series of native kidney oxalate nephropathy to date, from January 2015 to March 2023 at the Cleveland Clinic.

Results: Of 11900 kidney biopsies, we identified 60 native biopsies with oxalate deposits and excluded patients with clinically insignificant biopsies (n=12) or lack of data (n=17). 31 patients with native oxalate nephropathy were described. The mean age at diagnosis was 66.2 years (±12.1) and 58.1% were female. 87.1% had hypertension, 58.1% had diabetes, 42% had nephrolithiasis, and 77.4% had underlying CKD with a mean baseline creatinine of 1.8 mg/dL ±1.3. The mean creatinine at biopsy was 5.2 mg/dL ±1.7. Kidney biopsies showed abundant calcium oxalate crystal deposits, and 27 of 31 biopsies had additional diagnoses, the most common of which were acute tubular injury n=17 (54.8%) and diabetic glomerulosclerosis n=7 (22.6%). Severe and moderate interstitial fibrosis was present in 38.7% (n=12) and 51.6% (n=16) of biopsies respectively. 10 had a single etiology of ON, 10 had a multifactorial etiology (both enteric hyperoxaluria and high precursor intake) and 11 had an unclear etiology. Notably, only 7 patients had a history of gastric bypass. The mean duration of follow-up was 26.8 months and 26 patients had follow up data >1 year. Of these, 21 required dialysis and 5 were dialysis free at presentation. 5 of the 26 were deceased at 1 year, with 12 patients (38.7%) deceased at last follow up. 14 patients received targeted management while 12 patients did not receive targeted treatment and all 12 required hemodialysis. More patients (31.6%) had vitamin C intake post COVID pandemic (2020-2023) vs 16.7% prior to 2020.

Conclusions: Oxalate nephropathy presents as AKI or acute on CKD. The prognosis is poor with most patients requiring dialysis at presentation with high morbidity and mortality. Clinicians need to be aware of the risk factors associated with oxalate nephropathy to aid prompt diagnosis and management.

Funding: Private Foundation Support

SA-PO099

Multifactorial Rhabdomyolysis in an HIV Patient: Management of AKI

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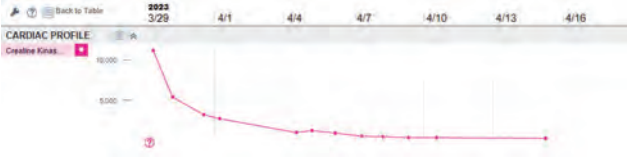
Introduction: Rhabdomyolysis is common in HIV patients with drug abuse history, however literature is scarce regarding management. In our multifactorial rhabdomyolysis case, CK level is more than 100,000 with proteinuria, which is a rare presentation. The findings in our case highlight the importance of individualized management approach based on the underlying etiologies and the patient's clinical status.

Case Description: In our case, a 32-year-old male with unknown past medical history presented to the emergency department with altered mental status. He was diagnosed with Strep Pneumonia, subsequently with HIV, HCV, polysubstance abuse (amphetamine, cocaine, and opiates) and later developed rhabdomyolysis with nephrotic range proteinuria. The patient received conservative treatment with 10-20 ml/kg of isotonic saline with 1 Liter of glucose 5% with 100 mmol of bicarbonate bolus. The goal was to maintain Urine output of 1 to 2 ml/kg/hour. Notably, there was a progressive improvement in the proteinuria, (from 4.5 grams per day to 1.45 grams per day). Considering the decline in proteinuria and the restoration of renal function, a renal biopsy was not planned at this stage. To support the patient's nutritional needs, a high protein diet was administered via a nasogastric tube, targeting a dosage of 1.6-1.8 grams per kilogram of body weight.

Discussion: This HIV patient with rhabdomyolysis and nephrotic range proteinuria who developed AKI due to multifactorial causes was treated with various management strategies- including pharmacological interventions targeting the specific etiologies, fluid therapy for volume resuscitation and electrolyte balance, and nutritional support. The efficacy of the conservative interventions was evaluated by improvement in renal function and reduction in proteinuria.

Trend of CK level

Day 1	3656	Day 5	76889	Day 11	22530
Day 2	>100000	Day 8	36445	Day 15	5414



Creatine Kinase Level trend

Protein Creatinine Ratio

SA-PO100

The Rise of Rhabdomyolysis in Philadelphia's Fentanyl Crisis

Rami Bzeih, David Jimenez, Jean Lee, Avrum Gillespie. *Temple University Hospital, Philadelphia, PA.*

Background: Philadelphia has experienced a recent surge of fentanyl use and unintentional overdose, particularly the area served by the Temple University Hospital System (TUHS). Patients admitted to the hospital for overdose are often found to have rhabdomyolysis and acute kidney injury (AKI). While opioids like heroin have been previously associated with causing rhabdomyolysis, it is our belief that fentanyl has exacerbated this problem. In this study, we determine whether there has been a rise in patients developing AKI from drug-associated rhabdomyolysis that correlates with the 50% increase of fatal fentanyl overdoses in Philadelphia over the past 6 years.

Methods: We conducted a retrospective cross-sectional study to examine trends in fentanyl-associated rhabdomyolysis and AKI. Our sample comprised 1060 patients aged 18-60 admitted to TUHS for drug-associated rhabdomyolysis. Data were collected from electronic medical records and screened for inclusion criteria. Patients with end-stage kidney disease or a hospital stay of less than 24 hours were excluded.

Results: From 2016 to 2022, the incidence of drug-associated rhabdomyolysis at TUHS has increased from 8.8 cases per month to 16.4 cases per month. Among those cases, the incidence of AKI rose from 5.8 cases per month to 13.8 cases per month. The greatest increase was noted between 2019 and 2020 (6.5 to 10 cases per month). Fentanyl was first tested in late 2018, and 60% of included patients since then were tested for fentanyl. Of those who were tested for fentanyl, positivity rate steadily increased from 52% in 2019 to 75% in 2023. Since 2016, AKI cases associated with other opioids declined from 67% to 16%. AKI cases positive for cocaine has remained around 43%.

Conclusions: Our findings suggest a strong correlation between the increased incidence of drug-associated rhabdomyolysis and AKI at TUHS and rising fentanyl abuse. This correlation was not observed with other drugs included in toxicology screens. Further research is required to ascertain the potential contribution of adulterants such as xylazine and phenylbutazone, and to develop effective harm reduction strategies to mitigate fentanyl-associated rhabdomyolysis and AKI.

SA-PO101

Hantavirus: A Rare Cause of Rhabdomyolysis

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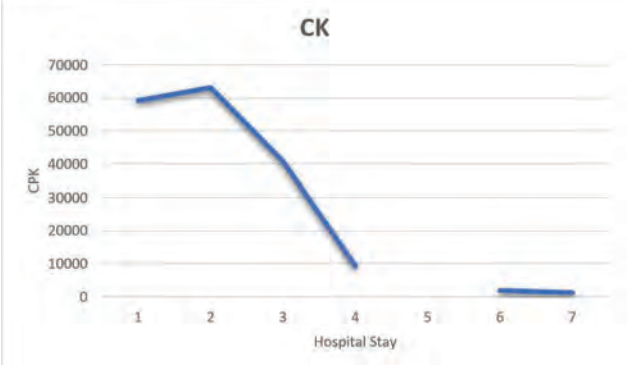
Introduction: Rhabdomyolysis has physical and nonphysical causes including toxins, trauma, and viral infections. Hantavirus presents flu-like symptoms and multisystem involvement including gastrointestinal, renal, and nervous systems.

Case Description: The patient is a 70-year-old male with a history of non-insulin-dependent diabetes, obesity, hyperlipidemia, arthritis, and chronic NSAID use who presented with altered mental status and inability to stand up after a fall eight hours prior. An initial examination found him disoriented, afebrile, and normotensive. Labs revealed a creatinine of 3.37 mg/dl and CK of 59100 U/L. CNS and renal imaging were all unremarkable. The patient became anuric on hospital day three and required continuous renal replacement therapy. On hospital day four he became febrile (101F). He was treated with aztreonam, vancomycin, cefepime, and empiric coverage with doxycycline. All blood cultures were negative. Collateral information was obtained from the family, who found his home in great disarray and infested with rats. This prompted testing for Hantavirus, which returned positive. The patient's renal function eventually recovered, with a creatinine of 3.26 mg/dl.

Discussion: Hoarders are at increased risk of exposure to Hantavirus due to contact with rodent droppings, saliva, urine in poorly ventilated areas. This is easily missed unless emphasis to social history including hobbies are explored. It is imperative to focus on The Social determinants of health for timely diagnosis and management.

Investigations

Blood culture	Negative
Urine Culture	Negative
ANA	Negative
Anti-Jo1 Ab	Negative
PM/Scl Ab	Negative
Antimitochondrial Ab	Negative



CPK trend

SA-PO102

Assessing Discharge Communication and Follow-Up of AKI: An Opportunity for Quality Improvement

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Background: Acute kidney injury (AKI) affects up to 20% of hospitalizations and is associated with increased chronic kidney disease, mortality, and healthcare costs. Proper documentation of AKI in discharge summaries is critical for optimal monitoring and treatment of these patients once discharged. This study aimed to evaluate the accuracy and quality of documentation of episodes of AKI at a tertiary care centre, in British Columbia, Canada.

Methods: This was a retrospective chart review study of adult patients who experienced AKI during hospital admission between January 1, 2018, and December 31, 2018. Laboratory data was used to identify all admissions complicated by AKI defined by KDIGO criteria. A random sample of 300 AKI admissions stratified by AKI severity (e.g., stage, 1, 2, and 3) were identified for chart review. Discharge summaries were reviewed for documentation of the following: presence of AKI, severity of AKI, AKI status at discharge, practitioner and laboratory follow up plans, and medication changes.

Results: Of the 300 discharge summaries reviewed, 38 were excluded. AKI was documented in 140 (53%) of discharge summaries and was more likely to be documented in more severe AKI: stage-1 38%; stage-2 51%; stage-3 75%. Of those with their AKI documented, 94 (67%) documented AKI severity and 116 (83%) mentioned the AKI status at discharge. 239 (91%) of discharge summaries mentioned a follow up plan with a practitioner, but only 23 (10%) had documented nephrology follow up. For laboratory investigations, 92 (35%) of summaries had documented recommendations. In summaries that included medications typically held during AKI, only about half made specific reference to those medications. For those with NSAIDS listed, 64% mentioned holding, and 9% mentioned a discharge plan. For those with ACEi/ARB, 38% mentioned holding these medications, and 46% mentioned a discharge plan. In ones with diuretics listed, 35% mentioned holding, and 51% included a discharge plan.

Conclusions: We found suboptimal quality and completeness of discharge reporting in patients hospitalized with AKI. This may contribute to inadequate follow up and post hospitalization care for this patient population. Strategies are required for increasing the presence and quality of AKI reporting in discharge summaries.

SA-PO103

Renal Malakoplakia in a Young Patient

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Introduction: Malakoplakia is a rare inflammatory disorder which commonly affects the genitourinary tract, but may also involve the gastrointestinal tract, lungs and skin. It is usually described in patients above age 40 years and is associated with infections and immunosuppressed conditions. We present a case of renal malakoplakia in a young female in the setting of *E. coli* urinary tract infection (UTI).

Case Description: A 32-year-old female with history of recurrent UTI, Raynaud's phenomenon, COVID-19, presented with 2 days of shortness of breath and lower extremity weakness. On examination, she was afebrile, tachycardic, hypotensive with diffuse petechial skin rash and hepatosplenomegaly. Labs showed leukocytosis, anemia, thrombocytopenia and acute kidney injury with creatinine 6.4 mg/dL (baseline 0.64mg/dL). Blood culture grew *E. coli*. CT abdomen pelvis showed marked bilateral kidney enlargement and continuous renal replacement therapy was started in the setting of worsening septic shock. The differential diagnosis of enlarged kidneys includes diabetes mellitus, cystic disease and infiltrative disease like amyloidosis, lymphoma, IgG4 related disease, hemophagocytic lymphohistiocytosis and malakoplakia. HIV and TB testing were negative. Kidney biopsy demonstrated pyelonephritis with focal micro-abscesses and diffuse CD163 positive inflammatory infiltrate consistent with macrophage/histiocytic cells. Von Kossa stain was positive with round inclusions in histiocytes, typical of Michaelis-Gutman bodies. Biopsy findings consistent with Malakoplakia. She was treated with antibiotics, bethanechol and ascorbic acid with recovery of kidney function sufficient to stop dialysis. Given intermittent fevers, persistent leukocytosis and enlarging left renal abscesses on CT, she underwent left nephrectomy 2 months into hospitalization. She was discharged home on oral minocycline.

Discussion: This case highlights the importance of considering malakoplakia in the differential diagnosis of nephromegaly, even in young patients. It is due to defective destruction of phagocytosed microorganisms by macrophages, although the underlying mechanisms remain unclear. Optimal therapy is uncertain, and this case emphasizes the importance of aggressive care.

SA-PO104

Kidney Epithelium Origin Cell-Free DNA: A Promising Biomarker in Prediction Sepsis-Induced AKI

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Background: Sepsis-induced acute kidney injury (SI-AKI) is a common complication of sepsis with high morbidity and mortality, with the diagnosis based on serum creatinine (Scr) and urine volume. Tracing the origin of the kidney epithelium origin cell-free DNA (Kidney-ep cfDNA) using the methylome atlas is a promising diagnostic biomarker for SI-AKI and has not been reported yet.

Methods: We extracted plasma cfDNA from 7 sepsis non-acute kidney injury (SN-AKI) and 9 SI-AKI patients for TET-assisted pyridine borane sequencing, used a reference methylation atlas of 40 cell types to analyze sequence reads to quantitate the relative contribution of cfDNA from different cell types by using the UXM fragment-level deconvolution algorithm. We multiplied the contribution by the total concentration of cfDNA, to obtain the concentration of Kidney-ep derived molecules. We determined the correlation of Kidney-ep cfDNA measures to SI-AKI, and then evaluated the diagnostic value of the Kidney-ep cfDNA. Differential methylation regions (DMR) were analyzed, and then we performed GO/KEGG pathway enrichment analysis using these DMR-related genes.

Results: Compared to healthy controls, all sepsis patients showed significantly elevated concentrations of cfDNA (P < 0.01). Compared to SN-AKI patients, SI-AKI patients had approximately 8.57-fold higher levels of cfDNA, consistent with the disorders of coagulation cfDNA (P = 0.022). The relative contribution and concentration of Kidney-ep cfDNA in SI-AKI patients was higher than in non-AKI patients (P = 0.003). The Area Under Curve (AUC) in differentiating SI-AKI from spesis patients reached 0.9206, which was higher than that of the cfDNA concentration (0.9206 vs. 0.8889). Also, there was a significant negative correlation between the concentration of kidney-ep cfDNA and the number of days after being diagnosed with SI-AKI (R=0.81, *P* = 0.028). Except for coagulation dysfunction, the concentration of Kidney-ep cfDNA was not affected by age, hypertension or septic shock (*P*<0.05). The pathways enriched the DMR genes, including complement and coagulation pathway, lymphocyte differentiation, etc.

Conclusions: Our study first showed the kidney-ep cfDNA is a novel biomarker of the SI-AKI diagnosis with real-time functional response.

SA-PO105

Chest Pain, Diarrhea, AKI, and Anemia: Uniting Them

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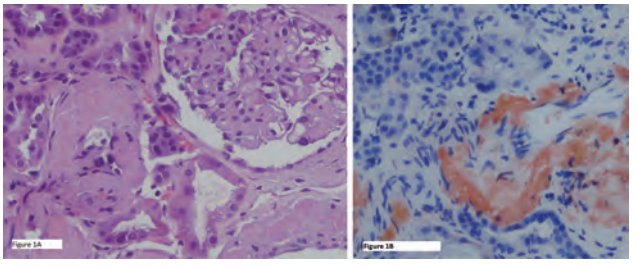
Introduction: Amyloidosis is a systemic disease with multiorgan involvement affecting 4000 Americans a year. Diagnosis is often delayed and overlooked. In this case a patient presents with many symptoms and a renal biopsy unites them.

Case Description: 69 year old male with pancreas and kidney transplant presents for chronic diarrhea for several weeks, chest pain, acute kidney injury (AKI) and anemia. GI panel positive for sapovirus. Cr improves with IV fluids but with ongoing diarrhea colonoscopy is done showing edematous colon. Chest pain persists and catheterization showed 60% proximal stenosis of the LAD and 40% left circumflex and RCA stenosis. He is discharged on aspirin. One week later, he has a rash and AKI with a Cr of 13.3. UA has eosinophils and cholesterol emboli is diagnosed. Dialysis is initiated and patient transferred for renal biopsy which is performed. The glomeruli had diffuse mesangial expansion by eosinophilic, amorphous, acellular material, walls of arteries and arterioles were expanded by the same material (Figure 1A). A Congo red stain was positive in glomeruli, arteries, and arterioles (Figure 1B). This is consistent with AL amyloidosis, lambda light chain type. Bone marrow biopsy shows plasma cell neoplasm involving 40 to 50% of bone marrow. Cardiac MRI is consistent with amyloid. Colon biopsy positive for amyloid. Patient was started on chemotherapy but expired.

Discussion: Amyloidosis is deposition of insoluble amyloid proteins that form B-pleated sheets. AL amyloid is composed of monoclonal gamma or kappa light chains. Light chains deposit in many organs and can present as anasarca, GI bleeding, dysphagia, weight loss, portal hypertension, diarrhea, chest pain, arrythmia and macroglossia. Diagnosis requires a biopsy of a fat pad or bone marrow and undergo evaluation for extent of organ involvement with cardiac MRI, coloscopy and skin biopsy. In this patient, due to his history of transplants, his work up was focused on infectious etiology for diarrhea. With the rarity of this disease, many are diagnosed late or not at all, which is why it is important to consider a unifying diagnosis for what may appear to be independent disease processes.



SA-PO106

Preoperative Serum Creatinine-to-Cystatin C Ratio and Risk of AKI After Cardiac Surgery

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Background: Postoperative acute kidney injury (AKI) is a serious complication after cardiac surgery, but risk stratification measures are limited. Decreased muscle mass is linked to negative outcomes, including kidney disease, in various clinical settings. More recently, the creatinine to cystatin C (Cr/Cys) ratio has shown correlation with muscle mass in several patients populations. This study aims to explore the association between preoperative serum Cr/Cys ratio and postoperative AKI in cardiac surgery patients.

Methods: Patients aged ≥18 years who underwent cardiac surgery at two tertiary hospitals between 2006 and 2020 were retrospectively evaluated. Their preoperative serum Cr/Cys ratios were categorized into quartiles. Primary outcomes were postoperative mild AKI (KDIGO stage 1) and moderate-severe AKI (KDIGO stage 2-3). Secondary outcome was length of hospital stay.

Results: Of the 2,354 enrolled patients (median age, 67.0 years; male, 65.2%), mild AKI and moderate-severe AKI were noted in 803 (34.1%) and 150 (6.4%) patients, respectively. Patients with higher Cr/Cys ratio had lower frequency of postoperative AKI and shorter lengths of hospital stay. Logistic regression analysis revealed that the odds ratios (ORs) [95% CI] for postoperative mild AKI and moderate-severe AKI decreased in a stepwise manner towards higher Cr/Cys ratio quartiles (mild AKI: Q2, 0.77 [0.61-0.97]; Q3, 0.75 [0.59-0.95]; Q4, 0.62 [0.49-0.79]; moderate-severe AKI: Q2, 0.67 [0.43-1.02]; Q3, 0.45 [0.28-0.73]; Q4, 0.54 [0.34-0.85] relative to the Q1, both *P* for trend <0.001). These associations were maintained after adjusting for confounding factors. Multivariable linear regression analyses revealed that patients in the 4th quartile of the Cr/Cys ratio had shorter hospital (-3.32 days, 95% CI, -5.34 to -1.30) stay than those in the 1st quartile.

Conclusions: Higher preoperative Cr/Cys ratios were associated with a lower risk of AKI development after cardiac surgery.

Table. Logistic regression for AKI and linear regression for hospital stay according to Cr/Cys ratio

	Univariable		Multivariable [a]	
Mild AKI	OR (95% CI)	*P*	OR (95% CI)	*P*
Q1	Ref		Ref	
Q2	0.77 (0.61 - 0.97)	0.029	0.61 (0.46 - 0.82)	0.001
Q3	0.75 (0.59 - 0.95)	0.016	0.50 (0.37 - 0.69)	<0.001
Q4	0.62 (0.49 - 0.79)	<0.001	0.32 (0.22 - 0.46)	<0.001
Moderate to Severe AKI				
Q1	Ref		Ref	
Q2	0.67 (0.43 - 1.02)	0.064	0.59 (0.36 - 0.98)	0.040
Q3	0.45 (0.28 - 0.73)	0.001	0.34 (0.18 - 0.62)	<0.001
Q4	0.54 (0.34 - 0.85)	0.007	0.36 (0.19 - 0.70)	0.002
Hospital stay	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Q1	Ref		Ref	
Q2	-2.90 (-4.47 - -1.32)	<0.001	-2.19 (-3.83 - -0.56)	0.009
Q3	-3.88 (-5.46 - -2.30)	<0.001	-2.71 (-4.50 - -0.92)	0.003
Q4	-4.62 (-6.20 - -3.04)	<0.001	-3.32 (-5.34 - -1.30)	0.001

[a] Adjusted for age, sex, BMI, HTN, DM, CHF, malignancy, eGFR, Hb, Alb, CPB time, contrast use, intraop inotropics, intraop transfusion, NSAID, Anti-plt agent, RASBs, Statin, diuretics, and antibiotics use

SA-PO107

Determination of Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Reference Intervals for Healthy Adult and Pediatric Individuals

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Background: Neutrophil gelatinase-associated lipocalin (NGAL) is a 25kDa protein implicated in multiple biological processes, including attenuation of apoptosis and differentiation of renal tubule epithelial cells and nephrons. NGAL is also produced and secreted by injured kidney tubule epithelial cells. As such, NGAL can serve as an early urinary biomarker for acute kidney injury (AKI). This multi-site, cross-sectional study aimed to establish reference intervals for urinary NGAL (uNGAL) in healthy pediatric and adult populations using a particle-enhanced turbidimetric assay.

Methods: Apparently healthy individuals, aged ≥3 months, were eligible for this study. Subjects with urinary tract infections, acute kidney injury (AKI) or a history of AKI, stage 4 or 5 chronic kidney disease (CKD), known congenital anomalies of the kidney and urinary tract, known urothelial, urological, or kidney malignancies were excluded from the study. Subjects with uncorrected congenital heart disease, having undergone solid organ or bone marrow transplantation, receiving renal replacement therapy, and having undergone surgery (urologic, nephrectomy, or correction of congenital heart disease) were also excluded. Six hundred eighty-eight (688) subjects were screened, 677 were eligible, and 629 (91.4%) were considered evaluable. Urine samples were collected and tested for NGAL and UTI.

Results: The following table describes the NGAL summary statistics and upper 95th reference intervals by age and gender.

Conclusions: These data demonstrate the normal urine NGAL reference intervals in apparently healthy pediatric and adult populations.

Funding: Commercial Support - BioPorto A/S

Table: NGAL Summary Statistics and Upper 95th Reference Intervals (by Age and Gender)

Age Categories	Male			Female		
	N	NGAL Mean ± SD	Upper 95th (90% CI)	N	NGAL Mean ± SD	Upper 95th (90% CI)
≥3 month to <2 years of age	42	50.48 ± 3.08	50 (50 to 70)	31	53.58 ± 13.07	94 (59 to 119)
≥2 years to <12 years of age	75	50.67 ± 0.58	50 (50 to 51)	64	57.59 ± 56.53	93 (58 to 193)
≥12 years to <22 years of age	72	50.15 ± 1.30	50 (50 to 54)	64	54.83 ± 16.77	89 (68 to 146)
≥22 years to <65 years of age	77	54.34 ± 24.57	74 (50 to 143)	81	59.3 ± 26.34	132 (82 to 176)
≥65 years of age	62	52.92 ± 15.38	80 (50 to 148)	81	57.52 ± 23.23	117 (68 to 240)

SA-PO108

Improved Outcomes with Early Nephrology Consultation After Biomarker Measurement

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Background: Novel urinary biomarkers, including Tissue Inhibitor Metallo-protease-2 and Insulin-like Growth Factor Binding Protein 7 ([TIMP-2]*[IGFBP7], T2*I7), have been developed to predict which patients are at risk for stage 2/3 AKI. While T2*I7 is approved as a risk stratification tool, data on its "real-world" use in conjunction with Nephrology consult and impact on AKI care is lacking.

Methods: We conducted a single-center prospective quality improvement study of ICU patients at risk for AKI or with KDIGO serum creatinine (SCr) stage 1 AKI. T2*I7 measurements and Nephrology consults were at the discretion of the primary ICU team. ICU providers were given KDIGO AKI-guideline-based practice recommendations based on T2*I7 results.

Results: Of 116 patients, 86(74%) had elevated T2*I7 ≥0.3. Of those, 30(26%) patients received nephrology consultation, 20 of whom had consultation within 1 day of T2*I7 measurement (early consult), and 10 had consults on days 2 or later (delayed consult). Patients with early and delayed consults had similar T2*I7 values (mean(SD) 3.0(3.1) vs 3.0(2.9), p=0.89), SCr at T2*I7 measurement (2.0(0.7) vs 2.0(0.5), p=0.75), and incidence of stage 1 AKI at time of T2*I7 measurement (15(75%) vs 9(90%), p=0.63). Despite more exposure to nephrotoxins, patients with early consults had significantly lower incidence of severe AKI, less dialysis, and improved mortality (p<0.05 for all) (Table). With renal consultation, T2*I7 was a poor predictor of severe AKI in 7 days (AUC 0.56(0.32-0.79), p=0.61).

Conclusions: Despite similar baseline characteristics and biomarker values, early nephrology consults were associated with improved outcomes and diminished the ability of T2*I7 to predict severe AKI. Future studies should continue to investigate if early kidney care, prompted by T2*I7, is beneficial in high-risk AKI patients.

Outcomes of Early vs Delayed Nephrology Consult

	Early Consult (n=20)	Delayed Consult (n=10)	p-value
Peak Change in SCr in 7 days (mg/dL)	2.7 (1.4)	4.7 (1.6)	0.003
Incidence of Stage 2 or 3 AKI in 7 days	9 (45%)	10 (100%)	0.004
Net I/O (mL) in 7 days	-1787.4 (6716)	+4973.7 (15540)	0.47
Diuretic Exposure	19 (95%)	8 (80%)	0.25
Exposure to Nephrotoxins (exposure x days exposed)	1.7 (2.4)	0.6 (1.0)	0.27
Length of Stay in ICU (days)	15.5 (11)	31.3 (23)	0.062
Total Length of Stay (days)	27.6 (16.5)	43.3 (21.0)	0.024
Inpatient Receipt of Dialysis	2 (10%)	7 (70%)	0.002
Inpatient Mortality	1 (5%)	4 (40%)	0.031

SA-PO109

Mortality Associated with the Neutrophil-Lymphocyte Ratio in Septic AKI Requiring Continuous Renal Replacement Therapy

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Background: Sepsis is an important cause of acute kidney injury in intensive care unit patients, accounting for 15–20% of renal replacement therapy prescriptions. The neutrophil-lymphocyte ratio, a marker of systemic inflammation and immune response, was previously associated with the mortality rate in multiple conditions. Herein, we aimed to examine how the neutrophil-lymphocyte ratio relates to the mortality rate in septic acute kidney injury patients requiring continuous renal replacement therapy.

Methods: Neutrophil-lymphocyte ratios of 6 and 18 were used for dividing neutrophil-lymphocyte ratios into three groups and, thus, were set higher than those in previous studies accounting for steroid use in sepsis. Cox proportional hazard models were used to calculate hazard ratios of mortality outcomes before and after matching their propensity scores.

Results: A total of 798 septic acute kidney injury patients requiring continuous renal replacement therapy were classified into three neutrophil-lymphocyte ratio groups: low (< 6), medium (6 ≤ x < 18), and high (≥ 18) (277, 115, and 406, respectively). The in-hospital mortality rates per group were 83.4%, 74.8%, and 70.4%, respectively (Table 1, $P < 0.001$). Per the univariable Cox survival analysis after propensity score matching, a high neutrophil-lymphocyte ratio was related to approximately 24% reduced mortality. The survival benefit of the high neutrophil-lymphocyte ratio group compared with the other two groups remained consistent across all subgroups, showing any P for interactions > 0.05.

Conclusions: A high neutrophil-lymphocyte ratio is associated with better clinical outcomes, such as low mortality, in septic acute kidney injury patients undergoing continuous renal replacement therapy.

Mortality outcomes according to the NLR results

	Total (n = 798)	NLR < 6 (n = 277)	6 ≤ NLR < 18 (n = 115)	18 ≤ NLR (n = 406)	P
On CRRT mortality (%)	61.4	70.4	60.9	55.4	<0.001
ICU mortality (%)	66.8	74.7	65.2	61.8	0.002
In hospital mortality (%)	75.6	83.4	74.8	70.4	0.001

NLR, neutrophil/lymphocyte ratio; ICU, intensive care unit; CRRT, continuous renal replacement therapy

SA-PO110

Higher IL-17A Levels Associate with AKI and Correlate with Biomarkers of Kidney Damage

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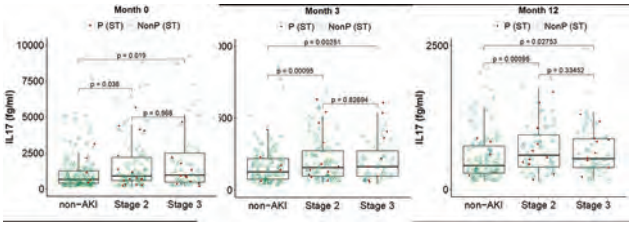
Background: AKI is associated with increased morbidity, mortality, and risk of CKD. IL-17A plays an important role in acute injury. We showed that IL-17A levels were elevated in critically ill patients with AKI and associated with hospital mortality and major adverse kidney events. IL-17A may be involved in AKI-to-CKD transition in AKI survivors. We hypothesize that IL-17A levels are elevated in hospitalized patients with AKI at diagnosis, and sustained elevation after discharge is associated with CKD incidence or progression.

Methods: Observational convenience sampling study of hospital survivors of Stage 2 or 3 AKI and controls without AKI from ASSESS-AKI study. Patients were classified as either "progression" or "non-progression" based on a composite of CKD incidence (≥25% decline in eGFR from baseline and achieving CKD stage ≥3), progression (≥25% decline in eGFR from baseline or <15 ml/min) or ESRD. IL-17A levels were evaluated at 0, 3 and 12 months post-AKI, and analyzed along with clinical and biomarker data over a period of up to 84 months.

Results: Among 171 AKI and 175 non-AKI participants, IL-17A levels were significantly elevated in AKI vs. non-AKI patients at 0M, 3M and 12M (p<0.05, Figure). IL-17A levels were significantly elevated in the progression vs. non-progression group, at the 3- and 12-month timepoints for outcomes occurring at 3-6 months and 12-84 months, respectively (p<0.05). In multivariable models that adjusted for demographics, comorbidity, eGFR and albuminuria, there was no independent association between IL-17A levels and the CKD outcome. IL-17A levels were positively correlated with kidney health biomarkers, including UNGAL, UIL-18, TNFa, and TNFRII at all three timepoints (p<0.001).

Conclusions: IL-17A levels were higher in hospital survivors that suffered from AKI when compared to those without AKI from diagnosis to post-discharge follow-up at 3 and 12 months, and according to AKI severity and post-hospitalization status of incident/progressive CKD. IL-17A levels were not independently associated with the CKD outcome but significantly correlated with several biomarkers of kidney health.

Funding: NIDDK Support, Other NIH Support - K23DK128562 awarded to AHF



SA-PO111

Risk Prediction Score for AKI in Critically Ill Septic Filipino Patients Admitted in Perpetual Succour Hospital: An Analytical Prospective Cohort Single-Center Study

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Background: Acute kidney injury (AKI) is a lethal complication of critical illness characterized by the rapid loss of the kidney's excretory function encountered in 50% of intensive care unit (ICU) admissions. Its impact on the outcome of critically ill patients makes AKI a significant cause of morbidity and mortality.

Methods: This is a prospective cohort study conducted in a tertiary hospital in Cebu from February to September 2020. The data of 2545 patients were identified by chart review but only 607 patients with a quick Sepsis Organ Failure Assessment Score (qSOFA) score of ≥2 were included in the pre-screening. A total of 198 septic ICU patients were enrolled. Demographic profile, laboratory results and outcome data were collated. Variables were screened then stepwise forward elimination was done to identify the significant predictors. An AKI risk score model was developed with binomial regression analysis by identifying independent prognostic factors. The diagnostic ability of the model was determined by the Area under the Receiver Operating Characteristics (AuROC).

Results: AKI developed in 155 (78%) patients. The significant predictors for Acute Kidney Injury were age, hypertension, atherosclerotic cardiovascular disease, weight, white blood count, creatinine, and BUN. An AKI prediction model with a cut off score of 161.9 was made with a fair diagnostic ability for predicting AKI at 0.79 based on AuROC.

Conclusions: The developed risk prediction tool using routinely available variables is found to be fairly accurate to predict the development of AKI among critically ill septic patients. This can aid clinicians to identify high risk population and will provide strategies for prevention, early diagnosis and treatment.

Table 14. The AKI Risk Predictors Based on the Binomial Logistic Regression for the Development of the AKI Predictive Model: Step 4

Predictors	OR	Conditions for the Model
Age	1.055	If ≥54 = score 1.055, else 0
Hypertension	1.907	If yes, = score 1.907, else 0
Atherosclerotic Coronary Vessel Disease	1.889	If yes = score 1.889, else 0
Admitting creatinine	1.944	If ≥1.07 = score 1.944, else 0
BUN	1.028	If ≥19.5 = score 1.028, else 0
Estimated weight	1.064	If ≥59 = score 1.064, else 0
WBC	1.030	If ≥7.56 = score 1.030, else 0
Total Score	**L321**	**If ≥161.9 = score as AKI**

*Cutoff Scores were based on the ROC Coordinates of the Curve with ≈ 0.80

The cut-off total score of 161.9 was used in the formulation of AKI detection as dictated by the receiving operating characteristic (ROC) based on the coordinates at ≈ 0.80 (*sensitivity/specificity*).

SA-PO112

Metabolomics Analysis and Classic Biomarkers to Predict Mortality in Patients with AKI and Kidney Replacement Therapy

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Background: Acute kidney injury (AKI) requiring kidney replacement therapy (KRT) is associated with mortality in critically ill patients. Serum metabolic biomarkers and markers of tubular damage might differentiate patients with a high risk of mortality.

Methods: Prospective cohort study of patients with critical COVID-19 in intensive care unit (ICU) with invasive mechanical ventilation (IMV) and who required KRT, admitted to Mar 2020 - Feb 2022. Patients with CKD stages 4 or 5 and kidney transplant were excluded. Urine SerpinA3, KIM-1, nGAL, HSP-72, and metabolomics analysis were measured on day 0 (start of KRT). Serum IL-6, IL-10, and TNF-alpha were also measured on day 0.

Results: Sixty patients were included, 52% died before discharge. The parameters measured at the beginning of the KRT were not different between living and dead patients (**Fig 1**). Of the urinary biomarkers studied, KIM-1 was the best mortality predictor (**Fig.2a**). The rest of the biomarkers had AUC minors (0.5-0.6) to predict this outcome. In the discriminant analysis of differential metabolites between the living (HD-A) and the dead (HD-D), p-cresol glucuronide was present in higher amounts in HD-D (**Fig.2b**).

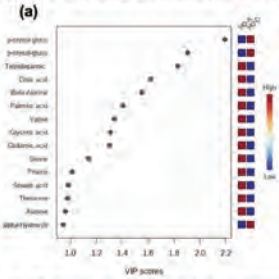
Conclusions: In this study it was observed that KIM-1 was the best predictor of mortality. In the metabolomics analysis, p-cresol glucuronide was the metabolite present in highest amounts among the deceased patients.

Figure 1. Clinical characteristics of patients at the beginning of KRT, divided according to the outcome of hospitalization live vs deceased.

	Live (n=29)	Deceased (n=31)	p-Value
Demographics			
Age, years	51 ± 12.2	56 ± 12.2	0.085
Male, n (%)	20 (69)	26 (84)	0.173
Body mass index, kg/m^2	31 (29-35)	29 (27-38)	0.240
Charlson index	1 (0-2)	2 (0-3)	0.323
SOFA score	10 (9-11)	10 (9-11)	0.542
Days of hospitalization at the beginning KRT	5 (2-12)	6 (4-12)	0.418
Days of IMV at the beginning KRT	3 (2-5)	6 (3-9)	0.079
Kidney function			
Baseline SCr, mg/dL	1 (0.8-1.2)	1 (0.9-1.2)	0.823
SCr at KRT initiation, mg/dL	5.1 (3.5-6)	4.2 (3.3-5)	0.162
Urine output at KRT initiation, ml	612 (280-1347)	994 (250-2112)	0.416
Laboratory at KRT initiation			
Leukocytes, x 1000/mm^3	12 (9-15)	12 (8-17)	0.784
C-reactive protein, mg/dL	16.2 (10.3-27)	19 (7.6-29.3)	0.906
Creatine kinase, U/L	369 (69-1049)	1013 (302-1852)	**0.023**
Lactate dehydrogenase, U/L	433 (313-552)	482 (335-586)	0.608
Ferritin, ng/mL	939 (532-1689)	1202 (613-1855)	0.276
PaO_2/FiO_2 ratio	144 (113-170)	123 (96-154)	0.141
Treatments in ICU at KRT initiation			
Carbapenems, n (%)	18 (62)	20 (65)	0.844
Vancomycin, n (%)	13 (45)	14 (45)	0.979
Antifungal therapy, n (%)	3 (10)	3 (10)	1.000
Norepinephrine, n (%)	22 (76)	27 (87)	0.327

Note. Continuous variables are expressed as median (interquartile range) or mean (standard deviation). **Abbreviations**. SOFA, Sequential Organ Failure Assessment score; KRT, kidney replacement therapy; IMV, invasive mechanical ventilation; SCr, serum creatinine; ICU, intensive care unit; PaO_2/FiO_2 ratio, ratio of arterial oxygen partial pressure to fractional inspired oxygen.

Figure 2. metabolomics analysis and biomarkers to predict mortality in patients AKI.



Biomarker	AUC (95% CI)	p-value
Urine biomarker		
KIM-1, µg/mg	0.68 (0.53-0.84)	0.03
HSP-72, µg/mg	0.51 (0.34-0.68)	0.32
NGAL, µg/mg	0.63 (0.47-0.79)	0.12
SerpinA3*, DPI/mg	0.52 (0.36-0.69)	0.78
SerpinA3**, µg/mg	0.64 (0.48-0.80)	0.10
Urine output >500ml	0.51 (0.37-0.66)	0.86
Urine output >1L	0.59 (0.44-0.73)	0.25
Plasma biomarker		
IL-6, pg/ml	0.57 (0.43-0.72)	0.31
IL-10, pg/ml	0.64 (0.50-0.79)	0.06
TNF-alpha, pg/ml	0.52 (0.37-0.67)	0.83

Abb. AUC, area under the curve.

(a) VIP schematic scores of partial least squares-discriminate analyses (PLS-DA) for HD-A vs HD-D. (b) Area under the receiver-operating characteristics curve of biomarkers for predicting mortality.

SA-PO113

Mortality Prediction of Plasma Presepsin in Septic Patients Requiring Continuous Renal Replacement Therapy

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Background: Presepsin is a more specific biomarker of sepsis, and many research results have been reported recently. However, since presepsin is highly affected by kidney function, acute kidney injury (AKI), especially the situation requiring continuous renal replacement therapy (CRRT), has a significant impact on presepsin dynamics and has not been elucidated. This study analyzed the relationship between plasma presepsin and mortality in patients requiring CRRT due to AKI.

Methods: From April 2022 to March 2023, patients who underwent a presepsin test just before CRRT were included. A total of 57 patients were enrolled, of which 35 were sepsis and 22 were non-sepsis. The predictive values of APACHE-II score, SOFA score, and plasma presepsin for 28-day mortality were analyzed using receiver operating characteristics (ROC) curve analysis.

Results: In predicting 28-day mortality in the overall cohort, area under the ROC (AuROC) values of APACHE-II score, SOFA score, and serum presepsin were 0.663, 0.731, and 0.636, respectively, which the presepsin showed the lowest predictive value. However, in the analysis of only sepsis patients, the AuROC values of APACHE-II score, SOFA score, and serum presepsin were 0.645, 0.681, and 0.802, respectively, which the presepsin was the best predictive marker for 28-day mortality. Moreover, in Cox regression analysis, high presepsin level was observed as an independent risk factor for 28-day mortality in sepsis patients (HR 3.823, P = 0.011).

Conclusions: Presepsin was not a useful marker of 28-day mortality in overall CRRT patients, including non-sepsis. However, in patients with sepsis, it was observed as the good predictive marker of mortality, which is thought to be because presepsin is a very specific marker for infection. Presepsin may be helpful in clinical practice for predicting mortality in CRRT patients with clinically suspected sepsis.

SA-PO114

Collagen Type III Biomarkers Are Prognostic for Adverse Outcomes After AKI

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Background: Acute kidney injury (AKI) is defined as a fast decrease in kidney function and may be associated with structural damage. Even though early markers predicting AKI are emerging, tools to monitor the long-term health risk of patients after AKI are still needed. The novel biomarkers PRO-C3 and C3M are reflecting collagen type III (COL3) formation and degradation, respectively. In this study, we evaluated the potential of these biomarkers of COL3 as prognostic biomarkers of adverse outcomes in patients after AKI.

Methods: We measured PRO-C3 and C3M in plasma samples collected 1 year after the episode of AKI, using novel ELISAs in 800 patients from the AKI Risk in Derby (ARID) study, who were then followed prospectively until year 3. 392 of the patients had been hospitalized for an episode of AKI, and 408 patients who did not sustain AKI were included as controls (non-AKI). Kidney disease progression (KDP) was defined as ≥25% decline in eGFR and a decline in eGFR stage.

Results: By year 3, a total of 42 (AKI=25/control=17) patients had KDP, 70 (43/27) died, 103 (62/41) had heart failure (HF), 193 (104/89) had cardiovascular events (CVEs), and 531 (267/264) were readmitted. We performed multivariate logistic regression analysis with KDP as outcome and Cox regression analysis with mortality, HF, CVE or readmission as outcome with backwards elimination including age, sex, ACR, baseline CKD and diabetes status, eGFR, PRO-C3 and C3M. For KDP, PRO-C3 was retained in the final model in the AKI (OR=1.02, P<0.05) but not the control group, whereas C3M was not retained in the final model in any of the groups. In the AKI group, PRO-C3 retained in the final models for mortality (HR=1.02, P<0.0001), HF (HR=1.01, P<0.05) and readmission (HR=1.00, P<0.05), whereas C3M was retained in the final model for CVEs (1.06, P<0.01). In the control group, PRO-C3 was only retained in the final model for HF (HR=1.01, P<0.01), and C3M was not retained in any of the models.

Conclusions: In this study we showed that biomarkers of COL3 are prognostic for adverse outcomes in patients after AKI. Our findings may indicate that these biomarkers identify patients with active fibrogenesis after AKI, suggesting that long-term renal injury after AKI is important for patient outcome.

SA-PO115

Plasma Humanin Level in AKI and CKD Patients

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Background: Humanin is a mitochondrial-derived cytoprotective peptide that reflects mitochondrial damage. Its level in the plasma of patients with AKI and CKD has not been reported yet. We aimed to determine the diagnostic value of humanin for kidney injury.

Methods: A total of 188 patients with kidney disease and 32 healthy controls were collected, patients with kidney disease were divided into AKI group (n=54) and CKD group (n=134) according to KDIGO definition. The plasma humanin level of each group was detected by enzyme-linked immunosorbent assay. ROC curves were used to analyze the diagnostic performance of humanin for AKI and CKD.

Results: A total of 188 patients (54 AKI, 134 CKD) and 32 healthy people were studied. The plasma humanin level in the AKI group and the CKD group was significantly higher than that in the healthy control group [576.5 (430.0-796.2) pg/mL vs 298.6 (188.8-366.4) pg/mL, p=0.0006 and 325.9 (207.3-631.4) pg/mL vs 298.6 (188.8-366.4) pg/mL, p=0.0164, respectively]. On the basis of receiver-operating characteristic analysis humanin could predict AKI and CKD [area under the curve (95% confidence interval) 0.869 (0.794-0.944) and 0.620 (0.529-0.711), respectively]. A cut-off point >413.2 pg/mL for humanin had a sensitivity of 0.78 and specificity of 0.91 in predicting AKI and a cut-off point >481.4 pg/mL for humanin had a sensitivity of 0.38 and specificity of 0.89 in predicting CKD.

Conclusions: Humanin is expressed in patients with AKI and CKD and may be a novel biomarker in response to kidney damage.

Funding: Government Support - Non-U.S.

SA-PO116

Dickkopf-3, a Key Driver of Renal Fibrosis, Is Increased in the Urine of Patients with AKI

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Background: The WNT–β-catenin system, an evolutionary conserved signaling pathway involved in morphogenesis and cell organization during embryogenesis, is usually suppressed in adulthood but can be re-activated in organ injury and regeneration. Dickkopf (DKK) proteins serve as inhibitors of WNT–β-catenin signaling. Animal models showed that DKK-3 is released by 'stressed' tubular epithelial cells and drives kidney fibrosis. However, the role of DKK-3 in human acute kidney injury (AKI) remains unknown. In the present study, we measured urinary DKK-3 in patients with AKI to test if urinary DKK-3 is useful to monitor the degree of tubular damage and/or recovery in human AKI.

Methods: AKI patients (n=66) who were treated in our department (December 2020 to December 2022) and healthy adults (n=16) were enrolled in this study. Written informed consent was obtained from all patients. Serum and urinary DKK-3 were measured by ELISA. The correlation of urinary DKK-3 with renal function, urinary protein level, clinical parameters and various AKI biomarkers were analyzed. This study was approved by the Ethics Committee on Human Research of our institutions (Approval number 2487).

Results: Compared to healthy subjects, urinary DKK-3 was significantly increased in AKI (1.02 ± 0.06 vs. 10.5 ± 1.26 ng/mL, p<0.001). There was no significant difference in urinary DKK-3 level between prerenal and renal AKI, but there was a significant increase according to the stage of AKI. There is a significant correlation of urinary DKK-3 with serum creatinine level, eGFR, urinary NGAL, and urinary beta2-microglobulin, but not with urinary protein level, urinary KIM1, or urinary NAG. Among the causes of AKI, urinary DKK-3 was markedly increased in patients with microscopic polyangiitis, in which urinary DKK-3 was significantly decreased after therapeutic intervention. In cases of kidney transplantation recipients, urinary DKK-3 was markedly increased at 1 day after transplantation but was decreased and became undetectable thereafter.

Conclusions: Urinary DKK-3 might be useful as a marker reflecting tubular damage as well as interstitial fibrosis in patients with AKI.

SA-PO117

Urinary DcR2/Cr Level Predicts Renal Outcome in Patients and Mouse Models with AKI

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Background: Acute kidney injury(AKI) is a well-recognized complication of critical illness with poor prognosis. Decoy receptor 2(DcR2), a senescent marker, is expressed specifically in senescent tubular epithelia. The aim of study is to investigate the association of urine DcR2 with renal outcome of AKI.

Methods: 153 biopsy-proven AKI patients were included from Daping Hospital, Army Medical University from January 2018 to October 2022. A composite renal endpoint included creatinine more than 50% higher than the baseline or ESRD after 90 days. All patients were divided into positive endpoints(n=75) and negative endpoints(n=78). The clinical characteristics were collected, and the uDcR2 levels were measured and normalized to urinary cre(uDcR2/Cr). By using correlation analysis, logistic regression and Kaplan-Meier curves, we explored the relationship between uDcR2/Cr and kidney outcome. We used experimental animals to further verify,and mice were randomly divided into 3 groups as follows: control, cisplatin, and aristolochic acid.

Results: The level of uDcR2/Cr was positively correlated with cystatin C and renal pathological acute scores, and negatively correlated with eGFR. Univariate logistic regression results increase the risk factors for poor kidney prognosis are age, female, with hypertension or(and) CKD, eGFR, Cystine C and uDcR2/Cr. Multivariate logistic regression analysis showed that the effect of uDcR2/Cr on renal outcome was statistically significant. After a median follow-up of 16 months, 75 participants achieve endpoint. The ROC curve was used to analyze the value of uDcR2/Cr for predicting kidney prognosis in AKI with an area under the curve of 0.72 and the cut-off value of 365ng/g Cr. The median time from at the time of AKI to endpoint in the uDcR2/Cr≥365ng/g Cr group(7.6 months) was significantly shorter compared to the uDcR2/Cr<365ng/g Cr group(36.6 months). To explore the trend of uDcR2 levels after AKI, uDcR2/Cr levels increased at 3d in cisplain-induced and aristolochic acid-induced AKI models compared with the control group, and the levels at 7d and 21d were still higher in the two models.

Conclusions: Urinary DcR2/Cr is closely associated to kidney injury and renal prognosis of AKI, suggesting that uDcR2/Cr could sever as a novel biomarker for predicting adverse outcomes in patients and mouse models with AKI.

Funding: Private Foundation Support

SA-PO118

Effects of Lanosterol Synthase Gene on the Development of AKI After Cardiac Surgery

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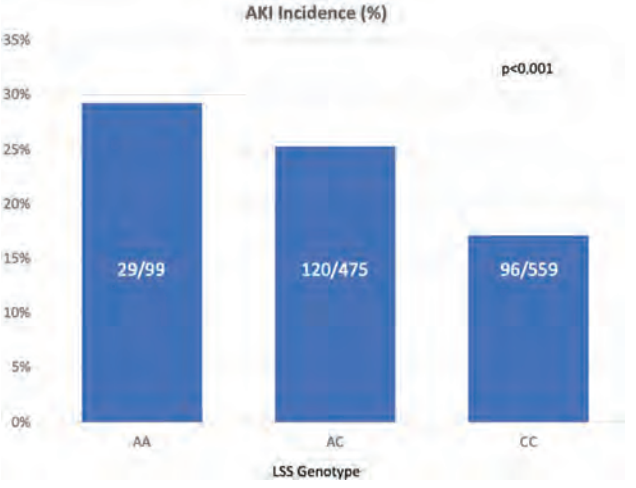
Background: Acute kidney injury (AKI) is a common post-surgery complication, significantly affecting morbidity and mortality. Recent studies reported that high plasma levels of endogenous ouabain (EO) are associated with worse kidney outcomes after cardiac surgery. Our group demonstrated that EO activity is affected by a missense variant (rs2254524 C → A, Val642Leu) in Lanosterol Synthase (LSS) gene. This work aims to analyze the relationship between this LSS polymorphism and the development of AKI after cardiac surgery.

Methods: 1237 patients undergoing elective cardiac surgery were enrolled in the study. For each patient, preoperative biological samples and LSS genotypes were collected. Primary outcome was AKI development according to KDIGO guidelines.

Results: 21.4% of patients developed AKI. Different preoperative clinical variables were analyzed, identifying five independent elements significantly correlated to AKI in multivariate logistic regression analysis: age (p<0.001), FE (p=0.005), NYHA class (p<0.001), reoperation (p=0.002) and complex surgical intervention (p< 0.001). No significant differences were observed between preoperative EO plasma levels and allelic variants of the LSS gene; moreover, patients with the less common A allele were not associated with a more severe preoperative clinical presentation, expressed as EuroScore. LSS minor variants (A) turned out to be significantly associated with the incidence of AKI (AA=29.3%; AC=25.3%; CC=17.2%; X^2 p=0.001). This evidence remains significant after correction for covariates associated with AKI previously reported (Log regression p=0.002; RR for AA variant: 2.09 IC95% 1.15-3.78).

Conclusions: Patients with at least one mutated allele of the LSS variant have a higher probability of developing AKI after cardiac surgery. We think these results could be of interest to further understand cellular mechanisms underlying AKI development.



SA-PO119

Low Cardiac Output During Cardiac Surgery Is Associated with Renal Tubular Injury Measured by Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Lee A. Goeddel, Natalie Waldron, Emily Rodriguez, James Buchanan, Wassim Obeid, Chirag R. Parikh. *Johns Hopkins University, Baltimore, MD.*

Background: Low cardiac output (CO) during cardiac surgery may contribute to renal hypoperfusion and AKI. It is challenging to associate intraoperative low CO to renal injury using serum creatinine as it is non-sensitive to injury and it its increases are delayed by 24-48 hours after surgery. We assessed the relationship between low CO and urinary neutrophil gelatinase-associated lipocalin (NGAL), which is a sensitive marker of renal tubular injury.

Methods: We enrolled 30 patients with preserved left-ventricular ejection fraction undergoing coronary-artery bypass surgery to collect urine samples at baseline, after cardiopulmonary bypass, and at intensive care unit (ICU) arrival. Cardiac index (CI) was calculated from continuous arterial waveform analysis that generates CI every five seconds and value of <= 2 L/min/m² was used as the threshold for low CI. We used the Meso Scale discovery platform to assess NGAL.

Results: Mean age was 62.7+/- 8 and 28% were female. On average, 210 ± 58 minutes of CI readings were available on each patient. Mean Low CI was 100.1± 73 minutes per patient. **Figure 1a** shows log2 NGAL at the three timepoints. Mean (SD) change from baseline to ICU arrival was (3.27 +/-3.89) pg/ml. On multivariable regression analysis adjusted for age, sex, and minutes MAP<65mmHg, each 10 minutes of CI <2 L/min/m² was associated with increased NGAL (beta 0.2; p=.078, **fig. 1b**). There was minimal association between changes in serum creatinine and low CI

Conclusions: Low CO during cardiac surgery appears to be associated with renal tubular injury and can be detected by urinary NGAL. This finding was independent of exposure to hypotension (minutes<MAP of 65 mmHg). Additional investigation of low CO and NGAL are warranted.

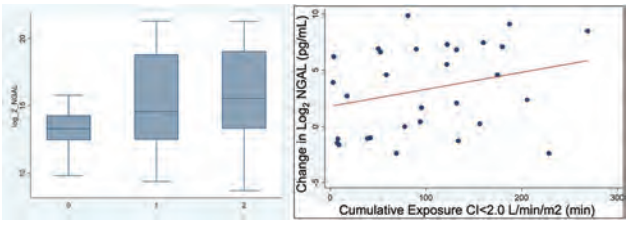


Figure 1: (a) Log2 NGAL increases from baseline (0), after cardiopulmonary bypass (1) to ICU arrival (2). (b) Low CI is associated with change in NGAL from baseline to ICU arrival.

SA-PO120

Association Between AKI and Biomarkers KIM-1, Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL), and Cystatin C in Patients Undergoing Cardiac Surgery

Bhupinder Singh, Jeannette Rodriguez, Ali C. Johnson, Richard A. Zager, Stacey Ruiz. *Renibus Therapeutics, Southlake, TX.*

Background: Patients undergoing cardiac surgery are at risk of developing acute kidney injury (AKI), which negatively impacts short and long-term clinical outcomes. Biomarkers that provide earlier detection of AKI may allow for timely intervention. Urinary excretion of kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), and cystatin C (CysC) is increased during experimental AKI. We investigated the association between these biomarkers and AKI in patients undergoing elective coronary artery bypass graft (CABG) and/or valve surgery on CPB.

Methods: Urine and plasma samples were collected from 121 adult patients who participated in a Phase 2 study designed to test the ability of an investigational drug (RBT-1) to induce an organ preconditioning response and prevent post-operative complications. AKI was defined as a ≥1.5X increase in serum creatinine (sCr) or oligoanuria through post-op Day 5 or need for dialysis. The study was neither powered nor enriched to test for potential RBT-1-induced AKI protection. Urine and plasma KIM-1, NGAL, and CysC were measured through post-op Day 3.

Results: Of the 121 patients, 22 (18.2%) developed AKI. Urinary levels of KIM-1 (uKIM-1) and CysC (uCysC) were higher in patients who did not develop AKI post-operatively (uKIM-1: 6.27 ng/mL vs 14.41 ng/mL [p=0.013]; uCysC: 2.92 ng/mL vs 6.45 ng/mL [p=0.011] for AKI vs No AKI). While uNGAL was higher in those who developed AKI (10.30 ng/mL vs 6.41 ng/mL), this result was not statistically significant (p=0.472). Correlation analyses indicated no relationship between max post-op sCr and uKIM-1 (r=0.0572), uCysC (r=0.2953), or uNGAL (r=0.3176). In contrast, plasma levels for these biomarkers were higher in patients who developed AKI post-op (KIM-1: 158 pg/mL vs 101 pg/mL; CysC: 2.39 mg/L vs. 1.61 mg/L; NGAL: 185 ng/mL vs. 126 ng/mL). Correlation analysis also showed a stronger relationship between max post-op sCr and plasma levels of CysC (r=0.7771, p<0.0001) and NGAL (r=0.7585, p<0.0001) at Day 3; no correlation was observed with KIM-1 (r=0.2941, p=0.001).

Conclusions: Urinary KIM-1, NGAL, and CysC did not correlate with AKI in this cohort of adults undergoing cardiac surgery. Plasma KIM-1, NGAL, CysC levels may hold greater promise and should be studied further.

Funding: Commercial Support - Renibus Therapeutics

SA-PO121

Exploring Lipid Biomarkers of Cardiac Surgery-Associated AKI Based on Lipidomics

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Background: Cardiac surgery-associated acute kidney injury (CSA-AKI) is a frequently occurring complication. Lipids played important roles in many biological pathways and could work as biomarkers of disease. The purpose of this study was to explore lipid biomarkers of CSA-AKI.

Methods: Plasma samples were collected when patients admitted to the ICU after cardiac surgery from 24 CSA-AKI patients and 31 controls. Lipidomic approach based on liquid chromatography mass spectrometer (LC-MS) was used to analyze plasma lipidomic alterations and potential biomarkers for CSA-AKI patients. Univariate and multivariate statistical analyses were utilized to screen the differential lipids between two groups.

Results: Lipidomics analysis detected 4053 lipid species totally. Differentially expressed lipids were screened based on the criteria variable importance at projection (VIP) value > 1, p value < 0.05, and fold change (FC) > 1.5 or < 0.67. Lipidomics identified that 65 lipids satisfied the criteria. The volcano plot showed the results of differential expression of lipids (figure 1). Heat map presented the relative levels of lipids (figure 2).

Conclusions: Lipidomics profiles could change significantly in CSA-AKI patients, and some lipid species were notably upregulated in the early stage of CSA-AKI, which could serve as potential biomarkers for CSA-AKI.

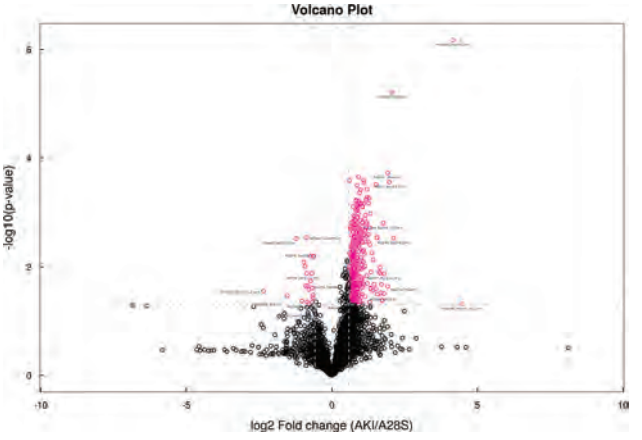

Figure 1. volcano spot

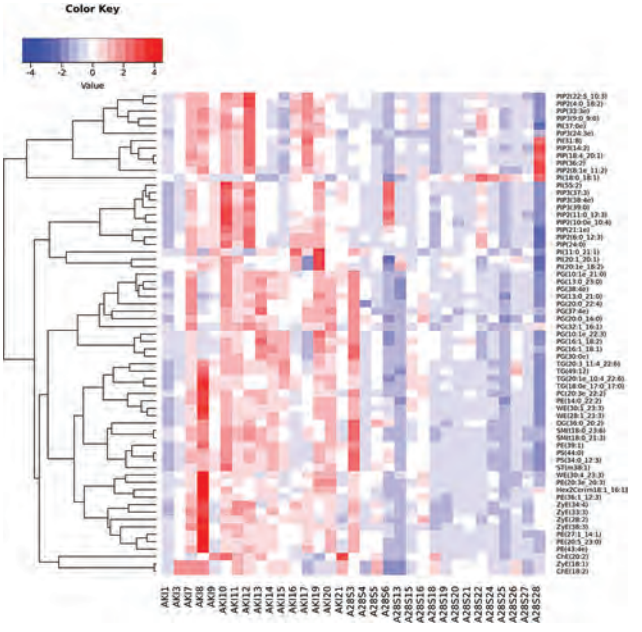

Figure 2. heat map

SA-PO122

Intra-Operative Shedding of Endothelial Glycocalyx in Cardiac Surgery-Associated AKI: A Prospective Longitudinal Cohort

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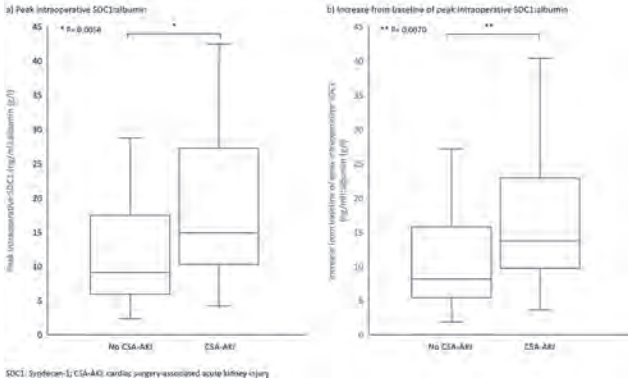
Background: This novel study aimed to consider the temporal association between microvascular disruption and cardiac surgery-associated acute kidney injury (CSA-AKI) by investigating dynamic endothelial glycocalyx changes.

Methods: We conducted a prospective observational cohort study of 61 patients undergoing non-emergency coronary artery bypass graft (CABG) surgery with serial sampling at set time-points in the pre, intra and post-operative period. We measured plasma syndecan-1 (SDC1), a major endothelial glycocalyx structural component, and calculated a ratio against plasma albumin (SDC1:alb) to take account of intraoperative haemodilution fluctuations. CSA-AKI within 48 hours was assessed using Kidney Disease Improving Global Outcomes (KDIGO) criteria. Demographic, clinical and surgical variables were considered in analysis.

Results: 14/61 (23.0%) participants developed CSA-AKI. Peak intraoperative SDC1:alb and increase from baseline of peak SDC1:alb were significantly higher in participants who subsequently developed CSA-AKI compared to those who did not (P=0.0063; P=0.008). (Figure 1) The best predictor variables of CSA-AKI were peak SDC1:alb (AUC 0.777) and urine protein:creatinine ratio (uPCR, AUC 0.840). After adjusting for uPCR and other key variables, odds of CSA-AKI in patients with peak SDC1:alb greater than the derived optimal cut-off of 23 were 11 times those with a lower peak SDC1:alb (OR 11.0 (95% CI 1.57- 106.91, P=0.021)).

Conclusions: This is the first demonstration of increased intraoperative shedding of SDC1, a core endothelial glycocalyx constituent, in CABG patients who subsequently developed CSA-AKI. These findings suggest endothelial glycocalyx disruption and microvascular dysfunction in CSA-AKI may provide a target for early therapeutic intervention and / or facilitate earlier identification of patients at greatest risk.

Figure 1: Comparison of SDC1:alb between patients who did and did not develop CSA-AKI



SDC1: Syndecan-1; CSA-AKI: cardiac surgery-associated acute kidney injury

SA-PO123

Growth Differentiation Factor (GDF)-15, a Stress-Induced Cytokine, Is Increased in Patients with AKI

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Background: Growth Differentiation Factor (GDF)-15, a member of the TGF-beta superfamily, is one of the stress response cytokines that promotes cell death. Under physiological conditions, GDF-15 is expressed in high levels in the placenta, prostate, and bladder. High circulating levels of GDF-15 have been associated with chronic inflammatory conditions including lung, liver and cardiovascular diseases, rheumatoid arthritis, and cancers. In the kidney, GDF-15 is expressed in renal tubules but its role in acute kidney injury (AKI) remains unknown. To address this issue, we measured urinary GDF-15 in patients with AKI to test if GDF-15 is involved in pathophysiology of human AKI.

Methods: AKI patients (n=86) who were treated in our department (December 2020 to December 2022) and healthy adults (n=19) were enrolled in this study. Written informed consent was obtained from all patients. Serum and urinary GDF-15 were measured by ELISA. Correlations of urinary GDF-15 with renal function, urinary protein level, clinical parameters and various AKI biomarkers were analyzed. This study was approved by the Ethics Committee on Human Research of our institutions (Approval number 2487).

Results: Urinary GDF-15 was detectable in healthy adults but was significantly increased in patients with AKI (5.1 ± 1.0 vs. 18.4 ± 1.5 ng/mL, p<0.001). Especially, urinary GDF-15 was markedly elevated in patients with ischemic AKI, drug-induced AKI, lupus nephritis, and ANCA-associated vasculitis. In most cases of AKI, urinary GDF-15 was decreased after therapeutic intervention. In cases of deceased donor kidney transplant recipients, urinary GDF-15 was significantly elevated at 1 day after transplantation but was decreased with improvement of kidney function thereafter. There was a significant correlation of urinary GDF-15 with urinary neutrophil gelatinase-associated lipocalin (NGAL), urinary kidney injury molecule-1 (KIM-1), urinary NAG, urinary β2-microglobulin, and urinary protein level, but not with serum creatinine level or L-FABP.

Conclusions: Collectively, urinary GDF-15 might be useful as a marker reflecting tubular stress and/or damage in patients with AKI.

SA-PO124

Urinary Follistatin Is a Marker Reflecting the Severity of Tubular Damage in Patients with AKI

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Background: Follistatin is an activin-binding protein that antagonizes the function of activin A, a member of TGF-beta superfamily. In animal models of acute kidney injury (AKI), the blockade of activin A by exogenous follistatin has been shown to attenuate kidney damage and improve renal function, suggesting that endogenous activin A negatively regulates tubular repair after AKI. Follistatin acts as a local modulator of activin A in many tissues. However, the role of follistatin in the kidney remains unknown.

Methods: To address this issue, we examined the localization of follistatin in normal human kidney and measured urinary follistatin in patients with AKI to test if urinary follistatin is useful as a marker for AKI. Patients with AKI (n=131) and healthy adults (n=13) were enrolled in this study. Serum and urinary follistatin was measured by ELISA. Correlations of urinary follistatin with other clinical parameters were analyzed.

Results: Follistatin was localized in renal tubules of normal kidney. Follistatin-producing cells were positive for Na-Cl co-transporter and uromodulin but were negative for aquaporin 1 or aquaporin 2. Urinary follistatin, undetectable in healthy adults, was significantly increased in patients with AKI (0.00 ± 0.00 vs. 458.1 ± 150.4 pg/mL, p<0.05) and was positively correlated with the severity of AKI. Urinary follistatin was significantly increased in patients requiring renal replacement therapy compared to those who did not. There was a significant correlation of urinary follistatin with urinary protein, alpha1-microglobulin, urinary NGAL, but not with urinary KIM-1, urinary L-FABP, urinary NAG, urinary beta2-microglobulin, serum creatinine. No correlation between urinary and serum follistatin was observed, suggesting that urinary follistatin is originated from the kidney but not from blood.

Conclusions: Collectively, follistatin produced by distal tubules of the kidney become detectable in the urine of AKI patients. Urinary follistatin might be useful to monitor the severity of acute tubular damage.

SA-PO125

Comparative Analyses of Classical Urinary Discriminators in Pre- vs. Biopsy-Proven Intrarenal AKI

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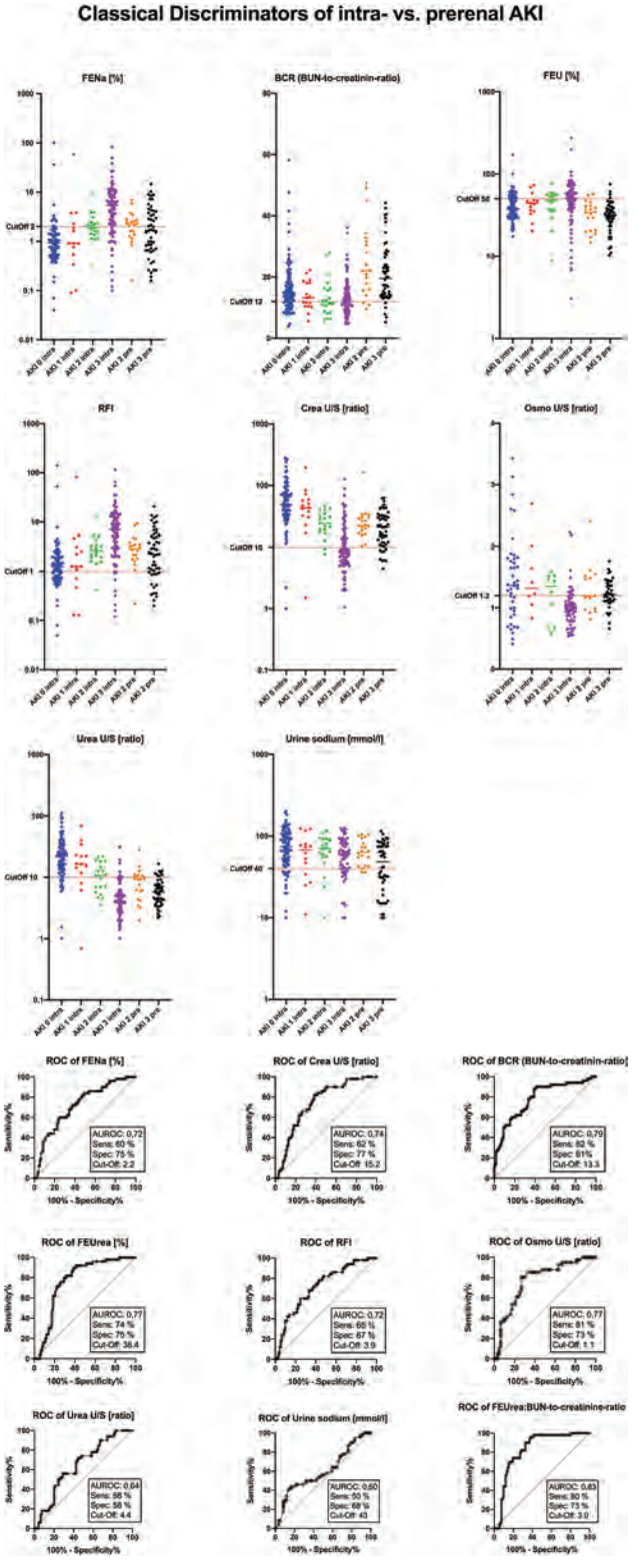
Background: The clinical distinction between prerenal and intrarenal acute kidney injury (AKI) remains challenging. Many biomarkers have been proposed, yet no comprehensive analyses of their performance has been conducted.

Methods: Classcial Urine AKI-Biomarkers of patients with biopsy-proven intrarenal AKI and prerenal AKI have been compared.

Results: Kindey urine composition handling showed alterations according to severity (Figure 1) of AKI in most discriminators. ROC analyses (of AKI 3 prerenal vs. intrarenal) showed some discriminatory power of the investigated classical biomarkers (Figure 2). Best performance was observed with BUN-to-creatinine-ratio (area-under-the-roc / AUROC = 0.79; sensitivity 60%, specificity 83%), worst with urine sodium concentration (AUROC 0.6; sensitivity 50%, specificity 68%). The ratio of FEUrea devided by BUN-to-creatinine-ratio yielded the best discriminatory power (AUROC 0.83; sensitivity 80%, specificity 73%).

Conclusions: This analysis is the first to comprehensively compare the discriminatory power of classic urine biomarkers to distinguish between prerenal and intrarenal AKI. To foster reliabilty the intrarenal group was based on kidney biopsy diagnosis. Overall, most parameters showed medium performance. We identified a new ratio (FEUra devided by BUN-to-creatinine-ratio), which performed best according to AUROC analysis.



SA-PO126

Fractional Excretion of Urea for the Differential Diagnosis of AKI: A Systematic Review and Meta-Analysis with Comparison to Fractional Excretion of Sodium

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Background: Differentiating between intrinsic and prerenal acute kidney injury (AKI) presents a challenge. This study aims to assess the performance of fractional excretion of urea (FEUrea) and compare it to fractional excretion of sodium (FENa) in distinguishing intrinsic from prerenal AKI.

Methods: We searched MEDLINE, Embase, CENTRAL, the Cochrane Library, and Scopus until July 2022. Studies evaluating FEUrea, with or without FENa, for differentiating AKI etiologies in adults were included. We assessed the methodological quality using the QUADAS-2/-C tools. We conducted a meta-analysis using the bivariate random effects model, with subgroup analyses to explore the impact of diuretic therapy on FEUrea performance. We performed direct statistical comparisons between FEUrea and FENa in the overall AKI patients and subgroups with and without diuretic therapy. Study protocol: PROSPERO, CRD42022341290.

Results: We included 11 studies with 1108 hospitalized patients. Among 8 studies (915 patients) evaluating FEUrea at 35% threshold, the pooled sensitivity and specificity for distinguishing intrinsic from prerenal AKI were 66% (95% CI, 49-79%) and 75% (95% CI, 60-85%), respectively. In a subset of 6 studies (573 patients) comparing FEUrea at 35% to FENa at 1%, there was no significant difference in sensitivity (69% vs. 86%, *P*=0.089) but a significant difference in specificity (81% vs. 64%, *P*=0.038). Additionally, In 302 patients not on diuretics, there were no significant differences in sensitivity (77% vs. 89%, *P*=0.410) or specificity (80% vs. 79%, *P*=0.956). In 4 studies with 244 patients on diuretics, FEUrea demonstrated lower sensitivity (52% vs. 92%, *P*<0.001) but higher specificity (82% vs. 44%, *P*<0.001) compared to FENa.

Conclusions: Both FEUrea and FENa have limited utility in differentiating intrinsic from prerenal AKI. FEUrea does not provide a superior alternative to FENa, even in patients receiving diuretic therapy.

Figure. Forest plot for the studies included in the meta-analysis of FEUrea at 35% for intrinsic versus prerenal AKI

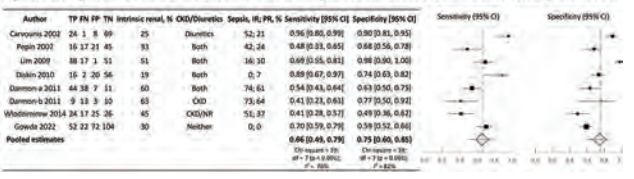

Table. Direct comparison between FEUrea at 35% and FENa at 1%

Test	Group/ subgroup	No. of studies; patients	Intrinsic AKI, %	Pooled sensitivity [95% CI]; I^2	Pooled specificity [95% CI]; I^2	Abs difference in sensitivity [95% CI, p]; Abs difference in specificity [95% CI, p]
FEUrea	All patients	6; 573	41	69% [48%, 84%]; 76%	81% [68%, 90%]; 77%	-20% [-44%, 3%, 0.089]; 16% [1%, 31%, 0.038]
FENa				90% [65%, 98%]; 86%	65% [56%, 74%]; 72%	
FEUrea	Not on diuretics	6; 302	44	77% [52%, 91%]; 86%	80% [64%, 90%]; 76%	-12% [-40, 16%, 0.410] 0.4% [-14%, 15%, 0.956]
FENa				89% [53%, 98%]; 85%	79% [72%, 85%]; 0%	
FEUrea	On diuretics	4; 244	42	52% [40%, 64%]; 78%	82% [54%, 95%]; 73%	-39% [-55%, -23%, <0.001] 38% [14%, 63%, <0.001]
FENa				92% [72%, 98%]; 50%	44% [31%, 58%]; 68%	

SA-PO127

Fractional Excretion of Urinary Sodium and Urinary Sediment Microscopy for Prediction of Response to Vasoconstrictors in Hepatorenal Syndrome Type 1

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Background: Because of diagnostic challenges around differentiating hepatorenal syndrome type 1 (HRS-1) from acute tubular injury (ATI), proper selection of patients who can benefit from vasoconstrictor therapy (VCT) remains suboptimal. We hypothesized that markers of tubular function or injury may correlate with therapeutic response to VCT.

Methods: Records from hospitalized patients with HRS-1 treated with VCT without shock were reviewed. We selected those who achieved ≥5 mmHg rise in mean arterial pressure (MAP) within 48 hours and had available fractional excretion of urinary sodium (FENa) (marker of tubular function) and microscopic examination of the urinary sediment (MicrExUrSed) (marker of tubular injury). Lower limit for urinary Na was <10 mEq/L. HRS-1 was diagnosed by ICA criteria + FENa <1% + no overt ATI by MicrExUrSed (abundant dark granular casts). Absence of ATI by MicrExUrSed was defined as bland sediment or only hyaline casts. The primary endpoint was percentage of change in serum creatinine (sCr) at the end therapy (day 7-14).

Results: A total of 44 patients with HRS-1 treated for 2-7 days with either norepinephrine (n=40) or midodrine/octreotide (n=4) were included. Median age was 52 (IQR 46-62), 41% female and 57% had alcoholic cirrhosis. At the start of VCT, median MAP was 71 mmHg (IQR 68-74) and median sCr was 3.8 mg/dL (IQR 2.8-4.9). Median FENa was 0.4% (IQR 0.29-0.49). FENa significantly correlated with change in serum Cr (r=0.395, p=0.007). Thus, lower FENa was associated with reduction in sCr. All patients with >30% reduction in sCr had FENa between 0.05 and 0.42%. Among those with MAP rise >10 mmHg (n=30), the correlation between FENa and change in sCr turned stronger (r=0.599, p=0.0004). Furthermore, the correlation between MAP rise and improvement

in sCr was stronger among those with absence of ATI by MicrExUrSed (n=24) (r=-0.579, p=0.003) compared to those with scattered elements of ATI (n=20) (r=-0.23, p=0.32). Among those with MAP rise >10 mmHg, 10 of 16 (63%) of those with no ATI by MicrExUrSed achieved >30% reduction in sCr compared to 4 of 14 (27%) of those with ATI elements (p=0.06).

Conclusions: Functional and injury urinary markers may offer predictive information respect to response to VCT in HRS-1.

SA-PO128

Kinetics of Mature Platelet Fraction as a Tool for Predicting the Time Course of Shiga Toxin-Producing Escherichia coli-Associated Hemolytic Uremic Syndrome (STEC-HUS)

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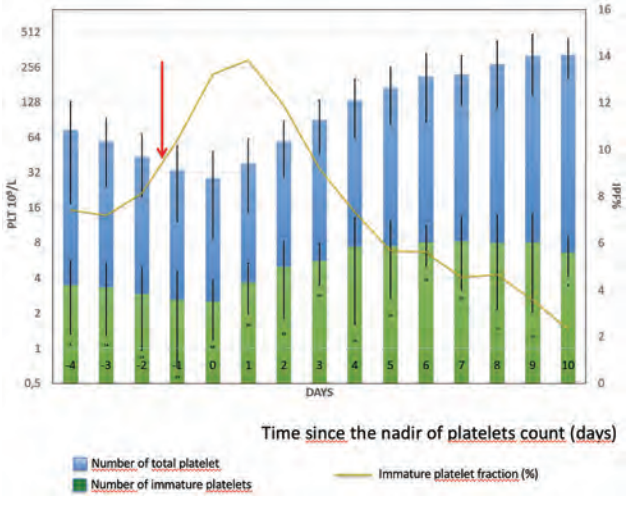
Background: Shigatoxin-related Hemolytic Uremic Syndrome (STEC-HUS) is a common thrombotic microangiopathy in children characterized by platelet consumption, hemolysis and kidney dysfunction. Being the time course of the disease relatively regular, the description of platelets kinetics, including reticulated platelets, may provide some useful insights for predicting the short-term course of the disease.

Methods: We considered all patients with STEC-HUS referred to our center during the last 5 years. Blood count for both total and reticulated platelets was performed daily with a XN-9000 hematology analyzer since admission until recovery. Results are expressed as absolute number and percentage of total.

Results: Fourty patients with documented STEC-HUS were studied. Results are displayed in the figure showing the time course of total and reticulated platelets in the coohort of patients (time 0 identifies the nadir of total platelets). When immature platelet fraction reaches the threshold of 10% the resolution of thrombocytopenia, thus the beginning of recovery, is approaching and is expected in 24-48 hours.

Conclusions: During the course of STEC-HUS the rise of immature platelet fraction above 10% anticipates (by 24-48 hours) the increase of total platelets count thus predicting the beginning of disease recovery.



SA-PO129

Through the Haze: Sailing the Turbid Waters of Uremic Ophthalmopathy

Caleb S. Pacheco-Molina, Jesus D. Vega-Colon, Maria E. Rivera, Jeaneishka M. Rivera Rios, Ileana E. Ocasio Melendez, Krystahl Z. Andujar-Rivera, Carlos G. Rivera-Bermudez, Lydwan Pérez Westerband. *Universidad de Puerto Rico Escuela de Medicina, San Juan, Puerto Rico.*

Introduction: Ophthalmic disease can be a consequence of many metabolic conditions, rarely is caused by uremia. This is an uncommon etiology of ophthalmic disease and there are only a few cases reported.

Case Description: A 45-year-old man with arterial hypertension, horseshoe kidney and a previous episode of acute kidney injury (AKI) presented complaining of a three-month history of bilateral blurry vision, eye pain and fatigue. Denied changes in urinary habits, recent infections, travel, toxic habits, NSAIDs use, or family history of kidney disease. Evaluation was remarkable for elevated blood pressure, 168/85 mmHg, and bilateral lower extremity edema. Ophthalmologic evaluation was notable for bilateral optic nerve inflammation. Laboratory results were remarkable for anemia, azotemia with BUN of 182.9 mg/dL, creatinine level of 29.5 mg/dL, severe hyperkalemia, and metabolic acidosis with HCO_3 level of 7.5 mEq/L. Urinalysis with findings of proteinuria, and hematuria with positive RBCs and WBCs without casts. Urine protein-creatinine ratio of 3.5 g/g. Workup for glomerular disease, vasculitides, HIV, HBV and HCV yielded negative results. Renal US showed small kidneys with increased cortical echogenicity compatible with intrinsic parenchymal disease, without hydronephrosis or nephrolithiasis. CT scan confirmed the presence of horseshoe kidney. Patient was started on hemodialysis with immediate improvement in visual symptoms. Follow up ocular evaluation was notable for improved optic nerve inflammation bilaterally. Head CT scan was negative for intracranial pathologies, as well as orbital CT scan. Patient was discharged home on hemodialysis and ophthalmologic symptoms continued improving.

Discussion: Uremic ophthalmopathy is a rare finding worth sharing. In the case of our patient that a clear etiology of renal injury was not found, it is more likely that the subject had progressive renal function decline for which he was not receiving appropriate care, and this finding might be secondary to chronic uremia. For this reason, it is fair to consider uremia as the cause of ophthalmopathy in patient in which other metabolic causes are not a clear culprit.

SA-PO130

Severe AKI due to Cortical Necrosis in Postpartum Patient

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Introduction: Severe post-partum AKI is rare in the United States, but has a challenging differential diagnosis that often includes atypical hemolytic uremic syndrome (aHUS), ATN and acute cortical necrosis (ACN). Establishing the diagnosis is critical to provide specific therapy. We present a case of aHUS in a post-partum patient in whom the diagnosis of aHUS was confounded by simultaneous influenza, peri-partum hemorrhage, and microangiopathic hemolysis, elevated liver enzymes, and HELLP syndrome, proteinuria, cardiomyopathy, and endometritis.

Case Description: A 33-year-old woman was hospitalized for hypovolemic shock and coagulopathy following term, vaginal delivery complicated by severe hemorrhage. She received RBC transfusion besides vasopressor support for several hours. Oligo-anuric kidney failure ensued requiring dialysis support. Echo showed severe global left ventricular dysfunction. CT with contrast was consistent with cortical necrosis of kidney. Platelet count of 63,000/uL, high LDH, low haptoglobin, and presence of schistocytes were consistent with microangiopathy. C3 and C4 and ADAMTS13 activity were normal. Liver chemistries normalized soon. UPR was elevated at 2.1. Empirical therapy for aHUS with Eculizumab was initiated with rapid improvement in platelet count and urine output but dialysis dependence persisted. Kidney biopsy performed that demonstrated cortical necrosis and could not confirm or reject a diagnosis of aHUS. Functional complement assays were nondiagnostic. Genetic profile was negative for mutations. Because of her clinical response, Eculizumab was maintained for 6-months. Unfortunately, patient remained dialysis dependent.

Discussion: Post-partum AKI can occur by a variety of mechanisms with variable prognosis and management. Eculizumab is specific treatment for aHUS but confers risk for infection and is expensive. Treatment of ATN or ACN is supportive, Alternative complement pathway functional and genetic profiles can facilitate diagnosis but results are delayed and may be non-informative as in this case. Kidney biopsy demonstrated cortical necrosis but patchy injury. ACN might have been demonstrable by CT or MRI by showing meduallary enhancement in the absence of cortical enhancement ("reverse rim sign") but were not obtained. Although aHUS was suspected based on hematologic and biochemical data, ACN appears to have been the dominant process.

SA-PO131

A Case of Atypical Manifestation of Uremic Encephalopathy: Acute Psychosis

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Introduction: Uremic encephalopathy UE is a cerebral dysfunction caused by the accumulation of toxins resulting from acute or chronic renal failure. The clinical presentation is broad, and the clinical course is always progressive when untreated. Patients generally exhibit the signs of UE when glomerular filtration rate is less than 15 ml/min/1.73 m2 and the symptoms usually include fatigue, nausea, restlessness, drowsiness and diminished ability to concentrate. Paranoia is sometimes described as a uremic presentation, but rarely do patients exhibit acute psychosis. Here we present a patient with acute psychosis as her first sign of uremic encephalopathy.

Case Description: The patient is a 66-year-old female with past medical history of CKD stage III with baseline 2.4 mg/dl, coronary artery disease status post percutaneous coronary intervention, HFpEF, DM2 who presented to the hospital after failing outpatient management of mastitis. Her hospital course was complicated by acute kidney injury stage II, mild hyperkalemia and acute pychosis. Her manifestations include vocalization of her displeasure of the hosptal, aggressive language, noncompliance to the treatment plan and severe paranoia. Patient did not have any psychiatric history. Her peak BUN was 59 and peak creatinine was 5.68 mg/dl. She was deemed to be competent by the psychiatry team. Antipsychotics were given for paranoia, but her conditions did not improve. However, her mental status improved drastically after two sessions of dialysis treatment.

Discussion: Timing of dialysis initiation is an important topic in nephrology. The current practice is to delay dialysis unless there is an absolute indication. Uremic encephalopathy is a clinical diagnosis and can have various presentations, most notably catatonia or hypoactive symptoms. Acute psychosis is a very atypical presention of uremia and can be missed as an indication for dialysis initiation. In our patient, delayed dialysis would significantly impacted the delivery of her overall care due to her psychosis.

SA-PO132

Cystatin C as a Diagnostic Marker for a Postoperative Urine Leak

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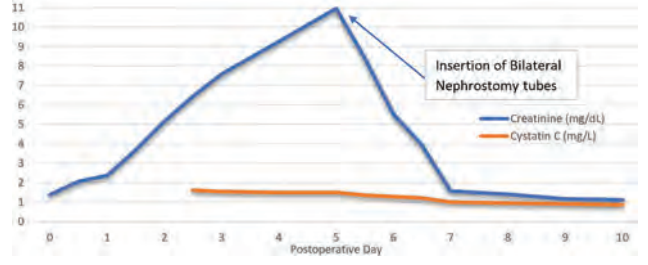
Introduction: Evaluating kidney function after urologic procedures can be challenging in the presence of complications such as urine leaks. This case report illustrates a scenario where serum creatinine provided misleading Glomerular Filtration Rate (GFR) estimations, prompting the use of cystatin C for diagnostic accuracy.

Case Description: A 67-year-old male with a history of prostate cancer underwent uneventful robotic assisted laparoscopic prostatectomy. Postoperatively, serum creatinine rapidly increased from a baseline of 0.9 mg/dL. On postoperative day (POD) 1, significant output from a Jackson-Pratt (JP) drain indicated possible urine leak. However, a CT scan on POD 2 did not show obstruction or leak. Due to ongoing suspicion, nephrology consultation recommended obtainng daily cystatin C, hypothesizing that elevated serum creatinine mirrored urine resorption rather than a GFR decline. On POD 5, discrepant serum creatinine and cystatin C values (10.95 mg/dL, 1.5 mg/L respectively) along with a JP drain fluid creatinine of >40 mg/dL led to the placement of nephrostomy tubes. Post-procedure, serum creatinine and cystatin C levels normalized and JP output decreased.

Discussion: This case highlights the use of cystatin C in diagnosing postoperative urine leaks and the limitations of using serum creatinine as the sole kidney function marker after urologic procedures. Despite a non-diagnostic CT scan, the divergent serum creatinine and cystatin C pointed towards a urine leak. The mild cystatin C elevation, which improved post nephrostomy tube placement, suggests some obstructive uropathy or intrinsic kidney injury. Our case aligns with a case by Saro-Nunez et al 2018, where cystatin C was similarly used for eGFR measurements in a urinoma. Cystatin C, correlates with residual kidney function in peritoneal dialysis patients, suggesting minimal transport across the peritoneal membrane. Considering creatinine's absorption in peritoneal and retroperitoneal spaces, cystatin C may offer a more reliable marker. This case highlights cystatin C's potential utility in urologic surgery complications like urine leaks, despite its rare use in acute kidney injury.



SA-PO133

Comparison of cROCK, KDIGO, and Their Combined Criteria for Detecting AKI in Hospitalized Adults with CKD

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Background: Acute kidney injury (AKI) in chronic kidney disease (CKD), also known as acute-on-chronic kidney disease (ACKD) increases the risk of CKD progression, major adverse cardiovascular events (MACEs), and all-cause mortality. Hou et al. set up a reference change value (**R**CV) of the serum creatinine (SCr) **O**ptimized **C**riterion for A**KI** in **C**KD (cROCK), which is defined as a >25% increase of SCr over 7 days. This study aimed to evaluate the ability of the novel criterion of **cROCK** to detect ACKD patients and then compared the effects of the criteria of cROCK and KDIGO in predicting long-term outcomes in ACKD patients.

Methods: This was a retrospective observational study with a 3-year follow-up period. The electronic medical records data of inpatients admitted to Xuzhou Central Hospital between January 2016 and June 2018 were screened. All included patients with CKD stage 3 were evaluated using cROCK, KDIGO, and their combined criteria. The renal composite endpoints, MACEs, and all-cause mortality were recorded as the clinical outcomes.

Results: A total of 812 patients was enrolled and assigned to 4 groups depending on the KDIGO and cROCK criteria (Fig 1). The baseline and follow-up data were described in Table 1. The cROCK detected 8.5% more ACKD events than KDIGO criterion (67.98% vs. 59.48%, $P < 0.001$). During the 3-year follow-up, 683 patients experienced renal composite endpoint events, with groups ranked from high to low percentage of free events as KDIGO(−)&cROCK(−), KDIGO(+)&cROCK(−), KDIGO(−)&cROCK(+), and KDIGO(+)&cROCK(+) (Fig 2A). 650 patients developed MACEs, with groups ranked as KDIGO(−)&cROCK(−), KDIGO(−)&cROCK(+), KDIGO(+)&cROCK(−), and KDIGO(+)&cROCK(+) (Fig 2B). 405 patients died with trends similar to MACEs (Fig 2C).

Conclusions: Compared to the KDIGO criterion, the cROCK detected more ACKD events. Combining the cROCK and KDIGO criteria might improve the predictive ability for long-term outcomes in ACKD patients.

Funding: Government Support - Non-U.S.

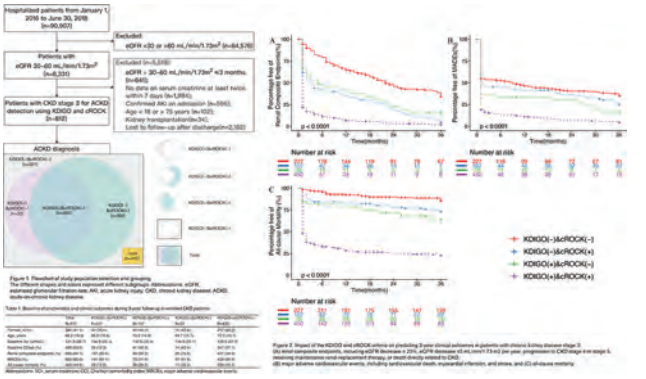

Table and Figure

SA-PO134

Smaller Kidney Volume Is Associated with AKI Following Cardiovascular Surgery, Especially Among Patients Treated with Renin-Angiotensin System Inhibitors

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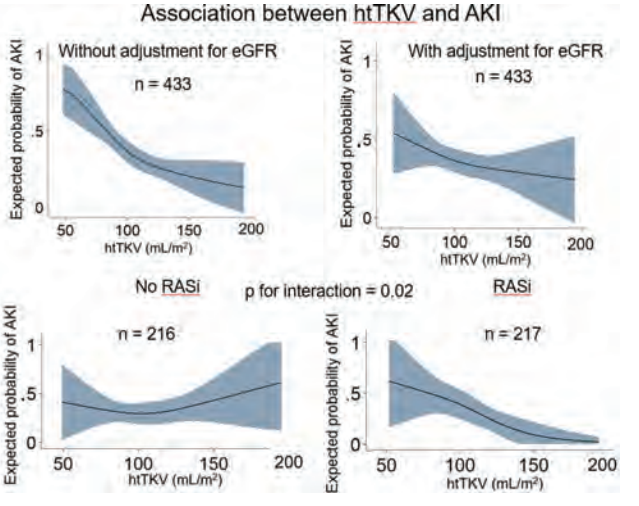
Background: Kidney volume might reflect atherosclerotic changes in the vascular bed in the kidney independent of eGFR and thus might be independently associated with postoperative AKI.

Methods: In this retrospective cohort study, we enrolled adults who underwent cardiovascular (CV) surgery from 2014 to 2021 at our facility and computed tomography (CT) scans within 6 months before surgery. We excluded those with multiple or large cysts, single kidney, serum creatinine >4 mg/dL, or undergoing kidney replacement therapy. Exposure of interest was height-adjusted total kidney volume (htTKV) measured by software using the three-dimensional CT reconstruction. The outcome was postoperative AKI defined by the KDIGO creatinine criteria. We employed logistic regression models and the results were shown as cubic spline curves. Effect modifications by renin-angiotensin system inhibitors (RASi, defined as angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers), loop diuretics, and non-steroidal anti-inflammatory drugs (NSAIDs) were assessed.

Results: Among 433 patients, 147 (33.9%) developed AKI. Those with smaller htTKV were older, less likely to be diabetic, had lower eGFR, and higher prevalence of CV comorbidities. Smaller htTKV tended to be associated with AKI even after adjustment for eGFR. Smaller htTKV was associated with AKI especially among the users of RASi (p for interaction 0.02). Loop diuretics and NSAIDs did not significantly modify the association between htTKV and AKI(p for interaction 0.44 and 0.42, respectively).

Conclusions: Smaller htTKV was associated with postoperative AKI independent of eGFR, especially among patients using RASi. Among patients with smaller htTKV, withdrawing RASi before CV surgery might be protective against post-operarive AKI.



SA-PO135

Combining Arterial and Venous Intrarenal Doppler Assessment for the Prediction of AKI After Cardiac Surgery

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Background: Acute kidney injury (AKI) is common after cardiac surgery and often hemodynamically mediated. The roles of ultrasound measures of intrarenal perfusion to predict AKI are yet to be determined. The objective of this study was to determine if point-of-care ultrasound Doppler measures of intrarenal arterial and venous flow predict AKI after cardiac surgery.

Methods: We conducted a secondary analysis of a prospective cohort study of adult patients undergoing cardiac surgery in whom ultrasound assessments were performed at ICU admission after surgery. AKI was defined by the KDIGO creatinine criteria. Intrarenal arterial markers included renal resistive index (RRI) and velocity-time integral normalized to peak systolic velocity (VTI/PSV), while venous markers included intrarenal venous flow (IRVF) categories and renal venous stasis index (RVSI). The area under the receiving operating characteristic (AUROC) curves were used to determine the predictive characteristics for post-operative AKI. The performance of individual markers were compared to a combined RRI and RVSI logistic regression model using the net classification index (NRI) and AUROC were compared with the DeLong test.

Results: We included 131 patients in total, with 47 patients (35.9%) developing post-operative AKI. All studied ultrasound markers showed moderate discrimination for the subsequent development of AKI (Table 1). More complex measurements (VTI/PSV and RVSI) were not superior to simpler indices (RRI and IRVF). In a multivariable model, both RRI (aOR:1.70, CI:1.09-2.66, p=0.02) and RVSI (aOR:0.85, CI:0.04-0.98, p=0.048) remained associated with AKI. The predicted probabilities from the model were slightly better than each index taken individually according to the NRI. However, the AUROC were not significantly different (Table 1).

Conclusions: Intrarenal arterial and venous Doppler indices moderately predict the development of post-operative AKI in cardiac surgery patients. However, combining arterial and venous Doppler indices only marginally improves prediction.

Echographic Parameters and AKI After Cardiac Surgery

Echographic Parameter	Postoperative Day 0			DeLong Test/Net Reclassification Index
	AUROC	95% CI	P Value	
RRI	0.64	0.55-0.74	0.006	p=0.38 / NRI: 0.32 (CI: -0.06; 0.69)
VTI/PSV	0.67	0.57-0.77	0.001	
IRVF Category	0.64	0.53-0.74	0.009	p=0.19 / NRI: -0.52 (CI: -0.82; 0.20)
RVSI	0.60	0.50-0.71	0.045	
Predicted probability of model: RRI + RVSI	0.69	0.59-0.78	<0.001	Vs RRI: p=0.50 / NRI: 0.50 (CI: 0.17; 0.84) Vs RVSI : p=0.38 / NRI: 0.38 (CI: 0.04; 0.70)

SA-PO136

Association of Aortic Pulsatility Index with Clinical Outcomes and In-Hospital eGFR Slope Among Patients Admitted for Acute Decompensated Heart Failure Requiring Hemodynamic Monitoring

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Background: Aortic pulsatility index (API), (systolic–diastolic blood pressure)/pulmonary capillary wedge pressure, is a hemodynamic parameter reflecting cardiac contractility and forward perfusion. We examined whether API is associated with mortality, cardiovascular (CV) outcomes and kidney outcomes among patients admitted for acute decompensated heart failure (ADHF).

Methods: For patients admitted for ADHF requiring invasive hemodynamic monitoring from 2015 to 2021, API was calculated at the time of pulmonary artery catheter placement. Mortality and end stage renal disease (ESRD) events were linked to the state death registry and the United States Renal Data System. Heart transplant (HT) and left ventricular assist device (LVAD) implantation events were obtained from the medical record. Cox proportional hazards regression models were used to evaluate the association between API quartiles and a composite endpoint of death, HT, or LVAD. Associations between API and baseline eGFR and in-hospital eGFR slope were evaluated using linear regression and linear mixed models, respectively. Cox proportional hazards regression models were used to evaluate quartiles of API and ESRD.

Results: Among 743 patients, mean (SD) age and baseline eGFR were 62 (14) years, 58 (27) ml/min/1.73m^2 respectively. Initial median (IQR) API was 1.8 (1.2, 2.7). Over median follow-up of 23 months, 259 (35%) died, 107 (14%) had HT, and 15 (2%) had LVAD implantation; 62 (8%) developed ESRD. In reference to the quartile with highest API, Quartile 1 (lowest API) was associated with increased risk of the composite outcome of mortality, OHT or LVAD. There was no association between API and baseline eGFR or in-hospital eGFR slope per week (0.42 [-1.69, 2.53]; 0.17 [-0.37, 0.71] per doubling API, respectively), nor any association between quartiles of API with ESRD.

Conclusions: Low API is associated with a higher risk of a composite of death and cardiovascular outcomes but not with baseline or in-hospital eGFR slope or development of ESRD.

Funding: NIDDK Support

Table. Hazard ratios ((95% CI) for composite outcome of death, heart transplant, or LVAD by API quartiles

	Quartile 1 (n=186)	Quartile 2 (n=184)	Quartile 3 (n=186)	Quartile 4 (n=187)
Initial median (IQR) API	0.9 (0.7, 1.0)	1.5 (1.3, 1.6)	2.1 (1.9, 2.3)	3.7 (3.0, 4.6)
Composite of Death, Heart Transplant, Left Ventricular Assistant Device Implantation				
N of Events	107	92	92	76
Unadjusted	1.74 (1.30, 2.33)	1.30 (0.96, 1.76)	1.34 (0.99, 1.82)	Ref
Adjusted	1.45 (1.04, 2.03)	1.19 (0.86, 1.64)	1.22 (0.89, 1.67)	Ref
End Stage Kidney Disease				
N of Events	15	21	13	13
Unadjusted	1.26 (0.60, 2.64)	1.61 (0.81, 3.22)	1.07 (0.49, 2.30)	Ref
Adjusted	1.07 (0.46, 2.48)	1.53 (0.73, 3.19)	1.07 (0.48, 2.35)	Ref

* Adjusted for age, sex, diastolic blood pressure, ejection fraction, baseline eGFR, home anticalcium (ACEi/ARB, ADNI, MRA); and in-hospital inotrope use.

SA-PO137

The Impacts of Skeletal Muscle Mass and Quality on Kidney Recovery of Patients with AKI Receiving Continuous Renal Replacement Therapy

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Background: Although there are increasing interests in kidney recovery after acute kidney injury (AKI), little is known about patients with severe AKI requiring continuous renal replacement therapy (CRRT). It is known that sarcopenia is associated with poor prognosis not only in chronic inflammatory conditions but also in acute disease. Recent study revealed that muscle mass and quality were significant determinants of mortality in patients with CRRT. However, few studies evaluated the effect of sarcopenia on kidney recovery in patients receiving CRRT.

Methods: We collected 2051 AKI patients who underwent CRRT from eight medical centers between 2006 and 2021. The skeletal muscle area (SMA) was measured from the automated software from CT images at 3rd lumbar vertebra within 15 days of CRRT initiation, and classified as normal attenuation muscle area (NAMA) and low attenuation muscle area (LAMA) according to muscle density. We used Fine and Gray model to investigate the effects of muscle index adjusted by body mass index (BMI) on kidney recovery.

Results: Of the 813 CRRT survivors, 682 (83.9%) patients were discharged without RRT. Increased SMA/BMI was independently associated with decreased risk of RRT dependence. Also, the 4th quartile of NAMA/BMI was significantly associated with decreased RRT dependence risk. However, non-significant effects of LAMA/BMI were observed.

Conclusions: In patients with severe AKI receiving CRRT, not only the quantity but also the quality of muscle affects RRT dependence.

SMA/BMI	Model1		Model2		Model3	
Q1 [0.99, 3.93]	ref		ref		ref	
Q2 (3.93, 4.74]	0.93	(0.74, 1.16)	1.01	(0.80, 1.27)	1.06	(0.83, 1.35)
Q3 (4.74, 5.56]	1.12	(0.91, 1.39)	**1.29**	**(1.01, 1.64)**	1.28	(0.99, 1.65)
Q4 (5.56, 9.76]	**1.35**	**(1.09, 1.66)**	**1.50**	**(1.17, 1.93)**	**1.48**	**(1.12, 1.95)**
Linear	**1.10**	**(1.04, 1.17)**	**1.12**	**(1.05, 1.20)**	**1.11**	**(1.03, 1.20)**
LAMA/BMI	**Model1**		**Model2**		**Model3**	
Q1 [0.08, 1.98]	ref		ref		ref	
Q2 (1.98, 2.43]	1.07	(0.87, 1.32)	1.14	(0.92, 1.41)	1.12	(0.90, 1.40)
Q3 (2.43, 2.97]	0.85	(0.69, 1.05)	0.97	(0.78, 1.20)	0.96	(0.76, 1.21)
Q4 (2.97, 6.51]	0.87	(0.71, 1.08)	0.98	(0.79, 1.21)	1.03	(0.81, 1.30)
Linear	0.93	(0.84, 1.02)	0.98	(0.89, 1.08)	1.02	(0.92, 1.14)
NAMA/BMI	**Model1**		**Model2**		**Model3**	
Q1 [0.05, 1.40]	ref		ref		ref	
Q2 (1.40, 2.12]	1.05	(0.84, 1.31)	1.10	(0.88, 1.38)	1.02	(0.80, 1.31)
Q3 (2.12, 2.99]	1.21	(0.97, 1.49)	1.27	(1.01, 1.60)	1.11	(0.86, 1.41)
Q4 (2.99, 7.44]	**1.52**	**(1.23, 1.87)**	**1.55**	**(1.21, 1.98)**	**1.38**	**(1.06, 1.81)**
Linear	**1.15**	**(1.08, 1.22)**	**1.14**	**(1.06, 1.23)**	**1.10**	**(1.02, 1.19)**

Model 1=crude

Model 2=Model 1+Sex+Age+Charlson comorbidity index+HTN+Sepsis

Model 3=Model 2+Creatinine+White blood cell+Hb+Albumin+PT INR+SOFA score+APACHE II score

SA-PO138

Contract Induced Nephropathy in Kidney Transplant Recipients: A Systematic Review and Meta-Analysis

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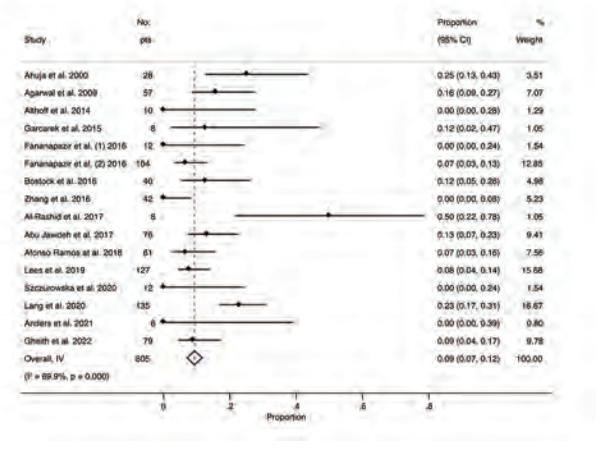
Background: Kidney transplant recipients (KTR) may be at higher risk of contrast induced Nephropathy (CIN) because of associated risk factors. The incidence proportion of CIN in native kidneys has been reported to be 9% in a recent meta-analysis with 0.5% requiring renal replacement therapy (RRT). We aimed to determine the incidence proportion of CIN in KTR.

Methods: Medline, Embase, and Cochrane databases were used to search the studies assessing the incidence of CIN in KTR from inception until January 2023. We applied Random effect model to estimate the incidence of CIN in KTR.

Results: Sixteen studies, including 805 contrast studies in KTR, were included in the analysis. The estimated incidence of CIN in KTR and CIN requiring RRT was 9.3% (95% confidence interval (CI) 7.1 % to 11.7%) and 1.1% (95% CI: 0.0% to 1.4%), respectively. None of the CIN patients required permanent RRT. In subgroup analysis, the incidence of CIN in KTR who received Iso-osmolar (300 mOsm/kgH20) vs hypo-osmolar CM (550 mOsm/kgH20) was 5.0% (95%CI: 0.8% to 11.2%) and 8.7% (95% CI: 5.6% to 12.2%), respectively. An estimated incidence of CIN in KTR who underwent coronary angiography was 14% (95% CI: 8% to 22%). Angiograms, including allograft renal artery angiograms (without angioplasty/stenting) and CT scans resulted in CIN in 12% (95% CI: 4% to 18%), in 8.6% (95% CI: 5% to 12% CI), respectively. CIN in KTR who underwent angioplasty/stenting to relieve renal artery stenosis (RAS) was 3%. There was complete reversal of CIN with successful therapeutic intervention for RAS, renal function improved above baseline. No graft loss was reported within 30 days post CM administration regardless of the type of CM administered.

Conclusions: The estimated incidence of CIN in KTR is 9.3%, equal to the incidence of CIN in native kidneys (9%). Therefore, it appears that the risk of CIN in KTR patients is not different than the general population.



Forest plot of incidence of CIN in KTR.

SA-PO139

Effect on Kidney Function Recovery Guiding Decongestion with Venus Evaluation by Ultrasound System (VExUS) in Patients with Cardiorenal Syndrome 1, A Randomized Control Trial

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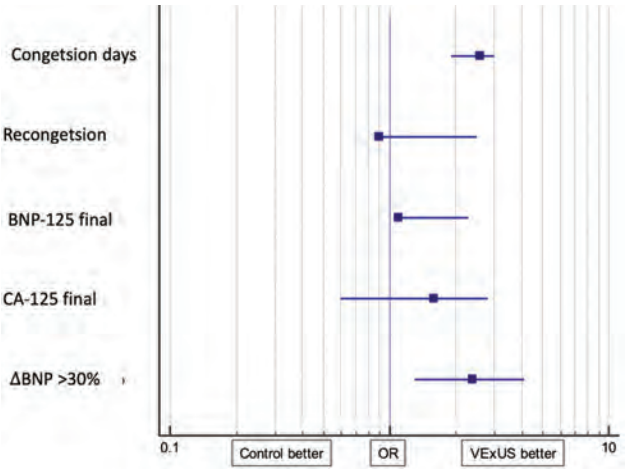
Background: In cardiorenal syndrome type 1 (CRS1) vascular congestion is a common complication, the Venus Evaluation by Ultrasound System (VExUS) could guide decongestion with diuretics effectively and thereby improve renal function and outcomes.

Methods: In this double-blind randomized clinical trial, patients with CRS1 were randomized to guide decongestion with VExUS compared to usual clinical evaluation. The primary and secondary endpoint was to assess kidney function recovery (KFR), days of hospitalization, mortality, changes in brain natriuretic peptide (BNP) and CA-125. Protocol register number is HCG/CEI-0836/22.

Results: During the period from March 2022 to February 2023, a total of 140 patients were randomized, 70 in the VExUS group and 70 in the Control group. KFR in the VExUS group, compared to Control, no significant difference was found. VExUS improve in more than twice the speed (in days) with which decongestion is achieved (OR 2.6, CI 1.9-3.0, p=0.01). With VExUS is two-fold more likely to reach a decrease of BNP >30% (OR = 2.4; CI 1.3-4.1, p = 0.01). Survival at 90 days was similar between groups. Recongestion, CA125 and mortality were similar between groups.

Conclusions: In patients with CRS1, we observed that VExUS guided decongestion, compared to clinical evaluation, did not improve the probability of KFR, but decongestion could be achieved more efficiently in fewer days.



SA-PO140

Discordance Between the Initial Etiological Diagnosis of AKI and that of the Nephrologist Based on a VExUS Study of Patients with AKI in an Acute Care Setting

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Background: Acute kidney injury (AKI) is associated with high morbidity and mortality. The correct diagnosis is essential for appropriate management because the treatments are very different between volume depletion, cardiorenal syndrome, hepatorenal syndrome, and acute tubular necrosis (ATN). We compare the initial diagnosis on presentation of AKI and the likely diagnosis based on the evaluation of a nephrologist based on a later chart review of the clinical course and diagnostic results.

Methods: In this single center, prospective, cohort study of ICU and ward patients who developed AKI during the admission we sought to determine the application of venous excess ultrasounds of intra-abdominal organs in discriminating the cause of AKI. We performed bedside US using a Logiq e BT12 machine, chart review and collection of baseline characteristics of all enrollees for 3 consecutive days. Baseline characteristics included: vital signs, 2D-echocardiogram, central venous pressure, right heart catheterization, urine electrolytes, urine protein-to-creatinine ratio, urine sediment. Ultra sonographers were blinded to the clinical diagnosis.

Results: We enrolled 80 patients with the initial diagnosis of AKI established by the primary care. Primary teams suspected ATN (23.5%), volume depletion (39.5%), hepatorenal (8.6%), cardiorenal (26%), and other causes (2.5%). The diagnoses posed by the primary care team were correct in 75% of the cases. ATN was mistakenly categorized as volume depletion 24% of the time and volume depletion as hepatorenal 29% of the time. Granular casts were present in 45% of ATN cases and 8% of non-ATN cases (p=0.0001), sensitivity 45%, specificity 92%. This includes 41% of misdiagnosed cases. As for VExUS, 70% of ATN cases were Grade 0, 64% of volume depletion, 50% of hepatorenal, and 33% of cardiorenal.

Conclusions: In a single-center prospective study of 80 patients with an initial diagnosis of AKI, the cause of AKI determined by the primary care team was discordant to that of the nephrology specialist in only 25% of the case. Urine sediment remains a useful tool in the diagnosis of AKI than VExUS. Future research is needed to examine the role of VExUS as a diagnostic tool.

SA-PO141

Hepatic Duplex: Can the Liver Be of Service to the Kidney in Diagnosing AKI?

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Background: Acute kidney injury (AKI) has a significant morbidity and mortality and better tools to diagnose the cause and inform the correct treatment are a research priority. We examined whether bedside venous duplex ultrasound of intra-abdominal organs differs in different causes of AKI.

Methods: A prospective single-center study of patients with cardiorenal, hepatorenal, acute tubular necrosis(ATN), and volume depletion acute kidney injury (AKI). Arrhythmias and body mass index (BMI)>30 were exclusions. Clinical data were obtained via chart review. Inferior vena cava diameter(IVC); hepatic vein and renal vein patterns; and Renal Resistive Indices(RRI) were obtained via Logic e BT-12 ultrasound. Sonographers were blinded from diagnoses. We used analysis of variance (ANOVA) for continuous variables and chi-square tests for categorical variables.

Results: We enrolled 81 AKI subjects, 34% with volume depletion, 19% cardiorenal, 35% ATN, 6% hepatorenal, and 3% other. Participants' mean creatinine 2.74 (±1.47) mg/dL. The IVC diameters in ATN, volume depletion, hepatorenal, and cardiorenal were 2,

1.87, 1.95, and 2.34 cm respectively (p=0.17). Diminished or reversed systolic hepatic duplex was seen in only 2 patients with volume depletion(p=0.0001), and both these patients had moderate tricuspid regurgitation and elevated pulmonary arterial pressures on echocardiogram. Similar hepatic duplex findings were noted on day 2 and day 3. Portal vein was continuous in 62.1% ATN, 60.7% volume depletion, and 31.3% cardiorenal patients(p=0.74). Renal venous flow was continuous in 18.8% of the cardiorenal patients(p=0.67). RRI was not different in ATN(0.65±0.05), volume depletion(0.67±0.07), hepatorenal(0.69±0.09), and cardiorenal(0.67±0.08, p=0.25).

Conclusions: Hepatic vein, but not IVC, renal and portal venous flow, nor RRI can differentiate types of AKI. This non-invasive bedside tool can help diagnose AKI and future trials will examine management.

SA-PO142

Association of Kidney Biopsy Needle Gauge with Post-Procedure Complications and Biopsy Adequacy

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Background: Narrower kidney biopsy gauge needles are thought to lead to fewer post-biopsy complications but could risk inadequate sampling for diagnosis. We examine the association of needle gauge with post-biopsy complications and sampling adequacy.

Methods: Using data from participants enrolled in the Yale biopsy cohort between 7/2020 and 4/2023, we tested the association of needle gauge (16G vs. 18 or 20G) with biopsy-related complications and number of glomeruli sampled using a chi-squared test for proportions for categorical outcomes or a Wilcoxon rank sum test for continuous outcomes.

Results: Of the 511 adult participants, median age was 60 (43,70), 49% were female, 60% were White, 33% were hospitalized and 52% underwent a biopsy for acute kidney injury. Those with 18G were more likely to have AKI (60% vs. 48%, P=0.01) and be hospitalized (40% vs. 29%, P=0.007). Needle gauge was not associated with seeking adverse post-biopsy complications, but participants who underwent a biopsy with narrower needle gauge required more imaging studies after biopsy (21% vs. 11%, p=0.004) primarily driven by concerns of hemoglobin drop. Narrower needle gauge was associated with fewer glomeruli available for diagnosis (11.5 [7.0-17.0] vs 14.0 [9.0-20.0], p<0.001).

Conclusions: Our data show that the narrower gauge biopsy needle was associated with fewer glomeruli available for diagnosis and greater need for postoperative imaging. However, we cannot rule out confounding by indication such that those at higher risk of complications underwent biopsy with narrower needle gauge. Further investigation into the complications associated with biopsy needle size controlling for detailed risk factors for post-biopsy complications is needed to confirm these findings.

Funding: NIDDK Support

Table of Kidney Biopsy Patients Complications

Post-biopsy complication	All patients (N=511)	18 G (n=326)	18 G or 20 G (n=185)	P-value*
Sought medical attention, n (%)	18 (4%)	10 (3%)	8 (5%)	0.43
Phone call	6 (33%)	3 (30%)	3 (38%)	
Office visit	1 (6%)	1 (10%)	0%	
ED visit	11 (61%)	6 (60%)	5 (63%)	
Additional imaging, n (%)	71 (15%)	34 (11%)	37 (21%)	0.004
For drop in Hb	7 (11%)	2 (6%)	5 (16%)	
For flank/back pain	23 (37%)	11 (35%)	12 (38%)	
For concern for bleeding	19 (30%)	12 (38%)	7 (22%)	
For hypotension	5 (8%)	2 (6%)	3 (9%)	
Reason not specified	9 (14%)	4 (13%)	5 (16%)	
Any hematoma found after biopsy, n (%	100 (21%)	58 (19%)	42 (24%)	0.17
Small	81 (81%)	45 (78%)	36 (86%)	
Medium/Large/>5 cm	19 (19%)	13 (22%)	6 (14%)	
Transfusions due to complication, n (%)	12 (30%)	7 (29%)	5 (31%)	0.89
Transfusion, IR intervention, or Medium/large hematoma, n (%)	28 (6%)	17 (5%)	11 (6%)	0.73
Total number of glomeruli obtained, median (IQR)	13.0 (8.0, 19.0)	14.0 (9.0, 20.0)	11.5 (7.0, 17.0)	<0.001

* χ^2 or rank sum test

SA-PO143

Erroneous Diagnosis of Acute Interstitial Nephritis on Gallium-67 Scintigraphy

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Introduction: Acute interstitial nephritis (AIN) and acute tubular necrosis (ATN) are common etiologies for acute kidney injury (AKI) in a patient with infection being treated with antibiotics. Kidney biopsy is the gold standard to distinguish between these diagnoses, but gallium-67 scintigraphy is sometimes used if a biopsy is considered high risk. We report a case where the gallium scan gave an erroneous result.

Case Description: We present a case of a 32-year-old male admitted for right elbow swelling, associated with fever to 100.4 for one day. Physical exam was significant for chronic venous malformations on the right arm, one of which was now tender to touch and palpation. Thrombophlebitis was suspected. Creatinine was 1.62 mg/dl which improved to 1.19 after 2 Liters of normal saline. Piperacillin/Tazobactam and Vancomycin were started. Blood cultures grew Pasteurella Multocida. Antibiotics were tailored towards this infectious agent. However, the patient remained febrile for three days after the bacteremia had cleared. Meanwhile, his creatinine rose from 1.19 to 2.81 in 72 hours. Urinalysis showed 100mg/dl protein, sterile pyuria and few granular casts. Renal ultrasound showed normal size and echogenicity. A gallium scan was done to identify the source of ongoing fever and revealed intense activity in the kidneys suggestive of interstitial nephritis. Kidney biopsy was done to confirm the diagnosis. Empiric Prednisone 1mg/kg/day was started while waiting for biopsy results. The biopsy showed ATN. Prednisone was then discontinued. Creatinine improved to 1.0 one week after discharge.

Discussion: Kidney biopsy is the gold standard for diagnosing acute interstitial nephritis but is not always attainable. Gallium-67 scintigraphy has emerged as an alternative modality to diagnose AIN. Graham et al showed 100% specificity but poor sensitivity when using an uptake cutoff of grade 5, which means the intensity of radioisotope uptake in the kidney is higher than in the liver. Few older studies have shown varying degrees of sensitivity and specificity. Our patient had a grade 5 uptake, yet the biopsy did not show AIN. Thus, our case highlights the limitations of the gallium scan in diagnosing AIN and confirms that when the clinical picture is unclear, biopsy may be preferred.

SA-PO144

Catheter-Directed Thrombectomy in Acute Renal Vein Thrombosis

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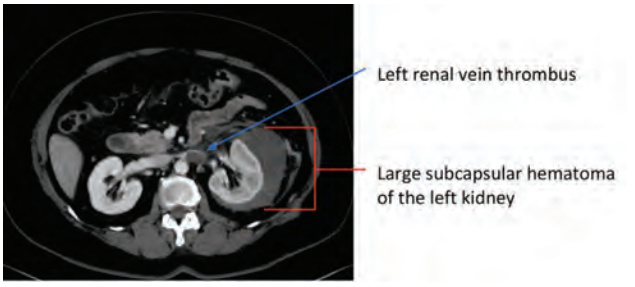
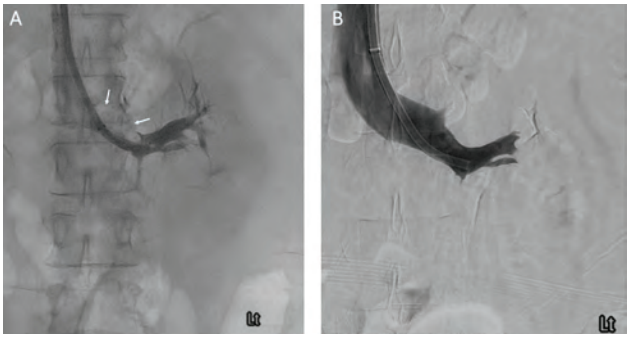
Introduction: Renal vein thrombosis (RVT) is a rare condition that can lead to severe complications including acute kidney injury or renal failure. Malignancy and nephrotic syndrome are the most common etiologies accounting for up to 66% and 20% of cases, respectively. The standard treatment for RVT is anticoagulation, but in the presence of declining renal function or contraindications, catheter-directed thrombectomy (CDT) can be considered.

Case Description: A 64-year-old female with CKD stage IIIa, hypertension and nephrolithiasis presented with acute left flank pain, AKI (creatinine 1.35mg/dL) and a 7cm left renal subcapsular hematoma with large RVT. Urinalysis revealed trace blood and protein with urine ACR of 8.2mg/mmol. On day three, kidney function declined to creatinine of 2.1mg/dL. Due to the rapid decline in kidney function and renal hematoma, precluding anticoagulation, CDT was performed. The clot was successfully retrieved and renal flow was restored. The creatinine approached baseline within a few days. Interestingly, the pathology demonstrated fragments of renal cell carcinoma within the thrombus despite no clear evidence of malignancy on CT or MRI imaging.

Discussion: We present the successful use of CDT for acute RVT secondary to renal cell carcinoma for diagnostic and therapeutic purposes. CDT permits rapid re-cannulization of the renal vein and facilitates faster renal recovery. Direct access permits interventions including venoplasty or stent placement for persistent stenosis or elastic recoil. To our knowledge, there are no previously reported cases of thrombectomy for acute RVT secondary to tumor thrombus. CDT is a potentially safe and effective treatment option for acute RVT, especially in the setting of declining renal function or contraindications to anticoagulation.





SA-PO145

Urinoma Treated with Transcatheter Arterial Embolization for Renal Artery: A Case Report

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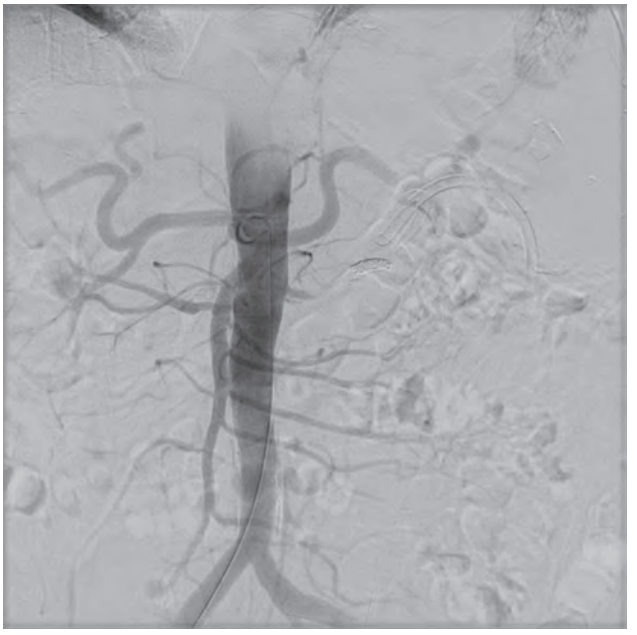
Introduction: Transcatheter arterial embolization (TAE) for renal artery was generally performed for renal cancer, aneurysm, polycystic kidney disease and bleeding. Here, we report a case of urinoma with the renal abscess successfully treated with TAE.

Case Description: A-79-year-old man with a past medical history of bladder cancer with total cystectomy and ileal conduit and ureterolithiasis with left ureteral stent was admitted to our hospital. He showed septic shock and disseminated intravascular coagulation (DIC) with the left renal abscess due to the dislodged left ureteral stent. He also showed acute kidney injury (AKI) and his serum creatinine was elevated to 7.37 mg/dL from baseline of 3.43 mg/dL a month before admission. He was given antibiotic for septic shock and underwent hemodialysis for AKI. He was also found to have hemorrhage from dorsal branch of the left renal artery due to DIC and performed the emergent TAE for that branch. After the TAE, we performed percutaneous drainage from the left renal abscess. However, fluid was continued to drain away from a tube inserted into the abscess. Laboratory findings showed the creatinine in the fluid was 17.09 mg/dL, and then we diagnosed as a urinoma. To treat the urinoma with infection, we performed TAE against the left renal artery to completely disrupt the renal function (Figure). After that, the fluid was dramatically decreased, the urinoma size was reduced, the abscess was fully improved, and the drainage tube was removed, though the maintenance dialysis was required.

Discussion: In this case, TAE was performed for disruption of renal function to treat the urinoma. Radical nephrectomy was also considered, but it was suspected difficult due to adhesions after infection. TAE may be the one of the treatment options for the urinoma.



SA-PO146

Cardiac Tamponade on Nephrologist-Performed Focused Cardiac Ultrasound

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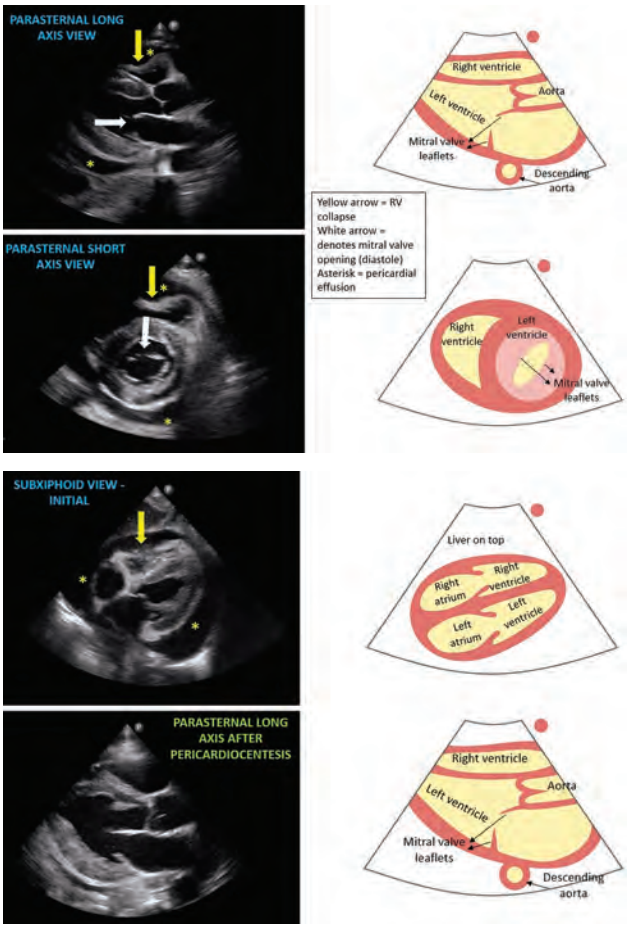
Introduction: Point of care ultrasonograhy (POCUS) has evolved as a component of physical examination in various specialties and nephrology is catching up quickly. Herein, we describe a case where focused cardiac ultrasound helped us appropriately manage AKI.

Case Description: A 59-year-old man with a history of untreated hypothyroidism presented with lower extremity swelling and shortness of Breath. Laboratory testing revealed a significantly elevated level of thyroid stimulating hormone of 43 mIU/mL (ref: 0.5-5). Chest X-ray showed an enlarged cardiac silhouette; transthoracic echocardiography demonstrated moderate to large circumferential pericardial effusion without tamponade and severely reduced LV systolic function. The patient was started on intravenous levothyroxine. The hospital course was complicated by hypotension requiring vasopressor therapy (presumed to be mixed septic and cardiogenic shock) and worsening renal function with oliguria. As assessing hemodynamics is a vital component of AKI evaluation, we performed POCUS, which revealed a plethoric inferior vena cava and a large circumferential pericardial effusion. Right ventricular diastolic collapse was clearly demonstrated (Figures 1 and 2) suggestive of tamponade physiology. The patient underwent emergent pericardiocentesis with removal of 450 mL of fluid resulting in cessation of the need for vasopressors as well as improvement in urine output.

Discussion: 1. POCUS (not limited to kidney) aids in the management of AKI. 2. Hemodynamics are dynamic. Having a recent formal echocardiogram should not preclude POCUS.



SA-PO147

Recovery of Chronic Thromboembolic Pulmonary Hypertension (CTEPH)-Associated Renal Failure After Pulmonary Endarterectomy (PEA)

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Introduction: Chronic thromboembolic pulmonary hypertension (CTEPH) is a recognized cause of severe pulmonary hypertension (PH). Acute Kidney Injury (AKI) is a common occurrence in advanced cases of CTEPH and often progresses to require permanent renal replacement therapy (RRT). We present two patients with CTEPH and AKI who had persistent need for RRT; however, after successful pulmonary endarterectomy (PEA) both patients experienced renal recovery and no longer required RRT.

Case Description: **Case 1:** A 43-year-old male with antiphospholipid syndrome was hospitalized with congestive heart failure (CHF) and AKI. He was diagnosed with CTEPH by ventilation-perfusion scan and pulmonary angiogram. He underwent a right heart catheterization (RHC) which confirmed the presence of severe PH, and his echocardiogram revealed RV dysfunction. Despite intense pharmacological treatment for PH, he continued to require RRT and was discharged home on peritoneal dialysis. Five months later, he underwent a successful PEA and within 48 hours, he recovered from needing RRT. Two years later, he continues to be dialysis-free and maintains a serum creatinine of 1.7 mg/dl. **Case 2:** A 57-year-old woman with known CTEPH was admitted due to worsening right-sided CHF and AKI. Her echocardiogram showed RV systolic dysfunction and severe tricuspid regurgitation. She initially required intensive critical care (ICU) management with vasopressors and continuous RRT (CRRT). After she stabilized, she underwent PEA and tricuspid valve repair. She was discharged on PH medications and dialysis. Renal recovery occurred over the next six months, following which she got off dialysis. Four years later, she was still dialysis free and had a creatinine of 1.96.

Discussion: This report demonstrates the reversal of dialysis-requiring AKI in CTEPH patients following PEA. PEA is a promising therapy for CTEPH with significant renal benefits and should be considered as the optimal treatment for patients with CTEPH and concomitant AKI.

SA-PO148

Meprin β Regulates Protein Kinase A-Mediated TGF-β Signaling in Ischemia/Reperfusion-Induced Kidney Injury

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Background: Ischemia/reperfusion (IR) is a leading cause of acute kidney injury (AKI) and is associated with high morbidity and mortality rates. Meprins, zinc metalloproteases have been implicated in the pathology of IR. Meprins are capable to proteolytically processing the catalytic subunit of protein kinase A (PKA-C) and several mediators of inflammation. The protein kinase A (PKA) signaling pathway plays an important role in renal fibrosis, promoting the production of transforming growth factor-β (TGF-β) and/or TGF-β-dependent molecules. The TGF-β signaling is involved in wound healing and tissue repair of injured kidneys. Activation of Smad2 and Smad3 is the major downstream event of the TGF-β signaling pathway. The objective of the current study was to determine how meprin β expression impacts PKA C-mediated TGF-β signaling in IR-induced kidney injury.

Methods: We used surgical procedures to achieve unilateral IR with contralateral nephrectomy in wild-type (WT) and meprin β knockout (βKO) mice. The mice were sacrificed at 96 h post-IR and kidney tissues obtained for analysis. Real-time PCR, and immunohistochemical staining, were used to evaluate the expression levels of PKA C and TGF-β. Statistical analysis utilized two way ANOVA.

Results: Real-time PCR data showed significant increases in mRNA levels of PKA C only in βKO kidneys after IR. In contrast, the mRNA levels for TGF-β were higher in both WT and βKO at 96 h post-IR Interestingly, the baseline mRNA levels for TGF-β were higher in meprin βKO mice. Immunohistochemical data showed significant increases in the levels of PKA C proteins in select kidney tubules of both genotypes after IR. Similarly, staining intensity for TGF-β were higher in select kidney tubules of both WT and meprin β deficient mice at 96 h IR. Immunofluorescence of kidney tissues with anti-meprin β, anti-PKA C and anti-TGF-β antibodies showed a positive correlation between meprin β expression and tubular PKA C and TGF-β levels in kidneys subjected to IR.

Conclusions: These findings suggest that meprin β regulates PKA C-mediated TGF-β signaling pathway in IR-induced kidney injury and provides new insights on the mechanisms underlying meprin β modulation of the pathophysiology of IR-induced renal injury.

Funding: Other NIH Support - NIH/NIGMS Grant # R35GM141537

SA-PO149

Role of LTBP4 in Kidney Injury: A Study on the Effect of LTBP4 on Angiogenesis and Inflammation in Renal Fibrosis

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Background: Transforming growth factor beta (TGFβ), a key player in renal fibrosis, is regulated by latent transforming growth factor beta binding protein 4 (LTBP4). However, we hypothesized that LTBP4 also plays a role in angiogenesis and inflammation, both TGFβ related and TGFβ independent. This is significant because the role of angiogenesis and inflammation in kidney injury is widely recognized.

Methods: We employed wild-type (WT) and *Ltbp4*^{PTKO}-/- [*Ltbp4* proximal tubule knockout (PTKO)] mice for our animal experiments. Additionally, we used human proximal tubule cells (HK-2 cells) transfected with LTBP4 lentiviral knockdown for *in vitro* cellular studies. To induce kidney injury, the mice underwent 30 min of bilateral renal ischemia-reperfusion injury (IRI) surgery. HK-2 cells were subjected to 24 h of hypoxia at 1% O_2, 5% CO_2, and 94% N_2 to simulate pathological kidney injury. Subsequently, molecular studies were conducted on mice kidney samples and HK-2 cells to assess the extent of injury and the expression of proangiogenic molecules and inflammatory cytokines.

Results: Our study demonstrated increased expression of LTBP4 in mice after kidney injury. Fourteen days post-IRI, *Ltbp4*^{PTKO}-/- mice showed more pronounced fibrosis than WT mice. Immunohistochemistry analysis revealed stronger positive staining for CD31, an endothelial marker, in WT mice than in *Ltbp4*^{PTKO}-/- mice. Moreover, WT mice exhibited higher expression of vascular endothelial growth factor (VEGF) than *Ltbp4*^{PTKO}-/- mice after undergoing IRI surgery. Transcriptomic analysis revealed upregulation of genes linked to angiogenesis in LTBP4-overexpressed HK-2 cells. Cellular studies reflected similar results in HK-2 cells, where VEGF expression was lower in LTBP4 knockdown cells. Additionally, inflammatory cytokines were upregulated in *Ltbp4*^{PTKO}-/- mice compared with those in WT mice after injury.

Conclusions: Our study findings show that LTBP4 plays a key role in regulating angiogenesis and inflammation during kidney injury. We demonstrated that LTBP4 partly has a protective effect in the progression of kidney disease. The increased angiogenesis and reduction in inflammation aid in the recovery of kidney injury and potentially mitigates long-term complications. These findings highlight the potential therapeutic avenues for utilizing LTBP4 in managing kidney injury.

SA-PO150

Role of SMPDL3b in Radiation-Induced Nephropathy

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Background: The kidneys are radiosensitive and dose-limiting organs for radiotherapy (RT) targeting abdominal and paraspinal tumors. Excessive radiation doses to the kidneys lead to radiation nephropathy (RN). In this study, we investigated a novel role for the lipid-modifying enzyme, sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b), in regulating the response of renal podocytes to radiation injury.

Methods: Podocytes were irradiated with either 4Gy or 8Gy and Ezrin, and apoptosis, DNA damage, and survival were quantified at different time points post-RT. For *in vivo* studies, 10–14 weeks old C57BL/6 received bilateral kidney irradiation of 14Gy or 6x5Gy with or without rituximab (50 mg/kg; IP, 1h before RT). 20 weeks post RT, glomerular filtration rate (GFR) was measured by transdermal monitors. Urine and serum samples were analyzed to quantify urinary albumin-to-creatinine ratio (ACR), serum BUN, and creatinine levels. Kidney cortex sections were stained with H & E, Periodic Acid-Schiff, Picrosirius red, and Masson's trichrome staining. Ultrastructural Changes in the glomerular filtration barrier were quantified by transmission electron microscopy.

Results: Podocyte survival decreased in a dose-dependent manner post-RT. SMPDL3b overexpression prevented RT-induced DNA damage and apoptosis in cultured podocytes. 24 h post-RT, Podocyte DNA damage and apoptosis increased significantly more in podocyte-specific knockout (pSMPDL3b-KO) mouse kidney cortex than in SMPDL3b wild-type mice (p 0.0166 and p = 0.0302, respectively). Fibrosis, glomerular basement membrane (GBM), and foot process width, mesangial expansion score, BUN, creatinine ACR increased significantly more in pSMPDL3B-KO mice than in SMPDL3b wild-type mice ($p < 0.05$). GFR decreased significantly in SMPDL3B wild type and pSMPDL3B-KO mice 20 weeks post-RT ($p < 0.05$). Rituximab treatment to SMPDL3b wild-type mice prevented SMPDL3b downregulation, podocyte loss, reduced fibrosis, mesangial expansion score, GBM thickness, and foot process width and significantly improved renal function (BUN, Creatinine, and ACR) post-RT ($p < 0.05$).

Conclusions: Rituximab treatment restored SMPDL3b basal expression levels and decreased radiation-induced podocyte injury and albuminuria. Our findings suggest SMPDL3b as a potential therapeutic target in radiation-induced renal damage.

Funding: Other NIH Support - NIH/NCI PQ12 1R01CA227493; W81XWH-22-1-0305; UM SJG 2023-01; 23L12, Other U.S. Government Support

SA-PO151

Renal IsoLG-Containing Antigen-Presenting Cells Modulate Endothelial Cells of Lymphatic Vessels via ET-3/ERB During Kidney Injury

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Background: Previously, we showed that sodium (Na^+) promotes the formation of the lipid oxidation product, isolevuglandins (IsoLGs) in antigen-presenting cells (APCs) which, in turn, have been linked to lymphangiogenesis and systemic hypertension. Lymphangiogenesis accompanies multiple experimental and human kidney diseases. Our recent studies show that albuminuric kidney injury leads to a high Na^+ environment within the kidneys and promotes renal accumulation of IsoLGs.

Methods: To induce nephrotoxic injury in mice, we used a sheep anti-glomerular antibody and harvested kidneys 3 weeks later.

Results: We observed a 370% increase in albumin: creatinine ratio, a 30% decrease in GFR, and increased systolic blood pressure (+20.1 mmHg) in nephrotoxin injured vs uninjured controls. Immunostaining of renal F4/80 expression, a macrophage marker, revealed a striking increase in the interstitium of nephrotoxic mice vs controls. Using flow cytometric analysis, nephrotoxin-injured kidneys were found to have elevated IsoLGs in monocytes and dendritic cells when compared to controls. Lymphatic endothelial cells (LECs) co-cultured together with APCs in a high Na^+ environment have increased IsoLGs as well as expression of endothelin receptor B (ETB), which are blocked with 2-hydroxybenylamine (2-HOBA) treatment. Additionally, when co-cultured with LECs, dendritic cells have increased IsoLG and expression of vasoactive peptide Endothelin-3 (ET-3) in response to a high Na^+ environment. Similarly, these observed increases are blocked with 2-HOBA treatment. Using RNA sequencing data and informatics in LECs co-cultured with APCs, we found high Na^+ significantly increased ET-3 in immune cells and ETB receptor in LECs.

Conclusions: These findings were validated using RT-PCR. Taken together, this data suggests LEC uptake of IsoLGs is potentiated by high Na^+ environment and interaction with inflammatory immune cells, and IsoLGs may play a role in the ET-3/ETB ligand: receptor intersection and crosstalk with LECs. The work was supported by NIH T32HL144446, 1P01HL116263, K01HL13049, R03HL155041, and R01HL144941.

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SA-PO152

Exposure to Systemic Hypoxia After Renal Ischemia Reperfusion Injury (IRI) Promotes Kidney Repair

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Background: We and others have shown that activation of hypoxic signaling prior to renal ischemia reperfusion injury (IRI) exerts renoprotective effects. However, it is unclear whether induction of hypoxia (Hx) after injury regulates kidney recovery. Here, we investigated how exposure to systemic hypoxia regulates post-IRI kidney repair.

Methods: Male C57/BL6 mice were subjected to uIRI via clamping for 25 minutes. 6-hrs post-injury, groups were placed in hypoxia chamber at 8% O2 for 24 or 72 hrs, while control groups remained in normoxia (Nx). Mice were then sacrificed and kidneys collected for bulk RNA-Seq, metabolomic analysis and histology, while serum was collected for metabolomic analysis.

Results: After exposure to 72 hrs of Hx or Nx following IRI, the Hx group was found to have significantly lower injury via kidney injury scoring on H&E stained tissue sections (3.3±0.5 Nx vs 2.2±0.4 Hx, P=0.02, n=4 Nx, n=4 Hx) and Kim1 gene expression (2.5 fold suppression compared to Nx, P=0.0002, n=4 Nx, n=4 Hx). Hypoxia exposure for 24 hours did not significantly reduce kidney injury scores, but did reduce Kim1 expression (P=0.03). KEGG/GO pathway analysis of RNA-Seq data at 72 hours revealed a prominent inflammatory signature in the downregulated genes, such as cytokine-cytokine receptor interaction, TNF and NF-κB pathways (KEGG), as well as immune response, inflammation response and cytokine production (GO), indicating hypoxia exposure attenuated post-ischemic renal inflammation. On the other hand, pathway analysis of upregulated genes showed significant enrichment for metabolic pathways such as tryptophan metabolism, PPAR signaling, glutathione metabolism, fatty acid degradation and retinol metabolism. Furthermore, quantitative assessment of kidney and serum metabolite profile using a comprehensive LC-MS metabolite panel, as well as a targeted LC-MS assay for tryptophan related metabolites were carried out. Here, we found significant increases in tryptophan pathway metabolites in kidney tissue and serum, such as kynurenine, xanthurenic acid, 3-hydroxy-anthranilic acid and NAD+.

Conclusions: In summary, exposure to hypoxia in the context of established ischemic injury promotes early reparative processes. Among the altered metabolic pathways, changes in tryptophan metabolism may contribute to the mechanisms by which hypoxia promotes adaptive repair.

Funding: NIDDK Support

SA-PO153

Modulation of Stimulator of Interferon Genes (STING) Signaling Differentially Affects Outcomes of AKI

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Background: Activation of cGAS/STING signaling leads to both type I interferon production and NFkB-dependent transcription in a Tbk1-dependent manner. During acute kidney injury (AKI), we recently described a population of innate immune cells expressing gasdermin D to be recruited to the surroundings of acute tubular necroses. Interestingly, these GSDMD+ cells seemed to signal back on the ongoing cell death, a concept termed necroinflammation. As recent work demonstrated a crucial role for free DNA and RNA fragments in the pathogenesis of AKI, we hypothesized that these might contribute to innate immune activation via the cGAS/STING pathway.

Methods: We tested STING-deficient mice in two established models of AKI, which reflect toxic tubular injury (cisplatin-induced AKI, CP-AKI) and redox stress (ischemia/reperfusion injury, IRI). Furthermore, pharmacological activation of STING by diABZI or inhibition by C-176 was investigated. Next to blood values, organ injury was determined by histological workup. Mechanistic insights were derived from immunohistochemistry and Western Blot analyzes in addition to cell culture experiments.

Results: STING-deficient mice were less susceptible to IRI as exemplified by less strongly elevated values of serum creatinine and urea as well as lower tissue injury scores, whereas STING activation by diABZI did not ameliorate AKI. In contrast, STING-deficiency did not influence CP-AKI, but co-treatment with diABZI led to massively accelerated lethality. We found this to be dependent on regulated cell death, which was neither apoptosis, necroptosis, nor ferroptosis. Interestingly, GSDMD-deficient mice (the effector protein of pyroptosis, already identified as a protective factor against cisplatin-induced AKI) could not be further sensitized by STING-activation. Western Blot analyzes from primary tissue confirmed a correlation between pSTING and both GSDMD expression and proteolytic activation.

Conclusions: We found STING to be critically involved in different models of AKI. Unexpectedly, the results of STING activation seem to be context-dependent, as STING-deficiency was protective in IRI, whereas concomitant STING activation accelerated lethality in CP-AKI. Further workup is ongoing to identify underlying mechanisms.

SA-PO154

Endonuclease G (EndoG) Inhibits DNase I-Mediated Apoptosis and DNA Repair in Kidney Tubular Epithelial Cells During Cisplatin Injury

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Background: We have previously shown that kidney tubular epithelial (KTE) endonuclease G (EndoG, EG) is induced by cisplatin and translocated from mitochondria to the nucleus during apoptosis. However, it is unknown whether EG causes apoptotic DNA fragmentation and how it leads to cell death. EG is the only apoptotic endonuclease found in the nucleus during apoptosis, has RNase activity, and induces inactive truncated isoform of another endonuclease, DNase I (DI).

Methods: We hypothesized that the role of EG in apoptosis depends on the presence of DI in the cell, and used cisplatin kidney injury *in vitro* and *in vivo* models to test this.

Results: To our surprise, although EG was often present in TUNEL-positive nuclei of KTE cells in mice treated with cisplatin (20 mg/kg), it did not colocalize with DNA fragmentation measured by TUNEL or with endonuclease activity measured by a fluorescent probe in apoptotic nuclei in cultured KTE NRK-52E cells. EG overexpression in DI-positive NRK-52E cells showed EG was not cytotoxic but instead protective against cisplatin injury (60 μM) as determined by flow cytometry. EG overexpression induced alternative splicing and inactivation of DI. When the same experiment was repeated using DI-negative HCC1954 cells, EG was cytotoxic and promoted cisplatin-induced cell death. Further study showed that EG was induced but was not cytotoxic in cisplatin kidney injury *in vivo*. After injection of cisplatin, no protection in EG null mice versus wild-type (WT) mice was observed by BUN, SCr, or histology. EG induction by cisplatin in WT mice was associated with the decrease of native DI expression and the appearance of inactive truncated DI. In addition to DNase I inactivation, an overexpression of EG in mouse KTE TKPTS cells induced mRNA alternative splicing (inactivation) of several DNA repair genes.

Conclusions: This study showed that EG acts as a proapoptotic enzyme in the absence of DI and it is anti-apoptotic in the presence of DI in KTE cells and the kidney during cisplatin injury. In addition, the overexpression of EG causes inactivation of several DNA repair genes thus likely causing an aggravation of the cisplatin injury.

Funding: Other NIH Support - NIGMS grant P20GM109005-06, Veterans Affairs Support

SA-PO155

14-3-3ζ Targets β-Catenin Nuclear Translocation to Maintain Mitochondrial Homeostasis, Promoting Balance of Proliferation and Apoptosis in Cisplatin-Induced AKI

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Background: Cisplatin, an extensively used chemotherapeutic agent for solid tumors, is limited in clinical use due to its side effects, especially nephrotoxicity. Cisplatin-induced acute kidney injury (AKI) is characterized by DNA damage, cell cycle arrest and mitochondrial oxidative stress. Recent work demonstrated that 14-3-3ζ plays important role in cancers, nerve disease and kidney disease, but the role and regulatory mechanism in cisplatin AKI remain to be further clarified.

Methods: Here, we found that 14-3-3ζ mRNA was upregulated in human kidney organoids (GSE145085) when treated with cisplatin, which was confirmed in experimental mice. Then, we used inhibitor for 14-3-3 (BV02) in animal experiment, knocking down and overexpressing 14-3-3ζ respectively in vitro experiments to test the role of 14-3-3ζ in cisplatin-induced AKI.

Results: The use of protein interaction inhibitor for 14-3-3 (BV02) aggregated drop of renal function, apoptosis, mitochondrial dysfunction and oxidative stress in cisplatin-induced AKI. Accordingly, increased apoptosis, cell cycle arrest, ROS production and lipid dysbolism in cisplatin-treated NRK-52E cells were exacerbated in cells knocking down 14-3-3ζ. Besides, blocking 14-3-3ζ both in vivo and in vitro suppressed β-catenin and its nuclear translocation, downregulating the expression of downstream gene cyclin D1 in cisplatin-induced damage. In contrast, overexpression of 14-3-3ζ relieved injury caused by cisplatin and promoted nuclear transportation of β-catenin. Further, a non-specific agonist of β-catenin BIO reversed the effects of knocking down 14-3-3ζ in cisplatin-induced damage in NRK-52E by activating β-catenin. The direct interaction between 14-3-3ζ and β-catenin was then verified.

Conclusions: Taken together, these findings indicate that 14-3-3ζ protects against cisplatin-induced AKI by improving mitochondrial function and balance of proliferation and apoptosis through facilitating β-catenin nuclear translocation.

Funding: Government Support - Non-U.S.

SA-PO156

Reno-Protective Effect of Ginsenoside Rg3 in Ischemia Reperfusion Injury Mice by Inducing Autophagy Flux

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Background: The protective effects of Ginsenoside Rg3 (Rg3) have been demonstrated through different mechanisms. Nevertheless, the specific evaluation of its renal-protective effect and the involvement of autophagy remain unclear. This study aims to examine how Rg3 induces autophagy flux and diminishes renal cell death in renal ischemia reperfusion injury (IRI).

Methods: C57Bl/6 mice were categorized into the subsequent groups: sham; sham treated with Rg3; IRI mice treated with saline; IRI mice treated with Rg3. Kidneys and blood samples were obtained 24 hours after the surgical procedure (sham and IR operation). Renal function, kidney histology, and the protein expression of autophagy markers were assessed.

Results: In the IRI mice group, there was an elevation of BUN and s-Cr levels compared to the sham group. However, the administration of Rg3 resulted in a reduction of BUN and s-Cr levels in the IRI mice. Furthermore, Rg3 treatment led to a decrease in renal injury, as evidenced by a lower renal tubular cell detachment and necrosis score in the IRI mice. The Rg3-treated IRI mice exhibited reduced oxidative stress and improved autophagy, characterized by increased levels of LC3 and Beclin-1, decreased levels of p62, and higher levels of renal ATP6E compared to the IRI mice treated with saline. Additionally, Rg3 treatment promoted the phosphorylation of AMPK in the kidneys of IRI mice.

Conclusions: Rg3 exhibits renal protection against renal IRI by enhancing autophagy flux.

SA-PO157

OTUD5 Mediates GPX4 Stability and Ferroptosis in Renal Tubular Cells During Ischemia-Reperfusion Injury

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Background: Acute kidney injury (AKI) is a severe kidney disease often linked with renal tubular cell ferroptosis, an iron-dependent, non-apoptotic cell death characterized by lipid peroxide accumulation. This can be triggered by ischemia-reperfusion (I/R) and typically results from decreased glutathione peroxidase 4 (GPX4) expression. However, the specific molecular events underlying GPX4 reduction following I/R remain poorly understood.

Methods: Our research involved identifying and characterizing the role of GPX4-interacting proteins in renal tubular cells. We also studied the susceptibility of renal regions to I/R injury using spatial transcriptomics. Both in vitro assays and in vivo experiments using mice with conditionally deleted Otud5 were employed to evaluate the function of OTU deubiquitinase 5 (OTUD5) in ferroptosis and AKI.

Results: OTUD5 was found to interact with and stabilize GPX4, conferring resistance to ferroptosis in renal tubular cells. During I/R, the inability of OTUD5 to deubiquitinate, triggered by mTORC1-mediated macroautophagy, led to GPX4 degradation and ferroptosis. Spatial transcriptomics revealed hyperactivity of cell ferroptosis and autophagy in the region between the kidney's inner cortex and medulla outstrip, susceptible to I/R injury. Functionally, OTUD5 deletion resulted in heightened renal tubular cell ferroptosis in vitro, and mice with tubular epithelial cell-specific Otud5 deletion demonstrated exacerbated AKI in response to I/R. Conversely, adeno-associated virus-mediated Otud5 delivery reduced ferroptosis and promoted renal function recovery.

Conclusions: Our findings unveil a novel autophagy-dependent ferroptosis module: I/R-induced OTUD5 macroautophagy leads to GPX4 degradation and tubular cell ferroptosis. Targeting this pathway may offer a potential therapeutic strategy for I/R-related kidney diseases.

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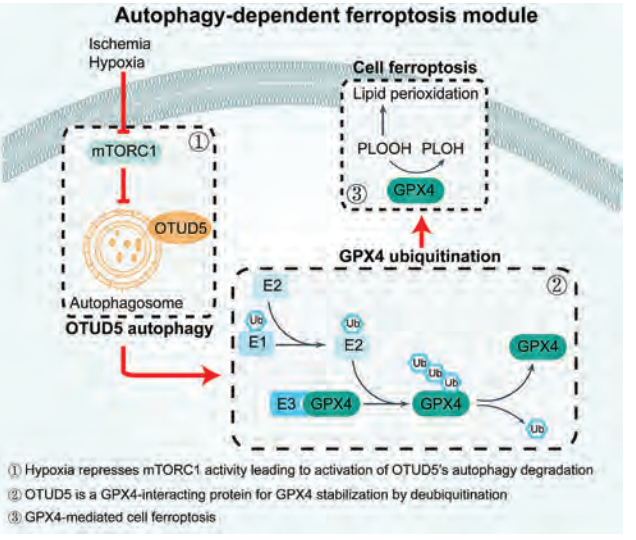

SA-PO158

Kidney HMGCS2 Protects Against Ischemic Kidney Injury

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Background: Evidence for abnormal renal fatty acid oxidation (FAO) in kidney disease suggests that dysregulated metabolism is a key component of kidney disease pathogenesis. Ketogenesis is a central metabolic pathway in which ketone bodies are produced from FAO. While the liver is the main ketogenic organ, the rate-limiting enzyme for ketogenesis, mitochondrial Hydroxymethylglutaryl-CoA synthase 2 (HMGCS2), is induced in the proximal tubule of the kidney during fasting. We previously demonstrated that HMGCS2 induced in the kidney does not contribute to the circulating pool of ketones during fasting and cannot compensate for hepatic ketogenic deficiency. We hypothesized that kidney HMGCS2 may be acting locally within the kidney to maintain normal function during metabolic stress or injury.

Methods: *Six2-Cre;Hmgcs2$^{fl/fl}$* (Six2^{Hmgcs2KO}) mice with kidney-specific *Hmgcs2* deletion and *Hmgcs2$^{fl/fl}$* littermate controls were subjected to ischemia/reperfusion injury (IRI). An acute kidney injury models with right nephrectomy and left IRI was used. Plasma creatinine and/or kidney mRNA/protein expression were assessed 24 hours after IRI. Using novel mouse models with proximal tubular hemagglutinin (HA)-tagged mitochondria with (*Ggt1-Cre;Hmgcs2$^{fl/fl}$;MITO-Tag*, Ggt^{Hmgcs2KO}-MT) or without (*Ggt1-Cre; MITO-Tag*, Ggt-MT) *Hmgcs2* deletion, proximal tubular-specific mitochondria were isolated using anti-HA magnetic beads after unilateral IRI. Fatty acid oxidation (FAO) capacity was measured using palmitoylcarnitine as a substrate and oxygen consumption rate was determined by Seahorse.

Results: Six2^{Hmgcs2KO} mice had significantly higher plasma creatinine levels and expression of kidney injury markers (*Kim1*) 24 hours after IRI compared to *Hmgcs2$^{fl/fl}$* littermate controls. Kidneys lacking HMGCS2 also had an increase in lipid droplet accumulation accompanied by a decrease in *Ppargc1a* expression, however there was no significant difference in renal *de novo* lipogenesis gene expression. Proximal tubular-specific mitochondria isolated 24-hour post IRI from Ggt-MT and Ggt^{Hmgcs2KO}-MT kidneys demonstrated that mitochondria lacking HMGCS2 had significantly lower basal and ADP-stimulated FAO capacity.

Conclusions: Our data provide evidence that proximal tubular HMGCS2 may play an important role in maintaining mitochondrial function and FAO capacity, resulting in protection against ischemic kidney injury.

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SA-PO159

Peroxisomal Inhibition Abolishes Dicarboxylic Acid-Mediated AKI Protection

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Background: Peroxisomes play important roles in metabolism, including in fatty acid oxidation (FAO). Interestingly, post-translational modification of lysine residues by succinylation promotes FAO and has also been linked to acute kidney injury (AKI). In addition, octanedioic acid (DC_8) is a dicarboxylic acid that, upon FAO, promotes hypersuccinylation. Finally, studies suggest that 10,12-tricosadiynoyl-CoA (TDYA) inhibits peroxisomal activity. Therefore, we hypothesized that DC_8 protects from AKI via hypersuccinylation of renal peroxisomes and that TDYA blocks this response.

Methods: To test the role of DC_8 in AKI, mice were fed with control or 10% w/w DC_8 diet, then, subjected to unilateral renal ischemia-reperfusion (IRI). Six days after IRI, mice underwent contralateral nephrectomy and were euthanized the following day. Supplementation was provided until sacrifice. To test if TDYA would promote an opposite response, we treated another cohort of animals with or without daily doses of 2mg/kg TDYA for 18 days. On the third day, animals began being fed on 10% DC_8 and underwent IRI as previously. Biochemical, histologic, and proteomic analyses were performed together with mitochondrial and peroxisomal activities.

Results: DC_8 prevented the rise of renal injury markers in IRI mice and improved morphology compared with controls, demonstrating efficient protection against AKI. Proteomics evidenced a substantial increase in peroxisomal succinylation in DC_8-fed animals, which was confirmed by immunofluorescence and peroxisomal FAO activity, while mitochondrial activity was shown to be preserved. Furthermore, TDYA completely abolished all the protective responses of DC_8 as it inhibited peroxisomal activity.

Conclusions: DC_8 supplementation drives renal hypersuccinylation, promoting a shift from mitochondrial to peroxisomal FAO, and protecting against AKI. Meanwhile, peroxisomal inhibition with TDYA completely inhibits this protection and confirms the important role of peroxisomal succinylation in AKI protection following DC_8 administration.

SA-PO160

Mitochondrial Morphology Regulates Proximal Tubule Cell Differentiation Status

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Background: Acute Kidney Injury (AKI) frequently occurs in hospitalized patients and predisposes them to developing chronic kidney disease (CKD). Our lab and others have shown prolonged proximal tubule cell (PTC) dedifferentiation in the form of maladaptive repair contributes to this AKI-to-CKD transition. One of the most striking histological features of dedifferentiated PTCs is fragmentation of the mitochondria, which occurs through the mitochondrial fission pathway involving dynamin related protein 1 (Drp1). While it is known mitochondrial fragmentation reduces mitochondrial function, it is unclear if fragmentation contributes to PTC dedifferentiation.

Methods: Mitochondrial morphology in kidney tissue was monitored using super-resolution microscopy. Using primary PTCs and LLC-PK1 cells treated with aristolochic acid (AA), we developed an in vitro model of PTC dedifferentiation. Mitochondrial fragmentation was suppressed with specific inhibitors. In vivo, inducible Drp1 KO mice ($Drp1^{\Delta PT}$) were used to regulated mitochondrial fragmentation and compared to wild-type (WT) littermates age 8-12. Kidney injury was induced by aristolochic acid nephropathy, repeat low-dose cisplatin, and bilateral ischemic reperfusion injury models. Dedifferentiation markers were measured by immunofluorescence, protein expression and mRNA levels.

Results: Using super-resolution imaging of kidney tissue, we found that dedifferentiated PTCs had greatly reduced mitochondrial volume and network length, indicating mitochondrial fragmentation. In vitro, AA treatment reproduced this phenotype by inducing mitochondrial fragmentation early after injury, which was followed by dedifferentiation at later time points. Pharmacological inhibition of mitochondrial fragmentation prevented PTC dedifferentiation. Similarly, knocking out Drp1 in vivo after kidney injury improved mitochondrial morphology and reduced markers of dedifferentiation in all three injury models tested. Improved mitochondrial morphology was associated with reduced kidney fibrosis in all three models.

Conclusions: Inhibition of mitochondrial fragmentation prevents proximal tubular cell dedifferentiation and reduces renal fibrosis. Interventions targeting mitochondrial health may lead to novel therapeutics to improve chronic kidney injury.

SA-PO161

A Novel RIPK3/BRD4 Small Molecule Inhibits Arsenical-Induced AKI

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Background: Arsenicals such as lewisite, cause blistering of the skin as well as lung, kidney, and multi-organ damage. The development of antidotes to warfare chemicals is a priority of the NIH CounterACT Program. To this end, we used single nucleus RNA sequencing (snRNAseq) to explore the nephrotoxic effects of phenylarsine oxide (PAO, a lewisite mimic) in an unbiased manner and synthesized a novel dual inhibitor (duali) that targets two necroptotic markers that are upregulated after lewisite exposure: receptor interacting serine/threonine kinase 3 (RIPK3) and bromodomain-containing protein 4 (BRD4). BRD4 plays a critical role in inflammation and redox metabolism. Here we identify transcriptional alterations in the kidney following arsenical-induced damage and test the hypothesis that the duali protects against injury using *in vivo* and *in vitro* models.

Methods: snRNAseq was performed on kidneys from mice treated topically with PAO (4mg/kg) or vehicle for 6 and 24 hours. Protective effects of duali were evaluated *in vitro* utilizing proximal tubule cells (PTCs). Cells were pretreated with duali 1 h before PAO and examined via immunostaining, western blots, and qPCR at 4, 20, or 24 hours. *In vivo* efficacy was assessed 24 h post PAO (4-6mg/kg). Duali was applied topically 30 min post PAO exposure.

Results: Duali treatment inhibits phospho- mixed lineage kinase domain-like pseudokinase (MLKL) and total RIPK3 and MLKL transcripts ($p < 0.05$) *in vitro*. We also observed a recovery of glomerular filtration rate in PAO exposed mice following duali treatment, which was associated with decreased expression of pRIPK3. snRNAseq in PAO treated mice revealed that fatty acid (FA) β-oxidation, FA biosynthesis, and PPAR-alpha pathways were upregulated in PTC and endothelial cells.

Conclusions: While the treatment with duali ameliorated PAO induced kidney injury, the mechanism of action remains to be elucidated. We have shown that cutaneous PAO exposure alters gene transcription and upregulates FA metabolism suggesting a compensatory response following metabolic perturbation. We conclude that our duali may be used as a potential therapeutic in arsenical-induced AKI. Future studies aim to confirm the precise mechanisms behind BRD4- and duali-mediated improvements of renal function.

Funding: Other NIH Support - NIH: The National Institute of Environmental Sciences

SA-PO162

Continuous Antithrombin III Infusion in a Clinically Relevant Sepsis Model

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Background: Despite unacceptably high mortality and economic burden, effective therapeutic strategies for sepsis remain elusive. Discrepancies between septic patients and animal models may be caused by drug pharmacokinetics, route, and timing of drug administration. Antithrombin III (AT) is an anticoagulant that might ameliorate sepsis-induced multiorgan dysfunction, though clinical trial results are conflicting due to variation in patient selection and drug regimens. AT has not been tested in clinically relevant sepsis models. AT has a short half-life, so we devised a method to continuously infuse drugs starting 6-12 h after cecal ligation and puncture (CLP). We asked, "Is AT effective in a clinically translatable sepsis model, and does the route of administration matter?"

Methods: We catheterized the mouse jugular vein, then connected the catheter to an osmotic minipump containing saline. After 1 wk stabilization, we performed CLP and replaced the minipump with one containing AT or saline. We set a 6-12-h time delay between sepsis induction and treatment by incorporating a 4 cm saline-filled catheter in the circuit. We measured the actual time lag with FITC-sinistrin and measured its systemic appearance with a transdermal fluorescence detector. Survival studies were conducted. In separate experiments, we collected blood, kidney, liver, and lung at 48 h for biochemical and histological tests. To examine the effect of administration route, we compared continuous AT infusion with saline infusion, and a conventional bolus AT injection.

Results: First, we detected a sustained fluorescence signal in the systemic circulation 5–6 hours after adding FITC-sinistrin to our drug administration system. Second, delayed, continuous AT infusion significantly improved 7-day survival compared to saline-infusion (65% vs. 29%, n = 21 /group, p = 0.018). Continuous AT infusion markedly improved survival vs. a single injection of AT (65% vs. 19%, n = 21 /group, p = 0.003). Continuous AT attenuated liver injury but not renal or lung injury in the histology and biochemistry analyses.

Conclusions: We created a clinically relevant murine sepsis model with both a continuous infusion and time lag. Survival was higher in continuous AT infusion than either single bolus injection or vehicle. Future studies will elucidate the mechanism of the survival benefit.

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

SA-PO163

Quantitative Proteomics Analysis of Differentially Expressed Proteins in Septic Mice Kidney With Humanin Treatment

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Background: Sepsis-associated acute kidney injury (SA-AKI), which carries a high morbidity and mortality in patients, has no effective therapeutic strategies and its mechanisms are not fully understood. Increasing evidence have already showed that renal mitochondrial dysfunction plays a pivotal role in sepsis. We aimed to determine the effects of humanin, a mitochondrial-derived cytoprotective peptide on kidney injury in septic mice, and look for differentially expressed proteins after humanin treatment.

Methods: A murine model (C57BL/6 mice, 8-10 weeks, male, n=6 for each group) was constructed by one single dose of intraperitoneally lipopolysaccharide (LPS) injection (10mg/kg, LPS group) or PBS (Control group). HNG (a potent analog of humanin) was intraperitoneally injected 15 minutes later with a dose of 1mg/kg (HN group). Blood urea nitrogen (BUN), serum creatinine (Scr) and Kim-1 was determined, kidney histology staining, renal inflammatory cytokines, mitochondrial function were evaluated. To analyze the global proteome of the kidney tissue, the 4D-Label-free quantification analysis was applied to screen differentially expressed proteins in 3 groups (n=3 for each group). The parallel reaction monitoring (PRM) was used to verify the selected target proteins.

Results: HNG significantly reduced serum levels of Scr and BUN in a dose-dependent manner (0.2mg/kg, 0.4mg/kg and 1mg/kg), inhibited renal expression of IL-6, IL-1β and HMGB1 and reduce the damage of mitochondria in renal tubular epithelial cells in LPS-induced AKI. Collectively, 5900 proteins were identified in the label free quantification mass spectrometry, 5111 of which were quantifiable. NF-kappa B, Toll-like receptor, NOD-like receptor or IL-17 signaling pathways were significantly enriched,among which 7 proteins were selected for verification by PRM, and they were CD14, Casp3, Rela, Gbp2, Gbp3, Gbp5 and S100a9.

Conclusions: Humanin improves mitochondrial function and alleviates renal tubular injury in LPS-induced AKI. The map of the global proteomics enables further understanding of SA-AKI and will provide great help for seeking more potential therapeutic targets for SA-AKI.

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SA-PO164

Differential Renal Responses to Dexamethasone in Rats and Mice Following AKI

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Background: Acute kidney injury (AKI) is a common cause of kidney failure and mortality. No treatments are approved, but the availability of novel diagnostic tools and biomarkers and better understand of human pathogenesis have increased the likelihood of developing an effective therapy. A major missing link to support successful clinical trials in this area is the lack of evidence that efficacy in preclinical models of AKI is translatable into humans. Because there is existing evidence of dexamethasone (dexa) beneficial effect in human (DECS trial) and rodent AKI, dexa was evaluated in ischemia-reperfusion (IR) induced AKI in rats and mice.

Methods: Dexamethasone was administered via IP injection to mice (12 mg/kg) and rats (3 mg/kg) 30 min before kidney ischemia reperfusion (IR). Plasma creatinine (pCre), transcutaneous GFR (tGFR) and kidney gene expression were evaluated 24h after the procedure.

Results: Dexa reduced plasma creatinine, kidney proinflammatory genes (IL-6, CCL2, IL-1β) and increased tGFR on day 1 after IR in rats but not in mice. Consistently, dexa treatment reduced plasma corticosterone levels (translational target engagement (TE) biomarker) only in rats. Kidney mRNA level of glucocorticoid receptor NR3C1 was downregulated in mouse IR but remained unchanged in rat IR. Similar plasma dexa concentrations were detected in rat and mice.

Conclusions: While the interpretation of these data is limited by the lack of availability of TE and plasma exposures in the DECS clinical trial, the differential responses observed in rat and mice may be attributed to downregulation of steroid receptor expression in mouse kidneys. Appropriate omics characterization together with translational biomarkers and compound exposures in humans and animals may provide significant insights and increase preclinical model translatability in AKI.

Funding: Commercial Support - Janssen

SA-PO165

Acute Exposure to Particulate Matter Affects Renin-Angiotensin System in the Kidneys

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Background: Recent studies have shown that exposure to fine particulate matter (PM) leads to systemic inflammation and furthermore increases the risk of cardiovascular disease. Epidemiologic studies have shown a significant association between exposure to PM and chronic kidney disease and progression to end-stage renal disease. In order to understand the underlying mechanism of PM to systemic effects, we examined the effects of acute exposure to high-concentration fine PM on kidney injury in an experimental mice model.

Methods: Unilateral Ureteral Obstruction (UUO) was induced in 10-week-old Sprague Dawley rats. For fine PM, we used Carbon black CP(CAS No 1333-86-4) dispersed in a specialized inhalation chamber. SD rats were exposed to high-concentration CP particles for 3 hours for 3 days in a nose-only inhalation chamber. Groups were divided into 1) Control, 2) UUO, 3) PM, 4) UUO + PM, 5) UUO+ PM+ ARB L158809 (Merck & Co, Inc, NJ, USA) by drinking water (1.5mg/kg/d).

Results: Weight loss was apparent in rats exposed to carbon black and PM exposure groups. Blood pressure was significantly elevated after the study in the PM and UUO groups. In the lung of PM exposure, renin, angiotensinogen, AT2R gene expression significantly increased and ACE2 decreased. In the kidney, the expressions of renin, and angiotensinogen were not changed after PM exposure, but ACE2 expression significantly decreased in the kidney and UUO further diminished the expression. ARB treatment restored the expression.

Conclusions: Altogether, these findings suggest that exposure to PM can affect the renin-angiotensin system in the kidney, in a different manner from other organs.

SA-PO166

Functioning and Molecular Mechanism of Histone Lactylation in AKI

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Background: Acute kidney injury (AKI) is a common clinical problem, which is defined as the abrupt deterioration of kidney function that results in a decreased glomerular filtration rate. Studies have demonstrated that AKI is associated with a reduced survival rate of patients, increased incidence of chronic kidney disease (CKD), and other complications.

Methods: Although lactylation has been widely studied in the context of cancer, inflammation, and regeneration, its role in AKI remains poorly understood. To address this gap, we conducted a comprehensive investigation into the effects and mechanisms of lactylation in ischemic AKI, utilizing flow cytometry, Western blot, PCR, immunofluorescence, Seahorse in vivo and in vitro.

Results: Our findings demonstrated that pan-lactylation and H3K18 lactylation were significantly reduced in tubular epithelial cells (HK-2 cells) and renal tissue under ischemia in vitro and in vivo. Interestingly, we found that ING2 expression were significantly reduced under ischemia and overexpression of ING2 could inhibit apoptosis of HK-2 cells. In mechanism, ING2 knockout or overexpression could regulate lactylation. Finally, ING2 could regulate lactylation through p300 and promoting histone lactylation could reverse ischemia-induced HK-2 cells injury and ischemia-reperfusion induced AKI in mice.

Conclusions: These results suggested that a unrecognized role of lactylation in kidney injury and a promising target for therapeutic intervention of AKI.

SA-PO167

Assessment of Extracellular Vesicles Isolated from the Culture Medium of Ischemic Renal Proximal Tubular Epithelial Cells

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Background: Extracellular vesicles (EVs) are membranous particles released by a cell into the extracellular environment. They play an emerging and important role in cell communication and have been implicated in a variety of pathological conditions including acute kidney injury and chronic kidney diseases. Our objective was to characterize the dynamics of extracellular vesicle release by proximal tubular epithelial cells exposed to hypoxia and reoxygenation (H/R).

Methods: Primary human renal proximal tubule epithelial cells (hPTECs, n=3) were exposed to 24 hours of 1% hypoxia followed by 3 hours of reoxygenation. Proximal tubule phenotype was verified by megalin immunofluorescence and EVs were isolated from the conditioned culture medium by ultracentrifugation (100.000g for 1h30min). Extracellular vesicle size and quantity were assessed by nanoparticle tracking analysis (NTA) and EV protein quantification.

Results: The immunofluorescence analysis indicated hPTECs were megalin-positive and this was not altered by H/R. NTA indicated that the H/R exposed cells released ~2-fold more EVs than normoxia ($p<0.05$). This was further supported by an increase in EV protein in conditioned media of H/R vs normoxia (1.08±0.17 vs 0.75±0.12 μg/μl, $p<0.05$). The mean particle sizes were not significantly different between H/R (153.5nm) and normoxia (145.8nm) groups.

Conclusions: Our initial data suggest that under hypoxia induces a shift in EV release from proximal tubule cells with greater EV release. These findings suggest that proximal tubule EV release may be altered in the context of ischemic kidney disease. Such changes may contribute to disease pathogenesis.

Funding: Government Support - Non-U.S.

SA-PO168

The Blood Transcriptome Is Reflective of Renal Tissue Injury in Endotoxin-Associated Acute Kidney Failure

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Background: MicroRNA (miR) regulate the translation of RNA involved in renal injury and recovery processes in endotoxin-associated acute kidney injury (sAKI). We previously identified the renal tissue response in sAKI as a series of temporally unique stages consisting of inflammation progressing to translation shutdown and organ failure. We hypothesize the blood miR and RNA (transcriptome) exhibits a response reflective of underlying renal tissue sAKI stage.

Methods: Kidney bulk RNAseq and miRNAseq were performed in an established murine model of sAKI at 0 (baseline) and 1,16 hr (injury) after endotoxin tail vein injection (LPS, n= 5 per timepoint). Total RNA (consisting of RNA and miRNA) extracted from bulk kidney tissue and whole blood (blood), DNAse treated, and globin depletion (blood only) performed. For each miR and RNA, libraries prepared and sequenced (miR: 10-15 million read depth/sample, RNA: 25-30 million read depth/sample) aligned to mm10 transcriptome (STAR). Counts were TMM normalized, log-transformed (counts-per-million, EdgeR), generating expression data. Pearson correlation between blood and kidney performed and common genes with $r>0.8$ and FDR <0.05 considered significantly correlated and pathway analysis performed (Pathfindr).

Results: Transcriptome analyses performed in the blood and the kidney revealed positively correlated miR (n=133 $r > 0.8$) and RNA (n= 388, $r >0.99$) shared between the blood and kidney at each timepoint. Pathway analysis revealed significant upregulation ($p <0.05$) of inflammatory, extracellular matrix/migratory pathways at 1 hr after LPS (NFKB pathway, cell-matrix adhesion, endothelial cell migration). At 16 hr after LPS there were shared alterations in transcription processing, miR regulation, viral responses, and catabolic processes. Analysis of the transcriptome shared between the blood and the kidney revealed parallel activation of RNA involved in the innate immune response and metabolic processes, regulated by miR (miR-144/Cxcl10, miR-298/Cd14, miR-345/Saa2).

Conclusions: Our data suggest that miR regulate RNA in several important sAKI-related pathways. These data demonstrate that the blood transcriptome may be reflective of underlying sAKI tissue stage indicating the utility of these transcriptomic biomarkers.

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SA-PO169

An IL10Ra-Mediated Regulation of T Regulatory Cells by Myeloid Cells in AKI

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Background: IL-10 is a cytokine with multiple effects in immunoregulation and inflammation. IL-10 can protect the kidney from ischemia-reperfusion injury (IRI) - a condition that causes tubular injury and dysfunction due to hypoxia and inflammation. IL-10 binds to its receptor (IL-10R) on the cell surface and activates intracellular signaling pathways that suppress the production of pro-inflammatory cytokines and pro-apoptosis factors. However, the mechanistic role of IL10Ra has not been investigated in AKI, especially during the resolving phase.

Methods: We generated IL10Ra$^{fl/fl}$ LysM-Cre mice for specific deletion of IL10Ra in myeloid cells and subjected them to bilateral or unilateral IRI (uIRI) followed by reperfusion for 13 days. The mice were analyzed for immunophenotypic, histopathological, biochemical, and molecular analysis to evaluate immune profile and pathophysiology. Bioenergetics with parameters of oxidative phosphorylation and glycolysis, along with Differentiation assays were performed to gain a mechanistic view of immunomodulation.

Results: Myeloid-cell-specific deletion of IL-10Ra led to a significant increase of CD4 effector memory cells and a marked reduction of regulatory T cells in the spleen as compared to IL-10Ra-sufficient controls. The expression of pro-inflammatory cytokines, co-stimulatory markers as well as activated CD8 T cells and CD8 effector memory T cells were also elevated in the KO mice as compared to the control. There were no differences observed in kidney function in KO mice subjected to bilateral IRI for 24 hours (Acute phase). However, when subjected to uIRI, the IL10Ra deletion led to reduced kidney function as shown by increased plasma Creatinine and BUN, increased tubular Injury score, and marked elevation of injury biomarkers KIM1 and NGAL. Interestingly, KO macrophages subjected to bioenergetics analysis revealed a reduction in mitochondrial respiration and altered potential in generating Foxp3^{+} T-regulatory cells (Tregs).

Conclusions: Our findings reveal a previously unrecognized link between mitochondrial dysfunction, Treg-differentiation, and IL10Ra signaling in resolving of AKI, and could also serve as a potential target for therapeutic modulation.

SA-PO170

Angiotensin II Type 2 Receptor (AT2R) Modulates CD4+ T Cells into Regulatory T Cells (Tregs) in Kidney Ischemia-Reperfusion Injury in Rats: Role of PP2A

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Background: Kidney ischemia reperfusion injury (IR) is the common pathophysiology of acute kidney injury (AKI) associated with immune cell infiltration including T cells. Male kidney is more susceptible to AKI than females. Recently, we have shown that IR causes infiltration of CD45+T cells in male rats and AT2R activation reduced renal CD45+ T cells infiltration and modulated CD4+T cells into anti-inflammatory Tregs ameliorating AKI. Infiltration of these cells in females and the mechanism of AT2R-mediated modulation of CD4T cells into Tregs are unknown.

Methods: Bilateral IR was performed on female SD rats for 30 mins. The rats were divided into 3 groups: sham, IR, and IR+C21 (AT2R agonist, i.p. 0.3 mg/kg b.wt). After 3 days kidney cells were isolated and analyzed with flow cytometry for investigating CD45+, CD3+, CD4+, and FoxP3+ Treg cells. Also B6 mouse splenic CD4+T cells were isolated using magnetically labelled anti-CD4, which were activated with anti-CD3/anti-CD28/ IL2/ TGFβ and treated with C21 alone or in the presence of AT2R antagonist PD123319, NO synthase inhibitor LNAME, PP2A inhibitor okadaic acid.

Results: The female rats showed CD45+, CD3+ and CD4+ T cells infiltration 3days after IR. However, the renal accumulation of CD45 and Tregs is lower in female (<1% of total kidney cells) compared to 3 days IR data in male (7%) rats- suggesting a sex difference. C21 administration reduced the CD45+ T cells infiltration, and increased CD4+FoxP3+ regulatory T cells population and reduced kidney injury as evident by reduced plasma creatinine. However, BUN and proteinuria analysis did not suggest any significant changes with AT2R activation at 3 day post-IR. The ex-vivo splenic CD4+T cells revealed that C21 treatment modulated the CD4+T cells into CD4+Treg cells as determined by 2- fold increase in transcription factor FoxP3 expression. AT2R antagonist PD123319 reduced 2- fold, suggesting the involvement of AT2R. The PP2A inhibitor okadaic acid remarkably attenuated C21-induced FoxP3 increase indicating while the NO synthase inhibitor L-NAME caused only a moderate reduction in C21-induced FoxP3 expression.

Conclusions: IR causes a lower immune cell infiltration in females than males and the AT2R-mediated protection and Treg modulation occurs via PP2A pathway.

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SA-PO171

Macrophage Subtypes Affect the Damage and Repair of Sepsis-Associated AKI by Regulating the Phagocytic Function of Kidney Epithelial Cells

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Background: Different subtype macrophages play different roles in acute kidney injury, but how they work is still not fully defined. This research highlighted the mechanism underpinning the clearance of dying cells and its impact on the surrounding environment including the phagocytotic function of kidney epithelial cells.

Methods: Mouse RAW264.7 cells (peritoneal macrophage cell line) were cultured, in which LPS or IL-4 was used to induce the M1 or M2 phenotype macrophages. The changes of phenotype were verified by Western Blot and flow cytometry. M1 and M2 macrophages were then co-cultured with TCMK-1 cells (kidney epithelial cell line) with or without LPS treatment for 24 h in a trans-well system. Inflammation cytokines were detected by quantitative real-time PCR (qPCR). Apoptotic cell death was accessed by Annexin V/Proidium iodid staining, while the phagocytotic capacity of TCMK-1 cells was evaluated by the uptake of FITC-labelled pHrodo E.coli Bioparticles® Conjugate, and then detected by a flow cytometer.

Results: RAW264.7 cells were successfully induced into M1 and M2, which were verified by increased iNOS expression, F4/80^{+}CD86^{+} cells and F4/80^{+}iNOS^{+} cells in M1 macrophages, and increased Arg-1 expression, F4/80^{+}CD206^{+} cells and F4/80^{+}Arg-1^{+} cells in M2 macrophages. In trans-well culture, M1 macrophages increased pro-inflammatory mediators including IL-1β, IL-6 and TNF-α in TCMK-1 cells, especially with LPS stimulation, but M2 macrophages raised anti-inflammation mediators. A similar change trend was revealed in the percentage of apoptotic TCMK-1 cells, together with Bax and EPOR protein expression. Most importantly, regardless of LPS, the phagocytotic function of TCMK-1 cells was decreased by co-cultured M1 macrophages, but it was enhanced by co-cultured M2 macrophages.

Conclusions: M1 macrophages affect adjacent kidney epithelial cells by releasing inflammatory mediators, inducing apoptotic cell death, compromising phagocytotic function and further repair, whereas M2 macrophages have opposite impacts.

SA-PO172

AKI Results in Sustained, Long-Term Alterations of Kidney Lymphatics

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Background: Acute kidney injury (AKI) is a serious clinical problem associated with significant morbidity and mortality that are inadequately addressed by current treatment options. The kidney endothelial system, comprised of blood and lymphatic vascular systems, responds dynamically to injury. In several models of AKI, kidney lymphatics undergo a process of expansion or lymphangiogenesis (LA). While this process is thought to be acutely protective, long-term alterations in kidney lymphatics following initial injury have never been assessed.

Methods: C57BL/6J mice subjected to bilateral ischemia-reperfusion injury (BIRI) or sham operation were followed for 1, 3, 6, and 9 months. Kidney function was monitored with serial measurements of serum creatinine (SCr) and transcutaneous glomerular filtration rate (GFR). Lymphangiogenic response was assessed by western blot and quantitative real-time PCR at end points. Large-volume confocal imaging followed by a three-dimensional tissue cytometry (3DTC) analytical approach was used to assess lymphatic architecture in relation to serial changes in kidney function.

Results: AKI was confirmed by reduced GFR and increased SCr 24 hours following BIRI. Kidney function improved over time, but BIRI mice had consistently reduced GFR relative to sham mice out to 9 months post-surgery. Histologic evaluation of glomerular and tubular damage showed a similar pattern. Expression of lymphangiogenic factors VEGF-C and VEGF-D, and lymphatic marker VEGFR-3 differed between sham and BIRI mice over time. 3DTC and volumetric tissue exploration and analysis of lymphatic architecture revealed BIRI mice consistently exhibited greater Lyve-1 than sham controls.

Conclusions: In the first long-term (9 month) study to evaluate kidney lymphatics following AKI, we show sustained alterations in the spatiotemporal dynamics of kidney lymphatic vasculature. Future studies will aim to elucidate the functional significance of injury-associated LA that persists beyond initial injury.

Funding: Veterans Affairs Support

SA-PO173

Impact of HIF Stabilizer ICA on Nrf2/Keap1 Pathway in Macrophages

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Background: Mice treated with HIF-stabilizer 2-(1-chloro-4-hydroxyisoquinoline-3-carboxamido) acetate (ICA) were protected from ischemia-reperfusion induced AKI, as were mice after treatment with Nrf2-inducer 1-[2-cyano-3-,12-dioxooleana-1,9(11)-dien-28-oyl] imidazole (CDDO-Im). However, the potential interactions of HIF and Nrf2/Keap1 pathways have not been studied in this context.

Methods: Bone marrow was isolated from wildtype (WT) and HIF1α-KO mice and differentiated into bone marrow-derived macrophages (BMDM). Cells were cultured for 5 days before treatment with vehicle, CDDO-Im (50nM), ICA (250μM) or CDDO-Im+ICA (50nM+250μM) for 24 hours. Cells were harvested and mRNA expression of Nrf2- (*Nqo1*) and HIF1α-target genes (*Hmox1, Glut1, Ldha*) using quantitative real time PCR was analyzed. Protein expression of Keap1, Nqo1 and HIF1α was studied by Western blotting. Statistical analyses were performed using one-way ANOVA and Dunnett post hoc test.

Results: In BMDM from WT mice, treatment with CDDO-Im, ICA or the combination of both (CDDO-Im+ICA) resulted in an upregulation of *Nqo1* mRNA expression (Vehicle: 1.3±0.2 vs. CDDO-Im: 4.4±1.3 ($p<0.05$); vs. ICA: 4.1±1.4 ($p>0.05$); vs. CDDO-Im+ICA: 4.4±1.5 ($p<0.05$)) and *Hmox1* (Vehicle: 1.3±0.2 vs. CDDO-Im: 1.7±0.4 ($p>0.05$); vs. ICA: 5.0±1.3 ($p>0.001$); vs. CDDO-Im+ICA: 4.1±0.6 ($p<0.001$)). This effect was not reversed in HIF1α-KO cells for *Nqo1* (Vehicle: 1.4±0.3 vs. CDDO-Im: 5.4±1.5 ($p<0.001$); vs. ICA: 3.9±0.1 ($p<0.05$); vs. CDDO-Im+ICA: 4.8±0.6 ($p<0.01$)). However, HIF1α-target genes *Hmox1, Glut1* and *Ldha* were significantly upregulated by ICA treatment in WT mice, but not by CDDO-Im or vehicle treatment. Western blotting confirmed these results at the protein level with a decrease of Keap1 expression (Vehicle: 1 vs. ICA: 0.7±0.5) and an increase of Nqo1 expression (Vehicle: 1 vs. ICA: 1.3±0.4) in WT and HIF1α-KO mice.

Conclusions: These *in vitro* studies demonstrate an upregulation of the Nrf2-target gene *Nqo1* following HIF-stabilizer, ICA, treatment. However, this effect was Hif1α independent. These results indicate a potential overlap of the two pathways HIF and Nrf2/Keap1 playing important roles in ischemic AKI. I*n vivo* studies in AKI-models are warranted to assess the impact on these dual effects.

Funding: Government Support - Non-U.S.

SA-PO174

Neutrophil Extracellular Traps (NETs) in the Peritoneal Cavity Contribute to Septic AKI (SAKI) via IL-17A Production in a Mouse Cecal Ligation and Puncture (CLP) Sepsis Model

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Background: There are no specific treatments for SAKI. We previously showed that the Toll-like receptor 9 (TLR9) pathway contributes to SAKI: (1) TLR9 is stimulated by mitochondrial DNA endogenously released during sepsis, (2) TLR9 activates interleukin (IL)-17A, and (3) knockout of TLR9 or IL-17A improves sepsis. Mitochondrial DNA was reported to stimulate NET formation via TLR9 in pulmonary graft dysfunction. Knockout of Peptidyl Arginine Deiminase 4 (PAD4), an enzyme essential for NET formation, completely abolished IL-17A accumulation during atherosclerosis in aorta. Treatment with Cl-amidine, a PAD inhibitor, improved survival after CLP. We hypothesized that NET formation in an infectious site could contribute to SAKI via IL-17A production in sepsis.

Methods: PAD4 KO, IL-17A KO and wild type (WT) controls were subjected to CLP. We assessed kidney function and IL-17A levels in peritoneal lavage fluid (PLF) and blood. Leukocyte infiltration in PLF, blood, and kidney were assessed by flow cytometry. NET formation in the cells in PLF was assessed by immunocytochemistry. To further investigate the effect of NETs on SAKI, we collected neutrophils from WT PLF at 18h after CLP and administered them intraperitoneally into PAD4 KO mice immediately after CLP.

Results: PAD4 KO and IL-17A KO attenuated SAKI and PAD4 KO decreased IL-17A levels in PLF and blood at 18h after CLP. CLP upregulated neutrophil infiltration into PLF, blood, and kidney at 18h. IL-17AKO attenuated neutrophil increase in blood and infiltration into kidney, but not in PLF. The cells in PLF at 18h after CLP contained >70% of neutrophils and formed NETs without any stimulation *ex vivo*. Adoptive transfer of WT neutrophils partially counteracted the protective effect of PAD4 KO against SAKI.

Conclusions: We found that PAD4 KO and 17A KO protected against SAKI, and PAD4 KO decreased IL-17A production in plasma and peritoneal cavity. IL-17A promoted neutrophil infiltration into blood and kidney after CLP. Adoptive transfer of WT neutrophils into the peritoneal cavity reversed the beneficial effect of PAD4 KO on CLP-induced SAKI. These findings suggest that NETs in the peritoneal cavity might contribute to a distant organ effect of SAKI via IL-17A production.

Funding: NIDDK Support

SA-PO175

Distant Organ Consequences of Renal Ischemia and the Effect of Renal Extracellular Vesicles (Exosomes)

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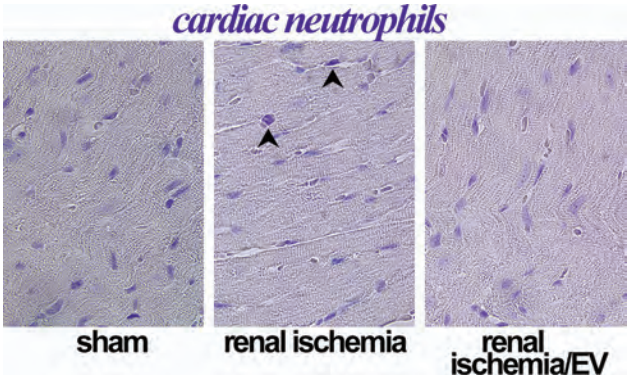
Background: Acute kidney injury is common, expensive and deadly. Morbidity and mortality remain very high; there is no specific treatment, yet the cause of death is frequently due to failure of extra-renal organs. We and others have demonstrated remote organ dysfunction and systemic inflammation following renal ischemia. We have also shown beneficial effects of extracellular vesicles (EV, exosomes) in models of renal injury. We hypothesized that EV would also decrease remote organ inflammation following renal ischemia. However, the effect of EV in the presence of renal failure could be limited.

Methods: The studies employed a well-characterized model of renal ischemia. Multiple time periods of ischemia were used in order to assess the effect of EV treatment independent of renal function. Both tissue and systemic inflammation as well as cell death were quantified.

Results: As in previous studies, markedly improved renal function and structure were found postischemia in groups treated with renal EV, given 24 hours after renal ischemia when renal failure had been established. Systemic inflammation, quantified as serum interleukin-1, -6 and tumor necrosis factor alpha, was significantly decreased in the treated group, even in the presence of prolonged ischemia. Tissue inflammation varied with the organ examined. The number of neutrophils in the heart decreased in the renal ischemia/EV group (figure 1). Anti-inflammatory interleukin-10 was significantly increased in all organs evaluated in the EV treated group, from 110-138% of sham levels. Evidence of apoptotic cell death was decreased in the heart in the EV treated groups.

Conclusions: Systemic and remote organ manifestations of inflammation after renal ischemia are amenable to treatment. Exosomes derived from renal tubule cells improve multiple abnormalities following renal ischemia.

Funding: Other NIH Support - NIAID, Veterans Affairs Support



Representative sections of esterase stained neutrophils in the heart following renal ischemia +/- exosomes

SA-PO176

Analysis of TCRαβ+CD4+CD8+ (Double Positive) T Cells in Normal and Diseased Kidneys in Both Mice and Humans

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Background: The roles of CD4, CD8 and double negative (DN) T cells are being increasingly recognized in normal and diseased kidneys. However, there is little information about kidney TCRαβ+CD4+CD8+ (double positive, DP) T cells. We therefore studied DPT cells in normal and diseased mouse and human kidneys.

Methods: Flow cytometry and single cell RNA-seq (scRNA-seq) were used to analyze kidney DPT cells in C57BL/6J mice at baseline, after ischemia reperfusion (IR) and cisplatin-induced AKI in comparison to CD4, CD8 and DN T cells. Effects of LCMV (virus) infection as well as gut microbiome were studied. Human kidneys from patients with renal cell carcinoma, with and without underlying ESRD were studied.

Results: DPT cells constituted a minor (0.16±0.03%) population of the total TCRαβ+ cells in normal mouse kidneys. AMNIS imaging flow cytometry confirmed the presence of both CD4 and CD8 co-receptors on individual DPT cells. DPT cells had significant Ki67 (87.4±3.3%) and PD1 (22.7±3.6%) expression. DPT cells had effector (69.6±7.5%) and central (18.3±3.5%) memory phenotype with significant IFNγ, TNFα and IL-17 expression. DPT cells expressed the metabolism-related proteins namely HKII, CPT1a and pS6. Percentage of DPT cells increased after ischemic AKI (0.47±0.11%, P=0.048) and cisplatin-induced AKI (0.40±0.14%, P=0.17) at 24 hrs compared to baseline. LCMV infection elevated kidney DPT cell percentage (0.40±0.08% vs 0.16±0.03%, P£0.01) and induced distinct functional and metabolic changes. Germ-free mice kidney DPT cell proportions and functional properties were comparable to WT mice. scRNA-seq analysis showed increased expression of *Klf2* and *Ccr7* and enrichment of TNFα and oxidative phosphorylation signaling related genes in DPT cells. Human kidneys contained high

DPT cell populations in both adjacent normal (median (IQR) = 0.97(.44-1.49)%) and cancer portion of (median (IQR) = 9.69(0.29-10.40)%) renal cell carcinoma tissue.

Conclusions: TCRαβ+CD4+CD8+ double positive T cells constitute a minor population of both mouse and human kidney T cells, with distinct features in normal and diseased kidney compared to other T cells. Future studies of this T cell population are needed to evaluate their roles in normal and diseased kidney.

Funding: NIDDK Support

SA-PO177

Coronin 1α Remodels Inflammatory Microenvironment to Dictate AKI Prognosis

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Background: T-cell-mediated immune response is a key mechanism in AKI onset. Our proteomics data indicate that coronin-1α is markedly induced in the kidneys after AKI, and it is highly expressed in T cells and macrophages to regulate immune cell activation, migration, and phagocytosis. As a protein first noted for its role in modulating actin dynamics and pathogen-host interactions, coronin-1α is spread throughout the cytoplasm and the cell cortex when the cell is resting. Once a pathogen enters the cell, coronin-1α binds to the phagosomal membrane, ensuring the binding and activation of calcineurin, ultimately stopping the fusion of lysosomes with phagosomes. Whether coronin-1α plays a role in AKI is unknown.

Methods: Male and female coronin-1α knockout (Coro1A-/-) mice were used to induce AKI by renal ischemia-reperfusion injury (IRI) at 1, 2, and 3 days (d) or cisplatin at 3d, respectively. A 3-month IRI model was constructed to evaluate AKI long-term outcomes in Coro1A-/- mice. AKI patients samples were employed. Global-/phospho-proteomics and single-nucleus RNA-Seq were utilized.

Results: After AKI, serum creatinine and blood urea nitrogen levels were largely preserved in Coro1A-/- mice compared with wild-type mice. Kidney morphological damages and the expression of the tubular injury markers and chemocytokines were consistently decreased in Coro1A-/- mice. Knockout coronin 1α effectively increased the clearance of apoptotic cells by macrophages. As a consequence, tubular cell proliferation was enhanced in Coro1A-/- mice. In the 3-month IRI model, Coro1A-/- mice exhibited significantly improved kidney function, histology and less fibrotic lesions. Mechanistically, global and phospho-proteomics revealed that inflammation-related signaling pathways were repressed after deleting coronin 1α, and T-lymphokine-activated killer-cell-originated protein kinase (TOPK) was the topmost differentially expressed protein in Coro1A-/- mice diseased kidneys. Single-nucleus RNA-Seq showed higher expression of TOPK in the isolated Coro1A-/- immune cells. *In vivo and ex vivo*, TOPK regulated an inflammatory microenvironment formation, enhancing apoptotic neutrophil clearance and providing favorable conditions to prime tubule repair and regeneration.

Conclusions: Coronin 1α is vital in determining AKI prognosis, and TOPK is a potential immune checkpoint in mitigating AKI.

Funding: NIDDK Support

SA-PO178

Glutamine Blockade After Severe AKI Reduces Kidney Fibrosis by T-Cell Metabolic Reprogramming

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Background: Metabolism regulates T cell function, and metabolic reprogramming by glutamine antagonism was previously demonstrated to reduce early injury in AKI. Given that T cells also mediate organ repair, we studied the effects of glutamine blockade on AKI repair and fibrosis.

Methods: Severe AKI was induced with 45 min unilateral ischemia in C57B6 mice. The glutamine antagonist, JHU083, was administered starting 24h after reperfusion. Kidneys were collected at 4 weeks and stained with Masson's trichrome. Kidney T cells were studied using spectral flow cytometry and machine learning-based analyses.

Results: Glutamine blockade by JHU083 reduced kidney fibrosis in both cortex (21.2±4.2 vs 4.0±0.6%, *P*=0.001) and medulla (17.3±3.2 vs 9.2±1.4%, *P*=0.038) compared to vehicle treatment (*n*=8 /each group). Unbiased high-dimensional analyses segregated T cells from JHU083-treated and vehicle groups. JHU083 increased double-negative (DN) T cells (CD4- CD8-), which have anti-inflammatory properties (6.3±0.7 vs 23.4±1.6% of αβT cells, *P*<.001, 2.2±0.3 vs 3.0±0.2 ×10^5 cells/g kidney, *P*=0.035) and naïve CD4 T cells (1.1±0.1 vs 12.8±2.2%, *P*<.001, 2.2±0.2 vs 6.3±0.7 ×10^4 cells/g kidney, *P*<.001), whereas effector-memory CD4 T cells decreased (92.8±0.8 vs 75.9±3.5%, *P*<.001, 1.8±0.1 vs 0.4±0.1 ×10^6 cells/g kidney, *P*<.001). JHU083 reduced CD4 T cell activation and proliferation (Ki67 94.2±0.5 vs 76.0±3.3%, *P*<.001; CD69 87.9±0.9 vs 77.2±1.8%, *P*<.001) as well as CD8 T cells (Ki67 93.5±0.5 vs 80.8±2.6%, *P*<.001; CD69 97.5±0.2 vs 94.2±0.6%, *P*<.001). JHU083 downregulated hexokinase II (normalized MFI, CD4 0.49±0.04 vs 0.18±0.04, *P*<.001; CD8 0.42±0.03 vs 0.27±0.04, *P*=.021), CPT1a (CD4 0.74±0.07 vs 0.13±0.03, *P*<.001; CD8 0.72±0.08 vs 0.27±0.04, *P*<.001), VDAC1 (CD4 0.73±0.08 vs 0.13±0.05, *P*<.001; CD8 0.77±0.07 vs 0.23±0.05, *P*<.001), and mTOR expression (CD4 0.58±0.04 vs 0.30±0.02 *P*<.001; CD8 0.29±0.03 vs 0.09±0.02, *P*<.001), but upregulated Tomm20 (CD4 0.16±0.04 vs 0.47±0.03, *P*<.001; CD8 0.28±0.05 vs 0.83±0.04, *P*<.001).

Conclusions: Reconstitution of T cell metabolism by glutamine blockade *after* severe AKI reduced kidney fibrosis, increased kidney DN T cells and decreased effector CD4 T cell activation. This is a novel approach to potentially mitigating AKI to CKD, as well as other causes of CKD progression.

Funding: NIDDK Support

SA-PO179

β2-Integrins Are Indispensable for HIF1α Activation in Neutrophils by Controlling Translational Initiation Factor Phosphorylation

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Background: In several inflammatory kidney diseases, circulating blood neutrophils migrate to sites with high cytokine but low oxygen concentrations. Migrating neutrophils interact with extracellular matrix proteins via β_2-integrins. We hypothesized that β_2-integrins control hypoxia-inducible factor 1α (HIF1α) activation under basal and inflammatory conditions.

Methods: HIF1α in human neutrophils was studied by immunoblotting, qPCR, bulk mRNA sequencing. Neutrophil suspension was achieved on polyhema, and adhesion on fibronectin (FN). Prolyl hydroxylases (PH) were inhibited with Roxadustat (ROX) and normobaric hypoxia (1% O_2). β_2-integrin signaling was analyzed by blocking and activating antibodies.

Results: We observed HIF1α protein in ROX-, but not GMCSF-treated neutrophils after 4h with a 3-fold synergistic effect by combined GMCSF/ROX treatment. Increased HIF1α protein was observed in neutrophils cultured on FN but not under stringent suspension conditions on polyhema. Importantly, HIF1α protein in combined ROX/GMCSF-treated neutrophils on FN was strongly reduced by blocking β_2-integrins and, conversely, induced by activating β_2-integrin antibodies on polyhema. The synergistic ROX/GMCSF effect as well as the blocking β_2-integrin effect for HIF1α protein were recapitulated under hypoxic conditions. Mechanistically, the HIF1α mRNA increase by GMCSF was necessary but not sufficient to explain the adhesion-dependent HIF1α protein induction. Importantly, GMCSF increased serine phosphorylation of eIF4E and 4EBP1 HIF1α translation initiation factors in neutrophils on FN in an β_2-integrin dependent manner. Synergistic HIF1α protein induction was demonstrated in neutrophils that transmigrated through FN towards GMCSF and ROX in vitro. Neutrophil bulk mRNA sequencing revealed HIF1α-dependent enrichment of cytoskeletal gene sets under inflammatory conditions. Finally, PH inhibition by ROX or hypoxia enhanced cytoskeleton-dependent neutrophil adhesion.

Conclusions: β_2-integrin engagement restricts HIF1α activation to neutrophils that emigrate from the blood to inflammatory sites under pharmacological or hypoxic conditions.

Funding: Government Support - Non-U.S.

SA-PO180

Clonal Hematopoiesis of Indeterminate Potential Associates with Severe AKI

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Background: Clonal hematopoiesis of indeterminate potential (CHIP) is the clonal expansion of hematopoietic stem cells due to somatic mutations like TET2 gene mutation, without evidence of hematologic malignancy or cytopenia. CHIP is associated with a pro-inflammatory state. The role of inflammation in acute kidney injury (AKI) among individuals with CHIP remains unclear.

Methods: Bone marrow cells (BMC) were collected from recipient mice (CD45.1 isotype), Tet2-deficient and control mice (CD45.2 isotype). Lethally irradiated male recipient mice underwent retroorbital injection of 5×10^6 BMC, consisting of 80% recipient cells and 20% *Tet2*-deficient (*Tet2*$^{-/-}$) or control (*Tet2*$^{+/+}$) cells. Flow cytometry confirmed successful engraftment and clonal expansion of *Tet2*-deficient cells, and then the chimeric mice underwent unilateral kidney vascular clamping with contralateral nephrectomy (Unx-IRI). Renal function was assessed by BUN and creatinine levels, and kidney macrophages were isolated for analysis.

Results: The chimeric mice with *Tet2*$^{-/-}$ BMC developed CHIP, indicated by flow cytometry of peripheral blood cells. *Tet2*$^{-/-}$ mice exhibited increased CD45.2 cells in the intrinsic myeloid kidney cell population. Following Unx-IRI, *Tet2*$^{-/-}$ mice had more severe kidney injury compared to control mice. Higher levels of tubule injury markers (KIM-1, NGAL) and more severe tubule injury were observed in *Tet2*$^{-/-}$ mice at 8 days after Unx-IRI. The kidneys of *Tet2*$^{-/-}$ mice displayed elevated expression of proinflammatory cytokines (Tnf, Il6, Il1b), chemokines (Ccl2, Ccl3), profibrotic genes (Tgfb, Ctgf, Acta2), and extracellular matrix-associated genes (Col1a1, Col3a1, Fn, Vim) compared to *Tet2*$^{+/+}$ mice. Macrophages isolated from the kidneys of *Tet2*$^{-/-}$ mice exhibited increased expression of proinflammatory cytokines both before and after injury. Additionally, increased co-expression of NLRP3 inflammasome and IL-1β with CD68-positive macrophages was observed in kidneys only in the CD45.2 macrophages and not in the CD45.1 macrophages.

Conclusions: This study demonstrates that CHIP is associated with an increased risk of severe AKI in this mouse model, potentially caused by enhanced infiltration of inflammatory cells into the kidneys and subsequent excessive production of proinflammatory cytokines and chemokines.

Funding: NIDDK Support

SA-PO181

AKI-Activated CCR2+ Classical Monocytes Drive Remote Lung Neutrophilic Capillaritis with Hypoxemia due to Ventilation-Perfusion Deficits and Endothelial Leakage

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Background: Acute respiratory distress syndrome and acute kidney injury frequently occur together in multiorgan failure patients and portend high mortality due to a lack of mechanistic understanding and therapeutic options. Pre-clinical animal models of this clinical kidney-lung interaction reveal that AKI induces remote lung inflammation with accumulation of neutrophils and interstitial macrophages in the lung, interstitial edema, and hypoxemia. How this remote lung inflammation is established and causes hypoxemia lacks understanding.

Methods: Flow-cytometry was used to determine the amount of classical/non-classical monocytes and of lung intravascular, marginated or extravasated neutrophils in the lung 24 hours after bilateral renal ischemia-reperfusion injury (IRI). Single-cell RNA sequencing (scRNAseq) analysis was used to study the remotely injured lung after AKI. In-vivo two-photon imaging was used to image lung neutrophils and monocytes after AKI. In vitro, permeability assays using primary lung endothelial cell monolayers were employed.

Results: After AKI, classical monocytes and neutrophils increased in the lung. Lung neutrophils accumulated in lung capillaries, impeded blood flow, and did not extravasate, unlike in LPS-induced direct lung injury, suggesting ventilation-perfusion deficits as important cause of the observed hypoxemia. scRNAseq analysis revealed that monocytes enter the lung and transition into interstitial macrophages. Depletion of $CCR2^{+}$ classical monocytes, but not of non-classical monocytes, blocked lung interstitial macrophage and neutrophil accumulation after AKI. In vitro, primary lung endothelial cell permeability in the presence of AKI serum was strongly enhanced when neutrophils from AKI mice, but not sham mice, were added.

Conclusions: $CCR2^{+}$ classical monocytes are required for neutrophil recruitment in remote lung inflammation after AKI and give rise to lung interstitial macrophages. In contrast to direct lung injury, AKI-induced remote lung inflammation after AKI shows massive neutrophilic capillaritis with neutrophil plugging of vessels that impedes capillary perfusion and thus oxygen uptake. This oxygenation deficit is further negatively affected by increased endothelial permeability.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO182

Plasma Sialic Acid as a Marker for Kidney Function Decline in Preclinical Models of AKI

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Background: Acute kidney injury (AKI) occurs in approximately 10–15% of hospitalized patients leading to high degree of mortality in clinic and is a major risk factor for CKD development and progression. Novel biomarkers could improve diagnosis and help define molecular pathways associated with AKI.

Methods: Untargeted metabolomics was performed on plasma samples from rat and mouse AKI models induced by ischemia reperfusion injury (IRI) using Rapidfire high throughput LC-MS technology. Samples from lean Sprague Dawley (SD) rats, and lean C57Bl/6J mice were collected 24 hours after IRI surgery using bilateral clamping. We also developed an obese and diabetic model of IRI, uninephrectomized (Unx) obese ZSF1 rats which are more susceptible to AKI compared to lean ZSF1 rats. AKI was confirmed by increased plasma Creatinine (pCr), increased kidney injury markers (KIM-1 and NGAL) and a decline in Glomerular Filtration Rate. Plasma sialic acids and creatinine levels were validated by targeted LC-MS/MS methods. Sialic acids were also measured in a Cecal slurry (CS)-induced Sepsis model of AKI in mice.

Results: A total of 20,472 spectral features were extracted from untargeted metabolomics and 123 of them were assigned putative annotations based on m/z and RT with the library of standards. Principal component analysis of the annotated metabolites showed distinct separation between AKI and control groups in all 3 models of IRI. Several gut-microbiome derived metabolites, uremic toxins and sialic acids were significantly increased across all models of AKI and correlated highly with plasma creatinine. Validation of free sialic acid using targeted LC-MS confirmed that plasma sialic acids are significantly increased in AKI and strongly correlated positively with plasma creatinine (Pearson r^2: 0.95 in CS, 0.91 in SD rat IRI, 0.77 in mouse IRI, and 0.60 in ZSF IRI, $p<0.0001$) in both IRI and sepsis models of AKI.

Conclusions: Increases in circulating free sialic acid, consistently observed in preclinical models for IRI or sepsis induced AKI, may be due to impaired filtration and could serve as a surrogate marker for AKI diagnosis

SA-PO183

Myeloid Cell Deletion of the Cationic Channel TRPM2, a Target of Uromodulin Inhibition, Is Protective in Murine Sepsis

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Background: Kidney-derived uromodulin is protective in a mouse model of sepsis, where it promotes proper myeloid cell function in the response to infection. One of the ion channel targets of uromodulin inhibition, cationic channel TRPM2, is expressed on myeloid cells and plays a role in their function. We therefore hypothesized that uromodulin modulates myeloid cell function in sepsis via TRPM2 and that its loss on myeloid cells would be protective in this setting.

Methods: A myeloid specific knockout of TRPM2 was generated by crossing a $TRPM2^{fl/fl}$ mouse with a myeloid cell specific Cre recombinase mouse ($LysM^{Cre}$). The resulting mice ($TRPM2^{fl/fl}$ $LysM^{Cre/+}$) and their littermate controls ($TRPM2^{fl/fl}$ $LysM^{+/+}$) were utilized in the cecal ligation and puncture model of sepsis. Animals were euthanized at various time points post-surgery to assess survival or to collect tissue and serum for imaging and biochemical studies. Immune cell distribution within the kidney will be measured using the Akoya Phenocycler system and immune cell signaling within the kidney is being analyzed by single-cell RNA-sequencing on the 10X Genomics platform.

Results: $TRPM2^{fl/fl}$ $LysM^{Cre/+}$ mice have increased survival and decreased sepsis severity at 48 hours post-surgery compared to $TRPM2^{fl/fl}$ $LysM^{+/+}$ controls. This is despite similar bacterial burden within the peritoneal organs of both genotypes at 24 hours post-surgery. To determine the potential mechanism for increased survival in $TRPM2^{fl/fl}$ $LysM^{Cre/+}$ animals, we harvested kidneys at 10 hours post-surgery and isolated immune cells for single cell RNA-sequencing. We found a reduction in transcriptional markers of immune defense in many cell types of $TRPM2^{fl/fl}$ $LysM^{Cre/+}$ mice. Markers of lymphocyte and natural kill cell mediated immunity were decreased despite the lack of expression of LysM in adaptive and innate lymphoid cells. This suggests that loss of TRPM2 on myeloid cell cells is blocking crosstalk between cells within the immune system to promote immune tolerance.

Conclusions: Myeloid cell knockout of TRPM2 is protective in a mouse model of sepsis. This is consistent with the previously described protective role for uromodulin in sepsis, as uromodulin is an inhibitor of TRPM2. This protection could be due to an increase in immune tolerance and prevention of death from septic shock.

Funding: NIDDK Support, Commercial Support - Dialysis Clinic, Inc.

SA-PO184

Integrin β1-Rich Extracellular Vesicles of Kidney Tissue Recruit Fn1+ Macrophages to Aggravate Ischaemia-Reperfusion-Induced Inflammation

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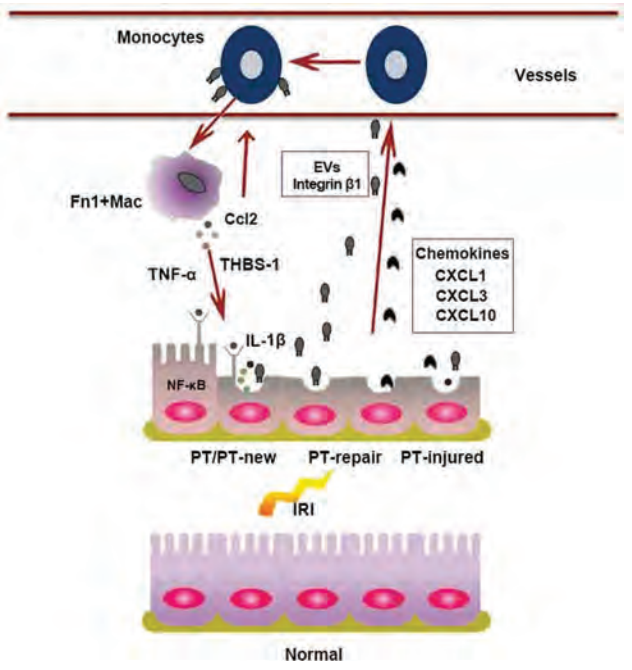
Background: Ischaemia-reperfusion injury (IRI)-induced acute kidney injury is accompanied by mononuclear phagocyte/macrophagocyte (MP) invasion and inflammation. However, the exact kidney-derived extracellular vesicle (EV)-carried proteins that mediate intercellular crosstalk remain elusive.

Methods: Multiomics analysis combining scRNA-seq data and kidney EV protein profiling was used to explore the transcriptomic diversity of proximal tubular cells (PTs) and MPs and differential protein expression of kidney EVs to elucidate how the PT-MP interaction amplifies local inflammation. Transmission electron microscopy, nanoparticle tracking analysis, co-immunoprecipitation, molecular docking, co-culture experiments, siRNA transfection technology, flow cytometry, RT-qPCR, western blotting, and immunohistochemistry were used for verification of functional experiments.

Results: Targeted adhesion and migration of various MPs were caused by secretion of multiple chemokines as well as the integrin β1-rich EVs by ischemic damaged PTs after IRI. These recruited MPs, especially Fn1+ Macs, amplified the surviving PTs' inflammatory response by secreting inflammatory factor TNF-α, Ccl2, and thrombospondin 1 (THBS-1), which could interact with integrin β1 to promote more MP adhesion as well as interact with CD36 to further promote the secretion of IL-1β from surviving PTs. However, blocking EVs with GW4869 maintained a moderate inflammatory response by reducing MP infiltration, promoting repair.

Conclusions: Our findings establish the molecular bases by which chemokines and kidney EVs mediate PT-MP crosstalk in early IRI and provide new insights into systematic intercellular communication.

Funding: Government Support - Non-U.S.



Summary of renal inflammation especially mediated by the intercellular crosstalk among PTs and MPs following IRI-AKI.

SA-PO185

Uromodulin Alleviates Interstitial Fibrosis in AKI to CKD Transition in a Cisplatin-Treated Rat Model via the Inhibition of EGFR Pathway

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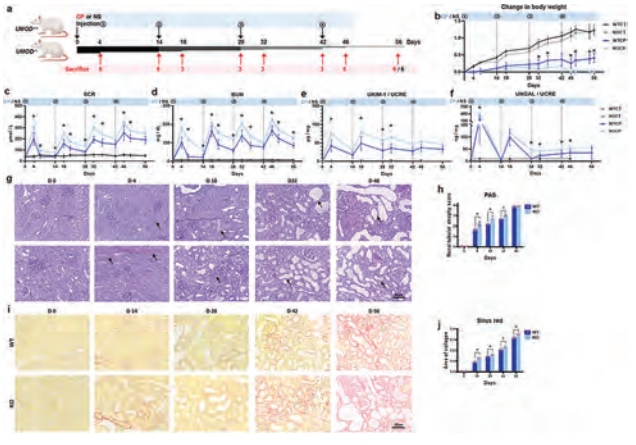
Background: Severe or recurrent acute kidney injury (AKI) episode is liable to cause the occurrence and acceleration of chronic kidney disease (CKD). Uromodulin has been reported as a protective factor for AKI and CKD. Here, we explored its role in the AKI-CKD transition.

Methods: Wild-type SD rats and *UMOD*$^{-/-}$ rats were given cisplatin at 3.2mg/kg for 4 times every 2 weeks to induce the transition of AKI-CKD. Serum, urine and kidneys were collected to assay the protect effect of uromodulin. Western blots, IHC and qPCR were used to investigate mechanisms. HK-2 cell culture in cisplatin was treated with or without uromodulin for further validation.

Results: *UMOD*$^{-/-}$ rats didn't develop spontaneous kidney injury or fibrosis. However, uromodulin deficiency accelerated the progression of AKI to CKD in our rat model, as evidenced by more serious kidney insufficiency and fibrosis. The levels of SCR, BUN, urinary KIM1 and NGAL were significantly increased in cisplatin-treated *UMOD*$^{-/-}$ rats compared with *UMOD*$^{+/+}$ rats. PAS and Sirius staining showed heavier renal lesion and fibrosis in *UMOD*$^{-/-}$ rats. During the transition of AKI-CKD, *UMOD*$^{-/-}$ rats showed elevated levels of fibrosis markers and over-activation of EGFR/ERK, according to Western blot and IHC. The native uromodulin supplement to cisplatin-stimulated HK-2 cells decreased the expressions of fibroblast markers and down-regulated the EGFR/EKR.

Conclusions: Uromodulin deficiency may exacerbate the progression of AKI-CKD transition induced by cisplatin via the overactivation of EGFR.

Funding: Government Support - Non-U.S.



SA-PO186

Kidney Damage Associated with Liver Fibrosis Is Differentially Orchestrated by YB-1 Depending on Its Cellular Origin

Xiyang Liu,[1] Daniela Hermert,[1] Anna Leitz,[1] Yingying Gao,[1] Jialin Wang,[2] Jürgen Floege,[1] Tammo Ostendorf,[1] Ute Raffetseder.[1] [1]*Department of Nephrology and Clinical Immunology, University Hospital RWTH-Aachen, Aachen, Germany;* [2]*Department of Nephrology, Zhongshan Hospital, Fudan University, Shanghai, China.*

Background: Acute kidney injury is a common and life-threatening complication of liver disease. In a previous study, we showed that the Y-box-binding protein (YB)-1 modulates the liver-kidney crosstalk. In a model of liver fibrosis (biliary duct ligation; BDL), mice with half-maximal *Ybx1* expression (*Ybx1*$^{+/-}$) exhibited significantly reduced liver damage, but the resulting kidney damage was increased. The purpose of the present study was to clarify the influence of organ/cell specific YB-1 expression on liver and kidney damage after induction of liver fibrosis.

Methods: For this purpose, BDL was performed as a liver fibrosis model in conditional *Ybx1* knockout animals with specific depletion in hepatocytes (*Ybx1*^{fl}*xAlfp*^{cre}), in myeloid immune cells (*Ybx1*^{fl}*xLysM*^{cre}) and in renal tubular cells (*Ybx1*^{fl}*xPax8*^{cre}).

Results: We found that targeting *Ybx1* in hepatocytes reduced liver fibrosis and kidney damage (e.g. tubular damage, *Ngal* mRNA expression)/fibrosis (e.g. collagen1A staining). Compared to WT animals, BDL mice with *Ybx1*-specific knockout in myeloid immune cells showed significantly reduced serum levels of liver enzymes but increased evidence of kidney damage and fibrosis. Finally, decreased expression of YB-1 in kidney tubular cells resulted in increased expression of fibrosis markers in the liver.

Conclusions: In summary, cell-specific YB-1 expression has a major influence on the respective organ damage in the context of the liver-kidney crosstalk. In addition, we document that renal YB-1 expression also has implications for liver fibrosis. Furthermore, the previously observed reduced liver damage with increased kidney damage occurring in the *Ybx1*$^{+/-}$ animals is best mimicked by a specific YB-1 reduction in immune cells.

Funding: Government Support - Non-U.S.

SA-PO187

Effects of Sodium-Glucose Cotransporter-2 Inhibitor (SGLT2i) on Renal Vascular Reactivity in Cirrhotic Rats

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Background: Variceal bleeding-associated hypotension may activate endogenous vasoconstrictors, leading to renal vasoconstriction and subsequent acute kidney injury (AKI) in cirrhotic patients. Sodium-glucose cotransporters-2 inhibitors (SGLT2i) are a new class of oral anti-hyperglycemic drugs with pleiotropic effects. In addition to the reductions in blood pressure and body weight, SGLT2i showed improvements in renal outcomes. The possible mechanisms included inhibition of inflammation and oxidative stress and a reduction in glomerular hyperfiltration via afferent arteriolar vasoconstriction. Cirrhotic kidney has the same picture of renal hyperfiltration with diabetic kidney. Therefore, the renoprotective role of SGLT2i in cirrhotic kidneys is worth evaluating.

Methods: Liver cirrhosis was induced in S-D rats with common bile duct ligation (CBDL). Rats received oral distill water or SGLT2i (Empagliflozin, 30 mg/kg/day) for 28 days. On the 28th day, AKI was induced by ischemic-reperfusion injury (IRI). On the 29th day, the following was investigated: (a) hemodynamic parameters, (b) serum glucose, BUN, Cr, ALT, AST, IL-1, IL-6, TNF-α, (d) in-situ kidney perfusion, (e) oxidative stress and western analysis of kidneys.

Results: SGLT2i treatment showed no significant change in serum parameters, but lower TNF-α ($p < 0.05$) in CBDL rats. Renal IRI enhanced renal vascular reactivity to endothelin-1 (ET-1) and led to significant increases in serum BUN and Cr (all $p < 0.05$), suggesting AKI. Compared with DW-treated rats, SGLT2i treatment abrogated IRI-related renal vascular hyper-reactivity to ET-1 (Fig) and showed lower BUN and Cr following IRI (all $p < 0.05$). The exact mechanisms of renal protection remained under analysis.

Conclusions: In conclusion, our results demonstrated beneficial effects of SGLT2i in kidneys of CBDL rats, including reduced inflammation, abrogated IRI-related renal vascular hyper-reactivity to vasoconstrictor, and protection from AKI. Therefore, SGLT2i might be recommended for cirrhotic patients.

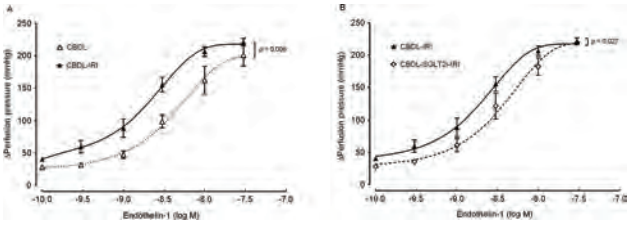

Fig. IRI increased renal vascular response to ET-1 in CBDL rats (A). SGLT2i treatment abrogated renal vascular hyper-reactivity to ET-1 following IRI (B).

SA-PO188

Transient Inhibition of the Sodium-Glucose Cotransporter 2 After Ischemia/Reperfusion Injury Ameliorates CKD in Rats

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Background: A severe episode of Acute Kidney Injury (AKI) can lead to Chronic Kidney Disease (CKD). The sodium-glucose cotransporter 2 (SGLT2) inhibitor, dapagliflozin, has exhibited nephroprotective actions in CKD, but the specific mechanisms remain elusive. We evaluated if a transient administration of Dapa after ischemia/reperfusion injury (IRI) prevents CKD.

Methods: Forty-one male Wistar rats (300-350 g) were randomized in: Sham surgery, IRI for 30 min (IR), and IRI + dapagliflozin (IR+Dapa). Daily treatment with Dapa was initiated 24 h after IRI and maintained only 10 days. After this period, one half of rats was euthanized for kidney functional, histological, and molecular analyses. The other half was followed for 5 months. Proteinuria was determined monthly; kidney function and fibrosis were evaluated at the 5th month. Differences between groups were analyzed through ANOVA with a significance level of $p<0.05$.

Results: Ten days after IRI, rats receiving Dapa exhibited an early restoration of renal blood flow (RBF) with a notorious reduction in RVR and a recovered Creatinine Clearance (CrCl) compared to the IR group alone. Importantly, IR rats persisted with detrimental changes in mitochondrial homeostasis indicated by a significant decrease in Sirtuin-3, a low Mitofusin/Drp1 ratio, and an abnormal mitophagy process with PINK1 up-regulation and reduced Parkin. There was a reduction in OXPHOS Complex I and less total NAD/NADH levels in this group. Interestingly, all these changes were prevented with SGLT2 inhibition. We also demonstrated that this short treatment prevented CKD after five months as indicated by proteinuria, CrCl, and fibrosis.

Conclusions: A short treatment with dapagliflozin after IRI is enough to prevent maladaptive repair and CKD in rats. This renoprotective effect seems to be mediated by an improved renal circulation and restoration of mitochondrial homeostasis. These findings highlight the relevance of the initial days of reperfusion, indicating that maladaptive repair can be modulated after severe AKI to prevent the development of long-term consequences.

Funding: Government Support - Non-U.S.

SA-PO189

Empagliflozin Protects Kidney by Preventing Autophagic Stagnation via Reducing Megalin-Mediated Reabsorption of Lipotoxic Albumin

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Background: Evidence from clinical studies such as DAPA-CKD and EMPA-KIDNEY trials suggests that sodium glucose cotransporter 2 (SGLT2) inhibitors confer renal protection regardless of the presence of diabetes, although the underlying mechanisms remain unclear.

Methods: We investigated the following aspects: 1) the impact of empagliflozin (EMPA) on lipotoxicity in kidney proximal tubular epithelial cells (PTECs) in both wildtype and inducible megalin knockout mice, 2) the effect of EMPA on albumin reabsorption in PTECs, 3) the influence of EMPA on autophagic activity, and 4) the effect of EMPA on ischemia-reperfusion injury (IRI) when autophagy and/or megalin are blocked.

Results: High-fat diet (HFD) induced the formation of cytosolic vacuoles (enlarged lysosomes containing phospholipids) in PTECs, which was alleviated by EMPA. Since vacuolar formation was rarely observed in HFD-fed inducible megalin knockout mice, we assessed megalin-mediated fluorescent albumin reabsorption in PTECs. HFD led to hyperreabsorption of albumin in both S1-2 and S3 segments, which was restored by EMPA. Subsequently, we measured plasma levels of 24 fractions of free fatty acids bound to albumin. EMPA improved the imbalanced lipoquality induced by HFD. Furthermore, employing inducible Atg5 knockout mice and GFP-MAP1LC3 transgenic mice, we found that EMPA mitigated the HFD-induced increase in autophagic demand and alleviated the stagnation of autophagy. Finally, we aimed to determine whether the reduced reabsorption of lipotoxic albumin and restoration of autophagic flux by EMPA improve the HFD-induced susceptibility to ischemic stress. The renoprotective effect of empagliflozin against IRI-induced acute kidney injury was attenuated when megalin and/or autophagy were blocked.

Conclusions: The reduction of toxic albumin reabsorption and prevention of autophagic stagnation in PTECs may be crucial for SGLT2 inhibition-mediated renoprotection.

Funding: Commercial Support - Japan Boehringer Ingelheim

SA-PO190

Gut Dysbiosis and Altered Gut-Derived Metabolites in Patients with Active Lupus Nephritis

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Background: Lupus nephritis (LN) is an important cause of acute kidney injury and chronic kidney disease. Emerging evidence suggests that gut dysbiosis may contribute to LN pathogenesis. We investigated gut dysbiosis and changes in gut-derived metabolites in LN patients.

Methods: Fecal samples were collected from 69 patients with kidney biopsy-proven Class III/IV±V LN (16 patients with active LN and 53 patients in remission). Age- and sex-matched samples from healthy subjects (n=15), patients with non-renal lupus (n=27), and patients with non-lupus chronic kidney disease (n=37) served as controls. Bacterial DNA was isolated from fecal samples and submitted to Novogene for shotgun metagenomic sequencing at an average depth of 41 million paired end reads with a read length of 150bp. Sequenced reads were processed to remove adapter regions and low-quality bases, and Phix and human contamination were filtered. High-quality reads were taxonomically profiled at different taxonomic levels using MetaPhlAn4. Microbial pathways and predicted metabolite abundance was assessed using HUMAnN3.6 pipeline and MelonnPan respectively.

Results: Three samples (1 LN and 2 non-renal lupus) failed quality control and were removed from analysis. Alpha and beta diversity were comparable between LN patients and controls. Active LN was accompanied by an increase in the abundance of *Megamonas funiformis* and *Ruminococcus torques* and a decrease in *Candidatus Avimicrobium caecorum* and *Alistipes shahii* compared to LN patients in remission and control groups ($P<0.05$, for all). Microbial pathways were similar in patients with active LN and remission, whereas fatty acid β-oxidation, hexitol degradation, ornithine degradation, and NAD salvage pathways were enriched in LN patients compared to healthy subjects. Analysis of microbiota-derived metabolites showed increased abundance of ADMA and chenodeoxycholate, and downregulation of pyridoxamine and nicotinic acid in patients with active LN compared to remission ($P<0.05$, for all).

Conclusions: LN is associated with gut dysbiosis and altered metabolite abundance. Whether these changes are of pathogenic significance remains to be established.

Funding: Government Support - Non-U.S.

SA-PO191

ACE2 Overexpression Mediates Spatial Distribution of Pathologic Features in AKI

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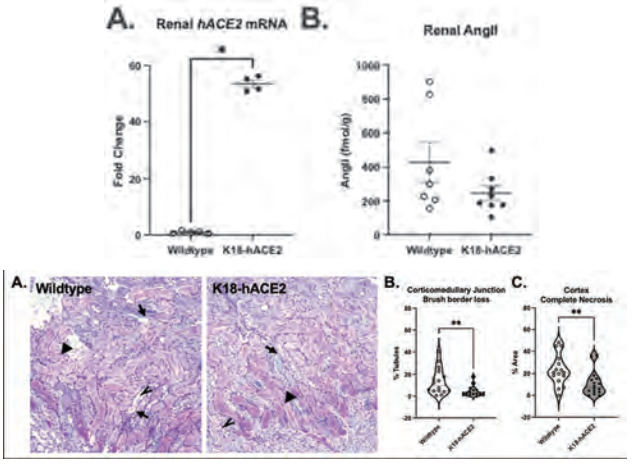
Background: Acute kidney injury (AKI) is a widespread health problem often caused by ischemia. Angiotensin II (AngII) drives pathologic changes in AKI. Angiotensin converting enzyme 2 (ACE2) metabolizes AngII and extinguishes its effects. While several studies have examined the role ACE2 plays in chronic kidney disease and hypertension, less is known about ACE2 in AKI. We hypothesize that ACE2 overexpression promotes recovery after AKI via AngII metabolism.

Methods: We use K18-hACE2 mice which overexpress human ACE2 in epithelial cells. Unilateral renal ischemia reperfusion (IRI, 25-min ischemia) with contralateral nephrectomy was performed on age-matched K18-hACE2 and wildtype (WT) littermates. Blood urea nitrogen (BUN), plasma creatinine (Cr), and histology was performed.

Results: Human hACE2 mRNA expression is increased in K18-hACE2 kidneys (53.5 ± 1.3-fold over WT mice; $p<0.05$, **1A**). At baseline, there was no significant difference in kidney AngII content in K18-hACE2 mice (428.4 ± 307.0 fmol/g vs 246.6 ± 122.8 fmol/g; **1B**). 24 hours after IRI, renal function (BUN and plasma Cr) was similarly decreased in WT and K18-hACE2 mice. Quantification of tubular injury revealed less brush border loss in the corticomedullary junction (CMJ) of K18-hACE2 kidneys (13.4 ± 11.6 in WT vs 4.3 ± 4.7, $p<0.01$, **2A, B**). In the cortex, overexpression of hACE2 caused lower levels of necrosis (23.2 ± 14.0 vs 10.9 ± 11.1 in WT, $p<0.01$, **2C**).

Conclusions: We show that K18-hACE2 mice are a valuable tool for understanding ACE2 in the context of kidney injury. Reduced brush border injury scores in CMJ, and lower cortical necrosis in K18-hACE2 mice following IRI suggests that ACE2 mediates regional differences in pathologic injury. Unchanged AngII at baseline may suggest that renal ACE2 mediates acute changes in AngII in association with control of spatial injury pattern. Examination of the injury and repair processes will elucidate the impact of ACE2 overexpression on injury mechanisms.

Funding: NIDDK Support, Private Foundation Support



SA-PO192

Loss of Tubular Angiotensin-Converting Enzyme 2 (ACE2) into the Urine with ACE2 Casts: A Key Pathophysiologic and Diagnostic Alteration in AKI?

Cosimo L. Cianfarini, Mina Shirazi, Jan Wysocki, Jiao-Jing Wang, Minghao Ye, Zheng J. Zhang, Daniel Batlle. *Northwestern University Feinberg School of Medicine, Chicago, IL.*

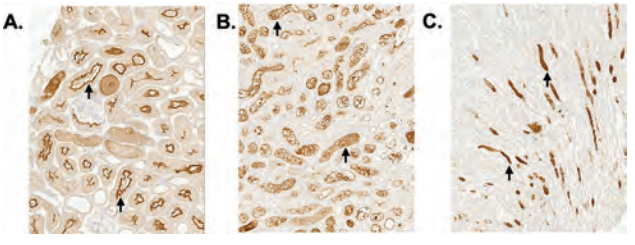
Background: In acute kidney injury (AKI) the renin angiotensin system (RAS) is overactive. ACE2 is a tissue RAS enzyme that is highly expressed in the apical tubular border in kidney cortex and corticomedullary region where it controls Angiotensin II degradation to form Angiotensin 1-7. We hypothesize that in AKI there is a loss of apical tubular ACE2 that amplifies RAS overactivity and results in worsening of proximal tubular injury.

Methods: We used the mouse model of AKI by ischemia-reperfusion-injury (IRI) in male C57BL/6 mice by clamping of the left renal pedicle for 30min followed by removal of the right kidney (unilateral IRI). Kidneys were harvested 48hrs after the surgery and stained for ACE2 by immunohistochemistry (IHC) and immunofluorescence (IF). Kidney ACE2 protein was assessed in membrane protein lysates and enzymatic activity measured using a fluorogenic substrate. ACE2 protein by western blot and enzymatic activity were assessed in mouse urine collected 48hrs post IRI.

Results: IHC and IF revealed a striking maldistribution of tubular ACE2 (Fig. A, B) compared to healthy control kidneys including spillage into the tubular lumen and presence of ACE2 positive luminal casts in the medulla (C) where ACE2 is usually absent. ACE2 protein in membrane lysates and enzymatic activity were reduced (37±3.5 vs. 100±5.6 ACE2/ß-Actin, p=0.0004 and 96±14 vs. 152±5.6 RFU/µg total protein/h, p=0.006). In the urine the full-length membrane bound ACE2 protein was increased (2606±1764 vs. 100±47 ACE2/µl urine, p=0.04) and activity in the urine sediment was increased as well (7.7±1.9 vs. 2±0.2 RFU/µg Cr, p=0.01). Moreover, ACE2 containing casts were recovered in the urine sediment.

Conclusions: In a mouse model of AKI caused by IRI there is a marked loss of ACE2 from the apical tubular border with deposition of ACE2 positive material in the medulla and increased urinary excretion of the full length membrane-bound ACE2. The deficiency of apical ACE2 not only results in the loss of its kidney protective effects but may also serve as a diagnostic marker of AKI.

Funding: Other NIH Support - NIAID, Private Foundation Support



SA-PO193

Urinary mRNA Profile in Recipients of Allogeneic Hematopoietic Cell Transplant with AKI

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Background: Allogeneic hematopoietic cell transplantation (HCT) is curative for hematologic malignancies but carries risk of acute kidney injury (AKI) in up to 80% within the first 100 days. The etiology of AKI is multifactorial and includes non-immune (ischemic, drug toxicity) and immune-mediated mechanisms. Herein we investigated whether AKI in HCT recipients is associated with a urinary cell three-gene signature validated for kidney graft recipients to detect intragraft inflammation (Suthanthiran et al. NEJM 2013).

Methods: We prospectively collected urine specimens at baseline, weekly while inpatient, and monthly outpatient until day 100, from individuals who had their first allogeneic HCT at MSKCC. AKI was defined as ≥ 7-day elevation of ≥ 1.5x baseline serum creatinine. Urine samples closest to the time of AKI and time from transplant-matched samples from patients without AKI were analyzed. Using RT-qPCR assay, we measured the absolute quantity of panel of mRNAs (T cell marker CD3e, proinflammatory chemokine CXCL10/IP10, and cytokine TGFB1), and 18SrRNA in urinary cells and calculated the CTOT04 molecular signature.

Results: A total of 32 urine samples from 32 HCT recipients were analyzed; 16 with AKI and 16 without AKI. There was no statistically significant difference in the urinary cell molecular signature score between the group with AKI and without AKI (Table).

Conclusions: Our findings suggest that AKI in HCT recipients is not associated with increased trafficking of activated T cells through the kidney. Ongoing studies in our laboratory to profile the transcriptome of urinary cells in an unbiased way using RNA-sequencing would likely yield molecular clues to differentiate causes of AKI in this patient population that is difficult to biopsy.

Urinary Cell Levels of mRNAs in HCT Recipients With and Without AKI

Type of urinary cell transcript	AKI (N=16) copies/µg total RNA	No AKI (N=16) copies/µg total RNA	P value
18S rRNA	1.55E+09	2.73E+09	0.82
TGFB1 mRNA	1.25E+04	1.17E+04	0.60
CD3e mRNA	3.53E+02	2.88E+02	0.80
CXCL10/IP10 mRNA	3.94E+02	7.97E+02	0.52
CTOT04 Signature*	-1.658	-1.793	0.82

*Validated molecular signature which correlates with kidney allograft-rejection (NEJM 2013 Jul 4;369(1):20-31).

SA-PO194

Dimensions of Urinary Muddy Brown Granular Casts and Waxy Casts and Clinical Correlations

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Background: Muddy brown granular casts (MBGC) have distinctive microscopic characteristics and are pathognomonic of acute tubular injury (ATI). Waxy casts (WxC) are found in a wider range of tubular and glomerular diseases. There is significant variability in MBGC and WxC size. We aimed to determine whether cast dimensions may correlate with clinical parameters.

Methods: Urine specimens from patients seen in inpatient nephrology consultation were collected. Cases with specimens containing MBGCs or WxC were sampled. At least 12 casts per case were imaged using SeBaCam® and SeBaView at 40x to 400x magnification. Using ImageJ, each cast was measured lengthwise 3 times and widthwise 6 times for MBGC, and 10 times for WxC. Clinical data was extracted from medical records. Data was analyzed by Spearman correlation and t-test.

Results: Twenty-one patients with MBGC and 18 patients with WxC were included. The primary etiology of acute kidney injury (AKI) was ischemic ATI in 61%, toxic ATI in 11% and acute glomerulonephritis in 28%. Mean (range) length for MBGC was 102 (33-317) µm and 223 (28-1714) µm for WxC. Mean (range) width for MBGC was 35 (9-110) µm and 43 (5-253) µm for WxC. For MBGC, width significantly correlated with height (r=0.535, p=0.012), whereas length significantly correlated with age (r=-0.436, p=0.048), FENa (r=0.698, p=0.008), urine chloride (r=0.896, p=0.001) and urine phosphate (r=-0.717, p=0.03). Further, mean MBGC length was found to be significantly longer in patients that received dialysis (p=0.057). WxC length did not correlate with age, need for dialysis or any other parameter, whereas WxC width significantly correlated with serum creatinine (sCr) value at the time of urine microscopy (r=0.855, p<0.001).

Conclusions: MBGC and WxC dimensions significantly correlated with various antropometric, chemical and clinical parameters. Correlation of MBGC length with need for dialysis as well as WxC with sCr suggest that cast dimensions may be related to severity of AKI. With implementation of automated image scanners and computational model training, these observations suggest that urinary cast dimensions may provide valuable diagnostic and prognostic information. Further larger studies are needed to verify and expand these observations.

SA-PO195

The Spectrum of Thrombotic Microangiopathy Related to Monoclonal Gammopathy

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Background: Patients with thrombotic microangiopathy (TMA) should be classified according to etiology to indicate targets for treatment, having impact on treatment and prognosis. Recent studies showed a high prevalence of monoclonal gammopathy (MG) in patients with TMA aged over 50 years. TMA was provisionally added as a MG of renal significance (MGRS) lesion by the International Kidney and MG Research Group. Recent studies suggested that complement dysregulation is common in this group. Here, we studied this premise in 7 patients with TMA and coexisting MG using complement measures, functional *ex vivo* endothelial cell tests, and genotyping.

Methods: Patients with TMA on kidney biopsy and/or peripheral blood were recruited from the Limburg Renal Registry and prospective COMPETE cohort. Patients with ADAMTS13-activity <10% or Shiga-toxin mediated disease were excluded. Patients were screened for rare variants and rearrangements in complement genes. Massive *ex vivo* C5b9 formation on endothelial cells, factor H autoantibodies (FHAA) or pathogenic variants in complement genes defined complement dysregulation. IgG was purified from serum to study monoclonal mediated complement activation. As a control, kidney biopsies of 27 patients with MGRS lesions were studied for morphologic features of TMA.

Results: Eighty-four out of 113 patients with TMA were screened for MG. Seven out of 84 patients presented with MG, classified as MGRS (*n*=6) and multiple myeloma (*n*=1). MG clustered in patients aged over 50 years (*n*/*N*=6/32, 19%). Severe acute kidney injury was noted in all patients. Four out of 7 patients presented with normal complement levels. Serum of one patient induced massive *ex vivo* C5b9 formation on the endothelium; IgG induced massive *ex vivo* C3c and C5b9 formation on the perturbed endothelium. Neither IgG nor C4d were found. No pathogenic variants were found. FHAA were present in 2 patients, without homozygous deletion of CFHR3-1. None of the MGRS patients presented with coexisting TMA on kidney biopsy or massive *ex vivo* C5b9 formation on the endothelium.

Conclusions: MG clustered in patients with TMA aged over 50 years. One patient with MG related TMA presented with alternative pathway activation. We found no evidence of TMA in a MGRS control group. With little evidence for complement dysregulation, the mechanism of MG induced TMA should be studied further.

SA-PO196

Monoclonal Gammopathy of Renal Significance (MGRS) Without Detectable Clones: Clinical Treatment Dilemma

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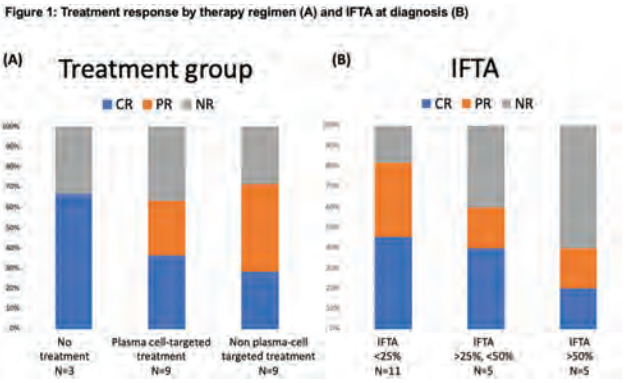
Background: Monoclonal gammopathy of renal significance (MGRS) is characterized by monoclonal immunoglobulin deposition in kidneys. However, monoclonal immunoglobulin is not always detectable in blood, urine, or bone marrow (BM). Treatment response and kidney outcome of MGRS without a detectable clone remains unclear.

Methods: In this single-center, retrospective cohort study, we identified 192 cases of monoclonal immunoglobulin deposition disease (MIDD) from our biopsy repository between 2010 to 2022, of which 86 had follow-up at our center. Inclusion criteria were: (1) negative serum protein electrophoresis and immunofixation, (2) normal serum free light chain ratio adjusted for kidney function, (3) no clone identified in BM, and (4) no specific hematologic diagnosis. We analyzed the best kidney response by therapies (no therapy, plasma cell (PC)-targeted vs. non PC-targeted targeted therapy). Those with at least one PC-targeted treatment were classified as the PC-targeted group.

Results: We included 26 native kidney and 2 transplanted kidney biopsies in this analysis. The median age was 58 (IQR 47-66) and 54% were male. The most frequent subtype of monoclonal immunoglobulin deposited in the kidneys was IgG3 kappa. 67% of patients who had proteinuria >1.0 g/gCr at diagnosis achieved complete response (CR)/ partial response (PR) regardless of the treatment regimen (Figure). Lower proportion of patients achieved CR if they had >50% interstitial fibrosis tubular atrophy (IFTA) at diagnosis. Two cases of MGRS in transplanted kidneys did not respond to treatment. Six out of 7 re-biopsies showed IFTA progression.

Conclusions: Treatments and outcomes of MGRS without a detectable clone were extremely variable. Re-biopsy provided limited information to assess disease activity or the need for additional treatment. More sensitive tools are needed to detect clones and to assess treatment response.

Figure 1: Treatment response by therapy regimen (A) and IFTA at diagnosis (B)



SA-PO197

Beyond Plasma Cell Disorders: Monoclonal Gammopathy of Renal Significance with Marginal Zone Lymphoma

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Introduction: Monoclonal Gammopathy of Renal Significance (MGRS) is well recognized with pre-malignant plasma cell disorders. We report a case of MGRS with nephrotic range proteinuria and rapid loss of kidney function in the context of Marginal Zone Lymphoma (MZL).

Case Description: A 65-year-old man with diabetes mellitus and heart failure is admitted for progressive kidney dysfunction. He has chronic kidney disease, baseline creatinine (Cr) 1.5mg/dL, presumably due to diabetes. On presentation, Cr was 2.1mg/dL. Urinalysis with 2+ proteins and 11-25 RBCs/HPF. 24h urine collection revealed proteinuria at 3.5g. 12.5cm kidneys of normal parenchymal thickness and echogenicity were noted on US with no hydronephrosis. Further workup showed C3 56mg/dL (nl: 86-166) and C4<2mg/dL (nl: 13-46). Serum monoclonal testing revealed a low-grade IgM kappa M protein at 0.09g/dL and a free light chain kappa to lambda ratio of 4.04 (nl: 0.26-1.65). A kidney biopsy showed membranoproliferative glomerulonephritis and IgM kappa restricted deposits. Serum cryoglobulins resulted as positive, type II with a monoclonal IgM Kappa and polyclonal IgG. IgM Cryoglobulin resulted at 17mg/dL with IgA and IgG cryoglobulin at 3 and 19mg/dl respectively. A clinico-pathologic diagnosis of cryoglobulinemia related MPGN was thus made. A bone marrow biopsy unmasked an underlying lymphoproliferative disorder consistent with MZL. CT imaging showed borderline diffuse adenopathy. As such, patient was started on Rituximab, Cytoxan, Vincristine and Prednisone. His kidney function worsened requiring dialysis. Despite cryoglobulins clearance, he remains dialysis dependent while on therapy for his MZL at four months post-diagnosis.

Discussion: Despite an improvement in recognition, MGRS remains a foreign entity both in the nephrology and hematology spheres. It is frequently thought of in the context of plasma cell neoplasms. This case illustrates an MGRS case occurring with an underlying B-cell clone and manifesting as MPGN with progressive kidney dysfunction and nephrotic range proteinuria. A high index of suspicion and a low threshold for kidney biopsy are key to making the diagnosis. As in this case, the kidney biopsy might be the only clue to the underlying lymphoma and a crucial diagnostic step with paramount therapeutic implications, both for kidney and overall patient survival.

SA-PO198

Renal IgG Heavy Chain (AH) Amyloidosis as Monoclonal Gammopathy of Renal Significance: From Accurate Diagnosis to Adequate Treatment

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Introduction: Monoclonal Gammopathy of Renal Significance (MGRS) is a B or plasma-cell clonal disorder that does not meet the criteria for cancer but produces a monoclonal immunoglobulin that leads to kidney injury. It can rarely manifest as AH amyloidosis, in which highly ordered heavy-chain fibrils deposit in the kidneys. We report a case in which a patient with MGRS was diagnosed and treated for renal AH Amyloidosis.

Case Description: A 77-year-old patient was referred to our Nephrology Clinic due to chronic kidney disease (1.4mg/dL baseline creatinine), proteinuria (2.2g/24h), monoclonal gamma spike (0.75g/dL), hypertension and feet paresthesia. Bone marrow biopsy showed 6% plasmocyte clonal proliferation. Eletrocardiogram, echocardiogram, myocardial scintigraphy and bedside kidney ultrasound were unremarkable. Further workup showed 8.7g/dL hemoglobin, 1.28mmol/L ionized calcium, rare eritrocytes and 2+ protein on urinalysis, 6.3 Kappa-to-Lambda ratio and 1058 mg/dL IgG. Renal biopsy was performed for suspected MGRS with glomerular involvement (images attached). AH Amyloidosis was diagnosed and CyBorD chemotherapy started. After 4 sessions, creatinine and blood urea nitrogen levels improved from 2.2mg/dL and 60.2mg/dL to 1.58mg/dL and 30mg/dL respectively. Proteinuria reached 0.86g/24h.

Discussion: This is a case of rare renal AH Amyloidosis diagnosed in a patient with hypertension, subnephrotic proteinuria and isolated kidney injury, which differs from the typical hypotension, nephrotic-range pronteinuria and multi-organ involvement seen in AL Amyloidosis. Since elevated serum free light-chain levels might be seen on both conditions, renal biopsy is vital for precise diagnosis and fibril deposit distinction. As new therapies are surging for MGRS and Amyloidosis, there is a need for prompt suspicion and accurate diagnosis, which can improve renal outcomes, mitigate disease burden and prevent overt malignancy such as multiple myeloma.

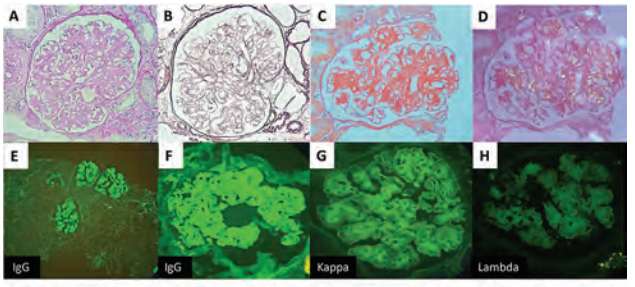

Figure 1 – Glomerulus showing global mesangial and segmental capillary loop deposition of PAS-pale, silver-negative substance (A. PAS, 400x; B. PAMS, 400x). The glomerular deposits are Congo Red-positive and show apple-green refringence under polarized light (C and D. Congo red, 400x), typical of amyloidosis. Diffuse global glomerular IgG positivity (E and F), with negative kappa and lambda (G and H).

Kidney Biopsy

SA-PO199

The Clinico-Pathologic Characteristics of Patients with Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits

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Background: Proliferative glomerulonephritis with monoclonal immunoglobin (Ig) deposits (PGNMID) is a rare form of monoclonal gammopathy of renal significance (MGRS). However, the Monoclonal (M) protein and hematologic clone is found in less than half of the cases.

Methods: We identified all patients with PGNMID from the Cleveland Clinic Kidney Biopsy Epidemiology Project from January 2015 to March 2023. Retrospective chart review was performed to obtain demographic and clinical characteristics.

Results: From 34 patients with PGNMID, 16 patients were excluded due to insufficient data. Of the 18 remaining patients, 67% were male and 78% of patients self-reported as white. The median age was 60 years, with 22% of patients < 50 years. Clinically, features at kidney biopsy were: hypertension (78%), acute kidney injury (72%), hematuria (78%), nephrotic syndrome (22%), and hypocomplementemia (23%). M protein was identified in 33% with an underlying clone identified in only 17% (3/18) of cases (MM, CLL and B cell lymphoma). Mean serum creatinine and proteinuria at biopsy were 3.2mg/dl (0.64 - 9.0) and 4.3 gm/dl (0 - 14.0gm) respectively. Regarding pathology, endocapillary hypercellularity (55%), pure mesangial (28%) and MPGN (16%) patterns were most common. The majority of patients (>65%) had mild chronicity and 1 case had crescents. IgG/Kappa was the predominant finding (83%), one patient had IgM/Kappa. Of 13 patients with IgG subclass staining, 77% had IgG3 and one case each of IgG1, IgG2 and IgG4. CyBorD and CyBord-Daratumumab were the most common chemotherapy regimens used, each accounting 35% followed by Rituximab in 12% of cases. Regarding outcomes, 18 patients had follow up data, with 8 (44%) progressing to ESKD post biopsy with mean duration of 7.8 months (0 - 13) and 44% had either complete (< 0.5 g) or partial remission (proteinuria reduction > 50% with stable eGFR) during follow up. No clinico-pathologic variables were predictive of response on univariate and multivariable analysis.

Conclusions: Our study adds to growing evidence of low clonal detection rate among patients with PGNMID and high rate of disease progression despite treatment. More studies are needed to better understand the true nature of this disease to hopefully guide therapeutic interventions.

SA-PO200

Triple Monoclonal Protein-Related Kidney Lesions in a Patient with Plasma Cell Dyscrasia

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Introduction: Toxic monoclonal protein typically results in a single type of kidney pathology due to biophysical properties of monoclonal protein. Multiple type of lesions is rarely reported. We report a patient with monoclonal gammopathy who has light chain cast nephropathy (LCCN), light chain proximal tubulopathy (LCPT) and thrombotic microangiopathy (TMA).

Case Description: A 57-year-old male with history of dermatomyositis and sarcoidosis on mycophenolate mofetil and prednisone who presented with fever, nausea, and loose stool for 3 days. He was diagnosed with concealed ruptured diverticulitis. He had a baseline creatinine (Cr) of 0.8-1.0 mg/dl but it was 1.47 mg/dl 3 months ago. Upon presentation, Cr was 2.81 mg/dl which continued to rise and peaked at 9.29 mg/dl requiring hemodialysis. Platelet (Plt) and Hemoglobin (Hb) were normal upon admission but continued to decrease along with the presence of hemolysis marker. ADAMTS13 activity was 28%. Kappa light chain (LC) of 16 mg/dl and kappa lambda (K/L) ratio of 7.17. Serum electrophoresis showed IgG kappa with M- spike of 0.2 g/dl. His urine analysis showed blood and granular cast, and his protein to creatinine ratio of 1.33 mg/mg. He underwent a kidney biopsy which showed kappa LCCN, TMA and non-crystalline LCPT with minimal interstitial fibrosis. Bone marrow biopsy showed less than 3% of kappa-restricted plasma cell. Complement study showed elevated sC5b-9. Given the finding of progressive TMA, he underwent plasma pheresis for 3 sessions as a bridging therapy before initiating anti-plasma cell therapy with daratumumab, bortezomib and dexamethasone. Due to recent infection, eculizumab was on hold. After the 1st cycle, he is still dialysis dependent but kappa free light chain came down to 3.83 mg/dl with K/L ratio 1.32. Hb and Plt improved but still has positive hemolysis marker so the plan is to start Eculizumab and continue chemotherapy.

Discussion: This case highlights the importance of toxic properties of monoclonal protein in causing kidney diseases. Triple monoclonal protein related kidney lesions can occur but rare. LCCN is a myeloma defining event but his LC (<50 mg/dl) and plasma cell burden is low (<10%) which makes this case very unusual. Sepsis-induced low flow stage may induce LCCN in this patient. Aggressive therapy is likely needed to eradicate the clone in order to achieve organ response.

SA-PO201

A Case of Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits Presenting as Hypertensive Emergency

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Introduction: Proliferative Glomerulonephritis with Monoclonal Immunoglobulin Deposits (PGNMID) is a subtype of monoclonal gammopathy of renal significance (MGRS), resulting from deposition of intact monoclonal IgG in glomeruli. Herein, we present the case of a 65-year-old who presented for new headaches and hypertensive emergency and was subsequently found to have PGNMID.

Case Description: A 65-year-old female with no significant past medical history developed new headaches and was treated with ibuprofen 800 mg TID for 5-months. Subsequently, she was found to have new hypertension with BP of 190/90 mmHg, serum creatinine of 1.0 mg/dl and nephrotic-range proteinuria of 5.4 g/g creatinine. Urinalysis was positive for protein and blood with no dysmorphic RBCs or casts on urine sediment. Labs also revealed new anemia and thrombocytopenia with elevated LDH, undetectable haptoglobin, and normal peripheral blood smear. Further serologic evaluation for C3, C4, ANA, cryoglobulin, ANCA, HIV, HBV, HCV, Anti-PLA2R, DAT, and ADAMSTS13 activity were normal/negative. Paraproteinemia evaluation with SPEP and UPEP were without evidence of M-protein, aside from a marginal free Kappa/lambda light chain ratio (1.8). Despite cessation of NSAIDS and adequate blood pressure control with amlodipine and losartan, proteinuria persisted with rising creatinine. Therefore, kidney biopsy was pursued which showed neutrophilic glomerulitis with a membranoproliferative pattern and rare fibrocellular crescents. Immunofluorescence showed only mesangial and capillary C3 and C1q deposits; however, pronase treated paraffin tissue unmasked IgG-kappa restricted subendothelial and mesangial deposits, diagnostic of PGNMID. She was treated with six cycles of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) resulting in initial improvement in proteinuria and serum creatinine. Repeat bone marrow was without residual plasma cells on flow cytometry.

Discussion: PGNMID is a MGRS that does not meet criteria for multiple myeloma or lymphoma, and a monoclonal immunoglobulin or abnormal bone marrow B cell clone is detected in only 30% of cases. Pronase treatment of paraffin tissue to reveal masked immunoglobulin deposits can provide insightful guidance in glomerular deposition diseases when routine immunofluorescence is not diagnostic.

SA-PO202

Proliferative Glomerulonephritis with Monoclonal IgG Deposits: A Mysterious Renal Disorder

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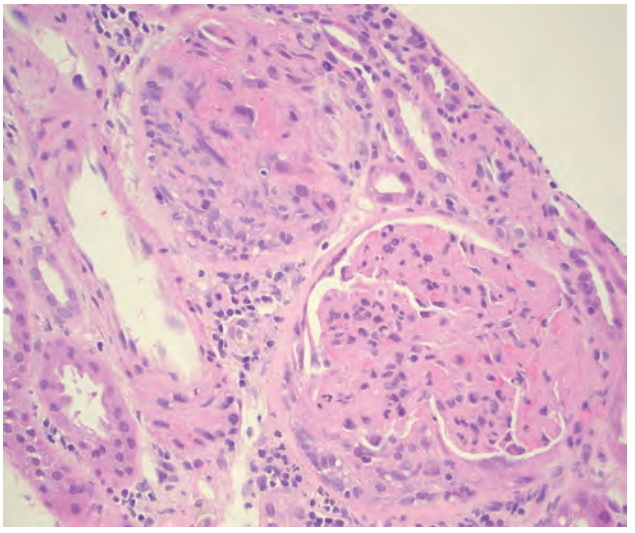
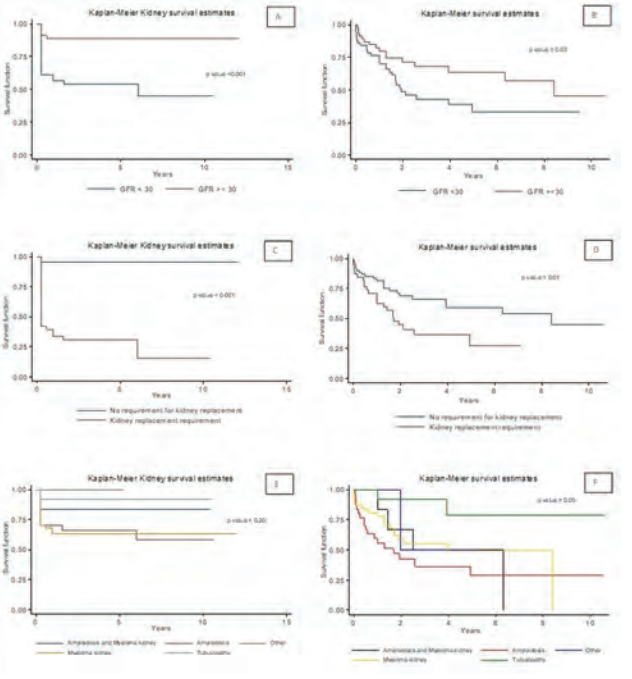
Introduction: Proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) is a rare form of glomerulonephritis characterized by glomerular monoclonal deposits. It predominantly presents with nephrotic range proteinuria and renal dysfunction. A third of patients with PGMID progress to ESRD. It is a renal-limited disorder, however, rare cases of PGNMID in association with CLL have been reported. Herein, we present a case of severe renal failure due to PGNMID in the setting of underlying CLL.

Case Description: An 88-year-old female with CLL presented with oliguric renal failure. Labs revealed an elevated serum creatinine level of 7.9 mg/dL (baseline 1.1 mg/dL), and nephrotic range proteinuria. Renal biopsy showed kappa-restricted immune complex-mediated proliferative and crescentic glomerulonephritis (Fig 1) with linear staining of glomerular capillary loops for IgG (3+), and kappa (3+) suggestive of PGNMID. It was presumed that her PGNMID was due to CLL and hence decision was made to continue with ibrutinib and assess hematological response.

Discussion: PGNMID, a rare form of GN, appears as one of the most mysterious renal disorders associated with monoclonal gammopathy. When present, it should raise the possibility of an underlying secondary etiology as hematological malignancies, especially CLL, have been recognized as a rare cause of PGNMID. Early recognition of PGNMID is a key factor for long term renal survival. Treatment therapy is aimed at monoclonal proliferation and hematological response. Identification of pathogenic clone is vital to guide treatment. The usual absence of any detectable clonal proliferation

makes its management challenging. Further studies in understanding the mechanisms of monoclonal deposition would help refine treatment strategies. This case highlights the importance of close monitoring and individualized treatment plans in the management of PGNMID.





SA-PO203

Prognostic Factors Associated with Renal Survival and Mortality of Renal Involvement Proven by Biopsy Associated with Monoclonal Gammopathy

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Background: Monoclonal gammopathies can generate a wide and diverse renal compromise that can condition the patient's prognosis. This study seeks to determine those factors associated with renal survival and mortality.

Methods: A retrospective cohort study of 98 patients older than 18 years with biopsy-proven renal involvement due to monoclonal gammopathy was conducted. For the analysis of renal and patient survival, the Kaplan Meier method was obtained, renal survival curves were compared with the histological diagnosis and the Log Rank Test was obtained. To determine the predictive factors at the time of biopsy that correlate with death and ESKD, univariate and multivariate cox analyzes were performed.

Results: The need for RRT was related to the combined outcome of ESKD and death (HR 4.86 CI 2.01-11.79). A GFR at the time of biopsy less than 30ml/min/1.73 was correlated with an increased risk of ESKD (HR 4.02 CI 1.38-11.71). Amyloidosis and age over 60 years are factors associated with higher mortality (HR 2.38, IC 1.22-4.86 and 1.96 IC 1.06-3.61 respectively). The presence of tubulopathy (myeloma Kidney) in renal biopsy was associated with better survival compared with other histological compromises (p 0.05).

Conclusions: The requirement of RRT and GFR less than 30 ml/min/1.73 were associated with adverse outcomes in patients with MGRS. Amyloidosis and age are factors negatively related to patient survival.

Funding: Private Foundation Support

Combined death and end stage chronic kidney disease

	Univariate (HR)	Multivariate (HR)
Age <60 years	1.58 (CI 0.88-2.85, p 0.12)	1.36 (CI 0.73-2.56, p 0.32)
GFR at biopsy ≤ 30 ml/min/1.73	3.53 (CI 1.90-6.54, p 0.000)	1.21 (CI 0.48-3.04, p 0.68)
Amyloidosis	1.08 (CI 0.61-1.92, p 0.76)	1.28 (CI 0.70-2.34, p 0.41)
Need for RRT	5.63 (CI 3.10-10.24, p 0.000)	4.86 (CI 2.01-11.79, p 0.000)

SA-PO204

A Rare Case of Proliferative Glomerulonephritis with Monoclonal IgA Lambda Deposits with Crescents

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Introduction: Proliferative glomerulonephritis with monoclonal immunoglobulin deposits (PGNMID) is an uncommon condition under the spectrum of renal disorders grouped under monoclonal gammopathies with renal significance (MGRS). Even more uncommon is the type of immunoglobulin (Ig) deposition other than IgG subclasses (IgG3 heavy chain being most common type of deposition) in PGNMID, which may be IgA or IgM as well as light chain only deposition.

Case Description: We report a 65 y/o Caucasian female patient (pt) with history of hypertension, recurrent urinary tract infections and non-obstructive nephrolithiasis with recent worsening of creatinine (Cr) to 1.3-1.6 mg/dL, with albuminuria 1.8 g/g, proteinuria 2.2 g/g and hematuria and negative nephritic workup. Pt was also noted to have low kappa/lambda light chain ratio (0.14) with significantly elevated free lambda light chains (206.23). No significant abnormalities were noted on serum protein electrophoresis, serum immunofixation electrophoresis or urine protein electrophoresis. While awaiting hematology consultation and renal biopsy the pt was admitted with low back pain and was noted to have new retroperitoneal mass/adenopathy concerning lymphoma. Pt developed progressive renal failure necessitating initiation of hemodialysis (HD). Retroperitoneal mass biopsy positive for diffuse large B-cell lymphoma (DLBCL) with renal biopsy notable for proliferative glomerulonephritis with monoclonal IgA lambda deposition with crescents in the setting of lymphoma and MGRS w/ monoclonal IgA lambda. The pt was started on R-CHOP chemotherapy (CT) for management of her DLBCL while continuing her on HD. Pt eventually achieved DLBCL remission as well as renal recovery with discontinuation of HD with 2 R-CHOP and 4 R-COEP cycles.

Discussion: PGNMID is a rare cause of renal disorder. Though it is usually recognized with deposition of IgG3 subclass heavy chains in glomeruli, it can rarely be recognized with deposition of other immunoglobulins like IgA and IgM as well as light chains. Treatment of this disease is based on clone directed therapy, which could lead to complete or partial remission in these patients. Our case is a one of the rarer cases as it involved uncommon monoclonal IgA lambda chain deposition and it is also associated with diffuse large B-Cell lymphoma.

SA-PO205

Cryoglobulinemic Thrombotic Microangiopathy: A Subtype of Monoclonal Gammopathy of Renal Significance

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Introduction: Monoclonal gammopathy of renal significance (MGRS) encompasses a set of disorders in which a cell clone secretes immunoglobulin that causes kidney damage without meeting criteria for a malignant plasma cell dyscrasia. These conditions often involve damage mediated by direct monoclonal Ig deposition, though less commonly include processes like thrombotic microangiopathy (TMA) without direct

antibody deposition in the kidney. Here, we present a case of kidney injury secondary to a cryoglobulin-mediated TMA responsive to steroids and clone-directed therapy.

Case Description: A 45-year-old African American woman with recent COVID-19 infection presented with weakness. Vital signs and exam were unremarkable. Labs were notable for creatinine of 8.3 mg/dL, hemoglobin 7.6 g/dL, platelet count 121 K/μL, and LDH 439 IU/L. Urinalysis revealed 4+ blood and 4+ protein with >182 RBC/hpf and muddy brown casts. PLASMIC score was 4. ADAMTS13 activity and functional TMA panel were normal. SPEP/UPEP showed monoclonal IgG lambda. Renal biopsy revealed chronic thrombotic microangiopathy. With a cryocrit of 2.5%, biopsy findings were most consistent with a cryoglobulinemic TMA with absence of paraprotein or immune deposits. She was discharged with a prolonged course of corticosteroids with clinical improvement. Six months later, she re-presented with recurrent AKI (creatinine 3.1 mg/dL), anemia, and thrombocytopenia. Renal function continued to worsen with repeat pulse-dose corticosteroids. Plasmapheresis and clone-directed therapy with bortezomib resulted in dramatic improvement in renal function (creatinine 1.1 mg/dL).

Discussion: Thrombotic microangiopathy is a less common manifestation of monoclonal gammopathy of renal significance and even more rarely associated with Type I cryoglobulinemia. This case demonstrates a paraprotein-mediated process causing disordered complement regulation leading to a TMA. To our knowledge, this is only the second reported case of severe acute kidney injury caused by a cryoglobulinemic thrombotic microangiopathy that was successfully treated with plasma exchange and clone-directed therapy. The role of these therapies in cryoglobulinemic TMA as well as consideration of eculizumab as a subsequent line of therapy in refractory cases merits ongoing discussion.

SA-PO206

Nephrotic Syndrome with Monoclonal Gammopathy of Undetermined Significance (MGUS): A Case Report

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Introduction: Nephrotic syndrome is characterized by proteinuria, edema, hypoalbuminemia, and hyperlipidemia. A diverse range of disorders has been associated with nephrotic syndrome. Causes of the nephrotic syndrome vary and it can show a vigorous expression of medical conditions. Therefore, it is necessary to establish and treat the etiology of nephrotic syndrome. Differential diagnosis for nephrotic syndrome is challenging due to possibility of nephrotic-range proteinuria by monoclonal gammopathy of undetermined significance (MGUS). Following is a case of a 60-year-old male diagnosed with MGUS concomitant with nephrotic syndrome.

Case Description: A 60-old-male was hospitalized in the nephrology division due to proteinuria, microscopic hematuria, edema in his both ankles and decreased renal function. To rule out glomerulonephritis, blood tests, urinanalysis, kidney biopsy, serum protein electrophoresis (EP), random urine protein EP and immune fixation EP were performed. Blood test results revealed hypoalbuminemia and dyslipidemia. Initial urinary protein-to-creatinine ratio (UPCR) level was 12.5 g/gCr. In the serum protein EP, the M protein was 0.2g/dL, and in the urine protein EP, Bence-Jones proteinuria was detected. The kidney biopsy revealed positive staining for ihC-CD68 in intraglomerular histiocytes; a high possibility of histiocytic glomerulopathy. As this condition has been reported to be associated with underlying hematologic diseases, we requested a consultation with the hematology department for further evaluation. The hematologist performed a bone marrow examination to differentiate between MGUS and myeloma, and to determine the percentage of plasma cells. On bone marrow examination, plasma cells constitute 4.7% of the nucleated cells on aspirate smears. Additionally, a PET scan did not reveal any evidence of primary malignancy or distant metastasis. The patient was diagnosed with MGUS as M protein level was less than 3g/dL, plasma cell ratio was less than 10%, and there were no accompanying myeloma symptoms. Furthermore, it was confirmed that there were no treatable diseases associated with histiocyte-related malignancy or plasma cell disorders.

Discussion: This case showed that MGUS might be a rare cause of nephrotic syndrome and thorough differential diagnosis for myeloma could be necessary to ensure not to miss the optimal treatment timing.

SA-PO207

Membranous Nephropathy Masquerading as Amyloid Nephropathy in a Multiple Myeloma Patient

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Introduction: Renal dysfunction is a common presentation in many plasma cell dyscrasias, including multiple myeloma. In these disorders, malignant plasma cells proliferate and produce monoclonal immunoglobulins (Ig). These Igs can result in myeloma cast nephropathy, light chain deposition disease, and most commonly, amyloid light chain (AL) amyloidosis. In AL amyloidosis, Ig light chains deposit into renal parenchymal tissue and cause proteinuria and progressive chronic renal failure. Therefore, dysproteinemia-associated kidney disease should be suspected in any patient with plasma cell dyscrasia and renal dysfunction.

Case Description: The patient was a 73-year-old Caucasian female first diagnosed with multiple myeloma, Durie-Salmon Stage IIIA, in 2014. She underwent chemotherapy and autologous stem cell transplant (SCT) in 2015, with complete remission. After SCT, she continued on maintenance immunomodulatory agents with a good hematological response. In 2022 she developed progressive lower extremity edema, worsening pain, and increased fatigue. Workup revealed proteinuria of 7g/24hr and increased urinary M-spikes. Given clinical suspicion for dysproteinemia- associated kidney disease, the patient underwent a repeat bone marrow and kidney biopsy. The bone marrow biopsy revealed myeloma plasma cells occupying only 5% of marrow. Kidney biopsy revealed immune complex deposits involving capillary loops in a subepithelial distribution, a finding consistent with membranous nephropathy (MN). Notably, Congo red staining was negative and ruled out amyloid deposits. Anti-phospholipase A2 Receptor (PLA-2R) immunostaining was negative, and nerve epidermal growth factor-like 1 (NELL-1) immunostaining was positive. Age-based cancer screening was initiated, and NSAIDS were discontinued.

Discussion: Herein, we present a case of NELL-1 positive MN in a patient with multiple myeloma. Membranous nephropathy is the second leading cause of nephrotic syndrome. MN can be idiopathic, related to infection, medication use (NSAIDs), or autoimmune diseases. Notably, NELL-1-positive MN has been linked to solid organ malignancies. Management of these patients should emphasize discontinuing possible causative agents and a thorough cancer screening. This case represents the importance of a thorough workup of nephrotic syndrome, even in patients with a high pretest probability of AL amyloidosis.

SA-PO208

The Meaningful Medulla: Apolipoprotein A-IV Amyloidosis

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Introduction: Apolipoprotein A-IV (ApoAIV) amyloidosis is a rare disease affecting the kidney. The few existing case reports cite limited proteinuria with renal decline. We report a case of ApoAIV amyloidosis presenting with acute renal failure and nephrotic range proteinuria.

Case Description: A 67-year-old man with a history of gout presented with 3 months of fatigue and leg swelling after mildly symptomatic COVID-19. Labs revealed a serum creatinine of 11.5 mg/dl, increased from 1.3 mg/dl at baseline. He had no diabetes or significant nonsteroidal use and no family history of renal disease. Urine protein-creatinine ratio was 4.7 g/g. Ultrasound showed increased renal echogenicity without obstruction. Renal biopsy sampled only medulla and revealed interstitial Congo red positive amyloid deposits without light chain clonality (Fig. a-c). He received a short steroid taper and started hemodialysis. Subsequent workup was notable for normal serum kappa:lambda light chain ratio, serum and urine electrophoresis, bone marrow biopsy, and PET/CT. A second renal biopsy sampled only cortex and showed focal and segmental glomerulosclerosis (FSGS) with incomplete podocyte effacement, 70% interstitial fibrosis and tubular atrophy (IFTA), moderate arterio- and arteriolosclerosis, and no amyloid deposits (Fig. d-f). Mass spectrometry of the medullary deposits showed ApoAIV amyloid. He remains on dialysis and has been listed for transplant.

Discussion: ApoAIV amyloid is a rare cause of renal amyloidosis, often presenting as progressive kidney failure with minimal proteinuria. Renal pathology is notable for amyloid deposits restricted to the medulla with cortical sparing. This patient additionally showed chronic pathological changes and proteinuria here is presumed to be due secondary FSGS. This case highlights an unusual presentation with nephrotic syndrome and the importance of mass spectrometry for amyloid subtyping.

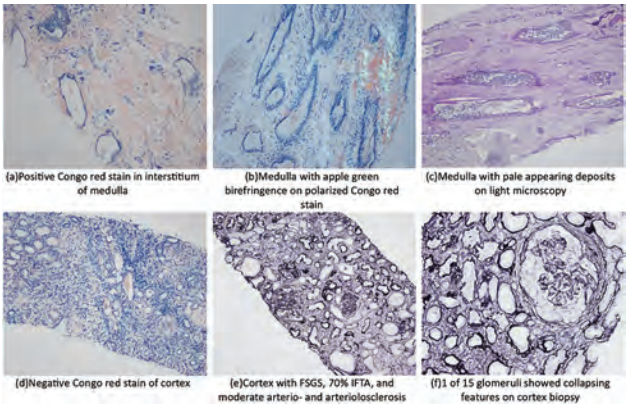

Figure: Biopsy Findings

SA-PO209

Abnormal Kidney Function in a Patient with Peri-Vascular AL Amyloidosis

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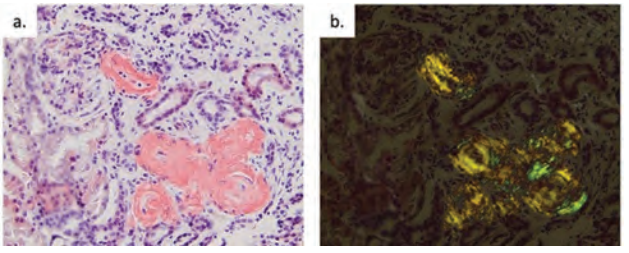
Introduction: Classic presentation of renal involvement of amyloidosis includes nephrotic syndrome due to amyloid fibril deposition in the glomerulus giving a "cauliflower" nodular appearance on light microscopy. Rarely amyloid deposits can be seen in a peri-vascular pattern and present with elevated creatinine and non-nephrotic range proteinuria. Patients with vascular limited amyloidosis are well described in AA amyloidosis but information about this pattern in AL amyloidosis is limited.

Case Description: We present a 71 year old white male with hypertension and IgG Kappa monoclonal gammopathy of undetermined significance present for screening colonoscopy. During the colonoscopy, a tubular adenoma was biopsied with findings consistent with AL kappa amyloidosis. On follow up evaluation, his creatinine rose from

a baseline of 0.9 mg/dL to 3.5 mg/dL. Upon chart review, 6 months prior his creatinine was already increased at 1.6 mg/dL. His work up was significant for a random urine microalbumin to creatinine ratio of 59 mg/g and urine protein to creatinine ratio of 742 mg/g. Serum kappa was 237 mg/l, serum Lambda 11.5 mg/l and Kappa/Lambda ration 20.6. Serum immunofixation Showed IgG Kappa monoclonal protein 673 mg/dl. Urine immunofixation showed monoclonal free Kappa light chains 73 mg/24hrs. Because of the degree of renal failure in the setting of non-nephrotic proteinuria and AL amyloidosis, he underwent renal biopsy. Renal biopsy confirmed AL kappa amyloid deposition in the vascular wall with little to no deposition in the glomeruli with 60% of cortex showing interstitial fibrosis and tubular atrophy.

Discussion: Immunoglobulin light chain amyloidosis can be deposited in diffuse pattern or vascular limited pattern. Our patient demonstrates a rare case of AL amyloidosis in a vascular limited pattern. He also had evidence of vascular involvement outside of the kidney as well. Further studies are needed to recognize this pattern of amyloid deposition.



Renal biopsy under Light microscopy shows amorphous hypoeosinophilic deposits in the vascular walls(a), which is positive by Congo red stain and shows bright apple-green birefringence under the polarized light (b).

SA-PO210

Membranous-Like Glomerulopathy with Masked IgG Kappa Deposits (MGMID) in a Patient with Sezary Syndrome

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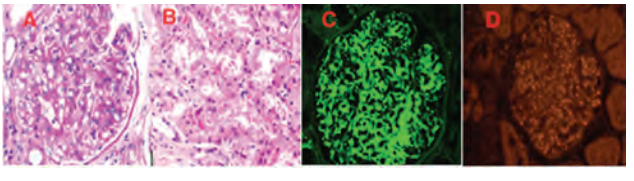
Introduction: MGMID is a rare pattern of glomerulonephritis (GN) that has recently been described in the literature and is characterized by sub-epithelial and/or mesangial immune deposits (Figure 1) that are masked to routine immunofluorescence but strongly stain for IgG and Kappa light chain after protease digestion. Commonly seen in young females < 40 years of age with a mean 24-hour proteinuria of 3.5 g (range 0.5-12.8) and have weakly positive antinuclear antibody titers. We present a patient with Sezary syndrome and nephrotic range proteinuria, and was found to have MGMID. To our knowledge, MGMID in Sezary Syndrome has not been reported yet.

Case Description: 65 year-old female with Sezary Syndrome on Mogamulizumab and type 2 Diabetes Mellitus (DM) presented for evaluation of albuminuria and was found to have nephrotic range proteinuria. She denied symptoms of volume overload. Her DM was well controlled. Her serological work up (Table 1) was negative. Kidney biopsy showed MGMID. She was treated with losartan and empagliflozin. Proteinuria decreased from 5.2 gm/day to 2.5 gm/day. Renal function continues to be stable, and she is currently continuing treatment with biweekly mogamulizumab for Sezary syndrome.

Discussion: This case emphasizes the need for research into this unique pattern of GN to figure out etiology and treatment. At this time, anti-proteinuric medications seem to be a reasonable option. Frequent presence of C3-only staining by routine immunofluorescence (IF) microscopy could lead to misdiagnosis as C3 GN in the absence of protease digested paraffin IF evaluation thereby underscoring the need to use paraffin IF. Serum Amyloid P (SAP) is also key to the diagnosis.

Laboratory values

Serum creatinine- 0.65 mg/dL (0.50-1.04); urine protein-creatinine ratio- 5.25 gm/gm; urine albumin-creatinine ratio- 3.7 gm/gm; urine analysis- 7 RBCs, 1 WBC; Hepatitis panel- Negative; Kappa-lambda ratio – 1.50; C3 and C4 are normal; ANA- negative; ANCA- negative; Hemoglobin A1c-6.3



A. PAS: Mild mesangial expansion within an enlarged glomerulus
B. H&E: Acute tubular injury with epithelial cell sloughing and epithelial simplification
C. Kappa (paraffin): Granular capillary and mesangial staining on protease digested paraffin-embedded tissue "unmasking" the immune deposits
D. Serum Amyloid P: Granular capillary and mesangial staining with SAP confirming the diagnosis of MGMID

SA-PO211

A Case of Membranous Nephropathy Secondary to Chronic Lymphocytic Leukemia in Association with a Novel Antigen

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Introduction: Membranous nephropathy (MN) is an uncommon presentation in patients with chronic lymphocytic leukemia (CLL). A novel target antigen has not been detected in MN associated with CLL. We describe a case of MN in association with CLL successfully treated with acalabrutinib and propose a novel antigen EGF-containing fibulin-like extracellular matrix protein (EFEMP2) as a possible target antigen in this disease.

Case Description: A 72-year-old male presented with bilateral lower extremity edema. His serum creatinine (Scr) was 1.7 mg/dL, serum albumin (SA) was 2.2 g/dL with 24-hour urine protein (24hUP) of 9g. Kidney biopsy revealed a PLA2R antibody negative and thrombospondin7A domain antibody negative MN with 1% of lymphocytic interstitial infiltrate consistent with CLL. He received rituximab (RTX) 1 g 2 doses 2 weeks apart. He went into partial remission with a 24hUP 1000 mg. He relapsed with reconstitution of B-cells due to which 2 additional RTX 1 g doses were given. However, he remained nephrotic despite RTX and a CD20+ B cell of 0. Subsequently, tacrolimus (TAC) 2 mg twice a day was initiated. He went into complete remission 1 year after TAC initiation but relapsed despite therapeutic levels of TAC. His 24hUP at the time of relapse was 13g with SA of 2.1 and Scr of 3.0. He received 2 doses of obinutuzumab 1 g 2 weeks apart for refractory MN. Despite that, he remained nephrotic over the next 4 months. He underwent a repeat kidney biopsy which demonstrated MN with 20% interstitial infiltrate that was PAX5, CD23, CD20 and CD5 stain positive consistent with clonal B-cell lymphoproliferation with features of CLL. Bone marrow (BM) biopsy showed CLL with 5-10% of the BM cellularity. CT chest and abdomen demonstrated widespread lymphadenopathy. Mass spectrometry of the first kidney biopsy showed moderate spectral count for EFEMP2 as the potential antigen in this case. He was initiated on Acalabrutinib 100 mg twice a day monotherapy. At last FU (12-month) he was in complete remission with Scr 2.4, 24hUP 370 mg and SA 4.5 without other therapies.

Discussion: Acalabrutinib monotherapy led to complete remission of MN with CLL. EFEMP2 is a possible target antigen in MN associated with CLL. Further studies are needed to confirm the presence of this antigen, disease association and outcomes in this patient cohort with MN and CLL.

SA-PO212

Clinical and Pathological Analysis of Five Cases of Immune Checkpoint Inhibitor (ICI)-Associated Membranous Nephropathy

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Introduction: Since ICIs have become a promising approach and have shaped a paradigm shift in tumor therapies, clinicians are increasingly confronted with immune-related adverse events (irAEs). Acute interstitial nephritis (AIN) is the most common renal irAE, and the treatment of ICI-AIN is based on ICI discontinuation and corticosteroids, which, in most cases, leads to recovery. On the other hand, ICI-associated membranous nephropathy (MN) is relatively rare, and its clinical and histological features and treatment remain unclear.

Case Description: We conducted a multicenter study on renal irAEs by the nationwide Onconephrology Consortium in Japan and analyzed five patients with ICI-associated MN. Patients received Nivolumab for NET, lung adenocarcinoma (two patients), ovarian cancer, and renal cell carcinoma. All patients presented with proteinuria after ICI initiation. Three patients responded to ICI discontinuation and immunosuppressive treatment, including corticosteroids and cyclosporine, and finally achieved remission, whereas two patients did not. The time from ICI administration to disease onset was longer (17.6 months) in treatment responders, whereas it was shorter (6 weeks) in patients with persistent proteinuria. Histologically, in all patients, immunofluorescence microscopy showed granular staining in the capillary walls for IgG (IgG1>4) and C3, and negative PLA2R staining, suggesting secondary MN. Two of the three remission cases showed granular staining for nerve epidermal growth factor-like 1 (NELL-1), which is frequently reported in malignancy-associated MN. The remaining remission case showed a lupus-like deposition pattern with high electron dense deposits in the subepithelial, intramembranous, and subendothelial areas. Two patients with persistent massive proteinuria showed negative NELL-1 staining and no dense deposit in subendothelial area.

Discussion: We revealed that the ICI-MN population is clinically and pathologically heterogeneous, and some patients showed proteinuria remission with treatment. The characteristics of slow-onset and NELL-1-positivity might be predictors of proteinuria remission. Our results speculated that ICI may induce underlying antibodies against tumor antigens such as NELL-1, leading to malignancy-associated MN, or may trigger immune responses, causing lupus-like MN.

SA-PO213

Bevacizumab-Associated Glomerular Microangiopathy: It's Not Always Thrombotic

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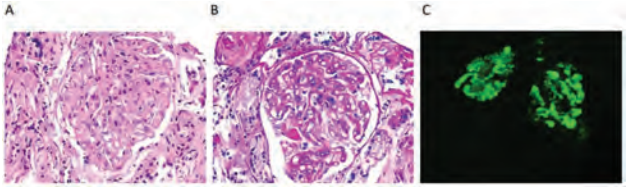
Introduction: Bevacizumab is a monoclonal antibody targeting vascular endothelial growth factor (VEGF). It has been associated with thrombotic microangiopathy (TMA) classically with fibrin thrombi on histology. Recent cases suggest a separate glomerular microangiopathy (GMA) with distinct histopathologic findings, including pseudothrombi, subendothelial dense materials, and full house pattern on immunofluorescence (IF). Herein, we describe a case of anti-VEGF therapy-induced GMA.

Case Description: A 52-year-old female with metastatic lung cancer for six years was referred for proteinuria. She was initially started on carboplatin, pemetrexed, and bevacizumab, then transitioned to bevacizumab monotherapy the past year. Other medical history includes undifferentiated mixed connective tissue disease. Urinary findings showed new-onset proteinuria with urine protein/Cr 5.1g/g with last urinalysis with no proteinuria four years ago. She had stable renal function creatinine 1.3-1.4mg/dl for the past two years, no thrombocytopenia, with normal haptoglobin and lactate dehydrogenase. Proteinuria workup was negative for complement abnormalities and monoclonal gammopathy. She had a positive ANA titer 1:320, with normal cryoglobulin and anti-double stranded DNA. Kidney biopsy showed (Figure) PAS-positive circulating materials and duplication of glomerular basement membrane on light microscopy. IF showed IgM and C3 staining. Electron microscopy showed subendothelial electron dense materials. These findings were most consistent with bevacizumab-associated GMA and bevacizumab was held. Proteinuria improved to 1.3g/g on follow up.

Discussion: As anti-VEGF therapy is commonly used, it is essential to recognize the glomerular findings of PAS-positive pseudothrombi that occur outside of previously reported fibrin thrombi. Pseudothrombi are thought to form as a result of VEGF inhibition, endothelial cell permeability and protein accumulation in the subendothelium. Differentiating this diagnosis from other causes of proteinuria is especially important in patients with history of autoimmune disease to avoid unnecessary use of immunosuppressants.



A. H&E. B. PAS. Pseudothrombi are seen in the capillaries. C. IF for IgM

SA-PO214

Calyceal Rupture of Horseshoe Kidney Following Chemotherapy

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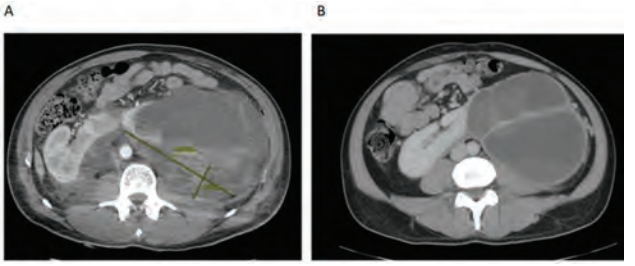
Introduction: Horseshoe kidney (HSK) is the most common congenital renal fusion anomaly. During embryogenesis, fusion of the kidneys prevents independent rotation and ascent. Vascular supply to HSK involves small arteries branching from aorta or renal arteries. Complications of HSK are pelviureteric junction obstruction, renal stones, infections, and tumors. Rupture of HSK has been reported in few case series and mainly due to trauma. Herein we describe a case of calyceal rupture of HSK in the setting of thrombocytopenia following chemotherapy.

Case Description: 40-year-old male with HSK was diagnosed with acute myeloid leukemia. Baseline imaging showed left renal atrophy with hydronephrosis. Labs showed normal renal function, creatinine 0.8mg/dl. He was started on induction chemotherapy with cytarabine and daunorubicin. Ten days later, he developed abdominal pain, distension, and hematuria. He was hypotensive, platelet count 25 K/mcL, hemoglobin 6.9 g/dL. CT scan showed increased severe left hydronephrosis, large volume hemorrhagic fluid with dilated calyces and large perinephric/retroperitoneal hemorrhagic fluid consistent with calyceal rupture. (Figure. A) He received 2 units of blood and platelets and underwent emergent interventional radiology (IR) embolization to multiple arterial branches of the kidney. Future cycles of cytarabine were carefully planned with heme, renal, urology, and blood bank.

Discussion: Bleeding and calyceal rupture was an unexpected potentially life threatening complication in this patient with known HSK. In patients planned for chemotherapy that can be complicated by thrombocytopenia, we recommend a) obtaining baseline renal imaging of HSK b) involving nephrology or urology early in the patient care and c) close monitoring and considering platelet transfusion with a higher platelet count threshold of 50K rather than 20K in collaboration with the blood bank given complicated arterial blood supply. In the event of hematuria and thrombocytopenia, we recommend early IR involvement for consideration of embolization.



(A) Calyceal rupture as described above (B) Repeat CT scan with decreased size of perirenal collection.

SA-PO215

Frequency and Characteristics of Chemotherapy-Associated Thrombotic Microangiopathy: Analysis from a Large Pharmacovigilance Database

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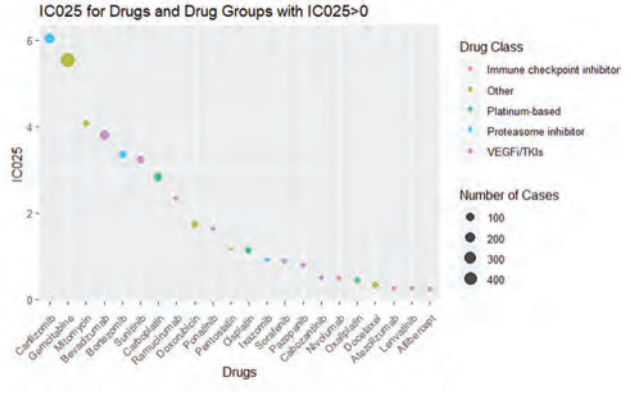
Background: Thrombotic microangiopathy (TMA) is a rare but detrimental complication of chemotherapy. We examined the frequency and characteristics of chemotherapy-associated TMA using a large pharmacovigilance database.

Methods: We utilized Vigibase, a global drug monitoring database containing over 30 million adverse reports, to examine the frequency of TMA after each of these drug classes: immune checkpoint inhibitors (ICPi), proteasome inhibitors (PI), platinums, tyrosine kinase inhibitors (TKI)/vascular endothelial growth factors inhibitors (VEGFi), conventional chemotherapy (gemcitabine and mitomycin) and other conventional chemotherapy (bleomycin, docetaxel, pentostatin and doxorubicin). The strength of association was determined using information component (IC), a measure of disproportionality between the observed and expected number of reports for a drug-event combination. A positive IC indicates that the number of observed reports exceeds the number of expected reports. We also analyzed characteristics of individual cases who had TMA.

Results: Between 2010 and 2023, there were 4703 reports of chemotherapy-associated TMA in 1099 individuals. The drugs with the highest IC were carfilzomib (5.92), gemcitabine (5.52), mitomycin (4.22), bevacizumab (3.87) and bortezomib (3.69) (**Figure 1**). Among cases where only a single agent was used, TMA was most common with conventional chemotherapy (n=379, 41.2%) followed by PI (n=228, 24.8%), TKI/VEGFi (n=185, 20.1%), and platinums. Time to TMA onset was shortest in patients receiving other chemotherapy (31 days, IQR 30-34) and PI (35 days, IQR 8-178) and longest for conventional chemotherapy (156 days, IQR 91-245). Though uncommon, ICPI-associated TMA was associated with the highest mortality rate (41%).

Conclusions: The drugs most commonly associated with TMA were PI, TKI/VEGFi and conventional chemotherapy. Time to onset was shortest for patients receiving other conventional chemotherapy, while ICPi-TMA was associated with the highest mortality.



SA-PO216

Rechallenging Gemcitabine with Eculizumab in a Patient with Gemcitabine-Induced Thrombotic Microangiopathy

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Introduction: Thrombotic microangiopathy (TMA) secondary to gemcitabine therapy (GiTMA) is a rare pathology that carries a poor prognosis, with nearly half of the cases progressing to end stage kidney disease. The mainstay of management is withdrawal of the offending drug and supportive care. Furthermore, a C5 inhibitor, eculizumab, has been successfully used in the treatment of GiTMA.

Case Description: A 78-year-old lady with a history of ovarian adenocarcinoma stage 4 on gemcitabine was referred for abnormal kidney function. She had CKD with a baseline serum creatinine (Scr) of 1.6-1.8 mg/dl. On this presentation, she had new onset hypertension and Scr was elevated to 2.8mg/dl. Hemoglobin was 8.7 mg/dl with elevated serum lactate dehydrogenase (539 U/L) and low haptoglobin (<20mg/dl). Urine analysis showed moderate proteinuria and hematuria with 30RBCs/HPF. Her spot urine protein-creatinine ratio (UPCR) was elevated at 1.5. A kidney biopsy was pursued which showed chronic thrombotic microangiopathy with severe glomerular capillary wall remodeling, 20% global glomerulosclerosis. Work up for causes of TMA was done including ADAMTS-13 level, antinuclear antibody level, HIV, direct antiglobulin levels, serum complement 3, serum complement 4, anti-neutrophilic cytoplasmic antibody levels and atypical HUS panel which came back unremarkable. Gemcitabine was thought to be the culprit medication and was withheld. Scr did not improve and the patient was initiated on eculizumab with an improvement in Scr to 2mg/dl. After a multidisciplinary discussion with oncology and the family, and based on the premise that gemcitabine was the only drug working for adenocarcinoma, it was decided to re-challenge Gemcitabine concurrently with eculizumab therapy. 3 months follow up showed Scr stable at 1.8mg/dl, normal LDH, Haptoglobin and a UPCR at 0.1.

Discussion: TMA secondary to Gemcitabine therapy is a rare condition. Physicians should have a high index of suspicion to diagnose GiTMA early in the course of the disease. Mainstay of management is discontinuation of gemcitabine and supportive care. Eculizumab has been tried in GiTMA with great success in improving hematologic and kidney parameters. However, continuation of Gemcitabine along with Eculizumab therapy is a novel strategy that has limited data. Further research is needed to validate this strategy.

SA-PO217

Gemcitabine-Induced Thrombotic Microangiopathy Treated with Eculizumab in a Patient with Pancreatic Cancer: A Case Report

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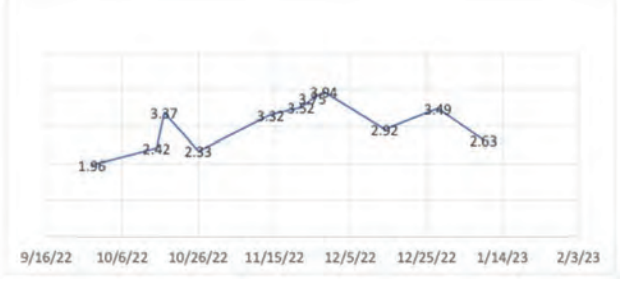
Introduction: Thrombotic microangiopathies (TMA) are characterized clinically by the presence of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, and ischemic organ injury. Drug-induced thrombotic microangiopathy (DITMA) is often under-recognized and under-reported. The incidence of gemcitabine-induced TMA (GITMA) has been reported to be between 0.02% and 2.2%.

Case Description: 67-year-old female with history of DM, Hypertension, CKD (B/L creat 1.8-2.0), Ca Pancreas s/p Whipple's on neoadjuvant chemotherapy (FOLFIRINOX followed by Gemcitabine/Abraxane) was admitted with history of frequent falls and worsening left upper and lower limb weakness for 3 days. She had received gemcitabine with cumulative dose of 15,000 mg/m2 for the preceding 1 year, with last dose 2 months prior to her presentation. On admission, her BP was 170/90 mm Hg, serum creatinine 3.5 mg/dl, serum albumin 3.1 g/dl, worsening anemia (hemoglobin 7.1 g/dl), thrombocytopenia (platelet count 89,000/mm^3), LDH 447 IU/L, with schistocytes on blood film. Urinalysis revealed RBC casts with urine microalbumin-creatinine 2400 mg/gm. ANA, ANCA, hepatitis B and C serologies were negative and complements normal. A diagnosis of GITMA was onsidered and she was stabilized with conservative measures. She was started on treatment with Eculizumab with which her renal functions improved with stable Hb.

Discussion: TMA occurring in a patient with a malignancy can be either malignancy or drug-induced. Mechanism of drug-induced TMA can be direct endothelial damage (type 1, dose dependent) or immune-mediated through the development of drug-dependent autoantibodies (type 2, none-dose dependent). Treatment of drug-induced TMA includes supportive therapy and withdrawal of the drug. Eculizumab has shown promise as an effective therapy for GITMA.



SA-PO218

Renal-Limited Thrombotic Microangiopathy from Bleomycin-Etoposide-Cisplatin Chemotherapy in a Young Male with Testicular Cancer

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Introduction: Thrombotic microangiopathy (TMA) is a systemic illness stemming from endothelial dysfunction. However some patients present with only renal-limited. In the context of chemotherapy, TMA is typically drug induced, classically associated with therapies such as gemcitabine and mitomycin with a delayed onset or with newer therapies such as tyrosine kinase inhibitors and anti-vascular endothelial growth factor (anti-VEGF) therapies any time during therapy. TMA can also be related to malignancy alone. However TMA has rarely been described in the context of testicular cancer and its therapies.

Case Description: We present a 33 year old caucasian male with past medical history of type 1 diabetes mellitus, CKD stage 3a/A3 due to genetic focal segmental glomerulosclerosis (FSGS) mitochondrial disorder with maternal inherited diabetes and deafness (MIDD) syndrome. His baseline Cr was 1.7 mg/dL with proteinuria of 4-5 grams over 24 hours despite maximal antiproteinuric therapy. He presented to the hospital with worsening edema, 20 pound weight gain, and rise in creatinine to 3.5 mg/dL. Proteinuria had dramatically increased to 11 g in 24 hours with microscopic hematuria. He was recently diagnosed with testicular cancer just two months prior and was now status post radical orchiectomy and is on cycle 2 of bleomycin, cisplatin, and etoposide. Just two weeks prior he was admitted for shiga toxin negative diarrhea and neutropenic fever in the setting of significant pancytopenia. Renal biopsy revealed active TMA with endothelial cell swelling seen on electron microscopy with stable moderate foot process effacement with mild to moderate chronic kidney disease. Unfortunately, due to his hypervolemia, he was initiated on renal replacement therapy followed by eculizumab with hopes his renal function would recover.

Discussion: Drug-induced TMA (DITMA) accounts for 10-13% of all TMA cases however its pathophysiology is unclear. Drugs which do not cause TMA when administered alone may do so when combined with other nephrotoxic agents. This is the second reported case of bleomycin-etoposide-cisplatin therapy related TMA. Understanding which chemotherapeutic combinations increase risk for TMA and how they affect the complement cascade can help prognosticate the degree of renal recovery and after treatment using complement inhibition therapy.

SA-PO219

Renal-Limited Thrombotic Microangiopathy due to Anti-VEGF/Tyrosine Kinase Inhibitor (TKI) Immunotherapy for Metastatic Renal Cell Carcinoma Presenting as Nephrotic Syndrome

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Introduction: Vascular endothelial growth factor (VEGF) inhibition may result in proteinuria, worsening hypertension, chronic kidney injury or glomerular disease. Recently, systemic VEGF inhibition has been reported to cause nephrotic disorders and thrombotic microangiopathy (TMA). We present a unique case of renal-limited TMA presenting as nephrotic syndrome in a patient on anti-VEGF/TKI immunotherapy for metastatic renal cell carcinoma.

Case Description: A 73-year-old male with history of metastatic renal cell carcinoma, managed with combination immunotherapy with axitinib and pembrolizumab, who presented with generalized swelling, increasing weight gain up to 30 lbs, heavy proteinuria, hypoalbuminemia concerning for nephrotic syndrome. Workup showed urine protein creatinine ratio of 14. Renal biopsy revealed renal-limited thrombotic microangiopathy, most likely attributed to anti-VEGF/TKI therapy. He had no evidence of immune complex deposition on electron microscopy; however, noted to have extensive foot process effacement which accounted for heavy proteinuria. His anti-VEGF/TKI therapy was discontinued and he is maintained on losartan and dapaglifozin with improvement in urine protein creatinine ratio to 7g upon followup.

Discussion: Our case suggests that renal involvement in patients on anti-VEGF/TKI immunotherapy may manifest as nephrotic-range proteinuria and clinically nephrotic syndrome with renal-limited histological TMA and cessation of anti-VEGF/TKI therapy results in significant improvement in proteinuria with possibility of re-challenge with immunotherapy. In such cases, other differentials may include minimal change disease or collapsing focal segmental glomerulosclerosis (FSGS). Cessation of anti-VEGF/TKI therapy results in significant improvement in proteinuria with possibility of immunotherapy re-challenge in the future. In case of concerns for renal sequelae with anti-VEGF/TKI involvement, prompt referral to nephrology for further evaluation is necessitated for appropriate and timely management.

SA-PO220

Renal Limited Thrombotic Microangiopathy (TMA) Secondary to Chronic Lymphocytic Leukemia (CLL): A Case Report

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Introduction: Chronic lymphocytic leukemia (CLL) is a monoclonal B cell lymphocytosis that produces a nephrotoxic monoclonal immunoglobulin (MIg). Complement-TMA and C3 Glomerulonephritis with systemic manifestations have been rarely reported associated to CLL. We report the first case of renal limited TMA secondary to CLL.

Case Description: 70-year-old female with a history of type 2 diabetes exceeding10 years, hypertension (HTN), and CLL diagnosed nine years prior presented with massive proteinuria with a UPCR a 10g/g, increased from 1.9 g/g six months prior along with lower extremity edema. The creatinine level was 0.84 mg/dL (eGFR around 74 mL/min/m^2) and at baseline. Her CLL had never been treated as she had been considered asymptomatic despite having a WBC count above 200000. Her UA showed pyuria and microscopic hematuria. The serological work-up was unrevealing except for trace cryoglobulin IgG lambda with a kappa lambda ratio at 0.34. A total body CT scan done 5 months prior to presentation had shown stable mild retroperitoneal lymphadenopathy and unchanged mild splenomegaly. A kidney biopsy showed early nodular sclerosis likely from diabetes along

with endothelial injury with glomerular basement membrane duplication and endothelial swelling suggestive of TMA on electron microscopy. Pronase immunofluorescence studies were negative for immune deposits. There was no evidence of peripheral TMA with stable hemoglobin and platelet counts and normal LDH and reticulocyte count. Complement studies revealed unregulated activity at the C3 and C5 convertase level with depleted CH50 levels. The patient's HTN and proteinuria were initially managed with losartan 50 mg daily, empagliflozin 10 mg daily and furosemide 40 mg daily, however as her UPCR increased to 17g/g, her nephrotic syndrome was deemed to be secondary to her CLL and she was initiated on ibrutinib. The proteinuria improved and is now 4.82 g/g three months later. In addition, her WBC count went down to 92.8k.

Discussion: The significant improvement in proteinuria after initiation of ibrutinib and the unregulated activity at the C3 and C5 convertase level suggests renal endothelial injury secondary to activation of the complement pathway by the MIg. Clinicians need to be aware of this potential complication of CLL to initiate treatment promptly.

SA-PO221

Renal TMA Presenting After Eight Years of Sunitinib Therapy

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Introduction: Thrombotic microangiopathy (TMA) is a rare side effect of Tyrosine Kinase Inhibitor (TKI) therapy that has almost always been reported as occurring within the first year of TKI initiation, with very few cases reported between two-three years. We report a case of renal-TMA occurring after eight years of TKI therapy.

Case Description: A 70-year-old male was seen for worsening renal function and edema in early 2022. He had a history of metastatic renal clear cell carcinoma treated with left renal resection in 2013 and was started on Sunitinib (TKI) in 2014. His baseline serum creatinine was 151 umol/L and peaked to 260 umol/L with urine protein: creatinine ratio (UPCR) of 857 mg/mmol at the time of referral. Physical exam revealed hypertension and bilateral lower extremity pitting edema. Rheumatologic work up, complement levels, and paraproteinemia panel were unremarkable. Renal biopsy revealed hyaline occlusive glomerular microangiopathy. Sunitinib was discontinued and within one week, his serum creatinine decreased from 260 umol/L to 182 umol/L. He was switched to Nivolumab in late 2022. After a year of discontinuation of Sunitinib, his serum creatinine and UPCR decreased from 260 umol/l and 857 mg/mmol respectively at referral, to 135 umol/l and 50 mg/mmol. The only other treatment that was leveraged was the optimization of his renin-angiotensin blockade using Irbesartan. No recurrence of renal dysfunction was noted after a year of follow-up and his hypertension and edema had resolved.

Discussion: To the best of our knowledge, our case is the first to highlight renal TMA occurring after three years TKI therapy. In previous case reports, renal recovery was seen with simply discontinuing the medication and supportive care such as renin-angiotensin inhibition, as was seen with our case. Some reports have used steroid therapy however these cases have almost always included stopping the offending agent as well. Mixed results have been reported with re-introducing TKI therapy. Take-away points from this case include: (1) Renal TMA can occur even after many years of TKI therapy, and should be monitored for as a possible long term side effect (2) Management involves obtaining renal biopsy, stopping the TKI, and supportive care to optimize hypertension and proteinuria (3) Further work is needed to understand if steroid treatment is effective and if re-introducing TKI therapy is safe

SA-PO222

Nirmatrelvir Plus Ritonavir-Induced Acute Interstitial Nephritis

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Introduction: Drug induced acute interstitial nephritis is an idiosyncratic delayed type IV hypersensitivity reaction that manifests 7-10 days after exposure to the culprit drug. We present a case of biopsy-proven drug-induced acute interstitial nephritis in a patient who received oral antiviral therapy for the treatment of COVID-19

Case Description: 73y woman with CKD stage II and resected HER 2+ Stage IIA Lung Adenocarcinoma actively treated with fam-trastuzumab and deruxtecan since December 2021, referred to our nephrology clinic for AKI noted on routine testing. One-year prior referral, baseline renal function was at 1.0-1.2 mg/dl. During initial encounter, patient reported traveling outside the US where she contracted COVID-19 and was given Paxlovid for treatment. Initial referral labs revealed WBC 8500cells/mm^3 and 1.9% eosinophils, SCr 1.8mg/dl, BUN 38mg/dl and renal ultrasound with normal echogenicity of both kidneys. Follow up labs after initial encounter showed SCr of 2.3mg/dl, BUN 36 and UA with moderate leukocyte esterase, negative nitrite, 4-6 RBC per hpf, >50 WBC cells/hpf and negative urine culture. Treatment with prednisone 60mg daily was started with plan to taper based on initial response. Over the next 3 months her SCr returned to 1.4 mg/dl while receiving tapering doses of prednisone

Discussion: Nirmatrelvir plus Ritonavir (Paxlovid™) was developed for the treatment and post exposure prophylaxis of COVID-19. While the exact mechanism for its association with acute interstitial nephritis is unknown, there is a distinctly dysregulating immunological response primarily a T cell–driven process. The withdrawal of the causative drug is fundamental as an initial step in management however in some cases corticosteroid therapy is initiated due to moderate to severe renal injury based on their potent anti-inflammatory effects and prevention of irreversible structural changes resulting in renal fibrosis

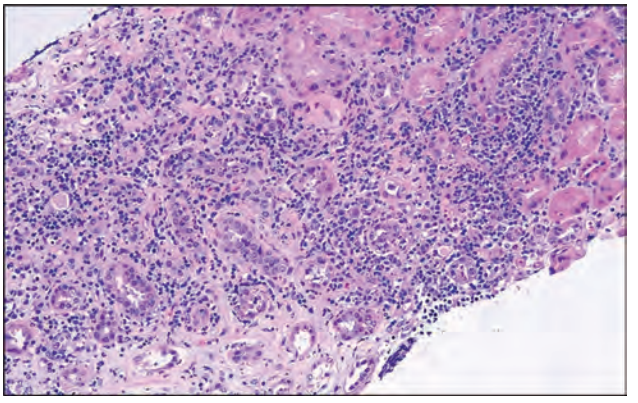

Fig1. Renal cortical tissue shows fairly diffuse active and chronic tubulo-interstitial inflammation. HEx200

SA-PO223

An Unusual Case of Kidney Infiltration by Heavy Chain Disease with Lamellar Inclusion Bodies

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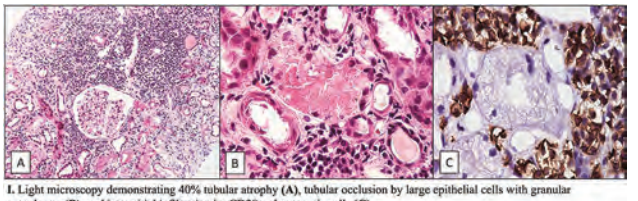
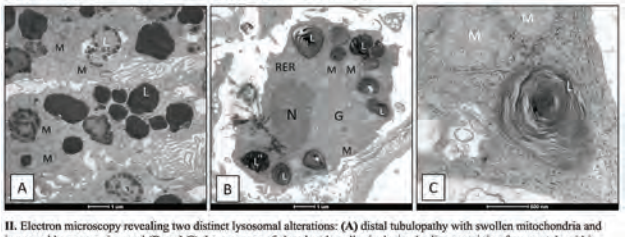
Introduction: Heavy chain diseases (HCDs) are rare B-cell proliferative disorders characterized by the production of a monoclonal protein composed of incomplete immunoglobulin heavy chains. To the best of our knowledge, we report the first case of renal HCD infiltrated by plasmacytic cells exhibiting distinctive lamellar inclusion bodies.

Case Description: A 65-year-old woman with systemic lupus erythematosus in remission with hydroxychloroquine and low-dose prednisone presented with fatigue, weakness, weight loss, and shortness of breath. Examination revealed pallor, hepatosplenomegaly, and inguinal lymphadenopathy. Laboratory tests showed anemia (Hb 5.2 g/dL), elevated creatinine (3.9 mg/dL, baseline 0.6), nephrotic-range proteinuria (6.2 g/day), and increased IgG levels (12,267 mg/dL). Imaging demonstrated bilateral kidney enlargement. Extensive workup for multiple potential etiologies was negative. Further analysis revealed a spike in the beta-1 region in serum protein electrophoresis and gamma-heavy chain presence in serum and urine immunofixation, with a normal free k/l light chain ratio. Bone marrow aspirate showed 6% plasmatic cells and a B-cell lymphoproliferative process with plasma cell differentiation and gamma heavy chain expression without light chain restriction. A kidney biopsy was performed (Fig 1). The patient underwent treatment with cyclophosphamide, bortezomib, and dexamethasone, resulting in kidney function improvement.

Discussion: The observed lamellar bodies are residual lysosomes often seen in lysosomal storage diseases, in subjects receiving lysosomotropic drugs, and rarely in plasma cell dyscrasias. In this case, they were located in the cytoplasm of plasma cells rather than in the tubules or podocytes, corresponding to heavy chain deposits. Kidney involvement is uncommon in HCDs, and its coexistence with lamellar inclusion bodies is even rarer, providing additional insights into this disease.



I. Light microscopy demonstrating 40% tubular atrophy **(A)**, tubular occlusion by large epithelial cells with granular cytoplasms **(B)**, and interstitial infiltration by CD38+ plasmacytic cells **(C)**.



II. Electron microscopy revealing two distinct lysosomal alterations: **(A)** distal tubulopathy with swollen mitochondria and increased lysosome size, and **(B and C)** the presence of abundant lamellar inclusion bodies containing few crystals within plasma cells.

Kidney Biopsy

SA-PO224

Atypical Hemolytic Uremic Syndrome (aHUS)/TMA in Genetically Predisposed Patients Treated with a Novel Agent for Relapsed/ Refractory Multiple Myeloma

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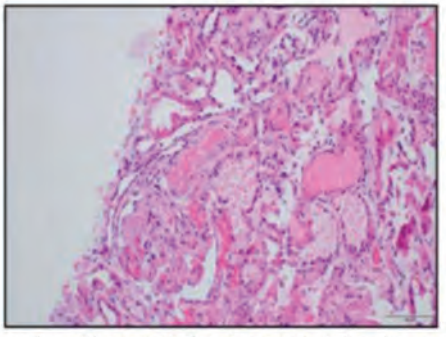
Introduction: A number of therapies are being studied to treat relapsed/refractory multiple myeloma (RRMM). Modakafusp alfa (TAK-573) is a novel candidate for treating RRMM. It is a first-in-class immunocytokine that delivers interferon alpha-2b (IFNα2b) to CD38+ cells, showing promising anti-myeloma activity.

Case Description: Here we present two adult males, ages 46 (Patient 1) & 56 (Patient 2) seen at MD Anderson Cancer Center, both with history of RRMM & enrolled in clinical study 2022-0497 G2A4 carfilzomib and modakafusp alfa. Both presented with oliguric AKI requiring RRT, new-onset thrombocytopenia, schistocytosis & transaminitis with elevated LDH. Both had genetic testing & kidney biopsy while admitted. Patient 1 is heterozygous for the extended CFH-H3 risk haplotype, consistent with increased risk for development/progression of atypical hemolytic uremic syndrome (aHUS). The kidney biopsy showed acute/active thrombotic microangiopathy (TMA)-like changes. Patient 2 is heterozygous for a CFHR1-3 deletion (strongly suggesting a large contiguous deletion of both CFHR1 and 3 genes). Patient 2's kidney biopsy also showed findings consistent with TMA features. Both patients had hemodialysis & eculizumab while inpatient & are continuing on hemodialysis on an outpatient basis.

Discussion: Both patients were recently started on carfilzomib & modakafusp alfa, a relatively new phase I/II clinical trial. Preliminary results from 2021 show modakafusp alfa caused side effects such as neutropenia, thrombocytopenia & mild reactions post-infusion. aHUS/TMA with AKI from modakafusp alfa has not previously been reported to our knowledge. Case reports of aHUS/TMA from carfilzomib do exist, however. We conclude that it is reasonable to perform genetic testing prior to initiating treatment with modakafusp alfa +/- carfilzomib, to mitigate the risk of aHUS/TMA as seen in our two patients.



H&E: glomerulus with congested and somewhat shrunken appearance, arteriole with fibrinoid necrosis, tubular epithelial injury.

SA-PO225

Digital Necrosis: Presenting Feature of Type 1 Cryocrystalglobulinemia

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Introduction: Type I cryoglobulinemia involves cryoprecipitable monoclonal Igs associated with multiple myeloma, Waldenstrom macroglobulinemia, or chronic lymphocytic leukemia (CLL). Some cryoglobulins can "crystalize", causing vaso-occlusive gangrene in addition to a glomerulopathy with a specific pattern of injury.

Case Description: A 64-y/o man presented with a purpuric ankle rash, and bluish discoloration of his fingers and toes (Fig. 1). Labs revealed AKI with pancytopenia, microscopic hematuria, and a urine Alb/Creat ratio of 500 mg/g. He had negative or normal testing for hepatitis B and C, HIV, Protein C and S activity, ANA, AntiDS-DNA, anti-scleroderma and anti-centromere antibodies, C3 and C4 levels, RF, antiphospholipid Abs, and ANCA. Serum immunofixation showed a monoclonal IgG kappa paraprotein. Cryoglobulin (CG) testing was negative X2. A renal bx demonstrated an MPGN pattern of injury with vascular thrombi, both with IgG kappa restricted staining on immunofluorescence. Electron micrographs revealed subendothelial and intraluminal electron-dense deposits with crystalline lattice-like substructures c/w cryocrystalglobulinemia (Fig. 1). Repeat CG testing showed a cryocrit of 5% that was also IgG kappa restricted on immunofixation. He received plasmapheresis and steroids. He developed AKI and required HD for a week after which his AKI resolved. He was eventually diagnosed with CLL and received clone-directed therapy with acalabrutinib. His digits required amputation, but his kidney tests normalized.

Discussion: The majority of CGs are "mixed" Type 2 & 3 associated with infections and autoimmune dz. Type 1 cryoglobulinemia is from a paraprotein produced by a plasma cell dyscrasia or a lymphoproliferative disorder. When the CGs form a crystalline substructure, they can cause vascular occlusion (his digits). Fortunately, his renal disease remitted. His presentation of digital ischemia suggested vasculitis, catastrophic anti-phospholipid syndrome, and cryoglobulinemia. The dx in this case ultimately depended on a renal biopsy and demonstrating the CG, a test that requires proper delivery and measurement.

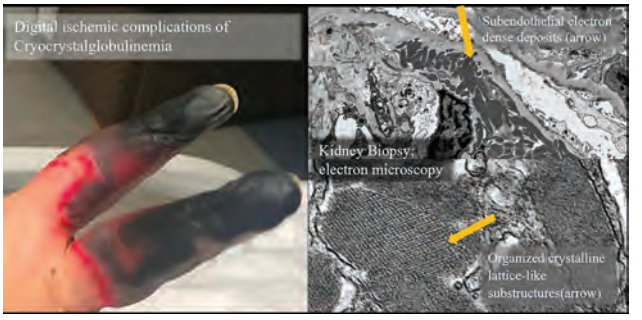

Fig. 1.

SA-PO226

Unmasking the Invisible: A Puzzling Case of Type 1 Cryoglobulinemic Glomerulonephritis with Hidden Immunoglobulin Deposits

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Introduction: Monoclonal immunoglobulins (Ig) occasionally yield false negative results on standard immunofluorescence (IF). Identifying these Ig is vital for determining the patient's disease pathogenesis and therapeutic intervention.

Case Description: A 60-year-old female presented with fever, dysuria, and flank pain. She was diagnosed with *E. coli* pyelonephritis and received ceftriaxone. Her symptoms resolved after a week, but she developed oliguria without urinary tract obstruction seen on ultrasound. Her urine examination revealed dysmorphic red blood cells and urine protein creatinine index of 5.5 g/g. Lab tests showed low C3, C4 levels, detectable cryoglobulins, elevated ASO titer and anti-DNase B. Serum protein electrophoresis (SPEP) showed IgG lambda monoclonal protein. Considering the patient's history of HCV infection, mixed cryoglobulinemia was suspected. A renal biopsy demonstrated diffuse endocapillary proliferation and focal membranoproliferative glomerulonephritis (MPGN) pattern with focal wire loops and hyaline thrombi. IF stains revealed isolated granular staining for C3 in the mesangium and capillary loops. Electron microscopy showed electron dense deposits in the mesangium and subendothelium with vague microtubular structures (20–25 nm). To differentiate GN with predominant C3 (post-infectious GN) from type I cryoglobulinemic GN with masked monotypic Ig deposits, paraffin IF with pronase digestion was performed. This method revealed the presence of IgG, lambda, C3, while kappa remained negative, leading to the final diagnosis of type I cryoglobulinemic GN. Bone marrow biopsy showed a normocellular trilineage marrow. The reatment was switched to a bortezomib-based regimen. Later her urine output improved, and serum creatinine declined to 2.25 mg/dL. Subsequent SPEP detected no monoclonal protein.

Discussion: High suspicion is necessary to avoid misdiagnosis in this case. Positive ASO and anti-DNase B, coupled with C3 dominant GN on renal biopsy, could have been erroneously diagnosed as post-infectious GN. Our case highlights the importance of performing paraffin IF with pronase digestion to detect masked Ig. This is crucial for patients whose kidney biopsy shows C3 dominant GN or MPGN pattern with concurrent monoclonal gammopathy or microscopic characteristics of cryoglobulinemic GN.

SA-PO227

Cryoglobulinemic Glomerulonephritis in the Setting of Chronic Lymphocytic Leukemia

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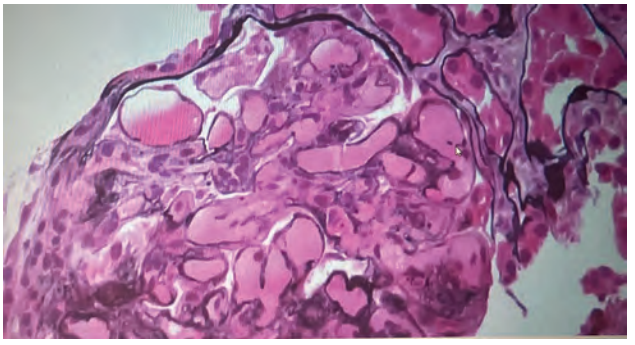
Introduction: Cryoglobulinemia is characterized by the presence of immunoglobulins that precipitate in vitro at temperatures below body temperature. End organ damage can occur due to hyperviscosity syndrome, more specifically in the kidney due to the formation of intracapillary (known as cryo-plugs), capillary wall and mesangial cryoglobulin deposits. This is referred to as cryoglobulinemic glomerulonephritis.

Case Description: A 76-year-old female with a history of biopsy proven chronic lymphocytic leukemia presented with dyspnea, edema, and weight gain. Evaluation was notable for hematuria and proteinuria, quantified at 5.8g/g. Serologies revealed an elevated C3 and undetectable C4. Serum cryocrit was 50 UL cryo/ml serum and serum viscosity was 1.4. Cryoglobulin isotyping showed monoclonal IgM-kappa (gamma), faint monoclonal IgM-kappa (beta) and faint monoclonal IgA-lambda (gamma) most consistent with type I cryoglobulinemia in view of her chronic lymphocytic leukemia. Kidney biopsy was obtained demonstrating prominent immune complex deposition in the form of numerous hyaline pseudothrombi with frequent duplication of the glomerular basement membrane most consistent with membranoproliferative glomerular injury. Patient met criteria for plasmapheresis due to the significantly elevated cryocrit and underwent one session. Afterwards, additional plasmapheresis was held and she was started on cyclophosphamide and rituximab. Patient continued to deteriorate and died due to respiratory failure.

Discussion: Type I cryoglobulinemia typically causes end organ damage through hyperviscosity with type II and III cryoglobulinemia doing so through vasculitis.

Atypical to our case was a serum viscosity at the lower limit of normal. We hypothesize that the degree of cryo-plugging was so high it resulted in hyperviscosity at the level of the glomerular capillary that was not detectable in the blood. The possibility of this constellation is important for clinicians to be aware of.



Cryo-plugging on light microscopy H&E stain

SA-PO228

Type I Cryoglobulinemic Glomerulonephritis in Solitary Kidney

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Introduction: Cryoglobulinemia (CG) is a disease in which immunoglobulins precipitate in serum at lower temperatures and then redissolve once warmed again. Glomerulonephritis (GN) is a common complication with type II and III CG but rarely documented with type I. We describe a patient with type I CG (IgM) induced GN without identified source.

Case Description: 66-year-old male with past medical history of a. fib, OSA, and solitary right kidney s/p nephrectomy at age 8 presenting with lower extremity edema and dyspnea on exertion found to be in hypertensive crisis. He denied hematuria or dysuria. Initial blood pressure of 212/104, started on nitroglycerin. Urinalysis with 2+ blood, >20 RBC, >500 protein, and granular casts. BMP electrolytes normal, BUN 37 mg/dL, creatinine 1.63 mg/dL (baseline 1.02). Normal TSH, metanephrines, and cortisol levels. Hepatitis panel negative. Negative renal arterial doppler. Nephritic workup with low C3, normal C4, and nephrotic range proteinuria (5.41 grams). SPEP with IgM monoclonal protein. Bone marrow biopsy negative, peripheral cytology with monoclonal B-cell population (CD5+, CD23-), cytogenetics negative. Renal biopsy IF studies IgM 3+, IgG 1-2+, C3 1-2+, and lambda 1+. EM with membranoproliferative pattern, focal hyalin thrombus, segmental fusion of foot processes, paired tubular structures identified in subendothelial spaces and pseudo-thrombus consistent with cryoglobulinemic GN. No subepithelial deposits. R-CHOP started for suspected lymphoma. Developed vasculitic lesions in mid-2021, C3 and C4 low, cryocrit positive for the first time. Transitioned to bendamustine with plasmapheresis. Second opinion felt lymphoma unlikely and started Velcade. Third opinion recommended ibrutinib with plasmapheresis for 4 weeks, renal function remains stable, blood pressure controlled but IgM band on serum immunofixation and urine sediment remain active.

Discussion: GN is common in mixed CG but extremely rare in type I, with our literature review showing 11 cases. Of those, 9 were due to hematolymphoid disease and the remaining 2 are IgG monoclonal bands. Our case shows that type I IgM CG can present with renal involvement and should be evaluated for in patients with unexplained AKI and positive IgM monoclonal protein with kidney biopsy. Furthermore, this case is unique in showing that renal biopsy can be done safely in a solitary kidney in order to have an accurate diagnosis.

SA-PO229

Monoclonal Gammopathy of Renal Significance (MGRS): An Alternative Pathway to C3 Glomerulonephritis (C3GN)

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Introduction: C3 glomerulonephritis (C3GN) is characterized by dysregulation of the alternative complement pathway and is commonly accompanied by a monoclonal gammopathy in older patients. These associated paraproteins are now increasingly recognized as the underlying drivers of complement dysregulation in many cases, which has important implications regarding treatment.

Case Description: An 86 year old male with a past medical history of atrial fibrillation and congestive heart failure presented with a ground level fall, sustaining a small subdural hematoma. On arrival, he was hypotensive secondary to atrial fibrillation with a slow ventricular response requiring an implantable pacemaker. He was hypoxic due to pulmonary edema seen on imaging. Labs showed a rise in serum creatinine to 3.89 mg/dl from a baseline of 1.0 mg/dl. Urine dipstick showed 3+ hematuria and a urine protein to creatinine ratio was measured at 2 g/g. He was presumed to have acute tubular injury and received intravenous diuretics with improvement in hypoxia. Nephrology was consulted to assist with diuretic management. Manual urine microscopy was performed which revealed numerous dysmorphic red blood cells (RBCs). Serologic testing was unremarkable except for a monoclonal IgG kappa paraprotein identified on immunofixation. We ultimately decided to pursue a kidney biopsy which revealed a C3 dominant crescentic glomerulonephritis with mesangial proliferation and rare mesangial electron dense deposits. The bone marrow biopsy showed hypercellularity with a polyclonal plasmacytosis. He was diagnosed with C3GN with monoclonal gammopathy and was started on treatment with bortezomib and steroids.

Discussion: We present a challenging case of acute kidney injury in an elderly male. Ultimately, the finding of dysmorphic RBCs on urine microscopy informed our decision to pursue a kidney biopsy, leading to a diagnosis of C3GN with monoclonal gammopathy. Recent evidence suggests that in many cases, dysregulation of the alternative pathway is driven by a monoclonal paraprotein. Furthermore, treatment directed towards the underlying hematologic disease has shown promise in achieving a renal response. For this reason, we elected to pursue treatment targeting the underlying hematologic disorder.

SA-PO230

Successful Obinutuzumab-Based Treatment of Chronic Lymphocytic Leukemia (CLL)-Associated Membranoproliferative Glomerulonephritis (MPGN) Lesion with Kidney Infiltration

Andrea Broka, Kuang-Yu Jen, Nasim Wiegley. *UC Davis Health, Sacramento, CA.*

Introduction: Chronic lymphocytic leukemia (CLL) is a mature B-cell neoplasm characterized by the accumulation of monoclonal cells in the blood and bone marrow with an indolent course. Extramedullary CLL with kidney involvement is rare, and treatments are based on retrospective studies and expert opinion. We present a patient with CLL-associated kidney involvement and successful complete remission after treatment with an Obinutuzumab-based regimen.

Case Description: A 68-year-old White man with CLL, chronic kidney disease and heart failure who presented with worsening edema and kidney function on outpatient labs. Workup showed creatinine (Cr) of 4.4 mg/dL (baseline 1.4) with urine protein/creatinine ratio >5g/g, white blood cell count of 83 x10^9/L (baseline) (Fig 1). Complement C3 was low, and Hepatitis panel, HIV, Rheumatoid factor, cryoglobulin, and C4 were negative. Kidney biopsy showed a membranoproliferative glomerulonephritis pattern of injury with cellular crescents, possible cryoglobulins, and focal involvement by CLL cells (Fig 2). Obinutuzumab-based therapy in combination with steroids, cyclophosphamide, and vincristine resulted in an improvement of kidney function and complete remission of nephrotic syndrome and CLL.

Discussion: CLL-associated MPGN pattern of injury with cryoglobulinemia and leukemic cell infiltration of the kidneys is a rare complication of CLL, more common in White elderly men compared to others. Previously, chemotherapy with rituximab plus other agents was the standard of care. However, Obinutuzumab has shown better efficacy compared to rituximab in patients with untreated CLL. Obinutuzumab is a second-generation anti-CD20 monoclonal Ab with enhanced antibody-dependent cellular cytotoxicity and superior progression-free survival. Detection of proteinuria or declining kidney function in patients with CLL should trigger evaluation and consideration of kidney biopsy. Prompt treatment with Obinutuzumab regimen can result in kidney recovery and improved patient outcomes.

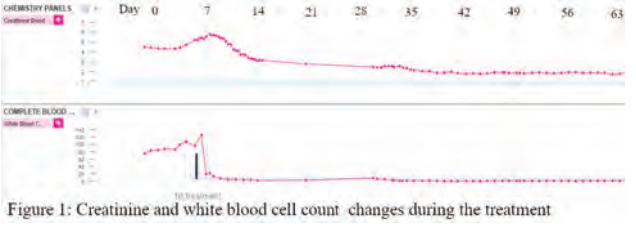

Figure 1: Creatinine and white blood cell count changes during the treatment

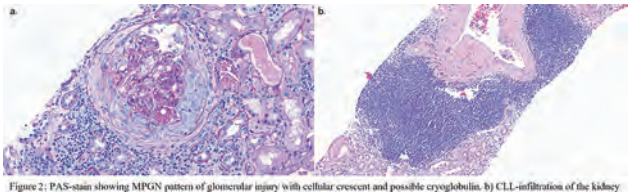

Figure 2: PAS-stain showing MPGN pattern of glomerular injury with cellular crescent and possible cryoglobulin. b) CLL-infiltration of the kidney

SA-PO231

Water, Water Everywhere: Not a Drop to Diurese

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Introduction: Anasarca is a common yet challenging symptom to manage, with common causes being cardiac, hepatic or renal failure. It is important to consider rarer etiologies when conventional therapies fail to respond.

Case Description: A 56-year-old woman with metastatic breast cancer, on Trastuzumab-deruxtecan presented with worsening anasarca and weight gain of 40kg. Workup ruled out heart, liver and renal failure(creatinine 0.6mg/dL) and nephrotic syndrome. Attempts at diuresis using various combinations (loop, thiazide, and carbonic anhydrase inhibitors) were unsuccessful and resulted in contraction alkalosis and worsening renal function. Due to lack of alternate diagnoses, we considered a diagnosis of capillary leak syndrome (CLS) possibly induced by trastuzumab-deruxtecan and filgrastim. We started amiloride 20mg and administered one dose of tocilizumab 800mg. Over the next

few days, daily urine output increased to 4L on furosemide 40mg with no contraction alkalosis or worsening renal function. She had steady improvement in volume status and decrease in weight (Figure 1). Patient was discharged on day 14 post tocilizumab with marked improvement in her functional status and edema, with weight back to baseline. She has not required re-hospitalization and her weight has remained stable on amiloride 20mg.

Discussion: Capillary leak syndrome refers to the collection of manifestations due to increased capillary permeability to proteins. Several drugs have been implicated such as gemcitabine, interleukins and monoclonal antibodies. Management of volume status is crucial in treating CLS but there is no well-established treatment protocol due to rarity of the condition. Cytokine release syndrome is a subset of CLS occurring in the setting of malignancy treatment or administration of monoclonal antibodies resulting in cytokine surge, endothelial cell injury and capillary leakage. Therapeutic options aim to block this cytokine storm with IVIG or steroids. This case highlights the success of tocilizumab, an interleukin-6 inhibitor for CLS induced by trastuzumab and filgrastim.

SA-PO232

Preliminary Results from a Genome-Wide Association Study (GWAS) in Bladder Cancer: Toward a Multi-Omics Approach

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Background: Bladder cancer is one of the most prevalent cancers, and its heterogeneity in clinical outcomes necessitates further investigation into the molecular mechanisms contributing to the disease to improve risk stratification, treatment, and prognosis. Here, we present the preliminary results of a GWAS in bladder cancer in an Italian cohort (N = 581) with paired genotyping and multi-omics data.

Methods: 594 individuals were genotyped with the Infinium OmniExpressExome-8 kit. PLINK2 was used for standard GWAS QC. The resulting dataset of 581 unrelated individuals consisting of 148 cases and 433 controls were imputed with the ToPMed panel (R2, GRC38). Logistic regression was performed on dosages under the additive model adjusting for age, sex, and principal components. Polygenic Risk Score (PRS) was calculated with PRSice-2 v2.3.5.

Results: 581 individuals (148 cases and 433 controls) and 594,108 SNPs remained after QC. Post-imputation QCs requiring SNP call rate (>95%), MAF (>1%) and Hardy-Weinberg ($P < 1 \times 10^{-6}$) within the cohort yielded a final set of 7,660,056 SNPs for GWAS. We identified three loci with suggestive association: chr10p15.3 (rs2605905, OR=3.06, $P = 1.53 \times 10^{-6}$; *DIP2C*), chr5p13.3 (rs5026245; OR = 2.14; $P = 3.83 \times 10^{-6}$; *ADAMTS12)*, and chr15q21.3 (rs17543144; OR = 2.03; $P = 4.46 \times 10^{-6}$; nearest gene *FAM214A*). The quantile-quantile plot showed no evidence of inflation ($\lambda = 0.969$) suggesting no residual population stratification. An interim assessment of the portability of existing PRS(PGS000782) on this cohort showed significant differences in means between cases and controls ($P = 2.17 \times 10^{-4}$).

Conclusions: An initial comparison of summary statistics between our cohort and larger bladder cancer cohorts deposited in the GWAS catalog showed consistent directionality in effect sizes at previously reported significant loci. Our GWAS may be underpowered for new discoveries but, leveraging on paired epigenomic and transcriptomic data available in our cohorts, we are well positioned for constructing multi-omics genetic correlations to dissect known and novel bladder cancer loci and provide insights into the pathobiology of disease. Finally, an interim assessment of PGS000782 showed portability in distinguishing cases from controls in this cohort.

Funding: Government Support - Non-U.S.

SA-PO233

Glomerular Pathology of Vascular Endothelial Growth Factor Inhibition: 12-Year Single-Center Experience

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Background: Vascular endothelial growth factor inhibitors (VEGF-I) are frequently used for cancer treatment. VEGF-I can cause proteinuria and acute kidney injury. Thrombotic microangiopathy (TMA) is common, but other glomerular pathologies are not well characterized. We aim to describe clinical characteristics and glomerular lesions associated with VEFG-I in a single center cohort.

Methods: We performed a retrospective chart review of patients treated with VGEF-I and underwent kidney biopsies from 2010 to 2022. Biopsy findings were reviewed by our pathologists.

Results: Nineteen biopsies were performed during 2010-2022 for kidney dysfunction in patients treated with VEGF-I. Eleven/19 had complete data. The median age was 62 (IQR 58-66) years, and the most common malignancy was renal cell carcinoma. TMA was found on 8/11 biopsies. Proteinuria was the most common reason for biopsy in patients with TMA. Three patients presented with other lesions besides TMA. One had anti-phospholipase A2 receptor-negative membranous nephropathy and both VEGF-I and pembrolizumab were stopped. She received prednisone with improvement in proteinuria. Another patient had known cryoglobulinemia with nephrotic range proteinuria exacerbated by VEGF-I peaking at 11g/day. Despite stopping VEGF-I and treating with prednisone+rituximab, he progressed to ESKD. Third patient had IgA nephropathy with diabetic changes, proteinuria progressed even after stopping VGEF-I (Table).

Conclusions: In this review of patients treated with VEGF-I undergoing kidney biopsy, we described the histological characteristics, clinical course, and outcomes. Our review adds information to the sparse literature on patients with renal dysfunction after receiving VEGF-I.

Patient	Gender	Age	Kidney Biopsy Findings	Primary Malignancy	Cancer Treatment	Outcome
1	F	55	PLA2R Negative Membranous Nephropathy, Minimal IgA Nephropathy	Renal Cell Carcinoma	Axitinib + pembroluzimab	N/A
2	M	59	Cryoglobulinemia Type II	Renal Cell Carcinoma	Pazopanib	Progression of Cancer
3	M	72	IgA Nephropathy Diffuse DM glomerulosclerosis	Hepatocellular Carcinoma	Atezolizumab + Bevacizumab	Progression of Cancer
4	F	51	Acute to subacute TMA	Ovarian Cancer	Bemcitabine + bevacizumab	Deceased
5	F	63	Subacute TMA	Colon Cancer	Bevacizumab	Disease progression, deceased
6	F	65	TMA	Glioblastoma Multiforme	Bevacizumab	Progression of Cancer
7	F	67	TMA	Endometrial cancer	Bevacizumab	Progression of Cancer, Decreased
8	M	62	Subacute TMA	Gastrointestinal stromal tumor	Imatinib, Noilotinib, Regorafenib, Sunitinib, Pazopanib, Imatinib + Dasatinib	Progression of Cancer
9	F	58	TMA	Ovarian Cancer	Bevacizumab	Progression of Cancer
10	M	60	TMA	Renal Cell Carcinoma	Nivolumab + Ipilimumab, + Cabozantinib	N/A
11	M	68	TMA	Renal Cell Carcinoma	Axitinb + Pembrolizumab	Progression of Cancer

SA-PO234

Bilateral Resection of Renal Cell Carcinoma with Postoperative Urinary Ascites

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Introduction: Urinary ascites is a rare complication of nephrectomy in the absence of bladder or ureteral injury.

Case Description: A man in his fifties with bilateral renal cell carcinomas underwent left total nephrectomy and right partial nephrectomy. He was treated with neo-adjuvant and adjuvant nivolumab. His pre-operative creatinine was 1.0 mg/dL. Two weeks post nephrectomies, he was hospitalized for anuric acute kidney injury. Urine microscopy revealed acute tubular necrosis (ATN). He had large-volume ascites, despite normal hepatic function, which was consistent with urine based on drained ascitic fluid creatinine level of 78.9 mg/dL. Serum creatinine peaked at 12.65 mg/dL and improved to 2.2 mg/dL after paracentesis and right ureteral stenting. Creatinine decreased to 1.9 mg/dL at discharge. He was readmitted two months later for Enterococcus faecalis bacteremia. CT IV pyelogram demonstrated active extravasation of contrast from the right renal pelvis and formation of a right perinephric urinoma which was 5.1 cm wide. Serum creatinine increased from 2.2 mg/dL on admission to 3.25 mg/dL by the time of hospital discharge. Follow-up imaging one month later demonstrated decrease in size of the right perinephric urinoma but with persistent extravasation of contrast from the right renal collecting system. Four months after right ureteral stent placement, the stent was removed and intraoperative retrograde pyeloureterogram showed no renal collecting system extravasation. His serum creatinine eventually settled at 1.9 mg/dL with a stable estimated glomerular filtration rate of 49 mL/min.

Discussion: Urinary ascites directly from the renal collecting system, as shown on imaging in this case demonstrates an unusual complication of bilateral nephrectomies. Loss of nephron mass, bacteremia, and post-operative ATN contributed to chronic kidney disease development, but estimation of renal function was likely clouded by reabsorption of creatinine from extravasated urine. The urinoma eventually became walled off and collecting system defects in the remaining kidney healed. Urinary leak leading to large volume ascites may occur post nephrectomy and should be considered in patients without hepatic injury. *The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

SA-PO235

A Case of Possible Malignancy-Related Polyangiitis Overlap Syndrome with Henoch-Schönlein Purpura and ANCA-Negative Pauci-Immune Glomerulonephritis as a Manifestation of Neuroendocrine Cancer

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Introduction: Henoch Schönlein purpura (HSP) is an immunoglobulin A (IgA) mediated small vessel vasculitis involving the skin, gastrointestinal tract, kidneys, and joints. It is often precipitated by infections but has also been reported with malignancies. Pauci immune crescentic glomerulonephritis (PICGN) is a cause of rapidly progressive glomerulonephritis (RPGN) and is usually ANCA positive with a paucity of immune complexes on renal biopsy. It is associated with microscopic polyangiitis (MPA), granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), or renal limited vasculitis. Polyangiitis overlap syndrome with features of more than one vasculitis has also been reported. We report a unique case of HSP and ANCA-negative PICGN in association with metastatic neuroendocrine cancer.

Case Description: A 54-year-old male with no medical history presented with fatigue, colicky abdominal pain, and dark urine for 2 weeks. He denied recent respiratory or gastrointestinal infection. He had new-onset hypertension (BP 163/96 mmHg), a purpuric rash on the buttocks and lower extremities, and acute kidney injury (AKI). Urinalysis showed hematuria, pyuria, and proteinuria. Skin biopsy showed IgA vasculitis consistent with HSP. Prednisone was started but he required hospitalization due to worsening AKI (BUN 36 mg/dL & creatinine 3.11 mg/dL). Workup showed anemia (Hb 12.8 g/dL), normal platelet count and coagulation profile, proteinuria of 1g/day, positive ANA (titer 1:80), negative anti-MPO & PR3 ANCA, anti-GBM, and anti smith antibodies. CT abdomen showed multiple liver masses and biopsy showed metastatic neuroendocrine cancer. Renal biopsy showed acute pauci immune necrotizing crescentic glomerulonephritis. Chemotherapy (carboplatin & etoposide) was initiated with steroids leading to the resolution of AKI.

Discussion: We report a unique case of HSP and ANCA-negative PICGN in association with metastatic neuroendocrine cancer. The difference in skin and renal biopsies indicates possible malignancy-related polyangiitis overlap syndrome. HSP and PICGN can be manifestations of occult malignancy, especially in adult males. Diagnosis of malignancy is crucial as remission of vasculitis may require both treatment of cancer and immunosuppressants.

SA-PO236

BK Virus Nephropathy (BKVN) in a Native Kidney of an Immunosuppressed Patient

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Introduction: BK virus nephropathy (BKVN) is common in kidney allografts but in native kidneys, BK reactivation is typically transient. However, there are a growing number of reports of native kidney fulminant BKVN in immunocompromised patients. We present a case of a patient with native BKVN mimicking an ifosfamide-related karyomegalic-like nephritis.

Case Description: A 53-year-old male with a past medical history of marginal zone lymphoma with transformation to diffuse B-cell lymphoma presented with worsening serum creatinine. He was in remission after chemotherapy including R-CHOP (2018-2019), R-ICE (2019), CD 19 CAR-T cell therapy (2019 –2020), fludarabine and cyclophosphamide lymphodepletion, and Obinutzumab with Brentuxumab vedotin (2020- 03/2021). 1 year after his last treatment, serum creatinine rose from a baseline of 0.99mg/dL to 2.13mg/dL. Urine protein-creatinine ratio was 223mg/g. Kidney biopsy showed interstitial nephritis with marked epithelial atypia, initially diagnosed as karyomegalic-like interstitial nephritis, likely related to treatment with ifosfamide. High-dose steroids were initiated without further improvement. Serum creatinine and UPCR increased when steroids were tapered. Cellcept was added to his regimen, as reported in other case reports, but his kidney function further declined. Cellcept was discontinued due to gastrointestinal side effects. An external review of pathology slides was obtained, and immunohistochemistry for Large T Antigen showed diffuse positivity, diagnostic of BKVN. Despite immunosuppression cessation the patient progressed to home hemodialysis.

Discussion: Non-kidney solid organ transplantation (32%) and hematologic malignancy (15%) are the most common associations with native kidney BKVN, which frequently progresses to end stage kidney disease. Pathologic hallmarks of BKVN in allografts such as plasma cell-rich infiltrates and nuclear inclusions are often subtle or absent in native BKVN. Interestingly, most cases of native BKVN associated with hematologic malignancy occur in the setting of ongoing treatment or active neoplasia, while this patient presented in remission. This case highlights the challenging nature of native BKVN diagnosis, and the importance of having a high index of suspicion for BKVN and other viral infections in patients with active or recent immunocompromise or immunosuppression.

SA-PO237

Diversity Outbred Mouse Model for Investigating Genetic Determinants of Cisplatin Nephrotoxicity

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Background: Cisplatin is a commonly used chemotherapy agent that is highly effective against several cancers. However, it has significant toxicity to several organs including the kidney. This has a significant impact on patient outcomes, as 50% of patients have to reduce dosages or discontinue use of cisplatin and up to 30% suffer from acute kidney injury (AKI). The causes of inter-individual variability in cisplatin nephrotoxicity are unknown, but evidence points to the involvement of genetic factors. We propose to use a mouse model with high genetic variability to identify potential gene candidates involved with modifying cisplatin nephrotoxicity. Here, we demonstrate the feasibility of using the Diversity Outbred mouse model, which was designed to mimic genetic heterogeneity in humans, in a small pilot study that demonstrates highly variable nephrotoxic response to chronic cisplatin administration.

Methods: Male and female Diversity Outbred mice (The Jackson Laboratory) were exposed to 9 mg/kg cisplatin subcutaneously weekly over 4 weeks (n = 8/sex) or to vehicle control (n = 4/sex). Three days after the last dose, plasma was collected and creatinine was measured by mass spectrometry and BUN was measured by a colorimetric assay at the UAB/SD O'Brien Center for Acute Kidney Injury Research.

Results: Control mice had plasma creatinine levels of 0.06±0.02 mg/dL [range: 0.04-0.08] in males and 0.07±0.02 mg/dL [0.06-0.11] in females. Compared to controls, cisplatin treated mice had significantly elevated plasma creatinine levels of 0.21±0.10 mg/dL [0.08-0.37] in males (p=0.0051) and 0.28±0.19 mg/dL [0.11-0.70] in females (p=0.016). Similarly, BUN was elevated in treated males (77.3±26.4 mg/dL [21.3-104.1] vs 26.5±8.4 mg/dL [18.1-36.5], p=0.00073) and females (65.7±27.5 mg/dL [21.9-92.0] vs 23.5±7.6 mg/dL [12.4-29.6], p=0.0030).

Conclusions: The Diversity Outbred mice display highly variable degrees of AKI after cisplatin exposure. While the majority of treated mice exhibited significantly elevated markers of AKI, some had markers similar to control mice. This model is suitable for quantitative trait loci (QTL) mapping to identify genes that modify susceptibility to cisplatin nephrotoxicity. Identification of these genes may enable pharmacogenetic application to tailor chemotherapy and enable development of adjunct therapies to limit cisplatin-induced AKI.

SA-PO238

Albuminuria Changes and Risk of Incident Cancer: The Stockholm CREAtinine Measurements (SCREAM) Project

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Background: A single albuminuria measurement is reported to be an independent predictor of future cancer risk. Whether progressive albuminuria (i.e. albuminuria changes) adds further prognostication is not known.

Methods: We included 64,303 subjects of the Stockholm Creatinine Measurements (SCREAM) project without a history of cancer and with at least 2 urine albumin-creatinine ratio (ACR) tests up to 2 years apart. Albuminuria changes were quantified by the fold change in ACR over 2 years, and stratified into the absence of clinically elevated albuminuria; albuminuria that remained constant; and albuminuria that increased; or decreased. The primary outcome was overall cancer incidence. Secondary outcomes were site-specific cancer incidences.

Results: During a median follow-up of 3.7 (IQR, 3.6-3.7) years, 5,126 subjects developed de novo cancer. After multivariable adjustment including baseline estimated glomerular filtration rate and baseline ACR, subjects with increasing ACR over 2 years had a 19% (HR, 1.19; 95% CI, 1.08-1.31) higher risk of overall cancer compared to those with absent albuminuria. No association with cancer risk was seen in the groups with decreasing or constant ACR. Regarding site-specific cancer risks, subjects with increasing ACR or constant ACR had a higher risk of developing urinary tract and lung cancer. No other associations between 2-year ACR changes and site-specific cancers were found.

Conclusions: Increases in albuminuria over a 2-year period are associated with a higher risk of developing overall, urinary tract, and lung cancer, independent of baseline kidney function and albuminuria.

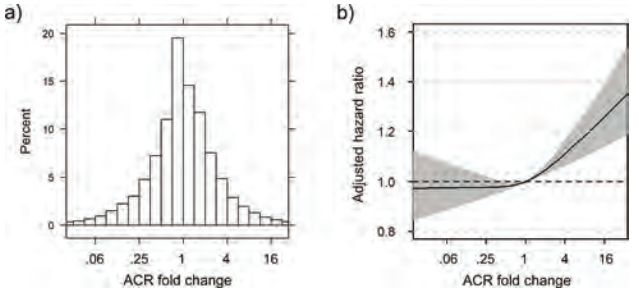

Figure 1. Distribution of 2-year ACR changes (panel A) and adjusted hazard ratio of overall cancer incidence associated with 2-year ACR changes (panel B). Restricted cubic splines of 2-year ACR changes with 3 knots at 0.1, 0.5, 0.9 quantiles of 2-year ACR fold change.

SA-PO239

Dripping Clues: Unveiling Diabetes Insipidus (DI), a Sneaky Presentation of Acute Myeloid Leukemia (AML)

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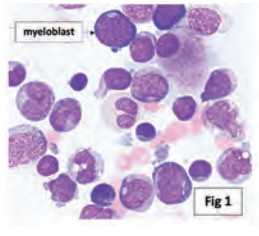
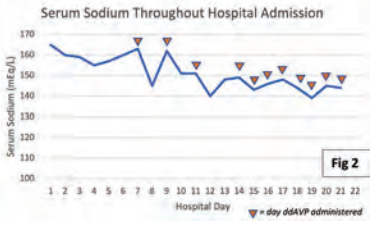
Introduction: DI is a rare complication of AML seen with cytogenetic defects especially monosomy 7 & inversion 3. It can occur before or after diagnosis of AML, with or without brain imaging abnormalities. Here, we report a case of hypernatremia from DI in a patient with AML.

Case Description: A 68-year-old male with no medical history presented to ICU with altered mental status & polyuria (urine output > 5L/day), noted to have hemoglobin 6.8 g/dL. Led to AML diagnosis based on blood and bone marrow tests (Fig1). Karyotyping revealed inversion 3 [inv(3)(q21q26)] & monosomy 7. His serum sodium (SNa) was high on admission at 168 mEq/L. Over the past 3-4 weeks, he had increased urination. Further evaluations, including an MRI of the brain, showed no abnormalities. Urine osmolality was 168 mOSm/L (other metabolic tests were normal). Treatment with diamino D-arginine vasopressin (ddAVP) (2- 4 mcg/day) & free water boluses improved SNa (Fig2) and urine osmolality. Diagnosis of probable central DI based on the response to ddAVP, was made. With his mental status improving, he was switched to oral desmopressin (0.05 mg BID) and maintained stable SNa (140-145 mEq/L) upon discharge. Unfortunately, due to the non-response to his therapy for AML (decitabine), he was transitioned to hospice.

Discussion: The pathogenesis of DI associated with AML (DI-AML) is not well understood. A possible mechanism is due to hypothalamic-pituitary infiltration of the leukemic cells or dysregulation of ADH due to dysthrombopoesis. Since approximately 90% of circulating ADH is associated with platelets, dysthrombopoesis in AML could lead to decreased levels and function of ADH. The 2 most common cytogenetic defects associated with DI-AML are monosomy 7 (80%) and inv-3 (46%). Patients with inv-3 and 50% involving monosomy 7 demonstrate activation of the MECOM [(MDS1 and EVI1 (ectopic virus integration site 1 protein homolog) complex] gene, leading to an increase in EVI-1 (a protein product). This disrupts the hypothalamic ADH secretion. We need more studies to prove an association between DI & AML. Our patient had features of CDI based on the evaluation & treatment response.





SA-PO240

Paraneoplastic Membranoproliferative Glomerulonephritis Associated with Neoplasm Transformation

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Introduction: Paraneoplastic glomerulonephritis is a rare complication of malignancy and early recognition could prevent ineffective and potentially harmful therapy. The mechanism is unclear and doesn't appear to be correlated with the tumor burden, invasion, or metastasis but possibly with the by-products of tumor cells. We present an interesting and rarely reported case of paraneoplastic proliferative glomerulonephritis with monoclonal IgG deposits (PGNMID) associated with Diffuse large B-cell Lymphoma (DLBCL) that responded to Cyclophosphamide/doxorubicin/prednisone/rituximab/Vincristine (R-CHOP).

Case Description: A 63-year-old woman with a history of hypertension, and chronic lymphocytic leukemia(CLL) failed two lines of therapy admitted to the hospital for a second opinion. She was recently admitted for severe acute kidney injury (AKI) attributed to chemotoxicity with partial recovery upon therapy cessation. On exam, the patient appeared hypervolemia, with labs notable for acute kidney injury. Urinalysis with hematuria and 3+ proteinuria; urine protein: creatinine ratio of 1.9gm/24hr. A secondary workup showed Low C3, M protein < 0.1 g/dL, and SPEP/IFE showed a small protein peak in the gamma region (IgG2 kappa). The renal biopsy showed Membranoproliferative glomerulonephritis with a monoclonal IgG deposit (IgG2 Kappa). PET scan significant for hypermetabolic soft tissue lesion in the oropharynx with tonsil biopsy confirming the transformation of CLL to DLBCL. The patient received R-CHOP with subsequent improvement in renal function and proteinuria.

Discussion: PGNMID has previously been reported to be associated with hematological malignancies, including CLL and lymphomas, solid malignancies, and infections, in addition to Monoclonal gammopathy of renal significance(MGRS). Effective treatment requires differentiating between these associated conditions as treatment is directed toward that disease. Our patient had confirmed hematologic malignancy at the time of PGNMID, the diagnosis for which paraneoplastic PGNMID is more reasonable than MGRS. The observed paraproteinemia is likely evolved as a part of an underlying immunoproliferative disorder. Increased free light chain level has been considered an adverse prognostic factor and early chemotherapy is emphasized for patients with PGNMID-associated hematological malignancies.

SA-PO241

A Case of Combined Light Chain Deposition Disease and Light Chain Cast Nephropathy

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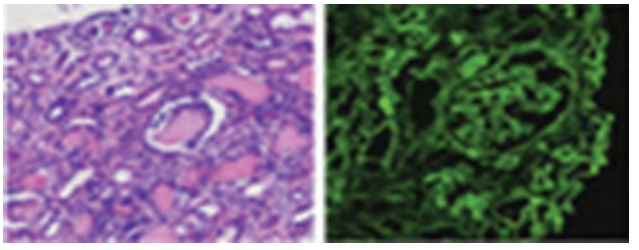
Introduction: Light chain cast nephropathy (LCCN) is the most common renal disease caused by multiple myeloma (MM). Light chain deposition disease (LCDD) is characterized by the tissue deposition of non-amyloid immunoglobulin (Ig) light chains. Cases of LCCN with coexistent LCDD remain sporadically documented in literature with reported incidence of 10-50%. Diligent histopathologic analysis is required for correct diagnosis. We report a case of acute renal failure in a patient with MM caused by combined LCCN and LCDD.

Case Description: 57-year-old male presented with several weeks duration of bilateral ribs pain requiring multiple doses of ibuprofen. Physical exam was rather unremarkable. Initial blood work indicated creatinine 13.95 mg/dL, potassium 7.5 mg/dL, calcium 14.8 mg/dL, and hemoglobin 9.1 g/dL. The skeletal survey revealed diffuse lytic lesions. Retroperitoneal ultrasound showed bilateral kidneys ~15 cm in size. Serum protein electrophoresis revealed restricted peak in the gamma region, κ- to lambda (λ)-FLC ratio 7501.38. The patient required urgent dialysis followed by 5 treatments with plasmapheresis. Once bone marrow biopsy confirmed myeloma, chemotherapy with Cytoxan-Bortezimib-Dexamethasone regimen was initiated. Renal biopsy showed tubules with hard casts, diffuse linear glomerular and tubular basement membranes all staining for k-LC on IF. Electron dense deposits were not observed on EM. Patient remained dialysis dependent however, passed away 18 months later.

Discussion: Diagnosis of combined LCCN-LCDD is challenging and can be easily missed without meticulous analysis of LM, IF, and EM. Zand's group at Mayo Clinic, in largest study to date, reported that < 50% of the patients with LCCN-LCDD had evidence of electron dense deposits on EM but had evidence of LCDD by IF. Worse renal and overall survival outcomes are observed in LCCN-LCDD patients compared to those with LCCN or LCDD alone with mortality rate of >50% within the first year of diagnosis. Therefore, early detection and treatment is crucial for renal function stabilization and further studies are needed to establish an optimal mode of therapy.



SA-PO242

Single-Cell Sequencing Analysis of Paired Peripheral Blood Mononuclear Cell (PBMC) and Bone Marrow Mononuclear Cell (BMMC) Samples from Amyloidosis (AL) Patients

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Background: Systemic light chain amyloidosis (AL) is the most common type of systemic amyloidosis. It has a variety of clinical manifestations and can involve multiple organs, kidney and heart are the most commonly affected organs. The diagnosis of AL depends on the presence of amyloid deposition of immunoglobulin light chain or heavy light chain as a precursor protein confirmed by biopsy, the existence of monoclonal immunoglobulin or free light chain in blood or urine, or the monoclonal plasma cells /B cells found in bone marrow examination. Previous studies have confirmed that single-cell sequencing is helpful to explore the pathogenesis of AL. Here, we performed single cell sequencing in AL patients with renal damage, and explored the specific clones and molecular characterization.

Methods: In this study, paired peripheral blood mononuclear cell (PBMC) and bone marrow mononuclear cell (BMMC) of 5 newly diagnosed AL patients and 3 healthy controls from Guangdong Provincial People's Hospital from March 2022 to June 2022 were collected. Single-cell sequencing and single cell repertoire sequencing were used to performed. Differentially expressed genes were obtained, and the related biological pathways were explored by GO and KEGG enrichment analysis.

Results: κ light chain (n=4) and λ light chain (n=1) were included in the 5 AL patients. UMAP map showed that AL patients had different expression patterns and contained more plasma B cells. GO and KEGG analysis showed that most of the marker genes were enriched in infection and binding related pathways. 274 differentially expressed genes were found between IGK and IGL cells. Using immune repertoire as comparison, specific clones were found such as the variable region of antibody V1-33 in subject AL2 was significantly expanded clones. Furthermore, the top five up-regulated genes were RHOB, CTSW, HSPA5, KRTCAP2 and MZB1, while the top five down-regulated genes were BTG1, CD79A, CD37, HLA-DRB1 and JUND.

Conclusions: Single-cell sequencing and single-cell immune repertoire sequencing revealed that AL patients contained more plasma B cells than healthy controls, most of the marker genes were enriched in infection and binding related pathways, and specific clonal amplification was found in some AL patients. The sequencing results can provide theoretical basis for the discovery of diagnostic biomarkers in AL patients with kidney damage in the future.

SA-PO243

A Novel In Vivo Model of Renal Cell Carcinoma (RCC) Angiogenesis

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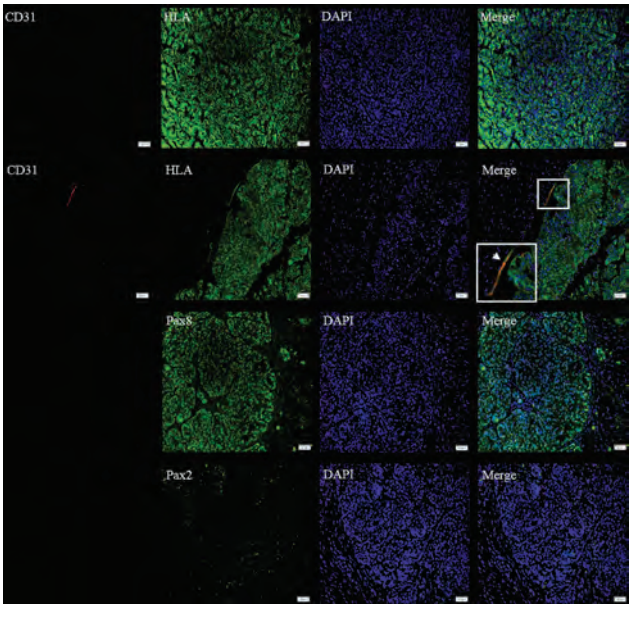
Background: Renal cell carcinoma (RCC) is the most common tumor in the kidney and currently lacks effective treatments. Remarkably, although RCC is an extremely angiogenic tumor, existing drugs aimed at inhibiting angiogenesis have shown disappointing results in patients. One potential reason for this discrepancy is the fact that most models used to dissect the molecular mechanisms of RCC angiogenesis involve transplantation of human tumor cells into mice, which results in development of host-derived vasculature, putting into question their clinical relevance. We have previously shown that combined transplantation of human kidney cells alongside human vessel forming cells into immunodeficient mice allows the generation of vascularized reno-vascular units. Herein, we aimed to develop a novel in-vivo model that will include RCC cells and vessels that are both human-derived.

Methods: We inoculated immunodefficient NOD-SCID mice with a combination of 10^6 fresh RCC cells and two types of human cells: (1) $5X10^5$ Endothelial Colony Forming Cells (ECFC); (2) $5X10^5$ Multipotent Stromal Cells (MSC), and analyzed the grafts following 3 weeks using immunostaining.

Results: Remarkably, the grafts developed into vascularized tumor units consisting of both RCC-like tissue, expressing classical markers of the tumor (e.g., PAX2 and PAX8), as well as human, HLA-positive blood vessels, contatining CD31+ endothelium, which were seen to feed the tumor tissue.

Conclusions: Taken together, this model represents a new purely-human inv-vivo model that allows studying the process of RCC angiogenesis, which could facilitate the uncovering of new mechanisms governing this critical process.

Funding: Private Foundation Support



SA-PO244

Elevated 1,25-Dihydroxy-Vitamin D Level: A Perplexing Case of Renal Sarcoma with Osteoclast-Like Giant Cells

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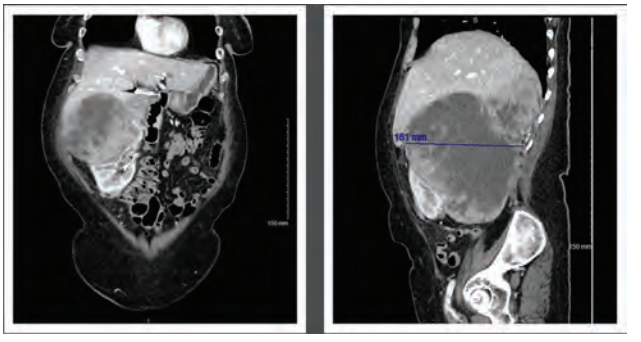
Introduction: Elevated 1,25 Dihydroxy vitamin D(DHVD) level is commonly attributed to increased macrophage activity in chronic granulomatous conditions such as sarcoidosis. There are no reports yet of DHVD elevation in renal tumors. Renal sarcoma is very rare accounting for 0.8–2.7% of malignant kidney tumors and coexistence with Extra-skeletal Osteoclast-like giant cell tumors (OGCT) is not yet reported.

Case Description: Our patient is 74 years old Caucasian female with history of HTN. She came to ER with complaints of right sided abdominal pain, also reported 18 lb weight loss and poor appetite. CT abdomen with contrast revealed Interval enlargement of the very large, heterogeneous right renal mass compatible with renal cell carcinoma now measuring up to 15.2 x 16.1 x 17.9 cm which directly invades the right hepatic lobe (hepatic invasion has increased) and possibly the posterior abdominal/chest wall. Laboratory data significant for total serum calcium level 15.0 mg/dl, 25 Hydroxy vitamin D level 33.6ng/ml, 1, 25 hydroxyvitamin D level 133 pg/ml, iPTH level 6.4 pg/ml and PTH related peptide level 1.7 pmol/L. She underwent radical nephrectomy with histopathology showing High grade dedifferentiated sarcoma, with multinucleated giant cells involving kidney and extending into liver segment 6 and 7 (19.2 cm), with lympho-vascular and perinephric adipose tissue involvement. Cytogenetics significant for CD 10 positive, RCC markers negative, MDM2 focally positive, High positive for PD-L1. One week postoperative, laboratory data significant for normalization of 1,25 DHVD level 9.6pg/ml, and serum calcium 8.7 mg/dl.

Discussion: Resolution of hypercalcemia and normalization of DHVD levels after Sarcoma resection in our patient is very unique. The most effective therapy for renal and retroperitoneal sarcomas is the gross total resection of the tumor. Increased rates of necrosis, poor differentiation, mitotic activity and increased histological grade are associated with a poor prognosis.



SA-PO245

A Case of Paraneoplastic ANCA-Associated Glomerulonephritis in a Patient with Non-Small-Cell Lung Carcinoma

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Introduction: Paraneoplastic glomerular diseases are rare immune-mediated disorders temporally correlated with the detection of an underlying malignancy. The association between malignancies and glomerular diseases has been most commonly described with solid tumors and membranous nephropathy. In contrast, Anti-Neutrophil Cytoplasmic Antibody (ANCA) vasculitis in patients with solid carcinomas is a rare occurrence.

Case Description: A 76-year-old female former smoker with a medical history of Sjogren's syndrome presented to our nephrology clinic to evaluate worsening kidney function. Two months prior, she was diagnosed with metastatic squamous cell carcinoma of the lung and received 1 dose of pembrolizumab 1 week prior to nephrology evaluation. She reported decreased appetite, weight loss, and fatigue. Physical examination was remarkable only for blood pressure of 152/68 mmHg. Laboratory findings showed worsening serum creatinine from a baseline of 1.6 mg/dL (two months prior) to a peak of 4.1mg/dL. Urinalysis showed positive blood with >20 RBCs per HPF and a urine protein and creatinine ratio of 5g/g. Serological workup showed positive anti-SSA, positive anti-MPO, and negative anti-PR-3 titers. She underwent a kidney biopsy which revealed a focal pauci-immune crescentic and sclerosis glomerulonephritis. The decision was to temporarily hold the immunotherapy and to start treatment with corticosteroids and Rituximab. A 2-month clinical follow-up showed a serum creatinine stable to 2.4mg/dL.

Discussion: In the last decade, there has been increased awareness of the association between malignancies, cancer treatment, and glomerular diseases. A paraneoplastic glomerular disease can be challenging to distinguish from a drug-induced or a primary glomerular disease in the setting of illness and treatment of underlying malignancy. Moreover, it poses an essential dilemma regarding management decisions concerning treatment for underlying cancer versus treating the glomerular disorder if the therapies cannot be given concurrently. In our case, we attributed the AAV to a paraneoplastic glomerular disease; the subacute rise in the creatinine coincided with the newly diagnosed lung cancer. One dose of immune checkpoint inhibitor was less likely the culprit. This case adds to the literature on this rare manifestation of AAV presenting as a paraneoplastic disease.

SA-PO246

IgG4-Related Disease with an Unusual Presentation

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Introduction: Immunoglobulin G4-related disease (IgG4-RD) is a chronic immune-mediated disease that can present with tumefactive lesions, fibrosis, and polyclonal IgG4-positive plasma cell infiltrate in nearly any anatomic site. It can manifest as lymphadenopathy, eosinophilia, and polyclonal hypergammaglobulinemia, and often mimics other hematologic conditions. However, the lack of a relationship between IgG4-related kidney disease and monoclonal gammopathy of renal significance (MGRS) warrants further investigation.

Case Description: 56-year-old male with spastic paraparesis secondary to cervical myelopathy due to severe cervical stenosis (C4-C5) with a history of chronic longstanding nasal congestion and obstruction. Started to have hyporexia, anosmia, weight loss, fatigue, rash and xerostomia for approximately 4 months. Accompanied by renal failure which was first detected 2 months prior to the onset of his symptoms. Urinalysis was negative and on microscopy had a bland appearance, ultrasound of the kidneys showed a mild bilateral increase in size. Further workup was relevant for Serum Free Kappa light Chains ratio of 9.7. Serum immunofixation was positive for IgG monoclonal protein with kappa light chain. Due to concern for myelodysplastic disorder, the patient underwent bone marrow biopsy which showed plasma cells that comprised 8-10 % of the nucleated hematopoietic bone marrow well-differentiated cells. There was no detectable clonal plasma cell population on flow cytometry prompting a diagnosis of MGUS for which he underwent kidney biopsy that revealed acute on chronic interstitial nephritis with many IgG4-positive plasma cells, suspicious for IgG4-RD. Currently receiving treatment with Rituximab and renal function has remained stable.

Discussion: This patient presented with xerostomia, constitutional symptoms, and development of renal failure, workup was diagnostic of MGUS. However, a kidney biopsy was performed and showed acute on chronic interstitial nephritis with IgG4-positive plasma cells, which leads to a diagnosis of IgG4-RD. An increased free light chain concentration has been reported in a variety of inflammatory and autoimmune diseases and reflects the polyclonal B lymphocyte activation in these pathologies. This presentation is fairly uncommon and the intention of this abstract is to make physicians aware of this for the future and warrant further investigation.

SA-PO247

Proximal Tubulopathy Secondary to Chronic Lymphocytic Leukemia After COVID-19 Infection

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Introduction: Light chain proximal tubulopathy is a rare kidney disorder that occurs when free light chains are filtered by the kidneys and then accumulate in the tubules, leading to kidney damage and dysfunction. This condition is often associated with multiple myeloma. While chronic lymphocytic leukemia (CLL) is not typically associated with light chain proximal tubulopathy, there have been rare cases reported in the medical literature. However, to our knowledge, no reports have been found of developing both conditions after a COVID-19 infection.

Case Description: A 60-year-old male with pre-DM presented were decreased appetite, fatigue, and dizziness his physical examination was unremarkable. Initial workup was significant for COVID-19 infection, serum creatinine of 3.2 mg/dL, GFR: 20 cc/min, however, was discharged for outpatient follow-up. Urinalysis showed proteinuria and hematuria (33 RBC per hpf), serum creatinine stable to 3.3 mg/dL, GFR: 20 cc/min, spot protein to creatinine ratio of 1.8 g, ANCA profile, hepatitis B and C serologies were non-reactive. Complement C3 slightly decreased 73 mg/dL (82-167mg/dL), serum-free light chains ratio of 14.6. Prior serum creatinine was 0.9 mg/ dl ~4 years prior. Kidney biopsy demonstrated focal endocapillary and extra capillary proliferative glomerulonephritis with apparent lgG1 kappa deposits (light chain proximal tubulopathy), supporting the diagnosis of monoclonal gammopathy of renal significance (MGRS). Hemato-oncology evaluation noted worsening weight loss since the COVID-19 infection and left supraclavicular and bilateral inguinal lymphadenopathy with palpable hepatosplenomegaly. He underwent a bone marrow biopsy showing atypical lymphocytosis, trisomy 12 in 45.5% of cells, and flow cytometry findings of the clonal B-cell population (60-65% of total), immunophenotypically represents (CLL). Treatment was started with Venetoclax, febuxostat, and obinutuzumab. His serum creatinine stabilized at 2.4 mg/dL with a GFR of 28 cc/min.

Discussion: Chronic lymphocytic leukemia rarely can present with deposition of free light chains in the kidneys leading to Light chain proximal tubulopathy. We present a case of a patient who had this presentation after having a COVID-19 infection. To our knowledge, there have been no reported cases of MGRS or chronic lymphocytic leukemia after a COVID-19 infection.

SA-PO248

A Case of Multicentric Castleman Disease Mimicking IgG4-Related Kidney Disease

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Introduction: Multicentric Castleman disease (MCD) is a benign lymphoproliferative disorder with heterogenous clinical symptoms and involves systemic organs in addition to lymph nodes. Case reports have documented mesangial proliferative glomerulonephritis, membranoproliferative glomerulonephritis, and amyloidosis in patients with MCD. Here, we report a case of MCD showing numerous IgG4+plasma cell infiltration in the kidneys.

Case Description: A 55-year-old man was referred to our hospital for high fever and diarrhea. His laboratory data revealed anemia, renal dysfunction (eGFR 30 mL/min/1.73m^2), polyclonal gammopathy (IgG 7130 mg/dL), an elevated serum IgG4 level (2130 mg/dL) and an elevated C-reactive protein level (8.0 mg/dL). Abdominal CT showed multiple lymph nodes swelling (axillary, hilar, para-aortic, and inguinal). Biopsy of the axillary lymph node showed expansion of the interfollicular areas by heavily infiltrating plasma cells. Renal biopsy showed a significant plasma cell infiltration into the tubulointerstitium. Immunohistochemical analysis revealed a 45% IgG4-positive:IgG-positive plasma cell ratio, which meets the diagnostic criteria for IgG4-related disease. Amyloid A deposition was found along the vessel walls. No abnormality was found in most glomeruli. IF showed no deposition of immunoglobulins and complements. Serological cytokine analysis revealed elevated levels of interleukin-6 (9.3 pg/ml) and vascular endothelial growth factor (VEGF) (1210 pg/ml). Human herpesvirus-8 was negative. Taken together with histological finding of lymph node biopsy, idiopathic MCD was diagnosed.

Discussion: Corticosteroid monotherapy resolved the serological and imaging abnormalities, but was partially effective. Additional therapy with tocilizumab is planned. Given that response to steroid therapy and prognosis are different between MCD and IgG4-related disease, diagnosis of MCD should be carefully made based on a combination of findings including organ distribution of disease, response to steroid therapy, and other pathological findings. Highly specific diagnostic biomarkers that can distinguish between these diseases are needed.

SA-PO249

Lysozyme-Associated Nephropathy Successfully Treated with Dasatinib in Chronic Myeloid Leukemia

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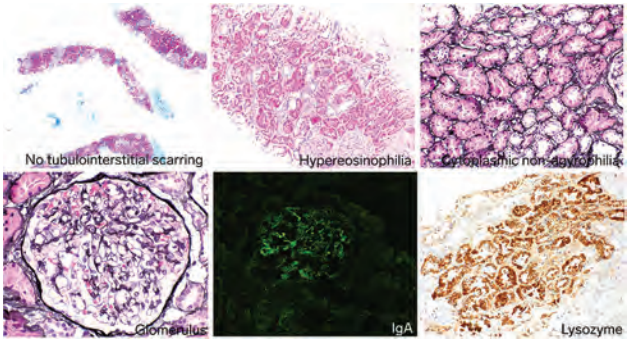
Introduction: Lysozyme-associated nephropathy (LyN) is a rare and underrecognized entity causing acute tubular injury. Serum lysozyme levels are elevated in chronic myelomonocytic leukemia and other forms of leukemia with myelomonocytic differentiation. We present a case of acute kidney injury (AKI) treated with dasatinib in the setting of chronic myeloid leukemia (CML) secondary to LyN.

Case Description: A 45-year-old man with a recent diagnosis of BCR-ABL-positive CML was referred to our clinic for abnormal renal function. At the time of CML diagnosis, his serum creatinine was 1.94 mg/dl and white blood cell count (WBC) was 203,000/microliter. He was treated with the tyrosine kinase inhibitor dasatinib and after six months his WBC normalized and creatinine improved to 1.6. His exam in renal clinic was notable for no hypertension or edema. Labs were significant for urine protein-creatinine ratio (UPCR) 0.2 g/g, kappa-lambda ratio mildly elevated to 1.85, and no evidence of Fanconi syndrome. Kidney biopsy revealed tubular injury with positive lysozyme staining in the proximal tubules and 2+ mesangial IgA staining with minimal interstitial fibrosis with a MEST-C score of 0. Since his CML was adequately treated, we concluded his lysozyme levels were likely improving. He continued dasatinib, and three months later creatinine improved further to 1.43 and UPCR was undetectable.

Discussion: Lysozyme is a cationic protein mainly produced by monocytes and macrophages. It is freely filtered at the glomerulus and reabsorbed in the proximal tubule via endocytosis. Excessive lysozyme production causes proximal tubulopathy and can result in AKI, Fanconi syndrome, and proteinuria. LyN is an underdiagnosed entity that often resolves with cytoreductive therapy. Interestingly, our patient had minimal proteinuria and no evidence of Fanconi syndrome, and we concluded his LyN had already responded to dasatinib by the time he was seen in renal clinic.



SA-PO250

Identification of Pathological Micro-Domains in Renal Carcinoma Biopsies Using High-Resolution Spatial Transcriptomics Signatures

Lavanya Muthukrishnan Iyer, Carolin Wiechers, Menglin Zheng, Silke Strassenburg, Leonie Neumann, Ramon Oliveira Vidal, Britta Seip, Timur Samatov, Rüdiger Fritsch, Uwe Andag. Spatial Team. *Evotec SE, Hamburg, Germany*.

Background: Kidney cancer globally ranks 14th in men, 9th in women, with most prevalence in North America and Europe. Clear cell renal cell carcinoma (ccRCC) arises in the proximal tubular epithelial cells (PTECs) and is currently treated with anti-angiogenic molecules and immune checkpoint inhibitors, leading to increased survival rates in responders. However, not all patients respond to these treatments. Here, we applied high-resolution spatial transcriptomics to biopsies of ccRCC patients, identified known markers of progression and gained novel insights into the micro-environments (ME) of affected kidney tissues.

Methods: FFPE tumor and healthy adjacent tissue biopsies from 2 ccRCC patients (ICD-10: C64) (51yr male-"A", 54yr female-"B") from Indivumed were assayed using 10x Genomics Visium CytAssist (FFPE human panel) and NanoString CosMx (1000-plex universal human panel, IF staining with CD298/B2M, PanCK, CD45, CD3) platforms.

Results: Initial analysis of Visium data revealed distinct differences between the two ccRCC patient tumors- while both patients showed a clear T cell response, we noted an extensive B cell response exclusively in patient A, whereas patient B showed a high number of proliferating tumor cells with angiogenesis. Within tumor A, we observed a striking correlation of the tissue ME to tumor PTECs function. While immune ME preserved normal PTEC metabolism, stromal ME comprised of fully transformed PTECs, highlighting that spatial ME plays a crucial role in tumor progression in ccRCC. Integrated analysis with a scRNAseq reference and CosMx further revealed rare populations of immune cells along the tumor edge within healthy adjacent tissue.

Conclusions: Overall, our high-resolution spatial transcriptomics data revealed patient-specific disease micro-domains and characterized molecular pathways in kidney cancer progression, paving the way for further analysis on distinct disease progression and unraveling potential therapeutic targets at the individual level.

SA-PO251

Characterization of Extracellular Matrix Composition in Wilms Tumor and Its Impact on Cellular Behavior

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Background: Wilms Tumor (WT) is a pediatric renal cancer that arises from abnormal kidney development. The extracellular matrix (ECM) in the tumor microenvironment plays a critical role in supporting normal and cancerous cells and is essential for tumor growth and development. This study aims to understand the differences in ECM composition between normal kidneys and WT samples and how these variations affect cellular behavior.

Methods: We decellularized normal kidneys and WT patient samples using an optimized decellularization technique. Second-harmonic generation (SHG) microscopy and two-photon excited fluorescence (TPEF), combined with immunohistochemistry, were used to characterize the decellularized matrices (dECM). Expression of various cancer-related proteins in WT dECM samples was compared to normal kidney dECM samples using Proteome Profiler Human XL Oncology Array. Changes in gene expression of seeded SIX2+CITED1+ WT and human fetal kidney (hFK) progenitor cells on different dECM scaffolds were examined by immunofluorescence and bulk RNA-seq.

Results: Our study found differences in ECM fiber expression in WT dECM, with the outer layer comprising dense and elongated fibers, followed by pocketed and mesh-like structures. WT dECM exhibited elevated levels of oncoproteins ERBB2/3, SERPINE1, and MMP2 compared to normal kidney dECM. The dECM supported the long-term survival, migration, and proliferation of WT and hFK cells. When seeded on different dECM scaffolds, WT and hFK cells showed altered transcriptomic profiles and changes in cellular behavior. WT and hFK cells on WT dECM exhibited variations in ECM binding proteins (integrins) and increased expression of EMT and cancer stem cell markers like vimentin and SOX9 compared to normal kidney dECM.

Conclusions: This study provides valuable insights into the role of the ECM in regulating cancer cell behavior. The findings have significant implications for developing physiologically relevant in vitro tumor models and identifying novel therapeutic targets and mechanisms.

Funding: Private Foundation Support

SA-PO252

Spontaneous Tumor Lysis Syndrome

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Introduction: Tumor lysis syndrome is a life-threatening oncological emergency characterized by metabolic abnormalities including hyperuricemia, hyperphosphatasemia, hyperkaliemia and hypocalcemia. These metabolic complications predispose the cancer patient to clinical toxicities including renal insufficiency, cardiac arrhythmias, neurological complications and potentially sudden death. TLS is typically associated with the start of chemotherapy; however, in some instances, spontaneous TLS may occur without prior exposure to chemotherapy. STLS is typically seen in high-grade hematological malignancies such as B-cell non-Hodgkin lymphoma.

Case Description: A 68-year-old male with a history of hypertension presented with fatigue, poor appetite, and generalized weakness. He had been previously admitted to another hospital for hematemesis and was diagnosed with high-grade B-cell lymphoma found in a gastric ulcer biopsy. He developed acute kidney injury and urinary obstruction during that hospitalization. On presentation to our hospital, he denied other symptoms and had no further episodes of hematemesis. Initial lab results showed extremely high uric acid (>33.1 mg/dl), abnormal values for phosphorus, calcium, and creatinine. The patient was diagnosed with AKI secondary to acute spontaneous TLS. Standard treatment was initiated with Rasburicase, the patient needed hemodialysis. Chemotherapy was initiated for the lymphoma. After five days, the patient's lab values improved, and he remained stable, transitioning to continuous renal replacement therapy.

Discussion: In conclusion, this case report underscores the importance of recognizing and promptly treating STLS in patients with high-grade hematological malignancies. Even in the absence of chemotherapy, STLS can occur and lead to severe metabolic abnormalities and renal dysfunction. Early intervention with appropriate pharmacological and supportive measures is crucial to prevent complications and improve patient outcomes. Further research and awareness are needed to better understand the pathophysiology and optimal management of STLS.

	Day 0	Day 1	Day 2	Day 3	Day 4	Day 5
Uric Acid (mg/dl)	>33.1	7.3	3.5	3.2	2.6	1.8
Phosphorus (mg/dl)	16.9	10.4	7.6	4.1	3.2	2.5
Calcium (mg/dl)	6.2	6.9	7.6	6.2	6.4	6.4
Creatinine (mg/dl)	6.5	5.5	2.9	1.7	1.4	1.1
BUN (mg/dl)	119	89	61	48	26	33

SA-PO253

Chronic Myelomonocytic Leukemia (CMML)-Related Glomerulopathy Without Lysozyme Nephropathy

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Introduction: Myeloproliferative neoplasms (MPN) are clonal hematopoietic cell disorders characterized by expansion of the myeloid lineages. We are increasingly recognizing myeloid disorders causing glomerular disease. Chronic Myelomonocytic Leukemia (CMML) is a unique MPN overlap which has a few glomerular presentations. We present a rare case of myeloproliferative glomerulopathy secondary to CMML and review the renal course as the neoplasm progressed.

Case Description: A 85-year-old male with past medical history of heart failure and CMML was admitted for acute kidney injury and proteinuria. Initial labs were significant for creatinine of 2.18 (baseline function of 1.1-1.3) mg/dl, 2.6g/day of total proteinuria and 1.8g/day albuminuria. Urinary sediment showed less than 3 red cells, 1-3 white cells, with occasional granular casts and free fat. Serological evaluation and infectious workup were unrevealing. Kidney biopsy was consistent with MPN associated with glomerulopathy. There was no evidence of lysozyme nephropathy even though serum lysozyme levels were elevated >10.8 mcg/ml. Post hospital, he was seen in clinic and was started on a course prednisone with improvement of pr/cr to 0.30 mg/mg and creatinine improved to 1.4 mg/dl. After completing steroids, his renal function and proteinuria began to worsen to >3 mg/dl and 1.48 mg/g, respectively. Additionally, he continued to have worsening leukocytosis (126x103/µl) and monocytosis. There were increasing peripheral blasts and serum lysozyme levels worsened to >19.3 mcg/ml. It was apparent that the patient's CMML progressed to AML with coinciding worsening renal parameters.

Discussion: Renal manifestations secondary to MPNs are rare. When it is present, those with elevated lysozyme are presumed to have lysozyme nephropathy, a sign of advanced hematological disease. In this case, the patient's proteinuria and renal function improved with steroids. Once stopped, his hematological parameters worsened, with laboratory evidence of peripheral blasts, indicative of progression to AML. This coincided with worsening lysozyme levels and precipitous decline in renal function. In conclusion, renal disorders in the context of myeloid neoplasms warrant thorough investigation as it may be a sign of worsening hematological disease and the potential role of steroids for nephroprotection should be explored.

SA-PO254

Piperacillin/Tazobactam Dosing Recommendation in Critically Ill Patients Receiving Tablo Kidney Replacement Therapy

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Background: Tablo kidney replacement therapy (KRT) machines provide flexibility in treatment duration, frequency, and effluent rates to treat ICU patients with AKI. These KRT options may clear piperacillin/tazobactam (PIP/TAZ) differently than conventional KRTs. This study's purpose was to predict PIP/TAZ doses likely to attain the efficacy targets in critically ill patients receiving Tablo KRT, using Monte Carlo simulation (MCS).

Methods: Pharmacokinetic models were developed using pertinent demographic & pharmacokinetic parameters to predict PIP/TAZ exposure in 5,000 virtual, anuric patients receiving 5 different KRT regimens (Table 1). PIP/TAZ doses with 0.5 or 4 hour infusions were simulated to assess the probability of target attainment (PTA). The 3 PIP efficacy targets used were 1) free plasma concentrations above the MIC for ≥50% of the dosing

interval (≥50% *f*T>MIC), 2) free concentrations for ≥50% of the dosing interval ≥4 times above the MIC (≥50% *f*T >4xMIC), or 3) 100% *f*T >MIC. Breakpoint MIC used was 16 mg/L for *P. aeruginosa.* TAZ target was ≥50% fT> threshold concentration of 4 mg/L. The toxicity risk of each PIP dose was predicted with using a safety threshold (157 mg/L). The smallest doses attaining PTA≥90% during 1-week of therapy were considered optimal.

Results: PIP/TAZ doses attaining the different efficacy targets in the 5 KRT settings are shown in Table.

Conclusions: MCS predicted the same PIP/TAZ doses for 3x/wk HD, daily HD, sequential HD/UF, and PIKRT while higher doses are necessitated for extended therapy. Higher doses were required for aggressive efficacy targets, but these were likely to increase the toxicity risk. These findings need clinical validation.

Funding: Commercial Support - Outset Medical

Table. PIP/TAZ Dosing Recommendations in 5 Tablo KRT regimens

Setting #	Tablo KRT Settings				PIP/TAZ Doses Attaining Different Targets		
	Type	Effluent Rate (mL/min)	Duration (hours)	Frequency	50% fT>MIC	50% fT>4xMIC	100% fT>MIC
1	HD	Qd 300	4	Mon-Wed-Fri	4.5g q12h*	4.5g q8h or 3.375g q6h*	3.375g q6h*
2	HD	Qd 300	4	Daily			
3	Sequential HD/UF	Qd 300 Quf 5	HD 4, then UF 20	Daily			
4	PIKRT	Qd 100	9	Daily			
5	Extended Therapy	Qd 50	24	Daily	3g q8h	4g q6h	3g q6h

HD: Hemodialysis; UF: Ultrafiltration; PIKRT: Prolonged Intermittent Kidney Replacement Therapy;
Qd: dialysate rate; Quf: ultrafiltrate rate
Doses may be administered over 0.5 or 4 hours.
*Doses should be given after HD in settings 1-3 but can be given before or after in setting 4.

SA-PO255

Drug-Drug Interaction Between Phosphate Binders and Daprodustat in ASCEND-D

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Background: Daprodustat (Dapro), a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI), is an oral alternative to erythropoiesis-stimulating agent (ESA) therapy and is indicated in the USA for the treatment of anemia of chronic kidney disease (CKD) in adults receiving dialysis for at least four months. Phosphate binders (PB) are widely prescribed for hemodialysis (HD) or peritoneal dialysis (PD) patients (pts) in the USA (66.1% and 57.8%, respectively). Previous studies indicate the absorption of some HIF-PHIs may be affected by co-administration with PBs.[1,2] However, results from a phase II study of Dapro indicate PB use does not have a major impact on hemoglobin (Hb) values. Here we examined the effect of PB use at baseline on Dapro treatment dose and Hb using data from the phase III ASCEND-D study (NCT02879305) (Singh AK, et al. *N Engl J Med.* 2021;385:2325–2335).

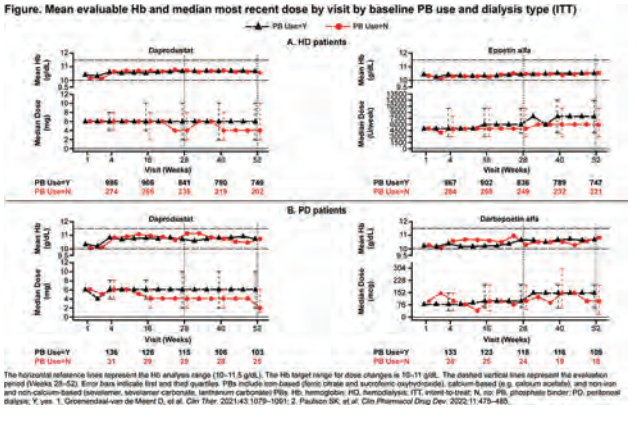
Methods: In ASCEND-D, 2964 pts with CKD undergoing dialysis and receiving ESAs were randomized in a 1:1 ratio to receive Dapro or injectable ESAs (epoetin alfa in HD pts or darbepoetin alfa in PD pts). Change in Hb and median doses from Weeks 1 to 52 was reported by baseline PB use and dialysis modality.

Results: 656 (22%) pts reported no PB use at baseline. In HD pts, the Hb profile in baseline PB users was generally indistinguishable from that in non-users, and the median Dapro/ESA dose was approximately one dose step higher than for pts with no PB use (**Fig. A**). While similar results were observed in PD pts, the number of pts reporting no PB use at baseline was too small to draw definitive conclusions (**Fig. B**). At Week 52, the majority of PB users and non-users had Hb within 10–11.5 g/dL, irrespective of treatment randomization.

Conclusions: This analysis demonstrated that baseline PB use had no major impact on the effect of Dapro on Hb levels in HD and PD pts.

Funding: Commercial Support - The study and this analysis were funded by GSK.

Figure. Mean evaluable Hb and median most recent dose by visit by baseline PB use and dialysis type (ITT)



The horizontal reference lines represent the Hb analyses range (10–11.5 g/dL). The Hb target range for dose changes is 10–11 g/dL. The dashed vertical lines represent the evaluation period (Weeks 28–52). Error bars indicate first and third quartiles. PBs include non-based (ferric citrate and sucroferric oxyhydroxide), calcium-based (e.g. calcium acetate), and non-iron and non-calcium-based (sevelamer, sevelamer carbonate, lanthanum carbonate) PBs. Hb: hemoglobin; HD, hemodialysis; ITT, intent-to-treat; N, no; PB, phosphate binder; PD, peritoneal dialysis; Y, yes. 1. Groenendaal-van de Meent D, et al. *Clin Ther.* 2021;43:1079–1091; 2. Paulson SK, et al. *Clin Pharmacol Drug Dev.* 2022;11:475–485.

SA-PO256

Exploring the Potential of Renal Dopaminergic System-Mediated Enhancement in Sodium Excretion by Canagliflozin

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Background: We have found that the renal dopaminergic system starts to activate along with the onset of diabetes/diabetic nephropathy, leading to sodium excretion before the occurrence of polyurea using spontaneously diabetic SDT rats. We raised the question of whether the SGLT2 inhibitors exert the natriuretic effects via the renal dopaminergic system in non-diabetic SD rats.

Methods: Sprague-Dawley (SD) rats (9-11 weeks old, male, N = 8 for non-treated rats, N=7 for canagliflozin-treated rats) were fed a commercial rodent diet. Canagliflozin (1.5-2mg/kg/day) dissolved with 200-250 mL of drinking water were orally administered every morning, from 14 to 25 weeks of ages. Blood samples were collected from the tail vein every week from the ages of 13 to 25 weeks, after which the body weight and the glucose levels. Each rat was individually housed in a metabolic cage for 24 h every week from the ages of 13 to 25 weeks and collected urine samples. At 26 weeks of age, rats were euthanized, perfused intracardially with saline containing heparin (20 IU/mL) and paraformaldehyde (PFA) for histological analyses.

Results: The plasma sodium concentration and blood glucose levels were similar across groups. But significant differences were observed in urinary sodium excretion, urinary glucose excretion, demonstrating the efficacy of canagliflozin. In mass spectrometry imaging analyses, mean values of cortical ionized L-DOPA intensity in canagliflozin-treated SD rats were significantly higher than the L-DOPA in non-treated SD rats. Also, we have observed that canagliflozin-treated SD rats exhibit significantly higher levels of reduced glutathione compared to control SD rats, suggesting a potential contribution to the reduction of renal oxidative stress.

Conclusions: Although further study needs to be conducted, we speculate that each mechanism, the activation of renal dopaminergic system and the suppression of oxidative stress, is another possible mechanism for kidney protection brought about by SGLT2 inhibitors. Possibly, the increased cortical reduction of oxidative stress may contribute to the detoxification caused by excess amounts of L-DOPA and DA.

SA-PO257

One Drug, Different Mechanisms of Side Effects: Linezolid-Induced Thrombocytopenia and Type B Lactic Acidosis

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Introduction: As the burden of antibiotic-resistant bacteria grows, we must understand the pathophysiology and management of rare side effects of Linezolid.

Case Description: 73 yo male with a history of HTN, CKD 3 [baseline serum creatinine(Scr) of 1 mg/dl], and lumbar radiculopathy status post lumbar fusion complicated by infections from Enterobacter cloacae, vancomycin-resistant Enterococci, and methicillin-resistant Staphylococcus aureus (MRSA) treated with- ciprofloxacin 500 mg twice daily for 60 days before admission, 30 days of tedizolid 200 mg daily, and Linezolid 600 mg twice daily for 9 days, leading to this admission. On admission, the patient had a Scr of 1.6 mg/dl, platelets of 93 K/UL, and lactate of 3.35 mmol/L. Lactate increased to 3.9 mmol/L on hospital day (HD) 1 and returned to normal limits by HD 2 mmol/L. He had a platelet nadir of 43 K/UL on HD 5, along with improvement in Scr to 1.1 mg/dl. Platelet count recovered to 570 K/UL 12 days after admission.

Discussion: Linezolid induced lactic acidosis and thrombocytopenia is diagnosed after excluding other conditions such as hypoxemia, anemia or low cardiac output. Approximately 30% of linezolid is eliminated via the renal route, with an elimination half-life of 5 to 7 hours with the therapeutic trough concentration being 2–8 μg/ml. In patients with impaired renal function, elimination half-life increases from 6.1 to 8.4 hours. Mitochondrial toxicity of linezolid causes severe lactic acidosis usually related to its toxic trough serum levels. Two mechanisms of LIT have been proposed; decreased platelet production via bone marrow suppression, and immune-mediated platelet destruction. Pharmacokinetic modeling of the two mechanisms found that suppression of platelet formation was the significantly more prominent mechanism of LIT. Immune-mediated platelet destruction typically develops within 7-14 days and recovers rapidly, whilst bone marrow suppression-associated thrombocytopenia develops gradually over multiple weeks and recovers gradually. The latter was observed in this case; a gradual decline and recovery of platelet counts. One has to consider reducing linezolid dose in patients with renal insufficiency on prolonged treatment to reduce toxicity amongst patients at low risk for treatment failure while being guided by therapeutic drug monitoring.

SA-PO258

Linezolid Adsorption During In Vitro Model of Hemoperfusion with Mini-Module of HA380 Cartridge

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Background: AKI due to sepsis is the result of a dysregulated host immune response to infection, with the production of inflammatory mediators and cytokines. Jafron HA380 cartridge has been specifically designed for cytokine storm in sepsis. Given the growing application of these hemoperfusion device, an unsolved problem is whether these polymers adsorb drugs, including antibiotics. *In vitro* experiments were conducted to determine its adsorption capacity towards Linezolid (LZD) antibiotic.

Methods: *In vitro* circulation was performed using a dedicated testing platform Galileo. A customized cartridge was built assembling mini-module components scaled in dimension towards HA380 and filled with 75g of HA380 beads (25% of the regular size). Blood pump was set at 250ml/min. Saline and human blood solutions enriched with 600mg of LZD have been tested for 2hrs. Samples were collected after the first passage (FP) through the cartridge and every 5 or 10min. LZD concentrations were measured. Adsorption was assessed considering the Removal Ratio:$RR(\%)=100x(C_0- C_t)/ C_0$.

Results: Experiment with saline solution was performed in duplicate. *In vitro* circulation confirms the affinity of beads material in binding LZD. The kinetics shows a rapid adsorption in the very first part of the experiments, after that the adsorption rate decreased due to the decrease of antibiotic available in the solution. After FP of the solution through the cartridge, a RR higher than 80% has been achieved. At the end of the experiments the adsorption reached about the 100% of RR. Blood circulation reinforced these results: the RR of FP was higher than 80%, and at the end the mass injected in the solution was almost entirely adsorbed (see table).

Conclusions: HA380 adsorbs significant amounts of LZD. Further investigation using a higher quantity of LZD is necessary to reach the saturation of the cartridge and understand the sorbent material capacity. These preliminary results highlight that there is an interaction that could affect the clinical outcome.

	Mass in the reservoir (mg)			RR (%)			Mass adsorbed (mg)		
Time point	Saline 1	Saline 2	Blood	Saline 1	Saline 2	Blood	Saline 1	Saline 2	Blood
0	603.9	598.2	674.1						
FP	88.8	88.5	102.0	85.3	85.2	84.8	515.1	509.4	572.0
5	26.3	7.6	70.1	95.6	98.7	89.6	577.6	590.5	603.9
10	11.0	2.7	54.6	98.2	99.5	91.9	592.8	595.4	619.3
15	5.2	1.8	33.0	99.1	99.7	95.1	598.6	596.4	641.0
20	3.2	1.4	19.7	99.5	99.8	97.1	600.6	596.8	654.3
30	2.0	1.1	10.7	99.7	99.8	98.4	601.9	597.0	663.3
40	1.5	0.8	7.4	99.7	99.9	98.9	602.3	597.4	666.7
50	1.2	0.8	6.3	99.8	99.9	99.1	602.6	597.4	667.8
60	0.9	0.6	4.9	99.8	99.9	99.3	603.0	597.6	669.1
70	0.7	0.5	4.7	99.9	99.9	99.3	603.1	597.7	669.4
80	0.7	0.4	4.2	99.9	99.9	99.4	603.2	597.8	669.8
90	0.6	0.3	3.8	99.9	99.9	99.4	603.3	597.9	670.3
100	0.4	0.3	3.5	99.9	99.9	99.5	603.5	597.9	670.5
110	0.4	0.3	3.2	99.9	99.9	99.5	603.5	597.9	670.9
120	0.4	0.3	3.2	99.9	99.9	99.5	603.5	597.9	670.8

SA-PO259

Use of Antiplatelet Drugs Targeting Platelet P2Y12 Receptor Is Associated with Reduced Risk for Infectious Death in Veterans with CKD

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Background: Platelets modulate thrombosis and inflammation, a hallmark of CKD pathophysiology. As a result, antiplatelet drugs are commonly used to reduce the risk of thrombosis in patients with CKD. Recent studies also demonstrated that platelet P2Y12 receptor inhibitors (P2Y12i) reduce inflammatory burden in patients with CKD, but their clinical impact on inflammation-related outcomes in CKD is not established. We investigated whether treatment with P2Y12i is associated with reduction in infection related deaths among patients with CKD.

Methods: We examined a national cohort of 90,701 US Veterans with incident CKD who were new P2Y12i users and 431,188 who never received P2Y12i. We used clinical trial emulation methods to examine the association of P2Y12i therapy with infectious deaths in competing risk regressions and cause-specific Cox models using propensity score (PS) overlap weighting to balance for baseline differences in demographics, comorbidities, laboratory values, and relevant medications use.

Results: Overall mean (SD) age was 69 (11) years, and eGFR was 69 (17) ml/min/1.73m^2; 95% were men; 16% were African Americans; 46% were diabetics. During a median follow-up of 6.8 years, there were 4,823 infectious deaths with 986 deaths in P2Y12i users (event rate and 95%CI: 0.87/1000PY, 0.82-0.92) and 3,837 deaths in non-users (1.45/1000PY, 1.4-1.5). P2Y12i therapy was associated with a reduced risk of infectious deaths in competing risk regressions and in cause-specific Cox models (Table).

Conclusions: In a large national cohort of Veterans with incident CKD, use of P2Y12i was associated with reduced risk of infectious deaths. The role of P2Y12i in the management of inflammation in CKD requires additional testing in prospective trials.

Funding: Veterans Affairs Support

Subhazard ratio and hazard ratio of a PS-weighed competing risk and cause specific Cox model in P2Y12i treated patients (vs. untreated) (n=521889).

		Competing Risk	P-value	Cox Model	P-value
	Event Rate per 1000PY (95% CI)	Subhazard Ratio (95% CI)		Hazard Ratio (95% CI)	
No P2Y12i Treatment (N=431,188)	1.45 (1.4, 1.5)	Referent	0.0016	Referent	<0.0001
P2Y12i Treatment (N=90,701)	0.87 (0.82, 0.92)	0.72 (0.58, 0.88)		0.45 (0.36, 0.57)	

SA-PO260

Torasemide Decreases Kynurenic Acid Production in Rat Kidney In Vitro

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Background: Loop diuretics are one of the most widely used agents in the treatment of congestive heart failure or arterial hypertension and related edemas. Torasemide is known to have longer time of action compared to other class representatives and thus more often chosen to stimulate diuresis. It was speculated that torasemide by volume depletion can be responsible for impaired kidney function, however direct nephrotoxic effect cannot be excluded. Tryptophan metabolites are well described uremic toxins. Among them kynurenic acid (KYNA) presents ambiguous effects. KYNA is a broad spectrum glutamatergic receptors antagonist, an agonist of cholinergic alpha-7-nicotinic receptors and a ligand of aryl hydrocarbon receptors. Direct precursor of KYNA, kynurenine (KYN) is metabolized through kynurenine aminotransferases (KATs). In animal models of hypertension KYNA was reported to cause natriuresis and lower the heart rate. On the other hand, it was observed that KYNA accumulated in the body proportionally to kidney function decline in animal and human studies. The aim of our study was to examine the influence of torasemide on KYNA synthesis and KATs isoenzymes activity, KAT I and KAT II, in rat kidney *in vitro*.

Methods: KYNA production and enzymes activity was analyzed in kidney homogenates and on purified enzymes after 2 hours incubation in the presence of L-KYN and torasemide in 6 different concentrations (1 μM, 10 μM, 50 μM, 100 μM, 500 μM, 1 mM). Due to limited drug's solubility torasemide was tested in kidney homogenates up to 500 μM concentration, whereas enzymes activity was analyzed up to 1 mM concentration. The amount of formed KYNA was quantified by high-performance liquid chromatography.

Results: Torasemide at 500 μM concentration decreased KYNA production to 68 % ($p < 0.05$) of control value. At 500 μM and 1 mM concentration torasemide inhibited KAT I activity to 78 % ($p < 0.05$) and 43 % ($p < 0.05$) of control value, respectively. Only at 1 mM concentration torasemide lowered KAT II activity to 17 % ($p < 0.01$) of control value.

Conclusions: We show for the first time that torasemide inhibits KYNA production and KATs activity in rat kidney *in vitro*. Further studies are warranted to investigate the impact of presented results on kidney function.

SA-PO261

Lack of Consistency in Loop Diuretic Strategies of Acute Heart Failure

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Background: Symptoms and signs of fluid overload are the primary reason for hospitalization of patients with acute heart failure (AHF). Intravenous loop diuretics (LD) remain the mainstay of therapy in this setting, with a significant subset of patients showing suboptimal response. The efficacy of combination diuretic therapy (CDT), a widely applied strategy to counter renal sodium avidity, is compared against LD-based regimens that are considered the standard of care. We sought to explore the consistency of LD use in contemporary trials of CDT in AHF.

Methods: Articles cited in the PubMed database using keywords "acute heart failure", "diuretic", and "congestion" were searched. Available data from clinical trials performed between January 2005 and December May 2023 were included. The studies were selected if 1) they were randomized controlled trials that explored the role of CDT in management of AHF, and 2) included loop diuretics as their control arm. Pertinent data on clinical and laboratory parameters (e.g. diuresis, weight change, and renal function) were extracted and reviewed.

Results: A total of 13 studies with 7,826 participants were included with a mean age of 72 years. They consisted of a variety of HF populations with a mean ejection fraction of 38% and an estimated GFR of 49 ml/min. The add-on agents were SGLT-2 inhibitors, acetazolamide, hydrochlorothiazide, spironolactone, and tolvaptan. There was substantial variation across studies both in the loop regimen and the reporting of decongestion markers (e.g. diuresis and weight change). The urine output on day-1 ranged from 1183 to 2400 ml (mean 1620.8 ±413 ml), while weight loss on day-1 was more consistent (0.94 to 1.2 kg; mean 1.04±0.1 kg).

Conclusions: While the current guidelines of AHF recommend intensifying LD therapy prior to CDT to enhance the decongestion process, there is no consensus on an optimal diuretic strategy. This study shows that 1) the LD regimens used in contemporary trials of CDT are highly variable, 2) the inconsistency in these regimens results in a highly variable diuresis as a marker of decongestion, and 3) a reliable comparison of the efficacy of add-on agents is challenging due to lack of consistency in the control arm. These results call for the development of an optimal LD strategy for AHF to help improve the decongestion process.

SA-PO262

Accelerating Drug Discovery for CKD Through Mendelian Randomization Analyses of Druggable Proteins

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Background: Drug repurposing can accelerate the discovery of treatments for chronic kidney disease. To identify potential therapeutic targets, we conducted Mendelian randomization analyses using genetic instruments for proteins targeted by approved drugs or drugs in clinical development.

Methods: Genetic instruments for 879 druggable proteins were derived from the Genotype-Tissue Expression (GTEx) project. Kidney outcomes included estimated glomerular filtration rate (eGFR), chronic kidney disease (CKD), and end-stage kidney disease (ESKD) derived from genome-wide association study summary statistics of European ancestry individuals in the Million Veteran Program (MVP). A drug target was considered significant if it met study-wide Bonferroni significance in the inverse variance weighted analysis for all three kidney outcomes stratified by diabetes status. Significant findings in MVP were replicated in the Chronic Kidney Disease Genetics Consortium (CKDGen). Analysis was performed using the TwoSampeMR package in R version 3.3.3 using the Vanderbilt Advanced Computing Center for Research and Education.

Results: Our study identified 69 independent drug targets within MVP ($p < 9.48E-06$). Shared targets in non-diabetic patients were Myosin Heavy Chain 7B (p_{eGFR} = 8.70E-08, p_{CKD} = 5.95E-17, p_{ESKD} = 5.80E-12) and Gonadotropin Releasing Hormone Receptor (p_{eGFR} = 3.61E-14, p_{CKD} = 1.94E-15, p_{ESKD} = 2.07E-09, 3.24E-17). Shared targets in diabetic patients were HLA-DRB1 (p_{eGFR} = 3.31E-54, p_{CKD} = 1.05E-53, p_{ESKD} = 1.72E-14), Glycoprotein Nmb (p_{eGFR} = 1.52E-14, p_{CKD} = 5.37E-16, p_{ESKD} = 2.31E-10), and Gonadotropin Releasing Hormone Receptor (p_{eGFR} = 2.56E-15, p_{CKD} = 5.45E-08, p_{ESKD} = 1.42E-08). All findings in MVP were replicated in CKDGen. The direction of effect was consistent across all findings, except for Gonadotropin Releasing Hormone Receptor which exhibited a positive effect in diabetic patients and a negative effect in non-diabetic patients.

Conclusions: Our findings highlight potential targets for therapeutic intervention in CKD. Pathway enrichment analyses are underway to explore underlying mechanisms. Further studies should confirm the causal relationship between druggable proteins and kidney outcomes.

Funding: Veterans Affairs Support

SA-PO263

Health Effects (Renal) Of Extra Strength Avmacol (HEROES) Study: Results from the Pharmacokinetic Phase of a Randomized Double-Blind Placebo-Controlled Trial

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Background: Increased oxidative stress is a major molecular underpinning of chronic kidney disease (CKD) progression. Decreases in the antioxidant enzyme glutathione-S-transferase μ-1 (GSTM1) due to a very common null gene variant have been shown to elevate oxidative stress and increase disease progression in animal and clinical studies. GSTM1 and many other antioxidant enzymes are regulated by the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway. This pathway can be upregulated by sulforaphane (SFN), which can be obtained naturally from cruciferous vegetables such as broccoli. Commercially available SFN supplements provide much greater consistency in dosage compared to dietary intake, and mouse studies have shown oral supplementation to be protective in CKD. We hypothesize that daily intake of SFN – in the form of Avmacol Extra Strength (ES) – will decrease CKD progression rate and decrease markers of oxidative stress and inflammation. We will test the safety, tolerability, and efficacy of Avmacol ES taken daily for 6 months in CKD Stages 3-4 in a randomized, double-blind, placebo controlled clinical trial.

Methods: A pharmacokinetic (PK) study was first performed to establish an optimal dose of Avmacol ES for CKD patients with eGFR of 25 – 45 mL/min/1.73m² to achieve similar peak concentrations and area under the curve (AUC) of plasma SFN observed in non-CKD patients. Subjects were given 2, 4, or 6 tablets once daily for 7 days. Plasma was collected at 0-8 h after the last dose. SFN levels were measured by LC/MS/MS.

Results: Peak plasma concentration (C_{max}) was reached between 2-4 h (t_{max}) in subjects taking 4 tablets (average C_{max}: 120 nM, AUC8h: 824 nmol h/L, n = 4) and in those taking 2 tablets (average C_{max}: 85.1 nM, AUC8h: 581.4 nmol h/L, n=4). No C_{max} was observed in those taking 6 tablets during 8h, and gastrointestinal (GI) side effects (SE) were significant. Both 2 and 4 tablets daily were well tolerated with minimal GI SE.

Conclusions: In CKD 3-4, SFN t_{max} is delayed compared to the 1-2 h t_{max} reported in non-CKD subjects. Avmacol ES 4 tablets daily is well-tolerated with greater and more consistent C_{max} and AUC than 2 tablets daily and is being used in the on-going randomized phase.

Funding: NIDDK Support, Commercial Support - Nutramax (providing drug and placebo)

SA-PO264

Magnetic Resonance Imaging Contrast Agent Safety: Prodigious Phosphorus in Renal Gadolinium-Rich Nanoparticles

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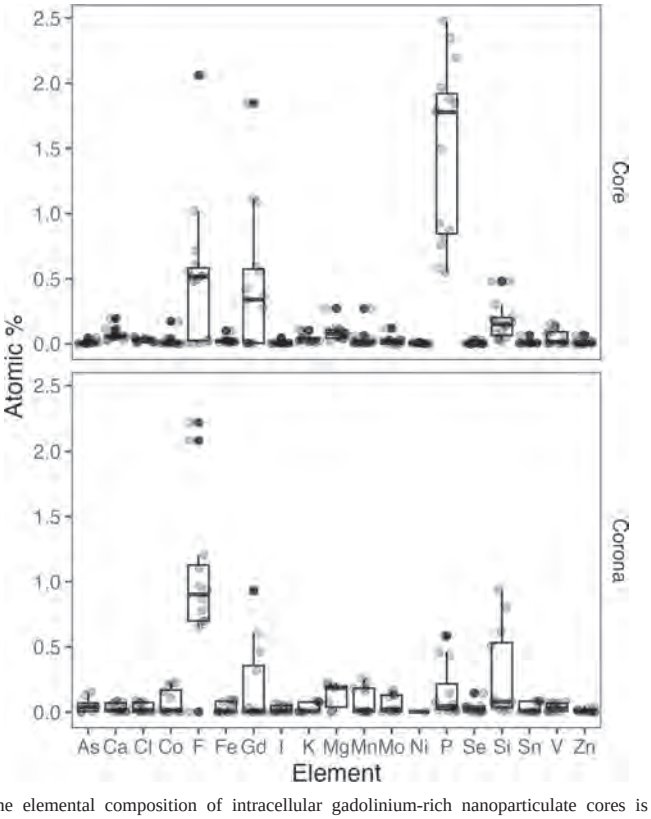
Background: Magnetic resonance imaging (MRI) contrast agent complications include fibrosis, kidney injury, and fatal gadolinium encephalopathy. Routine diagnostic imaging leads to the formation of gadolinium-rich nanoparticles in human kidneys. The mechanism is unclear.

Methods: Mice were treated with a MRI contrast agent. After four weeks of treatment and a washout period of 0.5 weeks, the kidneys were harvested. Flash-frozen kidney samples were homogenized in radioimmunoprecipitation assay buffer. Gadolinium-rich nanoparticles were purified from homogenate ultracentrifuged through sucrose gradients of different concentrations. We localized the nanoparticles using transmission electron microscopy (TEM). The elemental characterization of the nanoparticles was obtained using X-ray energy-dispersive spectroscopy (aberration-corrected scanning TEM, JEOL NEOARM). We compared quantities between core and coronal areas using a two-tailed t-test. We adjusted the p-values using the Benjamini-Hochberg (B-H) method to account for false discoveries.

Results: Electron-dense intracellular debris peppered the proximal tubular epithelium. The dendritic cores and coronas contained high levels of gadolinium. Among the elements, phosphorus was 9.5-fold higher in the cores ($p = 1.2 \times 10^6$).

Conclusions: There is more than one side to the argument concerning the safety of MRI contrast agents. Our findings suggest that nanoparticulate dendritic cores exhibit high phosphorus levels, which does not support the formation of $GdPO_4$ precipitate. These results contribute to understanding the mechanism of gadolinium-induced complications.

Funding: NIDDK Support, Other NIH Support - UL1TR001449, Veterans Affairs Support, Private Foundation Support



The elemental composition of intracellular gadolinium-rich nanoparticulate cores is glutted in phosphorus than the peripheral coronas.

SA-PO265

Hydralazine Adduct Formation on Myeloperoxidase Contributes to Development of Drug-Associated ANCA Vasculitis

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Background: Hydralazine exposure, an anti-hypertensive agent and a carbonyl scavenger, is associated with the development of ANCA vasculitis. We propose a pathogenic mechanism for hydralazine associated ANCA vasculitis hinging on formation of hydralazine adducts on myeloperoxidase (MPO), the primary immunogen for MPO ANCA.

Methods: *In vitro* hydralazine studies were performed using horse metmyoglobin (Mb) and human MPO. Hydralazine labeled Mb was digested by trypsin and peptides were analyzed with reverse phase HPLC and electrospray mass spectrometry. In addition, hydralazine labeled MPO was separated using PAGE gels and the hydralazine adduct was detected using an anti-hydralazine antibody. Commercially anti-MPO antibodies recognizing different portions of MPO were used to investigate the conformational change of the MPO heavy chain after hydralazine adducts formation. In addition, an immunoprecipitation assay was performed to detect hydralazine adducts on circulating MPO from patients. Furthermore, anti-MPO IgM and IgG antibodies were measured using ELISAs. Purified IgM and IgG from patients and healthy controls' plasma were investigated their ability to recognize control MPO or hydralazine labeled MPO.

Results: *In vitro* studies showed that carbonyl groups formation on primary amines of a protein in the presence of aldehydic products, such as acrolein, is required for hydralazine to bind a protein. Mass spectrometry data showed that hydralazine bound to a carbonyl group of Mb. Under similar conditions, hydralazine adducts were formed on MPO. Importantly, the hydralazine adducts on MPO could be detected in plasma from hydralazine associated ANCA patients but not from patients with non-hydralazine associated ANCA or healthy subjects. Using commercially anti-MPO antibodies, we demonstrated that hydralazine adducts formation on MPO resulted in conformation changes. In addition, purified IgG and IgM autoantibodies from hydralazine associated ANCA patients were reactive against hydralazine labeled MPO.

Conclusions: Under appropriate reactive conditions, hydralazine adducts were able to be formed on MPO in some subjects who were exposed to hydralazine. Hydralazine adducts induced MPO conformational changes which may facilitate autoantibody development, leading to hydralazine associated ANCA vasculitis.

Funding: NIDDK Support

SA-PO266

Dapagliflozin Ameliorates Cisplatin-Induced Nephrotoxicity by Upregulating Nuclear Factor Erythroid 2-Related Factor 2/Heme Oxygenase-1 Signaling Pathway: A Pre-Clinical Molecular Approach

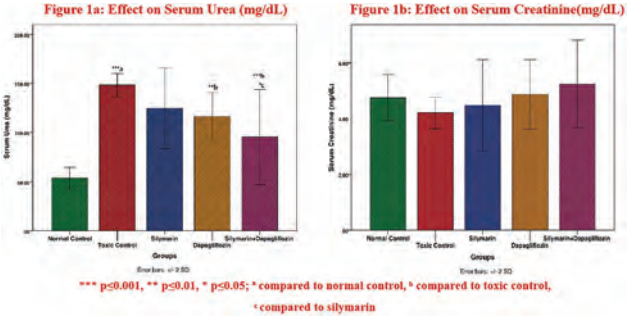
Anuradha A. Nair, Mohamed Farook, Nirmal N. Binu, Sofiya Khan, Mohamed Yehya Mohamed Mustafa, Mohammed M. Khan, Shakta Mani Satyam, Laxminarayana K. Bairy, Abdul Rehman. Dr. Satyam's Lab - DAPA CKD Team. *Ras Al Khaimah Medical and Health Sciences University College of Medical Sciences, Ras Al Khaimah, United Arab Emirates.*

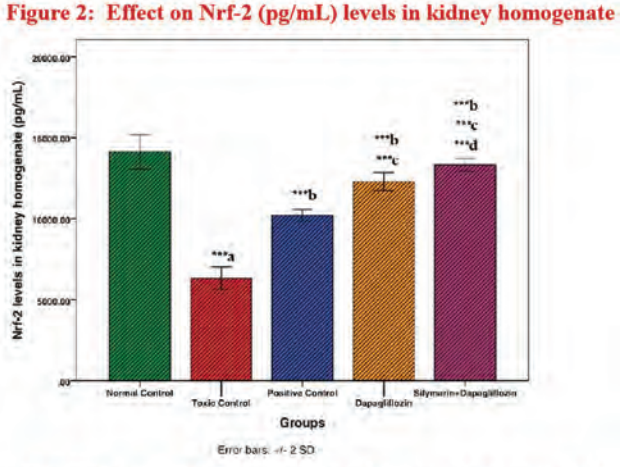
Background: A dose-limiting side effect of cisplatin administration is nephrotoxicity which impairs a patient's quality of life. No potent nephroprotective agent is available to combat cisplatin-induced nephrotoxicity. This study aimed to explore the nephroprotective potential of dapagliflozin and silymarin alone and in combination against cisplatin-induced nephrotoxicity in Wistar rats.

Methods: 30 adult Wistar rats were randomly divided into five groups (n=6/group): Group I- Normal control, Group II- Negative control, Group- III- Silymarin, Group IV- Dapagliflozin and Group V- Dapagliflozin + Silymarin. Nephrotoxicity was induced in Group II to Group V by administering cisplatin weekly for seven weeks. Biomarkers for kidney injury, inflammation, and oxidative stress were estimated following a histopathological examination of the kidney.

Results: Chronic kidney disease was significantly ($p<0.05$) demonstrated in cisplatin-intoxicated (negative) control compared to normal control rats. Dapagliflozin alone and in combination with silymarin significantly ($p<0.05$) reduced serum urea, creatinine, inflammatory cytokines, and oxidative stress markers compared to negative control.

Conclusions: The present study revealed that dapagliflozin alone and in combination with silymarin ameliorates cisplatin-induced nephrotoxicity in Wistar rats via stimulating Nrf2/HO-1 signaling pathway.





SA-PO267

Pharmacological Inhibition of Lysine-Specific Histone Demethylase 1 Protects Against AKI

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Background: Acute kidney injury (AKI) is a common clinical condition associated with increased mortality and morbidity. Current therapeutic options for this serious disorder are often limited and ineffective. Therefore, new therapeutic strategies are urgently needed to prevent or treat AKI. Macrophages play a critical role in the pathogenesis of cisplatin-induced AKI. However, the molecular mechanisms underlying macrophage activation in AKI are not fully elucidated. In this study, we investigated the role of lysine-specific histone demethylase 1 (LSD1) in the regulation of macrophage activation in the development of cisplatin-induced AKI.

Methods: To examine the role of LSD1 in cisplatin-induced AKI in vivo, wild-type C57BL6/J mice were administered intraperitoneally with a single dose of 20 mg/kg cisplatin to induce AKI and treated with GSK-LSD1, a selective LSD1 inhibitor, at 1 mg/kg or vehicle daily by intraperitoneal injection for 3 days. Cultured bone marrow-derived macrophages were used to examine the role and mechanisms of LSD1 in the regulation of macrophage activation in vitro.

Results: The expression of LSD1 was increased in macrophages in the kidney following cisplatin-induced AKI. Pharmacological inhibition of LSD1 with GSK-LSD1 protected the kidney from cisplatin-induced AKI and preserved kidney function in vivo. Furthermore, pharmacological inhibition of LSD1 with GSK-LSD1 suppressed macrophage activation, attenuated the NLRP3 expression, and inhibited inflammasome activation, resulting in reduced cleaved caspase 1 and IL-1β levels in the kidneys of cisplatin-induced AKI. In bone marrow-derived macrophages, pharmacological inhibition of LSD1 with GSK-LSD1 abolished macrophage activation and suppressed proinflammatory cytokine production. Moreover, GSK-LSD1 blocks NLRP3 expression and inflammasome activation in bone marrow-derived macrophages.

Conclusions: Our study identifies LSD1 as a critical regulator of NLRP3 expression and inflammasome activation in macrophages, leading to proinflammatory molecule production and development of cisplatin-induced AKI. Therefore, targeting LSD1 may represent a novel therapeutic strategy for AKI.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support

SA-PO268

Human Primary Renal Proximal Tubule 3D Spheroid Model for Kidney Injury and Drug Discovery

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Background: Renal proximal tubular epithelial cells (RPTECs) have a prominent role in maintaining kidney function by reabsorbing filtered nutritional substances, while allowing other substances to be excreted in the urine. RPTEC injury, cell death, and de-differentiation are mechanisms involved in kidney diseases including acute kidney injury (AKI). Human primary RPTECs isolated from normal human kidney tissue maintain the original phenotype *in vitro* for several passages and provide a translational advantage for studying nephron function and pathophysiology. Conventional two-dimensional culture methods frequently result in loss of tissue-specific RPTEC phenotypes partially due to changes of cell-cell communications and microenvironment. Hence, 3D models of RPTECs are being developed and used for drug discovery.

Methods: Primary hRPTECs were cultured in ULA spheroid plates for 4 days to form spheroids. Cellular injury was then induced by treatment with cisplatin or incubation in hypoxic chambers. Cytokine concentration, cell viability and apoptosis were measured by using commercial kits. RNA-seq were carried out, and pathway enrichment were analyzed by using Ingenuity Pathway Analysis software.

Results: Here we found that compared to 2D cultured cells, the hRPTEC 3D spheroid increased cisplatin induced injury responses and sensitivity with higher apoptosis and lower cell viability. Hypoxic condition induced significant increase of cell apoptosis and decrease of cell viability in hRPTEC spheroid. Transcriptomic analysis on the 3D hRPTEC hypoxia injury model identified similar pathway changes that found in *in vivo* in ischemic AKI models. Pathway analysis in this model supports a role of IL-17A in promoting hRPTEC inflammation and injury. In contrast, SIRT3 activator treatment protected hRPTEC from hypoxia injury likely by improving energy metabolism and mitochondria function.

Conclusions: 3D injury models in primary hRPTEC spheroid are more sensitive to cisplatin injury than 2D cultures and pathway analysis revealed pathway changes consistent with a role of IL-17. The models provide a physiological and pathophysiological tool, to evaluate the function and pathophysiology of the kidney with higher translational relevance and can be leverage for fast screening and evaluation of potential therapeutic targets for kidney diseases.

Funding: Commercial Support - JNJ

SA-PO269

Distinct Pharmacokinetics of AAV9 and AAVKP1 Enable Context-Dependent Efficient Renal Transduction

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Background: Recent progress in capsid engineering led to generation of numerous adeno-associated virus (AAV) vectors with novel phenotypes. However, they have not been evaluated in the context of renal gene transfer. Increased permeability of glomerular and peritubular capillary (PTC) is a common feature of CKD, but renal transduction in CKD kidney is yet to be characterized.

Methods: Renal transduction of 47 different AAV vectors following IV and renal vein (RV) administration was evaluated in C57BL/6J mice using NGS-based high-throughput method called AAV Barcode-Seq. Effect of CKD on renal transduction was assessed in X-linked Alport syndrome model mice. Select AAV vectors were individually vectorized and relationship between renal transduction and pharmacokinetics was evaluated.

Results: AAV Barcode-Seq followed by individual characterization revealed that proximal tubule (PT) and podocyte transduction is not attainable by IV administration of AAV vectors. On the other hand, AAVKP1 but not AAV9 transduced PT following RV administration. Assessment of injection path using fluorescent microspheres showed accumulation in the cortical interstitial space following RV administration. Interestingly, >10 times more AAVKP1 vectors were detected in the injected kidney ten minutes post RV administration compared to AAV9. These observations suggest that RV administration bypasses PTC and efficient interstitial retention of AAVKP1 enables PT transduction from basolateral side. In contrast to minimal urinary excretion of AAV vectors in healthy mice, excretion of AAV9 but not AAVKP1 was significantly increased in CKD mice by about 10^4 times following IV administration. Difference between AAV9 and AAVKP1 is explained by rapid blood clearance of AAVKP1 that shows >1000 times less blood concentration than AAV9 over eight hours post injection. Consistent with this observation, IV administration of AAV9 but not AAVKP1 achieved efficient podocyte and PT transduction in CKD kidney, suggesting that higher blood concentration of AAV9 facilitates access to podocytes and PT across leaky glomerular filtration barrier and PTC in CKD.

Conclusions: Our study underscores the important role of AAV pharmacokinetics in renal gene transfer. Appropriate selection of AAV vector depending on administration route and host condition is vital for successful gene therapy.

SA-PO270

RXFP1, the Relaxin Receptor, Is a Therapeutic Target Expressed in the Human Kidney, Not Rodent

Mark Lal,[1] Sean Eddy,[2] Jeffrey B. Hodgin,[2] Magnus Althage,[1] Pernille B. Laerkegaard Hansen,[1] Jaakko Patrakka,[3] Matthias Kretzler.[2] *[1]AstraZeneca PLC, Gothenburg, Sweden; [2]University of Michigan Michigan Medicine, Ann Arbor, MI; [3]Karolinska Institutet, Stockholm, Sweden.*

Background: RXFP1 is a G-protein coupled receptor (GPCR) potently agonized by its cognate ligand, relaxin. Historically named the pregnancy hormone following its identification and physiological description in rodents, relaxin is broadly recognized as a circulating hormone possessing several potentially clinically relevant cardiovascular-modulating and anti-fibrotic properties. It has long been recognized that there is remarkable diversity among species with regard to tissue source, regulation of synthesis and secretion, and physiological effects of relaxin. On the other hand, there is limited and inadequate understanding of RXFP1's tissue and cell expression across species, especially human.

Methods: Here, we describe the human target validation of RXFP1 in human kidney and highlight striking differences with rodent.

Results: As opposed to mouse and rat kidney, where RXFP1 is poorly expressed, RXFP1 is identified as one of the most highly expressed GPCRs in human glomeruli. Specifically, by single cell RNAseq, in situ hybridization and immunohistochemistry, we identify glomerular endothelial cells as the principal cell type expressing RXFP1. Through extensive analysis of human kidney expression data sets from patient biopsies, we find that RXFP1 expression correlates with kidney function and disease progression. We identified a 428 gene RXFP1 co-expression network (R>0.6, FDR<0.05) that was enriched for an endothelial cell gene signature.

Conclusions: These observations provide a vital foundation to building our pharmacologic understanding of relaxin/RXFP1 function in human and suggest that kidney-intrinsic target engagement may mechanistically explain the renal hemodynamic actions noted in clinical trials with relaxin. Great care needs to be taken to avoid conflation of relaxin's diverse physiological effects observed in species where RXFP1 cellular expression is not congruent with human.

Funding: Other NIH Support - NIH, Commercial Support - AstraZeneca

SA-PO271

A Novel and Unique Fc-Fusion Protein i-Body AD-214 Ameliorates Kidney Fibrosis Through Inhibition of Leukocyte Migration

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Background: Tissue fibrosis is the common pathological pathway in progressive chronic kidney disease (CKD). Current clinical practices are ineffective in limiting renal fibrosis. CXCR4 has been demonstrated to be central to the development of fibrosis. The usage of neural cell adhesion molecules as scaffolds by incorporating binding loops, mimicking the shape of shark antibody, allows construction of fully humanized single-domain antibody-like scaffold, designated as i-bodies. The i-body AD-214, which bind CXCR4 with high affinity, has been shown to be effective in limiting lung fibrosis. However, the role of AD-214 in renal fibrosis has not been investigated.

Methods: Renal proximal tubular cells (PTC) were incubated with TGFβ1 with/without AD-214 for 48 hours. Supernatant was collected and collagen-3 (Col-3) and collagen-4 (Col-4) were measured by Western blot. Mice with unilateral ureteral obstruction (UUO) were administrated AD-214 every two days from one day after UUO for 14 days. Changes in renal morphology were examined by H&E and PSR staining. Renal histology, mRNA, analysed by qRT-PCR, extracellular matrix (ECM) and leukocyte markers detected by immunohistochemistry (IHC) and kidney function, assessed by the blood urea nitrogen (BUN) and kidney injury molecule-1 (KIM-1) were examined. The *in vitro* scratch assay was conducted to investigate the impact of AD-214 on macrophage migration.

Results: AD-214 suppressed TGFβ1-induced overexpression of Col-3 and Col-4 by RPTEC cells compared to negative control. In UUO model, mice treated with AD-214 markedly ameliorated collagen deposition (30.4% reduction) relative to UUO+negative i-body treated group. IHC staining revealed that administration of AD-214 significantly attenuated the Col-4 and fibronectin (FN) deposition by 74.4% and 34.6% respectively relative to negative i-body treatment group. Consistently, physiological parameters BUN and KIM-1 were markedly reduced in mice treated with AD-214. Mechanism studies revealed AD-214 inhibited the infiltration of leukocytes including macrophages and neutrophils into UUO kidneys. In the *in vitro* scratch assay, AD-214 effectively inhibited the migration of macrophages induced by LPS.

Conclusions: Blocking CXCR4 using the i-body AD-214 is a promising therapeutic strategy to prevent the development of CKD.

Funding: Commercial Support - Adalta.Ltd, Private Foundation Support

SA-PO272

Optimized Normothermic Machine Perfusion of Kidney, Liver, and Combined Liver-Kidney to Predict Human Pharmacokinetics

Arianne Van Koppen, Reinout Stoop. *TNO, Leiden, Netherlands.*

Background: Robust translational models are key to predict the intestinal absorption, hepatic clearance (metabolic and biliary) and renal clearance of compounds. Ex vivo normothermic machine perfusion (NMP) of whole organs is a promising tool, especially

when combined with physiologically-based pharmacokinetic (PBPK) modeling to reliably predict human exposure levels. We aimed to optimize organ functioning during NMP and to demonstrate prediction of ADME data of model drugs (rosuvastatin, digoxin, metformin and furosemide) of liver and kidney combined with ex vivo intestinal absorption studies and PBPK modeling to predict the drug PK profile in humans.

Methods: Three ex vivo models were applied using porcine organs 1) the inTESTine system (n=3) to study apical to basolateral intestinal transport, 2) normothermic machine perfusion of ex vivo liver (n=3) to determine hepatic uptake, clearance and biliary excretion and 3) normothermic machine perfusion of ex vivo kidney (n=3) to determine renal clearance and urinary excretion.

Results: Intestinal absorption of digoxin and rosuvastatin were limited. Perfused porcine livers rapidly cleared rosuvastatin and digoxin from perfusate (hepatic extraction ratio of 0.82 and 0.31). Compounds were traced in bile after 10 min (rosuvastatin; 23%, digoxin; 51%, metformin and furosemide; ~0.2%). Renal excretion of rosuvastatin and digoxin was low, but high for furosemide and metformin (>90%).

Conclusions: NMP can be optimized to sustain organ functionality during perfusion. The combination of ex vivo gut, liver and kidney models with a generic PBPK model is a unique and powerful combination to predict ADME profile of (new) drugs, including the possibility to calculate the fraction that undergoes enterohepatic circulation. Future research is aimed at studying drug-drug interactions and the effects of disease processes.

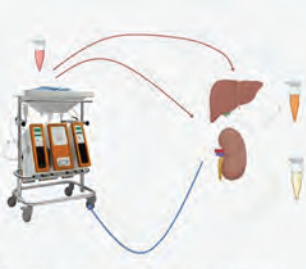

Figure 1. Graphical representation of combined ex vivo liver and kidney perfusion; generating perfusate, bile and urine fractions.

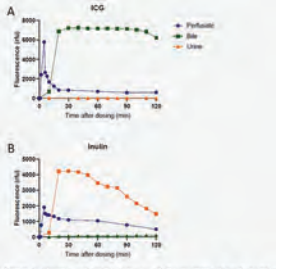

Figure 2. Hepatic and renal clearance of fluorescently labelled model compounds ICG (hepatic and biliary clearance) and inulin (renal and urinary clearance). (A) ICG is excreted into bile and not into urine (B) inulin excretion into urine and not into bile.

SA-PO273

Metabolomics of Drug-Induced Mitochondrial Biogenesis in Aged Mice Kidneys

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Background: Mitochondrial dysfunction is important in the aging process of many organs. We have shown that MC16, a drug candidate, induces mitochondrial biogenesis (MB) in mouse renal cortices and improves renal function in response to acute kidney injury. Thus, we hypothesized that stimulation of MB in aged mouse kidneys would improve global metabolomics in the kidney cortex.

Methods: Aged 22-month-old male C57B/6J mice were administered 1.0mg/kg MC16 or normal saline every other day over 21 days (n=8-9/group). Seven-month-old controls were administered normal saline every other day over 21 days (n=7). Kidneys were harvested and snap frozen in liquid nitrogen. Cortical biopsies were analyzed by Metabolon via multi-mass spectrometry. After mass normalization, log-transformation, and imputation, Welch's two-sample t-test was used to identify metabolites that differed significantly between treatment groups. A p-value of $p \leq 0.05$ and a false discovery rate of $q<0.10$ were used to identify global metabolite changes and correct for multiple comparisons.

Results: In total, the dataset of detected metabolites consisted of 1,010 biochemicals (BCs). Of these, 441 were statistically different in saline-treated old mice compared to young control mice, with 276 BCs increased and 165 BCs decreased. 140 BCs were statistically different in the MC16-treated old mice group compared to the saline-treated old mice group, with 72 BCs increased and 68 BCs decreased. Saline-treated old mice had reduced 1,5-anhydroglucitol and elevated glucose-6-phosphate, fructose-6-phosphate, and dihydroxyacetone phosphate compared to young control mice, indicative of enhanced glycolysis. Conversely, MC16-treated old mice had no statistical changes in glycolysis metabolites compared to young control mice. While both groups had elevated carnitine levels, MC16-treated old mice derived most of their carnitines from fatty acid metabolism, indicative of impaired fatty acid metabolism in the saline-treated old mice group.

Conclusions: These data reveal that global metabolomics can be utilized to identify various age-related kidney metabolic alterations within the renal cortices of mice. This approach will allow us to identify and monitor age-/disease- related metabolic changes in the renal cortex of mice to evaluate potential pharmacological agents that may alter/blunt the progression of renal dysfunction in future studies.

Funding: Other NIH Support - NIEHS T32 - University of Arizona Southwestern Environmental Health Sciences Center - Training Grant Award Number: T32 5T32ES007091-39, Veterans Affairs Support

SA-PO274

Development of Drug Efficacy Testing Platform for Glomerulonephritis

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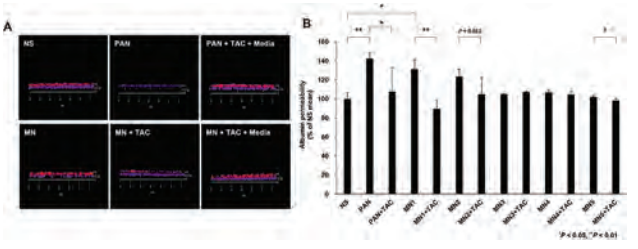
Background: There was little evidence for the treatment of glomerulonephritis (GN), although the guideline of GN was published. Therefore, we developed drug efficacy testing platform for GN using a 3D glomeruli tissue chip.

Methods: A gravity-driven glomerular-filtration-barrier (GFB) chip was designed with human podocytes and endothelial cells, allowing bi-directional flow in the bottom channel. Puromycin was used to induce glomerulonephritis (GN) models, and serum from membranous nephropathy (MN) patients was used to establish personalized models on the chip. The reproducibility of MN and the effects of tacrolimus were compared with clinical data. RFP-Gendo, WT1, and nephrin, representing the glomerular filtration barrier's molecular structure, were examined. Functional aspects of the GFB, such as cell viability and albumin permeability, were also evaluated.

Results: In the PAN-induced GN model, podocytes exhibited reduced levels of WT1 and nephrin, resulting in decreased albumin permeability and cell viability compared to the standard GFB. However, after the administration of tacrolimus, WT1 expression increased while nephrin expression decreased in the PAN-induced GN model. Tacrolimus also led to a reduction in albumin permeability and restoration of cell viability in this model. MN patients (MN1, MN2, and MN5) who received tacrolimus showed significant improvement. MN1 and MN2 had the most severe pathological injury among the enrolled patients. In the serum-induced MN1 and MN2 models on the chip, there was a significant decrease in cell viability compared to other groups, which was restored after tacrolimus treatment. Additionally, albumin permeability decreased in the MN1, and MN5 models following tacrolimus treatment on the chip. WT1 and nephrin expression increased in after tacrolimus treatment in the case of MN1 model, which had the most favorable response clinically.

Conclusions: The efficacy of tacrolimus was successfully evaluated using PAN-induced and serum-induced GN models on a chip that mimics the structure and function of the GFB. The GFB-mimicking chip holds promise as a personalized platform for assessing drug efficacy using patients' serum samples.

Funding: Government Support - Non-U.S.



SA-PO275

Endothelin Receptor Antagonists (ERAs) May Protect Against Rapid Kidney Function Decline: A Drug-Target Mendelian Randomization Study

Yixin Ma, Lubin Xu, Ruohuan Zhao, Limeng Chen. *Peking Union Medical College Hospital, Dongcheng-qu, China.*

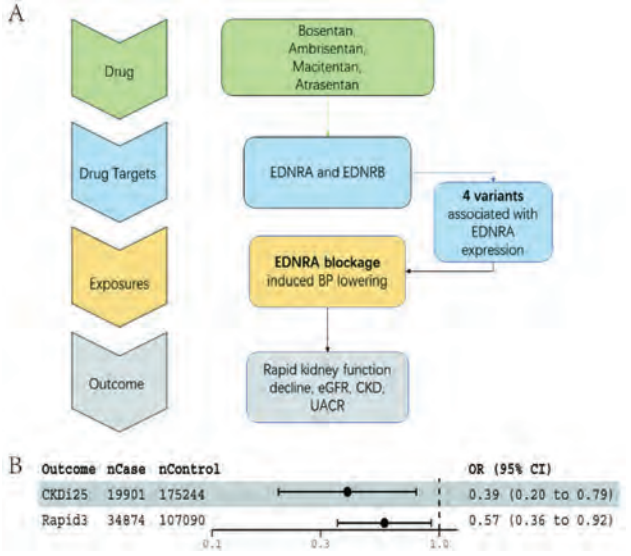
Background: Currently, the efficacy of ERAs to treat kidney disease is being tested in randomized controlled trials, positive effect in reducing albuminuria, preserving eGFR, and lower blood pressure has been reported. However, evidence from large randomized controlled trials comprehensively comparing the long-term renal effects of ERAs is lacking.

Methods: We applied a two-sample Mendelian Randomization approach to evaluate the causal effect of genetically mimicked ERA-induced blood pressure lowering on a series of kidney outcomes. Endothelin receptor (EDNR) SNPs associated with blood pressure and EDNR expression level were selected using GWAS summary data from the International Consortium of Blood Pressure (ICBP) and GTEx. GWAS summary statistics on kidney outcomes, including eGFR, proteinuria, and rapid kidney function decline, were drawn from CKDGen. We use fixed effects inverse variance weighted (IVW) meta-analysis of SNP-specific Wald estimates for primary analysis,the weighted median and MR-Egger methods for sensitivity analysis.

Results: Four EDNRA SNPs and no EDNRB SNPs met the inclusion criteria. Genetic mimicry of EDNRA blockage was associated with a lower risk of rapid kidney function decline (OR = 0.39, 95% CI = 0.20-0.79 for eGFR decline>25%, OR = 0.57, 95% CI = 0.36-0.92 for eGFR decline>3 unit per year) and a higher eGFR based on creatinine (β = 0.02, 95% CI = 0.01-0.04). Despite the significant proteinuria-lowering effect reported in clinical trials, we do not observe a causal effect for EDNRA inhibition on UACR, in the general population or the population with diabetes at baseline.

Conclusions: Mendelian randomization study suggests ERAs may protect against rapid kidney function decline through the blood pressure-lowering effect induced by EDNRA blockage.

Funding: Government Support - Non-U.S.



A: Study Design. **B:** The OR and 95% CI indicate the effect estimates of decrease in disease risk per 10 mmHg lowering of SBP via EDNRA inhibition.

SA-PO276

Sparsentan Receptor Occupancy Modeling, Clinical Actions, and Safety

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Background: In the PROTECT study, sparsentan, which targets both the endothelin type A (ET_AR) and angiotensin type 1 (AT_1R) receptors, reduced proteinuria vs active comparator in IgA nephropathy with minimal changes in fluid status. This contrasts with greater fluid retention, including heart failure hospitalization, in studies using agents targeting ET_AR alone (ERA). This may relate to differences in comorbidities; however, aspects of dual receptor binding by sparsentan may also be a factor. Since ET_AR blockers favor fluid retention while AT_1R blockers may promote fluid excretion, continual high blockade of AT_1R during ET_AR blockade may help maintain normal fluid balance. The pharmacokinetic (PK) properties of sparsentan were used to estimate diurnal changes in receptor occupancy (RO) at steady state in the PROTECT study.

Methods: Receptor affinities (Ki) were determined for sparsentan at ET_AR, ET_BR, and AT_1R using radioligand binding assays. PopPK modeling of sparsentan was used to derive 24-hour PK and RO profile of patients in PROTECT.

Results: Sparsentan receptor affinities and PK data of a typical IgAN patient in the PROTECT study are shown in Fig. 1A. The 24-hour plot of sparsentan RO for ET_AR, ET_BR, and AT_1R using PK data estimated for 400 mg daily shows RO is ~60%-90% for ET_AR, >95% for AT_1R, and <1% for ET_BR (Fig. 1B).

Conclusions: Sparsentan has a stable 24-hour relationship in relative RO of ET_AR to AT_1R in which AT_1R RO always exceeds ET_AR RO. In contrast, when a drug solely targets ET_AR, on top of AT_1R blockade, periods of relatively unaccompanied ET_AR antagonism may occur, representing a risk for fluid retention. This could partly explain the fluid retention seen with ERA and the minimal changes in fluid status seen with sparsentan.

Funding: Commercial Support - Travere Therapeutics, Inc.

(A)

Parameter	Value	Steady State Parameter	Value
Ki (ET_AR)	12.8 nM	Cmax	6470 ng/ml
Ki (AT_1R)	0.36 nM	Cmin	1266 ng/ml
Ki (ET_BR)	6582 nM	Half-life	9.6 hours
Protein binding	99%	AUC	63,600 ng.hr/ml

(B)

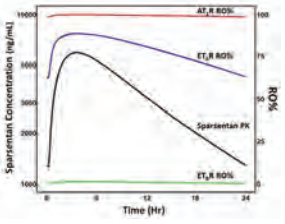

Fig 1: (A) Sparsentan receptor binding parameters and steady-state mean PK estimates from the PROTECT study. (B) Sparsentan receptor occupancies (right axis) over 24 hours for a single daily 400 mg oral dose in the PROTECT study, steady-state mean exposure (left axis).

SA-PO277

Targeted Mass Spectrometry to Detect and Quantify Circulating α-Klotho Isoforms

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Background: Progress in α-Klotho research has been stunted by the lack of reliable assays that can discriminate between various α-Klotho isoforms which potentially exert differential physiological roles. We designed a novel targeted liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay to detect and quantify the known circulating α-Klotho isoforms: soluble full-length Klotho (sFL-K), secreted KL1 (secKL1), soluble KL1 (sKL1) and soluble KL2 (sKL2).

Methods: We developed a parallel reaction monitoring-based (PRM) LC-MS/MS method that exploits unique peptide sequences present at the α2/β-cut site and the C-terminus of secKL1. During assay design, we tested enzymatic digestions of recombinant human sFL-K and secKL1 with commercially available proteases: trypsin, Lys-C, Asp-N, or chymotrypsin. After determining that chymotrypsin successfully created unique peptides covering the various α-Klotho isoforms, 11 synthetic peptides were used to optimize LC-MS/MS parameters and to determine limit of detection and quantification (LOD/LOQ) in solvent matrix. These peptides included chymotrypsin missed cleavages and deamidated Asn residues which were observed in our preliminary studies. We then utilized recombinant sFL-K and secKL1 proteins spiked into Top14 depleted plasma for further optimization and assessment of the assay.

Results: Only chymotrypsin digestion produced peptide signatures that cover the α2/β-cut site to differentiate between sKL1, sKL2 and sFL-K and the unique secKL1 C-terminus to identify secKL1 from sFL-K and sKL1. The LOD/LOQ for synthetic peptide signatures in solvent matrix ranged from 0.02/0.06 to 1.3/3.8 fmol. Synthetic peptides with an intact α2/β-cut site resulted in multiple peaks, most likely due to the high number of prolines in the peptide which can create distinct conformers that were resolved with application of a 60°C column heater. Deamidated peptides were detectable in depleted plasma matrix spiked-in with recombinant sFL-K and secKL1 proteins. sFL-K and sKL1 were detectable in human serum samples.

Conclusions: This is the first α-Klotho assay that can specifically detect and quantify different isoforms of circulating α-Klotho and overcome limitations of antibody-based methods. Further optimization for robustness, reproducibility as well as validation studies are required to assess α-Klotho isoforms in other sample types.

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SA-PO278

Identification of RNAs in Urinary Extracellular Vesicles for Detecting Renal Nrf2 Activation

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Background: NF-E2-related factor 2 (Nrf2), a master transcription factor, is known to be activated in response to oxidative stress, leading to producing antioxidant molecules. Renal oxidative stress condition can be estimated by measuring oxidative by-products and reactive oxygen species in urine. On the other hand, since activation of antioxidant molecules may mask renal oxidative stress condition, detecting renal Nrf2 activation is likely helpful for early detection of renal oxidative stress. However, little is known about the non-invasive detection method. Urinary extracellular vesicles (uEVs) released from renal epithelial cells contain RNAs that may serve as biomarkers for renal diseases. Here, we examined RNAs in uEVs after administration of bardoxolone methyl (BARD), an Nrf2 activator, in rats.

Methods: Male SD rats were randomly divided into two groups: the BARD (10 mg/kg intraperitoneally) and vehicle (75% corn oil/25% DMSO) groups. The urine was collected for 6 hrs after the administration, and uEVs were isolated. Kidneys were also obtained at 6 hrs post-treatment. RNAs were extracted from uEVs and kidneys and analyzed by next-generation sequencing and microarray techniques.

Results: Based on the blood and urine tests, BARD administration did not impair renal function. Microarray analyses revealed that 19 genes in the kidney and 211 genes in uEVs were significantly altered after BARD administration. Next-generation sequencing identified 958 genes that were significantly changed by BARD treatment in the uEVs. Of these genes, only two genes, Pir and Ephx1 were commonly increased in the kidneys and uEVs (Pir: > 3-fold, Ephx1: approximately 2-fold). Since the increase in Pir was higher than in Ephx1, we further investigated Pir as a potential biomarker for detecting Nrf2 activation. *In situ* hybridization revealed that BARD-treatment increased Pir expression in the proximal and distal tubules of the renal cortex. Moreover, we established the pre-amplification method of RNAs in uEVs and successfully detected Pir in uEVs by PCR.

Conclusions: Theoretically, Nrf2 is activated before the early onset of kidney diseases or under pre-oxidative stress condition. Thus, detecting Nrf2 activation in the kidney by measuring Pir in uEVs could be a potential tool to detect early kidney diseases.

SA-PO279

Prospective Evaluation of an Improved Eculizumab Initial Phase Dosing Regimen in Adult Patients with Atypical Hemolytic Uremic Syndrome

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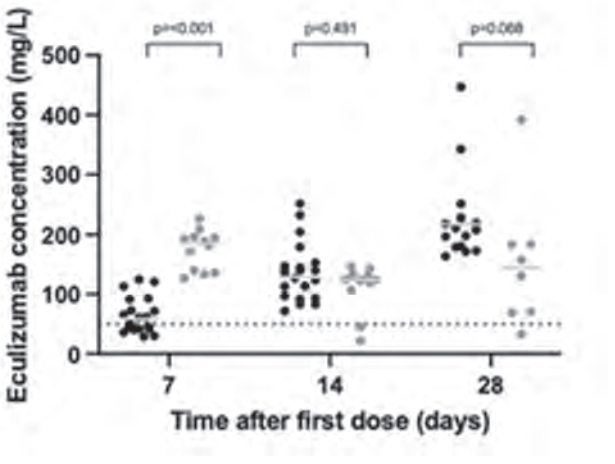
Background: Complete complement inhibition is often not achieved after the first dose of eculizumab due to subtherapeutic eculizumab concentrations (<50mg/L), while adequate complement inhibition is critical to prevent irreversible organ damage in aHUS. In this study we prospectively evaluated an improved initial phase dosing regimen.

Methods: The new regimen consisted of a weight-based loading dose on day 1 (>120kg: 2400mg; 90-120kg: 2100mg; 60-90kg: 1800mg; 40-60kg: 1500mg), followed by the standard biweekly 1200mg from day 15 onward. Eculizumab concentrations were measured to monitor therapy and compared with a historical cohort that received the standard dose. At each timepoint (day 7, 14, 28), we calculated the geometric mean eculizumab trough concentration and the fraction of patients with a subtherapeutic eculizumab concentration (<50mg/L) for both groups.

Results: 15 patients receiving the new dosing regimen and 22 patients receiving standard dose were evaluated. Baseline characteristics were similar across the groups. The eculizumab concentrations and the geometric mean concentrations on day 7, 14 and 28 are shown in Figure 1. Eculizumab concentrations were subtherapeutic in 42% (8/19), 0% (0/21) and 0% (0/16) of the patients on day 7, 14 and 28 respectively (standard dose) and in 0 (0/12), 20% (2/10) and 12.5% (1/8) of the patients on day 7, 14, and 28 respectively (new dose).

Conclusions: We prospectively confirmed improved early target attainment of a weight-based loading dose of eculizumab on day 1 followed by the maintenance phase dose from day 15 onward.

Funding: Government Support - Non-U.S.



Eculizumab concentrations for standard (black) and new initial phase (grey). Horizontal lines represents the geometric mean concentration. The dotted line represents an eculizumab concentration of 50 mg/L (threshold for complete C5 inhibition).

SA-PO280

Phase 3 COMMODORE Trials of Crovalimab in Paroxysmal Nocturnal Hemoglobinuria (PNH): Impact on Kidney Function

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Background: Complement inhibition is the standard of care in PNH and atypical hemolytic uremic syndrome (aHUS). Crovalimab (crova), a C5 inhibitor, enables rapid, complete and sustained C5 inhibition with subcutaneous self-administration in patients (pts) with PNH who are complement inhibitor-naive or switching to crova. Crova has non-inferior efficacy vs eculizumab (ecu) and a safety profile is consistent with that of other C5 inhibitors. Here we evaluate kidney function in the Phase 3 pts.

Methods: Pts with PNH received crova or ecu in one of the Phase 3 studies: global, randomized COMMODORE 1 (treatment-switch pts) and COMMODORE 2 (naive pts), or China-based, single-arm COMMODORE 3 (naive pts). In COMMODORE 1 and 2, pts receiving ecu could switch to crova after the primary treatment period. Data were pooled for safety and kidney function evaluation.

Results: 111 pts received ecu and 377 crova (192 naive, 185 switched to crova at study initiation or after primary period). Shifts in serum creatinine of ≥2 grade (gr) from BL occurred in 4.5% (5/111) of ecu pts vs 6.9% (26/377) of crova pts (8.3% [16/192] of C5 naive vs 5.4% [10/185] of switch pts; Table). Post-BL gr 3/4 shifts occurred in 1 ecu pt (BL: gr 2), 1 naive pt (BL: gr 0) and 4 switch pts (BL: gr 0). Shifts occurred much later than the onset of ecu-C5-crova immune complexes, suggesting the shifts were unrelated to switching. Urine protein, albumin and creatinine levels were not concerning. Type 3 hypersensitivity reactions, associated with complexes, occurred in 18% (33/185; 21 gr 1-2, 12 gr 3) of switch pts.

Conclusions: Serum creatinine shifts were comparable between ecu pts and pts who changed from ecu to crova or stayed on crova. Overall, the crova Phase 3 data show that the risk/benefit profile of crova is favorable in PNH and no new safety signals, including for kidney function, were observed. Crova is being evaluated for aHUS in the ongoing COMMUTE-a (NCT04861259) and COMMUTE-p (NCT04958265) studies.

Funding: Commercial Support - This study was funded by F. Hoffmann-La Roche, Basel, Switzerland

Table. Shifts in serum creatinine grade from BL.

Less than BL assessment | Equal to BL assessment | 1 grade increase from BL assessment | ≥2 grade increase from BL assessment

COMMODORE 1, 2, and 3	BL grade assessment	Maximum post-BL grade assessment, n (%)				
		0	1	2	3	4
Ecu (N=111)	0	89 (80)	4 (4)	5 (5)	0	0
	1	1 (1)	7 (6)	1 (1)	0	0
Median treatment duration, weeks (range) 22.1 (0.1, 26.1)	2	0	0	3 (3)	1 (1)	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Crova-naive (N=192)	0	143 (74)	9 (5)	15 (8)	0	1 (1)
	1	0	15 (8)	4 (2)	0	0
Median treatment duration, weeks (range) 52.1 (0.1, 107.9)	2	0	1 (1)	3 (2)	0	0
	3	0	0	0	0	0
	4	0	0	0	0	0
Crova switch (N=185)*	0	137 (74)	15 (8)	6 (3)	2 (1)	2 (1)
	1	2 (1)	10 (5)	6 (3)	0	0
Median treatment duration, weeks (range) 32.3 (0.3, 108.4)	2	0	0	3 (2)	0	0
	3	0	0	0	1 (1)	0
	4	0	0	0	0	0

BL, baseline. COMMODORE 1: NCT04432584; COMMODORE 2: NCT04434092; COMMODORE 3: NCT04654468.
* Includes patients who switched from ecu at beginning of study and those who switched from ecu to crova after the primary treatment period.

SA-PO281

Long-Term Outcomes Comparing Belatacept vs. Tacrolimus in Older and Marginal Kidney Transplant Recipients: A UNOS Database Analysis

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Background: Studies have shown that kidney transplantation with even a marginal kidney provides a survival advantage in older patients when compared to dialysis. Older kidney transplant recipients (KTR) of marginal organs where KDPI ≥85% are more likely to be negatively impacted by the nephrotoxic effects of calcineurin inhibitors. Hence, the aim of the study was to compare long term patient and graft outcomes in older and high KDPI KTRs stratified by Tacrolimus (Tac) vs Belatacept (Bela) maintenance immunosuppression.

Methods: We identified adult, first-time kidney only transplant recipients from 2010 to 2022 who received induction therapy and were discharged on Tac or Bela based maintenance immunosuppression from the UNOS database. Multivariate Cox regression models adjusting for several donor, transplant and recipient factors were used to compare long term outcomes Tac vs. Bela maintenance in KTRs with age ≥65 yrs, KDPI ≥85%, and donation after cardiac death (DCD).

Results: The results comparing Tac vs. Bela groups are detailed in Table 1. Bela use was associated with higher DCGF and death in KDPI ≥85% group ($p<0.05$). The rest of the long-term outcomes were similar between the groups.

Conclusions: The use of Bela in older KTRs recipients and DCD kidney recipients is associated with non-inferior outcomes, likely due to GFR advantage with Bela. Inferior outcomes in the Bela group among high KDPI KTRs could reflect selection bias. Other contributory factors could include higher risk for early rejections and opportunistic infections in the Bela group. These identified associations should be regarded as preliminary evidence, taking into account the retrospective nature of the study. They serve as a catalyst for future analysis.

Comparison of long-term outcomes in older and marginal kidney transplant recepients based on maintenance immunosuppression.

	Delayed Graft Function Tacro (%) vs. Bela (%); p	Patient Death HR (95%CI); p	Adjusted Overall Graft Failure HR (95%CI); p	Death Censored Graft Failure HR (95%CI); p
Recipient Age > 65 years Tac (n = 39855) vs. Bela (n = 1241)	9380 (23.54%) vs. 410 (33.04%); <0.001	0.88 (0.78-1.00); 0.057	0.98 (0.86-1.10); 0.723	0.89 (0.77-1.03); 0.109
KDPI >85% Tac (n = 9258) vs Bela (n = 422)	3273 (35.35%) vs. 177 (41.94%); 0.006	0.81 (0.66-0.99); 0.039	0.92 (0.76-1.10); 0.359	0.74 (0.59 - 0.93); 0.009
DCD Tac (n = 32,032) vs. Bela (n = 1068)	13821 (43.15) vs 538 (50.37); <0.001	0.87 (0.73 - 1.04); 0.139	0.99 (0.84-1.16); 0.904	0.85 (0.69 - 1.04); 0.108

SA-PO282

Association Between Mycophenolic Acid (MPA) Pharmacokinetics and In Vitro MPA Glucuronide (MPAG) Turnover by Gut Microbiota of Kidney Transplant Recipients

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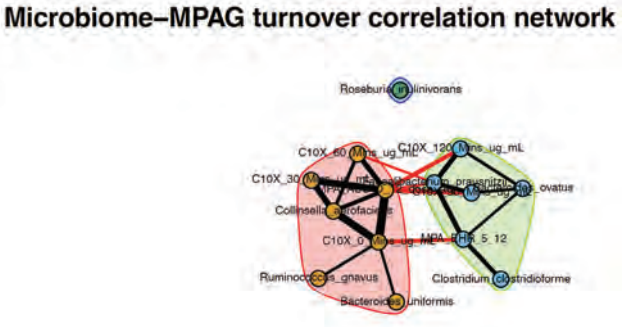
Background: Pharmacokinetic (PK) studies show enterohepatic recycling (EHR) of mycophenolic acid (MPA) due to MPA glucuronide (MPAG) hydrolysis by gut b-glucuronidases (BGUS). EHR increases MPA systemic exposure and likely enhances immunosuppression and toxicity in kidney transplant recipients (KTRs). We hypothesized that extensive EHR in-vivo would correlate with higher MPAG to MPA in-vitro.

Methods: 9 KTRs underwent simultaneous PK and stool collection at 30-60 days post-transplant. MPA % EHR was defined as MPA $AUC_{5\text{-}12\ hour}$ / $AUC_{0\text{-}12\ hour}$ x 100. Stool samples were anaerobically exposed to 100 mg/mL of MPAG in 7mL of YCFA (Yeast extract-Casein hydrolysate-fatty acids) broth, with aliquots collected at 0, 30, 60, 90 and 120 minutes. Total MPA and MPAG concentrations were assessed using mass spectrometry. Microbiota were characterized by 16S sequencing. We applied the Louvain Modularity Maximization algorithm to the correlation between in-vitro MPA levels, MPA PK, and BGUS producers present in >10% of samples (Threshold R=0.3).

Results: After exposure to MPAG, we observed an increase in MPA with a concurrent decrease in MPAG concentrations across all in-vitro samples. Further comparison showed a positive correlation between MPA AUC and in-vitro MPA at 0, 30, 60, 90 and 120 mins post incubation (R = 0.85, 0.68, 0.58, 0.48, 0.43 respectively, $p < 0.05$ at 0 and 30 mins). We included 7 out of 31 previously known BGUS producers in our network analyses, which suggested that the relative abundances of *B. uniformis*, *R. gnavus* and *C. aerofaciens* correlated with in-vitro MPA in the first hour and MPA AUC (FIG 1).

Conclusions: These data suggest that MPAG metabolism to MPA by the stool microbiome is correlated to the relative abundance of known BGUS producers. Further studies are needed to associate the extent of MPA PK with BGUS producers.

Funding: NIDDK Support



SA-PO283

Take Drug Interactions Seriously: Paxlovid in Transplant Patients Taking Tacrolimus

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Introduction: Kidney transplant recipients are highly susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and are eligible candidates for Paxlovid™ (nirmatrelvir and ritonavir), an antiviral medication that reduces morbidity associated with COVID-19 infection. Ritonavir effectively maintains serum concentrations of nirmatrelvir by inhibiting CYP3A but can also elevate levels of other drugs metabolized by this enzyme, including immunosuppressive medications. We describe a kidney transplant recipient who received Paxlovid and subsequently developed supratherapeutic tacrolimus levels after dose titration upward.

Case Description: A 65-year-old man with history of ESKD due to type 1 diabetes mellitus and renal transplant on tacrolimus (dosed at 0.5mg BID) presented to our ED with symptomatic COVID-19 infection, for which Paxlovid was initiated. Tacrolimus was held. He was hospitalized for two days and discharged with instruction to continue Paxlovid and hold tacrolimus until outpatient follow-up. The next day, he presented again with anuria, leg edema, and AKI. Tacrolimus level was 2.0 ng/mL and creatinine had risen from baseline 1.8 mg/dL to 2.7 mg/dL. Due to a concern for acute rejection, Paxlovid treatment was stopped, and he was given two 2mg doses of tacrolimus 12 hours apart before lab work revealed a sudden rise in serum tacrolimus level to 54 ng/mL on hospital day 2. Tacrolimus was again held. Serum levels trended down to therapeutic range within four days. AKI steadily improved with supportive care.

Discussion: The introduction of tacrolimus has transformed the field of kidney transplantation. Maintaining therapeutic serum levels remains challenging due to its metabolism by CYP3A, resulting in potential drug interactions and high tacrolimus levels that can lead to irreversible nephrotoxicity. Transplant recipients frequently receive Paxlovid, and tacrolimus is often held during treatment. After Paxlovid is dicontinued, 70-90% of CYP3A inhibition is relieved within 2-3 days, but may take longer with advancing age. Our case highlights the crucial need for cautious and conscientious resumption and dose titration of immunosuppression in the days after cessation of Paxlovid to avoid supratherapeutic and nephrotoxic serum levels of tacrolimus.

SA-PO284

Genistein Reduces Albuminuria by Inhibition of Caveolae-Mediated Endocytosis into Glomerular Endothelial and Epithelial Cells

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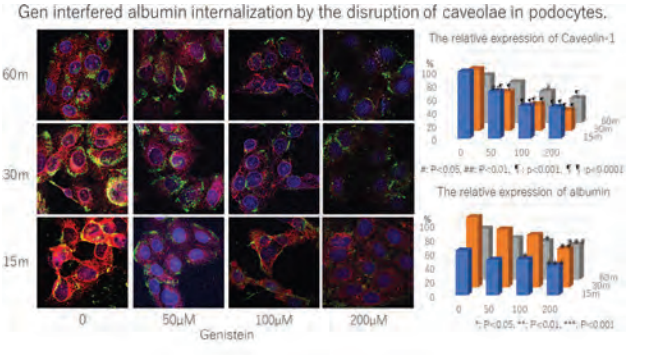
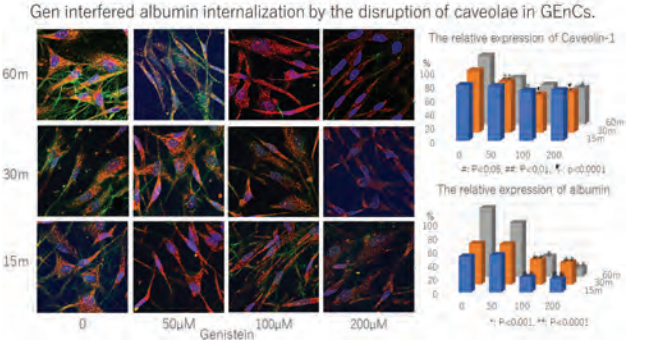
Background: We previously reported the intracellular trafficking pathway of glomerular endothelial cells (GEnCs) and epithelial cells (podocytes) through caveolae as the possibility of new etiology of albuminuria. The non-steroidal phytoestrogen belonged to potent soy isoflavone, genistein (Gen) inhibits Src kinase, which plays an important role of internalization of caveolae coated pits into cytoplasm as caveolae endocytosis. In this study, we analyzed the effect of Gen to reduce albuminuria by inhibiting albumin endocytosis through caveolae into GEnCs and podocytes.

Methods: After 1 hour pre-treating cells with 50, 100, or 200 μM of Gen, cells were incubated with time course treatment of albumin (15, 30, and 60 min), and then the expression of caveolin-1 (Cav-1), albumin, and p-Src were evaluated by immunofluorescence (IF) and western blots (WB) analysis. It was also analyzed whether 14 days treatment of Gen reduced albuminuria in the streptozotocin induced diabetic nephropathy modeled mice (STZ mice).

Results: Albumin and caveolin-1 (Cav-1) expression levels were significantly decreased with dose dependent manner of Gen in IF and WB analysis (Figure). The expression of p-Src was also decreased in WB analysis. In vivo study, though body weight and blood glucoses were not changed, Gen significantly decreased the urinary albumin/creatinine ratio in STZ mice (0.28 to 0.05, p=0.02) in comparison to non-treated STZ mice (0.21 to 0.14, p=0.37).

Conclusions: Gen interfered albumin endocytosis through caveolae by suppressing caveolae expression according to inhibit Src kinase and resulted in reduced albuminuria in STZ mice. These results indicated the possibility of Src kinase inhibitor, Gen as the new therapeutic approach to reduce albuminuria in diabetic nephropathy.





SA-PO285

Dexamethasone and Enalaprilat but Not SB525334 Exhibit Anti-Inflammatory Properties in Precision-Cut Kidney Slices (PCKSs) Obtained from Mice with Adriamycin-Induced Nephropathy

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Background: Precision cut kidney slices (PCKS) provide a valuable step between in vitro and in vivo testing. PCKS obtained from rodents exposed to adriamycin exhibit specific pathological features associated with glomerular and tubular injury, inflammation and eventual fibrosis. In this study, we have evaluated the effects of dexamethasone, enalaprilat, and SB525334 on inflammation and fibrosis in PCKS from kidney slices from adriamycin-treated mice.

Methods: Male mice were dosed with adriamycin (11.25 mg/kg, iv) to induce nephropathy. On Day 7 mice were humanely sacrificed and kidneys were cut at 250μm on a vibratome. Slices were cultured in Williams Medium E media. Tissue viability was evaluated at 0h to 96h by LDH assay and qPCR (versus control). Independent slices were treated with SB525334 (1μM), Dexamethasone (1μM) and enalaprilat (10μM) for 24 to 96h. Pro-fibrotic (Fn1, Col1a, Col3a, PAI1), pro-inflammatory genes (*IL-6, TNFα, IL-1*β and *CCL2*) and genes indicative of glomerular and tubular injury (nephrin, KIM-1 and WT1) were determined.

Results: PCKS were viable for 96h. All pro-inflammatory and pro-fibrotic gene expression were significantly increased from 24h onwards, p<0.001. Nephrin, *WT1* expression decreased, and *KIM-1* increased at 24h and remained elevated, p<0.001. SB525334 decreased the expression of all pro-fibrotic genes, p<0.001 but not the pro-inflammatory markers (NS) and increased nephrin and *KIM-1* (p<0.05, p<0.001) but had no effect on *WT1*. Dexamethasone significantly reduced *TNFα, IL-6, IL-1*β, *CCL2* (p<0.001) as well as *Fn1, Col1a, Col3a* and *PAI1* (p<0.001). Dexamethasone increased *WT1* and reduced *KIM-1* (p<0.05, p<0.001) but unchanged nephrin. Enalaprilat effects were limited, it reduced *IL-1*β (p<0.01) and increased *WT1* (p<0.05).

Conclusions: Dexamethasone and enalaprilat produced a reduction in inflammation and fibrosis (dexamethasone only) leading to protection of the functional unit of the kidney. In contrast, SB525334 effects were limited to fibrosis but the effects on kidney health were inconclusive. Taken together, inflammation plays a crucial role in adriamycin-induced nephropathy and PCKS present a reliable platform to test novel anti-inflammatory and anti-fibrotic therapies.

Funding: Commercial Support - Sygnature Discovery

SA-PO286

Antifibrotic Effects of Tadalafil, a Phosphodiesterase 5 Inhibitor, with PAI1 Downregulation via cGMP in Rats and Fibroblasts

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Background: Renal fibrosis is common in cases of renal dysfunction, and the development of therapeutic agents for renal fibrosis is desired. It was recently reported that phosphodiesterase 5 (PDE5) inhibitors, used for the management of erectile dysfunction and pulmonary hypertension due to increased cGMP, have renoprotective effects. Thus, in this study, we investigated whether tadalafil, a PDE5 inhibitor, has antifibrotic effects via cGMP in rats and renal fibroblasts.

Methods: Dahl salt-sensitive rats were used as a renal dysfunction model and divided into the following groups: normal salt (NS), high salt (HS), and HS plus tadalafil (HS+T). The NS group was fed a normal diet (0.3% NaCl), and the HS group and HS+T group were fed a high-salt diet (8% NaCl). Tadalafil (10 mg/kg/day) was orally given once a day. After 8 weeks, renal fibrosis was evaluated using AZAN staining. The mRNA expression level of the profibrotic factor, plasminogen activator inhibitor1 (PAI1), was also examined. Furthermore, NRK-49F cells, fibroblasts, were treated with the vehicle, transforming growth factor (TGF)β1 (2 ng/ml), or TGFβ1 + 8-Br-cGMP (1 mM). After 6 h, PAI1 mRNA expression levels and active PAI1 protein levels were measured.

Results: Collagen-rich areas visualized by AZAN-staining obviously increased in the HS group compared with that in the NS group and those areas decreased in the HS+T group compared with that in the HS group. Furthermore, while PAI1 mRNA expression in kidney tissue significantly increased in the HS group compared with that in the NS group ($P < 0.01$), it decreased in the HS+T group compared with that in the HS group ($P = 0.06$). The expression levels of PAI1 mRNA in TGFβ1-stimulated NRK-49F cells increased compared with those in the vehicle-treated cells. 8-Br-cGMP addition decreased the expression levels of PAI1 mRNA. Active PAI1 protein levels in the TGFβ1-stimulated cells was significantly upregulated compared with that of the vehicle-treated cells ($P < 0.01$) and that of the 8-Br-cGMP-treated cells was significantly downregulated compared with that of the TGFβ1-stimulated cells ($P < 0.01$).

Conclusions: Tadalafil shows antifibrotic effects, which may be due to the prevention of active PAI1 expression due to increased cGMP in fibroblasts.

SA-PO287

When Hepatic Therapy Backfires: Unraveling the Intricacies of Rifaximin-Induced Rhabdomyolysis Post-Transplantation

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Introduction: Rhabdomyolysis, a severe condition marked by muscle cell content leakage into circulation, manifests as weakness, pain, swelling, and myoglobinuria. It can result from diverse causes, leading to complications like acute kidney injury (AKI). We report a case of rifaximin-induced rhabdomyolysis.

Case Description: A 56-year-old male with a pancreas-kidney transplant, and cholestatic/drug-induced cirrhosis due to lacosamide (Stage 1 fibrosis on biopsy, now Stage IV). The initial presentation included weakness and altered mental state; labs revealed hyperammonemia (155 umol/L), elevated tacrolimus level (9.7 ng/mL), and creatinine (1.7mg/dL). He was started on intravenous fluids, rifaximin, lactulose, and continuation of his atorvastatin, resolved hepatic encephalopathy, and improved creatinine to 1.4 mg/dL. He returned three weeks later with increased weakness and leg pain. Labs showed elevated creatinine kinase (14614 U/L), creatinine peaking at 4.5 mg/dL, and a tacrolimus level of 8.9 ng/mL. A renal biopsy suggested acute tubular injury, rhabdomyolysis-induced pigment nephropathy, and borderline acute rejection. Management included pulse-dose solumedrol (500mg/3 days), followed by a taper, discontinuation of rifaximin, intravenous fluids, and dose reduction of tacrolimus, leading to resolution of rhabdomyolysis and improved kidney injury.

Discussion: In this case, rifaximin, a medication started during the patient's initial presentation, likely caused the rhabdomyolysis. Despite its limited gut absorption, hepatic impairment may enhance absorption. The mechanism could involve rifampin-induced mitochondrial oxidative stress in muscle, promoting myofibrillar proteolysis, similar to statin-induced rhabdomyolysis. This case underscores rifaximin's potential for inducing rhabdomyolysis, especially in patients with hepatic impairment.

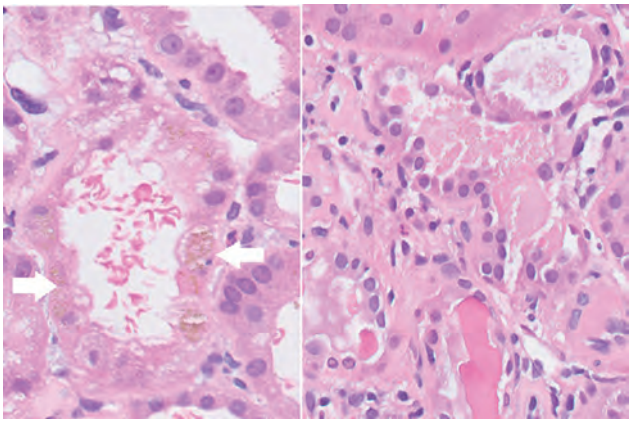

Figure 1: Hematoxylin and eosin stain of renal tubules notable for brown pigment in cytoplasm and granular cast

SA-PO288

AKI and Erythema Multiforme Associated with Helicobacter pylori Eradication Therapy: Not Invariably Drug Allergy

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Introduction: Helicobacter pylori (H. pylori) infection might lead to gastric carcinoma; hence, the elimination of H. pylori is pursued in infected individuals. One of the first-line therapeutic regimens consists of amoxicillin (AMPC), clarithromycin (CAM), and proton pump inhibitor (PPI). However, AMPC is an agent recognized for inducing interstitial nephritis and skin eruptions. PPI-associated interstitial nephritis has gained attention in recent years. Here, we present an intriguing case of a hypersensitive reaction following H. pylori eradication.

Case Description: A 70-year-old Asian male received a 7-day course of AMPC, CAM, and PPI for the treatment of H. pylori infection. Two days after completing the medication, his serum creatinine level was 0.89 mg/dL. The following day, he developed a febrile state accompanied by a generalized rash. By the fifth day after completing the treatment, he continued to experience fever along with a deteriorating skin rash. Laboratory investigations revealed the following findings: creatinine 2.82 mg/dL, C-reactive protein 16.7 mg/dL, procalcitonin 5.14 ng/mL, urinary NAG 88.8 IU/L, and urinary β2MG 155,000 μg/L. The patient was diagnosed with acute kidney injury and erythema multiforme. Additionally, rhabdomyolysis became evident. Pulse steroid therapy followed by oral prednisolone (0.8 mg/kg body weight) led to the amelioration of symptoms and full recovery of renal function. Kidney biopsy revealed acute tubular injury but not interstitial nephritis. Prednisolone was discontinued within three weeks. Leukocyte transforming test (LTT) and skin prick test for AMPC, CAM, and PPI yielded negative results, while LTT using H. pylori antigen showed a positive reaction. Consequently, the case was diagnosed as a hypersensitivity reaction against the eradicated H. pylori.

Discussion: Hypersensitivity reactions associated with the treatment of H. pylori infections were predominantly diagnosed as drug allergy. However, hypersensitivity against the eradicated H. pylori itself has recently been reported from Japan as a novel mechanism. To the best of our knowledge, this is the first case in which acute kidney injury manifested as complications. Recognition of this mechanism is crucial not only for dermatologist but also for nephrologist to prevent misdiagnosis.

SA-PO289

A Case of Drug-Induced Thrombotic Microangiopathy During Pulmonary Tuberculosis Treatment

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Introduction: Drug-induced thrombotic microangiopathy is a rare, but serious complication. Here, we report a case of severe rifampicin-associated TMA with acute kidney injury required renal replacement therapy during pulmonary tuberculosis treatment.

Case Description: A 67-year-old man diagnosed with pulmonary tuberculosis was referred to nephrology department for hematuria. The patient had a history of diabetes and hyperlipidemia. Isoniazid, rifampicin, pyrazinamide and ethambutol were administered after the diagnosis of pulmonary tuberculosis. And on the 7th day of tuberculosis treatment, gross hematuria and purpura were developed. Laboratory tests showed a hemoglobin level of 8.4 g/dL, a leukocyte count of $9.01x10^9$/L, a platelet count of $11x10^9$/L, a urea nitrogen of 132.8 mg/dL and a creatinine level of 13.8 mg/dL. Hemodialysis was initiated to control severe metabolic acidosis and uremic symptoms. Direct Coombs' test was positive and schistocytes were observed on peripheral blood smear. Hemolytic anemia with thrombocytopenia and acute kidney injury were suspected to be related to rifampicin. So, we discontinued the rifampicin and start therapeutic plasma exchange. In vitro test for drug-induced immune complex proved that hemolytic anemia was induced by rifampicin. After 4 sessions of plasma exchange, the patient's renal function was gradually recovered and hemodialysis was stopped.

Discussion: It is known that hemolytic anemia occurs because rifampin binds to circulating antibodies to form immune complex and attaches to the surface of red blood cells, which activates the complement cascade. Thrombocytopenia also occurs by an immunological mechanism induced by rifampin. Hemolytic anemia and thrombocytopenia are usually known to appear on the 3rd day to 3rd week of rifampin administration. Here, we report a case of severe thrombotic microangiopathy with acute kidney injury in which the etiology was identified with an immune complex test and successfully treated with plasma exchange.

Results of the drug-induced immune complex test

	O RBC	O RBC + anti-globulin
Patient's serum + drug	Positive	Positive
Patient's serum + AB serum + drug	Positive	Positive
Patient's serum + AB serum + PBS	Negative	Negative
Normal AB serum + drug	Negative	Negative
Normal AB serum + PBS	Negative	Negative

SA-PO290

Drug-Mediated Thrombotic Microangiopathy Associated with Eltrombopag

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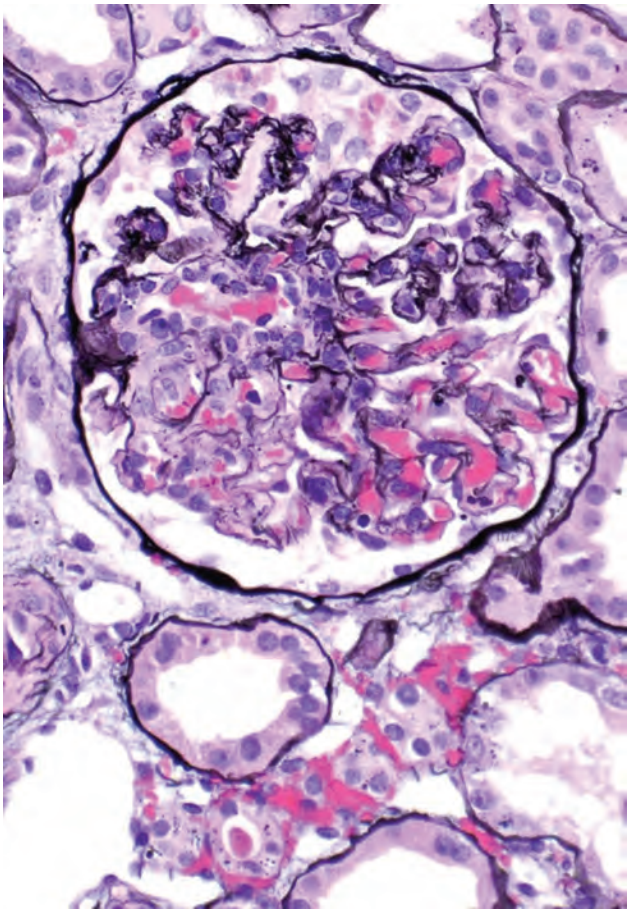
Introduction: Eltrombopag is a thrombopoietin-receptor agonist indicated in resistant chronic immune thrombocytopenia (ITP). This is the first report of full-blown biopsy-proven thrombotic microangiopathy (TMA) with acute kidney injury (AKI) and the nephrotic syndrome (NS) in an ITP patient on eltrombopag.

Case Description: 65-year-old woman with steroids and immunoglobulins resistant ITP presented with confusion, worsening thrombocytopenia, fever, and AKI. Eltrombopag was started 4 days prior to admission. Three weeks earlier, creatinine was 0.84 mg/dl, and platelets 84,000/uL. On admission, Creatinine was 5.22 mg/dl, and platelets 50,000/uL with schistocytes. LDH was 1,193 U/L. Urine protein-to-creatinine ratio was 6510 mg/g with hyperlipidemia and hypoalbuminemia. Blood and urine cultures, and direct Coombs were negative. Anticardiolipin antibodies, hepatitis B and C, and connective tissue disorders serologies were unremarkable. Pre-plasma exchange ADAMTS13 was normal. Eltrombopag was stopped, IV corticosteroids and hemodialysis (HD) were started. Renal biopsy showed focal cortical necrosis, ischemic changes in the glomerular capillary loops, and focal arteriolar fibrin thrombi with red blood cell fragmentation. After 7 daily plasma exchange sessions, platelets normalized and confusion resolved. Two months later she was taken off HD.

Discussion: There are four reports of eltrombopag-associated AKI, one was renal limited TMA, another in a patient with antiphospholipid syndrome, and two presented with AKI and NS. In this case report, Naranjo adverse drug reaction probability scale showed a score of 7 or a probable relationship between eltrombopag and TMA. Eltrombopag drug-mediated TMA is uncommon. Drug cessation, corticosteroids, plasma exchange and renal replacement therapy should be considered in the management of this disorder.



Ischemic glomerulus with fibrin thrombi

SA-PO291

Ophthalmological Safety of Hydroxychloroquine in CKD

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Background: Hydroxychloroquine (HCQ) is routinely used in advanced CKD for rheumatological disease, despite known concerns for its ophthalmological safety in older individuals and patients with CKD. Recently, HCQ has been implicated in therapeutically treating cardiovascular (CV) disease in patients with CKD.

Methods: We report the findings of the planned interim analysis examining the short-term ophthalmological safety of HCQ among all enrolled Veteran participants (n=100) in the **Ma**nagement of **C**V disease in c**K**d (MaCK) study, a phase 2b, randomized placebo-controlled trial aimed to examine the impact of HCQ on CV and renal outcomes. Blinded ophthalmological evaluations were done at baseline and at one-year after randomization by measuring visual acuity and evaluating macular health with autofluorescence(AVF), Humphrey's visual field (HVF), and optical coherence tomography (OCT), when clinically needed.

Results: Across the 100 Veterans aged 71.21±5.92, 95%male with eGFR of 40.04±7.72 and albuminuria of 438.0±784.4 mcg/gm of creatinine, randomized in 1:1 proportion between placebo:HCQ, worsening of visual acuity was similar across both groups (16 vs. 18, p >0.87). Ophthalmological symptoms prompted repeat macular health evaluation in 22 participants on follow-up with no significant difference between abnormalities detected on AVF (2 in each group), HVF (2 vs. 1 participant), and OCT (2 in each group).

Conclusions: Use of HCQ is safe from short-term ophthalmological perspectives among elderly, predominantly male participants with significant CKD.

Funding: Veterans Affairs Support

SA-PO292

Prevalence of Polypharmacy and Associated Adverse Outcomes in Kidney Transplant Recipients

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Background: Polypharmacy (PP) continues to increase, and is associated with numerous adverse clinical outcomes and mortality. Although the burden of medication in kidney transplant recipients (KTRs) is well-known, PP has not been characterized in detail in the KTRs. The aim of this study was to assess the prevalence of PP among KTRs and the association between PP and clinical outcomes in the KTRs.

Methods: A total of 972 KTRs from a prospective multicenter observational cohort study in Korea (KNOW-KT; The KoreaN cohort study for Outcome in patients With Kidney Transplantation) between 2012 and 2016 were included in the study. We investigated the association between the number of prescribed medications and adverse outcomes such as graft failure, all-cause mortality and cardiovascular events. PP was defined as the use of more than 10 medications per day at 1 year after kidney transplantation.

Results: The patients with PP were noted in 478 (49.2%) patients. The PP prevalence at 1, 2, 3, 5, and 8 years after transplantation was 49.2%, 36.5%, 35.7%, 36.3% and 24.6%, respectively. The prevalence of diabetes, dyslipidemia and history of cardiovascular disease was significantly higher in the PP group than in the non-PP group (the use of fewer than 10 medications; n= 494). The mean follow-up period was 6.9 years, and there were 69 graft failures, 63 new-onset cardiovascular diseases, and 36 deaths. When the effect of PP prescribed at 1-year post-transplant on clinical outcomes was analyzed, there was no difference in glomerular filtration rate between the non-PP and PP groups, and the hazard ratio of graft failure and death in the PP group was 1.07 (0.718 to 1.59) and 1.37 (0.71 to 2.64), respectively, compared to the non-PP group. However, multivariate analysis adjusted for classical risk factors showed that PP and medication counts independently increased the risk of new cardiovascular disease (adjusted HR 1.76 (1.051-2.950); p=0.032, adjusted HR 1.079 (1.00-1.164, p= 0.049), respectively) after KT.

Conclusions: These results showed that PP is common in KTRs, and considering the adverse effects of PP on KT outcomes, physician's attention and efforts are needed to systematically manage and prevent inappropriate PP after KT. Long-term and large-scale research is needed to establish management guidelines for PP in the future.

SA-PO293

The Relationship of Polypharmacy with Increasing CKD Stage

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Background: Previously, chronic kidney disease (CKD) and hemodialysis has been reported as the one of the risk factors of polypharmacy. However, it has been unclear the relationship of increasing CKD stage with the higher number of medications.

Methods: In this retrospective cohort analysis, 408 CKD patients (CKDG1 and 2 (n=23), CKDG3-5 (n=81) and CKDG5D (n=304) were conducted. We analyzed the backgrounds, the number and details of prescribed medications in January 2017, the number of patients who met STOPP (Screening Tool of Older Person's Prescriptions) criteria, and the risk factors for polypharmacy (6-9 medications) and hyper-polypharmacy (≧ 10 medications).

Results: The mean number of medications was significantly different among three groups and increased as the higher CKD stage (4.5±2.6 in CKDG1 and 2, 8.0±3.5 in CKDG3-5, and 9.7±3.5 in CKDG5D, p<0.001). The number of patients of polypharmacy and hyper-polypharmacy was increased as the CKD stage (polypharmacy: 26.1% in CKDG1 and 2, 72.8% in CKDG3-5, and 87.2% in CKDG5D, p<0.001, hazard ratio (HR) 3.23/ one stage increase, p<0.001, hyper-polypharmacy: 4.35% in CKDG1 and 2, 32.1% in CKDG3-5, and 51.0% in CKDG5D, p<0.001, HR 2.78/one stage increase, p<0.001). In STOPP criteria, the number of patients who had any duplicate drugs were significantly different among three groups and increased as CKD stage (4.35% in CKDG1 and 2, 14.8% in CKDG3-5, and 27.6% in CKDG5D, p=0.004), and patients who had benzodiazepines for > 4weeks were also significantly different (8.7% in CKDG1 and 2, 7.41% in CKDG3-5, and 24.7% in CKDG5D, p=0.001). Multivariate logistic analysis indicated that CKD stage and diabetes were independent risks for polypharmacy and hyper polypharmacy (polypharmacy: CKD stage; HR 1.62/ one stage increase, p<0.001, and diabetes: HR 2.23 (vs. without DM), p=0.007, hyper polypharmacy: CKD stage; HR 1.54, p<0.001, and diabetes: HR 1.64, p=0.017).

Conclusions: The number of medications, patients with polypharmacy, and the risk for polypharmacy were increased as higher CKD stage.

SA-PO294

Barriers and Facilitators of Pharmacist-Led Programs: Insights from Survey Among Providers

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Background: Hypertension is a leading cause of cardiovascular death in the United States (US). Despite current guidelines emphasizing strict blood pressure control, over half of the US population fails to reach the recommended goal. Clinical pharmacists can play a crucial role in a team-based approach to overcome these challenges. However, our previous survey found that pharmacists are underutilized despite positive attitudes among providers. To understand the barriers and facilitators of implementing pharmacist-led programs, we conducted a thematic analysis of survey data from providers.

Methods: To gain insights into the utilization of pharmacists, we conducted a survey among providers at a single academic institution and its affiliated Veterans Affairs (VA) hospital where the pharmacist-led medication management is routinely available. We conducted sentiment and thematic analyses of providers' narrative comments to better understand their attitudes and experiences with the utilization of pharmacists.

Results: The survey response rate was 37% (153 of 413 surveyed providers), with 36 providers (24%) providing comments. The majority of the providers (n=27, 75%) were Primary Care (PC) providers, with half of them (n=15, 50%) based in the VA practice. In the sentiment analysis, we observed more positive attitudes among PC APPs (n=5 of 8, 63%) compared to PC clinicians (n=7 of 19, 37%). Among VA PC clinicians (n=4), concerns were expressed. The thematic analysis results, summarized in Fig 1, highlight a lack of awareness among providers potentially leading to underutilization of pharmacists. However, there were other providers who expressed the value of pharmacists and held positive perceptions, likely based on their former experiences.

Conclusions: The lack of awareness among providers is a major barrier to implementing pharmacist-led programs.

Theme	Number of Mentions
Barrier: Lack of Knowledge/Information	10
Barrier: Concerns for Patient's Knowledge and Capability	7
Barrier: Concerns about Pharmacist Involvement	7
Facilitator: Need for Collaboration and Relationship Building	6
Facilitator: Positive Experiences with Pharmacists	5
Facilitator: Potential Benefits of Pharmacist Involvement	4

Barriers:

Lack of Knowledge/Information
- *"Neutral because I do not know."*
- *"I'm unaware of pharmacist availability in managing hypertension."*
- *"Don't know anything about the pharmacy-guided program."*
- *"Hard to judge, I have not seen it done."*
- *"I am not very familiar with pharmacist-guided management of BP meds."*
- *"Have not used pharmacists for blood pressure management."*

Concerns for Patient's Knowledge and Capability
- *"Unsurprisingly, it really depends on the patient as to the success and risk."*
- *"I don't have enough information about pharmacist-guided patient-driven self-titration, but I can tell you my patients are highly uneducated and I do not trust them to self-titrate their meds."*
- *"They are often confused with instructions even when written down. I think that is a very dangerous idea and I won't be referring patients for that service."*
- *"It can lead to confusion for patients."*
- *"Pharmacist involvement can lead to confusion for patients. Sometimes it leads to excessive lab draws. I would advocate nursing staff involvement for BP treatment and monitoring."*

Concerns about Pharmacist Involvement
- *"I never want the pharmacist involved in clinical decision making."*
- *"I do not require any assistance from individuals with no licensing authority to practice medicine."*
- *"I want to be in control of my patient's care."*
- *"I am ultimately responsible for them."*
- *"Hypertensive care is what I was trained to do."*

Facilitators:

Positive Perception of Pharmacist Involvement
- *"I think the pharmacist-guided approach makes a lot of sense."*
- *"I would love to have more pharmacist help in the outpatient clinics."*
- *"Pharmacists are an integral part of my practice and have been extremely helpful."*
- *"Depends on the pharmacist! But in general, after a diagnosis and secondary causes of hypertension ruled out, I'm happy to let my trusted clinical pharmacist assist with management."*
- *"Our pharmacists have guided me on multiple occasions."*
- *"I may be biased as my off-site clinic participated in some of the clinical trials of collaborative care both for hypertension and diabetes and it helped tremendously."*
- *"Having a clinical pharmacist in-house is an excellent resource for us clinicians."*
- *"I feel that involving a pharmacist in the treatment process helps us interact with patients more frequently than once every 2-3 months visits."*

Recognition of Pharmacist's Value in Clinic
- *"I find the pharmacist to be my most valuable asset in clinic."*
- *"Outstanding PACT pharm dx management at the IC VA, and I appreciate their care and excellent communications."*
- *"In my experience as a Heart Failure cardiologist, HF pharmacist take over HF medication titration in Heart Failure patients."*
- *"I am usually very satisfied having the pharmacist involved with HTN management."*
- *"Patients with advanced renal disease could work collaboratively with the pharmacy when needed."*
- *"Our clinical pharmacist at IRL provides a great service for our patients with suspected or confirmed hypertension."*

SA-PO295

Use of Guideline-Recommended Medication Therapy in a High-Risk CKD Population in the Kidney CHAMP Trial

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Background: Use of guideline-recommended medication therapy to improve kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) is suboptimal. Kidney CHAMP is a pragmatic randomized controlled trial evaluating the effectiveness of a population health management (PHM) approach to improve CKD care. The intervention leveraged electronic health records to identify patients with CKD at high risk of progression and communicate recommendations from a nephrologist-led e-consult and pharmacist-led medication review to primary care providers (PCP) randomized to the intervention group. We compared the use of guideline-recommended medication therapy in patients in the intervention group vs patients receiving usual care per their PCP.

Methods: Eligible patients were 18-85 years with high-risk CKD and not followed by a nephrologist. Guideline-recommended medication therapy included use of ACE inhibitor (ACEi) or angiotensin II receptor blocker (ARB) if baseline urine albumin-to-creatinine ratio (UACR) ≥ 300 mg/g, moderate or high intensity statin if baseline age ≤ 75 years, and SGLT2 inhibitor (SGLT2i) and/or GLP1 receptor agonist (GLP1RA). Changes in medication use between groups were tested using logistic regression via generalized estimating equations.

Results: Among 1596 patients enrolled, 58% were females, the mean age was 74 years, mean eGFR 37 mL/min/1.73m^2, and mean UACR 410 mg/g at baseline. Comorbidities included hypertension (95%), diabetes (64%), and cardiovascular disease (78%).

Over a median 18 month study period, ACEi/ARB use changed from 49% to 43% (p=0.10) vs 51% to 40% (p=0.005), statin use changed from 52% to 55% (p=0.55) vs 54% to 50% (p=0.25), and SGLT2i and/or GLP1RA use changed from 9% to 20% (p<0.001) vs 5% to 13% (p<0.001) in the intervention vs usual care groups, respectively. There was no between group difference in the change in ACEi/ARB (p=0.46), statin (p=0.12), or SGLT2i and/or GLP1RA (p=0.80) use.

Conclusions: A PHM approach did not improve use of guideline-recommended medication therapy in patients with high-risk CKD compared to usual care. This research supports a need to address barriers in the primary care setting, including therapeutic inertia and access to clear practice guidelines, and efforts to improve the delivery of CKD care.

Funding: NIDDK Support

SA-PO296

Outcomes of Australian and New Zealand Dialysis and Transplant Patients with Kidney Failure Attributed to Kidney Stones

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Background: Prevalence of kidney stones in the general population can reach 15-20%. Kidney stone formers (KSF), compared to non-KSF, have an increased risk of developing chronic kidney disease and kidney failure (KF). While risk factors, aetiology and outcomes in KSF is well established there remains little data for patients after they develop KF. We therefore set out to examine outcomes of KSF with KF (transplant or recieving dialysis).

Methods: Using the Australian and New Zealand Dialysis and Transpant (ANZDATA) registry we included adult patients with KF who recieved dialysis or transplant (1973-2020). We divided our cohort into KSF and non-KSF groups. For dialysis, we included haemodialysis and peritoneal dialysis to determine risk of mortality. A joinpoint model examined annual rates of KSF diagnosed with KF over time. A seperate analysis was conducted for transplant recipients to examine risk of mortaity and graft failure. Multivariate Cox regression analysis was used to determine hazard ratio (HR) and 95% confidence interval (CI) of outcomes.

Results: In the dialysis cohort 79,670 patients were followed (293,255 patient-years) with 871 (1.1%) having KF from calculi. Compared to non-KSF the KSF group were less likely to have diabetes (26%vs45%) or vascular disease (17%vs45%) and were older (61vs58 years), *P*<0.001. Proportion of KF with calculi as a cause declined annually by 2.7% (95%CI 1.9-7.4, *P*<0.01). There was no difference in mortality between KSF and non-KSF in patients in multivariate analysis (HR 0.93, 95%CI 0.86- 1.01, *P*<0.001). In the transplant cohort 25,052 patients were included, with 219 (0.9%) having KF from calculi. Pre-emptive transplant occurred in 2,221 (2.7%) of the whole group but only in 12 (1.3%) of KSF. Compared to the non-KSF the KSF group were less likely to be diabetic (20%vs12%) and older (48 vs 51 years) (*P*<0.001). There was no difference in mortality risk (HR 1.04, 95%CI 0.86-1.26) or graft failure (HR 1.01, 95%CI 0.77-1.34) between the two groups in multivariate analysis.

Conclusions: In Australia and New Zealand, KSF as a cause of KF is rare and declining over time. There is no difference in mortality risk between KSF and non-KSF in patients who start dialysis, or a difference in graft failure rate in those who received a transplant.

SA-PO297

Characterization of Nephrocalcinosis Phenotypes at Pediatric or Adulthood Ages of Onset

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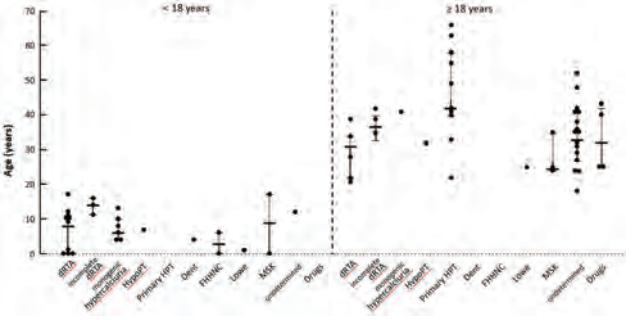
Background: This study aimed to compare the clinical and laboratorial presentation and etiology of Nephrocalcinosis (NC) at different ages of onset.

Methods: A retrospective study was conducted based on clinical and laboratorial data from medical records of outpatients aged < or ≥ 18 years old with radiologic evidence of renal parenchymal calcifications by computed tomography or renal ultrasound suggesting NC at presentation.

Results: A total of 81 patients, divided into 2 groups, 56 adults (44 F/12M, ≥18 yrs) and 25 pediatric (14F/11M, <18 yrs), were included**.** Pediatric patients were referred mostly because of hydroelectrolytic/metabolic disorders as the primary presentation of NC (84 vs 30%, p< 0.01), history of failure to thrive (48 vs 3%, p< 0,001) and deafness (28 vs 5%, p< 0,01), against higher association of NC with nephrolithiasis and more urological procedures in adults (70 vs 40%, p < 0.001 & 45 vs 24%, p= 0.056, respectively). Mean estimated glomerular filtration (eGFR) rate was lower in adults (88 ± 31 vs 108 ± 21 mL/min/1.73m2, p< 0.01). Molecular diagnosis could be established in 17/19 genetically tested cases corresponding to 21% of the whole sample. The individual distribution of underlying causes of NC per age are shown in the Figure. Distal renal tubular acidosis (dRTA) and monogenic hypercalciuria were statistically more frequent in the pediatric group (40 vs 13 % and 24 vs 11 %, p= 0.001, respectively) and primary hyperparathyroidism (HPT) and use of drugs were seen only in adults (14 and 7%). Undetermined or still under investigation cases were more common among adults. Cases of familial hypomagnesaemia with hypercalciuria and nephrocalcinosis (FHHNC), medullary sponge kidney (MSK), Lowe, Dent, Hypoparathyroidism (HypoPT) did not differ.

Conclusions: Adults with nephrocalcinosis exhibited reduced renal function at presentation possibly due to delay on diagnosis, worse clinical outcome or previous urological procedures. Molecular analysis could help to further elucidate clinical causes of NC in this group.



SA-PO298

Characteristic Alterations of Bone and Mineral Metabolism in Children and Adults with Nephropathic Cystinosis

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Background: The pathophysiology of nephropathic cystinosis (NC) associated bone disease is poorly understood.

Methods: We examined serum/plasma concentrations of 8 bone markers and routine parameters of mineral metabolism in 63 children (mean age 10.8 years) and 40 adults (mean age 28.3 years) with NC by ELISA and autoanalyzer. Data are given as age- and sex-dependent z-scores as a function of estimated glomerular filtration rate (eGFR).

Results: Pediatric and adult NC patients with eGFR > 60 ml/min/1.73 m² showed reduced z-scores for serum phosphate and calcium, and elevated bone-specific alkaline phosphatase (BAP) despite treatment for Fanconi syndrome. Hypocalcemia was more pronounced in children, whereas BAP z-scores were more elevated in adults (each p<0.001). Intact and total fibroblast growth factor 23 (FGF23) and parathyroid hormone levels were suppressed in NC patients with eGFR > 60 ml/min/1.73 m² (each p<0.001). FGF23 z-scores progressively increased in parallel with decreasing eGFR, reaching 6 SD in patients with eGFR < 30 ml/min/1.73 m², while calcitriol levels progressively declined. The Wnt signaling inhibitor sclerostin was increased by 1 SD in pediatric but not in adults NC patients irrespectively of eGFR. The osteoclast marker tartrate-resistant acid phosphatase 5b (TRAP5b) was increased by 1 SD (children) and 2 SD (adults) independent of eGFR despite the absence of hyperparathyroidism in the majority of patients (each p<0.001). Receptor-activator of NF-κB ligand (RANKL), an inhibitor of osteoclast activity, was reduced by SD 1.0 in pediatric but not in adult NC patients. Finally, the RANKL inhibitor osteoprotegerin (OPG) was increased by 2 SD in children with eGFR < 30 ml/min/1.73 m², whereas adult patients consistently showed reduced OPG z-scores.

Conclusions: Pediatric and adult NC patients show hypophosphatemia, hypocalcemia, hypovitaminosis D, and increased osteoblast activity indicating persisting rickets/osteomalacia despite treatment for Fanconi syndrome. Increased osteoclast activity despite counter regulation via OPG/RANKL and suppressed PTH levels suggests a primary osteoclast defect in NC resulting in increased bone resorption, which is more pronounced in children compared to adult patients.

Funding: Commercial Support - Chiesi

SA-PO299

Low Expression of Renal Claudin-2 Increases Medullary Pro-Inflammatory Macrophages and Calcification in Nephrectomy Patients with a History of Urinary Stone Disease

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Background: The transmembrane protein claudin-2 (Clnd2) is highly expressed in the proximal tubule and descending thin limb where it is key for ~70% of filtered Ca^{2+} reabsorption. Men with a rare missense mutation in Clnd2 manifest hypercalciuria and urinary stone disease (USD). However, the relationship of Clnd2 expression to renal calcification and interstitial cellular responses is not known. Thus, we examined Cldn2

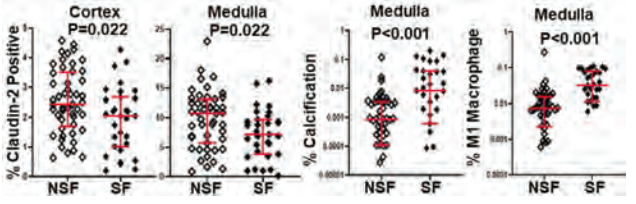
expression, interstitial calcification, and pro- and anti-inflammatory macrophages (Mφ's) in nephrectomy samples from patients with and without a USD history.

Methods: Non-cancerous kidney tissue sections from patients with (n=31 stone formers (SFs); 10F/21M) and without (n=50 non-stone formers (NSFs); 16F/34M) a history of USD were used for immunohistochemical analyses. Data are presented as median (25th, 75th percentile) and analyzed by Wilcoxon rank-sum test to identify statistically significant (P<0.05) differences between groups.

Results: Expression of Clnd2 protein in both cortex and medulla of kidneys was significantly (P=0.02) lower in SFs than NSFs. Renal medullary calcification (% calcification) and populations of M1 Mφ's (proinflammatory) were significantly (p<0.001) greater in SFs. There were no differences in the renal tissue population of M2 Mφ's (anti-inflammatory), age, body mass index, hypertension before surgery, serum creatinine, and eGFR between groups.

Conclusions: These results suggest that SFs have decreased expression of Clnd2 protein in the proximal tubule and thin descending limb of Henle's loop. This in turn may increase the formation of interstitial calcifications and populations of pro-inflammatory Mφ's in USD formers. NIDDK (DK135097) and Mayo Foundation.

Funding: NIDDK Support, Private Foundation Support



SA-PO300

Controls but Not Patients with Calcium Nephrolithiasis Secrete Less Urinary Uromodulin After Salt Loading

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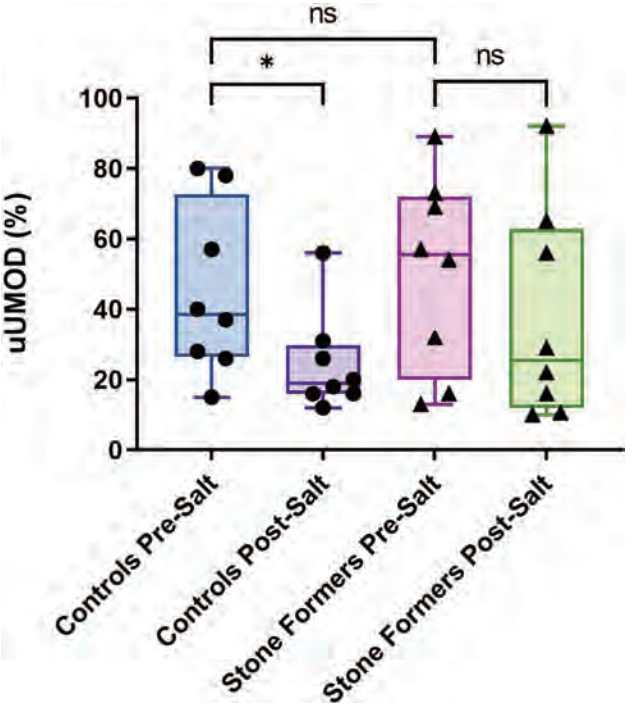
Background: Calcium is the most common constituent of kidney stones. Uromodulin (UMOD) enhances TRPV5 membrane abundance increasing renal Ca^{2+} absorption thus reducing hypercalciuria. UMOD stimulates Na^{+} absorption via NKCC2 causing hypertension. High salt intake is also risk factor for nephrolithiasis. We hypothesize that a higher urinary UMOD secretion with a high salt diet compensates for the higher stone risk by improving hypercalciuria.

Methods: This is a prospective, randomized, cross-over study. Stone-formers and controls were randomized to a control or a high salt diet for 2 days. After washout, the participants received the diet they were not exposed to previously. After each diet, we obtained 24-hour urine and fasting serum studies.

Results: At baseline, there was no significant difference for urinary UMOD secretion between stone-formers and controls. In contrast to our hypothesis, we found that urinary UMOD secretion was significantly reduced after the salt load in controls but not in stone-formers.

Conclusions: There was no lower baseline urine UMOD level in stone-formers. After salt loading, we show lower urinary UMOD secretion in controls but not in stone-formers. As UMOD enhances NKCC2 contributing to hypertension, acute downregulation of UMOD after a salt loading makes physiologically sense.



Salt-loading reduces uUMOD in controls only (P<0.05).

Table.1

	Controls	Stone Formers	*p*-Value
No.	8	8	NS
Age, yr	23-51	23-51	NS
Gender, M/F	3/5	3/5	NS
BMI Range	20-37	20-37	NS
Urine			
Ca^{2+}, mg/d	116.2 ± 61	235 ± 65.2	*<0.01*
pH	6.2 ± 0.34	6.45 ± 0.28	NS
Volume, ml	2.71 ± 0.5	2 ± 0.54	*<0.03*
Na^{+}, mEq/d	94 ± 57	120 ± 32.8	NS
K^{+}, mEq/d	50.5 ± 15	35 ± 9.7	*<0.03*
Uric acid, mg/d	668 ± 134.4	607 ± 118	NS
Creatinine, mg/d	1483.5 ± 268.7	1217 ± 322	NS
Mg^{2+}, mg/d	82.8 ± 52	86 ± 19.3	NS
Cl^{-}, mEq/d	117.6 ± 62.8	123 ± 38.8	NS
NH_4^{+}, mEq/d	33.4 ± 9	33 ± 9	NS
Citrate, mg/d	538.8 ± 188	385 ± 326	NS
Phosphorus, mg/d	666.4 ± 152.4	629 ± 118.3	NS
Oxalate, mg/d	19 ± 6.2	15 ± 5.7	NS
SO_4^{2-}, mmol/d	14.8 ± 5.5	12 ± 7.4	NS

Baseline.

SA-PO301

CYP24A1 Activity Associates with Phenotypic Traits in Idiopathic Hypercalciuria

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Background: Hypercalciuria is the most frequent abnormality in kidney stone formers. The underlying mechanisms remain unknown in most cases, hence the designation "idiopathic hypercalciuria". We hypothesized that the Vitamin D-inactivating enzyme CYP24A1 contributes to the pathogenesis of hypercalciuria in kidney stone formers.

Methods: We conducted association analyses between CYP24A1 activity, estimated by the Vitamin D metabolite diagnostic ratio (25(OH)-/24,25 $(OH)_2$ Vitamin D_3 ratio; VMDR), and the phenotype of participants in two observational cohorts of kidney stone formers, the Swiss Kidney Stone Cohort and the Bern Kidney Stone Registry. Linear and logistic regression models adjusted for multiple confounders, including plasma 25(OH) Vitamin D_3, were applied. Plasma 25(OH)- and 24,25 $(OH)_2$ Vitamin D_3 were quantified using an established, highly sensitive and specific LC-MS/MS assay.

Results: In total, 974 participants were included in the analysis. After multivariable adjustment, a higher VMDR (i.e. lower CYP24A1 activity) was associated with higher

total plasma calcium (β 0.07; 95% CI 0.01, 0.14; p = 0.02), ionized calcium (β 0.11; 95% CI 0.03, 0.18; p < 0.01) and absolute and fractional excretion of urinary calcium (β 0.06; 95% CI 0.00, 0.11; p = 0.04 and β 0.10; 95% CI 0.04, 0.16; p < 0.01, respectively). A higher VMDR was further associated with an increased risk of forming stones composed of calcium oxalate dihydrate (Odds ratio 1.64; 95% CI 1.22, 2.35; p < 0.01) and a reduced bone mineral density at the femoral neck (β -0.07; 95% CI 0.14, -0.01; p = 0.04). VMDR was not associated with plasma or urinary phosphate, 1,25 $(OH)_2$ Vitamin D_3 or parathyroid hormone.

Conclusions: Our study reveals that CYP24A1 activity is associated with traits previously linked to idiopathic hypercalciuria.

SA-PO302

Distinguishing Uric Acid Stone Formers from Type 2 Diabetics with Low Urine pH: The Role of Impaired Buffering

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Background: The prevalence of uric acid (UA) nephrolithiasis has increased in the past decades, particularly among patients with metabolic syndrome, and this lithogenicity is driven by acidic urine pH. Previous studies in these patients on random diets showed that this lower urine pH results from higher acid excretion and insufficient urinary buffering by ammonia. However, intrinsic vs. extrinsic contributors are hard to discern because diet was not controlled. In addition, patients with type 2 diabetes mellitus (T2DM) often exhibit an acidic urine, but only a minority develop UA stones. Here, we provide a comprehensive report of acid-base and stone risk parameters in UA stone formers (UASF) and non-stone forming controls with and without T2DM who were equilibrated and studied under a fixed metabolic diet.

Methods: A total of 74 UASF, 13 T2DM patients without a history of kidney stones, and 51 normal subjects without stones or diabetes (Ctrl) were studied. All participants were equilibrated on metabolic diet for at least 5 days. Blood and urine samples were collected for analysis of acid-base and stone risk parameters. Statistical analyses were performed to compare the stone risk profiles among the three groups.

Results: Participants were comparable with respect to demographic characteristics, with age range of 48-60 years (aligning with peak incidence of UA stones). UASF had slightly higher and Ctrl exhibited a lower body mass index. Under a fixed diet, UASF and T2DM exhibited lower urinary pH, higher net acid excretion (NAE), and lower levels of citrate and bicarbonate compared to Ctrl. The proportion of NAE excreted as ammonium (ammonium/NAE) was significantly lower in UASF [0.50 (95% confidence intervals: 0.46-0.54)] compared to T2DM [0.64 (0.53-0.76)] and Ctrl [0.74 (0.68-0.81)].

Conclusions: This study has the largest number of subjects evaluated on a controlled metabolic diet to date. We found a similarly high NAE in UASF and T2DM non-stone formers; the parameter that sets aside UASF was the significantly lower ammonium/NAE in UASF. An increased acid load to the kidney is an important contributing factor in the development of UA nephrolithiasis but it is not sufficient, and a defect in urinary buffering is necessary for its full pathogenesis.

Funding: NIDDK Support, Private Foundation Support

SA-PO303

Adherence to Potassium Citrate and Changes in 24-Hour Urine Stone Risk Parameters

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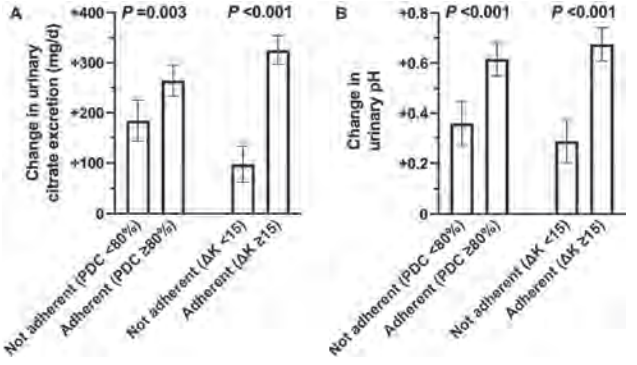
Background: Patient adherence to potassium citrate therapy for urinary stone disease (USD) is low. We assessed associations of potassium citrate adherence with changes in 24-hour urine parameters.

Methods: We identified adults enrolled in Medicare with USD, a baseline 24-hour urine collection (Litholink, 2011-2017), hypocitraturia or low urine pH, a prescription for monotherapy with potassium citrate tablets within 3 months, and a follow-up urine collection 6-12 months after baseline. We defined two measures of adherence: (1) percentage of days covered (PDC) over 0-3 months based on pharmacy claims and (2) change in urinary potassium (ΔK) between baseline and follow-up. We assessed the association between PDC and ΔK using an independent t-test and the association of adherence with changes in urinary citrate and pH using ANCOVA. Finally, we compared the strength of association of PDC and ΔK with these changes using a Wald test.

Results: Among 432 patients, 366 (85%) had hypocitraturia and 266 (62%) had low urine pH. Patients adherent to medication based on pharmacy claims (PDC≥80%) had a significantly higher mean ΔK compared to those not adherent to medication (+26.1 mEq/day vs. +17.9 mEq/day, *P*<0.001). The adjusted mean increase in urinary citrate and pH among patients adherent to medication significantly exceeded that of patients not adherent to medication (Figure). Compared to PDC, ΔK had a stronger association with change in urinary citrate (*P*<0.001) and pH (*P*=0.07), though the latter was not statistically significant.

Conclusions: Compared to pharmacy claims, the increase in urinary potassium was generally more predictive of increased urinary citrate and pH, emphasizing the value of urinary potassium as a measure of adherence.

Funding: NIDDK Support



Mean change in (A) urinary citrate and (B) pH stratified by adherence. Estimates are adjusted for age, sex, race, region of residence, dual eligibility, comorbidity score, and medication dose. Error bars represent 95% CIs.

SA-PO304

Differential Effects of Thiazide, Alkali, or Both on Urine Determinants of Stone Risk in Calcium Oxalate (CaOx) and Calcium Phosphate (CaP) Stone Formers

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Background: Thiazide type diuretics, potassium citrate (K-Cit), and lifestyle changes are used to prevent calcium kidney stones. Thiazides decrease stone risk by decreasing urine calcium (Ca). Citrate (Cit) is an inhibitor that decreases urine supersaturations (SS); however, it also increases urine pH and therefore Ca phosphate (CaP) SS. Thus, the effect of K-Cit on stone risk is complex.

Methods: To study the effects of common treatments for Ca stone risk we analyzed the 24-hour urinalysis of Calcium Oxalate (CaOx) and CaP stone formers (SF) by 4 different treatment types: lifestyle, K-Cit, thiazide, or both medications.

Results: Thiazides reduced urine Ca in both CaOx SF (-74±95 mg/day) and CaP SF (-102±100 mg/day). K-Cit alone and when combined with thiazide had no effect on urine Ca. K-Cit increased urine Cit in CaOx SF (252±306 mg/day), but not in CaP SF (36±353 mg/day). Thiazide decreased urine Cit among CaP SF (-118± 249 mg/day). K-Cit and thiazide combined increased Cit in CaOx SF (118±264 mg/day), but not CaP SF (94±217 mg/day). Urine pH rose in all groups except CaP SF on only lifestyle treatment. Among CaOx SF, pH increased in patients receiving K-Cit (0.6±0.6) and both (0.7±0.6) compared to patients receiving thiazide (0.1±0.5). There is a similar pattern among CaP SF receiving K-Cit (0.3±0.5), both (0.5±0.5), or thiazide (0.1±0.3). Thiazide decreased CaOx SS in both CaOx SF (-3.3±3.5) and CaP SF (-3.1±2.9). K-Cit did not lower CaOx SS in either CaOx or CaP SF. Thiazide decreased CaP SS in both CaOx SF (-0.5±0.9) and CaP SF (-0.8±0.9).

Conclusions: K-Cit had no significant effect on urine Ca and increased urine Cit levels in CaOx SF; however, increased urine pH lead to increased CaP SS for CaOx SF. The study raises questions about the best preventive treatment for patients with CaP stones and suggests that K-Cit may not confer the same benefits on CaP SF as it does on CaOx SF.

Funding: NIDDK Support

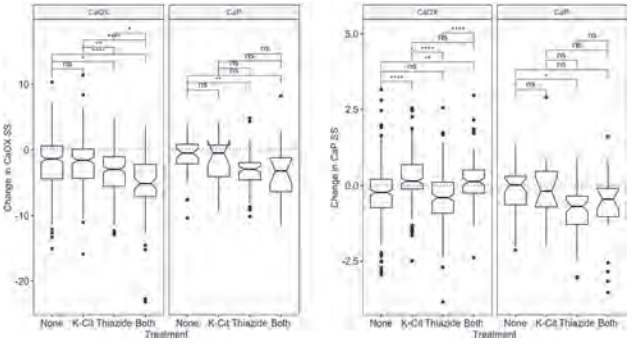

Figure 1. Boxplots of the change in urine CaOx and CaP SS by treatment group and stone type. Each includes t-tests comparing treatment groups.

SA-PO305

Effect of Hydrochlorothiazide on Bone Mineral Density in Patients with Kidney Stones: A Post Hoc Analysis of the NOSTONE Trial

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Background: Low bone mass and fractures are highly prevalent in patients with kidney stones. Thiazide diuretics lower urine calcium and hence may preserve bone mass. No placebo-controlled randomized trial (RCT) has been conducted to examine the impact of thiazide diuretics on bone mineral density (BMD) in patients with kidney stones.

Methods: We conducted a post-hoc analysis of the NOSTONE trial to assess a range of hydrochlorothiazide (HCT) doses or placebo on bone mineral density in patients with recurrent calcium-containing kidney stones. Computed tomography (CT) attenuation was measured at T12-L3 vertebrae in Hounsfield units (HU) at baseline and the end of the study, using a previously validated approach, with lower values corresponding to lower BMD. BMD measurements were performed by two independent readers blinded to the study intervention. Random-effects linear regression models were used to investigate treatment effects on changes from baseline.

Results: BMD measurements were available in 388 of 416 (93%) randomized patients. Median follow-up time was 2.92 years. At baseline, mean BMD was directly associated with eGFR (β 0.934 HU, 95% confidence interval [CI] 0.680; 1.189, p < 0.001) and inversely with age (β -2.208 HU, 95% CI -2.510; -1.907, p < 0.001). Mean BMD decreased by 6.4±15.7 HU in the placebo group, by 5.1±15.1 in the 12.5mg HCT group (β coefficient vs placebo, 0.368 HU, 95% CI -1.735; 2.472, p = 0.732), by 4.1±16.3 in the 25mg HCT group (β 0.926 HU, 95% CI -1.335; 3.187, p = 0.422), and by 4.8±15.9 in the 50mg HCT group (β 0.699 HU, 95% CI -1.450; 2.848, p = 0.524). No association was observed between HCT dose and change in BMD (p = 0.430). The results were confirmed in sensitivity analyses for eGFR, urinary calcium, body mass index, and in per-protocol analyses.

Conclusions: In patients with recurrent calcium-containing kidney stones, loss of bone mineral density was similar in patients receiving hydrochlorothiazide at a dose of 12.5 mg, 25 mg, or 50 mg or placebo once daily.

SA-PO306

Vascular Calcification in Kidney Stone Formers: The Impact of Age and Stone Composition

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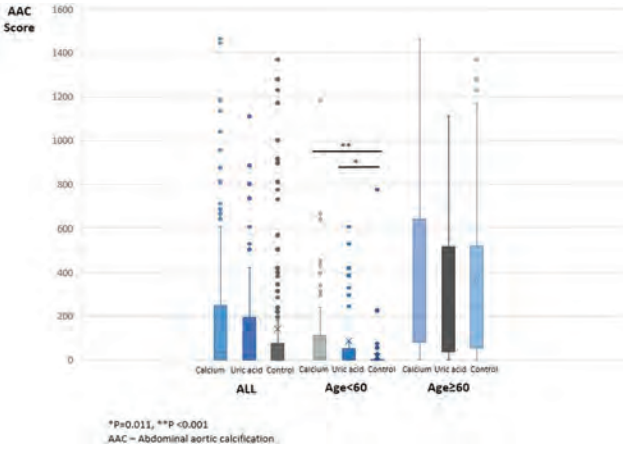
Background: Nephrolithiasis is a common condition, associated with increased cardiovascular morbidity. Previous observational studies have showed that kidney stone formers (KSF) have increased vascular calcifications (VC) and osteoporosis. However, data regarding the effect of age and stone component on VC in these patients is limited.

Methods: This is a retrospective, single center, matched case-control study. KSF with a pure stone analysis (uric acid stone or calcium oxalate) who were treated in the urology clinic of Shaare Zedek Medical Center from 2015 to 2021 were identified. Fully matched controls without history of nephrolithiasis were drawn from patients hospitalized or admitted to the emergency room of the same hospital. Abdominal aortic calcification (AAC) and vertebral bone mineral density (BMD) were assessed using available computed tomography (CT) imaging. KSF and non-KSF were compared for prevalence and severity of AAC and BMD.

Results: A total of 335 patients were investigated, 134 with calcium oxalate stone, 67 with uric acid stone, and 134 fully matched controls. Overall, the severity of VC, measured by the AAC score, did not differ significantly between the groups. However, in patients aged <60 years, both prevalence and severity of aortic calcification were significantly higher in calcium oxalate and uric acid stone groups compared to control (55.1%, 37.8% and 21.8%, p = 0.001, for the prevalence of aortic calcification and 95.4±187.5, 85.8±166.6 and 16.3±86.6, p = 0.001, for ACC score, respectively). The prevalence of osteoporosis was similar between the groups.

Conclusions: In this study, the prevalence and severity of VC was higher in younger KSF. These findings may suggest premature vascular calcification among patients with nephrolithiasis, both in calcium oxalate and uric acid stone formers.



SA-PO307

SYNB8802 Lowers Urinary Oxalate During a Diet-Controlled Study in Patients with Roux-en-Y Gastric Bypass

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Background: Patients with Roux-en-Y (RnY) gastric bypass surgery are at risk for development of intestinal malabsorption which can increase the absorption of dietary oxalate, resulting in enteric hyperoxaluria (EH). Hyperoxaluria may lead to kidney stone formation, kidney damage, and deposition of oxalate in other tissues and organs. SYNB8802 is an engineered probiotic bacteria designed to consume oxalate in the GI tract and reduce urinary oxalate (UOx) absorption.

Methods: Study SYNB8802-CP-002 was a Phase 1b, randomized, placebo-controlled, single-center inpatient study in subjects with a history of RnY gastric bypass surgery. Subjects were placed on a 12-day diet-controlled study containing 300 mg of oxalate and 400 mg of calcium. A diet and placebo run-in period of 3 days was followed by oral administration of increasing dose levels of SYNB8802 up to $3x10^{11}$ lives cells or placebo for 12 days. 24-hour urine was collected daily from days -3 to 12 and analyzed for urine oxalate content as well as other analytes.

Results: SYNB8802-CP-002 enrolled 11 subjects (median (SD) age 56 (8.6), 1 M/10 F) with a history of RnY gastric bypass, and no prior kidney stones. Seven subjects received SYNB8802 and 4 patients received placebo. Two placebo subjects were excluded from the efficacy analysis because of major protocol violations (antibiotic use and incomplete dosing). The oxalate diet resulted in a baseline mean (SD) UOx of 29.4 (2.3) mg/24h for the placebo and 32.5 (9.0) mg/24h for the SYNB8802. SYNB8802 lowered UOx by -41.0% (p<0.01) compared to -8.8% (p=0.73) for placebo but the change over placebo (-35.3%) did not achieve statistical significance (p=0.16). A post-hoc pharmacometrics model incorporating the effects of dose and frequency showed a significant UOx lowering of -37.3% [95% CI: 45.9, 28.3] relative to placebo (p<0.05). The most common adverse events were mild to moderate and GI related. There were no SAEs.

Conclusions: SYNB8802 was well tolerated in patients with RnY gastric bypass and demonstrated the capacity to lower UOx. SYNB8802 should be further evaluated in subjects afflicted with kidney stone disease and EH.

Funding: Commercial Support - Synlogic Therapeutics, Inc.

SA-PO308

Assessment of Health-Related Quality of Life in Primary Hyperoxaluria

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Background: Primary hyperoxaluria (PH) is a rare monogenic disorder; all 3 known forms are associated with frequent kidney stone events and a risk for chronic kidney disease. Here we assessed patient quality of life (QoL) metrics.

Methods: PH patients (pt) and caregivers were recruited by the Oxalosis and Hyperoxlauria Foundation. QoL was measured via disease specific questions plus validated instruments.

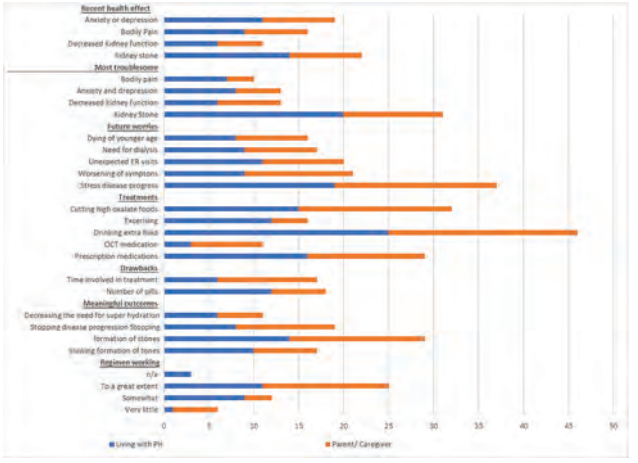
Results: Both PH pt (n=25) and caregivers (n=21) participated. The majority of PH cases were diagnosed as a child. The cohort included all 3 types (20 PH1, 15 PH2, 12 PH3). The majority (78%) of pt were diagnosed by genetic testing, 9% by liver biopsy, and in 13% pt did not know. Most pt (49%) formed their first stone as an infant or toddler, 23% as a preschool or school-age child, and 11% as teenagers. Only 4% formed their first stone as adults, and 13% never had a kidney stone. The main PH health concerns are shown in graph 1. Other significant health burdens are chronic kidney disease and fatigue. Adult pt see kidney stones as troubling compared to parents and caregivers (p=0.03). Socializing and traveling (34%, 10 adults, 6 children), attending school or work (23%, 4 adults, 7 children), and participating in sports (21%, 6 adults, 4 children) were the most impacted

activities of daily life in our sample. Anxiety regarding recurrent stone events and future kidney failure was high among all 3 PH types. PH 3 pt scored highest (least impacted) in all QoL domains, followed by PH 2 with the lowest scores for PH1.

Conclusions: Depression, anxiety, bodily pain, kidney stones and CKD are important QoL factors regardless of the underlying PH cause. These patient reported outcomes can be used to guide future treatment targets.

Sample characteristics

	Male	Female	Non-binary	Total
Living with PH	10	14	1	25
Parent or caregiver	13	8	0	21
Total	23	22	1	46



SA-PO309

Suboptimal Identification and Investigations of Renal Stones in a Tertiary Irish Centre: A Retrospective Analysis

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Background: Nephrolithiasis is a common medical problem with 10-20% of men, and 5% of women in Ireland having one kidney stone in their lifetime. Simple investigations and stone analysis can identify metabolic or structural factors that increase risk, allowing prompt treatment. There are clinical characteristics that should prompt these investigations, and this often requires multi-disciplineary approach.

Methods: EAU+ AUA recommend in depth metabolic screening for patients with these features: Young age Multiple or bilateral stones. Recurrent stone formers Structural kidney abnormalities Metabolic Co-morbidities that increase risk, Certain Stone Compositions We performed a retrospective analysis of patients admitted with stone disease between July 2022 and Feb 2023. We collected data on; Patient demographics Treatment choice First stone vs recurrent Testing of basic biochemistry Presence of Risk factors as above.

Results: We analysed 214 unique patient identifiers This consisted of 129 males and 85 female. Average number of stone episodes per month was 30.57. Mean age of patients was 50.25, with 19 patients under the age of 30yrs (9%). Age range 20-95yrs old. Patient presentation to our service was emergency in 158/214 (74%), 21 were elective admissions (10%), and emergency transfers from secondary hospitals consisted of 35/214 patients (16%). Inpatient admission with Medical Expulsive Therapy (MET) consisted of 15 of 214 patients (7%) 7 Patients were discharged home with MET (3%) 15 were admitted for ureteric stent placement alone(7%) 177 of the 214 patients were brought for ureteroscopy (83%) Looking at features as mentioned above that warrant screening, we note this of our population: 25% had recurrent or bilateral stones 9% had stone compositions that were high risk for recurrence 3% had co-morbidities that increase risk of recurrence as detailed above 9% under the age of 30yrs, and 28% under the age of 40. 5.6% had existent structural abnormalities.

Conclusions: There are a large proportion of patients that are at high risk of recurrence and thus a systematic and comprehensive approach is required to identify and investigate these patients. By proactively addressing this gap in patient care, we can enhance patient outcomes, reduce the burden of recurrent renal stones on healthcare systems, and ultimately improve the quality of life for individuals affected by this condition.

SA-PO310

A Case of Primary Pseudohypoparathyroidism Presenting with Normal Serum Phosphorus

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Introduction: Pseudohypoparathyroidism (PHP) is a very rare genetic disorder characterized by hypocalcemia/hyperphosphatemia secondary to parathyroid hormone (PTH), target organ resistance. PHP is a congenital disorder that is diagnosed in childhood. This is a unique presentation of a rare condition that was initially diagnosed in adulthood.

Case Description: We present a unique case of a 37-year-old woman who was referred for a second opinion before undergoing parathyroidectomy for a positive nuclear scan with an elevated intact parathyroid hormone (iPTH). She had a history of hypocalcemia beginning in her 30s with no family history for the same. Physical exam revealed short stature but no brachydactyly or intellectual disability. Initial findings showed a corrected serum calcium level was 8.3, iPTH 214, vitamin D 44, phosphate 3.6, magnesium 2.1, bicarbonate 25, and creatinine 0.9 and was placed on calcium supplementation and calcitriol. The urinary Fractional excretion of calcium was elevated and her bone density scan was normal. She was treated with a thiazide diuretic and an increase in the calcitriol dose which led to a corrected serum calcium 9.1 and iPTH 93. She did not undergo parathyroidectomy and we can conclude she likely has pseudohypoparathyroidism 1a or 1c.

Discussion: To our knowledge, this is one of the first reported cases of PHP diagnosed with normal serum phosphorus levels. The current literature review does not examine patients that have PHP despite having normal serum phosphorus levels. The goal of this case report was to increase awareness and education that PHP can be diagnosed later in life due to its varying phenotypic penetrance. Future studies can examine a larger cohort of patients that present with similar symptoms to determine the genetic cause. Above all, it is essential to provide knowledge to patients as well as physicians alike.

SA-PO311

Pseudo-Hyperphosphatemia: A Diagnostic Conundrum

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Introduction: Hyperphosphatemia is commonly seen in patient with chronic kidney disease however there are rare clinical situations where it can be seen in patients with normal renal function when interpretation of serum phosphate levels can be challenging due to potential analytical limitations. We present a case report demonstrating the diagnostic challenge of pseudo hyperphosphatemia to highlight the importance of high suspicion of spuriously elevated phosphate level.

Case Description: This is a 54-year-old female with history of multiple myeloma and diagnosed 1 year ago presented with fever and confusionI. In the ER and she was noted to have severe anemia and thrombocytopenia. In addition she was noted to have phosphorus level of 19.2 mg/dL with plasma creatinine was 0.55 mg/dL. Despite aggressive hydration and diuresis repeated measurement of phosphate levels showed persistent elevation and highest phosphate level being 25.7 mg/dL. After excluding common causes of hyperphosphatemia and noted resistance to treatment a diagnosis for spuriously pseudo hyperphosphatemia was made. This was attributed to analytic interference of elevated paraprotein level.

Discussion: True Hyperphosphatemia with normal renal function is a rarely reported condition. Clinicians should have a high suspicion for pseudo hyperphosphatemia/ spurious hyperphopahtemia due to analytical limitations to avoid expensive diagnostic work up, treatment and prologned hospital stay.

SA-PO312

The Dangers of Vitamin D Powder Supplements, Found Over-the-Counter, Causing Vitamin D Toxicity

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Introduction: Vitamin D toxicity is a rare but serious condition, potentially leading to death if not treated in a timely manner. This case highlights risks of misusing powder vitamin D supplements marketed directly to consumers.

Case Description: A 54-year-old female with no medical history presented with 4 days of headache, fatigue, nausea, vomiting, polydipsia, polyuria and constipation. She took no medications but had self-started vitamin D powder taking “a tablespoon daily in coffee for health and strong bones.” She learned vitamin D could decrease risk of COVID-19 infection as alternative to vaccination. Further investigation revealed this over-the-counter vitamin D powder was sold in 8 ounce bags with a 50 mg serving size equal to 5000 international units (IU) of Vitamin D3. Each bag contained 4,520 servings equaling 21,250,000 IU. “One tablespoon” of powder every morning equated to 1,328,125 IU, exceeding maximum recommended dose. Admission labs showed high Cr 1.76 mg/dL, calcium 14.4 mg/dL and ionized calcium 6.9 mg/dL but normal phosphorus 3.2 mg/dL, albumin 4.6 g/dL, PTH 26.3 pg/mL and TSH 1.21 uIU/mL. Renal US and CT imaging were unremarkable. EKG noted Osborn waves in leads II, III, aVF, V5, and V6, and QTc 412. 25-hydroxy vitamin D level was high at 650 ng/mL, 24-hour urine calcium was high at 410 mg/24 hr, 1,25-dihydroxy vitamin D was high at >600pg/mL. PTHrP, SPEP and UPEP with immunofixation were negative. Vitamin D toxicity was diagnosed with counseling for powder vitamin D supplement cessation. With IV hydration, calcitonin and bowel regimen, symptoms and calcium levels improved and patient was discharged with follow up.

Discussion: Vitamin D toxicity reported in literature recommends discontinuation of exogenous vitamin D. Previous case studies suggest glucocorticoids or bisphosphonates but clear guidelines for therapy are not identified. The most common cause of toxicity is excess exogenous intake greater than 10,000 IU/day causing 25-hydroxy vitamin D concentration >150ng/mL [1]. During COVID-19 pandemic, there was emphasis on supplements including vitamin D thought to protect against respiratory viral infections [5]. Our case elucidates risks of misusing over-the-counter supplements in a generation of changing trends in nutrition. Further studies should be performed to find treatments given risks of unintentional overdose.

SA-PO313

I Am in a Crystal Bind! A Case that Gave Us Ulcers

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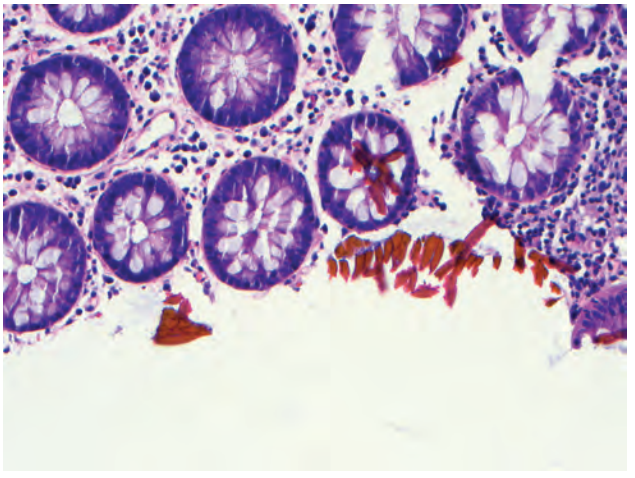
Introduction: In patients with ESKD, hyperphosphatemia has been shown to increase mortality. Common complications include vascular and heart calcification, as well as hyperparathyroidism. Managing hyperphosphatemia includes dietary modifications as well as phosphate binders. Sevelamer, a non-calcium phosphate binder, is commonly prescribed and usually well tolerated. Side effects of sevelamer are generally nonspecific and limited to nausea and gastrointestinal discomfort.

Case Description: A 37-year-old man with ESKD on intermittent hemodialysis, hypertension, congestive heart failure, and recent mitral and aortic valve repair presented with hematochezia and fatigue. His hemoglobin level was 5.9mg/dl upon admission. He was transfused and underwent an urgent colonoscopy, which revealed ulcerative mucosal injuries in the colon. Biopsy showed mucosal ulcers with sevelamer crystals. The patient was taken off sevelamer, stabilized, and switched to sucroferric/lanthanum for hyperphosphatemia and is stable at follow-up.

Discussion: Hyperphosphatemia is a common complication of end-stage kidney disease (ESKD) due to decreased renal elimination and continued intestinal absorption of dietary phosphate. Sevelamer, a non-calcium phosphate binder, is commonly used to control hyperphosphatemia. We present a case of a patient with ESKD on sevelamer, with lower gastrointestinal bleeding and endoscopic finding of colonic mucosal injuries with sevelamer crystals. Though reported in gastrology literature, nephrology reports show a paucity of discussion around this increasingly common adverse effect and the need for vigilance in ESKD.



Colon biopsy shows ulcerative mucosal injuries with typical reddish-brown crystals with a characteristic "fish-scale" pattern, described for sevelamer crystals.

SA-PO314

Three Patients with Recurrent Nephrolithiasis and Heterozygous ABCC6 Mutations

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Introduction: Pseudoxanthoma elasticum (PXE) is an autosomal recessive disease caused by mutations in the *ABCC6* gene, which encodes an ATP efflux transporter. Loss-of-function results in low extracellular PPi levels, which results in progressive ectopic deposition of CaP leading to skin papules, ocular lesions, and arterial calcification. The association between PXE and nephrolithiasis (stones) is known, though this has not been implicated in those who are heterozygous. We present three cases of recurrent stones without overt risk factors (Fig. 1), but with heterozygosity in *ABCC6*.

Case Description: Patient 1 45 yo F with recurrent CaP stones and nephrocalcinosis. Family history significant for mother with recurrent stones. Genetic testing showed *ABCC6* heterozygous variant of uncertain significance (VUS): c.1685T>C (p.Met562Thr). Skin biopsy and retinal exam did not reveal calcification. **Patient 2** 35 yo M with recurrent CaOx stones (20+) and numerous 2nd & 3rd degree relatives with stones. Genetic testing showed *ABCC6* heterozygous VUS: c.933C>A (p.Phe311Leu). **Patient 3** 24 yo F with recurrent CaOx/CaP stones and HTN. She had yearly stones since age 2 but an unknown family history. Genetic testing showed heterozygous for likely pathogenic variant in *ABCC6*: c3413G>A (P.Arg1138Gln) and heterozygous VUS for *PHEX* and *SLC34A3*, both associated with stones, without either phenotype.

Discussion: We hypothesize that heterozygous *ABCC6* mutations are underrecognized in recurrent stone disease, without extrarenal manifestations of PXE. Threshold for genetic testing of patients with recurrent stones without clear causes should be lowered given increasing testing availability. In vitro functional assays are underway to analyze the VUS mutations.

Vitals and Labs	Patient 1	Patient 2	Patient 3
Weights (lbs)	106-122	133-143	131-136
Blood pressures (mmHg)	97-139 65-91	134-151 85-104	112-141 74-93
Serum HCO_3 (mmol/L)	21.6-26.4	26.3-29.3	22-26.9
Serum calcium (mg/dL)	8.5-9.8	8.9-9.7	9.2-9.8
Serum phosphorus (mg/dL)	3.0-3.3	2.6-3.2	3.3-4.0
iPTH (pg/mL)	28-33	53	14
25-OH Vit D (ng/mL)	28-32	30.0	48.7, 79.2
1,25-OH Vit D (pg/mL)	**73.8-116.0**	57.9	**70.9, 99.6**
Serum Cr (mg/dL)	0.6-0.7	1.1-1.2	0.7-0.8
Urine pH	5.0-8.0	6.0-8.5	6.0-7.0

24hr urine collection	Patient 1	Patient 2	Patient 3
Total Volume (mL)	2,400	1,670	2,330
pH (-log[H^+])	6.70	6.7	6.5
Cr (mg)	1067	1344	851
Ca (mg)	**228**	89	68.2
P (mg)	295	559	320
UA (mg)	310	643	364
Na (mEq)	79	66	92
K (mEq)	30	54	51
Cl (mEq)	67	66	94
NH_4 (mEq)	17	29	15
Ox (mg)	19	16	9
Citrate (mg)	**295**	**336**	**449**
Osm (mOsm/kg)	177	-	195
SO_4 (mEq)	17	27	14
Mg (mg)	82	-	33

Metabolic workup for three patients including vitals, serum and 24 hour urine data

SA-PO315

A Case of Fibroblast Growth Factor 23-Induced Hypophosphatemia in Waldenström Macroglobulinemia

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Introduction: Fanconi syndrome and fibroblast growth factor 23 (FGF23)-induced hypophosphatemia are the main causes of hypophosphatemia due to renal phosphorus excretion in cancer patients. FGF23 induced hypophosphatemia is often associated with benign mesenchymal tumors of the mixed connective tissue type. As far as we know, this is the first case of FGF23 induced hypophosphatemia associated with Waldenström macroglobulinemia (WM).

Case Description: The patient was diagnosed with WM at the age of 74 years due to a lumbar compression fracture. Because he had severe neuropathy, he received rituximab as symptomatic WM. After treatment, clinical symptoms disappeared, and serum IgM decreased from 5800 mg/dl to 1800 mg/dl. Four years later, his serum IgM increased (3000 mg/dL) and serum phosphorus decreased (1.5–2.0 mg/dL). Six months later, he was referred to our nephrology department due to hypophosphatemia (serum phosphorus 0.8 mg/dL). He already received alphacalcidol 0.5 μg/day and alendronate 35 mg weekly. His serum IgM was 3263 mg/dL, serum creatinine was 0.98 mg/dl, corrected calcium was 9.6 mg/dl, parathyroid hormone was 39 pg/ml, 1.25-(OH)2 vitamin D was 11 pg/ml (normal range 20-60 pg/ml), and urine glucose was negative. The phosphate excretion rate was 44% and serum FGF23 was 91 pg/ml (normal range <30 pg/ml). The whole-body bone scintigraphy revealed bone destruction in the tenth thoracic vertebra. Contrast-enhanced CT showed multiple enlarged lymph nodes. He was diagnosed as FGF23-related hypophosphatemia due to WM. Sodium phosphate monobasic and tirabrutinib was initiated. Three months after treatment, serum IgM decreased to 423 mg/dl, and serum phosphate increased to 3.7 mg/dl.

Discussion: From the previous report, there are only three types of hematological malignancy that cause FGF23-related hypophosphatemia: diffuse large B-cell lymphoma, natural killer T-cell lymphoma and acute leukemia. We should also consider WM induce FGF23-related hypophosphatemia.

SA-PO316

Calciphylaxis in a Patient with Polymyositis and Absence of Renal Disease

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Introduction: Calciphylaxis is a rare and life-threatening disease in which calcium accumulates in small arteries and can cause tissue necrosis, thrombosis, and painful, non-healing skin ulcers. It is most often seen in patients with advanced choric kidney disease (CKD) but may occur when risk factors such as autoimmune or inflammatory conditions are present. We describe a case of calciphylaxis in a patient with polymyositis and acute kidney injury (AKI) without CKD.

Case Description: A 61-year-old man with polymyositis presented to the hospital with worsening dyspnea, and painful, lower leg wounds. He first noticed the leg wounds following a muscle biopsy for his polymyositis about 6 months prior to presentation; he reported the wounds increased in size since the biopsy. Medical history was significant for polymyositis on prolonged prednisone course, bronchiolitis obliterans organizing pneumonia, atrial fibrillation, hypertension, diabetes, and systolic heart failure. Physical exam revealed sinus tachycardia, coarse breath sounds with bilateral crackles. On his left leg, there were two tender-to-touch ulcers (~2x2 cm, clean-based, with dry yellow fibrinous exudate and surrounding hyperpigmentation). Laboratory data revealed a white blood cell count of 19.6 (81% neutrophils), blood urea nitrogen 52 mg/dl, creatinine 1.8 mg/dl (baseline 1 mg/dl), calcium 10 mg/dl, phosphorus 3.6 mg/dl, and lactic acid 4.1 mmol/L. He was admitted for further work-up of sepsis and AKI. Dermatology was consulted and took a biopsy of the wound which showed calcinosis with thrombotic vessels and fat necrosis consistent with calciphylaxis. Over the course of his hospitalization, the patient improved with antibiotics and fluids, and his AKI resolved. Blood cultures remained negative throughout his hospital stay, and antibiotics were adjusted accordingly by discharge. He was given clinic follow-ups with dermatology and rheumatology.

Discussion: To our knowledge, this is the first case of calciphylaxis reported in a patient with polymyositis and no underlying CKD. Clear treatment guidelines

for calciphylaxis are lacking and many physicians are not familiar with nonuremic presentations of calciphylaxis. We present this case to further advance awareness and knowledge of calciphylaxis occurring in the absence of advanced CKD.

SA-PO317

Bone Disease Related to Severe Vitamin D Deficiency in an Adult

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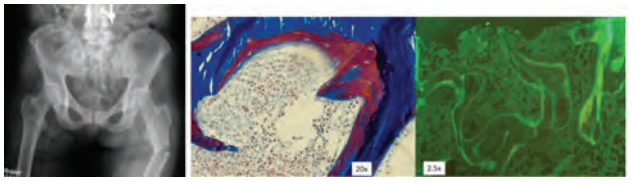
Introduction: Severe vitamin D deficiency (VDD) as a cause of bone disease is seen very rarely. While VDD can cause osteomalacia, associated secondary hyperparathyroidism (HPT) can also produce significant histopathological changes in the bone.

Case Description: A 60-year-old post-menopausal Caucasian woman, was admitted with a left subtrochanteric femur fracture in 2021, following a ground-level fall and underwent ORIF. She has had prior vertebral fractures, stage 3A CKD, and 30 pack year smoking history. Laboratory data revealed vitamin D (VD) <6.5 ng/ml, iPTH 492 pg/ml, calcium 7.9 mg/dl, ALP 602 U/l and BSAP >120 ug/l. Albumin, phosphorus, creatinine, and eGFR were 4.2 g/l, 2.9 mg/dl, 1.0 mg/dl, and 50ml/min, respectively. Imaging indicated diffuse sclerosis of the spine. Whole-body bone scintigraphy showed diffuse increased uptake throughout the skeleton in a "super scan" pattern. Forearm bone density showed a T-score of -2.6. Undecalcified bone biopsy of the iliac crest with double tetracycline labeling revealed a mixed pattern with high turnover, low mineralization and increased bone volume with areas of woven bone, with diffuse single labels on fluorescent microscopy (image). Malabsorption workup was inconclusive. Aggressive vitamin D replacement over a year, resulted in progressive normalization of VD, iPTH and BSAP levels, and improvement in radiological sclerosis.

Discussion: This patient presented with severe VDD in the setting of multiple fractures, with severe secondary HPT, bony sclerosis and renal osteodystrophy. The severity of HPT was out of proportion to her CKD and caused by VDD. Aggressive treatment with vitamin D resulted in marked reversal of bone abnormalities. With a fourth of the US population estimated to have VDD (<20ng/mL), it is important to consider VDD as a treatable secondary cause of and contributor to bone disease and fracture.



(Left) Femur fracture with varus angulation, increased sclerosis of the spine. (Center) Undecalcified bone biopsy (Masson-Goldner trichrome, 20x) showing mixed osteodystrophy with unmineralized osteoid, osteoblasts and multinucleate osteoclasts. (Right) Fluorescent microscopy (2.5x) showing isolated single labels with diffuse tetracycline deposition.

SA-PO318

The Pursuit of the Perfect Body: Need for Myocardial Revascularization and Dialysis After Polymethylmethacrylate Injection

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Introduction: Polymethylmethacrylate (PMMA) is a synthetic polymer, initially used to correct HIV-associated lipodystrophy. However, gluteal augmentation for aesthetic purposes are procedures that are increasingly performed all over the world, mainly in Latin America. PMMA can promote foreign body granulomas around its microspheres, leading to increased calcitriol synthesis and, consequently, hypercalcemia.

Case Description: A 58-year-old female patient with a history of arterial hypertension, type-2 diabetes mellitus and sleeve gastrectomy performed a gluteal bioplasty with PMMA 2 years ago. Thirty days after the procedure, the patient had type A anginal pain, acute myocardial infarction with ST-segment elevation and the need for myocardial revascularization. Upon admission, there was evidence of increased serum creatinine, associated with parathyroid-independent hypercalcemia and hyperphosphatemia. In the following 4 months, the patient progressed to end-stage chronic kidney disease and required renal replacement therapy. Renal biopsy showed 60% of tubular atrophy and interstitial fibrosis, with intratubular calcific casts. Positron emission tomography showed irregular densifications in the gluteal muscular plane (fig 1). Despite the previously described findings, no specific treatment was prescribed, as the proper diagnosis of hypercalcemia etiology was not done.

Discussion: PMMA injection promotes granulomatous reaction, with overexpression of 1α-hydroxylase. This leads to extrarenal production of calcitriol by macrophages, and subsequent hypercalcemia, associated with vascular calcification and nephrocalcinosis. This environment favors the onset of acute kidney injury and the progression of vascular damage. If not identified and treated quickly, it may predispose to ischemic events and progression to chronic kidney disease. As some patients have an unfavorable evolution even after treatment, the use of PMMA in large quantities should be prohibited.

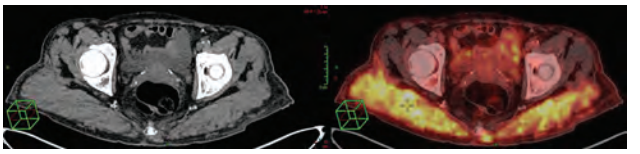

Fig 1

SA-PO319

When Woman Turns to Stone: Extraosseous Calcification in a Dialysis Patient

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Introduction: Extraosseous calcification (EC) involves vascular and soft tissue calcification, calciphylaxis and is a serious complication of chronic kidney disease (CKD), associated with mortality. EC is an active process arising from the complex interrelationship between electrolyte levels, cell differentiation, and dysregulation of many biochemical pathways. We report the case of a patient with diffuse EC.

Case Description: A female, aged 43, CKD of unknown etiology, on hemodialysis for four years. One year ago, the patient felt pain in the lower limbs, muscle weakness and hard edema in the legs. Seven months ago, she stopped walking, with disabling muscle weakness. On examination, edema in the lower limbs, palpable diffusely hardened nodules, and increased volume and pain in the right clavicle. No calciphylaxis. Admission exams (March 2023): intact parathyroid hormone (iPTH pg/dL) 4296, total alkaline phosphatase 706 U/L, calcium (mg/dL) 13, and phosphorus (mg/dL) 5.4. She was on paricalcitol 15 μg/wk and sevelamer 7.2 g/day. She has never tolerated cinacalcet. Previous exams confirmed a 2-year progressive increase in iPTH from 658 to 4296, monthly calcium average of 14 and phosphorus of 5.9. Paricalcitol was withdrawn. Radiology: extensive calcifications in the subcutaneous tissue of the legs and thighs, bilateral fracture of the femoral neck, brown tumor in the right clavicle, calcifications in the abdominal aorta and iliac arteries and calcifications in the mitral and aortic valves. Ophthalmology: calcifications in lower conjunctiva. Bone densitometry T score: lumbar spine -5.2 and femoral neck -4.2. Scintigraphy: capture in inferior parathyroids. The patient is awaiting parathyroidectomy.

Discussion: This is an unusual case of severe EC in a young, non-diabetic patient on dialysis for a short time. We confirmed the role of bone turnover disorders in the pathogenesis of EC, where the rapid progression of secondary hyperparathyroidism was a determinant of the patient's clinical manifestations. We emphasize the interrelation of bone and vessel, demonstrated by the severe loss of bone mass and the intensity of the EC. Nephrologists must understand the consequences of the mineral and bone disorder of CKD, so that interventions are early, in order to avoid very serious cases such as the one reported herein.

SA-PO320

The Developing Kidney Actively Negotiates Geometric Packing Conflicts to Avoid Defects

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Background: Ureteric bud (UB) tubules branch at the kidney's surface, where their tips specify sites of nephron induction through interactions with the surrounding cap mesenchyme. The extent of UB branching determines nephron endowment at birth (up to ~1 million in humans) and low nephron count poses a risk of hypertension and adult disease. Here, we examine physical and geometric factors involved in UB tip packing into a limited organ surface area and how UB morphology changes across developmental stages to accommodate branching.

Methods: We use confocal immunofluorescence of embryonic day (E)14-18 mouse kidneys and tissues to investigate the organization of UB and cap mesenchyme. Live kidney explants were treated with dispase to disrupt adhesion between the UB and mesenchyme and tubule retraction was measured by confocal microscopy. We used a computational model to predict branching tubule structures and defects that occur as a function of packing density, repulsion between tips, and node depth. Models were compared to our acquired data and previously published imaging studies of genetic mouse models.

Results: Surface packing density of UB tips increases between E14-18, accompanied by morphological changes in the size and shape of cap mesenchyme clusters and intervening stromal tissue boundaries. Branching tip morphologies change across this interval as well, with branch points progressively moving into deeper tissue layers. Physics-based computational modeling predicts these anatomical changes using geometric parameters. Consistent with model predictions, experimental measurements of tubule retraction following dispase treatment show that actomyosin-based forces are necessary for progressive restructuring of tubules. Our model also predicts conditions where 'packing defects' form, including colliding, or overlapping tubules ('short circuits') or tips being forced into deeper tissue layers ('buried tips'). We successfully reproduce the buried tips defect in microdissected kidney tissues and investigate published literature examples of mouse mutations that exhibit packing defects.

Conclusions: Our work indicates that the UB must actively restructure during development to avoid organizational defects. We suggest new classification criteria for branching morphogenesis-related congenital defects.

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SA-PO321

Probing Mechanical Regulation of Kidney Morphogenesis Through a Novel 3D Explant Culture Technique

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Background: Achieving proper tissue organization during kidney development plays a vital role in its subsequent functions. For example, congenital anomalies of the kidney and urinary tract can manifest as underdeveloped or disorganized tissue compartments that cause dysfunction or disease. While underlying genetic and molecular factors have been studied, there is little understanding of their interplay with tissue-level cell composition, geometry, and mechanics that together set the final organ structure. Here we address the limited capability to observe developing kidney tissues in a 3D context and seek to uncover the physical principles that set kidney architecture during embryonic development.

Methods: We incorporated a hydrogel droplet into a silicone ring device to encapsulate mouse embryonic day 13 (E13) kidneys for subsequent 3D culture. We tested different organotypic hydrogels (Matrigel, Collagen I) as embedding materials, and characterized their mechanical properties using microindentation. E13 kidneys grown in 3D gels and at in traditional air-liquid interface cultures were imaged every hour and fixed after 4 days.

Results: Our data showed that kidney morphogenesis proceeded in ECM-derived gel droplets, not just in air-liquid interface cultures. Both methods yielded similar numbers of ureteric bud branches and nephrons, as confirmed by immunofluorescence. Notably, our live branch tracking analysis revealed dynamic growth and rearrangement of ureteric tubules in unflattened kidneys for the first time. The mechanical properties of the embedding gel also impacted overall explant morphology. Low concentration Collagen I (0.3-1mg/ml, E<2kPa) best mimicked in vivo development. Matrigel (E<1kPa) failed to maintain the 3D integrity of the explant, resulting in partially flattened tissue. High concentration Collagen I (3mg/ml, E=4.2kPa) impeded development and lead to enlarged ureters in some samples, resembling certain congenital defects.

Conclusions: We present a 3D culture technique that not only supports ex vivo morphogenesis but also enables live imaging of mouse embryonic kidneys. Our data suggest organ ex vivo development is influenced by its mechanical environment. This work aims to transform long-term explant culture techniques and clarify the role of the mechanical environment in kidney development.

SA-PO322

Intracellular Acetyl-CoA Levels Are Pivotal for Nephron Progenitor Cell Fate Decisions

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Background: Low nephron endowment at birth correlates with the development of hypertension in later life. Nephron endowment at birth is governed by a delicate balance between nephron progenitor cells (NPC) self-renewal and differentiation. Previous studies showed that inhibition of glycolysis pushes NPC to differentiation and causes progenitor pool depletion.

Methods: Organ culture experiments: E12.5 embryonic kidneys cultured for 24h-48h in the presence of a vehicle or several pharmacological agents: the glycolysis inhibitor drug, YN1; the mitochondrial pyruvate carrier 1 blocker, UK5099; sodium acetate or canonical Wnt signaling activator (CHIR99021). Immunofluorescence was performed to characterize the observed phenotypes. Bulk. RNA seq. and Proteomics: NPCs were extracted by MACS (passage 0), cultured for 24h with the vehicle, CHIR, and YN1, and then processed for proteomics and bulk RNA sequencing. Data Analysis. Differential gene expression, pathway analysis, and GO enrichment analysis were performed in R.

Results: Here, we showed a direct relationship between glucose metabolism and NPC fate decisions. First, E12.5 embryonic kidneys cultured in the presence of YN1 showed reduced extracellular acidification rate (ECAR), and increased differentiation rate. Second, E12.5 embryonic kidneys stimulated with UK5099 showed an increased ECAR, reduced ATP production from oxidative phosphorylation, augmented NPC pool, and reduced differentiation. We compared the proteome and transcriptome of E13.5 NPC stimulated with either a CHIR or YN1 to dissect the molecular mechanism underlying these phenomena. Decreased cholesterol biosynthesis emerged as a top pathway targeted by both drugs. Inhibition of cholesterol synthesis stimulated NPC differentiation at the cost of cap mesenchyme depletion, which, in turn, phenocopied YN1 treatment. Acetyl-CoA links cholesterol production and glucose metabolism. Sodium-acetate is an alternative source of acetyl-CoA. Sodium-acetate supplementation increased cytosolic acetyl-CoA levels and cap mesenchyme size, without hindering NPC differentiation. Co-treatment with exogenous sodium-acetate abrogated the adverse effects of glycolysis inhibition.

Conclusions: This study identifies acetyl-CoA as a key metabolite for kidney development and sodium-acetate as a potential exogenous substrate to promote kidney growth and development

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SA-PO323

Real-Time ATP Imaging Reveals the Metabolic State During Kidney Development

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Background: Maternal malnutrition is associated with a reduced nephron number and an increased risk of hypertension and chronic kidney disease in later life. However, very little is known about what determines the nephron number, and about the metabolic state during nephrogenesis.

Methods: We focused on the cytosolic adenosine 5-triphosphate (ATP) level and its changes to examine an energy metabolism in embryonic kidneys. To explore the spatiotemporal dynamics of the cytosolic ATP level, we used transgenic mice expressing the cytosolic ATP-FRET biosensor, called GO-ATeam2 mice. We performed visualization and analysis of cytosolic ATP level in real-time *ex-vivo* imaging during branching nephrogenesis and examined the dependence of ATP production on glycolysis and oxidative phosphorylation during nephrogenesis.

Results: We succeeded in visualizing the cytosolic ATP level at a single cell level and investigated the spatiotemporal dynamics of the cytosolic ATP level in both ureteric bud (UB) and cap mesenchyme (CM) cells. The UB forms the collecting ducts through repeated bifurcation of the ureteric tree, while the CM differentiates into nephron epithelial cells. The reciprocal interaction between UB and CM cells is crucial for proper kidney development. During branching nephrogenesis, ATP levels of UB tip cells were significantly lower than those of UB stalk and CM cells. Glycolytic inhibition in the early phase of metanephric kidney (embryonic day E12.5) severely reduced the ATP level in both cells in a dose dependent manner, but ATP reduction was faster and more prominent in UB cells rather than in CM cells. In addition, the expression of specific markers for UB and CM cells were significantly reduced and electron microscopy images showed a loosening of cell-cell adhesion and irregular cell alignment in CM cells after glycolytic inhibition. Furthermore, glycolytic inhibition resulted in suppressed UB branching and reduced number of both branch segments and UB tips. On the other hand, these effects were not observed by an oxidative phosphorylation inhibitor.

Conclusions: The mice allowed us to perform real-time *ex-vivo* ATP imaging of embryonic kidneys. We found that UB branching was heavily dependent on glycolysis and that UB cells in the early branching phase were sensitive to glycolytic inhibition.

SA-PO324

Highly Parallel Production of Designer Kidney Organoids by Mosaic Patterning of Progenitors

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Background: Kidney organoids derived from human induced pluripotent stem cells (iPSCs) are a promising approach for congenital and adult disease modeling, regenerative medicine, and gaining fundamental understanding of organogenesis. However, organoids are limited in their production scale, reproducibility, and physiologic function and structure, posing a considerable barrier to their application. Thus, an important open question is the extent to which engineering control over culture conditions can guide organoids toward specific outcomes in composition and organization. Here, we study this by precisely controlling iPSC-derived kidney progenitor cell numbers and ratios in microwell-format organoid cultures.

Methods: We began by adapting transient 2D cell patterning technology to a microwell format suited for transition to long-term 3D organoid culture. We first applied our validated culture system to study the effect of initial nephron progenitor (NP) number on organoid morphogenesis. Since reciprocal interactions between NPs and ureteric bud (UB) tip cells influence nephron endowment during kidney organogenesis, a major predictor of kidney disease, we next examined how modulating ratios of these cells affects organoid morphogenesis.

Results: In our NP-only organoids, we discovered that throughout culture, organoid sizes directly depend on the number of initial NPs. Moreover, larger nephron organoids display a shift in final composition, with a significant increase in proximal tubule proportion from 40% to 61% from 2D cell pattern size diameters 200 to 500 μm. Preliminarily, we have found that regardless of cell ratio, transition of 2D mosaic cell patterns of NPs and UB tip cells to 3D suspension culture facilitates cell sorting and discrete compartment formation early in organoid development, which resembles physiologic organization. Furthermore, UB tip cells and NPs synergistically upregulate stromal cell populations.

Conclusions: Here, we contribute an integrated cell patterning and long-term culture platform that decouples organoid size from well geometry, enables 3D suspension culture, and maintains discrete organoid cultures. Our approach makes significant advances in organoid homogeneity relevant to drug screens and modeling of development and diseases as well as improved control over tissue interface formation crucial to engineered morphogenesis efforts.

Funding: NIDDK Support, Other NIH Support - NIH NIGMS MIRA R35GM133380 to Alex Hughes, Other U.S. Government Support

SA-PO325

Generation of Human Kidney Organoids with Three-Dimensional Vascular-Like Systems

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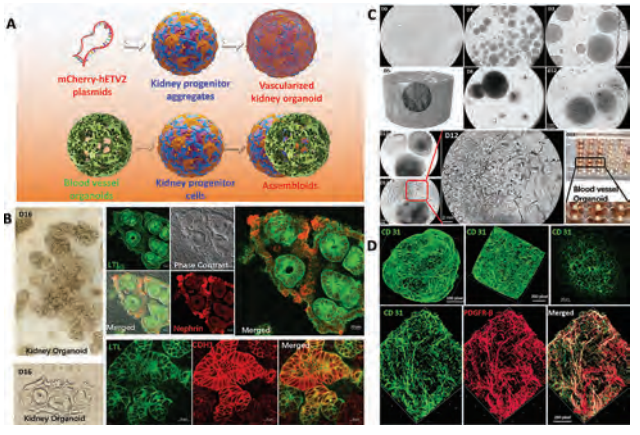
Background: Kidney organoids are hampered by their inability to imitate mature organ architecture since they are lack of vasculature, which creates essential niches. Here, we demonstrate two novel paradigms for generating three-dimensional vascularized kidney organoids.

Methods: Method 1. We differentiated the HiPSCs into kidney organoids and blood vessel organoids respectively. Then we co-cultured the 3D blood vessel networks with kidney progenitor aggregates to form the assembloids. Method 2. We induced the HiPSCs into the kidney progenitor aggregates. Then we transfected with mCherry-hETV2 plasmids into kidney progenitor cells. 7 days later, the organoid got matured.

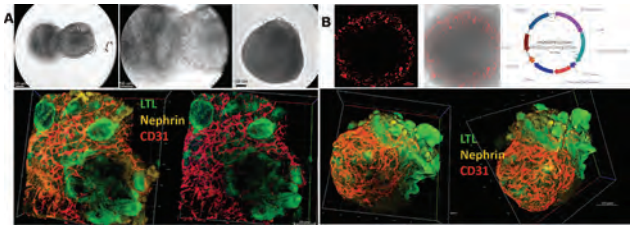
Results: Generation of assembloids from blood vessel networks and kidney progenitor aggregates To study organ-to-organ communication circuits within different organoids, we co-cultured the blood vessel organoid and kidney organoid. At later stage, the blood vessel networks penetrated the entire kidney organoid and assembled into multiple lineage organoids, enabling us to study the characteristic of the micro-physiological system within different organoids. **hETV2 promotes the vascularization of kidney organoids** We transfected with mCherry-hETV2 plasmids into the kidney progenitor aggregates. The hETV2 overexpressing kidney organoid positioned podocytes (NPHS1+) and tubular parts (LTL+) packed with numerous endothelial networks (CD31+).

Conclusions: 1) Blood vessel organoids penetrated the kidney progenitor aggregates, and formed entiely blood vessel networks within kidney organoids. 2) hETV2 transcription factor elicited the process of vascularization for kidney organoid.

Funding: Government Support - Non-U.S.



A. Schematic diagram, B. Kidney organoid, C. Blood vessel organoid, D. CD31 and PDGFR-β



A. Assembloid, B. hETV2 expressing organoid

SA-PO326

Deletion of Crkl Splice Isoforms in the Mouse Kidney Disrupts Intercompartmental Signaling Required for Progenitor Renewal and Branched Morphogenesis

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Background: We previously showed that haploinsufficiency and point mutations in *CRKL* drive kidney and urinary tract malformations in the DiGeorge, or 22q11.2, Syndrome (DGS) and in sporadic CAKUT, respectively. Here, we examined the developmental requirement of the two *Crkl* splice variants (T1 & T2) when conditionally and differentially deleted in the metanephric mesenchyme (MM).

Methods: We characterized phenotypic abnormalities in developing kidneys from mice with conditional deletion of both T1 and T2 ("No Crkl"), or only the T1 isoform ("T2 only"), specifically within the MM. Bulk and scRNAseq data were acquired and analyzed from embryonic kidneys isolated from 13.5 and 15.5dpc wild-type and mutant mice. IHC and ISH analyses were used to validate and identify key signaling pathways.

Results: At P0, both "No *Crkl*," and "T2 only" kidney phenotypes were characterized by severe hypoplasia and near-absence of nephrogenic progenitors (NP). Morphometric analysis of the renal collecting system at 13.5 and 15.5dpc shows a hyperbranched phenotype in "No *Crkl*" mutants, while expression of only T2 led to a hypobranched phenotype. Using our single-cell data to "deconvolve" bulk RNAseq data, we found an overrepresentation of early proximal tubule (ePT) markers in "No *Crkl*" mice, and an underrepresentation in "T2-only" mice, suggesting a cell type-based contribution to the divergent branching phenotypes. Both groups of mutants also showed an underrepresentation of NP markers, where scRNAseq and ISH analyses confirmed decreased expression of *Fgf8* and *Fgf9* in NPs and renal vesicle. Lastly, in-depth time-based analyses of bulk RNAseq datasets revealed 3 differentially regulated gene sets that may explain the divergent branching phenotype between the two mutants.

Conclusions: Genetic manipulation of *Crkl* confirms a crucial role in kidney development, where disrupted *Fgf8* expression suggests a cellular mechanism underlying renal hypodysplasia. Furthermore, disruption of splice isoform balance reveals a dichotomous pattern in early branching, suggesting a differential role for each isoform in regulating STOP and GO signaling associated with growth and branching morphogenesis.

Funding: NIDDK Support

SA-PO327

HNF4A Re-Expression Restores a Proximal Tubular Phenotype in Cultured Primary Cells

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Background: The tubular part of the nephron is composed of distinct segments. The transcription factor hepatocyte nuclear factor 4α (*HNF4A*) is a master regulator for the phenotype of the proximal tubules, controlling features such as brush border formation and transport. Culture of primary proximal tubular cells is an essential model system for kidney research, but during culture, the cells display a less differentiated phenotype with expression of markers associated with kidney injury. The aim of this study was to evaluate if HNF4A transduction of cultured primary proximal tubular cells could revert the cells to a more mature phenotype.

Methods: Primary proximal tubular cells obtained from human cortical kidney tissue were cultured and harvested at consecutive passages. The change in protein expression at different passages was evaluated using immunohistochemistry. *HNF4A* adenoviral transduction was performed on primary proximal tubular cells, followed by RNA sequencing and bioinformatic analysis. The effects of *HNF4A* transduction were furthermore analyzed by qPCR, Western blot, and immuno electron microscopy.

Results: Culture of primary proximal tubular cells resulted in major HNF4A loss. In contrast, the mesenchymal and injury marker vimentin was induced. HNF4A was successfully reintroduced by adenoviral transduction and this caused upregulation of known target genes associated with brush border formation, transport, and metabolism. Gene set enrichment analysis revealed pathways linked to absorption, transport, and digestion as well as microvilli and brush border. Using immuno electron microscopy, morphological features of proximal tubular cells could be visualized in HNF4A-positive cells.

Conclusions: In summary, human primary proximal tubular cells rapidly lose HNF4A expression during culture, but by reintroduction of HNF4A using adenoviral transduction, the cells regain expression of genes essential for brush border formation and transport. This suggests that HNF4A expression may improve the reliability of *in vitro* models of proximal tubular cells.

Funding: Government Support - Non-U.S.

SA-PO328

High-Throughput Discovery of Novel Therapeutic Candidates for Human Podocytopathies

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Background: Chronic kidney disease (CKD) impacts 12% of the world population. Currently, the best treatment options for patients experiencing advanced stages of CKD include dialysis or kidney transplantation. Therefore, there is an urgent need for novel therapies that address the underlying causes of kidney dysfunction and disease progression. Damage to podocytes is associated with CKD. In addition to comorbidities and predisposition factors, CKD occurrence can be aggravated by the administration of prescription drugs. These compounds include the chemotherapy drug Adriamycin (ADR), which exhibits off-target nephrotoxic effects in podocytes.

Methods: By employing our established protocol for hiPSC-derived podocytes, we developed a high-throughput screening (HTS) strategy to help discover new protective biomolecules and potential therapeutic candidates for podocytes. We screened the hiPSC-podocytes with a library of bioactive molecules and ADR. To eliminate the compounds that did not protect against ADR injury, the threshold for positive hits was considered above ADR control viability. These compounds were selected as potential hits and were subject to low-throughput secondary validation metrics.

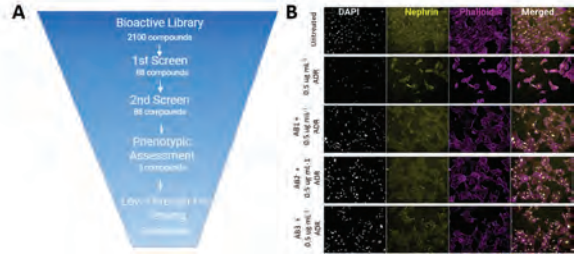
Results: The cells co-treated with the bioactive hits and ADR seemed to have been protected from ADR-induced injury by retaining healthy cell spread, and cytoskeletal

structures such as actin fibers. In subsequent 48hrs experiments, podocytes were pre-treated with the compounds in low-throughput environments, and podocyte cell viability and cytoskeleton arrangement were protected against ADR injury.

Conclusions: Our preliminary work led to the identification of three new compounds that protected human stem cell-derived podocytes from severe injury by ADR treatment *in vitro*. Ultimately, a podocyte-directed therapeutic could protect cells against known nephrotoxic drugs, potentially reducing the need for dialysis or kidney replacement in the future.

Funding: Other NIH Support - A.D.B. is a recipient of the NIH T32 Predoctoral Research Fellowship in the Center for Biomolecular and Tissue Engineering (CBTE) at Duke University (Grant No. 1 T32GM144291), Private Foundation Support

Figure 1



(A) Schematic of HTS and validations. (B) Fluorescent images of potential therapeutic hits compared to controls.

SA-PO329

T Cell-Mediated Immune Rejection of B2M Knockout Induced Pluripotent Stem Cell (iPSC)-Derived Kidney Organoids

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Background: "Stealth" induced pluripotent stem cell (iPSC)-derived kidney organoids represent an attractive strategy and could potentially be used in clinical transplantation. Genetic modification of the human leukocyte antigen (HLA) class I molecules in iPSCs prior to transplantation of their derived tissues could prevent immune rejection. Here we evaluated the effect of β2-microglobulin (B2M) knockout on T cell-mediated rejection of iPSC-derived kidney organoids.

Methods: Specific genetic modification achieved by CRISPR-Cas9 was used to knockout *B2M* gene expression and prevent HLA class I surface expression on iPSCs. Kidney organoid immunogenicity was determined in vitro by coculture with alloreactive T cells and in vivo following transplantation in humanized mice.

Results: We found that iPSC-derived $B2M^{-/-}$ kidney organoids were protected from T cell rejection *in vitro*. To evaluate *in vivo* protection, unmodified (control) and $B2M^{-/-}$ kidney organoids were transplanted in humanized mice that were engrafted with human peripheral blood mononuclear cells (PBMCs). Successful engraftment of the human PBMCs was validated and 4 weeks after PBMC injection we observed the infiltration of $CD4^+$ and $CD8^+$ T cells in the kidney organoids. There was no difference in the infiltration rate of $CD4^+$ and $CD8^+$ T cells, proliferation of T cells and T cell cytotoxicity between control and $B2M^{-/-}$ organoids. Control and $B2M^{-/-}$ organoids tissue integrity was similarly affected, showing tubulitis and loss of tubule integrity. Although the $B2M^{-/-}$ organoids were unable to express HLA class I on the cell surface, we found increased expression of HLA class II in control and $B2M^{-/-}$ organoids that were transplanted in mice with human PBMCs. HLA class II expression was expressed not only by endothelial, but also epithelial cells of the kidney organoid, posing an additional immunological barrier to the transplantation.

Conclusions: We conclude that knockout of the *B2M* gene alone is not enough to protect iPSC-derived kidney organoids from T cell mediated immune rejection and highlight the importance of HLA class II signalling in the graft rejection process.

SA-PO330

Therapeutic Potential of Induced Nephron Progenitor Cells and Their Extracellular Vesicles in Aristolochic Acid-Induced CKD: Insights from Organoid and Mouse Models

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Background: CKD affects 15% of US adults, with Aristolochic acid (AA) being a valuable model for CKD. We explored CKD therapies using induced nephron progenitor cells (iNPs) and their extracellular vesicles (iNP-EVs). iNPs are engineered HK-2 reprogrammed to a nephron progenitor phenotype using an inducible *piggyBac* transposon expressing *SNAI2, EYA1*, and *SIX1*. We compared the efficacy of iNP cells to iNP-EVs. EVs have similar benefits to injected stem cells while avoiding many associated pitfalls. This study investigated the potential therapeutic effects of iNPs and iNP-EVs on AA-induced renal injury in both iPSC-derived human kidney organoids and animal models.

Methods: Organoids were grown following established protocols and were treated with 10 μM AA for 48 hrs. AA was followed by 24 hrs of exposure to either iNPs or iNP-EVs. *In vivo* experiments were performed in NSG mice, an immunocompromised mouse strain, to avoid an immune response to iNPs. In brief, mice were injected with 2 mg/kg AA three times per week for two weeks; then, the injury was allowed to develop for an additional two weeks, then mice were treated with iNPs or iNP-EVs.

Results: iNP-treated organoids showed decreased Dickkopf-1 (DKK1) levels compared to EV-treated, untreated, and control organoids. Both iNPs and EVs treatment reduced macrophage colony-stimulating factor (M-CSF) compared to untreated organoids, with EV treatment showing a more pronounced effect. Immunofluorescent staining revealed increased alpha-smooth muscle actin (α-SMA) levels in AA-treated organoids, with lower expression in iNP and EV-treated organoids.

Conclusions: Analysis of tissue sections stained for α-SMA showed that the AA + iNP-EVs treated group had fewer myofibroblasts than the AA-only and AA + iNP-treated groups. All groups receiving AA had more α-SMA staining than the untreated control group. DKK1 is a Wnt signaling inhibitor, suggesting that iNPs may encourage proliferation through a non-exosomal mechanism. The M-CSF reduction suggests an iNP EV-dependent immunomodulatory effect. M-CSF is released from activated fibroblasts, so decreased M-CSF levels could indicate reduced numbers of myofibroblasts, supported by the improvement in α-SMA levels. In conclusion, iNPs and iNP-EVs may mitigate fibrosis in mouse and human models of AA-induced CKD.

Funding: Other NIH Support - NIH T32 ES007028, Veterans Affairs Support

SA-PO331

Kidney Organoid Transplantation Promotes Endothelial Cell Proliferation and Transition Toward a Human Fetal Arterial/Afferent Arteriolar-Like Phenotype

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Background: Kidney organoids (KORs) derived from induced pluripotent stem cells hold promise for regenerative medicine and kidney modeling. However, KORs lack proper vascularization, hindering maturation despite the emergence of endothelial cells (ECs). *In vivo* KOR transplantation prevents EC regression, enabling chimeric vascularization, blood perfusion, and nephron maturation. This study aimed to characterize the molecular effects of KOR transplantation on ECs.

Methods: Day7+12 KORs were transplanted into chicken embryos for 1 or 8 days, or further cultured *in vitro* for the same time period. FACS-sorted CD31+ KOR ECs underwent scRNA-seq (11,966 ECs). A human fetal kidney EC reference (8-17 weeks of gestation, >3,000 ECs) was created from publicly available scRNA-seq data. Immunostainings were performed to validate the findings.

Results: Both time and transplantation altered KOR EC transcriptomes, with the latter having a greater impact. KOR transplantation induced a metabolic transcriptome switch from oxidative phosphorylation to glycolysis, associated with hypoxia response geneset enrichment at day 1. At day 8, KOR transplantation prevented DNA damage response and decreased nuclear division, while upregulating antigen presentation, matrix deposition, angiogenesis, blood coagulation/circulation genesets, indicating response to blood perfusion. Consistent with angiogenesis, EC proliferation was increased in that condition (especially in M phase), as confirmed by Ki67 staining. ECs also underwent a major vein-to-arterial phenotypic transition, with a decreased pool of NR2F2+ ECs and the emergence of arterial ECs, and upregulated EC tissue-specific genes (especially kidney-related). Arterial ECs characterized by laminar shear stress response and Notch signaling, showed a similar transcriptome as human fetal kidney arterial/afferent arteriolar ECs. Transplantation-induced EC reprogramming involved *SOX7* transcription factor upregulation and regulon enrichment.

Conclusions: KOR transplantation led to the development of arterial ECs alike human fetal kidney artery/afferent arteriolar ECs, likely via SOX7 and blood flow exposure. These findings provide insights for the development of KOR vascularization strategies.

SA-PO332

Vessel-Promoting Factors npas4l/cloche and hand2 Act in Parallel to Inhibit Intermediate Mesoderm Specification

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Background: Proper organ formation depends on precise organ territories containing defined numbers of progenitor cells. Kidney progenitors reside in the intermediate mesoderm (IM), two bilateral stripes of cells in the posterior mesoderm. Previously we showed that the transcription factors Hand2 and Osr1 are essential for defining the dimensions of the IM by balancing the specification of IM and laterally adjacent vessel progenitors. Recently the transcription factor Npas4l/Cloche – well characterized as an early, essential regulator of vessel and blood progenitor formation – was shown to inhibit kidney development. Here we determine how kidney and IM specification is coordinated among *hand2*, *osr1*, and *npas4l*.

Methods: Taking advantage of the robust genetic, optical, and experimental benefits of the zebrafish model organism, we interrogate the IM at the single cell level. Here we employ a combination of loss and gain-of-function genetic analyses and whole mount RNA in situ and antibody staining.

Results: First, *hand2* and *osr1* regulate the development of *npas4l*-expressing lateral vessel progenitors (LVPs). Interestingly, like *hand2* loss-of-function, *npas4l* loss-of-function rescues *osr1* mutant kidney developmental defects. However, unlike in *hand2*; *osr1* double mutants in which LVP specification is restored, vessel progenitor formation is not rescued in *npas4l*; *osr1* mutants, suggesting that *hand2* and *npas4l* may implement different mechanisms to regulate kidney and vessel progenitor fates. Additionally, *npas4l* and *hand2* overexpression can inhibit kidney formation independent of one another's function suggesting the two factors can function in parallel to inhibit kidney specification. Importantly, like *hand2* mutants, *npas4l* mutants have expanded IM, but in *npas4l* mutants the increased IM is found outside *hand2*-expressing cells suggesting alternative sources of increased IM within the two mutants. Finally, consistent with parallel functions for *hand2* and *npas4l* in IM inhibition, *hand2*; *npas4l* double mutants have increased IM beyond that seen in either single mutant.

Conclusions: Together our findings reveal that proper kidney specification depends on parallel genetic pathways that inhibit IM specification while promoting vessel progenitor formation

Funding: NIDDK Support

SA-PO333

Profiling the Epigenetic Landscape of the African Spiny Mouse, A Mammalian Model of Kidney Regeneration

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Background: The African spiny mouse is the first mammal to demonstrate full restoration of kidney function without fibrosis after injury (Okamura et al., 2021) and provides an opportunity to elucidate mechanisms promoting kidney regeneration. The transcriptome of the spiny mouse and house mouse kidneys are the same, but its response to injury is remarkably different, indicating that epigenetic control of gene expression may be the key to its regenerative capabilities. We hypothesize that the African spiny mouse kidney is poised to respond differently before injury occurs through accessible chromatin for critical genes that are regulated by histone methylation.

Methods: Single nuclei ATAC-sequencing identified accessible regions of chromatin in normal African spiny mouse kidneys (n=3). Cleavage Under Targets and Release Under Nuclease (CUT&RUN) identified which regulatory elements were targeted by activating (H3K4me3) and repressive (H3K27me3) histone marks in spiny mouse kidney (n=2). Data was aligned to a spiny mouse reference genome we constructed with long-read DNA sequencing. For data analysis, we used Cellranger for ATAC-seq clustering, SEACR for CUT&RUN peak calling and HOMER for peak annotation and motif detection.

Results: Single nuclei ATAC-seq data mapped to the spiny mouse reference genome at >85%. Over 4,300 high quality peaks were generated from 27,000 cells, generating 10 distinct clusters. CUT&RUN sequencing data mapped to the reference genome at >95%. 2608 consensus H3K4me3 peaks and 1560 consensus H3K27me3 peaks were detected. Several key progenitor motifs marked by H3K4me3 were significantly enriched in the spiny mouse kidney ($p<0.01$) and had accessible chromatin based on ATAC-seq data, including *Nkx3.1*, *Osr1*, *Myb* and *Tead2*.

Conclusions: This work demonstrates that chromatin for nephrogenic progenitor genes in spiny mouse is accessible and poised for transcription through histone methylation. These experiments are being extended to injured kidneys of the spiny mouse to identify how gene regulation is controlled by histone marks in the setting of kidney regeneration. These results will have an important positive impact by providing targets and potential mechanisms for the redirection of kidney injury towards regeneration of functional tissue.

Funding: NIDDK Support, Private Foundation Support

SA-PO334

Inflammatory Cytokine Signaling in New Nephron Formation After AKI in Adult Zebrafish

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Background: Adult progenitor cells in the mesonephric zebrafish kidneys are required during neo-nephrogenesis replacing injured tubules by forming new nephrons. Single-cell RNA transcriptomes of adult kidney progenitor cells point to components of NF-kB and inflammatory cytokine receptors that may initiate stem cell-based nephrogenesis. Here, we present evidence that gentamicin induces inflammation-associated injury, which potentially stimulates stem cell-based nephrogenesis. The stimulatory effect on the progenitor cells to form new nephrons may be recapitulated by LPS injection without prior injury.

Methods: Adult zebrafish were injected *i.p.* with gentamicin or LPS at day 0. NF-kB signaling was determined 4 days post-injection (dpi) by NF-kB:GFP detection of the NF-kB reporter line *Tg(NF-kB:EGFP)* and NF-kB-associated gene expression using qRTPCR. Requirement of NF-kB signaling during regeneration was evaluated by pharmacological NF-kB inhibition. Bulk RNAseq from positive selected GFP^+ and $mcherry^+$ single cells by FACS was performed from kidneys 7 dpi by gentamicin injection using *Tg(lhx1a:EGFP;cdh17:mCherry)* fish.

Results: Gentamicin-induced kidney injury leads to increased tubular NF-kB reporter expression at 4 dpi and is associated with an upregulation of NF-kB target gene expression detected by qRTPCR. Additionally, gentamicin administration upregulated mRNA expression of GH receptors at 7 dpi, along with kidney progenitor markers osr1 and eya4. This was accompanied by an increased formation of new nephron aggregates, as indicated by elevated expression of Tg(lhx1a:GFP). Pharmacological inhibition of NF-kB signaling resulted in reduced expression of kidney progenitor markers, while LPS injection induced an upregulation of these markers. Bulk RNAseq analysis of positive-selected GFP+ Lhx1a+ cells at 7 dpi with gentamicin confirmed the induction of cytokine receptors in kidney progenitor cells.

Conclusions: Multiple pathways may converge on adult kidney stem cells to activate the formation of new nephrons. We propose that gentamicin-induced acute kidney injury (AKI) triggers inflammation, which, in turn, activates stem cells in the distal tubules. However, it remains unclear at this stage whether cytokine stimulation, such as that induced by LPS in the absence of injury, is sufficient to induce neo-nephrogenesis.

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SA-PO335

The Transcription Factor TCF21 Protects Stromal Cell Precursors During Kidney Development

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Background: Normal kidney development requires coordinated interactions between multiple progenitor cells. Foxd1+ cells are critical for normal nephrogenesis and their heterogeneity is increasingly appreciated. However, the molecular mechanisms and trajectories that drive the differentiation of Foxd1+ cells toward the renal stroma, capsule, mesangial cells, renin cells, pericytes, and vascular smooth muscle cells (VSMCs) are poorly understood. Tcf21 is a mesoderm-specific bHLH transcription factor critical for embryogenesis.

Methods: To investigate the developmental origins of Tcf21 effects on stroma, we performed single-cell RNA sequencing (scRNA-seq) on GFP+ cells from E14.5 *mTmG+;Foxd1Cre+;Tcf21$^{f/f}$* kidneys and control kidneys.

Results: Clustering of the entire dataset identified a large stromal population and a smaller representation of non-stromal lineages. Subclustering of stromal cells identified eight populations: proliferating, medullary/perivascular, 'Tcf21 mutant', nephrogenic zone/ureter, nephrogenic zone, collecting duct, ureteric associated stroma, and metanephric mesenchyme. Loss of Tcf21 resulted in a dramatic reduction in the proliferating, medullary/perivascular, nephrogenic zone, and collecting duct associated stromal populations. Immunostaining confirmed that mutants had severe reduction in the medullary and collecting duct stromal space of mutants. A unique cluster, exclusively present in mutant kidneys and named 'Tcf21 mutant', expressed high levels of extracellular matrix (*Spracl1*, *Fras1*), perivascular cells (*Rgs5*, *Akr1b7*), and endothelial cells (*Endomucin*) genes. Mutant cells showed upregulation of pathways involved in extracellular matrix organization, VSMCs and fibroblast proliferation, and negative regulation of angiogenesis.

Conclusions: These data underscore a role for Tcf21 in the emergence of the milieu of Foxd1+ derivatives, whereas loss of Tcf21 leads to stromal cell fate change that results in abnormal kidney development.

Funding: NIDDK Support

SA-PO336

Increased mTOR Signaling Secondary to a Human Integrin-Linked Kinase (ILK) Missense Variant Inhibits Nephrogenesis with Decreased ATP Generation

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Background: Signaling pathways that control nephrogenesis are critical to our understanding of kidney health and disease. Previously, we demonstrated increased mTOR signaling in vitro by overexpression of a CAKUT-associated human missense variant (T173I) of Integrin-Linked Kinase (*ILK*), a key regulator of renal development. Here, we investigate the hypothesis that ILK-T173I disrupts renal development in vivo via dysregulation of mTOR signaling.

Methods: mTOR signaling was analyzed in *Ilk*-T173I knock-in mice with *Ilk*-T173I replacing the WT *Ilk* allele. Morphogenic effects of *Ilk*-T173I on renal development were quantitated. Ureteric and non-ureteric cell populations were isolated by FAC sorting. Gene expression was analyzed by whole genome RNA microarray and qPCR. Cell proliferation and nephron maturation were evaluated by immunostaining and specific markers. Energy metabolism was characterized using the Seahorse assay.

Results: Homozygous *Ilk-T173I* knock-in mice were characterized by a 13.6% decrease in nephron number (n=6, P=0.04), a 35.2% decrease in ureteric branching (n=5, P=0.006) and an 88% increase in mTOR signaling (n=3, P=0.01). Rapamycin treatment of *Ilk-T173I*-knock-in embryonic kidney explants rescued ureteric branching to normal levels. Genome-wide RNA expression analysis in *Ilk-T173I*-knock-in ureteric and non-ureteric cell populations demonstrated elevated mTOR signaling in non-ureteric cells only. *Ilk-T173I*-knock-in non-ureteric populations expressed a 431% increase in *Osr1*

(n=3, P=0.002), a mesenchymal cell progenitor marker, and a 54% decrease in *Lhx1* (n=3, P=0.04), a marker for maturing nephrons. *Ilk-T173I* knock-in embryonic kidneys demonstrated a 2075% increase in phospho-Histone H3-labeled cells (n=3, P=0.0005), an indicator of cell proliferation, in the ureteric, nephrogenic and stromal lineages, and a 16.1% decrease in the percentage of S-shaped bodies (n=4, P=0.01), the mature form of nephrogenic intermediates. Metabolic profile of *Ilk-T173I*-knock-in, non-ureteric cells exhibited a 17% decrease in both oxidative ATP production (n=3, P=0.04) and total ATP production (n=3, P=0.02).

Conclusions: These data show that human Ilk-T173I variant impairs renal development in a mTOR-dependent manner, specifically acting within the non-ureteric cell population by increasing proliferation and disrupting maturation and cell metabolism.

Funding: Government Support - Non-U.S.

SA-PO337

PRRX1 Is a Master Regulator of Renal Fibroblast Cell Fate and Regulates Myofibroblast Activation in Response to TGF-β via Alteration of the Chromatin Landscape

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Background: Emerging evidence suggests that changes in the chromatin landscape in response to TGFβ likely contributes to the pathogenesis of diabetic kidney disease (DKD). Using iPSC derived kidney organoids, we have recently shown that TGF-β signalling to chromatin unleashes a programme of gene expression intiating fibroblast to myofibroblast activation. We hypothesise that SMAD3 and the Polycomb Repressive Complex 2 core component, EZH2, co-occupy regulatory regions within chromatin to deposit histone post-translational modifications (PTMs), thereby facilitating a chromatin landscape which drives fibroblast activation in DKD. Our data suggests that PRRX1 acts as a master transcription factor in regulating fibroblast to myofibroblast differentiation through association with SMAD3/EZH2. To characterise this proposed epigenetic mechanism, proteomic and transcriptomic analysis was performed on iPSC-derived kidney organoids treated with TGFβ1.

Methods: Histone extraction was performed on undifferentiated iPSCs, iPSC-derived nephron progenitor cells, iPSC-derived kidney organoids, and kidney organoids treated with recombinant TGFβ1. Histones were then subjected to LC-MS/MS for analysis of global histone modifications. Single cell RNA-sequencing (scRNA-seq) was performed on iPSC derived kidney organoids treated with EZH2 inhibitor, GSK343, for 1h prior to TGFβ1 treatment for 48 hours.

Results: Mass Spectrometry data revealed differential abundance of trimethylated lysine residues on Histone 3 (H3K27me3) between TGFβ treated and control, indicating dynamic changes in transcriptionally permissive states. scRNA-seq analysis of kidney organoids treated with TGFβ1 revealed cluster specific changes in PRRX1 expression in response to TGFβ1, specifically in stromal cells and activated myofibroblast clusters. These changes in PRRX1 in response to TGFβ1 were consistently observed in other fibroblast cell lines.

Conclusions: TGF-β is a key driver of chromatin dynamics as evidenced by H3K27me3 and likely contributes to gene repression through interaction between SMAD3 and EZH2. We propose that subsequent silencing of PRRX1 expression mediates fibroblast to myofibroblast activation and represent a tractable therapeutic target for the amelioration of fibrosis in DKD.

SA-PO338

Regeneration-Associated Cell-Derived Extracellular Vesicles Preserve Kidney Function After Acute Ischemia Injury

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Background: Under vasculogenic conditioning, pro-inflammatory cell subsets of peripheral blood mononuclear cells (PBMCs) shift their phenotype to pro-regenerative cells such as vasculogenic endothelial progenitor cells, M2 macrophages, and regulatory T cells, collectively designated as regeneration-associated cells (RACs). In this study, we evaluated the therapeutic efficacy of RAC-derived extracellular vesicles (RACev) compared with a vehicle-treated group using the rat kidney ischemia-reperfusion injury (K-IRI) model.

Methods: Human PBMCs were cultured with defined growth factors for seven and then two days to harvest RACs and RAC-ev, respectively. EV sizes were characterized by nanoparticle tracking analysis. Transmission electron microscopy revealed a bi-layered membrane structure and flow cytometry confirmed the presence of EV-specific markers (CD9, CD63, and Alix).

Results: Notably, systemic injection of RACev significantly decreased serum creatinine and blood urine nitrogen ($P < 0.01$ and $P < 0.005$) at day three after the onset of K-IRI than the control group. Histologically, the treatment group showed less fibrosis in the cortex and medullary areas ($P < 0.04$ and $P < 0.01$) compared to the control group. CD31 staining confirmed enhanced capillary densities at the cortex and medullary areas in the treatment group compared to the control group ($P < 0.003$). These beneficial effects were coupled with significant expression of angiogenesis (miR-126-3p/5p, miR-195-3p/5p, miR-146-3p/5p), anti-fibrosis (miR-133a-3p, miR-29b-3p), anti-inflammation (miR-10a-3p, miR-21-3p, miR-24-2p), and anti-apoptosis miRs by RACev. In vivo bioluminescence analysis showed preferential accumulation of RACev in the IR-injured kidney.

Conclusions: In conclusion, systemic transplantation of RACev improved kidney function via protecting from tissue fibrosis, anti-inflammation, and angiogenesis miR delivery to the ischemic tissue.

SA-PO339

Partitioning-Defective (Par1) Inhibition Protects Against Kidney Fibrosis in Mice

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Background: Partioning defective (Par) 1a and 1b (*MARK2/3*) expression is required for normal kidney development and increases in damaged tubules following tubular injury by unilateral ureteral obstruction (UUO) and folic acid (FA) injection in mice. *Par1a/MARK3* expression in human kidney tissues correlates with kidney fibrosis and eGFR. Par1a mutant (*Mark3*$^{-/-}$) mice are protected against kidney fibrosis following UUO and FA induced injury. We hypothesized tubular Par1a/b expression is maladaptive following kidney injury and sought to test the effect of tubular Par1a/b deletion and chemical Par1 inhibition on fibrosis following kidney injury.

Methods: We generated tubular conditional Par1a/b knock out mice (*Pax8-rtTA:tet-O-Cre:Mark2flox/flox:Mark3flox/flox*) mice. Tubular deletion was induced using doxycycline treatment 7 days prior to injury by UUO. Sham operated (for UUO) mice was used as control for the injury model. Both injured and uninjured uninduced *Pax8-rtTA:tet-O-Cre:Mark2flox/flox:Mark3flox/flox* mice and doxycyline treated *Mark2flox/flox:Mark3flox/flox* mice were used as controls. A MARK/Par-1 Activity Inhibitor (Sigma, 39621) was injected via IP injection for 3 days after UUO injury. Kidney phenotype was analyzed at 7 days post UUO injury or sham surgery.

Results: Par1a/b (*Mark2/3*) gene expression is highest in injured, dedifferentiated proliferating (Sox9 and Ki67+) tubular cells. Dual Par1a/b cKO mice were protected from injury induced fibrosis following UUO induced injury ($p=0.001$). MARK Inhibition after injury protected against UUO induced fibrosis.

Conclusions: Genetic tubular deletion of Par1a/b before injury and inhibition post UUO induced injury was protective against kidney fibrosis. Ongoing experiments are testing other models of kidney injury and mechanisms of Par1a/b protection.

Funding: NIDDK Support

SA-PO340

miR-17/-20a Alleviates Renal Interstitial Fibrosis by Repressing Frmd6 Expression in Renal Epithelia

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Background: An estimated 37 million Americans have chronic kidney disease (CKD), and its prevalence is increasing with higher rates of diabetes mellitus, hypertension and obesity. Regardless of the underlying etiology, renal fibrosis is the final manifestation of CKD. microRNAs (miRNAs) are endogenous, small non-coding RNAs that bind to target mRNAs and regulate their expression. In this study, we investigated the role of the *miR-17~92* cluster (comprises *miR-17*, *-18a*, *-19a*, *-19b*, *-20a* and *-92a*) in renal fibrosis.

Methods: Genetic mouse models of inducible epithelial-specific *miR-17~92* loss-of-function (*imiR-17~92*^{EpiLOF}) or gain-of-function (*imiR-17~92*^{EpiGOF}) were generated by crossing *Pax8Cre-rtTA; LC1-cre* mice with *miR-17~92* floxed mice or with a mouse line containing a constitutively active CAG promoter ahead of a *loxP*-flanked STOP cassette preventing transcription of the downstream *miR-17~92* sequence, respectively. Unilateral ureteral obstruction (UUO) and acute kidney injury (AKI) to CKD model were performed. Renal fibrosis was assessed by immunostaining with anti-collagen III and anti-α-SMA antibodies, followed by semi-quantitative analyses with ImageJ. The human proximal tubular epithelial cell line HK2 was transfected with either empty vector or a vector containing the *Frmd6 cDNA*. HK2 cells were used for experimental identification of *miR-17~92* target genes using PAR-CLIP.

Results: *miRs-17*, *-18a*, and *-20a* were upregulated in UUO and the AKI to CKD model. Interestingly, *imiR-17~92*^{EpiLOF} mice exhibited increased predisposition to renal fibrosis with aging and after UUO, which was accompanied by increased expression of known *miR-17~92* profibrotic targets, p-Stat3 and p-Smad3. Conversely, UUO-induced fibrosis was ameliorated in *imiR-17~92*^{EpiGOF} kidneys. *Frmd6*, an activator of Hippo signaling, was identified as a novel *miR-17/-20a* target. Frmd6 was increased in the tubular epithelium of obstructed *imiR-17~92*^{EpiLOF} kidneys compared to controls. Finally, overexpression of Frmd6 in HK2 cells resulted in increased expression of the mesenchymal markers *SNAI1* and *FN1*, and elevated secretion of collagen III in conditioned media.

Conclusions: Together, our findings indicate that the *miR-17~92* cluster in renal epithelia functions to limit fibrosis by regulating multiple pro-fibrotic pathways.

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SA-PO341

miR193a-VDR/RXR Axis and Renin Expression in the Transition of Parietal Epithelial Cells to Podocytes

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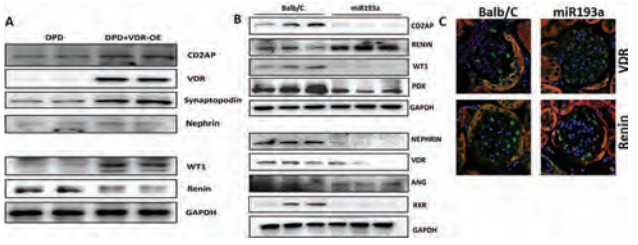
Background: Loss of kidney cells is a predominant cause of impaired kidney function in aging kidneys. Renin-expressing cells make a pool of renal progenitor cells, where the lack of renin expression determines their differentiation potential. Since microRNAs are the regulators of gene expression, we analyzed the role of the mir193a-VDR/RXR axis in regulating the renin expression and the stemness of Parietal Epithelial cells (PECs).

Methods: Human PECs were grown and analyzed for the expression of miR193a, renin, VDR, and RXR using real-time PCR and Western blotting. PECs were transitioned to podocytes by transfecting either miR193a plasmid or an inhibitor of miR193a. The PECs transition potential was also analyzed under the overexpression of VDR and RXR. Immunoprecipitation assays were performed to evaluate the potential interaction of VDR/RXR and Renin. Luciferase experiments were carried out to elucidate the binding of miR193a to VDR 3'UTR. In vivo, studies were carried out in control (Balb/C) and miR193a transgenic mice.

Results: Differentiated podocytes (DPD)-overexpressing (OE) VDR showed enhanced expression of VDR and podocyte markers but a decreased renin expression (Figure A). Renal tissues of miR193a transgenic mice not only showed attenuated podocyte markers (Nephrin, podocalyxin [PDX], WT1) and VDR/RXR but also showed enhanced renin expression when compared to control mice (Figures B and C). The miR193a expression inversely regulated the VDR expression, and the downing of VDR prevented hetero-dimerization with RXR contributing to poor reprogramming of PECs.

Conclusions: miR193a-VDR/RXR regulates renin expression and determines the efficient transition of PECs to podocytes.

Funding: NIDDK Support



A. Protein blots of differentiated podocytes (DPD) -overexpressing (OE) VDR were probed podocyte markers and renin. B. Protein blots of renal tissues of control (Balb/C) and miR193a transgenic mice were probed podocyte markers (Nephrin, PDX, WT1), VDR/RXR, renin and Angiotensinogen (Ang) expression. C. Immunolabeling of renal cortical sections of mice for VDR and renin.

SA-PO342

Modeling Kidney Development, Disease, and Plasticity with Clonal Expandable Nephron Progenitor Cells and Nephron Organoids

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Background: During kidney organogenesis, nephron progenitor cells (NPCs) self-renew and differentiate into nephrons, the functional units of the kidney. Dysregulation of NPC fates underlies a number of congenital kidney diseases while uncontrolled proliferation of NPCs in Wilms tumor is the most prevalent pediatric kidney cancer. Thus, a deeper insight into NPC biology is central to improving an understanding of kidney development, congenital disease and cancer, and to applying developmental insight to regenerating kidney functions.

Methods: A synthetic niche is formulated that allows the in vitro long-term clonal expansion of primary mouse and human NPCs, and induced NPCs (iNPCs) from human pluripotent stem cells. Nephron organoids are generated from cultured NPCs following a chemically-defined differentiation protocol. Genome-wide CRISPR screening is performed in the cultured NPCs to identify novel genes associated with kidney development and disease. Multiplexed CRISPR/Cas9 genome editing in the cultured NPCs generate a rapid, efficient, and scalable organoid model for polycystic kidney disease (PKD), allowing drug screening.

Results: Cultured iNPCs resemble closely primary human NPCs, generating nephron organoids with abundant distal convoluted tubule cells, which are not observed in published kidney organoids. The synthetic niche reprograms differentiated nephron cells into NPC state, recapitulating the plasticity of developing nephron *in vivo*. Scalability and ease of genome-editing in the cultured NPCs allow for genome-wide CRISPR screening, identifying novel genes associated with kidney development, congenital kidney diseases, and Wilms tumor. Cystic PKD organoid models are generated directly from genome-edited human NPCs in as short as 8 days. Proof-of-concept drug screening identified a drug candidate targeting epigenetic pathway.

Conclusions: These NPC and nephron organoid-based technological platforms have broad applications to kidney development, disease, plasticity, and regeneration.

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SA-PO343

TRIM72 Immunomodulatory Functions Protect the Kidney During Inflammation

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Background: TRIM72 (MG53) is a muscle-predominant protein and functions as a circulating myokine that appears to confer tissue protection during ischemia-reperfusion (I/R) acute kidney injury and UUO-mediated kidney fibrosis. We discovered the functional duality of TRIM72 in kidney protection serving as a membrane repair protein and also modulating the immune system by suppressing NF-kB signaling during kidney inflammation. Here we explored the biological role and therapeutic potential of engineered MG53-containing extracellular vehicles (EVs) in the treatment of kidney inflammation.

Methods: TRIM72 protein expression was characterized in human kidney, immortalized kidney parenchymal cell lines, and mouse proximal tubular epithelial cells derived from wildtype (*mg53* $^{+/+}$) or *trim*72-null (*mg53* $^{-/-}$) age and gender-matched mice. We investigated whether I/R- injured kidney recruits circulating TRIM72-containing EVs as a means of protection. Furthermore, we engineered TRIM72 expression in several cell systems and further investigated whether TRIM72 affected the cells' inflammatory cytokine profiles.

Results: TRIM72 expression was detected in total human kidney lysates and in immortalized human podocytes and mesangial cells. A serum pro-inflammatory cytokine panel confirmed elevation of pro-inflammatory cytokines in *trim*72-null mice. The relative fold increase in *trim*72-null mice compared to *wildtype* mice were: CXCL1--1.2; IL-2 --1.6; TNFa --1.38; IL-5 -- 2.8; IL-1--1.5. I/R-injured kidneys recruited TRIM72-containing EVs derived from C2C12 myotubes as shown by IVIS imaging of DiR-labeled EVs 2 hours post-injury. The kidneys from *trim*72 null mice that received C2C12 EVs over 4 weeks expressed comparable levels of TRIM72 to that of wildtype mice.

Conclusions: TRIM72 is detected in the kidney may be an endogenous inhibitor of pro-inflammatory cytokine expression. EVs loaded with TRIM72 are recruited to acutely injured kidneys, and can replenish renal TRIM72 levels in trim72 null mice. These results suggest that TRIM72-loaded EVs may be applied therapeutically to control kidney inflammation.

Funding: NIDDK Support, Other NIH Support - NIA, NIAID

SA-PO344

Development of a System for the Replacement of Animal Fetal Kidneys with Human Nephrons: Toward Clinical Application

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Background: Our focus is on "xenogeneic regenerative medicine," aiming to regenerate human nephrons using porcine fetal kidneys as a scaffold. Crucial to this approach is the replacement of porcine nephron progenitor cells (NPCs) with human NPCs. Previous studies using mouse models have shown complete replacement of the host nephrogenic niche with exogenous nephrons through Six2 (+) NPC suicide driven by diphtheria toxin (DT) or tamoxifen (TAM). However, there are limitations, such as DT's inability to target human NPCs and concerns about TAM's side effects. To facilitate future clinical applications, we have developed a novel inducible-caspase 9 (iCasp9) system. It activates the intrinsic apoptotic pathway upon the administration of a chemical inducer of dimerization (CID) without harming the surrounding renal tissue. Importantly, our study demonstrates efficient cell clearance using this new system in animal models.

Methods: Six2-iCasp9 mice were generated using TALEN-mediated gene modification. The knock-in site was positioned downstream of the exon to prevent lethality in homozygotes. CID was administered both *in vitro* to fetal kidneys and *in vivo* to neonatal mice with either Six2-iCasp9$^{+/+}$ or Six2-iCasp9$^{+/-}$ genotype. Additionally, exogenous mouse and rat progenitor cells, as well as induced human NPCs, were injected into Six2-iCasp9$^{+/+}$ fetal kidneys with CID administration.

Results: In the culture of Six2-iCasp9$^{+/+}$ fetal kidneys, treatment with CID induced efficient apoptosis of all NPCs within 18 hours, whereas the conventional TAM-driven model showed insufficient apoptosis at the same time point. *In vivo* administration of CID to neonates also led to the complete removal of NPCs. On the other hand, NPC removal was not observed in the Six2-iCasp9$^{+/-}$ mice. Following the injection of exogenous progenitor cells, successful nephron replacement was achieved in Six2-iCasp9$^{+/+}$ fetal kidneys.

Conclusions: We successfully developed an iCasp9 system that enables rapid and complete cell clearance, providing an optimal environment for NPC replacement and subsequent nephron regeneration in an animal model. The phenotypic differences between homozygotes and heterozygotes might be attributed to the varying levels of iCasp9 expression. This achievement marks a clinical advancement in the development of the porcine fetal replacement system.

Funding: Government Support - Non-U.S.

SA-PO345

The Role of Gata3 in Renin Cell Identity

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Background: Renin cells are precursors for other cell types in the kidney and show high plasticity in postnatal life in response to challenges to homeostasis. Our scRNA-seq studies revealed that the dual-zinc finger transcription factor Gata3, important for cell

lineage commitment and differentiation in many tissues, is expressed in mouse renin cells under normal conditions and homeostatic threats. Based on our Chip-seq data, we found an enhancer associated with Gata3 in renin cells. In addition, we identified a potential Gata3 binding site upstream of the renin gene leading us to hypothesize that Gata3 is essential for renin cell identity.

Methods: We studied 60 and 120-day-old mice carrying a conditional deletion of *Gata3* in renin cells: *Gata3$^{fl/fl}$;Ren1$^{dCre/+}$* (*Gata3-cKO*), and control *Gata3$^{fl/fl}$;Ren1$^{d+/+}$* counterparts. BUN and plasma renin levels were measured from blood samples collected by cardiac puncture. Ren1, Acta2, and Gata3 were visualized in kidney sections by immunohistochemistry. Histological analysis was performed on adult kidney sections with hematoxylin and eosin (H&E), periodic acid-Schiff (PAS) solution, or Masson's Trichrome chemical reactions. The juxtaglomerular area (JGA) index was calculated as a ratio of renin-positive JGAs per the total number of glomeruli and expressed as a percentage.

Results: *Gata3-cKO* mice have: 1) a marked reduction in Gata3 staining, demonstrating *Gata3* deletion in renin lineage cells; 2) a marked reduction of *Ren1* and *Akr1b7* mRNA levels in renin cells compared to controls; 3) a significant decrease in circulating plasma renin compared to controls under basal conditions and physiological threat; 4) a significantly reduced JGA index; 5) flattened JG cells compared to the plump and rounded morphology of control mice; 6) glomeruli with abnormal misplaced renin staining in the Bowman's capsule; 7) an absence of cubical epithelial cells in the Bowman's capsule, dilation of distal tubules, dilation of the glomerular capillaries and evidence of glomerular sclerosis and fibrosis. There was prominent glomerular hemorrhage with aneurysms and evidence of perivascular, peritubular, and periglomerular infiltration of inflammatory cells; 8) misplaced Acta2 staining in the intraglomerular mesangium, interstitium, and Bowman's capsule.

Conclusions: Our results suggest a role of *Gata3* in the identity of the cells of the renin lineage.

Funding: NIDDK Support

SA-PO346

Repetitive Administration of Cultured Human CD34+ Cells Improve Adenine-Induced Kidney Injury in Mice

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Background: There is no established treatment to impede the progression of diabetic kidney disease in human.

Methods: We evaluated the efficacy of cultured human CD34$^+$ cells with enhanced proliferating potential in chronic kidney injury model in mice. Human umbilical cord blood (UCB)-derived CD34$^+$ cells were incubated for one week in vasculogenic conditioning medium. This culture method significantly increased the number of CD34$^+$ cells (60-fold) and their ability to form endothelial progenitor cell colony-forming units (40-fold). Adenine-induced tubulointerstitial chronic kidney injury was induced in NOD/SCID mice, and cultured human UCB-CD34$^+$ cells were administered at a dose of 1×10^6/mouse on days 7, 14, and 21 after the start of adenine diet (cell therapy group n=18). In the control group (n=17), vehicle was administered at the same time point. Time-course of kidney function, pathological damage, and CD31-positive peritubular capillary density and macrophage infiltration in the kidney at the time of sacrifice (day 28) were evaluated.

Results: Repetitive administration of cultured UCB-CD34$^+$ cells significantly improved the time-course of serum creatinine levels in the cell therapy group compared with that in the control group (1.09 ± 0.09 mg/dL *vs* 1.41 ± 0.14 mg/dL on day 28, p =0.035). Both interstitial fibrosis area and tubular injury score were significantly reduced in the cell therapy group compared with that in the control group (interstitial fibrosis: 8.1 ± 5.4% *vs* 16.3 ± 7.0%, $p < 0.01$, tubular injury score: 1.48 ± 1.27 *vs* 2.83 ± 1.00, $p < 0.01$). Peritubular capillary density was significantly preserved in the cell therapy group compared with that in the control group (57.3 ± 6.4% *vs* 31.0 ± 6.1%, $p < 0.01$), and macrophage infiltration in the kidney tissue was dramatically decreased in the cell therapy group compared with those in the control group (1.3 ± 0.3% *vs* 14.4 ± 1.1%, $p < 0.001$).

Conclusions: Repetitive administration of cultured human UCB-CD34$^+$ cells significantly improved kidney dysfunction and chronic tubulointerstitial damage in adenine-induced kidney injury in mice *via* the protective effect of microvasculature integrity and anti-inflammatory effects. A clinical trial using cultured human UCB-CD34+ cells for progressive kidney disease might be expected.

SA-PO347

A Clinical Trial of Comprehensive Regenerative Treatment for Acute and Chronic Kidney Injury by Autologous Granulocyte-Colony Stimulating Factor (G-CSF)-Mobilized Peripheral Blood-Derived CD34+ Cell Administration

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Background: There has been no established treatment to improve severe acute kidney injury (AKI) and progressive chronic kidney disease (CKD) in human. We are performing a clinical trial of regenerative medicine using autologous G-CSF-mobilized CD34$^+$ cells for AKI and CKD.

Methods: After permission of government permitted ethical committee, a clinical trial of regenerative treatment for severe AKI and progressive CKD is now undergoing. Potential subjects comprised of patients with dialysis-dependent severe AKI or patients who could fortunately be withdrawn from dialysis treatment but did not recover to baseline renal function within 4 weeks after the onset of AKI (AKI arm), and patients with progressive CKD (CKD stage G3b and G4 with decrease of reciprocal serum creatinine more than 0.01mL/mg/month) (CKD arm). Autologous G-CSF-mobilized peripheral blood-derived CD34+ cells at a dose of $1x10^6$/kg body weight were administered into renal arteries, and safety and efficacy were evaluated.

Results: Until now, six patients (2 AKI patients with malignant hypertension and 4 CKD patients with IgA nephropathy) were registered, and 4 patients (2 AKI patients and 2 CKD patients) completed their follow-up after cell therapy. As for safety, no major adverse events were observed. AKI case 1 showed rapid increase of estimated glomerular filtration ratio (eGFR) from 9.2 at transplantation to 20.0 mL/min/1.73m^2 at 4 weeks after cell therapy, and further improved to 24.9mL/min/1.73m^2 at 52 weeks. AKI case 2 could be withdrawn from hemodialysis treatment one month after cell transplantation, and eGFR gradually increased to 12.8 mL/min/1.73m^2 at 52 weeks. eGFR in CKD case 1 decreased from 15.0 at transplantation to 10.2 mL/min/1.73m^2 at 6 months after cell therapy. However, eGFR in CKD case 2 increased from 15.2 at transplantation to 17.5 mL/min/1.73m^2 at 6 months after cell therapy. CKD case 3 and 4 are now under follow-up period.

Conclusions: Regenerative cell therapy using autologous G-CSF-mobilized CD34$^+$ cells might have beneficial effect in patients with severe AKI. In progressive CKD patients with severely decreased renal function, further patients' recruitment and clarification of the efficacy of this cell therapy is necessary.

SA-PO348

Benchmarking Mitochondrial Organization and Abundance in Organoids Against Fetal and Newborn Kidney Tissue

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Background: Proximal tubule (PT) epithelia are some of the most energy demanding cells in the body, and rely on mitochondria for a large variety of ATP-dependent functions. Fidelity of stem cell-derived kidney tissue depends on achieving similar mitochondrial function. Our previous investigations revealed a paucity of mitochondria in PT epithelia of human stem cell-derived organoids. In this study we benchmarked synthetic PT epithelia against natural PT epithelia, and used a screening approach to boost mitochondrial mass in organoid epithelia.

Methods: Mitochondria were localized by staining with anti-TOMM20, LTL and anti-HNF4A were used for PT. TMRM was used to identify energetically active mitochondria in kidney tissue.

Results: Human fetal kidney (HFK) and newborn mouse kidneys were stained for mitochondria and PT. Newly formed PT stain weakly for HNF4A and LTL have characteristic apically arranged mitochondria. The mitochondria translocate basolaterally as these cells differentiate and mitochondrial mass increases several-fold, suggesting an abrupt activation of biogenesis. Live tissue staining of newborn mouse kidney with TMRM reveals undetectable mitochondrial polarization in apical mitochondria of nascent epithelial cells, while cells with basolateral mitochondria show strong mitochondrial polarization. Presumptive PT epithelia in stem cell-derived organoids have almost exclusively apically located mitochondria, suggesting that these cells may be functionally immature despite HNF4A and LTL staining. Single cell data from HFK and organoids were mined for mitochondrial biogenesis, mitophagy and mitocytosis pathways. Compounds selected based on this analysis were tested for their capacity to modify mitochondrial mass and function in a flow cytometry-based screening assay using organoids with fluorescent reporters for mitochondria and for PT. As expected, modifiers of the biogenesis regulator AMPK modulate mitochondrial mass, but we also found unanticipated effects of modulating LRRK2, which determines mitochondrial positioning within the cell.

Conclusions: Subcellular localization of mitochondria serves as a hallmark of epithelial cell functional maturity in human stem cell derived kidney organoids, and modulating mitochondrial mass is an important step in developing high-fidelity human kidney organoids.

SA-PO349

Urine-Derived Stem Cell Administration Attenuates Renal Injury in an Adriamycin-Induced Nephropathy

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Background: Stem cell-based therapy as a potential alternative to conventional drug therapies for kidney diseases has attracted significant attention. While mesenchymal stem cells have been extensively studied in early clinical trials for various kidney diseases, research on urine-derived stem cells (UDSCs) remains limited. This study aims to evaluate the efficacy of UDSC administration in improving Adriamycin (ADR)-nephropathy using both an in vivo BALB/c mice model and an in vitro podocyte model.

Methods: 10 week-old male BALB/c mice were divided into four groups: sham, ADR, ADR+HS (single dose of UDSC), ADR+HM (three doses of UDSC) to establish the in vivo model. ADR was administered on day 0, followed by UDSC administration one week later. Necropsy and analysis were conducted on the 21st day. The urine albumin/creatinine ratio (ACR) was measured on days 0, 7, 14, and 21, and kidney

tissue was examined using light microscopy, immunofluorescence microscopy, and electron microscopy. In vitro, the protective effect of UDSC co-culture with ADR-treated podocytes was investigated through cell viability assessment and the expression of podocyte-specific markers, such as α-actinin-4 and synaptopodin.

Results: Both single-dose (ADR+HS) and multiple-dose (ADR+HM) UDSC administration significantly reduced the urine ACR levels compared to the ADR group. Histological analysis revealed notable improvements in renal tissue damage, including glomerulosclerosis and fibrosis, in both the ADR+HS and ADR+HM groups compared to the ADR group. Moreover, UDSC administration protected podocytes from damage, as indicated by increased foot process width. UDSC administration also enhanced expression of synaptopodin and α-actinin-4. Notably, ADR+HM showed a more pronounced effect on foot process width increase and improvement in the expression of α-actinin-4 and synaptopodin in podocytes compared ADR+HS. In vitro model, co-culture with UDSC significantly enhanced podocyte cell viability compared to ADR-treated podocytes alone. Furthermore, co-culture with UDSCs led to a significant increase in the expression of α-actinin-4 and synaptopodin in ADR-treated podocytes.

Conclusions: Administration of UDSCs demonstrates significant reduction in kidney damage in both in vivo and in vitro models of ADR-induced nephropathy.

SA-PO350

Depot-Specific Alterations in Visceral Adipose Tissue-Derived Mesenchymal Stem Cells in CKD: Insights from Single-Cell RNA Sequencing

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Background: Patients with chronic kidney disease (CKD) experience systemic conditions such as chronic inflammation, oxidative stress, and protein-energy wasting. While previous studies have explored inter-organ communication to understand these conditions, the specific changes occurring in adipose tissue within a uremic environment remain poorly understood. This study aimed to investigate the characteristics of visceral adipose tissue in CKD patients, with a focus on adipose tissue-derived mesenchymal stem cells (ADMSCs).

Methods: We collected retroperitoneal adipose tissue (RP) near the kidneys and omental adipose tissue (OM) from healthy kidney donors as well as CKD patients who underwent kidney transplantation or peritoneal catheter insertion. The characteristics of the stromal vascular fraction were evaluated using single-cell RNA sequencing. Additionally, adipose tissue fibrosis and the expression of thermogenic genes were assessed in the total adipose tissue from these two different depots.

Results: We harvested 66,668 cells. In the ADMSCs cluster of RP, CKD patients showed a significant upregulation of antioxidant genes, such as metallothioneins, SOD2, and GPX3. Gene Ontology and pathway analysis revealed that differentially expressed genes (DEGs) upregulated in CKD were related to ribosomal biogenesis and ferroptosis. We observed an increase in the S phase of the cell cycle in RP of CKD, accompanied by enhanced FOXO signaling pathway and cellular senescence to prevent DNA damage. In OM of CKD, DEGs specifically upregulated were related to ATP synthesis processes, including fatty acid β-oxidation, the TCA cycle, and oxidative phosphorylation in mitochondria. Additionally, the median cell size of adipocytes from CKD patients was significantly smaller than that of healthy controls, specifically in OM. Adipocytes of CKD OM showed a significant increase in the expression of thermogenic genes, such as UCP1, CIDEA, PGC1α, TBX1, and TMEM26.

Conclusions: We identified depot-specific alterations in ADMSCs and adipose tissue characteristics in CKD patients. Further investigations are needed to elucidate the potential role of these adipose tissue changes in the systemic conditions associated with CKD.

Funding: Government Support - Non-U.S.

SA-PO351

The Effects of Regulatory T Cell Induction by Mesenchymal Stem Cells Pretreated with Interferon-Gamma on Renal Inflammation and Fibrosis

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Background: Mesenchymal stem cells (MSCs) exert the anti-inflammatory effect by secreting various humoral factors, which contribute to the regeneration of damaged tissues. Interferon-gamma (IFN-γ) can enhance the anti-inflammatory effect of MSCs, and the enhancement of regulatory T (Treg) cell induction is thought to be an underlying mechanism. In this study, we investigated the effects of Treg cell induction by IFN-γ MSCs on renal inflammation and fibrosis.

Methods: Rats were subjected to contralateral nephrectomy and unilateral renal ischemia reperfusion injury (IRI) by clamping the renal artery. Subsequently, phosphate-buffered saline, untreated MSCs (control MSCs), or IFN-γ MSCs were administered to the renal artery. At 7 or 21 days after administration, rats were sacrificed and their kidneys were collected to examine renal inflammation and fibrosis. In addition, *in vitro* experiments were performed to examine expression levels of indoleamine 2,3-dioxygenase (IDO), the key regulator of Treg cell induction, in IFN-γ MSCs. Finally, we examined the therapeutic effects of IFN-γ MSCs transfected with IDO1 siRNA in IRI rats.

Results: Administration of IFN-γ MSCs induced Treg cells and inhibited infiltration of inflammatory cells in IRI rats more drastically than control MSCs. In addition, administration of IFN-γ MSCs more significantly attenuated renal fibrosis compared with administration of control MSCs. IDO expression levels in conditioned medium from MSCs were enhanced by pretreatment with IFN-γ. Functional experiments demonstrated that IDO1 knockdown in IFN-γ MSCs reduced their anti-inflammatory and anti-fibrotic effects in IRI rats by reducing Treg cell induction.

Conclusions: Our findings suggest that the increase of Treg cells induced by enhanced secretion of IDO by IFN-γ MSCs played a pivotal role in their anti-fibrotic effects. Administration of IFN-γ MSCs may potentially be a useful therapy to prevent renal fibrosis progression.

SA-PO352

Tonsil-Derived Mesenchymal Stem Cells Alleviate Gentamicin (GM)-Induced AKI by an Amelioration of Oxidative Stress and Apoptosis via an Incorporation into Damaged Renal Tubules

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Background: The therapeutic effect of mesenchymal stem cells (MSCs) in repairing damaged renal cells in AKI has been demonstrated. Human palatine tonsil is an attractive alternative high-yield source of adult stem cells since they are readily available from surgically removed waste tissue. The aim of this study is to investigate the therapeutic potential of T-MSCs in GM-induced AKI.

Methods: Twenty male Sprague-Dawley rats were divided into four groups: Control, GM (140 mg/kg/day, intraperitoneal injection for 10 days), GM+T-MSCs ($1x10^7$ cells, intravenous injection at 1 day after the 1st GM injection), and T-MSC group. To examine the intra-renal localization of T-MSCs, T-MSCs were labeled with PKH-26 red fluorescence before infusion. Measurement of BUN, Cr, proteinuria and histologic analysis including TUNEL staining were performed on 16 days of GM injection. Effect of T-MSC on renal tubular cells was also evaluated using a transwell co-culture system of NRK cells and T-MSC. Intracellular ROS was analyzed by measuring NOX activity, H_2O_2 generation, NOX mRNA expressions with DCF-DA staining.

Results: The infusion of T-MSCs in GM-induced AKI rats preserved renal function with a decrease in proteinuria. T-MSCs injection decreased apoptotic cells and the expression of Bax, cytochrome C, and cleaved caspase and increased Bcl-2. T-MSCs suppressed oxidative stress as reflected by a decrease in the level of urinary 8-OHdG with an increase in antioxidant enzymes (glutathione peroxidase and catalase) in the kidneys. Anti-human nuclei and PHK-26 staining demonstrated the localization of T-MSCs in the tubules of renal cortex. In-vitro study revealed that T-MSC or T-MSC-conditioned media ameliorated GM-induced NOX-1 expression, H_2O_2 generation, and apoptosis of NRK cells.

Conclusions: Our study demonstrated that T-MSCs ameliorated GM-induced AKI by directly incorporating into the damaged renal tubules, exerting anti-apoptotic and anti-oxidative effects.

Funding: Government Support - Non-U.S.

SA-PO353

Comparison of Therapeutic Effects of Adipose- and Bone Marrow-Derived Mesenchymal Stem Cells on Renal Fibrosis

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Background: Mesenchymal stem cells (MSCs) have garnered strong interest as a therapeutic tool for renal fibrosis. Although both adipose-derived and bone marrow-derived MSCs (ADSCs and BMSCs, respectively) suppress renal fibrosis, which of these two has a stronger therapeutic effect remains unclear. This study aimed to compare the antifibrotic effects of ADSCs and BMSCs from the same rats.

Methods: ADSCs and BMSCs were extracted from adipose tissue and bone marrow from same rats and cultured in serum-containing and serum-free medium, respectively. After renal ischemia-reperfusion injury, ADSCs and BMSCs were injected through the abdominal aorta. At 21 days post-injection, the rats were sacrificed, and their kidneys were analyzed. Next, ADSCs and BMSCs were infused into mice via tail vein, and 24h survival rate and pulmonary emboli were analyzed. In in vitro experiments, we compared the procoagulation factors and humoral factors in ADSCs and BMSCs.

Results: When cultured in serum-containing medium, ADSCs had a more potent inhibitory effect than BMSCs on renal fibrosis induced by ischemia-reperfusion injury in rats. ADSCs and BMSCs cultured in serum-free medium were equally effective in suppressing renal fibrosis. Mice infused with ADSCs (serum-containing or serum-free cultivation) had a higher death rate from pulmonary embolism than those infused with BMSCs. *In vitro*, mRNA levels of tissue factor, tumor necrosis factor-α-induced protein 6 and prostaglandin E synthase were higher in ADSCs than BMSCs, while that of vascular endothelial growth factor was higher in BMSCs than ADSCs. Although ADSCs had a stronger antifibrotic effect, these findings support the consideration of thromboembolism risk in clinical applications.

Conclusions: Our results emphasize the importance of deciding between ADSCs and BMSCs based upon the target disease and culture method.

Funding: Government Support - Non-U.S.

SA-PO354

Selected Renal Cells Improve Renal Function in a Canine Model of CKD

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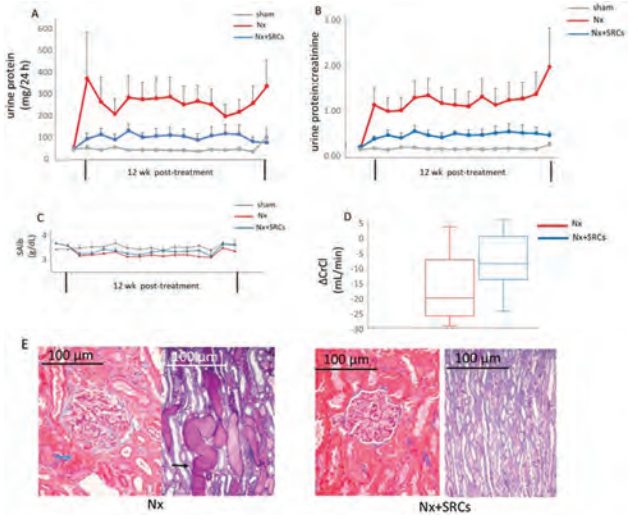
Background: Selected renal cells (SRCs) express podocyte, ureteric bud and cap mesenchyme markers associated with glomerular barrier function, renal filtration and urine concentration. In the present study we tested the hypothesis that cortical administration of autologous SRCs improves renal filtration and preserves renal microarchitecture in the canine subtotal nephrectomy (Nx) model of renal hypertensive chronic kidney disease.

Methods: SRCs were sourced from the excised contralateral kidneys of adult male mongrel dogs subjected to Nx. At weeks 15 and 43 post Nx, dogs were administered SRCs (~300x10^6 cells/dog into the remnant renal cortex, n=4) or placebo (n=4). Renal filtration was monitored over weeks 44 through 57 and renal microarchitecture (Masson's Trichrome) evaluated at sacrifice. A sham cohort served as control.

Results: There was no difference between the two Nx cohorts prior to randomization. SRC treatment was associated with increased body weight ($p<0.01$), reduced urine protein ($p<0.01$) and urine protein to creatinine ratio ($p<0.01$), and improved serum albumin ($p<0.01$) and creatinine clearance profiles ($p<0.05$, A-D). SRCs did not reduce blood pressure, rather their activity appeared to be directly related to preservation of renal microarchitecture evidenced by reduced - glomerular hypertrophy, tubular dilatation, cast deposition, inflammation and fibrosis (E).

Conclusions: These data suggest that SRCs, a standalone cell-based platform, has anti-inflammatory and anti-fibrotic activity and preserves glomerular and tubular microarchitecture and improves multiple indices of renal function in a large animal model of renal disease.

Funding: Commercial Support - ProKidney



SRCs improve renal filtration (A-D) and preserve renal microarchitecture (E) in a canine model of hypertensive chronic kidney disease.

SA-PO355

Renal Involvement After Pediatric Liver Transplantation: A Large Single-Center Cohort

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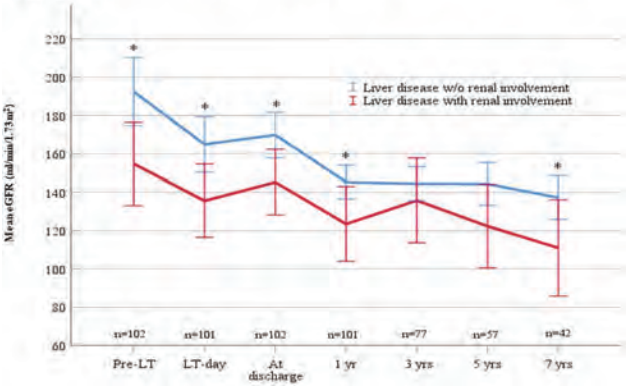
Background: Survival after pediatric liver transplantation has increased dramatically over the years, revealing extra-hepatic complications including impaired renal function. We conducted a large single center retrospective study to evaluate thoroughly renal outcomes after pediatric liver transplantation.

Methods: Pre and post-transplant data was collected from electronic charts of children who underwent liver transplantation at SCMCI from 2007-2020. Incidence of renal injury which included proteinuria, hypertension or decreased eGFR was documented. Additional renal assessment by renal ultrasound and the presence of acute kidney injury (AKI) was performed. Predictors for hypertension or decreased eGFR at last follow-up were identified using univariate and multivariate regression models.

Results: 121 children were followed for a median of 5.12 (IQR 2.94-7.3) years. After excluding 18 patients who died, or underwent renal transplantation, any renal injury was observed in 33.9% of the children, hypertension: 12.6%, proteinuria: 23.3%, and eGFR<90 mL/min per 1.73 m^2: 6.7% at their last follow-up. Reduction in eGFR was observed along the follow-up, and was accentuated in the first year post transplant (figure 1). AKI was seen in 41.7% of the children during follow-up. An abnormal renal ultrasound was seen in 44.7% of the children at last visit, significantly higher rates than before transplant, 10.7% ($p<0.001$). Abnormal renal ultrasound before transplant (OR=4.49, 95% CI 1.1-18.3) and liver disease with risk of renal involvement (OR=4.32, 95% CI 1.4-13.0) were found to be predictors for hypertension or decreased GFR at last follow-up.

Conclusions: Renal injury is very common in children after pediatric liver transplantation. Therefore, thorough renal pretransplant evaluation and follow-up are necessary for preserving and improving renal function.

Figure 1. Trends of estimated glomerular filtration rate (eGFR; mean, 95% CI) over the years in pediatric liver transplant patients.



*P< 0.05 Liver disease with renal involvement versus without. LT, liver transplant.

SA-PO356

Increasing Cardiovascular Burden Among Young Adults with Pediatric CKD at Time of Transition to Adult Care

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Background: Transition to adult care for young adults with pediatric chronic kidney disease (CKD) is critical phase of clinical care and may present challenges for cardiovascular disease (CVD) management. To investigate CVD burden among young adults, we assessed the prevalence of cardiovascular and metabolic comorbidities among participants > 18 years and compared to the same participants prior to age 18.

Methods: Using data from the Chronic Kidney Disease in Children (CKiD) study, we estimated prevalence of high blood pressure (elevated, Stage 1 or 2), obesity, and hyperglycemia before and after age 18 among those who reached young adulthood free of ESKD. Logistic models with generalized estimating equations for prevalence odds ratios (older vs. younger) for each comorbidity, adjusting for GFR, proteinuria and diagnosis.

Results: Among 313 participants who attained age 18 with an average GFR of 47 ml/min|1.73m2, the prevalence of high blood pressure (BP) was 38% among young adults (864 person-visits) with a median age was 19.8 [IQR: 18.8, 21.1], compared to 26% among the same participants prior to age 18 (1332 person-visits) at a median age 15.2 [12.8, 16.7] with an average GFR of 50. There were no significant differences in obesity (21% vs. 19%) or hyperglycemia (6% vs. 7%). Older age was associated with an unadjusted prevalence odds ratio for high BP of 1.70 (95%CI: 1.40 to 2.09), which remained significant in an adjusted model (OR: 1.63, 1.30 to 2.04).

Conclusions: Among young adults with pediatric CKD who had not reached ESKD, the prevalence of high BP was significantly higher compared to when they were younger. Adult nephrologists receiving patients with pediatric CKD should be vigilant for the potential worsening of BP control during the transition period.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

SA-PO357

Food Insecurity Is Associated with Short Stature, Slow Growth Velocity, and Lower Cognitive Function in the Chronic Kidney Disease in Children (CKiD) Cohort

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Background: Food insecurity is defined as the state of being without reliable access to an adequate amount of affordable and nutritious food. Food insecurity is associated with disparities in chronic kidney disease in adults; however less is known in children.

Methods: The Chronic Kidney Disease in Children (CKiD) study is a multicenter, observational cohort of children with eGFR 30-90ml/min/1.73m^2. Food insecurity screening was added in 2022 via the Hunger Vital screen. Cross-sectional analyses used Wilcoxon rank-sum test or Fisher's exact test, as appropriate, to determine the association between food insecurity and disease outcomes related to growth and cognition.

Results: Of the 181 participants included, 9% of subjects (n=17) reported food insecurity. Food insecure subjects had a median age of 9.7 (IQR, 8.4-17.9), median GFR of 42 (IQR, 26, 66), 53% were male, and 18% had glomerular disease. Food insecure patients had a higher prevalence of short stature and lower growth velocity. None of these patients were on growth hormone; however, food insecure patients were significantly more likely to be seen by a nutritionist (p=0.003). Food insecure patients performed less well on IQ tests (mean 89 vs 102, p=0.03) and were from households with lower income and maternal education. Follow-up analyses found the effect of food insecurity on IQ to be independent of maternal education.

Conclusions: Children with CKD and food insecurity, which is frequently associated with lower household income, and lower maternal education, are more likely to present with impairments in growth and lower performance on IQ testing. This study highlights the need to screen for food insecurity as early identification and intervention may improve CKD-related health outcomes. Further analyses will investigate the impact of food insecurity on longitudinal outcomes of CKD progression and cardiovascular factors.

Funding: NIDDK Support

SA-PO358

Performance of CKD-EPI GFR Estimating Equations in a Cohort of Young Adults with Pediatric CKD

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Background: The Chronic Kidney Disease in Children (CKiD) study previously documented an overestimation bias by the 2009 age-sex-race CKD-EPI eGFR among young adults aged 18 to 24 with a history of pediatric CKD. However, the recently updated 2021 race-free CKD-EPI equations have not been evaluated among young adults with a history of pediatric CKD.

Methods: Using CKiD data from young adults 18 to 25 years, we evaluated three CKD-EPI equations: 2021 SCr (with age and sex; AS), 2012 CysC, and the 2021 SCr-CysC (AS) Bias (eGFR - mGFR), accuracy (proportion within 10% and within 30%) and root mean square error (RMSE) were estimated.

Results: Among 313 person-visits, the median age was 19.4 years [IQR: 18.6, 20.6] and the median mGFR was 44.8 ml/min|1.73m^2 [IQR: 31.3, 65.1]. Table 1 summarizes agreement metrics. The average biases were +8.81 (95%CI: +7.09, +10.53), +3.73 (+2.04, +5.41), and +4.31 (+2.84, +5.78) for the SCr, CysC, and combined CKD-EPI equations, respectively. The proportion of eGFR within 30% of mGFR was 69.0%, 78.3% and 81.5%, respectively. The lowest RMSE was observed for the combined equation (11.75) and the creatinine-based and cystatin c-based equations RMSEs were 14.83 and 14.03, respectively.

Conclusions: Application of the new CKD-EPI SCr equation to CKiD data demonstrated overestimation of measured GFR and high root mean square errors. The cystatin-based and combination equations performed better than creatinine alone. As previously published, the race-free CKiD U25 equations had no significant bias (range: -0.89 to +0.70) and p30 between 85-90% among young adult participants, but performance is expected to be better in internal validation because it randomly differed from the data used to develop the U25 eGFR. For pediatric CKD patients transitioning to adulthood, care needs to be exercised when using disparate equations that yield abrupt differences in estimates of GFR. Use of U25 eGFR through 25 years is recommended for this population.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

Agreement between CKD-EPI eGFR and mGFR (bias, p10, p30, and root mean square error (RMSE) among 208 young adults participants in CKiD (≥ 18 years) with 313 assessments of mGFR

CKD-EPI eGFR	eGFR – mGFR (95% CI)	p10: eGFR within 10% of mGFR	p30: eGFR within 30% of mGFR	RMSE ml/min|1.73m2
2021 SCr-only	8.81 (7.09, 10.53)	26.2%	69.0%	14.83
2012 CysC only	3.73 (2.04, 5.41)	30.0%	78.3%	14.05
2021 SCr- and CysC-combined	4.31 (2.84, 5.78)	37.4%	81.5%	11.75

SA-PO359

Development of an Adaptive Clinical Web-Based Prediction Tool for Kidney Replacement Therapy in Children with CKD

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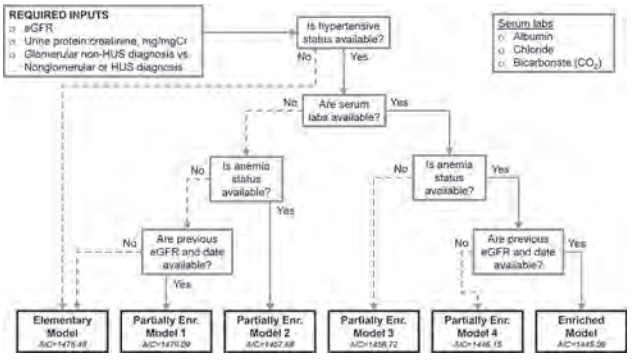
Background: Clinicians need improved prediction models to estimate time to kidney replacement therapy (KRT) for children with chronic kidney disease (CKD). We aimed to a) develop and validate a prediction tool using clinical variables for time to KRT from the Chronic Kidney Disease in Children (CKiD) study using statistical learning methods and b) to design an online calculator for clinical use.

Methods: We constructed an elementary model using eGFR, proteinuria and diagnosis as predictors in a parametric generalized gamma (GG) survival model and used penalized likelihood to identify optimal nonlinear combinations of these three. We then used random survival forest (RSF) to identify additional candidate predictors from a large panel of demographics and clinical markers. From the top predictors we used best subset selection, a learning method, to identify the best combination in an enriched GG model.

Results: Among 890 children, 9 candidate predictors were identified from 172 variables in RSF which were added to the elementary model. Best subset selection yielded an enriched model additionally based on blood pressure, 1 year change in eGFR, anemia, albumin, chloride and bicarbonate. Four additional partially enriched models were constructed for clinical situations with incomplete data and integrated as an adaptive tool (Figure). Discrimination was high in cross-validation (c= 0.86) and in an external European cohort (c= 0.85) with strong calibration. We designed an adaptive online tool for clinical use.

Conclusions: This clinical prediction tool for time to KRT in children was developed in a large, representative pediatric CKD cohort with an exhaustive evaluation of potential predictors and statistical learning methods. While models performed well internally and externally, further external validation of enriched models is needed.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI, Other U.S. Government Support



Decision tree describing adaptive prediction model based on availability of data. AIC statistics reported for each model (lower corresponds to lower error).

SA-PO360

Validating CKiD U25 eGFR Equations for Differing Body Habitus

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Background: The Chronic Kidney Disease in Children (CKiD) U25 eGFR equations provide unbiased estimates of glomerular filtration rate (eGFR) and strong levels of agreement with measured GFR (mGFR) for CKD patients 1-25 years old. However, the performance of these equations by body habitus has not been assessed.

Methods: Data were from the CKiD U25 validation set comprising 832 observations from 302 participants. Median age was 12 [IQR: 8,16] years and iohexol mGFR was 44 [32,61] mL/min/1.73m^2. We evaluated three U25 equations: creatinine, cystatin C and the average of the two. Within BMI categories (underweight, normal weight, overweight, obese), we summarize agreement as mean bias (eGFR-mGFR) and percent of eGFR within 30% of mGFR (P30). Mean bias was calculated from a mixed effects model to account for multiple observations per participant.

Results: All equations overestimated GFR in underweight subjects with the two cystatin C-based equations exhibiting statistically significant biases which persisted after adjusting for sex, age and GFR level. All equations underestimated GFR in overweight subjects but these biases were not significantly different than those in the normal weight subjects after adjustment. There was no bias observed in the obese category, suggesting this bias may not be a direct function of larger body habitus for age and sex. All three equations yielded lower P30 values in underweight compared to non-underweight subjects.

Conclusions: U25 eGFR slightly overestimated mGFR in underweight compared to non-underweight subjects, with U25 eGFR(cr) exhibiting the smallest bias of the three equations in this BMI group. The U25 equations performed well in non-underweight children, adolescents and young adults with CKD.

Funding: NIDDK Support, Other NIH Support - NICHD, NHLBI

	BMI Category			
	Underweight	Normal	Overweight	Obese
N subjects (observations)	44 (65)	204 (485)	87 (138)	63 (144)
Mean Bias (eGFR-mGFR), mL/min/1.73m2, Est. (95%CI)				
U25 eGFR(cr)	1.7 (-0.7, 4)	0.0 (-1.2, 1.2)	-2.0 (-3.8, -0.2)	2.1 (-0.4, 4.6)
U25 eGFR(cysC)	4.6 (1.8, 7.5)	-0.8 (-1.8, 0.2)	-2.0 (-3.8, -0.2)	-1.7 (-3.8, 0.5)
U25 eGFR(avg)	3.1 (0.9, 5.2)	-0.3 (-1.2, 0.6)	-2.0 (-3.5, -0.4)	0.1 (-1.7, 1.9)
P30: % eGFR within 30% of mGFR				
U25 eGFR(cr)	79%	88%	91%	81%
U25 eGFR(cysC)	75%	88%	90%	84%
U25 eGFR(avg)	80%	92%	95%	90%

1. Calculated from intercept only mixed effects model of eGFR-mGFR with subject-specific random intercept.

SA-PO361

Neonatal Risk Factors for CKD Progression in Children

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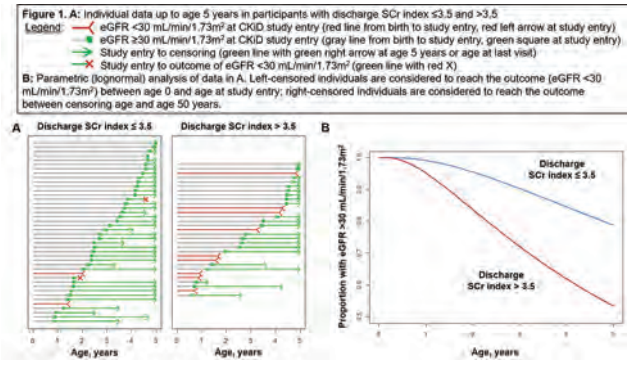
Background: Neonatal risk factors for childhood CKD include prematurity, acute kidney injury (AKI), and sepsis. It is not known how these factors, assessed in the 1st 90 days of life, are associated with early childhood kidney function in children with congenital kidney diseases.

Methods: Neonatal data including gestational age (GA); AKI or sepsis in first 90 days; and serum creatinine (SCr) at discharge was retrospectively collected on Chronic Kidney Disease in Children (CKiD) cohort study participants with congenital anomalies of the kidneys and urinary tract and other congenital kidney diseases. Participants with ≥1 CKiD study eGFR in follow up were included. SCr at NICU discharge was indexed to published mean SCr for GA and postnatal age (PMID: 34142253). We assessed univariate relationships between each predictor and incidence of eGFR<30 mL/min/1.73m^2 by age 5 years (eGFR<30$_{5y}$) and parametric survival for time to eGFR<30 mL/min/1.73m^2 (eGFR<30).

Results: 123 children (71% male; median [IQR] baseline age 3.0 [1.7, 4.3] y) had available neonatal data. 36% were premature (GA<37 weeks). Median [IQR] birth weight was 3.13 [2.60, 3.46] kg; discharge age was 21 [7, 40] days;median discharge SCr was 1.00 [0.65, 1.55] mg/dL; discharge SCr index was 3.3 [2.0, 4.5]. 40% had history of AKI; 13% had history of sepsis. Prematurity, AKI, and sepsis were not associated with risk of eGFR<30$_{5y}$. SCr index >3.5 at discharge was associated with 52% earlier time to eGFR<30. Cumulative incidence of eGFR<30$_{5y}$ was 21% for participants with discharge SCr index ≤3.5 and 47% for those with discharge SCr index >3.5 **(Figure 1)**.

Conclusions: SCr index >3.5 by 90 days of age was associated with a significantly higher risk of eGFR <30 mL/min/1.73m^2 by age 5 years in children with congenital kidney diseases in the CKiD cohort. Prematurity, AKI, and sepsis were not associated with CKD progression risk in this cohort.

Funding: NIDDK Support



SA-PO362

Ultrasound-Based Machine Learning Model and Renal Parenchymal Area as Predictors of Kidney Function Decline in Children with CKD

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Background: Few prediction models of kidney function decline include imaging features. Here, we apply machine learning-derived renal ultrasound features and compare the performance to renal parenchymal area (RPA) in the Chronic Kidney Disease in Children (CKiD) cohort study.

Methods: We determined the predictive performance of a previously developed machine learning algorithm among 119 subjects with non-glomerular chronic kidney disease (CKD) enrolled at 14 sites in the prospective CKiD study. The primary outcome was CKD progression defined as initiation of renal replacement therapy or 50% decline of estimated glomerular filtration rate (eGFR) assessed by the CKiD U25 equation. We assessed the predictive performance of three different models: (1) Clinical model (CM), (2) Deep Learning model (DLM), and (3) Deep Learning +Clinical model (DL+CM). The CM included baseline clinical features: age, eGFR, systolic blood pressure, urine creatinine, urine protein, and serum creatinine. The DLM used features extracted automatically from the first available kidney ultrasound. In a subset of 46 subjects, we compared the performance of ensembled models (3) DL+CM to (4) RPA +Clinical model (RPA +CM). The RPA model included age and the mean RPA values measured by an attending urologist and nephrologist blinded to outcomes. We used a random survival forest model to estimate CKD progression.

Results: Ninety-one subjects with a median age of 11.5 months, IQR [0.2, 78.2] at ultrasound were included in the DL+CM. CKD progression occurred for 20% over a median follow-up of 9 yrs, IQR [3.8,9.7]. For the subset of 46 subjects, median age at ultrasound was 9.7 months, IQR [1.4, 79.3] and CKD progression occurred in 28% over a median follow-up of 6.4 yrs IQR[4.1, 9.2]. Of the models presented, the DL+CM and RPA+CM had the best performance with C-index of 0.74 and 0.77, respectively.

Conclusions: Our ensemble models accurately predicted CKD progression using imaging features in children with CKD. The comparison of the performance of deep learning features and RPA was limited by the small sample size. These results in a prospectively enrolled cohort suggest that *early* ultrasound imaging features could identify children at greatest risk of CKD progression in clinical practice.

Funding: NIDDK Support

SA-PO363

Ultrasound Evaluation of Fibrosis in Pediatric Kidney Transplant Recipients

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Background: To evaluate doppler resistive indices, ultrasound elastography, and contrast ultrasound as imaging biomarkers of fibrosis in pediatric kidney transplants.

Methods: A prospective study of children with kidney transplant and healthy controls was conducted from February 2020 to May 2023. All subjects underwent ultrasound with spectral Doppler to measure resistive indices (RI) and shear wave elastography to assess renal stiffness. RIs were assessed in the upper, interpolar, and lower poles and median elastography values were averaged from 10 regions of interest. Kidney transplant recipients undergoing clinically indicated biopsies underwent contrast-enhanced ultrasound (CEUS) and Time-Intensity Curves were generated. CEUS time to peak, peak enhancement, perfusion index, area under the curve, and mean transit time were examined. All kidney allografts were classified as with interstitial fibrosis and tubular atrophy (IFTA) or without IFTA based on histopathology. Subjects with rejection were excluded. Kruskall-Wallis was used to compare RI and elastography between the three groups. Dunn test was used for post-hoc analysis. For the CEUS studies, Mann-Whitney analysis was used to compare allografts without vs. with fibrosis.

Results: 16 healthy control kidneys were examined among 8 subjects with median age 14.5 yrs. Among 11 kidney allografts, six (54.6%) were from living donors; median recipient age 16 yrs. Of the 11 allografts, 4 (33.3%) had IFTA (all grade 1). We found no difference in resistive indices (p=0.53) between allografts without vs. with fibrosis, or controls. Elastography measures differed between controls and all allografts (p=0.01); but did not differ between allografts with or without fibrosis. Among subjects with CEUS, mean transit time was the only parameter significantly prolonged in the allografts with fibrosis (vs. those without) (p=0.04).

Conclusions: In this cohort, RIs did not differ between groups. Tissue stiffness, by elastography, differed between controls and allografts but not between those with and those without fibrosis. CEUS detected differences in mean transit time between allografts with vs. without fibrosis, suggesting CEUS may be a sensitive biomarker to detect fibrosis. A larger sample and longitudinal data are needed for validation.

Funding: NIDDK Support

SA-PO364

Longitudinal Changes of Left Ventricular Diastolic Function and Fibroblast Growth Factor 23 in Young Hemodialysis Patients

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Background: Left ventricular diastolic dysfunction (DD) occurs early in patients on hemodialysis. Both traditional factors like hypertension and non-traditional factors including fibroblast growth factor-23 (FGF23) levels, erythropoietin, and treatment with vitamin D receptor activators such as paricalcitol may affect the progression of DD. Our objectives were to investigate the association of longitudinal changes of diastolic function with FGF23 levels and treatment with paricalcitol and erythropoietin in young dialysis patients.

Methods: Conventional and tissue Doppler imaging measurements and their respective age-adjusted Z-scores were used to measure early (E), late (A) diastolic transmitral flow velocities, corresponding mitral annular tissue velocities (e' and a'), and to evaluate DD in 20 young hemodialysis patients age 16.7±3.6 years. DD was defined as an abnormal Z-score of E, A, E/A or E/e' ratios. We analyzed associations of longitudinal DD changes with sequentially measured FGF23 levels, and with doses of erythropoietin and paricalcitol administered while on maintenance hemodialysis throughout a period of 7.1 ± 2.1 months.

Results: Compared with the standardized healthy age-matched controls, echocardiographic markers of diastolic function by Z-score cutoff revealed DD in 93% at baseline and 90% at follow-up. FGF23 levels were markedly elevated at baseline and follow up (25,238 ± 30,244 and 19,153 ± 25,191 RU/ml, respectively). FGF23 levels correlated only with the baseline mitral E/e' ratio, but not with any other measurement of diastolic function. Hypertension correlated with DD. Paricalcitol dose was associated with improved diastolic function while erythropoietin dose showed no correlation with FGF23 levels or diastolic function.

Conclusions: In young hemodialysis patients, DD is highly prevalent. Elevated FGF23 levels and hypertension may contribute to DD. Erythropoietin is neither associated with FGF23 levels nor with DD while paricalcitol may attenuate DD.

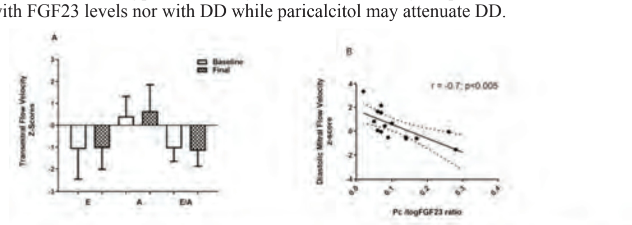

Figure A. Diastolic Function Z scores by Conventional Echocardiography in Hemodialysis Patients. The figure shows baseline and final transmitral early (E) and late (A) filling flow velocities and the E/A ratio obtained by 2-D imaging. Data expressed as Z-scores, average ± standard deviation.

Figure B. Regression of diastolic functional marker of late transmitral flow velocity z-score with the paricalcitol (Pc) dose. The Pc/log FGF23 ratio represents the Pc dose (µg/kg/week) divided by the calculated log FGF23 value.

SA-PO365

Urine Proteomic Profiling and Insights into CKD Progression in Children

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Background: Chronic kidney disease (CKD) progresses to end stage kidney disease (ESKD) and is associated with mortality rates that are 30-150 times higher than in the general pediatric population. We hypothesized that large scale proteomic measurements may provide insights to the molecular basis of CKD progression in children and may identify therapeutic protein targets.

Methods: In the CKiD Cohort Study, children with CKD were enrolled and eGFR was assessed annually. Among participants with an eGFR of 60-90 ml/min/1.73m^2 at baseline, 22 CKiD participants with CKD progression were matched by subtype of kidney disease to 22 CKiD participants without CKD progression. The primary outcome of CKD progression was defined as a composite of 50% decline in eGFR or ESKD. We measured 2904 urine proteins collected at the 6 month visit after enrollment using the Olink Proteomics Explore Assay.

Results: Of the 44 children included, the median age was 12 years, 66% were male, 68% had a glomerular cause of CKD, and baseline eGFR was 68 [IQR, 63, 81] ml/min/1.73m^2. In the full cohort, 38/2904 proteins were statistically significantly different (p-value cutoff of 0.000017 using the Bonferroni correction) when comparing those with CKD progression to those without CKD progression (Table). B-cell activating factor, Complement 2 (C2), and C5, all druggable targets, were more than 10-fold higher in children with CKD progression relative to those without progression. Pathway analyses demonstrated that TGF-β1, TNF, IL-1β, IL-4, IFN-γ, and angiotensinogen were key pathways activated in children with CKD progression.

Conclusions: Many urine proteins were elevated, and pro-inflammatory and pro-fibrotic pathways were upregulated in children with CKD progression. The application of large-scale proteomics to the study of CKD in children may inform pathomechanisms and identify new therapeutic targets.

Funding: NIDDK Support

Protein Symbol	Protein Name	Log Ratio	Location	Protein Type	Biomarker Application	Specific Drugs	p-value
AHSP	alpha hemoglobin stabilizing p	-4.31	Cytoplasm	other			1.54E-08
CNDP1	carnosine dipeptidase 1	-4.757	Cytoplasm	peptidase			5.21E-08
FABP4	fatty acid binding protein 4	-4.838	Cytoplasm	transporter	disease progression		2.07E-07
PPBP	pro-platelet basic protein	-3.640	Extracellular Space	cytokine			1.17E-07
TNFSF13B	TNF superfamily member 13b	-3.453	Extracellular Space	cytokine	efficacy,response to thera	belimumab,tabalumab,telitacice	3.11E-07
SERPINB8	serpin family B member 8	-2.820	Cytoplasm	other			4.23E-07
CA1	carbonic anhydrase 1	-3.248	Cytoplasm	enzyme		acetazolamide,benzthiazide	6.93E-07
BLVRB	biliverdin reductase B	-2.958	Cytoplasm	enzyme			6.71E-07
AMBP	alpha-1-microglobulin/bikunin	-4.241	Extracellular Space	transporter	safety,unspecified application		7.74E-07
PAGR1	PAXIP1 associated glutamate	-1.437	Nucleus	other			1.05E-06
FETUB	fetuin B	-3.582	Extracellular Space	other			1.27E-06
LIF	LIF interleukin 6 family cytoki	-3.378	Extracellular Space	cytokine	unspecified application		1.54E-06
SERPINA3	serpin family A member 3	-3.550	Extracellular Space	other	unspecified application		2.26E-06
TMSB10/TMSB4X	thymosin beta 4 X-linked	-2.144	Cytoplasm	other	diagnosis		3.33E-06
C2	complement C2	-2.422	Extracellular Space	peptidase			3.44E-06
PRSS2	serine protease 2	-4.008	Extracellular Space	peptidase			4.76E-06
C5	complement C5	-3.550	Extracellular Space	cytokine		[illegible]	4.91E-06
PDGFRA	platelet derived growth factor r	1.536	Plasma Membrane	kinase	efficacy,prognosis,safety	[illegible]	5.37E-06
ITIH5	inter-alpha-trypsin inhibitor he	-3.546	Extracellular Space	other			6.11E-06
KLK1	kallikrein 1	0.962	Cytoplasm	peptidase		[illegible]	6.40E-06
LCN15	lipocalin 15	-2.581	Other	other			8.74E-06
CXADR	CXADR Ig-like cell adhesion m	-2.232	Plasma Membrane	transmembrane receptor			9.04E-06
ABHD14B	abhydrolase domain containin	-2.758	Cytoplasm	enzyme			9.85E-06
APOA1	apolipoprotein A1	-1.600	Extracellular Space	transporter	diagnosis,efficacy,unspeci	[illegible]	1.34E-05
MB	myoglobin	-4.31	Cytoplasm	transporter	diagnosis,safety,unspecified application		1.29E-05
OSMR	oncostatin M receptor	-4.757	Plasma Membrane	transmembrane r	diagnosis,efficacy,unspecified application		1.34E-05
TNR	tenascin R	-5.83	Plasma Membrane	other			1.37E-05
JUN	Jun proto-oncogene, AP-1 tra	-1.251	Nucleus	transcription reg	prognosis,unspecified application		1.28E-05
CA2	carbonic anhydrase 2	-4.211	Cytoplasm	enzyme		acetazolamide,benzthiazide	1.34E-05
BTN2A2	butyrophilin subfamily 2 mem	-1.752	Plasma Membrane	other			1.35E-05
APOA4	apolipoprotein A4	-1.432	Extracellular Space	transporter	unspecified application		1.16E-05
FABP5	fatty acid binding protein 5	-2.367	Cytoplasm	transporter			1.30E-05
MBL2	mannose binding lectin 2	-3.579	Extracellular Space	other	diagnosis,efficacy		1.42E-05
ALCAM	activated leukocyte cell adhes	-2.24	Plasma Membrane	other	prognosis	[illegible]	1.53E-05
CBLN4	cerebellin 4 precursor	-1.320	Extracellular Space	other			1.55E-05
MSLN	mesothelin	-2.371	Extracellular Space	other	diagnosis,prognosis,unspe	[illegible]	1.74E-05
DPEP2	dipeptidase 2	-2.478	Plasma Membrane	peptidase			1.74E-05
IL1RAP	interleukin 1 receptor accesso	-2.760	Plasma Membrane	transmembrane receptor		CAN04	1.75E-05

Log Ratio is the Normalized Protein Expression (NPX) units (derived from count values) in log base 2 units of CKD Non-Progressors minus CKD Progressors

Top proteins of CKD progression by adjusted p-value using the Olink Proteomic Assay

SA-PO366

Serum FGF23 and Urinary Neutrophil Gelatinase-Associated Lipocalin (NGAL) Correlation with Glomerular Filtration Rate, Measured with a Reference Technique in Children with CKD

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Background: Prognosis of chronic kidney disease (CKD) is closely related to early diagnosis and initiation of nephroprotective measures. Current kidney injury biomarkers are suboptimal for predicting kidney disease progression. Fibroblast Growth Factor 23 (FGF23) is well described as an early marker that increases proportionally to worsening CKD stages in adults. Neutrophil gelatinase-associated lipocalin (NGAL) is known to increase early after acute kidney injury, as a marker of AKI severity, however, it has not been validated as an early marker in CKD. The aim of this study is to investigate the association between FGF23, NGAL and glomerular filtration rate (GFR) in children and evaluate their role in ascertaining moderate to severe CKD.

Methods: Children aged 5 to 20 years old requiring kidney function assessment following primary nephropathy, solid organ transplantation or secondary nephropathy were recruited prospectively in a tertiary hospital of Switzerland for a reference measure of their GFR, with simultaneous measurement of plasma FGF23 and urinary NGAL.

Results: 123 clearances were analyzed, in children mostly post solid organ transplantation (46%) or with primary nephropathy (37%). 42% had stage I CKD, 40% had stage II CKD and 12% had stage III or IV CKD. FGF23 was significantly higher in stage III or IV CKD (mean: 282.02 UI/ml ± 174.71) compared to stage I (mean: 143.76 UI/ml ± 178.61 ; p<0.001) or stage II (mean: 104.61 UI/ml ± 63.52; p<0.001). The area under the ROC curve for FGF23 to discriminate CKD stages I-II versus III-IV was 0.864 (95% confidence interval (CI): 0.780-0.947). NGAL values were more elevated in stage III or IV CKD (mean: 103.65 UI/ml ± 129.43) compared to stage I (mean: 36.19 UI/ml ± 100.36 ; p=0.016) or stage II (mean: 44.86 UI/ml ± 104.66; p=0.082). The area under the ROC curve for NGAL to discriminate CKD stages I-II versus III-IV was 0.688 (95% CI: 0.512-0.864).

Conclusions: FGF23 is significantly associated with decreasing GFR in children and discriminates for the presence of moderate to severe CKD in children. NGAL was not as strongly associated to decreasing GFR. Further studies are needed to evaluate FGF23 and NGAL as markers of CKD progression.

SA-PO367

Association Between N-Terminal pro-B-Type Natriuretic Peptide with CKD Progression in the CKD in Children Cohort

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Background: Elevations in the serum biomarker N-terminal pro B-type natriuretic peptide (NT-proBNP) are strongly associated with CKD progression in adults. It is unknown whether these associations are also seen in children with CKD, and may help identify a novel risk factor in this population. The objective of this study was to examine the association of NT-proBNP with CKD progression in youth with mild to moderate CKD.

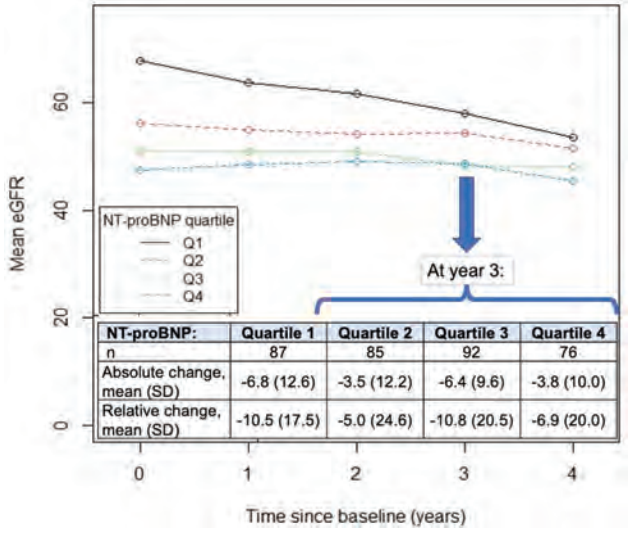
Methods: We measured serum NT-proBNP at the baseline visit of participants with available samples enrolled in the Chronic Kidney Disease in Children (CKiD) study (N=493). Included participants were aged 1-18 years with an eGFR of 30-90mL/min/1.73m^2. Exclusion criteria included history of kidney transplant, dialysis < 3 months, or structural heart disease. CKD progression was defined as a 40% decline in eGFR and/or progression to ESKD. We utilized nested Cox proportional hazards models to test the association between baseline NT-proBNP with CKD progression.

Results: Mean ±SD baseline NT-proBNP and eGFR were 127 ±173pg/mL and. 55 ±21mL/min/1.73m^2, respectively. Median duration of follow-up was 3.9 years and 107 (22%) met criteria for CKD progression. In unadjusted models, NT-proBNP was

associated with CKD progression (HR, [95% CI] per doubling: 1.36, [1.18, 1.56]). NT-proBNP was not associated with CKD progression in adjusted models (HR, [95% CI] per doubling: 1.06 [0.87, 1.29]). There was no interaction for participants with an eGFR above or below 45mL/min/1.73m2 (p= 0.84). Absolute and relative decline in eGFR was not different across baseline quartiles (**Figure 1**).

Conclusions: Unlike adults with CKD, NT-proBNP was not associated with CKD progression in a large, well-characterized cohort of youth with CKD. Potential explanations include physiologic differences across the lifespan and/or relatively short duration of follow-up.

Funding: Private Foundation Support



NT-proBNP:	Quartile 1	Quartile 2	Quartile 3	Quartile 4
n	87	85	92	76
Absolute change, mean (SD)	-6.8 (12.6)	-3.5 (12.2)	-6.4 (9.6)	-3.8 (10.0)
Relative change, mean (SD)	-10.5 (17.5)	-5.0 (24.6)	-10.8 (20.5)	-6.9 (20.0)

SA-PO368

Racial Differences in Outcomes in Children on Maintenance Dialysis Enrolled in the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS)

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Background: The NAPRTCS dialysis registry includes 8923 children from the last 30 years. We aim to describe racial differences in this cohort.

Methods: Children on maintenance dialysis at a NAPRTCS center are enrollment eligible. Demographic and clinical data are obtained at dialysis initiation and every 6-months until dialysis terminates. Before 2018 race was categorized as white, black or Hispanic, but race (white, black, other) and ethnicity are now separate. Outcomes include dialysis modality, cardiovascular health, time to transplant and survival.

Results: Table 1 shows clinical characteristics at dialysis initiation. There were more white than black children on both peritoneal dialysis (PD) and hemodialysis (HD), although a higher % of blacks were on HD. Those initiating HD with catheter access were more likely white than black (43% vs 29%); no racial difference with AV fistulas (36% white and 36% black). Mean Kt/V and URR were higher for non-black than black race on HD (1.61 vs 1.55, and 72.6 vs 70.7), with similar findings for PD mean Kt/V (2.45 non-black vs 2.14 black). More blacks than non-blacks had hypertension (48% vs 35%), left ventricular hypertrophy (32% vs 29%), and hypercholesterolemia (60% vs 20%). Over time, whites were transplanted more than blacks when listed for deceased donor transplants (50% vs 30% at 12 months; 87% vs 75% at 36 months). In those remaining on dialysis, survival was slightly higher for blacks than whites (89% vs 86% at 36 months).

Conclusions: White children have higher rates of kidney developmental anomalies, whereas racial differences are absent with FSGS frequency. Whites receive PD more than non-whites, whereas blacks receive HD at higher rates. Whites are more likely to initiate HD with catheter access. Regardless of modality, blacks demonstrate lower dialysis adequacy and more cardiac health sequelae. Whites are transplanted quicker than blacks. In children remaining on dialysis, 36 month survival is near 90% in both blacks and whites. Further study is needed to understand these disparities and to ensure optimal outcomes for all chronically dialyzed children.

	N	White	Black	Hispanic	Other
Dialysis Registrants	8923	49%	24%	19%	8%
Known Primary Diagnosis					
Hypoplasia/Dysplasia	1361	54%	19%	20%	7%
FSGS	1271	39%	39%	16%	6%
Known Initial Modality					
Peritoneal Dialysis	4616	53%	20%	20%	7%
Hemodialysis	3151	42%	30%	19%	9%

SA-PO369

Health-Related Quality of Life for Pediatric Patients with ESKD: A Systematic Review and Meta-Analysis of the PedsQL™

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Background: Health-related quality of life (HRQoL) studies demonstrate the impact of end-stage kidney disease (ESKD) on children's physical and psychosocial development. While several instruments measure HRQoL, few have standardized domains specific to pediatric ESKD. This review examines the published literature on the HRQoL among children with ESKD across differing renal replacement therapy (RRT) modalities, providing insight into the holistic care for these patients.

Methods: We conducted a literature review on pediatric HRQoL using the PedsQL™ 4.0 Generic Core Scale and the PedsQL™ 3.0 ESKD Module among 5 to 18-year-old patients. We queried PubMed, Embase, Web of Science, CINAHL, and Cochrane databases. Retrospective, case-controlled, and cross-sectional studies encompassing self/parent-reported PedsQL™ dimensional and total HRQoL scores were collected.

Results: Of 435 identified studies, 14 met the inclusion criteria. Meta-analysis demonstrated a significantly higher total HRQoL for healthy patients over those with ESKD [SMD: 1.44 (95% CI: 0.78 - 2.09); p<0.001] and across all dimensional scores. In addition, kidney transplant patients report a significantly higher total HRQoL than those on dialysis [PedsQL™ GCS, SMD: 0.33 (95% CI:0.14 - 0.53); p<0.001] and [PedsQL™ ESKD, SMD: 0.65 (95% CI: 0.39 - 0.90); p<0.001]. Kidney transplant patients also reported greater physical health scores than those on dialysis in self and parent/proxy reports of the PedsQL™ GCS [SMD: 0.51 (95% CI: 0.32 – 0.69); p<0.001] and [SMD: 0.30 (95% CI: 0.01 – 0.59); p=0.041], respectively.

Conclusions: Patients with ESKD report lower HRQoL in physical and psychosocial domains when compared to healthy controls. Pediatric transplant recipients showed better total HRQoL than dialysis patients, regardless of the specific modality, as observed on both PedsQL™ scales. This analysis demonstrates the need to identify areas of impaired functioning and produce congruent clinical recommendations.

Quality of Life Domains	Standardized Mean Difference (95% CI)	P	I^2 (95% CI); p-value
PedsQL™ 4.0 Generic Core Scales Total HRQoL			
Control (n=533) vs ESKD (n=330)	1.44 (0.78 - 2.09)	<0.001	93.36% (83.97% - 97.25%); p<0.0001
Transplant (n=285) vs Dialysis (n=192)	0.33 (0.14 - 0.53)	<0.001	27.89% (0.00% - 68.88%); p=0.2155
PedsQL™ 3.0 ESKD Module			
Transplant (n=148) vs Dialysis (n=127)	0.65 (0.39 - 0.90)	<0.001	0.00% (0.00% - 79.73%); p = 0.4249
Peritoneal Dialysis (n=49) vs Hemodialysis (n=17)	0.86 (0.27 - 1.45)	0.005	0.00% (0.00% - 21.0%); p=0.5150

SA-PO370

Clinical Outcomes in Children on Maintenance Dialysis: A Report of the North American Pediatric Renal Trials and Collaborative Studies (NAPRTCS) Registry

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Background: The NAPRTCS dialysis registry includes data on 8923 children receiving chronic dialysis.

Methods: Children on maintenance dialysis at any NAPRTCS center are eligible for registry enrollment. Data is collected at dialysis initiation and at 6-month intervals until dialysis termination. Clinical characteristics and outcomes compared across eras: 1992-2000, 2001-2010, 2011-2020.

Results: Hemodialysis (HD) as the initiating dialysis modality increased (34% in 1992-2000 versus 54% in 2011-2020), while peritoneal dialysis (PD) decreased (66% to 40%). HD catheters are placed in the jugular vein more often (87% in 2010-2020 vs 51% in 1992-2020). Use of double cuffed swan neck PD catheters placed with a downward oriented exit site increased over time (5% to 25%). Mean eGFR at dialysis initiation increased from 9.2 (1992-2000), to 11.2 (2011-2020) ml/min/1.73M2. Obesity has increased over time (17% affected 2010-2020). Hypertension was common regardless of the era (35% in 2010-2020 vs 39% for entire cohort). Height remains suboptimal, with average height Z scores of -1.34 within a month of dialysis initiation falling to -1.62 at 24 months, with growth hormone use in 30% of PD and 16% of HD children. Survival at 36 months of dialysis was > 90% with children initiating dialysis > 6 years old vs 77% initiating < 1 year old. A Cox proportional hazards model adjusted for age at initiation showed survival improved with initiation after 2000 (p<0.01). Infection accounted for 22% of deaths on dialysis in 1992-2000 but only 15% in 2011-2020, whereas cardiopulmonary causes of death stayed steady at 22%. Death from infection was higher in PD vs HD (23% vs 12%, p <0.01), though annualized rates for peritonitis fell from 0.93 (95%CI: 0.89-0.98) between PD initiations in 1992-1996 to 0.28 (0.21-0.35) between 2017-2022.

Cumulative incidence of transplant from the deceased donor waiting list increased, from 0.80 (95% CI: 0.75-0.84) in 1992-2000 to 0.91 (0.81-0.96) in 2011-2020.

Conclusions: Although survival on chronic dialysis has improved significantly over 30 years, hypertension, obesity, and growth delay in dialyzed children remain common morbidities. Infection rates and related mortality has decreased, but cardiopulmonary mortality has not, highlighting areas that can be improved upon in the future.

SA-PO371

Follow-Up of Low Estimated Glomerular Filtration Rate (eGFR) in Children in the US Military Health System (MHS)

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Background: For children, calculation of eGFR from serum creatinine (sCr) is typically not available in the electronic record and clinicians may fail to recognize an abnormal eGFR in the absence of previously known kidney disease. We retrospectively analyzed the extent of this issue in a large diverse pediatric population using the MHS Data Repository.

Methods: We extracted data for 1,561,622 children ages 1–17 enrolled in the MHS from 2016-2019, using the CKiD U-25 equation to calculate eGFR. Low eGFR was defined as the first occurrence of either <75 or <60 mL/min/1.73m^2. Follow-up was defined as a repeat sCr ≤90 days after the low eGFR. Children with > 8 sCr measurements or with the first low eGFR obtained ≤90 days from the end of 2019 without follow-up were excluded from analysis.

Results: sCr was measured in 128,033 (8.2%) of children. After exclusions there was at least one eGFR <75 and one <60 mL/min/1.73m^2 in 15,395 (12.0%) and 3168 (2.5%) children, respectively (Table). Follow-up sCr ≤90 days after low eGFR was performed infrequently; it was obtained in 9.7% vs 12.4% of children with eGFR <75 vs. <60 mL/min/1.73m^2, respectively. First follow-up sCr at >90 days were obtained in 13.2% vs.11.6% of children, and no follow-up labs were obtained in 77.1% vs. 76.1%. For eGFR <75 mL/min/1.73m^2, absence of follow-up labs within 90 days was associated with female sex (odds ratio [OR], 95% confidence interval [CI]=1.2, 1.1–1.3), ages 5–9 vs. 1–4 (OR, 95%CI=1.2, 1.03–1.4), ages 10–13 vs. 1–4 (OR, 95%CI=1.3, 1.1–1.6), and Black vs. White race (OR, 95%CI=1.2, 1.1–1.4). Sex, age, and race were not associated with lack of follow-up labs for GFR <60 mL/min/1.73m^2.

Conclusions: In the MHS, follow-up measurements of decreased eGFR in children were infrequent, suggesting a gap in recognition of reduced kidney function and a potential area for improvement. *The views expressed in this abstract are those of the authors and do not reflect the official position of the Henry M. Jackson Foundation for the Advancement of Military Medicine, Inc., the Department of Defense, the Department of Health and Human Services, or the US Government.*

Funding: Other U.S. Government Support

eGFR mL/min/1.73m^2	n	≤ 90 Days Follow-Up n (%)	> 90 Days Follow-Up n (%)	No Follow-Up n (%)
< 75	15,395	1500 (9.7)	2029 (13.2)	11,866 (77.1)
< 60	3168	392 (12.4)	366 (11.6)	2410 (76.1)

SA-PO372

Pediatric Nephrology Workforce in the United States and Access to Waitlist Registration in Children with ESKD

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Background: Nephrology is one of the pediatric subspecialties with the lowest workforce density in the US with minimal improvements noted over the last two decades. Pediatric nephrologists (PN) are critical partners in preparing children for kidney transplantation (KT), which is the preferred treatment modality. We hypothesized that geographic variations in the density of PN could associate with variations in the time to waitlist registration and living donor kidney transplantation (LDKT).

Methods: Retrospective cohort study of children <18 years who developed ESKD between 2016 to 2019 according to the United States Renal Data System. The number of active PN per state was estimated by the American Board of Pediatrics (ABP) in 2022 and state population <18 years was estimated by US Census Bureau Population Estimates in 2021. We examined the association between density of PN per 100,000 children and time to waitlist registration and LDKT using Cox models. Odds of preemptive waitlisting was examined using logistic regression models. All models used cluster (state) robust standard errors.

Results: We included 3,442 children, of whom 2,319 (67.4%) were waitlisted for kidney transplantation. The median density of PN/100,000 children/state was 0.85 (IQR 0.56 -1.19 (see Figure). The median time to waitlist registration was 0.65 years (IQR 0.32-1.16). Children residing in states with > 1 PN/100,000 had a 64% better access to waitlisting (HR:1.64, 95% CI 1.41-1.90); 2.8 times higher odds of preemptive waitlisting (OR:2.80, 95%CI 1.66-4.72) compared with children residing in states with < 0.4 PN/100,000; and 2.31 higher hazard of LDKT (HR: 2.31, 95% CI 1.40-3.82).

Conclusions: Lower density of pediatric nephrologists is associated with worse access to waitlist registration. Further studies to examine the implications of workforce availability and care of children with kidney disease are warranted.

Funding: NIDDK Support

Table 1. Hazard ratio (95% CI) for waitlist registration and odds ratio for preemptive waitlisting

	Pediatric nephrologist per 100,000 children		
	< 0.4	0.4 to 1.0	> 1.0
Waitlist registration			
Unadjusted	1	1.52 (1.25-1.86)	1.85 (1.54-2.23)
Adjusted *	1	1.32 (1.12-1.57)	1.64 (1.41-1.90)
Adjusted**	1	1.56 (1.28-1.90)	1.97 (1.64-2.34)
Preemptive waitlisting			
Unadjusted	1	2.53 (1.46-4.37)	3.28 (1.92-5.63)
Adjusted	1	2.09 (1.22-3.57)	2.80 (1.66-4.72)
Living donor transplantation			
Unadjusted	1	1.87 (1.23-2.82)	2.71 (1.92-3.84)
Adjusted *	1	1.48 (0.84-2.62)	2.31 (1.40-3.82)

* adjusted for age at ESKD onset, ESKD primary cause, neighborhood income, health insurance status.
** including only patients that were evaluated at the same state of residence at the time of dialysis initiation.

Figure 1. Density of pediatric nephrologists per state of US

SA-PO373

Abstract Withdrawn

SA-PO374

Lipid Levels in Pediatric Dialysis Patients with Glomerular and Non-Glomerular Disease

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Background: Children on dialysis have a 10-fold increase in cardiovascular disease (CVD) mortality when compared to the general population. The development of CVD in dialysis patients is in part attributed to progressive blood vessel calcification from CKD-MBD. Patients on dialysis are also more likely to have dyslipidemia, which further increases their risk of cardiovascular disease. While the prevalence of dyslipidemia in adult dialysis patients has been described, there is limited data on risk factors for pediatric dyslipidemia.

Methods: 2,043 pediatric patients (≤21 years) receiving maintenance hemodialysis (HD) or peritoneal dialysis (PD) with at least one lipid panel measurement were obtained from USRDS between 2001 and 2016. Disease etiology was classified as glomerular (n=1,029), non-glomerular (n= 701) and unknown (n= 313) and comparisons were made across etiologies. Linear regression models determined the relationship between disease etiology and log-transformed LDL, HDL, triglyceride (TG) and total cholesterol (TC) levels drawn within 12 months of USRDS entry.

Results: The median(IQR) age of the cohort was 13 (17, 19.4). The majority of the cohort received HD as a primary modality and there were no differences between ESKD etiologies. Adjusting for age, gender, race/ethnicity, modality, time with ESKD and using non-glomerular etiology as the reference, glomerular disease [%(95% CI)] was associated with 21%(14.8, 26.6) higher LDL, 19%(14.7, 23.8) higher TC, and 22.3% (15.5, 29.5) higher TG (p<0.0001 for all). There was no significant difference in HDL.

Conclusions: Pediatric dialysis patients with ESKD from glomerular causes have higher levels of Total Cholesterol, LDL, and Triglycerides compared to children with ESKD from non-glomerular causes. The long-term impact of this unfavorable lipid profile requires further investigation.

Table 1: Baseline cohort characteristics

	Glomerular Etiology	Non-Glomerular Etiology	Unknown Etiology	p-value
N (%)	1029 (50.4%)	701 (34.3%)	313 (15.3%)	
Age, median(IQR), yrs	17.7 (14.5, 19.7)	15.2 (10.6, 18.7)	17.7 (13.6, 19.6)	<0.0001
Sex, n (%)				0.0009
Male	523 (50.8%)	419 (59.8%)	178 (56.9%)	
Female	506 (49.2%)	282 (40.2%)	135 (43.1%)	
Race, n (%)				<0.0001
White	294 (28.6%)	318 (45.4%)	99 (31.6%)	
Black	335 (32.6%)	140 (20.0%)	93 (29.7%)	
Hispanic	331 (32.2%)	211 (30.1%)	107 (34.2%)	
Asian	43 (4.2%)	19 (2.7%)	8 (2.6%)	
Other/Unknown	26 (2.5%)	13 (1.9%)	6 (1.9%)	
Modality, n (%)				0.7
Hemodialysis	750 (73.2%)	506 (73.0%)	235 (75.3%)	
Peritoneal Dialysis	275 (26.8%)	187 (27.0%)	77 (24.7%)	
Insurance, n (%)				0.005
Public	546 (53.1%)	546 (53.1%)	172 (55.0%)	
Private	260 (25.3%)	260 (52.3%)	68 (21.7%)	
None	108 (10.5%)	44 (6.3%)	38 (12.1%)	
Unknown	115 (11.2%)	115 (11.2%)	35 (11.2%)	
Lipid Measurements (median[IQR])				
LDL, mg/dL	108 (78, 140)	87 (65, 111)	91 (67, 126)	<0.0001
HDL, mg/dL	38 (30, 49)	38 (30, 50)	38 (30, 47)	0.4604
Total Cholesterol, mg/dL	183 (146, 232)	162 (130, 192)	163 (135, 200)	<0.0001
Triglycerides, mg/dL	169 (116, 242)	147 (102, 223)	141 (101, 211)	<0.0001

Table 2: Lipid levels by disease etiology.

ref=non-glomerular disease	Glomerular Disease % diff (95% CI)**	Unknown Disease % diff (95% CI)
LDL, mg/dL	+21% (+14.8, +26.6) p<0.0001*	+5.4% (-1.2, +12.4) p=0.1
HDL, mg/dL	-1.4 (-5.4, +2.7) p=0.5	-0.5% (-5.7, +5) 0.8
Total Cholesterol, mg/dL	+19% (+14.7, +23.8) P<0.0001*	+5.9 (+0.72, +11.4) p=0.03*
Triglycerides, mg/dL	+22.3% (+15.5, +29.5) P<0.0001*	+5.7% (-2.1, +14.1) p=0.1

*p<0.05
**percent difference calculated according to the formula [(10^B)-1]x 100.
glomerular vs. non-glomerular disease classified according to Warady, AJKD, 2015
Covariates include race/ethnicity, age, gender, modality and time with esrd

SA-PO375

Persistent Increase in Serum Ferritin Levels Despite Converting to Permanent Vascular Access in Pediatric Hemodialysis Patients: Pediatric Nephrology Research Consortium Study

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Background: Our objective was to examine the change in serum ferritin levels after successful conversion to PVA among children who started hemodialysis (HD) using TCC.

Methods: Retrospective chart reviews were completed on subjects from 20 pediatric HD centers. All patients used TCC prior to PVA. Serum ferritin levels were collected at the creation of PVA and for two years thereafter. Statistical methods included hypothesis testing and statistical modeling after adjusting for relevant demographic variables.

Results: There were 11 (11%) arteriovenous grafts (AVG) and 87 (89%) arteriovenous fistulae (AVF). Their mean TCC use before PVA creation was 10.4± 17.3 months. Serum ferritin at PVA creation was elevated at 562.64± 492.34 ng/ml, further increased to 753.84± 561.54 ng/ml (p= <0.001) at first year and remained significantly elevated at second year 759.60 ± 528.11 ng/ml (p= 0.004). The serum ferritin levels did not show statistically significant linear association with respective serum hematocrit values. In a multiple linear regression model, there were three predictors of serum ferritin at first year PVA follow-up which showed significant association; steroid-resistant nephrotic syndrome as primary etiology (β = -438.93; 95% CI: [-845.41, -32.46]; p=0.035), being from a center enrolling >10 cases (β = 319.85; 95% CI: [2.02, 637.68]; p=0.049) and baseline serum ferritin level (β = 17.96; 95% CI: [3.38, 32.53]; p=0.017).

Conclusions: Increasing serum ferritin after conversion to PVA is concerning. This increase is not associated with serum hematocrit trends. Future studies should investigate the correlation of serum transferrin saturation and ferritin levels in pediatric HD patients.

SA-PO376

Exploring the Value of Assessing Hydration and Nutritional Status with Bioelectrical Impedance Analysis in Pediatric Chronic Dialysis

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Background: There is a lack of domestic and international clinical studies on the assessment of the hydration and nutritional status of children on dialysis by bioimpedance analysis-body composition monitor (BIA-BCM).

Methods: Children treated on dialysis in the nephrology department of the Children's hospital of Fudan University between July 1, 2021 and December 31, 2022 were assigned. A total of 100 children were described before and after 3 days of their dialysis, including basic information, biochemical indicators, imaging findings, and BIA-BCM indicators, exploring the correlation between BIA-BCM indicators and clinical indicators.

Results: Totally, 86 children with peritoneal dialysis and 14 children with hemodialysis were included. In peritoneal dialysis group, 19.77% and 36.05% had mild and severe water overload ; reduced LTI in 41.54% and increased LTI in 10.77%. In hemodialysis group, 35.71% with mild and severe water overload each; 3 cases with reduced LTI (Fig1). There was a significant linear relationship between BIA-BCM hydration indicators and clinical hydration indicators, and BIA-BCM nutritional indicators and clinical nutritional indicators (Fig2).

Conclusions: BIA-BCM can help guide the adjustment of clinical treatment regimens, and chronic dialysis children have some degree of improvement in hydration and nutritional status.

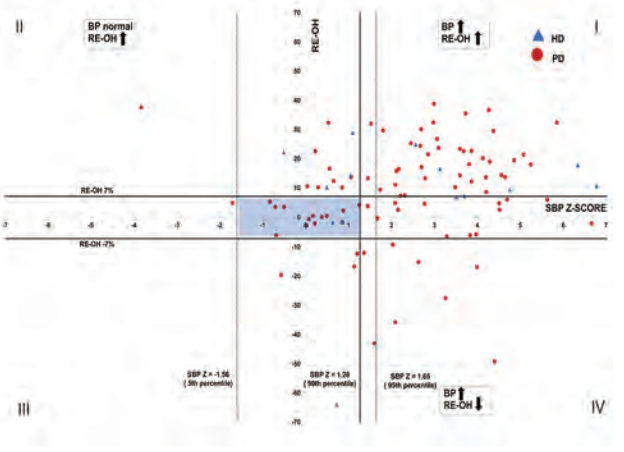

Figure 1

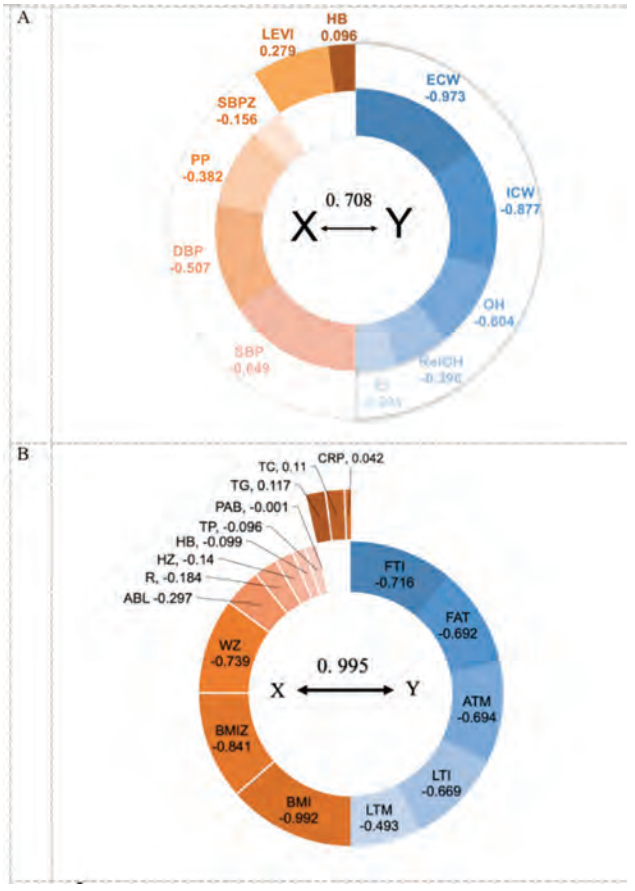

Figure 2

SA-PO377

Barriers to Growth Hormone (GH) Use in Children with CKD

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Background: GH is safe and effective in improving height in children with CKD. The purpose of this study was to identify barriers to GH use for the treatment of short stature in children with CKD.

Methods: Retrospective chart review identified children treated in the nephrology clinic at Le Bonheur Children's Hospital with estimated glomerular filtration rates (eGFR) ≤ 60 ml/min/1.73 m² via bedside Schwartz equation between January 1, 2017 until December 31, 2021. Males > 15 years old, females > 14 years old, and children < 3 years old were excluded. All children on GH at the most recent visit were included regardless of age, eGFR, or height percentile. Children having serum creatinine and height recorded within 7 days of one another during the study period were assessed. Barriers were evaluated for children not on GH with height percentiles ≤ 5%.

Results: 94 children were identified with eGFR ≤ 60 ml/min/1.73m². The cohort was 30% female, 51% black/African American, 41% white, 5% Hispanic/Latino, and had a median age of 11 years. Obstructive uropathy (27%), renal dysplasia (19%), and focal segmental glomerulosclerosis (13%) were the most common causes of CKD. 80 (85%) were not on GH and 14 (15%) were prescribed GH. Of the 14 patients on GH, 13 (93%) were male and 11 (79%) were white. Of the children not prescribed GH, 25 children (31%) had height percentiles ≤ 5% making them candidates for GH; there were 14 (56%) females, 13 (52%) black/African American, 9 (36%) white, and 2 (8%) Hispanic/Latinos in this group. Barriers identified were missed appointments/lost to follow up (8), severe developmental delay (7), severe hyperparathyroidism (4), delayed growth not identified by clinician (2), perceived adverse reaction (1), liver transplant (1), family declined treatment (1), and family reported not able to obtain (1).

Conclusions: Education on the importance of routine follow up appointments with more aggressive attempts to reschedule missed appointments may be beneficial in improving use of GH in children with CKD. Additionally, further education of families may lead to better control of hyperparathyroidism and other sequelae of CKD. The utility of GH therapy in children with severe neurologic impairments and CKD deserves further study. Finally, higher use of GH in white male children may suggest racial and gender inequality in provision of this treatment.

SA-PO378

Cognitive and Social Functioning of Infants and Preschoolers with Mild to Moderate CKD

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Background: Previously published data from the observational CKiD Study showed average neurocognitive function for a combined sample of infants and preschoolers with CKD, although 20% to 37% were deemed at-risk for selected neurodevelopmental difficulties (e.g., executive dysfunction). The current study expands upon previous findings with increased sample size and the examination of infants separately from preschool-age children.

Methods: Participants were 38 infants (Mean age=1.8 yrs) and 225 preschoolers (Mean age=4.8 yrs) recruited by CKiD Study sites. Infants were 76% male, with a median eGFR=49; preschoolers were 73% male, with a median eGFR=53. Measures included the Mullen Scales of Early Learning for infants, and the Wechsler Preschool and Primary Scale of Intelligence IV (WPPSI-IV) for preschoolers. Participants across both age bands received the parent-completed Ages & Stages Questionnaire: Social Emotional (ASQ:SE). Covariates included age, sex, maternal education, eGFR, hypertension, anemia/ESA use, proteinuria, seizure history, and abnormal birth history. Multivariate and logistic regressions were employed.

Results: After adjustment for covariates, infant Mullen Receptive Language (p=.02) and Expressive Language (p=.03) scores dropped with every 10% decline in eGFR. For the preschoolers, a 10% decline in eGFR (p=.004) and a doubling of proteinuria (p=.0002) were each associated with lower WPPSI-IV Verbal IQ. On the parent-completed ASQ:SE for the combined sample, about 13% were deemed at-risk for social-emotional problems, although the doubling of proteinuria was associated with at-risk status (p=.01).

Conclusions: CKD progression was associated with lower language-related abilities for infants and preschoolers, and this represents a novel finding in the CKD neurodevelopmental literature. The rate of parental concerns for social-emotional difficulties was equivalent to what might be expected in the typical population, although the doubling of proteinuria was associated with at-risk social status. Results highlight the need for early identification and ongoing developmental surveillance of young children with mild to moderate CKD, with further attention being devoted to early language and social development.

Funding: NIDDK Support

SA-PO379

Infectious Complications with Two Different Induction Regimens After Pediatric Kidney Transplantation

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Background: Pediatric kidney transplant recipients are vulnerable to clinically significant viral replication (VR) because of their need for intense induction and ongoing need for maintenance immune suppression (ISP). In this single-center study we compare the incidence of VR with CMV, EBV, parvovirus, BKV and infectious complications on an induction regimen with anti-thymocyte globulin (ATG) consisting of 3 mg/kg (HiATG) versus <3mg/kg (LoATG) and those who did not receive ATG (NoATG).

Methods: Retrospective analysis was performed in 59 patients with isolated kidney transplants from January 2018 to December 2021. The protocol for HiATG was a cumulative dose of 3mg/kg in the years 2018 -2019 which changed to 1 mg/kg in 2020-2021 for LoATG. Those with low pre-transplant vaccine response and/or low CD4 counts received NoATG. Induction ISP included basiliximab and methylprednisolone. VR was defined if PCR was > 137 copies/ml. Discontinuation of anti-metabolites or specific treatment for viral infection defined viral disease. Rejection was confirmed by kidney biopsy.

Results: Median age was 14 years (IQR: 9.5-17). There were no significant differences in the incidence of VR and rejection between HiATG and LoATG in the first 6 post-transplant months. All patients in NoATG had VR (See Table). Opportunistic infections were observed more often in NoATG. Although steroid avoidance was possible in LoATG and HiATG, time to steroid withdrawal was longer in LoATG (p = 0.02). Leukopenia was more prevalent in HiATG. After 6 months of transplant, VR occurred in 4 patients in each of HiATG and LoATG groups with one patient developing post-transplant lymphoproliferative disease during a mean follow-up period of 33±14 months.

Conclusions: Infectious complications occur in all induction regimens. In addition, maintenance ISP contributes to lowering host immunity. Differences in host response are likely to play a significant role in propensity to infections, highlighting the importance of individualizing ISP.

Clinical Characteristics in the First 6 Post-transplant Months

ATG dose (mg/kg) ‡	Patients†	Viral Replication†	Viral disease†	Opportunistic Infections†	Leukopenia†	Steroid free†	Steroid withdrawal days‡	Rejection†
3 (3-3)	25 (42)	14 (56)	5 (20)	1 (4)	11 (44)	21 (84)	7 (7-15)	2 (8)
1 (1-2)	30 (51)	18 (60)	3 (10)	1 (3)	8 (27)	25 (83)	19 (8-30)*	2 (7)
None	4 (7)	4 (100)	0	3 (75)	3 (75)	1 (25)	35	0

*P <=0.02; †N (%); ‡median(IQR)

SA-PO380

Norovirus Gastroenteritis in Pediatric Kidney Transplant Recipients: A Pediatric Nephrology Research Consortium Study

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Background: Norovirus can cause debilitating diarrhea in transplant recipients. Herein, we describe the clinical course and complications of norovirus infection in children with a kidney transplant.

Methods: Four transplant centers participated in this study. We included kidney transplant recipients who developed norovirus infection (confirmed by stool polymerase chain reaction or viral culture) between 1/1/2013 and 12/1/2019. Study variables are summarized as median and proportions. The estimated glomerular filtration rate (eGFR) was determined using the modified Schwartz equation. Acute kidney injury (AKI) was defined based on a change in eGFR per the pRIFLE criteria.

Results: Our cohort included 40 patients, 33 (82.5%) requiring hospitalization. The median age at transplant was 5.4 years (IQR:2.2, 1.2). Thirty-one patients (77.5%) were white, and 26 (65.0%) were male. The median time to diarrhea onset after transplant was 1.9 years (IQR:0.8, 3.8). The median diarrhea duration was 16 days (IQR:6.0,41.5), and that of hospitalization was 3 days (IQR: 2.0,8.0). During the norovirus infection, 17.5% developed neutropenia, 15% had a urinary tract infection, 17.5% had BK DNAemia, and 20% had EBV DNAemia. Furthermore, 52.5% developed AKI. We found no sustained decline in the median eGFR 12 months after diarrhea resolution (Table 1). Of the patients in the cohort, 2 lost their graft 6.8 and 30.0 months after the onset of diarrhea.

Conclusions: Norovirus can cause prolonged diarrhea in pediatric kidney transplant recipients complicated by AKI, neutropenia, and opportunistic infections. We found no sustained decline in eGFR over a 12-month follow-up. Multicenter, randomized controlled trials are needed to determine the most appropriate management strategy in children.

		All (N=40)	Norovirus + patients not hospitalized (N=7)	Norovirus + patients hospitalized (N=33)
		N (%)/Med [IQR]	N (%)/Med [IQR]	N (%)/Med [IQR]
Age (years)		5.34 [2.2, 11.2]	3.6 [2.0, 5.4]	7.6 [2.26, 11.69]
Sex	Male	26 (65.0)	4 (57.1)	22 (66.7)
Race	Asian	1 (2.5)	0 (0)	1 (3)
	Black/African American	4 (10.0)	2 (28.6)	2 (6.1)
	Hawaiian/Pacific Islander	1 (2.5)	0 (0)	1 (3)
	Other	3 (7.5)	0 (0)	3 (9.1)
	White/Caucasian	31 (77.5)	5 (71.4)	26 (78.8)
Donor Type	DD	17 (42.5)	3 (42.9)	14 (42.4)
ESRD Cause (%)	CAKUT	22 (55.0)	2 (28.6)	20 (60.6)
	cystic kidney disease	2 (5.0)	0 (0.0)	2 (6.1)
	Glomerulonephritis	2 (5.0)	1 (14.3)	1 (3.0)
	HUS	2 (5.0)	0 (0.0)	2 (6.1)
	Nephrotic syndrome	6 (15.0)	1 (14.3)	5 (15.2)
	Other	5 (12.5)	2 (28.6)	3 (9.1)
Maintenance IS	Prednisone, Tac, MMF	15 (37.5)	4 (57.1)	11 (33.3)
	Tac, MMF	20 (50)	3 (42.9)	17 (51.5)
	Other	5 (12.5)	0 (0)	5 (15.2)
Transplant to diarrhea time	days	681 [294.5, 1380]	1136 [693.5, 1391.8]	634 [225, 1354]
Duration of diarrhea	days	16 [6, 41.5]	24 [13, 40]	15 [6, 41.8]
Hospitalization Duration	days	3.00 [2, 8]	NA	3.00 [2, 8]
Weight loss during illness	Kg	1.1 [0.40, 1.9]	1.0 [0.15, 1.3]	1.5 [0.45, 2.2]
Neutropenia during illness (%)	Yes	7 (17.5)	0 (0)	7 (21.2)
Concomitant UTI (%)	Yes	6 (15.0)	0 (0.0)	6 (18.2)
Concomitant BK viremia (%)	Yes	7 (17.5)	1 (14.3)	6 (15.0)
Concomitant EBV DNAemia (%)	Yes	8 (20.0)	2 (28.6)	6 (15.0)
eGFR prior to diarrhea median (IQR)	ml/min/1.73m²	70.9 [51.9, 93.9]	78.3 [53.6, 87.8]	70.5 [52.2, 93.4]
Lowest eGFR during diarrhea median (IQR)	ml/min/1.73m²	54 [45.3, 67.2]	69.1 [48.6, 81.1]	50.9 [45.8, 65]
eGFR at diarrhea resolution median (IQR)	ml/min/1.73m²	75.7 [48.9, 91.2]	61.8 [43.8, 84.7]	76.2 [50.4, 91.8]
eGFR 6 months post diarrhea median (IQR)	ml/min/1.73m²	73.8 [52.8, 93.8]	85.1 [57.2, 92.7]	71.4 [52.8, 94.3]
eGFR 12 months post diarrhea median (IQR)	ml/min/1.73m²	72.9 [49.3, 93.3]	72.5 [56, 86.1]	73.3 [45.6, 93.7]
Acute kidney injury (pRIFLE)	I	4 (10)	0 (0)	4 (12.1)
	R	17 (42.5)	2 (28.6)	15 (45.5)
	no AKI	19 (47.5)	5 (71.4)	14 (42.4)

Table 1: Baseline Characteristics

SA-PO381

Clinical Characteristics and T-Cell Exhaustion in BK Polyomavirus Infection After Pediatric Kidney Transplantation

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Background: BK virus (BKV) is a significant cause of chronic kidney injury in kidney transplant recipients that results in allograft loss. Inhibitory receptors PD-1 and Tim-3 play a crucial role in regulating CD8 T cell function during chronic infection. The study's aim 1 was to determine the clinical characteristics of those who had BK viremia versus those who did not. Aim 2 was to document correlation between exhausted PD-1 and Tim-3 exhausted T cells during chronic BKV infection.

Methods: The retrospective case-control study was conducted from January 2008 to July 2022. The subjects were composed of a total of 32 pediatric KTRs and 12 with BKV viremia, in which 5 of 12 had BKVN were obtained. Peripheral blood mononuclear cells (PBMCs) were collected during episodes of BKV viremia. PD-1, Tim-3, and CD8 T cells were evaluated by multiparameter flow cytometry.

Results: BKV viremia was observed in 12/32 (37.5%) and BKVN in 5/32 (15.6%). Induction therapy was not significantly different between BKV and non-BKV viremia groups. The mean time for BK detection was 4.1 months after renal transplantation. Percent rise in serum creatinine correlated with intensity of viral load. The first-line therapy after identification of BKV viremia was a decreased dosage in Tacrolimus (100%) and intravenous immunoglobulin, and discontinuing mycophenolate mofetil. When reduction in immunosuppressant was not sufficient to decrease viral load, 4/12 (33.3%) of patients received leflunomide. High expression of PD1 and Tim-3 on CD8 cells with more severe T cells exhaustion was noted during chronic BKV infection. The treatment resistance was also accompanied with persistent high level of PD-1 and Tim-3 expression on CD8 T cells. There was no difference in the percentage of graft survival between BKV viremia and non-BKV viremia after 8 years' follow-up.

Conclusions: Patients with the highest viral loads and longest duration of BKV viremia are at risk of BKVN. Expression of PD-1, Tim-3 and CD8 T cell indicates chronic T cell partial exhaustion. BKV viremia and CD8 T cell exhaustion may be a surrogate marker for adjusting immunosuppressant reduction and intravenous immunoglobulin treatment.

SA-PO382

Use of the Seraph® 100 Microbind® Affinity Blood Filter in an Adolescent Patient with Disseminated Adenoviral Disease

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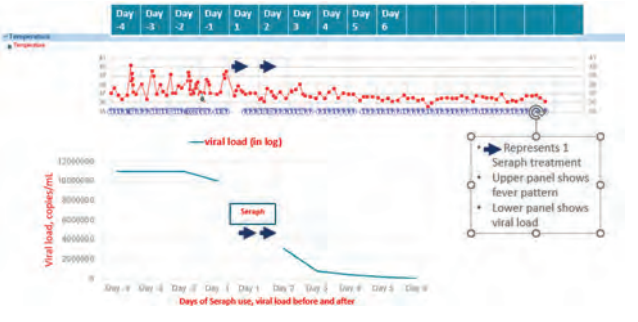
Introduction: Disseminated adenovirus infection can lead to high mortality and morbidity in immunocompromised patients. The Seraph® 100 Microbind® Affinity Blood Filter (Seraph 100) is a hemoperfusion device designed to adsorb pathogens when added to extracorporeal circuits. It has emergency use authorization for the treatment of COVID-19. Preclinical tests show a 62% reduction of adenoviral (ADV) load with Seraph 100, but this has not been reported in pediatrics.

Case Description: A 17 y.o. female s/p deceased donor kidney transplant (txp) for underlying FSGS, on chronic therapy with prednisone, tacrolimus, everolimus, presented 2 years post txp with dysuria, hematuria and fevers. She had AKI (creatinine of 2.3, baseline 0.8), elevated transaminases, and high serum ADV (> 10 million copies/mL). Kidney biopsy showed ADV nephritis with patchy areas of necrotizing interstitial inflammation and abundant viral inclusion bodies. Immunosuppression was discontinued but she remained febrile to 41° C, and had ADV levels >log 7 (> 10 million copies/mL). Cidofovir was not used due to AKI, and the risk of nephrotoxicity. After discussing the risks and benefits treatment with Seraph100 filter was started. She received 2 sessions in-line with continuous renal replacement therapy for a total time of 9 hours. Approximately 18 blood volumes were processed. ADV load decreased from 10 million prior to treatment to 148009 copies/mL (log 5.2) after the 2nd session. Fever curve (Fig 1) and transaminases improved. The ADV load continued to decrease despite not receiving additional sessions & restarting txp meds.

Discussion: Seraph® 100 filter was effective in reducing the ADV load in this adolescent patient with disseminated adenoviral infection post kidney txp, and led to an improvement in her clinical status. She tolerated treatment without significant adverse events. Teaching Point: The Seraph 100 uses heparin coated beads to bind pathogens, and can help debulk the infectious load. More studies are needed in pediatrics on its efficacy.



Clinical, viral response with Seraph

SA-PO383

Correlation Between Percentage Donor-Derived Cell-Free DNA (%dd-cfDNA) at Time of Allograft Biopsy and Rejection: Insights from the Multi-Center Pediatric Outcomes of Kidney Care in Renal Allografts (pOKRA) Study

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Background: The is prospective multi-center observational study to assess the accuracy of % dd-cfDNA as a biomarker for the detection of allograft rejection on simultaneous biopsy, in pediatric kidney transplant patients.

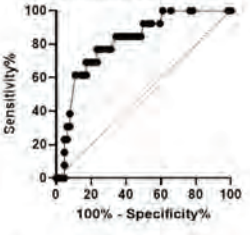
Methods: A total of 48 patients from 3 centers who underwent kidney biopsies within the first year post-transplantation were included in the study. We measured %dd-cfDNA levels using a targeted, multiplex PCR-based method analyzing single nucleotide polymorphisms. Patients were divided into two groups based on the presence or absence of allograft rejection, including subclinical rejection.

Results: We studied 77 samples of plasma %dd-cfDNA levels drawn on the same morning before kidney biopsies from 48 unique patients. Of 77 biopsies, 70 (91%) were surveillance biopsies, whereas 7 (9%) were diagnostic. We had 13 biopsy specimens from 12 patients with biopsy-proven acute rejection and 64 biopsy specimens from 44 patients without biopsy-proven acute rejection. At rejection, the %dd-cfDNA median (IQR) level was significantly higher at 1.2% (IQR, 0.5%-2.0%) than the quiescent group (median, 0.26%; IQR, 0.18%-0.49%). The area under the curve was 0.82 (95% confidence interval 0.70 to 0.93). Using a 1% cutoff, %dd-cfDNA had a specificity of 86 % (95% CI, 75% to 92%) and a sensitivity of 62 % (95% CI, 36% to 82%) in identifying active rejection. At the lower cutoff of 0.5%, %dd-cfDNA had a lower 75% specificity (95% CI, 63% to 84%) but higher 77% sensitivity (95% CI, 50% to 92 %) to discriminate biopsy-proven acute rejection from no rejection.

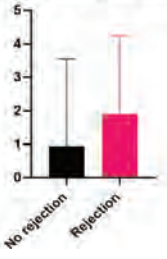
Conclusions: Prospective multicenter dd-cfDNA% levels timed to biopsy show a high accuracy with biopsy-proven acute rejection in children.

Funding: Commercial Support - CareDx

The area under the receiver operating characteristic curve for % dd-cfDNAto discriminate acute rejection



The bar graphs show the median (interquartile range) of the % dd-cfDNA in rejection versus no rejection.



SA-PO384

Using Eculizumab for Immediate Recurrence of ANCA Vasculitis in a Pediatric Kidney Transplant

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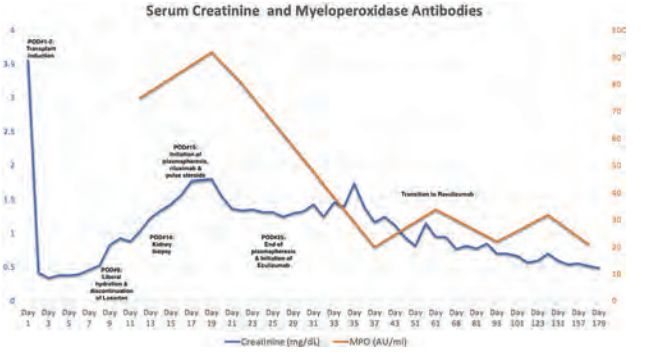
Introduction: ANCA associated vasculitis (AAV) is associated with poor renal outcomes with 20-30% of patients developing chronic kidney disease and up to 20-35% progressing to end-stage kidney disease. Recent advances have led to increasing interest towards complement inhibition as a potential treatment for AAV. We present a case of disease recurrence after pediatric kidney transplantation and the novel use of Eculizumab to salvage graft function.

Case Description: A 5-year-old Hispanic male with ESKD due to myeloperoxidase antibody positive ANCA vasculitis developed disease recurrence post-kidney transplant. Pre-transplant disease control required multiple rounds of high dose steroids, cyclophosphamide, azathioprine, and rituximab. Transplant induction included thymoglobulin and pulse-dose steroids with rapid taper. Mycophenolate (MMF) and tacrolimus (TAC) was started on POD 1 and 2 respectively. He developed gross hematuria on POD 5 with doubling of his serum creatinine (sCr) on POD 8. Kidney biopsy was done on POD 14 which showed pauci-immune glomerulonephritis and acute tubular necrosis without rejection. He was treated with plasmapheresis, pulse-dose steroids, and a dose of rituximab. Compassionate use of a C5a receptor inhibitor was sought and denied. Eculizumab, a C5 inhibitor was given instead on POD 28. With MMF, TAC, Eculizumab and steroid taper, his sCr improved. Two months later, he was transitioned to Ravulizumab. His kidney function remains stable and he continues to receive infusions without concerns of disease recurrence or serious infections.

Discussion: Previous reports of Eculizumab use for AAV led to our decision to use it for our patient with historically difficult to control AAV. This case illustrates a rare presentation of immediate disease recurrence of AAV in a pediatric kidney transplant and the successful use of C5 blockade. No specific treatment guidelines exist for childhood AAV, currently highlighting the need for further studies to evaluate efficacy and safety of complement inhibitors as treatment for childhood AAV.



SA-PO385

Lipoprotein Apheresis in Pediatric Post-Transplant FSGS

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Background: Focal segmental glomerulosclerosis (FSGS) is a common cause of end-stage renal disease (ESRD) in adolescents with a recurrence rate of >30% after transplant (txp). Lipoprotein apheresis (LDL-A) has been successfully used for post-txp FSGS recurrence (r-FSGS). It has also been used for drug resistant primary FSGS and de novo FSGS (d-FSGS) post-txp. We aimed to describe the efficacy and safety of LDL-A in pediatric patients with FSGS post-txp.

Methods: Retrospective, single center study at a tertiary care pediatric hospital. Outcomes were complete remission (CR) defined as Upc < 0.2; partial remission (PR) defined as Upc 0.2-2 and ≥ 50% reduction in proteinuria from baseline. All Upc in mg/mg.

Results: Five patients, age range 7-21 yrs (2 females; 4 r-FSGS, 1 d-FSGS) underwent LDL-A. Those with r-FSGS, 3 episodes were immediately post-txp, and 1 after 40 mths. D-FSGS was diagnosed 16 mths post txp in a patient with ARPKD. Two had a relapse requiring a 2nd course of LDL-A. Each course had 12 sessions using Liposorber® LA-15 system over a period of 9 weeks. Of those with r-FSGS, 3 had CR or PR at a median of 4 weeks after starting LDL-A. Patient 2 had >50% reduction in Upc from 34 (pre LDL-A) to a nadir of 3.3. A clinical relapse with increase in Upc to 11 was noted 4 months after 1st LDL-A. A 2nd course resulted in CR. Patient 3 with d-FSGS also had a >50% reduction in Upc from 15 (pre LDL-A) to a nadir of 2.7. A relapse with AKI (Upc 10.3, serum creatinine 7.3mg/dL) was seen after 11 months. A second course of LDL was attempted but patient did not respond, and was transitioned to chronic hemodialysis. No adverse events related to LDL-A were reported. Patient 3 had central line associated thrombus.

Conclusions: We report successful use of LDL-A in 5 pediatric patients. CR/PR was achieved in all with r-FSGS. In d-FSGS, there was significant decrease in proteinuria but no remission. The therapy was well tolerated with the only adverse event secondary to vascular access. More studies are needed to assess its efficacy in primary and d-FSGS post-txp.

	Patient 1	Patient 2		Patient 3		Patient 4	Patient 5
Primary disease	FSGS	FSGS		ARPKD		FSGS	FSGS
Post-txp disease	Recurrent FSGS	Recurrent FSGS		De novo FSGS		Recurrent FSGS	Recurrent FSGS
Age at txp	7	10		20		7	10
Peri-txp FSGS treatment	TPE, rituximab	TPE, rituximab		N/A		TPE, rituximab	TPE, rituximab
		Course 1	Course 2	Course 1	Course 2		
Time since txp (months)	0	0	6	16	28	40	0
Labs before initiating LDL-A							
Upc (mg/mg)	17.5	34.8	11.5	15.3	10.4	15.2	50.1
Lowest albumin (mg/dL)	1.6	2.5	2.1	2.6	2.9	2.6	2.2
Creatinine (mg/dL)	0.6	2.7	1.4	1.7	6.0	1.1	0.3
eGFR (mL/min/1.73m²)	64.2	27.7	42.5	41.9	9.1	47.7	127
Labs after completing LDL-A							
Upc (mg/mg)	3	9.7	0.21	2.7	9.3	1.6	<0.2
Lowest albumin (mg/dL)	3.0	2.0	3.9	3.7	2.7	3.2	4.6
Creatinine (mg/dL)	0.6	0.8	0.8	1.4	7.3	0.5	0.5
eGFR (mL/min/1.73m²)	67.6	64.1	66.4	53	7.1	89.3	80.7
Time to PR/CR (months)	4	N/A	1	N/A	N/A	1	1
Last Follow up							
Time since LDL-A (months)	30	24		Dialysis initiated after 2nd course of LA; Expired 3 months after dialysis initiation		2	1
Upc (mg/mg)	<0.2	0.7				1.6	<0.2
Lowest albumin (mg/dL)	4.6	4.0				3.2	4.2
Creatinine (mg/dL)	0.6	1.1				0.5	0.5
eGFR (mL/min/1.73m²)	81.2	54.1				89.3	91.9

FSGS, focal segmental glomerulosclerosis; ARPKD, autosomal recessive polycystic kidney disease; txp, transplant; TPE, therapeutic plasma exchange; LDL-A, lipoprotein apheresis; eGFR, estimated

SA-PO386

Diabetic Ketoacidosis in Pediatric Kidney Transplant Patient After Treatment for Rejection

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Introduction: New onset diabetes after transplantation (NODAT) is reported in 3-20% of pediatric kidney transplant (KT) patients. Diabetic ketoacidosis (DKA) has not been reported in a pediatric KT recipient. We report on the first case of DKA in a pediatric KT patient with NODAT after treatment of acute rejection.

Case Description: A 16yo, nonobese, female who received a deceased donor KT 4mos earlier was diagnosed with biopsy-proven acute T-cell mediated Banff class 1B and acute antibody mediated rejection in the setting of elevated creatinine. Her rejection was treated with thymoglobulin (total dose 5 mg/kg) and methylprednisolone (MP, total dose ~20 mg/kg). After her initial dose of MP, she developed hyperglycemia, was diagnosed with NODAT and managed initially with insulin and then with sitagliptin and metformin. Her hemoglobin A1c ranged from 5.3% – 7.1%. A subsequent kidney biopsy 21 months after KT showed acute T-cell mediated Banff class 1B and acute antibody mediated rejection. This episode was treated with MP (~30 mg/kg) followed by oral prednisone 60 mg daily (~1 mg/kg/day). Her hemoglobin A1c was 5.8% and she remained on sitagliptin and metformin. She presented 41 days later with new onset polyuria and polydipsia. She was found to have 3+ urine ketones, blood glucose 427 mg/dL, bicarbonate 12 mmol/L, anion gap 22 mmol/L, pH 7.23, beta-hydroxybutyrate 3.77 mmol/L, C-peptide 0.33 ng/mL, and hemoglobin A1c 12.4%. Her creatinine was at her baseline of 0.77 mg/dL and her trough tacrolimus level was 3.7 ng/mL on 4 mg XR tacrolimus daily. She was receiving prednisone 30 mg daily. Type 1 diabetes autoantibodies were negative: glutamic acid decarboxylase-65 antibody, insulin autoantibody, islet cell antibody 512, and zinc transporter 8 antibody. She was admitted and treated for DKA. Her insulin requirement was ~1.6 units/kg/day.

Discussion: Our patient's NODAT is likely related to intense steroid treatment for rejection and significant insulin resistance. At our center, we have implemented a multidisciplinary pediatric KT and diabetes clinic that promotes communication between providers and with patients. A single clinic visit streamlines care and facilitates management of NODAT. Recognition of the rare complication of steroid induced DKA in pediatric KT recipients is essential to provide prompt diagnosis and management.

SA-PO387

Neurocognitive Profile of Pediatric Kidney Transplant Candidates Aged 3 to 17 Years

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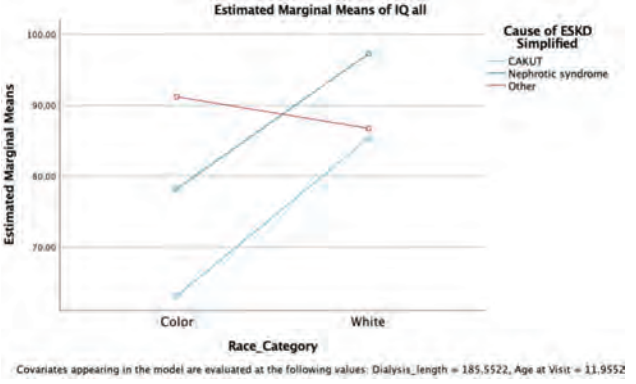
Background: Pediatric kidney transplant candidates frequently undergo pre-transplant neuropsychological evaluation. However, little is known about the neuropsychological profile of children awaiting a kidney transplant.

Methods: One hundred and one patients aged 3 to 17 years completed pretransplant neuropsychological evaluations at our center. Standardized tests were administered. Correlations between these test scores and age as well as dialysis duration were examined using Pearson Correlations. The effects of the cause of ESKD and race on test performances were evaluated using multivariate analysis of variance (MANOVA), adjusting for dialysis duration and age at testing.

Results: The mean age of our study cohort was 11.1 years (*SD*=4.2). The mean Full-Scale IQ of our cohort was significantly lower than general population at 87.3 (*SD*=16.8) (t= -6.64, p<.001). Age was significantly correlated with reasoning scores (r=.36, p=.003). Dialysis duration was negatively correlated with memory scores as measured by CVLT-C (r=-.323, p=.02) and visual organization scores as measured by the Rey-Osterrieth copy test (r=-.58, p=.003). After adjusting for age at testing and dialysis duration, the cause of ESKD was significantly associated with overall IQ (F(2)=3.3, p=.04) and verbal comprehension (F(2)=3.3, p=.05) performance (see figure). Race (F(1)=7.3, p=.009) and insurance type (F(1)=3.9, p=.05) were also significantly associated with verbal comprehension.

Conclusions: Pediatric kidney transplant candidates are at high risk for developing neurocognitive deficits, including lower overall IQ. Younger patients are at higher risk for abstract reasoning deficits, and patients with long dialysis duration are at higher risk for developing memory and visual organization difficulties. In addition, our results suggest that patients with CAKUT tend to have lower IQ scores versus patients with nephrotic syndrome, and white patients tend to perform better than patients of color on verbal abilities.



FSIQ

SA-PO388

Social Determinants of Health and Kidney Transplant Outcomes in Youth

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Background: Investigating how social determinants of health (SDoH) affect clinical outcomes is important in achieving health equity. The effect of SDoH on the pediatric transplant recipients is not well understood. Our aim was to investigate the association of adverse SDoH with kidney allograft outcomes in a diverse population of youth from a broad referral area.

Methods: In this single-center retrospective cohort study, data were extracted from the electronic health record using biomedical informatics methods. Inclusion criteria were youth 0-18 years who received a kidney transplant and had post-transplant care at our center from 9/25/2012 to 12/31/2022. Exposures were insurance type (public vs private), distance to transplant center, preferred language, and area deprivation index (ADI). Outcomes were graft survival, time to first biopsy-proven acute rejection (BPAR), and number of BPAR episodes. We used Kaplan-Meier estimates for graft survival and time to first BPAR. Cox proportional hazards regression models estimate the associations of exposures with time-to-event outcomes. For BPAR episodes, a negative binomial regression model, adjusted for time followed, assessed the relationship between outcome and exposure.

Results: Of 78 participants, 37% were female; median age at transplant was 8.5 years [IQR 3,14]; median follow-up was 5.0 years [IQR 4.1,7.0]. Event-free survival at 1 and 5 years was 100% and 92%. Median number of BPAR was 0 [IQR 0-2]. Public insurance, greater distance to transplant center, non-English language, and higher ADI were not associated with higher risk of graft failure or time to first BPAR. However public insurance was associated with greater BPAR episodes on unadjusted analysis [OR 3.33, CI 1.19-9.30] and after adjusting for race [OR 3.07, CI 1.08-8.73].

Conclusions: Several adverse SDoH were not associated with worse graft survival or faster time to BPAR in this interim analysis of pediatric kidney transplant recipients. However, having public insurance was associated with a greater number of BPAR. Public insurance may represent a risk marker for patients with greater healthcare needs and who may experience inequities in care. Ongoing quantitative and qualitative studies will clarify health-related social needs and patient experiences in this population to identify targeted interventions to achieve more equitable and optimal transplant outcomes.

Funding: Other NIH Support - The project was supported by the National Center for Advancing Translational Sciences

SA-PO389

Neighborhood Socioeconomic Deprivation Among Pediatric Kidney Transplant Recipients

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Background: Addressing social determinants of health is integral to kidney transplant management, although focus has only recently shifted to neighborhood-level effects. Using data from the Scientific Registry of Transplant Recipients, we describe the association between neighborhood socioeconomic deprivation and graft loss in pediatric kidney transplant recipients.

Methods: US recipients ≤18 years of age at time of listing who underwent kidney transplantation January 1st, 2010, to May 31st, 2022 (n=9,719) were included. Neighborhood deprivation was calculated using patient ZIP codes at time of listing and the Material Community Deprivation Index (MCDI), ranging from 0 (least deprived) to 1 (most deprived). Recipients were stratified into quintiles (Q). Kaplan-Meier and multivariable Cox proportional hazard estimates were calculated.

Results: The median MCDI for the most deprived neighborhoods (Q5) was 0.53 [IQR: 0.47, 0.84] compared to 0.23 [IQR: 0.06, 0.27] in the least deprived (Q1). Black and Hispanic patients were over-represented in the most deprived neighborhoods. As neighborhood deprivation increased, dialysis duration and deceased donation increased, while preemptive transplantation decreased. Recipients living in the most deprived neighborhoods had a 1.67 times greater risk of graft loss compared to the least deprived (CI: 1.42, 1.98).

Conclusions: Pediatric kidney transplant recipients with the highest levels of neighborhood socioeconomic deprivation had a greater risk of graft loss. Increased focus should be placed on contextual effects of neighborhood environment to address health disparities in pediatric kidney transplantation.

Funding: NIDDK Support

Table 1. Baseline characteristics stratified by Material Community Deprivation Index (MCDI) quintiles

Characteristics*	Overall n=9719	Quintile 1 n=1944	Quintile 2 n=1943	Quintile 3 n=1943	Quintile 4 n=1944	Quintile 5 n=1943
MCDI	0.37 [0.06, 0.84]	0.23 [0.06, 0.27]	0.31 [0.27, 0.34]	0.37 [0.34, 0.40]	0.43 [0.40, 0.47]	0.53 [0.47, 0.84]
Age (y)	13 [8, 16]	13 [8, 16]	12 [8, 16]	13 [8, 16]	13 [8, 16]	13 [7, 16]
Race/ethnicity						
Asian	412 (4)	151 (8)	97 (5)	59 (3)	83 (3)	42 (2)
Black	1523 (16)	215 (11)	238 (12)	326 (17)	452 (24)	580 (30)
Multiracial	153 (2)	42 (2)	46 (2)	46 (2)	29 (1)	12 (1)
Native American	77 (1)	8 (0)	14 (1)	14 (1)	15 (1)	26 (1)
Pacific Islander	52 (1)	15 (1)	14 (1)	14 (1)	7 (0)	2 (0)
White	7192 (74)	1515 (78)	1542 (79)	1488 (77)	1366 (73)	1279 (66)
Hispanic	2788 (28)	271 (14)	419 (22)	481 (25)	650 (31)	957 (49)
Insurance						
Private	3721 (38)	1203 (62)	856 (44)	679 (35)	539 (28)	356 (18)
Public	5910 (61)	725 (37)	880 (50)	1246 (64)	1391 (72)	1568 (81)
Diagnosis						
CAKUT	3091 (32)	633 (33)	656 (34)	630 (32)	576 (30)	596 (31)
Glomerulonephritis	1026 (11)	178 (9)	185 (10)	215 (11)	228 (12)	212 (11)
FSGS	1211 (12)	214 (11)	227 (12)	244 (13)	261 (13)	265 (14)
PKD	287 (3)	74 (4)	66 (3)	61 (3)	52 (3)	35 (2)
Other/Unknown	4104 (42)	847 (44)	802 (41)	793 (41)	827 (43)	835 (43)
Dialysis duration (y)	1.2 [0.6, 2.3]	1.0 [0.4, 1.9]	1.2 [0.6, 2.0]	1.2 [0.6, 2.3]	1.4 [0.7, 2.5]	1.5 [0.8, 2.7]
Deceased donor	6318 (65)	949 (49)	1144 (59)	1267 (65)	1402 (72)	1556 (80)
Preemptive transplant	2742 (28)	703 (36)	626 (32)	560 (29)	499 (26)	414 (21)

*Reported as median [IQR] for continuous variables and n (%) for categorical variables. Missing data: insurance, n=82; cold ischemia time, n=384. MCDI Material Community Deprivation Index, CAKUT congenital anomalies of the kidney and urinary tract, FSGS focal segmental glomerulosclerosis, PKD polycystic kidney disease

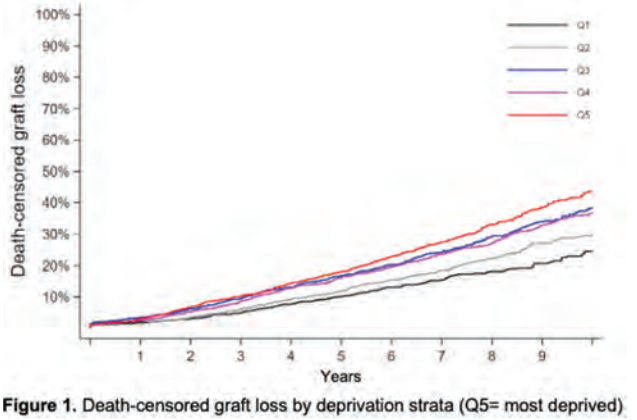

Figure 1. Death-censored graft loss by deprivation strata (Q5= most deprived)

SA-PO390

Recipient Proximity to Transplant Center in US Pediatric Kidney Transplantation

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Background: Recipient proximity to a transplant center varies greatly among US children with kidney failure. Prior studies of US children listed for kidney transplant demonstrated that less proximity to center was associated with greater risk of death on the waitlist. Using data from the Scientific Registry of Transplant Recipients, we describe the association between recipient proximity to transplant center and candidate evaluation and outcomes in US pediatric kidney transplant recipients.

Methods: US children ≤18 years of age at time of listing who underwent kidney transplantation from January 1st, 2001, to December 31st, 2019 (n=12,113) met inclusion criteria. Proximity to transplant center was calculated using recipient and transplant center ZIP codes at time of listing. Logistic and linear regression, in addition to multivariable Cox proportional hazard models, were utilized to analyze outcomes of interest.

Results: Seventy-five percent of recipients lived within 83 miles of a transplant center at time of listing. A majority of Black recipients (81.8%) lived within 83 miles (≤75th percentile) of a center, compared to 72.3% of white recipients. Twenty-three percent of recipients in the ≥75th percentile had a primary diagnosis of FSGS, versus 28% in the ≤25th percentile. Proportions of pre-emptive transplant and public insurance were similar across strata. There was no significant difference in survival across strata, with those with least proximity to center having no increased risk of graft failure (aHR 0.96, 95% CI: 0.87-1.06). There was no change in odds of living donor transplantation (aOR 1.01, 95% CI: 0.99-1.03) or delayed graft function (aOR 0.98, 95% CI: 0.95-1.02) with each 100-mile increase from center. Residing within the ≥75th percentile at time of listing increased waitlist time by 3% of one year (10.95 days, 95% CI: 0.6-6%).

Conclusions: No meaningful associations between recipient proximity to center and graft survival, waitlist time, living donor transplantation, or delayed graft function were detected. Future efforts should explore the impact of proximity to center on additional aspects of transplant access, recipient well-being, and caregiver burden.

Funding: NIDDK Support

Table 1. Multivariate Cox proportional hazard models on graft survival and linear regression for waitlist time

	10-year graft survival			Waitlist time		
	aHR*	95% CI	*P* value	Coefficient*	95% CI	*P* value
Distance to Transplant Center (quartiles)						
0-11.20 miles	Ref			Ref		
11.21-28.64 miles	0.95	0.86-1.04	0.22	-0.01	-0.04, 0.01	0.33
28.65-83.21 miles	0.95	0.86-1.05	0.29	-0.002	-0.02, 0.02	0.88
83.21-2888.37 miles	0.96	0.87-1.06	0.39	0.03	0.008, 0.06	0.02

*Adjusted for age at listing, gender, race/ethnicity, renal diagnosis, and living vs. deceased donor transplant.

SA-PO391

Distance to Transplant Center and Pediatric Kidney Transplant Outcomes and Access to Care

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Background: Reliable transportation is necessary for equitable healthcare access. Transportation insecurity poses a barrier to care, contributing to worse health outcomes in chronic disease. However its significance in pediatric transplantation is an area of ongoing investigation. Our aim was to assess the impact of distance to the transplant center on outcomes and post-transplant follow-up care in a geographically diverse cohort of pediatric transplant recipients.

Methods: In a single-center retrospective cohort study, data were extracted from the electronic health record using biomedical informatics methods. Inclusion criteria were youth 0-18 years who received a kidney transplant and had post-transplant care at our center from 9/25/2012–12/31/2022. Our exposure was distance to the transplant center, determined by calculating geodetic distance from participants' residence zip code to the transplant center. Outcomes were graft survival, biopsy-proven acute rejection (BPAR), hospitalization rates, and no-shows and cancelled appointments in the transplant clinic. We used Kaplan-Meier curves and Cox proportional hazards regression to estimate associations of exposures with outcomes.

Results: Of 78 participants, 37% were female; median age at transplant was 8.5 years (IQR 3,14); median follow-up was 5.0 years (IQR 1,7.0). The median distance to the transplant center was 29.0 miles (IQR 13.4,60.1); mean no-show proportion was 8.9% (SD 8.1%); mean cancellation proportion was 26.3% (SD 10.6%). Distance to the transplant center was not associated with higher risk of graft failure, shorter time to first BPAR, higher BPAR, and higher hospitalization rates. Greater distance from the transplant center was associated with a higher proportion of cancelled clinic appointments (p 0.0001, Beta coefficient 1.08 per 10 miles, 95% CI (0.63,1.54)).

Conclusions: Greater distance to the transplant center was associated with more clinic cancellations, which can cause delayed care resulting in negative effects on transplant health. Further study by collecting qualitative data on patient transportation access may help us understand the patient experience and what barriers can be mitigated to reduce appointment cancellations. By collecting qualitative data on patient transportation access in this population, we hope to better inform transplant maintenance and optimize long-term care.

Funding: Other NIH Support - The project was supported by the National Center for Advancing Translational Sciences

SA-PO392

Childhood Opportunity Index and Pediatric Kidney Transplant Health

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Background: Social Determinants of Health research has become increasingly important. The Childhood Opportunity Index (COI) is a composite of 29 variables affecting child health and well-being related to Health/Environment (HE), Social/Economic (SE), and Education (E). Research exploring the impact of COI on kidney transplant outcomes is lacking. Our aim was to assess association of COI with pediatric kidney transplant outcomes.

Methods: This was a single-center retrospective cohort study of kidney transplant recipients 0-18 years with post-transplant care at our center from 9/25/2012-12/31/2022. Exposures were overall COI and COI domains based on 2015 census tract data from diversitydatakids.org. Outcomes were graft survival, time to first biopsy-proven acute rejection (BPAR), number of BPARs, hospitalization rates, and transplant clinic no-show and cancellation rates. Statistical analyses included Kaplan-Meier, Cox proportional-hazards, and negative binomial regression models.

Results: Of the N=78 participants; median age at transplantation was 8.5 years [IQR 3,14]; median follow-up 5 years [IQR 4.1,7.0]. Event-free survival at 1 and 5 years was 100% and 92%. COI was not associated with graft survival, number of BPAR, hospitalization rates, or cancelled visits. COI-SE was inversely associated with time to first BPAR [p=0.010, HR=1.10, 95% CI 1.02-1.17]. Overall COI and COI-SE were inversely correlated with no-show rates [p=0.039, Beta coefficient=-0.41 per 5 units (95% CI -0.80,-0.02) and p=0.029, Beta coefficient=-0.43 per 5 units (95% CI -0.81,-0.05)]. Higher no-show rates were associated with worse graft survival [p=0.018, HR=1.38, 95% CI 1.06-1.79].

Conclusions: Lower COI-SE was associated with higher no-show rates which was associated with worse graft survival. Higher COI-SE was associated with shorter time to first BPAR, possible due to patients maintaining regular follow-up with more timely BPAR diagnosis. Higher no-show rates in individuals from areas of low COI-SE may

result in delayed BPAR diagnosis, which could increase risk of graft failure. Future study can assess if COI predicts other transplant or kidney disease outcomes. To better understand the effects that lower COI may have at the individual level, questionnaires can be used to identify barriers to care such as affordability, perceived cost, transportation, or ability to attend appointments.

Funding: Other NIH Support - The project described was supported by the National Center for Advancing Translational Sciences

SA-PO393

Revisiting Clinical Relevance of Radionucleotide-Based GFR Estimation and Comparison with CKiD U25 eGFR Equation in Pediatric Liver Transplant Patients

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Background: Renal dysfunction is common in patients with liver transplant recipients and can be present at the time of transplant or develop later during follow-up. Kidney function in these patients is monitored periodically by measuring glomerular filtration rate (GFR). In the absence of appropriate serum creatinine-based estimation equations in the past, GFR measurement by utilizing radionucleotide agent such as diethylenetriamine pentaacetate (DTPA) have been in common practice. The procedure involves IV line placements, radionucleotide agent administration, and blood draws. The value of newer GFR estimating equations such as CKiD U25 (derived form Chronic Kidney Disease in Children Under 25) have not been evaluated in these cases.

Methods: Retrospective analysis of all liver transplant patients since 1995 who had their GFR estimated by radionucleotide (99mTc-DTPA) for kidney function monitoring. The DTPA-GFR was compared with eGFR calculated by creatinine based CKiD U25 equation. All creatinine values were converted to isotope dilution mass spectrometry (IDMS) reference measurement. Patients with any missing data were excluded.

Results: 356 DTPA-GFR measurements (median 4 per patient; range 1 – 9) from 95 patients (57% males; median age at transplant 2.1 years, range 0.45 – 19.2) obtained at a median age of 10 years were available. 53 (15%) serum creatinine values were above the age specific reference range and the eGFR by U25 equation was <90 mL/min for all, while 40 had <90 mL/min, 11 had between 90 – 120, and 2 had >120 mL/min based on DTPA-GFR. 303 serum creatinine values were in normal range and the GFR was >120 mL/min in 94 (31%) by both methods. Of the rest of 209 values, U25 equation classified 147 (90 – 120 mL/min) and 18 (<90 mL/min); while DTPA-GFR classified 115 (90 – 120 mL/min) and 28 (<90 mL/min). The concordance between U25 and DTPA-GFR was ~50% for eGFR 90 – 120 mL/min, and ~15% for <90 mL/min, respectively. Overall, the correlation coefficient "r" between the two methods was 0.45 (p <0.0001).

Conclusions: In the absence of the gold-standard measurement, CKiD U25 equation appears to perform better than DTPA-GFR which is a time consuming, cumbersome and expensive procedure. Addition of serum Cystatin C is likely to further improve the eGFR estimation by CKiD U25 equation.

SA-PO394

Preventative Dental Practices and Cardiometabolic Health in Adolescents

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Background: Decreased utilization of dental services in adolescence has been linked to cardiometabolic disease in adulthood. The aim was to assess the relationship between preventative dental practices and cardiometabolic health in adolescents.

Methods: Analysis included children aged 13-17 years enrolled in the National Health and Nutrition Examination Survey (NHANES) from 2011-2018 who completed an oral health questionnaire. No dental care was defined as not having a dental visit in the past year. Financial barriers to seeking dental care were assessed among those without dental care. Cardiometabolic outcomes included obesity, elevated blood pressure (BP 120-129/<80 mmHg), hypertensive BP (BP≥130/80 mmHg), dyslipidemia (any abnormal lipid level), glucose intolerance (HOMA-IR), uric acid, glomerular hyperfiltration (estimated glomerular filtration rate [eGFR] ≥140 ml/min/1.72 m^2), and microalbuminuria (urine albumin:creatinine >30 mg/mg). Regression models adjusted for age, sex, self-identified race/ethnicity, household income, food insecurity, health insurance, household education, and body mass index (BMI) z-score examined associations using complex survey design procedures.

Results: Of 2,861 adolescents, 17.6% (0.9%) did not receive dental care in the past year and of those, 20.2% (1.9%) had financial barriers to accessing dental care. Adolescents without dental care had higher odds of overweight/obesity and dyslipidemia. Those with financial barriers had higher levels of non-HDL, lower levels of HDL, and higher odds of dyslipidemia (Table 1).

Conclusions: In a nationally representative population of adolescents, lack of preventative dental practices was associated with cardiometabolic health makers of overweight/obesity and dyslipidemia. In addition, financial barriers to health were associated dyslipidemia.

Funding: NIDDK Support

Table 1: Adjusted regression analysis of preventative dental practices and markers of cardiometabolic health

	No Dental Care in the last year (ref dental care in the last year) β (95% CI)	p	Financial Barrier (ref no Financial Barrier) β (95% CI)	p
SBPI	-.078 (-1.010, .854)	.868	-.892 (-3.501, 1.717)	.496
DBPI	.801 (-.775, 2.377)	.313	1.813 (-.653, 4.279)	.146
Total Cholesterol	-1.572 (-6.353, 3.208)	.513	4.880 (-2.109, 11.869)	.167
Triglycerides	-7.165 (-18.378, 4.048)	.206	-25.806 (-58.556, 6.994)	.119
Non-HDL	-.266 (-1.563, 1.031)	.683	7.946 (1.037, 14.854)	.025
HDL	.723 (-1.063, 2.510)	.421	-3.066 (-4.440, -2.456)	.026
LDL	-.845 (-4.532, 2.842)	.648	5.028 (-4.173, 14.228)	.276
HOMA-IR	.262 (-.003, .537)	.052	-.440 (-1.008, .128)	.127
Waist Circumference	-.666 (-1.784, .451)	.238	-1.032 (-3.613, 1.549)	.426
Urine albumin:creatinine	-.994 (-10.560, 8.572)	.836	7.075 (-1.999, 16.148)	.124
eGFR	-1.963 (-6.103, 2.176)	.347	-6.309 (-14.887, 2.269)	.146
Uric Acid	-.024 (-.163, .114)	.726	.025 (-.344, .393)	.894
BMI Z-score	-.097 (-.263, .071)	.253	.045 (-.226, .317)	.741
	Dental Care in the last year (ref No dental care in the last year) OR (95% CI)	p	**Financial Barrier** (ref no Financial Barrier) OR (95% CI)	p
Obese Status	1.114 (.125, 9.956)	.922	.987 (.096, 10.199)	.991
Obese and overweight status	.697 (.290, .990)	.044	1.449 (.687, 3.059)	.324
Pre-hypertensive Blood Pressure	1.142 (.774, 1.685)	.498	1.886 (.396, 8.911)	.419
Hypertensive Blood Pressure	1.193 (.502, 2.834)	.685	.316 (.077, 1.300)	.108
Insulin Resistance	.976 (.604, 1.578)	.920	.553 (.204, 1.498)	.239
Dyslipidemia	.663 (.471, .934)	.019	2.877 (1.123, 7.373)	.029
Albuminuria	.860 (.246, 3.011)	.811	.684 (.015, 32.335)	.844
Microalbuminuria	.807 (.553, 1.177)	.261	.943 (.508, 1.748)	.849
Hyperfiltration	1.100 (.582, 2.082)	.765	.279 (.039, 1.975)	.197

SA-PO395

Dental Caries and Cardiometabolic Health in Adolescents

Kristal Wong,[1] Srighana Nadella,[2] Mel Mupparapu,[2] Christine B. Sethna.[1]
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Background: Dental caries is the most common chronic disease in the pediatric population. Prior studies suggest that poor oral health may contribute to an increased risk of metabolic syndrome and cardiovascular risk in adulthood. The aim was to assess the association between dental caries and cardiometabolic risk in adolescents.

Methods: Analysis included adolescents aged 13-17 years enrolled in the National Health and Nutrition Examination Survey (NHANES) from 2011-2018 who completed an oral health questionnaire/exam. Untreated caries was defined as having one or more decayed teeth. Severity of dental caries was assessed by the Decayed, Missing, Filled Teeth (DMFT) score in permanent dentition (No caries, DMFT=0). Cardiometabolic outcomes included obesity, elevated BP (BP 120-129/<80 mmHg), hypertensive BP (BP ≥130/80 mmHg), dyslipidemia (any abnormal lipid level), glucose intolerance (HOMA-IR), uric acid, glomerular hyperfiltration (estimated glomerular filtration rate [eGFR] ≥140 ml/min/1.72 m^2), and microalbuminuria (urine albumin:creatinine >30 mg/mg). Regression models adjusted for age, sex, self-identified ethnicity/race, household income, food insecurity, health insurance status, household education, and body mass index (BMI) z-score examined associations using complex survey design procedures.

Results: Of 2,861 adolescents (age 14.97 [0.03] years, 55.3% [1.2%] male), 25.6% (1.3%) had untreated caries and 55.4% [1.3%] had DMFT ≥1. In adjusted models, untreated caries was significantly associated with higher HOMA-IR levels and lower eGFR values. Additionally, DMFT ≥1 was associated with higher odds of elevated BP compared to a DMFT of 0 (Table 1).

Conclusions: In a nationally representative study of adolescents, there was an association between untreated/more severe caries with cardiometabolic markers of BP and glucose intolerance.

Funding: NIDDK Support

Table 1: Adjusted regression analysis of dental caries with markers of cardiometabolic health

	Untreated Caries (ref Treated/No caries) β (95% CI)	p	Caries Experience (ref No caries experience, DMFT=0) β (95% CI)	p
SBPi	-.061 (-1.059, .936)	.903	.477 (-.489, 1.465)	.322
DBPi	-1.028 (-2.354, .299)	.126	-1.411 (-2.50, -.252)	.074
Total Cholesterol	.512 (-2.486, 3.510)	.734	2.358 (-.093, 4.809)	.059
Triglycerides	-.207 (-10.761, 10.348)	.969	.917 (-7.743, 9.578)	.833
Non-HDL	-.377 (-3.225, 2.471)	.792	1.319 (-1.289, 3.928)	.316
HDL	.899 (-.237, 2.014)	.119	1.039 (-.170, 2.247)	.091
LDL	-.714 (-5.281, 3.853)	.756	-.826 (-4.325, 2.672)	.639
HOMA-IR	.015 (-.212, .243)	.045	-.061 (-.275, .151)	.566
Waist Circumference	-.388 (-1.191, .415)	.338	.266 (-1.563, 1.031)	.683
Urine albumin:creatinine	-3.420 (-12.097, 5.256)	.434	-2.101 (-9.637, 5.435)	.579
eGFR	-5.463 (-8.493, -2.433)	<.001	-.391 (-3.959, 3.178)	.827
Uric Acid	.097 (-.056, .250)	.211	.031 (-.081, .143)	.580
BMI Z-score	.028 (-.093, .148)	.650	.038 (-.088, .165)	.545
	Untreated Caries (ref Treated/No caries) OR (95% CI)	**p**	**Caries Experience (ref No caries experience, DMFT=0) OR (95% CI)**	**p**
Obese Status	.809 (.134, 4.874)	.814	.820 (.079, 8.471)	.866
Obese and overweight status	1.071 (.762, 1.506)	.688	.849 (.611, 1.179)	.323
Pre-hypertensive Blood Pressure	1.161 (.878, 1.536)	.290	1.393 (1.023, 1.897)	.036
Hypertensive Blood Pressure	.598 (.321, 1.114)	.103	.639 (.362, 1.130)	.121
Insulin Resistance	.941 (.637, 1.390)	.757	.848 (.556, 1.292)	.436
Dyslipidemia	.917 (.602, 1.397)	.683	1.001 (.696, 1.441)	.996
Albuminuria	.905 (.388, 2.113)	.504	1.176 (.527, 2.626)	.687
Microalbuminuria	.908 (.637, 1.295)	.589	.935 (.671, 1.303)	.687
Hyperfiltration	.738 (.370, 1.472)	.382	.911 (.487, 1.703)	.766

SA-PO396

Hyperfiltration in Obese Diabetic BTBRob/ob Mice Can Be Measured Transcutaneously

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Background: Transcutaneous assessment of glomerular filtration rate (tGFR) has only been validated in lean mice. At 24 weeks obese diabetic mice display vasodilation of the afferent glomerular arteriole and increased glomerular size, yet do not differ in tGFR values from lean mice. Hence, we questioned if hyperfiltration can be assessed transcutaneously in obese diabetic mice.

Methods: We measured tGFR and FITC-sinistrin plasma clearance simultaneously in obese diabetic BTBR$^{ob/ob}$ and lean non-diabetic BTBR$^{wt/-}$ mice at week 12. At week 24 we assessed tGFR again and used tissue clearing and light sheet microscopy to assess glomerular size and vasodilation of the afferent arteriole in mice that were perfused with an infrared fluorescent dye.

Results: While at week 12 tGFR significantly differed between the groups with a faster clearance in the diabetic BTBR$^{ob/ob}$ mice (both $t_{1/2}$ of FITC-sinistrin (p=0.0081) and calculated GFR (p=0.0069)), no difference was found between diabetic and non-diabetic mice in tGFR at 24 weeks. In line with the increased tGFR, also FITC-sinistrin plasma clearance was significantly increased at week 12 in BTBR$^{ob/ob}$ mice (p=0.0140). At week 24 the diameter of afferent arterioles were significantly larger in BTBR$^{ob/ob}$ vs. BTBR$^{wt/-}$ mice (p=0.0007) and associated with increased glomerular size (p=0.0136).

Conclusions: The results indicate that hyperfiltration can be detected in diabetic mice by tGFR early in the course of disease. In keeping with the findings that no difference in tGFR was found at 24 weeks despite morphological parameters that indicate hyperfiltration, our data might be explained by progressive loss of functional nephrons later in the disease. Accordingly, this will reduce total glomerular filtration while increased glomerular pressure and dilation of the afferent glomerular arterioles (and presumably single nephron glomerular hyperfiltration) remain in nonsclerotic nephrons.

Funding: Government Support - Non-U.S.

SA-PO397

The Genetic Architecture of Diabetic Nephropathy in Mice

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Background: Diabetic nephropathy (DN) is the leading cause of end-stage renal disease in the United States and has a significant impact on human suffering. Leptin-deficient BTBR mice (BTBR$^{ob/ob}$) develop hallmark glomerular features of diabetic kidney disease in humans, whereas leptin-deficient C57BL/6J (B6$^{ob/ob}$) mice do not.

Methods: To identify the genetic loci that underlie this strain difference, we constructed an F2 intercross between BTBR$^{ob/ob}$ and B6$^{ob/ob}$ mice. We isolated kidneys from 460 F2 mice and used them to histologically score percent mesangial matrix and glomerular volume in ~50 glomeruli per mouse, yielding ~45,000 distinct measures in total. The same histological measurements were made in kidneys from B6 and BTBR mice when either lean or obese (*Lep*$^{ob/ob}$) at 4 and 10 weeks of age, allowing us to assess the contribution of strain, age, and obesity on glomerular pathology. All F2 mice were genotyped for ~5,000 single nucleotide polymorphisms (SNPs), ~2,000 of which were polymorphic between B6 and BTBR.

Results: We were able to identify a quantitative trait locus (QTL) on chromosome 7 at ~30 Mbp for percent mesangial matrix, glomerular volume, and mesangial volume. Two podocyte-specific genes in this region, Nphs1 (nephrin) and Kirrel2 (NEPH3 or filtrin), are physically located at the QTL and contain several high-impact SNPs (at splice regions or result in missense variants). Both are members of the immunoglobulin superfamily of cell adhesion molecules and localize to the podocyte slit diaphragm. Futhermore, mutations in these genes have been linked to chronic kidney disease in humans.

Conclusions: Our findings indicate genetic differences in genes known to be crucial to podocyte function and glomerular filtration barrier integrity as drivers of microstructural glomerular changes in diabetic nephropathy. Diabetic nephropathy is likely to be polygenic, with various genes, participating in various pathways, acting synergistically to affect susceptibility to the disease. Our study highlights Nphs1 and Kirrel2 and their role in podocyte function as genes that contributes to susceptibility to diabetic nephropathy and hallmark structural changes in the glomerulus. Genetic testing of a panel of gene variants may identify patients genetically predisposed to podocyte injury in diabetes and guide care to prevent nephropathy in diabetes.

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SA-PO398

Sexual Dimorphism in Glucose Metabolism in Type 2 Diabetic Mice

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Background: The prevalence of non-insulin-dependent diabetes has grown enormously over the last three decades and today this complication is a major global concern. According to the World Health Organization, the percentage of deaths attributed to high blood glucose is greater in males than females. This fact translates to experimental models of type 2 diabetes, in which obese male show increased blood glucose levels in comparison to female, despite the same degree of obesity. However, the mechanisms underlying this observation are still unclear. Thus, the aim of this study is to investigate the sexual dimorphism in glucose metabolism in BTBR WT and ob/ob mice.

Methods: The mice had blood glucose and body weight evaluated every two weeks. At the 16th week of age, euthanasia was performed to collect urine, liver and the kidneys. Albuminuria and gene expression of glucose metabolism enzymes were further performed.

Results: Preliminary data show that BTBR ob/ob mice, independently of sex, presented increased body weight in comparison to corresponding WT mice, but obese male were hyperglycemic than female throughout the experimental protocol. Diabetes and obesity induced albuminuria equally between males and females, which confirms loss of kidney function. In the liver, male and female BTBR ob/ob mice showed decreased *Pck1* and increased *Fbp*1 transcript levels, suggesting alteration of the gluconeogenesis pathway. However, female BTBR ob/ob mice had increased liver *Pkm* transcript levels than the corresponding male. In addition, liver *Pkm* transcript levels positively correlated with the blood glucose levels, which indicates sexual dimorphism in liver glycolysis. In the kidney, increased gene expression of the gluconeogenesis enzymes were observed in obese mice independently of sex, however, *Hk1, Pkm* and *Pfkp* transcript levels were upregulated only in females. Moreover, kidney *Pfkp* transcript levels positively correlated with blood glucose levels, suggesting also sexual dimorphism in kidney glycolysis. Gene expression of glucose transporters in the proximal tubule, SGLT2 and GLUT2, were only affected by obesity and diabetes and not by sex.

Conclusions: Collectively, these data show that there is a sexual dimorphism in gene expression of glycolysis enzymes in both liver and kidney, which may be associated with differences in blood glucose levels of male and female BTBR ob/ob.

Funding: Government Support - Non-U.S.

SA-PO399

TNF-α Pathway and Podocyte Dysfunction in Male and Female BTBR ob/ob Mice

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Background: Diabetic kidney disease (DKD) is the major cause of chronic kidney disease (CKD) in patients with diabetes. Studies suggest that tumor necrosis factor alpha (TNF-α) pathway signaling is important for DKD progression. TNF-α contributes to glomerular inflammation and injury, however, the mechanisms underlying this dysfunction, especially in podocytes, need to be further elucidated. Thus, the aim of this study is to elucidate how TNF-α may contribute to podocyte dedifferentiation in DKD and whether sexual dimorphism can modulate this process.

Methods: For this, male and female BTBR WT and ob/ob mice, a gold standard model of experimental type 2 diabetes and obesity were studied. The mice were observed up to a period of 16 weeks of age, and at the end of the experimental protocol, urine and kidneys were collected for analysis of albuminuria and gene expression. *In vitro*, immortalized mouse podocytes were treated with TNF-α for gene expression analysis.

Results: Preliminary data show that BTBR ob/ob mice presented elevated blood glucose levels, body weight and albumin excretion in comparison to WT mice. Among these parameters, blood glucose levels were affected by sex, as females were less hyperglycemic than males. In the kidneys, gene expression of TNF-α and TNF-α receptor

type 1 (TNFR1) were not statistically different among groups, but gene expression of TNF-α receptor type 2 (TNFR2) were upregulated in BTBR ob/ob mice independently of the sex. *Snai1* transcript levels were not changed, but there were an effect of sex and obesity on *Snai2* transcript levels. Females have higher gene expression of nephrin and podocin, but obesity reduces the expression of these genes, regardless of sex. *In vitro* experiments show that TNF-α treatment induced increased TNF-α gene expression and decreased *Snai2* transcript levels in podocytes.

Conclusions: In conclusion, these data suggest that BTBR ob/ob mice presented kidney inflammation, podocyte dysfunction and alteration of the cellular dedifferentiation pathway. Sexual dimorphism was observed in the gene expression of podocyte markers and *Snai2* transcript levels. *In vitro*, we confirmed the association of an inflammatory *millieu* with the dedifferentiation and inflammatory response of podocytes.

Funding: Government Support - Non-U.S.

SA-PO400

The Association Between Mechanosensitive Ion Channel Piezo2 Expression and Fibrogenesis in Hypertensive Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage kidney disease, and mechanical forces such as glomerular hyperfiltration are crucial in the pathogenesis and progression of DKD. We previously reported *Piezo2* expression in mouse kidneys and its alteration by dehydration and hypertension, however, the role of Piezo2 in DKD is still unclear. We aimed to elucidate *Piezo2* expression and regulation in mouse models of DKD.

Methods: We used two types of DKD models (high fat diet (HFD) and streptozotocin (STZ)-treated C57BL/6J mouse, and high salt (HS)-treated type 2 diabetic KK-A^y mouse) and non-diabetic control C57BL/6J mice. Blood samples and kidneys were collected at 29 weeks of age in HFD+STZ mice and 19 weeks of age in KK-A^y+HS mice. We examined blood and urine analyses, histopathologic and immunohistochemical evaluations of kidneys, and gene expression analysis. The localization of *Piezo2* expression was identified using in situ hybridization method.

Results: Both DKD models exhibited significant obesity, hyperglycemia, albuminuria, glomerular hypertrophy, mesangial expansion, infiltration of macrophages, and tubular vacuolization compared to control mice. These findings were more severe in KK-A^y+HS mice than in HFD+STZ mice. KK-A^y+HS mice showed hypertension. Fibronectin protein expression was significantly upregulated in the glomerular areas of KK-A^y+HS mice kidneys. In addition, there were no significant differences in interstitial fibrosis between HFD+STZ mice and control mice, whereas severe interstitial fibrosis was observed in KK-A^y+HS mice kidneys. In situ hybridization studies showed no significant difference in *Piezo2* expression between HFD+STZ mice and control mice, but *Piezo2* expression was increased and localized in the glomerular and interstitial regions in KKAy+HS mice. Real-time RT-PCR showed that *Piezo2* and *Fn1* mRNA were increased in KKAy+HS mice compared with control mice. Furthermore, *Piezo2* expression was strongly correlated with *Fn1* expression (ρ=0.92, P<0.001).

Conclusions: Our findings suggest that *Piezo2* expression is upregulated in glomerular and interstitial regions in the advanced stage of DKD with increased glomerular mechanical stress, and *Piezo2* is associated with kidney fibrosis.

SA-PO401

Effects of Electronic Cigarette Aerosol Exposure on Kidney Health in Diabetic/Obese Mice

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Background: Diabetes is one of the most important risk factor for chronic kidney disease (CKD) and end stage kidney disease. Tobacco smoking accelerates the progression of CKD of different etiologies including diabetes. However, whether e-cig use also has a deleterious effect on CKD progression is unknown. The aim of this study was to examine whether inhalation exposure of diabetic adult mice to e-cig aerosols, with and without nicotine, changes gene expression linked to kidney injury.

Methods: 7-8-wk-old BTBR obese mice, a model of type II diabetes, were exposed to: 1) filtered air (control); 2) Propylene glycol/ Vegetable glycerin PG/VG (1:1); or 3) PGVG (1:1) + Nicotine (36 mg/ml) for 10-wk (3hr/d; /5d/wk). After euthanasia, kidneys were collected for RNAseq and histology. After RNA extraction, bulk RNAseq was performed, followed by RNAseq libraries preparation with TruSeq Stranded Total RNA kit (Illumina). Libraries were sequenced and aligned against mouse genome. Differential gene expression analysis was performed with DESeq2 R/Bioconductor package. The 2nd kidney from each mouse was fixed in formalin and used to assess kidney injury in PAS-stained slides.

Results: Inhalation exposure of mice to PG/VG + nicotine resulted in gene expression changes in 724 genes, while only 3 genes were differently expressed in the PG/VG group, compared to controls. Kidney injury related genes (i.e., Rorc, Col4a3, EGFR, LRRK2, VDR), cancer related genes (e.g., Adamts1, Ccn1, Ackr3) and immune-regulatory (e.g., Ace2, Rorc, Cxcl6, Ccn1), were upregulated in the PG/VG + nicotine exposed group compared to controls. In the PG/VG only group, pro-inflammatory (Rorc) was upregulated, while inflammation-protective Nr1d and kidney injury-associated Mt1 genes were downregulated. Kidney histology showed mesangial expansion consistent with diabetic nephropathy, which was similar in all 3 exposure groups.

Conclusions: Long-term, repeated exposure of diabetic mice to e-cig aerosols containing nicotine induces significant changes in genes involved in CKD progression, cancer, and inflammation. This groundbreaking study reveals the kidney as a target of e-cig use and opens the door for further research concerning the impact of e-cig use on kidney health.

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SA-PO402

Novel Drug Screening Strategy to Explore Exosome-Targeted Intervention of Intraglomerular Cross-Talk for Diabetic Kidney Disease

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Background: Exosome (Exo), one of the extracellular vesicles, is an important mediator of intercellular communication in the regulation of physiological and pathophysiological processes. We reported the significance of intraglomerular cellular crosstalk centered on mesangial cells (MC) in the pathogenesis of diabetic kidney disease (DKD). However, the roles of Exo-mediated processes still remain elusive. The aim of this study is to explore novel exosome-targeted therapeutic strategy for DKD.

Methods: We focused on Exo as a possible key factor acting in a paracrine manner in glomeruli and examined the effects of mesangial cell-derived Exo (MC-Exo) on macrophages (Mφ) in culture. In order to identify new therapeutic agents, we established a high-throughput screening assay that can efficiently inhibit Exo-induced inflammation by use of validated library. We further investigated the effects of a candidate agent on DKD in vivo.

Results: MC-Exo stimulation activated NF-κB and increased the mRNA expression of TNFα and IL-1β in Mφ. The effects were significantly enhanced in Exo from MC cultured under high-glucose conditions compared to low-glucose conditions. DiO (fluorescent dye)-stained MC-Exo was colocalized with a cell-impermeant polar tracer, Cascade Blue™ hydrazide in Mφ, confirming that Exo was uptaken into Mφ by endocytosis. Next, from over 3,000 compounds, we screened drug candidates that could specifically and effectively suppress NF-κB activity and exosomal actions with minimum toxicity. Alvespimycin (Alv), an Hsp90 inhibitor, was identified as a final candidate. Treatment of diabetic rats with Alv improved proteinuria and mesangial expansion, along with suppressed mRNA expression of IL-1β and TNFα in glomeruli. Notably, the pre-final list of 28 compounds contained four Hsp90 inhibitors including Alv. Among them, Alv showed the highest inhibitory effect of Exo-uptake by FCM analysis.

Conclusions: Through our unique Exo-targeted drug screening, we successfully discovered alvespimycin, an Hsp90 inhibitor, which may ameliorate diabetic nephropathy. Alv inhibited Exo-uptake of Mφ and suppresses local inflammation in glomeruli, probably independent of Hsp90 blocking mechanisms. Exo-targeted intervention could be a novel and promising strategy for DKD.

SA-PO403

Investigation of Urinary Exosomal miRNA and lncRNA Expression Profiles and ceRNA Network in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is one of the major cause of end-stage renal disease (ESRD), it is important to detect diagnostic biomarkers of DKD. This study aims to explore expression profiles of urinary exosomal miRNA and lncRNA in DKD patients, and their possible regulatory mechanism in DKD.

Methods: We performed urinary exosomal miRNA and lncRNA profile in DKD, DM patients and healthy subjects, and analyzed biological functions of differentially expressed miRNAs and lncRNAs. And then we focused on the important mRNA ZEB1/2 which were related to DKD, constructed a ceRNA network.

Results: We identified differentially expressed 47 miRNAs and 61 lncRNAs of urinary exosome in DKD. GO and KEGG analysis showed target genes of miRNAs were involved in Iκ-BK/NF-κB, Wnt, PI3K-Akt pathway, autophagy and oxidation-reduction process. Differential lncRNAs participated in occurrence and development of DKD through peroxisome proliferator-activated receptor, cGMP-PKG pathway, autophagy and platelet activation. Furthermore, We constructed a ceRNA network with differentially expressed miRNAs, lncRNAs, ZEB1, ZEB2, and found that 7 lncRNA-miRNA- mRNA axes could promote the expression of ZEB1/ZEB2, which may play an important role in TIF of DKD.

Conclusions: In conclusion, Urinary exosomal lncRNA-miRNA may involved in the process of TIF in DKD through targeting transcription factor ZEB1/ZEB2, providing new directions to further clarify the pathogenesis and therapeutic targets of DKD.

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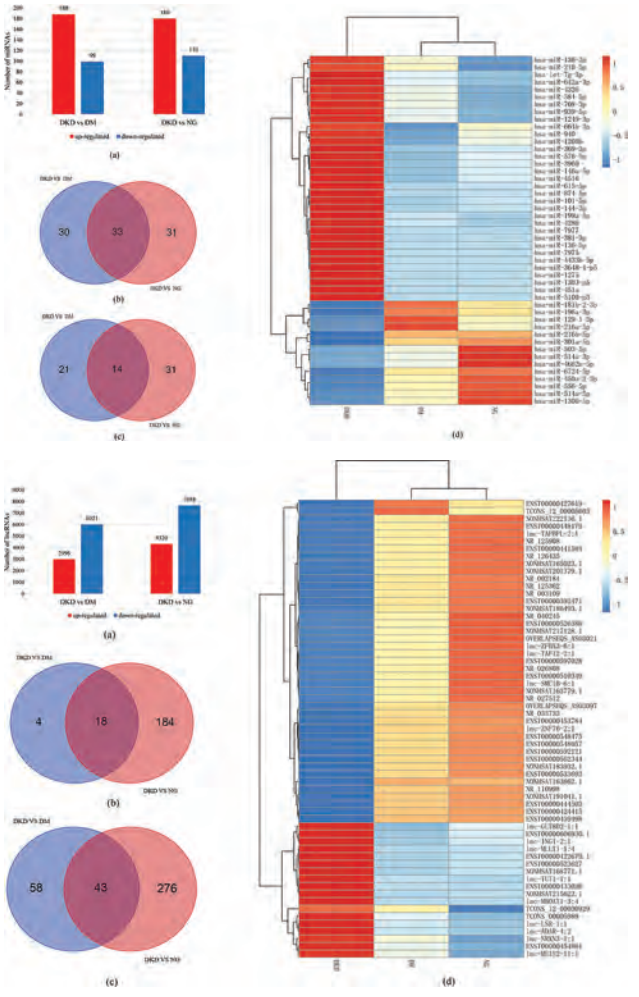

SA-PO404

Comparative Transcriptome Analysis of Spontaneously Diabetic Torii Fatty Rat Undergoing Salt Loading Alone or with Unilateral Nephrectomy

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Background: The Spontaneously Diabetic Torii (SDT) fatty rat is an animal model for type 2 diabetes and obesity. Salt loading and unilateral nephrectomy developed hypertension and diabetic nephropathy in this model early in the disease process. The current study aimed to identify risk factors for diabetic nephropathy and conduct transcriptome analysis using RNA-seq in SDT fatty and Sprague-Dawley (SD) rats.

Methods: Male SDT fatty and SD rats underwent distilled (Cont) or 0.3% NaCl (Salt) water loading from 10 to 20 weeks of age. Body weight, diet and fluid intake, systolic and diastolic blood pressure, blood glucose, and urine albumin level were assessed. Kidney sections were subjected to pathological analyses by H&E, PAS, and sirius red staining to investigate glomerular lesions and fibrosis. Whole kidney extracts underwent RNA-seq to analyze differentially expressed genes (DEGs) between strains, salt loading, and unilateral nephrectomy (Nx) at 9 weeks of age. Gene ontology (GO) analysis was performed on the DEGs using the DAVID analysis tool.

Results: Although no differences in body weight, diet and fluid intake were observed, blood glucose levels were significantly higher in SDT fatty than in SD rats, regardless of loading. Systolic and diastolic blood pressure, urine albumin, and glomerular lesion and fibrosis scores were significantly higher in SDT fatty (Salt) compared to SDT fatty (Cont), SD (Salt), or SD (Cont) rats. Using RNA-seq analyses, comparison of SDT fatty and SD strains showed 864 DEGs in Cont, 1500 in Salt, and 1599 in Salt/Nx. With respect to salt loading effects, in SDT fatty rats there were 481 DEGs in Cont vs. Salt, 365 in Cont vs. Salt/Nx, and 60 in Salt vs. Salt/Nx, whereas in SD rats, there were 57 DEGs in Cont vs. Salt, 167 in Cont vs. Salt/Nx, and 199 in Salt vs. Salt/Nx. GO analysis showed higher expression of genes involved in immune response and extracellular matrix related with inflammation in SDT fatty Salt or Salt/Nx compared to Cont rats.

Conclusions: Salt-treated SDT fatty rats showed elevated expression of inflammatory-related genes. This suggests a potential role of salt in promoting renal pathology in this model.

Funding: Government Support - Non-U.S.

SA-PO405

Oxidative Stress-Related Mitochondrial and Lysosomal Quality Control Mechanisms in Renal Cortex During the Normoalbuminuric Stage of Diabetes Mellitus

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Background: Oxidative stress during the normoalbuminuric stage of type 1 diabetes mellitus (DM) damages renal cortical mitochondria. Subsequent mitochondrial autophagy (mitophagy) produces autophagosomes destined for lysosomal degradation; hence, any lysosomes damaged in DM must be either repaired or degraded and removed in order for mitophagy to reach fruition. We aimed to determine if oxidative stress in DM triggers not only renal cortical mitophagy, but also lysosomal repair and elimination through lysosome-selective autophagy (lysophagy).

Methods: Four groups of rats (n=5 per group) received one of the following treatments: 1) STZ group: rats with DM induced by streptozotocin injection (STZ, 65 mg/kg, *i.p.*); 2) Sham group: rats receiving the STZ vehicle; 3) STZ+TLM group: STZ rats treated with telmisartan (TLM, an angiotensin receptor blocker; 10 mg/kg/day in chow); and 4) Sham+TLM group: TLM-treated Sham rats. Two weeks later, blood glucose levels, blood pressure, glomerular filtration rate (GFR), and urinary excretion of albumin and *N*-acetyl-β-D-glucosaminidase (NAG) were measured in each rat. Renal cortex homogenates were assayed for 3-nitrotyrosine (3-NT, an oxidative stress marker measured by HPLC), and Western blot was used to quantify proteins related to mitophagy (PINK1, BNIP3, LC3-II, p62), lysosomal repair (Galectin-3), and lysophagy (LAMP2, FBXO27).

Results: Blood glucose levels were higher in STZ rats than in Sham rats ($P<0.05$) and were unaffected by TLM. Blood pressure, albumin excretion, and NAG excretion were unaltered by STZ or TLM. GFR and renal cortical 3-NT levels were increased in STZ rats ($P<0.05$), and both changes were prevented by TLM ($P<0.05$). STZ rats had increased renal cortical LC3-II, PINK1, Galectin-3, and FBXO27 protein levels compared with Sham ($P<0.05$), with these effects prevented by TLM ($P<0.05$). BNIP3, p62 and LAMP2 levels did not differ among groups.

Conclusions: DM-induced renal cortical mitophagy, lysosomal repair, and lysophagy were blunted by the antioxidant effects of TLM, suggesting that these may be closely related quality control mechanisms triggered by oxidative damage.

SA-PO406

Liraglutide's Unveiled Renoprotective Mechanism in Type 1 Diabetes: Insights into Macrophage Polarization

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Background: Diabetic Kidney Disease is a major complication of type 1 (T1D) and type 2 (T2D) diabetes. While the GLP-1RA liraglutide, has shown promise in protecting the kidneys of individuals with T2D, its effects T1D are not well-studied. Additionally, the underlying mechanism through which liraglutide provides renoprotection in T1D or T2D requires further investigation. Macrophages are known to contribute to the development and progression of DKD. Upon infiltrating the glomeruli, they tend to adopt a pro-inflammatory M1 phenotype rather than an anti-inflammatory M2 phenotype. In addition to inflammation, excessive production of ROS is implicated in DKD progression. This study aims to investigate the renoprotective effects of liraglutide in T1D and examine its influence on shifting macrophage polarization towards the anti-inflammatory M2 phenotype by modulating NADPH oxidase.

Methods: C57/BL6J adult male mice were divided into 3 groups (n=5/group): C group, T1D group (induced by 3 consecutive doses of STZ), and T1D group treated with liraglutide (0.3 mg/kg twice daily). After a 13-week treatment period, the mice were sacrificed, and kidneys were isolated for analysis.

Results: Our results show that liraglutide improves kidney injury in T1D mice manifested by a reduction in kidney hypertrophy, BUN, ACR, proteinuria, glomerular hypertrophy, glomerulosclerosis, as well as glomerular collagen deposition. These findings were associated with decreased expression of inflammatory cytokines, as well as the M1 macrophage specific markers. Moreover, the levels of the anti-inflammatory cytokines were increased, and this was associated by an increase in the M2 macrophage specific markers. Furthermore, liraglutide treatment attenuated ROS production manifested by decreased NADPH oxidase activity through an inhibition of NOX2 and NOX4. Of interest, liraglutide treatment was associated with activation of the NADPH oxidases DUOX isoforms, indicating a more controlled and regulated ROS production, which may be involved in redox signaling and tissue homeostasis.

Conclusions: Our data highlight an anti-inflammatory renoprotective effect of liraglutide. This is manifested by a notable shift in macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, through the modulation of NADPH oxidase activity in T1D.

SA-PO407

MiR-200b Induces ZEB1-Mediated Upregulation of Matriptase and Affects Expression of Podocin: A Proposed Mechanism of Podocyte Effacement and Proteinuria in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is the leading cause of chronic kidney disease and a predominant reason for renal failure. Evidence from previous research indicates that abnormal expression of microRNAs (miRs) links closely to the occurrence and progression of DKD

Methods: Expression of miRs in urine samples from DKD patients and in cultured renal cells stressed with transforming growth factor beta 1 (TGF-β1) was evaluated by TaqMan assay. The emerging miR of interest and its downstream targets were analyzed in human renal sections, in cultured human podocytes and in zebrafish.

Results: Cell free urine screening showed increased abundance of miR-200b in samples from patients with DKD when compared to healthy controls. In situ hybridization confirmed expression of miR-200b in kidney specimens from DKD patients, but was not detected in healthy renal parenchyma. Transcriptome profiling of cultured human podocytes overexpressing miR-200b identified this miR as a regulator of the ZEB1 mediated matriptase (ST14)/ podocin pathway and found TGF- β1 and high glucose (HG) stress to be upstream activators of miR-200b expression in these cells. Immunofluorescence analysis of kidney sections from DKD patients showed increased expression of ST14 and decreased expression of podocin when compared to healthy controls. Furthermore, injection of a miR-200b mimic in zebrafish larvae caused an upregulation of ST14 and was accompanied by phenotypic changes such as edema, proteinuria and podocyte effacement.

Conclusions: Our results show that miR-200b is expressed in glomeruli and found at elevated levels in urine of DKD patients. Stressors such as high glucose or TGF-β1 can activate transcription of miR-200b in human podocytes, leading to increased levels of matriptase, a serine protease previously shown to cleave podocin. The observed decrease in podocin levels in glomeruli from DKD patients, together with the effect of a miR-200b mimic on proteinuria and ultrastructure of the pronephros in zebrafish positions miR-200b as a key regulator that modulates matriptase overactivation in DKD and warrants further studies.

SA-PO408

PACSIN2 Regulates the Inflammatory Response in Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is associated with hemodynamic and metabolic alterations including chronic low-level inflammation. Podocytes, the glomerular epithelial cells, are damaged by the inflammatory *milieu* in DKD *via* poorly understood mechanisms. Our study identifies protein kinase C and casein kinase substrate in neurons 2 (PACSIN2) as a new regulator of inflammation in the kidney.

Methods: This study relies on PACSIN2 knockout (KO) mice, in which we modeled DKD. We also used isolated human glomeruli and cultured human podocytes. We analyzed samples by quantitative Western blot, and immunofluorescence or immunohistochemical stainings.

Results: At the age of 12 months, compared to controls, PACSIN2 KO mice had paler kidneys, increased albumin to creatinine ratio, and altered glomerular vasculature. This coincided with increased circulating IL6, increased glomerular macrophage infiltration, and disrupted oxidative process in the glomeruli. Treatment of human glomeruli *ex vivo* with IL6 led to increased expression of PACSIN2. In cultured human podocytes, the expression and phosphorylation of PACSIN2 varied in response to inflammatory stimuli. PACSIN2 also interacted with NFkB and GSK3β depending on the stimulus. Diabetic PACSIN2 KO mice were lighter than diabetic controls, had lower glycaemia, lower albuminuria, and excreted less urine per 24h. We found no difference in macrophage infiltration and oxidative damage between diabetic WT and diabetic PACSIN2 KO mice. Nevertheless, the expression of NFkB and GSK3β was increased in glomerular lysates of diabetic PACSIN2 KO mice.

Conclusions: Our results indicate that lack of PACSIN2 alone causes kidney damage and increases inflammation in the glomeruli. In the context of DKD, lack of PACSIN2 improved metabolic and kidney parameters. Our study uncovers PACSIN2 as novel regulator of inflammation and highlights the contextual regulation of the inflammatory response in the glomeruli.

Funding: Private Foundation Support

SA-PO409

Exploring the Role of CXCL16 in Diabetic Kidney Disease: Insights into Inflammation, Lipid Disorders, and Therapeutic Potential of Curcumin

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Background: Diabetic nephropathy (DN) is a common complication of diabetes characterized by the progressive presence of albumin in the urine and the destruction of glomeruli. Elevated levels of soluble C-X-C chemokine ligand 16 (CXCL16) have been associated with inflammatory and lipid responses, which play a significant role in the development of renal dysfunction in patients with diabetes. However, the precise mechanisms through which CXCL16 affects DN are not yet fully understood.

Methods: To address this, we conducted a comprehensive study to investigate how CXCL16 contributes to podocyte injury in DN.

Results: CXCL16 were associated with abnormal lipid metabolism. The addition of CXCL16 to podocytes led to the formation of lipid droplets, along with increased expression involved in lipid synthesis and storage. CXCL16 treatment inhibited the movement of Nrf2 into the nuclei of podocytes. To explore potential therapeutic approaches, we evaluated the effects of curcumin, a compound known to activate Nrf2, on podocyte senescence and injury. Our results demonstrated that curcumin treatment reduced the accumulation of lipid droplets and mitigated podocyte injury, as evidenced by a decrease in cellular senescence. Importantly, we found that the protective effects of curcumin were inhibited when CXCL16 was reduced by CXCL16 siRNA. Meanwhile, curcumin treatment prevented CXCL16-induced oxidative stress and inflammation, preserved the expression of synaptopodin, and inhibited the abnormal movement of Nrf2. Through molecular modeling and docking analysis, we discovered that curcumin directly targeted a specific region in the CXCL16 protein, blocking its kinase activity. In a mouse model of DN, we validated the therapeutic potential of curcumin.

Conclusions: Taken together, our findings suggest that CXCL16 may serve as a promising therapeutic target for the treatment of DKD.

SA-PO410

Effects of Stimulating and Inhibiting IL11 Pathway in Kidney Fibrosis

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Background: IL11 has been widely implicated as a major downstream effector of TGFβ signaling driving fibrogenesis and extracellular matrix deposition in several organs including the kidney. Here, we aimed to test fibrotic effects of IL11 in in vitro and in vivo kidney disease models.

Methods: Primary renal fibroblasts and human precision-cut kidney slices (PCKS) were treated with TGFβ in the absence or presence of anti-IL11 mAb or anti-TGFβ as positive control. Fibrotic gene expression and ECM accumulation were measured with qRT-PCR, ELISA and picrosirius red (PSR) staining. The in vivo effects of IL11 on fibrosis and kidney function were tested on 12-week old db/db-UNX mice subject to daily subcutaneous dosing of recombinant mouse IL11 for 8 weeks (10, 100, 200 ug/kg). The anti-fibrotic effects of anti-IL11 were assessed using unilateral ureteral obstruction (UUO) mice that were treated with single-dose anti-IL11 and anti-TGFβ mAb. Renal tissues were probed for fibrotic marker expression. Kidney function was assessed by serum creatinine, Blood Urea Nitro (BUN), and urine albumin-creatinine ratio (uACR).

Results: In kidney fibroblasts and PCKS, TGFβ induced IL11, Fn1, Col4a1 and Col1a1. However, rhIL11 did not cause increase in fibrotic marker expression in these models. Furthermore, fibrotic marker expression and ECM accumulation were only partially inhibited by anti-IL11 in PCKS whereas no such effect was observed in primary kidney fibroblasts. Chronic administration of rmIL11 in db/db-UNX mice caused an increase in kidney weight, reduction in body weight and upregulated expression of FN, TIMP1 and Col1a1 genes, however no impact on renal function or accumulation of ECM was detectable in the IL11 treated mice. Both IL11 and TGFβ mAbs showed significant reduction in selective fibrotic markers compared to isotype control at Day 3 in UUO kidneys.

Conclusions: We demonstrated that IL11 expression is induced by TGFβ. However, either IL11 by itself or its inhibition failed to significantly impact fibrosis in vitro or kidney function in vivo. Collectively, these data suggest that other factors in renal milieu play a more important role than IL11 to drive fibrosis in the kidney.

Funding: Commercial Support - Janssen Pharmaceutical

SA-PO411

NLRP3 Inflammasome Activation Mediated by Lysyl Oxidase-Like 2 in Human Podocytes in Diabetic Condition

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Background: Diabetic kidney disease (DKD), a major complication of diabetes mellitus is a most common cause of kidney failure. Sterile inflammation is a hallmark of DKD. The NLR family pyrin domain containing 3 (NLRP3) inflammasome is a mechanism of sterile inflammation known to be activated by metabolic stimuli and reactive metabolites associated with DKD. Recently, lysyl oxidase-like 2 (LOXL2) has been reported to associate with tissue fibrosis, inflammation, and oxidative stress, all of which are implicated in the pathogenesis of diabetes and its complications. In this study, we investigated the expression of LOXL2 in human kidney and podocyte, and its contribution to NLRP3 inflammasome expression in podocyte with high-glucose condition.

Methods: We evaluated the expression of LOXL2 in human kidney using immunoflurorescence staining. Real-time PCR and western blotting analysis for LOXL2 mRNA and protein expression were performed using cultured human immortalized podocytes. After fully differentiated, cultured human podocytes were exposed to high glucose (HG) for 48 hours. Podocyte-specific LOXL2 knock-down cells using CRISPR-Cas9 was generated.

Results: By real-time PCR and immunofluorescence staining, LOXL2 expression was identified in human glomerulus and was significantly increased in that with diabetic kidney disease compared with normal control. mRNA of NLRP3 inflammasome expression was also significantly increased in podocyte with HG condition (6.79±0.32 vs. 1.60±0.26, $P<0.05$). Gene silencing of LOXL2 significantly reduced mRNA and protein expression of NLRP3 inflammasome in immortalized human podocytes with HG compared to controls. Western blot analysis showed that collagen I and phosphorylated Smad2 protein expression were significantly decreased in LOXL2 knock-down podocytes.

Conclusions: Our results showed that NLRP3 inflammasome activation may attenuated by gene silencing of LOXL2 in podocytes in diabetic condition.

SA-PO412

Inhibition of YAP Impairs the Expression and Function of WT1 in Diabetic Podocytes

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Background: Podocyte injury and loss are hallmarks of diabetic nephropathy (DN). The molecular mechanisms underlying these phenomena are poorly understood. Yes-associated protein (YAP) is a transcriptional coactivator that regulates cell proliferation, differentiation, and apoptosis. Nuclear YAP in podocytes is crucial for differentiation, cell survival, and structural maintenance. However, the role of YAP in diabetic podocyte injury is unclear

Methods: Inducible podocyte-specific YAP deletion (Yap^{podiKO}) mice and wild-type(Yap^{podWT}) mice were generated by crossing podocin.iCreERT2(+) mice with Yap gene floxed mice. Unilateral nephrectomized (UNX) Yap^{podiKO}, Yap^{podWT}, FVB/NJ mice, and mice with an inactive allele of the Wt1 gene ($Wt1^{CreERT2/+}$) were subjected to streptozotocin injections to induce type I diabetes. Proteinuria and diabetic podocyte injury were assessed. The expression of YAP, TAZ, WT1, TEAD1 and other podocyte-specific proteins in isolated glomeruli was analyzed by immunofluorescent staining or immunoblotting. The expression of these proteins was examined in primary cultured podocytes exposed to 25mM glucose with or without treatment of verteporfin, transfection of YAP siRNA or WT1 siRNA.

Results: In normal human and mouse kidneys, YAP was primarily localized in the nuclei of podocytes. However, diabetic podocytes exhibited increased phosphorylation and cytoplasmic retention of YAP. Diabetic UNX- Yap^{podiKO} and UNX- $Wt1^{CreERT2/+}$ mice were more susceptible to diabetic podocyte injury, as evidenced by earlier proteinuria and severe glomerulosclerosis compared to diabetic UNX-wildtype control mice. In vivo and in vitro studies revealed that YAP is a crucial coactivator of TEAD for Wt1 gene transcription in podocytes, and TEAD1 is an unrecognized downstream target of WT1 in podocytes. In the presence of high glucose, inhibiting YAP in podocytes impaired WT1 expression, and subsequent inhibition of TEAD1 and other wt1 target gene expression may contribute to diabetic podocyte injury.

Conclusions: Constitutively active YAP in podocytes plays a vital role in regulating WT1 gene expression and controlling the transcriptional function of WT1. In diabetic podocytes, inhibition of active YAP impairs WT1 expression, and subsequent inhibition of TEAD1 expression may represent an unrecognized mechanism of diabetic podocyte injury.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO413

AdipoR1 Is Reduced in Glomeruli in Type 2 Diabetes and Its Depletion in Podocytes in Vitro Impairs Integrin β1 Trafficking, Focal Adhesion Assembly, and Cell Adhesion

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Background: Adiponectin signals *via* adiponectin receptors 1 and 2 (AdipoR1/2) but the role of AdipoR1 in podocyte injury, and the regulation of AdipoR1 expression, remain unknown.

Methods: We carried out immunohistochemical stainings of kidneys of AdipoR1-deficient mice or people with type 2 diabetes (T2D). We treated podocytes with sera from lean and obese people, knocked down AdipoR1 lentivirally and overexpressed miR-221-3p in podocytes. Analyses included integrin endocytosis, adhesion and apoptosis assays.

Results: AdipoR1 and its binding partner APPL are downregulated in glomeruli of people with T2D without kidney disease and reduced AdipoR1 correlates with lowered podocyte number. In cultured podocytes, treatment with sera from obese people and overexpression of miR-221-3p reduce AdipoR1 expression. Expression of miR-221-3p is higher in glomeruli of people with T2D in comparison to controls, and the glomerular expression of miR-221-3p inversely correlates with AdipoR1-positive area. In cultured AdipoR1-knockdown (AdipoR1-KD) podocytes and mice depleted of AdipoR1, CD2AP, P-cadherin and synaptopodin are downregulated. This is coupled with reduced survival signaling and enhanced apoptosis and inflammation. AdipoR1-KD leads to mislocalization of APPL and impaired endocytic trafficking of active integrin β1. Focal adhesion (FA) appearance changes to plaque-like in AdipoR1-KD cells, resulting in increased mean FA area and decreased total cellular number of FAs. The expression of Arp3, which controls FA morphology, is reduced upon AdipoR1 knockdown and the cells show reduced re-adhesion.

Conclusions: Diabetes-associated mir-221-3p reduces AdipoR1 expression in podocytes. Lowered expression level of AdipoR1 in podocytes increases apoptosis and inflammation, impairs trafficking of active integrin β1 and alters FAs and cell adhesion. These alterations may contribute to kidney disease development in T2D.

SA-PO414

Diabetic Kidney Disease: Protein 4.1O Reduces YAP/TAZ Activation and Growth Factor-Induced Podocyte Migration

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Background: FRMD3 has been identified as a candidate gene for diabetic nephropathy and encodes for protein 4.1O. So far, four different protein 4.1O splice variants have been identified. The molecular function of these splice variants is unknown. In diabetic kidney disease growth factor signaling, Yes-associated kinase (YAP, and its paralogue TAZ) translocation into the nucleus and target gene transcription is increased. YAP/TAZ and growth factors have been shown to promote cell migration.

Methods: Human kidney biopsy samples from healthy and diabetic patients were stained for protein 4.1O with immunohistochemistry. HEK293T cells were stimulated with low (5 mmol/l), high (25 mmol/l) glucose concentrations or an osmotic control (5 mmol/l glucose + 19, 5 mmol/l mannitol). RNA was isolated and PCR performed. HEK293T cells expressed protein 4.1O splice variants or the control and were stimulated with low, high glucose or mannitol. After cell lysis, western blot was performed for phospho-YAP 397 and actin. Human podocytes were stably transduced with 4.1O splice variants. For migration assays, human podocytes were stimulated with 1 % FCS and different growth factors as well as its inhibitors.

Results: Protein 4.1O expression is detected in healthy human glomeruli by immunohistochemistry. In diabetic patients with CKD stage 3b to 5 and gross proteinuria protein 4.1O expression seems to be increased in podocytes. High glucose but not its osmotic control leads to enhanced transcription of FRMD3. Under high glucose condition protein 4.1O significantly increases YAP phosphorylation. This effect is abrogated if a splice variant lacking a c-terminal domain is expressed. Protein 4.1O reduces podocyte migration after growth factor stimulation compared to control and other splice variants. Treatment with a growth factor inhibitor does not alter podocyte migration in protein 4.1O and control cells.

Conclusions: Expression of protein 4.1O is increased in human diabetic kidney disease and under high glucose conditions. Protein 4.1O splice variants have differential effects on YAP/TAZ activation and growth factor induced migration. This improved understanding of protein 4.1O splice variant function helps to better understand its role in diabetic nephropathy.

SA-PO415

Blocking LFA-1 Reduces Diabetic Kidney Disease in a Mouse Model of Type 2 Diabetes

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Background: Diabetic dyslipidemia, characterized by elevated triglyceride-rich lipoproteins (TRLs), is a known risk factor for renal function decline. At the same time, macrophage accumulation has been observed in kidney biopsies in individuals with diabetic kidney disease (DKD). Thus, we wanted to test the role of monocyte infiltration in the progression of diabetic kidney disease.

Methods: BTBR wildtype (WT) and leptin-deficient (OB; diabetic) mice with LDL receptor deficiency were maintained on a high-fat diet to promote human-like dyslipidemia.

Results: OB diabetic mice with human-like dyslipidemia have a dramatic increase in DKD (glomerular size: 4164 ± 385 μm^2 in WT mice and 8299 ± 622 in OB mice, albuminuria to creatinine ratio: 374.3 ± 71.0 μg/mg in WT mice and 4648 ± 1021 in OB mice). This was associated with increased monocyte recruitment, glomerular macrophage accumulation, and glomerular foam cells, suggesting a pathogenic role for macrophages in DKD progression (Mac-2 positive cells per glomerulus in WT mice was 1.0 ± 0.2 and 6.8 ± 0.6 in OB mice). Notably, diabetes increased the expression of the adhesion molecule ICAM-1 in the glomerulus and in isolated kidney endothelial cells (ICAM-1 μm^2 per glomerulus in WT mice was 11.2 ± 3.1 and 54.7 ± 15.0 in OB mice) with a concomitant increase in monocyte binding partner, LFA-1. To test if LFA-1 facilitates monocyte infiltration into the kidney glomerulus and exacerbates DKD injury, we treated WT and OB mice with a control blocking antibody or an anti-LFA-1 blocking antibody (900 μg/week) for 4 weeks. Blocking LFA-1 did not affect blood glucose or lipid levels but resulted in a reduction in glomerular hypertrophy and urinary albuminuria in OB mice (glomerular hypertrophy: 6209 ± 346 μm^2 in control antibody-treated OB mice compared to LFA-1 treated OB mice 4844 ± 251, albumin to creatinine ratio: 1084 ± 157 μg/mg in control-treated OB mice compared to anti-LFA-1 treated OB mice 546 ± 164.0).

Conclusions: Together, these data suggest that diabetes promotes monocyte infiltration into the glomerulus, which in turn contributes to DKD.

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SA-PO416

The Insulin/Insulin-Like Growth Factor Axis Is Critically Important in the Kidney Podocyte Controlling Gene Transcription and Spliceosome Function

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Background: Insulin signalling to the podocyte via the insulin receptor (IR) is crucial for kidney function and insulin-like growth factor 1 (IGF1) signalling through the structurally related insulin-like growth factor 1 receptor (IGF1R) is also known to directly affect the podocyte. Since the IR and IGF1R may act redundantly in some contexts, this study sought to elucidate the role of the insulin/IGF1 axis in podocyte function using mouse and cell culture models deficient in both receptors.

Methods: To examine the effects of combined receptor loss *in vivo*, a transgenic mouse model with conditional inactivation of podocyte IR and IGF1R was generated. *In vitro*, conditionally immortalised genetic IR/IGF1R dual knockout podocytes were characterised using global proteomic and transcriptomic analysis.

Results: Podocyte specific IR/IGF1R knockout mice developed significant albuminuria and a severe renal phenotype with global sclerosis, renal failure and death occurring between 4 and 24 weeks. >90% loss of IR/IGF1R in cultured mouse podocytes was also detrimental resulting in >50% cell death 7 days after gene knockdown. Enrichment analysis of total proteomic data revealed a striking downregulation of gene ontology terms associated with DNA repair, splicing and RNA processing activity in IR/IGF1R knockdown cells. Long-read RNA sequencing was performed to obtain an overview of global splicing differences in the IR/IGF1R knockdown transcriptome and to determine the effect of spliceosome depletion on the transcriptomic profile of these cells. Analysis of this data revealed higher levels of intron retention and an increase in the proportion of transcripts containing premature termination codons in IR/IGF1R knockdown podocytes along with differential expression of fibronectin splice variants.

Conclusions: This work underlines the critical importance of podocyte insulin/IGF signalling and reveals a novel role for this extrinsic hormonal signalling axis in the maintenance of genomic integrity and in RNA processing by regulating spliceosome activity in this cell type.

Funding: Government Support - Non-U.S.

SA-PO417

Podocyte-Specific Deletion of SHP-1 Restored SUMOylation of Podocin and Reversed the Progression of Diabetic Kidney Disease

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Background: Both clinical and experimental data suggest that podocyte injury is involved in the onset and progression of diabetic kidney disease (DKD). Although the mechanisms underlying the development of podocyte loss is not completely understood, critical structure proteins such as podocin have been shown to play a major role in podocyte survival and function. We have reported that SHP-1 (a protein tyrosine phosphatase) expression is increased in podocytes of diabetic mice and glomeruli of patients with diabetes. However, the contribution of SHP-1 in podocytes has not been investigated.

Methods: Conditional podocyte specific SHP-1 deficient mice (Podo-SHP-$1^{-/-}$) have been generated to evaluate the impact of SHP-1 on renal function (albuminuria and GFR) and kidney pathology. Deletion of SHP-1 was performed at 4 weeks of age (prevention group; prior to the onset of diabetes) and after 16 weeks of diabetes (reversibility group). Mice were euthanized at 24 weeks of age for renal function and histology assessment.

Results: Elevated albuminuria and GFR seeing in the diabetic mice were preserved in the diabetic mice with specific podocyte ablation of SHP-1 at 4 weeks of age. Interestingly, late deletion of SHP-1 in podocytes after 16 weeks of diabetes also restored renal function and prevented kidney disease progression. Structural changes such as mesangial cell expansion, glomerular hypertrophy, GBM thickening, podocyte foot process effacement and podocyte loss induced by diabetes were also blunted and even reversed with deletion SHP-1 specifically in podocytes. Moreover, podocyte-specific deletion of SHP-1 at 4 weeks and 20 weeks of age prevented diabetes-induced expression of Coll IV, fibronectin, RhoA, and ROCK1, whereas it restored nephrin, podocin and TRPC6 expression. Mass spectrometry analysis revealed that SHP-1 reduced SUMO2 expression and is association with podocin which was also confirmed by immunoprecipitation and co-immunofluorescence in patients with diabetes kidney disease, while podocyte-specific deletion of SHP-1 allow to maintain podocin integrity and stability in a diabetic context.

Conclusions: Our data uncovered a new role of SHP-1 in the regulation of cytoskeleton dynamics and slit diaphragm protein expression and stability, and specific deletion of SHP-1 contribute to preserve podocyte function and even reverse DKD progression.

Funding: Government Support - Non-U.S.

SA-PO418

GSK3β: A Key Regulator of Glomerular Podocyte Injury in Diabetic Kidney Disease

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Background: Emerging evidence suggests that glycogen synthase kinase (GSK)3β, a critical transducer downstream of the insulin signaling pathway, acts as a convergent point for myriad pathways implicated in kidney injury, repair, and regeneration. However, its role in the pathogenesis of diabetic kidney disease remains highly controversial and was examined here.

Methods: Conditionally immortalized mouse podocytes were cultured under nonpermissive conditions and exposed to a diabetic milieu containing high ambient glucose and insulin as well as proinflammatory conditions, following GSK3β silencing, ectopic expression of a constitutively active GSK3β mutant (S9A), or treatment with tideglusib, a highly-selective small molecule inhibitor of GSK3β. Podocyte injury was assessed and signaling pathways examined.

Results: Upon diabetic insult, podocytes demonstrated prominent signs of cytopathic changes, marked by loss of homeostatic marker proteins like synaptopodin, increased oxidative stress and apoptosis, and stress-induced premature senescence, as evidenced by increased staining for the acidic senescence-associated-β-galactosidase activity, amplified formation of γH2AX foci, and elevated expression of mediators of senescence signaling, like p21 and $p16^{INK4a}$. Podocyte injury was associated with a reduction in inhibitory phosphorylation of GSK3β, denoting GSK3β hyperactivity. In podocytes overexpressing S9A, diabetic podocytopathy was worsened, concomitant with a desensitized insulin signaling activity, enhanced senescence response, impaired Nrf2 antioxidant response and the ensued exacerbation of oxidative damages. Conversely, GSK3β knockdown potentiated the insulin signaling, reinforced Nrf2 antioxidant response, and suppressed senescence, resulting in an improvement in podocyte injury. This protective effect was mimicked by tideglusib co-treatment, suggesting that GSK3β hyperactivity plays a key role in mediating diabetic podocytopathy.

Conclusions: Our findings suggest that GSK3β hyperactivity contributes to glomerular podocyte injury in diabetic kidney disease.

Funding: NIDDK Support

SA-PO419

Photobiomodulation Protects High-Fat Diet-Induced Diabetic Kidney Injury via Inhibition of Inflammation

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Background: Innovative therapeutic strategies for DKD are urgently needed due to limitations of current treatments. PBM, using red or near-infrared light to modulate cellular function, has gained increasing interest among available therapeutic strategies for many diseases due to its wide variety of positive effects, such as suppressing inflammation, improving mitochondrial activity, and alleviating oxidative stress, which are all inherent in DKD. However, the potential role of PBM in treating DKD has not yet been explored.

Methods: *In vitro*, human proximal tubular cells (HK2 cells) pre-treated with low dose (4.32 J) or high dose (8.64J) PBM were then incubated with TGF-β1 (2 ng/ml)

for 48 hours with or without PBM irradiation every 24h. *In vivo*, high-fat diet (HFD)-induced DKD mice were treated with low dose (7.2J) or high dose (18J) PBM 3 times per week commencing at 12 weeks of HFD and continue for 12 weeks. SHAM treatment was identical but with laser diodes switched off. Renal function, fibrotic and inflammatory markers were examined.

Results: *In vitro* results showed that TGF-β1 induced overexpression of fibronectin and tumour necrosis factor (TNF-α) ((*P*<0.01) at both mRNA and protein levels, which were significantly reversed by low (*P*<0.05) but not high PBM dose. Moreover, low but not high PBM dose significantly inhibited TGF-β 1-induced phosphorylation of p65 in comparison with the SHAM group. *In vivo*, low but not high PBM dose improved HFD-induced kidney injury with significant decreases in the levels of blood urea nitrogen, 24h albumin, and urine albumin-creatinine ratio (*P*<0.05). Furthermore, HFD-induced overexpression of collagen IV, TNF-α, a-SMA, TGF-β1, F4/80, and CD68 were reversed by low (*P*<0.05) but not high dose of PBM.

Conclusions: PBM exerts its reno-protective effect via inhibiting inflammation in in vitro and in high-fat diet-induced diabetic mice. This effect is biphasic, with PBM above the therapeutic dose showing no improvement in renal function.

Funding: Government Support - Non-U.S.

SA-PO420

C/EBPα Exacerbates Diabetic Nephropathy by Inducing ACSL4-Mediated Ferroptosis in Tubular Cells

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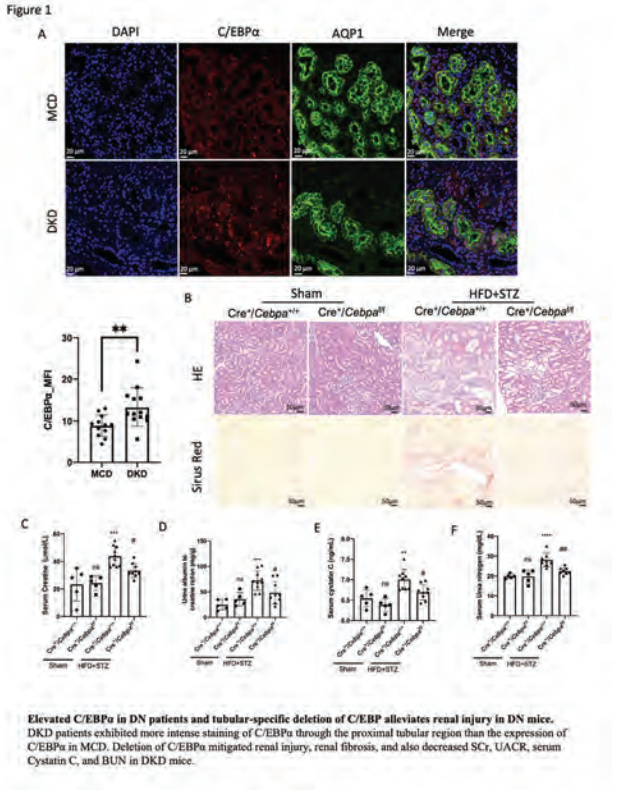
Background: Diabetic nephropathy (DN) is a serious complication of diabetes, leading to the progressive decline of kidney function. In this study, we examined the increased expression of CCAAT/enhancer binding protein alpha (C/EBPα) in DN patients and investigated its potential role in DN pathogenesis.

Methods: Pepck-Cre^{+}/*Cebpa*$^{+/+}$ (WT) and Pepck-Cre^{+}/*Cebpa*$^{fl/fl}$ (KO) mice were streptozotocin (STZ)-induced for diabetes. Renal histopathology, UACR, BUN, SCr, and Cystatin C levels were assessed for renal injury. Kidney tissues were analyzed for ferroptosis markers (GPX4, 4-HNE, MDA). C/EBPα transcriptional activity was examined using CUT&TAG, dual-luciferase, and ChIP-qPCR.

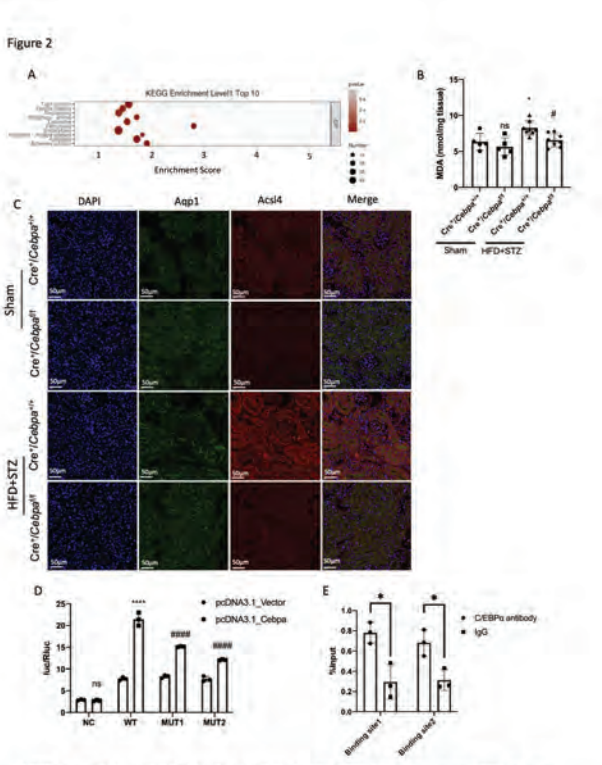
Results: STZ-treated WT mice showed more severe pathological injury, elevated SCr, cystatin C, BUN, and UACR. They also displayed pronounced signs of ferroptosis, including increased MDA, 4-HNE, and reduced GPX4. We further demonstrated that C/EBPα attenuated renal ferroptosis by binding to the TRS of ACSL4, a key enzyme of lipid peroxidation.

Conclusions: We discovered that C/EBPα regulated ACSL4 expression by binding to its TRS, triggering lipid peroxidation and subsequent ferroptosis. And knockout of C/EBPα could alleviate ferroptosis and ameliorate tubular injuries in DN.

Funding: Government Support - Non-U.S.



Elevated C/EBPα in DN patients and tubular-specific deletion of C/EBP alleviates renal injury in DN mice. DKD patients exhibited more intense staining of C/EBPα through the proximal tubular region than the expression of C/EBPα in MCD. Deletion of C/EBPα mitigated renal injury, renal fibrosis, and also decreased SCr, UACR, serum Cystatin C, and BUN in DKD mice.



C/EBPα attenuated ferroptosis by directly upregulating ACSL4. CUT&TAG-sequencing and KEGG pathway enrichment revealed a significant enrichment of genes in the ferroptosis signaling pathway. Knockout of C/EBPα mitigated ferroptosis in DN and decreased the expression of ACSL4. C/EBPα regulated the expression of ACSL4 by binding to its TRS sequence.

SA-PO421

PDIA4 Ameliorates Renal Tubular Pyroptosis via Suppressing IRE1a-sXBP1 Pathway in Diabetic Kidney Disease

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Background: Accumulating evidences imply the vital role of tubular injury in the pathogenesis of DKD, as well as of ER stress, the regulatory machinery of protein homeostasis. ER stress results in the activation of distinct unfolded protein response (UPR), and the effect of conserved UPR branch IRE1 on the diabetic tubular injury is still elusive.

Methods: We evaluated the activation of IRE1a/sXBP1 and NLPR3 inflammasome, as well as pyroptosis in the high glucose-stressed tubular cells. Furthmore, effects and underlying mechanism of PDIA4 on the activation of IRE1a induced by high glucose were investigated.

Results: We identified the activated IRE1α/sXBP1 and NLRP3 inflammasome, as well as pyroptosis via analyzing the differential genes expression in the diabetic tubules, which was further confirmed in the glucose-stressed tubular cells and biopsy samples from patients of DKD. Consistently, silencing down of IRE1α or administration of IRE1α inhibitor alleviates high glucose-induced NLRP3 inflammasome and pyroptosis. Furthermore, we revealed that PDIA4 suppresses the high glucose-induced tubular IRE1α/sXBP1. Immunoprecipitation and crosslinking assay demonstrated that high glucose promotes the dynamic interaction among PDIA4, Bip and IRE1α. That is, dissociation of Bip with IRE1α and Bip with PDIA4, while increase of PDIA4 with IRE1α. Bond of PDIA4 with IRE1α depends on -CHGC motif, and thus suppresses the activation of IRE1α/sXBP1. Dual-luciferase assay revealed that sXBP1 transcriptionally induces HSC70, hence results in the decrease of PDIA4 via CMA dependent degradation. In vivo, we overexpressed PDIA4 in two mouse models of DKD via injection of AAV9-PDIA4. Our data demonstrated the ectopic overexpression of PDIA4 alleviates the diabetic tubular injury and inflammation reaction, accompanied with the reduced IRE1α/sXBP1 and NLRP3 inflammasome.

Conclusions: Altogether, we revealed that the stress of high glucose activates IRE1α/sXBP1 pathway, NLRP3 inflammasome and pyroptosis in renal tubular cells. XBP1s reduces PDIA4 via induction of HSC70 and thus selective CMA degradation. Reciprocally, PDI4 exhibits inhibitory effect on IRE1α/sXBP1 pathway via bond with oligomerized IRE1α.

Funding: Government Support - Non-U.S.

SA-PO422

Screening for Small-Molecule Inhibitor for KIM-1 and Its Functional Validation in Kidney Fibrosis

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Background: Kidney Injury Molecule-1 (KIM-1) is a glycosylated protein upregulated following proximal tubular injury in humans and mice. With acute and chronic injury, KIM-1 mediates the uptake of apoptotic cells, oxidized lipids, advanced glycation end products (AGEs), and albumin-bound to long-chain fatty acids. Overexpression of KIM-1 causes chronic kidney disease (CKD) in mice.

Methods: We developed a cell-based high throughput functional assay for KIM-1 mediated uptake of DiI labeled ox-LDL and screened 14,414 unique compounds. After setting up a score based on each compound's potential to inhibit cellular ox-LDL uptake, we selected 240 potential hits and cherry-picked them from the primary screening. We performed secondary assays to confirm whether TW-37 quenches the fluorophore or it cleaves the extracellular domain of KIM-1 We employed cell-based binding assays, competitive inhibition assays, and Raman spectroscopy to investigate the binding of recombinant human KIM-1 to a top-hit molecule, TW-37.

Results: We found several hits, with TW-37 as the top hit. TW-37, a second-generation benzene sulfonyl derivative of gossypol, had the highest inhibitory effect on ox-LDL uptake. TW-37 is known to have Bcl2 inhibitory activity; however, Bcl-2 blockade with another specific Bcl-2 inhibitor, ABT-263, did not inhibit KIM-1-dependent ox-LDL uptake, showing that the effects of TW-37 and were not related to Bcl-2 inhibition. TW-37 is not toxic to epithelial cells at concentrations up to 11 μM. Our results from fluorescence quenching experiments confirmed that TW-37 does not quench DiI-fluorophore nor cleave KIM-1. *In silico* docking, experiments revealed a putative TW-37 binding pocket spanning residues 37 to 52 of KIM-1. Raman spectroscopy showed that TW-37 specifically binds to recombinant human KIM-1 and not to the BSA. TW-37 significantly decreased the cellular binding of ox-LDL and BSA-conjugated palmitic acid.

Conclusions: We have identified and characterized TW-37 as an inhibitor of KIM-1 binding. Thus, TW-37 has potential use as a therapeutic for treating kidney disease where chronic KIM-1-mediated uptake of lipid-laden albumin into the proximal tubule contributes to fibrosis and CKD.

Funding: NIDDK Support, Other NIH Support - American Heart Association

SA-PO423

Renal Tubule-Specific Angiotensinogen Knockout Ameliorates Diabetic Kidney Disease in Type 1 Diabetic Akita Mice

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Background: Angiotensinogen (AGT), the sole precursor of angiotensins in the renin-angiotensin system (RAS), is highly expressed in the renal proximal tubules (RPTs) of mice and patients with diabetic kidney disease (DKD). We reported previously that mice specifically overexpressing *Agt* in RPTs (*Agt*-Tg) develop hypertension and kidney injury. However, the pathophysiological roles of the intrarenal RAS in DKD progression is not well-defined. We investigated whether genetic deletion of *Agt* specifically in renal tubules (RT) could improve kidney injury in type 1 diabetic Akita mice.

Methods: We generated Akita mice with RT-specific *Agt* knockout (Akita Agt^{RT} KO) by crossbreeding Akita $Agt^{lox/lox}$ mice with Agt^{RT} KO (tubule-specific Pax8-Cre) mice. Male Akita Agt^{RT} KO, Akita $Agt^{lox/lox}$, non-diabetic $Agt^{lox/lox}$ and Agt^{RT} KO mice were studied at 20 weeks of age. Physiological data, kidney function, and urinary angiotensin II (Ang II) were assessed. Immunostaining on kidney sections, western blotting (WB) and real-time quantitative PCR (RT-qPCR) were performed to assess protein and gene expression in isolated RPTs.

Results: *Agt* deletion in RT did not significantly affect systolic blood pressure in Akita mice. Fasting blood glucose levels were lower in Akita Agt^{RT} KO vs. Akita mice. Glomerular filtration rate was increased in Akita mice, but was normalized in Akita Agt^{RT} KO mice. The urinary albumin-creatinine ratio (ACR) and Ang II levels were increased in Akita mice, but significantly decreased in Akita Agt^{RT} KO mice. Akita mice exhibited glomerular and tubular hypertrophy, tubular luminal dilation, and necrosis; these abnormalities were markedly attenuated in Akita Agt^{RT} KO mice. Podocyte number (defined by P57 and WT1 staining) was decreased in Akita mice, but was partially restored in Akita Agt^{RT} KO mice. Sodium-glucose cotransporter 2 (SGLT2) expression was lower in Akita Agt^{RT} KO mice than in Akita mice. Urinary glucose excretion was higher in Akita Agt^{RT} KO mice than in Akita mice.

Conclusions: Deletion of *Agt* in RT decreased hyperglycemia, glomerular hyperfiltration, ACR, kidney injury, and SGLT2 expression in Akita mice, demonstrating that inactivation of the intrarenal RAS attenuates DKD progression, at least in part, via down-regulation of SGLT2 expression.

Funding: Government Support - Non-U.S.

SA-PO424

Non-Steroidal Mineralocorticoid Receptor Antagonists (MRAs)-Finerenone Ameliorates Mitochondrial Dysfunction via PI3K/Akt Signaling Pathway in Diabetic Tubulopathy

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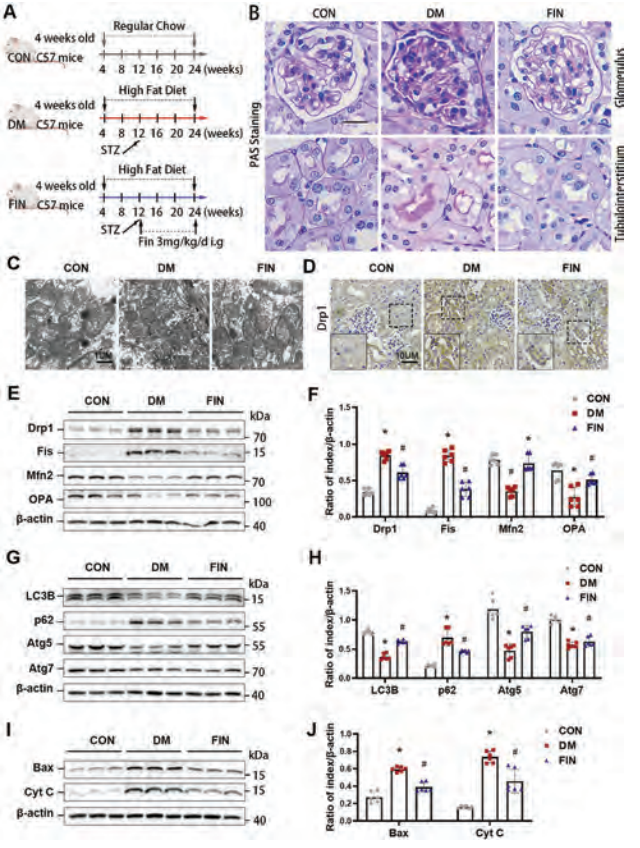
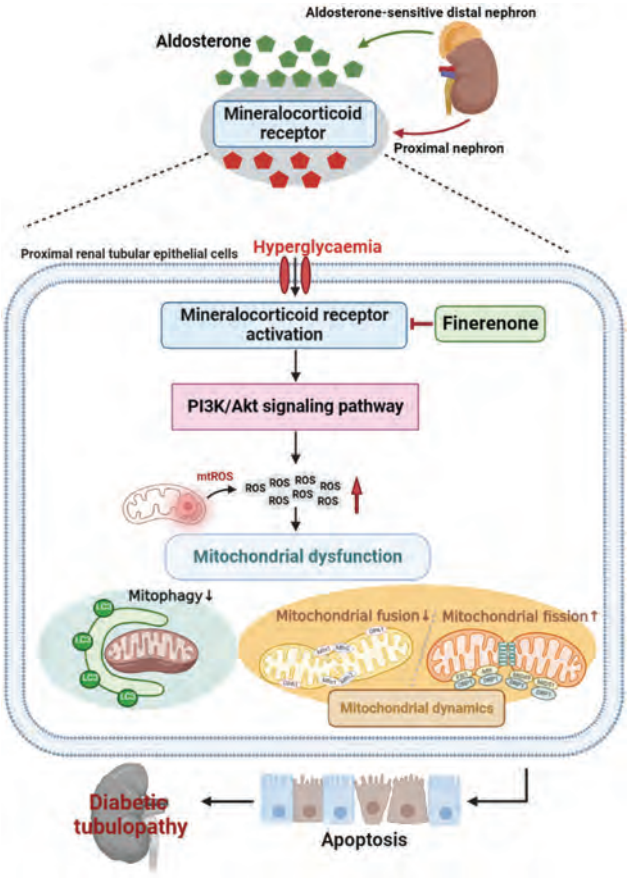
Background: Diabetic tubulopathy (DT) is gradually valued and elucidated as same as glomerular pathology in the pathophysiological perturbations of diabetic kidney disease (DKD). The mitochondria-centric view of DT is emerging as a vital pathological factor in metabolic diseases including DKD. Finerenone (FIN), a novel non-steroidal MRAs, attenuates proteinuria and fibrosis in tubules in DM, but these precise pathomechanisms remain unclear.

Methods: We investigated the role of mineralocorticoid receptor (MR) activation in perturbation of mitochondrial function via PI3K/Akt signaling pathway, including mitochondrial dynamics and mitophagy, under a DM state or hyperglycemia ambience.

Results: *In vivo*, the molecules were examined in kidneys of DM and FIN treatment mice as well. Notably, FIN administration partially attenuated mitochondrial fragmentation, oxidative stress, and apoptosis and restored mitophagy via PI3K/Akt signaling pathway both in HK-2 cells subjected to HG ambience and tubular cells of DM mice.

Conclusions: These results suggest a novel mechanism linking MR activation to mitochondrial dysfunction via PI3K/Akt signaling pathway during tubular injury in the pathogenesis of DKD and it provides evidence support for FIN as a agent for the treatment of DKD.





SA-PO425

Stable Isotope Resolved Mass Spectrometry in Individuals with Type 1 Diabetes Reveals that Diminished Renal Mitochondrial Function Precedes Clinical Diabetic Kidney Disease

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Background: Significant metabolic reprogramming occurs in diabetic kidney disease (DKD). Metabolomics studies of murine models of DKD demonstrate increased glucose metabolism and urinary and kidney lactate production. However, whether such changes occur in individuals with type 1 diabetes (T1D), and the temporal nature of such reprograming with respect to clinical DKD has not been systematically investigated. Stable isotope resolved mass spectrometry using [U-C13] glucose allows dynamic measurement and tracing of relevant glucose-derived metabolic pathways. We performed glycemic clamp study with [U-C13] glucose to evaluate how kidney metabolism is altered in T1D.

Methods: Euglycemic-hyperglycemic clamp studies with [U-13C] glucose were conducted in matched healthy control (HC), and in T1D individuals with established early DKD, and without clinical microvascular complications. All groups had similar estimated glomerular filtration rates (eGFR, CKD-EPI equation). Urine and plasma were collected throughout the course of the clamp study. Blood glucose levels were maintained at 100 mg/dl (±20) for the euglycemic clamp and 300 mg/dl (±20) for the hyperglycemic clamp arms of the study. Urine was analyzed with LC-MS for labeled urinary metabolites which reflect kidney metabolism.

Results: Urinary metabolites in the glycolytic and TCA cycle (mitochondrial) were detected in all three groups. Analysis of the TCA cycle metabolite isotopologues (malate, fumarate and α-ketoglutarate) under hyperglycemic clamp demonstrated significantly increased labeled glucose incorporation into the HC urine in comparison to T1D individuals with and without DKD. Incorporation into citrate and cis-aconitate were significantly elevated in the HC group only versus T1D DKD group.

Conclusions: These metabolic flux labeling studies suggest that T1D results in diminished kidney mitochondrial metabolism, compared to HC under hyperglycemic conditions. This difference was even more pronounced between HC and T1D with DKD. Our data strongly suggests that metabolic changes occur in T1D that results in reduced glucose mitochondrial metabolism, even prior to clinical DKD.

Funding: NIDDK Support, Other NIH Support - T32GM008322, Private Foundation Support

SA-PO426

SIRPα Contributions to Muscle Kidney Cross-Talk in Diabetic Kidney Disease

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Background: Fatty acid oxidation (FAO) is a preferred energy source for highly metabolic cells including cardiomyocytes and proximal tubular cells. The kidney is second only to the heart in mitochondrial numbers and oxygen consumption. ATP generation occurs mainly through fatty acid oxidation in the proximal tubular cells. Lipotoxicity has been linked to worsening kidney disease. Specifically, ATP depletion increases lipid accumulation, tubular necrosis and maladaptive repair ultimately leading to kidney dysfunction. Here we examined the role of muscle mediator, signal regulatory protein alpha (SIRPα) and its role in kidney FAO and function. Circulating serum SIRPα has been identified in patients with CKD, therefore we have examined the effects of SIRPα in a diabetic model of kidney disease.

Methods: Control flox mice, muscle (m)-specific and adipose (ad)-specific SIRPα knockout (KO) mice were subjected to a 60% high fat diet and compared to mice on standard chow. Metabolic processes including mRNA, protein expression, and oxygen consumption rates (Seahorse Bioscience) were identified. Triglyceride content was evaluated by triglyceride clearance assay.

Results: Control flox mice display elevated levels of serum SIRPα in response to HFD. mSIRPα KO mice but not adipose-specific SIRPα KO mice exhibit evidence of improved body weight, intracellular insulin signaling in peripheral tissues, and adipokine profile. Additionally, these mice demonstrate less intramuscular fat when compared to control mice on HFD. Also, exogenous SIRPα impaired proximal tubular FAO while reducing ATP production. Finally, kidney tissues in mSIRPα KO mice unlike adSIRPα KO mice displayed improved renal fatty acid oxidation, a reduction in kidney triglyceride content, less kidney fibrosis, and importantly protection against diabetic kidney disease (cystatin C similar to control) despite obesity-induced diet.

Conclusions: These results suggest the importance of the muscles contribution to kidney disease, specifically, myokine SIRPα in exacerbating diabetic kidney disease. Our discoveries provide insight in correcting metabolic defects associated with kidney FAO and to prevent diabetic kidney disease.

Funding: Private Foundation Support

SA-PO427

ALCAT1-Mediated Cardiolipin Remodeling Contributes to Podocyte Mitochondrial Dysfunction in Diabetic Kidney Disease

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Background: Recent studies suggested that mitochondrial damage resulting from abnormal cardiolipin remodeling was associated with the pathogenesis of diabetic kidney disease (DKD). AS a cardiolipin acyltransferase, ALCAT1 was confirmed to be involved in Parkinson's diseases and other aging-related diseases by regulating pathological CL remodeling. The purpose of this investigation was to determine the role of ALCAT1 in DKD.

Methods: We used db/db mice to conduct the in vivo experiments. Double immunolabeling and Western blots (WB) were performed to assess ALCAT1 distribution and expression in glomeruli. Mitochondrial structure was examined by transmission electron microscope (TEM). CL composition was assessed by lipidomics analysis. We cultured conditionally immortalized human podocytes to perform the in vitro studies. Lipidomics, TEM and WB analysis were similar to the in vivo study. Mitochondrial function was evaluated by mitochondrial membrane potential, mitochondrial ROS and ATP. The overexpression plasmids and siRNA were transfected to further investigate the changes of podocyte mitochondrial injury following overexpression or knockdown of ALCAT1.

Results: ALCAT1 expression was increased in glomerular podocytes of db/db mice and high-glucose (HG) cultured podocytes, accompanied by increased oxidized CL (ox-CL) and mitochondrial damage. ALCAT1 deficiency effectively blocked HG-induced ox-CL and podocyte mitochondria damage. In contrast, ALCAT1 upregulation enhanced ox-CL and mitochondria malfunction. Moreover, CL antioxidant SS-31 treatment markedly inhibited mitochondria dysfunction and cell injury. And SS-31 treatment could partly reverse the damage caused by ALCAT1 overexpression. We further found that ALCAT1 could mediate the key regulators of mitochondrial dynamics and mitophagy.

Conclusions: Our results demonstrated that ALCAT1-mediated cardiolipin remodeling played a crucial role in diabetic kidney disease and provided new insights for its treatment.

Funding: Government Support - Non-U.S.

SA-PO428

IL-6-ZIP14-GPX4 Axis Is Involved in Ferroptosis in Diabetic Kidney Disease

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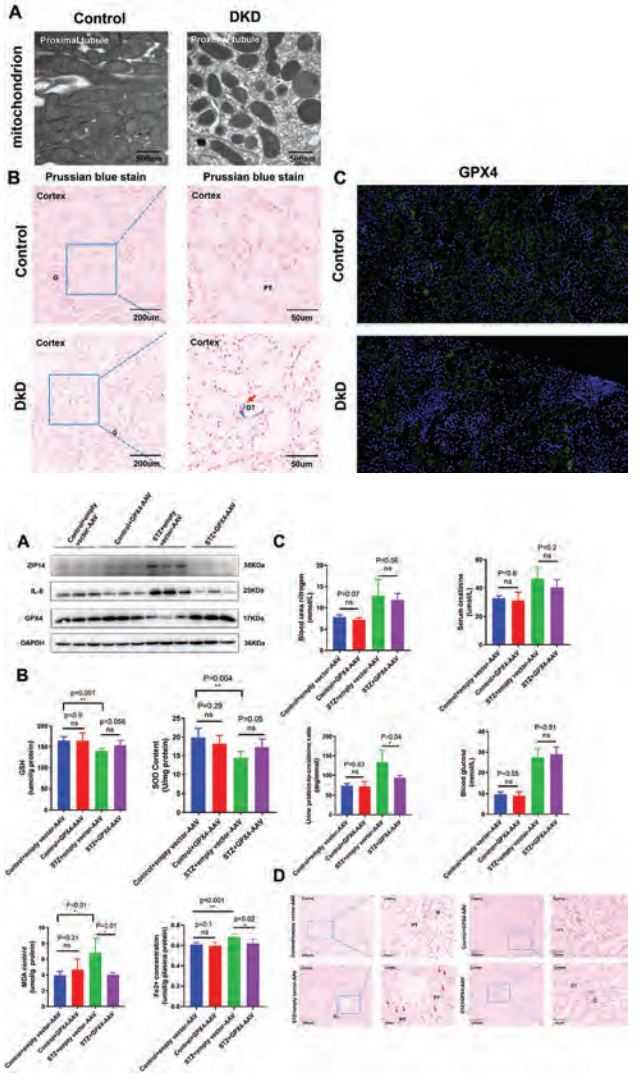
Background: Ferroptosis is caused by lipid peroxidation and iron accumulation. Our previous study have shown that ZIP14 is involved in ferroptosis in Diabetic kidney disease(DKD), but the mechanism is unknown. Interleukin-6 (IL-6) can specifically increase the expression of ZIP14. Thus, we hypothesize that IL-6-ZIP14-GPX4 axis is involved in ferroptosis in DKD.

Methods: Renal biopsies of patients with DKD were collected to detect the changes related to ferroptosis. We induced DKD in 8-week-old male rats with streptozotocin (STZ) and treated with GPX4-Adeno-associated viral (AAV) via tail vein to analyze the degree of renal injury. The expression of GPX4, IL-6 and ZIP14 was detecetd in kidney.

Results: The expression of GPX4 was down-regulated in DKD. While the levels of IL-6 and ZIP14 were up-regulated in kidney of STZ rats. Iron deposition was confirmed in kidney of DKD. The mitochondria of renal biopsy presented reduced mitochondrial volume and missing mitochondrial cristae. The levels of malondialdehyde (MDA), and Fe2+ in STZ group were higher than in the control. While the levels of GSH and SOD were lower than in the control. Over-expression of GPX4 decreased the expression of IL-6 and ZIP14 in kidney of STZ rats. Also, the urine protein-creatinine ratio, and the levels of both MDA and Fe2+ were decreased.

Conclusions: The IL-6-ZIP14-GPX4 axis is involved in ferroptosis in DKD.



SA-PO429

Long-Read Sequencing Identifies Loss of Proximal Tubule Spliceosome Gene Srsf7 as a Driver of Inflammation Through Alternative Splicing

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Background: Diabetic kidney disease (DKD) is the leading cause of end-stage renal disease worldwide, and SGLT2i have potent reno-protective effects, however the mechanism is unclear. Recently, the mRNA splicing factor *Srsf7* was shown in mice to be downregulated in DKD, and SGLT2i treatment specifically rescued *Srsf7* expression in the S1-segment of the proximal tubule (PT).

Methods: hTERT-RPTECs were treated with control or siRNA against *SRSF7* for 72h, then submitted for long-read (Nanopore) sequencing to more accurately capture alternative splicing. Reads were aligned using minimap2 then quantified with Salmon and analyzed for differential gene expression and differential transcript usage (DTU) using the R packages IsoformSwitchAnalyzeR and bambu.

Results: *SRSF7*-knockdown (KD) efficiency was >80%. Differential gene expression analysis also identified *SRSF7* as a top significantly down-regulated gene. *RSAD2* and *OAS2*, genes involved in viral inflammatory response, were identified as top upregulated genes, which was confirmed by significant increases in both gene and protein expression in *SRSF7*-KD cells. Gene Ontology analysis showed upregulation of biological processes related to viral response, NFkB signaling, and response to interferon, well as enrichment of these hallmark inflammatory pathways by GSEA. Conversely, processes related to cell cycle were downregulated in cells with *SRSF7*-KD, suggesting changes in proliferation. *MKI67* gene expression and BrdU incorporation were decreased in *SRSF7*-KD cells. The genes *SNAPIN*, *LGMN*, and *GGCT* were identified by both computational tools as having alternatively spliced isoforms between control and *SRSF7*-KD cells and were validated using RT-PCR. Genes with alternative splicing were enriched in pathways related to viral response/inflammatory signaling, mRNA alternative splicing, RNA metabolism, and apoptosis.

Conclusions: Decreased *SRSF7* in PT cells drives expression of pro-inflammatory genes and regulates splicing of inflammatory genes. Pro-inflammatory alternative splicing events in the S1 segment may thus drive DKD progression and SGLT2i are reno-protective by promoting an anti-inflammatory S1 transcriptome by rescuing Srsf7 expression.

Funding: NIDDK Support

SA-PO430

SGLT2 inhibition Alters Pdk4 and Ces1g Expression in a Mouse Model of Diabetes

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Background: Diabetes mellitus (DM) continues to be the major contributor to the development of chronic kidney disease (CKD). SGLT2 inhibitors (SGLT2i) have emerged as an important therapeutic intervention to slow the progression of CKD in patients with and without DM. However, the mechanisms by which SGLT2i confer a protective effect in CKD have not been fully elucidated. To further explore the protective mechanisms of SGLT2i in the kidney, we utilized Riboseq to examine the translatome in a mouse model of type 2 DM following SGLT2i treatment.

Methods: 8-week-old db/db (Kallis strain) and db/m (background control) mice were gavaged with 1mg/kg of dapagliflozin (dapa) or vehicle control daily for 4 weeks. Mice were subsequently euthanized and kidneys were harvested for bulk Riboseq and RNA seq.

Results: Riboseq analysis revealed that SGLT2i treatment of db/db mice significantly decreased kidney expression of pyruvate dehydrogenase kinase 4 (Pdk4). Given that Pdk4 is a known inhibitor of pyruvate dehydrogenase, this suggests SGLT2i alters glucose utilization and energy production in the kidney. Additionally, SGLT2i significantly increased the expression of Ces1g (carboxylesterase 1g) (Figure 1). Ces1g is involved in cholesterol and fatty acid utilization.

Conclusions: To our knowledge, this is the first report of SGLT2i effects on Pdk4 and Ces1g expression in the kidney. These data suggest that the protective effects of SGLT2i may include significant alterations in pathways regulating glucose and lipid metabolism. Ongoing studies will determine if direct manipulation of Pdk4 and/or Ces1g provides kidney protective effects in DM independent of SGLT2i.

Funding: NIDDK Support

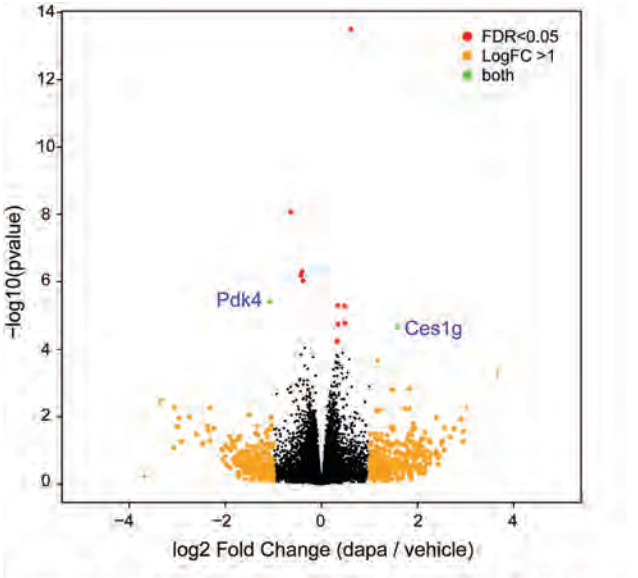

Figure 1: Volcano plot of gene expression in the kidney of db/db mice treated with SGLT2i vs vehicle control (Riboseq). Pdk4 is significantly decreased by SGLT2i. Ces1g is significantly increased by SGLT2i.

SA-PO431

Dampening Protein Translation Abrogates the Development of Albuminuria in a Diabetic Mouse Model

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Background: Diabetes remains a major cause of chronic kidney disease and end stage kidney disease. The pathophysiologic processes leading to the development of kidney disease in diabetes are poorly understood because it is not common practice to obtain kidney biopsies in diabetic patients without diabetic kidney disease (DKD). We have previously demonstrated that translation, the fundamental process in protein synthesis, is increased in the kidney in a mouse model of diabetes. This increase in translation was observed prior to the onset of DKD. Here we investigate whether direct inhibitors of protein translation, such as tetracyclines, can mitigate the development of proteinuria.

Methods: Db/db mice on a Kaliss strain background which are prone to developing manifestations of DKD over time were used. These mice demonstrate an increase in translation starting as early as eight weeks. Treatment with minocycline (50mg/kg daily x 4 weeks by gavage) was started at 8 weeks and the kidneys were harvested for polyribosomal profiling (PRP). In a parallel set of experiments, 6-week old Db/Db mice (n=10) were treated for up to 10 weeks with minocycline (50mg/kg daily in drinking water) and urine was collected weekly for measurement of albuminuria. Finally, a separate group of Db/Db mice were treated with the SGLT2 inhibitor (dapagliflozin; 1mg/kg, po) for 4 weeks and kidneys were harvested for PRP.

Results: Treatment with minocycline resulted in a 30% reduction in global protein translation as measured by PRP. Fifty percent of the vehicle control treated mice developed significant albuminuria (albumin/creatinine ratio between 0.6-6 μg/μg). In contrast, in all mice treated with minocycline allbumin/creatinine ratios < 0.5 μg/μg. Interestingly, SGLT2 inhibition also resulted in reduction of protein translation as measured by PRP.

Conclusions: Increased protein synthesis in the kidney is a feature of diabetes before the onset of DKD. Pharmacologic strategies to reduce protein synthesis may serve as a new therapeutic avenue to prevent the development of DKD.

Funding: NIDDK Support

SA-PO432

The Effect of Altered Branched-Chain Amino Acid (BCAA) Metabolism on Proteinuria and Mesangial Expansion in db/db Mice Treated with SGLT2 Inhibitor

Junichiro Hagita,[1,2] Toshiki Tsuboi,[1] Shoma Tsubota,[1] Sawako Kato,[1] Takuji Ishimoto,[2] Yasuhiko Ito,[2] Tomohito Doke,[1] Shoichi Maruyama.[1] *[1]Nagoya Daigaku Daigakuin Igakukei Kenkyuka Igakubu, Nagoya, Japan; [2]Aichi Ika Daigaku Daigakuin Igaku Kenkyuka Igakubu, Nagakute, Japan.*

Background: The protective effect of SGLT2 inhibitors on diabetic kidney disease (DKD) have been reported, however, underlying molecular mechanism remains unclear. Unbiased kidney metabolomics and transcriptome analysis for kidneys treated with SGLT2 inhibitors have been warranted. Although lowering blood glucose levels is believed to have a protective effect on DKD, recent studies have shown that SGLT2 inhibitors modulate branched-chain amino acid (BCAA) transporter expression and mTORC1 function, indicating the role of BCAA metabolism in DKD.

Methods: SGLT2 inhibitor, Tofogliflozin (5mg/kg/day) was given to the db/m and db/db mice for 8 weeks. The blood glucose levels, body weight and food intake were regularly examined. Urinary albumin and creatinine levels were measured. PAS, PAM, and collagen IV were stained in kidney FFPE sections. LC-MS and RNA sequence for kidney tissues was performed. The phosphoS6 (pS6) was stained with Nephrin in frozen kidney tissue to see the mTORC1 activation in mesangial cells. Mes13 were incubated with BCAA, and the levels of collagen IV and proteins associated with mTORC1 activation pathway were examined.

Results: Blood glucose levels were significantly reduced in db/db mice treated with Tofogliflozin compared to db/db mice ($p<0.01$). The proteinuria, mesangial expansion, and collagen IV accumulation were reduced in db/db mice treated with Tofogliflozin. The unbiased metabolomics study identified significant changes in 68 metabolites of kidneys from db/db mice compared to db/m mice ($p<0.05$). Tofogliflozin reversed the changes in 15 out of 68 metabolites. In addition to the metabolites associated with glycolytic or polyol pathways, the levels of BCAA were significantly reduced in kidneys treated with Tofogliflozin ($p<0.05$). The higher levels of collagen IV were confirmed in MES13 treated with BCAA. The protein levels of phosphorylated forms of S6 (pS6) and S6K (pS6K) indicating mTORC1 activation. The higher expression of pS6 in the mesangial region of db/db mice and reduction of their levels in Tofogliflozin-treated db/db mice was confirmed.

Conclusions: Unbiased metabolomics analysis identified the reduction of BCAA levels in kidneys treated with an SGLT2 inhibitor. The higher BCAA levels promote mesangial expansion by modulating mTORC1 activation.

Funding: Commercial Support - Kowa Company, Ltd.

SA-PO433

Renal Tubule-Specific NRF2 Deletion Downregulates SGLT2 and Angiotensinogen Expression and Ameliorates GFR and Kidney Injury in Akita Mice

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Background: Nuclear factor erthyroid-2 related factor 2 (NRF2) expression is increased in kidneys of mice and patients with diabetes. We have reported that overexpression of NRF2 in renal proximal tubular cells (RPTCs) increases sodium-glucose co-transporter 2 (SGLT2) and angiotensinogen (AGT) expression and exacerbates dysglycemia and progression of nephropathy in type 1 diabetic (T1D) Akita *Nrf2*$^{-/-}$/*Nrf2*^{RPTC} transgenic (Tg) mice (Diabetes 2021). However, the pathophysiological role of renal NRF2 in the progression of diabetic kidney disease (DKD) is not well understood. We now report the impact of *Nrf2* deletion specifically in renal tubules (RT) of Akita mice on the expression of SGLT2 and AGT in RPTCs in the setting of hyperglycemia and kidney injury.

Methods: Akita RT-specific *Nrf2* knock-out (Akita *Nrf2*^{RT} KO) mice were generated by crossbreeding Akita with *Nrf2*^{RT} KO mice using Pax8-Cre (through crossbreeding male *Nrf2* floxed mice with female RT-specific Cre deleter (Pax8-Cre) mice). Immunostaining on kidney sections, Western blot (WB) and real-time qPCR (RT-qPCR) were employed to assess protein and gene expression in isolated RPTs. Physiological and kidney morphological changes were assessed in male Akita *Nrf2*^{RT} KO, Akita *Nrf2*$^{lox/lox}$, non-diabetic *Nrf2*$^{lox/lox}$ and *Nrf2*^{RT} KO mice at the age of 10 to 20 weeks.

Results: SGLT2 and AGT expression in RPT were significantly lower in Akita *Nrf2*^{RT} KO mice cf. to Akita mice. Glomerular filtration rate (GFR) was increased in Akita mice but was normalized (reversed glomerular hyperfiltration) in Akita *Nrf2*^{RT} KO mice. Fasting blood glucose, glomerular tuft volume, RPTC volume, tubular luminal dilatation, tubular injury score, kidney weight and urinary albumin-creatinine ratio (ACR) were significantly increased in Akita mice vs nondiabetic *Nrf2*$^{lox/lox}$ and *Nrf2*^{RT} KO mice. These abnormalities were greatly reduced in Akita *Nrf2*^{RT} KO mice, except for fasting blood glucose. Fractional excretion of glucose was increased in Akita mice and increased further in Akita *Nrf2*^{RT} KO mice.

Conclusions: Our results show that RT-*Nrf2* deletion ameliorates GFR and kidney injury in Akita mice, indicating renal NRF2 is important in tubuloglomerular feedback via down-regulation of intrarenal SGLT2 and AGT expression.

Funding: Government Support - Non-U.S.

SA-PO434

Residues L667 and L658: Critical Players in the Functional Activation of SGLT2 by MAP17

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Background: Sodium-glucose cotransporter 2 (SGLT2) is crucial for renal glucose reabsorption. Unlike its family member SGLT1, SGLT2 requires an activator protein, MAP17, for its transport activity. However, the mechanism of this unique activation is unclear. A recent cryogenic electron microscope (cryo-EM) study predicted interactive residues on SGLT2-MAP17 complex, but their functional significance requires validation. This study aims to investigate the role of specific SGLT2 amino acid residues in the functional activation of SGLT2 by MAP17 and their effect on glucose transport.

Methods: Five SGLT2 residues predicted to interact with MAP17 were selected based on cryo-EM predictions and aligned sequences of SGLT2 homologues. Mutations (mostly to alanine or cysteine) were designed to assess the effects of side chain and polarity changes. Transport studies were conducted using Xenopus oocytes expressing wild-type SGLT2 (SGLT2-WT) proteins or mutants and co-expressing MAP17. Oocytes were microinjected with mRNA for SGLT2-WT or SGLT2 mutants, and MAP17 mRNA was co-injected. Negative controls included H_2O-injected oocytes and SGLT2-only-injected oocytes. Glucose transport in each oocyte was assessed by perfusing solutions containing 86 mM Na^+ and 20 mM glucose and measuring whole cell currents generated by glucose-activated Na^+ transport using two-electrode voltage clamp.

Results: Three SGLT2 mutations (L667C, L667M, and L658C) significantly inhibited glucose transport compared to SGLT2-WT. Specifically, L667C inhibited transport by 88%, L667M by 72%, and L658C by 70% ($p<0.01$). Notably, mutations F666A, F666Y, M661A, M661C, V665A and V665C did not significantly inhibit SGLT2 activity.

Conclusions: L667C, L667M and L658C mutations inhibited glucose transport potentially by disrupting the interaction between SGLT2 and MAP17, likely through altered hydrophobicity or disulfide bond formation. While other predicted interacting sites have a marginal contribution, L658 and L667 emerge as essential residues, displaying conservation and divergence among species and family members. This study confirmed the effects of cryo-EM predicted residues on SGLT2-MAP17 interaction and identified novel critical amino acids (L667 & L658) for SGLT2 function and MAP17 interaction.

Funding: Private Foundation Support

SA-PO435

Combination Therapy with Lisinopril and Dapagliflozin Rescues GFR Decline and Glomerular Damage in the KKAy Mouse Model of Diabetic Kidney Disease

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Background: We previously showed that male KKAy mice develop DKD with progressive decline of GFR upon high fat diet feeding together with a vasoconstrictor. In this study, efficacy of combination therapy with an ACE-inhibitor (lisinopril) and SGLT2-inhibitor (dapagliflozin) on renal function and histopathology was investigated.

Methods: Male KKAy mice underwent uninephrectomy (UNX). After recovery mice received high fat diet (45% LARD) and 50 mg/L LNNA in drinking water (wk0). At week 4, lisinopril (2.5 mg/kg/day and at week 8 dapagliflozin (5 and 20 mg/kg/day) were started. Body weight, blood glucose, food and water intake and albuminuria were determined regularly. GFR was measured transdermally by FITC-sinistrin clearance. Mice were terminated at week 16 and kidney histology was scored. Non-induced and induced non-treated mice were used as controls.

Results: Treatment of KKAy mice on HFD+LNNA with Dapagliflozin reduced blood glucose immediately. Combination therapy with lisinopril and dapagliflozin (5 mg/kg/day) rescued the progressive GFR decline to levels seen in non-induced chow-controls. Pathology showed that the percentage of healthy glomeruli increased from 14% to 26% after combination therapy (dapa 5). Interstitial fibrosis and tubular atrophy were signficantly reduced by combination therapy.

Conclusions: Male KKAy mice on a HFD and LNNA developed DKD resulting in CKD. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline and reduced glomerular damage. This indicates that the model is clinically relevant and can be used to study compound efficacy in both early and more advanced stages of DKD.

Funding: Commercial Support - Janssen, BPM, Government Support - Non-U.S.

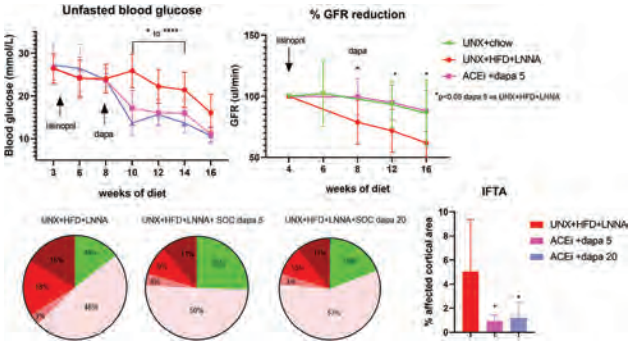

Figure 1: Dapagliflozin decreased blood glucose levels. Combination therapy with Lisinopril and Dapagliflozin rescued GFR decline, glomerular damage and interstitial fibrosis and tubular atrophy.

SA-PO436

Canagliflozin Inhibits Hedgehog Interacting Protein (Hhip)-Mediated Renal Tubular Cell Senescence in Type 1 Akita Mice

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Background: We have recently reported that hedgehog interacting protein (Hhip) activates sodium-glucose cotransporter 2 (Sglt2) expression and promotes tubular senescence-associated secretory phenotype (SASP) in murine diabetic kidney disease (DKD) (*Diabetiologia 2023*). However, the underlying mechanism(s) are poorly understood. Here, we aimed to elucidate the functional impact of the SGLT2 inhibitor, Canagliflozin (Cana) on tubular Hhip-mediated cell senescence in vivo and in vitro.

Methods: Akita renal proximal tubular cells (RPTC)-specific Hhip transgenic (Tg) mice (Akita/Hhip-Tg), Akita/non-Tg and their respective controls (Hhip-Tg or non-Tg) were studied. Cana was administered to Akita mice (Akia/Hhip-Tg vs. Akia/non-Tg) in water (10 or 30 mg/kg/day) from 6 to 20 weeks of age. Primary RPTCs and rat immortalized RPTC cells (IRPTCs) were also employed.

Results: Hhip-Tg mice were fertile and phenotypically normal cf. non-Tg. Compared to respective controls at 20-weeks, both Akita/Hhip-Tg and Akita/non-Tg mice displayed typical DKD dysfunction (hypertension, hyperglycemia, polyuria, increased urinary albumin/creatinine ratio and glomerular filtration rate) and dysmorphology (renal hypertrophy, glomerulosclerosis and tubulopathy). These features were more pronounced in Akia/Hhip-Tg than in Akita/non-Tg. Cana administration ameliorated DKD features in a dose-dependent manner. There was evidence of renal tubular SASP--Heightened β-galactosidase activity was seen in Hhip-Tg cf. non-Tg mice, and its activity was more pronounced in Akita/Hhip-Tg cf. Akita/non-Tg mice. In contrast, Cana more effectively inhibited tubular SASP in kidneys of Akita/non-Tg cf. Akita/Hhip-Tg mice. In IRPTCs, excessive Hhip gene expression through either engineered overexpression or high glucose (25mM D-glucose) stimulation promoted extracellular vehicle (apoptotic bodies and microvesicles)-mediated cellular senescence, and their effects were inhibited by the addition of canagliflozin (500nM).

Conclusions: Canagliflozin appears to be capable of offsetting DKD-related tubulopathy and tubular senescence, possibly, via the inhibition of excessive Hhip delivered extracellularly in DKD.

Funding: Government Support - Non-U.S.

SA-PO437

Cholesterol 25-Hydroxylase Protects Diabetic Kidney Disease by Regulating ADP Ribosylation Factor 4

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Background: Cholesterol 25-hydroxylase (CH25H) is a cholesterol hydroxylase which is actively involved in lipid metabolism. In kidney, CH25H predominantly expressed in endothelial cells and macrophages, which are renal resident cells and immune cells that have been proved of great importance in context of DKD progression. Intriguingly, the expression of CH25H is upregulated in diabetic mouse. In this study, we determined the effects of CH25H and its product 25HC in DKD.

Methods: C57BL/6J wild type (ch25h$^{+/+}$/lepr$^{+/+}$), ch25h KO (ch25h$^{-/-}$/lepr$^{+/+}$), diabetic (ch25h$^{+/+}$/lepr$^{db/db}$) and DKO (ch25h$^{-/-}$/lepr$^{db/db}$) were utilized in this study. The mice were sacrificed at the age of 24 weeks. C57BLKS/J male lepr$^{db/+}$ and lepr$^{db/db}$ mice were used for 25HC treatment study. In vivo studies were conducted with human umbilical vein endothelial cells and immortalized human podocytes.

Results: CH25H predominantly expressed in glomerular and peritubular endothelial cells. Lepr$^{db/db}$ and STZ-induced diabetic mice have an elevated level of CH25H mRNA level in glomeruli. Global deletion of ch25h in Lepr$^{db/db}$ mice aggravated DKD, showing more albuminuria and worse glomerular hypertrophy and mesangial matrix deposition, and can be alleviated by 25HC treatment. In vivo studies revealed that 25HC binds to a GTP-binding protein Arf4, enhancing its activity by inhibiting the interaction between Arf4 and its GTPase-activating protein Asap1. Interesting, Asap1 expressed mostly in endothelial cells and its expression is increased in the diabetic kidney. In Golgi apparatus, Arf4 activity is required for maintaining essential protein transportation and cellular function, while in cytosol Arf4 inhibits the activity of Aldolase and accumulation of methylglyoxal, thereby preventing cells from death.

Conclusions: Lacking of CH25H aggravated DKD and can be rescued by exogenous supplement of its catalytic product 25HC. 25HC protects DKD by maintaining Arf4 activity via inhibiting Arf4 interaction with its GAP Asap1. Activated Arf4 is required for promoting protein transportation in golgi apparatus and suppressing methylglyoxal production in cytosol, thereby preventing cells from injuries.

Funding: NIDDK Support, Veterans Affairs Support

SA-PO438

Targeting the LXR/mTOR Signaling Axis: A Novel Therapeutic Strategy for Modulating Autophagy in Diabetic Kidney Disease

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Background: Autophagy, vital for maintaining kidney homeostasis, is impaired in podocyte dysfunction and diabetes-induced podocyte injury. However, the underlying mechanisms behind autophagy alteration remain poorly understood. Both mTOR complexes and oxidative stress have been implicated as potential key players in diabetes-related autophagy imbalance, yet the mechanisms leading to their alterations are unclear. Additionally, the role of Liver-X-Receptor (LXR) in autophagy and its interaction with other pathways in diabetic kidney disease (DKD) is not well defined. This study aims to elucidate the role of the LXR/mTOR axis in autophagy and its connection to podocyte injury in type 2 diabetes (T2D)

Methods: In vitro experiments were performed using cultured human podocytes while in vivo experiments were conducted using control mice and T2D mice. T2D mice were treated with different pharmacological drugs to inhibit specific components of the mTOR complex: rapamycin for mTORC1, JR-AB2-011 for mTORC2, and PP242 for mTORC1/mTORC2. Another group of T2D mice was treated with T0 to activate LXR. In parallel, control mice were treated with Hydroxychloroquine (HCQ), an autophagy inhibitor, to further investigate the role of autophagy

Results: High glucose levels or hyperglycemia can lead to podocyte injury and dysregulation of autophagy. This is primarily caused by the production of reactive oxygen species (ROS) through NADPH oxidase activation. Additionally, LXR deactivation and mTORC1/mTORC2 activation contribute to these effects. Activation of LXR using T0 restores renal homeostasis by reducing proteinuria, reversing histological and phenotypical changes, and inhibiting NOX4. Moreover, LXR activation improves diabetes-induced autophagy alteration by restoring the expression of LC3B and p62. LXR activation also reduces the activation of both mTORC1 and mTORC2. Furthermore, inhibiting mTORC1, mTORC2, or mTORC1/2 pathways replicates the effects of LXR activation on ROS production and renal injury, but it does not affect the LXR pathway. Conversely, inhibiting autophagy in control mice using HCQ alone is enough to induce kidney injury

Conclusions: This study presents evidence for a novel role of LXR/mTOR in regulating oxidative stress and autophagy during the onset and progression of diabetic kidney disease (DKD)

SA-PO439

Phenotypic Features of Advanced Nephropathy in a Murine Model of Metabolic Syndrome: Focus on Sex Differences

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Background: Diabetes nephropathy (DN) which is often an integral part of obesity and metabolic syndrome (MS), is the most cmmon cause of ESRD in most countries. We had originally characterized nephropathy in ZSF rats, a rat model of DN and MS (Prabhakar S, JASN 2007). While male ZSF rats developed advanced features of DN and MS, the phenotypic features of female ZSF rats which have the same genetic background have not been well described. The goals of this study are to examine and compare the expression of MS in male and female ZSF rats at an advanced age.

Methods: Obese ZSF (ZDFxSHHF-fa/facp) model was developed by crossing lean female Zucker Diabetic Fatty (ZDF ./fa) and lean male Spontaneously Hypertensive Heart Failure (SHHF/Mcc-facp, ./fa) rats. Male and female CD rats were used as controls. Rats were monitored from 8th week of life and were fed normal rat chow (CD rats) or high calorie, high fat diet (Purina 5008) in the case of ZSF rats. The present report pertains to data obtained at 46 weeks of age. Blood pressure (BP) was measured by tail cuff plethysmography (Non-Invasive BP measurements using the Kent CODA system). Blood and urine were examined for glucose (Ascensia Contour glucometer) and protein levels. Body weights were measured weekly.

Results: The data here represent the results at 46th week in ZSF and CD rats, Obesity was first evident in ZSF rats at 20 wks but progressed steadily. Male ZSF rats were heavier than female ZSF rats (736±31 vs. 508±44gm p<0.0001) CD male rats were also heavier than female (802±111 vs. 306±31, p<0.0001) Male ZSF and CD rats did not differ significantly in their weights. Male ZSF rats developed significant hypertension compared to female rats (169/126 vs 139/89 p<0.05) CD males and female rats has similar BP (139±102 vs.136±90 mm/Hg p=NS). Proteinuria was was significantly high in male ZSF rats compared to female rats (>2 gm vs.1 gm) while CD rats had trace or no proteinuria. Male ZSF rats developed overt diabetes compared to mild diabetes in female ZSF rats.

Conclusions: These findings indicate that despite having similar genetic make-up, obese ZSF rats displayed major differenes in male and female sexes. In general male rats displayed more florrid features of metabolic syndrome. These observations warrant more intense investigations to explore the etiologic basis and factors to account for such differences between sexes.

Funding: Private Foundation Support

SA-PO440

KLF2 Agonists as a Novel Therapy for Diabetic Kidney Disease

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Background: Glomerular endothelial cell (GEC) dysfunction is a key event mediating the progression of diabetic kidney disease (DKD). Krüppel-like Factor-2 (KLF2) is induced by flow-mediated shear stress and has endo-protection via its anti-inflammatory, anti-thrombotic activation, and anti-angiogenesis effects. Our key observations : 1) In humans DKD, reduction of KLF2 expression is associated with the progression of DKD. 2) In cultured GECs, we find that KLF2 has anti-inflammatory effects and is a key and direct regulator of eNOS expression. 3) After induction of diabetes or unilateral nephrectomy to induce glomerular hyperfiltration, mice with endothelial cell-specific KLF2 deficiency develop more severe GEC injury and kidney disease as compared to wild type mice.

Methods: We generated an inducible endothelial cell-specific KLF2 overexpression mouse model to test whether overexpression of KLF2 protects GEC injury in DKD mice. We used Limited Rational Design (LRD) approach to design and synthesize KLF2 agonists. We screened KLF2 agonists in cultured GECs by using qPCR assay for eNOS and confirmed by western blot analysis. We utilized the drug affinity responsive target stability (DARTS) method to confirm the interaction of KLF2 agonists with KLF2. We treated db/db mice and BTBR ob/ob mice with KLF2 agonists

Results: Induction of KLF2 expression in endothelial cells in diabetic mice ameliorated albuminuria and glomerular injury with increased glomerular eNOS expression. Screening of KLF2 agonists identified that compound 6 (C-6) had the strongest stimulation on eNOS expression based on qPCR analysis and a dose-dependent stimulatory effect was also confirmed by western blot analysis. By DARTS approach, we confirmed that C-6 had direct interaction with KLF2 without regulation of its mRNA or protein expression, suggesting that C-6 increases the transcription of eNOS via enhancing the binding of KLF2 at eNOS promoter. To test whether C-6 has effects in vivo, we fed both db/db mice and BTBR-ob/ob mice with C-6 at 2.5mg/kg by daily gavage for 8 weeks and found a significant reduction of albuminuria and improvement of glomerular injury in these mice with no obvious toxicity. eNOS expression was also restored in the glomeruli of these diabetic mice by treatment of C-6.

Conclusions: KLF2 has a major protective role against GEC injury in DKD and KLF2 agonists could be developed as potential drugs for treatment of DKD.

SA-PO441

Discovery and Development of a Therapeutic Lead Compound for Diabetic Kidney Disease

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Background: Diabetic kidney disease (DKD) is a leading cause of kidney failure worldwide. We previously demonstrated that the accumulation of lipid droplets (LDs) in podocytes leads to lipotoxicity and cell death in DKD. Drugs that lower circulating lipids do not halt DKD progression. However, directly reducing LD accumulation in podocytes was shown to slow disease progression in experimental DKD. We hypothesize that a drug that specifically targets LD accumulation in podocytes will be effective at halting or reversing DKD progression.

Methods: We developed a phenotypic assay using immortalized human podocytes and deployed it to screen a combinatorial library representing over 45 million unique compounds. We performed mechanistic analyses on hit compounds using transcriptomic, proteomic, and phenotypic techniques. We conducted medicinal chemistry to improve drug-like properties and tested one compound in a murine model of DKD.

Results: We identified and synthesized a series of novel compounds that effectively inhibit LD accumulation in podocytes and protect them from injury and cell death. RNAseq analysis revealed that these compounds significantly reduce the expression of genes that mediate tumor necrosis factor (TNF)-signaling, a pathway associated with LD accumulation and podocyte injury, and alter the expression of lysosome-associated membrane glycoprotein (LAMP), a regulator of autophagy. Mechanistic studies demonstrated that these compounds robustly activate autophagy/lipophagy, leading to a significant reduction in LD accumulation in podocytes. We tested one compound with improved drug-like properties in an experimental model of DKD, *db/db* mice, and found that it significantly prevented the progression of DKD, as evidenced by a reduction in albumin-to-creatinine ratios (ACR) and the reduced pathological renal damage associated with DKD.

Conclusions: Our screening assay successfully identified compounds that protect podocytes from LD accumulation by inducing lipophagy. We developed a lead candidate from our initial hit series that demonstrates remarkable efficacy in preventing DKD progression *in vivo*. We are continuing lead optimization efforts toward generating a clinical candidate for testing in a clinical trial.

Funding: NIDDK Support, Private Foundation Support

SA-PO442

siRNA Inhibition of Lysophosphatidic Acid Receptor 1 (LPAR1) Attenuates Kidney Fibrosis and Improves Kidney Function in a Rat Model of Hypertensive CKD

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Background: LPAR1 plays an important role in fibrosis. Its expression is upregulated in kidneys of different injuries. We developed an LPAR1 siRNA-LNP that shows a good kidney cell distribution and improves kidney fibrosis and function in diabetic and Adriamycin-induced models of CKD. Here we demonstrate these efficacies in rats of hypertensive CKD.

Methods: Dahl salt-sensitive rats were fed an 8% high-salt diet for 6 wks and then treated with the LPAR1 siRNA-LNP at 1 or 2 mpk once/wk for 4 wks. A group with an ACEi, Perindopril treatment (Tx) at 3 mpk daily and a combination Tx group was also included in one study. Kidney LPAR1 knockdown, uACR, urine KIM-1 and Cystatin C, kidney hydroxyproline (HP), the expression of the key fibrogenic and inflammatory genes and others were measured. Histological changes were determined.

Results: LPAR1 siRNA Tx caused a dose-dependent reduction in uACR (>80% reduction at 2 mpk), urine KIM-1 and Cystatin C levels (both were nearly normalized at 2 mpk). The Tx also dose-dependently lowered blood pressure (systolic pressure dropped from ~176 to 142 mmHg in the 2 mpk group) and improved animal survival (~50% in control group vs 100% in 2 mpk group). The Tx significantly decreased kidney HP content. Histological analysis found that the Tx improved both glomerular and tubular histology including glomerulosclerosis and tubule-interstitial fibrosis. RNAscope analysis found that Tx at 2 mpk normalized LPAR1 expression. RNAseq analysis indicated that the Tx significantly lowered fibrogenic and inflammatory signaling activities and increased mitochondrial TCA cycle and oxidative phosphorylation activities. RT-PCR confirmed a down-regulation in expression of the key fibrogenic and inflammatory genes including TGFβ, CTGF, Col1a1, Col2a1, RAGE and NF-κβ. Though both LPAR1 siRNA and Perindopril lowered serum creatinine levels to a similar degree, LPAR1 siRNA showed a much better efficacy than the ACEi in improving kidney histology. Combination Tx showed additive effects on serum creatinine and kidney histology.

Conclusions: These data further demonstrated that siRNA inhibition of LPAR1 improves kidney fibrosis and function in rats of hypertensive CKD in addition to other models. Therefore, the LPAR1 siRNA-LNP could be a potential therapeutic for kidney fibrosis.

SA-PO443

Targeting Lysophosphatidic Acid Receptor 1 (LPAR1) with siRNA-Lipid Nanoparticles (siRNA-LNP) Is a Potential Therapeutic Approach for CKD -Associated Kidney Fibrosis

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Background: LPAR1 plays an important role in tissue fibrosis. Its expression is upregulated in kidneys (K) of different injuries. To explore if siRNA inhibition of its expression could be a therapeutic approach for K fibrosis, we developed a K-targeting LPAR1 siRNA-LNP.

Methods: A series of LPAR1 siRNAs were designed and screened in vitro. The activity of the selected lead siRNA was confirmed in vivo. A series of LNP formulations for delivery of siRNA to K were designed and screened in vivo. Cell distribution of siRNA in K was analyzed with different approaches. The selected lead LPAR1 siRNA-LNP was used to treat mice of DKD or rats of Adriamycin-induced CKD. LPAR1 gene knockdown, serum creatinine, uACR, K hydroxyproline (HP) and histological changes were determined.

Results: In vitro screen identified a lead LPAR1 siRNA of an IC50 ~10pM. The activity was confirmed in vivo. A lead LNP formulation was identified by showing >50% LPAR1 mRNA reduction in mouse K after a dose of 4 mpk and a higher siRNA accumulation in K than in liver or other tissues 24 hr after dosing. FACS analysis found that siRNA was delivered to majority of K cells including podocytes, mesangial cells, endothelial cells in glomeruli, and epithetical and non-epithetical cells in non-glomerulus part. Treatment (Tx) of mice with a single dose of a podocin siRNA-LNP significantly reduced podocin mRNA, further demonstrating the siRNA was delivered into podocytes. RNAscope analysis found that LPAR1 siRNA reduced LPAR1 mRNA level in different K cells. Tx of STZ-induced diabetic mice with LPAR1 siRNA at 4 mpk once a wk for 4 wks lowered K HP levels, and improved K fibrosis and tubular degeneration. Tx of BTBR *ob/ob* mice caused ~20% and 45% reduction in uACR after 3 and 9 wks of Tx, respectively. Tx of rats of Adriamycin-induced CKD at 2 mpk/wk for 4 wks normalized serum creatinine, lowered uACR by 60%, improved glomerulosclerosis, stopped worsening of glomerular atrophy, and reversed glomerular effacement and tubular dilation. The Tx effect lasted for >11 wks.

Conclusions: Above data demonstrated that siRNA inhibition of LPAR1 expression improves K fibrosis accompanied by an improved K function in multiple CKD models. Therefore, the siRNA-LNP could be a potential therapeutic for K fibrosis.

SA-PO444

Renal Cell Type-Associated Therapeutic Effects of Semaglutide in a Mouse Model of Hypertension-Accelerated Diabetic Kidney Disease

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Background: Obesity, hyperglycemia and hypertension are critical risk factors for development of diabetic kidney disease (DKD). While emerging evidence suggests that glucagon-like peptide-1 receptor (GLP-1R) agonists improve cardiovascular and renal outcomes in type 2 diabetes patients, their mode of action is presently unclear. Using paired bulk and single-nucleus RNA sequencing (RNAseq), we profiled renal transcriptome signatures of the long-acting GLP-1R agonist semaglutide alone and in combination with the ACE inhibitor lisinopril in a model of hypertension-accelerated, advanced DKD facilitated by adeno-associated virus-mediated renin overexpression (ReninAAV) in uninephrectomized (UNx) female *db/db* mice.

Methods: Seven weeks after ReninAAV administration and six weeks post-UNx, *db/db* UNx-ReninAAV mice were administered (q.d.) vehicle, semaglutide (30 nmol/kg, s.c.) or semaglutide (30 nmol/kg, s.c.) + lisinopril (30 mg/kg, p.o.) for 11 weeks. Endpoints included blood pressure, urine biochemistry, kidney histopathology as well as paired bulk and single-nucleus RNA seq. Cell type deconvolution was performed by referencing expression of treatment-affected genes across all major kidney cell types using single nuclei RNAseq.

Results: Semaglutide robustly reduced hyperglycemia, hypertension and albuminuria concurrent with reduction in glomerulosclerosis severity. Co-administration of lisinopril further ameliorated hypertension and glomerulosclerosis. Gene expression affected by both semaglutide mono- and combination treatment were primarily associated with the immune system and extracellular matrix remodeling. Semaglutide promoted discrete renal gene expression changes in *db/db* UNx-ReninAAV mice with notable suppression of macrophage-associated genes. Combined semaglutide and lisinopril administration resulted in more widespread transcriptome changes in several renal cell types, including macrophages, mesangial cells, podocytes and proximal tubule cells.

Conclusions: Semaglutide improves disease hallmarks in the db/db UNx-ReninAAV mouse model of advanced DKD and improves renal transcriptome signatures. Outcomes were further improved by combined antihypertensive standard-of-care.

Funding: Commercial Support - Gubra

SA-PO445

Effects of Nonsteroidal Mineralocorticoid Antagonist (Finerenone) in Western Diet-Induced Kidney Diseases

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Background: Mineralocorticoid receptor (MR) overactivation plays a crucial role in the pathogenesis of chronic kidney disease, several cardiovascular and arterial diseases. Recently the non-steroidal MR antagonist Finerenone (FN) was shown to have highly beneficial cardiac and renal protective effects. The purpose of these studies was to determine the mechanisms of the beneficial effects FN in kidney disease in a mouse model of western diet induced obesity and insulin resistance.

Methods: 2-month old C57BL/6J mice fed on low fat (LF) or western diet (WD) were treated with vehicle or FN for 6-months (prevention studies) or after 3 months on the LF or WD at 5 months of age, mice treated with vehicle or FN for 3 months (intervention studies) until they were 8 months old.

Results: Mice fed a Western diet (WD) had increased body weight and kidney weight, whereas Finerenone reduced kidney weight ratio without affecting body weight and blood glucose levels remained unchanged. WD-fed mice had higher plasma levels of TG and TC, reduced by FN. The WD fed mice exhibited significantly increased albuminuria and KIM1 which was decreased with FN. Kidneys of WD-fed mice showed increased expression levels of pro-inflammatory cytokines (MCP1, TGFβ), innate immunity pathways (TLR2, STING, STAT3), and fibrosis marker fibronectin and PAI-1, which were significantly reduced by FN. Interestingly, kidney cholesterol and ceramide levels were markedly increased in WD fed mice, which were reduced by FN. Electron microscopy revealed glomerular basement membrane disruption, podocyte foot process loss, and mitochondrial structural abnormalities in WD-fed mice, all improved by FN.

Conclusions: Our data shows that administration of Finerenone exhibits a renal protective role and prevents the progression of kidney disease in a mouse model of western diet induced obesity and insulin resistance.

Funding: Commercial Support - Bayer

SA-PO446

Linagliptin Increases Urinary Sodium Excretion via Deactivating Renal Epithelial Sodium Channel (ENaC) in Diabetic Rodents and Patients with Diabetes Mellitus

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Background: About half of patients with diabetes mellitus (DM) develop hypertension, leading to further organ damage. ENaC activation is linked to hypertension. Whereas SGLT2 inhibitors have drawn attention to its renoprotective effect, there are still several anti-diabetic agents available in clinic. However, which agent is the best partner of SGLT2 inhibitors remains unknown. In the present study, we investigated whether linagliptin (LINA), a DPP4 inhibitor, coordinates with SGLT2 inhibitor to attenuate diabetic nephropathy (DM-N) and explored the synergetic effect of LINA in diabetic and hypertensive rodents as well as patients with DM.

Methods: [1] SDT-fatty rats, an obese DM model, were given high salt water and categorized into four groups as followings; Sham, DM-N, DM-N treated with Empagliflozin for 12 weeks (EMPA), DM-N treated with 6-week EMPA followed by 6-week treatment with linagliptin (EMPA + LINA). [2] DOCA/salt mice, an ENaC-activated hypertensive model, were treated with EMPA or EMPA + LINA to investigate if LINA regulates ENaC activation. [3] Cultured distal tubules were treated with high sodium and glucose in the presence of EMPA, LINA, or GLP-1. [4] Urine samples were collected from patients with DM treated with LINA, EMPA, or the combination to investigate urinary sodium excretion.

Results: Tubular injury and renal fibrosis in SDT-fatty rats were improved by EMPA or EMPA + LINA. Along with lowered glucose level, renal dysfunction was attenuated by EMPA or EMPA + LINA. Urinary sodium excretion was increased by combination of the two when compared to EMPA alone. Renal ENaC was reduced with upregulation of Nedd4-2 by EMPA + LINA. Also, combination of the two attenuated hypertension with increase in urinary sodium excretion in DOCA/salt mice. Upregulation of Nedd 4-2 in DOCA/salt mice was prevented by the combination, but not EMPA alone. High sodium and glucose medium increased ENaC expression and suppressed Nedd4-2 expression, both of which were reversed by co-incubation with GLP-1 or LINA. Among the patients with DM, urinary sodium excretion was increased by combination of the two even when compared to EMPA or LINA alone.

Conclusions: LINA can become a potent to prevent the progression of DM-N through deactivating ENaC leading to increased urinary sodium excretion.

SA-PO447

Association of FRMD3 and ACE Gene Polymorphisms with Diabetic Nephropathy and Non-Diabetic Kidney Disease

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Background: FRMD3 and ACE gene polymorphisms have been suggested as an alternative test to differentiate diabetic nephropathy from non-diabetic kidney disease in patients with type 2 diabetes mellitus. This study was conducted to investigate the

relationship between FRMD3 and EA genes. and the clinical features of diabetic nephropathy. Objective: To determine the association of FRMD3 and ACE gene polymorphisms with diabetic nephropathy and non-diabetic kidney disease.

Methods: Patients who already had renal pathology findings were evaluated for ACE and FRMD3 polymorphisms. The subjects were classified into three groups; diabetic nephropathy, diabetic patients with other non-diabetic nephropathy and healthy patients. Polymorphisms of the ACE and FRMD3 genes were analyzed in each group.

Results: In a total of 200 patients from a reference medical center, the prevalence of GG, CG and CC was 45%, 43% and 12% respectively. There were no significant differences in clinical parameters, which consisted of disease duration, proteinuria, and complications in diabetic patients. The G allele was found mainly in patients with diabetic nephropathy (50.5%) while the C allele was found in patients with diabetes and other types of nephropathy (43.9%) ($p = 0.02$). There was a significant association between the CC genotype in patients with diabetes and other types of kidney disease compared to GG ($p = 0.001$). In addition, the C allele was 2.2 times more associated with diabetes and other kidney disease than the G allele ($p = 0.03$). The CC genotype was correlated with the risk of diabetes and other kidney disease than the GG and GC genotypes, with odds ratios of 6.6 and 4.5, respectively ($p = 0.02$).

Conclusions: Regarding the FRMD3 and ACE genes evaluated, the presentation of the C allele, especially homozygous CC, was associated with patients with diabetes and other types of nephropathy in patients with overt proteinuria. Therefore, renal biopsy is suggested in those with the C allele or the homozygous CC genotype.

SA-PO448

Dysregulated miR-936 as a Novel Diagnostic Marker for Diabetic Nephropathy: Meta-Analysis and Validation Study

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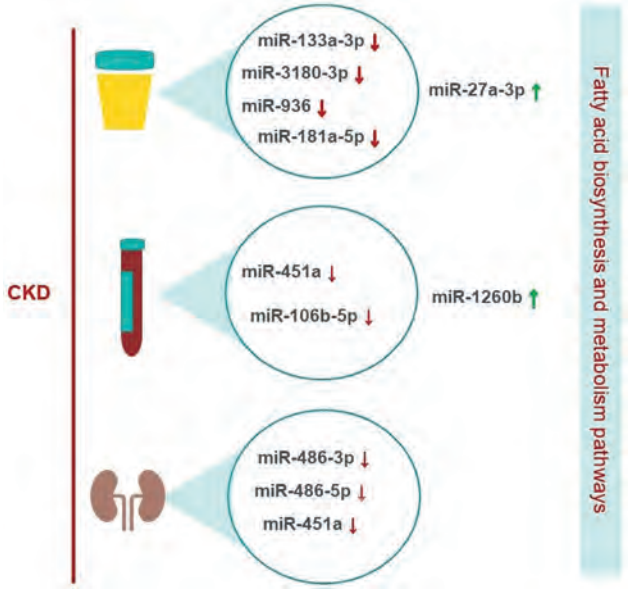
Background: MiRNAs are short non-coding ribonucleic acid molecules that bind to target messenger RNAs, resulting in their degradation and translational repression. They could be used as a diagnostic marker and nucleic acid therapy in chronic kidney disease (CKD).

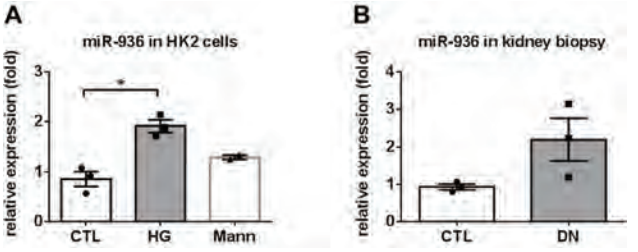
Methods: We used two consecutive methods to validate miR-936 in diabetic nephropathy (DN). First, investigating potential miRNA in CKD is explored from a meta-analysis of 32 miRNA profiling studies. The enrichment analysis was performed for target genes and molecular pathways utilizing DIANA mirPath v.3 and Reactome. Finally, for the first time, miR-936 was validated by qRT-PCR in kidney biopsy of DN patients and high glucose-induced HK-2 cells.

Results: Urinary miR-936 was one of the most down-regulated from a meta-analysis (Figure 1). The enrichment analysis found dysregulated miRNAs affecting fatty acid biosynthesis and metabolism pathways. MiR-936 was over-expressed in DN patient kidney biopsies (DN, n=3) compared to control kidney tissue (CTL, n=3) but did not reach statistical significance (Mann-Whitney test). HK-2 cells in high glucose (24 hours, 25 mmol/l, n=3) medium increased miR-936 expression by 2-fold (*$p<0.05$ by Kruskal Wallis test), while mannitol, osmotic control (20 mmol/l, n=3) had no effect.

Conclusions: The dysregulation of miR-936 expression in diabetic nephropathy is investigated, which will provide further research on the molecular mechanism of dysregulated miR-936 in diabetic nephropathy.

Funding: Government Support - Non-U.S.





SA-PO449

Label-Free Multimodal Imaging of Diabetic Kidney Disease Tissue

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Background: Accurate biomarker detection without sample destruction is critical for better utilization and preservation of biopsies. We developed a label-free multimodal imaging platform, combining hyperspectral SRS, MPF, and SHG. This approach reduces sample prep, enables the use of smaller biopsies, and details structural and biochemical changes in both 2D and 3D. Several histological stains are produced from the same sample without the need for serial reconstruction, and avoids unintended sample preparation effects such as lipid droplet fusion. Key insights include lipid subtype ratios, mesangial expansion, collagen fibrotic changes, and oxidative stress. Compatible with conventional methods, this platform affirms and deepens our understanding of DN to improve patient outcomes.

Methods: FFPE and fresh frozen renal tissue, subsequently fixed in 4% PFA, were sliced to 200µm and cleared with 8M urea and 0.2% TritonX. These samples were placed on glass slides and sealed under coverglass in water. SRS images used a tunable 500mW pump and 330mW 1031nm Stokes beams with a pixel dwell time of 40µs and a spectral resolution of 15cm-1. SHG was captured using the Stokes beam.

Results: 3D volumetric imaging provided more accurate mesangial volume fractions than single plane measurements, enabling the visualization of this expansion in DN. Relative distribution of ceramides and TAGs, as well as a greater degree of cholesterol esterification were observed in DN tubules. We also observed collagen fiber thickening and disarray, and oxidative stress. Findings were corroborated by routine IHC and IF.

Conclusions: This is the first all-in-one optical platform to visualize lipid subtype dysregulation, collagen thickening and anisotropy, oxidative stress, and mesangial expansion in DN in 2D and 3D. The spatial and chemical resolution afford multiplexed views of DN and maximizes sample utilization while maintaining flexibility.

Funding: NIDDK Support

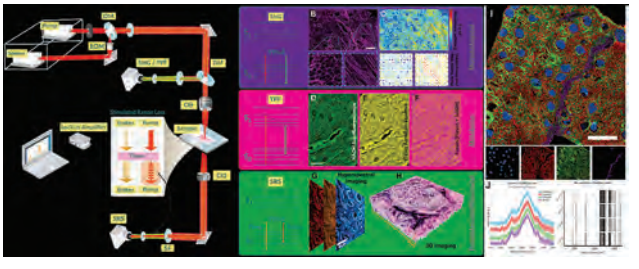

Fig 1.(A) Multiphoton laser microscopy system capable of (B) SHG imaging and (C) anisotropy analysis of collagen, (D-F) autofluorescence measurement of NAD[P]H and flavins, (G) SRS HSI, (H) 3D digital histology. (I) HSI segmentation. (J) Structure spectra plots.

SA-PO450

Long-Term Exposure to Ambient Air Pollutants and Increased Risk of ESRD in Patients with Type 2 Diabetes Mellitus and CKD

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Background: Limited data have examined the association between air pollution and the risk of end-stage renal disease (ESRD) in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD).

Methods: Data on air pollutants were obtained from the Beijing Municipal Ecological and Environmental Monitoring Center. Long-term exposure to air pollutants during the follow-up period was measured using the ordinary Kriging method. The outcome was defined as the occurrence of ESRD. Multivariate logistic regression analysis was used to estimate the association between air pollution and the risk of ESRD.

Results: 1,738 patients with T2DM and CKD hospitalized in Peking University Third Hospital from January 1, 2013, to December 31, 2021 were enrolled in this study. During a mean follow-up of 41 months, 98 patients developed ESRD. After adjusting for confounders, an increase of 10 $\mu g/m^3$ in $PM_{2.5}$ (odds ratio [OR] 1.19, 95% confidence interval [CI] 1.03–1.36) and PM_{10} (OR 1.15, 95% CI 1.02–1.30) concentration were positively associated with ESRD. An increase of 1 mg/m^3 in CO (2.80, 1.05–7.48) and an

increase of 1 μg/m³ in SO_2 (1.06, 1.00–1.13) concentration were also positively associated with ESRD. Apart from NO_2, all the above air pollutants have additional predictive value for ESRD in patients with T2DM and CKD, with $PM_{2.5}$ performing best.

Conclusions: In patients with T2DM and CKD, long-term exposure to $PM_{2.5}$, PM_{10}, CO, and SO_2 was positively associated with the risk of ESRD.

Funding: Government Support - Non-U.S.

	$PM_{2.5}$(per 10 μg/m³)		PM_{10}(per 10 μg/m³)		CO(per 1 mg/m³)		NO_2(per 10 μg/m³)		SO_2(per 1 μg/m³)	
Model	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value	OR(95% CI)	*P*-value
Unadjusted model	1.20 (1.06-1.36)	0.004	1.16 (1.03-1.30)	0.013	3.14 (1.27-7.78)	0.013	1.25 (0.99-1.59)	0.061	1.08 (1.02-1.14)	0.006
Model 1	1.19 (1.05-1.35)	0.007	1.15 (1.02-1.29)	0.021	3.05 (1.21-7.67)	0.018	1.25 (0.98-1.59)	0.066	1.07 (1.01-1.13)	0.013
Model 2	1.17 (1.03-1.33)	0.015	1.13 (1.01-1.27)	0.039	2.77 (1.09-7.05)	0.033	1.21 (0.95-1.54)	0.120	1.07 (1.01-1.13)	0.024
Model 3	1.18 (1.03-1.34)	0.014	1.14 (1.01-1.29)	0.030	2.75 (1.06-7.11)	0.037	1.22 (0.96-1.57)	0.109	1.07 (1.01-1.14)	0.022
Model 4	1.19 (1.03-1.36)	0.014	1.15 (1.02-1.30)	0.024	2.80 (1.05-7.48)	0.040	1.26 (0.98-1.61)	0.072	1.06 (1.00-1.13)	0.042

Model 1 adjusted for sex, age of diabetes onset, and duration of diabetes; Model 2 adjusted for variables in model 1 plus hyperlipidemia, using of lipid-lowering drugs, smoking status, insulin treatment, and heart failure; Model 3 adjusted for variables in model 2 plus baseline estimated glomerular filtration rate, mean arterial pressure, and body mass index; Model 4 adjusted for variables in Model 3 plus anemia, urinary protein, low-density lipoprotein cholesterol, glycated hemoglobin, and serum albumin.

Figure 1. Association between air pollutants and ESRD

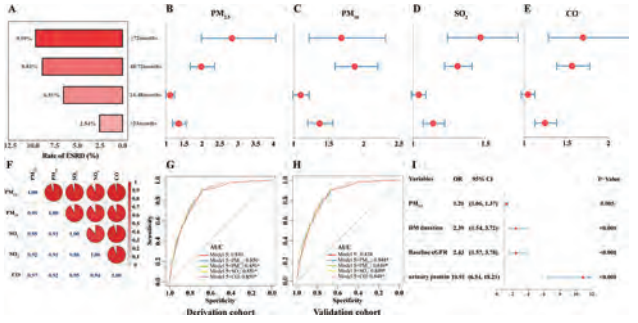

Figure 2. Subgroup analysis of follow-up time and prognostic efficacy of air pollutants

SA-PO451

Epidemiology of Diabetic CKD in Rural and Peri-Urban Bangladesh

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Background: Diabetes is often compounded with chronic kidney disease, and both diseases are becoming more prevalent. However, epidemiological data on Diabetic Chronic Kidney Disease (DCKD) is largely lacking in developing countries. We aimed to generate data in evaluating the prevalence of DCKD and associated risk factors in a selected rural community in Bangladesh.

Methods: We recruited study patients from the Mirzapur Demographic Surveillance System by stratified random sampling. We performed fasting blood sugar to screen patients for diabetes, and measured serum creatinine and urine albumin to creatinine ratio followed by a repeat measurement after 3 months to diagnose CKD. The GFR was estimated using the CKD Epidemiology Collaboration equation, and CKD was diagnosed using the Kidney Disease Outcomes Quality Initiative guidelines. Additionally, age, gender, marital status, occupation, educational background, income/month, smoking status, and sleeping hours were acquired during interviews. Physical examinations were performed to determine blood pressure, pulse rate, height, weight, waist circumference, and hip circumference. Moreover, blood samples were collected to measure serum albumin, hemoglobin, total cholesterol and triglyceride Chi-square test was performed for estimation of odds ratios (OR) and their 95% confidence intervals (CI) to determine the strength of association. Variables with *P*-values <0.05 were simultaneously included into the multivariate logistic model and adjusted odds ratio (aOR) and 95% CI were estimated.

Results: The prevalence of DCKD was 7.0% (61 cases of 872 screened participants). In multivariable analysis, associated factors for prevalent DCKD included hypertension (aOR 2.18, 95% CI 1.21-3.94), low serum albumin (aOR 2.24, 95% CI 1.00-5.00), and hypertriglyceridemia (aOR 2.14, 95% CI 1.21-3.79). However, there was no significant association between DCKD and those aged 46 years and more, sleeping duration less than 7 hours per day, present tobacco smokers, abdominal obesity, and hypercholesterolemia.

Conclusions: This epidemiological data on DCKD in rural and peri-urban Bangladesh revealed a 7% prevalence of DCKD. An early detection system to diagnose DCKD and the intervention should be scaled up to curb the risk factors, such as hypertension, low serum albumin, and hypertriglyceridemia.

Funding: Private Foundation Support

SA-PO452

Improving CKD Screening in Spanish-Speaking Patients with Poorly Controlled Type 2 Diabetes at a Rural Community Health Center

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Background: The American Diabetes Association (ADA) and Kidney Disease Improving Global Outcomes (KDIGO) consensus recommendations advise that patients with type 2 diabetes (T2DM) undergo annual screening with urine microalbumin creatinine ratio and estimated glomerular filtration rate. Less than half of patients with T2DM receive the recommend screening. This project aimed to increase CKD screening in Spanish-Speaking patients with poorly controlled T2DM (A1c>9) by 5% over 2 months at a community health center in rural North Carolina and evaluated secondary patient-centered outcomes of initiation of sodium glucose cotransporter 2 inhibitors (SGLT2i) and diagnosis with CKD.

Methods: We performed chart review querying for Spanish-speaking patients at SCCHC with T2DM with A1c>9 without a diagnosis of CKD (n=134). We then created a pop-up alert for patients without any CKD screening in the past year. We performed patient outreach to schedule appointments, offer counseling on CKD screening, and pend labs. Finally, we generated a flier for providers summarizing ADA and KDIGO guidelines for CKD screening and initial management.

Results: Only 43% of patients received full screening at baseline. Overall, the number of patients screened for CKD increased by 7%. 85% of patients with alerts in their charts who showed up for appointments received full screening. 50% of patients contacted through patient outreach scheduled an appointment and all patients who were seen in clinic following outreach received full screening. Only 29% of patients for whom the only intervention was provider education recieved complete screening. No diagnoses of CKD were made as a result of screening. There was an increase in prescription of an SGLT2i from 35% to 69% in patients recieving any CKD screening.

Conclusions: The improvement in CKD screening resulting from this project supports the need for pre-visit planning tools that highlight CKD screening, for patient education efforts, and for a one click 'Kidney Profile' lab order. The increased use of SGLT2i in patients recieving full screening supports a correlation between CKD screening and increased risk reduction therapy. Future efforts to increase appropriate CKD diagnosis and patient counseling following screening will be important for empowering patients to prevent disease progression.

SA-PO453

HbA1c-Dependent Projection of Long-Term Renal Outcomes

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Background: Diabetes mellitus is a major risk factor for the development of chronic kidney disease (CKD). An association between glycated hemoglobin (HbA1c) and decline of kidney function is well established. There is limited data addressing the prognostic value of baseline HbA1c to predict long-term renal outcomes regardless of diabetes status or anti-diabetic therapies.

Methods: In this single-center retrospective observational study, we analyze the effect of glycemic status on renal outcomes in a study population of $N = 19{,}285$ subjects over a median follow-up time of 69 months. The primary endpoint was defined as time to manifestation of moderate CKD (estimated glomerular filtration rate [eGFR] < 60 ml/min/1.73 m²) in subjects with unconstrained kidney function (eGFR > 60 ml/min/1.73 m²) at baseline. The secondary endpoint was defined as time to progression of CKD (eGFR < 30 ml/min/1.73 m²) in subjects with CKD stage III (eGFR 30 - 60 ml/min/1.73m²) at baseline. Endpoints were individually analyzed using interval- and right-censored datasets. For univariate time-to-event analysis, subjects were grouped into four cohorts by median HbA1c at baseline (HbA1c: < 5.7%, 5.7 – 6.5%, 6.5% – 8.5%, ≥ 8.5%). Covariate-adjusted hazard ratios were estimated applying multivariate parametric regression models on continuous HbA1c measures. A Cox proportional hazard based model was established to predict decline of kidney function based on discrete baseline HbA1c levels.

Results: Lowest baseline HbA1c levels were associated with the slowest decline of kidney function, highest baseline HbA1c levels with the fastest decline of kidney function (median time to primary endpoint for HbA1c < 5.7%: 16 years [95% CI: 13.6-17.8]; for HbA1c 5.7 - 6.5%: 14. years [95% CI: 12.4-15.4]; for HbA1c 6.5 - 8.5%: 9.9 years [95% CI: 8.6-11.7]; for HbA1c > 8.5: 7.1 [95% CI: 5,7 - 8,8], $P < 0.0001$). Similar trends were observed for the secondary endpoint. Covariate-adjusted time-to-event analysis confirms a concentration-dependent effect of HbA1c at baseline on both endpoints.

Conclusions: HbA1c is a strong predictor for kidney function decline, regardless of preexisting diabetes status or CKD stage. Lower HbA1c levels are associated with a lower risk of manifestation or progression of CKD.

Funding: Government Support - Non-U.S.

SA-PO454

Impact of SGLT2 Inhibitor on All-Cause Mortality Among Patients with Type 2 Diabetes with and Without CKD

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Background: SGLT2 inhibitors have been shown to improve survival among patients with chronic kidney disease (CKD) with and without diabetes. The long-term mortality benefit remains unclear. In addition, the existence of CKD among type 2 diabetes mellitus (DM) who are on SLGT-2 inhibitor can influence its mortality benefit. In this study, we wanted to compare mortality benefit among type 2 DM who are taking SGLT2 inhibitors and CKD to patients with normal renal function. We hypothesize that SGLT2 inhibitor should be started prior to the development of renal impairment among patients with type 2 DM.

Methods: In this retrospective study, we included all type 2 diabetes patients who presented to Dasman Diabetes institute for follow up from 2015 until 2022. The patients were divided based upon whether they were taking SGLT2- inhibitor or not and their CKD status. The main outcome was all-cause mortality.

Results: A total of 3569 patients were included. The all-cause mortality unadjusted hazard ratio (HR) for patients who were on SGLT2-inihbitor was 0.61 (95% CI, 0.41-0.89). After Adjusting for AgeGroup, gender, BMI and CKD stage, the adjusted HR ratio was 0.67 (95% CI, 0.45-0.99). The all-cause mortality HR for patients who were on SGLT2-inhibitor was 0.64 (95% CI, 0.43-0.95) which was adjusted for renal impairment. The HR for patients who had renal impairment who did not receive SGLT2 inhibitor was 4.41 (95% CI, 2.94-6.608). Whereas for patients who were on SGLT2 inhibitor and had renal impairment the adjusted HR was 2.82 (95% CI, 1.60-4.99) and 2.37 (95% CI, 1.31-4.27).

Conclusions: Over period of 8 years follow up, SGLT2-inhbitors were associated with lower all-cause mortality. The presence of CKD is associated with reduced survival suggesting that SGLT2 inhibitor should be started prior to the development of renal disease to improve survival. More research required to assess the optimal time to start SGLT2 inhibitor.

SA-PO455

Higher Glycemic Variability Increased the Risk of All-Cause Mortality in Patients with Diabetes Mellitus on Hemodialysis

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Background: Glycemic (HbA1c) variability has been recognized as an important predictor for the risk of cardiovascular events and all-cause mortality in patients with diabetes mellitus (DM) with and without renal failure. The aim of this study was to examine the association between HbA1c variability, as a measure of long-term glycemic control and the risk of all-cause mortality in patients with DM and HD.

Methods: Data of 2061 patients (collected between 2008 and 2018) with DM type 1 and 2 and HD were analyzed. HbA1c variability before and after HD was defined as the coefficient variation (CV), which was calculated as the ratio between the standard deviation (SD) and the mean of HbA1c. The relationships between HbA1c variability and mortality were examined by Cox models to estimate hazard ratios (HR) with and 95% confidence intervals (CI) in univariate and multivariate analyses, which was adjusted for demographics, laboratory findings and comorbidity. The patients were divided in seven groups, and we used the lowest CV group (CV≤0.5) as the reference group.

Results: During follow-up, 1071 (52%) deaths occurred. Through entire time of study each one unit increase of CV was associated with higher risk of mortality (HR 1.11, CI 1.02-1.23). Data before HD-start showed that 969 (47%) patients had HbA1c variability with CV>1, which increased to 1188 (58%) during HD. Patients in the group with the lowest CV≤0.5 had the best survival and 169 (8%) of these patients died. In a sub-analysis before HD-start, 597 (29%) of the patients had CV≤0.5, but during HD, 405 (20%) of the patients had CV≤0.5. The two groups with highest CV>2.8 had the highest risk of mortality and 305 (15%) of these patients died. In a sub-analysis before HD-start, 268 (13%) of the patients had CV>2.8, but during HD, 449 (22%) of the patients had CV>2.8. In the multivariate Cox analyses, the groups with highest CV (2.8-4.6 and >4.6) were associated with increased risk of mortality (HR 1.98, CI 1.54-2.47 and HR 1.99, CI 1.54-2.57) compared with the reference group.

Conclusions: Glycemic variability should be considered an important risk factor for mortality in patients with DM and HD. In patients with DM andHD, we highly recommend consistent monitoring of glucose homeostasis and regular evaluation of DM treatment.

SA-PO456

Preventing Hypoglycemia in ESRD Patients with Diabetes Mellitus: The Great Challenge

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Background: Patients with end stage renal disease who have coexisting diabetes mellitus are at an increased risk of developing hypoglycemia. With renal failure, patients have decreased renal gluconeogenesis, glucose reabsorption, and insulin clearance. ESRD patients accounted for about one third of all severe hypoglycemia episodes in hospitalized diabetics. Inadequate dose-adjustment of insulin could be a significant factor contributing to higher rates of hypoglycemia in these patients. In this study, we propose to add a text-based warning for physicians when ordering insulin in order to prevent overcorrection of glucose levels in these patients. Our long term goal is to create an individualized insulin sliding scale for patients with ESRD in order to prevent hypoglycemia and its sequelae.

Methods: We conducted an analysis on 1,178 hospitalized patients to evaluate the incidences of hypoglycemia in patients with co-existing diabetes mellitus and end stage renal disease. Our study aimed at understanding whether administering a lower average dose of insulin would decrease the overall number of episodes of hypoglycemia in these patients. The intervention was a text-based electronic reminder for physicians when they ordered insulin. The 2 groups studied were the pre-intervention group from October 2021 to June 2022 and post-intervention group from July 2022 to March 2023. There were 703 patients studied in the pre-intervention period and 474 patients in the post-intervention period.

Results: Upon analysis of the results, it was noted that there was no statistically significant difference between pre and post intervention groups in the number of hypoglycemic episodes. Although not statistically significant, we do see a reduced amount of total hypoglycemic episodes in patients post-intervention who had at least one prior hypoglycemic episode recorded. It should be noted that the cut off for hypoglycemia classification was changed during the course of this study which could have contributed to the lack of statistically significant results.

Conclusions: This study raises attention towards an important complication of end stage renal disease. Recurrent hypoglycemia can further complicate the course of acute illnesses. With the number of hypoglycemic episodes noted to be higher in the pre-intervention group, it is worthwhile to adjust insulin administration for these patients inpatient.

SA-PO457

Accuracy of Real-Time Continuous Glucose Monitoring in Hemodialysis Patients with Diabetes

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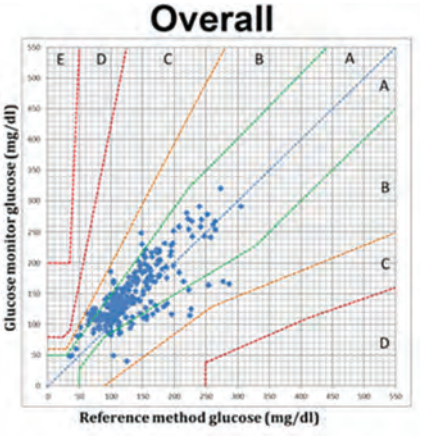
Background: HD patients with diabetes are at heightened risk of hypo- and hyperglycemia. Traditional glycemic markers (HbA1c) are less reliable in ESKD, and self-monitored blood glucose may not adequately capture glycemic status in HD patients given its infrequent nature. We thus sought to assess the accuracy of continuous glucose monitoring (CGM) as a more frequent (every 5-minutes), convenient, and automated method of glycemic assessment in a prospective HD cohort with diabetes.

Methods: Among 33 HD patients with diabetes hospitalized from 10/2020-5/2021, we conducted simultaneous glucose measurements using CGM measured by Dexcom G6 devices vs. blood glucose levels using capillary fingerstick or venous blood glucose, with the latter measured at least 4 times per day (before each meal and at night), plus every 30 minutes while receiving HD (total of 6-8 measures during HD). We assessed the agreement of CGM vs. blood glucose values using the mean absolute relative difference (MARD), defined as the average of absolute values of relative differences between CGM vs. blood glucose).

Results: The MARD was 19% overall and 18% and 22% during the non-HD and HD periods, respectively. Consensus error grid analysis showed all of sensor values in clinically acceptable zones A (allowable total error region typically associated with no harm) and B (small amount of data slightly outside the no harm zone but unlikely to cause significant harm).

Conclusions: In hospitalized HD patients with diabetes with concurrent CGM and blood glucose measurements, real-time CGM showed clinically acceptable performance and agreement with blood glucose. Further studies are needed to determine whether CGM can improve the glycemic management of HD patients compared to conventional approaches.

Funding: Commercial Support - Dexcom



SA-PO458

Efficacy of Continuous Glucose Monitoring (CGM) in People with Diabetes on Dialysis

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Background: Patients with diabetes on dialysis (DM) experience wide variations in glucose levels leading to increased risk of hypoglycaemia. Due to the inaccuracies of HbA1c in dialysis patients, JBDS-IP and KDIGO Diabetes Work Group recommend the use of CGM. We conducted a systematic review to examine current evidence for CGM use and its impact on clinical outcomes.

Methods: Search of MEDLINE and Embase databases was conducted. Clinical or observational trials in adults with DM on dialysis and CGM intervention reporting glycaemic outcomes were included. Data collected included patient characteristics, intervention and glycaemic outcome. Quality was evaluated using the NHLBI assessment tool.

Results: Of the 936 citations identified, 49 duplicates were removed. 887 screened by title and abstract. 9 full texts reviewed and a further 7 excluded due to duplications and failure to meet to selection criteria. Data was extracted for 2 studies (table 1), both 'good' quality, prospective before-and-after interventional studies with no control group. Joubert et al, (2015) showed mean CGM glucose level was 8.3 at baseline and 7.7mmol/L at the end of the CGM period ($p<0.05$). HbA1c decreased from 6.9 to 6.5% at the end of 12 weeks ($p<0.05$). Number of insulin adjustment was higher during the CGM compared to the SMBG period (2.1 vs 1.4, $p<0.05$). Mean CGM was lower on dialysis days (7.6 vs 7.8mmol/L, $p<0.05$). Képénékian et al, (2014) reported after 3 months with CGM-adapted insulin regimen, HbA1c decreased from 8.4 to 7.6% ($p<0.01$). Mean CGM values decreased from 9.9 to 8.9mmol/L ($p=0.05$). The frequency of glucose values >10mmol/L decreased from 41 to 30% ($p<0.05$), without significant increase in hypoglycaemia frequency. Insulin requirements increased from 70 to 82IU/d ($p<0.01$), without significant weight gain.

Conclusions: Evidence demonstrating impact of CGM on glycaemic outcomes in patients with DM on dialysis is lacking. Further trials with bigger sample size and longer follow up are needed to ascertain the benefits of CGM in these patients.

Author (year)	Country	Participant characteristics	Age (years)	Male to female ratio	Sample size	Comparator	Intervention	Outcome - Primary	Outcome - Secondary	Follow up duration
Joubert (2015)	France	Diabetic patients type 1 or 2. Haemodialysis (4h three times a week)	61 +/-15	8:7	15	SMBG	5 day CGM at 2 week intervals, antidiabetic drug adjusted accordingly	Change in CGM readings	Diabetic treatment changes and quality of life, AUC and MAGE, HbA1c levels	2x 6 week periods
Képénékian (2014)	France	T2DM treatment with insulin, HbA1c >47.5, maintenance dialysis more than 3 months	66 +/-9	19:9	28	baseline CGM and HbA1c	CGM adapted basal-bolus insulin regimen	Change in HbA1c	Body weight, insulin requirements, symptomatic hypoglycaemia, CGM parameters	3 months

Table 1 – Clinical demographic characteristics of included studies

SA-PO459

Association of Peripheral Neutrophil Count with Risk of Cardiovascular Mortality Among Adults with Diabetic Kidney Disease: Evidence from NHANES 2005-2010

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Background: Accumulating data shows that chronic inflammation has crucial pathogenic contributions in CKD patients with diabetes, but the contribution of neutrophils count in diabetic kidney disease (DKD) remains elusive.

Methods: We performed a cross-sectional study of 44,494 participants in the National Health and Nutrition Examination Surveys (NHANES) from 2005 to 2020. The prevalence of CKD and diabetes were calculated. The association of peripheral neutrophils count levels with kidney functions in DKD and cardiovascular disease (CVD) mortality were further explored using logistic regression and Cox proportional hazards models.

Results: Among the 2,643 patients with DKD from NHANES, the weighted mean of peripheral neutrophil count level was 4.97. When compared with patients with DKD in the lowest neutrophil count quintile, The highest quintile had the positively association with uACR and negatively relationship with estimated eGFR. During 2,215 person-years of eligible follow-up, 766 deaths (n = 237 deaths from CVD) occurred. In comparison to those in the those in the lowest neutrophil count quintile group, the highest quintile group had the HRs of 1.77 for all-cause mortality and 2.24 for CVD mortality in the fully adjusted model. A linear count-response relationship of peripheral neutrophil count with CVD mortality were also demonstrated (*P=0.002*).

Conclusions: Higher peripheral neutrophil count was significantly associated with an increased risk of cardiovascular mortality and poor kidney function among patients with DKD.

Funding: Private Foundation Support

Table 1 Association of neutrophil count level with kidney function in patients with diabetic kidney disease from NHANES 2005-2020 cohort

Kidney function measures	Median(CI)	Crude model*		Model 1†		Model 2‡		Model 3#	
		HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
uACR									
Q1	213.80(165.96,260.64)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2	293.99(205.32,382.67)	80.69(-18.32,179.70)	0.11	110.09(-18.53, 201.22)	0.02	114.17(-19.83,208.51)	0.02	101.34(-8.49,194.19)	0.03
Q3	287.67(189.46,385.88)	74.37(-32.24,180.98)	0.17	112.19(-0.68, 225.03)	0.05	120.77(-8.95,232.60)	0.03	103.84(-2.06,209.73)	0.05
Q4	447.60(314.12,581.07)	234.3(87.25,381.35)	0.002	281.76(137.95, 435.61)	<0.001	281.86(128.79,434.93)	<0.001	269.55(117.49,421.61)	<0.001
P for trend			0.004		0.001		<0.001		0.001
eGFR		Crude model		Model 1		Model 2		Model 3	
		HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
Q1	68.67(65.75,71.59)	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2	69.36(66.03,72.70)	0.69(-3.95,5.34)	0.77	-1(-3.96, 1.95)	0.5	-1.27(-4.07, 1.53)	0.37	-1.07(-3.79, 1.65)	0.44
Q3	69.81(66.55,73.07)	1.14(-3.23,5.51)	0.61	-1.4(-4.71, 1.80)	0.4	-1.95(-5.34, 1.44)	0.26	-1.66(-5.05, 1.73)	0.33
Q4	69.28(65.75,72.81)	0.61(-4.59,5.81)	0.82	-3.67(-6.91, -0.43)	0.03	-4.5(-7.64, -1.35)	0.01	-4.29(-7.43,-1.13)	0.01
p for trend			0.79		0.03		0.01		0.01

Data are n or weighted HR (95% CI). GFR is calculated using the CKD-EPI Creatinine Equation (2009). P values are for comparisons using the ANOVA for continuous variables with a normal distribution, the Kruskal-Wallis test for continuous variables with a skewed distribution.
*Crude Model: no adjusted; †Model 1: adjusted age, sex, and eth; ‡Model 2: adjusted Model 1+ smoke+ alcohol user; #Model 3: adjusted Model 2 + hypertension + hyperlipidemia.
Neutrophil count (*10^9) was quartered: Q1 (∞, 3.5]; Q2 (3.5,4.5]; Q3 (4.5,5.7]; Q4 (5.7, ∞)

Table 2 Associations of neutrophil count level with all-cause and CVD mortality in patients with diabetic kidney disease from the NHANES 2005–2018 cohort.

	No. death/no at risk	Crude model*		Model 1†		Model 2‡		Model 3#	
		HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
All-cause mortality									
Q1	194/403	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2	171/391	0.88(0.69,1.11)	0.28	0.89(0.70,1.12)	0.33	0.87(0.69,1.10)	0.25	0.86(0.68,1.09)	0.22
Q3	187/348	1.17(0.89,1.53)	0.26	1.27(0.99,1.64)	0.06	1.22(0.94,1.56)	0.13	1.22(0.94,1.57)	0.13
Q4	214/307	1.58(1.24,2.03)	<0.001	1.93(1.49,2.50)	<0.0001	1.77(1.36,2.31)	<0.0001	1.77(1.36,2.32)	<0.0001
p for trend			<0.0001		<0.0001		<0.0001		<0.0001
Cardiovascular mortality									
Q1	61/403	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Q2	52/391	0.87(0.57,1.32)	0.51	0.89(0.57,1.40)	0.62	0.86(0.54,1.37)	0.52	0.88(0.55,1.41)	0.59
Q3	58/348	1.19(0.77,1.82)	0.44	1.31(0.84,2.04)	0.24	1.26(0.78,2.05)	0.34	1.34(0.84,2.16)	0.22
Q4	66/307	1.75(1.13,2.71)	0.01	2.36(1.50,3.72)	<0.001	2.09(1.28,3.41)	0.003	2.24(1.38,3.64)	0.001
p for trend			0.01		<0.001		0.002		<0.001

Data are n or weighted HR (95% CI). P values are for comparisons using the ANOVA for continuous variables with a normal distribution, the Kruskal-Wallis test for continuous variables with a skewed distribution.
*Crude Model: no adjusted; †Model 1: adjusted age, sex, and eth; ‡Model 2: adjusted Model 1+ smoke+ alcohol user; #Model 3: adjusted Model 2 + hypertension + hyperlipidemia.
Neutrophil count (*10^9) was quartered: Q1 (∞, 3.5]; Q2 (3.5,4.5]; Q3 (4.5,5.7]; Q4 (5.7, ∞)

SA-PO460

Diagnosis of Renal and Cardiovascular Injuries in Type 1, Type 2, and Prediabetic Patients Using an Ensemble of Machine Learning and Deep Learning Methods

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Background: Diabetes is a growing global pandemic with serious complications such as renal and cardiovascular injuries. Diabetic nephropathy, characterized by decreased glomerular filtration rate (GFR) and albuminuria, is a microvascular complication of

diabetes. Cardiovascular disease, which can result in injuries to coronary, cerebrovascular, and peripheral arteries, is a macrovascular complication. Studies have shown that renal and cardiovascular diseases often co-occur in individuals with diabetes, but there is currently no machine learning algorithm that was used to diagnose the existence of both complications simultaneously.

Methods: For this study, a dataset of 273 diabetic patients is obtained from the American University of Beirut Medical Center (AUBMC). Chronic kidney disease is defined as a GFR lower than 60 ml/min and/or an albumin to creatinine ratio greater than 30. Cardiovascular disease outcome is measured by the presence of cardiovascular events such as myocardial infarction, heart failure, arrhythmias and valvulopathies. To balance the class distributions, the synthetic minority oversampling technique (SMOT) is used. The Random Forest and Artificial Neural Network models are employed to analyze the data and evaluate the relevance of each feature using feature importance methods. The grid search method is used to fine-tune the hyperparameters of the models.

Results: The Random Forest model achieved an accuracy of 91%. The Extreme gradient Boosting (XGBoost) feature importance method revealed that the most relevant features, in decreasing order of importance, were urine albumin mg/l, serum creatinine, age, LDL, total cholesterol, heart rate, phosphate, systolic blood pressure, carbon dioxide, and potassium. The Neural Network had 75% accuracy with Grid Search. The lower accuracy could be due to the small sample size (273 patients) for deep learning.

Conclusions: The results of the study show that machine learning can be useful in diagnosing renal-cardiovascular complications in diabetic patients.

SA-PO461

Differentiating Non-Diabetic Kidney Diseases from Diabetic Nephropathy in Type 2 Diabetes Mellitus Patients with Nephrotic Syndrome

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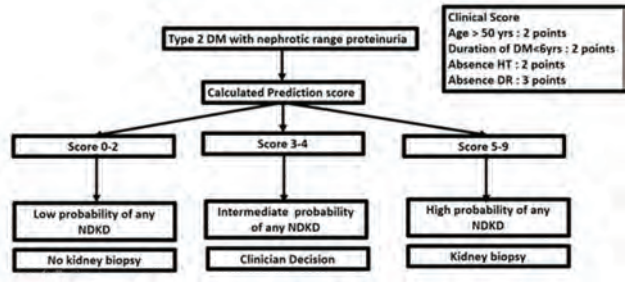
Background: Nephrotic syndrome (NS) in patients with type 2 diabetes mellitus (T2DM) encompass both diabetic nephropathies (DN) and non-diabetic kidney diseases (NDKD). This study aims to investigate kidney biopsies in T2DM patients who had NS to determine the prevalence of NDKD and analyze characteristic features that are associated with NDKD. The objective is to develop a clinical prediction score that can differentiate any NDKD cases from DN alone.

Methods: This study was done as a single-center, retrospective, cross-sectional observational design, patients diagnosed with T2DM who underwent kidney biopsy due to NS at Vajira Hospital between 2013-2021. All patients received diagnoses of either DN, isolated NDKD, or NDKD superimposed on DN, which were confirmed through pathological examinations. To identify factors correlated with NDKD, a multiple logistic regression analysis was performed. Additionally, a clinical prediction score was developed by assigning weights to the predictors' coefficients in a multivariable logistic model.

Results: A total of 273 patients were enrolled in this study, with 89 patients (32%) DN alone, 69 patients (25%) NDKD superimposed on DN, and 115 patients (42%) NDKD alone. The most prevalent NDKD causes were IgA nephropathy. The absence of diabetic retinopathy (DR) (adj.OR 2.89; 95% CI 1.61-5.2; p<0.001), age>50 years (adj. OR 2.26; 95% CI 1.29-3.93; p=0.004), duration of DM < 6 years (adj.OR 2.02; 95% CI 1.14-3.57; p=0.015), and absence of hypertension (adj.OR 2.058; 95% CI 1.08-3.89; p=0.026) significant associations with NDKD. From these 4 predictors, a prediction score was derived, wherein a score >5 indicated a higher likelihood of NDKD (AUROC of 0.75, 95%CI 0.63-0.86)

Conclusions: The prevalence of any NDKD in T2DM with NS is 67%. No DR, Age > 50 years, duration of DM < 6 years, and absence of hypertension have significant association with NDKD. A new clinical prediction score for distinguishing any NDKD from DN alone can defer kidney biopsy.



Algorithm using Clinical Prediction score

SA-PO462

Progression to ESKD in Type 2 Diabetes by Histological Findings: A Retrospective Cohort Study

Karina Haar,[1,2] Frederik Persson,[2] Iain O. Bressendorff,[3] Ditte Hansen,[3,4] Marie Møller,[3] Peter Rossing,[2,4] Rikke Borg.[1,4] PRIMETIME. *[1]Department of Medicine, Zealand University Hospital, Roskilde, Denmark; [2]Steno Diabetes Center Copenhagen, Herlev, Denmark; [3]Department of Nephrology, Copenhagen University Hospital – Herlev and Gentofte, Herlev, Denmark; [4]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark.*

Background: The risk of progression to end-stage kidney disease (ESKD) varies among individuals with type 2 diabetes (T2D). This study aims to investigate if the risk of progression to ESKD differ by biopsy-proven type of kidney disease.

Methods: We conducted a retrospective cohort study including all adults with T2D in Denmark from 1996-2020 who had a kidney biopsy performed. The individuals were previously classified as having diabetic nephropathy (DN) (n=599), non-diabetic nephropathy (NDN) (n=703), mixed disease (n=165), normal histopathology (n=49), or could not be classified (NC) (n=743). Using high-quality national registry data, the cohort was described with demographic, clinical, and laboratory data and comorbidity. Stratified analysis of progression to ESKD within the type of kidney disease was performed.

Results: The cohort consisted of 68% men with mean age 64.1+11.2 years at biopsy. At the time of biopsy, the DN group had systolic blood pressure (SBP) 144±20 mmHg and a body mass index (BMI) of 30.9±6.2 kg/m^2. They had a median and interquartile range [IQR] estimated glomerular filtration rate (eGFR) 39 [24.0, 59.2] ml/min/1.73m^2 and median [IQR] urine albumin-creatinine ratio (UACR) 2373 [890.2, 4183.5] mg/g. The NDN group had SBP 138±21 mmHg, a BMI of 30.8±6.5 kg/m^2, eGFR 29 [15.0, 58.0] ml/min/1.73m^2, and UACR 766 [95.5, 2394.5] mg/g. The mixed disease group had SBP 147±21 mmHg, a BMI of 31.7±6.1 kg/m^2, eGFR 25 [11.0, 48.0] ml/min/1.73m^2 and UACR 1863 [583.0, 3400.0] mg/g. We found a significant difference in the rate of renal progression ($p < 0.001$). During a median follow-up of 12.8 years, progression to ESKD occurred in 52% with DN, 42% with NDN, 53% with mixed disease, 25% with normal histopathology, and 41% with NC. Time to ESKD from diagnosis of T2D was significantly different within the type of kidney disease ($p < 0.001$); 13.2 [8.0, 17.9] median [IQR] years in DN, 7.8 [4.5, 12.8] years in NDN, 13.0 [7.8, 17.3] years in mixed disease, 6.3 [1.3, 11.1] years in normal histopathology, and 9.2 [5.1, 14.6] years in NC.

Conclusions: In people with T2D, we found the highest rate of ESKD in DN and mixed disease, but with the slowest time to progression. Analyses suggest that the risk of and time until progression to ESKD differs significantly within types of biopsy-proven kidney disease.

Funding: Private Foundation Support

SA-PO463

Progression to ESKD in Type 1 Diabetes by Histological Findings

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Background: Kidney disease in diabetes is a heterogeneous disease. To improve personalized medicine in people with diabetes, it is crucial to identify people at risk of progressing to end-stage kidney disease (ESKD). This study aims to investigate if progression to ESKD differs by biopsy-proven type of kidney disease in people with type 1 diabetes (T1D).

Methods: In this retrospective registry study, we included all Danish adults with T1D from 1996-2020 who had a kidney biopsy performed. The included individuals had diabetic nephropathy (DN)(n=132), non-diabetic nephropathy (NDN)(n=73), mixed disease (n=39), normal histopathology (n=5), or could not be classified (NC)(n=78). Demography, clinical presentation, laboratory values, and prevalence of comorbidity were described by compiling unique national registry data. Within the type of kidney disease, we analyzed progression to ESKD.

Results: The DN group consisted of 71% men with systolic blood pressure (SBP) of 146±21 mmHg and a body mass index (BMI) of 25.1±5.5 kg/m^2. In NDN and mixed disease groups 66% and 59%, respectively, were men. In NDN, mean SBP was 137±18 mmHg and they had a BMI of 24.6±3.5 kg/m^2. Those with mixed disease had a mean SBP of 135±21 mmHg and a BMI of 24.7±3.7 kg/m^2. Median and interquartile range [IQR] estimated glomerular filtration rate (ml/min/1.73m^2) and urine albumin-creatinine ratio (mg/g) were 37 [22.6, 54.1] and 2670 [935.4, 4390.7] in DN, 41 [14.0, 85.0] and 857 [304.5, 3860.5] in NDN, 27 [16.4, 71.8] and 1240 [435.0, 3472.0] in mixed disease, 29 [20.6, 36.5] and 201 [118.0, 984.7] in normal histology, and 35 [12.5, 62.5] and 436 [40.0, 2281.0] in NC, respectively. During a median [IQR] follow-up time of 22.6 [14.5, 30.4] years, 61% with DN advanced to ESKD, compared to 52% with NDN, 59% with mixed disease, and 46% with NC. There were no significant differences between groups. Likewise, there was no significant difference in median [IQR] time to progression of ESKD; 17.4 [12.0, 21.9] years in DN, 14.9 [9.1, 23.0] years in NDN, 19.6 [17.1, 27.4] years in mixed disease, 24.1 [19.3, 26.0] years in normal histopathology, and 18.5 [11.3, 24.8] years in NC.

Conclusions: In people with T1D, retrospective analysis of registry data did not find a significant difference in risk of progression to ESKD or time to ESKD within biopsy-proven type of kidney disease.

Funding: Private Foundation Support

SA-PO464

Preliminary Results from iBeat Ancillary Study: A Novel Bari Classification of Renal Damage in Diabetic Patients with CKD

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Background: Renal damage in diabetes is heterogeneous, kidney biopsy remains the gold standard for diagnosis. In this iBEAt sub-study, within the BEAt-DKD project (https://www.beat-dkd.eu/), we aimed to correlate imaging, clinical, molecular and histopathological data to dissect renal damage phenotypes.

Methods: We enrolled 83 patients to perform kidney biopsy (carried out in 64 patients), US and MRI, biofluids and clinical data collection.

Results: According to KDIGO 13 patients were in stage A1, 26 in A2 and 25 in A3, all ranging from G1 to G4. Histological classification by Mazzucco et al (PMID: 11920336) identified 31% of patients with class 1 (diabetic nephropathy-DN); 33% with class 2 (vascular and ischemic glomerular changes); 4% with class 3a (glomerular diseases and DN) and 31% with class 3b (other glomerulonephritis in the absence of DN). Since we observed heterogeneous histological lesions, we here propose a novel classification for diabetic patients with CKD. We recognized 3 different classes (DKD, NDKD, DKD+NDKD) and 6 different phenotypes including: a) in DKD (33%): pure metabolic (7%) and vascular metabolic (26%); b) in NDKD (63%): pure vascular (35%), immunological vascular (IgA, FSGS, MN; 9%), pure immunological (IgAN, FSGS; 19%); c) in DKD+NDKD overlapping phenotypes (4%). We observed differences of uACR (p=0.02) and proteinuria (p=0.005) among the different phenotypes of DKD and NDKD. PAS staining confirmed the increased mesangial expansion in DKD phenotype (p=0.04); vascular wall-to-lumen ratio discriminated vascular vs metabolic (p=0.04) and immunologic damage (p=0.05); renal resistive index discriminated among the phenotypes (p=0.02). We also performed single-cell RNASeq analysis of kidney biopsies mapping more than 61000 nuclei in different cell types, identifying differences between classes and phenotypes along the nephron and the vasculature (i.e. TNNT2 expression in podocytes was associated with vascular damage).

Conclusions: The integration of renal pathology, imaging and molecular data from the same patient has the potential to unlock new diagnostic criteria to address the heterogeneity of renal phenotypes, providing a new classification of renal damage in diabetes.

SA-PO465

Glomerular Crescents Are Associated with the Risk of Kidney Progression in Type 2 Diabetic Kidney Disease

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Background: Type 2 diabetic kidney disease (T2DKD) is the leading cause of chronic kidney disease and end-stage kidney disease. The heterogeneous phenotype of T2DKD complicates the approach to treating patients. While kidney biopsy is the gold standard for diagnosis, it is not perfect in predicting progression to end-stage kidney disease. Herein, we addressed whether the presence of glomerular crescents was associated with the outcomes in biopsy-proven T2DKD.

Methods: A total of 360 patients who were diagnosed as biopsy-proven DKD in the setting of type 2 diabetes but did not have other crescentic glomerulonephritis from 9 medical centers were reviewed. Hazard ratios (HRs) were calculated using a Cox regression model to evaluate the risk of kidney progression (i.e., ≥50% of decrease in estimated glomerular filtration rates) according to the presence of glomerular crescents.

Results: 11 patients (3.1%) had glomerular crescents in the biopsied tissues. During the follow-up period (median, 18 months; maximum, 18 years), the crescent group had a higher risk of kidney progression than no crescent group with adjusted HR of 2.71 (1.22–6.03) ($P = 0.014$). The relationship with kidney progression was more prominent in patients with high proportion of crescents than in those with low proportion.

Conclusions: The presence of glomerular crescents is associated with progression of T2DKD. Accordingly, histological monitoring of glomerular crescents may be needed to treat patients intensively.

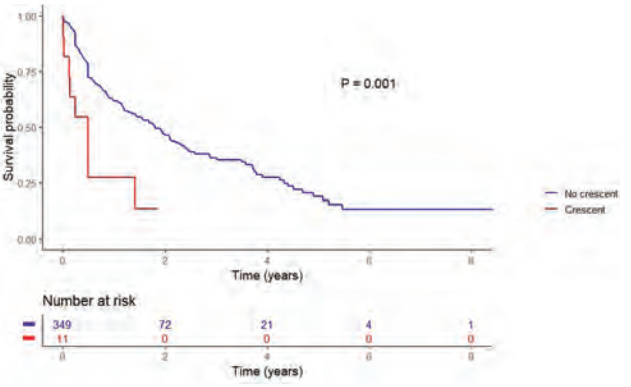

Fig 1. Kidney outcome curves for patients with and without crescents in the biopsied tissues. Kaplan-Meier curve depicted for patients without crescents versus those who had glomerular crescents in the biopsied tissues.

SA-PO466

Diversity of Kidney Biopsy Findings Among Diabetic Patients in the Cleveland Clinic Kidney Biopsy Epidemiology Project

Alvin G. Kwon,[1] Hanny Sawaf,[1] Shruti Shettigar,[2] Leal C. Herlitz,[1] Adam Kabuka,[2] Surafel K. Gebreselassie,[2] Shane A. Bobart.[2,1] *[1]Cleveland Clinic Foundation, Cleveland, OH; [2]Cleveland Clinic Florida, Weston, FL.*

Background: Patients with a clinical diagnosis of diabetes without other criteria to prompt kidney biopsy are often treated and managed as diabetic kidney disease (DKD). We sought to describe the spectrum of kidney biopsy findings among patients with diabetes and identify factors associated with finding DKD and non-DKD (NDKD).

Methods: We identified patients with a history of diabetes from the Cleveland Clinic Kidney Biopsy epidemiology project from January 2015 to September 2021 using available ICD-10 code data.

Results: Of 4128 patients with native kidney biopsies, 3503 had ICD-10 code data. We identified 1271 (36.3%) with an ICD-10 coded diabetes. Of these, 462 (36.3%) had DKD alone and 678 (53.3%) had NDKD alone, 105 (8.3%) had both DKD and NDKD and 26 (2.0%) were either normal or non-diagnostic. The most common diagnoses among those with NDKD were FSGS (23.6%), global glomerulosclerosis NOS (12.8%), ATN (8.9%) IgA nephropathy (8.0%) and ANCA vasculitis (7.4%) and membranous nephropathy (4.9%). When comparing types of NDKD between NDKD alone (n=678) and DKD+NDKD (n=105), global glomerulosclerosis NOS was more prevalent in NDKD alone group (13.9%, 5.7%). Oxalate nephropathy and PIGN were more prevalent in DKD+NDKD patients (4.8%, 0.9% and 11.4%, 3.5%, respectively). Aging and White race were positively associated with NDKD compared to DKD alone. (Table)

Conclusions: Of diabetic patients who underwent kidney biopsy, only 36.4% had DKD alone and 63.6% had additional diagnoses on biopsy. Aging had positive association with NDKD than DKD alone. Global glomerulosclerosis NOS, oxalate nephropathy and PIGN had different prevalence in NDKD versus DKD+NDKD. Further analysis is required and ongoing to determine factors associated with alternative diagnoses other than DKD among diabetes patients to guide the use of kidney biopsy in this setting.

Funding: Private Foundation Support

Factors associated with NDKD among diabetes patients in CCKBEP

Multivariable models (NDKD, n=783 vs. DKD alone, n=463)	Non-Diabetic Kidney Diseases OR (95% CI)
Model A	
Gender, female	0.85 (0.67, 1.08)
Age at time of biopsy, per 1 year older	0.020 (0.011, 0.028); beta coefficient
Race, self-identified White	1.42 (1.11, 1.82)
Model B	
Gender, female	0.84 (0.66, 1.06)
Age at time of biopsy, >70 years old	1.94 (1.46, 2.58)
Race, self-identified White	1.44 (1.13, 1.84)

SA-PO467

Diabetic Kidney Disease Phenotypes and Cardiovascular Outcomes

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Background: Adults with diabetic kidney disease (DKD) have high risk of major adverse cardiovascular events (MACE) and cardiovascular disease (CVD). However, variability in cardiovascular risk across DKD phenotypes remains poorly understood.

Methods: This is a longitudinal analysis of adults with diabetes from two cohorts, the National Health and Nutrition Examination Survey (NHANES, N=5,126) and the UK Biobank (N=27,059). We defined four distinct clinical phenotypes: no DKD (estimated glomerular filtration rate (eGFR)≥60ml/min and urinary albumin-to-creatinine ratio (UACR)<30mg/g), albuminuria only (eGFR≥60mg/ml and UACR≥30mg/g), decreased

eGFR only (eGFR<60ml/min and UACR<30mg/g), and albuminuria plus decreased eGFR (eGFR<60ml/min and UACR≥30mg/g). We used multivariable adjusted Cox proportional hazard models to assess CVD outcomes.

Results: In NHANES, the albuminuria only phenotype and the albuminuria plus decreased eGFR phenotype were associated with a 2.71-fold higher risk of CVD mortality (hazard ratio [HR] 2.71, 95% confidence interval [CI] 1.91-3.85) and a 2.75-fold higher risk (HR 2.75, 95%CI 1.80-4.21) compared to no DKD. In the UK Biobank, the albuminuria-only phenotype had a 2.01-fold higher risk of CVD mortality (HR 2.01, 95%CI 1.75-2.32) and a 1.54-fold higher risk of MACE (HR 1.54, 95%CI 1.41-1.68) compared to no DKD. Moreover, the albuminuria plus decreased eGFR phenotype had a 3.24-fold higher risk of CVD mortality (HR 3.24, 95%CI 2.38-4.40) and a 2.06-fold higher risk of MACE (HR 2.06, 95%CI 1.64-2.59) compared to no DKD. The decreased eGFR phenotype was associated with a 1.65-fold higher risk of CVD mortality (HR 1.65, 95%CI 1.24-2.18) and a 1.30-fold higher risk of MACE (HR 1.30, 95%CI 1.06-1.59) compared to no DKD.

Conclusions: Each DKD phenotype had varying risk of CVD mortality and MACE, indicating distinct clinicopathological characteristics. These findings emphasize the need for tailored management to prevent adverse cardiovascular outcomes in DKD.

Funding: Other NIH Support - Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R38HL143584

Table 1:

	No DKD	Albuminuria only	Decreased eGFR only	Albuminuria + decreased eGFR
*NHANES – Cardiovascular mortality				
Total Numbers	3005	1146	475	500
No. Events	231	174	98	131
Unadjusted	Referent	2.71[1.95-3.78]	4.47[3.12-6.40]	8.03[5.70-11.31]
Model 1	Referent	3.06[2.19-4.11]	2.04[1.43-2.90]	4.00[2.86-5.60]
Model 2	Referent	2.70[1.90-3.83]	1.82[1.24-2.65]	3.42[2.37-4.95]
Model 3	Referent	2.71[1.91-3.85]	1.52[0.99-2.31]	2.75[1.80-4.21]
*UK Biobank – Cardiovascular mortality				
Total Numbers	22191	3648	779	441
No. Events	788	319	106	110
Unadjusted	Referent	2.67[2.34-3.04]	4.21[3.43-5.15]	9.79[8.02-11.9]
Model 1	Referent	2.30[2.01-2.63]	3.27[2.65-4.03]	6.87[5.59-8.45]
Model 2	Referent	2.04[1.77-2.35]	2.60[2.09-3.24]	5.61[4.51-6.98]
Model 3	Referent	2.01[1.75-2.32]	1.65[1.24-2.19]	3.24[2.38-4.40]
UK Biobank – MACE				
Total Numbers	19826	3044	564	309
No. events	2,690	731	160	142
Unadjusted	Referent	1.91[1.76-2.08]	2.29[1.94-2.67]	4.37[3.69-5.17]
Model 1	Referent	1.69[1.56-1.84]	1.80[1.53-2.11]	3.20[2.79-3.80]
Model 2#	Referent	1.55[1.42-1.69]	1.73[1.46-2.05]	2.93[2.45-3.51]
Model 3	Referent	1.54[1.41-1.68]	1.30[1.06-1.59]	2.06[1.64-2.59]

*For NHANES:
Model 1: adjusted for age, sex, race or ethnicity, insurance, smoking status, BMI, survey year
Model 2: Model 1 + total cholesterol, hemoglobin A1c, systolic blood pressure, history of CVD, use of ACE/ARB, and use of statin
Model 3: Model 2 + eGFR
*For UK Biobank:
Model 1: adjusted for age, sex, race or ethnicity, smoking status, BMI, assessment center
Model 2: Model 1 + low density lipoprotein, hemoglobin A1c, systolic blood pressure, history of MACE (HF or MI or Stroke), use of anti-hypertensive medications, and use of statin
Model 3: Model 2 + eGFR
#No adjustment for history of MACE

Table 1

SA-PO468

Albuminuria Is Associated with Higher Carotid Plaque Volume Quantified by Novel 3D Ultrasound in Type 1 Diabetes

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Background: Carotid atherosclerosis is associated with progression of kidney disease. Novel 3D ultrasound (3DUS) methods to quantify carotid plaque volume (CPV) may potentially provide more accurate information on carotid atherosclerosis compared to conventional ultrasound methods. We investigated the association between CPV and albuminuria in individuals with type 1 diabetes (T1D) and healthy controls.

Methods: Total CPV (tCPV) was quantified using a novel 3DUS transducer (XL14-3, Philips Healthcare) and calculated as the sum of CPV bilaterally. Individuals with T1D were stratified based on historic albuminuria: normal (30 <mg/g), moderately (30-299 mg/g), or severely increased (≥300 mg/g). tCPV was Ln-transformed in all analyses. Association between tCPV and albuminuria groups was analyzed using linear regression with healthy controls as reference and adjusted for age, sex, systolic blood pressure, smoking, eGFR and LDL-cholesterol. Analyses were repeated solely including the T1D individuals, with the normal albuminuria group as reference, further adjusted for HbA_{1c}. Estimates per one standard deviation increase in Ln-tCPV with 95% confidence intervals are presented.

Results: A total of 120 individuals with T1D and 20 healthy controls were included, 48% were female and mean (±SD) age was 54±15 years. Of the individuals with T1D, 30 had normal, 45 moderately and 45 severely increased albuminuria. Median (IQR) tCPV in each group was: healthy controls 11.6 (6.0-41.6) mm^3, normal 13.0 (1.4-60.9) mm^3, moderately increased 29.2 (17.8-106.1) mm^3, and severely increased 46.3 (10.6-117.5) mm^3 albuminuria. Participants with moderately and severely increased albuminuria had higher tCPV compared to healthy controls after adjustment (0.42, CI [0.01-0.83], p=0.05) and (0.60, CI [0.13-1.06], p=0.01), respectively. Among T1D, individuals with moderately (0.38, CI [0.03-0.72], p=0.03) and severely increased (0.53, CI [0.13-0.94], p=0.01) albuminuria had higher tCPV than individuals with normal albuminuria.

Conclusions: Individuals with T1D and moderately or severely increased albuminuria had higher tCPV, measured with a novel 3DUS method, compared to individuals with normal albuminuria and healthy controls.

SA-PO469

SGLT2 Inhibition Improves Vascular Function in Patients with Type 2 Diabetes: A Double-Blind, Randomized, Placebo-Controlled Crossover Trial

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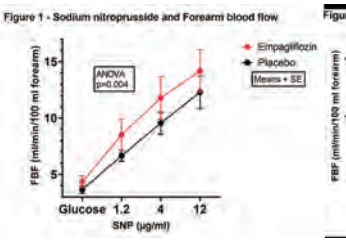
Background: Sodium glucose co-transporter 2 inhibitors (SGLT2i) reduce cardiovascular events and protect kidney function in patients with type 2 diabetes (DM2). Improved vascular function may be a part of the explanation for this. Vasodilatory capacity in patients with DM2 after SGLT2 inhibition was examined in this study.

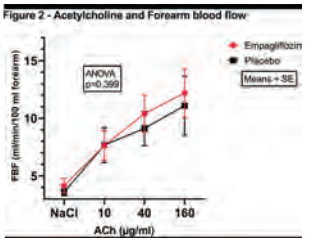
Methods: In a double-blind, randomized, placebo-controlled cross-over study, 15 patients with DM2 and preserved kidney function (eGFR > 60 ml/min/1.73 m^2) were included. Participants received four weeks of SGLT2i treatment (empagliflozin 10 mg) and matching placebo in a random order separated by a two-week wash-out period. At the end of each treatment period vascular function was evaluated by venous occlusion plethysmography. Forearm blood flow (FBF) was measured during intra-arterial infusion of acetylcholine (ACh) and sodium nitroprusside (SNP) in increasing concentrations, assessing endothelium-dependent and independent vasodilation, respectively. Repeated measures two-way ANOVA was used to compare absolute FBF between groups.

Results: The majority of participants were male (73 %). Mean age was 68±9 (SD) years (range 49-82), eGFR was 81±10 ml/min/1.73 m^2 and duration of diabetes was 16±9 years. Hypertension was diagnosed in 11 (73 %) participants and 4 (27 %) had cardiovascular disease. Both ACh and SNP dose-dependently increased FBF (Figure 1 and 2). FBF was significantly higher during SNP infusion after empagliflozin treatment as compared to placebo (p=0.004). No difference in FBF was found between empagliflozin and placebo during ACh infusion (p=0.399).

Conclusions: Empagliflozin improves endothelium-independent vasodilatation in patients with DM2, whereas no changes could be observed in endothelium-dependent vasodilation. These results suggest that SGLT2 inhibition positively affects vascular function, however the improvement does not appear to be related to improvement of the endothelial function.

Funding: Commercial Support - Boeringer-Ingelheim provided cost-free project medicine and matching placebo, Private Foundation Support, Government Support - Non-U.S.





SA-PO470

Validation and Application of Serum Urea Nitrogen-Based Protein Intake Assessment Equation in Diabetic Kidney Disease (DKD) Cohort

Qiuling Li, Wenjian Wang. *Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Guangzhou, China.*

Background: Our previous studies have established an equation based on serum urea nitrogen in CKD stage 3 patients prospectively, however, its application remains unknown in other stages patients. We aimed to verify the DPI equation in different CKD patients and explored the survival analysis. We applied this equation in our DKD cohort and NHANES cohort.

Methods: We retrospectively collected the clinical data from patients diagnosed with CKD in Guangdong Provincial People's Hospital from January 2015 to September 2022. End points included 50% reduction of eGFR, ESRD, and the occurrence of major cardiocerebrovascular event. We used Maroni's formula as a reference in our research to evaluate the applicability of DPI_{sUCR} equation and prognosis difference in patients with different DPI levels were further analyzed. In application cohort, we retrospectively collected the clinical data from patients diagnosed with DKD in Guangdong Provincial People's Hospital from January 2015 to September 2022 and NHANES cohort from 1999 to 2018 respectively. The endpoint events of different DPI levels were analyzed using the propensity score matching method to further confirm the clinical utility of this equation.

Results: The DPI_{sUCR} equation is more distinguishable in CKD stage 3 patients and DKD cohort, and it's well correlated with the DPI evaluated by Maroni's formula among CKD stage 1~2 and stage 4 patients as well as in DKD patients. Kaplan-Meier analysis showed patients with low DPI (<0.8 g/kg. d) has a better survival prognosis than high DPI (>1.0 g/kg. d) evaluated by DPI_{sUCR} equation or Maroni's formula, especially in CKD stage 3~4 patients. Analysis of data from 820 eligible valid cases in the DKD cohort revealed that, low protein diet improved outcomes. Also, analysis of data from 1723 eligible valid cases in the NHANES cohort revealed that, low protein diet improved outcomes and delay time to endpoint, especially in advanced CKD stage 3~4 patients. In the CKD cohort with diabetes history, restricted protein diets improved outcomes, and although there was a trend, there was no significant difference in results.

Conclusions: The DPI_{sUCR} equation is applicable in CKD stage 1~4 patients and DKD cohorts. Patients with DPI_{sUCR}≤ 1.0 g/kg. d generally have a better prognosis. Our study reveals DPI_{sUCR} equation identify patients with LPD effectively in CKD and NHANES cohort.

Funding: Private Foundation Support

SA-PO471

Effects of Probiotics and Fibers on Markers of Nephropathy and Endothelial Dysfunction in Persons with Type 1 Diabetes and Albuminuria

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Background: Recent data have pointed towards a link between gut microbiota and chronic kidney disease. Defects in the intestinal barrier due to microbial imbalance allow bacterial toxins to pass and cause systemic inflammation damaging the endothelium. Fibers serve as substrate for the beneficial bacterial strains, together with probiotics they have a positive effect on the gut environment, reestablish the microbial symbiosis and thereby strengthen the gut barrier in experimental models. We hypothesized that a supplement of fructo-oligosaccharides and probiotics would strengthen the gut barrier and protect the endothelium and kidneys.

Methods: A randomized, double blind, placebo controlled, crossover study including 41 persons with type 1 diabetes and albuminuria (urinary albumin-to-creatinine ratio (UACR) >30 mg/g) on renin-angiotensin-system blockade. Participants received synbiotic mix and matched placebo for 12 weeks in a random order with 6 weeks of washout. The primary end point was change from baseline to end of period in UACR (3 morning urine samples per visit). Secondary endpoints were: Change from baseline to end of period in endothelial glycocalyx thickness (perfused boundary region) and in inflammatory markers; end-of-period glomerular filtration rate (GFR) and ambulatory systolic blood pressure measured after each treatment period with synbiotic mix versus placebo.

Results: A total of 41 participants were randomized and 35 completed the study. Mean age was 58 (SD 10) years, 73% (n=30) were male, median UACR was 134 (IQR 63-293) mg/g, estimated GFR was 75 (30) ml/min/1.73m^2. There was no significant difference in UACR with a mean relative change (CI 95 %) from baseline to end-of-treatment of -3.0 (-18.4; 15.5) % in the synbiotic group and -12.0 (-29.6; 9.6) % in the placebo group with no significant difference between treatment periods (9.37 (-25.2; 44.0) percentage points; p = 0.60). No significant difference in the secondary end points was demonstrated.

Conclusions: Twelve weeks treatment with a supplement of synbiotic mix had no effect on UACR, perfused boundary region, inflammatory markers, GFR or ambulatory systolic blood pressure in subjects with type 1 diabetes and albuminuria.

Funding: Commercial Support - Novo Nordisk Foundation (Grant number: NNF OC0013659) and DSM Nutritional Products Ltd. Kaiseraugst, Private Foundation Support

SA-PO472

Safety and Efficacy of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) Among Patients with Type 2 Diabetes Mellitus (T2DM) and Advanced CKD and ESKD: A Systematic Review and Meta-Analysis

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Background: Evidence supporting the use of GLP-1RAs in T2DM patients and advanced chronic kidney disease (CKD) and end-stage kidney disease (ESKD) is scarce.

Methods: A literature search was conducted using MEDLINE, EMBASE, and Cochrane Database from inception through February 2023. The protocol for this review was registered in the International Prospective Register of Systematic Reviews (CRD 42023398452). Clinical trials and cohort studies reporting safety or efficacy outcomes of GLP-1RAs in adult patients with T2DM and advanced CKD (stage 5 CKD and ESKD) were included. Outcome measures included mortality, cardiovascular, blood glucose, and weight. Adverse events were assessed for safety. Estimates were pooled using random-efffects meta-analysis model.

Results: Eight studies (5 trials and 3 cohort studies) consisting of 27,639 patients with a median follow-up of 3 months (IQR 3, 12) were included in this meta-analysis. There was no difference in one-year mortality outcomes, but one cohort study found a significant long-term reduction in all-cause mortality with GLP-1RAs (HR 0.7; 95% CI 0.6, 0.9). GLP-1RAs significantly reduced cardiothoracic ratio (standardized mean difference, SMD of -1.2%; 95% CI -2.0, -0.4) and pro-BNP (SMD -335.9 pmol/L; 95% CI -438.9, -232.8), but did not significantly decrease systolic blood pressure compared to controls. GLP-1RAs significantly reduced mean blood glucose (SMD -1.1 mg/dL; 95% CI -1.8, -0.3) but not maximum blood glucose, blood glucose fluctuation, or HbA1c. GLP-1RAs resulted in significant weight loss (SMD -2.2 kg; 95% CI -2.9, -1.5). In term of safety, GLP-1RAs were associated with 3.8- and 35.7-time higher risk of nausea and vomiting, respectively, but were not significantly associated with higher risk of hypoglycemia.

Conclusions: Our study provides evidence supporting the safety and efficacy of GLP-1RAs among T2DM patients with advanced CKD and ESKD. While GLP-1RAs may have GI side effects, they demonstrate significant improvement on cardiovascular outcomes, blood glucose control, and weight reduction.

SA-PO473

Effects of Ertugliflozin by Uric Acid Quintile: Observations from VERTIS CV

Vikas Sridhar,[1] Francesco Cosentino,[2] Samuel Dagogo-Jack,[3] Richard E. Pratley,[4] Nilo B. Cater,[5] Margaret Noyes Essex,[5] Mario Maldonado,[6] Yujie Zhao,[7] David Cherney.[1] VERTIS CV Investigators. *[1]Department of Medicine, Division of Nephrology, University Health Network and University of Toronto, Toronto, ON, Canada; [2]Unit of Cardiology, Karolinska Institute & Karolinska University Hospital, Stockholm, Sweden; [3]University of Tennessee Health Science Center, Memphis, TN; [4]AdventHealth Translational Research Institute, Orlando, FL; [5]Pfizer Inc., New York, NY; [6]MSD (UK) Limited, London, United Kingdom; [7]Merck & Co., Inc., Rahway, NJ.*

Background: The sodium–glucose cotransporter 2 inhibitor ertugliflozin (ERTU) lowers serum uric acid (UA) levels. Using data from the VERTIS CV trial (NCT01986881), the impact of ERTU on eGFR and albuminuria was investigated in patients by baseline serum UA levels.

Methods: Patients with type 2 diabetes and atherosclerotic cardiovascular disease were randomized (1:1:1) to ERTU 5 mg, 15 mg (doses pooled for analyses), and placebo (PBO). Patients were categorized by baseline UA quintile (Table). UA over time, eGFR slopes (chronic from Weeks 6 to 260), and the time to first event of progression of albuminuria were analyzed for ERTU versus PBO.

Results: At baseline, there were notable differences by UA subgroup, such as sex, UACR, eGFR and diuretic use (Table). ERTU was associated with reductions in UA over time in all baseline UA subgroups (Fig. A). Treatment with ERTU resulted in a significantly slower rate of yearly eGFR decline in all UA subgroups compared with PBO (P<0.001; Fig. B). ERTU was associated with a reduced risk of albuminuria progression in all UA subgroups compared with PBO (Fig. C; $P_{interaction}$=0.34).

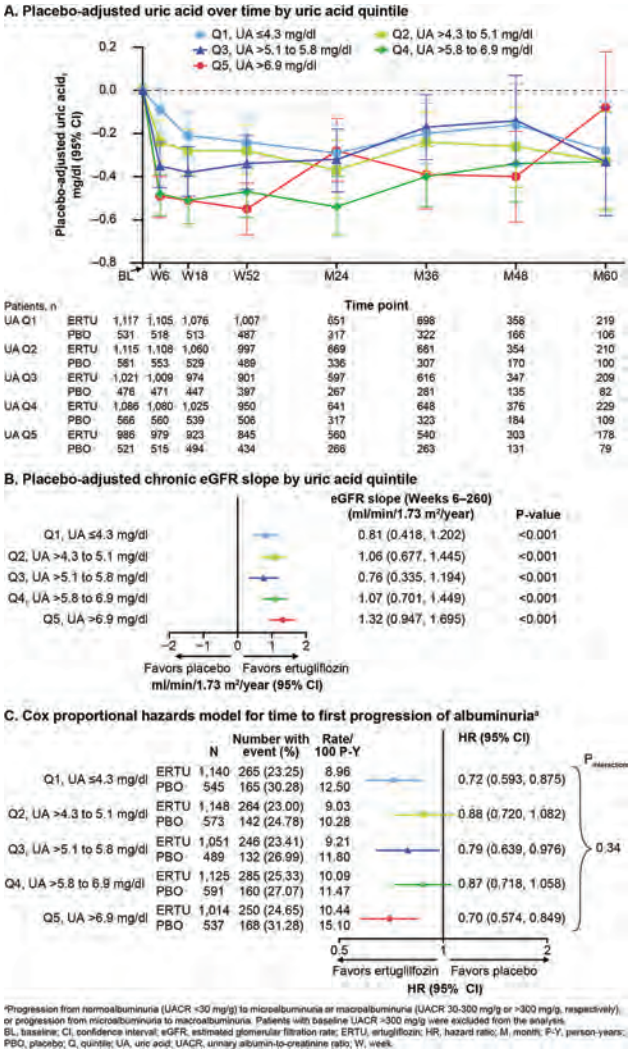
Conclusions: In VERTIS CV, ERTU reduced UA while attenuating eGFR decline and albuminuria progression, irrespective of baseline UA quintile.

Funding: Commercial Support - The study and this analysis were funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA, in collaboration with Pfizer Inc., New York, NY, USA. Medical writing and/or editorial assistance was provided by Moamen Hammad, PhD, and Melissa Ward, BA, both of Scion, London, UK. This assistance was funded by Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and Pfizer Inc., New York, NY, USA.

Table. Demographic and clinical characteristics by uric acid (UA) quintile (Q)

Variable	Q1, UA ≤4.3 mg/dl	Q2, UA >4.3 to 5.1 mg/dl	Q3, UA >5.1 to 5.8 mg/dl	Q4, UA >5.8 to 6.9 mg/dl	Q5, UA >6.9 mg/dl
N (%)	1,685 (20.5)	1,721 (21.0)	1,540 (18.8)	1,716 (20.9)	1,551 (18.9)
Female, n (%)	646 (38.3)	565 (32.8)	441 (28.6)	460 (26.8)	356 (23.0)
Mean age, years (SD)	63.4 (7.8)	64.1 (8.1)	64.6 (8.2)	64.7 (8.1)	65.1 (8.0)
Mean body mass index, kg/m^2 (SD)	30.6 (4.9)	31.3 (5.2)	31.9 (5.2)	32.2 (5.2)	33.5 (6.0)
Mean glycated hemoglobin, % (SD)	8.5 (1.0)	8.3 (1.0)	8.2 (0.9)	8.1 (1.0)	8.1 (0.9)
Median UACR, mg/g (range)	16.0 (1.0-7,239.0)	16.0 (1.0-5,357.0)	17.0 (1.0-6,884.0)	21.0 (1.0-8,584.0)	28.5 (1.0-9,548.0)
Mean eGFR, ml/min/1.73 m^2 (SD)	86.2 (15.7)	82.1 (16.6)	78.3 (17.5)	73.9 (18.2)	64.9 (18.9)
Antihypertensive use, n (%)	1,567 (93.0)	1,619 (94.1)	1,465 (95.1)	1,655 (96.4)	1,516 (97.7)
Diuretic use, n (%)	498 (29.6)	609 (35.4)	634 (41.2)	811 (47.3)	982 (63.3)

eGFR, estimated glomerular filtration rate; Q, quintile; SD, standard deviation; UA, uric acid; UACR, urinary albumin-to-creatinine ratio.



SA-PO474

Effects of Sotagliflozin on Anemia in Patients with Type 2 Diabetes (T2D) and Stages 3 and 4 CKD

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Background: Anemia is frequent in advanced diabetic kidney disease. Sodium-glucose cotransporter inhibitors (SGLTi) consistently increase hemoglobin (Hb) through multiple mechanisms. We examined the effects of sotagliflozin, a dual SGLT1 and SGLT2 inhibitor, on Hb in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD) stage 3 and 4, with and without anemia.

Methods: This was a pooled patient-level data analysis from two studies evaluating the efficacy and safety of sotagliflozin (200 and 400 mg) vs. placebo in patients with T2D and CKD 3 or 4 over 26 weeks. The effect of sotagliflozin on Hb, hematocrit, serum albumin, systolic blood pressure (SBP), body weight and estimated glomerular filtration rate (eGFR) was assessed in patients with anemia (defined as baseline Hb <13 mg/dL for men and <12 mg/dL for women) and without anemia.

Results: In the entire cohort, baseline mean Hb was 12.7 g/dL and sotagliflozin increased Hb from baseline to week 26 by 0.39 g/dL (200 mg; 95% CI 0.21-0.56) and 0.41 g/dL (400 mg; 95% CI 0.24-0.59) vs. placebo (p<0.0001). Of the 1064 patients randomized, 493 (46.3%) patients had anemia at baseline. The effect on Hb with sotagliflozin relative to placebo was more pronounced in patients without anemia over 26 weeks (Figure [doses pooled]). Sotagliflozin (doses pooled) increased odds of anemia resolving (odds ratio 1.95, p=0.017), with a trend towards decreased odds of anemia developing (odds ratio 0.75, p=0.41) over 26 weeks. The effect of sotagliflozin on serum albumin, SBP, body weight, and eGFR was generally consistent between patients with and without anemia. Sotagliflozin was generally well tolerated with similar safety profiles between anemia subgroups.

Conclusions: Sotagliflozin increased Hb in a rapid and sustained manner in patients with T2D and moderate-severe CKD over 26 weeks, and reversed anemia in a population at high risk of anemia.

Funding: Commercial Support - Lexicon Pharmaceuticals, Inc., The Woodlands, TX

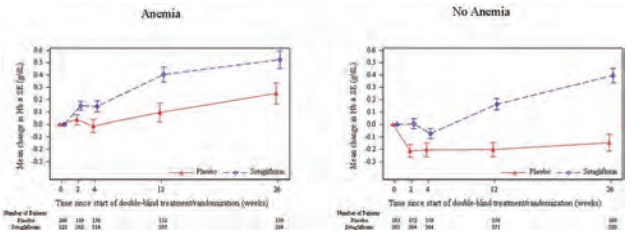

Figure. Mean change in hemoglobin from baseline over 26 weeks by anemia subgroup

SA-PO475

SGLT2 Inhibitor Therapy Ameliorates Anemia in Diabetic Kidney Disease

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Background: Sodium glucose cotransporter 2 inhibitor (SGLT2i) is a standard treatment for kidney and cardiovascular protection in diabetic kidney disease (DKD). Recent evidence suggests that SGLT2i may enahnce erythropoietin production. We perform a retrospective cohort study to determine the effect of SGLT2i on the hemoglobin level in patients with DKD.

Methods: We reviewed 670 DKD patients started on SGLT2i. Their hemoglobin level and estimated glomerular filtration rate (eGFR) 6 months before the use of SGLT2i, immediately before, and 6 months after the use of SGLT2i were reviewed.

Results: The hemoglobin level had a small but significant increase 6 months after SGLT2 inhibitor treatment from 12.89 ± 1.75 to 13.08 ± 1.94 g/dL (p < 0.0001). The absolute increase in hemoglobin level was 0.19 ± 1.06 g/dL; 274 patients (40.9%) had hemoglobin increase ≥ 0.5 g/dL, and 117 (17.5%) had an increase ≥1.0 g/dL. In contrast, the average hemoglobin level was 13.01 ± 1.75 g/dL 6 months before SGLT2i, which showed a significant decline to the pre-treatment level (p=0.001). The increase in hemoglobin after SGLT2i was most marked in CKD stage 3b (12.26 ± 1.81 to 12.68 ± 1.98 g/dL, p < 0.0001). There was no significant correlation between the change in hemoglobin level and the severity of albuminuria or HbA1c level.

Conclusions: SGLT2i has a small but significant beneficial effect on DKD-related anemia. The clinical impact of this effect deserves further studies.

Funding: Clinical Revenue Support

SA-PO476

ESKD-Free Survival Time in Patients with CKD and Type 2 Diabetes (TD2) in FIDELITY

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Background: End-stage kidney disease (ESKD) is a major health and economic burden; patients with reduced quality of life are at high risk of cardiovascular mortality. Finerenone significantly reduced the risk of cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in FIDELITY, a prespecified pooled analysis of the FIDELIO-DKD and FIGARO-DKD trials. Here, we estimated the ESKD-free survival time of patients treated with finerenone vs placebo.

Methods: Patients with T2D and CKD (albuminuria and estimated glomerular filtration rate [eGFR] ≥25–90 mL/min/1.73 m²) and on optimized renin–angiotensin system (RAS) inhibition were randomized (1:1) to finerenone or placebo. To estimate the population-level effect of finerenone, the restricted mean survival time for ESKD after 4.5 years of treatment in FIDELITY was extrapolated to 6,425,196 US patients with T2D and CKD according to the US National Health and Nutrition Examination Survey. The cumulative incidence and treatment effects of finerenone vs placebo for time to eGFR <10 mL/min/1.73 m² were also analyzed using a patient-based two-slope model extrapolated to 20 years.

Results: In FIDELITY, finerenone significantly reduced the risk of ESKD vs placebo (hazard ratio [HR]=0.80; 95% confidence interval [CI] 0.64–0.99; *p*=0.040). After 4.5 years of treatment with finerenone, the overall estimated time saved from ESKD for the US patient population vs placebo was 103,260 years (95% CI −3407 to 210,556). Using extrapolations based on 5000 Monte-Carlo simulations for the individual eGFR patient slopes, the cumulative incidence for time to eGFR <10 mL/min/1.73 m^2 showed a risk difference between treatments of −4.5%, −7.6%, −6.7% and −5.6% for 5, 10, 15 and 20 years, respectively, corresponding to a number needed to treat of 22, 13, 15 and 18 patients for finerenone. Treatment effects of finerenone vs placebo for time to eGFR <10 mL/min/1.73 m^2 showed a relative risk reduction of 21% (HR=0.79; 95% CI 0.76–0.82).

Conclusions: Treatment with finerenone and optimized RAS therapy was associated with a delay in time to ESKD in patients with CKD and T2D and may provide patient and healthcare cost-saving benefits.

Funding: Commercial Support - Bayer AG

SA-PO477

Discrepancy Between Lifetime vs. Five-Year Risk Estimates for ESKD in US Adults with Diabetes

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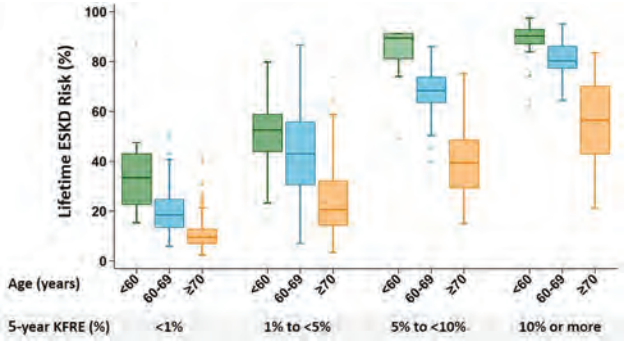
Background: The Kidney Failure Risk Equation (KFRE) estimates the short-term (2- or 5-year) risk of ESKD. Misinterpretation of this short-term risk as lifetime risk may lead to patient misunderstanding and suboptimal shared decision-making.

Methods: We analyzed data from 972 US adults aged 35-84 years with diabetes and eGFR 30 to <60 mL/min/1.73 m^2 who participated in the 1999-2020 NHANES. Each sample was weighted to represent the general US population. We used the KFRE to calculate 5-year ESKD risk, and the Swedish National Diabetes Register prediction model (Østergaard, CJASN 2022) to estimate the lifetime ESKD risk where we calibrated baseline hazards for mortality and ESKD based on the national databases. We compared the distribution of lifetime risk across KFRE categories, further stratified by age groups.

Results: The mean age of the study cohort was 71 years, 52% were female, the median HbA1c was 6.8%, and the median duration of diabetes was 15 years. The mean eGFR was 49 mL/min/1.73 m^2, and 53% and 43% had moderate and severe albuminuria, respectively. The 5-year risk of ESKD by KFRE (median 1.2% [IQR, 0.6% to 3.1%]) was consistently lower than the lifetime ESKD risk (median 22% [IQR, 12% to 42%]). This discrepancy was more pronounced in younger patients (**Figure**). For example, within the KFRE 1% to <5% risk category, the median estimated lifetime risk was 21% for age ≥70 years, 43% for age 60-69 years, and 53% for those <60 years.

Conclusions: The KFRE, a short-term ESKD risk estimate, substantially underestimates the lifetime risk of ESKD in patients with diabetes at every risk interval, particularly in the younger populations. Clinicians should consider lifetime ESKD risk estimates, rather than just short-term ESKD risk, when counseling patients with diabetes.

Funding: Other NIH Support - National Institute of General Medical Sciences



SA-PO478

Overall and Interindividual Effect of Four Different Drug Classes on Soluble Urokinase Plasminogen Activator Receptor in Albuminuric Type 1 and Type 2 Diabetes

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Background: Soluble urokinase plasminogen activator receptor (suPAR) is a biomarker active in multiple inflammatory processes and a risk factor of diabetic nephropathy. We evaluated the effect of four different drug classes on suPAR in type 1 and type 2 diabetes with albuminuria.

Methods: Post hoc analyses of a randomized, open-label, crossover trial including 26 adults with type 1 and 40 with type 2 diabetes with urinary albumin-creatinine ratio (UACR) ≥30 and ≤500 mg/g assigned to 4-week treatments with telmisartan 80mg, empagliflozin 10mg, linagliptin 5mg, and baricitinib 2mg separated by 4-week washouts. Plasma suPAR was measured before and after each treatment. SuPAR change after each treatment was calculated and, for each individual, the best suPAR-reducing drug was identified. Subsequently, the effect of the best individual drug was compared against the mean of the other three drugs. Repeated measures linear mixed-effects models were employed. Finally, treatment effect on UACR was correlated against treatment effect on suPAR, for each treatment and participant, assessed using Pearson's R.

Results: Baseline median (IQR) plasma suPAR was 3.5 (2.9, 4.3) ng/ml. No overall effect on suPAR levels was observed for any one drug. The individual best-performing drug varied, with baricitinib being selected for 20 (30%) participants, followed by empagliflozin for 19 (29%), linagliptin for 16 (24%), and telmisartan for 11 (17%). The individual best-performing drug reduced suPAR by 13.3% (95%CI: 3.7, 22.8; p=0.007). Difference in suPAR response between the individual best-performing drug and the other three was -19.7% (-23.1, -16.3; p<0.001). Baseline levels of suPAR and UACR were significantly correlated (R=0.28, p=0.029), but changes in UACR and suPAR after treatment were not correlated for any drug.

Conclusions: We demonstrated no overall effect of 4-week treatment with telmisartan, empagliflozin, linagliptin, or baricitinib on suPAR. However, individualization of treatment might significantly reduce suPAR levels and this mechanism is independent of UACR response.

Funding: Private Foundation Support

SA-PO479

Early Use and Effectiveness of Finerenone in US Patients with CKD and Type 2 Diabetes: A FOUNTAIN Platform Analysis

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Background: Based on evidence from clinical trials, finerenone reduces the risk of cardiovascular and renal complications among patients with chronic kidney disease (CKD) and type 2 diabetes (T2D). Evidence from finerenone use in real-world clinical practice is lacking.

Methods: Longitudinal (from July 2021 to latest data available) cohort study using two existing US electronic health record and insurance claim databases. Among individuals with both CKD and T2D, a single cohort of new users of finerenone is described (patient characteristics, comorbidities, comedications, and incidence rates of cardiovascular and renal outcomes, including eGFR and UACR changes over time).

Results: Preliminarily, results from an initial feasibility assessment show a total of 662 new users of finerenone who had a mean (SD) age of 72.1 (8.3) years with 46.6% being female. The most common comorbidities at baseline were hypertension (98.3%), hyperlipidemia (87.5%), peripheral vascular disease (66.8%), neuropathy (53.7%), retinopathy (35.5%), and congestive heart failure (34.4%); 9.9% of individuals had acute coronary syndrome and 6.5% experienced a stroke prior to finerenone initiation. Baseline comedication use was common with 70.5% of individuals using an angiotensin-converting enzyme inhibitor (ACE) or an angiotensin receptor blocker (ARB), 60.2% a beta-blocker, and 50.6% calcium channel blockers (CCB). Furthermore, 90.9% of finerenone users used anti-hyperglycemic medications, including insulins (46.6%), metformin (42.9%), sodium-glucose cotransporter-2 (SGLT2) inhibitors (42.3%), and glucagon-like peptide-1 (GLP-1) receptor agonists (35.2%). Complete results from the full Optum EHR and OM1 Real-World Data Cloud™ databases, including incidence rates of cardiovascular and renal outcomes, will be presented as part of the conference presentation.

Conclusions: Early evidence from patients who receive finerenone as part of clinical practice in the US suggests that finerenone is used independently of demographic and clinical characteristics. Furthermore, this analysis of early adopters suggests that finerenone is used as a complementary treatment option to other renal and cardiovascular protective medication-classes recommended for patients with CKD and T2D.

Funding: Commercial Support - Bayer AG

SA-PO480

Comparative Kidney and Cardiovascular Effectiveness of Empagliflozin Compared to Dipeptidyl Peptidase-4 Inhibitors in Patients with Type 2 Diabetes Mellitus

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Background: Placebo-controlled trials of sodium-glucose cotransporter-2 inhibitors (SGLT2i) demonstrated kidney and cardiovascular benefit for people with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). We used real-world data to compare the effectiveness and safety of empagliflozin to dipeptidyl peptidase-4 inhibitors (DPP4i) in patients with T2DM, with and without CKD.

Methods: We used electronic health record data from 20 large US health systems participating in PCORnet©. Using propensity overlap weighting, we compared the effectiveness of empagliflozin vs. DPP4i in patients with T2DM among those newly prescribed these medications between 2016-2020. Primary composite endpoint included first occurrence of 40% eGFR decline, incident ESKD, or all-cause mortality (ACM) through 2 years. We also assessed cardiovascular and safety outcomes.

Results: Among 62,197 patients, 32% initiated empagliflozin and 68% initiated DPP4i. Median follow-up was 1.1 years. Empagliflozin was associated with lower risk of the primary outcome compared to DPP4i (Table). Risk for ACM and a cardiovascular composite of stroke, myocardial infarction, or ACM were also lower in patients prescribed empagliflozin overall and in those with CKD. The difference in heart failure hospitalization risk between groups did not reach statistical significance. Genital mycotic infections and diabetic ketoacidosis were the only safety events more common in patients prescribed empagliflozin. Differences in risk for primary composite, 40% eGFR decline and ACM were also significantly lower in patients with CKD.

Conclusions: In a real-world population with T2DM with and without CKD, empagliflozin is associated with significantly lower risk for kidney and cardiovascular outcomes compared with DPP4i.

Funding: Commercial Support - Boehringer Ingelheim and Lilly

Table. Comparative kidney and cardiovascular effectiveness and safety of empagliflozin compared to DPP4i in patients with T2DM with and without chronic kidney disease: PCORnet®

	Overall			With Chronic Kidney Disease			Without Chronic Kidney Disease		
	Empagliflozin IR/1000 PY (N=20,279)	DPP4i IR/1000 PY (N=41,918)	Empagliflozin vs. DPP4i HR (95% CI)	Empagliflozin IR/1000 PY (N=3,669)	DPP4i IR/1000 PY (N=13,886)	Empagliflozin vs. DPP4i HR (95% CI)	Empagliflozin IR/1000 PY (N=16,907)	DPP4i IR/1000 PY (N=37,034)	Empagliflozin vs. DPP4i HR (95% CI)
Primary Outcome	26.71	36.46	0.75 (0.65 - 0.87)	44.45	66.36	0.68 (0.53 - 0.88)	22.65	29.86	0.79 (0.67 - 0.94)
40% decline in eGFR	12.15	16.42	0.75 (0.61 - 0.93)	16.58	26.89	0.63 (0.47 - 0.84)	11.14	11.92	0.81 (0.63 - 1.04)
Incident ESKD	3.36	4.88	0.68 (0.46 - 1.01)	8.26	12.78	0.64 (0.36 - 1.12)	2.23	2.98	0.75 (0.45 - 1.25)
Heart failure hospitalization	12.72	14.34	0.90 (0.73 - 1.11)	29.72	32.75	0.90 (0.65 - 1.24)	8.06	9.97	0.81 (0.60 - 1.21)
All-cause death	13.47	18.53	0.76 (0.62 - 0.92)	23.85	35.07	0.70 (0.50 - 0.98)	11.08	14.54	0.80 (0.62 - 1.02)
Cardiovascular composite[1]	23.90	30.70	0.81 (0.70 - 0.95)	40.63	55.04	0.75 (0.58 - 0.98)	20.06	24.26	0.85 (0.71 - 1.02)
Diabetic ketoacidosis	4.07	3.07	1.37 (0.89 - 2.09)	3.50	3.47	1.02 (0.39 - 3.68)	4.20	2.73	1.48 (0.91 - 2.38)
Genital mycotic infection	115.09	65.22	1.72 (1.54 - 1.88)	99.46	51.63	1.87 (1.50 - 2.34)	119.90	68.54	1.70 (1.54 - 1.87)
Severe hypoglycemia	9.41	10.69	0.90 (0.74 - 1.16)	14.85	18.77	0.80 (0.51 - 1.25)	8.16	8.75	0.96 (0.71 - 1.29)
Urinary tract cancer	4.67	5.04	0.96 (0.67 - 1.36)	8.78	8.85	1.01 (0.55 - 1.84)	3.72	4.12	0.93 (0.60 - 1.45)
AKI requiring dialysis	1.23	1.46	0.84 (0.43 - 1.65)	2.54	4.07	0.59 (0.21 - 1.63)	0.93	0.83	1.15 (0.46 - 2.91)

AKI, acute kidney injury; CI, confidence interval; IR, incidence rate; PY, person-years; T2DM, type 2 diabetes mellitus.
[1]Includes stroke, myocardial infarction, and all-cause death

SA-PO481

Interim Results from FINE-REAL: A Prospective Study Providing Insights into the Use of Finerenone in Routine Clinical Settings

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Background: Finerenone is a selective, nonsteroidal mineralocorticoid receptor antagonist, which improved kidney and cardiovascular outcomes in patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D) in phase 3 trials. Finerenone is approved in the European Union, US, China, and several other countries. FINE-REAL (NCT05348733) aims to provide insights on characteristics and treatment patterns of participants treated with finerenone in clinical practice.

Methods: FINE-REAL is a prospective, single-arm, non-interventional study of patients initiated on finerenone as part of their routine care in accordance with their country-approved label. The study, initiated in June 2022, is expected to be completed by January 2028.

Results: As of April 28, 2023, 574 participants have been enrolled. Baseline median UACR is 1,354 mg/g; however, UACR is unreported for 35% of participants (Table). Mean eGFR (mL/min/1.73 m^2 ([SD]) is 53 (23). Uptake of agents acting on the RAAS and of statins is 52% and 24%, respectively. Adverse events have been reported in 72 (12.54%) participants. Hyperkalemia has been reported in 17 (2.96%) participants, with all instances recorded as asymptomatic and none requiring hospitalization. Updated results from a later cut-off date, June 13, 2023, will be presented at the congress.

Conclusions: UACR is not routinely measured in a large proportion of patients in the real-world setting. In general, the uptake of guideline-recommended therapies for CKD associated with T2D is low (RAAS inhibitors and statins). Advocacy for greater adherence to standard of care could improve patient outcomes.

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Baseline demographic and disease characteristics	Total N=574; data cut-off date April 28, 2023	Baseline medications	Total N=574; data cut-off date April 28, 2023
Age, years (standard deviation [SD])	66 (11)	**Agents acting on the renin–angiotensin–aldosterone system (RAAS),** n (%)	299 (52)
Body mass index, kg/m^2 (SD)	33 (10)	**Angiotensin-converting enzyme inhibitor (ACEi),** n (%)	99 (17)
Median urinary albumin-to-creatinine ratio (UACR), mg/g	1,354	**Angiotensin receptor blocker (ARB),** n (%)	200 (35)
UACR >300 mg/g, n (%)	135 (28)	**ACEi + ARB,** n (%)	1 (<1)
UACR 30–300 mg/g, n (%)	138 (28)	**Insulin,** n (%)	199 (35)
UACR <30 mg/g, n (%)	42 (9)	**Sodium–glucose cotransporter 2 inhibitor,** n (%)	199 (35)
Individuals without evaluable UACR, n (%)	171 (35)	**Glucagon-like peptide-1 receptor agonist,** n (%)	150 (26)
Mean estimated glomerular filtration rate (eGFR), mL/min/1.73 m^2 (SD)	53 (23)	**Dipeptidyl peptidase-4 inhibitor,** n (%)	34 (6)
eGFR ≥60 mL/min/1.73 m^2, n (%)	151 (31)	**Statin,** n (%)	137 (24)
eGFR 30–59 mL/min/1.73 m^2, n (%)	273 (57)	**Previous mineralocorticoid receptor antagonist,** n (%)	11 (2)
eGFR 15–29 mL/min/1.73 m^2, n (%)	58 (12)		

SA-PO482

Predictors and Outcomes of Discontinuation of Glucagon-Like Peptide-1 Receptor Agonists (GLP-1 RAs) in CKD

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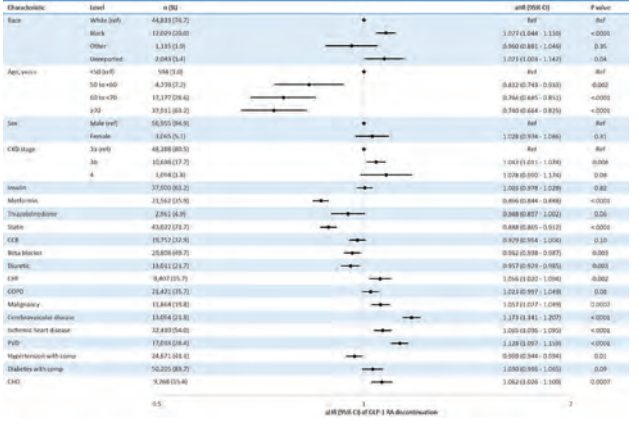
Background: GLP-1 RAs improve cardiovascular and kidney outcomes in patients with CKD but are underutilized. We aimed to study treatment discontinuation and its associations with patient-level characteristics and death among those with CKD.

Methods: Adults with CKD stages 3-4 were identified from the Veterans Affairs (VA) Corporate Data Warehouse from 2005-2022. Individuals who had an incident prescription for a GLP-1 RA were included, with the date of prescription used as the index date for the analysis. The primary outcome was treatment discontinuation, defined as an interruption in GLP-1 RA prescription for at least 90 days. Cox proportional hazards regression identified factors associated with time to treatment discontinuation and the association of treatment discontinuation with time to all-cause death, treating GLP-1 RA discontinuation as a time-varying covariate.

Results: Of 60,020 individuals who received a GLP-1 RA, 95% were male, 75% were White, 20% were Black, 63% were of age ≥70, and 80% had CKD stage 3a. Discontinuation (at least once) occurred in 28,407 (47%) GLP-1 RA users over a median (IQR) of 1.41 (0.72, 2.59) years of follow up. Black or unreported race, younger age, and concomitant vascular disease were associated with GLP-1 RA discontinuation (**Figure**). There were 9628 deaths. GLP-1 RA discontinuation, included as a time-varying covariate, was associated with all-cause death (HR 2.22 [95% CI 2.11, 2.34], P<0.0001) independent of age, sex, race, CKD stage, medical comorbidities, and concomitant medication use.

Conclusions: In CKD population, discontinuation of GLP-1RA is common and was associated with an increased risk of death. Additional studies exploring the reasons for short-term and long-term discontinuations of these agents are needed.

Funding: Other NIH Support - NHLBI, Veterans Affairs Support



SA-PO483

Increased Risk of Serious Hypoglycemia with Insulin Glargine in Veterans with Type 2 Diabetes: An Emulated Clinical Trial Observational Study

Amara Sarwal,[1,2] Jincheng Shen,[1,2] Ravinder Singh,[1,2] Mckenna R. Nevers,[1,2] Sydney E. Hartsell,[2,1] Guo Wei,[1,2] Robert E. Boucher,[1,2] Azeem M. Mohammed,[2] David Kim,[2] George Bissada,[2] Farahnaz Akrami,[2] Brad Adams,[1,2] Jesse Christensen,[1,2] Tom Greene,[1,2] Srinivasan Beddhu.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT; [2]University of Utah Health, Salt Lake City, UT.*

Background: Serious hypoglycemic events needing medical attention are significant complications of anti-glycemic therapy in type 2 diabetes (T2D), particularly in those with CKD. Therefore we examined the risk of serious hypoglycemic events with insulin glargine (IG) use compared to glucagon-like peptide-1 receptor agonists) GLP1-RA and sodium-glucose cotransporter-2 inhibitors (SGLT2i) in a national cohort of veterans.

Methods: We conducted an active comparator, new user design study of veterans (N = 30165) with T2D with CKD (eGFR < 60) on metformin who then initiated on IG or SGLT2i or GLP1-RA for the first time between 01/01/2018 to 12/31/2021. Those with any previous use of these agents were excluded. Administrative censor date was 03/31/2023. Serious hypoglycemic events needing medical attention were identified from ER/ urgent care visits or hospital discharge diagnosis with ICD10 codes using a validated algorithm. Inverse probability weights (IPW) were developed using propensity scores for the three drug classes. In IPW Cox models, the study drug classes were related to the risk of serious hypoglycemic events.

Results: 38.2% were initiated on IG, 12.7% on GLP1-RA and 49.1% on SGLT2i. Mean eGFR was 79.5± 20.1 ml/min/1.73m^2. There were 972 events over 78594 years follow-up. In IPW Cox regression, compared to GLP1-RA, the IG group had higher risk whereas the SGLT2i group had lower risk (Table 1).

Conclusions: IG is associated with higher serious hypoglycemia risk in CKD. The safety of IG in CKD needs to be reevaluated.

Table 1. Risk of hypoglycemia by drug class and CKD

	Event Rate	HR (95% CI)
Non-CKD (N= 128774)	0.71	
GLP1-RA (N = 16355)	0.52	1.00
Insulin Glargine (N = 49821)	1.09	1.59 (1.39, 1.82)
SGLT2i (N = 62598)	0.42	0.70 (0.60, 0.81)
CKD (N = 30165)	1.24	
GLP1-RA (N = 3787)	1.06	1.00
Insulin Glargine (N = 10901)	1.88	1.49 (1.21, 1.83)
SGLT2i (N = 15477)	0.74	0.67 (0.54, 0.83)

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Background: Insulin glargine (IG) is one of the most commonly used anti-glycemic agents in advanced CKD. However, there is a paucity of data in head to head comparisons of IG with newer agents like glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i). Therefore we examined the risk of mortality with insulin glargine use compared to GLP1-RA and SGLT2i use in a national cohort of veterans.

Methods: We followed the active comparator, new user design to emulate a trial to compare the effect of initiating on IG or SGLT2i or GLP1-RA among veterans with T2D on metformin who initiated any one of these three between 01/01/2018 to 12/31/2021 (N = 158,939). Those with previous use of these agents were excluded. Administrative censor date was 03/31/2023. Generalized propensity score based inverse probability weighting (IPW) was employed to control confounding in the observational data and facilitate comparisons among the three drug classes. In IPW Cox models, the study drug classes were related to the risk of mortality in those without and with CKD (eGFR < 60).

Results: 38.2% were initiated on IG, 12.7% on GLP1-RA and 49.1% on SGLT2i. 19% had CKD. There were 11,109 deaths over 368,347 patient-years of follow-up in non-CKD and 4,660 deaths over 80,043 patient-years in CKD patients. In IPW Cox regression, compared to GLP1-RA, the IG group had higher mortality risk in both the non-CKD and CKD subgroups whereas the SGLT2i group had lower mortality in the CKD subgroup (Table).

Conclusions: IG is associated with higher mortality risk in both non-CKD and CKD subgroups. These results suggest that the routine clinical use of IG needs to be reconsidered.

Table 1. Mortality events

	Event Rate	HR (95% CI)
Non-CKD (N= 128774)		
GLP1-RA (N = 16355)	1.96	1.00
Insulin Glargine (N = 49821)	4.14	1.70 (1.59, 1.83)
SGLT2i (N = 62598)	2.26	0.95 (0.88, 1.02)
CKD (N = 30165)		
GLP1-RA (N = 3787)	4.80	1.00
Insulin Glargine (N = 10901)	7.91	1.39 (1.26, 1.53)
SGLT2i (N = 15477)	4.31	0.82 (0.74, 0.90)

SA-PO485

Major Adverse Kidney Disease Events in a Real-World Population with Diabetes

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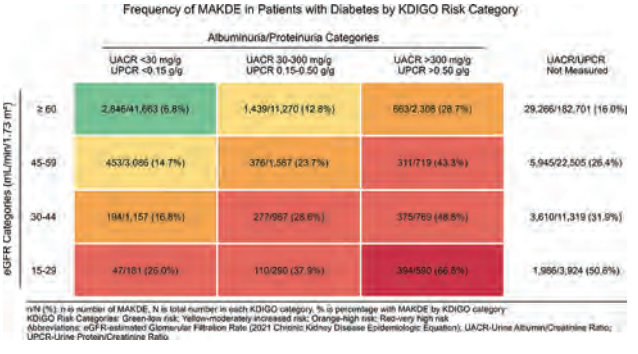
Background: Assessing risk for major adverse kidney disease events (MAKDE) helps target populations who could benefit from improved chronic kidney disease (CKD) awareness, detection, and intervention. In a real-world population with diabetes, we evaluated the frequency of MAKDE and Kidney Disease Improving Global Outcomes (KDIGO) risk categories during 2013-2020.

Methods: The study population was derived from electronic health records data in the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry at Providence and UCLA Health systems. Demographic and clinical characteristics were obtained for patients aged ≥18 years with diabetes. CKD was defined by eGFR <60 mL/min/1.73 m^2, UACR ≥30 mg/g or UPCR ≥0.15 g/g. MAKDE was defined as a composite of 40% eGFR decline from baseline, eGFR <15 mL/min/1.73 m^2, dialysis, or kidney transplant. Frequency of MAKDE was evaluated by baseline CKD status and KDIGO risk categories.

Results: Among patients with diabetes (N=285,036), 51% (n=144,016) were women and mean age was 61±16 years. At baseline, 21% (n=60,672) had CKD with mean eGFR of 56±24 mL/min/1.73 m^2 and median UACR of 58 (interquartile range [IQR] 33-164) mg/g. Frequency of MAKDE was 27% (16,180/60,672) in those with CKD and 14% (32,112/224,364) in those without CKD. Median follow-up was 2.3 (IQR 1.0-4.0) years. Among patients with CKD who had baseline eGFR and UACR/UPCR measurements, 37% were classified as high or very high KDIGO risk. MAKDE frequency increased by higher KDIGO risk categories (**Figure**).

Conclusions: MAKDE occurred commonly in a real-world population with diabetes. Compared to those without CKD, prevalence of MAKDE was twice as high in patients with CKD and more than one-third of them were in high or very high KDIGO risk categories when both eGFR and UACR/UPCR were measured.

Funding: Other U.S. Government Support



SA-PO486

A Quality Improvement Project to Increase CKD Screening in Diabetics

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Background: The ADA recommends that patients with DM should be screened for CKD annually with a urinary albumin (ACR) and serum creatinine (Scr). However, CKD screening remains low at 10-40%. In addition, ACEi or ARB's and SGLT2 inhibitors are under prescribed. We implemented a quality improvement project to increase annual screening for CKD in DM. We were also interested in whether increased CKD screening increased prescribing of ACEi or ARB's, SGLT2-inhibitors, and co-management with nephrology.

Methods: This is a quality improvement project of Kaiser members in the Portland Metro area between ages of 18-85 with DM (~40,000 pts). Patients with ESRD, on hospice or palliative care, <1 yr Kaiser enrollment, living in long term care facility, >66

with frailty and advanced illness, or >81 with frailty were excluded. Auto ordering of Scr and ACR in patients who had not had either lab resulted within the past year was rolled out on May 11, 2022. Providers received an EHR alert at time of visit reminding them that patients were due for labs. Patients also received automated letters, texts, and phone calls on their birthday to go to the lab. Data was collected cross sectionally at the beginning of the month and the percent of patients with Scr and ACR tested within the past year were reviewed monthly. Prescribing of ACEi/ARB, SGLT2-inhibitors, and nephrology co-management within 1 year was also tracked. Trends were reviewed using control charts.

Results: By 10 months after rollout, we saw an increase in ACR and Scr testing from 35% to 71%. We saw a small increase in ACEi or ARB use in patients with DM with hypertension and ACR ≥ 30 mg/gm from mean of 82% to 82.3%. There was no change in percent of patients with renal indication seen by nephrology which stayed around 28%. We saw an increase in SGLT2-inhibitors use in patients with renal indication from 10% to 16%. However, the improvement was occurring prior to rollout of the intervention making it unclear if the increase was a result of an increase in ACR and Scr testing.

Conclusions: Our findings suggest that use of auto ordered labs and automated outreach can result in significant improvement in CKD screening amongst diabetics. We saw a statistically but clinically insignificant increase in ACEi/ARB use after the intervention. We saw a larger increase in SGLT2-inhibitors use although we could not attribute this to increased ACR and Scr testing.

SA-PO487

Prescribing of Sodium Glucose Co-Transporter 2 Inhibitors Among Hispanic/Latino Individuals Within Duke University Health System

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Background: Type 2 diabetes (T2D) is a risk factor for cardiovascular disease, chronic kidney disease, and death. Lifetime prevalence of T2D in Hispanic/Latino individuals is over 50%. One medication class, the sodium glucose co-transporter 2 inhibitors (SGLT2is), improve cardiovascular and kidney outcomes among patients with T2D. Unfortunately, recent national evidence shows that racial and ethnic minority individuals with T2D, including Hispanics/Latinos, are less likely to receive SGLT2is compared to non-Hispanic White individuals. Prescribing patterns of SGLT2is within Duke University Health System (DUHS) are currently unknown. We examined prescribing rates and likelihood of SGLT2i prescribing among Hispanic/Latino individuals with T2D within DUHS compared to other races and ethnicities.

Methods: We extracted data from the DUHS electronic health record system to identify adults with T2D eligible to receive an SGTL2i. Starting in January of 2017, we defined eligibility as having a diagnosis code for T2D and an outpatient encounter with a hemoglobin A1C >6.5%. Patients were followed until either receiving an SGLT2i, losing eligibility (i.e., eGFR < 30 or A1C < 6.5%), death, or follow-up through December 31, 2022. We assessed time to SGLT2i prescribing based on race/ethnicity, accounting for competing risks in a subdistribution hazard model.

Results: Among adults with T2D (n = 6,653), Hispanic/Latino individuals had a lower cumulative incidence of SGLT2i prescriptions (10.1%) compared to both non-Hispanic Black (16.3%) and non-Hispanic White (17.5%) individuals (p=0.12). After adjusting for age, sex, type of health insurance, area deprivation index, and comorbidities, there was suggestion of a decreased likelihood of prescribing among Hispanic/Latino individuals when compared to both non-Hispanic Black (adjusted hazard ratio (aHR) 0.77 (95%CI: 0.53 – 1.11)) and non-Hispanic White (aHR 0.77 (95%CI:0.53-1.12)) individuals.

Conclusions: SGLT2is are prescribed at low rates among patients with T2D within DUHS, consistent with national trends. Likelihood of prescribing was lowest among Hispanic/Latino individuals, even after adjustment for key demographics and clinical comorbidities, when compared to their non-Hispanic Black and White counterparts.

SA-PO488

Use of Medicines to Protect Kidney Function Among Patients with Type 2 Diabetes (T2DM) and CKD in the United States

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Background: Newer classes of diabetes, kidney, and cardioprotective medicines, such as SGLT2i and GLP1a, have shown better outcomes among diabetic patients. We examined the use of SGLT2i and GLP1a among patients with T2DM and CKD in the US.

Methods: We identified 425,879 patients aged ≥20 years diagnosed with T2DM and CKD (mean age: 73.9 years) from Optum Clinformatics™ data. Medical history and specialist visits in 2019 were defined by ICD codes and provider ID (nephrology, cardiology, and endocrinology). We examined specific medicine use(SGLT2i, GLP1a, ACEIs/ARBs, and statins) in 2020. Combination therapy was defined as the overlapped use of medicines for ≥ 30 days. Logistic regression model was applied to examine factors related to medication use.

Results: SGLT2i use was observed among 5.5% of patients with type 2 diabetes and CKD, with higher usage in CKD stage G1–2 (6.2%) compared with other stages (G3: 4.6%, G4: 2.1%, and G5: 2.8%, $P < .0001$). About 8.0% of patients used GLP1a, with a higher usage in CKD stage G3 (7.9%) compared with early stages and advanced stages (G1–2: 7.5%, G4: 7.1%, and G5: 5.7%, $P < .001$). After adjusting for demographics and other covariates, having endocrinologist visits, being covered by Exclusive Provider Organization plans (compared to Health Maintenance Organization plans), and being covered by Point of Service plans, were found to be significant predictors of using SGLT2i and GLP1a (Table).

Conclusions: We document low use of SGLT2i and GLP1a among diabetic patients with CKD in 2020. Given encouraging results from several recent, large randomized clinical trials, especially with SGLT2i, our study suggests an ongoing need for investigating barriers and disparities in the real-world use of these medicines.

Funding: Other U.S. Government Support

Table. Associations[a] among CKD stage, insurance type, specialist visit, and use of kidney-protective medicines[b]

	SGLT2i				GLP1a				SGLT2i + Metformin[b]			
	Adjust OR	95% CI		P-value	Adjust OR	95% CI		P-value	Adjust OR	95% CI		P-value
CKD G stage												
G 1–2	1.20	1.18	1.22	<.0001	0.89	0.88	0.91	<.0001	1.48	1.44	1.51	<.0001
G 3	Ref				Ref				Ref			
G 4	0.53	0.51	0.55	<.0001	0.91	0.89	0.93	<.0001	0.28	0.26	0.31	<.0001
G 5	0.64	0.62	0.67	<.0001	0.68	0.66	0.70	<.0001	0.76	0.71	0.80	<.0001
Unknown	1.29	1.27	1.31	<.0001	0.91	0.89	0.92	<.0001	1.70	1.66	1.74	<.0001
Insurance type[c]												
HMO	Ref				Ref				Ref			
EPO	1.12	1.06	1.18	<.0001	1.24	1.18	1.30	<.0001	1.00	0.93	1.07	0.9946
POS	1.13	1.09	1.17	<.0001	1.17	1.13	1.20	<.0001	1.09	1.04	1.14	0.0003
PPO	0.90	0.88	0.93	<.0001	1.01	0.98	1.04	0.5508	0.83	0.79	0.87	<.0001
Others	1.06	1.04	1.08	<.0001	1.10	1.08	1.11	<.0001	0.98	0.96	1.00	0.0555
Specialist visit[d]												
Nephrologist	0.76	0.75	0.77	<.0001	1.04	1.03	1.05	<.0001	0.59	0.58	0.61	<.0001
Cardiologist	1.01	0.99	1.02	0.527	0.97	0.96	0.98	<.0001	0.99	0.97	1.01	0.1813
Endocrinologist	1.48	1.45	1.51	<.0001	2.03	2.00	2.06	<.0001	1.53	1.49	1.56	<.0001
	GLP1a+ Metformin[b]				Statin + any diabetic medicines[b]				ACEIs/ARBs + any diabetic medicines[b]			
	Adjust OR	95% CI		P-value	Adjust OR	95% CI		P-value	Adjust OR	95% CI		P-value
CKD G stage												
G 1–2	1.21	1.19	1.24	<.0001	1.01	1.00	1.02	0.0684	1.04	1.03	1.05	<.0001
G 3	Ref				Ref				Ref			
G 4	0.32	0.29	0.34	<.0001	1.08	1.06	1.09	<.0001	0.62	0.61	0.63	<.0001
G 5	0.57	0.54	0.61	<.0001	0.81	0.80	0.83	<.0001	0.48	0.48	0.49	<.0001
Unknown	1.42	1.38	1.45	<.0001	0.96	0.95	0.97	<.0001	1.07	1.06	1.07	<.0001
Type of Insurance[c]												
HMO	Ref				Ref				Ref			
EPO	1.16	1.09	1.23	<.0001	1.04	1.01	1.07	0.0218	1.07	1.04	1.11	<.0001
POS	1.11	1.06	1.16	<.0001	1.00	0.98	1.02	0.689	1.04	1.02	1.06	0.0002
PPO	0.97	0.93	1.01	0.1498	1.01	0.99	1.02	0.3683	1.01	0.99	1.02	0.402
Others	1.04	1.01	1.06	0.0012	1.06	1.05	1.07	<.0001	1.06	1.06	1.07	<.0001
Specialist visit[d]												<.0001
Nephrologist	0.69	0.68	0.71	<.0001	1.00	1.00	1.01	0.4096	0.78	0.77	0.78	
Cardiologist	0.91	0.89	0.93	<.0001	0.97	0.96	0.98	<.0001	0.78	0.78	0.79	<.0001
Endocrinologist	2.06	2.01	2.10	<.0001	1.52	1.50	1.53	<.0001	1.35	1.34	1.37	<.0001

Abbreviation: OR: odds ratio; CI: confidence interval; Ref: referent group; SGLT2i: sodium-glucose co-transporter 2 inhibitors; GLP1a: Glucagon like peptide 1 receptor agonists; ACEIs: angiotensin converting enzyme inhibitors; and ARBs: angiotensin receptor blockers

[a]Covariates were adjusted in the model, including age, sex, race/ethnicity, hypertension, cardiovascular disease (atherosclerotic heart disease, heart failure, cerebrovascular accident, peripheral vascular disease and other cardiac disease), and investigated antidiabetic medicines.

[b]Combination therapy was defined as an overlapped use of investigated medicines for more than 30 days.

[c]Type of insurance includes Health Maintenance Organization (HMO), Exclusive Provider Organization (EPO), Preferred Provider Organization (PPO), and Point of Service (POS) Plans.

[d]Reference is no specialist visit.

SA-PO489

Treatment Utilization and Disease Burden Associated with CKD Progression in Patients with Type 2 Diabetes

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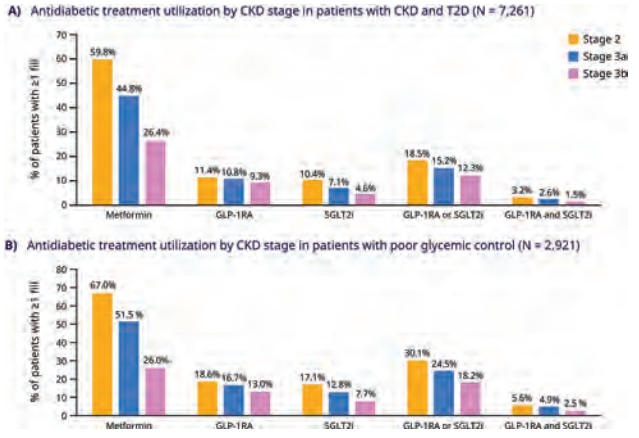
Background: Effective management of type 2 diabetes (T2D) is important for preventing/delaying complications, such as chronic kidney disease (CKD). This real-world, retrospective cohort study examined clinical characteristics and antidiabetic treatment utilization, particularly sodium-glucose cotransporter-2 inhibitors (SGLT2is) and glucagon-like peptide-1 receptor agonists (GLP-1RAs), in patients with CKD and T2D.

Methods: Data were obtained from the Merative™ MarketScan® Explorys Claims-Electronic Health Record Database (January 1, 2016, to September 30, 2021). Patients were aged ≥18 years and had ≥2 estimated glomerular filtration rate (eGFR) values between 15 and 89 mL/min, indicating the same CKD stage within a 90-day period. The first eGFR value qualifying for inclusion was the index date, and patients were continuously enrolled for 6 months pre-index and 12 months post-index. Patients had diagnoses of CKD and T2D in the pre-index period. Treatment utilization was reported by CKD stages 2–3b; all analyses were descriptive.

Results: : A total of 7,261 patients were included (mean ± SD age, 72.4 ± 10.6 years; 56.4% male). Patients had CKD stage 2 (28.0%), 3a (27.4%), 3b (29.5%), or 4 (15.1%). At pre-index, 4.2% and 7.8% of patients received SGLT2is and GLP-1RAs, respectively. At post-index, on average, 43.3% of patients across CKD stages 2–3b received metformin, 10.4% received GLP-1RAs, and 7.3% received SGLT2is; decreasing use of these agents was observed with CKD progression (**Figure**). In a subset of patients with poor glycemic control (glycated hemoglobin >7%; n=2,921), metformin, SGLT2i and GLP-1RA utilization was low; 18.2–30.1% received SGLT2is or GLP-1RAs (**Figure**).

Conclusions: Despite a large number of patients with comorbid CKD and T2D having poor glycemic control, SGLT2i and/or GLP-1RA utilization was low. Improved diabetes management is needed in this patient population.



SA-PO490

Limitations to the Use of Guideline-Directed Medical Therapy (GDMT) in Patients with CKD and Type 2 Diabetes Mellitus (DM) in the Primary Care Setting at an Inner-City Hospital in Bronx, New York

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Background: In 2022, KDIGO modified its GDMT for CKD and Type 2 DM patients to include SGLT-2 inhibitors (SGLT2i's) along with angiotensin converting enzyme inhibitors or angiotensin receptor blockers (ACEI/ARB) as first-line therapy. However, many patients are discontinued due to adverse effects of an initial decline in estimated glomerular filtration rate (eGFR), frequent yeast infections, urinary tract infections, and euglycemic ketoacidosis. We aimed to study which limitations affect practice patterns in our hospital.

Methods: We conducted a retrospective analysis of patients with CKD and Type 2 DM from the primary care clinics from North Central Bronx Hospital, a community hospital in Bronx, NY, from July of 2019 to July of 2022. Statistical analysis was performed using the SPSS program where dichotomic variables and their relationships were analyzed using Chi square and binary logistic regression.

Results: Out of 419 patients recruited, 66.8% were found to be prescribed an ACEI/ARB, while 20.5% were prescribed SGLT-2i's. A history of hyperkalemia showed a decreased odds ratio (OR) (0.460, 0.28-0.73 CI 95%, P=0.04), whereas a microalbuminuria check showed an increased OR (1.923, 1.2-1.9 95% CI, P=0.04) of an ACEI/ARB prescription respectively. CKD stage was also found to affect ACEI/ARB prescription with more patients been prescribed in stages 2, 3a, 3b (78.2%, 68.6%, 67.9%) and less in patients with CKD stages 4, 5, (55.6%,47.6%), respectively, P= 0.015. In the regression model, the only independent variable found to affect SGLT-2i prescriptions was microalbuminuria, where patients who had a microalbuminuria check within last year were more likely to have been prescribed an SGLT-2i OR=2.5, 1.11-3.12 CI 95%, p= 0.019.

Conclusions: A history of hyperkalemia and advanced CKD stage are limiting factors to prescribing ACEI/ARB, while not checking microalbuminuria are limiting factors to prescribing ACEI/ARB and SGLT-2 inhibitors.

SA-PO491

Change in Urine Albumin-to-Creatinine Ratio (UACR) and Health Care Resource Utilization (HRU) and Costs in Patients with Type 2 Diabetes (T2D) and CKD

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Background: UACR is an important measure of kidney damage, but the impact of changes in UACR on HRU and costs in patients with T2D and CKD is unclear.

Methods: We used the Optum electronic health records database (01/2007-09/2021) to identify adult patients with albuminuria, measured by UACR ≥30 mg/g (initial test) after diagnosis of T2D and CKD. UACR change was categorized as increased (>30% change), stable (-30% to 30%), or decreased (<-30%) based on the percent change between the initial test and the last test (between 183-730 days after the initial test). All-cause inpatient (IP) admissions, emergency room (ER) visits, outpatient (OP) visits, and total medical costs were evaluated during the 1 year after the last test. The association of UACR change with HRU was evaluated using Poisson regression, adjusting for key baseline characteristics. Medical costs (2022 USD) were estimated using a unit cost approach based on HRU frequencies.

Results: Among 144,814 patients eligible for the study, 81,084 (56%) had decreased, 31,766 (22%) had stable, and 31,964 (22%) had increased UACR. Compared with patients with stable UACR (IP admissions: 0.18 per-person-per-year [PPPY]; ER visits: 0.31 PPPY; OP visits: 19.13 PPPY; costs: $12,521), those with decreased UACR had similar HRU (IP: 0.17 PPPY; ER: 0.31 PPPY; OP: 19.90 PPPY) and annual medical costs ($12,329), while those with increased UACR had higher HRU (IP: 0.24 PPPY; ER: 0.35 PPPY; OP: 21.20 PPPY) and costs ($15,013). Compared with patients with stable UACR, those with decreased UACR had adjusted incidence rate ratios of 0.97 (95% CI: 0.93-1.01) for IP, 0.97 (0.94-1.01) for ER, and 1.02 (1.01-1.03) for OP. Patients with increased UACR had adjusted incidence rate ratios of 1.22 (1.17-1.28) for IP, 1.10 (1.05-1.15) for ER, and 1.07 (1.05-1.08) for OP compared with patients with stable UACR.

Conclusions: Among patients with T2D and CKD who had albuminuria, increases in UACR were associated with higher HRU and costs compared to patients with stable UACR, while decreases in UACR were associated with similar HRU and costs. Mitigating increases in UACR could yield economic benefits for this patient population.

Funding: Commercial Support - Bayer U.S. LLC

SA-PO492

Cost-Effectiveness Analysis of Dapagliflozin vs. Finerenone for Diabetic Kidney Disease

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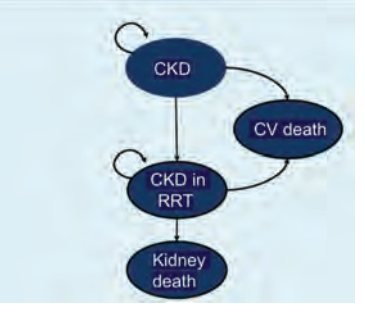
Background: Diabetic kidney disease (DKD) is the leading cause of end-stage chronic kidney disease (CKD) worldwide. CKD carries a health problem public health associated with high morbidity, mortality, high costs and low quality of life. It is necessary to implement risk reduction strategies, such as the use of selective sodium- glucose cotransporter inhibitors 2 (iSGLT2) and selective nonsteroidal mineralocorticoid receptor antagonist (MRA), reducing the risk of 20-40% of time to first onset of kidney failure, sustained decrease in eGFR, and renal or cardiovascular death.

Methods: A probabilistic economic model (Markov model) was developed to evaluate the cost-effectiveness of dapagliflozin versus finerenone for CKD. The model compared patients with dapagliflozin 10 mg per day versus finerenona 20 mg per day, added to standard treatment, in a cohort analyzed at 100 years of age. The states of CKD, progression to CKD with renal replacement therapy (RRT) requirement, renal and cardiovascular death were structured. The effect of dapagliflozin was estimated based on DAPA-CKD trial (HR 0.56; 95% CI, 0.45 - 0.68; $p < 0.001$) and the effect of finerenone based on FIDELTY trial (HR 0.77; 95% CI, 0.67–0.88; P = 0.0002). Probabilities, benefits, and costs of previous studies reported in literature were collected; to finally calculate the total costs, years of life gained adjusted for quality of life and the cost-effectiveness ratio.

Results: The total difference in cumulative life years was 3,979 for CKD in favor of dapagliflozin use. An incremental cost-effectiveness ratio, expressed in quality-adjusted life years, of $8,907 dollars was estimated with dapagliflozin versus $14,451 dollars with finerenone.

Conclusions: Dapagliflozina is cost-effective treatment versus finerenone for CKD, total difference $ 5,544 dollars for quality-adjusted life year.



SA-PO493

Overcoming Recruitment Obstacles in a Trial Examining Intradialytic Plantar Electrical Nerve Stimulation in Diabetic Hemodialysis Patients

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Background: Recruitment of patients on hemodialysis (HD) into a clinical trial is challenging (HD schedule, post-HD fatigue, polypharmacy, and physical and mental conditions). COVID-19 pandemic added an extra challenge (manpower, funding, and physical distance). We present challenges we faced in screening, recruiting, and retaining patients in our study of intradialytic plantar electrical nerve stimulation (iPENS).

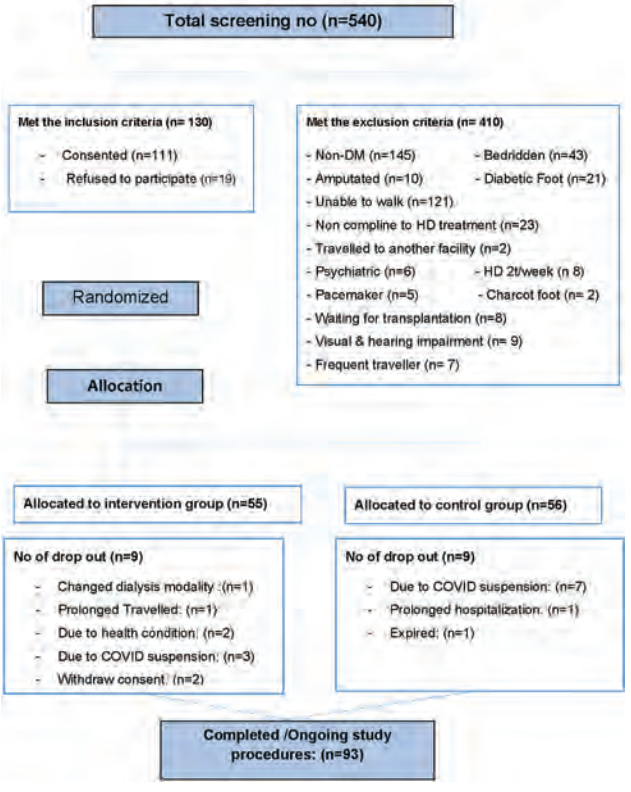
Methods: Our study design is a double-blind, randomized controlled trial. We used iPENS to improve gait, balance and mobility (assessed using wearable sensors) among diabetic patients undergoing HD. Patients received either 1-hour active iPENS or non-functional iPENS during every HD for 12 weeks. Our original target was to recruit 100 patients over 4 year study period.

Results: We screened 540 HD patients in 2018-23. 410 (76%) patients were excluded (mostly non-diabetic and non-ambulatory patients. 130 (24%) patients met the inclusion criteria, but 19 (14.6%) refused to participate (not interested in any extra tasks during HD). 111 patients consented, but 18 (16.2%) of patients dropped (mostly due to COVID-19 interruptions). In the end, 92 patients (17% of the total screened patients) completed the study. Our study faced 11 months interruption related to COVID-19 pandemic. No patients discontinued the study because of extra burden or side effects. Most patients reported positive feedback and experience, with many requesting to continue the intervention beyond the study duration.

Conclusions: Our study was successful in recruiting its target despite its complexity and the challenges it faced. Creating an innovative study design that suits patients' schedules was essential to our success.

Funding: Government Support - Non-U.S.

Figure 1: Therapeutic Plantar Electrical Stimulation Intervention During Hemodialysis to Improve Balance and Mobility, Study Flowchart



SA-PO494

Systolic Blood Pressure Modifies the Relationship Between Coronary Artery Calcification and Adverse Kidney Outcome: Results from KNOW-CKD

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Background: Previous studies have shown that elevated BP and coronary artery calcification (CAC) are risk factors for adverse kidney outcomes. However, the interaction between CAC and BP in relation to CKD progression has not well been studied. In this observational study, we aimed to evaluate whether systolic blood pressure (SBP) could modify the association between CAC and CKD progression in patients with CKD.

Methods: We analyzed 1698 participants with CKD stages G1 to G5 from the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD). Participants with kidney failure with replacement therapy (KFRT) and those with missing data for CAC and SBP were excluded. We categorized the participants according to their 1-year-mean systolic BP as controlled (SBP <120 mmHg) or uncontrolled (SBP≥120 mmHg) and the CAC status (Agatston score=0 or >0 AU). CKD progression was defined as a composite of halving eGFR from baseline value or onset of KFRT.

Results: During 10,023 person-years of follow-up (median 6.2 years), the composite outcome occurred in 689 (40.7%) participants. We found a significant interaction between the Agatston score and SBP for CKD progression (P=0.02). There were 90 (27.5%), 67 (37.0%), 219 (39.5%), and 313 (49.7%) composite outcome events in participants with controlled BP without CAC (group 1), controlled BP with CAC (group 2), uncontrolled BP without CAC (group 3), and uncontrolled BP with CAC (group 4), respectively. In multivariable cause-specific Cox model, the corresponding hazard ratios (95% confidence intervals) for groups 2, 3, and 4 were 1.25 (0.88-1.77), 1.44 (1.12-1.87), and 1.78 (1.35-2.34), respectively, compared with group 1. Sensitivity analysis using a different SBP cutoff of 130 mmHg yielded similar results.

Conclusions: The clinical implication of CAC for CKD progression may be influenced by the status of controlled SBP, and CAC is more strongly associated with adverse kidney outcome when SBP is not adequately controlled.

Funding: Government Support - Non-U.S.

SA-PO495

Are We Dismissing Type 2 Myocardial Infarction (MI) in ESRD? A Serious Note of Concern

Jorge Gutierrez, Chee Yao Lim, Kenneth Johan, Alberto Romero, Pinal Patel, Rahul Zain, Afsheen Afzal, Maria Angela Matabang, Betina Sinanova, Julian Ategeka, Laverne Yip, May Soe, Abdul Wahab, Richa Aggarwal, Vidya Menon. *Lincoln Medical Center, Bronx, NY.*

Background: Patients with ESRD and elevated troponin (cTn) have increased morbidity and mortality. The cTn elevation is often overlooked and categorized as chronic cTn elevation or demand ischemia. We aim to evaluate 30-day readmission and mortality at one year among hospitalized ESRD patients.

Methods: Adult patients with ESRD and elevated cTn admitted from 4/2020 to 4/2022 were included. The 4th Universal Definition of MI and cTn change ≥20% in patients with elevated cTn on admission were used to identify type 1 MI in ESRD. Patients were stratified into 2 groups: type 1 and type 2 MI. 30 days readmission rate and mortality during admission & 1 year were analyzed.

Results: Of the 376 patients hospitalized, 168 were classified as Type 1 or 2 MI and the rest were determined to have chronic elevation of cTn. 24 were classified as type 1 and 144 as type 2. Baseline characteristics were similar between both groups. 30 days readmission rate was 21% in the type 1 group vs 18% in the type 2 (p= 0.745). Mortality during hospitalization was 21% for type 1 vs 9% for type 2 (p= 0.083). Mortality was comparable at 1 year: 29% for type 1 vs 17% in Type 2. Risk of mortality in type 2 MI was higher with heart failure (OR 4.121, p=0.041), afib (OR 6.684, p=0.031) and hemoglobin <8 (OR 9.023, p=0.007). Patients with CVA (OR 0.080, p=0.010), chest pain on admission (OR 0.097, p=0.006), and atypical symptoms (OR 0.079, p=0.016) had better survival.

Conclusions: Type 2 MI is more common among ESRD patients. It has comparable outcomes at one year to type 1, highlighting the importance of strategies to accurately diagnose and risk stratify for better outcomes. Further research in this area, including the role of intervention, will enhance our understanding and improve clinical practices for this vulnerable population excluded in the ISCHEMIA-CKD trial.

SA-PO496

Are We Closing the Loop in Patients with ESRD Too Soon?

Jorge Gutierrez, Kenneth Johan, Chee Yao Lim, Alberto Romero, Pinal Patel, Maria Angela Matabang, Afsheen Afzal, Rahul Zain, Richa Aggarwal, Vidya Menon. *Lincoln Medical Center, Bronx, NY.*

Background: Cardiovascular (CV) disease remains the leading cause of death in ESRD patients. Myocardial infarction (MI) is associated with poorer outcomes compared to the general population. A recent consensus by the Standardized Outcomes in Nephrology Hemodialysis (SONG-HD) group defines MI type I in ESRD patients if they have changes in EKG, symptoms, and a rise or fall of troponin (cTn) within 6 to 12

hours of more than 20% if elevated or more than 50% if normal on admission. We aimed to study the outcomes of patients with ESRD and elevated troponin according to this new consensus.

Methods: This retrospective single center study included patients with ESRD admitted with elevated troponin from April, 2020 to 2022. Patients with a single cTn on admission, repeated cTn less than 6 hours apart from the initial, admitted for cardiac arrest or trauma were excluded. Patients that met criteria for type I MI according to the SONG-HD group consensus were included for the study. Baseline characteristics and mortality up to 1 year were analyzed using descriptive statistics.

Results: After stratifying according to exclusion and inclusion criteria a total of 24 ESRD patients were admitted during this period for type I MI. 4 patients received ACS protocol (ACSP) and PCI within 30 days with a mortality of 0%, 12 patients only ACSP with a mortality of 25% and 8 patients no intervention with a mortality of 50%. 14 patients were documented as type I MI and 10 patients were not due to the lack of guidelines at that time. Out of the 14 patients, 3 received ACSP and PCI within 30 days, with a mortality rate of 0%, 9 only ACSP with a mortality of 11% and 2 received no intervention with a mortality rate of 50%. Out of the 10 patients not identified as type 1 on hospitalization, mortality was 50%.

Conclusions: To date there are no clinical trials about the benefit or harm of revascularization in patients with ESRD. The ISCHEMIA-CKD study reports no benefit in initial invasive strategy when compared to conservative strategy in patients with CKD stage 3 and 4. Though our sample size is small, it brings to light the recurrent question about the role of early cardiac catheterization/PCI among patients with type 1 MI with ESRD while highlighting the importance of early and accurate recognition of type 1 MI in this high risk population.

SA-PO497

Etelcalcetide Use Affects Changes in Agatston Coronary Artery Calcium (CAC) Score in Maintenance Dialysis Patients

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Background: Dialysis patients are known to be at high cardiovascular risk, and the Agatston CAC score, a measure of coronary artery calcification, has been associated with cardiovascular events. Recently, calcimimetics such as etelcalcetide have been used to manage secondary hyperparathyroidism, but their effect on vascular calcification is unknown. Therefore, the present study investigated whether etelcalcetide use affects changes in Agatston CAC scores in maintenance hemodialysis patients.

Methods: This historical cohort study included 192 patients undergoing maintenance hemodialysis who had Agatston CAC score of 100 or higher and were not using calcimimetics other than etelcalcetide. Propensity score matching was performed by age, gender, diabetes mellitus, Ca, iP, and intact PTH. In addition, we examined whether there was a difference in etelcalcetide use and the rate of change in Agatston CAC score after one year.

Results: In the two groups of patients matched for background factors by propensity scores (18 patients each), the Agatston CAC score change was significantly lower in the etelcalcetide use group ($p = 0.0284$).

Conclusions: Etelcalcetide use in maintenance dialysis patients may reduce coronary calcification.

SA-PO498

Empagliflozin in Patients with Acute Heart Failure and Diuretic Resistance: Preliminary Data from the DRIP-AHF-1 Trial

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Background: Diuretic resistance is common in acute heart failure and associated with poor clinical outcomes. Chronic kidney disease (CKD) is a major determinant of diuretic resistance. Association of furosemide with sodium-glucose cotransporter 2 inhibitors can potentially overcome diuretic resistance in acute heart failure patients with CKD.

Methods: This is a prospective, single-arm, observational, open-label clinical trial. Patients admitted with acute heart failure with estimated glomerular filtration rate (eGFR) of 15-45mL/min/1.73m^2 and diuretic resistance, defined as a urinary output (UO)<300mL in the 2 hours post 1-1.5mg/kg IV furosemide, were recruited. These patients received 25mg of empagliflozin 2 hours post a second IV furosemide bolus of 1-1.5mg/kg, administered at least 5 hours after the initial furosemide bolus. Primary outcome is the 3-hour UO post furosemide+empagliflozin on the first day of the study, compared with furosemide alone. Secondary outcomes include fractional excretion of sodium (FENa) and total urinary sodium excretion.

Results: From 32 patients screened, 6 patients met inclusion criteria and consented to participate. Median age was 80 (75-84) years, 67% were male, median ejection fraction was 40 (40-55) % and median baseline eGFR 18 (17-25) mL/min/1.73m^2. All patients had a strong response to furosemide after empagliflozin administration (Table)

Conclusions: Our preliminary data shows that empagliflozin at a dose of 25mg, when added to high dose IV furosemide in patients with acute heart failure, low eGFR and diuretic resistance, is capable of increasing urinary output and urinary sodium excretion.

Funding: Private Foundation Support

Data for the primary and secondary outcomes

Patient number	UO 3h post FST (mL)	UO 3h post Empa+FST (mL)	FENa 3h post FST (%)	FENa 3h post Empa+FST (%)	Na excretion 3h post FST (mmol)	Na excretion 3h post Empa+FST (mmol)
#1	215	290	4.7	7.6	14.4	22.0
#2	345	650	2.3	8.5	19.7	57.9
#3	290	515	7.2	11.3	27.8	55.6
#4	490	775	8.0	11.4	54.8	88.4
#5	80	310	3.3	6.4	6.0	27.0
#6	340	605	5.0	12.4	30.9	67.8

Empa - Empagliflozin; FENa - Fractional excretion of sodium; FST - Furosemide stress test; Na - Sodium; UO - Urinary output

SA-PO499

Effect of Renal Denervation on Plasma Adipokines Concentrations in Patients with Resistant Arterial Hypertension

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Background: Adiponectin, leptin and visfatin are synthesized by adipocytes. Adiponectin has anti-diabetic, anti-atherosclerotic, anti-thrombotic, anti-inflammatory, and cardioprotective properties. Leptin has hypertensinogenic properties. Visfatin seems to be a marker of endothelial dysfunction and vascular damage. Renal denervation (RDN), is proposed as method of treatment in patients with resistant arterial hypertension (RAH). This single-center, interventional clinical study aimed to assess the effect of RDN on plasma adipokines (adiponectin, leptin and visfatin) concentration in patients with RAH.

Methods: Eighteen patients (9 women, 9 men) aged 53.2±6.5 years with RAH who underwent RDN using Simplicity catheters (Medtronic, Inc., Northridge, CA) were enrolled in the study. Plasma adiponectin, leptin and visfatin concentration was determined before and 6 months after RDN using: the Human Adiponectin ELISA Kit (Otsuka Pharmaceutical Co, Tokyo, Japan), the Human Leptin RIA HL-81K (Linco Research, Inc., Missouri, USA) and Visfatin c-terminal ELISA Kit (Phoenix Pharmaceuticals Inc., Karlsruche, Germany), respectively.

Results: Systolic and diastolic blood pressure was reduced 6 months after RDN (mean ± standard deviation; 196.6±28.2 and 162.9±15.6; $p<0.001$ as well as 117.9±26.4 and 90.7±8.6 mmHg; $p<0.001$), respectively). Body mass index (BMI) before and 6 months after RDN was similar (mean ± standard deviation, 31.0 ± 4.4 and 31.3±4.4 kg/m^2; $p=0.8$). Plasma adiponectin concentration increased significantly 6 months after RDN (median with interquartile range; 5.78 (3.70;10.47) and 7.58 (5.60;10.64) μg/mL, $p=0.009$). Plasma leptin and visfatin concentration measured before and 6 months after RDN did not change significantly (median with interquartile range; 5.78 (95% CI 27.5 (14.0;39.0) and 22.5 (12.0;32.0) ng/mL; $p=0.13$, as well as 4.45 (3.70;5.00) and 4.70 (4.10;6.00) ng/mL; $p=0.23$, before and 6 months after RDN, respectively).

Conclusions: 1. Renal denervation may increase plasma adiponectin concentration but did not influence plasma leptin and visfatin concentration in patients with RAH. 2. Increased plasma adiponectin concentration may participate in the cardiovascular benefits in these patients, however long term clinical consequences of this observation need further investigations.

Funding: Government Support - Non-U.S.

SA-PO500

Efficacy and Safety of Renal Denervation in the Maintenance Hemodialysis Patients with Hypertension: A Single-Center Study

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Background: Hypertension, a characteristic symptom in patients undergoing maintenance hemodialysis (MHD), is strongly linked to elevated hospitalization and mortality rates. Percutaneous renal denervation is a novel adjunctive treatment for hypertension, and we observed its efficacy and safety in patients undergoing maintenance dialysis.

Methods: Hypertension patients who underwent hemodialysis for more than 3 months were recruited. The eligible patients were between 18 and 70 years old, with office systolic blood pressure ranging from >150 mmHg to <180 mmHg, while concurrently taking three or more stable doses of antihypertensive medications for at least 6 months. Before enrollment, patients underwent a 28-day standardized treatment with antihypertensive medications. Those whose office systolic blood pressure remained between ≥150 mmHg and ≤180 mmHg after the treatment were included. Patients were subjected to follow-up assessments at 1, 3, and 6 months. The primary endpoints were a change in office systolic blood pressure, and changes in antihypertensive medication types and dosages from baseline to 6 months for the renal artery denervation.

Results: Between April 2021 and April 2023, among 26 enrolled patients, 12 patients who fulfilled the qualifying criteria underwent RDN surgery. The average age of the 12 patients was 43.4±10.60 years, with an average duration of dialysis of 2.4±1.14 years. At 3 months, the office systolic blood pressure reduction was -21.1mmHg(SD 5.7). At 6 months, the office systolic blood pressure reduction was -17.3mmHg(SD 3.8). At 6 months, only one patient required a reduction in the dosage of one medication, while the remaining patients maintained consistent types and dosages of medications as prior to the procedure. There were a total of 3 cases of adverse events, with 2 cases of minor hematoma at the femoral artery puncture site and 1 case of rectal bleeding in a patient with hemorrhoids.

Conclusions: At 6 months of follow-up,RDN produced a clinically meaningful blood pressure reduction,independent of concomitant antihypertensive medications. The application of RDN in patients undergoing maintenance hemodialysis is efficacy and safety.

Funding: Government Support - Non-U.S.

SA-PO501

Pooled, 12-Month Renal Safety and Blood Pressure (BP) Reductions Using the Symplicity Spyral Radiofrequency Renal Denervation Catheter

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Background: Renal denervation (RDN) targets the sympathetic nervous system to lower blood pressure (BP). Impact on long-term renal function after RDN is less well known. We report the 12-month BP reductions and renal safety after RDN from the largest existing database, using the latest generation, multi-electrode, radiofrequency (RF) Symplicity Spyral™ catheter.

Methods: A broad spectrum of patients with hypertension were enrolled in the SPYRAL HTN Global Clinical Program, consisting of 4 major studies; SPYRAL First-In-Man, SPYRAL HTN-OFF MED, -ON MED and Global SYMPLICITY Registry (GSR). GSR is an all-comer registry for patients with uncontrolled hypertension, including chronic kidney disease (CKD), whereas patients enrolled in the SPYRAL HTN-OFF and -ON MED trials required to have OSBP ≥150 and <180 mmHg and ODBP ≥90 mmHg. OFF MED patients were required to have a drug washout period prior to treatment and did not take drugs for the first 3 months. ON MED patients were on a stable 1-3 antihypertensive drug regimen for 6 months. All were treated with RF RDN using the Spyral catheter. We pooled reductions in office and 24-h ambulatory BP, safety outcomes include changes in the estimated glomerular filtration rate (eGFR) and renal artery stenosis incidence (>70%, confirmed by angiography).

Results: As of March 2023, 1,539 patients received RF RDN using the Spyral catheter. Patients at baseline were 58±12yrs old, 38.2% female, 30.1% had type 2 diabetes, eGFR was 77.9±24.4mL/min/1.73m^2, 21.6% had CKD stage 3 or more, OSBP was 164±22mmHg and ASBP was 152±17mmHg. 12 months after RDN, OSBP changed by -15.9 ± 23.2 (n=970; p<0.001) and ASBP changed by -10.0±15.7 (n=660; p<0.001). Significant diastolic BP reductions were also observed. eGFR changed minimally by -2.6mL/min/1.73m^2 (n=805; p<0.001). There was no incidence of renal artery stenosis (>70%).

Conclusions: In this large, pooled population of patients receiving RF RDN using the Spyral catheter, there were significant and consistent BP reductions through 12 months. There was no incidence of renal artery stenosis, and eGFR change was consistent with the natural progression of the aging hypertensive population. These data highlight the safety and efficacy of RF RDN as an adjunctive therapy to antihypertensive drugs to treat high BP.

Funding: Commercial Support - Medtronic Inc

SA-PO502

Mineralocorticoid Receptor Antagonist (MRA) Use Among CKD Patients Before and After the Transition to Dialysis: A Real-World Observation from an Integrated Health System

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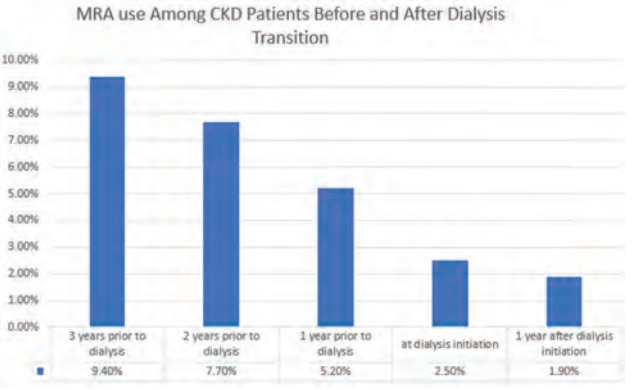
Background: MRAs may improve outcomes in the end-stage kidney disease (ESKD) population, but their use has been limited due to potential side effects and concerns. Among a large, diverse real-world population of incident ESKD patients, we evaluated MRA use prior to and one year after the transition and its associations with short-term all-cause hospitalizations and mortality.

Methods: A retrospective cohort study within Kaiser Permanente Southern California was performed among CKD patients (eGFR≤45) who transitioned to dialysis between 1/1/2007 and 12/31/2017. MRA (spironolactone and eplerenone) use was defined as two or more pharmacy dispensations. MRA use was evaluated as ever, within 3, 2, and 1 year before dialysis, at dialysis initiation, and 1 year after dialysis. Multivariable logistic regression was performed to assess the patients' characteristics related to the use of MRA.

Results: Among 6,812 CKD patients who transitioned to dialysis, 18.3% used an MRA at any time before dialysis and decreased prior to the initiation of dialysis (Figure 1). Among 5,655 ESKD patients who survived, MRA use was 1.9% at 1 year after dialysis. Dialysis patients on MRA were more likely to be non-Hispanic White (OR: 1.87; 95% CI: 1.12-3.12), Asian (OR: 1.82; 95% CI: 1.07-3.09), on peritoneal dialysis (OR: 1.67; 95% CI: 1.10-2.55), and have uncontrolled hypertension with higher hypertensive medication use. The 1 year RR for hospitalization (1.00; 95% CI: 0.81-1.23) or all-cause mortality (0.99; 95% CI: 0.52-1.88) was not significant among MRA vs. non-MRA users.

Conclusions: MRA use was low (1.9%) after transitioning to dialysis. Uncontrolled hypertension but not heart failure was associated with MRA use. Given potential benefits, MRA use in dialysis may represent an area of focus in managing the dialysis population.



SA-PO503

Impact of Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers on Cardiovascular Events and Mortality in Dialysis Patients: A Meta-Analysis of Randomized Controlled Trials

Muhammed Khaled Elhadi Elfaituri, Taha K. Elfaituri, Hazem Faraj, Ahmed Msherghi. *University of Tripoli Faculty of Medicine, Tripoli, Libya.*

Background: Cardiovascular disease is the leading cause of mortality among patients with end-stage renal disease undergoing dialysis. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are commonly used to manage hypertension in this demographic. Despite their widespread use, the decisive impact of these medications on cardiovascular outcomes and all-cause mortality within the dialysis patient population remains to be fully elucidated. This systematic review and meta-analysis of randomized controlled trials (RCTs) sought to accurately quantify the effect of ACEIs and ARBs on a composite of fatal and non-fatal cardiovascular events, cardiovascular mortality, and all-cause mortality among patients undergoing dialysis.

Methods: A systematic search of PubMed, EMBASE, and the Cochrane Library was conducted up to January 2023, focused on RCTs assessing the effects of ACEIs and ARBs on the specified outcomes in dialysis patients. Two reviewers undertook independent data extraction, and any discrepancies were resolved through consensus. The pooled Odds Ratio (OR) with 95% confidence intervals was calculated using a random-effects model. All statistical analyses were performed using R version 4.0.3 with the metafor and meta packages.

Results: A total of 4 RCTs involving 1,502 patients (755 patients on ACEIs/ARBs and 747 controls) were identified. The results revealed that ACEIs and ARBs were not associated with a significant reduction in the composite of fatal and non-fatal cardiovascular events (OR 0.86, 95% CI 0.57-1.28, I^2=66%), cardiovascular mortality (OR0.78,95%CI0.55-1.12,I^2=0),orall-causemortality(OR0.87,95%CI0.66-1.13,I^2=8%). Notably, heterogeneity was observed among the included studies.

Conclusions: The findings of this meta-analysis of RCTs did not provide clear evidence of a significant benefit of ACEIs and ARBs on cardiovascular outcomes or overall survival in dialysis patients. However, given the heterogeneity observed among the included trials, further, high-quality RCTs are warranted to strengthen these findings. Clinicians should consider this lack of definitive evidence when weighing these medications' potential benefits and risks for patients undergoing dialysis.

SA-PO504

PRN Blood Pressure Medication Use in VA Hospitals

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Background: Pro Re Nata blood pressure medications (PRNBP) are commonly used to treat inpatient asymptomatic hypertension. Recent studies in non-Veteran populations suggest this may increase risk of ischemic events and in-hospital mortality. To date, the extent and characteristics of PRNBP use in VA hospitals is unknown.

Methods: We obtained National VA Corporate Data Warehouse (CDW) data on medical/surgical floor hospitalizations in FY16-20 lasting ≥ 3 days for Veterans who were not on dialysis and ≥18 years old. We validated an algorithm to identify PRNBP versus no-PRNBP use in VA national data by comparing CDW data with individual chart review (30 charts per group). We applied this algorithm to report the frequency and characteristics of hospitalizations with and without PRNBP use in patients already on scheduled BP medications.

Results: 577,136 hospitalizations (381,896 unique Veterans) met our criteria at national VA hospitals. An algorithm to identify PRNBP use in VA hospitals was 97% sensitive and 100% specific. Using this algorithm, of the 577,136 hospitalizations, 142,506 (24.7%) received PRNBP defined as a one-time or PRN order. 309,126 of the 577,136 hospitalizations had scheduled BP medications (224,001 unique Veterans). We chose the first hospital stay of each unique Veteran as the unit of study (n=204,990); of these, 87,975 received at least one PRNBP during the stay and 117,015 did not. Age and BMI for those with and without PRNBP were similar (mean±SD age: 70.5±11.5 vs

70.5±11.3; BMI: 29.5±6.7 vs 30.1±6.8; standard mean difference (SMD)<0.1). Admission systolic BP was higher in the PRNBP group (mean±SD: 146.4±25.4 vs 137.0±20.8; SMD=0.4) as was mean systolic BP (138.8±17.2 vs 130.7±13.7; SMD=0.5). Stays with PRNBP had median±IQR 2.0±3.0 doses given. Hydralazine and metoprolol were the most common PRNBP (27% each). Length of stay was slightly longer for those who received PRNBP (median±IQR: 6.0±6.0 vs 5.0±4.0; SMD=0.2). Mean baseline serum creatinine was 1.3±0.9 for PRNBP vs 1.2±0.8 for those without PRNBP (SMD=0.09).

Conclusions: The highly sensitive and specific algorithm to identify PRNBP use in VA hospitals found that inpatient PRNBP use was very common and occurred among those with higher admission BP. This cohort is the largest to date to study PRNBP use and will be the basis of future study to examine the clinical outcomes of PRNBP use in VA hospitals.

Funding: Other NIH Support - T35, Veterans Affairs Support

SA-PO505

Blood Pressure Changes with Intensive Urate Lowering in Uncontrolled Gout Patients with and Without CKD

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Background: Hypertension rate is high in uncontrolled gout (UCG) patients (pts) and associated with gout and hyperuricemia. In adults, allopurinol had little effect on BP, but intensive urate-lowering with pegloticase reduced systolic (SBP) and diastolic (DBP) BP. BP changes during pegloticase use (MIRROR RCT trial) were examined.

Methods: UCG pts (SU≥7mg/dL, oral ULT failure/intolerance, and ≥1 gout symptom) were randomized 2:1 to oral MTX (15mg/wk) or PBO as cotherapy to pegloticase (8mg biweekly, 52wks). After 2wk MTX tolerance period and 4wk MTX/PBO Run-in, pts began pegloticase+MTX/PBO (Day 1). Sitting BP was measured before MTX (baseline [BL, Wk -6]) and pegloticase (Wk -4, Day1) exposure and every 2wks thereafter. Preinfusion, on-treatment BP data were included. Mean(±SD) change from BL (CFB) was examined by treatment group and BL eGFR (<60, ≥60ml/min/1.73m^2).

Results: 152pts (89% men, 55±13yrs, 14±11yr gout history, 76% tophi, 11±14flares/yr) were randomized (100 MTX, 52 PBO). Groups were similar at BL, including SBP (MTX vs PBO: 133±13 vs 131±15mmHg) and DBP (82±9 vs 83±10mmHg). SBP initially decreased in both groups but more in MTX pts by Wk24 (CFB: -6±16 vs -1±18mmHg). CFB was sustained in MTX pts thru Wk52, but fluctuated after Wk24 in PBO pts (n≤19; **Figure**). In MTX pts, DBP was below BL thru Wk52 (CFB: -2±8mmHg). In PBO pts, DBP first declined, but returned to BL by Wk52 (CFB: +1±12mmHg). Pts with BL eGFR≥60 (SBP: 133±13mmHg, DBP: 83±9mmHg; N=98) and <60 (130±15mmHg, 80±7mmHg; N=46) had similar BP CFB early in treatment but by Wk24 was more pronounced in ≥60 group (trend persisted thru Wk52, **Figure**).

Conclusions: BP decreased during pegloticase therapy in CKD and nonCKD pts. After 6mo, pts cotreated with MTX and without CKD had more pronounced changes. These data support a possible role of urate, and potentially MTX, in regulating BP particularly in nonCKD pts with gout. Further study is needed.

Funding: Commercial Support - Horizon Therapeutics plc

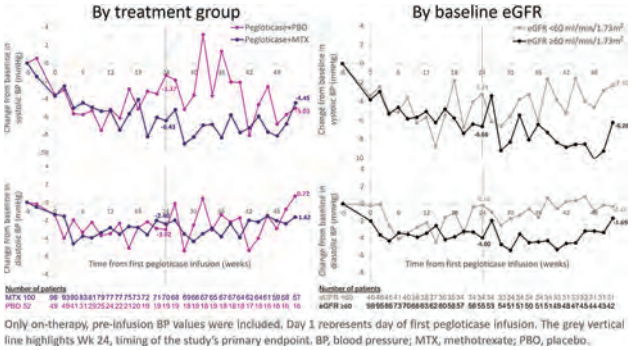

Figure. Mean change from baseline (before MTX, Wk -6) in BP during biweekly pegloticase (8 mg) treatment.

SA-PO506

Sacubitril/Valsartan Improves Cardiac Function in Dialysis Patients

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Background: Heart failure is a common disease characterized by activation of adverse neurohormonal systems and high mortality and mortality rate. Noteworthy, cardiovascular diseases are well known complication of CKD, especially in ESRD, where dialysis patients are 7- 8 times more likely to encounter cardiac arrest than the general population. Sacubitril/Valsartan (Sac/Val) is a dual inhibitor/blocker of neprilysin and angiotensin II receptor, which exert cardioprotective effects among patients with reduced and preserved ejection fraction (HFrEF & HFpEF). Unfortunately, the drug is not approved for subjects with advanced CKD and dialysis patients due to safety concern. The current study examined cardiac and renal effects of Sac/Val in dialysis patients.

Methods: The study was approved by the Nazareth Hospital EMMS Human Research Review Committee and carried at Nazareth Hospital. All patients provided informed consent. Thirteen chronic dialysis patients with HFrHF (FE<40%) were recruited. All patients received conventional dialysis regimens (3 sessions a week for HD; daily dialysis for PD) and all received conventional treatment for CHF and other background illnesses. Patients were treated with Sacubitril/Valsartan at incremental doses 2X50 up to 2X200 mg/day and blood samples were collected and ECHO was performed at baseline and after 3 and 6 months after treatment. Also, quality of life was assessed by Cardiomyopathy Questionnaire (Kansas City KCCQ-12) before and after life after Sacubitril/Valsartan adminsitration.

Results: Administration of Sac/Val to dialysis patients with HFrEF for 6 months gradually improved EF independently of morphological changes in cardiac geometry, as was assessed by echocardiography, and hemodynamic alterations. Specifically, EF was 32.1±1.15% at baseline and increase to 41.15±1.78% (P<0.01) and 48.63±4.72 (P<0.005) following 3 and 6 months of treatment with Sacubitril/Valsartan, respectively. This improvment was associated with significanly reduction in pulmonary artery systolic pressure (PASP). Interestingly, the quality of life significantly improved after Sacubitril/Valsartan treatment. No major adverse effects were reported in the present study, supporting the safety of Sacubitril/Valsartan at least in these patients and for the applied follow up period.

Conclusions: Collectively, these findings support the use of Sac/Val as cardio protective agent in dialysis patients with HFrEF.

Funding: Private Foundation Support

SA-PO507

Heart Failure (HF) in the SGLT2 Inhibitor (SGLT2i) and GLP1 Receptor Agonist (GLP1-RA) Era: Does Hypertension (HTN) Matter?

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Background: Whether uncontrolled HTN modifies the potential protective effects of SGLT2-I and GLP1-RA on HF is unknown.

Methods: We conducted an active comparator, new user design study in a national cohort of veterans (N = 129,186) with type 2 diabetes (T2D) on metformin without HF at baseline and initiated on an SGLT2i, GLP1-RA or insulin glargine (IG) for the first time between 1/1/18 and 12/31/21 and followed until 3/31/23. In Cox models, we examined whether the associations of SBP categories with HF risk modified by the drug class.

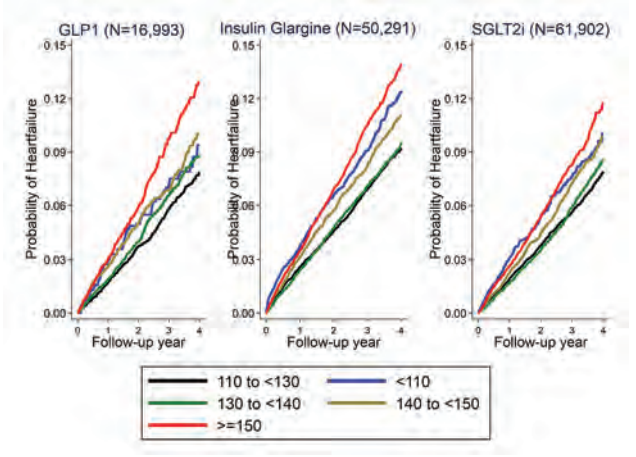
Results: 13.1% were initiated on GLP1RA, 38.9% on IG and 47.9% on SGLT2i. There were 8,850 HF events over 355,990 person-years. Within each of the drug classes, those with SBP 110 to 130 mmHg had the lowest and > 150 mmHg the highest incidence of HF (Fig). In a multivariable Cox model adjusted for SBP levels, demographics, comorbidity, CKD stages and other variables, compared to GLP1RA, IG had higher risk of HF but SGLT2i had similar risk (Table). In the same model, there was a graded association of SBP levels with the risk of HF (Table). The product interaction term of drug classes and SBP categories was not significant (p = 0.65).

Conclusions: HTN remains a significant risk factor for HF in veterans with T2D initated on SGLT2i or GLP1RA.

HF risk by Drug Class and SBP groups

Predictor	HR (95% CI)
Drugs	
GLP1	Reference
Insulin Glargine	1.19 (1.11, 1.27)
SGLT2i	0.93 (0.87, 0.99)
SBP Groups	
<110	1.20 (1.10, 1.31)
110 to <130	Reference
130 to <140	1.03 (0.97, 1.09)
140 to <150	1.21 (1.13, 1.29)
≥150	1.42 (1.33, 1.52)

Product interaction term = 0.65



SA-PO508

Effect of Baroreflex Activation Therapy on Blood Pressure: A Randomized Sham Clinical Pilot Trial on Behalf of the BAT Team

Daniel Gordin,[1,2] Johan R. Simonsen,[1] Pirkka Vikatmaa,[1] Ilkka T. Tikkanen.[1,2] On Behalf of the BAT Team. *[1]HUS Helsingin yliopistollisen sairaala, Helsinki, Finland; [2]Minerva Foundation Institute for Medical Research, Helsinki, Finland.*

Background: Baroreflex activation therapy (BAT) is a promising treatment option for individuals with resistant hypertension. No randomized sham controlled trials have been done thus far.

Methods: This investigator-initiated randomized, double-blinded sham-controlled pilot trial included five Finnish patients with resistant hypertension. Participants were found eligible if they were 18-70 years old with a daytime systolic ambulatory blood pressure (ABP) of ≥145 mmHg, and/or a diastolic ABP ≥95 mmHg. Patients were on ≥3 antihypertensive drugs including a diuretic. A witnessed drug intake prior to ambulatory blood pressure measurement (ABPM) was implemented. The Barostim Neo System was implanted for modulation of the autonomic nervous system by direct electrical stimulation of the carotid baroreceptors. One month after implantation, all participants were randomized to either 8 months BAT-system on or BAT-system off followed by continuous BAT for all participants (Figure). ABPM was performed per protocol. The primary outcome was defined as a change in systolic ABP after 8 months of BAT, compared to pharmacotherapy.

Results: BAT decreased mean daytime systolic blood pressure by 11.8 mmHg in three participants randomized to BAT, while in the two remaining participants randomized to continuous pharmacotherapy mean systolic daytime blood pressure increased by 8.7 mmHg. When pooling daytime systolic 24-hour ABP, BAT was associated with a 9.2 mmHg lower mean blood pressure (143.5 mmHg [95% CI:142.2-144.9] vs 152.7 mmHg [151.1-154.2], <0.0001). In linear mixed models with the BAT-system's status as a fixed effect, daytime SBP at baseline and after 8 months of follow-up were compared between individuals on BAT and continuous pharmacotherapy. BAT was associated with a reduction in mean daytime SBP of -11.7 mmHg (P<0.0001).

Conclusions: BAT may lower systolic blood pressure in individuals with resistant hypertension. Large-scale studies are needed to support this assumption.

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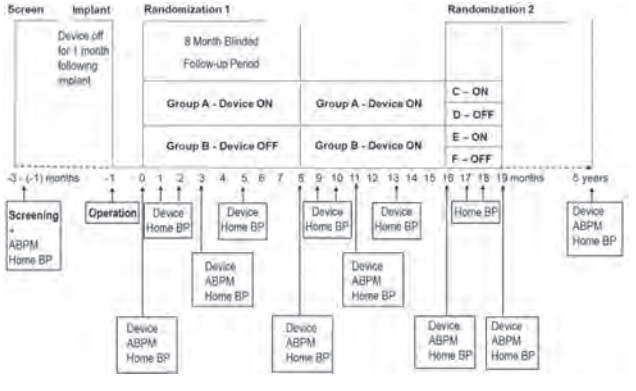

SA-PO509

A Clinical Study to Evaluate and Compare the Blood Pressure (BP) Measurements Taken at Peridialysis Time, at Home, and with Ambulatory BP Monitoring (ABPM) Machine in Hemodialysis Patients

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Background: The study was conducted to find variability of BP measurements obtained at Peridialysis time & at Home with respect to ABPM which would help in better understanding of HTN & its control in HD patients.

Methods: The observational study was conducted in 50 ESRD patients undergoing HD at our centre. BP measurements were taken at baseline & at 6 months during follow up. For each case, BP measurements were taken at Pre HD, Intradialysis, Post HD at Home with calibrated digital BP machine and compared with 44 hours Ambulatory BP recorded with calibrated ABPM machine. The data was analysed both at baseline & at follow up, to find which BP taken at Pre HD, Intradialysis, Post HD & at Home showed highest agreement with the 44 hr Ambulatory BP.

Results: At baseline 44(88%) of cases at baseline were hypertensive (Average BP ≥130/80mmHg over 44 hr monitoring) based on ABPM. Average Home BP had the least difference with average BP by ABPM [SBP diff (2.88 ± 1.44), DBP diff (1.98 ± 1.17)] followed by Median Intradylitic BP{ SBP diff 3.2 ± 4.69 DBP diff 3.52 ± 3.36}. Both Pre HD & Post HD BP vary widely compared to ABPM. On Bland Altman analysis, range of agreement was narrowest with Home BP{SBP 5.64, DBP 4.58). Peridialysis time BP {Pre HD ((SBP 11.23 to 22.49, DBP 4.15 to 15.93) Median intradialytic(SBP-5.99 to12.39, DBP-3.06 to10.10) & Post HD (SBP-31.24 to 3.44, DBP-18.30 to 2.42)} had wide range of agreement with ABPM. **At 6 month follow up** Average Home BP had the least difference with average BP by ABPM {SBP diff (2.82 ± 1.27), DBP diff (2 ± 1.48)}. Both Pre HD & Post HD BP vary widely compared to ABPM. On Bland Altman analysis, range of agreement was narrowest with Home BP{SBP 4.99, DBP 5.82}. Peridialysis time BP {Pre HD ((SBP 10.33 to 22.39, DBP 4.77 to 17.31) Median intradialytic(SBP-10.55 to 20.55, DBP-3.06 to10.10) & Post HD (SBP-3.44 to10.92, DBP-19.08 to 4.40)} had wide range of agreement with ABPM.

Conclusions: Home BP can be an alternative to ABPM for diagnosing HTN in HD patients considering it to be more practical compared to cumbersome ABPM. At dialysis unit, Median Intradylitic BP may be an alternative to ABPM for diagnosing HTN when home BP measurements are not available. Pre HD & Post HD BP measurements should not be used to make diagnosis & treatment of HTN in HD patients.

SA-PO510

Does Home Blood Pressure Monitoring Improve Blood Pressure in CKD?

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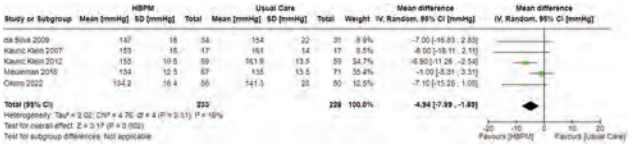
Background: Uncontrolled hypertension is a well-established risk factor for kidney disease progression, cardiovascular disease, and death in patients with chronic kidney disease (CKD). Home blood pressure monitoring (HBPM) is commonly utilized to optimize blood pressure (BP) control in the general population with hypertension. However, it is unclear whether HBPM improves BP control in CKD. We conducted a systematic review and meta-analysis of studies assessing the efficacy of HBPM in reducing BP in patients with CKD.

Methods: A multi-database search was completed to identify interventional studies that included HBPM as an intervention and included change in BP as an outcome. Additional studies were identified by internet and citation searches. Studies were not limited by country but were restricted to those printed in English.

Results: Of 12,100 abstracts screened, 13 manuscripts met the inclusion criteria and included 883 patients across the spectrum of CKD. Six studies included subjects with pre-dialysis CKD, 4 included subjects on hemodialysis, 2 included transplant patients, and one with a mixture of these groups. Eight out of the 10 manuscripts reported a significant change in systolic BP and 5 reported a significant change in diastolic BP. Two manuscripts reported increased achievement of goal BP. Notably, only 5 studies included a control arm and were included in the meta-analysis. Our results, shown in the **Figure**, indicate that HBPM improves systolic BP. Similar results were obtained for diastolic BP.

Conclusions: While few studies have evaluated if utilization of HBPM is effective in reducing BP in patients with CKD, results of this meta-analysis suggest that HBPM may improve BP control in CKD.



SA-PO511

Apelin Offers Cardiovascular and Renal Benefits in Health and CKD

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Background: Chronic kidney disease (CKD) affects 1 in 10 people and cardiovascular disease is its commonest endpoint. Despite standard-of-care, outcomes remain poor and new therapies are needed. Apelin, an endothelium-dependent vasodilator and inotrope, is a potential novel treatment. We examined the cardiovascular and renal actions of apelin in health and CKD.

Methods: Patients with stable, non-diabetic CKD and age- and sex-matched healthy volunteers were recruited to a randomized, double-blind, placebo-controlled study. Subjects received pyroglutamated apelin-13 ([Pyr^1]apelin-13 (1 nmol/min and 30 nmol/min) or placebo on two study visits. Blood pressure, impedance cardiography and pulse wave velocity were examined. Iohexol and para-aminohippurate clearances determined glomerular filtration rate (GFR) and effective renal blood flow (ERBF), respectively. Tubular function was assessed *via* urinary electrolyte and free water excretion.

Results: Twelve patients with CKD and 12 healthy volunteers were recruited. Baseline characteristics are shown in **Table 1.** Compared to placebo, in health and CKD 30 nmol/min [Pyr^1]apelin-13 reduced mean arterial pressure by ~3% and systemic vascular resistance index by ~10-15%, and increased cardiac index by ~10-15% ($p<0.05$ for all comparisons). In health and CKD, 1 nmol/min and 30 nmol/min [Pyr^1]apelin-13 had similar effects on renal endpoints. ERBF increased by ~15% ($p<0.01$ compared to placebo in both groups). In CKD only, GFR fell by ~4 mL/min, filtration fraction by ~3% and proteinuria by ~25% ($p<0.01$ compared to placebo for all). [Pyr^1]apelin-13 promoted natriuresis and free water clearance in health and CKD. Overall, the effects of apelin were prolonged in CKD.

Conclusions: Apelin has cardiovascular and renal benefits in CKD. If maintained long-term these would improve cardiovascular and renal outcomes. Clinical trials of long-acting oral apelin analogues are justified in CKD and other conditions with impaired salt and water balance.

Baseline characteristics

	Healthy volunteers	Chronic kidney disease
Age, years	48±4	48±4
Male sex (%)	8 (67)	8 (67)
Mean arterial pressure, mmHg	90±6	95±8
Systemic vascular resistance index, dynes*cm*cm-5 m2	2548±397	3013±613
Pulse wave velocity, m/s	5.8±0.2	6.6±0.3
Glomerular filtration rate, mL/min	98±5	41±5
Protein:creatinine ratio, mg/g	0	344(141-1273)

SA-PO512

Apelin Increases Forearm Blood Flow in CKD

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Background: Chronic kidney disease (CKD) is a global health emergency. It is independently associated with cardiovascular disease. Despite current treatment patients still progress to kidney failure and/or die from cardiovascular causes. There is an unmet need for newer therapies and apelin, an endothelium-dependent vasodilator and potent inotrope, is an attractive therapeutic target. Clinical studies find apelin improves endothelial function in health and heart failure. We examined the local vascular actions of apelin in CKD.

Methods: Patients with stable, non-diabetic CKD and age- and sex-matched healthy volunteers were recruited to a randomised, placebo-controlled study. Baseline blood pressure and pulse wave velocity were measured. Gold-standard venous occlusion plethysmography was used to examine endothelial function in response to incremental intra-arterial doses of acetylcholine (7.5, 15 and 30μg/min, endothelium-dependent vasodilation), sodium nitroprusside (1, 2 and 4μg/min, endothelium-independent vasodilation), and pyroglutamated apelin-13 ([Pyr^1]apelin-13; 0.3, 1, 3, 10, 30 and 100nmol/min). Circulating tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 assessed endogenous fibrinolysis.

Results: Fifteen patients with CKD (mean age 55±4 years; 53% male) and 15 healthy volunteers (mean age 51±3 years; 67% male) were recruited. In comparison to health, patients with CKD had a higher blood pressure (mean arterial pressure: 102mmHg *versus* 93mmHg, $p<0.05$) and increased pulse wave velocity (7.5±2.2 m/s *versus* 6.0±0.9m/s, $p<0.01$). Similar dose-dependent vasodilation to acetylcholine and sodium nitroprusside was seen in both groups. [Pyr^1]apelin-13 dose-dependently increased forearm blood flow to a maximum of ~30% in both health and CKD ($p<0.01$ compared to baseline for both). Net tPA antigen release increased 20-70 fold in both groups, with a trend to a greater release in CKD.

Conclusions: In optimally managed patients with CKD, apelin promotes vasodilation and may regulate fibrinolysis. If maintained longer-term with systemic treatment, apelin would reduce cardiovascular risk. Systemic studies are needed to investigate the haemodynamic and renal effects of apelin in CKD.

SA-PO513

Relationship Between Iron Deficiency and QTc Prolongation in Japanese Maintenance Hemodialysis Patients

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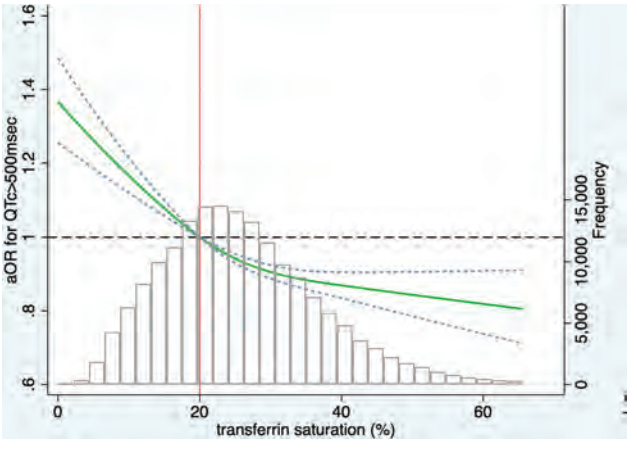
Background: QT interval prolongation is a risk factor for fatal arrhythmias and other cardiovascular complications. Causes of QT interval prolongation in hemodialysis (HD) patients is not fully understood. It has also recently been reported that lower transferrin saturation (TSAT), one of the marker for iron deficiency, is associated with cardiovascular complications in patients with CKD. We hypothesize that iron deficiency may be associated with QT interval prolongation in HD patients.

Methods: We identified 175,448 eligible patients from a nation-wide database receiving thrice-weekly HD in Japan. The cross-sectional study was conducted on adult maintenance HD patients enrolled in the 2019 Japanese Society for Dialysis Medicine Annual Survey. Logistic regression analysis was performed with serum ferritin (S-fer) and TSAT as explanatory variable and QTc prolongation (QTc >500 msec) as outcome, adjusted for possible confounding factoes.

Results: A total of 175,448 patients were included in the analysis of this study. The mean QTc (standard deviation) was 451.7 (36.1) msec. 13,343 (7.6%) of subjects have suffered from QTc >500 msec. On multivariate analysis, the adjusted odds ratios [95% confidence interval] for QTc prolongation in the groups with TSAT ≤ 20% and S-Fer >100 ng/mL, TSAT ≤ 20% and S-Fer ≤ 100 ng/mL, TSAT > 20% and S-Fer ≤ 100 ng/mL with the group with S-Fer > 100 ng/mL and TSAT > 20% as the control group, were 1.12 [1.05, 1.20], 1.19 [1.14, 1.25] and 0.99 [0.95, 1.04], respectively. A J-curve relationship was observed between TSAT and QTc prolongation (Figure).

Conclusions: This study suggests that decreased TSAT (≤20%) may be associated with QTc prolongation in maintenance HD patients. Iron deficiency may play some role for prolonging ventricular repolarization time independent of other risks in HD patients.



A J-curve relationship was observed between TSAT and QTc prolongation

SA-PO514

Characteristics and Prediction of Tumor Recurrence in Patients with Pheochromocytoma and Paraganglioma: A Single-Center Experience in Taiwan

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Background: Both pheochromocytoma and paraganglioma are rare catecholamine-producing neuroendocrine tumors. Surgical resection is the only curative treatment for these tumors. Patients receiving tumor resections, however, still probably encountered tumor recurrence. To our best knowledge, it's still with unclear clinical presentation of these catecholamine-producing tumor and lack of useful parameters to predict recurrence after tumor resection. The aim of this study is to find predictors of tumor recurrence in patients with these two rare neuroendocrine tumors.

Methods: This study was conducted at a tertiary medical center in Taiwan retrospectively. Data collection by chart review was undertaken in a 2000-bed private university hospital in Taiwan between January 2000 and December 2021. In total, 310 patients with pathologic diagnosis of pheochromocytoma or paraganglioma were enrolled.

Results: The study subjects were grouped as PCC and PGL and then further classified to sympathetic PPGLs and parasympathetic PPGLs according to the tumor origin. This study include 156 patients of PCC and 154 patients of PGL which larger tumor size, more symptoms of headache, arrythmia, diaphoresis, anxiety, and mass effects, more comorbidity of hypertension and hyperglycemia, higher urine epinephrine level, and higher renin level were significantly noted in patients with PCC. The other classification of the subjects including 247 patients with sympathetic PPGLs and 63 patients with parasympathetic PPGLs who have significant larger size of tumor, more symptoms of arrythmia, diaphoresis, body weight loss, and chest tightness without ischemic heart disease, and more comorbidity of hypertension and hyperglycemia in the group to sympathetic PPGLs. Of the subjects, there are 14 patients categorized as the

recurrent group, and 289 patients categorized as non-recurrent group. Comparing with non-recurrent group, recurrent group are younger (p=0.03407), and have more genetic ancestry (p=0.02062).

Conclusions: Our study demonstrates the characteristics of PCC and PGL and several clinical parameters such as age and genetic ancestry are associated with tumor recurrence after tumor resection in patients with PCC or PGL. It will help clinician to closely monitor disease status after tumor resection.

SA-PO515

Differences in Cardiovascular Phenotype and Pharmacotherapy Between Patients with ESKD Based on Transplant Eligibility

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Background: Cardiovascular disease (CVD) is a major cause of death in end-stage kidney disease (ESKD) patients, linked to traditional and non-traditional risk factors. The ISCHAEMIA-CKD trial indicated no benefit from early invasive treatment for coronary artery is disease (CAD) in advanced kidney disease. Hence, optimizing conservative medical therapy is crucial. We conducted post-hoc analyses using CYCLE-HD trial data to compare structural and functional heart disease and pharmacotherapy in patients active and not active on the transplant waiting list.

Methods: 130 hemodialysis patients underwent cardiac MRI for comprehensive cardiovascular phenotyping (2015-18). Appropriate comparison tests were used depending on data distribution. If initial testing revealed a significant difference, ANCOVAs were used to adjust for age.

Results: 71/130 patients were active and 59/130 were not active on the transplant list. The 'active' group were younger (53 (40, 61) vs 66 (57, 75) years). 68% vs 79% were male, 69% vs 64% had hypertension, 20% vs 10% had dyslipidemia, 30% vs 48% had diabetes. There were no significant differences in medication use: 15% vs 8% on an ACE inhibitor or ARB, 48% vs 41% on a beta blocker, 50% vs 37% on a calcium channel blocker, 28% vs 32% on aspirin, 45% vs 61% on a statin. After adjusting for age, left ventricular (LV) ejection fraction, global longitudinal, and circumferential strain were significantly lower in the 'not active' group and LV mass index was higher (Table 1).

Conclusions: In this analysis, pharmacotherapy to mitigate CVD was poor irrespective of transplant listing status. CV phenotype was different between those listed and those not listed. Greater attention must be paid to optimising CV pharmacotherapy in both groups of patients to improve CV outcomes.

Table 1: Cardiac MRI characteristics

	Active, n=71	Not active, n=59	p-value*	ANCOVA
LV mass index (g/m²)	58 (48, 77)	60 (52, 76)	*	F= 3.8
Global native T1 (ms)	1269 ± 39	1280 ± 42		F=1.1
PWV (m/s)	7 (6, 9)	9 (7, 13)	*	F=0.0
LV ejection fraction (%)	57 (51, 62)	54 (41, 61)	*	F=8.9*
Global longitudinal strain (%)	-15 (-16, -12)	-13 (-15, -10)	*	F=7.3*
Global circumferential strain (%)	-17 (-19, -14)	-15 (-19, -12)	*	F=5.7*

LV; left ventricle, PWV; pulse wave velocity, *p≤0.05, ANCOVA adjusted for age

Table 1: Cardiac MRI characteristics

SA-PO516

Comparative Safety and Effectiveness of Statins in Kidney Transplant Recipients

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Background: Recent observational studies suggest that statins are well-tolerated and may lower all-cause mortality in kidney transplant recipients. A specific type of statin may be preferrable over other types, given the unique pathophysiological challenges in this population. We compared the safety and effectiveness outcomes between statins in a national cohort.

Methods: Using the USRDS data, we studied adult kidney transplant recipients in 2006-2018 who started atorvastatin, pravastatin, simvastatin, rosuvastatin, or lovastatin post-transplant. Those who used statins pre-transplant or had the outcome of interest before transplant or statin initiation were excluded. Those who used multiple statins were censored at the initiation of the second statin. We analyzed Medicare institutional claims to ascertain various safety/effectiveness outcomes (see Table 1) and Medicare pharmacy claims to ascertain statin use. Deaths were captured from multiple sources including Social Security and CMS data. We used Cox regressions to compare mortality and the safety/effectiveness outcomes between statins, after adjusting for multiple recipient-, donor-, and transplant-related risk factors.

Results: Our cohort included 16,967 recipients; 7,885 used atorvastatin, 4,065 used pravastatin, 3,617 used simvastatin, 1,207 used rosuvastatin, and 193 used lovastatin. Compared to atorvastatin users, pravastatin users showed lower risk of all-cause mortality (aHR=0.82 [95% CI; 0.72-0.94]), cardiovascular mortality (aHR=0.73 [95% CI; 0.55-0.98]), myocardial infarction (aHR=0.79 [95% CI; 0.62-1.00]), and hemorrhagic stroke (aHR=0.57 [95% CI; 0.33-0.98]). Simvastatin users showed lower risk of all-cause mortality (aHR=0.88 [95% CI; 0.78-0.98]), cardiovascular mortality (aHR=0.75 [0.58-0.97]), and hemorrhagic stroke (aHR=0.55 [95% CI; 0.35-0.86]). Other outcomes did not differ between statins (Table 1).

Conclusions: Pravastatin and simvastatin might be preferrable over atorvastatin in kidney transplant recipients. Further research addressing other cardiovascular risk factors and statin dose is needed.

Funding: NIDDK Support

Table 1. Association of Statin Types with Various Safety and Effectiveness Outcomes in 16,967 Kidney Transplant Recipients with Post-Transplant Statin Initiation.
Estimates are adjusted hazard ratios (95% CI). Bold indicates statistical significance (p<0.05).

Outcomes	Atorvastatin	Pravastatin	Simvastatin	Rosuvastatin	Lovastatin
Effectiveness Outcomes					
All-cause mortality	REF	**0.82 (0.72-0.94)**	**0.88 (0.78-0.98)**	0.91 (0.72-1.14)	0.63 (0.38-1.03)
Cardiovascular mortality	REF	**0.73 (0.55-0.98)**	**0.75 (0.58-0.97)**	0.61 (0.34-1.11)	0.16 (0.02-1.15)
Congestive heart failure	REF	1.01 (0.85-1.21)	0.93 (0.79-1.09)	0.97 (0.71-1.33)	0.98 (0.56-1.69)
Ischemic stroke	REF	0.78 (0.61-1.00)	0.92 (0.74-1.15)	0.92 (0.61-1.38)	0.91 (0.40-2.04)
Myocardial infarction	REF	**0.79 (0.62-1.00)**	0.86 (0.70-1.07)	1.23 (0.86-1.77)	0.82 (0.36-1.87)
Cardiac catheterization	REF	1.17 (0.87-1.57)	1.05 (0.80-1.37)	0.69 (0.38-1.25)	1.03 (0.36-2.92)
Coronary artery bypass grafting	REF	0.91 (0.55-1.51)	0.72 (0.43-1.18)	1.66 (0.74-3.75)	0.57 (0.06-5.43)
Safety Outcomes					
New-onset diabetes	REF	1.00 (0.82-1.21)	1.00 (0.84-1.18)	0.84 (0.58-1.22)	1.05 (0.55-1.99)
Hemorrhagic stroke	REF	**0.57 (0.33-0.98)**	**0.55 (0.35-0.86)**	0.43 (0.15-1.24)	0.50 (0.06-3.94)
Cataract	REF	1.13 (0.95-1.34)	0.97 (0.82-1.14)	1.10 (0.82-1.48)	0.76 (0.40-1.43)
Liver injury	REF	1.35 (0.70-2.61)	1.32 (0.78-2.21)	0.45 (0.10-2.13)	2.63 (0.69-10.03)
Rhabdomyolysis	REF	0.61 (0.29-1.26)	1.15 (0.65-2.05)	1.73 (0.61-4.90)	0.84 (0.15-4.83)

SA-PO517

Comparing Long-Term Blood Pressure Management in Kidney Transplant Patients: Immediate-Release vs. Extended-Release Tacrolimus

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Background: Tacrolimus (Tac) is a first-line anti-rejection medication with immediate-release (Tac IR) and extended-release (Tac ER) versions. Hypertension is a common adverse effect of Tac, but the longitudinal blood pressure control between kidney transplant recipients receiving Tac ER and Tac IR has never been studied.

Methods: A retrospective, single-center cohort study used data from the University of Pennsylvania Health System. Adult patients aged 18+ who started tacrolimus immediately after kidney transplantation between January 1st, 2016, and December 31st, 2019, were included. The primary outcome was time-varying systolic and diastolic blood pressure (SBP and DBP) documented through December 31st, 2021. Baseline and time-varying variables were collected, and the secondary outcome was the incidence of hypertensive crisis. Sensitivity analysis was performed using time-constant exposure based on the type of Tac patients received at four months post-transplant. A logistic regression model, a 3-step marginal structural model, and a 2-tailed Fisher's exact test were used for analysis.

Results: 654 patients with 16,382 BP entries were analyzed. Black patients were 2.32 times more likely to receive Tac ER (p=0.001). Patients taking Tac ER had a 1.87 mmHg lower SBP than those taking Tac IR (p=0.009), but no difference in SBP in the sensitivity analysis with a time-constant exposure at a 4-month cutoff. No significant differences were observed in DBP in both the main and sensitivity analyses. A total of 9 patients experienced a hypertension crisis; 8 were on Tac IR, and 1 was on Tac ER. No statistical difference in the occurrence of hypertension crises between the two groups was found.

Conclusions: Post-transplant patients taking Tac ER show a slightly lower SBP than those on Tac IR, without a significant difference in hypertensive crisis incidence.

Funding: Other NIH Support - pharmacoepidemiology T32

Evaluating Mean SBP and DBP in Patients on Tac ER vs Tac IR Through a Marginal Structural Linear Mixed Effects Model

Tac ER vs Tac IR	Coefficient (95% CI)	P value	Intra-cluster Variation
Time varying exposure			
SBP	-1.87 (-3.28, -0.47)	0.009	0.26
DBP	-0.31 (-1.25, 0.64)	0.527	0.37
Sensitivity analysis with 4 months cutoff			
SBP	1.49 (-1.01, 4.00)	0.242	0.29
DBP	1.53 (-0.40, 3.45)	0.120	0.39

SA-PO518

Association Between Progression of Coronary Artery Calcification and Development of Kidney Failure with Replacement Therapy: Findings from KNOW-CKD Study

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Background: A higher burden of coronary artery calcification (CAC) is a strong risk factor of adverse cardiovascular and kidney outcomes. However, clinical implications of longitudinal change in CAC remain unknown. Here, we evaluated whether the progression of coronary artery calcification can predict development of kidney failure with replacement therapy (KFRT).

Methods: A total of 1,173 participants with chronic kidney disease (CKD) G1 to G5 without kidney replacement therapy were included from KNOW-CKD (Korean Cohort Study for Outcomes in Patients With Chronic Kidney Disease). Participants were

categorized into 3 groups according to the change in CAC score between baseline and year 4 (non-progressors, ≤0 AU; moderate progressors, 1–199 AU; severe progressors ≥200 AU). The primary outcome was the development of KFRT.

Results: During a follow-up period of 4,690 person-years (median, 4.2 years), the primary outcome occurred in 230 (19.6%) participants. The incidence of KFRT was 37.6, 54.3, and 80.9 per 1000 person-years in non-, moderate, and severe progressors, respectively. In multivariable cause-specific hazard model, the hazard ratios (HRs) for the moderate and severe progressors were 1.77 (95% CI, 1.06–2.95) and 2.52 (95% CI, 1.06–6.00), respectively, compared with non-progressors. A sensitivity analysis using a different definition of CAC progression, with a threshold of 100 AU, also yielded similar results.

Conclusions: The progression of CAC was associated with an increased risk for development of KFRT in patients with CKD.

Funding: Government Support - Non-U.S.

SA-PO519

Additive Risk for Pericardial Effusion of Exposure to Either Hydralazine or Minoxidil and Advanced CKD

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Background: Vasodilatory antihypertensives hydralazine and minoxidil have been linked to the development of pericardial effusion. However, most of the available evidence comes from small cohort studies or case series. Furthermore, because advanced chronic kidney disease (CKD) is associated with uremic pericardial effusion, it is not clear whether hydralazine or minoxidil independently confer a risk for pericardial effusion in advanced CKD. We aimed to examine this question in a large patient database.

Methods: We retrospectively reviewed records of adult patients who underwent transthoracic echocardiography (TTE) between 2017 and 2022 to identify those diagnosed with pericardial effusion. Exposure to either hydralazine or minoxidil within 3 months prior to the TTE was probed, as well as demographic and clinical characteristics, including CKD status. Advanced CKD included stage 4 or 5 CKD or end-stage kidney disease. Cases of mesothelioma or tuberculosis were excluded.

Results: A total of 153,678 unique patients with TTE entered the analysis. Pericardial effusion was found in 1,441 (0.94%). By multivariate logistic regression, exposure to hydralazine [OR 1.58 (CI 1.4–1.8), p<0.0001)], exposure to minoxidil [OR 4.48 (CI 2.8–7.2), p<0.0001)], advanced CKD [OR 2.30 (CI 1.7–3.1), p<0.0001)], coronary artery disease [OR 1.21 (CI 1.1–1.4), p=0.0011)], and female sex [OR 1.33 (CI 1.2–1.5), p<0.0001)], were independently associated with increased risk of pericardial effusion, whereas age, race, diabetes mellitus and hypertension were not. The rate of pericardial effusion was greater in those exposed to vasodilators: 1.4% of hydralazine users (n=24,650) compared to 0.8% of nonusers (n=121,118) (p<0.0001), and 5.4% of minoxidil users (n=354) compared to 0.9% of nonusers (n=153,414) (p<0.0001). Among those with advanced CKD (n=2,337), the incidence of pericardial effusion was overall higher and significantly associated with exposure to either hydralazine (3.3% vs 1.7% for nonusers, p=0.022) or minoxidil (6.5% vs 2.1% for nonusers, p=0.043).

Conclusions: Hydralazine and minoxidil confer an increased risk for pericardial effusion that augments the increased risk associated with advanced CKD. Because these agents are frequently prescribed in advanced CKD, close monitoring is advised.

SA-PO520

Renalism: An Obstacle to Left Heart Catheterization in CKD Patients

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Background: "Renalism" is the reluctance of clinicians to conduct contrast-based studies such as left heart catheterization (LHC) on individuals with chronic kidney disease (CKD). Non-ST-elevation myocardial infarction (NSTEMI) often requires LHC and delay can lead to increased mortality and adverse cardiovascular outcomes.

Methods: The National Inpatient Sample Database 2016-2018 was used to sample patients presenting with NSTEMI. Baseline demographics and comorbidities were collected using ICD-10-codes. Patients less than 18 years old, missing data, and with end-stage renal disease were excluded. Patients were stratified into CKD 1-2 vs CKD 3-5. 1:1 propensity matching was performed to match the two cohorts. Mortality and cardiovascular outcomes were compared in CKD 3-5 patients who underwent LHC and those who did not.

Results: Of 427,593 NSTEMI patients, 79,284 had CKD 3-5. CKD 3-5 patients were less likely to have LHC and had increased mortality. After matching, CKD 3-5 was independently associated with less LHC. During regression analysis, CKD 3-5 patientsthat underwent LHC were 2.9 times less likely to have in-hospital mortality compared to patients that did not undergo LHC. Additionally, LHC in CKD 3-5 patients was also associated with decreased cardiovascular outcomes and acute kidney injury (p<0.001).

Conclusions: Alteration in practice-based guidelines due to risk of contrast-induced nephropathy leads to less LHC in CKD patients and increased mortality and adverse cardiovascular outcomes. Further studies are needed to evaluate the risks and benefits of contrast-based studies in this patient cohorts.

Outcomes of CKD Stage 3-5 patients that underwent left heart catheterization

Outcomes	P-value	Odds Ratio	Lower 95% CI	Upper 95% CI
Unmatched				
Mortality	<0.001	0.390	0.352	0.432
Acute Kidney Injury	<0.001	0.651	0.626	0.678
Acute Heart Failure	<0.001	0.696	0.667	0.725
Cardiac Arrest	<0.001	0.752	0.658	0.859
Length of Stay (Coefficient)	<0.001	-1.080	-1.218	-0.942
Matched				
Mortality	<0.001	0.342	0.319	0.366
Acute Kidney Injury	<0.001	0.724	0.702	0.746
Acute Heart Failure	<0.001	0.838	0.814	0.864
Cardiac Arrest	<0.001	0.731	0.666	0.803
Length of Stay (Coefficient)	<0.001	0.396	0.295	0.498

SA-PO521

Cardiovascular Risk Prediction Improvement Using Algorithm- or Formula-Based Pulse Wave Velocity: Analysis of CARTaGENE

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Background: Carotid-femoral pulse wave velocity (PWV) is the gold-standard measurement for aortic stiffness and a well-established surrogate marker for cardiovascular disease. Faster and less resource-intensive methods to estimate PWV (using either formulas or integrated pulse wave analysis algorithms) have been developed but their incremental predictive value for cardiovascular outcomes remains unclear.

Methods: We studied individuals aged between 40 and 69 from the population based CARTaGENE cohort (Quebec, Canada). Baseline PWV was assessed using a previously described estimation formula (formula- based PWV, or f-PWV; using age, sex, and systolic blood pressure) or estimated with the ARCSolver algorithm from central waveform characteristics obtained with the SphygmoCor device (algorithm-based PWV, or a-PWV). Major adverse cardiovascular events (MACE: cardiovascular mortality, non- fatal stroke, non-fatal myocardial infarction) during a 10-year follow-up were obtained from medico-administrative databases. Cox proportional hazards models were employed to obtain associations between PWV and MACE after adjustment for existing cardiovascular risk prediction scores (ASCVD [from revised pooled cohort equations], SCORE-2).

Results: 17,548 individuals were included and 2,263 experienced a MACE during follow-up. Mean PWV values at baseline were 8.4 ± 1.4 m/s (f-PWV) and 7.9 ± 1.3 m/s (a-PWV). Both f-PWV (HR= 1.52, 95% CI [1.47-1.58]) and a-PWV (HR=1.60 [1.54-1.66]) were predictive of MACE in unadjusted models. The association between a-PWV and MACE remained significant after adjustment for ASCVD (HR= 1.14 [1.08-1.20]) and but not after adjustment for SCORE-2 (HR= 1.06 [1.00-1.13]). In contrast, f-PWV was not associated with increased MACE after adjustment for either prediction score (HR= 1.02 [0.97-1.08] for ASCVD; HR= 0.95 [0.89-1.00] for SCORE-2). Similar trends were observed after stratification for tertiles of baseline cardiovascular risk.

Conclusions: Algorithm-based PWV, but not formula-based PWV, improves cardiovascular prediction beyond what is achievable with recognized prediction tools.

SA-PO522

Rates and Outcomes of Cardiac Surgery for People Receiving Long-Term Dialysis or Kidney Transplantation in Australia

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Background: Rates of coronary artery disease and cardiac valve disorders are higher among people with kidney failure (KF). Cardiac surgery (CS - coronary artery bypass grafting [CABG] and valve replacement surgery) are important treatment options for these, but may carry substantial risks. Utilising data linkage of two registries with national coverage, we examined rates and outcomes of CS among patients receiving long term dialysis or with a kidney transplant.

Methods: Data were linked probabilistically between the Australia & New Zealand Dialysis & Transplant Registry and the Australian & New Zealand Society of Cardiac & Thoracic Surgeons Cardiac Surgery Database. Thirty-day mortality adjusted for risk factors was compared for 3 groups based on status at time of surgery (dialysis / kidney transplant / non-kidney failure [KF]) using multiple logistic regression. The study population included all eligible CS in Australia from 2001-2019.

Results: Demographics are shown in the Table. Crude 30-day mortality was highest among the dialysis group then the transplant and non-KF groups. Mortality progressively improved over time. Adjusted for procedure type and other comorbidites, excess mortality persisted for the KF groups. The odds ratio for 30 day mortality for CS in the dialysis group was 3.4 [2.7-4.2] and for the transplant group was 2.4 [1.4-4.2]. Adjusted analyses

showed increased risk of mortality were seen for valve replacement (vs CABG), urgent surgery, comorbidities and those with greater dialysis vintage. Mortality at 24 months was 32 [29-35]% for the dialysis group and 16 [12-20]% for the transplant group.

Conclusions: Among KF patients requiring CS, early mortality rates are substantially increased, especially when other comorbidities are present or surgery is urgent. While the risks of not operating are not known for these cohort, these data will inform and support careful consideration of the risks of cardiac surgery in this group.

Funding: Government Support - Non-U.S.

	Dialysis	Transplant	Non-KF
Number	1639 (74% male)	353 (75% male)	150741 (73% male)
Age (median (IQR) ; years)	63 (55-71)	64 (55-69)	68 (59-71)
Diabetes (%)	58	44	29
Procedure type (Isolated CABG / Isolated valve replacement / combined)	955/301/244	131/98/55	80606/30754/15298
Unadjusted 30 day mortality [95% CI]	6.5 [5.3-7.8]%	4.5 (26-7.3)%	2.2 (2.1-2.3)%

SA-PO523

Association of CKD and Cardiovascular Disease Risk with All-Cause Mortality: A Mediation Analysis in Chinese Adults

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Background: To evaluate the complex relationship of chronic kidney disease (CKD) and cardiovascular disease (CVD) risk with mortality in different age groups and the mediation effect of CVD risk among Chinese adults.

Methods: A total of 7533 participants from the China Health and Nutrition Survey (CHNS) cohort were included in this study. CKD was defined as eGFR <60 mL/min/1.73m^2. Framingham risk score (FRS) was used to assess CVD risk. The interaction, joint association of CVD risk and CKD on mortality, and subsequent mediation effect were evaluated using multivariable Cox regression.

Results: CHNS cohort recorded 266 deaths over a mean follow-up time of 5.04 years. The all-mortality rates among adults with CKD and high CVD risk were significantly higher than healthy controls (22.48 and 21.30 per 1000 person-years). The adjusted hazard ratios (aHR) were 1.70 (95% CI 1.27-2.28) and 1.62 (95%CI 1.26-2.09), respectively. There was a negative interaction between CKD and CVD risk on mortality. The association between CKD and mortality was stronger in low+medium CVD risk group (aHR=1.87, 95% CI 1.20-2 .91). Besides, mortality hazard was highest in CKD patients with high CVD risk (aHR=3.14, 95% CI 1.92-5.14). Mediation analysis showed that CVD risk mediated 33.4% of the effect of CKD on all-cause mortality (p<0.001). After adjusting for the moderator of age, the mediation proportion was 7.2%-10.3%.

Conclusions: Comprehensive strategies including lifestyle modifications, diet restrictions, and cardio-nephrology multidisciplinary treatment for mitigating CVD risk in CKD patients should focus on middle-aged people and early disease detection.

Funding: Government Support - Non-U.S.

SA-PO524

Constipation and Risk of Death and Cardiovascular Events in Hemodialysis Patients

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Background: Constipation is common in dialysis patients and primary care. Recent studies have disclosed its independent associations with the increased risk of mortality or cardiovascular disease in the general population. In this study, we aimed to investigate the association of constipation with clinical outcomes using a large cohort of hemodialysis (HD) patients in Korea.

Methods: This retrospective, population-based cohort study used HD quality assessment data from the Korean Health Insurance Review and Assessment (HIRA) during the period between January 2015 and June 2021. Public medical insurance registration is mandatory in Korea, and HIRA is an independent agency that reviews and assesses healthcare benefit costs. Constipation was defined as the number of total prescribed laxatives of ≥ 180 during the baseline one year period. The primary endpoint was evaluated as the development of all-cause mortality and cardiovascular events including myocardial infarction (MI) and stroke. Each event was identified as the relevant International Classification of Disease (ICD)-10 diagnosis as the major diagnostic code and procedural codes for the health insurance claims.

Results: A total of 35,230 patients over the age of 19 years old were included in the study, and the mean follow-up period was 54.2 month. Overall, 25.9% of HD patients were identified as having constipation, which seemed to be higher than the reported 15-20% in the general population. The most frequently used laxatives were lactulose/lactitol. In Cox proportional hazard model, constipation was associated with increased all-cause mortality (hazard ratio [HR], 1.16; 95% confidence interval [CI], 1.09–1.23) and ischemic stroke (HR, 1.16; 95% CI, 1.0.–1.32) after multivariable adjustment for demographics, prevalent comorbidities, and medications. Constipation was not significantly associated with MI and hemorrhagic stroke after multivariable adjustments although the crude cumulative incidence of each was higher in patients with constipation.

Conclusions: Constipation was associated with higher risk of all-cause mortality and incident ischemic stroke independently of known cardiovascular risk factors in prevalent HD patients. Further studies are needed to determine whether constipation serve as one of the indicators of poor health or is a possible causal factor to cardiovascular disease.

SA-PO525

The Role of Blood Pressure Load in Ambulatory Blood Pressure Monitoring in Adults: A Review of Current Evidence

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Background: In the field of ambulatory blood pressure monitoring (ABPM), the concept of the blood pressure load (BPL), defined as the percentage of readings above a certain threshold, has been in general use since the 1990s. However, the benefits of using this index in adults have not been clearly demonstrated, and accordingly it has not been integrated into the major blood pressure diagnosis and treatment guidelines. In this manuscript, we present the first comprehensive review of the current evidence regarding the possible associations of BPL with target organ damage and clinical outcomes, the major determinants for its role and utility in blood pressure measurement. We put a particular emphasis on studies exploring whether BPL has added benefit to the mean blood pressure indices.

Methods: Our review is based on a search of PubMed for all articles containing the combination of the MeSH term "Blood Pressure Monitoring, Ambulatory" and "blood pressure load" or "BP load", last performed on April 13th, 2023. We also scanned the references from articles found on the PubMed search. We included all the articles for which we could find full text in English examining the associations of BPL as defined above with clinical outcomes or organ damage.

Results: While a couple dozen studies aimed to assess the association of the blood pressure load with target organ damage, the cumulative sample size is small. Almost all of the studies are retrospective, and none are interventional. Though the associations of the BPL with various measures of target organ damage are evident, the available literature fails to demonstrate a clear and consistent added value for the BPL over the mean blood pressure indices.

Conclusions: The BPL has been a part of the ABPM report for more than 3 decades worldwide, yet we have found no previous paper reviewing the evidence for its use. Based on our analysis, we summarize that while the associations of BPL with target organ damage are clear, it is inconclusive whether the addition of BPL to the mean blood pressure indices has any advantage. There is a clear need for further research in this field, including large-scale prospective trials with long-term follow-up to elucidate the possible benefits of incorporating BPL into clinical practice.

SA-PO526

Why We Treat Asymptomatic Blood Pressure Elevations in the Hospital

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Background: In the hospital, asymptomatic blood pressure elevations (ABPE) are often treated with Pro Re Nata blood pressure medications (PRNBP). There is no evidence to support this practice, and recent literature suggests it may be harmful. Provider and nursing rationale and motivations for treating ABPE are not well understood.

Methods: We recruited clinical providers and nurses from inpatient non-ICU settings for 1 on 1 semi-structured interviews. Based on the Theoretical Domain Framework Interviews were coded in a rolling fashion by a multidisciplinary group until theme saturation was achieved.

Results: We interviewed 10 providers (years in role): 5 internal medicine/hospitalist physicians (10-22), 1 midlevel provider (8), 4 housestaff (2-7); and 6 nurses (1.7-4 years). Definitions for HTN "emergency" vs "urgency" varied within each group with respect to threshold for definition and for treatment. Providers and nurses felt that treatment varied by patient factors and nursing experience or stress level, while nurses felt there was variability by provider. All noted hospital factors that could affect BP including pain, stress, measurement technique, diet, substance abuse, and missed medications. Most providers felt that using PRNBP would lead to more harm than good, though some noted benefit to titrate scheduled medications, quick nursing response and less calls to doctor. Some providers feared being viewed as negligent by nursing or patients if they did not treat. Factors related to rapid response thresholds and need for MD to push IV medications at the bedside also influence provider and nursing actions. Nurses cited goal of keeping vitals in the normal range using PRNBP. Some providers felt guidelines needed regarding thresholds for treatment of inpatient ABPE. For buy in from providers, education of providers and nursing regarding new literature to support guidelines would be helpful to change practice. A few providers stated that adding alerts in the medical record or penalties to change practice is not desirable while another said alerts would be helpful. Nurses did not feel a need for any change to practice save to make PRNBP more accessible in the computer system.

Conclusions: Education of providers, nursing and patients regarding goals for ABPE with an algorithm for an approach to management may be helpful to optimize treatment of ABPE in the hospital.

Funding: Veterans Affairs Support

SA-PO527

Health Care Utilizations and Costs in the Year Following an Incident Major Thrombotic Cardiovascular Event (MTCVE) in Patients with and Without ESKD

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Background: Patients with end-stage kidney disease (ESKD) are at higheran elevated risk of major thrombotic cardiovascular events (MTCVEs) and use moresubstantial healthcare resources than compared to patients without ESKD. There is limited information on costs following MTCVEs in patients with ESKD.

Methods: Cohorts of Medicare fee-for-service beneficiaries aged ≥66 years were created using data from the US Renal Data System (USRDS) for ESKD patients receiving in-center hemodialysis (HD) and a 20% sample of Medicare claims for non-ESKD patients. We included patients experiencing a new MTCVE (myocardial infarction, ischemic stroke, venous thromboembolism, or critical limb ischemia) between 2015-2018. Adjusted all-cause healthcare resource utilization (HCRU) and cost outcomes were assessed for 1 year following the index event.

Results: Table 1 and Figure 1 detail HCRU and costs, respectively, in the year following each type of MTCVE. Patients with ESKD had much higher rates of all-cause hospitalization than non-ESKD patients, with the largest magnitude of difference in patients with VTE. Rates of ICU admissions, inpatient days, emergency and outpatient encounters were significantly higher in ESKD patients even after demographic adjustment. Adjusted costs of care were higher in ESKD patients compared with non-ESKD patients across all encounter and MTCVE types, with some variation in costs attributable to specific encounter types.

Conclusions: In the year after an incident MTCVE, patients with ESKD had significantly higher all-cause HCRU and costs of care than non-ESKD patients who experienced the same type of MTCVE. These differences persisted even after adjustment.

Funding: Commercial Support - Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Rahway, NJ, USA

Figure 1. Per person per year healthcare costs in the year following an incident MTCVE in patients with and without ESKD, by event type and cost category (2019 USD, in hundreds)

SA-PO528

Evaluation of Plasma Sphingolipids as Mediators of the Relationship Between Kidney Diseases and Cardiovascular Events

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Background: Patients with chronic kidney disease (CKD) are at higher risk for cardiovascular events. Sphingolipids are a family of circulating lipids with regulatory and signaling roles that are strongly associated with both eGFR and cardiovascular disease. We examined whether circulating sphingolipids partially mediate the associations between eGFR and cardiovascular events.

Methods: We measured the circulating concentrations of 4 ceramides and 4 sphingomyelins with the fatty acids 16:0, 20:0, 22:0, and 24:0, in plasma from 3,463 participants in the Cardiovascular Health Study without prevalent cardiovascular disease. We tested the adjusted mediation effects by these sphingolipids of the associations between eGFR and incident cardiovascular disease via quasi-Bayesian Monte Carlo method with 2,000 draws, using a Bonferroni-corrected p value for significance of 0.00625.

Results: The mean (±SD) eGFR was 70 (±16) mL/min/1.73 m², and the mean age was 76 (±5) years. Lower eGFR was associated with higher plasma ceramide and sphingomyelin 16:0, and lower ceramides and sphingomyelins 20:0 and 22:0. Lower eGFR was associated with risk of incident heart failure and ischemic stroke, but not myocardial infarction. Five of eight sphingolipids partially mediated the association between eGFR and heart failure. The strongest mediators were ceramide-16:0 (proportion mediated 14%, 95% CI 8-23%) and sphingomyelin-16:0 (proportion mediated 10%, 95% CI 5-17%). No sphingolipids significantly mediated the association between eGFR and ischemic stroke (**Table**).

Conclusions: Plasma sphingolipids partially mediated the association between lower eGFR and incident heart failure. Altered sphingolipids metabolism may contribute to heart failure in patients with CKD.

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Table: Mediation by individual sphingolipids of the associations between eGFR and cardiovascular outcomes using a quasi-Bayesian Monte Carlo method with 2,000 draws

Sphingolipid	Heart failure		Ischemic Stroke	
	Proportion mediated (95% CI)	p-value	Proportion mediated (95% CI)	p-value
Ceramide-16:0	**0.14 (0.08, 0.23)**	**<0.001**	-0.05 (-0.15, 0.00)	0.04
Ceramide-20:0	0.04 (0.01, 0.09)	0.02	0.03 (-0.12, 0.28)	0.54
Ceramide-22:0	**0.04 (0.01, 0.09)**	**<0.001**	0.01 (-0.09, 0.17)	0.58
Ceramide-24:0	0.02 (0.00, 0.05)	0.07	0.01 (-0.05, 0.11)	0.57
Sphingomyelin-16:0	**0.10 (0.05, 0.17)**	**<0.001**	0.00 (-0.17, 0.18)	0.96
Sphingomyelin-20:0	**0.04 (0.01, 0.08)**	**0.002**	0.00 (-0.10, 0.11)	0.95
Sphingomyelin-22:0	**0.07 (0.03, 0.13)**	**<0.001**	0.02 (-0.10, 0.24)	0.55
Sphingomyelin-24:0	0.03 (0.01, 0.07)	0.01	0.01 (-0.06, 0.11)	0.67

BOLD FONT indicates significance at the Bonferroni-adjusted p-value < 0.00625
Proportional effect is the percentage of the association between eGFR and the cardiovascular outcome that is mediated by the sphingolipid of interest.
Adjusted for age, sex, clinical location, smoking, BMI, alcohol use, LDL-C, HDL-C, triglycerides, SBP, diabetes, prior TIA, and use of fibrates, statins, and antihypertensive medications. Additionally, ceramide 16:0 was adjusted for ceramide 22:0, sphingomyelin 16:0 was adjusted for sphingomyelin 22:0, ceramides 20:0-24:0 were adjusted for ceramide 16:0, and sphingomyelins 20:0-24:0 were adjusted for sphingomyelin 16:0

SA-PO529

Plasma Uromodulin and Cardiovascular Outcomes in Adults with Hypertension and CKD

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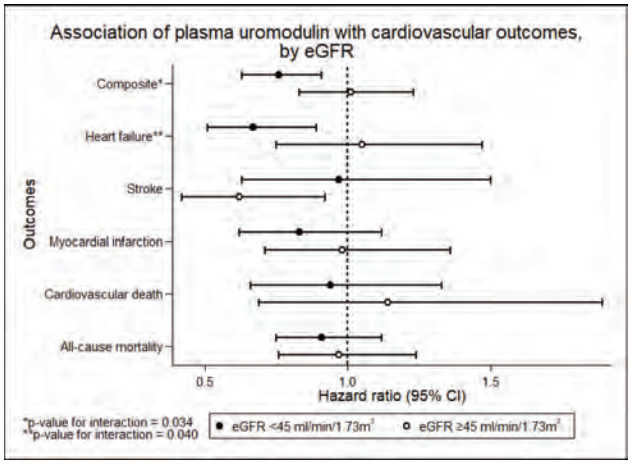
Background: Uromodulin (UMOD) is an emerging kidney tubule biomarker that may improve identification of persons at elevated cardiovascular (CV) risk beyond conventional markers. We evaluated the association of plasma UMOD with CV outcomes in CKD.

Methods: This was a secondary analysis of the Systolic Blood Pressure Intervention Trial (SPRINT), in which an intensive systolic blood pressure (SBP) target reduced risk of CV events and mortality. We measured plasma UMOD at baseline in participants with eGFR <60 ml/min/1.73 m² (N = 2302) and evaluated its association with a composite primary outcome of nonfatal myocardial infarction (MI), acute coronary syndrome without MI, acute decompensated heart failure (HF), stroke or CV death. Hazard ratios (HR) were estimated using Cox proportional hazards models adjusted for demographic and clinical variables, including eGFR and albuminuria.

Results: Median follow-up was 3.9 years, mean eGFR was 46 (IQR: 36–55) mL/min/1.73 m² and median plasma UMOD was 17.2 (IQR: 12.3–23.2) ng/ml. In the lowest UMOD quartile, 105 out of 575 (18.3%) experienced the primary outcome compared to 57 out of 575 (9.9%) in the highest. After multivariable adjustment, higher UMOD was not significantly associated with the primary outcome in the overall cohort. Of the component outcomes, each SD higher UMOD was associated with 30% lower risk of stroke (HR 95%CI: 0.51–0.95, p <.01) only. The association of UMOD with the primary and HF outcomes differed by eGFR (p for each interaction <.05) (Figure). Each SD higher UMOD was associated with 24% lower risk of the primary outcome (HR 95%CI: 0.63–0.91) and 33% lower risk of HF (HR 95%CI: 0.51–0.89) in those with eGFR <45 ml/min/1.73 m² (p <.01 for both), but not among those with eGFR ≥45 ml/min/1.73 m².

Conclusions: Higher plasma UMOD in hypertensive persons with CKD is associated with lower risk of stroke and, among those with lower eGFR, lower risk of CV and HF events.

Funding: NIDDK Support



SA-PO530

Association of Serum Magnesium with Atrial Fibrillation in Patients Requiring Peritoneal Dialysis

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Background: It has been known that morbidity of atrial fibrillation (AF) in chronic kidney disease is higher than in general population. Age, obesity, diabetes mellitus (DM), and cardiovascular disease, these are thought to be one of the risk factors of AF. Hypomagnesemia is also potential risk factor of AF in hemodialysis patients, while it has not been studied in peritoneal dialysis (PD) patients. Hence, we examined association between of serum magnesium (sMg, mg/dL) with AF.

Methods: A nation-wide, cross-sectional study was performed by using data from Japanese Renal Data Registry, which encompasses a nationwide population dialysis centers, corrected at the end of 2019. The inclusion criteria were as follows: only PD patients, aged≥20. The exclusion criteria were as follows: missing data for Mg and history of AF. Among 332599 dialysis patients, 2366 PD patients were enrolled into this study finally. They were divided three groups according to the lower and upper level of sMg general reference value of 1.8 and 2.6, named low-, normal-, and high-sMg group respectively. Odds ratio (OR) for AF was calculated in each group compared with normal-sMg group by logistic regression analysis. AF was diagnosed by rest 12-leads electrocardiogram.

Results: Mean age was 63±13 years, 65.1% of them were male, 47.8% had DM. Mean sMg level was 2.14±0.58, and 4.3% had AF. In unadjusted model, the odds for AF was significantly increasing in low-sMg group compared with normal-sMg group (OR 2.23, p=0.0003), while high-sMg group did not show significant increment or decrement of OR for AF. After adjusting of confounding variables of age, sex, DM, and current smoker, same trend had seen between low and norml sMg groups.

Conclusions: Hypomagnesemia was closely associated with AF in PD patients. Preventing hypomagnesemia may reduce the incidence of AF in PD patients. We may need to monitor the sMg level regularly and pay attention more to hypomagnesemia to prevent AF in PD patients.

Odds ratio for AF in three groups divided by sMg

	Model 1			Model 2			Model 3		
	OR	95%CI	p	OR	95%CI	p	OR	95%CI	p
Mg, mg/dL									
1.8<	2.23	1.44-3.46	0.0003	2.12	1.36-3.30	0.0008	2.05	1.30-3.22	0.0018
1.8-2.6	1			1			1		
2.6<	0.93	0.47-1.85	0.85	0.99	0.49-1.96	0.98	0.97	0.47-2.00	0.94

Adjusted factor: Model 1; unadjusted. Model 2; age, sex. Model 3; age, sex, diabetes mellitus, current smoker

SA-PO531

Biomarkers of Kidney Tubule Health and Retinal Microvascular Signs: The Multi-Ethnic Study of Atherosclerosis

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Background: Both the retina and kidney can be damaged by microvascular disease. Here, we examined the association between biomarkers for kidney tubule health and retinal microvascular signs in persons who participated in The Multi-Ethnic Study of Atherosclerosis (MESA).

Methods: Among 470 MESA participants, we measured 6 plasma biomarkers of kidney tubule health: KIM-1, MCP-1, SuPAR, TNFR 1 and 2, and YKL-40 and 6 urinary biomarkers of kidney tubule health: A-1MG, EGF, IL-18, KIM-1, MCP-1, and YKL-40. Retinal microvascular measurements were assessed from fundus photography: central retinal arteriolar and venular equivalents (CRAE and CRVE, respectively). We used multivariable linear regression models to test the associations between kidney tubule health markers and CRAE and CRVE. Final model was adjusted for age, race, gender, BMI, hypertension, LDL, HDL, smoking, urine albumin, urine creatinine and eGFR.

Results: Mean age was 60±10 years and mean eGFR was 92±13ml/min/1.73m². The prevalence of HTN and current smoking was 36% and 14%, respectively. The mean CRAE and CRVE was 144±14 μm and 214±21 μm, respectively. In adjusted continuous models, each 1 SD higher plasma KIM-1, and urine KIM-1 concentrations were individually associated with narrower CRAE. Each 1 SD higher plasma SuPAR concentrations were individually associated with wider CRAE and CRVE (Figure). There was no significant association between remaining biomarkers and CRAE and CRVE.

Conclusions: In this study of community-living individuals without CKD, diabetes, or CVD, selected kidney tubule health markers are associated with subtle retinal microvascular changes. These findings suggest that microvascular disease may impact the kidney tubules, above and beyond the glomerulus.

Table: Association of plasma and urine biomarkers with retinal microvascular changes among MESA participants.

CRAE (n=470)	Unadjusted β, 95% CI	Fully Adjusted β, 95% CI
pKIM1 (pg/ml)	-6.94 (-11.60, -2.29)*	-5.14 (-9.84, -0.45)*
pMCP1 (pg/ml)	-2.52 (-10.94, 5.89)	0.28 (-8.01, 8.56)
pTNFR1 (pg/ml)	-3.39 (-10.76, 3.98)	1.80 (-5.69, 9.29)
pTNFR2 (pg/ml)	-9.53 (-18.69, -0.37)*	-5.90 (-15.01, 3.20)
pSUPAR (pg/ml)	6.99 (-1.22, 15.26)	9.15 (0.89, 17.40)*
pYKL40 (pg/ml)	-3.62 (-7.71, 0.47)	0.09 (-4.34, 4.53)
uKIM-1 (pg/ml)	-3.63 (-7.02, -0.25)*	-5.68 (-10.15, -1.22)#
uMCP-1 (pg/ml)	-2.21 (-5.68, 1.26)	-0.51 (-3.94, 2.93)
uEGF (pg/ml)	3.016 (-1.80, 7.83)	0.49 (-4.31, 5.28)
uYKL-40 (pg/ml)	-1.63 (-4.70, 1.44)	-1.52 (-4.55, 1.52)
uA1M (mg/l)	-6.96 (-12.95, -0.97)*	-3.26 (-9.32, 2.80)
uMOD (ng/ml)	1.43 (-2.55, 5.40)	0.19 (-3.74, 4.12)
CRVE (n=470)	**Unadjusted β, 95% CI**	**Fully Adjusted β, 95% CI**
pKIM1 (pg/ml)	-2.32 (-9.25, 4.62)	2.30 (-4.65, 9.25)
pMCP1 (pg/ml)	9.72 (-2.68, 22.12)	9.24 (-3.01, 21.49)
pTNFR1 (pg/ml)	-0.13 (-11.02, 10.77)	5.58 (-5.56, 16.73)
pTNFR2 (pg/ml)	-5.38 (-18.90, 8.20)	-5.41 (-18.67, 7.85)
pSUPAR (pg/ml)	19.52 (7.39, 31.65)#	21.49 (9.39, 33.59)##
pYKL40 (pg/ml)	-3.25 (-9.30, 2.81)	-2.40 (-8.30, 3.50)
uKIM-1 (pg/ml)	0.99 (-4.03, 6.02)	-0.02 (-5.03, 4.99)
uMCP-1 (pg/ml)	4.58 (-0.53, 9.70)	2.78 (-2.39, 7.95)
uEGF (pg/ml)	7.48 (0.39, 14.57)	4.59 (-2.41, 11.59)
uYKL-40 (pg/ml)	1.83 (-2.69, 6.36)	1.90 (-2.59, 6.39)
uA1M (mg/l)	-1.01 (-9.91, 7.88)	-6.15 (-15.01, 2.71)
uMOD (ng/ml)	4.04 (-1.82, 9.90)	3.06 (-2.63, 8.74)

*P <0.05, #P<0.01, ##P<0.001. Biomarkers were log transformed. The table showed β of CRAE and CRVE per 1 SD change in biomarkers level. Unadjusted = biomarker alone, Fully Adjusted: adjusted for unadjusted + age, race, gender, BMI, HTN, LDL, HDL, smoking, urine albumin, urine creatinine, eGFR. CRAE: central retinal artery equivalent, CRVE: Central retinal vein equivalent.

SA-PO532

Subclinical Primary Aldosteronism and eGFR Decline

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Background: Primary aldosteronism (PA), characterized by renin-independent aldosterone secretion, is the most common and modifiable form of secondary hypertension. Overt PA predisposes to disproportionately high rates of cardiovascular and kidney disease, independent of blood pressure (BP). Growing evidence suggests that milder forms of renin-independent aldosteronism (ie, Subclinical PA) are highly prevalent yet their clinical significance remains uncertain.

Methods: Prospective study of 536 participants aged 40-69 yr and on no BP medications from the randomly sampled, population-based CARTaGENE cohort (Canada). Using aldosterone and renin levels from enrollment, we employed multivariable linear regression models to measure the association between the aldosterone-renin ratio (ARR) and eGFR (via the 2021 CKD-EPI$_{Cr/CysC}$ equation) measured at enrollment and after 5-7 years of follow-up.

Results: The mean (SD) age, eGFR, and systolic BP were 55 (7) years, 107 (13) mL/min/1.73m^2, and 132 (11) mmHg, respectively. Higher ARR was successively associated with steeper annual eGFR decline with ARR Tertile 3 having a 74% steeper decline than ARR Tertile 1 (1.18 vs. 0.68 mL/min/1.73m^2/yr, P=0.01; **Fig. 1**). On multivariable linear regression, higher ARR was associated with steeper annual eGFR decline (P=0.03; **Fig. 2**).

Conclusions: In a randomly sampled, population-based cohort of individuals on no antihypertensive medication, Subclinical PA was associated with steeper eGFR decline, independent of BP. Subclinical PA may serve as a potentially modifiable risk factor to prevent or slow CKD.

FIGURE 1: ANNUAL EGFR DECLINE BY ARR TERTILE

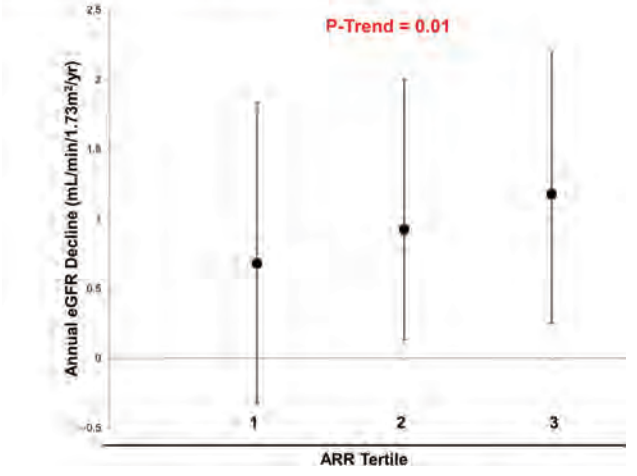
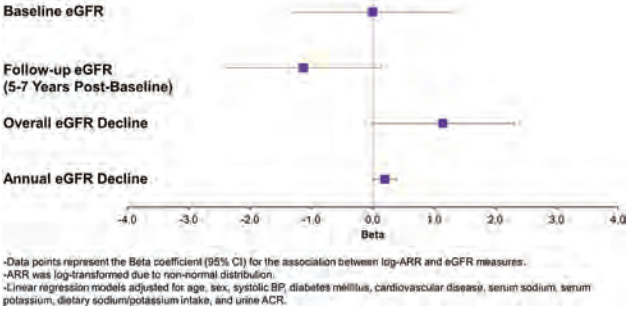


FIGURE 2: ARR AND eGFR ASSOCIATIONS



-Data points represent the Beta coefficient (95% CI) for the association between log-ARR and eGFR measures.
-ARR was log-transformed due to non-normal distribution.
-Linear regression models adjusted for age, sex, systolic BP, diabetes mellitus, cardiovascular disease, serum sodium, serum potassium, dietary sodium/potassium intake, and urine ACR.

SA-PO533

Abstract Withdrawn

SA-PO534

Galectin-3 and Mortality in Relation to Vascular Calcification in Incident Hemodialysis Patients

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Background: Vascular calcification is a recognized risk factor for mortality in hemodialysis patients. Galectin-3 (Gal-3), a key regulator of fibrosis, inflammation, and cell proliferation, has been implicated in adverse outcomes in several pathological conditions such as heart failure and chronic kidney disease. The study aims to determine whether elevated Gal-3 levels may affect vascular calcification and how these effects may contribute to mortality risk in hemodialysis patients.

Methods: Serum Gal-3 was measured in patients from the incident hemodialysis cohort (n=477, age 68.5 ± 12.6 years) and the cut-off value for predicting mortality was estimated by area under the receiver operating characteristic (ROC) curve (AUC). The extent of aortic arch calcification (AAC) was assessed by chest X-ray. We performed a causal mediation analysis to investigate the effect of Gal-3 on mortality via vascular calcification. Mortality data were obtained with a median follow-up of 42 months.

Results: Serum Gal-3 levels were closely associated with age (r=0.131, p=0.004), coronary artery disease history (r=0.117, p=0.010), brain natriuretic peptide levels (r=0.154, p=0.004), high-density lipoprotein (HDL) cholesterol (r=-0.176, p=0.001), high-sensitivity C-reactive protein (hs-CRP) (r=0.183, p=0.002), and AAC score (r=0.249, p<0.001). At a cut-off level of 37.0 ng/mL, the AUC for predicting mortality was 0.718 with sensitivity and specificity of 60.2% and 74.7%, respectively. Multivariate Cox regression analysis showed that higher Gal-3 levels increased all-cause mortality by 2.2-fold (95% confidence interval [CI] 1.38-3.45, p=0.001). The results of the mediation analysis suggested that this association was partially mediated by vascular calcification. Both the indirect effect between Gal-3 and mortality through vascular calcification (β=0.0068, bootstrapped 95% CI 0.0020-0.0138) and the direct effect of the Gal-3 on mortality (β=0.0370, bootstrapped 95% CI 0.0205-0.0594) were significant.

Conclusions: This study suggests a possible mechanism linking serum Gal-3 and increased mortality in hemodialysis patients, providing evidence for a significant role of Gal-3 in vascular calcification.

SA-PO535

Dialysis Transition in Patients with and Without Heart Failure in a CKD Population

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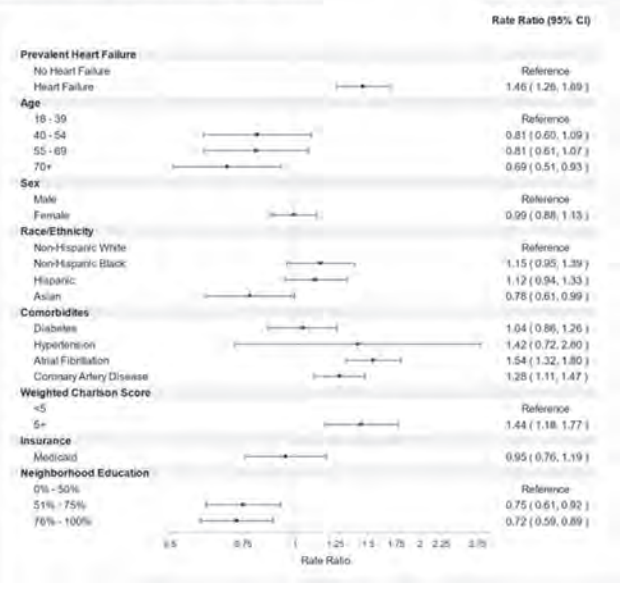
Background: CKD and heart failure (HF) frequently coexist and are associated with worsened outcomes. We sought to compare CKD patients with and without HF who transitioned to dialysis.

Methods: Retrospective study between Jan 2007 and Dec 2018 among incident CKD adult patients who initiated dialysis within Kaiser Permanente. Incident CKD identified as≥2 consecutive eGFR≤45 at least 90 days apart with one prior eGFR≥60. Prevalent HF determined by ICD coding for HF. Dialysis setting (inpatient vs outpatient) and dialysis access (among HD) at initiation were determined for patients with vs without HF. Multivariable logistic regression used to estimate odds ratios (OR) and 95% Cl for inpatient dialysis initiation and catheter use.

Results: 6,812 CKD patients initiated dialysis. 2,498 had HF [71% preserved EF (HFpEF), 20% reduced EF (HFrEF), and 9% unknown EF]. Inpatient dialysis start occurred in 18.5% with HF vs 9.6% without HF. Catheter use at dialysis start occurred in 58.5% with HF vs 51.9% without HF. Inpatient dialysis start OR (95% Cl) were 1.73 (1.30, 2.29), 1.42 (1.22, 1.66), and 1.45 (1.17, 1.79) for HF unknown EF, HFpEF, and HFrEF compared to no HF. Inpatient dialysis start OR were 1.46 (1,26, 1.69), 0.69 (0.51, 0.93), 0.99 (0.88, 1.13), 1.54 (1.32, 1.80), 1.28 (1.11, 1.47), 1.44 (1.18, 1.77), and 0.72 (0.59, 0.89) for HF vs no HF, age>70, female, AFib, CAD, Charlson score>5, and education level 76-100%, respectively. Catheter start OR were 1.04 (0.99, 1.10), 0.85 (0.76, 0.95), 1.04 (0.99, 1.10), 1.21 (1.14, 1.29), 0.98 (0.93, 1.04), 1.20 (1.12, 1.29), and 0.86 (0.79, 0.93) for HF vs no HF, age>70, female, Afib, CAD, Charlson score>5, and education level 76-100%.

Conclusions: HF patients were more likely to start dialysis inpatient. HFrEF was associated with inpatient and catheter at dialysis start. Our findings question whether CKD patients with HF may benefit from earlier and differential dialysis transition strategies.

Forest plot of rate ratios for inpatient dialysis initiation among incident CKD patients (N = 6,812)



SA-PO536

Association of Antihypertensive Medications with Cardiovascular (CV) Outcomes in Patients with CKD

L Parker Gregg,[1,2] Aaron R. Perkins,[3] Hui Yang,[3] Vijay Nambi,[1,2] Susan Hedayati,[4] Sankar D. Navaneethan,[1,2] Carlos A. Alvarez.[3,4] *[1]Baylor College of Medicine, Houston, TX; [2]Michael E DeBakey VA Medical Center, Houston, TX; [3]Texas Tech University Health Sciences Center School of Pharmacy - Dallas, Dallas, TX; [4]The University of Texas Southwestern Medical Center, Dallas, TX.*

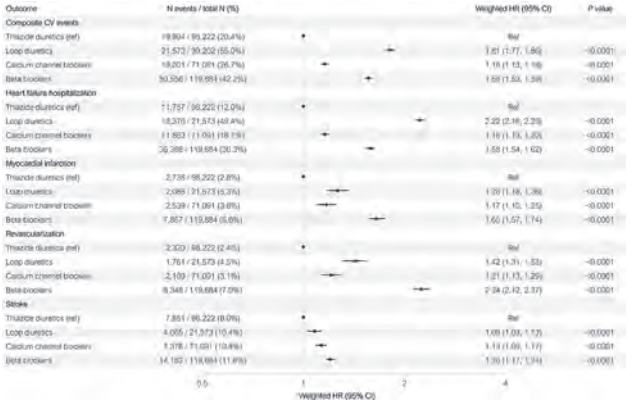
Background: Angiotensin converting enzyme inhibitors (ACEi) and receptor blockers (ARB) are first line for hypertension in patients with CKD. Whether the second agent prescribed is associated with CV events is less clearly established.

Methods: Using the Veterans Affairs Corporate Data Warehouse, we identified veterans with CKD stages 1-5 based on estimated glomerular filtration rate and albuminuria from 1/1/2010 to 12/31/2016. We selected individuals prescribed an ACEi/ARB as monotherapy for hypertension at or prior to the time of prescription of a second antihypertensive agent (*index date*), grouped by thiazide diuretics (TD), loop diuretics (LD), calcium channel blockers (CCB), and beta blockers (BB). The primary outcome was the composite of hospitalization for heart failure or fatal or non-fatal myocardial infarction or stroke, or revascularization. Inverse probability of treatment weights (IPTW) were generated using generalized boosted methods, and Cox proportional hazards regression assessed associations between medications and CV events.

Results: Of the 328,399 participants, 98,222 (30%) were prescribed TD, 39,202 (12%) LD, 71,091 (22%) CCB, and 119,884 (36%) BB. The mean age was 71 years, 97% were men, 72% were White, and 18% were Black. Compared to the other groups, TD users were younger, more likely to be female, and less likely to have CKD stages 4 or 5. Heart failure was more common among users of LD (36%) and BB (18%) compared to TD (3%). Weighted standardized differences demonstrated that characteristics were balanced between groups after IPTW. There were 111,124 composite CV events. Compared to TD, increased hazard of CV events was seen for LD, CCB, and BB users (**Figure**).

Conclusions: Although residual indication bias cannot be excluded, these data suggest that there may be an increased risk of CV events with LD, CCB, and BB compared to TD in those with CKD. Examination of the reasons to initiate these agents is warranted.

Funding: Veterans Affairs Support



SA-PO537

Kidney Function Predicts New-Onset Cardiorenal Events and Mortality in Primary Aldosteronism: Approach of the 2021 Race-Free eGFR Equation

Chun-Fu Lai, Yen-Hung Lin, Vincent Wu. Taiwan Primary Aldosteronism Investigation (TAIPAI) Study Group. *National Taiwan University Hospital, Taipei, Taiwan.*

Background: Individuals with primary aldosteronism (PA) exhibit glomerular hyperfiltration, which may conceal underlying kidney damage. We aimed to investigate whether baseline estimated glomerular filtration rate (eGFR) is associated with cardiovascular outcomes in this population.

Methods: This observational cohort study enrolled 760 coronary artery disease-naïve patients diagnosed with PA between January 1, 2007 and December 31, 2018 (male, 45%; mean age, 52.3 ± 11.9 years). The baseline eGFR was calculated using the 2021 Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which includes serum creatinine and cystatin C but omits the race variable. Outcomes were composite cardiovascular events (total death, non-fatal myocardial infarction, and coronary revascularization procedure), all-cause mortality, and adverse kidney events.

Results: During a mean follow-up of 5.8 ± 3.2 years, new-onset composite cardiovascular events occurred in 47 patients, with a crude incidence rate of 10.9 per 1,000 person-years. Multivariable Cox proportional hazards analysis showed that baseline eGFR was independently associated with composite cardiovascular events (hazard ratio [HR], 0.98 [95% CI, 0.97–0.99]). Penalized splines smoothing in multivariable regression analysis demonstrated that the risk of composite cardiovascular events increased negatively and linearly when patients had a baseline eGFR less than 85 mL/min/1.73m^2. Patients with baseline eGFR <85 mL/min/1.73m^2 were independently associated with higher risks of composite cardiovascular events (HR, 2.39 [95% CI, 1.16–4.93]), mortality (HR, 4.63 [95% CI, 1.59–13.46]), and adverse kidney events (sub-distribution HR, 5.96 [95% CI, 3.69–9.62], with mortality as a competing risk). (Figure 1A-C)

Conclusions: Our data support interpreting baseline eGFR as a predictor for new-onset adverse cardiorenal events and emphasizes the importance of the early detection of kidney function impairment in hypertensive patients with PA. We also firstly point to the validity of the 2021 race-free CKD-EPI equation in patents with PA.

Funding: Government Support - Non-U.S.

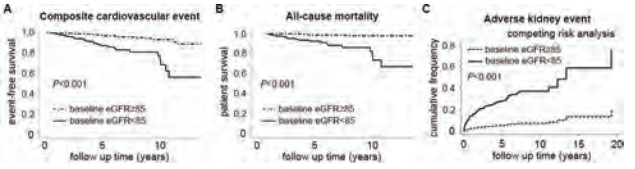


Figure 1. Clinical outcomes of interest in patients stratified by the baseline kidney function.

SA-PO538

Blood Pressure Is Not Controlled to <130/80 mm Hg in Majority of Veterans with High Atherosclerotic Cardiovascular Disease (ASCVD) Risk

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Background: Blood pressure (BP) control remains the most effective intervention to prevent cardiovascular disease (CVD). The American College of Cardiology/American Heart Association (ACC/AHA) hypertension guideline recommends a BP goal <130/80 mmHg for adults with high CVD risk which includes individuals with existing ASCVD, diabetes mellitus (DM) or chronic kidney disease (CKD). Few studies have examined the proportion of Veterans with CVD, DM or CKD with BP controlled to <130/80 mmHg receiving care within Veterans Affairs patient aligned care teams (PACT).

Methods: Vital sign data were obtained from 98,433 Veterans aged 18 to 85 years with a hypertension diagnosis during a PACT visit within eight Veteran Integrated Service Network 12 medical centers from January 1,2019, through March 1,2020. BP control was examined by high CVD risk (age ≥ 65 years and/or CVD, DM or CKD) and by presence of CVD, DM, CKD based on ICD10 diagnosis codes, or estimated glomerular filtration rate < 60 ml/min/1.73 m^2 on two occasions based 90 days apart prior to the end of the study period. BP control was defined as a systolic BP <130 mmHg and diastolic BP <80 mmHg based on BP recorded during the last PACT clinic visit during the study period.

Results: The mean age was 68.5 years (SD 12.7) and 93% were male. Among the 89,537/98433 Veterans with high CVD risk, BP was controlled to <130/80 mmHg in 37.5% and <140/90 mmHg in 76.5%. Among subgroups, BP was controlled to <130/80 mmHg in 42.8% (5313/12,414) with CKD, 39.8% (13,484/33,880) with diabetes, 45.3% with CVD (13,402/29,584) and in 47.1% (1810/3845) with CKD, DM and CVD. In contrast, BP was controlled to <140/90 mmHg in over 75% of Veterans with CKD, DM and/or CVD. (Figure 1).

Conclusions: The majority of Veterans with high CVD risk did not have BP controlled to < 130/80 mmHg. Strategies are needed to improve BP control in Veterans with high CVD risk.

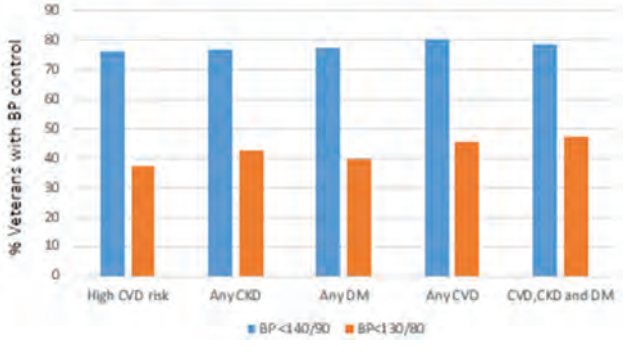

Figure 1.

SA-PO539

Association Between Birth Weight Z-Score and Blood Pressure in Young Adults

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Background: Low birth weight (BW) has been associated with increased risk of hypertension later in life. The aim of this study was to examine the association between BW weight z-score and blood pressure (BP) indices in healthy young adults.

Methods: Participants were recruited from a cohort of 970 adults aged 20-22-years who participated in a population-based study of BP in 9-10-year-old Icelandic children. All participants underwent 8 resting clinic BP measurements during two separate visits and an ambulatory BP (ABP) measurement. Birth weight and gestational age obtained from the Icelandic Birth Registry were used to calculate BW z-scores based on a standardized growth chart by Niklasson & Albertsson-Wikland. Pearson correlation coefficient and multivariable linear regression were used for analysis.

Results: Of 170 young adults who completed the follow-up study, 102 were women (60%). The mean clinic BP was 120/65 mm Hg in men and 112/66 mm Hg in women. The mean BW for men was 3625±736 g and 3646±592 g for women. A negative correlation was observed between BW z-score and both systolic and diastolic ABP (r= -0.14, p=0.026 and -0.10, p=0.20, respectively). When the sexes were analyzed separately the correlation between BW z-score and systolic ABP was statistically significant only in women (r=-0.24, p=0.014). In women the association between BW z-score and diurnal systolic ABP was significant (r=-0.26, p=0.013) while the correlation with nocturnal systolic ABP was not (r=-0.16, p=0.097). When adjusted for body mass index a significant association was detected between BW z-score and both systolic and diastolic ABP in young women (beta= -1.7, p=0.02 and beta= -1.2, p=0.01, respectively). This association was stronger for both diurnal systolic and diastolic ABP (beta= -1.8, p=0.02, and beta= -1.4, p=0.02), than for nocturnal ABP (beta= -1.4, p= 0.08, and beta= -0.79, p= 0.2). In men, BW z-score did not have a significant association with either ABP (systolic, r=-0.002 p=0.9; diastolic, r=-0.1 p=0.4) or clinic BP (systolic, r=-0.07 p=0.4; diastolic, r=-0.02 p=0.8) at follow-up.

Conclusions: Low BW z-score has a strong association with systolic ABP in young women and this relationship is stronger for diurnal systolic ABP.

SA-PO540

Prevalence of Aldosterone Breakthrough in a Cardiometabolic Clinic and Association with Albuminuria

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Background: Type 2 diabetes (T2D) and chronic kidney disease (CKD) patients have cardiovascular and renal benefits when treated with renin-angiotensin system (RAS) blockers. Some of these patients are known to exhibit a rise in aldosterone levels while on RAS blockers, called aldosterone breakthrough. The aim of our study is to assess the prevalence of aldosterone breakthrough in our clinic and its association with albuminuria.

Methods: Patients from a cardiometabolic clinic with available plasma aldosterone concentration (PAC) levels were screened. Exclusion criteria included: not taking a RAS blocker for at least 10 months, current treatment with a mineralocorticoid receptor antagonist (MRA) and an Aldosterone to renin ratio suggestive of primary hyperaldosteronism. Patients with a PAC>400pmol/L were considered to have aldosterone breakthrough.

Results: 64 patients met the inclusion criteria with 21 (33%) showing aldosterone breakthrough. Patient characteristics are shown in the Table. No significant differences in baseline characteristics were seen in patients with or without aldosterone breakthrough except for higher albuminuria in the breakthrough group. The prevalence of CKD was numerically higher in the breakthrough group. Similar trends were seen when aldosterone breakthrough was defined as a PAC level above the median of our sample.

Conclusions: Aldosterone breakthrough is prevalent in patients from a cardiometabolic clinic and is associated with higher albuminuria. Patients with aldosterone breakthrough can potentially draw more benefit when treated with an MRA.

Baseline characteristics based on the presence or absence of aldosterone breakthrough

Characteristic	Aldosterone breakthrough	No aldosterone breakthrough	p value
Age (years, median [IQR])	67 (64-77)	67 (61-75)	0.58
Sex (male, [n,%])	15 (71)	28 (65)	0.61
Hypertension (n, %)	19 (90)	37 (86)	0.62
Type 2 diabetes (n, %)	20 (95)	40 (93)	0.73
Heart Failure (n, %)	13 (62)	23 (53)	0.52
Chronic kidney disease* (n, %)	16 (76)	22 (51)	0.06
SGLT2i (n, %)	16 (76)	35 (81)	0.63
Albuminuria (mg/g, [median (IQR)])	264 (76-1118)	34 (0-1013)	0.02
PAC (pmol/L, [median (IQR)])	549 (498-839)	227 (151-291)	<0.01

*defined as eGFR<60mL/min/1.73m2

IQR - Interquartile range; PAC - Plasma aldosterone concentration; SGLT2i - sodium-glucoseco-transporter 2 inhibitors.

SA-PO541

Low-Grade Albuminuria and Cardiovascular Mortality Among Healthy Adults

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Background: Albuminuria is associated with cardiovascular events among adults with underlying cardiovascular disease and diabetes, even at low levels of urinary albumin excretion. We hypothesized that low-grade albuminuria is associated with cardiovascular death among healthy adults.

Methods: We included adults participating in the 1999-2014 National Health and Nutrition Examination Survey (N=18,696). We excluded those with urinary albumin-to-creatine ratio (UACR) >30mg/g, baseline cardiovascular disease, hypertension, diabetes, estimated glomerular filtration rate <60ml/min/1.73m^2, those who were currently pregnant, and those who had received dialysis in the last year. We assessed the relationship between log-transformed UACR and cardiovascular and all-cause mortality using multivariable Cox proportional hazards models. Models were adjusted for age, sex, race or ethnicity, survey year, BMI, insurance, smoking, A1c, systolic blood pressure, total cholesterol, serum albumin, statin use, and eGFR.

Results: Mean age was 38.1 years (standard deviation 14.0) and 53.4% were female. The median length of follow up was 12.2 years [interquartile range 8.4-16.4 years]. In adjusted models, each doubling of UACR was associated with a 34% higher risk of cardiovascular death [HR 1.34 (95% confidence interval (CI) 1.10-1.63)] and a 28% higher risk of all-cause mortality [HR 1.28 (95% CI 1.16-1.41)]. The highest tertile of UACR was associated with an 84% higher risk of cardiovascular death [HR 1.84 (95% CI 1.18-2.89)] and 59% higher risk of all-cause mortality [HR 1.59 (95% CI 1.29-1.97)], compared with the lowest tertile **(Table 1)**.

Conclusions: Higher levels of albuminuria in the "normal" range < 30 mg/g in healthy individuals nevertheless predict cardiovascular and all-cause mortality.

Funding: Other NIH Support - Research reported in this publication was supported by the National Heart, Lung, and Blood Institute of the National Institutes of Health under Award Number R38HL143584

Table 1.

	Continuous UACR		UACR Tertile 1 (0.12-4.29mg/g)	UACR Tertile 2 (4.29-7.12mg/g)	UACR Tertile 3 (7.12-29.94mg/g)
	HR (95% CI)	p-value	HR (95% CI)	HR (95% CI)	HR (95% CI)
Cardiovascular mortality					
No. of events	179		50	39	90
Unadjusted	1.80[1.33-1.91]	<0.0001	Reference	0.90[0.52-1.57]	2.75[1.89-3.99]
Model 1	1.31[1.08-1.59]	0.005	Reference	0.74[0.41-1.32]	1.79[1.17-2.74]
Model 2	1.37[1.13-1.67]	0.002	Reference	0.76[0.41-1.41]	1.90[1.27-3.06]
Model 3	1.34[1.10-1.63]	0.005	Reference	0.72[0.39-1.32]	1.84[1.18-2.89]
All-cause mortality					
No. of events	964		250	296	438
Unadjusted	1.39[1.26-1.53]	<0.0001	Reference	1.25[1.00-1.57]	1.91[1.55-2.35]
Model 1	1.26[1.15-1.38]	<0.0001	Reference	1.15[0.90-1.47]	1.54[1.25-1.91]
Model 2	1.30[1.18-1.43]	<0.0001	Reference	1.24[0.96-1.59]	1.66[1.34-2.07]
Model 3	1.28[1.16-1.41]	<0.0001	Reference	1.20[0.93-1.53]	1.59[1.29-1.97]

Model 1: adjusted for age, sex, race or ethnicity, insurance, smoking, survey year, BMI
Model 2: Model 1 + hemoglobin A1c, total cholesterol, systolic blood pressure, serum albumin, statin use
Model 3: Model 2 + eGFR

Table 1

SA-PO542

Effect of Intensive Blood Pressure Control on Kidney Outcomes: Long-Term EHR-Based Post-Trial Follow-Up of SPRINT

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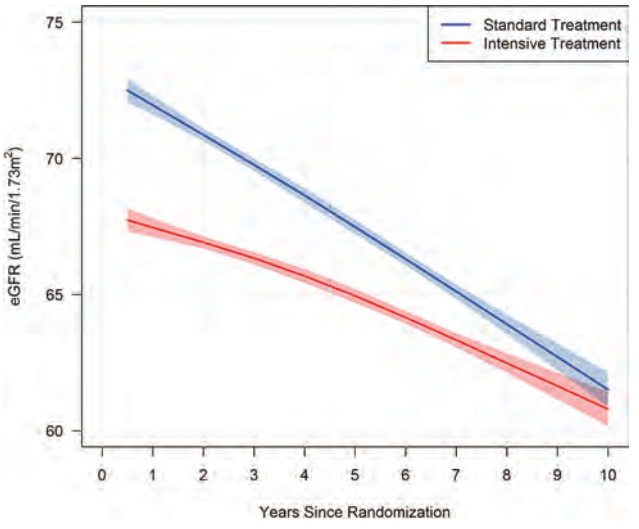
Background: Intensive blood pressure (BP) lowering in SPRINT produced acute decreases in kidney function and increased the risk of AKI. We evaluated the effect of intensive BP lowering on long-term changes in kidney function using trial data supplemented with outpatient EHR creatinine values.

Methods: SPRINT data were linked with EHR data from 49 (of 102) SPRINT study sites. The primary outcome was the slope of decline in eGFR calculated using trial and outpatient EHR values. Secondary outcomes included a ≥30% decline in eGFR to <60ml/min/1.73m^2 and a ≥50% decline in eGFR in participants with eGFR ≥60 and <60ml/min/1.73m^2 at baseline, respectively.

Results: EHR creatinine values were available for a median of 8.7 years for 3041 participants. The long-term slope of decline in eGFR was -1.09 ml/min/1.73m^2/year (95% CI -1.17 to -1.01) in the standard treatment group and -0.72 ml/min/1.73m^2/year (95% CI -0.80 to -0.64) in the intensive treatment group (P <0.001). Among participants without CKD at baseline, intensive compared to standard treatment was associated with an increased risk of a ≥30% decline in eGFR during the intervention (hazard ratio (HR) 3.29, 95% CI 2.35, 4.60), but not during the post-intervention observation phase (HR 1.09, 95% CI 0.84, 1.42). There was no significant effect of intensive treatment on eGFR decline in those with CKD at baseline. Estimates of kidney outcomes during the intervention period were similar when using SPRINT and EHR creatinine values.

Conclusions: Intensive BP lowering was associated with a lesser slope of decline in eGFR compared with standard BP lowering during long-term follow-up in SPRINT. However, there was no consistent benefit of intensive BP lowering on secondary kidney outcomes.

Funding: Other NIH Support - NHLBI



Long-term slope of eGFR including both SPRINT and EHR creatinine values starting 6 months after randomization

SA-PO543

The Impact of Chronic Fluid Overload, Water Imbalance (Tonicity), and Sodium Toxicity on Mortality of Hemodialysis Patients

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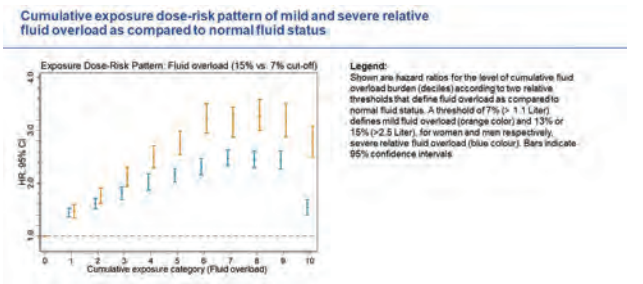
Background: Chronic fluid overload, water imbalance and plasma sodium toxicity (tonicity) contributes to high mortality in hemodialysis-dependent (HD) patients and the interplay remains unclear. In this retrospective cohort, we aimed to determine the dose-response relationship and interplay between cumulative burden of fluid overload (FO) as measured by body composition (BCM)-measurement, plasma and dialysate sodium on all-cause mortality.

Methods: Incident HD-patients with a valid BCM-measurement ≤90 days of renal replacement therapy were eligible. Cumulative exposure was quantified by counting the months spent in exposure status and categorized in deciles or quartiles. Exposure status was defined as FO, hypo and hypernatremia (<135, >145mmol/l) and dialysate sodium ≤138mmol/l. A threshold of 7% defined mild and 13% or 15%, for women and men, severe relative FO. 7% <- normal fluid status was defined as fluid depletion. Hazard Ratios (HR) for defined conditions were estimated from Cox regression frailty model and adjusted for clustering by country and clinics and potential confounding variables.

Results: 68,196 incident HD-patients from 875 clinics in 25 countries were followed-up to ten-years (2010-2020), during which 21,644 patients died. The mortality risk associated with FO increased with cumulative exposure burden, mild FO (>1.1 Liter) showed a steeper increase pattern with HR peaking at 3.28 (95%CI: 3.00 to 3.59) than clinically severe FO (>2.5 Liter) (HR peak 2.47(2.33-2.63) compared to normal fluid status (figure 1).

Conclusions: The effect of FO on mortality is large and mandates a sensitive definition to quantify the risk. The dose-response effect of FO is better assessed using the 7% cut-off definition for mild as compared to severe FO. This suggests that the use of a stricter FO definition, could lead to better control of fluid status and improved outcomes.

Funding: Commercial Support - Fresenius Medical Care, Government Support - Non-U.S.



SA-PO544

Bioelectrical Impedance Parameters as Earlier Predictors of Mortality/ Survival in Ecuadorian Hemodialysis Patients

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Background: Bioelectrical impedance analysis (BIA) is a non-invasive test to assess body composition and water distribution. Nutritional and volume disturbances are related with mortality in hemodialysis (HD) population. Few is known about BIA parameters as mortality/survival predictors. The aim of the study was to study BIA parameters as mortality/survival predictors in HD patients.

Methods: Observational-prospective-cohort study from April 2021-2023 in one HD center. BIA analysis was performed in HD patients and parameters significatively related with mortality and survival were identified. ROC curves, regression and correlation analysis were performed in BCM parameters identified.

Results: A total of 115 patients were included, 9 (7,8%) died. Phase Angle (PA) (4.64°±1.11vs3.12°±0.62;p:0.01), Lean Tissue Index (LTI) (12.41Kg/m²±3.14vs9.75Kg/m² ±2.95;p0.02), Intracellular Water (ICW) (15.26L±3.53vs13.23L±4.97;p=0.03) were related with survival. Correlation analysis found positive correlation of PA (p<0.001), LTI (p=0.02) and ICW (p= 0,03) with survival. Age (53.98y±14.75vs70.67y±7.14; p<0.001) and E/I ratio (0.97±0.14vs1.17±0.16;p<0.001) were related with mortality. Age (p=0.002) and E/I ratio (p=0,005) had positive correlation with mortality.

Conclusions: Phase Angle, Intracellular water, E/I ratio, and Lean Tissue Index of a single non-invasive BIA can be used as earlier predictors of survival and mortality in HD patients allowing premature identification and intervention in this group of patients to reduce mortality risk.

Table 1. Baseline characteristics and variables with statistical significance of studied population.

Variables studied. (N=115)	Results
Male gender (%)	56,5
Age (mean ± SD) years	55,2 ± 14,9
Body Mass Index (mean ± SD) kg/m²	25,61 ± 4,16
CKD Etiology (%)	
- Diabetes	29,6
- Others	70,4
Comorbidities (%)	
- Diabetes	26,1
- Hypertension	47,8
- Others	26,1
*HD vintage (months)	72 (36 – 108)
Deaths	9
Mortality prevalence	7,8%
° Variables with statistical significance with survival	
Variables	Cut-off (Sensitivity %, Specificity %)
Phase Angle (p<0,001)	≥ 3,26 (S:88, S: 44)
Lean Tissue Index (p 0,02)	≥ 10,35 (S:72, S:33)
Intracellular Water (p 0,02)	≥ 13,15 (S: 68, S:33)
° Variables with statistical significance with mortality	
Age (p<0,001)	≥ 64,5 (S:88, S:27)
E/I ratio (p<0,001)	≥ 0,99 (S:78, S:23)
*HD vintage values expressed in median and interquartile range (25 – 75). ° P-values obtained with student T-test in mortality and survival	

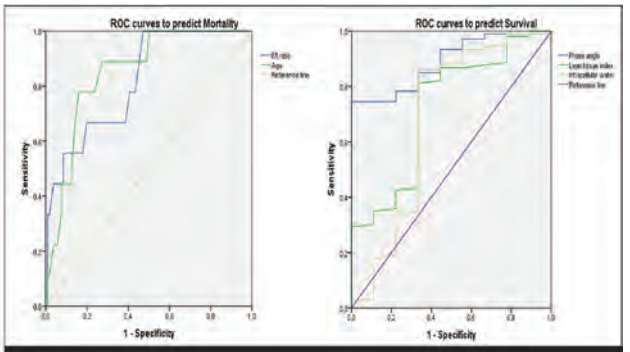

Figure A. ROC curves of BIA parameters associated with mortality and survival.

SA-PO545

Kidney Sodium MRI: Extending the Concept of Residual Kidney Function in Hemodialysis

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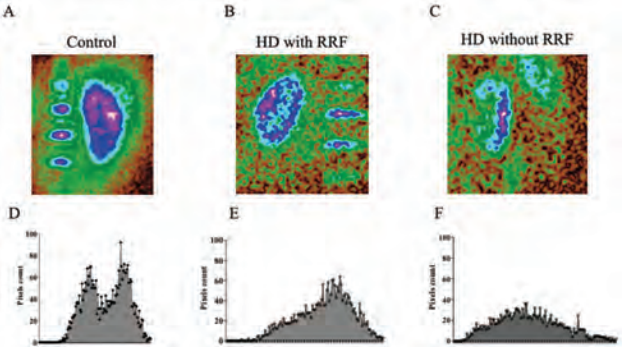
Background: It is widely recognized that persistence of even modest amount residual kidney function (RKF) is associated with improved outcomes, in hemodialysis (HD) patients. The concept of RKF, as currently utilized, is exclusively based upon urine volume and small solute clearance-requiring complete interdialytic urinary collection. This makes accurate and consistent assessment measurement challenging and difficult to implement in clinical practice. More importantly it focusses almost exclusively on glomerular function, rather than a more inclusive consideration of overall kidney function to incorporate assessment of renal tubular mass. The aim of this study was to test the feasibility of obtaining useable ^{23}Na-MRI kidney images, in the setting of dialysis dependance (as compared to normal subjects without CKD) and initially describe the associations between directly imaged medullary sodium content and other components of a more conventional approach to the definition of RKF.

Methods: We included 21 healthy volunteers and 17 HD participants, fasted for eight hours prior to their study visit. Urine samples were collected to measure urinary osmolarity, before MRI scan.

Results: Median (IQR) fasting medulla to cortex ratio was significantly higher 1.56 [1.5 – 1.61] in healthy volunteers compared to HD patients 1.22 [1.13 – 1.3], p<0.0001. Medulla to cortex ratio and median urinary osmolarity were correlated (r=0.87, p<0.0001) in the whole population. We found a significant association between HD vintage and medulla to cortex ratio whereas we did not find any association with urine volume. Sodium signal intensity distribution within healthy kidney describes two different peaks-relating to well defined cortex and medulla; whereas HD participants displays only a single peak indicative of the markedly lower sodium concentration.

Conclusions: The application of kidney sodium MRI to the study of RKF in patients receiving maintenance HD is practical and provides a previously unavailable ability to interrogate the function of remnant tubular mass.



SA-PO546

Analysis of Microcirculatory Flow Changes After Hemodialysis

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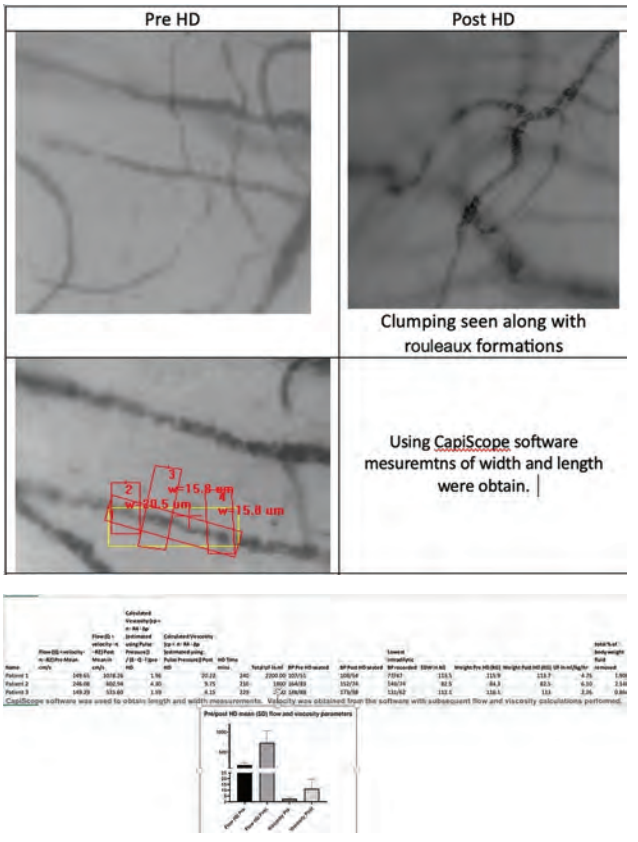
Background: During HD there appears to be a viscosity change in RBCs which leads to a decrease in their deformability changing to a rouleau formation with concurrent increases in viscosity. Increases in both whole blood and plasma viscosity are corelated with increases in HTN as wells as adverse cardiovascular changes.

Methods: Changes to the microcirculation in HD patients have previously been documented by Bemelmans et al by viewing the sublingual mucosa. Microcirculation impairment is an independent predictor of organ dysfunction and death which can be assessed via capillaroscopy examination. We adapted a commercial orthogonal polarization spectral imaging camera to perform capillaroscopy of the conjunctival tissue bed. Unlike the sublingual mucosa, the bulbar conjunctiva demonstrates hemodynamic features not dissimilar to the cerebral cortex.

Results: Early findings demonstrate a profound abnormality in RBC aggregation and RBC density in the microvasculature post-HD figure 1, along with a calculated increase in viscosity via software analysis (Figure 2). Although the etiology of these findings is unclear, it correlates with the observed increase in cardiovascular events seen among ESRD patients in the immediate days following dialysis.

Conclusions: Although the Fåhraeus–Lindqvist effect predicts viscosity decrease with an increase in microcirculatory flow, our study findings demonstrate that in HD, an increase in flow is proportional to an increase in viscosity. Rouleau formation post-HD is abnormal and is postulated to be responsible for the increase in viscosity noted. The increase in viscosity appears unrelated to UF but to HD itself.



SA-PO547

Changes in the Glymphatic System Before and After Dialysis Initiation in Patients with ESRD

Jiyae Yi, Sihyung Park, Yang Wook Kim, Bongsoo Park, Yoo jin Lee, Changmin Heo, Yeongrok Oh, Byeongo Choi. *Inje University Haeundae Paik Hospital, Busan, Republic of Korea*.

Background: This study evaluated 1) glymphatic system function in patients with end-stage renal disease (ESRD) before dialysis initiation compared to healthy controls, and 2) changes in glymphatic system function after renal replacement therapy including dialysis in patients with ESRD using the diffusion tensor image analysis along the perivascular space (DTI-ALPS) method.

Methods: This prospective study was conducted at a single hospital. We enrolled 14 neurologically asymptomatic patients who initiated hemodialysis or peritoneal dialysis for ESRD, as well as 17 healthy controls. The patients underwent magnetic resonance imaging (MRI) before and 3 months after dialysis initiation, and the DTI-ALPS index was calculated. We compared the DTI-ALPS index before and after dialysis initiation between patients with ESRD and healthy controls.

Results: The DTI-ALPS index differed between patients with ESRD before dialysis initiation and healthy controls (1.342 vs. 1.633, p=0.003) but not between patients with ESRD before and after dialysis initiation (1.342 vs. 1.262, p=0.386). A positive correlation was observed between DTI-ALPS and phosphate levels (r=0.610, p=0.020) in patients with ESRD.

Conclusions: We confirmed glymphatic dysfunction in patients with ESRD but observed no differences before or after dialysis initiation. This may be related to uremic toxins that are not removed by dialysis in patients with ESRD. The results of this study could be used to develop the pathophysiology and treatment of patients with ESRD.

SA-PO548

Near-Infrared Spectroscopy in Hemodialysis

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Background: Near-infrared spectroscopy (NIRS) is a noninvasive monitoring of cerebral oxygenation commonly used in monitoring for ischemia in surgical patients. Sensors are placed to measure oxygenation in the designated area. Infrared waves pass through a regional area to detect deoxygenation prior to widespread ischemia. During Hemodialysis (HD), ESKD patients are known to have abnormalities in cerebral blood flow, but few studies have looked at changes in cerebral oxygenation during HD in these patients. The aim of this study was to evaluate cerebral regional O2 saturation (rSO2) during HD, and to assess any correlation with vital signs such as blood pressure (BP) and heart rate.

Methods: Six inpatients with ESKD undergoing dialysis were enrolled. We used the FDA cleared device, INVOS PM 7100 patient monitor (K211561) and the INVOS Adult rSO2 sensor (K182868) produced by Medtronic. A sensor was secured on each side of the scalp, to measure temporal lobe oxygenation. NIRS monitor was placed at the beginning of HD and was removed 5 minutes after the session ended. Baseline was established during the first five minutes of the treatment. Desaturation was defined as a 20% or greater relative reduction from baseline local blood oxygen level for at least 1 minute.

Results: Patients' ages ranged from 59-85 years. Baseline rSO2 was adequately obtained in all patients. Desaturation was observed in one out of six patients (Figure). This was a 25% desaturation lasting for 2 minutes and 40 seconds, during which patient was asymptomatic and without change in vital signs. The same patient had a one-time drop in BP to 87/46 but no desaturation was observed during this time. Another patient had a one-time drop in BP to 91/63, without any desaturation observed in this time.

Conclusions: This pilot study was conducted to establish baseline cerebral oxygenation data for ESKD patients undergoing HD. Though a small sample size, this approach has potential to reveal interesting and useful insights to effects of HD on neurological function. We are continuing to gather patients and will use this group to establish norms of NIRS in ESKD patients.

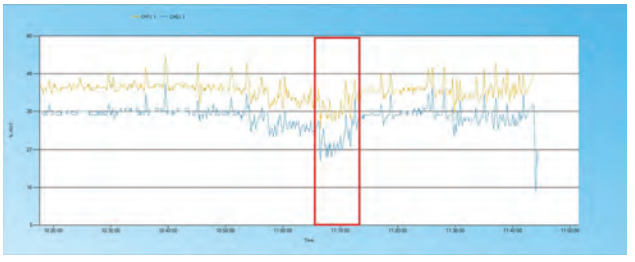

Figure: NIRS data of patient with desaturation marked in red box

SA-PO549

Cerebrovascular Function and Brain Structure in Hemodialysis Patients

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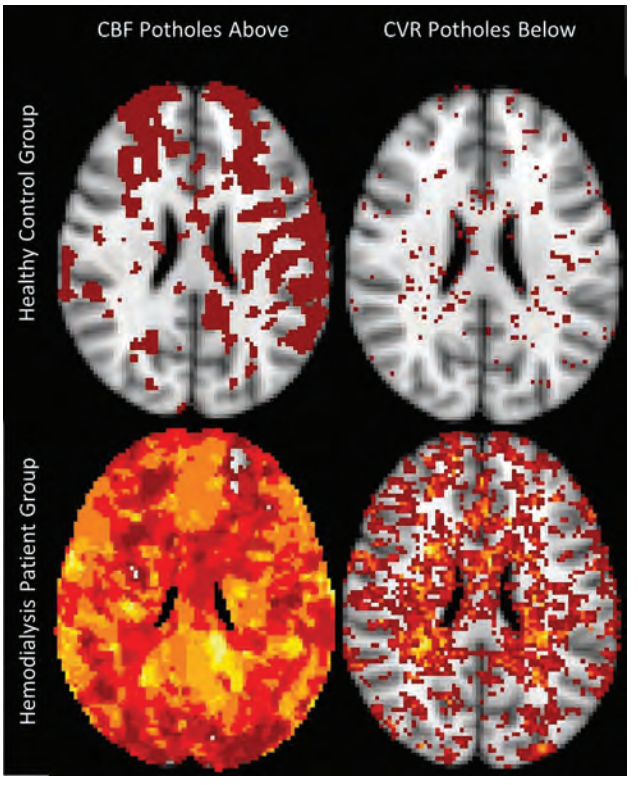
Background: Hemodialysis (HD) patients often have decline in cerebral blood flow (CBF) and cerebral oxygen saturation during HD. Cerebrovascular reactivity (CVR) measured at rest may be able to identify individuals susceptible to intradialytic hypoperfusion and ischemic brain injury. We hypothesized that HD patients would have decreased CVR and increased CBF relative to controls and that decreased CVR would be related to structural brain lesions.

Methods: In 10 HD patients and 10 controls, we measured cortical thickness and white matter hyperintensity (WMH) volume from the T1 and T2 FLAIR respectively, CVR from a breath hold during BOLD CVR fMRI, and arterial transit time and CBF from arterial spin labelling. Differences in these measures between the groups were tested by averaging across the tissue and with a pothole analysis. We correlated cortical thickness and WMH volume with cerebrovascular variables to assess the relationship between brain structure and cerebrovascular health in HD patients.

Results: Compared to controls, the HD cohort had decreased cortical thickness, increased WMH volume (p=0.002, p=0.004), and increased white matter CBF (p=0.02). Pothole analysis demonstrated a greater number of increased gray and white matter CBF voxels (p=0.03, p=0.02) and a greater number of decreased gray and white matter CVR voxels (p=0.02, p=0.01). No significant relationships were found between cortical thickness or WMH volume and CVR or CBF.

Conclusions: HD patients have structural injury with decreased cortical thickness and increased WMH. Notably, HD patients had increased CBF and decreased CVR. However, we did not find that decreased CVR correlated with decreased cortical thickness or increased WHM in this pilot study.

Funding: NIDDK Support, Private Foundation Support



Pothole count of higher CBF and lower CVR. Brighter yellow indictes a greater prevalence of potholes in that location

SA-PO550

Early Detection of White Matter Changes Through MRI Brain Diffusion Tensor Imaging (DTI) in ESRD Patients on Hemodialysis

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Background: Neurological complications like stroke and cognition disorders contribute to morbidity and mortality in CKD patients significantly. It has been postulated that neurological adverse events and renal dysfunction in CKD patients are related at the pathogenesis level. Neurological changes in the brain in CKD patients can be detected by Magnetic resonance studies at a stage earlier than overt clinical symptom manifestation.

Methods: After obtaining approval from the Institutional Ethics Committee, 30 patients with end-stage renal disease on hemodialysis and 10 age-matched control persons without kidney disease underwent routine biochemical studies and an MRI brain on a 3T scanner. Fractional Anisotropy and Mean Diffusivity were calculated for corpus callosum genu and splenium, anterior and posterior corona radiata, pons, and cerebellar hemispheres on both sides. Conventional MRI images were evaluated for changes in small vessel disease. Student's unpaired T-test was used to determine if the difference in results were statistically significant.

Results: 18 out of 30 hemodialysis patients and three out of 10 control patients had white matter changes of small vessel disease detectable in conventional MRI sequences. Fractional anisotropy was significantly low for corpus callosum genu ($p<0.003464$ and $p<0.007437$, right and left sides respectively) and anterior corona radiata ($p<0.04272$ and $p<.001653$, right and left sides respectively) in hemodialysis patients than control. No significant difference in fractional anisotropy was noted for other locations. Mean diffusivity was higher at corpus callosum genu and anterior corona radiata in hemodialysis patients than in age-matched controls but did not reach statistical significance ($p>0.05$).

Conclusions: There are white matter changes detectable by DTI imaging in a quantitative manner in anterior corona radiata and corpus callosum genu in hemodialysis patients that is absent in age-matched control persons without renal disease. Further research is needed to use these early quantitative DTI changes to build robust predictive models for prognostication that will lead to comprehensive renal and neurological clinical management in CKD patients.

SA-PO551

Intrinsic Prefrontal Functional Connectivity According to Cognitive Impairment in Patients with ESRD

Yeongrok Oh, Bongsoo Park, Yang Wook Kim, Sihyung Park, Yoo jin Lee, Changmin Heo, Jiyae Yi, Byeongo Choi. *Inje University Haeundae Paik Hospital, Busan, Republic of Korea*.

Background: This study aimed to investigate differences in intrinsic prefrontal functional connectivity according to the presence of cognitive impairment in patients with end-stage renal disease (ESRD) using functional near-infrared spectroscopy (fNIRS).

Methods: We prospectively enrolled 37 patients with ESRD who were undergoing hemodialysis for more than six months and had no previous history of neurological or psychiatric disorders. The NIRSIT Lite device was used to acquire fNIRS data, and the NIRSIT Lite Analysis Tool program was used to process the data and generate a functional connectivity matrix. We obtained functional connectivity measures by applying graph theory using BRAPH program from the connectivity matrix using the BRAPH program. All patients with ESRD underwent a Korean version of the Montreal Cognitive Assessment (MoCA-K) to assess their cognitive function.

Results: Of the 37 patients with ESRD, 23 had cognitive impairment, whereas 14 patients showed no cognitive impairment. Intrinsic prefrontal functional connectivity was significantly different between groups. The network measures of the strength, global efficiency, and mean clustering coefficient were lower (4.458 vs. 5.129, p=0.018; 0.397 vs. 0.437, p=0.028; 0.316 vs. 0.421, p=0.003; respectively) in ESRD patients with cognitive impairment than those without cognitive impairment. There were no significant correlations between MoCA-K scores and clinical characteristics.

Conclusions: We demonstrated a significant association between cognitive function and intrinsic prefrontal functional connectivity in patients with ESRD. ESRD patients with cognitive impairment have reduced connectivity and segregation in the prefrontal brain network compared with those without cognitive impairment.

SA-PO552

Urea Clearance in a Large-Animal Hemodialysis Benchtop Model Using Nanoporous Silicon Nitride Membranes

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Background: Over three-quarters of a million Americans live with the daily complications of end-stage renal disease (ESRD), and 71% of those are on some form of hemodialysis (NIH NIDDK 2020). One major shortcoming with current hemodialysis is the non-ambulatory nature of the treatment, with many patients undergoing treatment for four hours, three times a week. Our goal is to make conventional renal replacement therapy more compact, allowing for ambulatory dialysis. To accomplish this, our lab has previously devised and utilized nanoporous silicon nitride (NPN) membranes that demonstrated a 20% urea clearance in a small-animal model (Hill et al., 2020). We modified the NPN membranes for use in a large animal benchtop model by increasing the surface area while maintaining a pore size of 0.35-μm. NPN membranes with a pore size of 35-nm were also developed for testing in the large-animal model with the goal of consistent dialysis of uremic toxins without loss of other important macromolecules and blood components (e.g., albumin and white blood cells).

Methods: The large-animal hemodialysis benchtop model consists of a 500 mL circulating analyte (20 mM urea-spiked 1x phosphate-buffered saline (PBS) or whole heparinized bovine blood) flowing across an NPN membrane counter to 1x PBS, circulating at a rate of 50 mL/min and 120 mL/min respectively. The NPN membranes are contained in a stable 3D-printed housing unit that allows for effective flow-through and the ability to gather transmembrane pressure readings, without damage to the chip. Small samples (~100 μL) were collected from the body of the dialyzed analyte every five minutes for the first thirty minutes, and every fifteen minutes thereafter, over the course of two hours.

Results: The clearance results of the NPN membranes in the dialysis of urea-spiked 1x PBS and blood show a decrease in urea concentration in the analyte over a time of two hours, consistent with that seen in the small-animal model. This data suggests that NPN membranes are effective dialyzers of metabolic waste products, such as urea, in a large-animal model of ESRD.

Conclusions: This study demonstrates the effectiveness of microporous and nanoporous silicon nitride membranes for dialyzing small metabolic waste products in a large-scale animal model.

Funding: NIDDK Support

SA-PO553

Impact of Protein Fouling on Middle Molecule Removal During Initial Dialysis Phase

James P. Kennedy,[1] Karlee Emal,[1] Joanie Werner,[1] Chih-Hu Ho,[1] Adam M. Zawada,[2] Skyler Boyington.[1] [1]*Fresenius Medical Care North America, Ogden, UT;* [2]*Fresenius Medical Care Deutschland GmbH, Sankt Wendel, Germany*.

Background: Deposition of plasma proteins to the dialyzer membrane during the initial dialysis phase strongly reduces removal capacity of middle molecules such as β2-microglobulin (β2-m). Hydrophilic membrane modification with polyvinylpyrrolidone (PVP) has been shown to reduce protein fouling and to stabilize dialyzer performance during dialysis treatment. In the present study we investigated the impact of initial protein fouling on middle molecule removal by different dialyzers, including the novel FX CorAL with PVP enriched and stabilized surface of its Helixone *hydro* membrane.

Methods: This *in vitro* study included the following dialyzers: FX CorAL 80 (Fresenius Medical Care), Revaclear 400 (Baxter), Diacap Pro 19H (B. Braun), ELISIO 17H and Cellentia 17H (both Nipro). Protein deposition to the membrane was simulated during a recirculation experiment with bovine plasma for 30 and 60 min. β2-m clearance was determined in a single-pass setup with bovine plasma at three time points (before protein fouling [0min], after 30min and 60min protein fouling). Clearance values were normalized based on the membrane surface size.

Results: Across all five investigated dialyzers, mean β2-m clearance reduced by 18.7% after 30min of plasma recirculation (0min: 35.2±9.3ml/min/m^2; 30min: 28.7±7.5ml/min/m^2). After additional 30min of plasma recirculation, β2-m clearance only slightly decreased (60min: 28.4±7.9ml/min/m^2; -1.1% vs 30min). When comparing the clearance reduction by the different dialyzers, the FX CorAL showed low β2-m clearance decrease while having the highest β2-m clearance values throughout the experiment (0min: 47.2±3.4ml/min/m^2; 30min: 39.8±0.9ml/min/m^2; 60min: 40.0±1.3ml/min/m^2) as compared to Revaclear (0min: p<0.001; 30min: p<0.001; 60min: p<0.001), Diacap Pro (p<0.01; p<0.001; p<0.001), ELISIO (p<0.01; p<0.001; p<0.001) and Cellentia (p<0.001; p<0.001; p<0.001).

Conclusions: Efficient removal of middle molecules while preserving vital proteins such as albumin is pivotal for patients requiring renal replacement therapy. To prevent loss of dialyzer performance during treatment, novel hydrophilic membranes, such as FX CorAL's Helixone *hydro* membrane, has been shown to reduce protein fouling and to stabilize performance during treatment, especially during the initial dialysis phase.

SA-PO554

Hydrophilic Membrane Modification Improves Filtration Characteristics of Dialyzer Membranes

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Background: While efficient removal of uremic solutes and accumulated water is pivotal for the well-being of patients requiring kidney replacement therapy, the removal capacity of a dialyzer decreases during dialysis treatment due to adsorption of plasma proteins to the membrane. Hydrophilic membrane modification with polyvinylpyrrolidone (PVP) has been shown to reduce protein adsorption and to stabilize permeability of the membrane during treatment. The present study compares water permeability changes of polysulfone membranes, including the PVP enriched and stabilized membrane of the novel FX CorAL dialyzer.

Methods: This *in vitro* study included the polysulfone-based FX CorAL 600, FX CorDiax 600 (both Fresenius Medical Care) and xevonta Hi15 (B. Braun) dialyzers. Protein fouling to the membrane was simulated during a recirculation experiment with bovine milk for 4h. The decrease in filtration flow (Q_F) at constant inlet flow (Q_{IN}, 400ml/min) and transmembrane pressure (TMP, 75mmHg) (setup 1) as well as the increase in TMP at constant Q_F (100ml/min) and Q_{IN} (400ml/min) (setup 2) were continuously determined during recirculation.

Results: Across all dialyzers, Q_F at constant Q_{IN} and TMP decreased strongly in the first 20min and then slowly for the remaining time (20min: -50.8±15.9ml/min; 4h: -66.9±29.2ml/min). Likewise, the TMP at constant Q_F and Q_{IN} increased first strongly and then slowly (20min: +21.9±3.9mmHg; 4h: +39.0±5.9mmHg). The FX CorAL showed the lowest reduction in Q_F (20min: -30.6±8.2ml/min; 4h: -32.6±13.4ml/min) as compared to FX CorDiax (20min: -61.0±3.7ml/min, p=0.001; 4h: -78.2±21.4ml/min, p=0.017) and xevonta (20min: -60.8±3.4ml/min, p=0.001; 4h: -90.0±5.5ml/min, p=0.006). In line, the FX CorAL showed lowest increase in TMP (20min: +18.3±1.5mmHg; 4h: +32.7±2.1mmHg), as compared to the FX CorDiax (20min: +21.7±3.8mmHg, p=0.214; 4h: +39.9±4.8mmHg, p=0.078) and xevonta (20min: +25.8±0.8mmHg, p=0.015; 4h: +44.4±3.0mmHg, p=0.011).

Conclusions: Protein adsorption to the membrane is the major factor for the initial decrease of dialyzer membrane permeability during hemodialysis. Hydrophilic membrane modification with PVP reduces protein fouling and stabilizes the removal capacity of solutes and water during dialysis treatment.

SA-PO555

Uremic Toxins Are Adsorbed by the Model 3 Wearable Artificial Kidney (WAK)

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Background: Elimination of uremic toxins is necessary for effective renal replacement therapy. Previous WAK data showed that its sorbents adsorb beta2 microglobulin, uric acid, hippuric acid, indoxyl sulphate and indoleacetic acid. We aimed to show the WAK3 effectively purifies dialysate from additional toxins.

Methods: Discarded dialysate from 8 dialysis patients was placed in a reservoir and recirculated for 4 hours through the the WAK3 charcoal cartridge. Samples were obtained before and after the fluid passage through the cartridge and analyzed LC-MS. Metabolites

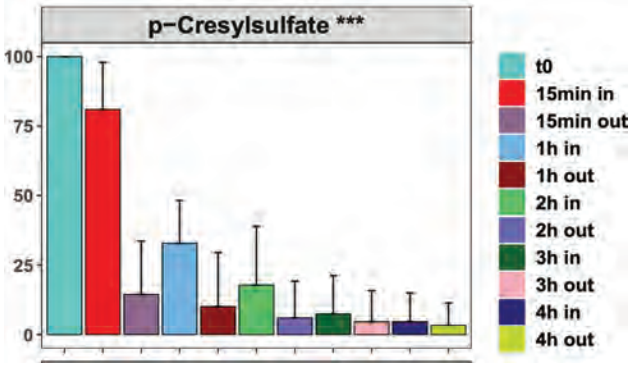
were separated on a LunaNH2 (Phenomenex) HILIC column and detected with a Q Exactive orbitrap mass spectrometer (Thermo Scientific). Statistical analysis was done with a one-way Anova test.

Results: the concentration of ADMA, homocitrulline, homocysteine, kynurenine, p-cresylsulfate, phenol, and phenylacetylglutamine, and methylguanidine in the spent dialysate decreased by 87.93% (p= <0.001) at a dialysate pulse flow rate of 30 ml/min. after 4 hours of recirculation through the WAK sorbent cartridge

Conclusions: The WAK3 effectively adsorbs uremic toxins from dialysate supporting the notion that the device may be effective in treating dialysis patients.

Percentage of toxin removed from dialysate after 4 hours of recirculation through the WAK3 charcoal sorbent

TOXIN	% removed	p-value
Methylguanidine	74.4%	<0.001
ADMA	93.98%	<0.001
Homocitrulline	80.19%	<0.001
Homocysteine	72.33%	<0.001
Kynurenine	97.5%	<0.001
p-Cresylsulfate	96.71%	<0.001
Phenol	95.54%	<0.001
Phenylacetylglutamine	92.85%	<0.001



SA-PO556

Can Oral Potassium Binders Be Added to Dialysate to Improve the Efficacy of Hemodialysis?

Rouzbeh Tehrani,[1] Avrum Gillespie,[2] Juliana Alderfer.[1] *[1]Temple University, Philadelphia, PA; [2]Lewis Katz School of Medicine at Temple University, Philadelphia, PA.*

Background: Can commercially available oral potassium (K+) binders (sodium zirconium cyclosilicate, ZS-9) be added to the dialysate to improve diffuse clearance and reduce dialysate usage while decreasing blood-dialysate K+ gradients?

Methods: This is an in-vitro hemodialysis experiment using 1 liter of freshly collected Li-heparinized porcine blood dialyzed with an average blood flow rate of 30 mL/min and dialysate flow of 50 mL/min, two peristaltic pumps, Fresenius Optiflux hemodialysis membranes, and CitraPure dialysate concentrate (Rockwell Medical). For the potassium management experiment, 5 g of ZS-9 was added to 1 L of dialysate. Dialysate K+ was set to 4 mmol/L for the management of the potassium concentration gradient (delta C_K). ZS-9 leaching to blood was tested by examining blood specimens after 5-hour hemodialysis, using highly concentrated Nano-Slurry (10 to 20 g/l) dialysate and increased transmembrane pressure (reversed), and measuring the reverse filtrate for nanoparticles for turbidity and nanoparticle materials using inductively coupled plasma mass spectrometry.

Results: In experiment 1, blood K+ was 5 mmol/L and dialysate K+ was 4 mmol/L plus ZS-9 (delta C_K=1), by 60 minutes using recirculated dialysate, serum K+ had decreased to 3.5 mmol/L and dialysate K+ 3.0 mmol/L. In experiment 2, the blood K+ was 8 mmol/L and the dialysate 4 mmol/L plus ZS-9 (delta C_K=4), by 60 minutes using recirculated dialysate, the serum potassium was 4 mmol/L. In experiment 3, the starting serum potassium was 8 and the bath was 4 K+, after the addition of ZS-9, potassium dropped to 5.8 at 20 minutes, and then after the addition of ZS-9 at 40 minutes, potassium dropped to 2.5mmol/L and maintained at equilibrium. The addition of ZS-9 in increments was to manage C_K gradient throughout the treatment. No suspended particles and no trace amount of Zr or Si were detected passing through the membrane from dialysate to blood.

Conclusions: The addition of commercially available K+ binder, sodium zirconium cyclosilicate (ZS-9), effectively lowered potassium using recirculated dialysate while maintaining a minimal concentration gradient throughout the treatment. The addition of K+ binders to dialysate can be incorporated into a novel hemodialysis machine that can recirculate dialysate and offer the management of K+ throughout the treatment.

SA-PO557

Can Oral Phosphate Binders Be Added to Dialysate to Improve the Efficacy of Hemodialysis?

Rouzbeh Tehrani,[1] Avrum Gillespie,[2] Juliana Alderfer.[1] *[1]Temple University, Philadelphia, PA; [2]Lewis Katz School of Medicine at Temple University, Philadelphia, PA.*

Background: Can commercially available polymeric phosphate binders, Sevelamer carbonate (SC), be added to the dialysate to improve diffuse clearance and reduce dialysate usage while decreasing blood-dialysate phosphate gradients? Sevelamer carbonate is an orally administered, non-absorbed phosphate-binding anion exchange resin. It is a buffered form of Sevelamer hydrochloride.

Methods: This is an in-vitro hemodialysis experiment using 1 liter of freshly collected Li-heparinized porcine blood with an average blood flow rate of 30 mL/min and dialysate flow of 50 mL/min, two peristaltic pumps, Fresenius Optiflux hemodialysis membranes, and CitraPure dialysate concentrate (Rockwell Medical) which was diluted and the pH adjusted using sodium bicarbonate (Solcart B, B.Braun). For the phosphate experiment, 3 tablets of SC were crushed and added to the dialysate, 2700 mg of active-SC/L. SC leaching to blood was tested by (i) examining blood specimens after prolonged 5-hour hemodialysis, (ii) using highly concentrated SC-added dialysate (5 to 10 g/L) and increased transmembrane pressure, and measuring the reverse filtrate for SC particles.

Results: For the hyperphosphatemia experiment, the start serum phosphorus was 8 mg/dL. After 30 minutes of dialysis, the phosphorus was 5.5 mg/dL. SC was added and the phosphate dropped to 2.5 mg/dL at 100 minutes. SC was then added again and phosphate dropped to 2 mg/dL. No suspended particles were detected passing through the membrane from dialysate to blood.

Conclusions: The addition of Sevelamer Carbonate (SC) effectively lowered phosphate using recirculated dialysate and can be incorporated into a novel hemodialysis machine that can recirculate dialysate, reducing water consumption for both in-center and home hemodialysis. While SC effectively reduced phosphate levels, its addition to the dialysate has been found to influence the dialysate pH. Therefore, careful consideration must be given to pH adjustment when utilizing SC. Maintaining appropriate dialysate pH is crucial for ensuring patient safety and optimizing dialysis outcomes.

SA-PO558

Improving the Efficacy and Efficiency of Hemodialysis by Adding Nanoscale Activated Carbon (Nano-Slurry) Sorbent to the Dialysate

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Background: Improving the efficacy and efficiency of dialysate for hemodialysis has the potential to improve patient outcomes and reduce waste and energy consumption. Currently, hemodialysis relies mostly on diffusive clearance across a gradient between the patient's blood and the dialysate. We demonstrate that the addition of nanoparticle sorbents to the dialysate can improve the efficiency of hemodialysis and can allow for the reuse of dialysate.

Methods: This is an in-vitro hemodialysis experiment using Li-heparinized porcine blood, two peristaltic pumps, Fresenius Optiflux hemodialysis membranes, and CitraPure dialysate concentrate (Rockwell Medical) which was diluted and the pH was adjusted using medical-grade sodium bicarbonate (Solcart B, B.Braun). One liter of freshly collected porcine blood was dialyzed with an average blood flow rate of 30 mL/min and dialysate flow of 50 mL/min. Nanoscale activated carbon (Nano-Slurry) was tested in this study. The mass of added adsorbents (0.5 to 5 g/l) varied depending on the adsorbent type, targeted blood toxin, and expected removal rate. Absorbent leaching to blood was tested by using highly concentrated Nano-Slurry (10 to 20 g/l) dialysate and increased transmembrane pressure by increasing the dialysate flow rate to 1000 mL/min and measuring the reverse filtrate for nanoparticles by turbidity with a near-infrared turbidity meter.

Results: In the single-pass experiment, creatinine was removed in half the time when using Nano-Slurry dialysate. We then did our recirculated dialysate experiment and the Nano-Slurry, creatinine rapidly equilibrated in the control experiment at 30 minutes whereas, the recirculated Nano-Slurry dialysate continued to remove creatinine at the end of the experiment, 100 minutes. BUN rapidly lowered from 17 mg/dL to 7mg/dL, below the calculated equilibrium at 20 minutes. For the absorbent leaching experiment, the reverse filtrate had turbidity that remained unchanged pre- and post-experiment with a measure of 0.03 NTU.

Conclusions: Nano-Slurry improved the efficiency in both in-vitro single pass and recirculated hemodialysis models. The addition of nanoscale adsorbents improved the efficiency of dialysis and can be incorporated into a novel hemodialysis machine that can recirculate dialysate, reducing water consumption for both in-center and home hemodialysis.

SA-PO559

Animal Models for Studying Protein-Bound Uremic Toxin Removal

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Background: Protein-bound uremic toxins (PBUTs) are linked with the progression of chronic kidney disease (CKD) and higher morbidity and mortality risks. Conventional dialysis does not effectively remove PBUTs due to their binding to plasma proteins. Therefore, novel approaches to improve PBUT clearance are being developed, but these require validation before clinical trials can be initiated. To gain more insight into suitable CKD animal models we conducted a semi-systemic review to document PBUT concentrations in various models and species.

Methods: The search yielded 1163 records which were included for abstract screening, of which 66 were included for data extraction (Figure 1). All data were extracted by one researcher, after which the data were independently validated by a second researcher. Two specific types of injury were distinguished and analyzed as subgroups for the effect on PBUT levels: nephron loss models (e.g. 5/6th nephrectomy) and tubular damage models (by administration of tubulotoxins, e.g. adenine).

Results: PBUT concentrations were reported in studies using rats (n=43), mice (n=16), dogs (n=3), cats (n=4), goats (n=1), and pigs (n=1). Most studies in rodents reported mean uremic concentrations of plasma indoxyl sulfate (IS) close to or in the range of human ESKD, with the highest concentrations in tubular injury models (121.7 μM (89.3 μM – 154.1 μM); mean (95% CI), n=15 rat studies). Compared to nephron loss models in rats, a greater rise in plasma IS compared to creatinine was found in tubular injury models (factor 11.2 versus 6.3 for nephron loss models), likely due to the fact that tubular secretory function was relatively more affected than glomerular filtration. The small number of studies and heterogeneity of the data reported precluded detailed analysis of large animal models or other PBUTs.

Conclusions: Tubular injury models in rats appear to be suitable models to mimic human ESKD for *in vivo* validation of innovative PBUT-lowering strategies.

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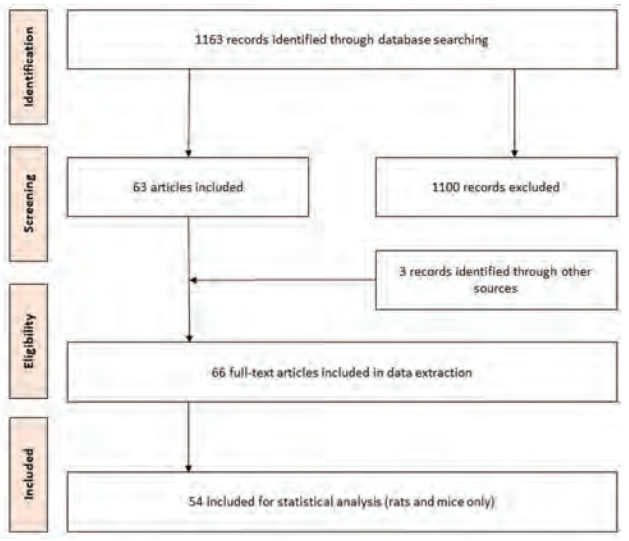

Figure 1. Article selection process.

SA-PO560

A Chronic Intermittent Hemodialysis Pig Model for Functional Evaluation of Dialysis Filters

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Background: Performance evaluation of new dialysis filters is primarily performed *in vitro*, which can lead to differences in clinical results. Currently, data on filter performance and safety are available only for actual hemodialysis patients. Herein, we aimed to establish an *in vivo* dialysis model that could be extrapolated to humans.

Methods: A bilateral nephrectomy porcine model of renal failure was established, in which a double-lumen catheter for human dialysis was subsequently placed in the external jugular vein under general anaesthesia, the tip of which was fixed to the back (Fig 1). Hemodialysis was performed every other day in the same manner as in humans, during which various clinical data were evaluated. The utility of hemodiafilters coated with and without vitamin E (V-RA and ABH™) was subsequently compared using this model.

Results: Hemodialysis treatment was successfully performed in bilaterally nephrectomised pigs under the same dialysis conditions as humans (4 h per session, 3 times a week, for 2 weeks). In accordance with human clinical data, regular dialysis alleviated renal failure in pigs, allowing for sufficient activity. The vitamin E-coated filter showed a significantly greater reduction rate of advanced oxidation protein products (AOPP) during dialysis and a lower quantity of fibrinogen adhesion at the first dialysis on postoperative day 1 than ABH (Fig 2).

Conclusions: Herein, we successfully constructed a pig model of chronic hemodialysis that mimics the pathophysiology and dialysis condition of patients undergoing hemodialysis. This model will be useful for evaluating the performance and safety of dialysis filters before market release.

Funding: Commercial Support - Asahi Kasei Medical Co. Ltd.

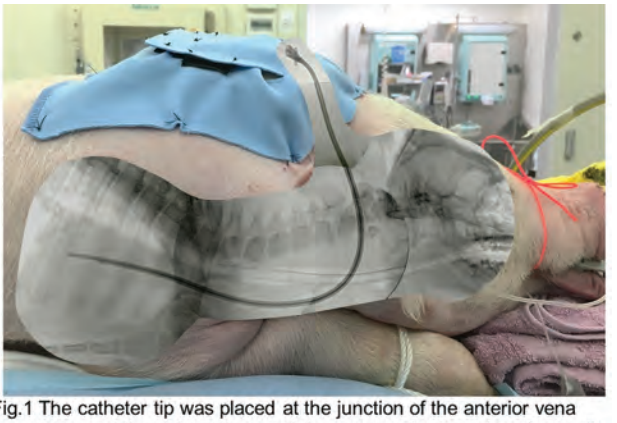
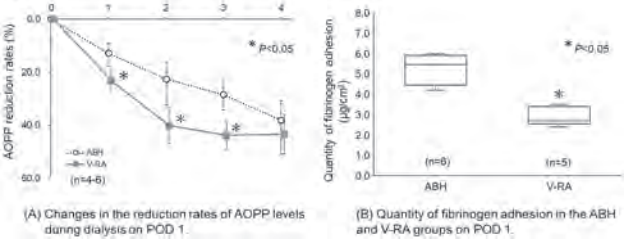


Fig.1 The catheter tip was placed at the junction of the anterior vena cava and the right atrium, and the access site was placed dorsally.

Fig 2.



(A) Changes in the reduction rates of AOPP levels during dialysis on POD 1

(B) Quantity of fibrinogen adhesion in the ABH and V-RA groups on POD 1

SA-PO561

Amino Acid Loss During a Hemodialysis Session Depending on Membrane Materials

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Background: Dialysis-related factors including nutrient loss during a hemodialysis (HD) session may have an important impact on protein energy wasting especially in elderly or malnourished dialysis patients. In this study, we examined dialysate amino acid (AA) loss during a HD session and compared clear space (CS) of AA among three different membranes including acrylonitrile and sodium methallyl sulfonate blend (AN 69) which has significantly smaller amount of albumin loss.

Methods: In 6 maintenance HD patients (6 women), pre-HD plasma basic 20 AA profiles were analyzed in three consecutive HD sessions (blood flow 200ml/min, 4 hours) with different membranes. Simultaneously, dialysate AA losses in each session are measured by continuous effluent collection (2L/hr) from the drainage line. The membranes studied were: cellulose tri-acetate (CTA), polysulfone(PS), and acrylonitrile and AN 69. All membranes had similar surface area of 1.5 square meters. We measured CS using the pre-dialysis plasma AA concentration and AA losses in dialysate, and compared CS among the three membranes.

Results: The total amino acid (TAA) loss for each HD session was 8.2 (5.9-10.0) g for CTA, 8.0 (6.1-9.5) g for PS, and 7.3 (5.0-8.4) g for AN69 (p=0.32). Average of CS for each AA is 21(16-25) L for CTA, 19(16-27) L for PS, 18(15-24)L for AN69 (p=0.36). Total CS for AA is 400(311-474) for CTA, 362 (302-505) L for PS, 344 (292-451)L for AN69 (p=0.36).

Conclusions: A total of 7 to 8 grams of AA are lost per HD session. No superiority of AN69 for reducing AA loss was not observed in this study.

SA-PO562

Bisphenol Levels in Hemodialyzers

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Background: Bisphenol A (BPA)-based materials are widely employed across various industries, including dialysis. As concerns for BPA's health risks rise, bisphenol S (BPS)-based materials are increasingly used. However, BPS safety requires further evaluation. To support thorough risk assessments on bisphenols and their exposure for hemodialysis patients, extractables (E) and leachables (L) from 8 commercially available dialyzers were tested.

Methods: For E, dialysate and blood sides of each dialyzer were incubated statically at 37°C with 95% ethanol (EtOH) and collected after 72 hrs. For L, bloodlines, dialysate and blood sides were filled with 17.2% EtOH and recirculated at 300 mL/min and 37°C for 24 hrs. Bloodline controls were run using the recirculation setup. Bisphenols were quantified by liquid chromatography-mass spectrometry using standard addition and stable-isotope labeled standards.

Results: BPA (0.43 - 32.82 µg/device) and BPS (0.02 - 2.51 µg/device) were detected in E from dialyzers and housings made with BPA- and BPS-containing materials (Figure 1). In L, BPA was only detected in one dialyzer made of BPA-containing membrane and housing material. BPS (0.08 - 1.44 µg/device) was detected in L of dialyzers made with BPS-based materials. BPA/BPS were not detected in bloodline controls, cellulose-based membranes, and in Fresenius Medical Care's FX CorAL 120 dialyzer, a member of the recently FDA-cleared CorAL dialyzer family.

Conclusions: Dialyzers have varied bisphenol amounts based on raw materials and manufacturing process used for housing and membranes. FX CorAL exhibited no detectable bisphenols, as opposed to other dialyzers with synthetic membranes, where varying amounts of bisphenols were detected. To understand the BPS toxicological profile, additional studies should be performed and evaluated as rigorously as BPA.

Funding: Commercial Support - Fresenius Medical Care

Dialyzer type	Manufacturer	Membrane materials	Housing materials	Sterilization	BPA (µg/device)		BPS (µg/device)	
					E	L	E	L
FX CorAL 120	Fresenius	PS/PVP	PP	In-line steam	ND	ND	ND	ND
Theranova 500	Baxter	PAES/PVP	PC	Steam	0.73	ND	0.02	0.08
Elisio 21H	Nipro	PES	PP	Gamma ray	ND	ND	1.37	0.96
Sureflux 21UX	Nipro	Cellulose Triacetate	PP	Gamma ray	ND	ND	ND	ND
Solacea 21H	Nipro	Asymmetric triacetate	PP	Gamma ray	ND	ND	ND	ND
Xevonta Hi23	B. Braun	Amembris PS/PVP	PC	Gamma ray	32.82	2.48	1.99	1.44
Revaclear 400	Baxter	PAES/PVP	PC	Steam	0.43	ND	0.27	0.15
Bain B-20HF	Bain	PES	PP	Radiation	ND	ND	2.51	0.62

- PS – polysulfone, PVP – polyvinylpyrrolidone, PP – polypropylene, ND – not detected, PAES – polyarylethersulfone, PC – polycarbonate, PES – polyethersulfone.
- PS and PC are BPA-based materials, PES is BPS-based material, while PVP, PP, cellulose or asymmetric triacetate are neither BPA- nor BPS-based materials.
- Different sterilization processes are indicated.
- 95% ethanol is extractable, 17.2% ethanol is leachable.
- All samples were analyzed in duplicate for three technical replicates.
- For the 95% EtOH extracts, the BPA and BPS amount in extracts of blood side and dialysate side were combined and reported as the total amount in each sample for each dialyzer. For calculating the extraction mass in extractables, the extraction volume and density of 0.8 g/ml for 95% EtOH was used. For leachables, no density adjustment was used as the density of 17.2% EtOH is close to 1 g/ml.

Figure 1: BPA and BPS extraction mass in extractables (E) and leachables (L) of tested dialyzers.

SA-PO563

Endotoxin Retentive Performance of the Fresenius FX CorAL Dialyzer

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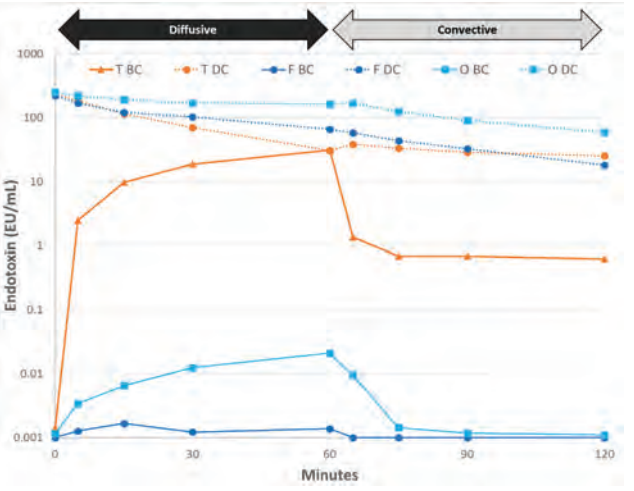
Background: Many dialyzer innovations focus on improving solute removal or sequestration of target molecules. However, these improvements may impact peripheral dialyzer functions, such as prevention of pyrogenic substances from entering patient blood. This study explored the transmembrane flux and retention of endotoxins for the following dialyzers: FX CorAL 80 and Optiflux F180NRe (Fresenius Medical Care), and Theranova 400 (Baxter International). FX CorAL (F), a new dialyzer featuring novel Helixone hydro membrane, Optiflux (O), a membrane known for endotoxin performance, and Theranova (T), a medium cut-off (MCO) membrane.

Methods: *In-vitro* experiments used culture filtrates of *P.* aeruginosa (ATCC 27853) and *S.* maltophilia (ATCC 13637) spiked into saline to create a solution containing > 200 EU/mL. Dialyzers were challenged under diffusive and convective test configurations, with samples taken during both configurations at 5, 15, 30, and 60 minutes. Samples were analyzed for endotoxin using a kinetic turbidimetric LAL assay with a detection limit of 0.001 EU/mL.

Results: Diffusive transmembrane flux of endotoxin was observed for all dialyzers, with F and O nearly 10^3 lower than T. Maximum diffusive endotoxin concentrations: F = 0.0016 EU/mL; O = 0.0209 EU/mL; T = 30.98 EU/mL. Convective endotoxin flux decreased over time for all dialyzers, with T plateauing higher than O or F. Log reduction values were calculated from convective samples at 60 minutes: T = 1.61; F = 4.26; O = 4.72.

Conclusions: Endotoxin retention of dialysis membrane is a final barrier in the transfer of pathogens to patients. This is an important membrane quality, since endotoxins present in dialysate will contribute to chronic inflammation in patients. FX CorAL demonstrates endotoxin retentive performance similar to Optiflux, and better than Theranova. Improved understanding of endotoxin removal mechanisms may lead to enhanced endotoxin retention in parallel with dialysis membrane development.

Funding: Commercial Support - Fresenius Medical Care



SA-PO564

Effect of Dialysis Treatment on Structural Brain Connectivity in Patients with ESRD

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Background: End-stage renal disease (ESRD) patients are known to have reduced structural and functional brain connectivity associated with cognitive function. However, the effect of dialysis treatment on brain connectivity is not understood. This study was designed to evaluate effects of dialysis treatment on structural brain connectivity in patients with ESRD.

Methods: This prospective study was conducted with 20 ESRD patients with pre-dialysis and 35 healthy controls. The patients underwent T2-weighted and three dimensional T1-weighted magnetic resonance imaging (MRI) before and 3 months after dialysis initiation, and cortical thickness was calculated. We applied a graph theoretical analysis for calculating the structural co-variance network based on the cortical thickness. We compared the cortical thickness and structural co-variance network between ESRD patients with pre-dialysis and healthy controls, and between ESRD patients with pre-dialysis and those with post-dialysis.

Results: The mean cortical thickness in both hemispheres was lower in ESRD patients with pre-dialysis than in healthy controls (2.296 vs. 2.354, p=0.030; 2.282 vs. 2.362, p=0.004; respectively), and it was higher in ESRD patients with post-dialysis than in those with pre-dialysis (2.333 vs. 2.296, p=0.001; 2.322 vs. 2.282, p=0.002; respectively). In analysis of the structural co-variance network, the assortative coefficient was lower in ESRD patients with pre-dialysis than that in healthy controls (-0.062 vs. -0.031, p=0.029), and it was higher in ESRD patients with post-dialysis than those with pre-dialysis (-0.002 vs. -0.062, p=0.042).

Conclusions: We found that there were differences in cortical thickness and structural co-variance network before and after dialysis in ESRD patients. This indicates that dialysis treatment affects structural brain connectivity and will contribute to understand the pathophysiologic mechanism of cognitive function alterations resulting from dialysis treatment in ESRD patients.

SA-PO565

Uromodulin in Kidney Failure

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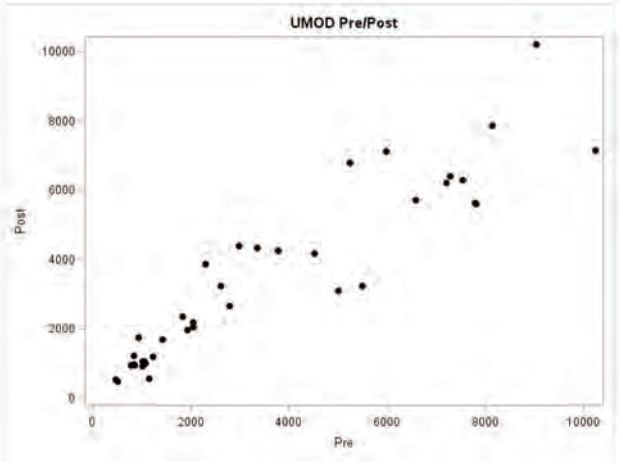
Background: Uromodulin (UMOD) is a 95 kDa glycoprotein produced exclusively by the loop of Henle. UMOD is detectable in urine and blood and levels may represent functional renal tubular mass. To address this question, we measured serum UMOD in chronic dialysis patients to evaluate its potential utility as biomarker of kidney function and to assess its dialyzability.

Methods: Serum samples were obtained immediately before and after hemodialysis through dialysis access and immediately frozen at -20. All samples were assayed undiluted within 6 months, using a sandwich ELISA assay platform (Invitrogen ®; Thermo-Fisher), with assay sensitivity down to 40 pg/mL. Estimated glomerular filtration rate (eGFR) was

determined using the median of all available pre-dialysis eGFR values within a month of the sample collection date. Age, sex, dialysis vintage, and target weight were collected. Descriptive analyses and Spearman correlation coefficients were performed.

Results: Pre- and post-dialysis levels were obtained from 38 individuals. Values were non-normally distributed (Fig1). Median UMOD pre-dialysis was 2450 (IQR=1060- 5981) pg/mL, and post dialysis was 2870 (IQR=1050-5640) pg/mL, with median difference =16 (!QR=-600-470) pg/mL, P=0.8. UMOD>8000 pg/mL were in the 95th percentile. Pre- and post- dialysis UMOD values were highly correlated (R=0.93, P<0.001 and did not correlate with eGFR, age, sex, dialysis vintage or target weight.

Conclusions: Low levels of UMOD are detectable in patients with end stage kidney failure. There is no evidence of removal of UMOD with hemodialysis. Further evaluation of UMOD as a biomarker of potential kidney recovery after acute injury or transplantation or indicator of preserved residual renal function is worth further investigation.



Uromodulin Levels Before and After Hemodialysis

SA-PO566

Is the Donnan Equilibrium Still Intact in High-Volume Hemodiafiltration?

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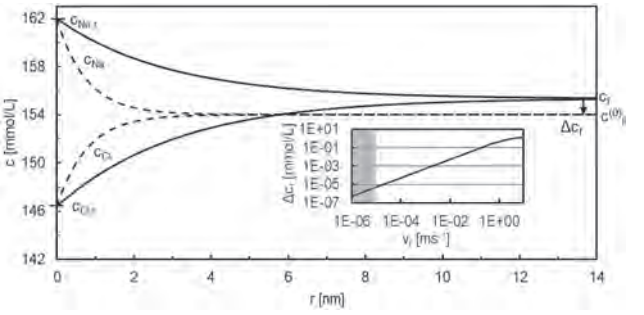
Background: High convective flow in high-volume hemodiafiltration has raised concerns that intradialytic electrolyte balance might be changed compared to standard HD, requiring adaptions of dialysate electrolyte prescription. The presence of charged proteins in the blood which are too large to penetrate the dialyzer membrane cause an asymmetric small ion distribution governed by the Gibbs-Donnan equilibrium (GDe). Derivations of GDe in most cases ignore the hydrodynamic drag from transmembrane fluid flow. We studied the effect of this flow by numerical simulations in an extended model.

Methods: The Nernst-Planck equation was extended by an advective term taking into account the hydrodynamic transmembrane flow as an additional driving force for ion transport. For the simplest case of two oppositely charged monovalent permeable ions a set of differential equations was derived. This allowed for a numerical calculation of permeable ion concentrations on both sides of the membrane depending on the transmembrane flow speed. The deviation of ion concentrations from their equilibrium values was analyzed for different ion species and concentrations for a large range of transmembrane flow rates.

Results: Even in the case of a non-zero convective flow, equilibrium concentrations are already reached a few nm from the inner membrane boundary, thus still within the membrane pores (cf. Fig. 1). These concentrations differ slightly from what is expected from classical Gibbs-Donnan equilibrium. However, in a typical HDF treatment, where transmembrane flow speed is less than 10^{-5} ms^{-1} this deviation is less than 6 10^{-5} mmol/L.

Conclusions: Even in high volume hemodiafiltration the transmembrane flow has negligible influence on the equilibrium electrolyte concentrations.

Funding: Commercial Support - Fresenius Medical Care Deutschland GmbH



Na^+ and Cl^- concentrations in filtrate (c_{Na} and c_{Cl}, resp.) at transmembrane flow speed v_f = 0 (dashed lines) and v_f = 10 ms^{-1} (solid lines). c_f and $c^{(0)}{}_f$: equilibrium concentrations at v_f > 0 and v_f = 0, resp.; $\Delta c_f = c_f - c^{(0)}{}_f$. Gibbs-Donnan ratio r_D = 0. 95.Insert: Δc_f as a function of v_f; shaded region: range of flow speeds in medical applications.

SA-PO567

Noninvasive Assessment of Liver Disease and Outcomes in ESKD

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Background: People with ESKD often exhibit risk factors (diabetes mellitus, obesity and hypertension) for non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH). NAFLD and NASH both associate with increased cardiovascular risk and by 2030 NASH will be the leading cause of cirrhosis. Little is known about prevalence and clinical outcomes of NAFLD and NASH in ESKD. We report updated interim results from this study non-invasively evaluating liver disease in ESKD.

Methods: This prospective observational study involves 451 prevalent patients with ESKD receiving dialysis for >3 months at 5 UK kidney units. A FibroScan (Echosens) measured hepatic steatosis using controlled attenuation parametrography and fibrosis using transient elastography. Survival analyses were performed using Kaplan-Meier estimates and a Cox regression model for multivariate analysis.

Results: Median patient age was 62. 61% of patients were male. 93% had hypertension, 48% diabetes and 63% hyperlipidaemia. 33% had a BMI of greater than 30kg/m^2. 27% had suspected NAFLD and 12% suspected NASH. There was increased mortality with suspected hepatic fibrosis grades F2-4 (19.1% vs 2.5% in grades F0-1). Kaplan-Meier survival curves are shown in Figure 1. Mortality in participants with suspected hepatic fibrosis grades F3-4 was significantly increased after adjustment for other predictors of survival (Figure 2).

Conclusions: There is significant burden of suspected hepatic steatosis and fibrosis in ESKD. Suspected F3-4 fibrosis is an independent risk factor for mortality in this interim analysis. Strategies to improve liver health in advanced kidney disease may be of benefit.

Funding: Commercial Support - Associates of Cape Cod, Inc

Figure 1 Overall survival by Fibrosis stage

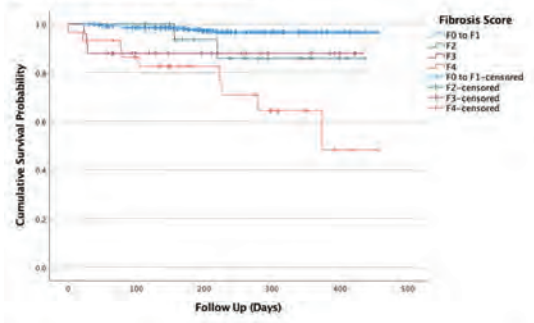
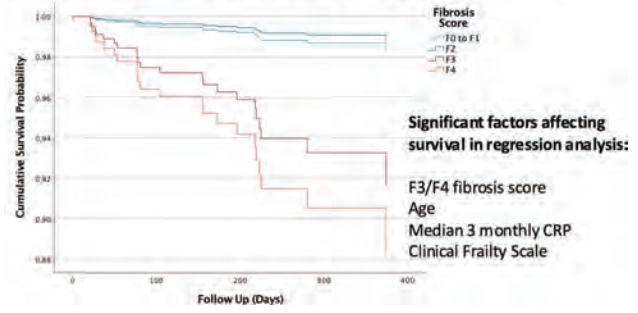


Figure 2 Cox proportional hazards regression model of survival by Fibrosis stage



SA-PO568

The Relationship Between Myocardial Fibrosis and Physical Activity in Individuals Receiving Hemodialysis

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Background: Individuals with end stage kidney disease receiving haemodialysis have high levels of myocardial fibrosis, which is thought to contribute to their excess cardiovascular burden. In addition, these individuals are physically inactive, which directly associates with high levels of cardiovascular and all-cause mortality. However, the relationship between physical activity levels and myocardial fibrosis has not previously been explored.

Methods: This is a post-hoc analysis of baseline data from the CYCLE-HD trial. Participants wore an accelerometer on the upper arm for 7 days; average steps per day were calculated by dividing the total number of steps by days worn. Global, septal and non-septal native T1 times (a surrogate of myocardial fibrosis) were acquired using cardiac MRI. Spearman's correlation and multiple linear regression analyses (adjusting for age, gender and diabetes) were performed to investigate associations between steps per day and T1 variables.

Results: Data for 102 participants were included. Mean steps per day were 3180±282. Steps per day had a significant negative correlation with global native T1 (-0.308; P = 0.002), non-septal T1 (-0.287; P = 0.004) and septal T1 (-0.275; P = 0.005). This relationship persisted after adjustment (Table 1).

Conclusions: Increased physical activity defined by average daily step count, associates with lower levels of myocardial fibrosis. Overall the levels of physical activity were low (comparable to levels reported in other studies), however these data indicate that even these levels (below recommended guideline levels) may be beneficial. Longitudinal studies are needed to understand the mechanisms behind these findings.

Table 1. Multiple linear regression showing the association between steps per day, Native T1, Non-septal T1 and Septal T1

	Standardised coefficients β (95% CI)	P-value
Steps per day and CMR (n=102)		
Native T1	-0.004 (-0.007 to -0.001)	=0.003
Non-septal T1	-0.004 (-0.006 to -0.001)	=0.009
Septal T1	-0.004 (-0.007 to -0.001)	=0.007

*There was no significant association between myocardial fibrosis and other variables (age, gender and diabetes) in the regression analyses.

SA-PO569

Assessing Muscle Mass and Radiodensity via Chest CT for Prognostic Insights in Hemodialysis Patients

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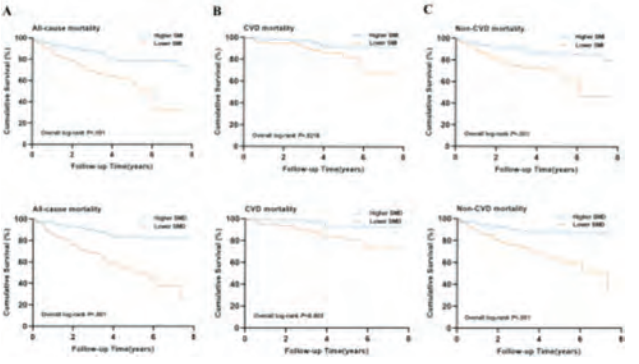
Background: CKD often leads to PEW, which in turn contributes to the development of sarcopenia. This condition is strongly associated with increased mortality. Consequently, evaluating muscle mass in HD patients is of significant clinical relevance. However, the relationship between muscle mass measured by Chest CT and prognosis for HD patients remains unclear.

Methods: Between January 2015 and December 2019, we conducted a retrospective study involving HD patients in a hemodialysis center. Chest CT scans at T12 level were analyzed using segmentation software to assess SMI and SMD.

Results: A total of 303 patients were included, with a mean age of 55.4± 16.6 years and a median follow-up period of 4.6 years. During the follow-up period, 78 deaths occurred. Sex-specific cut-offs of SMI and SMD were determined using maximally selected rank statistics analysis: 96 patients(31.6%) with SMI <30(male) or <24.35(female) cm^2/m^2 and 99 patients(32.6%) with SMD <38.61 (male) or <31.44(female) HU were categorized as having lower SMI and lower SMD, respectively. Patients with lower SMI and lower SMD consistently demonstrated an increased risk of any cause deaths, as evidenced by Kaplan Meier survival curves. After adjusting for confounding factors using mult ivariate Cox proportional risk models, lower SMI and lower SMD were independently associated with a higher risk of all-cause mortality and non-cardiovascular mortality. This association persisted in subgroup analyses and competitive risk model. Adding SMI and SMD to the established risk model improved the C-index from 0.78 to 0.82 (P < 0.001), with similar results observed in NRI and IDI. Decision curve analysis revealed that the prognostic model incorporating both SMI and SMD yielded the highest net benefit for predicting all-cause mortality.

Conclusions: SMI and SMD measurements derived from chest CT-T12 images provide valuable prognostic information, potentially enhancing the criteria for chest CT use in sarcopenia studies among HD patients.



Kaplan-Meier analysis of any cause mortality.

SA-PO570

Association Between Muscle Quality Measured by Computed Tomography and Valvular and Thoracic Aortic Calcification in Maintenance Hemodialysis Patients

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Background: Extra-coronary calcification (ECC) is independently associated with Cardiovascular disease (CVD). Low muscle mass is known to be related to vascular calcification. We evaluated whether muscle quality measured by computed tomography was associated with the risk of ECC in maintenance hemodialysis (MHD) patients.

Methods: The patients who underwent MHD in our Blood Purification Center from January 1, 2020 to December 31, 2022 were enrolled. Chest computed tomography images were collected and an open-source software 3D Slicer (version 5.0.3) was used to assess muscle quality (by skeletal muscle density, SMD, HU) at L1 level. The whole thoracic aorta calcification scores (TACS) and calcification scores of the 3 segments of thoracic aorta, including ascending thoracic aorta (ATACS), aortic arch (AoACS), and descending thoracic aorta (DTACS) were measured by 3D Slicer. 2-dimensional ultrasonic echocardiography was used to assess the number of calcified valves and patients were divided into 3 groups. We used multivariable linear regression analysis and cumulative logit model respectively to explore relationships between SMD and ECC.

Results: The age of 1076 patients was (57.98±14.49) years old, 59.3% of patients were male and the median dialysis age was 52 (17, 96) months. SMD was significantly negatively associated with TACS (model 1 [adjusted for age and sex]: standardized coefficient [β], -0.38 [95%CI, -0.51 — -0.24, P<0.001]; model 2 [adjusted for all factors in model 1 plus body mass index, smoking status, history of drug usage and past history]: β, -0.39 [95%CI, -0.52 — -0.25, P<0.001]; model 3 [adjusted for all factors in model 2 plus primary disease, dialysis vintage and laboratory results (albumin, interleukin-6, uric acid, et al)]: β, -0.44 [95%CI, -0.60 — -0.29, P<0.001]). Similarly, SMD was negatively correlated with ATACS, AoACS and DTACS. Additionally, increased SMD reduced the

risk of cardiac valve calcification (model 1: odds ratio [OR], 0.92 [95%CI, 0.89 — 0.95, P<0.001]; model 2: OR, 0.91 [95%CI, 0.88 — 0.95, P<0.001]; model 3: OR, 0.90 [95%CI, 0.86 — 0.95, P<0.001]).

Conclusions: This is the first study evaluating the association between skeletal muscle quality and ECC in MHD patients. We identified significant negative associations between muscle quality and specific markers of ECC.

Funding: Government Support - Non-U.S.

SA-PO571

Intradialytic Plantar Electrical Stimulation Boosts Mobility and Physical Activity in Frail Patients: A Randomized Controlled Trial

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Background: Frailty is notably pervasive in hemodialysis (HD) patients and contributes to diminished physical activity, poor quality of life, and mortality risk. Our study aimed to assess the efficacy of a targeted intradialytic plantar E-stim intervention to enhance mobility in frail diabetic HD patients.

Methods: Participants randomized into intervention group (IG, n=35) and control group (CG, n=33). IG received plantar E-stim treatment and CG had a non-operational device both for 1 hour with their HD sessions for 12-week period. To assess daily physical activity, participants wore a monitoring pendant for two consecutive days both at the onset of the study and following the 12-week intervention.

Results: The IG and CG showed no significant differences in age, sex, BMI, or frailty rates. Remarkable group x time interaction effects were noted in terms of physical activity (total standing transition: p=0.017; total walking transition: p=0.015) and mobility capacity (total steps: p=0.040) among frail patients. The IG demonstrated notable enhancements in standing (+18.12%, Cohen's d=0.315) and walking transitions (+17.10%, Cohen's d=0.476) from baseline to the 12-week mark. In contrast, the CG displayed a decrease in physical activity (Standing: -14.80%, Cohen's d=0.281; Walking: -23.59%, Cohen's d=0.365). Mobility capacity decline was less in IG (-3.48%, Cohen's d=0.048), while CG saw a significant reduction (-52.85%, Cohen's d=0.644).

Conclusions: This study highlights that intradialytic plantar E-stim substantially enhances both physical activity and mobility, particularly among frail HD patients. Given these findings, it is recommended that E-stim be integrated as an adjunctive measure to routine HD treatment.

Funding: Government Support - Non-U.S.

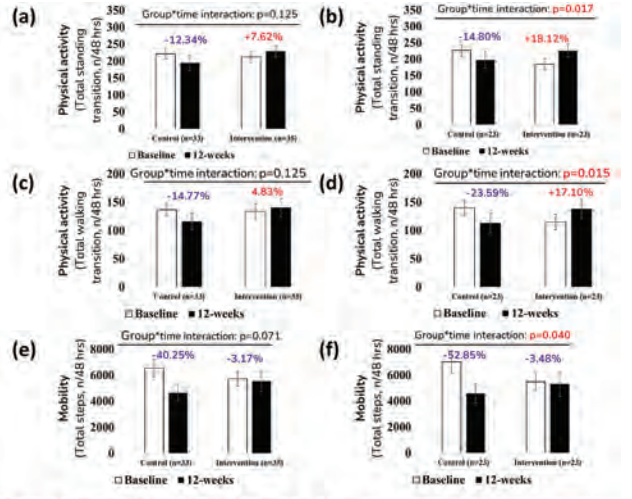

Figure 1. Changes of daily physical activity for 48 hours: (a), (c), and (e) reflect all participants including non-frail patients; and (b), (d), and (f) includes only frail patients.

SA-PO572

Roles of Irisin, a Myokine on Uremic Sarcopenia

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Background: The prevalence of sarcopenia is high in patients with CKD. Further, sarcopenia is reported to be closely associated not only with reduced physical activity but also with mortality. Recently, it has been noticed that skeletal muscles immediately after exercise secrete bioactive substances called myokines, which are associated with metabolic improvement and muscle mass increase. Irisin, one of the myokines, has been found to play an important role in the maintenance of endothelial function, thus contributing to the development of atherosclerotic vascular diseases. Furthermore, Irisin is known to be decreased in CKD condition and its levels are associated with the severity of atherosclerosis, possibly contributing to the increase in cardiovascular complications in CKD. In this study, we investigated the role of Irisin in uremic sarcopenia.

Methods: In the clinical study, we examined the relationship between serum Irisin and sarcopenia, exercise intensity, and atherosclerosis in 65 hemodialysis patients in our hospital. In vivo study, we performed 5/6 nephrectomy on C57BL/6J mice as a CKD model, and the exercise group received an exercise intervention for 10 weeks. We measured serum Irisin, the expression levels of FNDC5 (a precursor of Irisin) in skeletal muscle, serum creatinine, muscle mass, and grip strength, and evaluated renal lesions, especially endothelial damage by PAS staining and glycocalyx staining.

Results: In dialysis patients, Irisin levels tended to be lower in the patients with low physical performance/activity. The same tendency was also found between Irisin levels and the markers of atherosclerosis such as ABI or Agatston score. In vivo study, the expression levels of FNDC5 were significantly decreased in the skeletal muscle of CKD model mice compared to sham mice. Along with decreased Irisin levels, glomerular endothelial injury assessed by glycocalyx staining and glomerular sclerosis was observed in the CKD model. Exercise intervention significantly not only ameliorated FNDC5 expression and increased serum Irisin levels but also halted progressive renal dysfunction by inhibiting endothelial damage in CKD model mice.

Conclusions: These observations suggest that impaired Irisin release could be a culprit for CVD in CKD, which could be restored by exercise training.

SA-PO573

Sarcopenia with Central Obesity Is Associated with an Increased Risk of All-Cause Mortality in Maintenance Hemodialysis Patients

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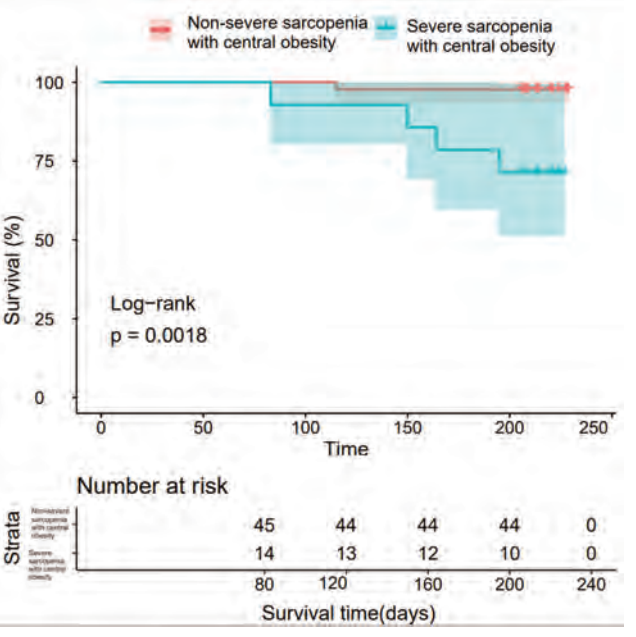
Background: Sarcopenia, a common condition found in maintenance dialysis (MHD) patients, is known to be linked to higher rates of illness and death. Several studies have indicated that central obesity can predict cardiovascular mortality in MHD patients. However, there is a knowledge gap regarding the impact of sarcopenia with central obesity on the survival of MHD patients.

Methods: This retrospective, observational, cohort study enrolled MHD patients on Sept 1-31, 2022. The Asian Working Group for Sarcopenia criteria and the waist hip rate (WHR) were used to diagnose sarcopenia with central obesity. Additionally, demographic, body composition, clinical laboratory and body composition by bioimpedance were collected. The primary outcome is all-cause mortality with MHD patient.

Results: A total of 59 MHD patients were included in this study, specifically, the prevalence of sarcopenia was 44.1% and the prevalence of sarcopenia with central obesity was found to be 49.2%. Over a median follow-up period of 214 days, a total of 5 (8.5%) deaths occurred. Univariate Cox regression analyses revealed several factors associated with an increased risk of mortality, including age (HR: 0.055; p=0.098), 5-time chair stand test (HR: 0.044; p=0.029), and severe sarcopenia with central obesity (HR: 2.651; p<0.001). However, in the multivariate analysis, only severe sarcopenia with central obesity remained independently associated with all-cause mortality (HR: 2.734; p=0.015), indicating that severe sarcopenia with central obesity was linked to an increased risk of all-cause mortality in MHD patients.

Conclusions: It is crucial to consider the presence of central obesity when evaluating the correlation between sarcopenia and adverse outcomes in individuals undergoing dialysis.



SA-PO574

Sarcopenia Prevalence According to Short Daily and Conventional Hemodialysis Regimens: Preliminary Findings from the SARC-HD Study

Heitor S. Ribeiro,[1] Marvery P. Duarte,[1] Fábio A. Vieira,[1] Victor M. Baião,[1] Priscila M. Varela,[4] Jacqueline F. Monteiro,[3] Antonio Jose Inda-Filho,[2] Otavio Nobrega.[1] *[1]Universidade de Brasilia, Brasilia, Brazil; [2]Centro Universitario ICESP, Brasilia, Brazil; [3]DaVita Brasil Participacoes e Servicos de Nefrologia Ltda, Rio de Janeiro, Brazil; [4]IdealCor, Brasília, Brazil.*

Background: Sarcopenia is a skeletal muscle disorder characterized by the loss of muscle strength, muscle mass, and performance, and is highly prevalent in patients undergoing hemodialysis (HD). Despite the increasing interest and clinical recognition, there is little understanding of how sarcopenia evolves across users of different modalities of HD regimens. Therefore, we investigated the prevalence of sarcopenia according to short daily and conventional hemodialysis regimens.

Methods: This cross-sectional multicenter study included eight dialysis units in Brasilia, Brazil, and enrolled adult patients undergoing HD for ≥3 months. Muscle strength was evaluated by handgrip strength and five-time sit-to-stand test. Calf circumference was used to estimate muscle mass, and physical performance through the 4-m gait speed test. Stages of sarcopenia were defined according to the revised European Working Group on Sarcopenia in Older People. Patients were stratified according to the hemodialysis regimen, short-daily (5 to 6 sessions/week, duration ~2h30) and conventional (3 sessions/week, duration ~4h).

Results: The study enrolled 258 patients (66% male, 58.3 ± 0.9 years), 45% on conventional HD. The overall prevalence of probable sarcopenia (low muscle strength), sarcopenia, and severe sarcopenia was 26.7%, 26.7%, and 8.5%, respectively. No significant differences were found in the prevalence of sarcopenia, low muscle mass, and low physical performance between patients undergoing short daily and conventional HD (30.3% vs. 22.4%; $P > 0.05$). The low muscle strength was significantly higher in patients undergoing short daily compared to those receiving conventional HD (19.0% vs. 32.0%; $P = 0.024$).

Conclusions: Our multicenter study revealed a high prevalence of sarcopenia; however no significant difference was observed in prevalence between different HD regimens. Nevertheless, patients on short daily regimens had a higher prevalence of low muscle strength. This highlights a potential association between the HD regimen and the primary manifestation of sarcopenia, precisely muscle strength.

SA-PO575

Body Composition and Coronary Artery Calcification in a Prospective Hemodialysis (HD) Cohort: A Substudy of the NIH THYROID-HD Trial

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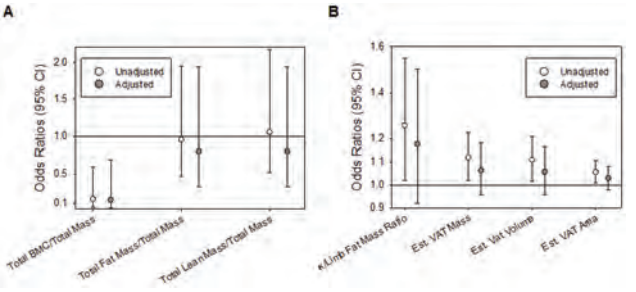
Background: HD patients have a high burden of coronary artery calcification (CAC), which is associated with CV mortality. We examined the relationship of body composition assessed by dual-energy x-ray absorptiometry (DXA) with CAC measured by cardiac CT in a prospective HD cohort.

Methods: In a substudy of the multi-center NIH THYROID-HD Trial, we examined associations of specific DXA body composition metrics (ratios of total body mineral content (BMC)/total mass, total fat mass/total mass, total lean mass/total mass) with elevated CAC Agatston scores (>400 Hounsfield units) in HD patients with upper reference and subclinical hypothyroid range TSH levels (>3.0-10.0mIU/L) using logistic regression. In secondary analyses, we examined the relationship between novel DXA visceral adiposity metrics (trunk/limb fat mass ratio, visceral adipose tissues (VAT) mass, VAT volume, VAT area) and elevated CAC scores.

Results: In 189 HD patients with baseline DXA and CAC measurements, the median (IQR) of CAC scores was 388 (29, 1978). Each +Δ0.02 increase in total BMC/total mass ratio was associated with lower risk of elevated CAC in adjusted analyses: OR (95%CI): 0.14 (0.03, 0.69) (**Fig A**). In unadjusted analyses, higher trunk/limb fat mass ratio (+Δ0.2), VAT mass (+Δ100 g), VAT volume (+Δ100 cm^2), and VAT area (+Δ100 cm^2) were each associated with higher risk of elevated CAC: ORs (95%CIs): 1.26 (1.02, 1.55), 1.12 (1.02, 1.23), 1.11 (1.02, 1.21), and 1.06 (1.01, 1.10), respectively (**Fig B**). While adjusted analyses narrowly missed statistical significance, point estimates showed higher CAC risk with higher VAT values.

Conclusions: In a subcohort of patients from the NIH THYROID-HD Trial, higher BMC/total mass was associated with lower risk of CAC, whereas higher visceral adiposity value was associated with higher CAC risk. Further research is needed to determine if VAT reduction lowers CAC risk in HD patients.

Funding: NIDDK Support



SA-PO576

Body Composition and Its Response to Intradialytic Exercise in Kidney Failure: A Combined Analysis of the PEDAL and CYCLE-HD Randomised Controlled Trials

Khai Ping Ng,[1] Jamie H. Macdonald,[2] Robin Young,[3] Daniel S. March,[4] Matthew Graham-Brown,[5] Tom Mercer,[6] Sharlene A. Greenwood,[7] James Burton,[5] Indranil Dasgupta.[8] *[1]University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom; [2]Institute for Applied Human Physiology, Bangor, United Kingdom; [3]University of Glasgow, Glasgow, United Kingdom; [4]University of Leicester, Leicester, United Kingdom; [5]University of Leicester Department of Cardiovascular Sciences, Leicester, United Kingdom; [6]Queen Margaret University Division of Dietetics Nutrition Biological Sciences Physiotherapy Podiatry and Radiography, Musselburgh, United Kingdom; [7]King's College London Centre for Nephrology Urology & Transplantation, London, United Kingdom; [8]University Hospitals Birmingham NHS Foundation Trust, Birmingham, United Kingdom.*

Background: Patients with kidney failure on hemodialysis (HD) are at high risk of sarcopenia obesity, highlighting the need for effective nutrition and exercise strategies to improve long-term outcomes. This post-hoc analysis of the PEDAL and CYCLE-HD studies aimed to 1) determine the clinical utility of fat tissue index (FTI) and lean tissue index (LTI) in comparison to body mass index (BMI) and 2) assess the effect of a 6-month intradialytic exercise intervention on FTI and LTI compared to usual care.

Methods: BMI, FTI and LTI were *a priory* secondary endpoints in both the PEDAL and CYCLE-HD trials. BMI was classified as per WHO definitions. FTI and LTI were determined by Bioelectrical Impedance Analysis (BIA) and classified as per the MONDO study, that found an FTI of 4-15kg/m^2 and an LTI of 15-20kg/m^2 were associated with best survival.

Results: Across both studies, 298 participants had BIA measurement at baseline; with 209 at baseline and 6-months. Mean age was 58±15 years, 65% male, median HD vintage 1.3 years (IQR 0.5-3.4) and mean BMI of 28.3±6.3kg/m^2. BMI correlated with FTI (r=0.79; p<0.0001). Of those with healthy BMI (n=198), 17% were over-nourished by FTI (>15kg/m^2) and 74% undernourished (LTI <15kg/m^2). Conversely, among those with an FTI of 4-15kg/m^2, 14% were categorised as overweight or obese by BMI. There was no significant correlation between BMI and LTI; 24% had BMI ≥30kg/m^2 and LTI <15kg/m^2 (sarcopenic obesity); only 16% had both FTI of 4-15kg/m^2 and an LTI of 15-20kg/m^2. With intradialytic exercise, there was no significant difference between the groups in change over 6 months for LTI (-0.33, CI -1.08-0.41; p=0.4) or FTI (0.16, CI -0.69-1.00; p=0.7), regardless of compliance.

Conclusions: This study highlighted issues of body composition misclassification using conventional BMI cut-offs in HD patients. Only a minority of patients had both LTI and FTI within the range associated with best survival. The majority of patients had hidden sarcopenia with nearly 75% with normal BMI being sarcopenic. 6-months of intradialytic exercise did not improve body composition, suggesting alternative interventions are required to target fat and lean tissue mass and enhance patients' survival.

SA-PO577

Changes in Modified Creatinine Index Following Bone Fractures in Patients Undergoing Maintenance Hemodialysis

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Background: Previous research has shown associations between lower skeletal muscle mass and a subsequent increased risk of bone fractures in hemodialysis patients. However, limited data exist on whether fractures lead to a loss of muscle mass in this population.

Methods: We analyzed a historical cohort study of 2,292 patients undergoing maintenance hemodialysis in Japan. We compared longitudinal changes in modified creatinine index (mCI) as a surrogate marker of muscle mass in a subcohort of patients who experienced fractures during the 7-year study period and those who did not, matched by propensity score at 1:3. Follow-up started immediately prior to the occurrence of fracture in the fracture group and at study enrollment in the non-fracture group.

Results: During a median follow-up of 5.4 years (IQR, 2.5-7.0 years), 113 patients experienced clinical fractures, among which 84 patients had data on mCI over time. With the use of propensity-score matching, 66 patients who experienced a clinical fracture were matched with 198 patients who did not sustain a fracture. While the mCI remained virtually unchanged in the non-fracture group, there was a progressive decrease in mCI in the fracture group, with a 3.0% decrease from baseline at 1 year and an 8.0% decrease at 5 years. Similar findings were obtained for changes in nutritional indicators such as serum albumin and body mass index.

Conclusions: In patients undergoing maintenance hemodialysis, the occurrence of clinical fractures may lead to a subsequent reduction in muscle mass, as indicated by the modified creatinine index. Whether interventions to prevent muscle mass loss following a fracture improve clinical outcomes warrants further investigation.

SA-PO578

Metabolites Associated with Mortality in Hemodialysis Patients

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Background: Uremic toxins contributing to the increased risk of death in hemodialysis patients remain largely unknown. We used untargeted metabolomics profiling to identify plasma metabolite associated with mortality in hemodialysis patients.

Methods: We created a cohort of 465 participants from the Longitudinal US/Canada Incident Dialysis (LUCID) study in which we profiled 498 known plasma metabolites measured on an untargeted platform. We assessed the association between metabolites and 1-year mortality adjusting for age, sex, race, cardiovascular disease, diabetes, BMI, albumin, KT/V, dialysis duration, and country. We used limma, a metabolite-wise linear model with empirical Bayesian inference, and two machine learning models, LASSO and random forest (RF), for analysis. We corrected for batch effects in metabolite abundances using the removal of unwanted variation (RUV) method, and we accouted for multiple testing by false discovery rate (q) below 10%. We defined mortality-metabolite associations as robust if significant in the limma model ($q<0.1$) and at least of medium importance in both LASSO and RF models (metabolite is above the 70th percentile for the variable importance measure).

Results: The mean age was 61 years, 88% were male, 54% had diabetes and 48% had cardiovascular disease. There were 44 deaths (9.5%). The mean duration from dialysis initiation to metabolomic profiling was 62 days. We identified two metabolites significantly associated with 1-year mortality; mesaconate (HMDB0000749) and quinolate (HMDB0000232) ($q<0.1$ and high importance by both LASSO and RF). We identified 29 additional metabolites associated with 1-year mortality ($q\geq0.1$) with high and/or medium importance by both LASSO and RF.

Conclusions: We identified two metabolites significantly associated with an increased 1-year mortality risk in incident hemodialysis patients. Mesaconate is an intermediate in the glutamate degradation pathway and has not been previously designated as a uremic toxin. Quinolate is a product in the kynurenine pathway and has been previously considered as a uremic toxin. Our study identifies additional metabolites that could be further investigated for mechanisms of uremic toxicity and potetial targeted interventions to prevent poor outcomes.

SA-PO579

The Geriatric Nutritional Risk Index (GNRI) to IL-6 ratio as a Predictor of Mortality in a Long-Term Follow-Up of Hemodialysis Patients

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Background: Persistent inflammation is an important cause of protein-energy wasting, which is a potent predictor of mortality. Therefore, regular monitoring of inflammatory biomarkers concurrently with nutritional risk screening may be clinically useful for estimating mortality risk in dialysis patients.

Methods: In this multicenter prospective cohort study comprising 325 maintenance hemodialysis patients (38% female; median age, 66 years; age range, 20-91years), we investigated the effect of the ratio of geriatric nutritional risk index (GNRI) to plasma C-reactive protein (CRP), Interleukin-6 (IL-6) and Pentraxin 3 (PTX3) levels on 10-year all-cause mortality. We used Cox proportional hazards models to estimate mortality risk.

Results: A total of 170 (52.3%) patients died during the observation period. When adjusting for age, sex, dialysis vintage, diabetes mellitus and cardiovascular disease, patients with higher log GNRI/IL-6 had a significantly lower mortality risk (Hazard ratio [HR]: 0.58, 95%CI: 0.41-0.82; P=0.002). Higher log GNRI/CRP (HR:0.74, 95%CI:0.62-0.91, P=0.006) and higher log GNRI/PTX3 (HR:0.46, 95%CI:0.22-0.93, P=0.03) are also related to lower mortality risk.

Conclusions: The ratio of GNRI to plasma inflammatory proteins levels, especially the ratio of GNRI to IL-6, may be a useful biomarker for assessing mortality risk in hemodialysis patients. Nutritional risk screening is expected to improve the mortality prediction power of inflammatory biomarkers.

SA-PO580

Endothelial Glycocalyx Injury due to Hemodialysis Induces Intradialytic Hypotension

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Background: Hemodialysis (HD) plays a pivotal role in replacing renal function for patients with end-stage renal failure. When the patients undergo hemodialysis, HD complications, such as intradialytic hypotension and arrhythmia, are inevitable. The vascular endothelial glycocalyx, which exists on the inner surface of vascular endothelial cells and maintains vascular homeostasis, has been suggested to be impaired by hemodialysis. However, it is unclear whether the endothelial glycocalyx injury is associated with HD complications.

Methods: We enrolled the patients who underwent outpatient hemodialysis at Gifu Seiryu Hospital between April 2022 and July 2022 (346 hemodialysis sessions). Patients aged <20 years. This single-center retrospective study evaluated the association between syndecan-1, an endothelial glycocalyx dysfunction marker, and complications of hemodialysis. Complication events, as the primary outcome, were defined as intradialytic hypotension, arrhythmia, and subjective symptoms such as chest pain, nausea, general malaise, and leg cramps during HD. Patients undergoing outpatient maintenance HD at Gifu Seiryu Hospital undergo blood tests at the beginning of each month. The GEE model was used to reveal the association between the serum syndecan-1 concentration in pre-HD and hypotension. Age, sex, and BNP were included in the model as covariates to adjust for confounders.

Results: In total, 92 patients were enrolled. The median HD period was 40 months. The most common primary illness was diabetic nephropathy. In pre-HD, the median serum syndecan-1 concentration was 67.7 ng/mL. In post-HD, the median serum syndecan-1 concentration was 98.3 ng/mL. According to the generalized estimating equations (GEE) model adjusted for age, sex, BNP, and amount of water removed per hour, no association was found between serum syndecan-1 concentration in pre-HD and appearance of intradialytic hypotension (odds ratio (OR): 1.001, P<0.741). However, a GEE model using the same adjustment factors showed that the greater the amount of change in serum syndecan-1 concentration before and after HD, the more complications appeared (OR: 1.005, P<0.013).

Conclusions: The study revealed that the quantitative assessment of the endothelial glycocalyx injury by measuring the concentration of serum syndecan-1 during HD is associated with intradialytic hypotension.

SA-PO581

Variability of Troponin I Levels in Patients on Chronic Haemodialysis over One Week

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Background: Patients undergoing chronic haemodialysis (HD) have remarkably higher risk for major adverse cardiovascular events. Haemodynamic and volume changes inbetween dialysis sessions lead to constant cardiac burdain and strain which could increase cardiac troponin levels without signs and symptoms of an acute coronary syndrome (ACS). This makes it more difficult to diagnose acute disorders. Primary goal was to evaluate the basal troponin values of HD patients on their first weekly treatment (the highest volume overload) and observe value oscillations during the week.

Methods: Data of 67 patients (24 female, 43 male) undergoing chronic HD programme at Dubrava University Hospital were collected after aquiring informed consent. Troponin levels were measured multiple times during the period of one week, using Beckman Coulter High-Sensitivity Troponin I (hs-cTnI) assay - before every HD session, after the first session that week and the day after the first session, what resulted with 3 to 5 values per patient depending on the dialysis regiment. Upper reference limit (URI) for hs-cTnI is <14.9 ng/L for female patients and <19.8 ng/L for male patients.

Results: Before the first session, mean basal hs-cTnI was 30,6ng/L (range 5,1 ng/L - 211,2 ng/L), with differences in male (34,6ng/L – 75% higher than URI) and female patients (23,8 ng/L – 60% higher than URI). More male patients had hs-cTnI levels in the reference interval, 51% opposed to 36% of female patients. However, more male patients had values higher than 50 ng/L (6 males, 1 female). The highest mean value was measured after the first dialysis session of the week (32,7 ng/L) and the lowest before the last session in the week (25,8 ng/L). A 7-percent rise in mean value was recorded after one dialysis session. The coefficient of variation (CV) was measured for each patient and the mean CV for hs-cTnI values was 19,6% (2% - 67%) with significant difference between female (13,5%) and male (23%) patients.

Conclusions: Our results show that hs-cTnI values were elevated in 54% of patients on chronic HD without signs of ACS with mean value of 30,1 ng/L out of all the measurements. During one week hs-cTnI values were acceptably stabile with variability of 20%. Patient's hs-cTnI mean value could be taken as a personal basal value for comparison when diagnosing ACS.

Funding: Government Support - Non-U.S.

SA-PO582

Comparative Analysis of Cardiovascular Performance in Hemodialysis and Heart Failure Patients

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Background: Patients on hemodialysis (HD) exhibit significant impairment in cardiovascular functional capacity that may be comparable to those with non-CKD associated heart failure. The problem is that to-date, no studies have directly compared cardiovascular functional differences between patients on HD compared with non HD patients with heart failure with reduced ejection fraction (HFrEF) and HF with preserved ejection fraction (HFpEF). We hypothesized that patients on HD exhibit unique exercise ventilatory response patterns compared to those with HFrEF and HFpEF.

Methods: We conducted a cross-sectional analysis of patients on thrice-weekly HD versus HFpEF (EF ≥40%) and HFrEF (EF <40%) patients who underwent cardiopulmonary exercise test (CPET) at Indiana Universtiy. A total of 90 patients (age=55 [13] years; n=30 per group) were included in this analysis.

Results: There were no group differences in age, sex, or diabetes (all p's>0.05). The HD group had a higher prevalence of hypertension (p<0.001), lower hemoglobin (Hgb; p<0.001), and lower beta blocker (BB) use (p<0.001) compared to both HFrEF and HFpEF, and a higher proportion of smokers compared to the HFpEF group (p=0.017). After adjusting for these covariates, peak oxygen uptake (VO_2Peak) was lower in the HD (12.9 [12.0-14.1] mL/kg/min) and HFrEF (13.0 [12.2-14.3] mL/kg/min) groups compared to HFpEF (16.3 [15.5-17.6] mL/kg/min; p=0.028). Percent of heart rate reserve (% HRR) was lower in the HD group (37.8 [31.6-39.8]; p=0.011) compared to both HFrEF (57.0 [20.9-59.1]) and HFpEF (61.0 [54.8-63.0]). Additionally, VE/VCO_2 slope was lowest in the HD group compared to HFpEF and HFrEF (p<0.001). Hgb, smoking, VE/VCO_2 slope, and %HRR were significantly associated with VO_2Peak in the HD group; this differered with sex, race, VE/VCO_2 slope, and %HRR for HFrEF, and sex, BB use, and %HRR for HFpEF.

Conclusions: Patients on HD exhibit similar declines in VO_2Peak as those with HFrEF without significant CKD undergoing evaluation for heart transplant, exemplifying the dramatic effects of CKD on cardiovascular health. Chronotropic incompetence and impaired skeletal muscle reserve may be predominant drivers of impaired VO_2Peak in HD patients, while impaired lung capacity and cardiac output may be predominant drivers in patients with HFrEF and HFpEF.

SA-PO583

Correlation of Cardiac Function by Transthoracic Ultrasound and State of Inflammation in Asymptomatic Young Patients (18-40 Years), with Hemodialysis: A Single-Center Experience

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Background: Cardiac pathology is currently one of the leading causes of mortality worldwide, with chronic kidney disease being a major risk factor for cardiovascular-related deaths, especially in patients undergoing renal replacement therapy. Patients undergoing renal replacement therapy, such as hemodialysis, are subject to frequent changes in volume and persistent systemic inflammation. However, early monitoring and management of heart failure in young patients with chronic kidney disease are often lacking.

Methods: The aim of this observational, descriptive, and cross-sectional study was to evaluate the degree of cardiac dysfunction and inflammatory profile in young, asymptomatic hemodialysis patients, by analyzing their medical records, clinical analysis to evaluate the inflammatory profile of hemodialysis patients and performing a transthoracic echocardiogram.

Results: The study included 24 hemodialysis patients with a median age of 29 years (range 24-38 years) and no history of systemic arterial hypertension or cardiac disease at the time of data collection. There was a direct correlation between anemia and systolic dysfunction (p=0.013), as well as anemia and diastolic dysfunction (p=0.043). In relation with inflammatory profile we founded that elevated levels of ferritin were correlated with a higher degree of diastolic dysfunction (p=0.023), and low ferritin levels were associated with pericardial effusion (p=0.043).

Conclusions: Asymptomatic young patients on hemodialysis present with subclinical cardiac dysfunction associated with metabolic and inflammatory disorders. The presence of pericardial effusion was not associated with elevated inflammatory parameters, therefore detection of pericardial effusion by echocardiography is necessary for adequate control and preservation of cardiac function.

Tabla 4.* Correlación de variables analíticas con la *disfunción sistólica.

Laboratorios	Con DS *N*= 5	Sin DS *N*= 19	valor de *p*
URR %, *n* (%)			
Ideal >65%	3 (60)	15 (78.9)	0.384
No ideal <65%	2 (40)	4 (21.1)	
Ácido úrico mg/dl, n (%)			
<7.5	4 (80)	16 (84.2)	0.822
>7.5	1 (20)	3 (15.8)	
Anemia, *n* (%)			
Sí	4 (80)	4 (21)	**0.013**
No	1 (20)	15 (79)	
Ferritina, *n* (%)			
Baja	3 (60)	4 (22)	0.233
Normal	1 (20)	7 (36)	
Alta	1 (20)	8 (42)	
Transferrina, n (%)			
Baja	2 (40)	9 (47.3)	0.804
Normal	3 (60)	9 (47.3)	
Alta	0	1 (5.4)	

SA-PO584

Cardiac Autonomic Innervation Is Decreased in Postmortem Tissue from Individuals with ESKD Compared with Those Without

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Background: Cardiac innervation changes can lead to an imbalance in neural activation and arrhythmias. Although described in other disease states, changes in cardiac innervation have not been studied in ESKD.

Methods: Age and DM matched cases with ESKD and controls without ESKD (10/group) who underwent autopsy at NYU-affiliated hospitals (2012-2020) were identified. Demographic and CV history was collected from autopsy and medical records. Case and controls were selected based on availability of LV anterior wall sections without extensive fibrosis in the area of interest. We performed H&E staining, and immunohistochemistry for S100 (all nerves), Tyrosine hydroxylase (TH, sympathetic nerves) and trichrome staining for fibrosis. Staining and fibrosis were quantified within regions of interest in the epi-, mid- and endocardial ⅓ as density per mm^2 (primary outcome) or fibrosis %.

Results: Mean age: ESKD 66.7 vs. controls 65.6 y, sex: 50% female in both groups and DM was (80% in both groups), whereas 60% were Black in the ESKD group vs. 40% in the control group. All ESKD patients had ischemic heart disease vs. with 30% of controls. Most common cause of death: myocardial infarction (50% in ESKD, 30% controls) followed by pump failure. Overall nerve density was lower in ESKD compared to controls: S100 density in the mid (63.97/mm2 vs. 106.7/mm2, P=0.04) and endocardial (62.6/mm^2 vs. 203.2/mm^2, P=0.003) thirds. Sympathetic nerve density was lower in dual-stained sections, particularly in the endocardial region (65.9/mm^2 vs. 180.6/mm^2, P=0.002). Fibrosis was higher in those with ESKD in all regions (epi= 0.009 vs. 0.005, mid= 0.024 vs. 0.006, endo=0.033 vs. 0.006, P= <0.05 for all). Fibrotic area was not correlated with nerve density (overall and for sympathetic nerves) in regions of interest (P> 0.05 for all).

Conclusions: Reduced overall nerve density and sympathetic innervation observed in ESKD. Further studies are needed to evaluate cardiac innervation patterns in ESKD and its link to arrhythmia.

Funding: Private Foundation Support

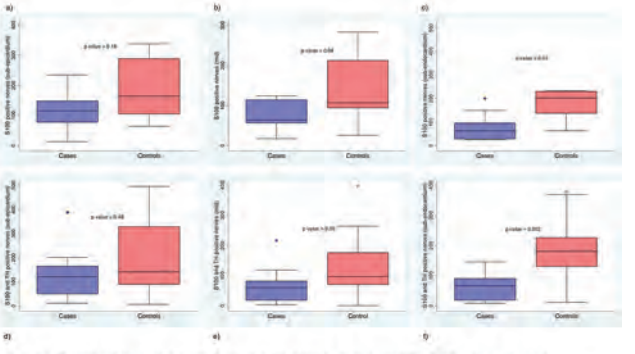

Figure: Top panel S100 positive and dual positive nerve density the sub-epicardial region (a,d), mid (b,e) and sub-endocardial regions (c,f)

SA-PO585

Automatic Detection of Intradialytic Paroxysmal Atrial Fibrillation and Flutter in Single-Lead ECG

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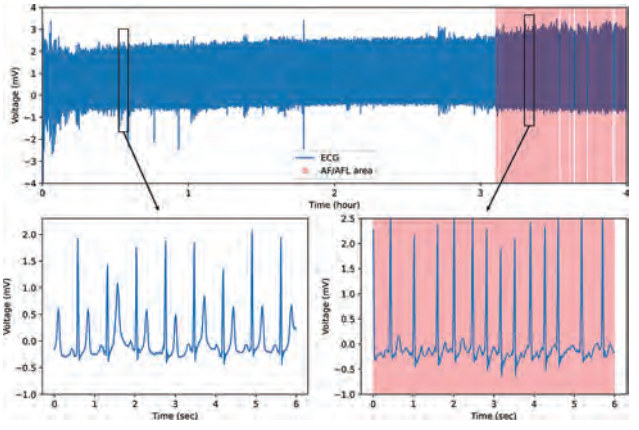
Background: Intradialytic paroxysmal atrial fibrillation and flutter (AF/AFL) can result in hemodynamic instability and suboptimal dialysis dose. To achieve appropriate prevention and management of intradialytic paroxysmal AF/AFL, the first step is precise detection during hemodialysis session. Herein, we developed a Transformer-based model to automatically segment AF/AFL in single-lead echocardiography (ECG) by self-supervised learning and masked signal modelling.

Methods: To develop a model, we used 11 open source databases containing 5,684-hour ECG signals from 2,017 patients. To validate a model, intradialytic ECG signals were retrieved from 4-hour 30 hemodialysis sessions at Seoul National University Hospital. AF/AFL was defined as ≥10-second duration, and the Swin Transformer model with wide window-size was adopted as a main architecture. The model performance was evaluated with F1 score.

Results: The model achieved F1 scores of 0.9612 and 0.9731 in segmenting AF/AFL and other rhythms, respectively. Throughout cross-database, F1 scores ranged between 0.8889 and 0.9896 depending on the prevalence of AF/AFL. Ablation analysis identified that the performance was attributable to pretraining with masking random signals and unlabeled database. The present model was superior to previous models in detecting AF/AFL particularly when training and testing databases were matched. When applying to intradialytic ECGs, the model showed favorable performance in segmenting AF/AFL areas.

Conclusions: The model with self-supervised learning and masked signal modelling maintains robust performance in various databases, which will help automatic detection of intradialytic paroxysmal AF/AFL.



SA-PO586

Clearance of Cardiac Troponins Depends on Hemodialysis Mode: A Randomized Cross-Over Trial

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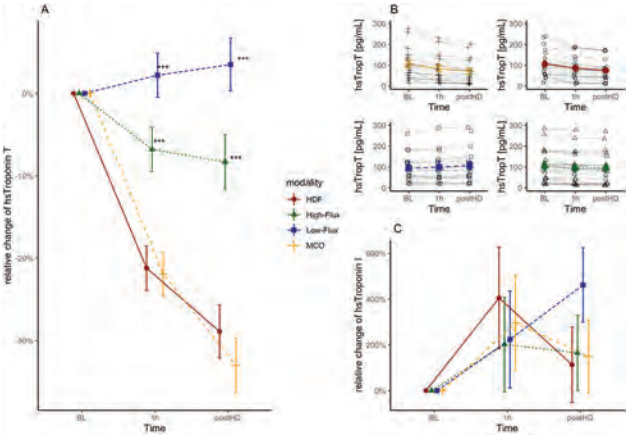
Background: Diagnosis of acute myocardial infarction (AMI) is difficult in hemodialysis (HD) patients as they less likely present typical features, thus, diagnosis relies on biomarkers. There is inconclusive data on cardiac Troponin (cTn) kinetics during HD without considering membrane characteristics.

Methods: We included prevalent, clinically stable HD patients and measured cTns (cTnT and cTnI) concentrations before, during and after HD with different modalities (low-flux HD, high-flux HD, hemodiafiltration [HDF] and medium cut-off (MCO)-HD). Treatment characteristics were standardized and similar between groups. The primary aim was to compare relative changes of cTns from baseline to after 1 hour of HD (Δ1h) for different dialysis modalities with secondary outcomes including absolute and relative changes of cTns during and after HD, using linear mixed models accounting for subjects, sequence, period and treatment.

Results: Of 20 patients, one patient was excluded because of NSTE-AMI, thus, 19 were included in final analysis. Of those 47.4 % were female (mean age 65.5±13.4 years, median dialysis vintage 19 months (min. 3, max. 165)). Different Δ1h were observed for MCO (least square mean [LSM] -21.9 ± 2.7%) vs. low-flux (+2.2 ± 2.7%, p<0.001) and MCO vs. high-flux (LSM -6.8 ± 2.7%, p<0.001) with no difference for MCO vs. HDF (LSM -21.2± 2.7%, p=0.81). Similar results were observed post HD. For absolute changes, LSM for MCO were -21.2 (± 3.2 pg/mL), -6.4 (± 3.2 pg/mL) for high-flux, -20.2 (± 3.2 pg/mL) for HDF treatment and +2.3 (± 3.2 pg/mL) for low-flux HD after one hour. There was no clear trend in cTnI kinetics.

Conclusions: Standard diagnostic AMI algorithms cannot be applied during HD. A Δ of >20% of cTnT, recommended by the SONG-HD MI group, occurs without evidence of ACS when MCO-HD or HDF are applied.



SA-PO587

Serum Endocan as a Risk Factor for Aortic Stiffness in Patients on Maintenance Hemodialysis

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Background: Endocan is secreted by the activated endothelium and plays a central role in inflammation and endothelial dysfunction, angiogenesis and vascular smooth muscle cell proliferation, it is associated with cardiovascular disease. This cross-sectional study aimed to assess the relationship between serum endocan levels and carotid–femoral pulse wave velocity (cfPWV) in patients on maintenance hemodialysis (HD).

Methods: Blood samples and baseline characteristics were collected from 122 HD patients. Serum endocan concentrations were measured with an enzyme-linked immunosorbent assay kit. Aortic stiffness was defined as a cfPWV of more than 10 m/s, while cfPWV values ≤ 10 m/s defined the control group, according to the ESH-ESC 2018 guideline.

Results: Of the 122 HD patients, aortic stiffness was diagnosed in 53 (43.4%) and higher percentages of diabetes ($p < 0.001$), hypertension ($p = 0.030$), were of older age ($p = 0.007$) and had higher systolic blood pressure ($p = 0.011$) and endocan levels ($p < 0.001$) in those with aortic stiffness than those without. After adjusting for factors significantly associated with aortic stiffness by multivariate logistic regression analysis, serum endocan (odds ratio [OR]: 1.566, 95% confidence interval [CI]: 1.224–2.002, $p < 0.001$), age (OR: 1.040, 95% CI: 1.001–1.080, $p = 0.045$), and diabetes (OR: 4.067, 95% CI: 1.532–10.798, $p = 0.005$) were independently associated with aortic stiffness in patients with chronic HD. Multivariable forward stepwise linear regression analysis also confirmed that the logarithmically transformed endocan level (β =0.405, adjusted R^2 change = 0.152; $p < 0.001$) was an independent predictor of cfPWV values. The area under the receiver operating characteristic (ROC) curve predicting aortic stiffness by serum endocan level was 0.713 (95% CI: 0.620–0.806, $p < 0.001$).

Conclusions: Serum endocan level positively correlates with cfPWV and is also an independent predictor of aortic stiffness in maintenance HD patients.

SA-PO588

The Association Between Adipokines and Cardiovascular (CV) Risk Factors in Hemodialysis Patients

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Background: Non-traditional risk factors in cardiovascular (CV) disease among hemodialysis (HD) patients include mineral bone disease and extracellular volume overload. Adiponectin is an adopokine that has an inverse relationship with CV disease in the general population, but studies in HD patients show conflicting results regarding its association with CV morbidity and mortality. We explored associations between adiponectin and leptin with various CV risk factors in a subset of an HD cohort.

Methods: We conducted a cross-sectional study of hypertensive HD patients. We measured adiponectin and leptin with ELISA from frozen plasma obtained in a midweek treatment. BP was measured per HD protocol. And we obtained pre and post HD measurements of ECV with bioimpedance spectroscopy. We conducted Pearson correlation and multiple linear regression analysis to determine associations between adipokines and other clinical variables.

Results: There were 24 participants who had adiponectin levels (mean 12238 [504] ng/mL) with 58% men, 58% Black, and 50% with diabetes. There were no differences in adiponectin based on sex, race or diabetes. Adiponectin correlated negatively with fat free mass (r=-0.51, p=.02) and dry weight (r=-0.44, p=.03). Leptin correlated positively with

fat mass (r=0.7, p=.004) and dry weight (r=0.6, p=.003), but had a negative correlation with ECV bodyweight (r=-0.8, p=.00001). Table 1 shows adiponectin was signficantly associated with dry weight, BP, phosphate, and ADMA (with independent associations of phosphate and ADMA).

Conclusions: Adiponectin was associated with known CV risk factors in a small cohort of HD patients, although phosphate was the only independent predictor. Leptin was associated with anthropometric measurements, consistent with findings from others. The association between phosphate and adiponectin is novel and warrants further investigation.

Funding: NIDDK Support, Veterans Affairs Support

Table 1:Linear regression (univariate and multivariate) analyses using plasma adiponectin as the outcome

	Univariate		Model 1		Model 2	
	Standardized Regression Coefficient	P. Value	Standardized Regression Coefficient	p-value	Standardized Regression Coefficient	P. Value
Phosphate	0.4	0.04	0.4	0.02	0.3	0.05
ADMA	0.4	0.05	0.4	0.02	0.3	0.05
Average Systolic BP	0.4	0.04	0.3	0.1		
Systolic BP(pre-HD)	0.5	0.02	0.4	0.06		
Estimated Dry Weight	-0.5	0.03				

SA-PO589

Association of Bioimpedance Parameters with Changes in Blood Pressure During Hemodialysis: A Secondary Analysis of the Frequent Hemodialysis Network (FHN) Daily Trial

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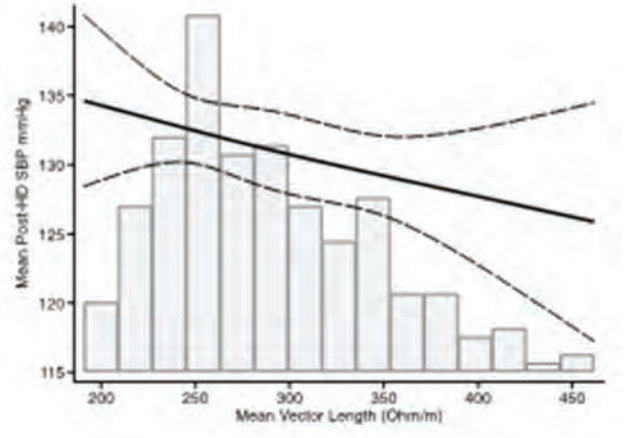
Background: Intra-dialytic hypertension (IDHyper) affects 5-15% of patients and is associated with cardiovascular and all-cause mortality. Hypervolemia is thought to be a major etiological factor, yet the association of objective measures of volume with IDHyper is not well described.

Methods: In post hoc analyses of the FHN Daily Trial (n=234), using data from baseline, 1, 4, and 12 months (n=800), random effects regression was used to assess the association of bioimpedance measures of volume and general health (vector length and phase angle) with post-HD SBP (continuous) and any increase in SBP (categorical) from pre- to post-HD. Models were adjusted for randomized group, age, sex, race, BMI, vascular access, HD vintage, hypertension, heart failure, diabetes, residual urea clearance, pre-HD SBP, hemoglobin, phosphorus, and eKt/V.

Results: Mean age was 50 ±14 years; 39% were female; 43% were Black. Shorter vector length (per 50 Ω/m) was associated with higher post-HD SBP (3.1 mmHg; 95%CI 2.0, 4.2; Fig. 1) and higher odds of IDHyper (OR 1.64; 95%CI 1.13, 2.39). The lowest tertile of vector length (vs. highest) was associated with higher post-HD SBP (6.3 mmHg; 95%CI 3.3, 9.3) and a trend toward higher odds of IDHyper (OR 2.09 95%CI 0.81, 5.35). Narrower phase angle (per 1 degree) was associated with higher post-HD SBP (1.0 mmHg; 95%CI 0.3, 1.6), and higher odds of IDHyper (OR 1.33; 95%CI 1.03, 1.72). The lowest tertile of phase angle (vs. highest) was associated with higher post-HD SBP (5.5 mmHg; 95%CI 2.6, 8.4) and higher odds of IDHyper (OR 2.74; 95%CI 1.11, 6.76).

Conclusions: Bioimpedance measures of volume status are independently associated with higher post-HD SBP and risk of IDHyper. Incorporation of bioimpedance measurement at individual HD sessions may help identify a subgroup of patients at risk of IDHyper.

Funding: NIDDK Support



Mean vector length and mean post-HD SBP

SA-PO590

Use of Novel and Conventional Cardiac Biomarkers to Assess Cardiovascular Risk in Hemodialysis Patients

Zachary J. Neronha, Andy Chuu, Frank J. O Brien. *Washington University in St Louis School of Medicine, St Louis, MO.*

Background: Hemodialysis patients experience greatly increased morbidity and mortality. Although the underlying etiology is not completely understood, volume overload likely plays an important role given their elevated risk of cardiovascular disease and especially heart failure. Biomarkers are commonly used to clinically assess volume status in cardiology patients, but cardiac biomarker use in dialysis patients is complicated by an incomplete understanding of biomarker clearance during dialysis and the complex interplay of renal and cardiac causes of volume overload. Here, we investigate a panel of conventional and novel cardiac biomarkers in a group of hemodialysis patients catagorized by their baseline ejection fraction.

Methods: We performed a descriptive, prospective cohort study utilizing a group of hemodialysis patients at the Chromalloy American Kidney Center, an outpatient hemodialysis center in St. Louis, MO serving approximately 150 ESRD patients. Study enrollment was randomized, and consisted of 35 patients seperated into 3 groups with ejection fractions <40%, 40-50%, and >50% based on a recent echocardiogram. The mean age was 62 and 94% were African American. Pre-dialysis blood was drawn to measure NT-proBNP, high-sensitivity troponin T (hsTnT), galectin-3, growth differentiation factor-15 (GDF-15), and soluble ST2 (sST2).

Results: Randomization produced a distribution of patients across the cohorts that was relatively equivalent in age, ethnicity and gender and differed with respect to EF. Preliminary data suggests that within our cohort, ejection fraction influenced novel cardiac biomarker expression. Patients with a lower ejection fraction had biomarker expression more suggestive of volume overload than those with preserved ejection fraction. Those with an EF of >50% also had a high level of cardiac biomarker expression.

Conclusions: Preliminary analysis of the baseline characteristics of this patient cohort suggests cardiac biomarker expression is influenced by ejection fraction. More study is needed to evaluate how cardiac biomarker data varies with volume optimization, and any predictive value it may have for major adverse cardiovascular events. We therefore plan to follow this patient cohort for an additional year to assess any changes in biomarker expression, future adverse events, and the impact of volume optimization on biomarker expression.

SA-PO591

Duration of Hemodialysis as an Amplifier of Thrombolytic Deficit and Oxidative Stress in ESRD

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Background: Thrombo-inflammation and oxidative stress increase as kidney function declines. Additionally, the incidence of thromboembolic events is several times higher in patients with end-stage renal disease (ESRD) on hemodialysis (HD). However, the mechanism underlying the increased risk for thrombotic events has not yet been thoroughly investigated. The aim of this study is to measure the level of biomarkers of thrombo-inflammation and oxidative stress in ESRD patients on HD and to investigate the association of those levels with HD duration.

Methods: In this cross-sectional study, levels of oxidative stress-related, and thrombo-inflammatory biomarkers, as well as blood cell count values were determined in plasma samples of ESRD patients undergoing HD at a single healthcare center. Time between sample collection date and the initiation of HD was correlated with the measured biomarker levels. Commercially available normal human plasma samples were used as a healthy control group.

Results: The study included 96 patients with median age of 64 years (interquartile range-IQR 50-74), and 40 healthy control plasma samples. The median time since initiation of HD in ESRD group was 62 months (IQR 25-94). The levels of tissue-type plasminogen activator (tPA) and functional plasminogen activator inhibitor 1 (PAI-1) were significantly higher in ESRD patients, compared to control group (Med 4.2 vs 0.4 ng/mL and Med 7.0 vs 3.2 IU/mL, respectively). Significant positive correlation of tPA and functional PAI-1 levels was observed with the time spent on HD in months (r=0.32, p=0.03 and r=0.35, p=0.02, respectively). Those biomarkers were entered into age-adjusted logistic regression model showing predictive potential of HD duration on functional PAI-1 levels only (OR 0.32, p=0.03) (Table 1).

Conclusions: Increase of functional PAI-1 during the time spent on HD clearly suggests that the risk of developing thrombotic complications may rise over time due to the increase of fibrinolytic deficit which is modulated by an upregulation of functional PAI-1 in ESRD patients on HD.

Biomarker (unit)	OR	95% CI	p
tPA (ng/mL)	0.130	-0.016 - 0.041	0.388
Functional PAI-1 (IU/mL)	0.323	-0.078 - -0.005	0.028

Table Footer

HD – hemodialysis; tPA – tissue-type plasminogen activator; PAI-1 – platelet activator inhibitor 1; OR – odds ratio; CI – confidence interval

SA-PO592

The CompAct-HD Trial Reports an Acute Complement Activity-Associated Inflammatory Response Within 15 Minutes of Starting Hemodialysis

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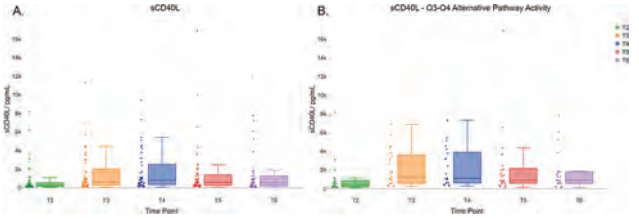
Background: It is well established that kidney patients experience aberrant complement pathway activation. A heightened inflammatory state is thought to contribute to excess cardiac deaths and cardiovascular events in those undergoing hemodialysis (HD). The aim of the CompAct-HD trial is to characterize complement activation and biomarker response to blood-membrane-circuit interaction during HD.

Methods: Six timed intradialytic blood samples were collected in 300 HD patients during a standard treatment with ultrapure water and high flux membranes. Complement activity potential was determined from timepoint 1 and inflammatory biomarkers from timepoints 2 to 6. Highly multiplexed assays enabled us to determine 60 biomarkers of complement activation and inflammation from a single blood sample.

Results: The 6 blood samples for each patient revealed changes in inflammatory biomarkers within 15 minutes (T3, sCD40L, panel A) of starting dialysis. There was a wide range in the magnitude of this response between individuals. Most biomarker levels increased, peaking during the first hour of dialysis and then fell; not always to the level at the start of dialysis. Interrogating the data for sCD40L to remove patients with Alternative Pathway activity in the first and second quartile showed that patients with complement activity above the median experienced a larger median inflammatory response at all time points (panel B).

Conclusions: Patients with an elevated complement activation potential experienced an exaggerated acute intradialytic inflammatory response within 15 mins of HD treatment, which did not always resolve to baseline by the end of the dialysis session.

Funding: Commercial Support - Invizius Ltd



SA-PO593

Immune Response of Heterologous vs. Homologous Prime-Boost Regimens with Adenoviral Vectored and mRNA COVID-19 Vaccines in Immunocompromised Patients

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Background: Due to rare but major adverse reactions to the AstraZeneca adenoviral ChAdOx1-S-nCoV-19 vaccine (ChAd), German health authorities recommended adults under 60 who received one dose of ChAd, to receive a second dose of the BioNTech mRNA BNT162b2 vaccine (BNT) as a booster. Studies in the general population suggest an enhanced efficacy of the heterologous (ChAd-BNT) compared to the homologous (BNT-BNT) vaccination regimen. However, an analysis of the efficacy in patient populations with a high risk of severe COVID-19 due to acquired immunodeficiency is still missing.

Methods: We therefore compared both vaccination regimens in healthy controls, patients on dialysis and patients with rheumatic diseases concerning the humoral and cellular immune response.

Results: The humoral and cellular immune response differed substantially in healthy controls compared to patients with acquired immunodeficiency. Overall, the most significant differences between the two immunization regimens were found in neutralizing antibodies. These were higher after a heterologous immunization. Healthy controls responded well to both vaccination regimens. However, the formation of neutralizing antibodies was more pronounced after a heterologous immunization. Dialysis patients, on the other hand, only developed an adequate humoral and particularly cellular immune response after a heterologous immunization. Rheumatic patients also - to a weaker extent compared to dialysis patients - benefited from a heterologous immunization.

Conclusions: In conclusion, the heterologous COVID-19 vaccination regimens (ChAd-BNT) seem to have an advantage over the homologous vaccination regimens, especially in immunocompromised patients such as patients with end-stage kidney disease treated with hemodialysis.

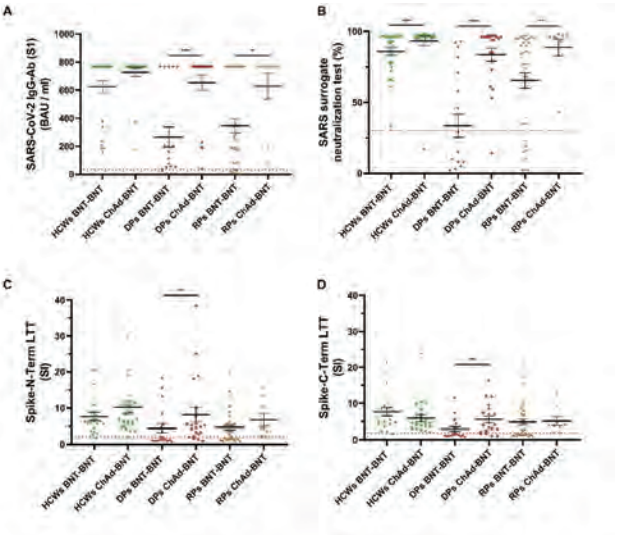

Figure 1. Scatterplots of humoral and cellular response to homologous (BNT-BNT) or heterologous (ChAd-BNT) COVID-19 vaccination regimens in participants with different medical conditions. All plots display geometric means with standard error of the mean (SEM). Statistical significance was assessed by Mann-Whitney U test. *, p<0.05, **, p<0.01, ***, p<0.001. HCWs, healthcare workers; ChAd, ChAdOx1-S-nCoV-19 vaccine; BNT, BioNTech mRNA BNT162b2 vaccine; DPs, dialysis patients; RPs, rheumatic patients; LTT, lymphocyte transformation test. (A) Scatterplots of SARS-CoV-2 IgG-Ab (S1) (BAU / ml). Red dotted line indicates the threshold value at 35.2 BAU / ml, n = 0, 0, 4, 0, 8, 0. (B) Scatterplots of SARS surrogate neutralization test (%). Red dotted line indicates the threshold value at 30%, n = 0, 1, 12, 1, 8, 0. (C) Scatterplots of Spike-N-Term LTT. Red dotted line indicates the threshold value at 1.9 SI, n = 1, 0, 11, 3, 15, 0. (D) Scatterplots of Spike-C-Term LTT. Red dotted line indicates the threshold value at 1.9 SI, n = 1, 0, 12, 4, 16, 0.

SA-PO594

Clinical and Biological Profile and Factors Associated with High Blood Lead Levels in Chronic Hemodialysis Patients in a Western French Guiana Hospital Center

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Background: Lead is toxic to the body. Its chronic intoxication combines various clinical and biological disorders that can be life-threatening. In French Guiana, lead poisoning is particularly worrying, as the incidence rate is nearly sixty times higher than in metropolitan France. In chronic hemodialysis patients, lead levels are often higher and can lead to several adverse consequences. Hence, the interest of this study, which is to describe the clinical and biological characteristics of chronic hemodialysis patients with high blood lead levels and to identify the associated factors to draw attention to its screening and the prevention of its complications.

Methods: Descriptive and analytical cross-sectional study that included 65 patients on chronic conventional hemodialysis: with an annual biological assessment in December 2022, including a serum lead assay. The outcome was the notion of hyper lead level, defined by a lead level > 85 µg/l. We described the clinical, biological, and dialytic parameters of patients with hyper lead levels and in logistic regression, we identified the factors that are correlated according to a significance threshold P<0.05.

Results: In total, 54% of patients had hyper lead levels, of which 2/3 were female. They were older, with an average age of 62. No patients had occupational exposure to lead. 94% were hypertensive and half were diabetic. 1/4 had anaemia and all had resistance to erythropoietin. Their ferritin levels were slightly lower, with an average of 721 µg/l. The mean albumin was 30 g/l, pre-albumin was 28 g/l, the mean parathyroid hormone was elevated at 1355 ng/ml, NT-pro BNP at 9144 ng/ml. The mean CRP was 10.8 mg/L. They had collapsed residual diuresis and natriuresis with averages of 150 ml and 12 mmol/24 hours, respectively. There was a significant positive correlation between elevated BLL and young age and negative correlation with female sex, low serum albumin, prealbumin, protein and ferritin levels, and collapsed residual diuresis.

Conclusions: High blood lead levels are common in the Guyanese chronic hemodialysis population in which it is correlated with female sex, malnutrition, iron deficiency and residual poor renal function and probably with resistance to erythropoietin treatment. It is necessary to screen in at-risk populations to prevent complications associated with it.

SA-PO595

Validity and Adequacy of Animal Models in Haemodialysis Research: A Systematic Review

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Background: With the worldwide dialysis population growing rapidly, there is an urgent need for hemodialysis (HD) innovations. However, before novel HD technologies can be implemented, extensive preclinical testing is required. Currently, there is no consensus on the most suitable animal model (species, type and validation of kidney injury etc.) for HD innovation research, nor are there gold standards for reporting efficiency outcomes.

Methods: This review, registered in PROSPERO (CRD42022307144), involved a systematic search in PubMed and Embase for relevant studies up to February 4th 2022. After removing duplicates, 5723 abstracts were screened for eligibility by three independent reviewers. Inclusion was based on publication of a HD intervention in any animal model with adequate kidney failure. Data from individual reports were subsequently extracted using predefined parameter sheets.

Results: Of the 5723 abstracts screened, 195 records were included as full text and 41 full text articles were included for data-extraction. Data extraction has been completed for all articles, but only qualitative analysis has been conducted thus far. Studies most frequently used dogs (54%), followed by rats (27%), pigs (8%), goats (6%), sheep, and cats (both 2%). Dog studies were primarily conducted before 2010, with a shift towards other large animals observed thereafter. Relevant descriptives such as strain, sex, weight, and age were not systematically reported, with only 4 (9%) records reporting all four parameters and 23 (49%) not reporting two or more. Regarding kidney injury, 42 (89%) studies used an acute kidney injury model, with kidney injury induced via surgery in 43 (91%) studies. One study validated the presence of kidney injury by measuring eGFR, while all other studies reported urea, creatinine, or both parameters. Finally, 30 reports (64%) performed only a single dialysis session per animal.

Conclusions: Use of dogs in HD research has significantly declined over the past decades, potentially due to a shift in public ethical perception. A notable concern is the overall inadequate adherence to the ARRIVE guideline for reporting. Our findings indicate no apparent improvement in reporting quality over time, highlighting the necessity for clear guidelines to drive innovative HD research.

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SA-PO596

Hyperammonemia in Multiple Myeloma (MM): Rare but Serious Complication

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Introduction: MM is characterized by abnormal plasma cell proliferation and clinical manifestations such as hypercalcemia, renal insufficiency, anemia, and bone lesions. Encephalopathy associated with MM can stem from hypercalcemia, hyperviscosity, or uremia. In rare cases, certain myeloma cell lines can cause hyperammonemia which can result in cerebral edema, high intracranial pressure, and high mortality rates. We present a case of hyperammonemic encephalopathy complicating relapsed refractory MM (RRMM) following an autologous stem cell transplant.

Case Description: A 62-year-old African American woman with RRMM following an autologous stem cell transplant presented with bone pain, increasing lethargy and confusion. Laboratory studies showed anemia, thrombocytopenia, low Kappa-Lambda ratio and normal calcium levels. Despite a normal liver function test, she had elevated ammonia levels, peaking at 157.3 umol/L. Her blood gas indicated chronic primary respiratory alkalosis (pH 7.51, PCO_2 23mmHg, HCO_3^- 18mmol/L) due to ammonia-stimulated ventilation. A head CT was negative for acute pathology. Findings were consistent with MM-induced hyperammonemic encephalopathy. Lactulose and rifaximin were started, but her ammonia level remained elevated. To aid in ammonia clearance, she underwent continuous renal replacement therapy (CRRT) at a a dose higher than standard (~35mL/kg/hr), while receiving aggressive chemotherapy (DCEP). After four days, there was an improvement in her ammonia level and mentation, and CRRT was discontinued. However, the patient was readmitted for hyperammonemic encephalopathy and ultimately transitioned to hospice care due to treatment failure.

Discussion: Hyperammonemic encephalopathy should be considered in MM patients with decreased consciousness. The exact mechanism is unclear but may be related to the production of ammonia by myeloma cell lines or to myeloma-related humoral factors which can affect amino acid metabolism leading to hyperammonemia. While rare, this manifestation may indicate an advanced disease state and an unfavorable prognosis. Management lacks consensus, but chemotherapy is crucial. Lactulose and rifaximin may reduce ammonia levels; however, renal replacement therapy is more effective in ammonia clearance and may prevent complications from prolonged hyperammonemia, including cerebral edema.

SA-PO597

A Case of Hepatic Encephalopathy During Hemodialysis

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Introduction: Hepatic encephalopathy (HE) is a serious neurological complication of portal hypertension (PH). A variety of dialysis-related factors can increase the risk of HE.

Case Description: A 50-year-old male with a history of nodular regenerative hyperplasia complicated by PH and recurrent ascites despite transjugular intrahepatic portosystemic shunt (TIPS) and kidney failure on hemodialysis (HD), hospitalized 2 times in 2 months for recurrent episodes of altered mental status (AMS) during HD sessions. The etiology of the AMS was suspected to be due to HE after an acute episode of confusion was witnessed during an inpatient HD treatment. Subsequent evaluation during this witnessed episode suggested worsening alkalosis during the course of his treatment (Table 1). Therefore, in subsequent HD treatments, his prescription was modified to lower blood flow rates and use of a lower bicarbonate (HCO3) bath (25 instead of 35). During the following 3 inpatient sessions, there were no more episodes of AMS. He subsequently underwent a TIPS revision which led to a complete resolution of his recurrent episodes of AMS.

Discussion: Ammonia exists in the blood as NH3 and $NH4^+$, but only NH3 can cross the blood brain barrier (BBB). Respiratory and metabolic alkalosis favors the production of NH3, and its CSF concentration can increase 2-3 fold. As a result, we suspect that in patients with PH who have undergone TIPS, HD can augment their risk of HE. Moreover, intradialytic hypotension (IDH) can lead to increased portosystemic shunting and increased ammonia levels. In this individual, the recurrent episodes of AMS occurring exclusively during HD sessions can plausibly be explained by a presumed increase in NH3 levels crossing the BBB and precipitating HE. The use of a lower HCO3 bath (25), and prevention of IDH, successfully temporized the patient while he awaited revision of his TIPS procedure.

	On admission	During AMS episode	Post HD session with HCO3:25 bath
Na	139	141	140
K	4.7	3.2	4.2
Cl	102	97	100
Carbone Dioxide	17	28	21
BUN	48	17	35
Creatinine	5.98	3.1	4.91
pH	7.6	7.65	
PCO2	22	27	

SA-PO598

Hydroxocobalamin-Triggered Blood Leak Detection During Hemodialysis in a Liver Transplant Patient

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Introduction: High-dose intravenous hydroxocobalamin, known as Cyanokit, is routinely administered for vasoplegic shock, a life-threatening complication from cardiac surgery when conventional vasopressors are insufficient to maintain an appropriate mean arterial blood pressure goal. In liver transplant patients, hydroxocobalamin use has become more common for vasoplegia and to decrease time on pressor dependence post-transplant. After liver transplant, some patients with acute kidney injury require continuous renal replacement therapy (CRRT) followed by transition to intermittent hemodialysis (iHD). Hydroxocobalamin is mostly excreted in the urine and has a half-life of 26-31 hours. It also has a deep red color, causing discoloration of body fluids, including urine and dialysis effluent. iHD machines have a light sensor to detect small blood leaks into the effluent as a safety feature to prevent unwitnessed hemolysis or bleeding into the filter. Interestingly, hydroxocobalamin is detected as a blood leak, which halts the hemodialysis procedure. Hydroxocobalamin does not affect CRRT, so patients remain on CRRT for approximately 5 days and then transition to iHD.

Case Description: A 67 year-old male with decompensated NASH cirrhosis and acute kidney injury from hepatorenal syndrome requiring dialysis underwent a liver transplant. He received hydroxocobalamin and was transferred to the SICU where he was started on CRRT briefly, and, given no pressor requirement, iHD was initiated. However, the iHD machine detected hydroxocobalamin as a small blood leak and stopped the procedure. CRRT was restarted. iHD was restarted after another 72 hours and no complications were noted.

Discussion: Hydroxocobalamin-triggered blood leak detection is common and causes increased time on CRRT. Fresenius iHD machine has a photometric sensor consisting of a green and red light transmitter and a photodetector. An alarm is triggered when green light is absorbed by blood and hydroxocobalamin is capable of triggering this alarm. Alternatives to allow for earlier transition to hemodialysis are other iHD machines that have different sensors that do not detect hydroxocobalamin, empirical adjustment of dialysate and blood flow to decrease detection of hydroxocobalamin, and treating intraoperative vasoplegic syndrome with methylene blue instead of hydroxocobalamin, which does not impair iHD.

SA-PO599

Purpuric Rash After Starting Hemodialysis: Not the Immediate Suspect

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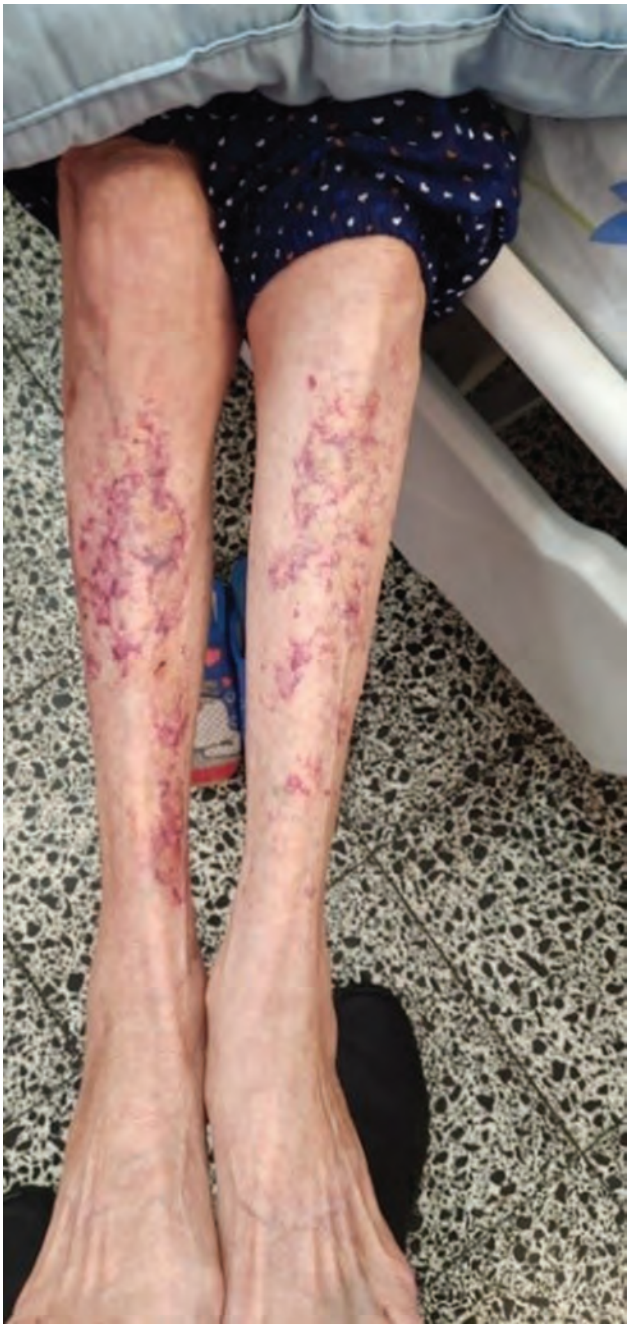
Introduction: Hemodialysis patients are at risk to develop vitamin C deficiency. Several factors can contribute to vitamin C deficiency, including potassium restricted diet, hemodialysis clearance of water soluble vitamins and increased oxidative stress leading to vitamin C utilization. However, clinical manifestation of scurvy is rare or overlooked. Herein, we report a case of scurvy in a hemodialysis patient.

Case Description: A 74-year-old patient with end stage kidney disease due to diabetic nephropathy has been treated with hemodialysis since 2020. During 2022, she was hospitalized several times due to pulmonary edema. A purpuric rash with perifollicular erythema was noted on her lower legs (Figure A). She also complained of gingival bleeding. Laboratory exam demonstrated undetectable vitamin C level (less than 4 mg/L), hypoalbuminemia and elevated CRP. Based on her dermatologic findings and labs results, a diagnosis of scurvy was made. After 2 months of daily vitamin C supplement, her symptoms and rash resolved, without episodes of pulmonary edema. Echocardiography demonstrated improved LV function (EF 35% improved to 45%), suggesting a therapeutic role for vitamin C repletion.

Discussion: Recommendation of Clinical Practice Guidelines for Nutrition in CKD about regular vitamin C supplementation is opinion based. The absence of rigorous recommendation stems from lack of double blind randomized controlled clinical trials that explored the potential beneficial effect of vitamin C supplementation and possible deleterious effect of calcium oxalate supersaturation, accumulation and deposition. This case is a reminder that scurvy can occur in hemodialysis patients and may contribute to cardiovascular complications. A high clinical awareness is warranted in order to diagnose this treatable devastating disease.



SA-PO600

Recurrent Severe Hypersensitivity Reactions Following New Start of Hemodialysis

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Introduction: Hypersensitivity reactions are a known complication of dialysis. Most cases are due to ethylene oxide, membrane filters, or medications. We present a case of a patient with recurrent hypersensitivity reactions on dialysis despite numerous changes to his dialysis configuration.

Case Description: A 78 yo male with chronic kidney disease and hypertension presented to our hospital with anuric AKI requiring hemodialysis (HD). A few minutes prior to the end of his first HD session, he developed hypotension for which treatment was stopped. 90 minutes into his second session, he developed hypotension, loss of consciousness (LOC), and ventricular tachycardia, all of which resolved after treatment was stopped. He had no significant electrolyte abnormalities, no ischemic changes on EKG, and his hemoglobin was stable. No other patients who underwent HD that day had a similar reaction. During his next 4 sessions, he developed LOC and hypotension requiring norepinephrine despite switching dialysis machines and reverse osmosis machines, as well as using a hypoallergenic dialyzer (Cellentia-19), priming the circuit with 2 liters of saline, and pre-treatment with diphenhydramine, cimetidine, and prednisone.

His symptoms occurred progressively sooner with subsequent HD sessions and resolved each time with discontinuation of treatment. An IgE level was elevated but an ethylene oxide IgE level, C3/C4, and tryptase were normal. An ethylene oxide IgE level obtained 1 month later was normal. He tolerated treatment with a NxStage machine with gamma sterilized tubing but did not tolerate a subsequent attempt using an Optiflux dialyzer and NovaLine bloodlines. He did tolerate further treatments with a Revaclear dialyzer and Novaline bloodlines. The patient became progressively debilitated with difficult road to recovery. He elected to forgo further HD treatments and opted for comfort-oriented care.

Discussion: This patient developed a constellation of symptoms most consistent with severe anaphylactoid reactions on dialysis. Through a series of trial and error of adjusting different components of his dialysis apparatus, he was found to be non-tolerant of ethylene oxide treated components and tolerant of the gamma irradiated ones. This case demonstrates the potential severity of dialysis reactions and the importance of considering every step and component in evaluating the cause.

SA-PO601

A Unique Case of Dialysis Hypersensitivity Reaction in a Critically Ill Patient on Continuous Renal Replacement Therapy

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Introduction: Allergic reactions are well-established life-threatening complications of dialysis, however these reactions pose a diagnostic challenge in critically ill patients on continue renal replacement therapy (CRRT) who may have other severe illnesses confounding the picture. We present a case of a dialysis-related anaphylactic type reaction to a CRRT system sterilized with ethylene oxide (EtO).

Case Description: A 48-year-old male with hypertension and undifferentiated inflammatory arthritis presented with shortness of breath and dark tarry stools. The patient's initial work up was significant for anemia with hemoglobin 4.1 gm/dL and concern for pneumonia. The hospital course was complicated by acute hypoxic respiratory failure requiring mechanical ventilation, septic shock requiring vasopressor support, and AKI secondary to ATN with peak creatinine 4.01 mg/dL from prior baseline 0.94 mg/dL. Nephrology was engaged for initiation of CRRT due to worsening pulmonary edema in the setting of oliguria >72 hours. The patient experienced repeated episodes of severe hypotension upon starting CRRT which required escalation of vasopressor doses. These episodes persisted despite extra rinsing of the filter with albumin and saline. He also experienced repeated episodes of circuit clotting despite anticoagulation with heparin and citrate. There was high suspicion for a dialysis-related reaction to the EtO sterilized CRRT system and the patient was transitioned to intermittent hemodialysis with a steam sterilized system which was tolerated without any complications. He underwent another session without incident and ultimately experienced kidney recovery.

Discussion: This case highlights the importance of having high clinical suspicion for dialysis related reactions, particularly in the ICU setting when the diagnosis may be more challenging. We believe the patient's repeated severe hypotension when starting CRRT was likely due to an IgE mediated hypersensitivity to the EtO sterilized CRRT system. EtO, a chemical known to cause type A dialysis reactions, is no longer used to sterilize most dialyzers however it is important to recognize several CRRT systems as well as dialysis tubing and ancillary components may still use EtO. Due to this, it is imperative to increase provider education and awareness of dialysis reactions particularly in the complex ICU setting.

SA-PO602

Dialysis in Diabetic Ketoacidosis (DKA)? Profound Acidemia in the Setting of Diabetic Ketoacidosis Triggered by Inferior ST-Elevation Myocardial Infarction (STEMI)

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Introduction: Diabetic ketoacidosis (DKA) is a life-threatening condition that can cause severe acidemia impairing cardiac contractility and vascular tone. The role of bicarbonate therapy remains controversial. We present a case of severe DKA triggered by an myocardial infarction that required continuous venovenous hemodialysis(CVVHD) for severe acidemia.

Case Description: A 32 year old female with poorly controlled Type 1 Diabetes mellitus was brought to the ED unresponsive. Family reported preceding nausea, vomiting, and confusion after heavy alcohol use and skipping insulin. She was hemodynamically stable but obtunded with dry mucous membranes and Kussmaul respirations. VBG showed a pH<6.8, pCO2 16mmHg, bicarbonate<2mmol/L, potassium 6.7mmol/L and lactate 9.9mmol/L. Serum glucose was 1255mg/dL, BHB >4.5mmol/L, and creatinine 2.24mg/dL (baseline 0.7mg/dL). ECG revealed ST elevations in inferior leads. The patient received bicarbonate based crystalloids along with insulin. Two hours later, VBG showed persistent severe academia (pH 6.85) and a rising serum Troponin. Despite improving urine output, given severe acidemia, CVVHD was started (effluent dose: 30ml/kg/hr). The patient's pH normalized and a left heart catheterization was done revealing an 80% thrombotic lesion in the RCA which was stented. Dialysis was continued for 8 hours with careful attention to potassium balance. Kidney function recovered with creatinine dropping to 1.01mg/dL after 24 hours. Overshoot alkalosis with mild alkalemia (pH 7.49) followed and was managed expectantly. Patient was discharged two days thereafter with appropriate follow-up.

Discussion: DKA is a life threatening condition triggered by infections, stroke, malignancy, myocardial infarction, or medical nonadherence. In addition to managing DKA, timely identification of the underlying trigger is critical to patient outcomes. The role of bicarbonate therapy in DKA is controversial and the role of renal replacement therapy in severe cases remains undefined. This case illustrates the use of bicarbonate based fluids and ultimately CVVHD successfully to control the patient's severe metabolic derangement to expedite timely revascularization. Hourly assessments with careful attention to potassium balance and acid base status is critical to this strategy.

SA-PO603

Managing Phosphate Repletion During Continuous Renal Replacement Therapy in the Setting of Severe Hyperbilirubinemia

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Introduction: Continuous renal replacement therapy (CRRT) is commonly used for critically ill patients with acute kidney injury. Among CRRT-associated adverse effects, hypophosphatemia is common. Strategies to prevent or treat hypophosphatemia include protocolized phosphate replacement and use of dialysate/replacement solutions containing phosphate. Most patients on CRRT require phosphate supplementation, particularly after the first 48 hours. Our facility, which uses dialysate without phosphate, has a replacement protocol guided by serum phosphate levels drawn every 6 hours.

Case Description: A patient with acute-on-chronic alcoholic liver disease and hepatorenal syndrome was treated with continuous veno-venous hemodialysis without replacement fluid: Blood flow rate 300 ml/min and dialysate flow rate 29 ml/kg/hr. The patient had severe jaundice with total bilirubin of 35 mg/dL. This rendered the colorimetric assay of serum phosphorus inaccurate and not reportable. Protocolized phosphate replacement based on serum levels became impossible. To measure serum phosphate without bilirubin interference, we measured phosphate levels in the effluent as a surrogate. Simultaneously, we measured serum urea nitrogen (SUN) and effluent dialysate urea nitrogen (EDUN), as a quality control measure to assess dialysate saturation.

Discussion: During CRRT, 90-100% dialysate saturation is assumed to occur for small molecules with sieving coefficients near 1.0, such as urea and phosphate. EDUN (56mg/dL) agreed closely with SUN (52.4mg/dL), demonstrating that effluent dialysate was saturated and in equilibrium with plasma. Dialysate phosphate was 4.6mg/dL. We inferred that dialysate phosphate was reasonably equivalent to serum phosphate and were able to circumvent bilirubin interference with serum phosphate assay. The patient received protocol-driven phosphate replacement, guided by dialysate effluent phosphorous measurements, which ranged between 2.4-5.1mg/dL. The use of effluent phosphorus levels as a serum phosphorus surrogate provides a novel approach for guiding phosphate replacement in patients with severe hyperbilirubinemia. *The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

SA-PO604

Dialyzing or Hemolyzing? A Case of Continuous Renal Replacement Therapy (CRRT) Filter Hemolysis

Tyler Maggio, Iiro Honkanen. *University of Iowa Hospitals and Clinics, Iowa City, IA.*

Introduction: Evidence of hemolysis in the inpatient setting evokes a broad differential. Devices are frequently employed to support vital organ functions that can introduce an additional mechanism for hemolysis that expands the differential. Here we describe a case of hemolysis secondary to filter induced lysis as part of a continuous renal replacement therapy (CRRT) circuit.

Case Description: A 43-year-old man presented with altered mental status, shortness of breath, and hypotension. He had a history of systolic heart failure, CKD stage 4, Type 2 diabetes, and chronic normocytic anemia. Workup was pertinent for worsening ejection fraction with elevated NT-proBNP consistent with cardiogenic shock with AKI on CKD for which he remained oliguric despite diuretic challenge. CRRT was initiated on day 2. On hospital day 16 the hemoglobin dropped to a nadir of 5.9 g/dL that did not respond appropriately to blood transfusions. Plasma free hemoglobin was elevated with undetectable haptoglobin. Direct antibody testing was negative. Liver enzymes, fibrinogen, and platelets were stable. There was concern for intradialytic hemolysis based on amber tinge in the effluent dialysate bag and otherwise unrevealing workup. CRRT pressures were reviewed and within normal ranges and no kinks were identified in the circuit. Plasma free hemoglobin was measured pre and post filter which identified a 20% increase from 1017 to 1282 mg/dL. The CRRT circuit was discontinued with subsequent improvement in serum hemoglobin and normalization in plasma free hemoglobin. No additional evidence of hemolysis was identified. The CRRT circuit was resumed with a new filter from a different lot on hospital day 18 with no further hemolysis observed.

Discussion: Hemolysis is a serious condition that may be associated with worse morbidity and mortality in the setting of severe illness. CRRT access sites as well as the individual components of the circuit serve as potential sources of mechanical hemolysis. Plasma free hemoglobin can be sampled at various points of the circuit to suggest the source of hemolysis. Once an implicated component has been identified, the circuit should be reset with monitoring for improvement of hemolysis. CRRT use is increasing in ICUs, so clinicians should be aware that filter induced mechanical hemolysis is a rare but plausible cause of hemolysis that can be easily corrected.

SA-PO605

Iron Poisoning and the Utility of Continuous Renal Replacement Therapy (CRRT)

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Introduction: Iron poisoning is a rare life-threatening condition. The primary method for iron removal remains chelation therapy, and continuous renal replacement therapy (CRRT) should be utilized as an adjunctive therapy. We describe a case on the role of RRT in iron chelation for severe iron poisoning.

Case Description: An 18 Year old man with unremarkable past medical history presented to the hospital with intentional overdose secondary to ibuprofen and iron. He was initiated on chelation agent, deferoxamine, and referred to our center for transplant evaluation. Initial iron profile was significant for an iron level of 320 ug/dL. Peak iron levels of > 3000 ug/dL were seen 3 hours after presentation and trended to < 90 ug/dL 48 hours after presentation. Baseline serum creatinine of 0.5-0.8 mg/dL, and at the time of his presentation was 0.78 mg/dL and so toxicology recommended initiation of CRRT to ensure deferoxamine clearance. Imagining studies did not demonstrate iron deposits in the kidneys. 5 days after ingestion, the patient successfully underwent hepatitis C virus positive orthotopic liver transplant. He was eventually liberated from renal replacement therapy 7 days after initiation.

Discussion: This case highlights the important supportive role of CRRT in the management of iron overdose. Iron poisoning can lead to significant hemodynamic instability, including hypotension and fluid shifts and it can also lead to direct toxic effects. Iron poisoning can also lead to electrolyte derangements such as hyponatremia, hyperkalemia, or metabolic acidosi. In both instances, CRRT helps maintain fluid balance by allowing for precise control of fluid removal, replacement, and electrolyte adjustments. Additionally, chelating agents are mostly excreted in the urine unchanged. In cases where iron chelation therapy is utilized, especially if there is any renal impairment, CRRT can assist in removing the chelating agent from the bloodstream and preventing its accumulation and potential adverse effects. Of note hepcidin and pro-hepcidin have molecular weights of 2.7 KDa and 10 KDa, respectively, and, therefore, may be removed by CRRT, which uses membranes with a cut-off of 35 KDa. Nephrologists should be liberal in the use of CRRT especially if patients are receiving chelation therapy or have any degree of renal insufficiency.

SA-PO606

Ifosfamide-Induced Neurotoxicity Treated with CRRT

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Introduction: Ifosfamide is an alkylating chemotherapeutic agent with wide application in treatment of multiple gynecological cancers. Encephalopathy is one of the worrisome complications of ifosfamide therapy occurring in about 10-40% of the patients. We discuss a case of a 63-year-old female who developed ifosfamide-induced encephalopathy after an acute kidney injury (AKI).

Case Description: 63 year old female patient with past history of uterine adenocarcinoma. She required multiple lines of chemotherapy, the latest regimen included doxorubicin and ifosfamide. Her clinical course was complicated by obstructive uropathy from the uterine mass and she required bilateral nephrostomy tube insertion. She also had recurrent AKI, severe metabolic acidosis and hypokalemia that was attributed to tubular toxicity from Ifosfamide. Her creatinine partially recovered and remained ~2 mg/dl with eGFR of 27 ml/min. She also had ifosfamide induced neurotoxcity and was successfully treated by IV methylene blue. She was admitted for her 3rd cycle of chemotherapy. On admission, her creatinine was 2.6 mg/dl. Her kidney function initially improved with IV fluids however worsened again and her creatinine peaked at 2.69 mg/dl. Both nephrostomy tubes were patent and kidney ultrasound showed no hydronephrosis. Her hospital course was complicated by altered mental status, CT scan brain showed no acute intracranial findings. She was treated for ifosfamide induced neurotoxicity with IV methylene blue however her mental status worsened, and she was transferred to the ICU. It is also notable that the patient was treated with aprepitant for nausea earlier in her admission and may have contributed to slowed metabolism of ifosfamide and decreased response to methylene blue. She was started on CVVHD given the concern of poor renal clearance of ifosfamide. She received 4 days of CVVHD, her mental status gradually improved, and the dialysis line was removed.

Discussion: This case illustrates the successful use of CVVHD in a patient with suspected ifosfamide neurotoxicity. An acute kidney injury along with use of aprepitant made the patient more prone to accumulation of toxic metabolites, which was not responsive to methylene blue. With increasing therapeutic options for cancer treatment, the nephrologist's role in handling medication side effects will continue to expand.

SA-PO607

A Tale of Two Lines: Line Positioning Affecting Ability to Tolerate CRRT

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Introduction: Continuous renal replacement therapy (CRRT) is the modality of choice for delivering dialysis to patients with hemodynamic instability. However few patients have a precipitous drop in blood pressure with initiation of CRRT warranting discontinuation, followed by prompt improvement in blood pressure. Some of this drop in blood pressure could be secondary to removal of vasopressors by CRRT. The degree of blood pressure drop is likely related to the proximity of vasopressor delivery to the arterial end hole of the hemodialysis catheter and the prescribed clearance. We report a patient who tolerated CRRT when the vasopressors were infused through a distal port of a Trialysis (Power-Trialysis, short-term triple lumen dialysis) catheter instead of PICC (peripherally inserted central catheter) line which was delivering the pressors close to arterial end hole of the Trialysis catheter.

Case Description: A 64-year-old female who was being treated with antibiotics through a right arm PICC for leg stump infection was transferred to ICU due to acute kidney injury and septic shock. Norepinephrine and vasopressin were infused as vasopressors through the PICC. A right internal jugular Trialysis catheter was inserted to initiate dialysis. CRRT was attempted twice with precipitous drop in blood pressure within 3-5 mins needing significant increase in vasopressor dose, warranting discontinuation of CRRT. A prompt rise in blood pressure and decrease in vasopressor dose to that pre CRRT was noted following discontinuation of CRRT. The possibility of vasopressors being removed by CRRT was suspected due to the proximity of the tip of the PICC to the Trialysis catheter arterial end hole. CRRT was reattempted after switching vasopressors infusion from the PICC to the distal port of the Trialysis catheter. Patients' hemodynamics stayed stable affirming the suspicion of vasopressor removal by CRRT.

Discussion: Inadvertent removal of vasopressors should be considered as a potential cause of hemodynamic instability during CRRT initiation. Risk can be mitigated by infusing the vasopressors away from the arterial end hole of dialysis catheter either distally or proximally, which can be achieved by repositioning the tip of catheter.

SA-PO608

Dialysis Disequilibrium Syndrome in a Patient with a Relatively Low Blood Urea Nitrogen (BUN)

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Introduction: Dialysis disequilibrium syndrome (DDS) is characterized by a range of neurologic symptoms that can affect patients when they first start hemodialysis (HD) or after multiple missed HD sessions.

Case Description: A 39-year-old patient with a history of lung transplant 5 years ago for idiopathic pulmonary fibrosis, stage 5 chronic kidney disease secondary to CNI toxicity, was admitted with severe nausea/vomiting. On physical examination his BMI was 20, normal vital signs, and no pericardial rub or asterixis were noted. Laboratory results: sodium 135, potassium 4.1, creatinine 8.9, blood urea nitrogen (BUN) 65, bicarbonate 18, blood venous gas 7.26/41. Hemodialysis (HD) was initiated (duration 2 hours, blood flow rate: 200 mL/min, dialysate flow rate: 400 ml/min, dialysate sodium: 138 mEq, dialysate bicarbonate: 25 mEq/L, fluid removal: 0.5L, urea reduction rate: 50%), immediately after his first HD, the patient complained of nausea, vomiting, and moderate to severe headaches. DDS was suspected and 100 ml of 3% hypertonic saline was administered with rapid resolution of the symptomatology, a subsequent head CT scan did not show cerebral edema.

Discussion: DDS is an uncommon but serious complication after HD initiation primarily caused by cerebral edema. The pathogenesis is not clearly defined. The generation of osmotic gradients due to the rapid reduction of extracellular urea and other osmoles could create a transient osmotic gradient between plasma and brain cells. Rapid correction of metabolic acidosis during HD could lead to intracellular cerebral acidosis. Risk factors include first HD, extremes of age, markedly elevated BUN (>175 mg/dl), and conditions associated with increased permeability of the blood-brain barrier (BBB). Hypertonic saline or mannitol to reduce the osmotic gradient is recommended as a treatment. Preventive measures include limiting the BUN clearance to <40%, the use of sodium modeling, or the prophylactic use of hypertonic saline or mannitol. The development of DDS in this patient was unexpected, considering his low BUN and the HD prescription that was used. Potential explanations include the generation of organic osmoles in uremic patients other than urea, that increase the permeability of the BBB and act as osmotically active substances generating an osmotic gradient. The prompt treatment led to full neurologic recovery.

SA-PO609

Dialyzing Brain Dead

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Introduction: Organ transplantation has been increasing worldwide, many of the patients die on wait list. The clinical progression of hemodynamic instability after brain death leads to possible loss of organs that could be harvested. Here we present a case of a twenty-six-year-old male who received kidney replacement therapy after being declared brain dead and was able to successfully donate his organs as per his organ donation status.

Case Description: A twenty-six-year-old male admitted after a motor vehicle accident, was found to have multiple fatal injuries including intracranial hemorrhage. Unfortunately, he succumbed to his injuries and was declared brain dead. He subsequently developed oliguric acute kidney injury (AKI) due to acute tubular necrosis as noted on urine sediment with muddy brown casts, leading to volume overload and hyperkalemia. Nephrology was consulted for stabilization before organs could be procured. Patient was started on Extracorporeal Kidney-Replacement Therapy in the form of Sustained low-efficiency dialysis (SLED). Continuous kidney replacement therapy (CKRT) might have been a preferred option, but due to non-availability of CKRT at our center SLED was initiated. SLED was done to minimize the hemodynamic changes. The heart and

left kidney were evetually procured and successfully transplanted. Family played an important role in deceased organ procurement and helped with every manner.

Discussion: Nearly half of discarded kidneys from 2010-2020 were from donors with AKI. Management of organ donor with AKI is often curtailed due to hemodynamic and electrolyte instability. Dialysis can correct the effects of AKI, but is rarely started after brain-death. Extracorporeal kidney-replacement therapy following brain death has not been extensively explored, CKRT has been studied to some extent. Brain dead patients with AKI treated CKRT have a favorable outcomes in organ donation. At our center, a brain-dead patient received dialysis in the form of SLED which improved hyperkalemia and volume overload, enabling the successful organ procurement. There is a need for further investigation into dialysis after death for organ procurement. Any intervention or treatment provided after death creates an ethical dilemma. There is a need to examine the ethical considerations and guidelines around the use of extra-corporeal kidney replacement therapy in brain dead patients for organ procurement.

SA-PO610

The Role of Duloxetine for Management of Persistent Hypotension in ESKD

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Introduction: Uremic neuropathy is a known complication of end stage kidney disease (ESKD) that has significant morbidity and mortality. It can present as distal sensory, motor neuropathy, or autonomic dysfunction that worsen over several months. ESKD patients can develop intra-dialytic hypotension or persistent hypotension due to sympathetic and parasympathetic dysregulation characterized by preserved cardiac index, absence of reflex tachycardia, anhidrosis and reduction is systemic vascular resistance. Here, we evaluate the use of duloxetine, a serotonin–norepinephrine reuptake inhibitor, for management of persistent hypotension in ESKD on hemodialysis.

Case Description: 33-year-old lady history of ESKD started on hemodialysis for 19 years that over the past 5 years patient has been experiencing progressive and persistent hypotension. 5 years ago, her blood pressure was 90/50mmHg and now it is constantly 40/20 mmHg. Underwent cardiac, and endocrine investigation of hypotension with no specific cause. Therefore, thought to be associated with uremic neuropathy causing autonomic dysfunction. Despite intensifying hemodialysis, use of midodrine, hydrocortisone, and fludrocortisone, patient had no improvement in hypotension. Due to the severe hypotension the patient developed bilateral ischemic retinopathy and vision loss, multiple small bowel ulceration, and peripheral neuropathy. Patient was started on duloxetine 40mg daily trial for peripheral neuropathy. Within one week of therapy, patient noted improvement in neuropathic pain and in addition, blood pressure increase to 50/26. With Blood pressure improvement, patient developed diffuse and constant pulsing headaches required oral analgesic. Upon discontinuing duloxetine, headaches resolved and blood pressure returned to her baseline (41/19).

Discussion: Duloxetine has been commonly used for treatment of depression and anxiety in addition to peripheral neuropathy. One of the known side effects of duloxetine is hypertension, which is thought to be due to increase in norepinephrine levels, therefore, agonizing alpha-receptor, arterial vasoconstriction and increase systemic vascular resistance. Hence, duloxetine has a potential role in management of uremic neuropathy and an alternative treatment of persistent hypotension in ESKD.

SA-PO611

One-Year Effect of Deferoxamine in Sickle Cell Disease with ESRD Patient on Hemodialysis

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Introduction: Sickle cell disease patient may develop Iron overload due to multiple transfusions. Iron chelation is recommended for treatment. Deferoxamine is eliminated through the kidneys and bowels. In ESRD the elimination is only by bowels. It can be removed by hemodialysis as reported. We are reporting the changes in serum Iron, Ferritin, hospital admission rates and transfusions frequency in an ESRD patient with sickle cell disease after using Deferoxamine for a year.

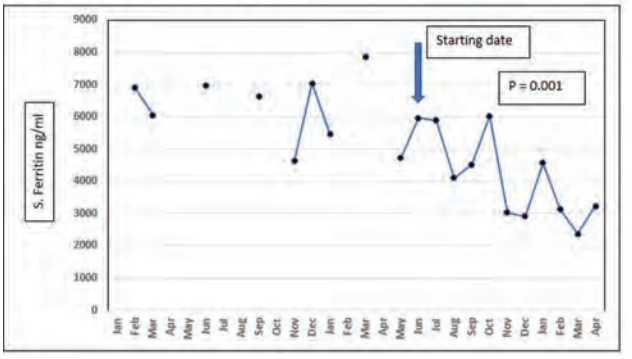
Case Description: 29 years old patient with Sickle cell disease. ESRD for 3 years, started with PD and transitioned to HD 3X weekly for the past year. He had recurrent admission for painful and hemolytic crises with frequent blood transfusions. Iron levels increased up to 235 micgm/dL (45-160) and Ferritin reached 7973 ng/ml (20-300). Hb remains low 3-5 gm/dl (14-18). Deferoxamine was started after review, discussion and assessment, at 1gm IV after each dialysis in June 2022 until May 2023.

Discussion: Deferoxamine is proven to be used with heavy metal intoxication. It is cleared through the kidneys and bowels. In patients with impaired renal function elimination of Deferoxamine will be reduced. Hemodialysis is reported to improve the clearance. Limited data is available on using the drug with Iron overload among dialysis patients. In our patient, we started Deferoxamine at 1gm IV infusion over 1 hour after each dialysis for a year. It was noticed to reduce the Ferritin significantly by 48%. An insignificant reduction trend was observed in S. Iron of 23%. The monthly admission rates for the patient was increased. Other causes needs to be excluded. There was an insignificant decrease in the number of PRBC transfused monthly.

Mean annual monthly admission rate, units of PRBC transfused, S. Iron and Ferritin.

Variables	2021 Mean (SE)	2022 Mean (SE)	2023 Mean (SE)	p value
Monthly admissions	1.2 (0.34)	2.3 (0.7)	3.6 (0.7)	0.001
Monthly transfusions	1.6 (0.5)	1.8 (0.37)	1.2 (0.4)	NS
S. Iron		138 (22)	108 (30)	NS
S. Ferritin	6375 (378)	5050 (476)	3360 (356)	0.001

Graph (1): Ferritin level over the follow up months:



SA-PO612

A Rare Case of Ocular Myasthenia Gravis in a Patient with ESRD

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Introduction: Myasthenia gravis (MG) is a rare autoimmune disorder caused by defective neurotransmitter transmission at the neuromuscular junction. The overall prevalence is about 150 to 200 cases per million. MG typically presents with fluctuating weakness and fatigability of ocular, bulbar, limb, and/or respiratory muscles. Very rarely, patients may present with isolated ocular symptoms, also known as ocular MG.

Case Description: An 82-year-old Hispanic woman with a past medical history of type II diabetes mellitus, hypertension, and end-stage renal disease (ESRD) on hemodialysis (HD) presented with sudden-onset ptosis of the right eyelid. Her vital signs were stable, and the rest of her physical exam was unremarkable. She underwent a computed tomography (CT) scan of the head and magnetic resonance imaging of the brain, both of which were unremarkable. A thyroid function test was normal and a CT of the chest looking for a thymoma was negative. Neurology was consulted and there was a high clinical suspicion for ocular MG. An ice pack test was performed and demonstrated improvement of her ptosis. She was started on pyridostigmine with improvement of her symptoms. Muscle-specific kinase and acetylcholine-binding antibody assays were negative, which is not uncommon in patients with ocular MG.

Discussion: Ocular MG is an extremely rare disease. In patients with ESRD on hemodialysis, it is an even rarer phenomenon. In addition, patients on HD are known to be at increased risk for stroke, a diagnosis often included in a list of differentials considered when assessing patients with physical manifestations of MG. It remains paramount to rule out acute stroke in patients with ESRD on HD presenting with motor deficits. However, it is also important to consider rarer etiologies, such as ocular MG, in the list of differential diagnoses.

SA-PO613

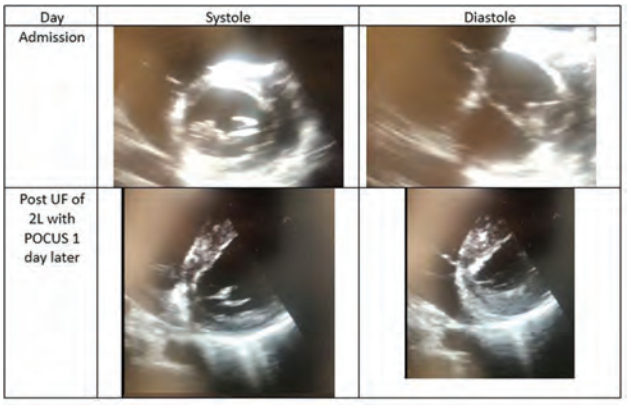
D-Sign Seen on Point-of-Care Ultrasound (POCUS) from Volume Overload and Used to Avoid CT Pulmonary Embolism (CT-PE) in Severe Contrast Allergy Patient

Sylvester Barnes IV.[1,2] *[1]Loyola University Chicago Stritch School of Medicine, Maywood, IL; [2]Edward Hines Junior VA Hospital Cooperative Studies Program, Hines, IL.*

Introduction: A 50y M w/ PMHx of osteosarcoma c/b chemotherapy induced cardiomyopathy now s/p OHT (11/10/17), severe iodine contrast allergy resulting in previous anaphylaxis, ESRD on HD (TTS) with last dialysis one day prior to admission, and RCC with metastases was brought to the ED for low O2 levels at home of 78%. Significant medications include fentanyl patch 25mcg every 72hours, oxycodone 5mg q8 prn, gabapentin 300mg TIW on MWF, tacrolimus, and prednisone. Obtained vitals are BP of 164/82, HR 81, RR 18, 87%O2 sat improved to 96% on 2L NC. The patient is drowsy on exam, lungs clear to auscultation, HR is RRR with no JVD noted, no cyanosis in nail beds or lips. Labs are significant for a negative troponin I, negative viral respiratory panel, BNP 2813pg/nl increased from 1620pg/ml three months prior, and D-Dimer 2655 ng/ml. CXR showed mild interstitial pulmonary edema and a small right pleural effusion. The patient's pain medication was held but there was a concern for possible PE secondary to his underlying malignancy and decreased O2 levels.

Case Description: Bedside POCUS showed cardiac flatting of the interventricular septum with an eccentricity index > 1 ; "D" sign indicating right heart strain. This patient's D sign pattern was observed only in diastole which is more indicative of fluid overload then PE. CT PE protocol was planned for the following day with starting of prophylaxis planned to start the following day as well. The pt underwent HD with removal of 2L of fluid. The next day repeat POCUS was performed showing resolution of the "D" sign along with oxygenation improvement.

Discussion: The patient was discharged the next day without a PE CT scan, EDW adjustment for his dialysis and lower pain medication. The use of POCUS helped to identity a right heart strain pattern with an eccentricity index >1 in diastole only. The POCUS findings before and after HD negated the need for additional studies which in this patient carried significant risk secondary to his severe contrast allergy.



SA-PO614

The Uncertainty of Bleeding Risk Monitoring for ESKD Patient on Continuous Anticoagulation Infusion

Man Kit Michael Siu, Ekamol Tantisattamo, Samir D. Patel. *University of California Irvine, Irvine, CA.*

Introduction: Patients with end-stage kidney disease (ESKD) are at increased risk of bleeding due to: chronic anemia, uremic platelet dysfunction, vascular calcification, and dialysis-related complications. Additionally, the risk of venous thromboembolism is also heightened, making anticoagulation management challenging. This case report presents the unfortunate outcome of an ESKD patient who experienced acute intracranial bleeding after initiation of heparin infusion for ischemic digits, leading to death.

Case Description: Patient is a 38-year-old female with ESKD secondary to diabetes mellitus (DM) on peritoneal dialysis (PD) and a history of scleroderma. She presented with progressive digit pain and discoloration. During hospital stay, she developed worsening respiratory status due to ESBL pneumonia, requiring intubation. She was started on epoprostenol given concern for Raynaud's crisis, as well as heparin infusion for severe atherosclerotic vascular disease with stenosis. Unfortunately, hospital course was further complicated by a non-operable intraparenchymal bleed with cerebral edema and herniation, leading to eventual extubation and transition to comfort care.

Discussion: Bleeding events in ESKD patients, ranging from bruises and bleeding at venipuncture sites to intracranial hemorrhage, significantly contribute to mortality and morbidity. Furthermore, blood transfusions can lead to alloimmunization and limit future transplantation options. In this case, several factors contributed to the adverse events. Team factors, including limited communication between the medical teams involved, may have hindered comprehensive management given patient's ongoing anticoagulation need. Patient factors, such as multiple comorbidities (ESKD, cardiovascular disease on aspirin) and the initiation of epoprostenol (a potent platelet aggregation inhibitor), further increased bleeding risk. Lastly, hospital policies, such as specific protocol tailored to ESKD patient that minimizes bolusing and allow for slower infusion rates could have potentially prevented these adverse events and improve patient outcomes.

SA-PO615

Improving Medication Errors in Hospitalized Hemodialysis Patients

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Background: The kidney is a key organ for the excretion of several medications and their metabolites. Medical errors relating to dosing and/or timing of medications in patients on hemodialysis (HD) may have serious adverse events. This project was designed to identify and prevent common medications errors in HD patients.

Methods: A quality improvement project was conducted at the University of Pittsburgh Medical Center Presbyterian Hospital from May 2021 to March 2023. Nephrologists identified HD patients and created a single Powerchart list to be electronically reviewed by a dedicated pharmacist who ensured appropriate dosing and timing of renally dosed medications. We included patients admitted to the hospital that were on HD, with acute kidney injury or end stage kidney disease. We excluded patients from units that had on-site dedicated pharmacists or evidence of HD held for more than one week.

Results: A total of 1723 reviews have been completed on 668 patients. Our analysis revealed that 1065 medications were being appropriately dosed and 146 medications required interventions. Of those that required intervention, 125 medications were rescheduled to be given after dialysis and 21 medications required dose adjustment (chart 1). Common medications identified are demonstrated in chart 2.

Conclusions: Approximately, 12% of medications reviewed required an intervention for dose/timing adjustment and 10% were defaulted to be given prior to dialysis. A pharmacist, via electronic review, was able to reduce these potential errors and next steps may include utilizing Electronic Medical Records solutions to automate error reduction.

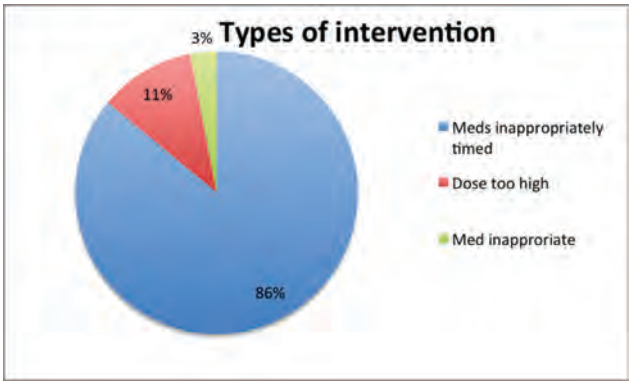


Chart 1

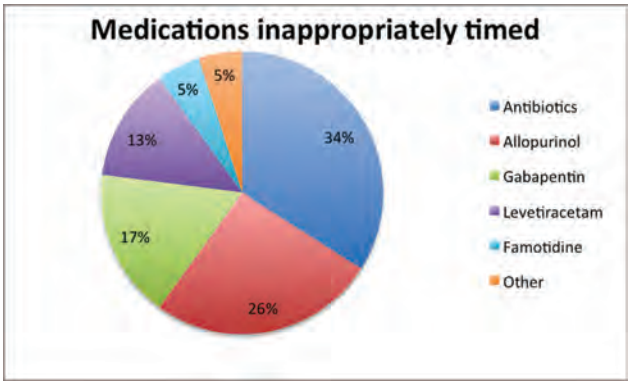


Chart 2

SA-PO616

Medication Reconciliation in Veterans Receiving Dialysis at Edward Hines VA Hospital: A Quality Improvement Initiative

Juan J. Cintrón-García, Roberto Guerrero, Holly J. Kramer, Karen A. Griffin, Kavitha Vellanki. *Loyola University Health System, Maywood, IL.*

Background: Polypharmacy, commonly defined as use of 5 or more medications, is associated with higher morbidity, fall risk, functional decline and disability. We aimed to identify prevalence of medication discrepancy and possible risk factors in veterans receiving dialysis at Hines VA hospital.

Methods: Eligible patients were asked to bring all pill bottles at least once during the study period, October 2022 to March 2023. Medical records were then reviewed to identify discrepancies. Collected data included age, race, sex, cause of end stage renal disease (ESRD), dialysis vintage time, dialysis modality, no: of providers involved, no: of prescribed medications and presence of care giver at home. Cognitive screening was done using Montreal Cognitive Assessment Test (MoCA).

Results: A total 48 patients participated in the study. Baseline characteristics are shown in Table 1. 32 patients had at least one medication discrepancy. Compared to patients that completed MoCA (36/48), those that declined (12/48) had higher percentage of medication discrepancies (75% vs. 63%) despite having a caregiver (71% vs. 61%) (Image 1). 11 of the 12 patients declining MoCA were receiving hemodialysis (HD).

Conclusions: We found high prevalence of medication discrepancy in our veteran ESRD patients. MoCA scores were not associated with medication discrepancies, but those declining MoCA or with poor overall interest tended to have more discrepancies. Our study limitation is small sample size of a single center veteran population.

Funding: Veterans Affairs Support

Baseline characteristics of study population

Age in years	Average age: 68
Race	29-African American 17-White 2-Other race
Sex	46-Male 2-Female
Cause of ESRD	29-DM 6-HTN 3-GN 10-Other
Dialysis vintage time in years	Average 3.7 years
Modality of dialysis (HD vs. PD)	41-HD 7-PD
No: of providers involved in care	Average: 3
No: of prescribed medications	Average: 9
Mean MoCA score (N = 36)	20 (total score = 30)

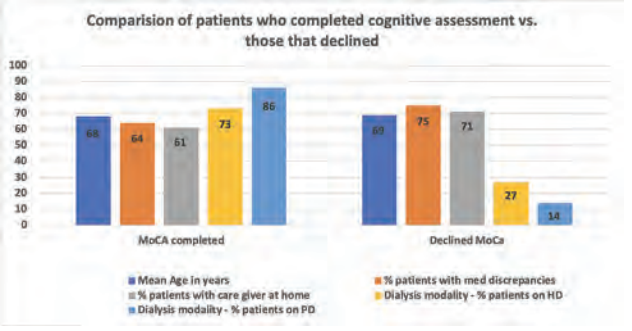


Image 1

SA-PO617

Efficiency of a Fully Integrated Hemodialysis (HD) Machine in the Acute Care Setting

Nazli Atefi,[1,2] Nasha Elavia,[1,2] Zain Haq,[1,2] Jagman S. Chahal,[1,2] Abutaleb A. Ejaz,[1,2] Ami M. Patel.[1,2] *[1]VA Medical Center Baltimore, Baltimore, MD; [2]University of Maryland Medical System, Baltimore, MD.*

Background: Tablo™, which is a fully-integrated, adaptive hemodialysis (HD) machine with an internal water purification system without requiring traditional water treatment resources, has a 300 mL/min restriction in the maximum attainable dialysate flow rate (DFR). We investigated the efficiency of Tablo™ in the acute hospital setting.

Methods: We conducted a prospective, single-center analysis. All Veterans with ESKD, who completed ≥ 3hrs of hemodialysis with available blood urea nitrogen pre- and post-treatment, from February 2023 to May 2023 were included. Urea reduction ratio (URR) and calculated Kt/V were compared for selected variables.

Results: 38 Veterans with total of 69 HD sessions met the inclusion criteria for analysis. Participants were 94.2% males, mean age 67.2±10.2 years, dialyzed for 211.3±9.1 mins, blood flow rate (BFR) 354.1±13.1mL/min, with Optiflux F160 (43.5%) and F180 (56.5%) dialyzers, average ultrafiltration 1.9±0.6 L, arteriovenous fistula (26%), arteriovenous graft (5.7%) and central venous catheter (68.3%). Kt/V and URR for full cohort was 1.21±0.2 and 59.5±6.7%, respectively. 43.5% and 27.5% of the sessions achieved adequate Kt/V (≥1.2) and URR (≥65%), respectively. Mutivariable analysis by subclasses are shown in Figure1. Access type, duration of treatment, dialyzer type or BFR were not predictors of adequate Kt/V on multivariate analysis. Despite a favorable trend, significant statistical differences were not observed in Kt/V or URR between the use of Optiflux F160 and F180 dialyzers at same BFR (350 mL/min) and treatment duration (3.5 or 4 hrs).

Conclusions: The restriction of DFR to 300 mL/min with Tablo™ system compromises adequacy of dialysis in acute care setting. This may be mitigated by prolonging session times, albeit at the expense of higher resource utilization. Future studies are necessary to compare adequacy of Tablo™ and conventional dialysis machines using higher typical DFR in a larger cohort.

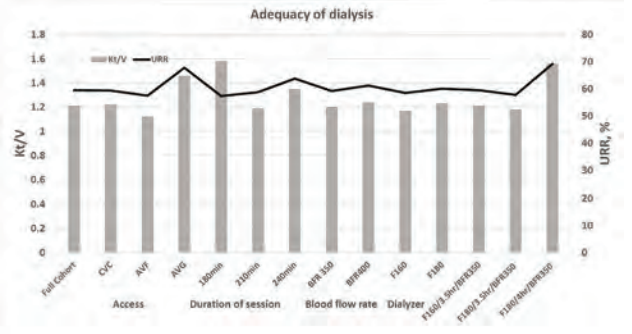


Figure 1 Multivariable analysis of dialysis adequacy with Tablo ™

SA-PO618

Blood Flowrate Accuracy with Dality Hemodialysis System

Clayton Poppe, Nicholas Hyun, Blaine Murakami. *Diality, Irvine, CA.*

Background: As laid out by Williams, Jensen, Gillum and Nabut,[1] blood flow accuracy in hemodialysis machines often does not match the manufacturers' stated accuracy at high blood flowrates. Flowrates might be lower by as much as 80-100 ml/min at a setpoint of 500 ml/min. This compares to the stated accuracy of +/-10% by most hemodialysis machine manufacturers. This difference in blood flowrate can lead to a reduction in Kt/V of 8.4%, depending on the dialysate flowrate. The Diality Hemodialysis System corrects for the factors responsible for reducing the expected flowrate leading to more accurate control of the blood flowrate and thus a higher Kt/V that better matches the theoretical value for dose delivered. [1] Williams HF, Jensen K, Gillum D, Nabut J. Blood pump speed vs. actual or "compensated" blood flow rate. Nephrol Nurs J. 2007 Sep-Oct;34(5):491-9, 525. PMID: 18041451.

Methods: The challenge in controlling blood flow is that parameters that are appropriate for high blood flows may not work a low flowrates. An algorithm that predicts the flowrate from independent variables is used to control the blood flow using a Proportional-Integral-Differential (PID) control methodology. The factors feeding into this algorithm are independently correlated with changes in blood flow. These include: - Pump head speed - Inlet and Outlet Pressures - Tubing Aging - Temperature

Results: The graph on the left-hand side of Figure 1 shows the accuracy of blood flow control at 100 ml/min while the graph on the right-hand side shows the accuracy of blood flow control at 500 ml/min. The green line represents the measured flow from a reference flowmeter while the orange line represents the algorithmically calculated flow from the device. Actual flowrates are well within the stated accuracy of +/-10% for both low and high flowrates.

Conclusions: Understanding the variables that lead to changes in blood flow and using them to control blood flow in real time can leads to better blood flow accuracy. This in turn can lead to higher average Kt/V for higher treatments with high blood flowrates.

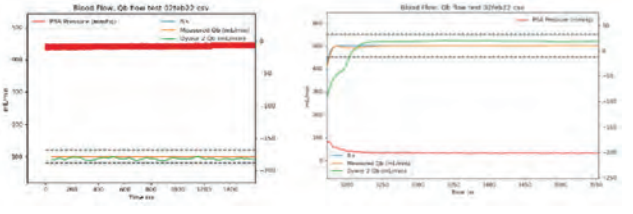


Figure 1: Blood Flowrates of 100 ml/min (right) and 500 ml/min (left)

SA-PO619

Increasing Incidence and Prevalence of Patients on Kidney Replacement Therapy over the Last 40 Years in Uruguay

Leonella Luzardo,[1,2] María Laura Ceretta,[1] Alejandro Ferreiro,[1,2] Valentina Oroza,[1] Maria C. Gonzalez-Bedat.[1] *[1]Uruguayan Dialysis Registry, Montevideo, Uruguay; [2]Nephrology Center, Montevideo, Uruguay.*

Background: From 1980 onwards chronic dialysis (CD) and kidney transplantation (KT) are accessible for the entire population.

Methods: The aim of this study is to describe the trends in the incidence (I), the prevalence (P) and the survival of patients on KRT over the last 40 years.

Results: The P increased from 41 to 1227 pmp (Fig 1). The P on CD increased from 38 on 1981 to 820 pmp in 2020. The P of patients on KT increased from 3 on 1981 to 407 pmp in 2020. The growth of the I and P of CD and KT was higher in the first 2 decades (1981-2000) (278% vs 48%, 533% vs 113%, 1592% vs 23% and 3066% vs 291%) (Fig 2). The growth of the P rate of KT was 10 times higher than the CD P rate. The age on admission to CD increased from 44.3±13.5 in 1981 to 62.2±17.1 years in 2020, while those over 65 years increased from 3.0 to 52.4%. The crude M on CD increased from 14.8 in 1993 to 17.0/100 patient-y, but no changes were observed in the adjusted analysis. The M rate in CD was 17 times higher than that of the general population (Table 1).

Conclusions: The I and P of patients with CKD on KRT in Uruguay have increased between 1981 and 2020 with a higher percentage growth in the P rate of KT. Despite the increasing admission of patients older than 65 years, M has remained stable in recent years.

Comparison between mortality rate among chronic dialysis patients and the uruguayan general population

All ages	17
< 65	39
65-74	8
75-84	5
» 85	2

CD: chronic dialysis patients GP: general population

Figure 1. Incidence and prevalence of CD and KT and CD mortality during the 40 study years period.

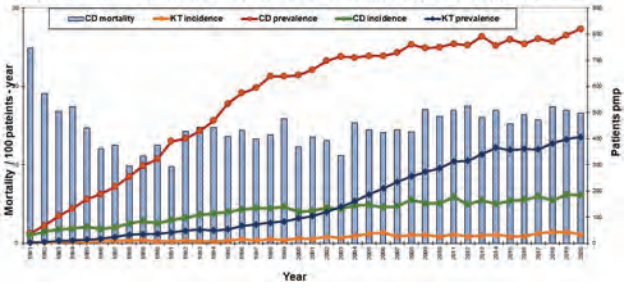
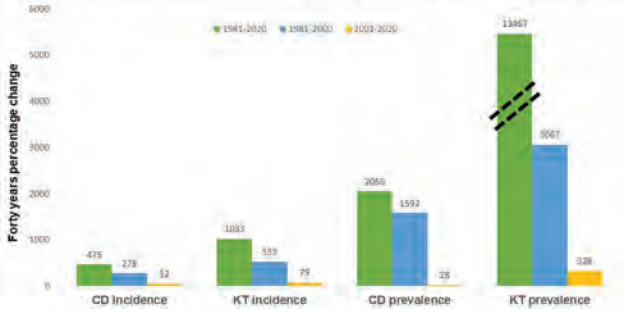


Figure 2. Incidence and prevalence of CD and KT percentage change during the 40 study years period.



SA-PO620

Implementing a Protocol for Incremental Hemodialysis in Incident Patients with ESKD: A Quality Improvement Project

Ali Taha,[1] Alexander Messina,[1] Alexander Tom,[1] Reman I. Altar,[1] Nancy Filteau,[1] Daniel Blum,[2] Emilie Trinh,[1] Catherine L. Weber.[1] *[1]McGill University Health Centre, Montreal, QC, Canada; [2]Hopital General Juif, Montreal, QC, Canada.*

Background: Incremental hemodialysis (HD) is the process whereby the frequency of HD is adapted to the patient's residual kidney function, initially starting at twice a week with an increase based on clinical indications. Incremental HD potentially facilitates the transition to HD, reduces patient and caregiver burden, improves quality of life and reduces costs. We sought to increase the number of patients commenced on incremental HD at a tertiary care academic center and to develop a safe process to monitor these patients.

Methods: We performed a prospective cohort quality improvement study. Starting November 1 2022, we aimed to start 75% of eligible incident chronic HD patients on incremental HD within 1 year. Eligible patients were defined as medially stable with no acute, active medical issues, and no indication for more frequent HD. The primary outcome measure was percentage of incident ESKD patients started on incremental HD. The balancing measure was the number of patients requiring transition to three-times per week HD. The incremental HD process was developed with input from all stakeholders.

Results: Between November 1 2022 and March 31 2023, among 35 incident chronic HD patients, 14 were eligible for incremental HD, of which 9 started incremental HD. As of May 2023, 6 patients remain on two-times per week HD and 3 patients required an increase to three-times per week HD. The process developed included a) a patient information sheet about incremental HD b) nursing education, c) a nurse led protocol whereby the patient performs a 24 hour urine collection for volume and the nurse completes a safety checklist every 6 weeks, and d) an alert system for the MD to review the patient's HD prescription if they have uremic symptoms, are volume overloaded or hyperkalemic.

Conclusions: We successfully initiated 64% of eligible incident HD patients on incremental HD, of which two-thirds remained on twice-weekly HD. Our next steps will involve feedback from patients and healthcare staff through quantitative and qualitative surveys with the goal of optimizing our protocol and expanding it to all dialysis units at our center.

SA-PO621

A Vulnerable Population: Case Series Examining Involuntarily Discharged Hemodialysis Patients in an Urban, Predominantly Black US Population

Zikora U. Nnadike,[1] Anjuli Shah,[1] Carol A. Gray,[2] Loren C. Cobb,[3] Christopher M. O'Donnell,[1,2] Jose E. Navarrete,[1,2] Jason Cobb.[1,2] *[1]Emory University School of Medicine, Atlanta, GA; [2]Emory Healthcare, Atlanta, GA; [3]Meharry Medical College, Nashville, TN.*

Background: An overlooked population is the number of insurable involuntarily discharged hemodialysis (HD) patients receiving maintenance HD. Presented is a case series examining involuntarily discharged HD patients receiving maintenance HD in inpatient settings in an urban US population.

Methods: Retrospective chart review of potential involuntarily discharged HD patients from 2020 – 2023 observed at Emory Hospitals and Grady Memorial Hospital. Studied were insurable end stage kidney disease (ESKD) patients who started HD as inpatient and were seen for inpatient dialysis >60 days and patients involuntarily discharged from a HD center.

Results: Among the 25 ESKD patients – all Black race and 68% male. 13 discharged for noncompliance, 8 discharged for disruptive behavior, 3 for insurance reasons, and 1 undetermined. HD vascular access – permcath (n=13), arteriovenous graft (n=4), and arteriovenous fistula (n=8). Observed hospitalizations for HD ranged from 3 to 298. The 3 patients discharged for insurance reasons included 2 patients initiated on HD as an inpatient and declared ESKD and received HD as an inpatient >60 days. Suspected noncompliance prevented them from being accepted despite being insurance eligible. 16 patients received a second chance outpatient HD center, and 1 was discharged from the second chance HD unit.

Conclusions: This case series brings attention to a vulnerable nephrology population. Most of the patients were discharged for subjective reasons like noncompliance and the impact of biases are hard to determine, but the patients being 100% Black is remarkable. The high level of success with second chance HD center placement demonstrates a need for interventions. More data is needed to examine geographic variances, economic impact, and the psychological toll emergency-only inpatient HD is having on these patients.

SA-PO622

Characteristics and Outcomes of High-Acuity Patients Referred for Outpatient Dialysis

Gopa B. Green,[1] Eric D. Weinhandl,[1,2] Graham E. Abra,[1,3] Tejas Gopal,[3,1] Juan D. Ordonez,[1] Wael F. Hussein.[1,3] *[1]Satellite Healthcare, San Jose, CA; [2]University of Minnesota Twin Cities College of Pharmacy, Minneapolis, MN; [3]Stanford University School of Medicine, Stanford, CA.*

Background: Dialysis-requiring hospitalized patients with co-morbid high-acuity needs are challenging to place in outpatient dialysis centers, leading to extended hospital stays. In 2018, we established a program for physician evaluation of high-acuity referrals for admittance to outpatient dialysis centers. The program provides care coordination with the discharging hospital, necessary dialysis-related medical equipment, and training of center staff to manage need for bed or bariatric bed, left ventricular assist device (LVAD), tracheostomy, behavioral issues requiring supervision, infection with communicable organisms, or other high-acuity co-morbid conditions. Little is known about the safety or efficacy of outpatient dialysis for high acuity patients.

Methods: We describe the characteristics and outcomes of patients referred to the program from January 2018 through April 2023.

Results: The program received 468 referrals, of which 149 (31.8%) initiated dialysis at outpatient dialysis centers of a mid-size non-profit dialysis provider. 304 patients were excluded due to reasons including inadequate staffing or space, clinical instability, and overly complex management needs. The most common indications for admission were the need for a special gurney or bed (99 patients), tracheostomy (22), and LVAD (8). The mean (SD) age was 62.7 (14.0) years, 41% were female, and 59% had diabetes. 21% of patients had a central venous catheter at the time of referral into the program. During 152 patient-years of follow-up, re-hospitalization rate at 1 month was 37%, with an admission rate of 2.7 per patient-year and 21 hospital days per patient-year. Despite this, 94% of the patients' survival time was spent out of the hospital. Survival rates at 3, 6, and 12 months were 76%, 71%, and 59% respectively.

Conclusions: A program that utilizes nephrologist evaluation, care coordination, additional equipment, staffing, and training can facilitate hospital discharges and address the care needs of high-acuity patients undergoing dialysis in the outpatient setting. Despite high comorbidity, these patients can benefit from being out of the hospital the majority of their time post admission to the dialysis center.

SA-PO623

Nephrologist Involvement in the Multi-Organ Failure Patient with Artificial Liver Support Systems: Experience of the Single-Center Extracorporeal Therapy Program in Mexico

Abel Humberto V. Compean,[1,2] Pedro Morales Molina,[1,2] Diana Maldonado Tapia,[1,2] Monica Lopez Mendoza,[1,2] Pamela Prado,[1,2] Claudia B. López,[1,2] Irving G. Ramirez,[1,2] Julio C. Nieto,[1,2] Beatriz R. Cerezo Samperio,[1,2] Juan D. Diaz Garcia.[1,2] *[1]Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico; [2]Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico.*

Background: The role of the nephrologist in intensive care is critical and includes the implementation of extracorporeal therapies, such as combined artificial hepatic-renal support, which provides time for rapid inclusion in an emergency liver transplantation program or recovery from acute failure. The most used methods are the molecular adsorbent recirculating system (MARS) and single-pass albumin dialysis (SPAD).

Methods: Objective: To expose the experience in the multiorgan support of critically ill patients with extracorporeal liver and kidney support therapies at the Centro Medico Nacional 20 de Noviembre. Retrospective study of patients with acute liver failure from 2016 to 2023 who underwent MARS or SPAD therapy.

Results: Of 21 patients, 43% were women and 57% men, with an average age of 38 years. The etiology of the liver disease was autoimmune in 47%, hepatitis A infection in 19%, cryptogenic in 14%. Ten of these patients had a previous liver transplant, 47% with recurrence of the disease or chronic rejection; the indication for liver support was 66% for acute chronic liver failure and 34% for acute liver failure, with SOFA score 9.8±8, MELD

score 25±15. Five patients received MARS and 16 SPAD, with a total of 63 sessions (average of 3 sessions per patient), with a bilirubin clearance rate of 29.2% (3-47%). Acute kidney injury was present in 62%, of these 54% required CRRT. We found an average survival of 6 months (1 to 56 months) and mortality of 80%.

Conclusions: The use of MARS or SPAD is a therapeutic bridge that allows clinical improvement of the patient or liver (re)transplantation in acute liver failure. Despite the high mortality, there is substantial room for improvement that favors comprehensive care processes in the critically ill patient. Survival of these patients varies according to the severity and availability of donated organs.

SA-PO624

Rural Alaskan Experience Insourcing Innovative Dialysis Technology

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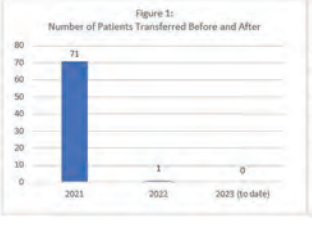
[1]Mat Su Regional, Palmer, AK; [2]Outset Medical, San Jose, CA.

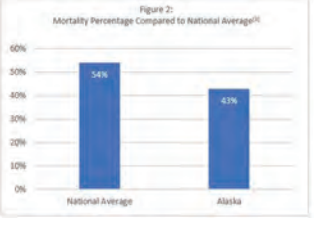
Background: Patients requiring dialysis in rural areas often face obstacles for treatment such as distance to care, financial limitations, and mistrust of the medical community. Studies have revealed moving geographic location of medical services closer, has a positive impact on health, economic and psychosocial states. Alaska has a paucity of acute dialysis services outside of the major cities like Anchorage and Fairbanks, leading to significant cost and complexity to the delivery of care to patients in these areas. Mat Su Regional hospital is a 125-bed hospital located an hour from Anchorage and operationalized a dialysis service line to improve access to care for rural patients in Palmer, AK using an innovative dialysis system, Tablo®. This describes the first year of Intermittent Hemodialysis (IHD) and Sustained-Low Efficiency Dialysis (SLED) treatments.

Methods: A retrospective chart review through the hospitals Electronic Health Records (EHR) was performed on all IHD and SLED treatments since implementation in February 2022.

Results: Since implementation of dialysis services in February 2022, there were 340 combined IHD and SLED treatments in the hospital. Only 1 patient was transferred for care compared to 70 patients the year prior. Training for ICU nursing staff consisted of Tablo hub training modules, 2-hour hands on training and 2- 12-hour treatments with preceptor on the device. In the ICU there were 23 unique patients with 65 total SLED treatments. CLABSI rate was 0% and mortality rate was 43% (Fig 1) with 70% of those patients being male. Most treatments where longer than 10 hrs. (98%) and 49% used automated saline flushes as method for anticoagulation and 9% of treatments ended due to clotting (Fig 2). There was a 4.3% COVID rate.

Conclusions: Implementation of a new dialysis service line using Tablo decreased hospital transfers and displacement of patients in rural Alaska. Mortality rates were slightly better than national averages as were clotting events. Training of staff was relatively easy which allowed hospital wide adoption. More research is needed to increase dialysis services into rural areas for better patient outcomes.





SA-PO625

Building a Framework for Enhancing Dialysis Services in Conflict-Affected Regions: A Multi-Level Action Plan

Sami Alasfar,[1] Hani S. Alashawi,[2] Saleh Kaysi,[4] Gilbert M. Burnham.[3] *[1]Mayo Clinic Arizona, Scottsdale, AZ; [2]Health Cluster, Gaziantep, Turkey; [3]Johns Hopkins University Center for Teaching and Learning, Baltimore, MD; [4]UVC Brugmann, Brussels, Belgium.*

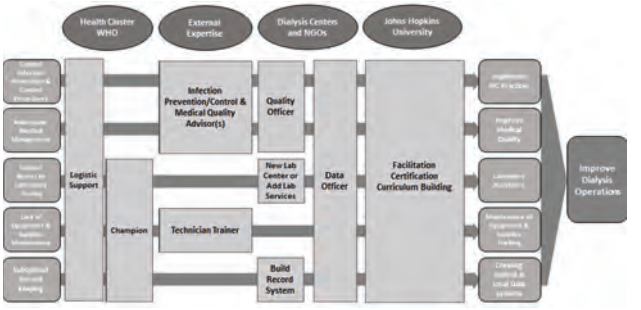
Background: The provision of dialysis to patients with ESKD in areas affected by conflict poses various challenges. Reports have shown a high incidence of hepatitis B&C among patients on hemodialysis (HD) & poor HD operations in Northwest (NW) Syria, an area enduring armed conflict. A framework is necessary to address the hindrances to HD in such environments.

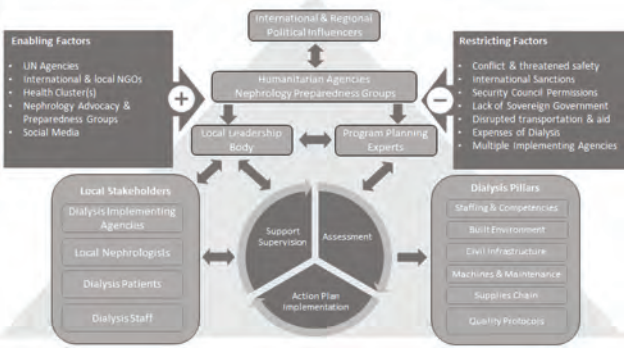
Methods: The Health Cluster Hub in Turkey is collaborating with Johns Hopkins University to spearhead a quality improvement initiative for HD in NW Syria. Objectives are to address difficulties of HD in this region and enhance care delivered by NGOs administering HD. The project comprises 3 phases: baseline asssement, setting up basic standards & action plan, and putting a support supervision system, alongside creating a framework to attain these targets.

Results: The 1st phase involved a survey of HD centers and 2 workshops utilizing the fishbone technique & theory of change models to map the necessary changes. Through this phase, an action plan (Fig 1) was developed and involved various stakeholders with different objectives. The 2nd phase focused on building quality curricula, which were subsequently taught through courses, creating a record system, & establishing minimal standards for HD centers. Furthermore, a framework was created to address dialysis services in NW Syria and other conflict settings (Fig 2).

Conclusions: As it is the responsibility of the nephrology community and humanitarian agencies to ensure quality care for patients with ESKD, we propose a comprehensive framework to enhance HD care in unstable areas. This framework involves engaging all stakeholders in care delivery, establishing minimum standards, and mitigating risks to patients.

Funding: Government Support - Non-U.S.





SA-PO626

Association of Predialysis Education Choice with Optimal Starts in ESRD

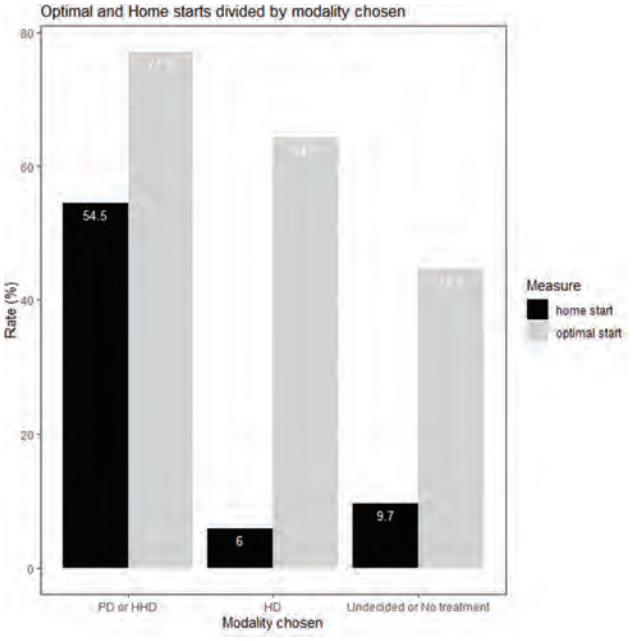
Ken J. Park, Cynthia Tai, Daniel E. Carl. *Kaiser Permanente Northwest, Portland, OR.*

Background: Published studies have shown that choosing home dialysis after modalities education pre-dialysis is associated with higher likelihood of starting on home dialysis (PD or home HD). However, the relationship between patients' dialysis choice after modalities education and optimal starts (receipt of preemptive kidney transplant, initiation of HD with arteriovenous graft or fistula, or initiation of PD) is unknown. We were interested in whether choosing a home modality was associated with higher likelihood of having an optimal start.

Methods: Our retrospective cohort consisted of 525 patients from Kaiser Permanente Northwest who progressed to ESRD (defined as receipt of preemptive kidney transplant, HD, or PD) from January 1, 2019 to December 31, 2022 and had attended modalities education pre-dialysis. Multiple logistic regression was used to examine the association of patients' dialysis choice with having an optimal and home dialysis start.

Results: Hemodialysis was chosen by 26% and home dialysis by 54% of patients. Patients were undecided or chose no treatment in 20% of the cohort. Univariate analysis showed that compared to choosing HD or being undecided / choosing no treatment, patients who chose home dialysis were more likely to start optimally (77% vs. 64% vs. 45%, $p < 0.005$) and to start on home dialysis (55% vs 6% vs. 10%, $p < 0.005$). After adjusting for race, age, diabetes, and gender, patients choosing home dialysis had 3.8-fold ($p < 0.005$) and 1.6-fold ($p = 0.04$) higher odds of starting optimally and a 11.3-fold and 18.3-fold higher odds of starting on home dialysis ($p < 0.005$) compared to the undecided/ no treatment group and hemodialysis group respectively.

Conclusions: Choice of home dialysis after modalities education was associated with a higher likelihood of having an optimal and home dialysis start.



SA-PO627

It Takes Time: Developing a Standardized Strategy to Improve Timely Modality Education and Home Dialysis Choice Rates in Patients with Advanced Kidney Disease in Toronto, Canada

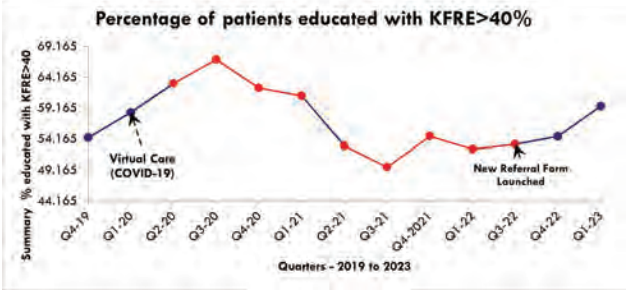
Declan Lu, Sijia Zheng, Bailey Paterson, Lisa Dubrofsky, Bourne L. Auguste. *University of Toronto, Toronto, ON, Canada*.

Background: Patients with progressive chronic kidney disease (CKD) should receive timely education that allows them to choose a treatment path that aligns with their care goals and lifestyle. Home-based dialysis modalities have been associated with increased quality of life and reduced health care costs. Modality education has been shown to increase rates of home dialysis as the initial dialysis strategy. Delays in timely education may reduce home dialysis choice rates. Barriers to timely modality education include lack of a standardized referral process, physician practice variation and patient preparedness to engage in discussion. The aim of this study was to assess whether the implementation of a standardized referral process could increase the rates of timely modality education and home dialysis choice.

Methods: This was a quality improvement study performed at a single center in Toronto, Canada between 2019-2023. Patients with a 2-year Kidney Failure Risk Equation ($KFRE^2$) of >= 40% were recommended for modality education as outlined by the provincial regulatory body. Rates of modality education and home dialysis choice were recorded on a quarterly basis both before and after implementation of a standardized referral process.

Results: 1451 encounters were identified between 2019-2023. Prior to initiation of a standardized referral process, 647/1134 (57.1%) of eligible patients received modality education and 218/647 (33.7%) of educated patients choose home dialysis as their preferred modality. After initiation of a standardized referral process, 177/317 (55.8%) of eligible patients received modality education and 54/177 (30.5%) of patients choose home dialysis as their preferred modality.

Conclusions: There was no significant change in modality education or home dialysis choice rates after initiation of a standardized strategy. Timing of education should not be restricted to arbitrary cut-off values but requires ongoing mentorship and support of patients at an early stage of disease course.



SA-PO628

Shared Decision-Making Intervention Regarding Dialysis Modality in Patients with Stage 5 CKD

Hark Rim,[1,2] Byeonghwa Bak,[1,2] Ye na Kim,[1,2] Ho Sik Shin,[1,2] Yeonsoon Jung.[1,2] *[1]Kosin University Gospel Hospital, Busan, Busan, Republic of Korea; [2]Kosin University College of Medicine, Transplantation Research Center, Busan, Republic of Korea*.

Background: Patients with kidney failure must make complicated decisions about the dialysis modalities used either at home or in-hospital. Different options have varying levels of impact on patients' physical and psychological conditions and their social life. The purpose of this study was to evaluate the implementation of an intervention designed to achieve shared decision making (SDM) in patients' options for dialysis.

Methods: SDM was performed after consent was written for stage 5 chronic kidney disease patients before dialysis, and 435 cases were performed in 408 patients from December 16, 2019 to June 30, 2021. Among these, 101 patients were compared by SDM measurement scale, patient satisfaction, disease recognition scale survey, and dialysis method.

Results: The average age of participants was 56 years, with a gender composition of 55 males (54.5%) and 46 females (45.5%). Following SDM, the final dialysis methods decided upon by patients and clinicians were peritoneal dialysis (67 patients, 66.3%), hemodialysis (22 patients, 21.8%), and kidney transplantation (1 patient, 1.0%).

Conclusions: Among participating patients, SDM was effective when used to decide on dialysis treatment, and patients were satisfied with the dialysis method decision process. On the disease awareness scale, those who participated in this project had relatively high positive and low negative perceptions, so it can be concluded that SDM was relatively effective. The implementation of SDM was helpful in selecting patients' best dialysis methods, and SDM scale results were higher in the peritoneal dialysis group than in the hemodialysis group.

Table 2
Shared decision making measurement scale results.

Questionnaire items	4 Points or higher
1) My attending physician made it clear that a decision was needed.	97.3%
2) My attending physician wanted to know exactly how I was involved in making the decision.	87.4%
3) My attending physician said that there were several options to choose from depending on my health condition.	89.2%
4) My doctor explained in detail the pros and cons of each treatment option.	92.8%
5) My attending physician helped me understand the information.	93.7%
6) My doctor asked what my preferred treatment was.	91.0%
7) My doctor and I thoroughly evaluated the different options for treatment.	84.6%
8) My doctor and I chose treatment together.	88.3%
9) My doctor and I agreed on a course of treatment.	90.1%

Table 8

Choosing the right dialysis method for you.

What is most important to you?
1. Health-related considerations
I want to protect my heart.
I want to protect my bones, joints, and nerves.
I want to live according to my will.
I do not want to be a burden to my family.
I want to keep my quality of life as high as possible.
I want to spend a day without the burden of dialysis.
I do not want to go on dialysis every day.
I want to see a doctor regularly.
I can control my daily routine by myself.
I lead a regular life.
I plan and act in my daily life.
I enjoy exercising.
2. Dialysis environment
I want to go to the hospital as little as possible.
I am more comfortable with expert dialysis.
I like being in a familiar environment.
I hate environmental changes.
I like to experience new things.
I like watching TV.
I find it difficult to lie down for long periods of time.
I am afraid of needles.
I tend to be very conscious of other people's eyes.
I tend to depend a lot on my spouse for my daily life.
I need someone to take care of me.
I do not want a dialysis machine in my house.
3. Daily life
I want to spend as much time as possible with my family.
I live with and take care of my elderly parents.
I am raising a child.
I have to go to school or go to work.
I should be able to eat and drink what I like.
I sweat a lot, so I shower or bathe often.
I tend to care about my appearance.
I take a lot of time to get used to new things.
I have no one to take care of me.
I love to travel and never give up.
I travel abroad a lot.

SA-PO629

Provider Peritoneal Dialysis (PD) Education Can Increase Continuous Ambulatory Peritoneal Dialysis (CAPD) Utilization Without Increased Peritonitis

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Background: CAPD use is low (<10%) in the US and Automated Peritoneal Dialysis (APD) is the preferred modality of PD (Peritoneal Dialysis). There are many reasons for increased APD utilization, but the perceived bias of healthcare providers toward CAPD may be a driver. CAPD is presumed to have greater burden and higher peritonitis rates, but APD may have greater complexity, more frequent alarms, storage needs, and time attached to a machine. We hypothesized that an education program on the physiology of PD, benefits of CAPD, monitoring KPIs (key performance indicators), and thrice daily exchanges on initiation with ongoing support would increase CAPD utilization without increasing peritonitis rates.

Methods: The program was implemented between 7/22 and 11/22 in 17 Fresenius Kidney Care home units across 3 established PD markets with variable CAPD utilization (7%(I), 13%(II) and 19%(III)). Adults who started PD between 2/22 and 4/23 were included. Outcomes reviewed include new CAPD starts, peritonitis rates, and conversion to hemodialysis (HD) therapy during the five months before and five months after participation in the pilot program.

Results: 215 patients started CAPD during the analysis period. CAPD starts increased from 59% of all new starts (n=111) in the 5 months prior to pilot start to 79% (n=104, p=0.0003) during the initial 5 months of the pilot. Conversion from CAPD to APD declined from 20/111, 18%, to 5/104, 4.8%, from the two periods. 100% of conversions were from a single market (I). Overall CAPD penetration rose in every market (I-61%, II-32%, III-30%) and 36% overall. Peritonitis rates among the new starts improved in the CAPD group, but not in the CCPD group. CAPD group peritonitis rates decreased significantly from 1/32.5 patient months to 1/238 patient months (RR=0.13, p=0.03). CCPD peritonitis rates increased with new starts from 1/55 patient months to 1/40.7 patient months, but the difference was not significant. The rate of conversion to HD remained consistent between the two time periods.

Conclusions: CAPD may offer advantages to many patients in the USA and may be underutilized. Education on PD physiology, potential benefits of CAPD, initiation awareness programs, and ongoing support with review of KPIs can lead to greater utilization of CAPD without an increased peritonitis risk.

Funding: Commercial Support - Fresenius Medical Care

SA-PO630

Incidence of Fungal Peritonitis and Exit Site Infections Among Peritoneal Dialysis Patients in a Mid-Sized Dialysis Provider

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Background: Fungal infections are a relatively rare complication of peritoneal dialysis (PD). These infections include fungal peritonitis, an especially serious complication, and fungal growth at the catheter exit site. Surprisingly little is known about the epidemiology of fungal infections among PD patients in the United States. We estimated the incidence of fungal peritonitis and exit site infection (ESI) in a multi-center cohort of PD patients.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. We identified patients who initiated PD between January 1, 2011, and March 31, 2023, and retained those that initiated PD during the first year after diagnosis of end stage kidney disease. Patents were followed until the earliest of first fungal infection (either peritonitis or ESI), death, conversion to hemodialysis, kidney transplantation, recovery of function, or April 30, 2023. We estimated the cumulative incidence of each of fungal peritonitis and ESI, and used Cox regression to estimate associations of age, sex, diabetes, and time-varying modality subtype (continuous ambulatory, automated) with the risk of fungal infection.

Results: The cohort included 5743 patients. Overall, 135 patients experienced a fungal infection: 94 patients experienced peritonitis at a mean of 27.9 months after PD initiation, 43 patients experienced an ESI at a mean of 32.0 months after PD initiation, and 2 patients experienced both complications. The cumulative incidence of fungal peritonitis was 0.9% at 2 years after PD initiation and 1.7% at 4 years. No associations with fungal peritonitis were statistically significant, although age of 18-44 years, relative to 45-64 years, and continuous ambulatory PD were associated with lower hazard. At 3 months after fungal peritonitis, the cumulative incidence of conversion to hemodialysis was 80.4%. The cumulative incidence of fungal ESI was 0.4% at 2 years after PD initiation and 0.7% at 4 years. At 3 months after fungal ESI, the cumulative incidence of conversion to hemodialysis was 18.6%.

Conclusions: Fungal infection is a rare event in PD patients, with little overlap between fungal peritonitis and ESI. Fungal infection tends to occur late in the course of PD. Fungal peritonitis is highly likely to be followed by PD discontinuation in the short run.

SA-PO631

Risk Factors for Peritoneal Dialysis Failure: Retrospective Cohort Study

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Background: Patients who start intermittent peritoneal dialysis (IPD) as a bridge therapy to continuous ambulatory peritoneal dialysis (CAPD) may present failure of the IPD technique before starting due to multiple factors. The principal factors identified with loss of technical were peritonitis, tunnelitis, and definitive failure. The aim of this study was to estimate the incidence of technique failure in IPD patients with the IPD program at the General Hospital of Mexico.

Methods: Retrospective cohort study that included 199 patients with IPD, was reviewed the patient records of peritoneal dialysis, during the period between January 2008 and May 2023. The incidence was estimated, as and risk factors for technique failure.

Results: A total of 199 patient records were included; 58% (115) were men, with a mean age of 45.4±14.9 SD years, 65% (127) had diabetes type 2, and 94% had systemic hypertension. In the 62% (123) patients, the initiation of renal function replacement therapy was urgent. It was identified that in 70% (139) of patients, the first catheter was placed percutaneously and 30% (60) was surgical. The catheter type was pig tail in the 93% (185) of the cases. the loss of technique was identified in 24% (48) of patients, including as causes of etiologies events of dysfunction that required catheter replacement and events of peritonitis, the analysis of the first event of peritonitis increased the risk of loss technique (OR 10.1, 95%IC 4.8- 21, p=0.0001). In the follow-up period, 35% (70) of the patients were present with at least one event of peritonitis, 40% (80) presented dysfunction; and 30% turned to hemodialysis.

Conclusions: The principal factor associated with losing the technique was peritonitis, even when the patient did not use dialysis outside of the hospital. Peritonitis is a frequent and serious complication of peritoneal dialysis (PD), representing the most common cause of conversion to hemodialysis in the long term. It is necessary to integrate strategies for the care and management of the ambulatory catheter during IPD.

SA-PO632

Peritoneal Dialysis-Related Mycobacterium abscessus Infections: A Case Series

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Background: Catheter-associated infections are an important cause of morbidity and catheter loss in people using peritoneal dialysis (PD). *Mycobacterium abscessus* is a rapidly growing non-tuberculous mycobacterium (NTM) that has innate antimicrobial resistance. *M. abscessus* is an uncommon etiology of PD catheter associated infections, with only a handful of cases reported and only 2 cases reported in USA. Thus, there is a lack of evidence-based guidance on management of *M. abscessus* PD catheter infections. During routine clinical care, we encountered several patients with PD related infections due to *M. abscessus*. We sought to determine risk factors for *M. abscessus* PD catheter associated infections and describe treatment outcomes.

Methods: This is a retrospective study in which medical records from one 700-bed tertiary care hospital and one regional dialysis center were reviewed. Information was abstracted to a study-specific case report form. Epidemiological, clinical characteristics, M. *Abscessus* complex subspecies, managements and fate of PD were explored. This study was approved by relevant IRBs.

Results: We identified 7 patients diagnosed with *M. abscesses* PD catheter infection. Among these 7 patients, 4 (57%) presented with symptoms suggestive of peritonitis and 3 (43%) with exit site infections (ESI) / tunnel infections. 7% were males (4/7) with median age of 42 years (range 42-88). Original kidney disease was diabetic nephropathy in 57% (4/7) and mean time on PD before developing NTM infection was 20.5 months. Subspecies were identified in 6 (85%) and revealed 4 (57%) with *abscessus* and 2 (28%) with *massiliense*. 5 patients (72%) were managed with upfront PD catheter removal and antibiotics with good outcomes. PD catheter salvage was attempted in two patients (28%) initially presenting with ESI. One of these patients progressed over a year to peritonitis and tunnel abscess due to *M. abscessus* despite continued antibiotics. The other was shifted to hemodialysis (with PD catheter removal) after persistent *M. abscessus* ESI in the context of antibiotic intolerances.

Conclusions: *M. abscessus* is an important cause of PD catheter-associated infections. Management of peritonitis and tunnel infections requires catheter removal and prolonged antimicrobial therapy. Catheter removal should be considered in people with ESI.

SA-PO633

Peritonitis-Free Survival in Peritoneal Dialysis According to Staphylococcus spp. Nasal Carriage

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Background: Mexico ranks second with the highest prevalence of peritoneal dialysis (PD) in Latin America. Yucatan in Mexico has the highest prevalence of obesity, diabetes, and kidney stones, the main risk factors for progression to kidney failure (KF). The Agustín O'Horan General Hospital receives patients with chronic kidney disease without affiliation to any health service in which PD is the first line treatment for KF. In our center, PD associated peritonitis continues to be a major cause of hospitalization, PD failure, transition to hemodialysis, and even death. Previous reports suggested that nasal carriage of Staphylococcus spp (SS) conferred an increased risk of PD related peritonitis, however this notion has been challenged by new evidence.

Methods: We conducted a prospective study from March 1st 2022 to March 31st 2023. We included all incident PD patients who underwent nasal swabbing prior to PD catheter placement. Patients were followed up for at least 30 days after the PD catheter placement and the time of first peritonitis was recorded. We compared the peritonitis free survival between SS nasal carriers and PD patients with nasal culture negative (CN).

Results: 172 patients started PD during the study period. Fifty one patients were excluded due to contamination or the absence of a nasal swab sample prior to PD catheter placement. 121 patients were included in the study, 54.54% were women, the mean age was 51.6 years, and 61% of the population had type 2 diabetes. Thirty four patients had a positive nasal culture for SS and all of them were treated with intranasal mupirocin. Patients were followed for at least 30 days after PD catheter placement with a mean follow up of 138.9 days. Data were censored for patients who had mechanical complications, did not develop peritonitis or were lost to follow up. 46 cases of peritonitis occurred during the follow up. The etiology of PD related peritonitis included 17 SS, 14 non SS, 8 polymicrobial and 7 CN peritonitis cases. Peritonitis free survival in nasal carriers of SS was 76.2 days compared to 69.3 days in patients with CN. There was no significant difference in peritonitis free survival between the two groups.

Conclusions: Nasal carriage of SS does not appear to have an impact on peritonitis free survival. The benefit of performing a nasal culture prior to PD catheter placement remains to be elucidated.

SA-PO634

Peritonitis Impact on Technique Failure and Time to First Peritonitis Event in Peritoneal Dialysis: A Retrospective Multicenter Cohort Study in the National Health System of the Dominican Republic

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Background: Peritonitis is a concern in peritoneal dialysis (PD) as it is a common complication that impacts outcomes and technical survival. It is a frequent cause of technique failure. The aim of this study is to estimate the impact of peritonitis on technique failure and determine the time to the presentation of the first peritonitis event.

Methods: A retrospective, multicenter, and descriptive cohort study was conducted on patients enrolled in the home PD program of the National Health System of the Dominican Republic. Peritonitis was diagnosed based on the ISPD guidelines. The analysis included incident PD patients enrolled between January 1st, 2016, and December 31st, 2022. Demographic data were collected and presented as mean ± SD for quantitative variables, while qualitative variables were reported as absolute and relative frequencies. A binary logistic regression was performed for the possible association between variables of interest using Odds Ratio, with a confidence interval of 95% and p value < 0.05. To assess survival, only peritonitis events were considered using Kaplan-Meier curves and the Log-Rank test.

Results: We studied 4,476 incident patients with a median follow-up of 693 days, with a range of 30 to 2,465 days. The mean age was 57 ± 15 years, and 58% of the patients were males. Among the patients, 393 (8.7%) experienced a peritonitis event, with 53 (1.1%) having two events, and 10 (0.22%) patients experiencing three or more events. Out of those who had peritonitis, 79% were cured, 12% transitioned to hemodialysis (HD), and 7.9% died. The median time to the first peritonitis events was 474 days (CI 431-517) The factors associated with the development of peritonitis were patients older than 65 years (OR: 1.94; 95%CI: 1.49-2.52: p<.001) and having been on therapy for more than a two-year period (OR: 2.86; 95%CI: 2.10-3.88).

Conclusions: in this analysis, factors such as older age and a longer duration of therapy were associated with an increased risk of developing peritonitis. The time at the first event is higher than reported in other studies. These highlight the importance of implementing preventive strategies and close monitoring in PD.

Funding: Commercial Support - Macrotech

SA-PO635

Prognosis and Treatment of Peritoneal Dialysis-Associated Infection by Nontuberculous Mycobacteria

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Background: Nontuberculous Mycobacterium (NTM) can lead to infections related to peritoneal dialysis (PD) catheters, defined as exit site infection and tunnel infection, and PD related peritonitis. Current guideline lacks clarity regarding the indication for catheter removal and the optimal duration of treatment for these infections. Therefore, the aim of this literature review is to analyze the accurate treatment approaches and prognosis associated with NTM-related PD catheter infections and peritonitis.

Methods: We conducted a literature review of published cases of PD catheter-related infection and peritonitis by NTM in PubMed, Embase, and Ichu-shi databases up to August 2022.

Results: A total of 362 cases were included in the analysis. Among these cases, 226 (62%) were male, with the mean age of 57 years. Diabetic nephropathy accounted for 22% of cases as the most common cause of end-stage kidney disease (ESKD). Mycobacterium abscessus was identified as the most prevalent pathogen, found in 38% of cases. The distribution of cases was as follows: 39% categorized as catheter-related infection alone, 26% as peritonitis alone, and 25% as both catheter-related infection and peritonitis. Only 57% of cases yielded positive NTM cultures on the initial attempt. In 18% of cases, other bacteria, mainly Corynebacterium or diphtheria, were identified in the initial culture, while the first bacterial culture was negative in 24% of cases. Antibiotics alone were used to manage 43% of patients, while 44% eventually required catheter removal. The average duration of antibiotics was 4.8 months. Notably, six cases of peritonitis resulted in death without catheter removal.

Conclusions: This case series represents the largest sample size in NTM-related catheter-related infection and peritonitis. Early submission of acid-fast bacilli smear and culture should be considered, especially when bacterial cultures are either gram positive rods or negative. Catheter removal may be considered as the appropriate management at the early stage of NTM infection.

SA-PO636

Urine Dipstick: A Point-of-Care Tool for the Diagnosis of Peritoneal Dialysis-Associated Peritonitis

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Background: PD-associated peritonitis is a complication that impacts the morbidity and mortality of patients. The ISPD recommends diagnosing peritonitis when at least two of the following criteria are met: clinical features such as abdominal pain or cloudy dialysis effluent, dialysis effluent WBC > 100/μL with > 50% PMN, or positive dialysis effluent culture. The Spanish Society of Nephrology suggests using a urine dipstick for early diagnosis based on a new strip designed to test PD fluid.

Methods: A prospective study was conducted at the Hospital Universitario Dr. José Eleuterio González, evaluating consultations for PD-associated peritonitis from the emergency department to the nephrology department during August 2022 through February 2023. After a 2-hour exchange, samples were taken the strip testing (Siemens multistix10 SG) were to the laboratory for cytochemical analysis, culture. The strip results were read after a waiting time of 2 minutes and were interpreted by a nephrologist.

Results: 30 patients were screened, confirming the diagnosis of PD-associated peritonitis based on the strip and cytochemical results. The demographic data shown in Figure1. The strip showed a sensitivity of 73% and specificity of 100% when using a cutoff of 3 crosses. However, these values changed when using a cutoff of 2 crosses, resulting in a sensitivity of 95% and specificity of 100%.

Conclusions: Urine dipsticks are feasible, and cheap tools that can be useful for the diagnosis of PD-associated peritonitis with great sensibility and specificity saving time for the initiation of the antibiotic. It also helps conserve resources and enables patients to continue their treatment outside the clinic using a simple method.

	N =30
Gender	
Female	18 (60%)
Male	12 (40%)
Age	49 years
Comorbidities	
Mellitus diabetes	25 (83.3%)
Arterial hypertension	29 (96.7%)
Residual kidney function	547 ml
Time in dialysis	471 Days
Change line	
No	16 (53.3%)
Yes	14 (46.7%)
Dialysis Solution	
1.5%	7 (23.3%)
2.5%	23 (76.7%)
Time of symtoms	3.83 Days
Effluent WBC	3,370
Culture	
Negative	13 (43.3%)
Pseudomona aeruginosa	4 (13.3%)
Stahp aureus	3 (10.0%)
Stahp epidermidis	3 (10.0%)
Klebsiella pneumoniae	2 (6.7%)
Achromobacter xylosoxidans	1 (3.3%)
Corynebacterium amucolatum	1 (3.3%)
Enterobacter cloacae	1 (3.3%)
Serratia marcenses	1 (3.3%)
Sthap aureus mrsa	1 (3.3%)

SA-PO637

Does Final Peritoneal Dialysis Catheter Tip Position Predict Early Catheter Dysfunction?

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Background: It is believed that, for a functioning peritoneal dialysis (PD) catheter, the inserter needs to place the catheter in an optimal position. Exact tip position within the pelvis in relation to the pubic symphysis can be determined at time of placement for fluoroscopically guided PD catheters.

Methods: A retrospective cohort of adult PD patients in London, Ontario, who underwent percutaneous PD catheter insertion using fluoroscopy from 2013 to 2017 were reviewed. The distance between the top of the pubic symphysis and the bottom of the catheter coil was measured using Citrix software of stored images. Univariate and multivariate backward stepwise logistic regression analyses were conducted for the outcome of early catheter flow dysfunction versus each of final catheter tip position and baseline covariables included age, sex, race, body mass index (BMI), cause of Kidney Failure and number of prior abdominal surgeries with P-value <0.2 for variable inclusion in stepwise regression. Early catheter flow dysfunction was defined as the failure to achieve sufficient inflow/outflow to maintain any modality of PD, refractory to non-procedural interventions, and necessitating a repositioning procedure within 3 months of PD start.

Results: 286 patients who underwent fluoroscopic catheter insertion during the study period had a trial of PD. Of 35 patients who experienced early catheter dysfunction, 31/35 underwent a repositioning procedure. There was no difference between final catheter tip position of catheters that did or did not experience early flow dysfunction [catheter-tip to pubis symphysis median distance (Q1-Q3) 37 (29-53) vs 38 (26-50) mm, p=0.62]. In univariate analyses, no variable was associated with a significant difference in frequency of catheter dysfunction. Backward stepwise multivariate analyses of catheter dysfunction retained BMI, age and cause of Kidney Failure with only BMI significantly associated with frequency of early catheter flow dysfunction (OR 1.07 ± 0.04, p=0.04).

Conclusions: Final pelvic PD catheter tip position, relative to the pubic symphysis at time of fluoroscopic insertion, was not predictive of early catheter flow dysfunction. In light of this, the frequent focus of inserters on “optimal” placement may be unwarranted.

SA-PO638

Peritoneal Dialysis and Technique Survival in Diabetic Patients

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Background: Management of end stage renal disease (ESRD) in diabetic patients is an ongoing challenge. Despite potential adverse metabolic effects, peritoneal dialysis (PD) is considered safe and suitable in diabetic ESRD treatment. Previous descriptions of poor technique survival have been contradicted by recent studies, in line with improved dialysis technique and reduced technique-associated complications. We evaluated technique survival in diabetic patients on PD.

Methods: Clinical records of incident PD patients from 2000-2022 were examined. Kaplan-Meier method and log-rank test were used to compare technique survival rate between diabetic and non-diabetic patients. Adjusted HR were calculated using Cox regression.

Results: A total 235 incident PD patients were included, 23% diabetic. Mean age of PD onset 54 ± 15 years. Patients with diabetes mellitus (DM) were older (61 ±14 vs 41 ±15 years), mostly male (74 vs 24%), with higher cardiovascular (CV) burden (p<0.05). Assisted PD modality was more prevalent in this group (29 vs 5%, p<0,05). Median technique survival in DM and non-DM patients was 31 (CI 95% 22-39) and 52 months (CI 95% 42-62), respectively (p=0.002). Main reasons for PD suspension included technical failure (39%) and PD-associated infectious complications (35%). No significant difference in Infectious complications was observed between the two groups (35% vs. 44%, p= 0.513). Modality suspension due to autonomy loss was higher in DM group (12% vs. 3%, p= 0.05). In the univariate model, rate of technique failure was higher in the DM group (HR=1.9, CI 95% 1.2-2.8, *P* = 0.003). This association was not verified in the multivariate model. Due to protocol changes in PD prescription after the availability of biocompatible solutions, separate time period analysis before and after 2008 revealed HR 4.7 (CI 05% 0.75-29.0 P=0.097) and HR of 1.3 (CI 95% 0.3-2.2, p=0.415), respectively.

Conclusions: Decreased technique survival in DM patients was not verified when considering separate time period analysis, with better outcomes in recent years. This reflects technical improvements, biocompatible solutions and prescription tailoring. CV management remains key, and strategies to mitigate the menace of autonomy loss are essential in this subgroup, including helper signaling and increased support for assisted PD.

SA-PO639

Success Rates and Safety of Two Non-Guided Percutaneous Catheter Placement Techniques for Peritoneal Dialysis in Urgent-Start Dialysis: A Single-Center Experience Retrospective Cohort Study

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Background: The optimal technique for catheter placement in uremic patients remains debated. In our center we have been using our non-guided percutaneous modified Seldinger technique. With the availability of the peritoneal dialysis catheter kit in our center, we modified our non-guided Seldinger technique for patients with urgent start dialysis requirement.

Methods: This was a single-center retrospective cohort study of patients hospitalized with urgent-start dialysis requirement of a single center in Mexico City. We aimed to summarize the success rates and safety of our two percutaneous non-guided insertion methods.

Results: A total of 117 patients with urgent-start dialysis requirement were included. Two percutaneous catheter insertion techniques were used, the non-guided percutaneous modified Seldinger technique 62.9% and the non-guided percutaneous modified Seldinger technique with peritoneal dialysis catheter kit technique 48.1%. The mean age of the patients was 54.92 ± 13.49 years, 40.5% were women, the mean body mass index (BMI) was 25.79 ± 4.77 kg/m2, BUN 95 ± 57 and the median in-hospital stay was 19.28 (10-20) days. Overall, 73.3% had diabetes, 76.7% hypertension, and the time from admission to catheter insertion was 7 (3-10) days. The analysis showed that the patients who underwent placement with peritoneal dialysis catheter kit had fewer replacement requirement (p=0.028), and there was no difference in migration, peritonitis, and catheter leak between both groups.

Conclusions: The use of the peritoneal dialysis catheter kit in urgent start dialysis requirement proved less catheter replacement.

Variables	Peritoneal dialysis catheter kit (n= 27)	Non peritoneal dialysis catheter kit (n= 90)	p value
Age (years)	56.26 ± 12.6	54.52 ± 13.79	0.171
Body Mass Index (kg/m2)	25.2 ± 4.95	25.95 ± 4.73	0.066
Type 2 Diabetes (%)	77.5	70.4	0.067
Hypertension (%)	70.4	78.7	0.689
Replacement (%)	0	15.7	0.028
Catheter migration (%)	7.4	14.6	0.329
Leak (%)	1.9	3.1	0.625
Peritonitis (%)	7.4	5.6	0.732

SA-PO640

Evaluation of Impact of Residual Renal Function on Clinical Outcome, Quality of Life, and Prognosis in Patients on Continuous Ambulatory Peritoneal Dialysis (CAPD)

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Background: Residual renal function (RRF) in patients with ESRD receiving dialysis is defined as the ability of the native kidneys to eliminate water and uremic toxins. It provides small solute clearance, has role in maintaining fluid balance, phosphorus control, and removal of middle molecular uremic toxins, and contributes significantly to the overall health. It is a powerful predictor of mortality.

Methods: A Prospective Observational Study conducted in Apollo Hospitals, Guwahati for 1year. Study Population included all patients who were initiated on CAPD during this study period after excluding those fulfilling exclusion criteria. Their RRF was calculated as the average of urea clearance (Kru) and creatinine clearance (Crcl) in 24 hrs urine sample. All patients were followed up at regular intervals - at the time of initiation of CAPD, 3 and 6 months with clinical, laboratory parameters, prognostic markers.

Results: Following observations were made during the study: Total number of cases was 50 with mean age of 61.6 years with majority (54%) in elderly age group (>60 years) with a male to female ratio of 2.57:1. Most common co-morbidities were hypertension (92%), diabetes (60%), CAD (26%), hypothyroidism (24%). Native kidney diseases observed were diabetic nephropathy (52%), hypertensive nephropathy (50%), chronic glomerulonephritis (14%), chronic tubulointerstitial diseases (4%). Mean renal reserve deteriorated over time from 4.27 ml/min/1.73m2 at baseline to 4.11 ml/min/1.73m2 at 3 months and 3.91 ml/min/1.73m2 at 6 months ($p<0.01$). 36% cases showed a fall of renal reserve >0.5 ml/ min/ 1.73 m2 and 36% showed low renal reserve (0.5 ml/ min/1.73 m2). These cases were observed to be significantly associated with lower urine output, hemoglobin, platelet, sodium, albumin, bicarbonate, vitamin D levels and higher creatinine, potassium, PTH, phosphorus levels, higher degree of malnutrition, depression, co-morbidities, poorer quality of life parameters ($p<0.01$), more incidence of respiratory infections, peritonitis and also higher mortality.

Conclusions: Our study showed low RRF deteriorates over time. A significant correlation between low RRF at baseline and malnutrition, depression symptoms, poor quality of life and solute clearance. Hence preservation of RRF is an essential marker of patient prognosis in CAPD.

SA-PO641

Predictors of Long-Term Patient and Technique Survival in Home Hemodialysis Patients

Koji Tomori, Tsutomu Inoue, Yusuke Watanabe, Hiroaki Amano, Hirokazu Okada. *Saitama Ika Daigaku, Iruma-gun, Japan.*

Background: Home Hemodialysis (HHD) enhances patient quality of life and survival, yet it also increases the risk of access-related complications due to the frequency of treatments. The influence of these complications on long-term treatment survival, particularly in patients with arteriovenous fistulas (AVF), remains unclear. Therefore, our study aims to follow AVF patients over a prolonged period to evaluate long-term treatment survival and identify its predictors in HHD patients.

Methods: We conducted an observational study involving all incident HHD patients at our facility from 2001 to 2020. The cumulative incidence of all-cause mortality and procedure failure (TF) as a composite outcome was calculated at 5- and 10-year intervals. Cox proportional hazards models were used to identify patient characteristics or comorbidities that predicted TF and death.

Results: A total of 77 patients (age of 50.7 years, 15.6% female, and 23.4% with diabetes) were included. All patients self-punctured their AVF, and the median frequency of dialysis was five sessions per week. During a median follow-up of 116 months, we observed 11 deaths and 19 instances of TF. Unadjusted 5- and 10-year adverse event-free survival was 83.5 and 67.2 %, respectively. Both age (aHR 1.09) and diabetes (aHR 4.17) were significantly associated with TF. Cardiovascular disease was the most frequent cause of death, and VA trouble was the primary cause of TF. VA-related TF occurred after 100 months of HHD initiation.

Conclusions: Although the long-term prognosis of HHD patients was favorable, access-related TFs occurred more frequently in patients with long-term HHD. Thus, careful management of VA is important to improve treatment survival.

SA-PO642

Reframing the Role of Buttonhole Cannulation (BHC) in the Home Hemodialysis (HHD) and Self-Care Settings: Outcomes of BHC as a Primary Technique in a Large Single-Center HHD Program

Waleed Zafar, Maria Bermudez. *Geisinger Medical Center, Danville, PA.*

Background: HHD remains underutilized in the U.S. Fear of needle insertion is one of the main patient barriers for widespread adoption of HHD. BHC, once considered the preferred method for self-cannulation given patient- and fistula-friendliness, has fallen out of favor due to concerns about infectious complications. The quality of evidence concerning potential risks of BHC is low. We describe experience from a single center HHD program regarding utilization of BHC technique.

Methods: Patients currently enrolled in the HHD program were surveyed regarding the use of BHC. Since the program predominantly utilizes BHC, we also evaluated the incidence of bacteremia in all patients enrolled in the HHD program between 2008 and 2022.

Results: Between 2008 and 2022 a total of 76 patients were ever enrolled in the HHD program at a single center of whom 18 (23.7%) were currently active, 13 were successfully transplanted, 19 transitioned to in-center hemodialysis and 23 died. No episodes of bacteremia were documented in the HHD program over this period. 14 of the 18 currently active patients who had arteriovenous fistulas were surveyed and 13 of them used BHC technique. All but 2 patients did short daily HHD with remaining two doing nocturnal HHD. Demographics and results from the survey are presented in table 1.

Conclusions: Our 14-year single center experience with BHC has helped develop key elements for the successful implementation of this technique: a single cannulator per fistula, multidisciplinary patient-centered selection, longitudinal education, strict infection control, and reliable nursing support. These have shown to be important in patient and care partner empowerment as well as low incidence of infectious and noninfectious complications.

Table 1: Results of survey about accessing AVF among patients currently enrolled in the HHD program (n=14).

Characteristic		N (%)
Age	Less than 49 years	5 (35.7)
	50 – 69 years	6 (42.9)
	70 or older	3 (21.4)
Sex	Male	8 (57.1)
	Female	6 (42.9)
Diabetes		7 (50.0)
Received Kidney Transplant		3 (21.4)
Duration since starting any type of renal replacement therapy	Less than a year	2 (14.3)
	1 – 2 years	6 (42.9)
	3 – 5 years	4 (28.6)
	More than 5 years	2 (14.3)
Ever been on Peritoneal dialysis		3 (21.4)
Ever been on In-center dialysis		14 (100.0)
Duration on In-Center dialysis	Less than a year	8 (57.1)
	1 – 2 years	1 (7.1)
	3 – 5 years	2 (14.3)
	More than 5 years	3 (21.4)
Technique to access fistula	Buttonhole	13 (92.9)
	Rope ladder	1 (7.1)
Primary person to access fistula	Partner	8 (57.1)
	Self	6 (42.9)
Factors that help in reducing needle related distress	Nursing support	2 (16.7)
	Education about cannulation	1 (8.3)
	Increasing confidence my or partner's ability to cannulate	9 (64.3)
Frequency of pain while accessing fistula	Never or rarely	10 (71.4)
	Sometimes, very often or always	4 (28.6)
Frequency of infiltration while accessing fistula	Never or rarely	14 (100)
	Sometimes, very often or always	-
Frequency of prolonged bleeding while accessing fistula	Never or rarely	13 (92.8)
	Sometimes, very often or always	1 (7.1)
Frequency of aneurysm formation while accessing fistula	Never or rarely	13 (92.8)
	Sometimes or very often	1 (7.1)
Frequency of inability to complete dialysis because of difficulty with cannulation	Never or rarely	14 (100.0)
	Sometimes or very often	-
Frequency of fistula infection since starting buttonhole technique	Never	14 (100.0)
	Once	-
	Twice or more	-
Felt supported by the team when having issues with fistula	Almost always or often	14 (100.0)
	Sometimes, seldom or never	-

SA-PO643

A Nephrologist-Driven Percutaneous Peritoneal Dialysis Catheter Insertion Service Increases the Prevalence of Peritoneal Dialysis: A Single-Centre Experience in Singapore

Sreekanth Koduri. *Changi General Hospital, Singapore, Singapore.*

Background: The incidence and prevalence of end stage kidney disease(ESKD) requiring dialysis is increasing all over world, including Singapore. Despite the well documented benefits of peritoneal dialysis(PD) in offering better quailty of life and preservation of residual renal function, only around 15% of prevalent ESKD patients are on PD in Singapore. The aim of the study is to report the success of a percutaneous PD catheter insertion service in increasing the prevalence of PD in a large academic renal centre.

Methods: The number of prevalent PD patients was stagnant in our centre, over last 5years, despite the consistent growth in the number of ESKD patients requiring dialysis during this period. From early 2022, the interventional nephrologists started a percutaneous PD catheter insertion service. Based pre-determined criteria, the patients were selected for appropriate method of PD catheter insertion by the nephrologists, as illustrated in figure 1.

Results: Since 2022, 75.9% of the PD catheters were inserted percutaneously by interventional nephrologists. The complication rates were very low with no episodes of bowel perforation, major bleeding or PD peritonitis within 2weeks of catheter insertion. There was one episode (1.5%) of exit site infection within 2weeks of catheter insertion. Since the introduction of this service, the number of prevalent PD patients increased by 55% by May 2023 when compared to December 2021(104 vs 67prevalent patients), as illustrated in figure 2.

Conclusions: Percutaneous PD catheter insertion by nephrologists, with appropriate selection of patients, is safe and reliable. This service provides timely access creation and increases the penetration of PD.

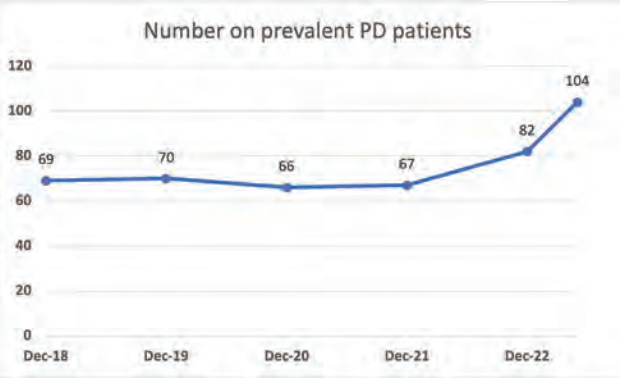


Figure 2

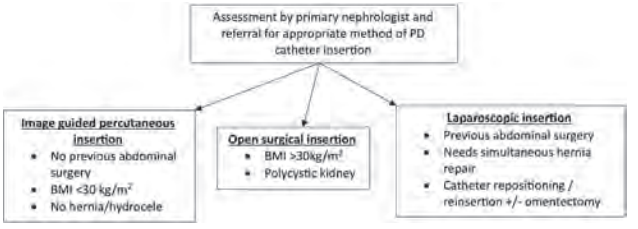


Figure 1

SA-PO644

Longevity of Percutaneously Placed Peritoneal Dialysis (PD) Catheters: Single-Center Study

Alexis Lorio,[1] Mahnoor Liaqat,[1] George L. Parra,[2] Claire Juhas,[1] David I. Nweke,[1] Akwe Nyabera,[3] Manoj Bhattarai,[3] Shweta Bansal.[3] *[1]The University of Texas Health Science Center at San Antonio Joe R and Teresa Lozano Long School of Medicine, San Antonio, TX; [2]The University of Texas Health Science Center at San Antonio Graduate School of Biomedical Sciences, San Antonio, TX; [3]The University of Texas Health Science Center at San Antonio Division of Nephrology, San Antonio, TX.*

Background: Percutaneously placed PD catheters are shown to have similar short-term (1 year) outcomes as compared to surgically placed catheters and have been used increasingly. Data on the longevity of these catheters are sparse.

Methods: We conducted a retrospective chart review study of 114 catheters in 91 patients who initiated PD between 2014 and 2020 at University Health System home dialysis center. The last follow-up was December 2022. PD catheters were placed percutaneously (n=81) either by interventional radiologists or nephrologists, or by laparoscopic surgery (n=33) when there were concerns of hernia or adhesions due to prior extensive abdominal surgery or refractory peritonitis. Demographic and clinical data were analyzed using descriptive statistics.

Results: In the percutaneous group, mean age was 46.4±13 years, 66% were male, mean BMI was 29±6 kg/m^2 and diabetes was the cause of kidney failure in 69% of patients. The surgical cohort had similar demographics except mean BMI was 31.2±7.6 kg/m^2. Median longevity of an individual catheter determined from PD start to cessation was 90.4 (30.6, 158.8) weeks for the percutaneous and 68.7 (29, 123) weeks for the surgical group. Reasons for catheter removal are shown in Figure 1. The percutaneous group had 0.26 episodes of peritonitis per patient-year, while the surgical group had 0.40 episodes per patient-year. The most common mechanical complications were slow drain and leakage, and these were similar between the two groups. Non-randomization precludes comparison analysis between the groups.

Conclusions: This single-center experience demonstrates that percutaneously placed PD catheters are a viable alternative for long-term PD therapy. Further studies from large centers or databases are needed to confirm our findings which have implications for the direction of PD programs to allocate resources appropriately.

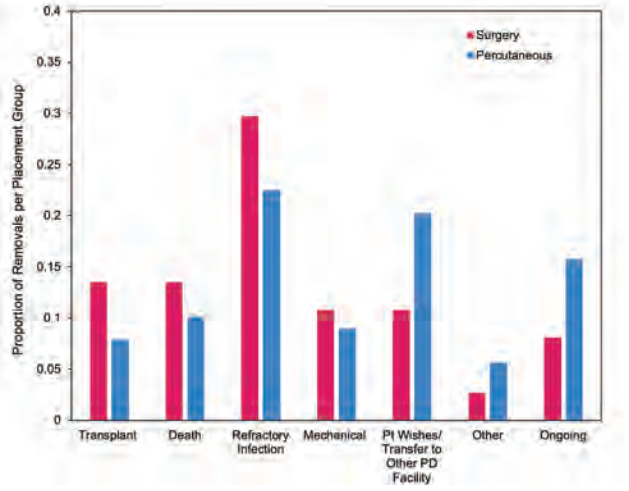


Figure 1

SA-PO645

Medical Peritoneal Dialysis Catheter Insertion Can Increase Peritoneal Dialysis (PD) Patient Population: A Single-Centre Study

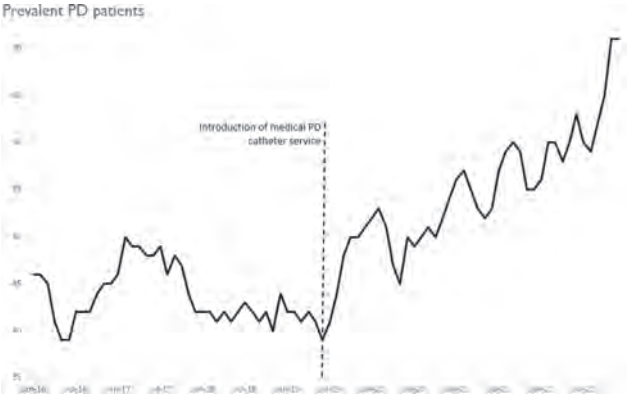
James Talbot-Ponsonby, Yasir Z. Khan, Daniel Jones, Seema Shrivastava, Edward Stern. *St George's University Hospitals NHS Foundation Trust, London, United Kingdom.*

Background: Peritoneal dialysis (PD) can offer improvement in quality of life and treatment costs compared to hemodialysis. Access to PD is often limited by cather insertion facilities. PD catheters can be inserted surgically (laparoscopic or open, both typically under general anaesthesia) or medically (percutaneous, under local anaesthesia). We examined the benefits of introducing a medical PD catheter service in a tertiary renal unit in addition to a surgical service which was already available.

Methods: Safety data (incidence of peritonitis within 90 days and of catheter malpositioning) were reviewed in the electronic health record from July 2017-June 2019 (surgical insertions alone) and July 2019-June 2021 (medical and surgical insertions). PD prevalence was tracked over 6 years.

Results: From June 2017-July 2019 there were 44 surgical catheter insertions compared to 63 (33 medical, 30 surgical) from July 2019-June 2021: a 43% increase in incident PD patients. There was no significant difference in early peritonitis (14% in surgical vs 15% in medical, P=0.77) or malposition (7% in surgical vs 9% in medical, p=0.70). Prevalent PD patients fell by 15% from 2016-2019 but grew by 79% in the 3 years after introduction of medical catheter insertions.

Conclusions: Introducing percutaneous PD catheter insertion by nephrologists was associated with an increase in PD patients with no increase in complications. Contraindications to medical insertion include significant obesity or previous major abdominal surgery. A hybrid medical/surgical service allowed most patients to be offered PD while avoiding general anaesthesia and minimising operating theatre usage. A limitation in this study is the groups arenot matched for complication risk: technically challenging patients will tend to be offered surgical insertion. Nevertheless, we demonstrated that introduction of medical PD catheter insertion can grow the PD population without an increase in complications.



SA-PO646

Surgical Outcomes Associated with Simple vs. Complex Peritoneal Dialysis Catheter Placement

Ankur Shah,[1,2] Susie L. Hu,[1,2] Christina A. Raker.[1,2] *[1]Brown University Warren Alpert Medical School, Providence, RI; [2]Rhode Island Hospital, Providence, RI.*

Background: Patients receiving peritoneal dialysis are dependent upon stable, reliable access to their peritoneal cavity via a surgical or percutaneously placed catheter. Advanced laparoscopic catheter placement has been demonstrated to have better catheter related outcomes compared to simple placement. In this study, we report baseline characteristics and 30 day surgical outcomes of simple versus complex laparoscopic PD catheter placement in a national US based cohort.

Methods: We conducted a retrospective analysis using the NSQIP database from January 1, 2013, to December 31, 2018. Patients who underwent peritoneal dialysis catheter placement were identified using relevant Current Procedural Terminology (CPT) codes. Simple catheter insertion was defined as the absence of additional procedures while complex was defined as catheter extension or omentopexy. Data on patient characteristics, surgical approach (simple or complex), and postoperative outcomes were extracted. The primary outcomes of interest included death, length of stay, and surgical site infection.

Results: A total of 9,593 patients who underwent laparoscopic peritoneal dialysis catheter placement were included in the analysis. Of these 89.95% received simple catheter placement, while 10.05% underwent advanced techniques. Patients who underwent complex catheter placement had no difference in mortality (adjusted odds ratio (aOR) 0.54, 95% Confidence Interval (CI) 0.19 – 1.52, p = 0.25), surgical site infection (OR 0.59, 95% CI 0.34 – 1.03, p = 0.06), or prolonged length of stay (>7 days) (OR 0.95, 95% CI 0.51 – 1.78, p = 0.87) compared to patients receiving simple catheter placement.

Conclusions: This study demonstrates that advanced peritoneal dialysis catheter placement techniques are associated with similar surgical outcomes compared to simple techniques. It is already known that patients receiving advanced catheter placement have lower rates of catheter tip migration, flow obstruction, and better long term catheter survival. These findings suggest that the adoption of advanced techniques may lead to improved long-term catheter related outcomes without sacrificing short term surgical outcomes.

Funding: Clinical Revenue Support

SA-PO647

Evaluating the Impact of the Advancing American Kidney Health Executive Order on Global Search Interest: An Interrupted Time Series Analysis

Ankur Shah,[1,2] Roger Chou,[1] Susie L. Hu,[1,2] Christina A. Raker.[1,2] *[1]Brown University Warren Alpert Medical School, Providence, RI; [2]Rhode Island Hospital, Providence, RI.*

Background: AAKH aimed to improve kidney health outcomes by transforming the kidney care landscape. Understanding the general impact of such policy interventions is crucial for public health surveillance and policy planning.

Methods: We conducted a retrospective analysis using Google Trends data from for two time periods: January 1, 2013 to December 31, 2018, and January 1 2019 to December 31, 2021. Search interest data were extracted using relevant keywords related to kidney health and care. An interrupted time series analysis was performed to assess the impact of the AAKH executive order on global search interest trends. Segmentation was conducted at the time of policy implementation (July 2019) to compare pre- and post-intervention periods.

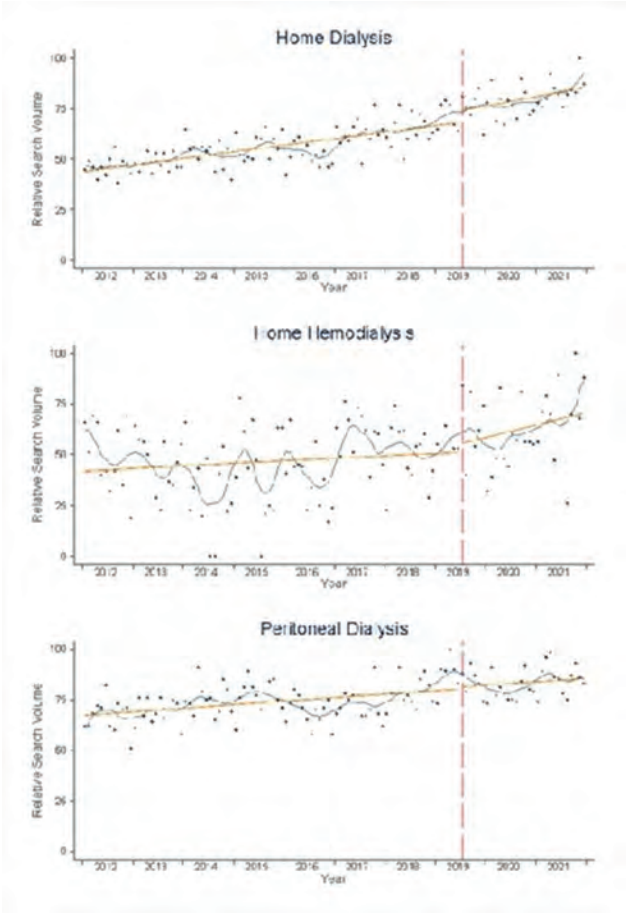
Results: Overall, interest in home dialysis, home hemodialysis, and peritoneal dialysis were steadily increasing in both the USA and globally. In the USA and globally, relative interest in peritoneal dialysis outweighed home hemodialysis. Home hemodialysis had the greatest variability in RSV with 2014 and 2015 had zero RSVs, leading to the observed dip in the lowess curve.

Conclusions: AAKH has not increased awareness of home dialysis beyond the nephrology community. More steps must be taken to raise awareness and understanding of home dialysis.

Funding: Clinical Revenue Support

HOME DIALYSIS						
	Level Change Post-AAKH			Trend Change Post-AAKH		
	Mean (95% CI)			Mean (95% CI)		
	Within-group	Between-group	P	Within-group	Between-group	P
USA	5.93 (-0.16 to 12.0)	-5.27 (-13.3 to 2.73)	0.20	0.13 (-0.17 to 0.43)	0.38 (-0.02 to 0.77)	0.06
Global	11.2 (6.0 to 16.4)	Ref.		-0.24 (-0.50 to 0.01)	Ref.	
HOME HEMODIALYSIS						
	Level Change Post-AAKH			Trend Change Post-AAKH		
	Mean (95% CI)			Mean (95% CI)		
	Within-group	Between-group	P	Within-group	Between-group	P
USA	4.16 (-10.8 to 19.1)	-6.2 (-25.1 to 11.9)	0.48	0.42 (-0.44 to 1.28)	0.43 (-0.60 to 1.45)	0.41
Global	10.8 (-0.15 to 21.7)	Ref.		-0.005 (-0.55 to 0.54)	Ref.	
Peritoneal Dialysis						
	Level Change Post-AAKH			Trend Change Post-AAKH		
	Mean (95% CI)			Mean (95% CI)		
	Within-group	Between-group	P	Within-group	Between-group	P
USA	0.85 (-5.83 to 7.53)	-3.52 (-12.9 to 5.86)	0.46	0.003 (-0.31 to 0.31)	0.22 (-0.22 to 0.65)	0.33
Global	4.37 (-2.22 to 11.0)	Ref.		-0.21 (-0.52 to 0.09)	Ref.	

Comparison of USA vs. Global changes in trends pre- and post-AAKH by segmented linear regression.



USA trends in relative search volume, 2012-2021

SA-PO648

Peritoneal Dialysis Offers Similar Outcomes to Hemodialysis in Hospitalized Patients Admitted with COVID-19

Ankur Shah,[1,2] David Painter,[1] Susie L. Hu,[1,2] Christina A. Raker.[2,1] *[1]Brown University Warren Alpert Medical School, Providence, RI; [2]Rhode Island Hospital, Providence, RI.*

Background: The COVID-19 pandemic has resulted in hundreds of millions of infections and more than 6 million deaths worldwide. Maintenance dialysis patients were at uniquely high risk for both acquisition and morbidity and mortality related to COVID-19. Our studies objective is to assess outcomes by dialysis modality using a large, population based database in the United states. Specifically, we sought to quantify the effects of dialysis modality on hospital mortality, length of stay, and hospital charges. This work will be useful in public health planning and resource utilization for a future respiratory pandemic.

Methods: We retrospectively identified patients in the 2020 National Inpatient Sample with primary diagnosis code of COVID-19 and ICD-10-PCS codes for hemodialysis or peritoneal dialysis. Descriptive statistics were performed on demographic, comorbidities, hospital, and outcome variables. Primary outcomes were Mortality and secondary outcomes were Length of Stay and Hospital Charges. Linear and Logistic Regression with survey weights were used to develop models accounting for demographic, clinical, and hospital factors.

Results: A total of 54,580 COVID-19 patients with ESKD were identified in the NIS database, of which 1,730 patients were on PD and 52,850 patients were on HD. After adjusting for demographic and clinical factors, there was no significant difference in in-hospital mortality between PD and HD patients (adjusted odds ratio [aOR] = 1.13, 95% confidence interval [CI]: .85-1.49, p=.389). Similarly, LOS (adjusted mean difference (aMD)= -.344, 95% CI: -1.52-.84, p=.569) and hospital charges (aMD = -4868.31, 95% CI: -27562.54-17825.92, p=.674) did not significantly differ between the two groups.

Conclusions: This study provides evidence that COVID-19 infection requiring hospitalization in PD patients is associated with similar outcomes compared to HD patients. PD patients had similar in-hospital mortality rates, lengths of stay, and hospital charges. These findings suggest that both PD and HD patients with ESKD are equally vulnerable to the morbidity and mortality COVID-19, although PD patients are able to better shield from acquiring the virus. Further research is needed to explore additional factors that may influence outcomes and to guide clinical decision-making for ESKD patients during the COVID-19 pandemic.

Funding: Clinical Revenue Support

SA-PO649

Creatinine Clearance Predicts Longitudinal Phosphate Levels Irrespective of Achieved Urea Kt/V: A Peritoneal Dialysis-MONDO Analysis

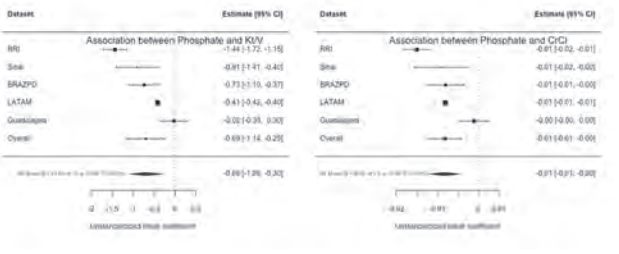
Murilo H. Guedes,[1] Maria Ines Diaz Bessone,[2] Lili Chan,[3] Andres E. De la Torre Quiroga,[4] Ariella E. Mermelstein,[5] Guillermo Garcia-Garcia,[4] Vincent Peters,[6] Constantijn Konings,[7] Adrian M. Guinsburg,[2] Thyago P. Moraes,[1] Peter Kotanko,[5] Jochen G. Raimann,[5] Jaime Uribarri.[3] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Fresenius Medical Care Holdings Inc, Waltham, MA; [3]Icahn School of Medicine at Mount Sinai, New York, NY; [4]Hospital Civil de Guadalajara, Guadalajara, Mexico; [5]Renal Research Institute, New York, NY; [6]Tilburg University, Tilburg, Netherlands; [7]Catharina Ziekenhuis, Eindhoven, Netherlands.*

Background: Serum phosphate (PO4) is associated with worse outcomes among kidney failure patients, and its dialysis clearance is not well predicted by small solute kinetics. Guidelines in peritoneal dialysis (PD) recommend using urea Kt/V over creatinine clearance (CrCl) to monitor dialysis adequacy. We hypothesize that this recommendation may lead to suboptimal PO4 control. We designed this study to evaluate if CrCl predicts longitudinal PO4 irrespective of achieved Kt/V.

Methods: We performed a longitudinal analysis of multiple cohorts of incident PD patients – Fresenius Medical Care Latin America (FMC-LATAM), Renal Research Institute (RRI), Mount Sinai Hospital, Hospital Civil Guadalajara, and the BRAZPD cohort. The exposures were first available Kt/V and CrCl after 90 days of PD initiation. The outcome was longitudinal PO4. Results were pooled using a random-effects metanalysis. The primary estimate was the linear coefficient from linear mixed regression models with random effects. Models were then compared by log-likelihood ratios (LLR) to assess the information added by CrCl on models with Kt/V.

Results: 16.796 patients were included – RRI (n=653), Sinai (n=131), BRAZPD (n=171), LATAM (n=15631), and Guadalajara (n=210). Mean ages ranged from 45 (Guadalajara) to 58 years (Sinai). In most datasets, Kt/V and CrCl were associated with longitudinal PO4 despite adjusting for sex, age, and PO4 binder use. The pooled estimates, despite being heterogeneous, confirmed the results (**Figure**). For all datasets, including CrCl on models adjusted with Kt/V improved information (LLR tests $p < 0.05$ for all datasets).

Conclusions: Among incident PD patients, CrCl predicts longitudinal PO4 irrespective of achieved urea Kt/V. Our results suggest that CrCl may be an important measurement in clinical practice to monitor PO4 clearance in PD patients.



SA-PO650

Effect of Roxadustat vs. Erythropoietin on Nutritional Status in Peritoneal Dialysis Patients: A Retrospective Study

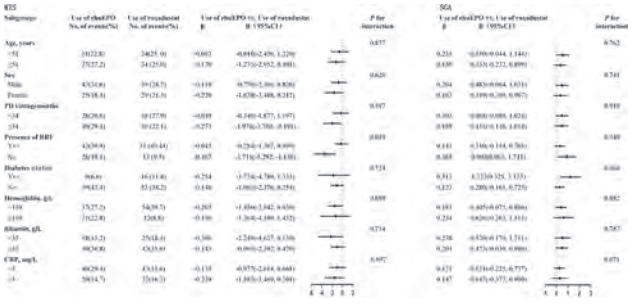
Xiao J. Luo, Qimei Luo, Xianrui Dou. *Shunde Hospital of Southern Medical University, Foshan, China.*

Background: Roxadustat have been used to treat renal anemia in patients undergoing dialysis. The effect of roxadustat on nutritional status in peritoneal dialysis (PD) patients remains uncertain. We aimed to explore the effect of roxadustat on nutritional status, and explore the possible modifiers for the association in PD patients.

Methods: The current study included 136 PD patients with renal anemia. The primary efficacy endpoints included changes from baseline in nutrition-related parameters. Linear regression analysis was performed to analyze the correlation between use of roxadustat with Subjective Global Assessment (SGA) and Malnutrition-Inflammation Score (MIS). Logistics regression analysis was used to evaluate the risk factors for the indicators of MIS.

Results: After a median treatment observation of 20.0 (25^{th}-75th, 16.0–21.0) months, the changes from baseline in serum albumin, prealbumin, total cholesterol, high-density lipoprotein cholesterol, blood urea nitrogen and creatinine levels were not significantly different between two groups. Besides, the use of roxadustat was inversely associated with MIS (β, -0.263; 95% CI: -2.430, -0.096), and was positively associated with SGA (β, 0.440; 95% CI: 0.046, 0.834). Additionally, compared to patients in rHuEPO group, those with the use of roxadustat were associated with more dietary intake (OR, 0.405; 95% CI: 0.190-0.865) and fewer gastrointestinal symptoms (OR, 0.365; 95% CI: 0.164-0.809). The inverse association between the use of roxadustat with MIS was stronger in patients without RRF (*P* for interaction=0.019).

Conclusions: In short, this study found that the use of roxadustat was inversely associated with MIS and positively associated with SGA in PD patients.



SA-PO651

Profiles of Iron and Anemia Indices and Associations in Mental Health Among Incident Peritoneal Dialysis Patients in Brazil and the United States

Vladimir Rigodon,[1,2] Peter G. Pecoits,[1,5] John W. Larkin,[2] Yue Jiao,[2] Len A. Usvyat,[2] Franklin W. Maddux,[2] Peter Kotanko,[3,4] Roberto Pecoits-Filho,[1,5] Thyago P. Moraes,[1,5] Murilo H. Guedes.[1,5] *[1]Pontificia Universidade Catolica do Parana, Curitiba, Brazil; [2]Fresenius Medical Care, Waltham, MA; [3]Renal Research Institute, New York, NY; [4]Icahn School of Medicine at Mount Sinai, New York, NY; [5]EPICENTER - Center for Epidemiology and Clinical Research, Curitiba, Brazil.*

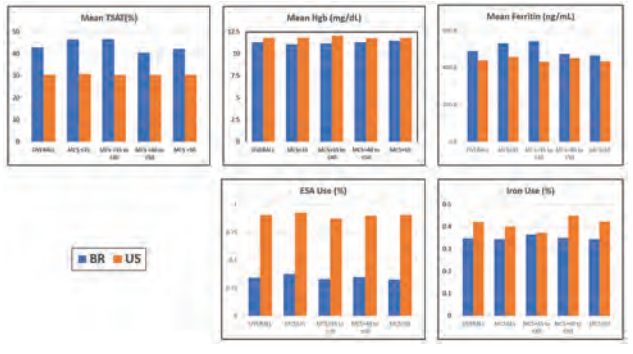
Background: Management of iron stores and anemia are important to maintaining quality of life in dialysis, yet the associations in mental health are unknown in Peritoneal Dialysis (PD). We aimed to identify and describe the trends in KDQOL mental component summary (MCS) scores and cohort characteristics in patients starting PD in Brazil (BR) and the United States (US), with a focus on iron and anemia indices and related medication use.

Methods: Patients included data on adults who started PD between Dec 2004-Jan 2011, that had ≥1 TSAT, hemoglobin (Hgb), ferritin, and KDQOL result within the first 180 days of PD. We described the BR and US cohort characteristics based on the following MCS categories: ≤35, >35-≤40, >40-≤50, >50. Higher MCS scores show better mental health. This preliminary analysis is descriptive, and it does not include multivariable adjustments.

Results: In both cohorts (BR=2022 vs US=1657), age (mean age BR=57.3 vs US=55.6) and albumin levels were consistent (both 3.7 g/dL). The US cohort had fewer males (BR=45% vs US=54%) and more patients with a white race (BR=62% vs US=72%). TSAT levels and erythropoietin stimulating agent use were higher in the US vs BR (**Figure**). Lower MCS scores were associated with higher ferritin & TSAT levels in BR, though not observed in the US. Higher MCS scores were positively associated with IV iron use in the US, but not observed in BR. Younger patients showed the lowest MCS scores in the US, while the inverse was found in BR.

Conclusions: In this preliminary descriptive analysis, we found some unique profiles in iron and anemia markers associated with mental health outcomes. Although some of these findings may be related to practice patterns, iron and anemia management may potentially influence the mental health of patients at PD initiation. Further investigations are needed to understand this relationship and its implications for patient care and outcomes.

Funding: Commercial Support - Pontificia Universidade Catolica do Parana, Fresenius Medical Care, BaxterHealthcare



SA-PO652

Higher Iron Deficiency Rates Among Incident Peritoneal Dialysis Patients Without Anemia in Brazil and United States

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Background: The profiles of iron deficiency (ID) are undefined in the peritoneal dialysis (PD) population. This study examines the prevalence of and patient characteristics associated with ID states and the coexistence of anemia in incident PD patients in the United States (US) and Brazil (BR).

Methods: We used data from adults starting PD at 122 clinics in BR and >2500 clinics in the US. We included patients who had at least ≥1 hemoglobin (Hgb), ferritin, and transferrin saturation (TSAT) measurement within 180 days of PD start. ID was defined as TSAT <20%. ID states were categorized as: a. functional ID, no anemia (TSAT <20%, ferritin ≥200 ng/mL, Hgb ≥10 g/dL), b. functional ID with anemia (TSAT <20%, ferritin ≥200 ng/mL, Hgb <10 g/dL), c. absolute ID, no anemia (TSAT <20%, ferritin <200 ng/mL, Hgb ≥10 g/dL), and d. absolute ID with anemia (TSAT <20%, ferritin <200 ng/mL, Hgb <10 g/dL).

Results: Patients starting PD in BR (n=1,365) and the US (n=12,303) had mean age of 59.8 (BR) & 55.2 (US) years, 46.4% (BR) & 55% (US) were male, 61% (BR) & 70% (US) were of a white race. ID was present in >10% of incident PD patients, with a slightly higher prevalence in BR (~4 percentage points). Rates of ID states were relatively consistent in BR and US for functional and absolute ID in patients without anemia, and these represent ≥80% of all ID cases (**Figure 1**). However, functional and absolute ID rates among patients with uncontrolled anemia were ≥3 fold higher in BR vs US.

Conclusions: Prevalence of ID at PD start is >10.6% and ID primarily exists in patients without anemia in both BR and US. Current recommendations suggest ID screening in patients with low Hgb, considerations that may be having implications on patient care. For instance, patients with functional ID had mean ferritin >400 ng/mL, yet levels were >150 ng/mL higher in those with vs without anemia. Ongoing research is underway to understand the trajectories and outcomes associated with ID in PD.

Funding: Commercial Support - Pontificia Universidade Catolica do Parana, Fresenius Medical Care, BaxterHealthcare

Figure 1: Characteristics of Incident PD Patients with Iron Deficiency in Brazil and United States

Parameters	Overall		Functional ID, no anemia		Functional ID with anemia		Absolute ID, no anemia		Absolute ID with anemia	
Country	BR	US	BR	US	BR	US	BR	US	BR	US
Patient n	1365	12303	71	497	21	67	86	696	25	44
ID prevalence (%)	14.8	10.6	5.2	4.0	1.5	0.5	6.3	5.7	1.8	0.4
Age (years)	59.8	55.3	61.5	58.4	58.7	51.6	57.3	55.0	58.9	48.4
Male (%)	46.4	55.0	53.5	53.0	47.6	61.0	37.2	48.0	24.0	34.0
White race (%)	61.1	70.0	56.3	69.0	61.9	58.0	73.3	76.0	48.0	77.0
Albumin (g/dL)	3.5	3.6	3.4	3.5	3.6	3.1	3.5	3.5	3.4	3.3
Hgb (g/dL)	11.3	12.0	11.6	11.7	9.1	9.4	11.8	11.9	9.1	9.4
TSAT (%)	44.1	30.7	15.3	17.4	16.2	17.2	15.5	16.4	14.6	14.9
Ferritin (ng/mL)	424.2	445.5	489.5	475.5	582.5	665.6	91.6	93.9	100.2	88.6

BR: Brazil; US: United States; PD: peritoneal dialysis; ID: iron deficiency; Hgb: hemoglobin; TSAT: transferrin saturation

SA-PO653

Constipation and Clinical Outcomes in Peritoneal Dialysis: Results from Thailand PDOPPS

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Background: Patient-reported outcome measures (PROM) has gained international recognition as important predictors of clinical outcomes in peritoneal dialysis (PD). We sought to understand the associations between patient-reported constipation and clinical outcomes.

Methods: Constipation was determined in patients across 22 facilities in Thailand Peritoneal Dialysis Outcomes and Practice Patterns Study (PDOPPS) during 2014-2017. Constipation was diagnosed using both objective assessment tools (Bristol Stool Form Scale [BSFS]) and self-reported questionnaire, constipation severity score [CSS]). BSFS is a 7-level scale visual inspection of feces (from 1 to 7, from hard to softer) based on its texture and morphology. Whilst the CSS measures duration (1 item) and severity (7 items: frequency of bowel movement, difficulty, pain, completeness, attempt duration, defecation assistance, frequency of attempt failure) of constipation and is a self-filled questionnaire, with participants being asked to respond on a 5-point Likert scale coded.

Cox proportional hazards model regression was used to estimate associations between constipation and clinical outcomes, including mortality, hemodialysis (HD) transfer and peritonitis.

Results: 634 of 975 randomly selected PD patients from 22 facilities reported their constipation by using BSFS and CSS. In this questionnaire, the patients rated their constipation as well as a change in constipation over time. Constipation was common in the PD population, particularly in patients with older age, marriage, diabetes, lower educational level, and worse nutritional status (including lower time-average serum albumin and phosphate concentrations). Interestingly, self-reported constipation at baseline was significantly associated with shorter time to first and higher rates of peritonitis (hazard ratio [HR] 1.74, 95%CI 1.29-2.34) and death (HR 2.43, 95%CI 1.82-3.24) but not HD transfer (HR 1.25, 95%CI 0.7-2.21) after adjusting for age, gender, PD vintage, comorbidities, shared frailty by study sites, and serum albumin.

Conclusions: Patient-reported constipation was independently associated with higher risks of peritonitis and all-cause mortality, but not HD transfer. This warrants further investigation to identify effective interventions.

SA-PO654

Role of Remote Monitoring in Automated Peritoneal Dialysis: Impact in SONG-PD (Standardized Outcomes in Nephrology-Peritoneal Dialysis) and Results from RPM-APD Multicenter Study

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Background: The use of remote monitoring (RPM) in automated peritoneal dialysis (APD) has shown lower hospitalization rates in those patients who used this technique in addition to another series of clinical advantages such as greater technique survival. The present study evaluated the association between RPM use and SONG-PD outcomes.

Methods: A prospective observational multicenter cohort study included 232 patients in 16 Hospitals. A RPM program was used in 176 of the patients and 56 were treated with APD without RPM. The primary outcomes were standardized outcomes in Nephrology (SONG)-PD clinical outcomes and quality of life (EQ-5D-L). Data was recorded al least during 6 months. Propensity score matching (PSM) 1:1 was used to evaluate the association of RPM exposure with outcomes.

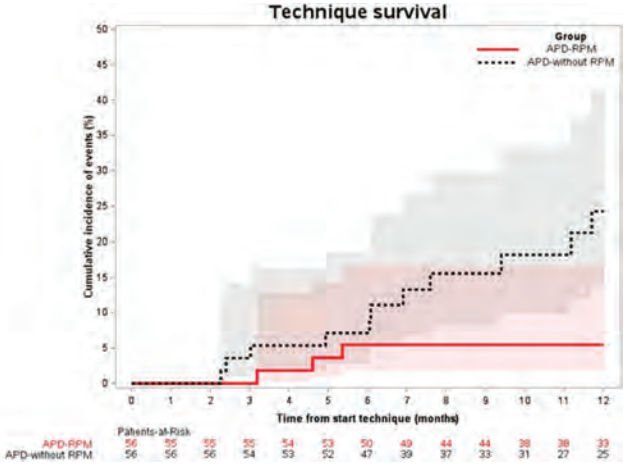
Results: There were no differences between baseline and demographic characteristics. Before PSM, APD with RPM (n=176) vs without RPM (n=56) was associated with less mortality (n=1 vs n=4)(HR (95%CI): (0.08 (0.01-0.69) (p=0.020) and with better technique survival (n=10 vs n=11) (HR (95%CI): (0.25 (0.11-0.59) p=0.001). After PSM, APD with RPM continued to associate con with better technique survival (figures 1 and 2)

Conclusions: The use of an RPM program in APD patients may be associated with better technique survival. RPM could be a tool for improvement of APD therapy.

Funding: Commercial Support - Baxter Health Company

Table 1. Clinical Outcomes Associated with RPM in Matched Sample

Outcomes	APD- RPM N=56	APD-without RPM N=56	OR (95%CI)* HR (95%CI) IRR (95%CI)	P value
Primary outcomes				
PD associated infection[1]	12 (21.4)	13 (23.2)	0.90 (0.37-2.21)	0.821
Infections per patient-year	0.34 (0.79)	0.30 (0.63)	1.11 (0.49-2.56)	0.792
Cardiovascular disease[2]	9 (16.1)	2 (3.6)	3.92 (0.84-18.2)	0.081
Mortality	1 (1.8)	4 (7.1)	0.24 (0.03-2.16)	0.204
Technique survival[1]	3 (5.6)	11 (21.6)	0.23 (0.06-0.83)	**0.024**



SA-PO655

Association Between Age, Frailty, and Change in Health-Related Quality of Life After Dialysis Initiation?

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Background: Despite its key importance, changes in health-related quality of life (HRQOL) after dialysis start are still poorly understood. This study aimed to assess the association between age, frailty and changes in HRQOL during the transition to home dialysis and in-center hemodialysis (ICHD).

Methods: HRQOL was measured using the KDQOL-SF questionnaire. Frailty was evaluated at study baseline using the Clinical Frailty Scale. Changes in physical component summary (PCS), mental component summary (MCS), and kidney-specific domains (burden, symptoms/problems and effects of kidney disease) were assessed in linear regressions comparing scores 6-months before and 6-months after dialysis start, with adjustment for age, frailty, dialysis modality and gender.

Results: Among a cohort of 121 CKD patients, 59 patients initiated dialysis (68 ±13 years, 61% ICHD and 39% home dialysis). HRQOL trajectories, stratified by age and frailty are illustrated in Figure 1. After adjustment, there were no statistically significant predictors associated with score changes at six months. There was however a nearly significant interaction between age and frailty (p=0.052) for MCS whereby frailty was associated with a trend towards decreased MCS for patients <65 years (*B* -18.1, 95% CI -37.4; 1.2, p=0.06), without a significant change in older patients. We also observed a trend towards improved score in the Problems/Symptoms in patients >65 years (vs. <65 years) after dialysis start (*B* 10.7, -0.3; 21.7, p=0.055).

Conclusions: This small prospective study showed that age and frailty may be associated with HRQOL after dialysis start, although we did not identify statistically significant associations. It demonstrates the importance of individualizing the choice of kidney replacement therapy, avoiding generalizing the expected evolution of patients on the basis of isolated characteristics such as age or frailty.

Figure 1. Crude trajectory of HRQOL before and after dialysis initiation

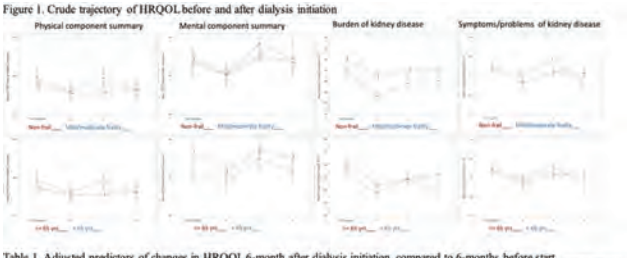

Table 1. Adjusted predictors of changes in HRQOL 6-month after dialysis initiation compared to 6-months before start

Variables	PCS			MCS			Effect			Burden			Symptoms/Prob.		
	B	95% CI	P-value	*B*	95% CI	P-value	*B*	95% CI	P-value	*B*	95% CI	P-value	*B*	95% CI	P-value
Home dialysis *vs. ICHD*	-3.0	-10.5; 4.5	0.42	5.3	-7.1; 13.7	0.20	4.3	-12.7; 21.3	0.61	-5.9	-23.4; 12.0	0.51	-1.2	-11.9; 9.4	0.81
Women *vs Men*	1.3	-4.8; 7.6	0.65	-0.9	-7.7; 5.9	0.78	-4.9	-18.4; 8.7	0.47	8.3	-6.3; 23.0	0.25	1.7	-7.0; 10.5	0.68
Age ≥65 yrs *vs <65 yrs*	1.5	-6.3; 9.3	0.70	3.7	-5.0; 12.4	0.39	2.3	-15.4; 20.0	0.79	5.9	-12.6; 24.4	0.52	10.7	-0.3; 21.7	0.055
Mild/moderate frailty *vs non-Frail*	-5.0	-13.4; 3.3	0.22	-18.1	-37; 1.2	0.06	9.2	-8.9; 27.3	0.31	5.3	-14.6; 25.0	0.59	-9.3	-21.2; 2.5	0.12
Age*Frailty (>65yrs /frailty vs. *<65 yrs /non-frail*)				21.8	-0.2; 43.9	0.052									

SA-PO656

International Comparison of Home Dialysis Uptake: A Multi-Registry Analysis from the INTEGRATED Research Group

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Background: There is a wide variability in home dialysis use from a high of 50% of patients receiving home dialysis in New Zealand to less than 10% in France. We aimed to compare patterns and predictors of home dialysis uptake across different registries.

Methods: This multi-national registry study of home dialysis included data from Australia, New Zealand, Canada, France and USA. Analyses were performed independently in each registry using identical statistical approaches. Multivariable adjusted clustered Cox models were used to evaluate predictors of home dialysis initiation within the first year of kidney replacement therapy (KRT), excluding pre-emptive transplantation.

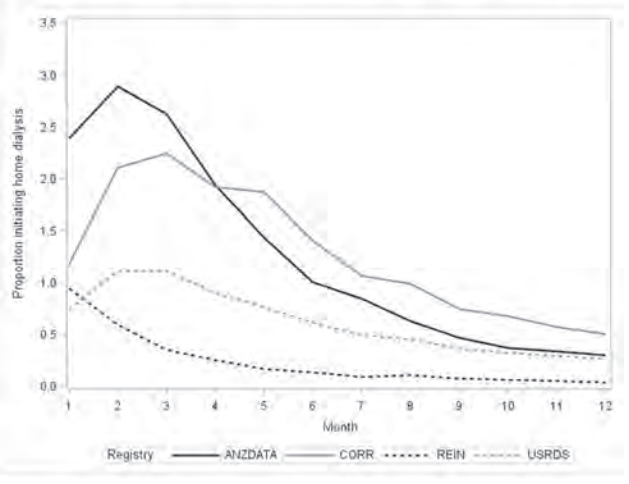
Results: The proportion of patients starting KRT on home dialysis was 29% in ANZDATA, 22% in CORR, 9.2% in REIN and 8.8% in USRDS. Patterns of transfer from in-center hemodialysis to home dialysis varied between countries, with a marked increase in the proportion of transfer to home dialysis 3 months after KRT start in CORR, ANZDATA and USRDS. After adjustment for patient-related characteristics, patients were most likely to initiate home dialysis within the first month of KRT in all registries. There was a diverging association between sex and home dialysis uptake; females had a lower use of home dialysis in Canada and Australia/New Zealand, and higher use in France and USA.

Conclusions: This study showed marked international differences in the pattern of home dialysis uptake within the first year of KRT. Further work should aim to identify how practice patterns, and governance strategies can mitigate these differences to improve access to home dialysis.

Funding: Private Foundation Support

Table 1. Adjusted clustered Cox model of home dialysis initiation within one year after KRT initiation

Figure 1. Percentage of patients transferred from in-center hemodialysis to home dialysis, excluding patients starting on home dialysis, within the first year of hemodialysis initiation, for the three registries



SA-PO657

Is the Cost of the New Home Dialysis Techniques Still Advantageous Compared to In-Centre Hemodialysis?

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Background: Three main factors should be considered in the economic evaluation of home dialysis: the progressive reduction in the cost of consumables for in-centre hemodialysis (IC-HD), the widespread use of incremental Peritoneal Dialysis, and the renewed interest in Home Hemodialysis (H-HD). Registries data on incidence and prevalence of dialysis modalities are heterogeneous, showing widespread underemploy of home dialysis. Based on results in clinical and quality of life benefits, underemploy could be no more justified.

Methods: We compared the direct and indirect costs of PD (53 patients), H-HD (21 patients) and IC-HD (180 patients) by measuring the dialysis activity performed from January 1, 2019 to December 31, 2019 at the San Giovanni Bosco Hub Hospital, Turin (Italy). A cost analysis of the different dialysis techniques (DP and HD, home and hospital) was also carried out.

Results: To obtain comparable weekly costs, the following strategy was applied: a) calculating the average weekly frequency of dialysis sessions based on the dialysis modality. b) normalizing the cost of individual sessions per patient per week. c) calculating the monthly and yearly costs. PD proved to be the least expensive (€ 23,314.79 per patient per year), while H-HD has a lower average cost than IC-HD (€ 35,535.00 vs € 40,798.98).

Conclusions: Our data analysis confirms the low cost of Continuous Ambulatory PD and PD. Compared to all other hemodialysis modalities and even Automated Peritoneal Dialysis, Home Bicarbonate Hemodialysis has the lowest costs and the weekly cost of Frequent Home Hemodialysis was found to be comparable to that of In-Centre Bicarbonate Hemodialysis.

SA-PO658

First-Year Impact of the ESRD Treatment Choices (ETC) Model

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Background: The ETC Model is intended to boost use of home dialysis and kidney transplantation among Medicare fee-for-service beneficiaries with ESRD, while reducing Medicare expenditures and preserving quality of care through performance-based Medicare payment adjustments to ETC participants. We examined impacts in the first year of the ETC Model (2021).

Methods: CMS randomly selected 91 Hospital Referral Regions (HRRs) and four HRRs from Maryland for the ETC Model, with mandatory participation from ESRD facilities and Managing Clinicians. We used difference-in-differences (DiD) regression models to compare changes in outcomes in the 95 ETC HRRs with those in 211 comparison HRRs between 2017-2019 and 2021. We used data from Medicare claims, the ESRD Quality Reporting System, the Scientific Registry of Transplant Recipients, and the In-Center Hemodialysis Consumer Assessment of Healthcare Providers and Systems survey to evaluate impacts on dialysis modality, transplant, utilization, Medicare spending, and patient experience of care.

Results: ETC HRRs constituted 31% of HRRs nationwide and included 2,519 ESRD facilities, 4,749 Managing Clinicians and 99,699 beneficiaries in 2021. Home dialysis increased similarly in ETC (11.8 to 14.7% of patient months) and comparison (12.8 to 15.8%) areas, yielding a non-significant (NS) DiD estimate of -0.11%. Home dialysis training increased 9% more in ETC vs. comparison areas ($p<0.05$). Transplant waitlisting showed a slower decline in ETC (19.5 to 19.0%) vs. comparison (21.1 to 19.8%) areas (DiD=0.83%, ($p<0.1$). Living donor kidney transplant rates fell similarly in ETC and comparison areas (DiD=0.005, NS). Although not directly incentivized by ETC, deceased donor transplants increased more in ETC (3.2 to 4.5 transplants per 1,000 patient months) vs. comparison (3.3 to 4.1) areas (DiD=0.37, $p<0.1$). There was no early impact on hospital utilization, overall Medicare spending and in-center hemodialysis patient experience of care.

Conclusions: Through the first year of the ETC Model, there was evidence of modest gains in home dialysis training, transplant waitlisting and deceased donor transplants, but no impact on home dialysis use or living donor transplants. These are early findings. Future analyses will consider the impact of provider infrastructure development and increased payment adjustments.

Funding: Other U.S. Government Support

SA-PO659

Factors Affecting Survival Rate in Diabetic Patients Who Underwent Immediate-Start Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) patients with diabetes mellitus (DM) are known to have poorer survival compared to PD patients without DM. However, there are few studies on risk factors associated with patient survival in diabetic end-stage renal

disease (ESRD) patients underwent PD. The aim of this study was to identify factors independently associated with patient survival in diabetic ESRD patients who received immediate-start peritoneal dialysis (ISPD) without a break-in-period.

Methods: In this retrospective cohort study, 178 consecutive patients who started PD at Konkuk University Hospital from August 2005 to March 2023 were enrolled, and 144 patients with ISPD were finally analyzed. These patients were divided into the DM and the non-DM group. The primary outcomes were factors independently associated with patient survival in the DM group, estimated using a Cox proportional hazards regression model. Kaplan-Meier method was used to calculate patient survival rates.

Results: Among 144 patients, 93 (64.5%) had diabetes. The 1-, 5-, and 10-year patient survival rates of the DM and non-DM group were 97.6%, 86.9%, 35.1% and 98.4%, 92.1%, 65.6%, retrospectively. Compared to the non-DM group, the DM group had significantly higher age and body mass index (BMI), and significantly lower hemoglobin and serum albumin levels. However, only CVD was independently associated with patient survival in the DM group in univariate analysis, and this association was confirmed in multivariate analysis (Table 1).

Conclusions: Our study showed that CVD was the only factor independently associated with patient survival in ISPD patients with diabetes. Other factors such as age, BMI, hemoglobin, and serum albumin level did not appear to affect patient survival in diabetic ESRD patients who underwent ISPD without a break-in period.

		Multivariable	
Variables		Hazard ratio(95% CI)	P-value
Age		1.00 (0.96-1.04)	0.983
BMI(kg/m²)	25<BMI<30	1.20 (0.33-4.43)	0.781
	BMI> 30	1.95 (0.46-7.85)	0.364
CVD		3.12 (1.03-9.44)	0.044
Uric acid		1.15 (0.92-1.41)	0.206
Smoking		2.31 (0.58-9.18)	0.233

Table 1. Multivariable Cox regression analysis for 10-year patient survival in the diabetic group

SA-PO660

Healthcare Resource Utilization (HCRU) in Prevalent Dialysis Patients Undergoing Peritoneal Dialysis in the United States

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Background: CKD is associated with increased HCRU. The US prevalence of patients (pts) undergoing peritoneal dialysis (PD) has more than doubled since 2000. We characterized the HCRU rate in prevalent PD pts in the US.

Methods: This observational cohort study used 2017–2019 United States Renal Data System data. Adults (≥18 years [yrs]) undergoing PD on Jan, 1 2018 (index) and with 6 months of Medicare fee-for-service coverage prior to index (incl.) were included. Follow-up was from index until death, loss of Medicare coverage, kidney transplantation, or Dec 31, 2019. All-cause HCRU was measured as the total number of services provided/total follow-up time (rate per patient-year [PY]).

Results: 20,647 PD pts were included (median age, 62.2 yrs; median dialysis duration, 2.7 yrs; **Table 1**). Diabetes was the most prevalent comorbidity (55.4%) and cause of ESKD (39.9%). Median follow-up was 2 yrs. During follow-up, rate of hospitalization was 1.52 per PY; of intensive care unit use 0.37; of skilled nursing facility (SNF) use 0.29; and of emergency department (ED) encounters 1.09 (**Table 2**). Consultation rates were highest for nephrologists (15.72). Pts treated in units with the largest numbers of pts (>100) had generally lower HCRU; pts outside of large metro areas had a lower hospitalization, but higher outpatient and ED encounters rates.

Conclusions: In the US, PD pts had 1.52 hospitalizations and 1.09 ED encounters per PY. Pts treated in units with >100 pts had generally lower HCRU rates.

Funding: Commercial Support - Funded by GSK (Study 213716)

Table 1. Baseline characteristics

Baseline characteristics	
Total, N (%)	20,647 (100)
Median age, years (25th, 75th percentile)	62.2 (51.0, 71.0)
Male sex, n (%)	11,322 (54.8)
Median dialysis duration, years (25th, 75th percentile)	2.7 (1.3, 4.4)
Race, n (%)	
Non-Hispanic white	11,037 (53.5)
Non-Hispanic black	5,094 (24.7)
Hispanic	2,810 (13.6)
Other	1,706 (8.3)
Medicare/Medicare dual enrollment, n (%)	7,020 (34.0)
Part D drug coverage low-income subsidy	
No part D coverage	4,969 (24.1)
Without low-income subsidy	6,894 (33.4)
With low-income subsidy	8,784 (42.5)
Comorbidities in baseline period, n (%)	
Diabetes	11,439 (55.4)
Atherosclerotic heart disease	5,382 (26.1)
Heart failure	5,093 (24.7)
Other cardiac disease	4,192 (20.3)
Peripheral vascular disease	3,792 (18.4)
Dysrhythmia	3,017 (14.6)
Chronic obstructive pulmonary disease	2,439 (11.8)
Stoke or transient ischemic attack	1,910 (9.3)
Acute myocardial infarction	1,142 (5.5)
Liver disease	878 (4.3)
Gastrointestinal disease	593 (2.9)
Cause of end-stage kidney disease, n (%)	
Diabetes	8,242 (39.9)
Hypertension	6,346 (30.7)
Glomerulonephritis	3,141 (15.2)
Other/unknown/missing	2,918 (14.1)

Table 2. Rates of healthcare resource utilization in prevalent peritoneal dialysis patients (rate per patient-year)

	Service setting							Physician speciality			
	Inpatient										
	All	ICU	Intermediate care unit	General ward	SNF	ED*	OB*	OP	Nephrologist	Cardiologist	Endocrinologist	Internal medicine & family doctor
Overall, rate per patient-year	1.52	0.37	0.50	0.003	0.29	1.09	0.20	6.73	15.72	4.11	0.47	9.70
Residence area												
Large metropolitan area	1.54	0.38	0.52	0.004	0.28	1.02	0.20	6.13	15.90	4.20	0.52	9.88
Non-large metropolitan area	1.48	0.40	0.42	*	0.31	1.34	0.20	8.96	15.04	3.55	0.29	9.04
Dialysis facility size†												
<30	1.57	0.39	0.47	*	0.30	1.11	0.21	7.46	15.28	4.22	0.56	10.03
30–<60	1.56	0.39	0.50	*	0.34	1.11	0.21	7.33	15.73	4.13	0.50	10.26
60–100	1.57	0.39	0.51	0.002	0.31	1.11	0.20	8.90	15.75	4.23	0.46	9.87
>100	1.47	0.34	0.51	0.005	0.25	1.07	0.20	8.27	15.73	4.05	0.46	9.36

*Number of events <11; †Not leading to hospitalization; ‡Measured by patients per facility.
ED: emergency department; ICU: intensive care unit; OB: observational stay; OP: outpatient; SNF: skilled nurse facility

SA-PO661

Effect of ESRD Prospective Payment System on Utilization of Peritoneal Dialysis in Patients with Kidney Allograft Failure

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Background: The Center for Medicare and Medicaid Services introduced ESRD Prospective Payment System (PPS) in 2011 to increase the utilization of home dialysis modalities, including peritoneal dialysis (PD). Several studies have shown a significant increase in PD utilization after PPS implementation. However, its impact on patients with kidney allograft failure remains unknown.

Methods: We conducted an interrupted time series analysis using data from the United States Renal Data System that include all adult patients with allograft failure who started dialysis between 2005 and 2019. We compared the PD utilization in the pre-PPS period (2005-2010) to the fully implemented post-PPS period (2014-2019) for early (within 90 days of dialysis initiation) and late (91-365 days) PD experience.

Results: 27507 adult recipients with allograft failure started dialysis during the study period. There was no significant difference in early PD utilization between pre-PPS and post-PPS period in either immediate change called "step change" (0.3% increase; 95%CI: -1.95%, 2.54%; p=0.79) or rate of change over time called "slope change" (0.28% increase per year; 95%CI: -0.16%, 0.72%; p=0.18). Subgroup analyses revealed a trend toward higher PD utilization in post-PPS period in for-profit and large-volume dialysis units. There was a significant increase in PD utilization in post-PPS period in those units which had low PD experience in the pre-PPS period (2.2% increase; 95% CI: 1.31, 3.22; p<0.01). Similar findings were seen for the late PD experience.(Table)

Conclusions: PPS did not significantly increase the utilization of PD in patients initiating dialysis after allograft failure.

	Pre-PPS period, % [a]	Post-PPS period, % [b]	Step change, % [c]	P-value	Slope change, % per year [d]	P-value
Overall	15.8	18.8	2.64 (-8.25, 0.97)	0.15	-0.44 (-1.24, 0.36)	0.27
Age						
≥ 36 yr	13.1	16.0	-0.99 (-5.51, 3.53)	0.66	-0.36 (-1.40, 0.64)	0.45
< 36 yr	19.3	23.3	-5.09 (-11.03, 0.85)	0.09	-0.60 (-1.92, 0.72)	0.35
Sex						
Male	13.4	16.4	-0.29 (-4.80, 4.23)	0.90	0.28 (-0.72, 1.28)	0.59
Female	19.4	22.2	-8.01 (-12.59, 0.58)	0.07	-1.44 (-2.92, 0.004)	0.05
Race						
White	17.3	20.8	-1.49 (-6.13, 3.15)	0.52	-0.66 (-1.68, 0.36)	0.20
Black	12.2	13.5	-1.92 (-6.88, 3.04)	0.44	0.20 (-0.92, 1.32)	0.72
Others	16.9	23.4	-20.02 (-34.59, -5.46)	<0.01	-2.44 (-5.68, 0.80)	0.13
Facility profit status						
For-profit	15.7	18.4	-2.41 (-6.17, 1.35)	0.20	-0.44 (-1.28, 0.40)	0.28
Not-for-profit	17.0	21.4	-1.15 (-11.46, 9.16)	0.82	0.16 (-2.12, 2.44)	0.89
Facility affiliation status						
Affiliated	15.4	18.2	-2.54 (-6.94, 1.65)	0.25	-0.68 (-1.68, 0.28)	0.16
Independent	17.7	21.3	1.53 (-9.12, 12.18)	0.77	1.52 (-0.84, 3.88)	0.20
Facility size						
Small	12.4	18.8	-0.91 (-7.75, 5.93)	0.79	-0.44 (-1.96, 1.08)	0.55
Medium	9.3	15.9	-0.23 (-6.29, 5.82)	0.94	-1.28 (-2.6, 0.09)	0.06
Large	21.1	20.7	-2.91 (-8.27, 2.45)	0.28	0.52 (-0.68, 1.72)	0.37
Facility previous PD use						
Low	0.3	4.8	2.51 (1.03, 3.96)	<0.01	0.16 (-0.16, 0.52)	0.33
Medium	7.9	15.2	3.33 (-4.15, 10.82)	0.37	-0.28 (-1.92, 1.40)	0.75
High	35.4	33.1	-9.61 (-16.29, -2.92)	<0.01	-1.26 (-2.76, 0.20)	0.09

ESRD PPS, End-Stage Renal Disease Prospective Payment System; PD, peritoneal dialysis
a. Pre-PPS period: Q2 2005 - Q4 2010
b. Post-PPS period: Q1 2014 - Q4 2019
c. Instant change of the proportion of early PD attempt after PPS.
d. Long-term change in increase rate of the proportion of early PD attempt (% per year) after PPS.

Effect of PPS on late PD experience in patients with allograft failure

SA-PO662

Fewer Communities Left Behind: Peritoneal Dialysis (PD) Initiation Patterns by Health Service Area in an Era of Expansion

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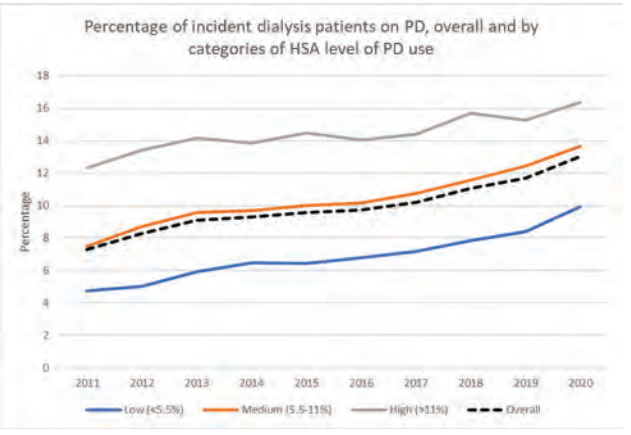
Background: Use of peritoneal dialysis (PD) has historically varied by community and region, with racially diverse, urban, and northeastern areas having lower utilization of PD than rural, less diverse, and western areas. The trend of PD utilization since 2010 in the communities impacted by these disparities is unclear.

Methods: We used the United States Renal Database System to examine patterns of PD use in Health Service Areas (HSA) in the US. We assigned each of the 754 HSAs with ≥20 prevalent dialysis patients in 2009-2010 into "high" (>11% of dialysis patients using PD), "medium" (5.5-11%) or "low" (<5.5%) PD use categories. We then identified incident dialysis patients from 2011-2020 and described patient characteristics and trends in percentage of patients using PD on day 1 of dialysis according to HSA PD-use category. We used logistic regression with adjustment for demographics to determine whether changes in PD use differed across HSA categories.

Results: 1,195,588 incident dialysis patients were included. In the 2011-2020 period, low-use HSAs had a lower percentage of incident dialysis patients who were White (48.1% vs 63.2%) and a higher percentage of incident dialysis patients living in urban areas (86.3% vs 69.4%) or in the Northeastern US (38.8% vs 8.9%) compared with high-use HSAs. The percentage of patients initiating PD increased in each category of HSA (Figure). The adjusted odds of a patient initiating PD increased more in low-use HSAs (OR per 5 years 1.49, 95% Confidence Interval [CI] 1.45-1.52) than in medium or high-use categories (OR 1.37, 95% CI 1.35-1.39; OR 1.16, 95% CI 1.13-1.19, respectively).

Conclusions: During the 2010s, PD use increased more rapidly in areas where the modality had previously been less-utilized, suggesting that the national increase in PD utilization was geographically robust and did not result in widening differences among HSAs.

Funding: NIDDK Support, Clinical Revenue Support



SA-PO663

Characteristics of Registered Research in Peritoneal Dialysis, Past and Present

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Background: Recent national policy changes and the continued growth of peritoneal dialysis (PD) as a therapy for end-stage kidney disease has renewed interest in this modality. The objective of this study was to describe the current landscape of PD clinical trials to assess trends and gaps in clinical research.

Methods: An advanced search was completed through ClinicalTrials.gov, yielding 248 studies. Descriptive statistics and Fisher exact tests were used for statistical analysis.

Results: Most studies were completed (197, 79.4%), did not indicate a phase (143, 57.7%), were academically sponsored (156, 62.9%), or conducted in Asia (88, 35.5%). There has been overall growth in PD clinical trials since 1995. Drug studies were more likely to be completed, industry-sponsored, or have surrogate as the primary outcome compared to device, procedure/behavioral, and other studies (17, 77.2%, 16, 72.7%, 71, 72.5%, respectively; p = 0.030; 2, 9.1%, 2, 9.1%, 5, 4.1%, respectively; p < 0.001; 13, 59.1%, 15, 68.2%, 78, 79.5%, respectively; p < 0.001).

Conclusions: Despite growth in PD research worldwide, more studies are being conducted outside the U.S., and static investment in U.S. government sponsored PD research risks not achieving the goal of increasing availability of home dialysis.

SA-PO664

Mobile Technology to Explore Real-Time Symptom Data and Physical Activity in People Receiving Peritoneal Dialysis

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Background: Fatigue is a frequent and debilitating symptom that contributes to poor quality of life for people receiving peritoneal dialysis (PD). The fatigue experience and factors that may influence it (e.g., mood and physical activity) are poorly understood for people receiving PD, in-part, due to the recall instruments typically used to assess fatigue. Mobile ecological momentary assessment (mEMA) is a survey method that captures data in real-time using mobile phone technology, which has not been trialled in this cohort. The aim of this study was to explore the real-time fluctuations and associations between fatigue, mood and physical activity using mEMA.

Methods: A seven-day longitudinal study was conducted with adults receiving PD. Participants completed fatigue (0-130 [No Fatigue - Severe Fatigue]) and mood (0-10 [Happy - Sad]) Likert scales, via a mobile app, five times each day and concurrently wore an accelerometer to capture physical activity. A feasibility questionnaire was completed via the app on the eighth day.

Results: Forty-eight adults (mean age 61.0+13.5 years) completed the study. Relative to mean wake up score, within-day fluctuations were observed with fatigue less severe from mid-morning to early afternoon (10am-1pm: -9%) before increasing later in the afternoon (4pm-7pm: +14%), peaking at bedtime (+27%). Associations between fatigue and mood were observed with a 1-unit change in mood score conferring a 5.2-unit change in fatigue *(p<0.01)*. Acute relationships were observed with every 1-minute of physical activity associated with a -0.53 *(p<0.01)* and -0.01 *(p<0.05)* change in fatigue and mood score, respectively. Overall adherence to the app-based surveys was 73%. Most participants reported mobile phones and the mEMA app being easy to use with some seeing potential in mEMA to assist with the management of their kidney condition, as a self or external monitoring tool.

Conclusions: The results suggest that targeting either fatigue or mood through intervention may be effective for improving both symptoms, with physical activity-based interventions a potential strategy to mitigate fatigue and poor mood. Furthermore, mEMA, and mobile phones, were feasible to capture symptom data with potential to be employed in future research or, as part of improved care.

SA-PO665

A Proof-of-Concept Study: Metoprolol Tartrate Is Readily Cleared by Peritoneal Dialysis

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Background: The dialyzability of cardioprotective β-blockers such as metoprolol and carvedilol is well-known. Even so, there is no consensus on the choice between metoprolol vs. carvedilol due to studies with conflicting results. The situation is worse for PD patients since the data on PD clearance of β-blockers is far more scarce. Furthermore, some authors have linked β-blockers to UF failure without a clear mechanism. In this proof-of-concept study, we aimed to develop a technique for determining the metoprolol tartrate (MT) level in the effluent and serum samples of PD patients. The completed version of the study will also include metoprolol succinate and carvedilol levels, which we expect to be the first study to investigate that phenomenon.

Methods: We selected nine patients on stable doses of MT aimed at a resting pulse<70/min. All predialysis samples were taken on the dry abdomen. Regardless of APD or CAPD status, an exchange with 1.36% glucose solution was done. After a 2-hour dwell time, post-dialysis blood samples and effluent samples were collected. In addition, pre and post-pulses and ECGs were recorded. The blood samples were analyzed with the HPLC 1220 ® (High-performance liquid chromatography) instrument. The peaks at 262 nm were recorded, and the AUC values were calculated based on the standard analysis. A similar process was followed for the effluent.

Results: The mean age was 58±11 years. Drug doses and baseline pulse rates were similar. The mean pre-PD MT levels were 134±66 ng/mL, and post-PD levels were 51±28 ng/mL. The average effluent drug concentration was 81±51 ng/mL, and the delta change between pre-post dialysis was 60±11%. Patients on APD had numerically higher MT baseline and post-dialysis concentrations, but the difference was insignificant (p=0,190). Residual renal function and transporter types did not affect drug levels. Pre and post-dialysis pulse rates were statistically similar; no tachycardia event was observed.

Conclusions: We have shown that effluent has very high levels of MT. This might be the link to the so-called β-blocker-related UF failure. Furthermore, we have proven that PD readily clears MT. After the completion of the study with the addition of metoprolol succinate and carvedilol levels, we hope to facilitate the "β-blocker" debate in the field of peritoneal dialysis.

SA-PO666

Peritoneal Dialysis Patients Exhibit Quantifiable Neurocognitive Impairment but Not Acute Ischemic Brain Injury: A Magnetic Resonance Spectroscopy and Diffusion Tensor Imaging Study

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Background: Patients receiving hemodialysis (HD) are known to suffer recurrent ischemic multiorgan injury, which effects the vulnerable vascular beds of the brain. These acute cerebral insults are associated with significant white matter (WM) injury, ultimately leading to neurocognitive impairment. PD patients are not subject to the equivalent circulatory stress as HD patients suggesting PD is relatively neuro-protective. Our objective was to utilize an imaging-based approach previously applied to a HD cohort to examine the acute intradialytic effects of PD.

Methods: Patients completed a neurocognitive battery (The Montreal Cognitive Assessment (MoCA), Trails Making Test (TMT), and Cambridge Brain Science (CBS)), an intradialytic MRI scan encompassing diffusion tensor imaging (DTI, WM integrity), and a proton magnetic resonance spectroscopy (^{1}H-MRS, neurochemistry). Imaging and neurocognitive assessments were performed before PD exchange, with repeat imaging after 90 minutes of dwell time.

Results: 12 patients receiving PD were studied. Patient demographics included (mean±SD): 67±8 years of age, 75% male, 75% diabetic, dialysis vintage 18±10 months, ultrafiltration 0.58±0.36L, and PD exchange 8.3% with 2.5% and 91.7% with 4.25% dextrose. Neurocognitive impairment (%impaired) was evident by the TMTA/B measuring attention (A=92%) and executive function (B=42%). CBS tasks are classified by their contribution to verbal, short-term memory, and reasoning domains. The verbal weighted domain component score demonstrated the most impairment (46%). Finally, 2/12 patients (17%) exhibited global impairment detected by the MoCA. DTI imaging demonstrated no acute effects on WM integrity. However, ^{1}H-MRS detected a 21% increase in brain glucose concentration (p=0.006).

Conclusions: PD patients exhibited quantifiable neurocognitive deficits, but did not suffer acute intradialytic WM injury, supporting that PD may have neuro-protective benefits. PD dwell did result in brain hyperglycemia, indicative of acute metabolic stress. This may translate into an alternative hypothesis for progressive neurocognitive impairment via advanced glycation end-products, but further research is necessary.

Funding: Private Foundation Support

SA-PO667

Retinopathy Is Associated with Impaired Cognition in Patients Undergoing Peritoneal Dialysis

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Background: This study was aimed at examining the relationship between retinopathy and cognitive impairment in patients undergoing peritoneal dialysis (PD).

Methods: Forty-eight men and 59 women (age range: 21 to 78 years) undergoing PD were included in this **c**ross-sectional study. Retinal microvascular characteristics, such as geometric changes in retinal vascular including tortuosity, fractal dimension (FD), and calibers, were assessed. Retinopathy (such as retinal hemorrhage or microaneurysms) was evaluated using digitized photographs. The Modified Mini-Mental State Examination (3MS) was performed to assess global cognitive function.

Results: The prevalence rates of retinal hemorrhage, microaneurysms, and retinopathy were 25%, 30%, and 43%, respectively. The mean arteriolar and venular calibers were 63.2 and 78.5 mm, respectively, and the corresponding mean tortuosity was 37.7 ± 3.6 and 37.2 ± 3.0 mm^{-1}. The mean FD was 1.49. After adjusting for age, sex, education, mean arterial pressure, and Charlson index, retinopathy was found to be negatively associated with 3MS scores (regression coefficient, -3.71, 95% confidence interval: -7.09 to -0.33, P = 0.03).

Conclusions: Retinopathy, a condition common in patients undergoing PD, was associated with global cognitive impairment.

Funding: Government Support - Non-U.S.

Evaluation of retinal microvascular characteristics

	Total	Without Retinopathy	With Retinopathy	P value
Entries	214	122 (57.01)	92 (42.99)	
Mean caliber of arteriole (μm)	63.20(55.68-69.80)	64.19(57.71-70.00)	61.45(55.56-68.80)	0.350
Mean caliber of venule (μm)	78.53(71.46-88.11)	78.15(69.54-88.51)	79.03(72.42-86.24)	0.874
AVR	0.80 ± 0.13	0.81± 0.13	0.80 ± 0.12	0.589
Mean tortuosity of arteriole (mm-1)	37.74 ± 3.60	37.34 ± 3.36	38.27 ± 3.86	0.067
Mean tortuosity of venule (mm-1)	37.24 ± 2.98	37.32 ± 2.89	37.12 ± 3.11	0.631
Fractal dimension	1.49 (1.47-1.51)	1.50 (1.48-1.51)	1.48 (1.45-1.51)	<0.001
Microaneurysms, n (%)	65 (30.37)	23 (18.85)	42 (45.65)	<0.001
Retinal hemorrhage, n (%)	54 (25.23)	12 (9.84)	42 (45.65)	<0.001
Drusen, n (%)	9 (4.21)	5 (4.10)	4 (4.35)	>0.99
Soft exudates, n (%)	14 (6.54)	1 (0.82)	13 (14.13)	<0.001
Hard exudate, n(%)	30 (14.02)	7 (5.74)	23 (25.00)	<0.001
AV nicking, n(%)	53 (24.77)	25 (20.49)	28 (30.43)	0.1315

AVR, arteriole-to-venule ratio; AV nicking, arteriovenous nicking.

Table 1 Evaluation of retinal microvascular characteristics

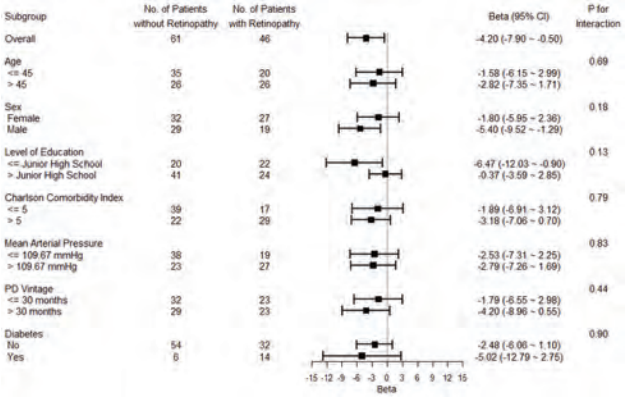

Figure 1 Subgroup analysis of associations between retinopathy and 3MS scores.

SA-PO668

A Novel Mouse Model of Peritoneal Dialysis-Related Encapsulating Peritoneal Sclerosis

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Background: Encapsulating peritoneal sclerosis (EPS) is a severe complication in patients undergoing peritoneal dialysis (PD), with a high mortality rate. However, the insufficiency of knowledge pertaining to the etiology of EPS hampers the development of effective pharmacotherapeutic treatment, and there is a deficiency in pre-clinical models that can recapitulate the progression of the human disease. Thus, we aimed to develop an efficient and realistic mouse model of PD-associated EPS that could mimic the disease characteristics observed in humans.

Methods: Eight-week-old male C57BL/6J mice received a daily intraperitoneal injection of a combination of 4.25% PD solution and SHS (containing 0.1% chlorhexidine gluconate and 15% ethanol dissolved in saline), along with lipopolysaccharide (LPS) administration once a week. And Saline group was given intraperitoneal injection of the same volume of 0.9% saline (daily) as the control. 3 weeks later, ultrasounic and histochemical examines

were used to detect abdominal changes in mice, and then RNA sequencing (RNA-seq) was performed to uncover the potential molecules and signalings in the pathogenesis of EPS.

Results: In EPS group, 76.67% mice survived and all surviving mice developed significant and diffuse peritoneal adhesion at the end of experiment. Ultrasounic and histopathological analyses demonstrated peritoneal thickening and extensive intra-abdominal adhesion. Combined with the immunohistochemical results of mice sacrificed at weeks 2 and 4, we revealed the dynamic process of adhesion formation in EPS models. Finally, the RNA-seq of peritoneal tissue showed marked fiber deposition and inflammatory cell infiltration dominated by macrophages in EPS group. These results observed in our mouse model were consistent with the characteristics of EPS patients.

Conclusions: Our novel mouse model of PD-associated EPS is efficient to replicate the key features of EPS occured on patients, and provide a promising platform to investigate the molecular pathophysiology and treatment strategy of EPS.

SA-PO669

Optical System Shows Promise for Online Detection of Peritonitis in Peritoneal Dialysis

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Background: Peritoneal Dialysis (PD) is associated with significant patient morbidity and mortality. Prompt peritonitis diagnosis and treatment is crucial and may be limited by the lack of early patient or care partner recognition of peritonitis signs and symptoms thereby delaying clinical presentation and treatment and adversely impacting peritonitis treatment outcomes.

Methods: The Intelligent Dialysis Assistant (IDA), a new electronic automated ambulatory PD exchange device (part of liberDi's Digital Dialysis Clinic) provides aseptic PD exchanges. The IDA is fitted with an inline WBC sensor that can transmit online detection of white blood cells (WBC) in the PD effluent and aid in the early diagnosis of peritonitis. To check the capabilities of the sensor in- vitro, we created PD solutions with a range of 150- 16,000 cells/μL to mimic PD effluent peritonitis conditions.

Results: The sensor installed in the IDA (part of liberDi's Digital Dialysis Clinic) was able to detect the different concentrations of white blood cells in the solution (from 150 through 16,000 cell/μL), with a high linear correlation (R^2 =0.98).

Conclusions: A point-of-care testing system for detecting peritonitis using a sensor is a promising approach that may improve the prompt diagnosis and treatment of peritonitis in PD patients. The ability of the installed sensor in the IDA to detect low concentrations and volumes of white blood cells suggests that may be a reliable tool to detect peritonitis in the PD effluent and will require validation via further clinical studies.

Funding: Commercial Support - liberDi

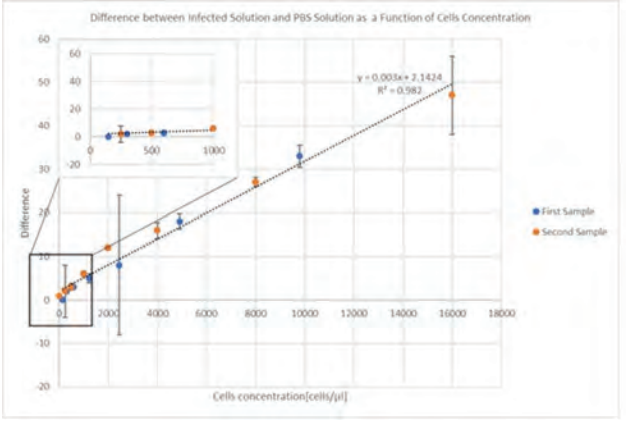

Figure 1 illustrates how the differences in optical system readings between the infected solution and the reference solution varies with different concentrations of white blood cells for two tested blood samples, as well as the average of those samples. Each point denotes 103 readings.

SA-PO670

The Effect of Far-Infrared Therapy on the Cardiovascular and Infection Events in Peritoneal Dialysis Patients

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Background: Long-term peritoneal dialysis (PD) may be associated with cardiovascular (CV) and infection complications. A previous case reprt has shown that far-infrared (FIR) therapy may improve abdominal discomfort due to encapsulating peritoneal sclerosis in PD patients. Since there is little information concerning this issue, we conducted this study in order to evaluate the possible effects of FIR therapy on the CV and infection events of PD patients.

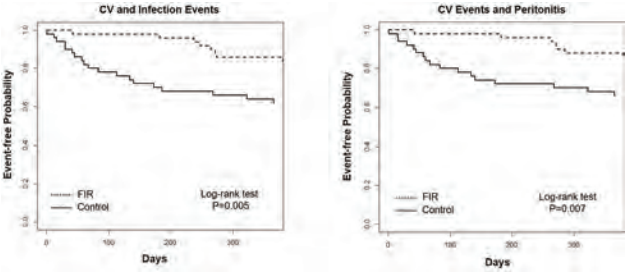
Methods: A total of 99 PD patients were enrolled and randomly divided into FIR and control groups. WS TY101 FIR emitter (WS Far Infrared Medical Technology Co., Taipei, Taiwan) was used to conduct the FIR therapy. The irradiating power density was set at 20 mW/cm^2 and the top radiator was set at 20 cm above the abdomen. Both groups underwent FIR therapy for 40 minutes twice daily during the first and last exchange of each PD session for 1 year. The outcome measures include (1) CV events such as 3P-MACE (3-point major adverse cardiovascular events [consisting of non-fatal stroke, myocardial infarction, and CV death]), coronary artery disease (CAD), and hospitalized heart failure (HHF) and (2) infection events such as pneumonia and peritonitis.

Results: Peritonitis was found to be statistically significant (hazard ratio (HR)=0.418, P=0.017) while two combinations of events were also found to be significant (CV and infection events [HR=0.338, P=0.007] & CV events and peritonitis [HR=0.336, P=0.012]). The survival curves showed that the FIR group had a slower occurrence of CV and infection events, as well as CV events and peritonitis, than the control group. The log-rank tests for both CV and infection events & CV events and peritonitis showed a significant difference (P=0.005, 0.007, respectively) between the two groups.

Conclusions: FIR therapy may significantly lower the risk of CV and infection events, as well as CV and peritonitis events.

Funding: Government Support - Non-U.S.

Event Type	Control N=50	FIR N=49	HR	P
3P-MACE, CAD, and HHF	7 (14)	8 (16.33)	0.270	0.103
Peritonitis	14 (28)	11 (22.45)	0.418	0.017*
CV and infection events	19 (38)	17 (34.69)	0.338	0.007*
CV events and peritonitis	17 (34)	17 (34.69)	0.336	0.012*



SA-PO671

Impaired Sodium Dipping Is Associated with Poor Blood Pressure Control in Patients on Peritoneal Dialysis

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Background: Overhydration is often found in patients on peritoneal dialysis (PD). There is no clear association between fluid overload and hypertension in this population. Since short dwells are associated with decreased sodium removal because of peritoneal sodium sieving, we hypothesized that impaired sodium dipping may be associated with worse blood pressure (BP) control.

Methods: This is a cross-sectional analysis of prevalent patients on PD. We evaluated sodium dipping (dialysate sodium dipping after 1 hour with 4.5% glucose bag), fluid overload (excess extracellular volume ≥ 0.39 measured by bioimpedance spectroscopy) and BP control (high BP was defined as office-measured values > 140/90 mmHg).

Results: 47 patients (age 52 ± 18 years, 53% men) were included. Overhydration was found in 62% of patients and high BP in 34% of patients; sodium dipping < 5mmol/L was found in 57% of patients. (Table 1) These patients were characterized by a higher percentage of high BP (81.3% vs 18.8%, p=0.018), despite similar use of antihypertensive drugs, and no difference in overhydration status, membrane transport profile, cycles/volume PD prescription, ultrafiltration volume, and residual renal function. Sodium dipping < 5mmol/L remained significantly associated with high BP in a fully adjusted model (HR 11.8, 95% CI 2.0-68, p=0.006).

Conclusions: The association between lower sodium dipping and poor BP control suggests that dialytic sodium removal should be included as an important parameter of PD adequacy.

Table 1

	Na dipping ≥ 5 mmol/L	Na dipping < 5mmol/L	p
Extracellular water/Total body water	0.38 ± 0.02	0.39 ± 0.01	0.993
Systolic BP, mmHg	126 ± 23	137 ± 23	0.067
Serum Na, mEq/L	140 ± 3	141 ± 3	0.109
Renal Kt/V	1.2 ± 0.5	1.2 ± 0.6	0.890
Ultrafiltration, mL	556 ± 427	628 ± 440	0.579
Use of antihypertensive, %	43.6	56.4	0.751
Classes of antihypertensive, n (%) 0-1 2 ≥ 3	- 7 (35) 10 (50) 3 (15)	- 10 (37) 9 (33.4) 8 (29.6)	0.396

SA-PO672

CA-125 Is a Good Biomarker of Overhydration in Peritoneal Dialysis Patients

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Background: Volume management in peritoneal dialysis (PD) patients is crucial due to the impact of fluid overload on cardiovascular and non-cardiovascular morbimortality. Clinical examination itself has a poor diagnostic accuracy for minor deviations from normohydration, highlighting the necessity for supplementary tools. The aim of this study was to evaluate the association between serum biomarkers (CA-125 and NT-proBNP) and volume status, assessed through bioimpedance analysis, upon initiation of PD technique and follow-up.

Methods: Single-centre observational cross-sectional study including PD patients that started technique between 2017 and 2023. Demographic and clinical data were collected from electronic records. Parameters evaluated were clinical examination, serum biomarkers, bioimpedance and dialysis adequacy.

Results: A total of 79 patients (51 male) were included with a median age of 59 (IQR 23) years. Baseline (T0) PET showed 77.2% high or high-average transporters. Follow-up (T1) PETs were performed after a median of 18 months (IQR 19). All the patients started with continuous ambulatory peritoneal dialysis (CAPD). Median weekly Kt/V was 2.3 (IQR 0.7). The median residual renal function (RRF) and residual diuresis were 5.9 (IQR 4.9) mL/min/1.73m2 and 1.5 (IQR 1.1) L (5.1% anuric), respectively. Median CA-125 at T0 and T1 were 16.2 U/mL (IQR 17.8) and 13.4 U/mL (IQR 16.1), respectively, which were not statistically different. The median overhydration index at T0 and T1 was 1.55L (IQR 2.5) and 1.1L (IQR 2.3) (p=.001). There was a positive association between D/P of creatinine and CA-125 (r=.25, p=.03) and a negative association between weekly Kt/V and CA-125 (r=-.25, p=.035), both at T0. There was also a positive association between NTproBNP and CA-125 levels at T1 (r=.44, p<.001) and between the NTproBNP variation from T0 to T1 and the CA-125 variation from T0 to T1 (r=.352, p=.004). There was no association between the variation of hydration status and the variation of NT-proBNP and CA-125 levels.

Conclusions: Serum NT-proBNP and CA-125 show a positive correlation, which suggests these biomarkers might be used interchangeably in the evaluation of the patients' hydration. Effective management of hypervolemia improves clinical outcomes. Prospective studies are needed to better understand the use of CA-125 as a surrogate marker of hypervolemia.

SA-PO673

CCL18-PITPNM3 Mediates Macrophage-Mesothelial Cross-Talk and Promotes Peritoneal Dialysis-Associated Peritoneal Fibrosis

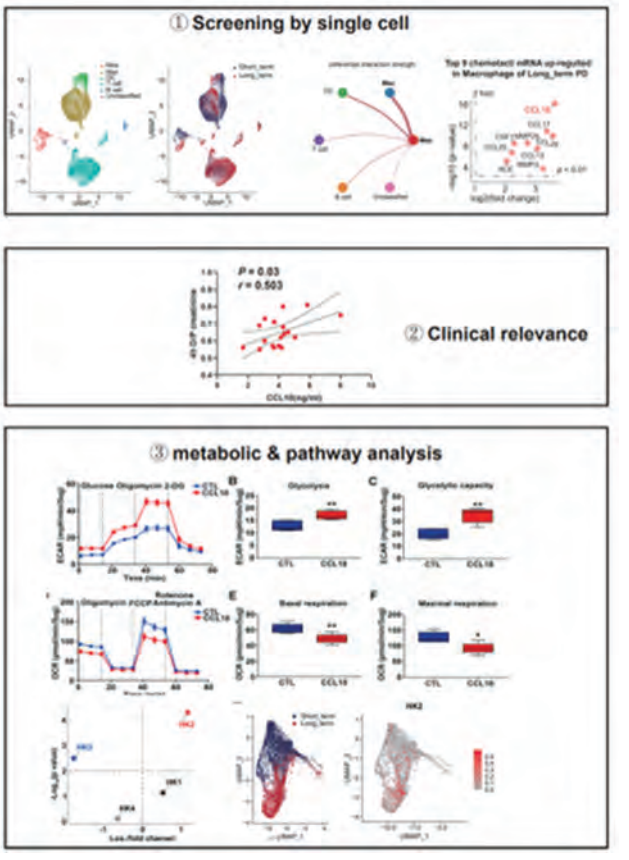
Yuxiang Sun, Qiang Huang, Hui Peng. *Third Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China.*

Background: Peritoneal dialysis (PD) is one of the replacement therapies for end-stage renal disease. After long-term PD(LPD) treatment, about 50% of patients will develop peritoneal fibrosis and ultrafiltration failure. Macrophages and metabolic reprogramming have been confirmed to play an important role in PD-related peritoneal fibrosiss.

Methods: We performed scRNA-seq on perfusate cells from patients receiving PD treatment and explored the functions of specific cell types in the development of PD-related peritoneal fibrosis. By cell communication analysis, we interrogated crosstalk among different cell types in PD effluent. Then we used western blot, qPCR and seahorse to investigate the downstream pathway.

Results: We discovered that LPD promoted interactions between macrophages and mesothelial cells. We also found that LPD induced the M2 polarization of macrophages. CCL18 was identified to be the most significantly M2-type macrophage-secreted factor upregulated in LPD patients. Moreover, the increased concentration of CCL18 in the PD effluent of LPD patients was related to the high peritoneal transport. It was found that PITPNM3 was the most abundant and significantly elevated receptor for CCL18 in the mesothelial cells of LPD patients. Knocking down PITPNM3 receptor ameliorated EMT of mesothelial cells induced by CCL18. Finally, we discovered that CCL18-PITPNM3 could promote the expression of glycolysis enzyme HK2 by activating the PI3K-Akt-cMyc signaling pathway.

Conclusions: PD promoted macrophage M2 polarization and increase CCL18 secretion. CCL18 binds to PITPNM3 in mesothelial cells activating the PI3K/Akt/cMyc. HK2 signaling pathway, so as to enhance the glycolysis and EMT of mesothelial cells and lead to PD-related peritoneal fibrosis.



SA-PO674

Mesothelial Extracellular Vesicles Promote Fibroblast Activation via Delivering of Integrin-Linked Kinase in Peritoneal Fibrosis

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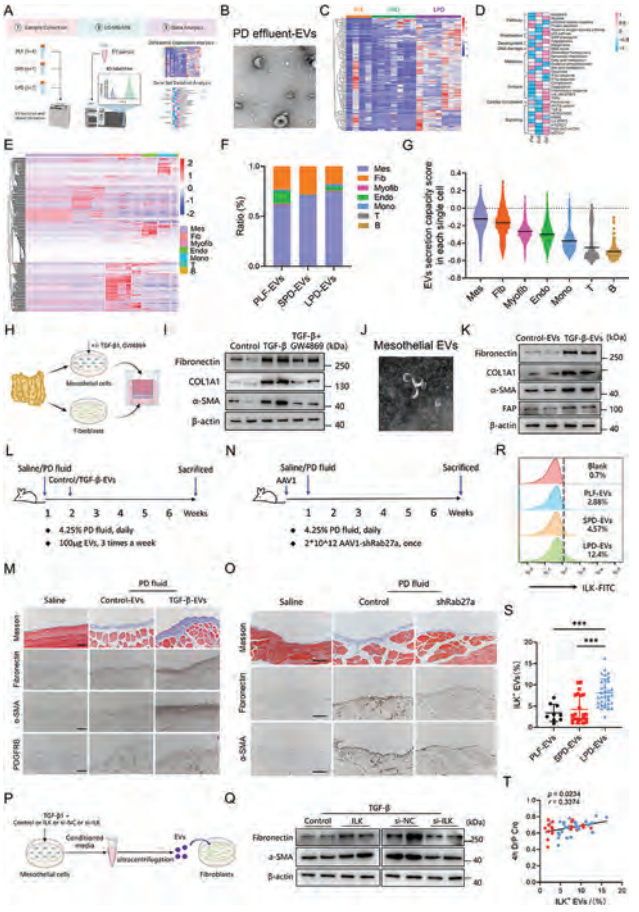
Background: Varieties of cell-cell communications among peritoneal cells play a significant role in peritoneal fibrogenesis induced by peritoneal dialysis (PD). Extracellular vesicles (EVs) have been confirmed to involve in intercellular communication by transmitting various molecules. However, their roles and functional mechanisms in peritoneal fibrosis remain to be determined.

Methods: We performed combined analysis of PD effluent-derived EV proteomics and peritoneal single-cell RNA sequencing to determine the cell source of PD effluent-derived EVs. We blocked mesothelial EVs secretion via GW4869 or shRab27a, and injected mesothelial EVs into mice treated with PD fluid. We detected the percentage of ILK^+ EVs in PD effluent by flow cytometry.

Results: Using integrative analysis of EV proteomics and single-cell RNA sequencing, we characterized the EVs isolated from PD patient's effluent and revealed that mesothelial cells are the main source of EVs in PD effluent. We demonstrated that transforming growth factor-β1 (TGF-β1) can substitute for PD fluid to stimulate mesothelial cells releasing EVs, which in turn promoted fibroblast activation and peritoneal fibrogenesis. Blockade of EVs secretion by GW4869 or Rab27a knockdown markedly suppressed PD-induced fibroblast activation and peritoneal fibrosis. Mechanistically, injured mesothelial cells produced EVs containing high level of ILK, which was delivered to fibroblast and activated them. Clinically, the percentage of ILK positive EVs in PD effluent correlated with peritoneal dysfunction.

Conclusions: Our study highlights that peritoneal EVs mediate communications between mesothelial cells and fibroblasts to initiate peritoneal fibrogenesis. Targeting EVs or ILK could provide a novel therapeutic strategy to combat peritoneal fibrosis.



SA-PO675

Intraperitoneal Pressure Induces Peritoneal Dialysis-Related Peritoneal Fibrosis and Stampede Phenomenon Through CD44 Signaling

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Background: Peritoneal dialysis (PD) is a widely used sustainable kidney replacement therapy. Prolonged use of peritoneal dialysis fluids is associated with mesothelial-mesenchymal transition, peritoneal fibrosis, and eventual ultrafiltration (UF) failure. However, the impact of intraperitoneal pressure (IPP) on the peritoneum remains unclear.

Methods: In this study, we employed a mouse PD model and human Met-5A cells to investigate the influence of pressure on the peritoneum and mesothelial cells. We utilized repeated, chronic infusion of glucose-free phosphate-buffered saline (PBS) to increase IPP and examined its effects.

Results: We observed that increased IPP induced peritoneal fibrosis and upregulated the expression of cluster of differentiation 44 (CD44) in mesothelial cells (Figure 1). Pressurization led to a mesenchymal phenotype, the expression of fibrotic markers and inflammatory factors, increased cell proliferation, and cell migration in Met-5A cells. The mouse PD model and human peritoneum equilibrium tests showed a positive association between higher IPP and both increased small solute transport and decreased net UF. The treatment of CD44 neutralizing antibodies prevented pressure-induced phenotypic changes in mesothelial cells, while a CD44 inhibitor oligo-fucoidan ameliorated pressure-induced peritoneal thickening, fibrosis, and inflammation in PD mice.

Conclusions: Our findings suggest that IPP plays a crucial role in peritoneal fibrosis in PD. CD44-mediated mesothelial changes and inflammation are involved in these processes. The experiments of CD44 blockade showed its potential as a therapeutic approach for PD-related peritoneal fibrosis and UF failure.

Funding: Government Support - Non-U.S.

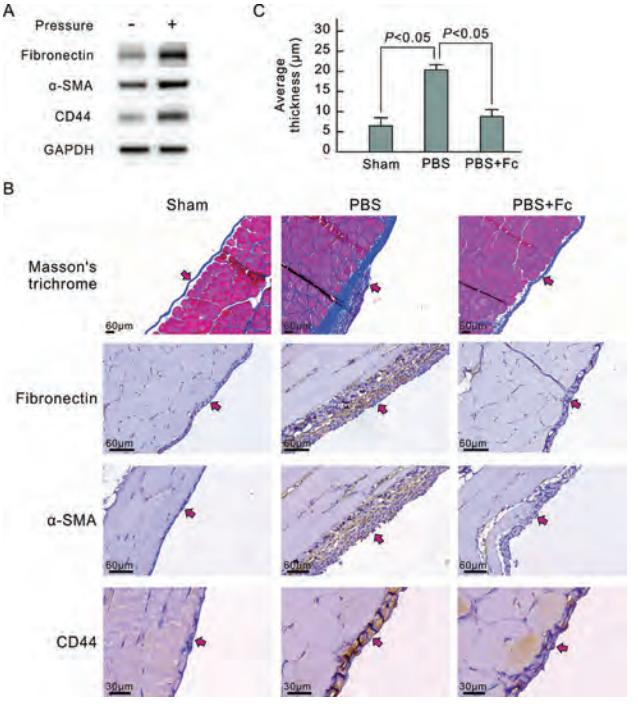

Figure 1. Pressure-induced CD44 expression and peritoneal fibrotic changes, thickening and "stampede" phenomenon.

SA-PO676

FG4592 Ameliorates Peritoneal Dialysis-Associated Peritoneal Fibrosis

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Background: Inflammatory responses in the peritoneum contribute to peritoneal dialysis (PD)-associated peritoneal fibrosis. Previous studies showed that FG4592 (Roxadustat) suppressed inflammation in renal ischemia-reperfusion injury, alcohol-induced alcoholic liver disease. To date, FG4592 has become widely used for the treatment of anemia in patients undergoing dialysis. However, the role of FG4592 in the progression of peritoneal fibrosis has not been clarified. In this study, we used a PD rat model to investigate the effects of FG4592 on PD-associated peritoneal fibrosis.

Methods: A rat model of peritoneal fibrosis was induced via intraperitoneal injection of 4.25% PD fluid at a dose of 100mL/kg daily for 4 weeks. To investigate the effect of FG4592 on peritoneal fibrosis, rat were intraperitoneally injected with FG4592 at 1mg/kg per day. Rats were randomly divided into three groups: rats injected intraperitoneally with saline equivalent to the amount of PD fluid were defined as the control group (n=6), rats injected with 100mL/kg PD fluid were defined as the PD group (n=6) and rats injected with 100mL/kg PD fluid plus FG4592 were defined as PDF+FG4592 group (n=6). After 28 days of PD treatment, PET was performed on each rat before the rats were kills. The parietal and visceral peritoneal tissues were collected for Masson's thichrome staining, western blotting and real-time PCR.

Results: Compared with the PD group, those of the PDF+FG4592 group showed increased net ultrafiltration volume. Masson's trichrome staining showed that those of the PD group showed thickness of the submesothelial compact zone, and the histological change was accompanied by decreased peritoneal transport of glucose and sodium, and increased peritoneal transport of creatinine and albumin. In contrast, administration of FG4592 prevented the thickening of the peritoneum and improved the peritoneal transport function presenting as increased transport of glucose and sodium, and decreased transport of creatinine and albumin. Injection of 4.25% PD fluid significantly increased the mRNA levels of IL-1b, TNF-a and MCP-1 in the visceral peritoneum, and treatment with FG4592 effectively decreased their expression. Results of western blotting demonstrated that FG4592 inhibited the formation of fibronectin, collagen I and vimentin at protein levels.

Conclusions: FG4592 alleviates the development of peritoneal fibrosis in a rat model of PD.

SA-PO677

Matrix Metalloproteinase-10 Deficiency Has Protective Effects Against Peritoneal Inflammation and Fibrosis via NFκB Pathway Inhibition

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Background: One of the most common causes of discontinuation of peritoneal dialysis is impaired peritoneal function. However, its molecular mechanisms remain unclear. We have previously demonstrated that MMP (matrix metalloproteinase)-10 gene expression is significantly increased by microarray analysis of peritoneal fibrosis mice, but its function has not been elucidated yet.

Methods: Chlorhexidine gluconate (CG) was intraperitoneally injected to wild-type and MMP-10 knockout mice to elucidate the role of MMP-10 on peritoneal injury. We also examined function of peritoneal macrophages and mesothelial cells obtained from wild-type and MMP-10 knockout mice, and human MMP-10-overexpressing RAW 264.7 cells and MeT-5A cells. In addition, we investigated MMP-10 expression on human peritoneal biopsy specimen, and association between serum proMMP-10 and peritoneal permeability determined by peritoneal equilibration test (PET).

Results: MMP-10 was expressed in positive cells for WT1, a mesothelial marker, and also for MAC-2, a macrophage marker, in the thickened peritoneum of both mice and humans. Serum proMMP-10 levels were well correlated with peritoneal permeability indicated by D/P Cr. Peritoneal fibrosis, inflammation, and high peritoneal permeability induced by CG were all ameliorated by MMP-10 deletion, with reduction of CD31-positive vessels and VEGF-A-positive cells. Expression of *Ccl2*, *Tnfa*, and *Il6* and phosphorylation of NFκB subunit p65 at S536 were suppressed in both MMP-10 knockout macrophages and mesothelial cells in response to lipopolysaccharide (LPS) stimulation. Overexpression of MMP-10 in RAW 264.7 and MeT-5A cells upregulated mRNA expression of pro-inflammatory cytokines with phosphorylation of NFκB subunit p65.

Conclusions: Inflammatory responses induced by MMP-10 are mediated through NFκB pathway, and that systemic deletion of MMP-10 ameliorates peritoneal inflammation and fibrosis caused by MMP-10-induced NFκB activation of peritoneal macrophages and mesothelial cells.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO678

Peritoneal Endothelial Hyaluronan in Glycocalyx Is Decreased in Peritoneal Dialysis Patients Treated with Conventional Solutions

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Background: Peritoneal membrane dysfunction in peritoneal dialysis (PD) is primarily attributed to angiogenesis; however, the integrity of vascular endothelial cells can affect peritoneal permeability. Glycocalyx is a bioactive gel-like layer and is known to play roles in maintaining a negative charge, regulating coagulation, and controlling microvascular permeability. Degradation of glomerular hyaluronan, a component of the endothelial glycocalyx, leads to proteinuria and structural damage. One hypothesis suggests that development of encapsulating peritoneal sclerosis (EPS) is triggered by protein leakage due to vascular endothelial injury. We therefore investigated the expression of hyaluronan of glycocalyx in peritoneal membrane of normal and diseased conditions.

Methods: We studied the expression of hyaluronan in a total of 254 peritoneal membrane tissues of PD patients and chlorhexidine-induced peritonitis model. Five healthy donors of kidney transplants were used as control. Peritoneal hyaluronan expression was visualized using biotin-labeled human hyaluronan-binding protein (HABP). CD31, CD68 and ratio of luminal diameter to vessel diameter (L/V ratio) were also evaluated.

Results: Hyaluronan expression was much lower in the PD patients undergoing long-term PD treatment with conventional solution than those treated with low-GDP, pH-neutral solutions ($p<0.001$). There were no significant differences in the number of vessels or macrophages between the groups. In EPS cases, L/V ratio and hyaluronan expression significantly decreased in those treated with conventional solutions. The extent of hyaluronan loss correlated with the severity of vasculopathy ($r^2=0.524$, $p<0.0001$). Hyaluronan expression in EPS patients treated with conventional solutions declined even though the L/V ratio was relatively high. In peritonitis of human and animal model, hyaluronan expression were preserved in spite of the inflammatory conditions.

Conclusions: Peritoneal hyaluronan in endothelial glycocalyx was more preserved in patients treated with low-GDP, pH-neutral solution. Loss of hyaluronan in the glycocalyx may induce proteins leakages, leading to the development of EPS in the patients treated with conventional solution.

SA-PO679

The Response of Mesothelial Cells to Fibrotic Stress Is Influenced by Carnitine Acetyltransferase (CrAT)

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Background: Long exposure to high glucose in peritoneal dialysis (PD) can lead to peritonel fibrosis (PF), resulting in a decline in ultrafiltration capacity. Transforming growth factor-beta (TGF-beta) plays a crucial role in PF, and it is influenced by the hyperglycolytic state induced by glucose-based PD solutions. Now, new biocompatible PD solutions is being developed, incorporating two complementary approaches: reducing glucose and use osmotic-metabolic agents that offer metabolic benefits to counteract excessive local and systemic glucose exposure. One such agent is L-carnitine. This study aims to investigate the impact of L-carnitine and carnitine acetyltransferase (CrAT), a key enzyme in L-carnitine metabolism, on the modulation of TGF-beta's pro-fibrotic effects.

Methods: CrAT overexpression in mesothelial cells (Met5A) was obtained by a transfection of a plasmid encoding CrAT ORF. The expression of CrAT was assessed at both the gene and protein level using real-time PCR and Western blot. Metabolomic analyses were conducted on WT and CrAT-overexpressing cells. Wild-type (WT) and CrAT-overexpressing cells were also exposed to different concentrations of L-carnitine (50 μM and 2 mM) in the presence and absence of TGF-beta. The expression of markers associated with PF and inflammation was examined.

Results: CrAT overexpression was confirmed and unsupervised hierarchical clustering analysis revealed distinct metabolic profiles between WT and CrAT-overexpressing cells. Notably, their response to TGF-beta differed: treatment with TGF-beta at a physiological L-carnitine concentration (50 μM) significantly increased the expression of fibrotic and pro-inflammatory markers, alpha-SMA, vimentin, IL-6 and IL-1β in WT cells. The exposure to supra-physiological L-carnitine levels reduced the increase of these markers in WT cells. In CrAT-overexpressing cells, TGF-beta failed to modulate alpha-SMA, VIM, IL-6, and IL-1β.

Conclusions: CrAT overexpression could provide valuable insights into the mechanisms by which L-carnitine metabolism effectively regulates the progression of fibrosis and inflammation in PD. Utilizing L-carnitine as an osmo-metabolic agent in PD solutions has the potential to significantly decelerate the advancement of PF.

SA-PO680

Role of Plasminogen Activator Inhibitor-1 (PAI-1) on Phenotype Transition and an Induction of Oxidative Stress in Human Peritoneal Mesothelial Cells (MCs)

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Background: The epithelial-to-mesenchymal transition (EMT) of MCs is an early mechanism of peritoneal dysfunction in peritoneal dialysis (PD). Plasminogen activator inhibitor-1 (PAI-1) was initially known as an inhibitor of fibrinolysis by hindering the proteolytic activity of tissue type plasminogen activator and urokinase-type plasminogen activator, and recently reported to regulate EMT of cancer cells. However, there are no studies on the role of PAI-1 in peritoneal EMT and fibrosis.

Methods: For in-vitro experiment, EMT was evaluated by morphological changes of MCs and the expression of E-cadherin and α-SMA by real-time PCR, WB and ICC. E-cadherin promoter activity, activation of Smad2/3, Erk1/2, AKT, nuclear translocation of snail and MMP expression were assessed. ROS generation was assessed by DCF-DA, MitoSox staining, and NOX mRNA expression. For in-vivo, PD mouse model (C57BL/6) was established by daily infusion of 4.25% glucose-based dialysate (100mL/kg/day) for 4 weeks via intraperitoneal catheter with or without oral administration of PAI-1 inhibitor (Tiplaxtinin, 5mg/kg/day). In 4 weeks of PD, dialysate/plasma ratio of creatinine (D/P_{Cr}) and the 2-hour-dialysate/initial dialysate ratio of glucose (D/D_0 glu) were measured. Effects of Tiplaxtinin on EMT, peritoneal thickening and an expression of markers of oxidative stress were investigated.

Results: TGFβ (1 ng/ml) stimulation resulted in an increased expression of PAI-1 mRNA and protein in MCs. TGFβ-induced EMT was ameliorated by siPAI-1 or Tiplaxtinin (20 μM). TGFβ-induced nuclear translocation of snail and decrease of E-cadherin promoter activity were also alleviated by siPAI-1. siPAI-1 inhibited TGFβ-induced activation of Smad2/3, Erk1/2, AKT and MMP2 expression. Tiplaxtinin alleviated NOX- and mitochondria-mediated ROS production. In mouse PD model, Tiplaxtinin ameliorated the changes in D/D_0 glu and D/P_{Cr}. Also, Tiplaxtinin administration also resulted in a decrease in peritoneal thickness and fibrosis and an increase in ratio of reduced to oxidized glutathione and SOD2.

Conclusions: PAI-1 plays a role in peritoneal EMT and fibrosis, and modulation of PAI-1 expression/activity in MCs could be a novel strategy to prevent peritoneal fibrosis in PD patients.

Funding: Government Support - Non-U.S.

SA-PO681

Unveiling the Role of Mesothelial Cells in Methylglyoxal-Induced Peritoneal Fibrosis

Yu-Syuan Wei, Pei-Shiue J. Tsai. *National Taiwan University, Taipei, Taiwan.*

Background: Being one of the renal replacement therapies for end-stage kidney disease patients, peritoneal dialysis (PD) maintains the lives of about 11% of dialysis patients. However, morphological and functional changes in the peritoneum, which is called peritoneal fibrosis (PF), are inevitable during long-term PD. PF can gradually progress into ultrafiltration failure and has a high correlation with encapsulating peritoneal sclerosis, a complication with high mortality. Despite the presence of glucose degradation products (GDPs) produced by heating high glucose-containing dialysate is considered to be the key component to initiating PF, and methylglyoxal (MGO) is one of the most important GDPs; however, the mechanisms of how MGO induces PF, especially the involvement of mesothelial cells, is still unclear.

Methods: Human mesothelial cells (MeT5A), were cultured and treated with different concentrations of MGO. Cell viability and production of free radicals were evaluated first. Next-generation sequencing was then performed to assess the transcriptomic changes after MeT5A was treated with MGO for 6 hours and 24 hours. Differential expression genes (DEGs) and pathway enrichment analysis based on databases of KEGG and gene ontology (GO) were further analyzed.

Results: When compared with control MeT5A, 2009 and 2516 DEGs were detected, respectively, after 6 or 24 hours of MGO stimulation. GO enrichment analysis showed that most DEGs that appeared at 6 hours were related to extracellular matrix organization (p=0.01); while DEGs that appeared at 24 hours were related to extracellular matrix organization (p=0.00002), type I interferon signaling pathway (p=0.002), wound healing (p=0.006), cell adhesion (p=0.01) and angiogenesis (p=0.01). Although epithelial-to-mesenchymal (EMT) was considered an important phenomenon in peritoneal fibrosis, genes that related to EMT, such as *SNAI1*, *SNAI2*, *CDH1*, and *VIM*, were not significantly changed under our experimental setup. Moreover, proteins that are known to activate fibroblasts trans-differentiation into myofibroblasts, except for *TGFB1*, genes such as *IL1B*, *PDGFA*, *PDGFB*, and *PDGFD* were upregulated significantly.

Conclusions: Our study showed that when mesothelial cells were treated with MGO *in vitro*, they tended not to develop EMT but promoted pro-inflammation response and the activation of fibroblasts.

Funding: Government Support - Non-U.S.

SA-PO682

PPARα Modulator Ameliorates Methylglyoxal-Induced Peritoneal Fibrosis

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Background: Peritoneal inflammation and fibrosis remain major obstacles to the long-term maintenance of peritoneal dialysis. In this study, we investigated whether PPARα agonism ameliorates peritoneal inflammation and fibrosis in methylglyoxal (MGO) induced peritoneal injury in mice, as well as in cultured human peritoneal mesothelial cells (HPMCs) and THP-1 cells.

Methods: Peritoneal fibrosis was induced by intraperitoneal injection of MGO in male C57/B6 mice for 3 weeks. The mice were fed normal chow diet with a specific PPARα modulator, pemafibtare (0.3 mg/kg), 3 weeks before MGO injection, and then peritoneal tissues were examined. *In vitro* study, HPMC and THP-1 cells stimulated with IFN-γ were examined with or without pemafibrate treatment.

Results: Pemafibrate increased PPARα expression in the peritoneum. Pemafibrate significantly decreased MGO-induced cell density and peritoneal thickening. In immunohistochemical staining, pemafibrate reduced the number of fibrosis markers α-SMA, TGF-β1, and FSP-1 positive cells and deposition of collagen I and III, the expression of the inflammatory cytokine TNF-α, and macrophage infiltration. In addition, pemafibrate improved the deterioration of the dialysate-to-plasma (D/P) ratio of BUN and glucose and reduced TGF-β1 expression in the dialysate. *In vitro* studies, pemafibrate inhibited IFN-γ-induced activation of fibrosis markers (TGF-β1, fibronectin) in HPMC. In THP-1 cells, pemafibrate promoted anti-inflammatory M2 macrophage polarity and inhibited inflammatory M1 macrophage cytokine production, including IL-1β. Moreover, Pemafibrate suppressed not only AP-1 signaling pathway but also NLRP3 inflammasome and caspase-1 activation in HPMC.

Conclusions: The specific PPARα modulator, Pemafibrate ameliorates peritoneal fibrosis by inhibiting peritoneal inflammation.

SA-PO683

The Role of Myocardin-Related Transcription Factor-Serum Response Factor Signaling in Peritoneal Mesothelial Cells

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Background: Peritoneal membrane failure is a critical complication of long-term peritoneal dialysis treatment. Peritoneal fibrosis has been known to be involved in the development of peritoneal membrane failure. Therefore, clarifying the mechanisms of peritoneal fibrosis is important. Thus far, myocardin-related transcription factor (MRTF) - serum response factor (SRF) signaling is known to drive the development of various fibrosis. Focal adhesion (FA) and lysyl oxidase (LOX) family mediating collagen cross-linking are also known to contribute to the development of organ fibrosis. However, the involvement of MRTF-SRF signaling in the expression of FA components and LOX family in peritoneal fibrosis is unclear. In this study, we investigated the contribution of MRTF-SRF signaling to the expression of FA components and LOX family using peritoneal mesothelial cells (PMC).

Methods: Mouse primary PMCs were stimulated with transforming growth factor (TGF)-β_1. Then, the expressions of α_1 chain of type I procollagen (Col$I\alpha_1$), FA components and LOX family were evaluated. In addition, the effects of MRTF-SRF signal on their expressions were evaluated in TGF-β_1-stimulated PMCs treated with siRNA targeting MRTF-A/-B or MRTF-SRF inhibitor (CCG-1423).

Results: TGF-β_1 induced the expression of Col$I\alpha_1$, LOX family and FA components (integrins and integrin linked kinase) in PMCs. Their expressions were reduced with siRNAs targeting MRTF-A/-B. In addition, the expressions of FA components were also reduced with CCG-1423. Taken together, TGF-β_1 induced the expression of Col1α_1, LOX family and FA components dependent on MRTF-SRF signaling in PMCs.

Conclusions: MRTF-SRF signaling may contribute to the development of peritoneal fibrosis through TGF-β_1-induced FA components and LOX family in PMCs.

SA-PO684

Histone Lactylation Facilitates Peritoneal Mesothelial Cell Senescence and Promotes Peritoneal Dialysis-Associated Fibrosis

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Background: Peritoneal fibrosis (PF) is a serious clinical complication in patients undergoing long-term peritoneal dialysis (PD). Recently, histone lactylation has been found to increase with glycolysis and intracellular lactate levels, leading to chronic organ damage. Here, we investigated the role and mechanism of histone lactylation in PD-associated fibrosis induced by high-glucose dialysate.

Methods: Mouse models of PF were constructed by 4.25% glucose peritoneal dialysate combined with methylglyoxal. We used a lactylation enhancer (rotenone) and a lactylation inhibitor (oxamate) to validate the effects of histone lactylation in vivo and in vitro. The parietal peritoneum samples and cultured peritoneal mesothelial cells (PMCs) were analyzed for the senescence, fibrosis, glycolysis, and histone lactylation levels. We generated DcR2 (a senescent marker) knockout mice to verify the effects of histone lactylation by clearing senescent cells. Single-cell RNA sequencing (scRNA-seq) was used to characterize the heterogeneity of PMCs clusters under different lactylation intervention conditions.

Results: We found that lactate and glycolysis levels were significantly higher in the PF group compared to the control group, and immunoprecipitation results also showed enhanced levels of histone lactylation modifications in the PF group. In vitro, we also verified that PMCs exhibited enhanced levels of lactate and lactylation in response to stimulation by high glucose, while we found an increasing expression of cell senescent marker (P16, P21, and DcR2) and senescence-associated secretory phenotype. Then we found that PMCs senescence was significantly enhanced in the lactylation-enhanced group, while the lactylation-inhibited group alleviated PMCs senescence. In the PF model of DcR2 knockout mice, compared with the wild group, the peritoneal thickness and the expression of fibrotic markers were significantly reduced. The transcriptomic analysis using scRNA-seq revealed the activation of senescence-related pathway in PMCs clusters of PF group, whereas the senescence-related pathway was down-regulated in the lactylation-inhibited group. The results indicated that histone lactylation may promote PF through PMCs senescence.

Conclusions: Histone lactylation may play a vital role in the progression of PD-associated fibrosis by promoting PMCs senescence.

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SA-PO685

MMP-12 Inhibitor Ameliorates the Peritoneal Fibrosis in a Peritoneal Dialysis (PD) Mouse Model

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Background: Continuous exposure to non-physiological fluids during peritoneal dialysis (PD) is associated with pathological responses, such as sustained microinflammation, leading to tissue fibrosis and angiogenesis. We reported that submesothelial expression of matrix metalloproteinase-12 (MMP-12), an elastin proteinase secreted by macrophages, was enhanced by continuous exposure to peritoneal dialysis fluid(PDF). In this study, we investigated the effects of MMP-12 inhibitor on peritoneal fibrosis.

Methods: Morphological changes of the peritoneum in a PD mouse model were histologically analyzed in a peritoneal dialysis fluid (PDF) group (intraperitoneal PDF instillation once a day for 6 weeks), a control group (saline), and a MMP-12 inhibition group (PDF + MMP-12 inhibitor).

Results: Elastica van Gieson staining showed that the elastin just below the mesothelial cell layer was disorganized and fragmented in the PDF group, compared with the control group. Elastin fragments were observed also in collagenous thickened submesothelial tissue in the PDF group, not in the control group. In the MMP-12 inhibition

group, no degradation of the elastin or no elastin fragments in submesothelial tissue was observed. Mesothelial cell swelling, peritoneal thickening, and increased collagen fiber expression observed in the PDF group were significantly suppressed in PDF+MMP-12 inhibition group.

Conclusions: The results suggest that MMP-12 induced by PDF instillation could be associated with local microinflammation in the peritoneal tissue, suggesting that MMP-12 may be an therapeutic target to relieve peritoneal damage.

SA-PO686

An Unusual Dietary Cause of Hyperphosphatemia and Hypocalcemia Mimicking Tumor Lysis Syndrome

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Introduction: In healthy individuals, high dietary phosphate intake is rarely emphasized since there is no correlation proven between phosphate intake and serum inorganic phosphate concentration. Hyperphosphatemia has a variety of etiologies other than traditionally focused cellular shifts. High phosphorus could cause more acute kidney injury (AKI) events and acute phosphate nephropathy can cause AKI in rare cases. Additionally, COVID-19 infection can alter the physiology of phosphate regulation and the severity of AKI. Here we present a patient with COVID-19 infection and sudden onset severe hyperphosphatemia and hypocalcemia in the setting of AKI who was revealed to have a substantial dietary intake of phosphate that improved with the improvement of AKI.

Case Description: The patient is a 52-year-old male who presented with shock in the setting of COVID-19 pneumonia. Further laboratory tests found that he had severe hyperphosphatemia (10.0 mg/dL), hypocalcemia (6.5 mg/dL), and AKI with a serum creatinine that peaked at 8.53 mg/dL. Ionized calcium was also low at 0.96 mmol/L and his uric acid level was elevated at 11.1 mg/dL. These electrolyte derangements initially raised concern for tumor lysis syndrome (TLS). However, there was no evidence of malignancy on physical examination or imaging. It was noted after further history taking that the patient drank 2 liters of soft drinks daily. This unusual diet in the setting of severe AKI likely led to hypocalcemia. The patient's renal function improved with the improvement of his shock. The resolution of the patient's AKI also normalized his hyperphosphatemia and hypocalcemia.

Discussion: In the setting of AKI, dysregulation of the phosphate transporter may interfere with phosphate balance. Although hyperphosphatemia is commonly seen in patients with severe AKI, a dietary cause of severe hyperphosphatemia leading to hypocalcemia is not well recognized. This patient's phosphate intake through soda alone was 300-400 mg a day and phosphorous from food additives is absorbed at a much higher rate than natural sources. This intake likely precipitated a sudden hyperphosphatemia in the setting of the patient's AKI which resulted in hypocalcemia, mimicking TLS. Further studies investigating hyperphosphatemia being the cause of hypocalcemia in instances other than TLS should be followed.

SA-PO687

Intravenous Ferric Carboxymaltose-Induced Severe Hypophosphatemia

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Introduction: Hypophosphatemia (HP) is a rare and severe adverse effect of some intravenous (IV) iron formulations. Here, we present a case of a patient with severe HP after receiving IV ferric carboxymaltose (FCM) due to renal phosphate wasting with high Urine fractional excretion of PO4 (FEP).

Case Description: A 19-year-old female was initially evaluated in the clinic for Iron deficiency due to heavy menstrual bleeding. She received one dose IV FCM because of inability to tolerate oral medications due to gastroparesis. A few days later she had severe generalized bone pains along with weakness, fatigue, nausea, chills, and headache. Labs showed isolated low serum phosphorous (S. PO4) of 1.9 mg/dl (normal 2.5-4.5 mg/dl). She was started on oral potassium-phosphate (K-PO4). Due to persistent HP and symptoms, she was admitted for further management. At the time of admission, labs revealed persistent HP. Remaining serum electrolytes were within normal range. Urine FEP was >55% with high 24-hour PO4 in the urine of 2.305g/24 hours (0.400-1.300). This favored renal PO4 wasting. Fibroblast growth factor (FGF-23) was 58 pg/ml (normal range was <59 pg/ml as per Mayo Clinic lab). She was managed with IV as well as oral PO4 supplements. She was discharged on oral PO4 supplements along with calcitriol. Follow up clinic visit within 1 month showed that her S.PO4 levels normalized to 4 mg/dl. She was able to come off oral PO4 supplementation. This further supports that it was a short-term effect from IV FCM use.

Discussion: HP has been reported with the use of IV iron preparations, more commonly with IV FCM as compared to other IV formulations. IV FCM induced HP is typically associated with increase in FGF-23 which causes increase in urinary phosphate excretion and suppression of 1,25(OH)2D concentration. Common symptoms include generalized weakness, fatigue, bone, and muscular pain. It is recommended to measure S. PO4 in patients who present with the above-mentioned symptoms. Measuring FEP or TMP/GFR (maximum rate of tubular phosphate reabsorption to the glomerular filtration rate) to confirm intravenous iron-induced renal phosphate wasting has been suggested. Treatment options include activated vitamin D along with phosphate supplements and therapeutic anti-FGF23 antibody.

SA-PO688

The Association Between Urine Oxalate and Citrate May Not Be Diet Driven

Megan Prochaska, Fredric L. Coe, Elaine M. Worcester. *University of Chicago Division of the Biological Sciences, Chicago, IL.*

Background: Higher urine oxalate excretion has been associated with higher urine citrate excretion and the magnitude of the association is larger in non-kidney stone patients compared with kidney stone patients. The mechanism for this association may be due to simultaneous dietary intake oxalate and citrate in fruits and vegetables or transporter linkage of SLC26A6 and NaDC1 in the kidney.

Methods: Eleven participants, including 3 kidney stone patients, were admitted to the clinical research center and given sodium oxalate. Timed pre-sodium oxalate (1) and post-sodium oxalate (6) urine samples were collected every hour. Urine composition was measured and excretion rates of oxalate and citrate calculated at each period. Mean and standard error were graphed per period and mixed methods longitudinal models were generated to compare change over time versus pre-oxalate value (Period 1) of oxalate and citrate excretion.

Results: Eight of the 11 participants were women with mean age 54 years. Urine oxalate and citrate excretions were higher than pre-oxalate (Period 1) at Periods 4 to 6, and Periods 4 and 5, respectively (Figure 1).

Conclusions: After consumption of sodium oxalate participants had an increase in urine oxalate excretion, as expected, but they also had an increase in urine citrate excretion. The association between oxalate and citrate excretion may not be completely driven by dietary intake.

Funding: NIDDK Support

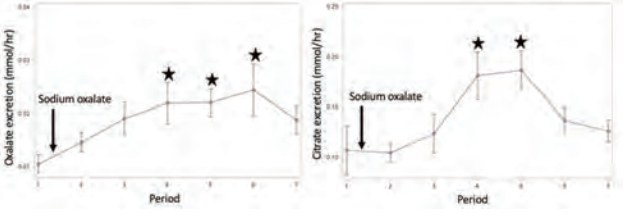

Figure 1. Excretion of oxalate and citrate per study period. Period 1 represents pre-sodium oxalate baseline value. Periods 2-7 are post-sodium oxalate and timed every 1 hour. Starred periods denote where an indiviudal period was statistically higher than Period 1 in the mixed methods longitudinal model.

SA-PO689

Quantitative Assessment of Overall Acid-Base Balance in Humans

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Background: Kidney stones are common and understanding mechanisms contributing to stone formation is important in developing effective prevention and treatment strategies. This study aimed to investigate the impact of various predictors on urine pH and acid-base homeostasis, which play a significant role in kidney stone formation.

Methods: Kidney stone patients and non-kidney stone patients provided 24-hour urine collections while at home and eating a free choice diet. A pH titration analysis was performed and acid-base parameters were measured in the urine to assess acid-base balance. Basic statistics and linear models were developed to characterize change in urine acid-base chemistry as a function of demographic and urine factors.

Results: There were 246 participants with mean age 54 years, 133 female, and 190 kidney stone patients. In multivariate analysis, higher age was associated with lower urine pH (-0.005 per year, $p<0.001$) but there was no association by sex. In separate multivariate models, male sex was associated with lower acid excretion (-0.6 meq/mM creatinine, $p<0.001$) and lower urine anions (-0.5meq/mM creatinine, $p<0.01$) compared with female. In separate multivariate models, higher age was associated with higher urine anion (0.02 meq/mM creatinine per year, $p<0.001$) and higher titratable acidity (0.01 meq/mM creatinine per year $p<0.001$).

Conclusions: This study provides valuable insights into the relationships between demographic factors and urine acid-base chemistry. The association between age and sex with urine pH, urine anions, acid excretion, and titratable acidity underscores the importance of age and sex as factors in acid-base balance. This may also suggest different mechanisms for kidney stone formation in older adults and between men and women and is consistent with known data that stone types may change with aging and there are differences between men and women.

Funding: NIDDK Support

SA-PO690

Nephrolithiasis as a Manifestation of Primary Hyperaldosteronism Secondary to Adrenal Adenoma

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Introduction: The primary hyperaldosteronism has been considered a rare cause of secondary hypertension with a prevalence up to 12% The variability of presentation of this syndrome is too wide and sometimes it is not the usual one The following is a case of a patient who started with hypertension and recurrent kidney calculi due to primary hyperaldosteronism caused by an adrenal adenoma.

Case Description: 33 years-old male with no significant medical history who presented to hospital due to hypertensive episodes Outpatient laboratory tests were performed and hypokalemia plasma renin activity was requested and reported 0.39 and aldosterone at 20 Primary hyperaldosteronism was suspected After that the patient begins with intermittent episodes of lower abdominal pain, irradiated to right groin and hematuria. Laboratory tests creatinine 0.77 urea 21 Na 145 k 2.5 A renal Doppler ultrasound was performed and reported bilaterally renal calculi the intrarenal circulation was in normal parameters in both kidneys Abdominal tomography was practiced where bilateral renal lithiasis is observed and a stone in the upper third of the right ureter of 3.2 mm diameter A ureterolithotomy was performed the analysis of the calculus reported 60% calcium oxalate 40% calcium phosphate During the following 4 years the patient continued with episodes of urolithiasis without other alterations In the last episode the patient presented again in the emergency room due to abdominal pain and a well-defined hypodense nodular image towards the left adrenal gland was found in the abdominal tomography related to adenoma and multiple intrarenal stones microcysts and simple cysts were observed with presence of free intravesical stones The patient received medical management and lithotripsy was performed after 1 month a laparoscopic radical left adrenalectomy was performed without complications.

Discussion: There are few cases reported in the literature of patients with primary hyperaldosteronism and recurrent nephrolithiasis It has been reported that chronic mineralocorticoid administration and primary hyperaldosteronism facilitate renal calcium excretion This case alerts us of the importance to remember the renal physiology of calcium in hyperaldosteronism and it is one of the most variable presentations and for which the patient will seek medical attention quickly.

SA-PO691

Characterization of a Cohort with Kidney Stones and Enteric Hyperoxaluria

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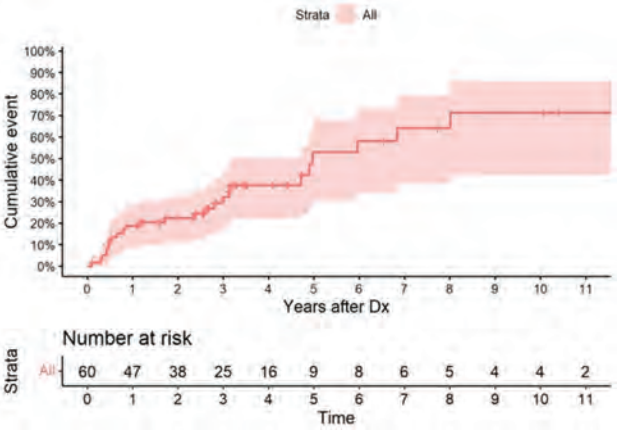
Background: Enteric hyperoxaluria (EH) is a risk factor for kidney stones. The relationship between risk factors and the natural history remains poorly defined. To address this knowledge gap, we created an EH patient registry.

Methods: The electronic medical record at all 3 Mayo Clinic sites was searched to identify patients with a known cause of EH, 24-hour urine oxalate (Uox) ≥40mg, and history of kidney stones. Symptomatic stone events were defined by the presence of renal colic, stone passage associated with urinary tract infection or hematuria, or procedure for stone removal.

Results: We report on data from the first 74 abstracted patients. The largest group of 34 (46%) had bariatric surgery (29 (85%) of these were Roux En-Y Gastric Bypass (RYGB)), 20 (28%) inflammatory bowel disease (IBD), 11 (15%) pancreatic insufficiency, 5 (7%) short bowel syndrome, 1 (1%) celiac, and 1 (1%) other fat malabsorptive conditions. Mean age at first stone diagnosis was 48.6 ±14.1 years and BMI 31.6±8.71 kg/m^2. EH diagnosis was on average 8 years after first stone event and mean UOx was 65.3±30.9 mg/24 hr. Follow-up after EH diagnosis was available for 60/74 patients, 78% of whom had a prior stone event (average n=4, 45%>2 events). Those with bariatric surgery were more likely to be female (p=0.002), have a higher BMI (p<0.001), and experience asymptomatic kidney stones before surgery (p=0.02). After a median follow-up of 3 years, the 5-year cumulative stone event rate after EH diagnosis was 52.9% (Figure) and did not differ by EH cause.

Conclusions: EH patients experience a high rate of stone recurrence of up to 53% at 5 years regardless of underlying etiology. RYGB is the single most common cause, however other conditions associated with fat malabsorption are also common. These preliminary data strongly support continued efforts to develop a robust EH patient registry to identify specific phenotypic features that are associated with stone disease risk to inform study design for novel therapeutics.



SA-PO692

Injection of Silicone for Cosmetic Gluteal Augmentation Leading to Hypercalcemia

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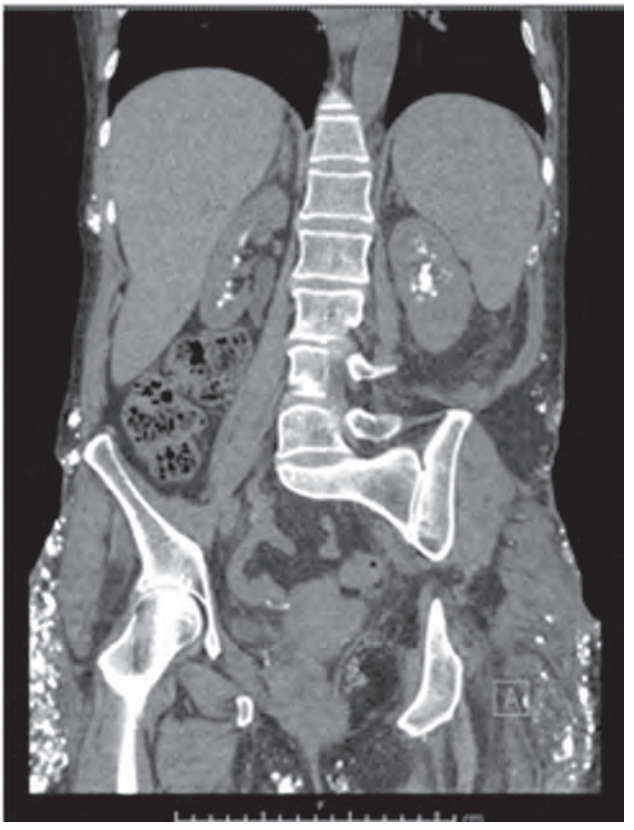
Introduction: Hypercalcemia can be seen in many common Granulomatous disease such as Sarcoidosis, Tuberculosis, and Granulomatosis with Polyangiitis (PTH-indipendent). Silicon injection for cosmetic procedures have also been associated with granuloma formations and subsequent hypercalcemia.

Case Description: 58 yo Hispanic female presents for evaluation of chronic non-healing bilateral gluteal wounds. She has a history of CKD stage 3, nephrolilithiasis, and chronic hypercalcemia not previously worked up. She also has a history of Silicon injections into bilateral Gluteal regions in Mexico for cosmetic purspose 25 years ago. LABS: Sodium-136 mmol/L, Potassium-5.0 mmol/L, Chloride-104 mmol/L, CO2-22 mmol/L, BUN-62 mg/dL, Creatinine-2.21 mg/dL, Calcium-11.0 mg/dL, Corrected Calcium-12.92mg/dL, Albumin-1.6 g/dL, Phosphorus-3.6 mg/dL, Magnesium-2.1 mg/dL, SPEP/UPEP Normal, TSH-1.665 uIU/mL, PTH<2 pg/ml, PTH-RP-16 pg/ml (WNL), Vitamin D 25-OH 12ng/ml, Vitamin D2 1,25-OH 8 pg/ml, Vitamin D3 1,25-OH 60pg/ml, Urine 24H Calcium 283.8 mg/24 HR, Alk Phos 246 U/L.

Discussion: Investigation revealed **depressed** PTH, **Low** vitamin D25 level and **elevated** Vitamin D2-1,25 level. Imaging including CT and PET showed evidence of significant long standing calcified granulomas. Patient also had biopsy of the gluteal wounds which showed foci of foreign body-type multinucleated giant cell reaction and extensive calcifications. Normally conversion of Vitamin D 25-OH to Vitamin D2 1,25 OH occurs in the kidney via a 1-hydroxylase enzyme that is under the physiologic control of PTH, FGF-23, and the serum phosphourus level. In granulomatous diseases, this conversion is occurring independent of these controls inside giant cells. The high levels of converted Vitamin D2 1,25-OH causes increased intestinal calcium absorption and increased bone resorption leading to hypercalcemia.



CT of Abdomen showing extensive soft issue calcified granulomas in gluteal tisssue

SA-PO693

An Unusual Case of Hypercalcemia

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Introduction: Antibiotic-eluting calcium sulfate beads are a method of local antibiotic delivery in infections of prosthetic material. Advantages include fewer off-target effects and greater antibiotic concentration at the site of infection than with systemic antibiotics. Hypercalcemia is a rare complication of this that has received little study to date.

Case Description: A 67-year-old man who had undergone endovascular repair of an abdominal aortic aneurysm years prior, presented with septic shock. CT demonstrated a collection in the residual aneurysm sac suggestive of an infected graft. The patient underwent graft removal with gentamicin-eluting beads placed retroperitoneally. He received 6g of calcium chloride intraoperatively and 4g of calcium gluconate over post-operative day (POD) 1; with no additional supplementation afterwards. On POD4, a basic metabolic panel showed worsening acute kidney injury (baseline sCr 0.9 mg/dL) and hypercalcemia (Table 1). Multiple etiologies for hypercalcemia were considered, including immobilization and malignancy, but none was thought to explain the acuity of the rise. The intravenous calcium administered perioperatively was expected to have been excreted by this time, and he was not on any medications associated with hypercalcemia. Workup revealed appropriately low PTH, PTHrP and low-normal Vitamin D 25-OH and 1-25 OH, pointing to the antibiotic-eluting calcium beads as main etiology. The patient was treated with aggressive fluid resuscitation and 4 doses of calcitonin, with improvement in serum calcium and creatinine as seen in Table 1.

Discussion: We present a case of hypercalcemia resulting from intraoperative placement of gentamicin-eluting calcium beads, which can occur 72-hours after insertion, and illustrates the importance of recognizing potential toxicity of local antibiotic vehicles.

Chemistries during post-operative period

Blood chemistry value	POD1	POD4	POD14
Na	144	149	145
K	3.9	3.4	3.4
Cl	111	121	108
HCO3	17	13	21
BUN	42	45	35
Cr	1.67	1.81	1.37
Ca	8.6	11.7	10.0
iCa	1.23	1.87	1.39
Phos	4.6	3.7	2.2

SA-PO694

Calcitriol-Mediated Hypercalcemia in Mesothelioma

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Introduction: Hypercalcemia (hyperca) is common in several hematological and solid organ malignancies however hyperca has rarely been reported in mesothelioma. We report an unusual case of calcitriol mediated hyperca in mesothelioma.

Case Description: An 80-year-old gentleman with stage IV chronic kidney disease was admitted for severe hyperca. Serum calcium (Ca) corrected for hypoalbuminemia 15 mg/dL. He was diagnosed with right lung mesothelioma two months prior followed by first cycle of nivolumab/ipilimumab(Nivo/Ipli) a month prior. He had mild hyperca 6 months prior to mesothelioma diagnosis which progressed despite stopping vitamin D and Ca supplementation. Workup shown in Table 1. Initial imaging revealed concern for lytic lesions of pelvis however subsequent workup including serum free light chains, serum and urine protein electrophoresis, bone and PET scan were negative for plasma cell dyscrasias. Further Imaging revealed 2.3cm left renal mass suspicious of renal cell carcinoma (RCC) however PET scan did not show any uptake into the kidneys. After acute treatment of hyperca the patient continued treatment with immunotherapy(IT) to which he responded.

Discussion: Hyperca from malignancy occurs from either tumor secretion of parathyroid hormone-related protein or tumor production of calcitriol etc. Calcitriol induced hyperca from Nivo/Ipli has also been reported. In our case calcitriol mediated hyperca from mesothelioma is the most plausible etiology. Even though calcitriol levels prior to IT are not available hyperca developed prior to starting IT. Workup of hematologic malignancy was negative and PET scan did not show FDG uptake by the renal mass. Finally his Ca levels improved with further IT and improvement in mesothelioma. Although FDG uptake in RCC has a lower sensitivity and Nivo/Ipli can also treat RCC we believe the time-course of events makes mesothelioma the more plausible etiology.

Table 1

Test	Value
Calcium (mg/dL)	14.3
Albumin (g/dL)	2.8
Corrected Calcium (mg/dL)	15.3
Ionized Calcium (mg/dL)	7.1
Phosphorus (mg/dL)	3.6
PTH (pg/mL)	16.6
PTHrP (pmol/L)	<2
25-hydroxyvitamin D (ng/mL)	52.7
1,25-hydroxyvitamin D (pg/mL)	83.4
Serum and Urine Protein Electrophoresis	No monoclonal spike identified

SA-PO695

Hypercalcemia Associated with Severe Tophaceous Gout

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Introduction: Refractory gout remains a persistent challenge leading to significant functional impairment. Hyperuricemia is strongly associated with chronic kidney disease. Severe hypercalcemia from gout is a rare phenomenon and we, herein present a case with chronic tophaceous gout presented with severe hypercalcemia leading to acute kidney injury (AKI).

Case Description: 40-year-old male with history significant for chronic tophaceous Gout presented to the emergency department from clinic for further evaluation of hypercalcemia and AKI noted on the laboratory results. His symptoms were arthralgias and muscle weakness. Vital signs notable for blood pressure of 150/70 mmHg, Heart rate 92 beats per minute. Laboratory results significant for serum creatinine 3.80 mg/dL (baseline of 1.3 mg/dL), calcium 12.9 mg/dL, albumin 2.9 g/dL, corrected calcium is 13.4 mg/dL, ionized calcium 1.76 mmol/L, phosphorus 4.7 mg/dL, parathyroid hormone 11.1 pg/mL, Thyroid stimulating hormone is 3.58 ulU/mL, 25-hydroxy vitamin D 48.6 ng/mL,1-25, dihydroxy vitamin D was 85.9 ng/mL, uric acid is 11 mg/dL, PTHrP 3.3 pmol/L, work-up for myeloma was negative. X-Ray of the extremities showed multifocal partially calcified tophaceous gout. CT scan of the chest, abdomen and pelvis with no evidence of lymphadenopathy or granulomatous process. Biopsy of the skin lesions was consistent with Gout with calcifications. Given the above findings, it was thought to be secondary to increased production of 1,25 dihydroxy vitamin D (calcitriol) due to granulomatous inflammation caused by severe gout and he was treated with calcitonin x 3 doses, intravenous hydration and prednisone 40 mg daily. His calcium improved to 10 mg/dL, and was discharged home.

Discussion: The most common cause of hypercalcemia is primary hyperparathyroidism, however in the hospital setting it is malignancy. Chronic tophaceous gout results in granulomatous inflammation leading to increased production of calcitriol resulting in hypercalcemia. This is extremely rare and our case illustrates the importance of understanding the pathophysiology for hypercalcemia in chronic gout. Treatment includes primarily corticosteroids.

SA-PO696

Refractory Hypercalcemia: Unmasking Pneumocystis jirovecii Pneumonia in a Renal Transplant Recipient

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Introduction: Refractory hypercalcemia in renal transplant recipients is a challenging consequence of Pneumocystis jirovecii pneumonia (PJP). Accurate diagnosis is crucial, as PJP can present subtly, leading to increased mortality rates. In renal transplant patients, hypercalcemia frequently accompanies PJP and serves as a vital diagnostic clue. In this report, we present a case of refractory hypercalcemia resulting from PJP in a renal transplant recipient, highlighting the need for effective recognition and management.

Case Description: A 57-year-old male with a history of renal transplant, currently on immunosuppressive therapy, who was admitted to the hospital with fevers and general malaise. Laboratory findings revealed marked hypercalcemia (15.6 mg/dL) with suppressed parathyroid hormone (PTH) levels. Extensive Infectious investigations, including urinalysis, chest x-ray, commuted tomography (CT) of the chest, abdomen, and pelvis, blood cultures, viral panel tests yielded no significant findings. Despite administration of isotonic saline, calcitonin, and bisphosphonates, the patient's hypercalcemia remained unresponsive. Further laboratory studies revealed normal PTH-Related Protein (14 pg/mL), elevated 1,25 dihydroxy vitamin D (133 pg/dL), and normal 25-dihydroxy vitamin D (52 ng/dL). Due to persistent fever in an immunosuppressed individual, an extensive infectious investigation was conducted, including tests for various viruses and pathogens. A breakthrough was achieved when the qualitative PCR test for PJ returned positive. The patient was promptly initiated on systemic steroids and atovaquone therapy targeting PJP. Serum calcium returned to normal after completion of therapy.

Discussion: Hypercalcemia in renal transplant patients with PJP results from a granulomatous-like mechanism. Macrophages and monocytes in granulomas play a vital role by producing 1-alpha hydroxylase, converting calcidiol to calcitriol, the active form of Vitamin D. Calcitriol stimulates increased calcium absorption in the intestines and kidneys and calcium mobilization from bone tissue, leading to hypercalcemia. Therefore, when evaluating a renal transplant patient presenting with hypercalcemia, it is crucial to consider PJP as a potential differential diagnosis.

SA-PO697

Neonatal Hypocalcemia and Maternal Hypercalcemia: Exploring the Potential Connection to Parathyroid Adenoma and CaSR Mutations

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Background: This study aims to investigate the relationship between neonatal hypocalcemia and maternal hypercalcemia, and to explore potential genetic predispositions related to parathyroid adenoma and CaSR mutations in mothers.

Methods: Neonates presenting with late-onset (≥3 days) hypocalcemic tetany or seizures, low serum total calcium, high serum phosphorus, and inappropriately low or normal iPTH levels suggestive of hypoparathyroidism were prospectively enrolled. Hypomagnesemia, high phosphate intake, and kidney function impairment were excluded. Following enrollment, all mothers were evaluated for potential causes of neonatal hypocalcemia.

Results: Seven full-term newborns (six males, one female) and their mothers were enrolled. All newborns were diagnosed with transient hypoparathyroidism secondary to maternal hypercalcemia. To investigate the cause of maternal hypercalcemia, maternal serum calcium, phosphorus, iPTH levels, and parathyroid scans were assessed. Five mothers were found to have parathyroid adenoma, and one was confirmed to have a CaSR loss-of-function genetic mutation. All newborns were treated with oral calcium gluconate combined with cholecalciferol or calcitriol. After approximately one month of treatment, serum calcium and phosphate levels normalized, and the iPTH-Ca correlation was restored. Following parathyroidectomy in mothers with parathyroid adenoma, serum calcium levels normalized, but elevated iPTH levels persisted for months. The mother with the CaSR loss-of-function mutation exhibited a similar trend in serum calcium and iPTH levels.

Conclusions: This study underscores the importance of evaluating maternal calcium homeostasis in cases of neonatal hypocalcemia and highlights a potential genetic association between neonatal symptoms and maternal parathyroid adenoma and CaSR mutations. Further research is warranted to understand the genetic basis and optimize management strategies for both conditions.

SA-PO698

Trends in Serum Parameters Levels According to Renal Function Following Denosumab

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Background: Osteoporosis and chronic kidney disease (CKD) are major risk factors for fracture. Denosumab is widely used to treat osteopenia in patients with CKD; however, its effect on phosphate, calcium, and parathyroid hormone (PTH) levels has not been fully elucidated.

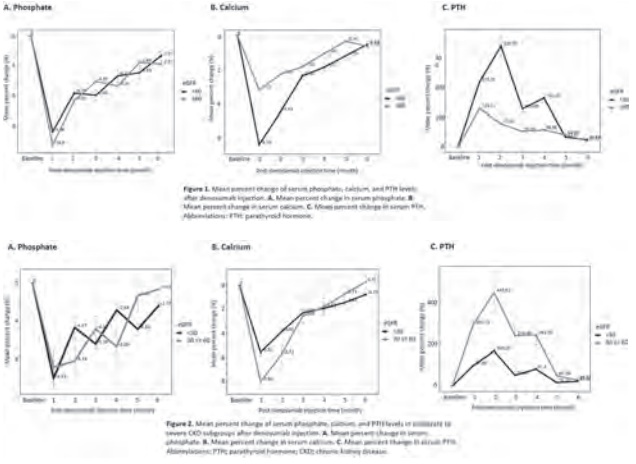
Methods: A retrospective observational study was performed on patients from three hospitals in Korea who were treated with denosumab between November 2016 and December 2021. We compared the mean percentage change in serum phosphate, calcium, and PTH levels from baseline to six months post-denosumab treatment. Among the 11 586 patients (median age, 70.0 years; 89.2% female) included in this study, 10 069 (87.9%) had an estimated glomerular filtration rate (eGFR) over 60 mL/min/1.73 m^2 and comprised the preserved kidney function group. Patients with an eGFR under 60 mL/min/1.73 m^2 (n = 1 517) comprised the reduced kidney function group.

Results: One month after denosumab administration, serum calcium (preserved kidney function group: -3.18%; reduced kidney function group: -6.35%) and phosphate levels (preserved group: -10.9%; reduced group: -9.56%) decreased and serum PTH levels increased (preserved group: +123.54%; reduced group: +216.93%). However, all parameters returned to baseline six months after treatment. Six months after denosumab treatment, a higher rate of hypocalcaemia was observed in the reduced kidney function group relative to that of the preserved kidney function group (4.5 and 8.3%, respectively, $p < 0.001$).

Conclusions: One month post-denosumab treatment, serum phosphate and calcium levels significantly decreased and PTH levels increased; however, these changes were transient. When using denosumab in reduced kidney function patients, close monitoring and replacement of calcium and vitamin D are required.

Hypocalcemia at baseline and 6 months after denosumab treatment

	Overall	Reduced kidney function group (%)	Preserved kidney function group (%)	P-value
	N=11,586 (100.0)	N=1,517 (13.1)	N=10,069 (86.9)	
At baseline	883 (9.1)	137 (10.4)	746 (8.9)	0.091
At 6 months after denosumab treatment	287 (5.0)	67 (8.3)	220 (4.5)	<0.001



SA-PO699

Licorice-Induced Hypocalcemia: A Rare Outcome of Chronic Licorice Consumption

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Introduction: A syndrome mimicking mineralocorticoid excess resulting in hypokalemia, hypertension, and hypernatremia is a common occurrence after chronic licorice consumption, according to various published case reports. However, licorice induced hypocalcemia with eunatremia is rarely reported. The authors present a case of a patient diagnosed with hypocalcemia due to excessive licorice consumption.

Case Description: 69 year old male presented to our department with primary complaints of oral numbness, muscle cramping, and paresthesia. On admission, he was hypertensive (160/90mmHg) with a heart rate of 84 bpm. An initial lab analysis showed hypocalcemia [Ca, 2.7 mg/dL], hypokalemia [2.7 mEq/dL], and hypomagnesemia [1.1 mg/dL]. The patient was immediately started on IV potassium and calcium replacement, and spironolactone. Dietary history revealed that the patient had been consuming licorice excessively since 2 and half months due to its presumed anti-inflammatory action. The replacement therapy was continued to day 3 and then stopped. The laboratory results were monitored till day 7. Follow-up on day 28 showed normal values as summarized in Table 1.

Discussion: Glycyrrhetic acid and Glycyrrhizic acid are two components of Licroice root extract that have been shown to mimic mineralocorticoid excess by inhibiting enzyme 11ßhydroxysteroid which converts cortisol to cortisone. This results in an increased plasma half-life of cortisol, which binds to aldosterone receptors in renal tubules and activates them. Eventually, the volume overload increases sodium, calcium, and magnesium delivery to the distal tubules. Sodium is absorbed in exchange for calcium and magnesium which induces hypocalcemia and hypomagnesemia. Low magnesium

also impairs the function of the Parathyroid hormone. Licorice is quite popular among the geriatric American population because of its assumed anti-oxidant properties and this case report highlights the significance of physician's knowledge regarding its chronic use and but life-threatening complication of hypocalcemia.

Table 1: Laboratory analysis

Day	Potassium [mEq/dL]	Calcium [mg/dL]
1	2.7	5.7
3	3.3	7.1
7	3.9	8.2
28	3.8	8.1

SA-PO700

Years of Hypomagnesemia due to an HNF1B Mutation

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Introduction: Mutations in the hepatocyte nuclear factor 1B (HNF1B) are an inherited cause of renal malformation that is accompanied by magnesium wasting and a distal tubular dysfunction like Gitelman syndrome. We describe a patient in late adulthood who has hypomagnesemia and an HNF1B mutation.

Case Description: A 39-year-old female presented with intractable nausea and loose stools. She denied any family history of kidney disease. Her laboratory findings revealed a magnesium of 1.0 mg/dL and a potassium of 3.3 mg/dL. Her FeCa was < 0.1% and FeMg was 5.6%. She reported multiple visits to her PCP for IV magnesium infusions twice per week in addition to oral supplementation. She otherwise denied any symptoms of paresthesia or numbness. Genetic testing was performed and revealed a deficiency in HFNB1. She was started on amiloride in an effort to decrease magnesium supplementation. Her subsequent visit revealed a magnesium of 1.4 mg/dL. Renal ultrasound also revealed an innumerable amount of bilateral renal cysts, one of which measured 2.5 cm on the upper pole of the right kidney. No solid renal mass was identified.

Discussion: HNF1B is a transcription factor that is highly expressed in multiple organs that include the kidney, pancreas, and liver. It plays a role in morphological renal development in the form of cystic kidney disease, but also can increase the risk of renal tubular dysfunction and progressive CKD. An HNF1B-related hypomagnesemia may be associated with alteration of the Na/K ATPase in the distal convoluted tubule (DCT). Hypocalciuria occurs when sodium reabsorption in the DCT is impaired, as in Gitelman syndrome and in mutation of the *FXYD2* gene. Our patient likely had longstanding subclinical HNF1B-related hypomagnesemia but was exaggerated in late adulthood by gastrointestinal losses. She has been asymptomatic but still requires frequent magnesium infusions despite amiloride use.

Pertinent lab findings of the patient

Parameter	Initial Presentation	Follow-up 5 months later	Normal Range
Creatinine (mg/dL)	0.68	0.88	0.6-1.3
Magnesium (mg/dL)	1.0	1.4	1.5-2.5
Calcium (mg/dL)	9.5	9.9	8.6-10.3
Phosphorus (mg/dL)	3.4	3.9	2.1-4.7
Albumin (g/dL)	Not obtained	4.6	3.5-5.7
FeCa (%)	< 0.1	< 0.1	> 1
FeMg (%)	5.6	Not obtained	< 4
PTH (pg/mL)	29.5	50.0	12.0-88.0

SA-PO701

Diagnostic Dilemma of a Case of Complex Refractory Hypomagnesemia

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Introduction: Magnesium (Mg^+) diisorders are usually less common & not well investigated. Renal Mg^+ wasting can be associated with Barter syndrome, Gitelman syndrome, Familial renal magnesium wasting, Hepatocyte nuclear factor-1-beta gene mutations, Epidermal growth factor gene mutation, or Cyclin M2 mutations.

Case Description: A 69-year-old white female with PMH of CKD Stage 2, HTN, DM, Sarcoidosis, presented with severe chronic hypomagnesemia. Her daughter also has chronic hypomagnesemia. She was on pantoprazole & HCTZ for >7 years, HCTZ was discontinued 1 year prior to the presentation. Now on oral & Mg^+ IV infusion (4 gm/month). Other medications included Spironolactone, Gabapentin, Glyburide, Lantus, Aspirin, and Mepolizumab. Pantoprazole was discontinued, continued on oral Mg^+, but increased Mg^+ IV infusions (4 gm/week). Despite these changes her Mg^+ level was still ranging between 0.9 to 1.3 mg/dL. Later stopping spironolactone was also unsuccessful to improve the Mg^+ level, but her K^+ dropped to low normal. Workup as follows: Na^+ 140 mmol/L, K^+ 3.4 mmol/L, Cl^- 102 mmol/L, CO_2 27 mmol/L, BUN 8 mg/dL, Creatinine 0.7 mg/dL, Glucose 205 mg/dL, Ca^+ 9.7 mg/dL, Phosp 4.2 mg/dL & Mg^+ ranging between 1.0 to 1.3. UA- normal. 24-hour urine lytes: Mg^+ 59.4 mg, Ca^+ 68 mg/dL, K^+ 50 mmol, Na^+ 90 mmol. 24-hour Creatinine 0.8 g. Urine Mg^+ 4.4 mg/dL. Fractional excretion (FE) of Mg^+ 6.87%.

Discussion: A daily excretion of >10 to 30 mg or a FE of Mg^+ above 3 to 4% in a person with hypomagnesemia & normal kidney function, indicates renal Mg^+ wasting. In contrast, a 24-hour urinary Mg^+ excretion of <10 mg or a FE of Mg^+ <2% usually indicates an extrarenal Mg^+ losses (typically GI). Our patient's FE of Mg^+ is 6.87%, & 24-hour urine Mg^+ was 59.4 mg. Gitelman syndrome (GS) is the most common form of familial renal Mg^+ wasting. Bartter syndrome (type 3) that resemble GS, may also present with hypomagnesemia. The 24-hour urine calcium/creatinine ratio is 85 mg/g. The upper range for the urine calcium/creatinine ratio in adults is about 200 mg/g. The lower limit of normal for calcium excretion is unknown. A spot urine calcium/creatinine ratio of <70 mg/g has been proposed to define hypocalciuria in adults when Gitelman syndrome is suspected. Our patient has a spot ratio of 19 mg/g. The patient is undergoing genetic testing to identify the etiology of hypomagnesemia.

SA-PO702

Gitelman-Like Syndrome Associated with Seizure Secondary to Chronic Proton Pump Inhibitor Use and Alcohol Consumption: Case Report of Undetectable Magnesium

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Introduction: Magnesium (Mg2+) is the second most common intracellular cation, acting as a cofactor in over 300 metabolic reactions. Magnesium metabolism depends on integrated actions between the kidney and intestine. There are descriptions of reductions in intestinal and renal absorptive capacities by use of a proton pump inhibitor (PPI) as well as by alcohol consumption, but undetectable serum magnesium is not common. We describe a case of severe hypomagnesemia in a patient who has been a chronic user (for 8 years) of PPIs and consumes alcohol daily.

Case Description: Male, 73 years old, hypertensive, diabetic, sarcopenic admitted due to generalized tonic-clonic seizure. He was using antihypertensive drugs (Atenolol 50 mg / day; Lisonopril 20mg / day and Amlodipine 5 mg / day), in addition to the chronic use of Omeprazole (40 mg / day). He had a habit of daily drinking (01 bottle of wine a day) and eating meat, with low intake of vegetables and legumes. In admission exams, the following were identified in the blood: Hb: 12.3 g/dl, creatinine (Cr): 1.0 mg/dl, Mg less than 0.1 mmol/L (RV 0.7 – 1.2 mmol/L) potassium 3.6 mEq/L (RV 3.5 – 5.0 mEq/L), sodium 139 mEq/L, chloride 106 mmol/L, HCO3-: 27.2 mEq/L, PTH: 82.9 pg/L ml. Urinary tests showed: Volume 1.5 L/day; uMg: 2.16 mmol/day; Mg excretion fraction (FeMg) 6%; uCa 13.5 mg/day; uNa 100mEq/day; uCr 46.6mg/dl; uK 11.8 mEq/L; FeK 7%. Omeprazole was suspended and intravenous Mg replacement was started, followed by maintenance with oral Mg replacement. Levels normalized after 2 weeks. The patient was discharged from the hospital using oral Mg at a dose of 260 mg/day of elemental Mg for outpatient follow-up.

Discussion: We describe a case of severe hypomagnesemia in an elderly patient with a history of chronic use of PPIs associated with daily alcohol consumption and low intake of legumes. He also had metabolic alkalosis and hypocalciuria, findings compatible with Gitelman-like syndrome. There was normalization and maintenance of adequate levels of magnesium after discontinuation of PPI and alcohol consumption, demonstrating the role of these factors in this disorder.

SA-PO703

Correction of Refractory Hypomagnesemia by SGLT2 Inhibitor

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Introduction: Correcting hypomagnesemia can be difficult due to limited gastrointestinal (GI) absorption of oral Magnesium (Mg) supplements, diarrhea with high dose supplement, and lack of effective agents to decrease renal losses. The reported prevalence of hypomagnesemia is 14%-48% in type 2 diabetic patients. With the growing use of Sodium-Glucose Cotransport 2 Inhibitors (SGLT2i) for cardiac protection, renal protection and proteinuria, etc., post hoc analyses have shown the association of SGLT2i use with increased blood magnesium. A few clinical case reports also demonstrated improvement of hypomagnesemia with SGLT2i. The mechanism by which SGLT2i correct hypomagnesemia is unclear.

Case Description: 74 year old male passed out at a restaurant 4 years ago, he was found to have serum magnesium (Mg) of 0.8mg/dL. Mg supplement was started. He again had severe hypomagnesemia when evaluated for photophobia. Since then he also got intermittent iv Mg. Mg was maintained at 1.4-1.6 mg/dL. Other medical issues include type 2 diabetes, hypertension. No chronic nausea, vomiting; no PPI or diuretic use. He is well nourished, not alcoholic. HbA1c was 6's - 8's. eGFR was >60 cc/min, no microalbuminuria. Work-up showed renal Mg wasting as fractional excretion of Magnesium (FEMg) was 6% when plasma Mg was 1.6 mg/dL in 2/2022. SGLT2i (empagliflozin 12.5mg daily) was added in March 2022, plasma Mg increased to 1.8 mg/dL 1 month later, then to 2.0 mg/dL 3 months later. Plasma Mg has been remain at 2.0 mg/dL over the following 10 months. The increase of plasma Mg from 1.6 to 2.0 mg/dL was associated with decrease of FEMg from 6% to 3%. After plasma Mg stablized at 2.0 mg/dL, FEMg was 13% and 10% on 2 occasions. See Table.

Discussion: GI loss or renal losses are the two major etiologies of hypomagnesemia. This patient had refractory hypomagnesemia despite oral and intermittent iv supplements. His elevated FEMg in presence of hypomagnesemia was consistent with renal wasting. The initiation of SGLT2i rapidly normalized plasma Mg. While plasma Mg remains at 2.0 mg/dL in the following months, the FEMg increased again. This increased most likely represents appropriate renal handling in responding to GI Mg intake.

	2/22/22	4/5/22	7/19/22	2/28/23	4/3/23
Mg (mg/dL)	1.6	1.8	2.0	2.0	2.0
FEMg (%)	6	6	3	13	10

SA-PO704

The Drug that Keeps Giving: Hypomagnesemia Fixed by SGLT2 Inhibitor

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Introduction: Sodium-glucose cotransporter 2 (SGLT2) inhibitors are widely used in patients with kidney disease to improve clinical outcomes. They are known to increase serum magnesium levels. There are rare case reports of these helping treat hypomagnesemia with or without urinary losses of magnesium. We present a case report to add to this data in treating refractory hypomagnesemia with a significant improvement in serum magnesium levels.

Case Description: A 72-year-old frail woman with a past medical history of type 2 diabetes mellitus and gastric bypass surgery presented to the emergency department with complaints of worsening fatigue and refractory chronic hypomagnesemia. The patient had experienced generalized weakness, tremors, and reduced appetite for many months. The patient had known chronic hypomagnesemia, hypokalemia, hypocalcemia, and alkalosis, thus a concern for Gitelman syndrome. She was prescribed oral supplementations without significantly improving serum magnesium levels. Her home medications included metformin and pantoprazole. At the time of presentation, the patient had normal vitals, though she was very frail, demented, and resting tremors in her hands. serum magnesium was 0.9 mg/dl. The pantoprazole was discontinued, and oral and intravenous magnesium supplementation was started with a slight improvement in the serum magnesium levels to 1.2 mg/dl. Next, amiloride was added. However, she developed diarrhea likely secondary to the magnesium salts, which added to her gastric losses and inability to tolerate oral repletion. The fractional excretion of magnesium (FeMg) was 69% consistent with renal magnesium wasting, but the genetic tests for Gitleman came back negative. Subsequently, we added an SGLT2 inhibitor with marked improvement in serum magnesium levels to 2.3 mg/dl and complete resolution of tremors.

Discussion: In patients with significant urinary magnesium wasting, supplementation often fails to improve serum magnesium levels. Clinical trials have shown that SGLT 2 inhibitors can improve hypomagnesemia in diabetic patients with urinary magnesium wasting. However, data on their efficacy in nondiabetic patients with hypomagnesemia is scarce. SGLT2 inhibitors may be considered in patients with intractable hypomagnesemia, representing a possible new tool in this challenging clinical disorder.

SA-PO705

Urinary Phenotyping in Mesoamerican Nephropathy

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Background: Mesoamerican nephropathy (MN) is a leading cause of CKD in Central America. Studies suggest an underlying tubulointerstitial nephritis with coexisting electrolyte wasting in affected individuals. The Colt-MRC cohort is a community-based study in Nicaragua, which recruited individuals at risk of MN, measuring serum creatinine (Cr) and collecting questionnaire data and biosamples at annual study visits for 7 years. In this sub-study, we aimed to compare the urinary phenotype of individuals from the cohort who develop early kidney injury (EKI) – defined by a significant decline in eGFR from a healthy baseline, with healthy controls (HC) and those with established MN (eMN).

Methods: We compared concurrent serum and urine samples from EKI cases pre and post decline in eGFR to two samples from HC matched for age, sex, community and study visit, and samples from two consecutive study visits from un-matched eMN participants (Table 1). All serum and urine samples were tested for: Cr, Na, K, PO_4 & Mg, and fractional excretions (FE) of electrolytes were calculated. Urine was also tested for MCP-1 (ELISA) and corrected for urine Cr. Data were analysed using mixed-effects modelling.

Results: FE of all electrolytes were raised in the eMN group, but serum Na and Mg were lower. MCP1 was significantly raised in cases in the visit post EKI compared to pre-EKI, HC and eMN. See Table 1.

Conclusions: Urinary MCP1 levels are higher in cases after incident EKI versus HC and eMN, suggesting acute inflammation at the onset of MN that subsequently subsides. Participants with eMN had raised FE of all measured electrolytes, a common feature of CKD due to decreased nephron mass. However, they also had lower serum Na and Mg, with 50% exhibiting clinical hypomagnesemia, which is not a feature of CKD and suggests ongoing impairment of tubular function in established MN.

Funding: Private Foundation Support, Government Support - Non-U.S.

Mean values	HC (n=43)		EKI (n=43)		eMN (n=21)	
	Visit 1	Visit 2	Visit 1 (pre-decline)	Visit 2 (post-decline)	Visit 1	Visit 2
No. Males	36 (84%)		36 (84%)		21 (100%)	
Age (years)	25	26	25	26	26.5	27.5
eGFR ml/min/1.72m^2	118	114	111	84.5	46.5	46
Serum PO_4 (mmol/L)	1.14	1.2	1.21	1.2	1.2	1.15
FE PO_4 (%)	7.2	7.2	8.4	8.5	14.5*	12.9*
Serum Mg (mmol/L)	0.82	0.82	0.8	0.8	0.7*	0.7*
FE Mg (%)	3.4	3.8	3.9	4.9	11.7*	12.4*
No. Mg <0.7mmol/L	1 (2.3%)	2 (4.6%)	4 (9.2%)	2 (4.6%)	10 (48%)	11 (52%)
Serum Na (mmol/L)	140.6	140.1	140.2	140.2	139.4**	138.4**
FE Na (%)	0.9	0.9	1.1	1.1	2.1*	2.1*
Serum K (mmol/L)	4.5	4.5	4.3	4.3	4.4	4.3
FE K (%)	7.8	8.7	8.5	10.3	17.8*	18.6*
MCP-1/Crt (ng/mmol)	4.8	3.6	5	11.7~	6.1	9.2

*p<0.001 **p<0.05 eMN vs HC & EKI ~p<0.05 post-decline EKI vs pre-decline, HC and eMN.

SA-PO706

A Mystery Solved: Getting a "Grip" on Unexplained Hypermagnesemia in a Patient on Continuous Cyclic Peritoneal Dialysis (CCPD)

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Introduction: Hypermagnesemia should not occur in a patient on RRT without an exogenous source. We present a pt in whom a [Mg] level of 6.0 mg/dL was found in which there was no history of intake of any Mg containing mediations or supplements despite multiple inquiries.

Case Description: A 27 year old black woman with anuric ESKD secondary to Alport's disease on CCPD presented with a 1-wk history of weakness and syncopal episodes. She reported "blackout" and "spacing out" spells, each lasting a few seconds. She also noted new upper extremity weakness, spontaneously dropping items from her hands. She reported compliance with home PD (1.5 mEq/L [Mg] dialysate). She denied use of laxatives or supplements. She works as a chef and denied any recent increase in Mg containing foods. In the ED her VS were unremarkable except for a BP of 170/90. Her laboratory values were typical for ESKD except for a serum [Mg] of 6.0 mg/dL (nl 1.7-2.7). Her EKG demonstrated a prolonged QTc. She received IV calcium, and her QTc normalized. She was admitted to the hospital and started on rapid exchange PD with a dialysate [Mg] of 0.5 mEq/L. Her neurologic episodes and muscular weakness resolved. Upon further investigation (by the dietician), the patient noted that she recently started rock climbing 4 times per week using climber's chalk to improve her grip (the chalk helps keep hands dry to provide a stronger grip) which upon research was found to be made of magnesium carbonate (Figure 1). Her [Mg] improved in the hospital and decreased further at home with change to a lower [Mg] dialysate and stopping her rock climbing (Fig. 1).

Discussion: Magnesium is easily excreted by the kidneys when renal function is normal, so hypermagnesemia requires a large exogenous source in the setting of renal insufficiency. The exact mechanism by which she absorbed Mg from the climbing chalk remains uknown. Although a dialysate [Mg] of 1.5 mEq/L (0.75 mmol/L) is slightly high relative to a normal serum [Mg], her markedly elevated [Mg] of 6.0 mg/dL (2.5 mmol/L) had to be from an exogenous source that required "Dr. House" like investigation to solve.

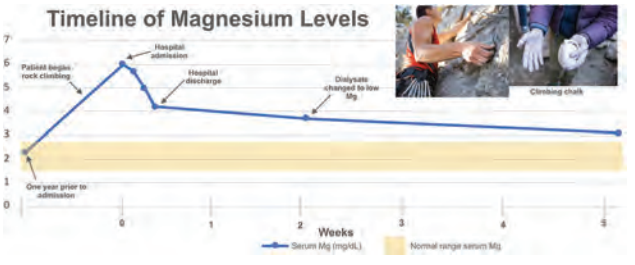


Figure 1. Clinical course of magnesium

SA-PO707

Clinic-Level Fluid Quality Score Associates with Fluid Overload Hospitalizations

Tory Scoggins, Patricia Mccarley, Amanda S. Rivenbark, Amanda Stennett, Brian S. Ash, Kathleen Yatsuhashi, Kellie Y. Becker, Caitlin Monaghan, Sheetal Chaudhuri, John W. Larkin, Jeffrey L. Hymes. *Fresenius Medical Care, Waltham, MA.*

Background: Fluid overload (FO) is a primary cause of hospitalization in the dialysis population. A national dialysis network established a Fluid Action Group (AG) system to help identify patients on hemodialysis (HD) with clinical presentations associated with

hypervolemia to prompt timely evaluations/interventions. Fluid AG assignments for patients are used to calculate a Fluid Clinical Quality Score (CQS) for each HD clinic. This analysis investigated if Fluid CQS was meaningfully associated with FO hospitalizations.

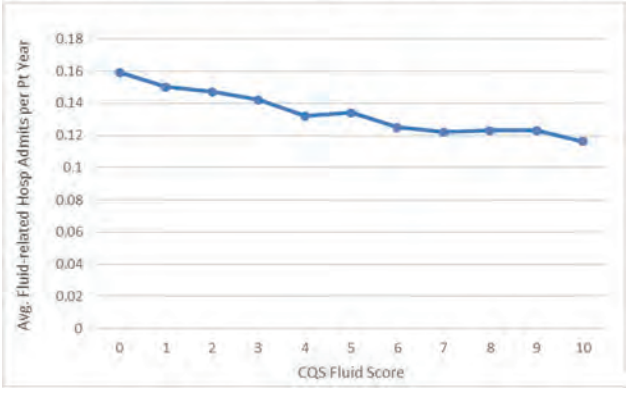
Methods: Fluid AG scoring assigns patients into groups representing a low-to-high FO risk based on the presence of post-HD hypertension coupled with excess interdialytic fluid gains, missed/shortened treatments, unchanged/increased estimated dry weights, and/or multiple blood pressure medications. Fluid CQS Score was calculated based on percent of patients in AGs with the median scoring 5, top decile scoring 10, and bottom decile scoring 1. Data on the Fluid CQS and the average rolling 12-month hospitalization rate considering exposure time were collected from 9/2022- 2/2023. FO hospitalization rate was averaged for each level of the Fluid CQS.

Results: Among patients treated at 2,705 clinics, we observed an inverse relationship between higher Fluid CQS scores and lower FO hospitalization rates ($R^2 = 0.93$). Average FO hospitalization rate was 25% lower at clinics with a Fluid CQS score of 10 vs 1 (0.16 vs 0.12 FO admissions/patient year at clinics with a Fluid CQS score of 10 vs 1, respectively). Consistent trends were observed during each month individually.

Conclusions: Fluid CQS appears to be meaningfully correlated with FO outcomes observed at a clinic and can be viewed as a surrogate marker of the management of fluid control. Further investigations are needed to understand the effectiveness of interventions being performed based on Fluid AG for individual patients.

Funding: Commercial Support - Fresenius Medical Care

Figure 1: Association between Fluid Clinical Quality Score (CQS) and fluid-overload hospitalizations



SA-PO708

Hypertension, Hypokalemia, and Psychosis: A Case Report of Ectopic ACTH Production from Pulmonary Carcinoid Tumor

Amara Sarwal, Siddhartha Kakani, Josephine Abraham. *University of Utah Health, Salt Lake City, UT.*

Introduction: Pulmonary carcinoid tumours are a rare cause of ectopic ACTH [1]. Herein, we present a case of ectopic ACTH production presenting as acute psychosis due to a pulmonary carcinoid tumor.

Case Description: 63 year old male with rheumatoid arthritis and hypertension presented to the Emergency Department with erratic behavior and altered mental status. Initial workup revealed profound hypokalemia to 1.8 mmol/L, sodium of 152 mmol/L, bicarbonate at 34 mmol/L and serum creatinine at 1.02 mg/dL. Urine toxicology was positive for marijuana. He was also found to be hypertensive at 152/101. Patient noted excessive sweating for 1.5 years along with weight loss of 20 pounds in the last month. Contrasted imaging of the abdomen did not reveal any masses in the adrenals, although did note bilateral adrenal hyperplasia. Hyperaldosteronism was ruled out. 24 hour cortisol was 9948 ug/d with elevated ACTH of 229 pg/mL. Patient's behaviour was thought to be due to acute psychosis from the hypercortisolism, and he was started on ketoconazole with improvement in symptoms. Contrasted imaging of the chest revealed a 1.9cm right upper lung nodule that had been stable since 2020. Unfortunately, patient developed PJP pneumonia, causing a delay in surgical resection. Patient underwent wedge resection a month later, with pathology revealing 1.4cm well differentiated carcinoid tumor with positive ACTH immunostaining.

Discussion: Metastases in pulmonary neuroendocrine tumors have been reported at <15% of cases[1]. >80% of cases of pulmonary carcinoids are curative with surgery [1]. Our patient had a nodule that had been unchanged for years prior to presentation. After ruling out any other causes for ectopic ACTH, we decided to pursue further evaluation of the lung nodule.

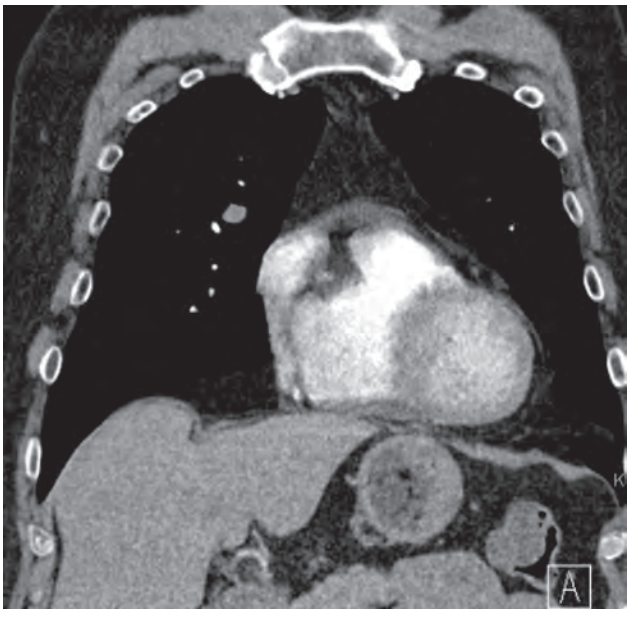


Figure 1. Right sided middle lobe nodule

SA-PO709

Comparison Between Longitudinal Kidney Function and Volume Changes in Association with Heart Failure Outcomes Among Discharged Patients in EVEREST

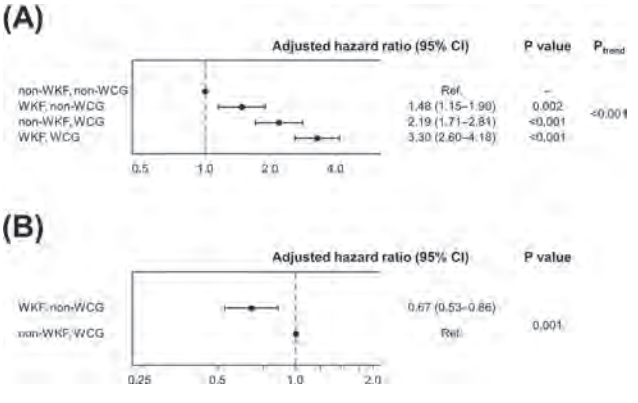
Tatsufumi Oka, Hocine Tighiouart, Wendy I. McCallum, Marcelle Tuttle, Marvin Konstam, James Udelson, Mark J. Sarnak. *Tufts Medical Center, Boston, MA.*

Background: Decongestion can result in kidney function decline. The relative clinical importance of changes in kidney function and changes in volume status remains uncertain in outpatient HF settings.

Methods: This post-hoc analysis of the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (EVEREST) trial analyzed patients who survived HF hospitalization. As time-varying exposures, worsened kidney function (WKF) and worsened congestion (WCG) were defined as any decrease in eGFR and any increase in B-type natriuretic peptide (BNP) in comparison with values at discharge, respectively. We examined the association of 4 groups (non-WKF, non-WCG group; WKF, non-WCG group; non-WKF, WCG group; and WKF, WCG group) with the composite of cardiovascular death or HF re-hospitalization, particularly focusing on the comparison between WKF, non-WCG and non-WKF, WCG groups. Marginal structural models, which can create a balanced pseudo-population throughout follow-up, were applied to account for time-dependent confounding.

Results: Among 3666 patients, median age, eGFR, and BNP at discharge were 67 years, 57.9 mL/min/1.73 m^2, and 441.9 pg/mL, respectively. During follow-up (median, 44 weeks), 631 patients died due to cardiovascular disease and 1160 experienced HF re-hospitalization. After adjustment for time-dependent confounders, a significant trend was observed in the association between the 4 groups and study outcome with the highest risk in WKF, WCG group (Figure A). Patients in WKF, non-WCG group had a 33%-lower risk of the composite outcome than those in non-WKF, WCG group (Figure B).

Conclusions: WKF-WCG categories discriminated the risk of HF outcomes in discharged patients with HF. Patients in WKF, non-WCG group had fewer adverse HF outcomes than those in non-WKF, WCG group, suggesting the importance of sustaining decongestion over preserving kidney function.



SA-PO710

Dare to Diurese: Lymphedema in a Patient with Spina Bifida

Maheen Khan, Neev Patel, Yashvi Pethani, Martin Brigham, Adrian P. Sequeira. *LSU Health Shreveport, Shreveport, LA.*

Introduction: Evaluation of edema is a common part of medical practice. While there are myltiple etiologies that can cause edema, diuretics are cornerstone of management and have the potential to be overused. We present one such case in a patient with lymphedema from spina bifida. Patients with spina bifida carry 100 times higher risk of developing primary lymphedema compared to healthy individuals[2]. Lymphedema praecox, the most common form of primary lymphedema, has its onset between age 2 and 35 and has a female to male ratio of 10:1[3].

Case Description: A 28-year-old female with past medical history of spina bifida presented to the ED with worsening lower extremity swelling and light-headedness. Prior evaluation by PCP endocrinologist, and cardiologist were unremarkable. She was on lasix 80 mg twice a day, metolazone 2.5 mg twice a day, spironolactone 50 mg daily and 80 mEq of oral potassium. On arrival, BP was 72/40 mm Hg, pulse 70 per minute, and respiratory rate 40/min. physical exam showed non-pitting edema ib bilateral lower extremities. Labs showed Na 132, K 2.3, Cl 89, Cr 0.8. EKG revealed inverted T waves in anterior leads and prolonged QT interval. Echocardiogram was unremarkable with ejection fraction 55%. Diuretic withdrawal, fluid resuscitation, and potassium replacement corrected her electrolyte and hemodynamic abnormalities. Further evaluation for hypokalemia revealed aldosterone 261 ng/L, renin 100 ng/L, ACTH < 5.0, AM cortisol 3.9, TSH 2.067. Upon evaluation by Nephrology, primary lymphedema was deemed to be the cause of nonpitting edema. Pt was discharged on Lasix 80 mg daily and KCl 40 mEq daily.

Discussion: The case reports highlights a few key points including: 1. recognizition of lymphedema in patients with spina bifida 2. importance of evaluation of peripheral edema and it's causes in all patients 3. cautious use of diuretics and mineralocorticoid receptor agonists especially when used in conjunction 4. frequent monitoring of electrolytes when patients are on diuretics and 5. de-escalation of therapies when edema is refractory to therapy or side effects are frequent.

SA-PO711

Therapeutic Plasma Exchange-Related Hypotension: A Comparison of Replacement Fluids

Andrew Yanik,[1] Amara Sarwal,[1] Jamie P. Dwyer,[1] Srinivasan Beddhu,[1] Robert E. Boucher,[1] Josephine Abraham.[1] *[1]University of Utah Health, Salt Lake City, UT.*

Background: Therapeutic plasma exchange (TPE) is used to remove specific pathogenic entities or replace substances that are physiologically lacking. TPE requires replacement fluid administration due to plasma losses, and the most common replacement fluids are albumin and saline. There is limited literature regarding the effect of different replacement fluids on TPE-related hypotension. This study aimed to compare TPE-related hypotension between groups receiving partial-saline and 100% albumin.

Methods: This is a retrospective, single-center study from the University of Utah. Patients who were 18 years old or older and had diagnoses necessitating TPE were considered eligible participants. 2272 TPE sessions were performed in 333 patients from 1/1/2020 and 3/3/2023. All patients before 3/1/22 received partial saline, and all patients after this received 100% albumin. Episodes of TPE-related hypotension were investigated and compared between these two groups using logistic regression models to relate TPE group to the incidence of each type of hypotensive event, with adjustment for SBP, DBP and indication for TPE.

Results: The mean age of the patients was 50.5 years and 48.6% were male. The partial-saline group accounted for 1432 sessions and the 100% albumin group accounted for 840. Hypotension occurred in 32.4% of TPE sessions in the partial saline group, and 31.7% in the albumin group (OR=1.01, 95% CI 0.83-1.23, p=0.865). When analyzing individual criteria of hypotension between the partial saline and albumin groups respectively, the results show: 4.82% vs 2.86% (SBP <90 mmHg OR=1.70, 95% CI 1.03-2.78, p=0.035), 16.13% vs 11.31% (MAP <65 OR=1.39, 95% CI 1.05-1.83, p=0.02), 21.37% vs 22.26% (SBP drop >20 mmHg OR=0.98, 95% CI 0.7-1.23, p=0.84), and 3.84% vs 2.50% (SBP drop >40 mmHg OR=1.74, 95% CI 1.00-3.03, p=0.05). When analyzing the composite of an SBP drop below 90 mmHg, MAP <65, and SBP drop by >40 mmHg, events occurred in 19.41% and 14.05 % of the partial saline and albumin groups, respectively (OR=1.41, 95% CI 1.09-1.80, p=0.007).

Conclusions: Partial saline recipients are significantly more likely to have a hypotensive event. This may reflect support for using 100% albumin as replacement fluid during TPE, reinforcing the physiologic rationale for colloid replacement.

SA-PO712

Differentiating Vasopressin Withdrawal Syndrome from Gestational and Central Diabetes Insipidus: A Learning Case Study

Panupong Hansrivijit,[1,2] Annie Liu,[1,2] Pui Susan W. Cheung.[1] *[1]Massachusetts General Hospital, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA.*

Introduction: Differentiating vasopressin withdrawal syndrome (VWS) from gestational diabetes insipidus (GDI) and central diabetes insipidus (CDI) in a pregnant woman is challenging. Prolonged administration of exogenous vasopressin can lead to negative feedback on endogenous anti-diuretic hormone (ADH) production from the posterior pituitary gland. CDI can occur following a shock leading to pituitary infarction and usually co-exists with anterior pituitary axis deficits given their enriched blood supply. Finally, GDI is mediated by placenta-derived vasopressinase which degrades endogenous ADH and exogenous vasopressin. GDI typically presents in the 2nd and 3rd trimester and can persist up to 4-6 weeks postpartum. A baseline urine analysis and serum copeptin level is a useful tool in the diagnosis of polyuria in pregnancy.

Case Description: A 32-year-old, 24^{+2}-week pregnant female was admitted to the Intensive Care Unit for peripartum cardiomyopathy requiring Impella device placement. She was started on phenylephrine and vasopressin for hypotension on hospital day (HOD) 1. On HOD13, vasopressin was stopped, and she became polyuric with nine liters of urine output leading to some issues with the Impella device. Urine osmolality was 100 mosm/kg. Vasopressin was then restarted with resolution of polyuria. Nephrology was then consulted. Fortunately, urine analysis was collected on the day of admission and showed urine specific gravity of >1.030. While on vasopressin, the serum sodium was 129 mmol/L, urine osmolality was 678 mosm/kg, copeptin level was <2.8 pmol/L. Anterior pituitary axis work-up was unremarkable. She delivered on HOD21 while on vasopressin. Vasopressin was successfully discontinued on HOD22 with a bridge using desmopressin. Eventually, desmopressin was completely stopped on HOD37 (16 days after delivery).

Discussion: This patient's presentation favors VWS over GDI. First, the urine specific gravity on admission suggested presence of ADH effect which argues against GDI. Second, low copeptin level was auggestive of VWS. The copeptin level is expected to be within reference range in GDI or elevated in the setting of cardiogenic shock. Finally, absence of anterior pituitary axis dysfunction would make CDI very less likely. In conclusion, urine chemistry and copeptin level are essential in the diagnosis of polyuria in pregnancy.

SA-PO713

Running Dry: The Thirsty Journey of Postpartum Diabetes Insipidus

Jeaneishka M. Rivera Rios, Ileana E. Ocasio Melendez, Krystahl Z. Andujar-Rivera, Caleb S. Pacheco-Molina, Carlos G. Rivera-Bermudez, Jesus D. Vega-Colon, Maria E. Rivera. *Universidad de Puerto Rico Escuela de Medicina, San Juan, Puerto Rico.*

Introduction: Diabetes insipidus (DI) is a rare complication of pregnancy, occurring in 1 in 30,000 pregnancies. During pregnancy or the postpartum period, DI can be associated with excessive vasopressinase activity secreted by the placental trophoblasts, which increases the degradation rate of vasopressin.

Case Description: A 28-year-old female G2P1A0 with a trichorionic triamniotic pregnancy at 27 3/7 weeks gestation, was admitted to the hospital due to preterm premature rupture of membranes (PPROM) and later developed preeclampsia. After an emergent cesarean section, she developed acute respiratory distress syndrome requiring endotracheal intubation, was treated for hyperthyroidism and transfused with one packed red blood cells. On day 6 following delivery, the patient developed polyuria, no polydipsia reported while sedated on mechanical ventilation. Laboratory investigations showed normoglycemia, normocalcemia, hypokalemia, hypomagnesemia, hypernatremia (serum sodium level of 151 mEq/L), a urine output of 6.5 L/day, and a urine specific gravity of 1.005. Total placenta weight was found to be 770 g (normal 500-600 g in a full-term pregnancy). Treatment with synthetic analogue 1-deamino-8-D-arginine vasopressin resulted in decreased urine output, increased urinary osmolality, and normalization of sodium levels. The patient was discharged from the hospital with no signs of DI or additional complications. Endocrinological follow-up confirmed that there were no underlying metabolic disorders.

Discussion: This case highlights the diagnostic complexity of transient diabetes insipidus in the postpartum period. It is a rare complication that can occur following pregnancy and delivery, especially in patients with pre-existing medical conditions. Diagnosing DI during pregnancy can be challenging due to physiological changes, which can make interpreting results difficult. A high index of suspicion for vasopressinase-induced DI should be considered in the presence of risk factors such as preeclampsia, hepatic dysfunction, and multiple gestation.

SA-PO714

Arginine Vasopressin Deficiency in the Hypoxic Brain

Leanna V. Ritchie, Abdul Basit, Lyle W. Baker. *Mayo Foundation for Medical Education and Research, Jacksonville, FL.*

Introduction: Hypernatremia is an electrolyte disorder most commonly related to limited access to water or suppression of the thirst compensatory mechanism. Uncommonly hypernatremia may be associated with interruption in the anti-diuretic hormone (ADH) cascade either from a central (pituitary) or nephrogenic etiology. ADH is released in response to elevated serum sodium from the posterior pituitary gland to bind with V2 receptors in the distal tubules and collecting ducts in the kidney to facilitate water reabsorption. If this phenomenon is interrupted, termed arginine vasopressin deficiency (AVD), a patient may present with hypernatremia and polyuria. The most common etiologies of AVD are secondary to infiltrative disease, primary or secondary tumors and traumatic brain injury.

Case Description: Here presented is a case of a 58 year old female with a past medical history remarkable for hypertension, diabetes, seizure disorder and obesity who presented to the hospital after cardiac arrest. The patient had asystole and achieved return of spontaneous circulation after 1 hour of advanced cardiac life support. Following cardiac arrest she developed hypernatremia with polyuria. CT head indicated global hypoxemic brain injury. The patient had absent brainstem reflexes. The patient developed acute kidney injury secondary to renal ischemia and was started on continuous veno-venous hemofiltration (CVVH). Despite renal replacement therapy the patient developed hypernatremia with polyuria. Initially free water flushes were initiated, however the patient developed refractory hypernatremia. Renal replacement therapy was discontinued. Urine osmolality was 259 mOsm/kg, consistent with AVD. The patient's urine volume

reduced in response to desmopressin administration with correction of hypernatremia. She was diagnosed with central AVD secondary to anoxic brain injury. Unfortunately neurological evaluation identified brain death and the patient was terminally extubated.

Discussion: This case has a unique etiology secondary to hypoxic injury versus a trauma, infiltrative disease or brain mass. The pathophysiology of AVD post hypoxic brain injury is poorly understood. It is hypothesized that damage to the hypothalamus or posterior pituitary gland may hinder ADH secretion. This is an uncommon presentation of cerebral injury post cardiac arrest and may be a negative prognostic indicator for recovery.

SA-PO715

Spontaneous Development of Diabetes Insipidus in a Healthy Female: A Rare Case of Central Diabetes Insipidus in the Nephrology Clinic

Allison Mitchell, Hania Kassem. *The University of Texas Medical Branch at Galveston Development Office, Galveston, TX.*

Introduction: Diabetes Insipidus (DI) is a rare complication resulting from vasopressin (AVP) deficiency [central (CDI)] or AVP resistance [nephrogenic (NDI)] leading to polydipsia, polyuria, and hypernatremia. We present a case of CDI in the nephrology clinic setting including diagnosis, imaging, and treatment.

Case Description: A 46-year-old female presented to nephrology clinic with polydipsia and polyuria that began 3 months prior. Her primary complaints were extreme thirst requiring consumption of approximately 20L of water over 2 to 3 days with large volume urination every hour. Initial laboratory findings were consistent with diabetes insipidus: high-normal sodium (Na) of 145, creatinine of 0.55mg/dL, low urine osmolality of 140 mOsm/kg, and low serum AVP (which resulted 2 weeks later). Due to high suspicion for CDI, patient was started on a trial of oral desmopressin 0.1mg daily which was increased over two weeks to desmopressin 0.2mg BID. Patient subsequently improved with resolution of symptoms and labs showing: normal serum Na (140 mmol/L) with improved urine osmolality (494 mOsm/kg). MRI brain showed diffuse thickening of the pituitary infundibulum in the absence of posterior pituitary bright spot and a small meningioma over the left anterior temporal lobe supporting a diagnosis of Langerhans cell histiocytosis (LCH). Patient was referred to neurology and oncology for further evaluation.

Discussion: LCH is a rare disorder characterized by abnormal proliferation of Langerhans cells, histiocyte-like cells, of unknown cause. This disorder is rarely seen in adults (1-2 per million) and is twice as likely to be diagnosed in males. LCH affects the central nervous system by affecting the pituitary infundibulum leading to the initial presentation of DI. An elevated serum Na along with dilute urine in a patient with polyuria and polydipsia was strongly suggestive of DI, which led to the decision of work up and treatment without requiring a confirmatory water deprivation test. Desmopressin dosing titration required close monitoring with patient counseling about decreasing fluid intake once urine output decreases and being aware of the signs of hyponatremia. This was a unique case in the outpatient nephrology setting of a rare disease in an unlikely patient demographic.

SA-PO716

A Deep Dive into Diabetes Insipidus

Billy Zeng, Sijie Zheng. *Kaiser Permanente, Oakland, CA.*

Introduction: Central diabetes insipidus (DI) is a disease caused by absent antidiuretic hormones production, leading to symptoms of polyuria and polydipsia. Head trauma is a typical cause of central DI. We present a case of new onset partial central diabetes insipidus where recurrent scuba diving was considered a likely trigger.

Case Description: A 58-year-old female presented with polyuria, nocturia, and thirst for one month that started after an annual scuba diving trip. Past medical history was notable for anxiety. She was recently prescribed buproprion prior to these symptoms. Physical exam was unremarkable, serum sodium 145 mmol/L, serum osmolality 305 mOsm/Kg, 24-hour urine volume >2.8 L, and urine osmolality 180 mOsm/Kg. She was empirically started on DDAVP to relieve nocturia symptoms and scheduled for a water deprivation test. Nocturia symptoms improved immediately after started DDAVP. Water deprivation test (Figure 1) showed mild elevations of urine osmolality with water deprivation and substantial increase of urine osmolality with DDAVP administration indicative of partial central DI. An MRI was performed, showing an absent neurohypophysis on T1 sequence. According to the patient, a previous head MRI was normal. On further review of the patient's social history, she went on annual scuba diving vacations for many years.

Discussion: To our knowledge this is the first report of central DI associated with scuba diving. Previous studies have shown that recreational diving can cause a reduction of 20% cerebral blood flow, decompression while ascending can also cause brain injury. We hypothesize that repeated exposure to such hypoxic conditions may have caused injury to the posterior pituitary, with potentially some injury associated with each dive until eventually enough posterior pituitary function was affected, resulting in dysfunction of antidiuretic hormone production or release.

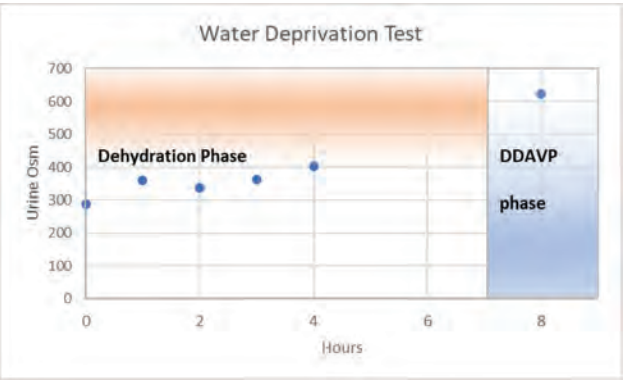


Figure 1. Water deprivation test. Urine osmalality was measured each hour. DDAVP administered at hour 7.

SA-PO717

A Case of Iatrogenic Hyponatremia from Adrenal Insufficiency

Guangchen Zou. *Johns Hopkins University, Baltimore, MD.*

Introduction: Adrenal insufficiency can cause hypersecretion of ADH and lead to hyponatremia. A patient with panhypopituitarism developed severe hyponatremia when hydrocortisone were inadvertently held.

Case Description: A 47-year-old male was admitted for aspiration pneumonia. He had medulloblastoma in his teens and had resection and radiation therapy complicated by panhypopituitarism, and recurrent ischemic strokes with residual right-sided hemiparesis. He was on levothyroxine, hydrocortisone, aspirin, clopidogrel and pravastatin at home. Pneumonia improved and he had a percutaneous gastrostomy tube placed. He was then NPO for a gastric emptying study and his hydrocortisone was inadvertently held and not restarted afterwards. He was restarted on continuous tube feeding (Osmolite 1.2 at 55 ml/h) along with enteral water flushes (150 ml q4h). His sodium was normal since admission for 14 days but dropped from 142 to 117 over 3 days. Systolic blood pressure were 100s-140s. Creatinine was 0.4 mg/dL and potassium was 4.6 mmol/L. Urine sodium was 193 mmol/L, potassium was 37.7 mmol/L and osmolality of 577 mOsm/Kg. Tube feeding were held and he was restarted on hydrocortisone. He was edematous and was given IV furosemide 20 daily. His sodium improved and repeat urine studies 3 days later showed urine sodium of 24 mmol/L. He was later restarted on tube feeding with TwoCal HN. Sodium level remained within normal range 2 weeks later. He was discharged to a skilled nursing facility.

Discussion: Serum sodium dropped when his hydrocortisone was held while being started on tube feeding. Very high urine sodium level which decreased after restarting hydrocortisone were consistent with SIADH from adrenal insufficiency. Clinicians should be careful not to withhold hydrocortisone inadvertently for patients with adrenal insufficiency. For patients with SIADH, serum sodium level should be carefully monitored when they are being started on tube-feeding.

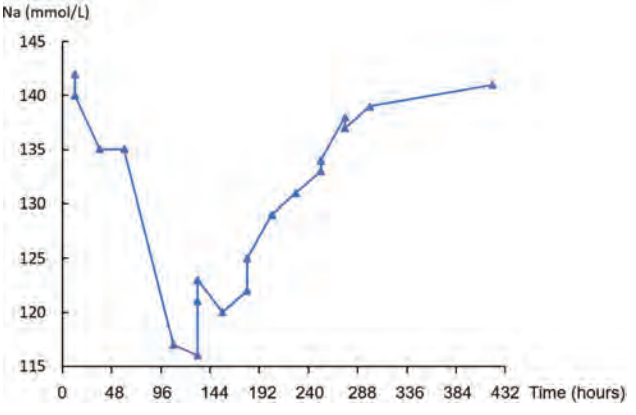


Figure 1. Serum sodium trend. Last dose of hydrocortisone was 14 h before time 0. Hydrocrotisone restarted at 106 h.

SA-PO718

Diagnosing Acute Intermittent Porphyria with SIADH

Mandy Hsu,[1] Abdul-Jawad Majeed,[1] Kevin C. Roe.[2] *[1]Penn State College of Medicine, University Park Program, State College, PA; [2]Mount Nittany Medical Center, State College, PA.*

Introduction: We present a case of acute intermittent porphyria (AIP) presenting with SIADH. AIP is a rare and often overlooked diagnosis. The case highlights the importance of considering AIP when a patient presents with SIADH. Delay in diagnosis led to delayed treatment, multiple emergency department visits and hospitalizations, and unnecessary testing.

Case Description: A 20-year-old female with a history of anemia and anxiety presented with nausea, vomiting, and abdominal pain. She experienced symptoms for two months and underwent extensive evaluation and prior hospitalization. She described the pain as diffuse, inconsistent, and varying in severity. Prior evaluation included upper endoscopy, colonoscopy, CT scans, X-rays, gynecologic evaluation with pelvic ultrasound, and psychiatric consultation. Laboratory evaluation was consistently notable for hyponatremia with serum sodium ranging from 120-130 mEq/L. Hyponatremia was first attributed to dehydration and anorexia treated with IV fluids, free water restriction and salt tablets. However, when euvolemia was achieved a low serum sodium (129 mmol/L) with inappropriately elevated urine osmolality (331 mOsm/kg) persisted. Once the diagnosis of SIADH was determined, a nephrology consultant recognized the association with AIP. Testing for urine porphobilinogens confirmed the diagnosis. The patient was transferred to a tertiary care center to receive appropriate treatment with hemin infusion. Symptoms improved but evidence of SIADH persisted.

Discussion: Early recognition of AIP is often difficult given the rarity of the disease and because the presentation is variable and nonspecific. Our case demonstrates how the presence of low urine sodium levels may help lead to a diagnosis of AIP. This diagnosis may have been missed had the potential cause of SIADH not been taken into consideration. Prompt diagnosis of AIP is important so hemin therapy can be started early to manage future acute attacks and prevent long-term consequences, such as chronic neuropathic pain. Given that the patient had numerous differential diagnoses, it is important to consider the relationship between SIADH and AIP when presented with repeated unexplained abdominal pain, nausea, and vomiting. Teaching points: -Identify the underlying cause when managing SIADH. -AIP and SIADH have an established relationship. SIADH may result from damage to hypothalamus and hypothalamic-hypophyseal tracts in AIP.

SA-PO719

Pressor Dose Vasopressin-Induced Acute Hyponatremia

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Introduction: Vasopressin infusion is commonly used in intensive care unit for circulatory shock but has rarely been associated with hyponatremia. We describe a case of severe hyponatremia in a patient receiving vasopressin infusion that improved upon discontinuation.

Case Description: A 54-year-old, 74-kilogram male, with a history of interstitial lung disease, was admitted to the intensive care unit for acute hypoxic respiratory failure and shock due to COVID-19 pneumonia. A vasopressin infusion, at 0.03 units/minute, was initiated as an adjunctive medication to Norepinephrine. The patient's sodium level decreased from 136 mEq/L to 122 mEq/L over the first 15 hours. Urine output over this time was 1.2 Liters. Once vasopressin was discontinued, the urine output increased to 300 mL/hour with an osmolarity of less than 100 mOsm/kg. The serum sodium rapidly normalized to 135 mEq/L in 9 hours. The patient required desmopressin and a five percent dextrose infusion for treatment of overcorrection of hyponatremia.

Discussion: Vasopressin, at doses of 0.03 units/minute, is a common medication given in the intensive care unit to support circulatory collapse. Vasopressin can exert antidiuretic effects through interaction with V2 receptors in the renal collecting duct cells by incorporation of aquaporin 2 channels allowing passive free water reabsorption across an osmotic gradient. This results in water intoxication with subsequent hyponatremia. In our patient, discontinuation of Vasopressin resulted in a prompt diuresis and correction of hyponatremia.

SA-PO720

Polyuric Hyponatremia: A Case of Salt Wasting

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Introduction: Renal salt wasting has been described in association with several chemotherapeutic agents, yet the diagnosis may prove elusive as the initial work up may reveal findings consistent with the much more common diagnosis of syndrome of inappropriate anti-diuretic hormone (SIADH). Here we described a case of renal salt wasting (RSW) associated with two chemotherapeutic agents and identify the key diagnostic features to differentiate RSW from SIADH.

Case Description: A 29 male with Stage IV testicular rhabdomyosarcoma undergoing inpatient chemotherapy with Etoposide, Ifosfomide and Cisplatin developed acute hyponatremia with a serum sodium drop from 134mEq/L to 123mEq/L in under 48 hours. Urine studies revealed a urine sodium of 168mmol/L, urine potassium 18.8mmol/L, with a negative electrolyte free water clearance and a urine osmolality of 536mOsm/kg. Initial concern was raised for SIADH given inability to excrete free water, further supported by a diagnosis of active malignancy. Additional evaluation revealed that the patient was polyuric with a daily urinary volume of six liters. Additionally, he was hypotensive with evidence of volume depletion on exam. Urinary evaluation revealed normoglycemic glucosuria and aminoaciduria consistent with proximal tubular injury. The patient required 11 liters of hypertonic saline (HTS) to maintain his serum sodium at near normal levels over a two week course. With on-going supportive management, he was weaned off HTS and transitioned to salt tablets which eventually were discontinued as an outpatient upon completion of his chemotherapy.

Discussion: RSW shares several features with SIADH but this case highlights key differentiators. SIADH is regarded as a state of impaired free water excretion and low urine volumes with maintained volume status resulting from augmented release of arginine vasopressin despite there being no appropriate physiologic stimulus. RSW also exhibits impaired free water excretion but is accompanied by high urine volumes as a defect in tubular sodium reabsorption drives solute diuresis, an accompanying drop in serum sodium and hypovolemia. Cisplatin and Ifosfamide have been noted to cause proximal tubule injury which can manifest as isolated renal salt wasting or in association with Fanconi's syndrome, as was seen in this patient. Urinary volume, concurrent medication use and assessment of volume status serve as important features in differentiating RSW from SIADH.

SA-PO721

An Under-Recognized Complication of Chylous Leak: A Case Report of Rapidly Developed Hyponatremia

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Introduction: Chylous leak is a documented complication of thoracic duct perforation, with co-morbidities including high output volume depletion, hypoalbuminemia, immuno-compromised states, and electrolyte imbalances. Our goal is to demonstrate the importance of adequate and frequent electrolyte monitoring, including serum sodium, as hyponatremia is an overlooked complication that leads to sudden critical clinical statues for the patient. Our case portrays a moderate hyponatremia within 4 days of clinical presentation of chylous thoracic leak.

Case Description: Our case is of a 32 year old male with a past medical history of asthma, presenting after a motor vehicle accident. His course was found to be complicated by recurrent pleural effusions, with bilateral chest tube placement, and high outputs of 5 liters total per day. Chemistry studies demonstrated elevated triglycerides, cholesterol, in concordance with chylous leak, with low fat diet, TPN, midodrine, and octreotide initiation for treatment of the chylous leak. In addition, patient had an intractable headache and nausea, with subsequent development of a hyponatremia as low as 125, with urine sodium <10, urine osmolality of 1100, mOsm/kg, serum osmolality of 267, bicarb of 15, and a Cr of 0.7, at baseline. The clinical picture involved addressing nutrition demands with multi-disciplinary nutrition discussion for enteral feeding regimen, augmented with TPN, increasing salt intake to 3g three times daily, and a bicarb saline infusion to increase solute repletion at rates of 200cc/hr until repeat IR embolization was completed for the thoracic duct laceration. Patient's sodium was improved within 6 meq each day, with a final sodium of 135, with no residual neurologic symptomatology.

Discussion: Different etiologies lead to chylous leaks, including iatrogenic surgery, malignancy, and trauma. The morbidities associated with chylous leak in our case involved dangerous circulatory complications, with 4-5L of fluid per day needing supplementation, in addition to electrolyte repletion including bicarbonate and sodium. This case report is aimed to raise awareness for early monitoring of electrolyte levels in patients with high output effusions, to carefully monitor sodium, and to consider early consultation for nutrition, and diagnostic studies, to guide punctual clinical management.

SA-PO722

Etiology of Severe Hyponatremia in COVID-19 Patients Compared with Hyponatremia with Non-COVID-19 Patients by Urine Osmolarity and Sodium

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Background: Lung diseases are known to be associated with hyponatremia and the Syndrome of Inappropriate Antidiuretic Hormone (SIADH). As COVID-19 cases surged during the pandemic, hyponatremia among COVID-19 cases were reported, suggesting an increase in the incidence of SIADH. This study attempts to evaluate for potential causes of severe hyponatremia (HN) prior and during the COVID-19 pandemic.

Methods: Single center, observational retrospective study comparing severe HN (serum sodium 125 mEq/L or less) presenting to Westchester Medical Center Emergency room between 2019- 2022. Demographic variables, urine osmolarity (Uosm), urine sodium (UNa) were collected from EMR. COVID-19 infections were diagnosed by PCR. A total of 477 charts were reviewed. Patients were divided in two groups, severe HN without COVID-19 in the year of 2019 and those with COVID-19 between 2020 and 2022.

Results: 38 patients presented with severe HN and COVID-19 compared to 105 Non- COVID-19 patients in 2019. Complete urinary measurements were found in 26 COVID-19 patients & 66 Non-COVID-19 patients. 16 out of 26 COVID-19 patients preented with concentrated urine, Uosm >300. In patient with Uosm >300 Osm/kgH20 and UNa >20 Meq/L, 31% were COVID-19 positive and 24% Non-COVID -19, In patient with Uosm >300 and UNa < 20, 31% were COVID-19 positive compared to 33% Non COVID-19. Of those presenting with dilute urine Uosm <300, 38% were COVID-19 patients & 42% were Non-COVID-19 patients.

Conclusions: Severe Hyponatremia among COVID-19 and Non COVID-19 patients did not show a significant difference in etiology when comparing predictors Uosm and UNa. Despite other reports suggesting a higher incidence of SIADH, this was not evident in our severe HN COVID-19 patients.

SA-PO723

Prevalence of Hyponatremia in Dengue-Infected Patients: Relationship with Systemic Inflammation

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Background: Dengue infection is becoming more prevalent worldwide and is associated with systemic inflammation. Systemic Inflammation is associated with non-osmotic release of ADH. Purpose: To evaluate the prevalence of hyponatremia in newly infected patients and its relationship with systemic inflammation.

Methods: Cross-sectional study in 375 patients with newly diagnosed dengue infection at Hospital Posadas in Argentina. Diagnosis was confirmed by IgM serology or PCR. Hyponatremia was defined as serum sodium concentration <135 mEq/L.

Results: Hyponatremia was present in 30.13% of the patients at admission. In multivariate logistic regression model, the OR for hyponatremia adjusting for age and sex was significant in the patients over 65 years, OR 6.034 (IC95 2.652-13.728) p= 0.001. We also analyzed the relationship of hyponatremia with C-reactive Protein (CRP). In multivariate logistic regression model adjusted for age, sex and CRP, OR for hyponatremia was significant in the group of patients with elevated CRP, OR 3.37 (IC95 1.439-7.895) p= 0.005. We found a negative correlation between serum sodium and CRP (Spearman correlation coefficient rho= - 0.283; p=0.002).

Conclusions: 1: The prevalence of hyponatremia is high in newly infected patients with dengue; 2: Degree of hyponatremia correlated with severity of inflammation.

SA-PO724

A Case of Asymptomatic Isotonic Hyponatremia Following Transurethral Bladder Resection

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Introduction: Hyponatremia is a known, uncommon sequelae of transurethral resection (TUR) of the prostate or bladder. This is usually attributed to perioperative fluid absorption of glycine used during bladder irrigation. However, a less observed occurrence of hyponatremia related to this procedure is due to fluid absorption after a bladder perforation.

Case Description: We present an 85-year-old male who experienced gross hematuria and was found to have a bladder mass requiring TUR of the bladder. During this procedure, the patient underwent bladder irrigation with glycine 1.5% solution. Post operatively, the patient was initiated on continuous bladder irrigation (CBI) with normal saline solution. The morning of the surgery, his serum sodium level was 140 mEq/L. The post-procedure metabolic panel (drawn 12 hours after his TUR) was 130 mEq/L. This sodium was repeated 5 hours later, and was found to be 128mEq/L (Figure 1). Serum osmolality, urine osmolarity and urine sodium were 288 mosm/kg, 297 mosm/kg, and 132 mEq/L respectively. On physical exam, the patient was euvolemic, and had a tender but soft abdomen. These findings were consistent with isotonic, euvolemic hyponatremia. CT urethrogram was performed, which identified an anterior bladder perforation. CBI was discontinued, and he was started on a moderate fluid restriction. His serum sodium improved to 132mEq/L in about 20 hours (Figure 1).

Discussion: Bladder perforation is an uncommon cause of acute isotonic hyponatremia, due to the retention and reabsorption of urine. Transurethral resection of prostate tissue has historically been associated with isotonic hyponatremia due to intraoperative glycine administration and absorption. Our patient likely had a mixed picture, with both causes contributing to the sodium level. This case highlights the importance of ruling out bladder perforation when hyponatremia is found after a TUR procedure.

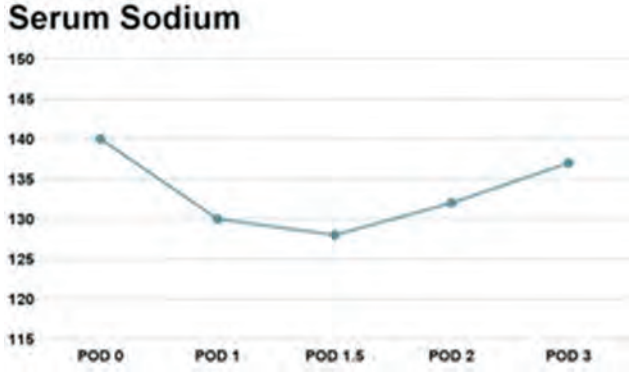

Figure 1: Serum Sodium (mEq/L) vs Postoperative Day (POD)

SA-PO725

Severe Hyponatremia Following Melphalan Use: An Important Recognition

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Introduction: Hyponatremia has been associated with adverse outcomes in various underlying diseases. In cancer patients, syndrome of inappropriate antidiuretic hormone (SIADH) has been a recognized complication of many chemotherapy agents. Melphalan has been reported to cause SIADH in the pediatric population. Still, no previous cases were reported in adults. Here we present a rare case of severe hyponatremia as a complication of melphalan chemotherapy.

Case Description: A 67-year-old female with a history of multiple myeloma achieving partial response on classical bortezomib regimen presented for an autologous stem cell transplant. The patient underwent a high dose of melphalan preconditioning regimen (200 mg/m2) 48 hours prior to the transplant. Serum sodium was 140 mmol/L before melphalan induction. The next day, the patient reported mild nausea. On the third day, serum sodium was 119 mmol/L repeatedly. Further workup showed serum osmolality of 253 mOsm/kg and normal renal function. Urine studies revealed a urine osmolality of 352 mOsm/kg and urine sodium of 41 mmol/L. No other associated symptoms were reported. The patient remained hemodynamically stable, and appeared euvolemic on the exam suggesting that SIADH as the etiology of hyponatremia. The decision was made to proceed with the transplant using only 1 L 0.9% Normal Saline for stem cell infusion. The repeat serum sodium level at 6 hours interval was 134 mmol/L, an increase of 15 mmol/l from the last measured level. Given this rapid correction was noted just after 48 hours of the development of hyponatremia, a re-lowering rescue strategy was applied with desmopressin and an infusion of dextrose 5% in water to avoid osmotic demyelination syndrome. The re-lowering strategy was stopped when serum sodium reached a level of 126 mmol/L, and the patient was then treated with fluid restriction (< 1 Liter/day) until serum sodium gradually increased to a normal level.

Discussion: Melphalan-induced SIADH is a rarely reported complication, particularly in adults. It has been hypothesized that alkylating agents, including melphalan, increase the release of anti-diuretic hormone, leading to hyponatremia. This case underlies the importance of monitoring sodium levels closely after melphalan infusion in adult cancer patients and avoiding high water and hypotonic fluids intake in patients receiving drugs that can trigger SIADH.

SA-PO726

Acute Peripartum Hyponatremia due to Oxytocin

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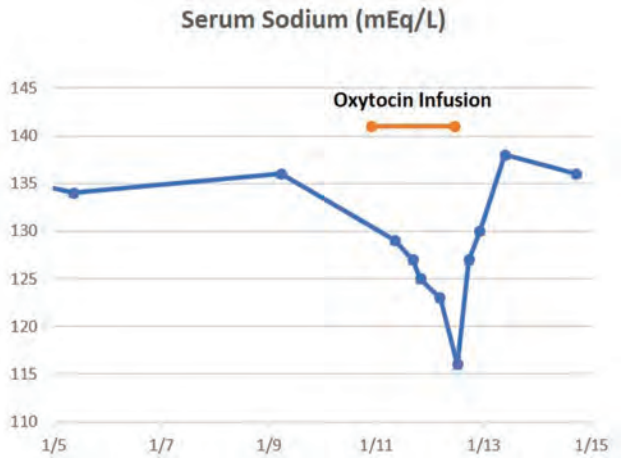
Introduction: Medication-induced hyponatremia is common in hospitalized patients. In addition, the physiology of pregnancy predisposes to hyponatremia. We present a case of oxytocin-induced peripartum hyponatremia.

Case Description: A 40-year-old woman with diabetes and hypertension is admitted for induction of labor at 34 weeks of pregnancy for preterm rupture of membranes. Admission serum sodium (Na) was 136 mEq/L. Oxytocin was given as an infusion over 36 h at a maximum rate of 0.034 units/min and followed by a bolus of 30 units IV for postpartum bleeding. The first Na level after oxytocin started was 129 [Figure]. At hour 30 of the infusion, Na dropped to 123 and then reached a nadir of 116 an hour after the oxytocin was discontinued. Urine studies revealed osmolality 227 mOsm/L and Na 68 mEq/L. Fluid intake was restricted, urine output increased to ≥700 mL/h for 6 h, and Na levels rapidly normalized over the next 20 h.

Discussion: Along with systemic vasodilation and arterial underfilling, pregnancy is characterized by a reset of the osmotic set point for antidiuretic hormone (ADH) release, predisposing to hyponatremia. Pregnancy-specific causes of hyponatremia include syndrome of inappropriate ADH from hyperemesis gravidarum, Sheehan syndrome, and oxytocin-induced hyponatremia. Oxytocin and ADH are cyclic nonapeptides that differ by only 2 amino acids and are synthesized by overlapping groups of neurons in the hypothalamic supraoptic and paraventricular nuclei. Both bind G protein-coupled receptors with significant overlap in affinity. This cross-reactivity gives oxytocin an ADH-like effect. While well described in the literature, oxytocin-induced hyponatremia is likely underrecognized. Nephrologists and obstetricians alike must be aware of this form of medication-induced hyponatremia, allowing for appropriate monitoring and prompt recognition to prevent the maternal and fetal morbidity associated with hyponatremia in pregnancy.



SA-PO727

A Rare Cause of Worsening Hyponatremia in Pulmonary SIADH

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Introduction: Primary adrenal insufficiency is a relatively rare entity with most cases in the United States secondary to auto-immune or genetic processes. Here we present a rare case of tuberculous adrenalitis presenting as worsening hyponatremia in a patient with SIADH.

Case Description: 50-year-old male from Mexico, with medical history of pulmonary tuberculosis and chronic hyponatremia (SIADH secondary to tuberculosis), presented with complaints of generalized weakness, nausea and vomiting for 4 days. Initial lab evaluation was significant for hyponatremia of 119. This was a significant change from patient's previous mild hyponatremia readings in 130s which had responded to salt tablets and fluid restriction in the past. This led to further investigation into the cause of this worsening hyponatremia not responsive now to salt tablets or fluid restriction. Labs were significant for low cortisol with no increase seen with ACTH stimulation test, suggestive of primary adrenal insufficiency, subsequently confirmed by high ACTH. Imaging revealed interval worsening of pulmonary tuberculosis with left upper lobe opacity, scattered patchy opacities and tree-in-bud nodularity in lingula, left lower lobe and right upper lobes. Bilateral adrenal hyperplasia and retroperitoneal adenopathy were noted on abdominal CT scan. Patient was re-started on RIPE therapy and hydrocortisone and fludrocortisone supplementation requiring higher doses due to RIPE. Patient's symptoms improved and sodium stabilized in 130s after therapy initiation.

Discussion: Adrenal insufficiency generally appears in tuberculosis cases after 90% glandular destruction. Most patients with active disease have bilateral adrenal enlargement seen on imaging and biopsy is generally not required in cases with evidence of extra-adrenal tuberculosis. This case was unique as there was clear evolution in the cause of hyponatremia with worsening infection. It also highlighted the importance of investigating worsening of chronic hyponatremia in patients with pulmonary tuberculosis. Lastly, it should be highlighted that even with treatment of the infection, adrenal function rarely seems to return to normal likely due to anatomical destruction of the gland, emphazing the importance of early detection and medication compliance in this disease.

SA-PO728

The Prevalence of Hyponatremia in the United States

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Background: Hyponatremia (serum sodium [corrected for hyperglycemia] < 135 mmol/L) is the most common electrolyte abnormality. Hyponatremia prevalence has been estimated in higher risk settings (e.g. 15% - 30% in hospitalized patients) using more recent data, while data regarding overall prevalence date back to surveys conducted prior to 2005. Using data from a nationally representative sample, we estimate the overall prevalence of hyponatremia in the US adult population using pooled data from population-based cross-section samples from 1999 – 2020, providing an analytic sample nearly 4-fold larger than used in previous estimates.

Methods: NHANES (National Health and Nutrition Examination Survey) produces national estimates that are representative of the total noninstitutionalized civilian US population. Typically conducted every 2 years, each cycle provides a nationally representative cross-sectional survey of approximately 10,000 persons, more than half of whom are adults providing serum samples. Multiple cycles can be combined to provide estimates with even greater precision. This study used pooled NHANES data from 1999 – 2020 (n = 55,731) to estimate the overall prevalence of hyponatremia across the general US adult population, as well as by gender and age subgroups. Observed data were used in the primary analyses, with missing data imputed in secondary analyses.

Results: Overall prevalence of hyponatremia in US adults is estimated to be 2.05%. As shown in the table, prevalence is higher in women ($p < 0.001$) and increases with age ($p < 0.001$). Based on US census data, it is estimated that in 2022, 5,944,024 US adults had hyponatremia. Secondary analyses based on imputed data showed very similar results.

Conclusions: Approximately 6 million US adults had hyponatremia in 2022, a prevalence of about 2%. Prevalence was higher in women and increased with age. As the population ages, the prevalence of hyponatremia in the US will likely increase.

Funding: Commercial Support - NephCentric

Prevalence of Hyponatremia by Age and Gender

Age Group	18 - 29	30 - 39	40 - 49	50 - 59	60 - 69	70 - 79	80 +	Total
Female	2.24%	2.35%	2.45%	2.16%	2.59%	4.60%	6.10%	2.53%
Male	0.59%	1.01%	1.61%	2.01%	2.35%	2.90%	5.12%	1.55%
Total	1.41%	1.69%	2.04%	2.09%	2.48%	3.85%	5.72%	2.05%

pooled NHANES data from 1999 - 2020

SA-PO729

Comparison of Local, Regional, and National Annual Trends of Hyponatremia Prevalence Rates in Hospitalized Patients

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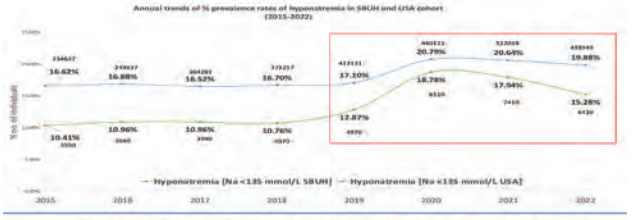
Background: Hyponatremia is the most common electrolyte abnormality among hospitalized patients. A high prevalence of hyponatremia among patients with COVID-19 has been reported in the literature. However, there is a paucity of data assessing hyponatremia's prevalence rates in the pre-and post-COVID-19 pandemic period.

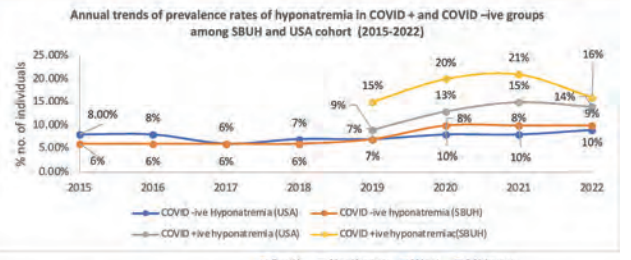
Methods: We used the TriNetX database (Stony Brook healthcare and the US-network (52 organizations)) to identify adults with hyponatremia (Na <135mmol/L) and normal-natremia (Na 135-145mmol/L) within the first 24hrs of inpatient or ED visit from Jan 1, 2015, to Dec 31, 2022.

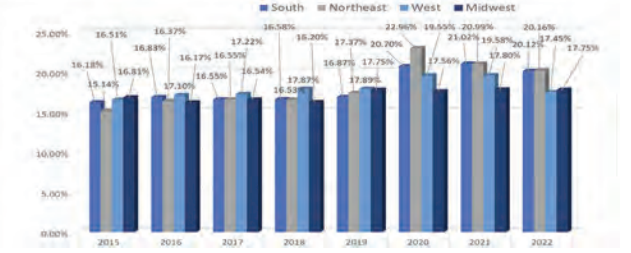
Results: Hyponatremia prevalence was 14% (40,570) in the SBUH cohort (298,130) and 19% (3,066,241) in the US cohort (16,395,015), respectively. Hyponatremia rates increased from 10% (4070) to 18% (6510) in the SBUH cohort, as compared to 16% (371,257) to 20% (460121) in the US cohort from 2019 to 2022. The rise of hyponatremia rates was 15% to 21% in SBUH in COVID +ive group compared to 7% to 10% in COVID -ive group from 2019 to 2021. Hyponatremia rates increased regionally from 2019 to 2022, with the highest rates of 22% and 20% noted among the Northeast and South regions in 2020. Hyponatremia among COVID-19 patients was associated with a significantly higher risk of ICU admissions, mechanical ventilation, and death.

Conclusions: Hyponatremia rates have been increasing locally, regionally, and nationally since 2019. Relatively higher prevalence rates were seen during the 2019-2021 period but were higher in both COVID-19 +ive and COVID-19 -ive groups, with a notably higher rise in hyponatremia rates among patients with COVID-19.

	COVID +ive Hyponatremia (Na <135) n(5030)	COVID+Normonatremia(Na 135-145 mmol/L) n(15,830)	Hazard ratio(CI)
Death	1030(20%)	1900(12%)	1.76(1.593 1.828) p < 0.001
Mechanical Ventilation	710(14%)	1340(8.4%)	1.6(1.531 1.1816) p < 0.003
ICU admissions	1570(31%)	2870(18%)	1.7(1.6,33 1.815) p <0.001







SA-PO730

Risk Factors of Under-Correction in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial

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Background: The under-correction of hyponatremia, non-optimal correction, is insufficient to improve cerebral edema, associated with increased mortality. Few prospective studies have identified the individuals at high risk of under-correction under controlled hypertonic saline treatment.

Methods: We conducted a post hoc analysis of a prospective randomized controlled study – the SALSA (Efficacy and Safety of Rapid Intermittent Correction Compared With Slow Continuous Correction With Hypertonic Saline) trial in 178 patients with glucose-corrected serum sodium (sNa) ≤125 mmol/L. Six subjects without sNa values during the entire follow-up period were excluded from the study. Under-correction was defined as sNa of less than 5 mmol/L within 24 hours or sNa of less than 10 mmol/L or 130 mmol/L within 24-48 hours.

Results: Mean age was 72.8 years old and mean sNa concentrations were 118.2 mmol/L. Over 48-hour intervention period, mean changes in sNa at 24 hours and 48 hours were 8.6 and 11.5 mmol/L, respectively. Twenty-six of 172 patients (15.1%) experienced under-correction (10 patients within 24 hours and 21 patients within 48 hours). The under-correction group received more amount of hypertonic saline (486 ml vs 932 ml, P <0.001) and had less urine output for 48 hours (4117 mL vs 2647 mL, P = 0.004). High levels of urine osmolality, serum calcium and creatinine and lower levels of body mass index, systolic blood pressure, uric acid, and albumin were associated with greater risk for under-correction. The etiologies of hyponatremia and infusion methods of hypertonic saline were not associated with under-correction.

Conclusions: Among patients with symptomatic severe hyponatremia under controlled hypertonic saline treatment, under-correction occurred in 15% and were associated with baseline patient's information.

SA-PO731

Response of Relowering Treatment and Clinical Significance in Severe Hyponatremia: A Post Hoc Analysis of the SALSA Trial

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Background: Relowering treatment has been performed in overly rapid correction of hyponatremia and its response may be numerous. However, few studies evaluated response of relowering therapy and its relationship to prognosis in patients with treating hyponatremia.

Methods: One hundred seventy-eight patients with glucose-corrected serum Na (sNa) ≤125 mmol/L were included. Eighty-seven out of 178 patients (in total 207 cases) underwent relowering treatment. Relowering regimen was 5% dextrose infusion of 10 ml/kg over 1hour if sNa level increase is ≥10 mmol/L or ≥18 mmol/L within 24 or 48 hours, respectively. Patients with concurrent desmopressin use or without sNa level after relowering were excluded. Eighty-seven patients (age 73.1 years, male 43.7%, and mean initial sNa 117.0 mmol/L) were classified into responder group (RG) (≥ 2 mmol/L) (34/87) and non-responder (NRG) (< 2mmol/L) (53/87) group according to decrease of sNa after relowering treatment. Overcorrection was defined as increase in the sNa level by >12/18 mmol/L within 24/48 hours.

Results: Mean of sNa at time of relowering treatment and delta sNa from initial sNa were 128.6 mmol/L and 11.7 mmol/L, respectively. Among 87 patients with relowering treatment, overcorrection occurred in 9/34 (26.5%) of RG and 27/53 (50.9%) of NRG (P = 0.024). Median value of sNa decreases by 1 mmol/L (interquartile -1 to 3 mmol/L) in total, 4 mmol/L (interquartile 3 to 6 mmol/L) in RG, 0 (interquartile -2 to 1 mmol/L) in NRG after treatment. Lower initial sNa level (adjusted odd ratio [OR] 0.86, P=0.008), lower initial potassium level (adjusted OR 0.28, P=0.003), NRG (adjusted OR 3.41, P=0.032) were associated with overcorrection.

Conclusions: Our findings indicate that a decrease in sNa levels less than 2 mmol/L following relowering therapy may predict overcorrection in hyponatremic patients treated with hypertonic saline.

SA-PO732

Use of Serum Osmolality to Guide Management of Severe Hyponatremia Outside of Detectable Range

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Introduction: Hyponatremia is common, and it is heterogeneous in its clinical presentation (ranging from mild and asymptomatic to critically low with severe symptoms, such as seizures). Competent management entails identifying the etiology and monitoring sodium closely to avoid overcorrection. Consequently, a challenge arises when the serum sodium is below measurable range for the lab. In such cases, it is more difficult to discern the starting sodium and therefore prevent overcorrection. This case demonstrates use of serum osmolality to estimate sodium in these cases.

Case Description: A 44-year-old male with a history of alcohol abuse was admitted to the hospital due to decompensated cirrhosis. He presented with jaundice, shortness of breath, and swelling in his lower extremities. Sodium on admission was < 106mg/dL, which is lower than the lower limit of calculation for the laboratory. Serum osmolality 219 mOsm/kg, urine Na <20 mmol/L, urine Cl <20 mmol/L, urine osmolality 413, BUN/Cr 7/0.66, serum alcohol level 113.7mg/dL. Despite receiving 3% hypertonic saline for 24 hours, his sodium continued to be below 106mg/dL, even on blood gas analysis. In order to determine the initial sodium level upon admission and the rate of correction, we used the following formula: serum osmolality = 2(Na) + BUN/2.8 + Glucose/18 + EtOH/3.7 (where 219 = 2x Na + other values). According to this formula, the estimated initial sodium level was 94 mg/dL, and subsequent measurements using this formula showed appropriate correction. The patient remained on 3% hypertonic saline for 48 hours, and two days later, his sodium level reached 107. At this point, the administration of 3% saline was discontinued, and the patient was given intravenous Lasix on a daily basis due to suspected hypervolemic hyponatremia in the context of liver cirrhosis. The sodium levels continued to improve slowly, reaching 140 on the eighth day of hospitalization.

Discussion: The patient in this case presented with critically low sodium below detectable range and severe symptoms, necessitating a precise plan of care for improving sodium promptly but also without overcorrecting. Using simple algebraic calculations involving the serum osmolality formula, the patient's sodium was reliably estimated. This guided sodium correction without any episodes of overcorrection in this already critically ill patient.

SA-PO733

Modified Formula to Predict a Change in Serum Sodium in Patient with Hyponatremia Requiring RRT

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Introduction: Hyponatremia is a common and feared electrolyte imbalance encountered, but rapid correction of sodium is what most physicians dread. In patients with hyponatremia requiring RRT, controlling the rate of sodium correction can be challenging & often requires the use of a hypotonic solution to dilute the dialysate. Here we present a case of a patient with hyponatremia pending liver transplant, who was started on CVVHD & rather than using a hypotonic solution we used a slower dialysate flow rate to prevent rapid correction of sodium.

Case Description: 39 year old male with decompensated cirrhosis presented with acute, asymptomatic hypervolemic hyponatremia. Initial labs showed S.Na 120, S.Osm 273, U.Osm 328, U. Na 49, BUN 74, Creatinine 2.36, CO2 17, normal TSH & cortisol. Despite fluid restriction, hypertonic saline, furosemide & tolvaptan, his sodium did not improve and fluctuated between 120-124. He also developed worsening renal failure needing initiation of CVVHD. To avoid overcorrection of sodium, the following modified formula was used to predict the rate of correction: [{**Dialysate Na** (140) - **Patient's Na** (120)} /**TBW** {0.6 X patient's weight(141)}] X **Dialysate flow Rate**(1L/hr) **= Rate of sodium correction** (~0.23mEq/L/hr) In our patient we used Qd (Dialysate flow Rate) as 1.5L/hr to get 0.35mEqL/hr as the rate of sodium correction His sodium corrected to 127 on day 1,131 on day 2 and plateaued at 134 on day 3.

Discussion: Rapid correction of hyponatremia in cirrhosis runs a higher risk of patients developing osmotic demyelination syndrome. On CVVHD there is a risk for rapid correction if adjustments like diluting the dialysate with a hypotonic solution to reduce the dialysate sodium, are not made. The above formula helps us adjust the dialysate flow rate so that we can predict the rate of sodium correction to be <8mEq/24hrs, thus preventing an overcorrection of hyponatremia. Various factors can affect the serum sodium in patients on CVVHD like IV infusions, insensible losses, etc. which explains why there wasn't an exact correction of sodium as predicted in this patient. However by setting an upper limit of sodium correction using a slower dialysate flow on CVVHD we could prevent overcorrection of hyponatremia. If predicted change in hourly serum sodium is higher, consider adding hypotonic solution to avoid overcorrection.

SA-PO734

Urea for the Treatment of Hyponatremia: A Two-Center Experience

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Background: Oral urea is an effective treatment for hyponatremia, especially in patients with the syndrome of inappropriate antidiuresis (SIAD). However, data are limited and no predictors for treatment response have been identified. Here, we report our two center experience on efficacy, safety and tolerability of oral urea to correct hyponatremia.

Methods: Retrospective study including hospitalized patients at the Erasmus Medical Center, The Netherlands and University Hospital Basel, Switzerland who received oral urea for hyponatremia (plasma sodium (pNa) <135 mmol/l) between August 2018 and September 2022. The primary outcome was the rise in pNa until discontinuation of urea and/or discharge. The secondary outcomes included the risk of overcorrection (rise in pNa >10 mmol/l in 24h) and urea discontinuation due to side effects. Linear regression analyses were performed to identify predictors for pNa rise.

Results: In 138 patients (median age 69, 53% males, 92% SIAD) 159 urea treatment episodes (median dose 30 g/d) were identified. Concomitant fluid restriction (median 1L/24h) was prescribed in 88%. Under urea, pNa rose from 127 mmol/L (IQR 123–129) to 134 mmol/L (IQR 131–136) in 4 days (IQR 2–7) and pNa normalization was achieved in 47% of the cases. Higher baseline pNa and more liberal fluid intake were associated with a lower pNa rise (-0.7 mmol/L, 95%CI -0.8 to -0.6 and -0.4 mmol/L, 95%CI -0.6

to -0.2, respectively). In contrast, longer treatment duration and higher estimated glomerular filtration rate (eGFR) were associated with a greater pNa rise (0.3 mmol/L, 95%CI 0.1 to 0.4 and 0.2 mmol/L, 95%CI 0.1 to 0.4, respectively). Patients who reached normalization were treated significantly longer than those who did not (median 6 vs 3 days). Overcorrection occurred in 6 patients (4%, rise 13 ± 2 mmol/L in 24h). Urea was discontinued in 12 patients (9%) due to poor palatability and/or gastro-intestinal symptoms. No treatment-related serious adverse events, including osmotic demyelination syndrome occurred.

Conclusions: In this largest cohort reported to date, oral urea effectively corrected hyponatremia with a relatively low rate of overcorrection and side-effects. Higher baseline pNa and more liberal fluid intake were associated with a lower pNa rise, whereas longer treatment and higher eGFR were associated with a greater pNa rise.

SA-PO735

Serum Osmolality Testing and Preserved GFR Are Associated with Improved 30-Day Mortality in Severely Hyponatremic Patients

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Background: Despite UK guidelines advocating paired osmolalities and urinary sodium, inadequate investigation of hyponatremia is common. Although many hospitals suggest serum osmolality as an initial test, it is unclear whether this approach improves outcomes. We have built a logistic regression model to explore the association between serum osmolality (sOsm) testing status and mortality in severely hyponatremic patients. We also examined renal function to identify if this conferred greater risk.

Methods: We analyzed sodium values on admission from 87,174 patients in a large UK tertiary hospital. We extracted U/E, measured osmolalities, age, and blood glucose. Since we wanted to isolate the effect of a sOsm test, it was important to control for its value. In the absence of a measured osmolality, we therefore derived a calculated osmolality using the first glucose and urea available within 24h. We validated this by regressing 753 measured and estimated osmolalities ($R2 = 0.6958$, $p < 0.001$). 30-day-mortality was modeled with covariates 'Sodium Result', 'sOsm value (calculated if measured not available)', 'age', 'GFR' and an interaction term identifying if testing was associated with improved mortality when sodium was <126meq/L.

Results: Testing for serum osmolality in patients with sodium values <126meq/L was associated with lower 30 day mortality (coefficient -1.527, $p<0.001$), as was preserved eGFR ($p<0.01$) and younger age ($p<0.001$). Of 1187 patients with Na+<126meq/L, just 39.4% received a sOsm test within 7 days of admission.

Conclusions: In this large hospital cohort, a low proportion of patients received a serum osmolality when severely hyponatremic. Performing serum osmolality testing is associated with lower 30 day mortality. Patients with impaired renal function were at increased risk. Not being able to identify patients who were admitted for palliation or identifying further clinical predictors of mortality were important limitations. This is the first large study where sOsm has been calculated in place of a measured value to model the impact of the test itself on outcomes, a technique which could be used on other datasets. The results of this analysis have led to the adoption of an electronic alert to prompt sOsm testing, the impact of which will be measured in 3 monthly intervals.

SA-PO736

Chronic Hyponatremia Is Independently Associated with Mortality at Each Stage of CKD

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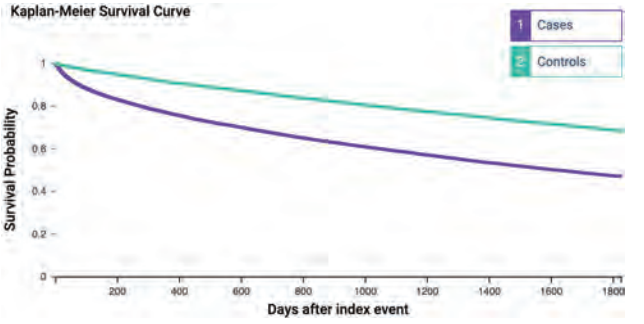
Background: Prior studies have shown hyponatremia is associated with mortality among patients with CKD. What is not clear is whether or not hyponatremia is a marker of underlying disease severity or if hyponatremia is associated with mortality independent of the severity of the underlying CKD and other comorbid conditions. The objective of this study is to determine if chronic hyponatremia (> 90 days duration) is independently associated with mortality and secondary outcomes at all stages of CKD.

Methods: All adult patients with CKD with chronic hyponatremia (cases) and without chronic hyponatremia (controls) between 2012 and 2018 were eligible for inclusion. The groups were matched for demographics and CKD stage using propensity scores. TriNetX research network was used to identify cohorts. The follow-up time was 5 years after CKD diagnosis. Primary outcome was mortality. Secondary outcomes were cerebrovascular, cardiovascular, infectious, thrombotic and neurodegenerative outcomes. All outcomes were analyzed as time to event using Kaplan-Meier analysis and summarized as hazard ratios. Subgroup analysis was performed for each CKD stage.

Results: The analysis included 25,944 cases and 25,944 matched controls. The mean age for cases was 66.3 (SD 15.8) and 65.9 (SD 16) years in controls. Patients in the cases group had higher chances of death (HR: 2.11, 95% CI: 2.05-2.18, $p<0.001$), stroke (HR: 1.92, 95% CI: 1.82-2.02, $p<0.001$), sepsis (HR: 4.17, 95% CI: 3.99-4.36, $p<0.001$), ischemic heart disease (HR: 1.7, 95% CI: 1.65-1.74, $p<0.001$), myocardial infarction (HR: 2.42, 95% CI: 2.31-2.54, $p<0.001$), CHF (HR: 2.32, 95% CI: 2.24-2.41, $p<0.001$), pneumonia (HR: 2.29, 95% CI: 2.20-2.37, $p<0.001$), cellulitis (HR: 2.06, 95% CI: 1.92-2.14, $p<0.001$), PE (HR: 2.09, 95% CI: 1.92-2.27, $p<0.001$) and dementia (HR: 1.66, 95% CI: 1.56-1.76, $p=0.005$). Subgroup analyses indicated consistent trends in each CKD stage.

Conclusions: At each of stages of CKD, 1 and 2 collectively, 3, 4 and 5, chronic hyponatremia is independently associated with morbidity and mortality.



SA-PO737

Overcorrection in the Management of Hyponatremic Patients [Na+] ≤125 mmol/L Following Emergency Department Admission

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Background: Hyponatremia (HN) is the most common electrolyte abnormality. Treatment of a low serum sodium [Na^+] level needs to be gradual to avoid overcorrection (OCx). We studied patients who were overcorrected and why.

Methods: Patients admitted to Westchester Medical Center via the Emergency Department from 2019 - 2022 with [Na^+] ≤125 mmol/L were included. An OCx is defined as a [Na^+] correction > 8 mmol/L in 24 hours. Slowing or reversing the OCx is considered a reversal. The use of hypertonic saline (HTS), serum and urine osmolarity (UOs), urine sodium, and the duration were recorded.

Results: 477 patients were studied per the inclusion-exclusion criteria. 43% were on HN-associated medications averaging 1.83 (+/- 0.89) per patient with loop diuretics the most common. Cirrhosis was the most common HN-associated chronic disease, and renal consultation was requested in 58% (275/477). OCx occurred in 89 (19%) of patients, with a higher odds ratio (OR) in patients with UOs<300 (OR 3.9) and in whom HTS was administered (OR 4.5). Psychoactive medications were more common in OCx versus diuretics (27 vs 8%) and chronic diseases less likely in OCx (31.5 vs 60%). The rate of OCx was 9.2 +/- 6.1mmol/L in 24 hours. Reversal of treatment was seen in 50% of OCx and risk was increased in patients with UOs <300 (OR 4.3) and HTS (OR 9.4).

Conclusions: OCx is associated with predictors UOs and HTS. Patients presenting with Na<125, on psychoactive medications, and lacking HN-associated chronic diseases should prompt an immediate renal consult to adequately assess HN physiology, underscore the need for UOs, and assess the selection of empiric fluids. While many of these findings are in general associated with HN, this study also highlights their association with OCx.

Table 1: Baseline Characteristics

	Total population (n=477)	OCx (n=89)
Males	254 (53%)	39 (44%)
Average age (years)	62.74 (+/- 16.04)	61.52(+/-16.83)
Patients on any HN-inducing Medication*	203 (43%)	40(45%)
Loop Diuretic	158 (33%)	7(8%)
Thiazide Diuretic	50 (10%)	13(15%)
Psychoactive Medication	86 (18%)	24 (27%)
Kidney Disease	86 (18%)	14(16%)
Liver Cirrhosis	137 (29%)	10(11%)
Congestive Heart Failure	64 (13%)	4(4%)

Table 2: Total Adequate Correction vs Overcorrection

	Adequate Correction (n=388)	Overcorrection (n=89)	p-value
Average Initial Sodium (mmol/L)	121.68 (+/- 3.82)	118.94 (+/- 4.33)	**<.001**
Empiric IV Fluids	209 (54%)	68 (76%)	**<.001**
Hypertonic Saline	16 (4%)	18 (20%)	**<.001**
Renal Consult	215 (55%)	60 (67%)	**0.038**
Average Time to Renal Consult (hours)	25.12 (+/- 45.36)	13.51 (+/- 17.25)	0.065
Full Lab Workup	121 (31%)	40 (45%)	**0.013**
Average Time to Workup (hours)	24.28 (+/- 54.28)	14.09 (+/- 37.92)	**0.019**
Urine Osmolarity < 300 mmol/L*	90 (36%)	45 (68%)	**<.001**
Length of Stay (days)	12.13 (+/- 13.30)	9.98 (+/- 14.89)	0.058

SA-PO738

Use of Copeptin to Diagnose Nephrogenic Diabetes Insipidus Secondary to Hypercalcemia

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Introduction: Diabetes insipidus (DI) is a condition characterized by polyuria caused by inadequate antidiuretic diuretic hormone (ADH) activity. Differentiating between central and nephrogenic DI is usually accomplished by an indirect water deprivation test, which is effective, however inconsistencies in sample collecting can confound results. An emerging method of determining the etiology of DI is through the measurement of Copeptin, a moiety which is cleaved off the pro-ADH molecule and is a surrogate marker for ADH levels. Here, we discuss a case of a nephrogenic DI, in which a Copeptin level was used to assist in diagnosis.

Case Description: A 23-year-old woman presented to the hospital with abdominal pain and vomiting. She was found to have necrotizing pancreatitis and a calcium of 16 mg/dL. She was treated with IV fluids, calcitonin and zoledronic acid. An ultrasound and sestamibi scan revealed a parathyroid adenoma. The patient then developed hypernatremia up to 167 mmol/L with urine osmolality of 130 mosmol/kg, despite daily fluid resuscitation. Workup for differentiating central from nephrogenic DI included TSH, cortisol, MRI brain which were unrevealing. The patient had no response to DDAVP 0.1 mcg or 2 mcg subcutaneously. However, with a higher dose of 4 mcg, the urine osmolality increased to 307mosmol/kg and sodium decreased by 2 mmol/L. Given the incomplete response to DDAVP, nephrogenic DI was diagnosed and treated with a thiazide diuretic and D5W until her sodium normalized. Copeptin levels returned at more than double the upper limit of normal, confirming the diagnosis of nephrogenic DI. This further confirmed hypercalcemia as the culprit and parathyroidectomy was planned after discharge.

Discussion: Copeptin can be a useful tool in differentiating nephrogenic DI from central DI. Response to DDAVP or water deprivation tests are widely used, however in our patient, as in many cases, the results were difficult to interpret as the lab collection times and urine output measurements were inconsistent. An elevated copeptin level provided a simplified way to assess the patient's level of ADH and confirm the diagnosis of nephrogenic DI. ADH is an unstable molecule and degrades quickly, thus cannot easily be measured directly. However, copeptin is a stable, surrogate marker for ADH levels and can be measured alone or in combination with water deprivation.

SA-PO739

From Shock to Sprinklers: A Rare Case of Polyuria in the ICU

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Introduction: Arginine vasopressin deficiency (AVD), previously known as central diabetes insipidus, is most commonly idiopathic, a result of a tumor, neurosurgery, or trauma. Here, we present a case of massive polyuria caused by transient vasopressin deficiency in an ICU patient after discontinuation of therapeutic vasopressin used for septic shock.

Case Description: A 56-year-old man with a history of COPD, AIDS, R ear Squamous Cell Carcinoma, was admitted for COPD exacerbation. His course was complicated by respiratory failure requiring mechanical ventilation and septic shock due to R ear infection, managed with vasopressin. When stopped after two days, urine output went from an average of 1.5 to a peak of 8.2 L/day, associated with serum sodium rise from 130 to a peak of 148 mmol/L. Urine osmolality reached a nadir of 57 mOsm/kg and serum copeptin level was 3 pmol/L. Concerned for AVD, IV vasopressin was restarted and desmopressin was trialed, both resulting in resolution of polyuria, urine osmolality peaking at 547 mOsm/kg, and normalization of serum sodium. Oral desmopressin was initiated. ACTH, AM Cortisol, LH, TSH and prolactin levels were normal. Brain MRI did not reveal structural abnormalities. After eight days of serum sodium 135-145 mmol/L and urine output 2-3L/day, desmopressin was tapered off and patient was discharged. Sodium levels off desmopressin 12 days later were stable. Further review of his chart revealed a similar presentation following cessation of vasopressin during a hospitalization for septic shock five years prior, resolving without intervention.

Discussion: Vasopressin is released by the posterior pituitary gland in response to thirst, hyperosmolality, and hypotension. Analogs are used to treat catecholamine-resistant shock, and abrupt cessation has been reported to lead to transient AVD. Neurosurgical and cardiothoracic surgical patients have been reported to be at risk. We present a case of AVD in sepsis. Prior case series have proposed downregulation of V2 receptors as a mechanism for the polyuria and hypernatremia, however, a low normal copeptin level in the face of hypernatremia suggests that suppression of endogenous arginine vasopressin is a more likely process. Given the recurrent nature of AVD in this patient, future research is needed to identify predisposing factors.

SA-PO740

Unintended Consequences: Severe Hypernatremia and Metabolic Alkalosis Following Baking Soda Ingestion for Urine Drug Screen Evasion

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Introduction: Baking soda, also known as sodium bicarbonate, has various uses such as cleaning and treating conditions like metabolic acidosis and acid reflux. However, baking soda overdose can lead to fatal adverse events. We report a case of severe hypernatremia caused by intentional abuse of sodium bicarbonate to alter a urine drug screening (UDS) test result.

Case Description: We report a case of an individual found unconscious in a courthouse restroom. Initial findings revealed hypoglycemia to 55mg/dL and seizure activity upon EMS arrival. The patient was encephalopathic, prompting intubation. Formal laboratory tests showed critical hypernatremia, hypokalemia and metabolic alkalosis with Na>180, K=2.4, Cl=111, CO2>50, pH in blood gas=7.56. Further information was obtained from the patient's mother, revealing that the patient likely ingested baking soda with water before the UDS in an attempt to manipulate the test results. Interestingly, the initial UDS on admission returned negative for methamphetamine, but a repeat test done two days later resulted positive. The nursing staff also found white powder in the patient's bag. After mixing the powder with vinegar, bubbles were observed, raising suspicion of a baking soda ingestion. Sodium correction using D5W and LR, was initiated along with antiepileptic drugs in conjunction with serial lab monitoring to ensure that sodium levels were appropriately lowered. Unfortunately, the patient deteriorated further with development cerebral edema and brain herniation.

Discussion: Metabolic alkalosis occurs from an accumulation of $HCO3^-$ or an inability to eliminate excess $HCO3^-$. This case involved a patient with severe hypernatremia and metabolic alkalosis due to exogenous alkali intake from baking soda, presenting with seizures and encephalopathy. The initial blood gas indicated an acute metabolic alkalosis with respiratory compensation. Cytotoxicity resulting from seizure and fluid shifts from rapid changes in sodium levels can explain the cerebral edema. Notably, a simple test demonstrating the reaction between vinegar and baking soda can be done to confirm the substance and may change the clinical course.

SA-PO741

A Man with Serum [Na] 163 mM Who Is Not Thirsty

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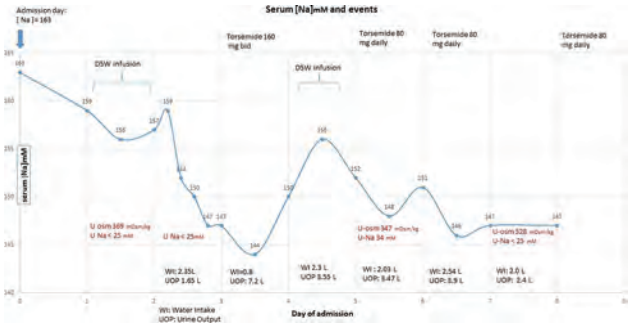
Introduction: Lack of thirst sensation is a rare cause of hypertonicity, as thirst is the main defense to maintain isotonicity and normal intracellular volume. Hypertonicity is sensed by osmoreceptor cells, which control thirst and ADH release. The ability to sense/act on thirst is both necessary and sufficient to prevent dehydration, with ADH playing a supportive role by increasing the kidney water absorbtion. We present a case of a patient who developed hypertonicity due to an acquired injury resulting in defects in both thirst (resulting in hypodipsia) and ADH release (resulting in reduced water retention).

Case Description: A 60-year-old man with a history of CHF, DM, HTN and CKD ([Cr] 1.5 mg/dL) was admitted for cardiogenic shock. He was managed with diuresis and discharged with Torsemide and water/salt restrictions. During the admission, [Na] increased from 132 to 154 mM. Four days after discharge, he was re-admitted when follow-up laboratory tests showing serum [Na] of 163 mM and urine osmolality of only 369 mOsm/L. Surprisingly, he did not complain of thirst. He was treated with D5W, reduced Torsemide dose, and daily water consumption of ~ 2.5 L. Within two days, serum [Na] corrected to 144 mM. CT head did not show a brain lesion (cardiac defibrillator precluded MRI). A transient resumption of Torsemide and liberation of water consumption led to an immediate worsening of hypernatremia. He was discharged with serum [Na] of 147 mM and instructions to keep strict water intake of ~3 L per day. To date, the patient is isotonic.

Discussion: Our patient developed severe hypernatremia, which—although initially promoted by water restriction and Torsemide—was maintained by a remarkable lack of thirst sensation and urine concentration defect. Most of the patients with this rare condition, are young and have an identified CNS etiology (e.g. tumor), whereas our patient was 60 years old without a brain lesion. We conclude that our patient developed hypertonicity due to a rare combination of lack of thirst (hypodipsia) and partial arginine vasopressin deficiency and was treated successfully with an increased water intake.



SA-PO742

Unusual Polydipsia-Polyuria Syndrome, Hypernatremia, and Hypercopeptinemia: What Is the Diagnosis?

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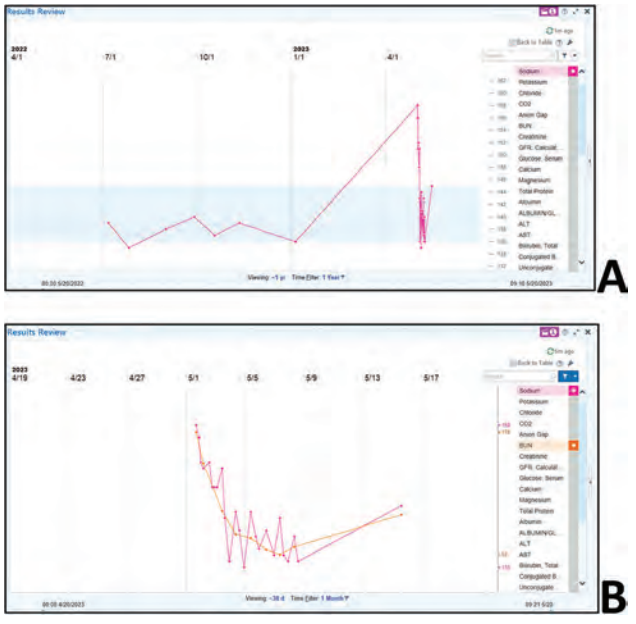
Introduction: Polydipsia-Polyuria Syndrome (PPS) can represent central diabetes insipidus (DI), nephrogenic DI or primary polydipsia (PP). Correct differentiation is crucial; Copeptin assay is useful. We describe PPS, hypernatremia, and hypercopeptinemia: Is this a new syndrome?

Case Description: A 76-yo female with Alzheimers disease was evaluated for dizziness, fatigue, incessant thirst, and chest pain. She was drinking excessively even from public faucets and had increased very wet diapers. The daughter restricted water intake at home. Vitals signs were stable. Physical examination was unremarkable. Sodium was 158 mmol/L, BUN 178 mg/dL, creatinine higher at 1.46 mg/dL, BNP 2000 pg/mL. Chest radiograph and non-contrast head CT were non-diagnostic. She received IV D5W and drank to thirst. Sodium normalized (Figure A). BUN trajectory was a near mirror image of Na trajectory (B). Incessant thirst persisted. Copeptin was 79.7 (<13.1) pmol/L. She was discharged with a diagnosis of PP and a Psychiatry referral.

Discussion: Does our patient have partial nephrogenic DI from AKI, drug-induced SIADH (?Sertraline), and/or PP, or a combination thereof? Hypernatremia on admission probably reflected true water deficit following forced restriction of water intake at home by the daughter in the few days preceding the admission. Follow up would require a delicate balance of controlled water intake. Psychiatry management of suspected PP could include behavioral therapy, health education, relaxation techniques and positive reinforcement. Her dementia could be a barrier. Recent evidence supports a role for GLP-1 agonists in PP. Several unanswered diagnostic and therapeutic questions around PPS remain and call for further research.



Na and BUN trajectories

SA-PO743

Identification and Characterization of a Novel CASR Mutation Causing Familial Hypocalciuric Hypercalcemia

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Background: Although familial hypocalciuric hypercalcemia type 1 (FHH1) is primarily caused by monoallelic mutation in calcium-sensing receptor (*CASR*) gene, the characterization of the newly-identified CaSR mutation linked to clinical response to calcimimetics remains limited.

Methods: A 45-year-old male presenting with hypercalcemia, hypocalciuria, and inappropriately high parathyroid hormone (PTH) had a good response to cinacalcet (total serum calcium from 12.5 to 10.1 mg/dl). Sanger sequencing of *CASR*, *GNA11*, and *AP2S1* genes was performed in this family. The simulation model was used to predict the function of the identified mutant. The *in vitro* studies including immunoblotting, immunofluorescence, cycloheximide chase study, Calbryte™ 520 calcium (Ca^{2+}) detection, and half-maximal effective concentration (EC50) were examined.

Results: The patient was identified to carry a *de novo* heterozygous *CASR I554N* mutation, located in the cysteine-rich domain (residues 542–612) crucial to affect the ligands (Ca^{2+}) binding. This missense mutation was pathogenic based on the different software prediction models and ACGME criteria. The simulation model showed *CASR I554N* mutation decreased its binding energy with Ca^{2+}. Human *CASR I554N* mutation attenuated the stability of CASR protein, reduced the expression of p-ERK 1/2, and blunted the intracellular Ca^{2+} response to gradient extracellular Ca^{2+} (eCa^{2+}) concentration. EC50 study also showed calcimimetics rescued the function of *CASR I554N* mutation.

Conclusions: This novel *CASR I554N* mutation decreases CASR stability and its binding affinity with Ca^{2+}. Its correction of blunt response to eCa^{2+} by calcimimetics may support the therapeutic effect of cinacalcet for this patient.

Funding: Government Support - Non-U.S.

SA-PO744

Combined Consideration of Sex, Genotype, and Total Liver Volume Progression Determines the Risk of Hospitalization in an International Multicenter Cohort of Autosomal Dominant Polycystic Liver Disease

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Background: Autosomal dominant polycystic liver disease (ADPLD) is a rare disease with female preponderance, majorly based on pathogenic variants in PRKCSH or SEC63. Clinically, ADPLD is characterized by vast heterogeneity ranging from asymptomatic courses to highly symptomatic hepatomegaly. Little is known to predict disease progression at early stages hindering clinical management and genetic counselling. By establishing genotype-phenotype correlations, this study aims to improve disease prognostication in ADPLD.

Methods: We analyzed an international cohort from ten tertiary centers with 265 ADPLD patients harboring pathogenic variants in PRKCSH or SEC63. Genotypes were correlated with in-depth phenotypic data including normalized age-adjusted liver volume (nTLV) and PLD-related hospitalization (liver event).

Results: 185 (70%) patients with ADPLD-PRKCSH and 80 (30%) patients with ADPLD-SEC63 were included (76% females). Classifying individual nTLV into predefined, age-adjusted progression groups yielded predictive risk discrimination for future liver events independent of sex and genetic defect **(Fig. 1A)**. Additionally, severe disease in terms of onset of liver events was more likely in patients with PRKCSH variants as compared to those with SEC63 variants **(Fig. 1B-C)**. A newly developed clinical score consisting of basic genotype and patient sex was able to discern mild courses from moderate and severe disease.

Conclusions: Both imaging and clinical genetic scoring have the potential to inform ADPLD-patients on their risk of developing symptomatic disease. Hereby, the combination of female sex, PRKCSH-disease, and rapid progression of hepatomegaly is associated with the greatest odds of PLD-related hospitalization.

Funding: Government Support - Non-U.S.

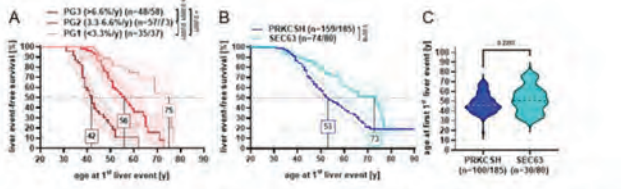

Fig. 1 (A) Risk classification for liver events stratified into age-adjusted progression groups (PG) defined by differential yearly change in normalized total liver volume (nTLV) (<3.3%/year – mild PG1 in pink; > 3.3 – 6.6%/year – moderate PG2 in red; >6.6%/year –severe PG3 brown). Liver event-free survival showed significant discrimination for all groups (median age 42 yrs (PG3) versus 56 yrs (PG2) versus 75 yrs (PG1). **(B)** Survival analysis stratified by basic genotype shows an increased likelihood of experiencing symptomatic liver events in *PRKCSH* individuals compared to *SEC63* individuals (median age 53yrs vs. 73yrs,, p<0.0018). **(C)** Comparison of symptomatic disease cases only did not yield significant differences in age at event (46yrs for *PRKCSH*- versus 50 yrs for *SEC63*-alteration, p=0.22).

SA-PO745

Outcomes of Foam Sclerotherapy for Large Kidney/Liver Cysts using Multi-Stage (Same/Next Day) and Multiple Sequential Procedures

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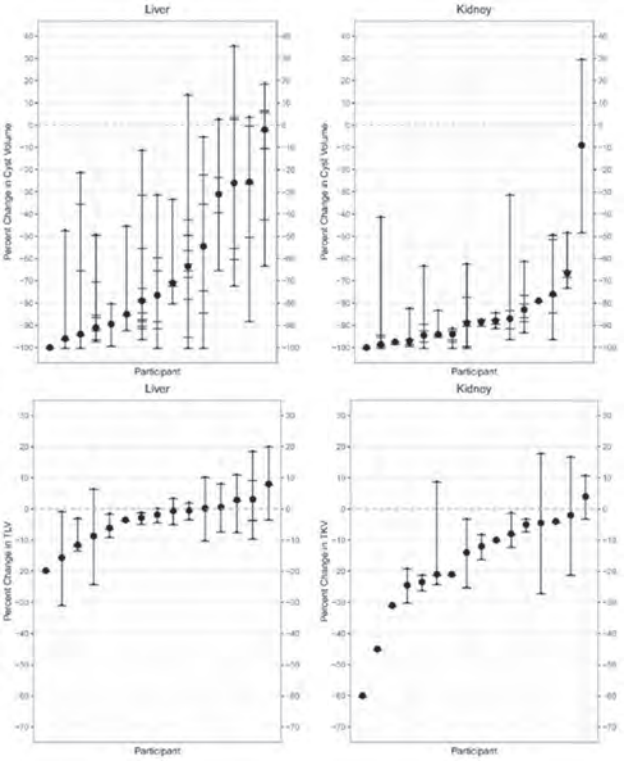
Background: We have been performing sotradecol foam sclerotherapy (SFS) outpatient procedures to ablate liver/kidney cysts. SFS has led to substantial reductions in Targeted Kidney & Liver Cyst (TKCV/TLCVs), total kidney/liver volumes (TKV/TLV), improved QOL, & augments cyst volume reduction in addition to tolvaptan (kidney cysts) & octreotide (liver cysts). We examined efficacy in individuals with multiple large cysts who opt to undergo multiple or multi-stage SFS (same day or 2 consecutive days).

Methods: Kidneys & liver were segmented using a deep-learning algorithm & cysts segmented using semi-automated segmentation software, pre & 4+ mo post SFS. Wilcoxon tests assessed %Δ pre/post SFS. Median % Δ TKCV/TLCVs were calculated (per-patient) by taking median %Δ of targeted cysts within patient & compared to outcomes from single stage cyst procedures.

Results: For **multiple liver procedures**,(n=15) median Δ% TKCV/TLCVs was -76.5% [IQR, -90.3%, -42.8%, P<0.001] & ΔTLV % -1.9% [IQR, -7.4%, 0.42%, P=0.11] (**Fig 1**). For patients undergoing **multiple kidney procedures** (n=16), median % ΔTKCV was -88.8% [IQR, -95.1%, -82.0%, P<0.001] & Δ% TKV -13% [IQR, -23.8%, -4.9%, P<0.001]. Only 5 had **multi-stage liver procedures;** median Δ% TLCV post SFS -73% [IQR, -93%, -71%, P=0.06], & only 2 underwent **multi-stage kidney procedures**; median Δ% TKCV -52%[IQR, -73.5%, -31%, P=0.5].

Conclusions: Multiple SFS procedures led to substantial reductions in TKCV/TLCV/TKV/TLV; data on patients who underwent multi-stage procedures were sparse, but still demonstrated positive results. SFS is feasible & convenient for patients seeking ablation of multiple cysts in a single 1 or 2 day session. Multiple & multi-stage SFS appear to be effective for patients with high cyst burden mainly due to a limited number of large cysts, with good patient satisfaction.

Funding: NIDDK Support, Private Foundation Support



Percent Change in Targeted Cyst Volumes, Liver & Kidney Volumes.Black bars: % Δ of each cyst. Black dots: median % Δwithin each participant. Dashed line: 0% change.

SA-PO746

The Clinicopathologic and Genetic Characteristics of Autosomal Recessive Polycystic Kidney Disease Presenting in Adulthood

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Background: Autosomal recessive polycystic kidney disease (ARPKD) is a rare ciliopathy that causes massively enlarged kidneys and pulmonary hypoplasia in perinatal children, frequently leading to fetal demise. In the survivors, ductal plate malformation often causes congenital hepatic fibrosis and Caroli disease. However, the spectrum of presentation and disease varies considerably.

Methods: We examined the clinicopathologic characteristics of *PKHD1*-defined ARPKD. Genetic testing was performed using whole exome sequencing.

Results: Three unrelated families (4 adult individuals) were identified to harbor disease-causing *PKHD1* variants sequenced by the Irish Kidney Gene Project. The average age of initial presentation was 16.5 ± 18.6 years. In family (1), we identified biallelic *PKHD1* variants (NM_138694.4: c.2702A>C;p.N901T & c.107C>T;p.T36M) in a female patient with congenital hepatic fibrosis and non-enlarged cystic kidneys, during the evaluation of elevated creatinine. She had gradually progressed into ESKF at 53 years of age. In family (2), the renal-limited phenotype of PKD was identified in two siblings. No liver involvement was identified. The two siblings detected a homozygous missense variant in the *PKHD1* gene, NM_138694.4: c.5221G>A;p.V1741M. Patients progressed to ESKF at ages 36 and 40 years, respectively. In family (3), the index patient presented with predominant hepatic phenotype - recurrent cholangitis, portal hypertension, and Caroli disease at clinical disease-onset aged 48 years. A liver biopsy was performed and demonstrated marked liver fibrosis with numerous multifocal cystic dilatation of intrahepatic ducts. She was found to have multiple small bilateral kidney cortical cysts with impaired function. At the last assessment, aged 61 years, she developed slowly progressive kidney insufficiency, with a serum creatinine of 201 μmol/L and creatinine clearance of 23 ml/min about 15 years after her presentation. Exome-sequencing revealed pathogenic biallelic *PKHD1* variants (NM_138694.4; c.8068T>C; p.W2690R and c.338delG; p.G113Dfs*4).

Conclusions: While ARPKD is remarked with early-onset and high disease mortality, these cases illustrate disease heterogeneity, and *PKHD1*-defined ARPKD is not merely a pediatric disease.

SA-PO747

An Updated Analysis of the Irish Kidney Gene Project Registry

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Background: Over 700 genes have been implicated in monogenic nephropathies (MN), a significant cause of chronic kidney disease (CKD), but their prevalence is often underestimated. Diagnosing MN can personalize clinical management with better-informed choices of therapies and targeted disease surveillance and influence prognosis and genetic counseling for patients and their families. Herein, we provide an update on the diagnostic yield of various technologies (exome sequencing, targeted gene panel, and *MUC-1* sequencing) and immunostaining utilized by the Irish Kidney Gene Project (IKGP).

Methods: All results from the multidisciplinary genetic kidney clinic between January 2014 and March 2023 were analyzed in this prospective cohort study. All clinic visit records were analyzed for clinical and genetic factors associated with solved cases. Using the guidelines of the American College of Medical Genetics and Genomics, pathogenic or likely pathogenic variants were evaluated as disease-causing.

Results: Through the IKGP, 593 families (976 individuals) had been sequenced, of which 49.4% (482/976) were female. At the last follow-up, 58.5% of patients, with an average age of 42.3 ± 16.5 years, had reached end-stage kidney disease. We were able to demonstrate a likely-pathogenic/pathogenic variant in 47.4% (281/593) of families, encompassing 52 distinct monogenic entities. Three phenotypes accounted for up to 82% of positive results in genes related to autosomal dominant polycystic kidney disease (*PKD1* (number for families (*n*)=155), *PKD2* (*n*=23), *IFT140* (*n*=4)), autosomal dominant tubulointerstitial kidney disease (*UMOD* (*n*=8), *MUC1* (*n*=10), *HNF1B* (n=2), and *DNAJB11* (n=1)), and COL4A-related phenotypes (*COL4A5* (*n*=20), monoallelic *COL4A4* (*n*=1), *COL4A3* (monoallelic *n*=5; biallelic n=3)). Disease-causing variants identified in the remaining 42 genes comprised 17.4% of the solved families. In 31.1% (*n*=24) of the 77 families referred with *a priori* diagnosis of CKD of undetermined cause were found to have a known monogenic cause.

Conclusions: The use of broad genomic strategies had a high success rate, especially in the presence of family history.

SA-PO748

Incompletely Penetrant Variants Underlie the Familial Variability in Disease Progression in Adults with ADPKD

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Background: Although familial variability is one of the most prominent characteristics of autosomal dominant polycystic kidney disease (ADPKD), its molecular causes remain unknown. We hypothesize that co-inheritance of additional *PKD1* or *PKD2* variants with a pathogenic inactivating variant may contribute to familial disease progression.

Methods: Family members with clinically diagnosed polycystic kidney disease were recruited. Primary disease-causing variants were identified using ADPKD targeted next-generation sequencing panel. Additional variants (AV) were investigated using the criteria listed below: 1) rare (allele frequency <0.01), 2) missense variants in exonic or splicing regions, and 3) SIFT and PolyPhen predicted to be detrimental to protein formation variants were included. All AVs were deemed as variants of uncertain significance. We compared the progression to end-stage kidney failure (ESKF) between families with AV (at least one member with an additional ADPKD variant per family) and families with only primary variants.

Results: A total of 115 families with ADPKD (338 individuals, 55.9% female, 53.8% progressed to ESKF) were included; 60 different truncating *PKD1* variants, 37 non-truncating *PKD1* changes, and 7 *PKD2* variants. 31 (26.9%) families (52 individuals) had at least one patient with AV. Among these families, those with non-truncating *PKD1* variants and AV had a lower mean age of ESKF than in families without additional variants (46 ± 10.1 vs. 52.35 ± 11.6, $p = 0.041$). The mean age of ESKF was not different between families with truncating *PKD1* and *PKD2* variants based on AV, 47.8 ± 8.4 vs. 47.3 ± 9.2 and 61.5 ± 3.5 vs. 67.3 ± 11.6, respectively. In a multivariate Cox mixed-effects model (adjusted for sex, early-onset of hypertension, early-onset urological events, and primary ADPKD variants), we identified an independent effect of the additional variants on familial disease progression [multivariate shared frailty model $p = 0.0015$].

Conclusions: Our findings suggest that familial variability in ADPKD may be explained by co-inheritance of additional damaging variants, particularly in families with *PKD1* non-truncating variants.

SA-PO749

ADPKD Comorbid Conditions at a PKD-Focused Center

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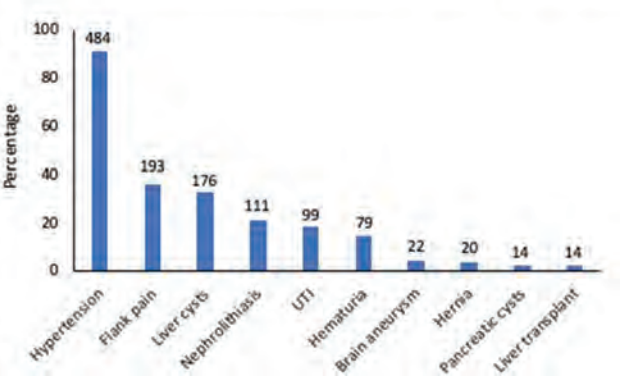
Background: We are a center providing multidisciplinary care to patients with autosomal dominant polycystic kidney disease (ADPKD). We sought to evaluate the prevalence of common co-morbid conditions in our patient population.

Methods: We used the Epic Systems electronic medical record (EMR) at our institution to perform a search for clinical data on patients with ADPKD seen in our health system. We used the following ICD-10 codes: hypertension (I10, I15.1, N28.89), flank pain (R10.9, G89,29), hematuria (R31.0, R31.1, R31.9, R31.2), pancreatic cysts (D49.0, K86.2, Q45.2), hernia (K45.0, K42.9), brain aneurysm (Q28.3, I72.9, I67.1, I71.21, I71.9, I71.4, Z86.79), nephrolithiasis (N20.0), liver cysts (Q44.6, K76.89), urinary tract infection (UTI, N39.0), liver transplant (Z94.4), and family history of PKD (Z84.1). We performed chart review to validate data on a subset of patients.

Results: 556 unique patients were identified out of a total of 3561 Nephrology clinic visits at our center since 2011. The median age was 48 years old [IQR 35-62]. 301 patients (54.1%) were women. A majority of patients identified as White (302, 54.3%), 42 (7.6%) Black, 95 (17.1%) Asian, 62 (11.2%) LatinX, and remainder Other race categories. The mean (SD) systolic blood pressure (SBP) obtained from office visit measures was 133.3±17.8 mmHg and mean (SD) diastolic blood pressure (DBP) was 77.0±11.4 mmHg. The median [IQR] estimated glomerular filtration rate (eGFR) was 60.0 [38.5, 93.0] ml/min/1.73m^2. Median [IQR] urine albumin to creatinine ratio was 19.5 [8.6, 99.7] mg/g. 63 (11%) patients had received a kidney transplant. Co-morbidities are shown in the Figure. We found that brain aneurysm was inaccurately coded due to automatic generation of a diagnosis of cerebral aneurysm when ordering magnetic resonance angiography (MRA) at our center; only 22 out of 74 patients with screening had a true positive brain aneurysm after chart review.

Conclusions: EMR data can identify ADPKD patients for both coordinated care and research purposes. Further efforts to quality control true positive cerebral aneurysm coding at our center are needed.

Figure. Prevalence of co-morbidities in UCSF PKD Center of Excellence



SA-PO750

Autosomal Dominant Polycystic Kidney Disease: Prevalence of Pericardial Effusion

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is associated with a variety of extrarenal manifestations. Previous studies reported a prevalence of pericardial effusion (PE) in ADPKD of up to 35% in U.S. cohorts. Our study is the first to evaluate systematically the prevalence and determinants of PE in a non-U.S. ADPKD cohort.

Methods: Clinically stable ADPKD patients from a specialized outpatient clinic were reviewed retrospectively. Magnetic resonance imaging and computed tomography scans were investigated regarding the presence of PE (≥4mm). Imaging findings were linked to clinical characteristics.

Results: 208 out of 286 ADPKD patients had imaging suitable for evaluation of PE. We detected PE with a mean size of 6.8±3.3mm in 17 patients (8.2%). The prevalence of autoimmune diseases was higher in patients with PE (11.8% versus 2.1%, p=0.022). Overall, we observed a clear female preponderance with a prevalence of PE of 7.8% in females (3.8% in male patients). PE dimension was generally larger in patients with known PE etiology other than ADPKD. Presence and size of PE were not associated with signs of rapidly progressive disease, ADPKD genotype, patient age, body mass index, medications, and other parameters. Exploratory investigation of individual characteristics of patients with PE by regression tree analysis suggested renal functional impairment, sex, and proteinuria as candidate variables.

Conclusions: The prevalence of PE in our cohort was up to four times lower than previously reported and showed a clear female preponderance. The low prevalence of PE compared to recent U.S. data may point to an unknown environmental factor as a cause of PE in ADPKD. Furthermore, our data suggest that patients with a PE size >10mm deserve further attention, as they may have additional non-ADPKD related pathologies.

SA-PO751

Polygenic Effects on the Risks of Intracranial Aneurysms Among Patients with ADPKD

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Background: Patients with autosomal dominant polycystic kidney disease ADPKD are at an increased risk of intracranial aneurysms (IA). Although there is an ongoing debate on who to screen, current strategies do not provide a personalised evaluation on risk of development and progression of IA. In this study, we aimed to identify the association of risk of IA in patients with ADPKD and genome-wide polygenic scores (PGS).

Methods: All adult ADPKD patients enrolled in the Irish Kidney Gene Project who underwent cerebral image screening for IA were included. Using previously published array SNP genotype data, we created PGS for six traits (hypertension (HTN) albuminuria, total kidney volume (KV), intracranial aneurysm (IA), and stroke, and glomerular filtration rate(GFR). Using PRSice2 software, PGS were calculated, and each trait was quantified categorically into three groups (high PGS >70%, average PGS 31%–70%, and low PGS <30%). To identify potential IA-specific risk factors, the polygenic effects of each GPS trait were compared between patients with and without IA using logistic regression.

Results: A total 226 participants (mean age 57.1 ± 14.4 years, 59.7% female) were assessed for IA-specific genomic risk stratification. 213 (88%) patients had hypertension, and 140 patients progressed to kidney failure at mean age 49.4 ± 10.4 years. Family history of IA was confirmed in 75 (33.1%) patients. Forty-seven (20.8%) patients had intracranial aneurysms, with 31.9% having multiple IA. Compared to the average (31%–70%) PGS distribution for each trait, the distribution of high or low PGS did not have a differential impact on the risk of IA development in patients with ADPKD.

Conclusions: Our current method did not identify a significant polygenic effect for the risk of IA in ADPKD patients, possibly due to the small sample size. To test this hypothesis, a larger study would be needed.

SA-PO752

Prevalence and Characteristics of Intracranial Aneurysms and Cerebral Hemorrhage in Patients with Autosomal Dominant Polycystic Kidney Disease in the Japanese Nationwide Database

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Background: Selective screening for cerebral aneurysms in patients with autosomal dominant polycystic kidney disease (ADPKD) is recommended worldwide. In this study, we analyzed data from a cohort of Japanese patients with ADPKD, for which universal screening is recommended. We describe the prevalence and characteristics of intracranial aneurysms and cerebral hemorrhage in patients with ADPKD.

Methods: We examined the nationwide registry data of 4447 patients with ADPKD who held a new certificate of medical subsidy from the Japanese Ministry of Health, Labor, and Welfare from 2015 to 2017. We investigated the screening rates and risk factors for intracranial aneurysms, and prevalence of intracranial aneurysms and intracranial hemorrhage in patients with ADPKD. To analyze the diagnostic rate of intracranial aneurysms, we also compared the prevalence of intracranial aneurysms between patients who received MRI and those who did not.

Results: Overall, 693 patients (15.6%) had intracranial aneurysms, and 256 (5.8%) had intracranial hemorrhage. The MRI screening rate for intracranial aneurysms in patients with intractable diseases was 78.2%. The prevalence of intracranial aneurysms in patients who underwent MRI increased to 19.2% (odds ratio [OR] =9.33) compared with that in patients who did not (2.5%). The prevalence of intracranial aneurysms in MRI-screened patients was 22.6% in patients aged ≥ 50 years, 19.4% in patients with hypertension, and 21.5% in female patients. Hypertension (OR=1.46; P=0.002), age ≥ 50 years (OR=1.39; $P < 0.001$), female sex (OR=1.52; $P < 0.001$), and CKD stages 4–5 (OR=1.29; P=0.005) were risk factors associated with intracranial aneurysms. Female sex was found to interact with age and was not a risk factor for intracranial aneurysms in patients under 50 years of age but was a risk factor for intracranial aneurysms in those over 50 years of age ($P < 0.05$ for the interaction).

Conclusions: Screening with MRI improved the diagnostic rate of intracranial aneurysms in patients with ADPKD, which is particularly important for attributes at risk for intracranial aneurysms such as patients aged ≥50 years, with hypertension, female sex, and CKD stages 4–5.

SA-PO753

Targeted Genetic Testing with Broad Panel Informs Secondary Genetic Factors in Polycystic Kidney Disease

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Background: Currently, a major obstacle in autosomal dominant polycystic kidney disease (ADPKD) research is the low number of African American (AA) patients in clinical studies and lack of studies evaluating a potential interaction of *APOL1*-related nephropathy with ADPKD. In this pilot study, we aimed to identify the causal and secondary variants in a cohort including AA patients.

Methods: Genetic testing was performed using a commercially available next-generation sequencing-based 382 gene kidney disease panel. Pathogenic (P), likely pathogenic (LP) variants and variant of uncertain significance (VUS) were reported. Demographic data and urine protein creatinine ratio (UPCR) were obtained from electronic medical reports.

Results: Genetic testing was performed for 13 ADPKD patients (9 men and 4 women, mean age 56±10 yrs, Table 1). Five individuals were found to have heterozygous *PKD1* mutations (2 with P variants, 1 with LP variant, 2 VUSs). Two individuals were found to be heterozygous for a *PKD2* P variant. Six individuals had no identified P, LP variants or VUS in *PKD1* or *PKD2*. There were 5 AA patients and all have *APOL1* renal risk variants. Mean UPCR of AA patients were significantly higher than European American patients (2.15±1.27 vs 0.57±0.95 g/g, p=0.035). Of these AA patients, one had two *APOL1* risk alleles (G1/G2), one with homozygous G1/G1 and 3 had heterozygous *APOL1* G0/G1 risk allele.

Conclusions: Use of broad panel genetic testing in patients with PKD identifies factors underlying disease variability and progression. This preliminary data suggests the importance of genetic testing for *APOL1* risk variants in AA ADPKD patients. Proteinuria may be an important sign of APOL1 associated kidney disease in AA ADPKD patients.

Funding: Private Foundation Support

Table 1. Genetic test results and proteinuria levels of patients with polycystic kidney disease

Age/sex	Ancestry	Zygosity	*PKD1* / *PKD2* Variant	ACMG	Zygosity	Other Gene Variant	ACMG	UPCR (g/g)
48 / F	EA	Het	*PKD1* c.412C>T (p.Arg138*)	P	-	-	-	0.17
49 / M	EA	Het	*PKD1* c.[662T>C;1617G>C;2879G>A] (p.[Leu221Pro;Gln539His;Gly960Asp])	LP	Het	*NF1* c.7285C>T (p.Arg2429*)	P	0.62
48 / M	AA	Het	*PKD1* c.9397+1G>A	P	Hom	*APOL1* c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met]) (G1)	RA	2.7
61 / F	EA	Het	*PKD2* c.843+1G>A	P	-	-	-	0.6
53 / M	AA	-	-	-	Het	*APOL1* c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met]) (G1) c.1164_1169del (p.Asn388_Tyr389del) (G2)	RA	NA
66 / M	AA	-	-	-	Het	*APOL1* c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met]) (G1)	RA	3.64
69 / M	EA	-	-	-	-	-	-	0.1
69 / F	AA	Het	*PKD2* c.973C>T (p.Arg325*)	P	Het	*APOL1* c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met]) (G1)	RA	0.8
52 / M	AA	-	-	-	Het	*APOL1* c.[1024A>G;1152T>G] (p.[Ser342Gly;Ile384Met]) (G1)	RA	1.46
57 / M	EA	Het	*PKD1* c.8602T>C (p.Ser2868Pro)	VUS				2.86
49 / M	EA	Het	*PKHD1* c.274C>G (p.Arg92Gly)	VUS	Het	*RET* c.2711C>T (p.Ser904Phe)	LP	0.06
65 / M	EA	Het	*PKHD1* c.2936C>T (p.Thr979Ile)	LP				0.07
37 / F	EA	Het Het	*PKD1* c.10861C>T (p.Arg3621Trp) *PKD1* c.4376T>C (p.Leu1459Pro)	VUS VUS				0.07

Abbreviations: AA: African American, ACMG, The American College of Medical Genetics and Genomics Criteria, EA: European American, F, female; Het, heterozygous; Hom, homozygous; LP, likely pathogenic; M, male; NA, not available; P, pathogenic; RA, risk allele, UPCR: urine protein creatinine ratio
* Translation termination (stop) codon

SA-PO754

"Genotype-First" Approach to Analyzing the Diversity and Prevalence of Genes in a Cohort of Cystic Disease Patients

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Background: Cystic kidney diseases are one of the most prevalent forms of monogenic kidney diseases. Variants in *PKD1* and *PKD2* reportedly comprise 93% of genetic causes of cystic kidney diseases with variants in other genes (i.e. *IFT140, GANAB,* etc) accounting for a small proportion. As variants in these less common genes lead to milder or atypical presentations, a "phenotype-first" approach to identifying cases with cystic disease may lead to an underestimation of their contribution. Using comprehensive genetic testing, we present a "genotype-first" approach that identifies contributions of cystic kidney and/or liver disease, providing real-world insights.

Methods: A retrospective analysis of results from patients tested with a 385 renal gene panel (the Renasight™ test) was performed. Cases were selected based on having one pathogenic (P) or likely pathogenic (LP) variant in a gene associated with autosomal dominant cystic disease (*PKD1/2, IFT140, HNF1B, UMOD, ALG9, GANAB, SEC63, PRKCSH).*

Results: Among 41,182 total cases reviewed, 3698 (9.0%) had positive results in a cystic gene, 23 of which (0.6%) had findings in more than one cystic gene. P/LP variants in *PKD1/2* comprised the majority (74.0%, n=2,739) of the positive findings. A total of 1113

variants were identified in *PKD1/2*, of which 67% were private to a single case. Behind *PKD1/2*, variants in *IFT140* (9.6%; n=357), *HNF1B* (8.2%, n=304) and *UMOD* (4.6%, n=171) comprised small but significant proportions of the positive cases. Findings in each of the remaining cystic genes (*ALG9, GANAB, SEC63, PRKCSH*) had prevalence < 1.0%.

Conclusions: This study, representing the largest real-world experience, provides new insight into estimates of the prevalence of cystic disease causing genes in a "genotype-first" approach. While our observation of private mutations in *PKD1/2* is consistent with prior reports, we showed that *PKD1/2 were* etiologically implicated in a smaller proportion of cases than has previously been reported. These new insights into the genetic landscape of cystic disease will have important implications for clinical practice given the prognosis and implications for management differ greatly between *PKD1/2* and the other genetic causes.

SA-PO755

Population Analyses to Determine Genetic Causes of Kidney Cysts

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is a genetically heterogeneous disease with two major and at least seven minor genes. Information on the phenotypic penetrance of variants in these genes is biased as their analysis is usually limited to known ADPKD populations. In addition, the full genetic causes of kidney cysts may not be fully identified because kidney clinic patients are usually screened. Large populations with detailed clinical/imaging data and whole exome sequencing (WES) allow genotype- and phenotype-first approaches to clarify kidney cyst genetics. The Mayo Clinic Biobank (MCBB; n=52,865) is a population-based cohort with clinical records and WES that can allow these approaches to be employed.

Methods: In a phenotype-first approach, ICD9/10 codes and other diagnoses of kidney cysts have been employed to identify ADPKD and kidney cyst populations in the MCBB. WES data associated with these groups are being screened for likely causative variants. In the genotype-first approach, we are screening for loss-of-function (LoF) and known pathogenic variants in the ADPKD genes in MCBB participants. Examination of clinical records and imaging will determine the cystic disease penetrance of these variants.

Results: Using 15 renal/hepatic cyst related ICD codes, we identified a total of 1,093 individuals in the MCBB (2.08%). Of these, 184 were coded as ADPKD (0.35% in the MCBB), 579 with other cystic kidney phenotypes (1.10%), 294 with a single cyst (0.56%), and 36 with just liver cysts (0.07%). Analysis of the MCBB for patients previously diagnosed with ADPKD identified 108 patients; reassuringly, 101 (93.5%) were also found with the ADPKD ICD codes. MCBB also contains 50 patients previously diagnosed with kidney cysts; 26 had cystic ICD codes. Utilizing CPT codes, we have found that 1,013 (92.7%) of these patients have available imaging data (MRI, CT, or ultrasound). Manual inspection is underway to verify the phenotypes, and genetic variants from 341 PKD/ciliopathy genes are being retrieved for these patients. LoF and known pathogenic variants in all ADPKD genes are also being identified in the whole MCBB for the genotype-first analysis.

Conclusions: Population-based analyses can better explain the genetics of kidney cysts and penetrance of ADPKD genes, and the MCBB is ideally suited for this analysis.

Funding: NIDDK Support

SA-PO756

Genome-Wide Copy Number Analysis in 11,754 Trios Identifies Human Gene Knockout Patients Including 12 Patients with NPHP1 Whole Gene Deletions

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Background: Whole genome sequencing (WGS) to detect rare genetic diseases is becoming increasingly common. However, pipelines to analyse copy number variants (CNV) are underutilised.

Methods: Using a bespoke CNV analysis of Genomics England 100,000 Genomes Project (100kGP) WGS data from 11754 parent-child trios, we searched for homozygous deletions overlapping with a gene, or "whole gene", or contiguous gene deletions across the 22 autosomes. We filtering for frequency (<0.5% in a control cohort of 15440 cancer patients within 100kGP population) and for autosomal recessive inheritance mode. Identified regions of deletions were also analysed in 18877 additional rare disease singletons within the 100kGP.

Results: A homozygous ~150kb whole gene deletion of *NPHP1-MALL* on chromosome 1, which aligned with a known region containing segmental duplications (SD), was the most frequent observation among all autosomal recessive (AR) OMIM-morbid genes, identified in 3 parent-child trios. Clinical phenotypes were consistent with this genotype including nephronophthisis and retinal dystrophy. We extended our analysis to look for *NPHP1* whole gene deletions in 18877 additional singletons within the 100kGP. This reverse genetics approach identified an additional 9 patients with whole gene deletions and matching phenotypes. The frequency of heterozygous *NPHP1* whole gene deletion was assessed in a control cohort of 15440 cancer patients within 100kGP and was found to be 0.35%.

Conclusions: In conclusion, NPHP1 was the most frequently observed AR OMIM-morbid gene knockout in our trio analysis. Homozygous whole gene deletions in *NPHP1* may be easily missed using standard WGS pipelines which don't assess fully for CNVs and a targeted read-depth approach to identify CNVs in parent-patient trios and singletons is valuable in identifying these deletions.

SA-PO757

Recessive Variants in NEK1 and NEK8 Are Associated with Cystic Kidney and Kidney Stone Disease

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Background: ~9-20% of chronic kidney disease patients have a Mendelian genetic cause. Mice with biallelic deleterious variants in *Nek1* and *Nek8*, encoding NimA-related serine/threonine kinases, develop adult-onset cystic kidney disease. In humans, biallelic *NEK1* and *NEK8* pathogenic variants are associated primarily with severe fetal/neonatal disease with multiple congenital anomalies including kidney malformations (14/16 congenital renal onset). It remains unclear if variants in these genes cause later onset kidney disease.

Methods: Variants in *NEK1* (NM_001199397.3) and *NEK8* (NM_178170.1) were detected by panel, exome or genome sequencing in >5457 families with cystic kidney or kidney stone disease (Boston Children's Hospital), with renal/urologic disease patients (Genomics England), with suspected hereditary kidney disease (University of Chicago), or with clinical genetic testing identifying bi-allelic *NEK1/8* variants (GeneDx, University of Iowa, University Medical Center Groningen).

Results: Six families (seven individuals) with cystic kidney disease and/or kidney stone disease were identified with rare recessive variants in *NEK1* (two) or *NEK8* (four). Deleterious variants exhibited rare population frequency (gnomAD genome database), ≥2 deleterious *in silico* prediction scores (PolyPhen2.0, MutationTaster, SIFT, CADD) and strong amino acid conservation in vertebrate orthologues. All *NEK1* variants (p.Ala313Thr; p.Met564ValfsTer35; p.Ser909Cys) and four of five *NEK8* variants (p.Thr41Ile, p.Ile170Phe, p.Ser224Cys, p.Arg294His) were novel, while one *NEK8* variant (p.Arg599*) was previously reported. Clinical phenotyping revealed cystic kidney disease (5/7), nephrolithiasis and/or nephrocalcinosis (3/7), nephromegaly (3/7), and chronic kidney disease (3/7). Age of kidney disease diagnosis ranged from age 5-18 years. In contrast, no deleterious bi-allelic variants were observed in exome data from 1285 non-disease control subjects.

Conclusions: Recessive *NEK1* and *NEK8* variants were identified in individuals with non-congenital cystic kidney and kidney stone disease, suggesting a novel association between *NEK1/8* variants and later-onset kidney disease.

Funding: NIDDK Support

SA-PO758

TMEM67 Allelic and Other Effects Drive Vast Phenotypic Heterogeneity Across a Broad Spectrum of Ciliopathies

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Background: Ciliopathies are genetically and phenotypically heterogeneous inherited diseases, impacting multiple organs systems, including kidneys. Kidney phenotypes include polycystic kidney disease (PKD) and renal cystic dysplasia, and genes associated with integrity/function of primary cilia. *TMEM67* variants are found in several ciliopathies, with varying severity, including Meckel (MKS), Joubert syndromes (JBTS), and nephronophthisis (NPHP). MKS is the most severe, including perinatal lethality, PKD, CNS defects, CHF, and polydactyly. Whereas NPHP, tubulointerstitial nephritis and cysts, is the mildest. It is currently unclear how *TMEM67* variants cause such an array of phenotypes and disease severity.

Methods: To investigate the pathogenicity, penetrance, and pathomechanisms of *TMEM67* missense variants (19) across these diseases, we employed *in vitro* exogenous expression systems and patient derived cell lines to assess TMEM67 maturation/trafficking to the apical plasma membrane (glycosylation status/western blotting, surface immunolabelling/flow cytometry, and immunofluorescence [IF] imaging) and primary cilia transition zone [TZ; IF], and primary cilia protein composition (IF).

Results: All the MKS-associated *TMEM67* missense variants that we assessed, are fully penetrant (7/7), and abolish trafficking of TMEM67 to the cell surface and TZ (1/1, patient cells). Whereas only a subset in the milder JBTS (7/13) and NPHP (2/5) diseases, are fully penetrant, and incompletely penetrant/mild and apparent neutral alleles are present (~31 and 60%, respectively). Interestingly, many of these variants (11/19) are misfolded and can be partially or completely rescued by enhancing folding conditions, even for the fully penetrant variants found in MKS (~57%). In addition, absence of TMEM67 from the TZ, perturbs trafficking of other ciliary proteins, inversin and ARL13B.

Conclusions: Our preliminary studies assessing 19 *TMEM67* variants (MKS, JBTS, and NPHP) have revealed that: 1) allele penetrance correlates with disease severity to some degree (TMEM67 maturation/trafficking), 2) perturbed TMEM67 maturation/trafficking

represents a common pathomechanism, resulting from defective TMEM67 folding in many cases; and 3) fully penetrant membrane trafficking variants also perturb primary cilia protein composition and TMEM67 TZ localization.

Funding: NIDDK Support, Private Foundation Support

SA-PO759

Multiple Unilateral Subcapsular Cortical Hemorrhagic (MUCH) Cystic Disease of the Kidney: First Case in Brazil of a Possible New Clinical Entity of Unknown Etiology

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Introduction: The occurrence of MUCH Cystic Disease of the Kidney was described in 14 patients from the USA, France, Canada and Japan by Yoshida et al. in 2019. We describe the first similar case in Brazil.

Case Description: A 36-year-old hypertensive Brazilian man was referred to our Nephrology Clinic due to nephrotic syndrome (NS) along with acute kidney injury requiring dialysis. An extensive investigation of systemic diseases associated with NS (viral serologies, syphilis, autoimmune diseases and neoplasms) was negative. Abdominal MRI showed multiple subcapsular cortical hemorrhagic cysts in the left kidney with normal right kidney. The cysts measured <1cm on average, the biggest one 2.5cm. The signal was hyperintense on T1 and hypointense on T2-weighted MRI, suggesting hemorrhagic content. Biopsy of the right kidney revealed focal segmental glomerulosclerosis (FSGS), tip lesion variation, added to acute tubular necrosis in recovery phase. Complete remission of NS and recovery of renal function were achieved after 8 weeks of immunosuppressive treatment.

Discussion: Yoshida et al described 14 cases with distinctive renal image findings, similar to the presented. No patients had positive family history of kidney disease. 6 of them underwent genetic evaluation and results were negative for renal cystic disease. The characteristics of the cysts (unilateral, subcapsular with hemorrhagic content) suggest a different etiology from that of the classic APKD1/2, ARKD or medullary cystic kidney disease. Whole genome sequencing is currently being processed. None of the patients previously described had NS nor FSGS, suggesting a non-causal association. These clinical and radiological findings might be features of a new non-inherited renal cystic disease.

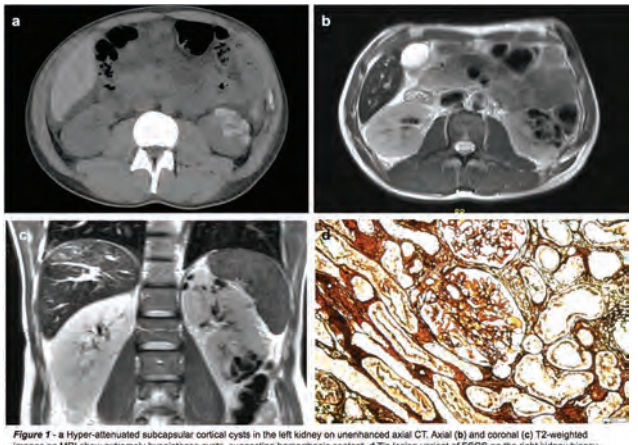

Figure 1 - a Hyper-attenuated subcapsular cortical cysts in the left kidney on unenhanced axial CT. Axial (b) and coronal (c) T2-weighted images on MRI show extremely hypointense cysts, suggesting hemorrhagic content. d Tip lesion variant of FSGS on the right kidney biopsy (PASM,original magnification× 200).

SA-PO760

A Rare Case of Polycystic Kidney Disease due to Pathogenic Variants in the ALG9 and TTC21B Genes

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Introduction: *ALG9* is a novel disease gene that accounts for <1% of cases on the polycystic kidney disease (PKD) spectrum. Pathogenic mutations of the *TTC21B* gene are associated with nephronophthisis, characterized by tubulointerstitial disease and kidney cysts. Animal studies suggest that *TTC21B* modifies the phenotype of PKD due to the *PKD* gene mutation. Whether *ALG9* interacts with *TTC21B* is unknown. We present a rare case of PKD due to heterozygosity for pathogenic variants in *ALG9* and *TTC21B*.

Case Description: A 65-year-old Hispanic woman with well-controlled human immunodeficiency virus, osteoporosis and nephrolithiasis presented for evaluation of chronic kidney disease, proteinuria, and bilateral kidney cysts. Serum creatinine fluctuated between 1.1-1.3 mg/dL (eGFR 44-54 ml/min/1.73m^2) with no hematuria. Urine protein-creatinine ratio was 442 mg/g. Replacing tenofovir in her antiretroviral regimen did not improve kidney function. Kidney ultrasound revealed slightly enlarged kidneys of 12.4 cm on the left and 11.5 cm on the right, increased parenchymal echogenicity as well as numerous bilateral cysts, some of which were complex. A CT abdomen showed 4 cysts in the left kidney and 3 cysts in the right kidney that were >8 mm in diameter, as well as innumerable bilateral cysts that were too small to count. There were no liver cysts. She reported had no known family history of cystic kidney disease. Genetic test revealed a heterozygous *ALG9* nonsense, loss of function mutation (c.1219C>T, p.Arg407*) and a heterozygous *TTC21B* variant that resulted in a frame-shift (c.2913dup, p.Val972Serf*11). Using UCSC Genome Browser, we found evidence that *ALG9* and *TTC21B* both interact with ubiquitin C.

Discussion: *ALG9* encodes a-1,2-mannosyltrasnsferase, which adds specific mannose molecules to a *N*-glycan precursor in the endoplasmic reticulum lumen. *ALG9* mutation is associated with a milder phenotype than *PKD* mutations. *TTC21B* encodes a retrograde intraflagellar transport protein. A previous case reported that *TTC21B* heterozygous variants exacerbated the phenotype of PKD due to *PKD1* mutation. The interactions between *PKD* genes and *TTC21B* were validated in animal studies. However, whether *ALG9* interacts with *TTC21B* is unknown. Addressing this knowledge gap will help define the prognosis and guide treatment therapy in patients like ours.

SA-PO761

HNF1B Nephropathy Mimicking Autosomal Dominant Polycystic Kidney Disease: A Case Report

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Introduction: Hepatocyte nuclear factor1beta (HNF1B) nephropathy is characterized by hypomagnesemia, hyperuricemia, congenital anomalies of the kidneys and urinary tract (CAKUT), and multiple small cortical cysts without kidney enlargement. It also involves multi-organ manifestations including insulin-deficient diabetes (or maturity-onset diabetes of the young [MODY]), pancreatic exocrine dysfunction, liver dysfunction and neurodevelopmental abnormalities including autism spectrum disorder (ASD). We present a rare case of HNF1B nephropathy with atypical large kidney cysts mimicking autosomal dominant polycystic kidney disease (ADPKD).

Case Description: A 37-year-old male with ASD initially presented with hypertensive emergency. The patient reported occasional flank pain and distension but no other symptoms. The patient was estranged from his father, and his mother had normal kidney function without cysts. There was no known history of kidney failure, aneurysms, or sudden death in his extended family. Physical examination revealed distended abdomen with palpable organomegaly. Laboratory results showed elevated creatinine levels (2.41 mg/dl) and reduced eGFR (33 ml/min/1.73 m2) with an eGFR decline of 5 ml/min/1.73 m^2 in the last year. Fasting blood glucose levels and liver function tests were normal. CT showed innumerable bilateral kidney cysts, the largest of which measured 19 cm on the right and 12 cm on the left, and an enlarged spleen. An initial diagnosis of *de novo* ADPKD was suspected. Genetic testing of *PKD1* and *PKD2* found no responsible variant, leading to a broader cystic gene panel sequencing. A heterozygous 1.26 Mb deletion (chr17:g.34842466_36104935del), encompassing whole *HNF1B* gene was detected. Cascade screening showed that the patient's mother was unaffected.

Discussion: HNF1B nephropathy displays substantial phenotypic heterogeneity. We present a case of HNF1B nephropathy clinically mimicking ADPKD with extreme kidney enlargement and loss of kidney function, without hypomagnesemia, hyperuricemia, or MODY. Phenocopies are not uncommon, and this case further exemplifies the role of genetic testing to obtain a concrete diagnosis. This case report contributes to the understanding of phenotypic variability in HNF1B nephropathy and emphasizes the importance of considering this diagnosis in patients with large kidney cysts.

SA-PO762

Glomerulocystic Kidney Disease with Concurrent Thin Basement Membrane Disease in an Adult Male

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Introduction: Glomerulocystic kidney (GCK) is a rare condition that presents as progressive renal insufficiency and is typically found in pediatric patients with only a few cases described in adults. GCK is defined by the dilation of Bowman space to 2-3 times that of normal size and more than 5% of glomeruli are involved. Patients with GCK have rapid development of renal insufficiency in less than 1 year and most progress to ESRD. Multiple cases of GCK have been reported; however, GCK with concurrent TBMD has an even rarer occurrence.

Case Description: A 30-year-old Asian male patient with history of bilateral glaucoma and gout with no family history of renal disease was admitted for evaluation of urinary retention and renal insufficiency. Foley catheter was placed with 900 ml of yellow urine suggesting urinary obstruction. Physical exam reveals no flank tenderness. Renal ultrasound showed increased echogenicity of the kidneys, without hydronephrosis. No renal stones, perinephric stranding, hydronephrosis, or cysts in organs were noted on CT. The patient underwent a renal biopsy with preliminary findings consistent with obstructive nephropathy. Patient's renal function did not improve with foley insertion. GN serology was unrevealing. UA with 4-10/HPF RBC, 2+ Hb and 1+ protein. Biopsy was reviewed again with renal pathologist, and the findings were consistent with GCKD with concurrent thin basement membrane and chronic tubulointerstitial disease. The patient was started on hemodialysis and referred to genetics clinic. A pathogenic variant was detected in the COL4A1 gene and heterozygous pathogenic variants in the ECHS1 & ITPA genes.

Discussion: To our knowledge, this is the first case of GCK with concurrent TBMD with pathogenic variants of the COL4A1, ECHS1, and ITPA genes. Previous literature has identified 5 main types of GCK: GCK in PCKD, hereditary, syndromic, obstructive,

and sporadic. Our case is most consistent with hereditary variant of GCKD. This has been reported in one case study by Hashimoto et al. in which no pathogenic mutations in genes had been identified. A pathogenic COL4A1 gene can lead to hereditary angiopathy with nephropathy, aneurysms, and associated with renal cystic lesions and basement membrane involvement as seen in our patient. GCKD with concurrent TBMD can present in adulthood. This case report highlights this rare presentation of GCKD.

SA-PO763

PAGE Phenomenon in a Crossed Fused Renal Ectopia: A Rare Phenomenon in a Rare Anomaly

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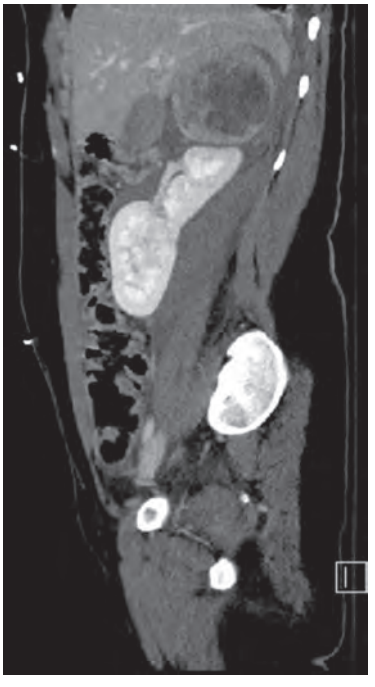
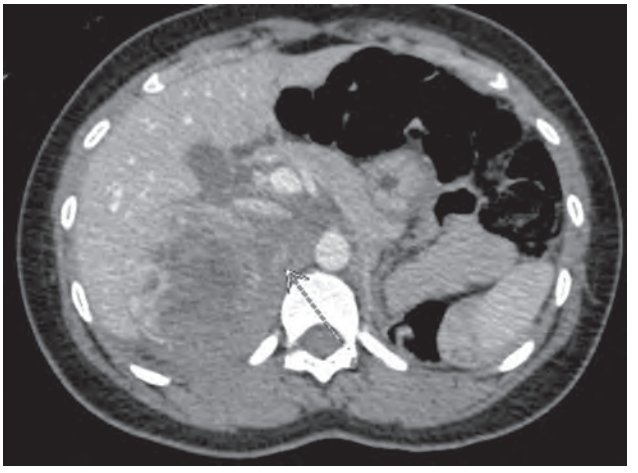
Introduction: PAGE phenomenon is rare. It occurs due to an external compression of the renal parenchyma, usually by subcapsular hematoma. Crossed fused renal ectopia (CFRE) is another rare finding. We present an unusual case of a young female with CFRE complicated by PAGE kideny due to pheochromocytoma.

Case Description: A 28 yo F with CFRE presented with Rt flank pain for 3 days. Pain was severe, radiating to the back, associated with nausea. She denied vomiting and headache. In the ED, she was found to have hypertensive urgency, BP 202/117, HR 103 bpm. PE was significant for RLQ tenderness with no rebound or rigidity. Blood work showed Hgb of 11.3 g/dL. CMP, including BUN and Cr were wnl. US of the abdomen showed diffuse echogenic appearance of the Rt kidney with scattered cysts. CT Urogram showed large Rt retroperitoneal and subcapsular hematoma and a heterogenous right suprarenal mass. She was admitted to the ICU and was treated with Nicardipine drip. Urine catecholamines were significantly elevated. Patient was stabilized and was transferred to urologic oncology surgeon for intervention.

Discussion: PAGE kidney is rare and is commonly traumatic or iatrogenic. However, it can be caused by an adrenal mass. It carries high morbidity especially in patients with solitary kidney and CFRE. Urgent intervention is warranted to salvage the kidney.



CT Abdomen showing CFRE



CT Abdomen showing Rt adrenal mass with active bleeding.

SA-PO764

Case Report: Mosaic TSC2/PKD1 Contiguous Gene Deletion Syndrome

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Introduction: A rare overlap of tuberous sclerosis complex (TSC) and autosomal dominant polycystic kidney disease (ADPKD) can occur when large deletions impact the adjacent *TSC2* and *PKD1* genes, leading to *TSC2/PKD1* contiguous gene deletion syndrome. We present a case of *TSC2-PKD1* contiguous gene deletion syndrome with somatic mosaicism where initial genetic testing did not identify a pathogenic variant.

Case Description: A 21-year-old female patient was referred to the McMaster Kidney Genetics Clinic with clinical features consistent with TSC, including childhood epilepsy, multiple bilateral brain tubers, angiofibromas, ash leaf lesions, and bilateral kidney cysts. There was no family history of TSC or PKD. In childhood, she was diagnosed with bilateral renal angiomyolipomas (AMLs) on ultrasound. Her most recent creatinine was 0.75 mg/dL with eGFR of 117 ml/ min/1.73m^2. Magnetic resonance imaging of the kidneys at age 18 revealed numerous bilateral kidney cysts including complex heterogenous cysts in an atypical lopsided distribution (Mayo class 2) but no evidence of fat containing AML. Clinical genetic testing with capillary sequencing and multiplex ligation-dependent probe amplification (MLPA) for *PKD1, PKD2, TSC1,* and *TSC2* did not identify a responsible pathogenic variant. A follow up cystic kidney disease gene panel was arranged which identified a deletion spanning exons 15-46 of *PKD1* and exons 32-42 of *TSC2* predicted to be in 35% of the patient's circulating white blood cells, suggesting somatic mosaicism and a diagnosis of *TSC2-PKD1* contiguous gene deletion syndrome.

Discussion: Through unexpectedly low read depths, next generation sequencing gene panels can identify deletions. However, detection of somatic mosaicism can be challenging as the variant allele frequency can be above the expected 50% for a heterozygous deletion. Patients with somatic variants may present atypically with more subtle phenotypic features than patients with classical pathogenetic variants. Patients with TSC can have small kidney cysts, though their phenotype should be quite clinically distinct from ADPKD. Our case demonstrates an example of mosaic *TSC2-PKD1* contiguous gene deletion syndrome and the improved sensitivity for somatic genetic variants with gene panel sequencing over traditional capillary sequencing and MLPA.

SA-PO765

Tolvaptan Use in Patients with Autosomal Dominant Polycystic Kidney Disease and Gilbert Syndrome

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Introduction: Jinarc therapy is contraindicated in patients with elevated liver enzymes. Gilbert's syndrome, one of the most common genetic disorder, is characterised by mild fluctuating unconjugated hyperbilirubinemia. A search of the available medical literature did not identify any studies or information that evaluated the use of tolvaptan in patients with ADPKD and Gilbert's syndrome. We present two cases with ADPKD and Gilbert's syndrome, in whom treatment with tolvaptan was initiated.

Case Description: Case 1 was a 31- year-old male patient and Case 2 was a 34-year-old female sibling. They have rapidly progressive ADPKD and a family history of Gilbert's syndrome. Blood testing for systemic markers of liver function were performed prior to and two weeks after initiation of Jinarc, continuing monthly thereafter. Their renal function was normal. Both patients received Jinarc 45 mg in the morning and 15 mg in the afternoon, and the dose was not increased during first 4 months of follow-up. A sustained urine osmolality (Uosm) of 280 mOsm/kg was achived in both patients. Case 1 had Uosm between 65 nad 138 mOsm/kg and Case 2 between 43 and 287 mOsm/kg. Case 1 had mild hyperbilirubinemia prior to tolvaptan initiation but no significant additional elevation of bilirubin was observed during treatment. Case 2 had an increase in bilirubin immediately after starting treatment but it remained < 2 ULN thereafter. The table presents the bilirubin values in both patients before and during tolvaptan therapy. All other parameters of potential hepatocellular injury, including hepatic transaminases, were within the normal range in the first 4 months.

Discussion: In two young adult siblings with rapidly progressive ADPKD and a benign Gilbert's syndrome we cautiously started treatment with tolvaptan. We observed an isolated elevated serum bilirubin in the absence of the other criteria for hepatic injury. We feel that patients with Gilbert's syndrome can also be considered for tolvaptan therapy. Still, safety studies in patients with impaired bilirubin glucuronidation are warranted.

Total and direct bilirubin presented for cases 1 and 2.

	Prior tolvaptan	After 2 weeks	1 month	2 months	3 months	4 months
Total bilirubin, mcgmol/L Case 1	37	35	24	25	28	30
Case 2	19	28	30	22	31	31
Direct bilirubin,mcgmol/L Case 1	10	13	10	10	11	11
Case 2	5	10	11	8	11	12

SA-PO766

Phenotypic Variabilities of Neonatal Autosomal Recessive Polycystic Kidney Disease

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Introduction: Autosomal Recessive Polycystic Kidney Disease (ARPKD) is caused by a mutation in the PKHD1 gene and is an inherited cause of chronic kidney disease in children. The most typical presentations in neonates are a history of oligohydramnios, massively enlarged kidneys, and the Potter sequence with pulmonary hypoplasia that can lead to respiratory insufficiency and perinatal death. Extra-renal manifestations include congenital hepatic fibrosis, cholangitis, and portal hypertension. A subset of ARPKD patients can have a predominant liver phenotype.

Case Description: We report the variable clinical manifestations of three cases of neonatal ARPKD. Case 1 is the male neonate with enlarged ventricles in the brain, atypical extra-renal manifestation, and confirmed the diagnosis by genetic testing. Although he did not require renal replacement therapy in the neonatal period, he developed severe hypertension at 3 months. Case 2 was born with a history of oligohydramnios and required ventilator support for 3 days. His neonatal course was unremarkable and developed hypertension at 8 weeks of life. He received a renal transplant at 4 years of age. Case 3 is a full-term neonate who developed pulmonary hypoplasia, was on a high-frequency ventilator at birth, and required initiation of dialysis and nephrectomies in the neonatal period. Clinical and laboratory findings of cases are shown in Table 1.

Discussion: It should be aware of variable presentations of ARPKD cases and some may require aggressive management of nephrectomies and dialysis in the neonatal period. Due to its multi-system effects, a multidisciplinary team of nephrologists, gastroenterologists, surgeons, and neonatologists help families of patients make informed treatment decisions.

Fig. 1: Clinical and laboratory findings of 3 neonatal cases with ARPKD

	CASE 1	CASE 2	CASE 3
Gestational age (weeks)	33	31	36
Birth weight(Grams)	2053	1500	2600
Oligohydramnios	Yes	No	Yes
Pulmonary hypoplasia	None	None	Yes
Renal Ultrasound findings	Normal sized kidneys, bilateral pelviectasis and cysts	Enlarged kidneys with the pelviectasis and cysts.	Very enlarged kidneys >9 cm bilaterally with multiple tiny cysts
Extra-renal manifestations	Ventriculomegaly, colpocephaly.	Hepatic cysts	Pulmonary hypoplasia, hepatic fibrosis
eGFR at 28 days of life (mL/min/1.73m^2)	37.7	27	8
Serum Creatinine at 14 and 28 days of life (mg/dL)	0.5	0.6	2.3
Initiation of dialysis before 28 days (Yes/No)	No	No	Yes

eGFR- estimated kidney function based on serum Creatinine (0.41 x Height (cm)/ serum Cr (mg/dl)), (eGFR <15 ml/min/1.73 m^2- End Stage Renal Disease)

Fig 1. Clinical and laboratory findings of 3 neonatal ARPKD cases

SA-PO767

Discovery of a Novel Candidate Gene Implicated in X-Linked Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is characterized by typical imaging findings and a family history and ~90% of cases have a genetic explanation. In contrast, the underlying genetic basis of adult-onset sporadic cystic kidney disease remains incompletely elucidated, with ~30% of patients in our cohort remaining unexplained by variants in established cyst-related genes, leading to inconclusive diagnoses. These individuals were presumed to harbor potentially unreported mutations in novel candidate genes associated with PKD.

Methods: An NGS panel screening was conducted to analyze 69 known genes associated with renal cysts in adult patients with no familial history of the condition. Whole genome sequencing was performed on 47 unrelated individuals who did not exhibit any pathogenic candidate variants, aiming to identify novel genes implicated in renal cyst formation.

Results: Candidate gene A, located on the X chromosome, exhibited missense variants found in three male patients aged 74 (PT570), 80 (PT698), and 58 (PT1216) years, respectively. These patients demonstrated renal function impairment with estimated glomerular filtration rates (eGFR) of 53.5, 21.8, and 20.2 ml/min/1.73m^2, respectively. Hypertension was a shared characteristic among all patients, while no complications associated with hepatic cysts were observed. The protein product of gene A was found to be expressed in the primary cilia of human renal tubules. Kidneys from 12-month-old male knockout mice lacking gene A exhibited vacuolation of tubular cells and tubular dilation, providing evidence that gene A is a novel causative gene involved in cyst formation.

Conclusions: Gene A is a newly discovered gene associated with PKD, demonstrating X-linked inheritance, which is uncommon in inherited cases of PKD. Further accumulation of cases is warranted for a more comprehensive understanding.

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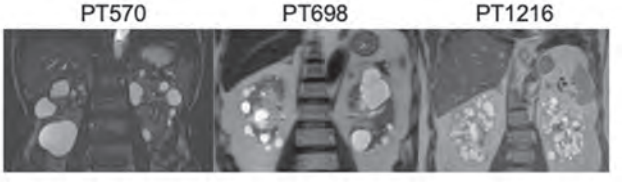

SA-PO768

Determine the Pathogenic Mechanism Underlying Infantile ADPKD Caused by a Novel Monoallelic NEK8 Mutation

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Background: ADPKD is mainly caused by mutations in *PKD1* and *PKD2* that encode polycystins, PC1 and PC2, respectively. Current evidence suggests that the dosage of PCs in primary cilia controls the severity and progression of ADPKD. But the molecular mechanisms mediating the trafficking of PCs into primary cilia remain unclear. NEK8 is the only known protein kinase residing in primary cilia, in the Inversin compartment, and is associated with a syndromic ciliopathy when both alleles are mutated. Interestingly, a novel monoallelic *NEK8* mutation (p.Arg45Trp) was recently identified in 3 Mayo families with early onset PKD without extrarenal manifestations. This finding suggests that the mutation selectively causes PKD, and thus represents a unique tool for investigating the molecular mechanisms specifically regulating renal cystogenesis.

Methods: Mutagenesis Transfection CRISPR/Cas9 Immunostaining Kinase assay Fluorescence

Results: To understand how p.Arg45Trp (R45W) affects NEK8, we inactivated *Nek8* in IMCD3 cells, and then re-expressed wild type (WT) or R45W variant NEK8. Primary cilia in *Nek8*$^{-/-}$ cells were truncated but were rescued equally well by NEK8-WT and NEK8-R45W, which show comparable expression and stability. The level of GPR161 in cilia remained the same with or without *Nek8*. Yet, ANKS6 as a binding partner of NEK8, lost its localization in *Nek8*$^{-/-}$ cilia, which was fully recovered by reexpressing NEK8-WT or R45W. These data suggest that the overall structure of primary cilia is not affected by the R45W mutation. However, we observed that PC2 levels significantly decreased in *Nek8*-null cilia; a defect rescued by NEK8-WT but not R45W, although the total protein level of PC2 appeared comparable. Our results indicate that the R45W mutation specifically impairs PC2 in cilia. Moreover, we showed that the autophosphorylation of NEK8-R45W was significantly decreased compared to NEK8-WT, implying a partial loss of kinase activity. This suggests that adequate NEK8 kinase activity is necessary for supporting the normal level of PC2 in cilia.

Conclusions: We found that a novel ADPKD variant of NEK8 (R45W) selectively repressed the ciliary level of PC2. In future, we will seek NEK8 partners in cilia that are specifically affected by this single-point mutation in NEK8. Our work will provide critical information to the understanding of PC trafficking in cilia and ADPKD etiology.

Funding: Other U.S. Government Support

SA-PO769

Molecular Testing in a Clinical Laboratory Cohort Reveals Significantly Increased Incidence of PKD1 Truncating Variants in ADPKD Patients with Pediatric-Onset vs. Adult Presentation

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a multisystem disorder characterized by multiple kidney cysts and extrarenal features. *PKD1* and *PKD2* (likely) pathogenic (L/PATH) variants cause 95% of ADPKD. Although the majority of ADPKD cases present in adulthood, approximately 1-2% have onset before age 15. While severe presentation is usually associated with truncating *PKD1* variants in adults, the variant spectrum in pediatric ADPKD cases is not well-established.

Methods: We examined the age distribution and variant spectrum in pediatric and adult cases in a retrospective study of 1582 cases referred for next generation sequencing multi-gene panel clinical testing for Cystic Kidney Disease (CKD). Testing included sequence and copy number analysis of *PKD1, PKD2, PKHD1* and other genes associated with renal cysts.

Results: The pediatric sub-cohort accounted for nearly one-third of cases tested. Our analysis revealed a diagnostic rate of 42% for the entire cohort and involved 13 genes (40% within adult and 46% within pediatric sub-cohorts – including ADPKD patients with prenatal onset). Diagnostic cases primarily had L/PATH variants in *PKD1* (69%) or *PKD2* (16%), but also included *HNF1B* (2% adult, 16% pediatric), bi-allelic *PKHD1* (1% adult, 7% pediatric) and *GANAB* (2% adult, 2% pediatric). Truncating *PKD1* L/PATH variants were significantly enriched in both our pediatric (p-value<0.001) and adult (p-value<0.001) sub-cohorts. A statistically significant association was found between the age groups and variant types (p-value<0.05), with 68.9% of L/PATH variants in pediatric patients being *PKD1* truncating compared to 59.8% in adults.

Conclusions: Consistent with published data, our results indicated that *PKD1* L/PATH variants, particularly truncating, were the cause of the majority of ADPKD, regardless of age of onset or presentation. Additionally, we found that *PKD1* truncating variants were more significantly enriched in the pediatric cohort compared to adults. Lastly, findings from clinical genetic testing for patients with CKD may inform clinical management, guide decision-making for reproductive and familial cascade testing, and generate research questions to better characterize genotype-phenotype correlations that may impact future patient care.

SA-PO770

Benefits of Genetic Testing in Patients with Polycystic Kidney Disease (PKD)

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Background: Autosomal Dominant Polycystic Kidney Disease (ADPKD) is the most common inherited kidney disease, responsible for ~10% of end stage renal disease. The most common mutated genes are PKD1 or PKD2 and ~90% of patients have an identifiable genetic variant within the two. While genetic testing has identified these mutations and their predictive values, the specific clinical significance is still not well defined. Additionally, comprehensive screenings have successfully identified PKD1 and PKD2s roles in ADPKD, but there are still patients who have no mutation detected in either gene.

Methods: Data recorded by electronic medical record of patients with image diagnosed PKD at a single nephrology clinic was collected and analyzed. Natera Genetic testing results identified genetic variants. Family history (FH) was used to determine genetic predisposition.

Results: Forty patients with PKD were identified between December 2020 and December 2022. Twenty Seven were positive for a PKD1/PKD2 mutation, 7 of which had a variant of uncertain significance (VUS) of PKD1/PKD2. Seventeen of these 27 had a positive FH of PKD, while 8 were negative and 1 unknown. Three patients did not have a PKD1/PKD2 mutation, but tested positive for mutations COL4A1, COL4A4 and TTC21B. Lastly, there were 3 patients with negative results, one of which has a FH.

Conclusions: Eighty Five percent of the patients in our cohort have a PKD1/PKD2 mutation or PKD1/PKD2 VUS, with some VUSs becoming pathogenic at a later time. However, 30% of those patients do not have a FH. The genetic study thus confirmed the diagnosis and helped predict their prognosis. The existence of heterozygous PKHD1 together with Col4A4 mutation may be the culprit of the kidney cysts in patients with Alport syndrome. The patients with true negative results remain unclear, but the sequence data will contribute to the nationwide database and help identify the true variants. Our experience advocates that the benefit of genetic testing is imperative to detecting and identifying true causative variants and that this can provide prognostic information for patients with ADPKD.

Table 1 Genetic Profiles of patients without PKD1/PKD2 mutation

Case #	PKD1/PKD2 VUS	VUS	Carrier Variant/Carrier of VUS	Family history
1	PKD1	Duplication of Exons 22-34	ATP7B; MOCOS; LRP2; ANK26; LRP4	Yes
2	PKD1	c.11695C>G (p.Leu3899Val) c.10290G>A (p.Val3430=)	HBB, BBS7, APOL1 (heterozygous),SLC3A1; AGPAT2; IFT122; WFS1; CYP27B1	Yes
3	PKD1	c.1529G>C (p.Arg510Pro)	GLI2; MNX1; CREBBP; LMX1B; CFI; LRP2; PLCE1; MEFV; COX10; SLC26A1	Yes
4	PKD1	c.9454C>T (p.Arg3152Trp)	PRKCSH; ITGB4; SLC26A1; AGPAT2; NPHP4; MEFV	No
5	PKD1	c.8809G>A (p.Glu2937Lys)	BBS1,HNF1A,NEK8	Yes
6	PKD2	c.1748T>A (p.Met583Lys)	FLCN; ALMS1; IQCB1; CYP11A1; MEFV; BBS2	Yes
7	PKD1 PKD2	c.266A>C (p.Asn89Thr),c.266A>C (p.Asn89Thr) c.709+4A>G (p.?)	TSC2; C3; FREM1; MYO1E; CUBN; G6PC; PLCE1; HPS1; SLC4A4; ELP1	Yes
	Non-PKD/PKD2 VUS	**Mutation**		
8	COL4A1	c.2095+1G>T (p.?)	BBS9; CEP164; FANCI	Yes
9	TTC21B.	c.2500C>T (p.Gln834*)	LPIN1	No
10	COL4A4	c.4599T>G (p.Tyr1533*)	HBB;PKHD1	No
11	None	N/A	Negative	No
12	None	N/A	Negative	No
13	None	N/A	SLC7A9; CLCN2; XDH; BBS12; BBS10; LRP2; NEDD4L	Yes

SA-PO771

Elucidating the Genetics of Unresolved PKD in a Large Unselected Cohort

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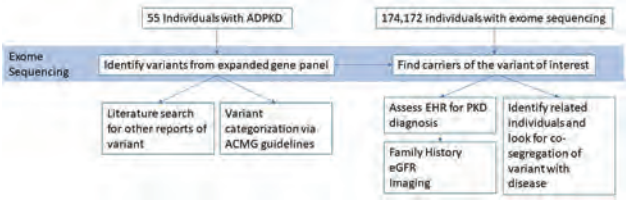
Background: We reported on 235 individuals with typical, mild or atypical PKD from an unselected cohort of 174,172 individuals with exome sequencing. Variants in 11 known cystic genes *(PKD1, PKD2, ALG8, ALG9, DNAJB11, GANAB, HNF1B, IFT140, PKHD1, PRKCSH,* and *SEC63*) were identified in 76.5% of these individuals, leaving 55 with no candidate causal variant.

Methods: The 55 individuals with unresolved genetics consisted of 37 with typical, 6 mild and 12 atypical PKD. We expanded the analysis to include 121 cystic genes identified by the Kidney Cystic and Ciliopathy Disorders Gene Curation Expert Panel in an attempt to identify candidate causal variants. Exome sequencing combined with EHR was leveraged to identify rare variants from these genes in these individuals. Variants were evaluated in the general population for cosegregation with disease and evidence of PKD in carriers.

Results: 47/55 individuals had at least one rare variant (MAF<0.001) including 13 with protein truncating variants in the 121 genes. Two unrelated individuals, one with mild and one with atypical PKD have the same *BICC1* frameshift variant: *His141ThrfsTer16* (10:58786953:T:TC). Another with typical PKD is a carrier of two missense variants in *BBS2*. This individual has several unaffected 1st degree relatives who are carriers of one the variants of *BBS2*. Additional efforts are underway to determine other candidate variants as well as their penetrance.

Conclusions: Genetic variants in genes other than *PKD1* and *PKD2* may play a significant role especially in atypical or mild PKD. Exome sequencing in an unselected cohort is a powerful approach to demonstrate the phenotypic and genetic variability of PKD and in determining penetrance.



SA-PO772

Complex Genetic in Autosomal Dominant Polycystic Kidney Disease (ADPKD)

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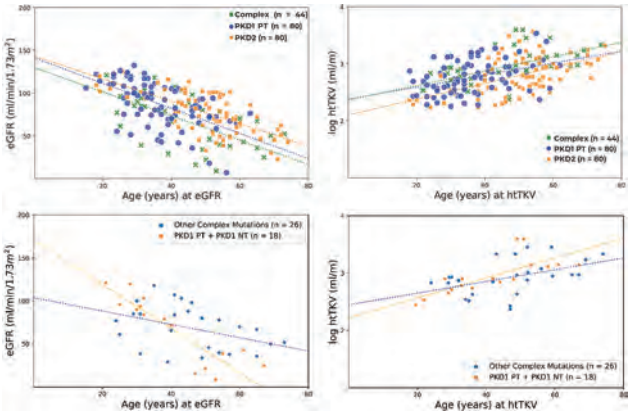
Background: ADPKD is genetically heterogeneous and primarily due to mutations in *PKD1* or *PKD2*. Complex inheritance with biallelic *PKD1* or digenic *PKD1* and *PKD2* mutations (a.k.a. complex genetic) has been reported in a small number of families. Here, we report the prevalence and genotype-phenotype correlation of patients with complex genetic from the extended Toronto Genetic Epidemiology Study of PKD.

Methods: All study patients underwent *PKD1* and *PKD2* mutation screening by targeted Next-Generation sequencing (NGS) and multiplex ligation-dependent probe amplification in mutation-negative cases. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF≤1%) deleterious variants of high and moderate impact as predicted by multiple predictive algorithms. Patients with complex genetic were defined as those with two pathogenic mutations in *PKD1*, or in *PKD1* and *PKD2*. Phase was determined in all patients with *PKD1* biallelic mutations.

Results: We found genetic complexity in 47/993 (4.7%) of families with an identifiable *PKD1* or *PKD2* mutations. Preliminary results from 44 of 53 patients in these families suggest that patients with a *protein-truncating (PT)* and a *non-truncating (NT) PKD1* mutation have more severe disease (by eGFR and TKV; see figure) than patients with two *PT-PKD1* mutations *in-cis*, two *NT-PKD1* mutations *in-trans*, or *PKD1* and *PKD2* digenic mutations.

Conclusions: In this large cohort study from a single geographic region, we found that patients with genetic complexity in ~5% of families with a known *PKD1* or *PKD2* mutation. Delineating complex genetic by NGS has important implications for genetic counselling and may improve clinical prognostication in ADPKD.

Funding: Government Support - Non-U.S.



SA-PO773

ADPKD and Collagen Genes (COL4A3, COL4A4, COL4A5)

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Background: The familial hematuria diseases are a heterogeneous group of monogenic conditions caused by mutations in one of the collagen IV genes: COL4A3/A4/A5 that are expressed in the glomerular basement membranes (GBM) and are responsible for the most frequent forms of microscopic hematuria (MH), Alport syndrome, and thin basement membrane nephropathy (TBMN). Data suggest that about 1% of the world population may have MH and TBM, a frequency leads to occasional superimposition of TBMN with other glomerulopathies. Autosomal Dominant Polycystic Kidney Disease (ADPKD) is a major genetic disorder affecting up to 12.5 million individuals worldwide and it is the fourth most common global cause for renal replacement therapy. Two are the principle causative genes: PKD1 and PKD2. The aim of the study was to describe a cohort of clinically ADPKD patients (pts) studying collagen IV genes COL4A3/A4/A5.

Methods: We performed NGS with Sophia Genetic "Nephropathies Solution" Panel on clinically ADPKD pts. This panel includes 44 genes (target region 105.8kb) involved in different types of nephropathies. We considered variants that are categorized as Vous, likely pathogenic or pathogenic (Class 3, 4 or 5 of ACMG) in COL4A3, COL4A4 and COL4A5 genes.

Results: We found 13 (6.3%) clinically potentially interesting (Class 3, 4 or 5 of ACMG) variants in collagen genes in 250 consecutive clinically ADPKD pts. We found 2 pts PKD1, PKD2, PKHD1 negative: 1pt variations carrier COL4A4 NM_000092.5: c.2908C>T (p.Gln970Ter) and c.2756A>G (p.Glu919Gly); 1 pt carrier COL4A3 NM_000091.5: c.609+3_609+6del and COL4A5 NM_000495:c.169G>A p.(Gly57Arg). We also found 4 pts with 4 Vous variants in collagen genes combine with at least 1 pathogenic or likely pathogenic variant in PKD1 or PKD2 genes. We found 3 pts with likely pathogenic variants in COL4A4 or COL4A3 genes combined with Vous or likely benign variants in PKD1 or PKD2 genes and 1 pt with 1 variant likely pathogenic in COL4A3 and 1 likely pathogenic variant in PKD1.

Conclusions: The study outlines the importance to consider also collagen genes even if we have a clear clinical manifestation of ADPKD. Analysis of genes involved in these 2 pathologies could lead to better understand the phenotype-genotype correlation at least in patients with both conditions.

SA-PO774

Intraflagellar Transport 140 Mutations in Taiwan Polycystic Kidney Disease

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Background: Autosomal dominant polycystic kidney disease (ADPKD) is primarily caused by *PKD1* and *PKD2*, followed by a small portion of cases caused by GANAB and DNAJB11. Other genes, including *ALG8, ALG9, PKHD1,* and *COL4A* can cause similar cystic ab-normality and mimic ADPKD. We previously performed the genetic analysis in a total of 920 ADPKD families and identified nearly 70% of the genetic causes. However, many families remained undiagnosed or had only a variant of uncertain significance identified. We performed exome sequencing in a total of 286 families aiming to identify their disease-causing genes.

Methods: A total of 286 probands from 286 families were included in this study. The study was approved by the institutional review boards of the Kaohsiung Medical University Hospital. Nextera Flex for Enrichment and Exome panel (CEX V2, Illumina) was used for exome library creation. The resulting fastq data were aligned to the reference human genome sequence and performed nucleotide variant calling using the DRAGEN Bio-IT platform (Illumina). The VCF file was analyzed in CLC Genomics Workbench (Qiagen). FastreeR was used to calculate distances, build phylogenetic trees, and perform hierarchical clustering between the samples.

Results: A total of 11 families were identified to have 6 different heterozygous *IFT140* truncation or obligatory splicing variants, including p.Glu51*, p.Leu540*, p.Gln667*, p.Asp738fs, p.Tyr923fs, and p.Gln1162* in the Taiwan ADPKD cohort. Two recurrent mutations, p.Glu51* and p.Leu540* were identified. Phylogenetic analysis showed that the two families with the p.Leu540* variant should be close relatives, while the 5 families with p.Glu51* have various degrees of kinship. Most affected individuals have relatively fewer and larger kidney cysts than classical ADPKD individuals. Their kidney function deterioration rate differs significantly in these 11 affected individuals.

Conclusions: Our data showed that heterozygous *IFT140* pathogenic mutations represented a small but significant 1.2 percent of ADPKD in Taiwan. All our *IFT140* pathogenic mutations are different from the report by Senum *et. al.* in 2022, although 4 of them existed in the GnomAD database. Missense variants of *IFT140*, as well as variants in the other intraflagellar proteins, were also identified. However, their role in the pathogenicity of ADPKD needs further evidence and functional analysis.

Funding: Government Support - Non-U.S.

SA-PO775

Monoallelic IFT140 Pathogenic Variants in Adult Polycystic Kidney Disease Patients Without Family History

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Background: *IFT140* encodes a subunit of intraflagellar transport complex A, which is involved in retrograde ciliary transport. *IFT140* is known as a causative gene of Meinzer-Sardino syndrome, an autosomal recessive ciliopathy that presents with short-costothoracic dysplasia. Recently, heterozygous variants in *IFT140* were reported to cause autosomal dominant polycystic kidney disease (ADPKD). We investigated the presence of *IFT140* pathogenic variants in patients with polycystic kidney disease without family history.

Methods: We performed a comprehensive genetic analysis in 151 adult polycystic kidney patients without family history. Targeted genes were 69-92 genes including *IFT140* responsible for 6 hereditary cystic kidney diseases (ADPKD, autosomal recessive polycystic kidney disease, nephronophthisis, nephronophthisis-related ciliopathies, autosomal dominant tubular interstitial kidney disease, and autosomal dominant polycystic liver disease).

Results: Through this analysis, 50 patients (33%) had pathogenic variants in *PKD1* or *PKD2* genes. Additionally, 4 patients had pathogenic variants in other genes (*HNF1B*, n = 2; *OFD1*, n = 1, *PKHD1*, n = 1). In 6 of 97 patients (6%) who did not have any apparent pathogenic variant in known causative genes, heterozygous pathogenic variants were detected in *IFT140* gene (frameshift variant, n = 3; nonsense variant, n = 2; splicing variant, n = 1). None of the patients with heterozygous pathogenic variants in *IFT140* had liver cysts. Additionally, although total kidney volume were large (median, 1357 ml), renal cysts were asymmetric and atypical. Furthermore, the patients with *IFT140* pathogenic variants were older (median, 59.5 years old) and had better renal function (median eGFR, 57.2 ml/min/1.73m^2) at the time of genetic analysis.

Conclusions: *IFT140* should be considered as the responsible gene for polycystic kidney disease, even in the patients had no family history.

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Identification of Transcripts Critical to Tuberous Sclerosis Complex (TSC)-mTOR Axis Dysregulation in Tuberous Sclerosis Complex Renal Cystic Disease

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Background: Tuberous sclerosis complex (TSC) is an autosomal dominant disorder caused by mutations in TSC1 or TSC2 genes, and affects over two million individuals worldwide. In the kidney, TSC is associated with the development of cysts and angiomyolipomata, leading to renal failure. The cyst epithelia in various models of *Tsc* knockout mice (e.g., principal cell specific KO of *Tsc1* or *Tsc2*, pericyte specific KO of *Tsc1*, and heterozygote *Tsc2*$^{+/-}$), as well humans with TSC is overwhelmingly comprised of hyper-proliferating A-intercalated cells (ICs). Deletion of Foxi1, the transcription factor critical to the acid secretion and IC viability, completely abrogated the cystogenesis in *Tsc1* KO mice.

Methods: RNA-seq analyses comparing the renal transcriptome of Wildtype (WT), *Tsc1 KO*, *Tsc1*/*Foxi1* dKO, and *Foxi1* KO mice were used to identify the differentially expressed transcripts (DET) that were activated in *Tsc1* KO (exhibiting many cysts) and downregulated in *Tsc1/Foxi1* dKO (that had no cysts) mice. The expression levels of mRNAs and proteins of interest were confirmed by northern and western blot analysis, and their localization was ascertained by immunofluorescence microscopy.

Results: RNA-seq analyses identified arginine vasopressin receptor 1a (*Avpr1a*) and the oncogene c-*Kit* (a receptor tyrosine kinase) as DET with robust activation in the kidneys of *Tsc1 KO* mice and complete abrogation in *Tsc1/Foxi1* dKO mice. Northern and Western blot analyses confirmed the increased expression of *Avpr1a* and c-*Kit*, and immunofluorescence displayed abundant labeling of both proteins on the basolateral membrane of ICs lining the cysts in *Tsc1* KO mice. KEGG enrichment analysis and expression studies showed the activation of MAPK and PI3K/AKT pathways, which are critical in AVPR1 and c-KIT signal transduction. Further, Tsc2 in ICs lining the cysts was shown to be phospho-inactivated on multiple ERK, AKT and RSK1 target sites.

Conclusions: The activation of AVPR1a and c-KIT oncogene, in association with enhanced ERK1/2 signaling and TSC2 inactivation, point to a novel pathway that disrupts the TSC/mTORC1 axis in ICs and leads to unregulated cell growth in TSC cystogenesis

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Tuberous Sclerosis Complex (TSC) Renal Cyst Extracellular Vesicles (EVs) Have Unique miRNA and Protein Profile

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Background: Over one million people worldwide have tuberous sclerosis complex (TSC), and half exhibit renal cystic disease. There is an unmet clinical need as there are no approved therapies. We identified that TSC renal cystogenesis is a cell non-autonomous disease process. To address this, we investigated the role of extracellular vesicles (EVs) as a novel mechanism of renal cystic disease to find new therapeutic options. Understanding the mechanism(s) for TSC-associated renal cystogenesis has significant ramifications. Similar to the renal cystic disease-associated renal cell carcinoma seen in von Hippel Lindau disease, TSC-associated renal cystic disease also is associated with renal cell carcinoma in 4-5% of the patient. An in-depth understanding of renal cystogenesis and the abnormal proliferation that leads to renal cell carcinoma will lead to better prevention strategies and therapies.

Methods: After Institutional Review Board approval, we isolated TSC patient derived EVs and performed tunable resistive pulse sensing, electron microscopy, dynamic light scatteringm and western blot analysis to characterize the EVs. We also performed mass spectroscopy for protein analysis, and RNASeq to better understand the miRNA and lncRNA associated with this diease state. For comparison, we used TSC serum derived EVs. For the analysis we used unsupervised clustering with hierarchical clustering and Pearson's correlation coefficients as well as a principal component analysis.

Results: The EVs from the human cyst fluid showed the expected cup shape morphology. Western blot analyses revealed a signature for small EVs, which also contained aquaporin 2, supporting their origin from principal cells. Sizing by TRPS and DLS revealed the EVs were approximately 140 nm in diameter at a concentration of 10^9 EVs per ml. There was strong agreement among DLS, TRPS, and TEM sizing methods. The protein analysis revealed three major groups of proteins that clearly distinguish the EVs isolated from the renal cyst from the EVs isolated from plasma. These experiments clearly reveal the the cyst EVs are unique when compared to EVs derived from patients with TSC. Furthermore, there were unique miRNA and lncRNA signatures for the EVs isolated from the cysts.

Conclusions: EVs in TSC patient cyst fluid continue unique protein and RNA signatures that may offer new avenues into the biology of the diease, and more importantly, into possible therapeutic approaches.

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Characterization of Exosomes Isolated from the Kidneys of Wild-Type (WT) and Tsc1 Knockout (Tsc1 KO) Mice

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Background: TSC is caused by mutations in TSC1 or TSC2 genes. Cysts are a major renal manifestation of TSC and can lead to end stage kidney disease. In human and mouse models of TSC the cystic epithelium is overwhelmingly comprised of genotypically normal A-intercalated cells (AIC). This suggests the presence of signals that alter the proliferation of AIC. EXO are membrane-bound particles generated by cells and mediate cellular communication, function, and growth. We posit that EXO are important mediators of dysregulated proliferation of AIC lining the cysts in TSC. To this end, we isolated, characterized, and identified the differences in the RNA content of EXO from WT and *Tsc1* KO mice.

Methods: EXO from kidney explants were isolated by size exclusion chromatography. The isolated EXO were characterized by western blot analysis, transmission electron microscopy (TEM), and fluorescent nanoparticle tracking analysis (fNTA). EXO RNA was isolated and run through cDNA library preparation methodology for Nanopore sequencing and mapped to the mouse transcriptome.

Results: TEM studies showed that EXO sizes range from 50 to 300nm. The fNTA studies revealed that greater than 70-77% of isolated particles were EXO with a size range of 50 to 300nm. The EXO were of similar size and distribution; however, the number of EXO was significantly higher in the preparations from the kidneys of *Tsc1* KO mice. Isolated EXO were highly enriched for CD63 and RAB27A markers. RNAseq analysis revealed that 145 transcripts were differentially represented ($p<0.05$) in the EXO isolated from the kidneys of *Tsc1*KO vs. WT mice. These included 24 lncRNAs (4 previously identified), 1 vtRNA, 107 mRNAs, and 8 pseudogenes. Enrichment analysis revealed numerous pathways that differed between *Tsc1* KO and WT exosomes, with significant fold enrichment found in the mTOR and phospholipase D signaling pathway and those of glycerophospholipid metabolism. The mRNA for *SLC25A26*, a mitochondrial protein that functions in S-adenosylmethionine (SAM) S-adenosylhomocysteine (SAH) exchange, and *Lpin2* were substantially enriched in *Tsc1* KO, mice.

Conclusions: LPIN2 and SLC25A26 may affect mTOR activation via SAH levels and DAG signaling, respectively, pointing to a potentially novel mechanism in TSC cystogenesis.

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CFTR Absence Affects Kidney Structure and Function

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Background: Cystic fibrosis (CF) is an autosomal recessive disorder arising from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and leads to impaired ion transport across epithelial cells. CFTR plays a critical role in renal progenitor self-renewal during nephrogenesis suggesting that altered CFTR expression could impair nephron endowment and predispose to renal hypodysplasia. During aging, chronic kidney disease (CKD) is morecommon in people with cystic fibrosis (PwCF) than in non-CF individuals. Here, we evaluated the effect of the absence of CFTR on the kidney structure in young mice.

Methods: Kidneys from 7–9 week old C57BL/6J mice expressing wild-type (WT) CFTR or G542X CFTR (CFTR KO; N=2/group/sex) were formalin-fixed and paraffin-embedded. We performed morphometric analysis of glomerular and tubular structures using PAS staining. Glomerular density was assessed by counting the number of glomeruli using light microscopy (n=3/kidney). Cortical area of the kidney was measured using Amira software. Glomerular density was expressed as the number of glomeruli per unit area (glomeruli/mm^2). Lotus tetragonolobus lectin staining of proximal tubules was performed to evaluate presence of the functional glomerulo-tubular junctions (GTJ). Absence of Lotus positive cells in Bowman's capsule defined the loss of GTJ.

Results: The mean renal cortical area was 31% smaller in KO male, compared to WT male. Thecorresponding kidney weight was 25% lower in KO male. The mean cortical area was 8% biggerdespite 20% lower kidney weight in KO female, compared to WT female. Glomerular densitywas 40% and 33% higher in KO male and female, compared to WT male and female, respectively. The loss of GTJ connections was higher in the KO groups (49% and 65% in KO males and females, compared to 27% and 40% in the WT counterparts).

Conclusions: Decreased kidney weight, smaller mean cortical area, higher glomerular density, and loss of GTJ connections in KO groups support the critical role of CFTR in the kidney and suggest that CFTR dysfunction may predispose PwCF to CKD. Increased mean cortical volume despite a lower kidney weight and loss of GTJ connections in KO females emphasize that the impact of CFTR absence is modulated by sex-specific factors.

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SA-PO780

Novel Regulatory Networks of CFTR in the Kidneys

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Background: Cystic fibrosis (CF) is an autosomal recessive genetic disorder arising from mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene and leads to impaired ion transport across epithelial cell membranes. While the most affected organs in people with CF (PwCF) are the lungs and digestive system, advancements in clinical care and novel high efficiency CFTR modulator therapy have increased life expectancy for most PwCF, unveiling impacts on other organs, including the kidneys. Adult PwCF have up to 20-fold higher risk of end stage kidney disease. In vitro studies suggest that CFTR may regulate renal metabolic pathways and protect from fibrosis, but nothing is known about such role in vivo. We performed single-nuclei (sn) multiomic analysis to elucidate the molecular mechanisms underlying CFTR role in the kidney.

Methods: Kidneys from 7–9-week-old male and female C57BL/6J mice expressing wild-type (WT) CFTR or CFTR G542X (CFTR KO [1]; N=1/group/sex) were subjected to nuclei isolation, Chromium Single Cell Multiome Assay, and snRNA-seq and ATAC-seq profiling. We annotated clusters and assigned cell types based on the expression pattern of knowledge-based cell type marker genes. We assessed the linkage between differentially expressed genes and accessible chromatin regions. This enabled the identification of potential regulatory elements and molecular changes in CFTR KO kidneys.

Results: We detected 27K of high-quality cells in both snRNA-seq and snATAC-seq. In WT and KO groups we identified reads corresponding to Cftr region, predominantly in the proximal tubuleepithelial (PTE) cells. Feature linkage plots corresponding with ATAC accessibility peaks (1Mbrange) and expression of CFTR gene across different cell types showed a robust positive and negative correlation network in the proximity of CFTR gene along with higher overall peak strength in KO groups.

Conclusions: The novel transcriptional and epigenetic CFTR regulatory networks suggest a novel role of CFTR in the kidney and emphasize that CFTR dysfunction may predispose PwCF to CKD.

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CFTR Modulators Mitigate Autosomal Recessive Polycystic Kidney Disease

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Background: ARPKD caused by mutations in PKHD1 results in systemic and portal hypertension, fibrosis of the liver, hepatosplenomegaly, and fusiform dilation of the collecting ducts that progresses to end-stage renal disease.

Methods: We injected in pkhd1del3-4/del3-4 (del3-4) deletion model mice with 30 mg/kg of VX-809 every other day for 30 days beginning at 5 days of age or 4 months old and necropsied the mice after 30 days of treatment.

Results: Untreated 5-month-old del3-4 mice had serious liver disease with numerous cysts. Fig.1A illustrates this wide range of cyst sizes, with cysts that are very large in some parts of the liver, and in other parts, numerous but smaller. VX-809 had a profound effect in reducing cysts of all sizes, including the largest ones, as illustrated in Fig.1A&B. The summary data in Fig.1C show that VX-809 had profoundly reduced the larger cysts and was remarkedly effective in reducing even the smaller cysts. We stained liver sections in 5-week-old mice with Ki67, a marker of proliferation, and with CK19, a cholangiocyte marker. There was a substantially (~50-fold) higher percentage of del3-4 cells that were positively stained for both Ki67 and CK19, demonstrating that increased proliferation occurred within the bile duct. VX-809 reduced the staining by one-half. Further experimentation found using confocal microscopy that CFTR is located at the apical membrane in cholangiocytes from the del3-4 mice. VX-809 reduced the CFTR at the apical membrane but increased it at the basolateral membrane.

Conclusions: These data indicate that VX-809 reduces proliferation and the presence of CFTR at the apical membrane while increasing CFTR at the basolateral membrane. Demonstration of liver cyst reduction increases the therapeutic potential of VX-809 as a treatment of ARPKD.

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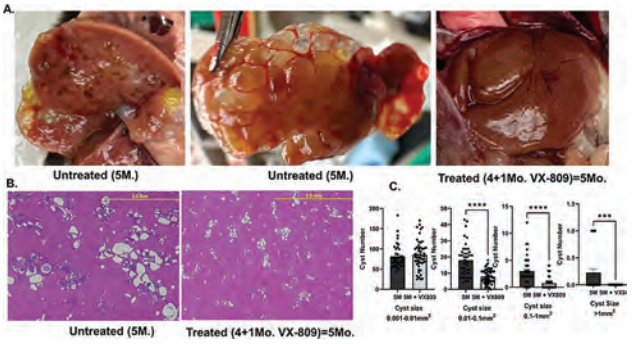

Fig 1: Livers from *Pkhd1*$^{del3\text{-}4/del3\text{-}4}$ *(del3-4)* mice **A.** Photos of livers. Please note the massive cysts in the untreated mice vs. lack of cysts in the treated mice. **B**. Pictures of H&E staining. **C.** Summary of cyst size. Note the reduction in cyst size following treatment with VX-809.

SA-PO782

The Pkhd1del3-67 Deletion Disrupts Local Genomic Architecture Resulting in Reduced Expression of Tfap-2b in the Developing Eye and Peters Anomaly

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Background: Mutations in *PKHD1*, a gene that spans ~500kb, cause Autosomal Recessive Polycystic Kidney Disease (ARPKD). Mice with genomic deletion from intron 2 through the 3'UTR of *Pkhd1* develop eye and teeth abnormalities. While neither phenotype has been associated with ARPKD, a transgenic mouse strain with a genomic rearrangement mapping close to the *Pkhd1* locus and a strain with *Tfap2b* deletion in Neural Crest Cells (NCC) develop similar eye pathology.

Methods: We recorded eye weights and intraocular pressures (IOP) of *Pkhd1*$^{del3\text{-}67/del3\text{-}67}$ mice and litter mate controls from P7 through P28 and performed histological evaluation of their eyes from E15.5 through P28. We generated *Pkhd1*$^{del3\text{-}67/+}$;*Tfap2b* $^{ko/+}$ transheterozygotes and evaluated their eye, kidney and liver phenotypes.

Results: All *Pkhd1*$^{del3\text{-}67/del3\text{-}67}$ mice developed Peters anomaly, a form of anterior segment dysgenesis, with elevated IOP, corneal opacities and most having enlarged globes. Retinal ganglion cell (RGC) number was normal at P7 but decreased by P28. Adult eyes had disruption of the iridocorneal angle with the iris adherent to the cornea, a finding associated with angle closure glaucoma. E15.5 mouse eyes had less compact cornea with large gaps within stroma and cornea and lens adhesion. *Pkhd1* expression was low in all cell types of normal E15.5 eyes. *Tfap2b* expression was normal in pre-migratory and migrating NCC of *Pkhd1*$^{del3\text{-}67/del3\text{-}67}$ but decreased in corneal endothelium and angle tissue at E15.5, suggesting a defect in NCC-derived cells after they have already populated the eye cup. *Pkhd1*$^{del3\text{-}67/+}$; *Tfap2b* $^{ko/+}$ developed eye and incisor abnormalities like those of *Pkhd1*$^{del3\text{-}67/del3\text{-}67}$ but had phenotypically normal livers and kidneys.

Conclusions: Our results suggest that the eye and incisor abnormalities observed in *Pkhd1*$^{del3\text{-}67/del3\text{-}67}$ mice likely result from disruption of local genomic architecture compromising *Tfap-2b* expression in NCC-derived cells, rather than from loss of expression of *Pkhd1*. This model will be useful for studying the complexities of *Tfap-2b* gene regulation and interventions that prevent RGC loss in glaucoma. GWAS studies have identified SNPs in *PKHD1* associated with elevated IOP. Our data may suggest a possible explanation for this relationship.

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Differential Regulation of MYC Expression by PKHD1/Pkhd1 in Human and Mouse Kidneys: Phenotypic Implications for Recessive Polycystic Kidney Disease

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Background: ARPKD (MIM 263200) is caused by mutations in *PKHD1*, which encodes FPC. We previously showed that: 1) MYC/Myc is overexpressed in human ARPKD and mouse *Cys1*$^{cpk/cpk}$ (*cpk*) kidneys, but not in several *Pkhd1* mutants; 2) the FPC C-terminal domain (FPC-CTD) upregulates, while cystin downregulates, the *MYC/Myc* P1 promoter; 3) mouse and human FPC-CTD differ in subcellular localization (Yang, 2021). Here we present new data from informatic analyses and FPC-CTD overexpression in mouse and human renal epithelia.

Methods: Evo-devo mammalian organ database was queried for developmental expression patterns of cystogenes. ClustalOmega and WebLOGO3 were used to analyze the vertebrate FPC conservation. Immunoblotting and qRT-PCR were used to quantify proteins and mRNA.

Results: *PKHD1* mRNA expression peaked before *CYS1* mRNA in fetal human kidney; in contrast, *Cys1* mRNA expression peaked before *Pkhd1* mRNA in the developing mouse kidney. Developmental expression patterns of *MYC/Myc* mRNA were similar in human and mouse kidneys, peaking in early fetal development and gradually decreased thereafter. Sequence alignment of 102 vertebrate FPCs revealed higher conservation score of the extracellular (1.9) than the intracellular cytoplasmic (1.5) domain. *Cys1* mRNA and cystin protein were downregulated by 80% and 70%, respectively, in mIMCD-3 cells stably overexpressing mFPC-CTD. Stable hFPC-CTD overexpression in TERT immortalized human renal epithelial (hTERT-HRE) cells was unsuccessful, suggesting cytotoxicity. Transient hFPC-CTD overexpression in hTERT-HRE cells did not alter cystin expression.

Conclusions: Higher expression of *Cys1* vs. *Pkhd1* in the developing mouse kidney and the suppression of *Myc* expression by cystin could contribute to the low renal MYC expression in *Pkhd1* mutant mice. In contrast, the relatively lower levels of *CYS1* vs. *PKHD1* in developing human kidney may preclude a cystin-driven protective effect for renal cystogenesis. In addition, the low cross-species conservation of the FPC-CTD suggests functional differences that may contribute to differing susceptibilities to *PKHD1/Pkhd1* mutations and the disparate renal phenotypes.

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Spontaneously Occurring Pkhd1 Mutation (Pkhd1cyli/cyli) with Altered Renal mRNA Processing and Hormonally Sensitive Hepato-Biliary Disease

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Background: ARPKD (MIM 263200) is a hereditary hepato-renal fibrocystic disorder that causes early childhood morbidity and mortality. Mutations in the *PKHD1* gene, which encodes fibrocystin/polyductin complex (FPC), causes all typical forms of ARPKD. Several mouse strains carrying diverse, genetically-engineered disruptions in the orthologous *Pkhd1* gene do not exhibit the classic ARPKD renal phenotype. Here we present the phenotypic and molecular characterization of new mouse model with a spontaneous recessive *Pkhd1* mutation which causes isolated cystic liver (*cyli*) disease.

Methods: A backcross mating scheme and MIT microsatellite makers were used map the *cyli* mutation. DNA sequencing was used to identify the *cyli* mutation. Kidneys and livers were harvested for HE histology. *Pkhd1* mRNA and FPC protein expression were analyzed by RT-PCR, qRT-PCR, Oxford Nanopore sequencing, and immunoblotting.

Results: We mapped the *cyli* mutation to Chromosome 1 and identified an insertion/deletion mutation within *Pkhd1* exon 48, which was predicted to result in a premature termination codon (UGA). *Pkhd1*$^{cyli/cyli}$ (*cyli*) mice exhibited progressive hepato-biliary pathology and longitudinal analysis revealed that pregnancy exacerbated liver disease severity in female mutants. Renal cystic disease was not observed in mutants aged to 6-months. Abundance of *Pkhd1* mRNA was lower in *cyli* than in wild-type kidneys. Several alternatively spliced *Pkhd1* transcripts, all containing exon 48, were detected in *cyli* kidneys. We identified an AAAAAT motif in exon 48 immediately upstream of the *cyli* mutation that could enable ribosomal frameshifting and nonsense mediated decay (NMD) escape.

Conclusions: The *cyli* mutation caused cystic liver similar to the hepato-biliary disease in human ARPKD. The low abundance of *Pkhd1* transcripts in *cyli* kidneys suggests an escape from NMD. Ribosomal frameshifting could allow production of sufficient amounts of FPC for renoprotection in the *cyli* mouse. Further analysis will be required to assess differences in ribosomal frameshifting activity in renal epithelia from the *cyli* mouse and humans with truncating *PKHD1* exon 48 mutations.

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SA-PO785

Functional TRPV4 Status Sets the Rate of Cytogenesis in Autosomal Recessive Polycystic Kidney Disease (ARPKD) During Variations in Dietary Potassium

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Background: Autosomal Recessive Polycystic Kidney Disease (ARPKD) manifests as a progressive growth of the fluid-filled cysts in the collecting duct. Cystic cells are characterized by the impaired intracellular Ca^{2+} signaling ($[Ca^{2+}]_i$), elevated cAMP levels to drive augmented proliferation. Mechanosensitive TRPV4 channel plays a dominant role in maintaining $[Ca^{2+}]_i$ homeostasis and flow-sensitive $[Ca^{2+}]_i$ signaling in the collecting duct. Systemic TRPV4 stimulation with GSK1016790A impedes cystogenesis in ARPKD models. Previously, we demonstrated that high dietary K^+ regimen elevates both activity and expression of renal TRPV4.

Methods: Here, using fluorescence microscopy and systemic measurements, we tested how regulation of renal TRPV4 function by dietary K^+ intake modulates the rate of cystogenesis and mechanosensitive $[Ca^{2+}]_i$ signaling in cystic cells of PCK453 ARPKD rats.

Results: One month treatment with both high KCl (5% K^+) and KB/C (5% K^+ with bicarbonate/citrate) diets significantly augmented renal TRPV4 expression in PCK453 rats in comparison to that on the regular diet (0.9% K^+). We next explored $[Ca^{2+}]_i$ levels in freshly isolated renal cysts upon application of TRPV4 agonist GSK1016790A and high flow. Treatment with KCl diet significantly augmented TRPV4-dependent Ca^{2+} influx in cystic cells. Unexpectedly, rats on KB/C intake exhibited diminished elevation of $[Ca^{2+}]_i$ concentration in cystic cells in response to both high flow and the agonist comparing to the control. High KCl diet reduced cAMP levels in cystic cells. In contrast, KB/C diet led to the increased cAMP-dependent signaling in cystic cells of ARPKD rats. At the systemic level, high KCl diet significantly decreased kidney-to-bodyweight ratio and reduced the cystic area in kidneys of PCK453 rats. High KB/C diet accelerated ARPKD progression and renal injury leading to a marked increase in the cystic area and particularly the number of cystic dilations in the renal cortex. Of note, application of TRPV4 antagonist GSK2193874 reversed beneficial effects of high KCl diet.

Conclusions: Overall, we demonstrate that TRPV4 channel activity negatively regulates cAMP levels in cystic cells thus attenuating (high activity) or accelerating (low activity) ARPKD progression. Augmenting TRPV4 activity by increased dietary K^+ intake may have therapeutic potential in PKD.

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Ultrasound and 3D Imaging Characterisation of a Rat Model of Polycystic Kidney Disease

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Background: Polycystic kidney disease (PKD) is a congenital fibrocystic disorder for which there is no curative treatment. Consequently, PKD is classified as a medical condition with high unmet therapeutic need. Animal models with improved clinical translatability can optimally inform about potential efficacy of novel drug candidates for PKD. The polycystic kidney (PCK) rat is an established genetic model of PKD with natural history and renal histologic abnormalities that resemble the human disease. Gubra has established a PCK rat breeding program to enable fast turnaround time of preclinical drug discovery within PKD. In this study, we have characterised disease progression in the PCK rat to aid in designing future pharmacological intervention studies.

Methods: Male PCK (PCK/CrljCrl-Pkhd1pck/Crl) and control (CRL:CD(SD)) rats were randomised into study groups based on body weight (10 weeks). At the age of 17 and 25 weeks, rats underwent ultrasound assessment of kidney volume, urine collection for quantification of albuminuria, and plasma sampling for urea and creatinine analysis. At termination, kidneys were collected and total kidney volume, cyst number and volume were analysed using quantitative 3D imaging.

Results: Compared to age-matched control rats, PCK rats displayed marked albuminuria at 25 weeks of age. Plasma urea was progressively increased at both 17 and 25 weeks, while plasma creatinine was only increased at week 25. *In vivo* ultrasound measurements revealed that total kidney volume progressively increased (25 wks.: 4909 mm^3) compared to control rats (2174 mm^3). 3D light sheet imaging enabled whole-kidney counting of cysts and quantification of cyst volume (control: 10.9 mm^3 vs 25 wks.: 413.5 mm^3) as well as the total kidney volume that correlated to kidney ultrasound results.

Conclusions: The PCK rat displays hallmarks of PKD, characterized by age-dependent progressive increase in biomarkers of kidney injury, kidney hypertrophy and cyst formation. *In vivo* ultrasound and *ex vivo* quantitative whole-kidney 3D light sheet imaging is highly instrumental for detailed assessment of progressive kidney disease in the PCK rat. Accordingly, these imaging modalities are instrumental as key endpoints for assessment of potential therapeutic effects of preclinical drug candidates in the PCK rat model.

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SA-PO787

Prevalence of APOL1 Variants in Persons with Proteinuric CKD

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Background: *APOL1* variants (*G1* or *G2*) are the genetic cause of progressive, proteinuric nephropathies referred to as APOL1-mediated kidney disease (AMKD). The prevalence of *APOL1* variants, which are common in persons of recent African ancestry, is not well known as *APOL1* genotyping is not routine in kidney disease care. We report data from a new interim analysis on the prevalence of *APOL1* genotypes in proteinuric chronic kidney disease (CKD).

Methods: This ongoing global study is enrolling up to 2500 participants of recent African ancestry with FSGS or proteinuric (UPCR >0.5 g/g) nondiabetic kidney disease (NDKD) to determine the percent of participants with 2 *APOL1* variants, including by genotype category, and identify potential participants for trials evaluating APOL1 therapies. During a single visit, a blood sample is collected to determine the *APOL1* genotype (validated PCR assay); genetic counseling is available.

Results: Interim analysis included 1463 participants. Among 392 participants with FSGS and 1071 with NDKD, 184 (46.9%) and 248 (23.2%) have 2 *APOL1* variants, respectively (**Table**). Most participants with 2 *APOL1* variants and proteinuric CKD are >30 to ≤60 years old (n=321/432; 74.3%).

Conclusions: The high prevalence of 2 *APOL1* variants in participants with recent African ancestry and proteinuric CKD emphasizes the importance of *APOL1* genotyping in kidney disease care to inform disease management and enable referral for clinical trials of APOL1-targeted therapies.

Funding: Commercial Support - Vertex Pharmaceuticals Incorporated

Table. Baseline Demographics and *APOL1* Genotyping Results

	FSGS N = 392	Proteinuric NDKD N = 1071	Total N = 1463
Age, years, mean (SD)	42.9 (13.1)	51.1 (13.3)	48.9 (13.7)
Region or country, n (%)			
North America			
United States	279 (71.2)	937 (87.5)	1216 (83.1)
South America			
Brazil	8 (2.0)	10 (0.9)	18 (1.2)
Europe	105 (26.8)	124 (11.6)	229 (15.7)
United Kingdom	60 (15.3)	81 (7.6)	141 (9.6)
France	30 (7.7)	28 (2.6)	58 (4.0)
Spain	14 (3.6)	13 (1.2)	27 (1.8)
Netherlands	1 (0.3)	1 (0.1)	2 (0.1)
Belgium	0	1 (0.1)	1 (0.1)
***G1/G1, G1/G2, or G2/G2 APOL1* genotype, n (%)**	184 (46.9)	248 (23.2)	432 (29.5)
G1/G1	93 (23.7)	116 (10.8)	209 (14.3)
G1/G2	74 (18.9)	108 (10.1)	182 (12.4)
G2/G2	17 (4.3)	24 (2.2)	41 (2.8)
***G1/G1, G1/G2, or G2/G2 APOL1* genotype by region or country, n/N (%)[a]**			
North America			
United States	123/279 (44.1)	210/937 (22.4)	333/1216 (27.4)
South America			
Brazil	2/8 (25.0)	0/10	2/18 (11.1)
Europe	59/105 (56.2)	38/124 (30.6)	97/229 (42.4)
United Kingdom	36/60 (60.0)	31/81 (38.3)	67/141 (47.5)
France	23/30 (76.7)	4/28 (14.3)	27/58 (46.6)
Spain	0/14	1/13 (7.7)	1/27 (3.7)
Netherlands	0/1	1/1 (100.0)	1/2 (50.0)
Belgium	0	1/1 (100.0)	1/1 (100.0)
***G1/G1, G1/G2, or G2/G2 APOL1* genotype by age category, n/N (%)[b]**			
<18 years	3/4 (75.0)	0/2	3/6 (50.0)
≥18 to ≤30 years	42/78 (53.8)	14/61 (23.0)	56/139 (40.3)
>30 to ≤45 years	70/135 (51.9)	64/275 (23.3)	134/410 (32.7)
>45 to ≤60 years	57/130 (38.0)	130/549 (23.7)	187/699 (26.8)
>60 years	12/25 (48.0)	40/184 (21.7)	52/209 (24.9)

***APOL1:* *Apolipoprotein L1*; FSGS:** focal segmental glomerulosclerosis; **n:** number of participants in the specified category; **N:** number of participants; **NDKD:** nondiabetic kidney disease; **SD:** standard deviation

Notes: Eligible participants are at least 12 years of age and of African ancestry or geographic origin (Black, Caribbean, African American, Sub-Saharan African, Cuban, Mexican, Puerto Rican, South or Central American, or other Spanish culture/origin). For more information about the study, please see https://apol1program.com. This table includes participants in the Full Set with a genotyping result as of 31 March 2023. Percentages were calculated based on the number of participants in the Full Set, unless otherwise specified.

[a] Percentages were calculated based on the total number of participants in each region/country per disease state.
[b] Percentages were calculated based on the total number of participants in each age category per disease state.

SA-PO788

Small Molecule Inhibition of APOL1 Reverses Albuminuria in a Chronic Mouse Model of APOL1-Mediated Kidney Disease

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Background: Two coding variants in the *APOL1* gene (G1 and G2) confer a greater risk for progressive, proteinuric kidney disease in individuals of African ancestry. Available therapies do not address the causal genetic driver of disease, highlighting the need for novel efficacious APOL1-targeted treatments. We have previously shown that pharmacologic inhibition of APOL1 pore function ameliorates albuminuria in an acute mouse model of APOL1-mediated kidney disease (AMKD). Here we describe the development of a chronic mouse model of AMKD with robust albuminuria and glomerulosclerosis and demonstrate that inhibition of APOL1 with a small molecule attenuates these features of AMKD.

Methods: A novel model, heterozygous for the APOL1 G1/G2 variants, was developed for these studies in addition to the homozygous APOL1 G2 mouse model previously described. Continuous increased APOL1 expression was achieved by infecting mice with an adeno-associated virus (AAV) engineered to express interferon-γ (IFN-γ). These mouse models were used to assess the effect of APOL1 small molecule inhibition on glomerular injury and urinary albumin-to-creatinine ratios (UACR).

Results: Administration of AAV-IFN-γ in APOL1 transgenic mice increased interferon levels and signaling after virus injection and led to sustained APOL1 induction, elevated UACR, and glomerulosclerosis on both genetic backgrounds. Oral administration of an APOL1 inhibitor robustly attenuated chronic IFN-γ–induced albuminuria in APOL1 transgenic mice.

Conclusions: Small molecule inhibition of APOL1 attenuates albuminuria in a chronic mouse model of AMKD. These findings support continued development of precision medicines for patients with AMKD.

Funding: Commercial Support - Maze Therapeutics

SA-PO789

APOL1 Risk Variants Induce Mitochondrial Dysfunction in Patient-Derived Kidney Organoids

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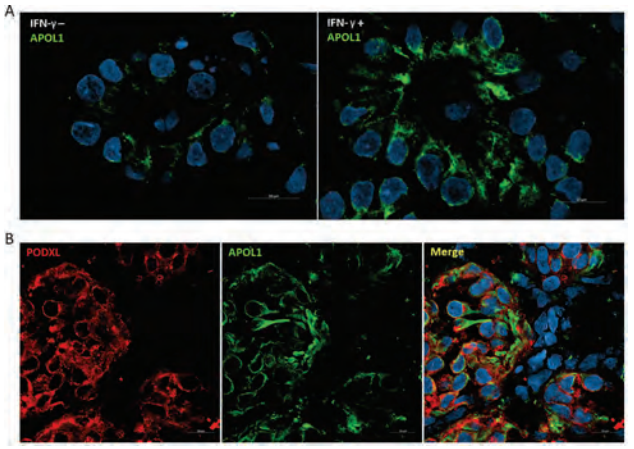
Background: Apolipoprotein L1 (*APOL1*) high-risk genotypes cause CKD in the presence of interferon gamma (IFN-γ). To elucidate mechanisms, patient-derived induced pluripotent stem cells (iPSCs) were used to generate a kidney organoid model of *APOL1* nephropathy.

Methods: iPSCs were generated from fibroblasts of two patients with APOL1 nephropathy homozygous for G1G1 and G2G2 risk variants (RV). Isogenic control of the G2G2 patient iPSCs was created with CRISPR-Cas9 gene editing. Kidney organoids were generated using G1G1, G2G2 and isogenic control iPSCs. Organoids were treated with IFN-γ and analyzed by single cell transcriptomics, immunofluorescence imaging and mitochondrial respiration assay.

Results: APOL1 gene expression was upregulated in all genotypes following IFN-γ. Single cell transcriptomics of organoids 3 days post IFN-γ treatment showed APOL1 induction was mainly in podocytes, confirmed with colocalized immunolabeling of APOL1 and podocalyxin. RV podocytes showed significantly decreased expression of nuclear DNA-encoded OXPHOS related genes, while mitochondrial DNA-encoded gene expressions were increased. Further, a novel subpopulation in RV podocytes was identified, characterized by a metabolic switch to glycolysis. Next, glomeruli were isolated from RV and isogenic control organoids to assess oxygen consumption rate and reactive oxygen species (ROS). In RV glomeruli, maximal respiration rate upon IFN-γ treatment did not increase, unlike in the isogenic control, and ROS levels were 30% higher.

Conclusions: We generated a kidney organoid model of *APOL1* nephropathy using patient-derived RV and isogenic control iPSCs. Exposure of *APOL1* RV organoids to IFN-γ induced podocyte mitochondrial dysfunction and may provide a mechanism for development of CKD. This model supports further research in mechanisms and potential therapeutics for *APOL1* nephropathy.



APOL1 expression increased upon IFN-γ treatment (A), specifically in the podocyte population (B).

SA-PO790

APOL1-Inflammation and Hypoxia Axis in Ischemic Donor Kidneys

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Background: The presence of two *APOL1* renal risk variants (RRVs) in donor kidneys negatively impacts kidney allograft survival. We examined the effects of *APOL1* RRVs on APOL1 expression and compared the differences in cytokine and APOL1 expression patterns between preservation methods cold storage (CS) and normothermic machine perfusion (NMP).

Methods: Discarded deceased donor kidney pairs underwent 6-hour NMP (n=6) and CS (n=6). Perfusion, biochemical, and histologic parameters were recorded. Paired donor kidneys with different *APOL1* genotypes were compared with regard to the aforementioned parameters and gene expression under NMP and CS. DNA is extracted and genotyping for *APOL1* RRVs G1 (rs73885319) (rs60910145) and G2 (rs71785313) were performed by Sanger sequencing.

Results: Donor genotyping showed 5 kidney pairs with G0/G0 and a kidney pair with heterozygous G0/G1 RRV. Kidneys were successfully perfused, with improved renal blood flows and resistance over the course of perfusion, and evidence of urine output (Table 1). Transcriptomic analyses showed different expression patterns between *APOL1* G0/G0 kidneys and G0/G1 kidney, particularly under NMP (Fig. 1). The kidney with *APOL1* G0/G1 showed higher fold increase in expression of APOL1, TGF-β and IFN-γ compared to kidneys with G0/G0 under 6 hrs of NMP. Overall, APOL1 expression was significantly correlated with KIM1 (r=0.87, p<0.001), TGF-β (r=0.83, p=0.001), IFN-γ (r=0.77, p=0.004) and HIF-1α (r=0.81, p<0.001) in all kidney pairs.

Conclusions: Donor kidney with *APOL1* G0/G1 RRV demonstrated different transcriptomic response to alternative preservation methods. Further studies needed to clarify the interplay between APOL1, inflammation and kidney injury in the setting of allograft ischemia and reperfusion.

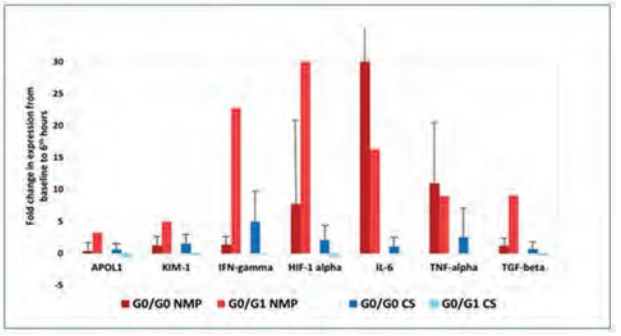
Funding: Private Foundation Support

Table 1. Characteristics of ischemic nonutilized donor kidneys

	K1 CS	K1 NMP	K2 CS	K2 NMP	K3 CS	K3 NMP	K4 CS	K4 NMP	K5 CS	K5 NMP	K6 CS	K6 NMP
APOL1 RRVs	G0/G0		G0/G0		G0/G1		G0/G0		G0/G0		G0/G0	
Donor type	DCD	DCD	DCD	DCD	SCD	SCD	DCD	DCD	SCD	SCD	DCD	DCD
Age	58	58	59	59	70	70	14	14	57	57	56	56
Sex	F	F	F	F	F	F	F	F	F	F	F	F
KDPI (%)	88	88	88	88	100	100	CRRT	CRRT	69	69	74	74
Previous HMP	+	+	+	+	-	-	+	+	-	-	+	+
CIT (hours)	42	42	32	32	17	17	39	39	51	51	31	31
Urine output (mL/hour)	0	58	0	108	0	75	0	3	0	4	0	17

Abbreviations: CIT: cold ischemia time, CS: Cold storage, CRRT: continuous renal replacement treatment, DCD: donation after circulatory death, HMP: Hypothermic machine perfusion, KDPI: kidney donor profile index, NMP, Normothermic machine perfusion, RRVs: renal risk variants, SCD: standard criteria donor

Figure 1. Histogram of RT-PCR results based on *APOL1* genotype [G0/G0 (n=5) vs G0/G1 (n=1)] showing the differences in relative gene expression profile on baseline and at 6 hours of normothermic machine perfusion (NMP) vs cold storage (CS).



SA-PO791

Single-Nucleus RNA Sequencing Analysis of Interferon-Exposed APOL1 High-Risk Transgenic Mouse Reveals Distinct Injury Patterns in Podocytes and Endothelial Cells

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Background: *APOL1* high-risk genetic variants, termed G1 and G2, compared to the common variant G0, cause focal segmental glomerulosclerosis (FSGS), collapsing glomerulopathy, and arterionephrosclerosis in individuals with sub-Saharan African ancestry. Gene expression profiles of glomerular cells in APOL1-mediated cell injury have not been studied at the single cell level. We performed single-nucleus RNA sequencing (snRNA-seq) of glomeruli from wild-type (WT) and bacterial artificial chromosome (BAC)/APOL1-G0 and -G1 transgenic mice following interferon-g administration.

Methods: BAC/*APOL1* transgenic mice received a single dose of interferon-g, administered retro-orbitally, and were euthanized 24 hours later. Glomeruli were isolated and nuclei were captured for snRNA-seq. The snRNA-seq data from BAC/APOL1-G0, BAC/APOL1-G1 and wild-type mice were integrated and analyzed using Seurat4. Podocytes and glomerular endothelial cell clusters were identified by expression of known marker genes. Subclustering and pseudotime analysis were performed to identify cell subpopulations and their characteristic gene signatures.

Results: The combined analysis of snRNA-seq datasets identified podocyte clusters expressing *Nphs1* and glomerular endothelial cell (GEC) cluster expressing *Ehd3* and *Hecw2*. *APOL1* was expressed by podocytes and endothelial cells. Expression levels were similar between *APOL1*-G0 and *APOL1*-G1 expressing cells within each cluster. Podocytes and GECs showed similar gene expression patterns of early injury but distinct patterns with more severe injury. Genes specific to the podocyte severe injury cluster in BAC/*APOL1* mice showed higher expression in human FSGS *APOL1* high-risk urinary podocytes, compared to APOL1-low-risk podocytes.

Conclusions: Following interferon administration to BAC/APOL1 mice, we observed a unique gene expression profile in a *APOL1*-G1 risk allele mouse compared to a *APOL1*-G0 mouse. *APOL1* was expressed in podocytes and GECs. However, the gene expression patterns of injury in these two cell types were different and may reflect different roles by which these cells contribute to glomerular pathology in APOL1 glomerular disease.

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SA-PO792

HIV-1 Protein Nef Acts in Synergy with APOL1-G1 to Impair Nephrocyte Function by Inhibiting Autophagy and Endocytosis Pathway

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Background: Individuals carrying APOL1 risk alleles G1 and G2 have higher chances of developing HIV-associated nephropathy (HIVAN). The role of APOL1 in HIVAN is mostly derived from studies done in cultured renal cells or clinical genetic

studies. However, very little is known about how APOL1 risk alleles and HIV-1 genes interact *in vivo* to induce HIVAN. The basic mechanisms responsible for the synergistic renal pathological effects of APOL1 risk alleles and HIV-1 are still unclear.

Methods: Because *Drosophila* nephrocyte, is remarkably similar, both structurally and functionally, to the mammalian podocyte, here we generated transgenic flies selectively expressing APOL1 nephropathy risk Alleles G1 and HIV-1 protein Nef in *Drosophila* nephrocytes. We then investigated the structural and functional effects on the fly nephrocytes.

Results: As transgenic flies with APOL1-G1 aged, we found nephrocyte function declined, cell size increased, the structure of the slit diaphragms defected, and nephrocytes died prematurely. Furthermore, we showed that the expression of APOL1-G1 impaired the nephrocyte function by affecting the acidification of organelles by inhibiting the endocytosis pathway. Next, we noticed that the expression of HIV-1 protein Nef facilitated these nephrocyte impairments. We further found that expressing of HIV-1 protein Nef in nephrocytes induced the accumulation of autophagosomes and inhibited the autophagy pathway, which facilitated the impairments of the acidification of organelles, and functional structure of nephrocytes.

Conclusions: These results suggested that Nef and APOL1-G1 lead to the increased risk of renal failure through their synergistic regulation of the autophagy and endocytosis pathway, which will provide new therapeutic targets to prevent HIV-associated nephropathy.

Funding: NIDDK Support

SA-PO793

Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics and Outcomes During Index Hospitalization Diagnosis in the Era of C5 Inhibitor Therapy (C5i)

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Background: C5i therapy has significantly improved clinical outcomes for aHUS. Due to its rarity, there are few previous large aHUS retrospective cohort studies and these are limited to patients from outside the US, children, and/or prevalent patients from before the era of C5i. This study sought to describe the clinical characteristics and outcomes in one of the largest and most diverse incident adult US aHUS cohorts treated with C5i to date.

Methods: This was a retrospective cohort study of adult aHUS patients in the US diagnosed during hospitalization, derived from the US Premier Healthcare Database, which contains ~25% of all US hospitalizations (1/2011–6/2021). aHUS was defined as the presence of a diagnostic code for thrombotic microangiopathy (TMA) or HUS and a treatment code for C5i in the absence of a diagnostic code for secondary causes of TMA or HUS. Prespecified clinical and outcome data were collected and analyzed using descriptive statistics.

Results: The cohort comprised 634 patients with a median age of 51 years (interquartile range [IQR] 32–64). The majority were female (67.2%), White (61.5%), and non-Hispanic (76.3%). Baseline co-morbidities included hypertension (70.3%), chronic kidney disease (30.4%), and diabetes (18%). Median intensive care unit (ICU) and hospital stays (IQR) were 6 (3–11) and 20 days (14–32), respectively. The median time from admission to C5i was 9 days (5–15). For patients receiving corticosteroids (CS) (78.5%) and therapeutic plasmapheresis (TPE) (69.1%), the median time from admission to treatment was 2 days (1–5) and 3 days (2–5), respectively. Median treatment durations for CS and TPE were 17 days (8–28) and 5 days (3–12). Renal replacement therapy (RRT) was initiated in 77.3% of patients and discontinued prior to discharge in 51% of these patients. In-hospital mortality was 12.3%, and 22.7% of patients required follow-up in skilled care facilities.

Conclusions: Despite the substantial clinical benefits from C5i, aHUS remains a morbid disease, as shown by hospital and ICU stay duration, RRT incidence, discharge care requirements, and mortality described in this US cohort. Future efforts should focus on improved time to treatment and developing novel therapies.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO794

Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics and Treatment Patterns Associated with Mortality During Index Hospitalization

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Background: aHUS is caused by dysregulation of the alternative complement pathway and is associated with significant morbidity and mortality. C5 inhibitors (C5i) improve thrombotic microangiopathy (TMA) response and renal recovery. This study described clinical characteristics and treatment patterns associated with mortality using real-world evidence from one of the largest, most diverse incident aHUS cohorts in the US during the C5i era.

Methods: This was a retrospective cohort study of 634 incident hospitalized adult aHUS patients, derived from the US Premier Healthcare Database, which contains ~25% of all US hospitalizations (1/2011–6/2021). aHUS was defined as the presence of a diagnostic code for TMA/HUS *and* a treatment code for a C5i in the absence of a diagnostic code for secondary causes of TMA/ HUS. Demographic and clinical characteristics were analyzed using t-test, Wilcoxon rank test, Fisher's exact test or Chi-squared test as appropriate.

Results: Overall, 78 patients (12.3%) died during hospitalization. Of 285 patients with mortality data post-discharge, 30- and 365-day mortality rates were 4% and 9%, respectively. In-hospital aHUS mortality was associated with older median age (63 vs 49 years, p<0.001), diabetes (30% vs 16%, p=0.003), longer median intensive care unit stay (14 vs 5 days, p<0.001) and hospital stay (31 vs 20 days, p<0.001), but not race, ethnicity, gender, history of hypertension, or CKD. In-hospital mortality was associated with a longer median delay between admission and therapeutic plasmapheresis (TPE) (5 vs 2 days, p<0.001) and C5i (15 vs 8 days, p<0.001). Although not associated with exposure or time until corticosteroids (CS), mortality was associated with duration of CS use (27 vs 16 days, p<0.001) and time from C5i initiation to CS discontinuation (14 vs 6 days, p=0.02). Mortality was associated with increased median time to renal replacement therapy (RRT) (5 vs 3, p<0.001) but not RRT requirement.

Conclusions: Delayed TPE, RRT, and C5i treatment and prolonged CS exposure are associated with increased mortality in aHUS. Future efforts should be made to reduce any treatment delays and develop more targeted, steroid-sparing treatments.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO795

Atypical Hemolytic Uremic Syndrome (aHUS) Clinical Characteristics Associated with Renal Replacement Therapy (RRT) Initiation During Index Hospitalization and RRT Requirement After Discharge

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Background: aHUS is caused by dysregulation of the alternative complement pathway and is associated with significant renal morbidity. This study described the clinical characteristics and treatment patterns associated with RRT, using real-world evidence from one of the largest and most diverse incident aHUS cohorts in the US during the C5 inhibitor (C5i) era.

Methods: This was a retrospective cohort study of 634 incident hospitalized adult aHUS patients derived from the Premier Healthcare Database, which contains ~25% of all US hospitalizations (1/2011–6/2021). aHUS was defined as presence of a diagnostic code for thrombotic microangiopathy (TMA) or HUS *and* a treatment code for a C5i in the absence of a diagnostic code for secondary causes of TMA or HUS. Demographic and clinical characteristics were analyzed using t-test, Wilcoxon rank test, Fisher's exact test or Chi-squared test as appropriate.

Results: The in-hospital RRT initiation rate was 77%. Compared with patients not requiring RRT, those who initiated RRT were significantly more likely to be White (64% vs 53%, p=0.04), have a history of heart failure (22% vs 9%, p<0.001), and have a longer median duration of intensive care unit (6 vs 4 days, p<0.001) and hospital (22 vs 16 days, p<0.001) stay. Age, sex, ethnicity, hypertension (HTN), CKD, and diabetes were not associated with RRT requirement. Patients receiving in-hospital RRT had a longer delay between admission and therapeutic plasmapheresis (TPE) (3 vs 2 days, p=0.007) or C5i (10 vs 7 days, p=0.006), but not corticosteroids (CS). RRT was discontinued by discharge in 51% of survivors. RRT requirement at discharge was associated with a history of HTN (79% vs 66%, p=0.004) and CKD (37% vs 26%, p=0.02) but not with age, race, ethnicity, sex, or diabetes. In-hospital RRT discontinuation was associated with TPE (84% vs 65%, p<0.001) and CS (81% vs 73%, p=0.04) but not with time between admission and C5i, TPE, or CS.

Conclusions: In patients with aHUS, preservation of renal function remains a challenge. Treatment and time to treatment are associated with renal outcomes. Future efforts should be made to measure the effect of aHUS treatment delay.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO796

Rapid Nephrogenomics in Intensive Care for Early Intervention in Adult Thrombotic Microangiopathies

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Background: Nephrogenomics, represents the study of genetic factors influencing kidney function and diseases. The field has rapidly advanced in recent years due to the development of high-throughput sequencing technologies such as next-generation sequencing (NGS). Thrombotic microangiopathy (TMA) encompasses various genetically driven diseases with some of them could benefit from early intervention (C5 blocking, VitB12 therapy). Structural variants (SV) in the CFH/CFHR gene region leading to the formation of gene fusions constitute a specific molecular diagnostic bottleneck associated with 5% of complement dependent TMA (c-TMA) cases. However, the highly repetitive character of sequences in this region, makes it difficult to detect these SVs when using standard short-read sequencing. Our current turn-around time for the diagnosis of TMA (3 weeks) is too long in some clinical context. Ultra-fast sequencing techniques using long reads Nanopores technologies can provide efficient and versatile cost-effective analysis in a matter of hours.

Methods: Here we report diagnostic results of Nanopore sequencing with adaptive sampling in TMA, which is a method to enrich sequences or genes of interest. We lower our TAT to 5 days with long reads sequencing and adaptive sampling. We established a rapid molecular diagnosis that allows time-decision making on the use of anti-C5 treatment for complement-mediated TMA (c-TMA), as averting unnecessary costly and potentially harmful therapy in patients who will in any case not respond to the anti-C5 treatment.

Results: With rapid and long reads sequencing, we were able to diagnosis a case of independent complement-TMA with a variant in *MMACHC*. We also retrospectively validated the detection of known SVs in four samples on which MLPA (Gold standard method to identify SV) analysis was performed. We were able to detect all the SVs in these samples such as CFH-CFHR1 hybrid, CFHR1-CFH hybrids of different sizes and a deletion of CFHR1-CFHR3.

Conclusions: Thus, rapid genomics using nanopore technologies can provide valuable insights into disease detection and treatment efficacy improving patient diagnosis and prognostic, enabling optimal and early therapeutic intervention.

Funding: Government Support - Non-U.S.

SA-PO797

Unusual Case of Thrombotic Microangiopathy (TMA) in the Setting of Severe Hypertension

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Introduction: 22-year-old female with a past medical history of hypertension since age 3, left ventricular hypertrophy since childhood, and hypokalemia and metabolic alkalosis who was referred for severe active on chronic thrombotic microangiopathy in the setting of difficult to control blood pressure. Her blood pressure had been previously well controlled but developed refractory hypertension starting in 12/2020. She had been on Nifedipine and Losartan but developed bilateral lower extremity edema in 2021 and was switched to Verapamil and Enalapril. She was continued on Amiloride and due to uncontrolled blood pressure, was switched from Hydralazine to Labetalol with better blood pressure control. Despite the combination of enalapril and amiloride, she remained with low levels of potassium.

Case Description: Previous work-up for secondary hypertension had been negative and patient had no family history of HTN. Renal biopsy in 2021 showed chronic-active thrombotic microangiopathy, largely affecting blood vessels, focal segmental and diffuse global sclerosing glomerulopathy, severe tubular atrophy and interstitial fibrosis, severe and diffuse chronic changes, and advanced IFTA and global glomerulosclerosis. TMA secondary to TTP, anti-cardiolipin syndrome, scleroderma, drugs, and infection were ruled out. Patient had a positive ANA but negative ENA and no clinical or laboratory signs of lupus. Genetic testing for complement regulatory proteins that are associated aHUS were unrevealing.

Discussion: At time of referral, we performed genetic testing and patient was found to have compound heterozygous mutations in HSD11B2 gene, which results in apparent mineralocorticoid excess (AME) an autosomal recessive disorder. Patient progressed to end stage renal disease. She received a deceased donor kidney transplant after a short course of peritoneal dialysis. Post-transplant course was complicated with prolonged hypotension secondary to chronic adrenal suppression, and responded well to Florinef. This case highlights the heterogeneity of TMA presentation and inform providers on management of hypotension after kidney transplantation in patients with AME.

SA-PO798

Primary Atypical Hemolytic Uremic Syndrome Presenting with Raynaud Phenomenon Triggered by COVID-19

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Anthony Provenzano.[2] *[1]East Carolina University Brody School of Medicine, Greenville, NC; [2]Eastern Nephrology Associates PLLC, Greenville, NC.*

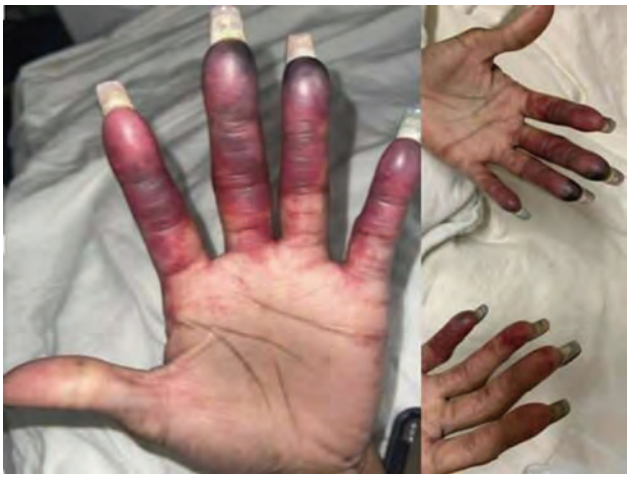
Introduction: COVID-19 has been linked to atypical hemolytic uremic syndrome (aHUS), although skin manifestations are rarely reported.

Case Description: A 48-year-old female with Mixed connective tissue disease (MCTD) presented after COVID-19 with Raynaud's phenomenon. Blood film showed schistocytes, ADAMTS13 level was 45%, before PLEX therapy. Labs (Coombs, antiphospholipid, CH50, hepatitis, HIV) were unremarkable but she had a positive RNP antibody and ANA with a titer of 1:320. Renal biopsy showed thrombotic microangiopathy and 20% interstitial fibrosis. Genetic testing revealed a heterozygous MCP/CD46 gene mutation. She needed 2 months of hemodialysis, but symptoms, platelets, and creatinine improved with ravulizumab initiation.

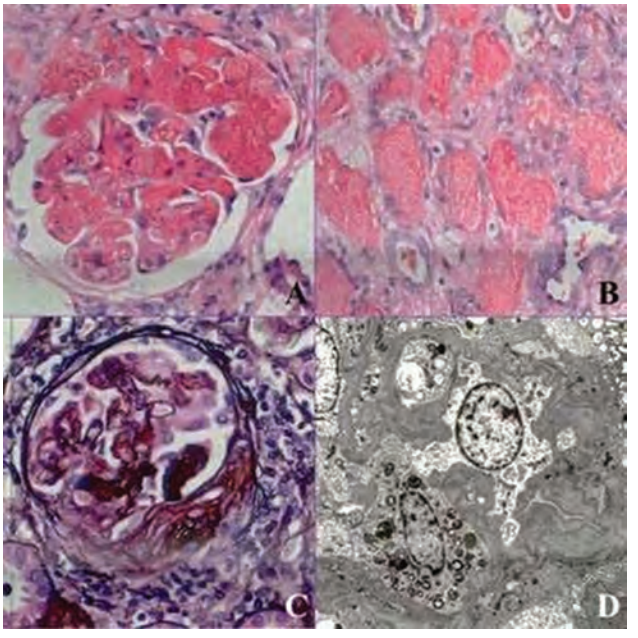
Discussion: Our case highlights skin involvement in primary genetic aHUS and the potential association between MCP/CD46 gene mutation and MCTD, which is rarely reported.

Results

Hemoglobin (mg/dL)	11
Platelets (mcL)	20
Creatinine (mg/dL)	8.44
Blood Urea Nitrogen (mg/dL)	84
Haptoglobin (mg/dL)	22
Lactate dehydrogenase (U/L)	5000



Raynaud's Phenomenon



A Global fibrin thrombus
B Acute tubular necrosis
C Segmental sclerosis, adhesions, and GBM corrugation
D Mesangiolysis and increased lamina rara interna.

SA-PO799

Complement-Mediated Hemolytic Uremic Syndrome due to CD46 Pathogenic Variant Unmasked by COVID-19

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Introduction: Complement-mediated hemolytic uremic syndrome (HUS) is rare, with an estimated incidence of 10 cases per 1,000,000 children in the U.S. Only 5 to 10 percent of these cases are from *CD46* gene variants. We report the case of a pediatric patient with a history of COVID-19 infection, presenting with severe thrombocytopenia, anemia and renal dysfunction who was found to have an extremely rare mutation in *CD46*.

Case Description: A previously healthy 3 y/o male presented with fever, abdominal pain, anorexia, and dark colored urine for 5 days. He had recent history of COVID-19. Mother denied him having had diarrhea. He had no prior history of kidney diseases and family history was non-contributory. Physical exam was remarkable for scleral icterus, and diffuse abdominal tenderness. Laboratory workup showed anemia (hemoglobin: 6.4 g/dL), thrombocytopenia (21 x 10^3µL), acute kidney injury (BUN 102 mg/dL, plasma creatinine 2.45 mg/dL), and schistocytes in peripheral blood smear. He also had hyperbilirubinemia (total bilirubin 2.4 mg/dL, direct bilirubin 1.7 mg/dL), elevated lactate dehydrogenase (2,991 U/L), gross hematuria and nephrotic range proteinuria (urine protein to creatinine ratio 4.6 mg/mg). Clinical picture was consistent with thrombotic microangiopathy. Further workup revealed a negative direct antiglobulin test, normal complement C3 and C4 levels, and normal ADAMTS13 activity level. Stool was negative

for Shiga toxin. We suspected this was a case of atypical HUS (aHUS) in the setting of recent viral infection (COVID-19). Genetic panel for aHUS was ordered, and patient was started on Eculizumab (human anti-C5 monoclonal antibody).

Discussion: Patient's clinical status significantly improved after the first dose of Eculizumab. Platelet count and BUN normalized. Hemoglobin and plasma creatinine improved significantly (8.5 g/dL and 0.8 mg/dL respectively). LDH was down trending by the time of discharge (1238 U/L). Genetic panel revealed an extremely rare heterozygous nonsense variant in exon 5 of the *CD46* (c.486T>A, p.Cys162Stop) confirming our working diagnosis. This case demonstrates the importance of prompt recognition of aHUS, early genetic/functional testing for complement-mediated aHUS and early initiation of Eculizumab to reduce the risk of permanent kidney damage. It also shows that COVID-19 infection may act as trigger for complement-mediated aHUS.

SA-PO800

Partial Rescue of Complement-Induced Organ Injuries in a Factor H Mutant Mouse by MASP3 Deficiency

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Background: Complement is activated through three canonical pathways: classical pathway (CP), lectin pathway (LP) and alternative pathway (AP). MASPs was known as a component of LP, but according to recent reports, MASPs was also participate AP. *MASP1* gene knock-out mice (MASP-1/3 lacked) showed no AP activity and furthermore, MASP3 was clarified that it was responsible for the AP activation through maturation of pro factor D. These findings open the door to developing MASP3 targeting therapy for AP mediated disease, but we need to confirm blocking MASP3 is truly effective in vivo. In this study, we tested whether MASP3 deficiency abrogate phenotypes of a murine atypical HUS(aHUS) model with complement factor H point mutation.

Methods: We generated MASP3 knockout mice ($MASP3^{-/-}$) and crossed with complement factor H mutant mice($FH^{R/R}$) which showed thrombotic microangiopathy and systemic thrombophilia as we previously reported. We then compared $FH^{R/R}$ $MASP3^{-/-}$ with littermates, $FH^{R/R}$ MASP3 wild type($FH^{R/R}$) in survival, hemoglobin or platelet level, and histologic change in major organs including kidney.

Results: We found that MASP3 deficiency rescued $FH^{R/R}$ from thrombocytopenia, anemia and renal failure. They were also prevented from large vein thrombi in liver and kidney. However, about 30% of $FH^{R/R}$ $MASP3^{-/-}$ died of extra-renal organ injuries such as intestinal injury, pulmonary hemorrhage and cerebral ischemia. We measured LPS based AP activity with 20% serum from mice and found that a complement AP activity in $FH^{R/R}$ $MASP3^{-/-}$ was significantly lower than that in $FH^{R/R}$, but higher compared with that in $FH^{R/R}$ $FD^{-/-}$.

Conclusions: These findings demonstrated that MASP3 could be therapeutic target for complement AP mediated diseases, but it is important to assess whetheher residual AP activity by pro-FD cause tissue injury in each setting.

Funding: Other NIH Support - NIAID

SA-PO801

An Unusual Case of Lupus-Associated Atypical Hemolytic Uremic Syndrome Presenting with Diffuse Alveolar Hemorrhage and Acute Renal Failure

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare genetic disease characterized by acute renal injury (AKI), thrombotic microangiopathy (TMA), and other end-organ damage. It occurs when genetic mutations alter complement regulatory proteins, most commonly complement factor H. As a diagnosis of exclusion, it presents a unique diagnostic challenge. Eculizumab, a monoclonal antibody against complement C5, is the treatment of choice for primary aHUS.

Case Description: A 43 year old male with past medical history of systemic lupus erythematosus, Grave's disease, and hypertension presented to our institution with respiratory distress, hemoptysis, and subjective fevers. He had recently been treated with intravenous antibiotics after sustaining a cat bite. On presentation, he was profoundly hypoxic with elevated D-dimers, thrombocytopenia, and diffuse bilateral alveolar infiltrates. Patient was subsequently intubated, and serial bronchiolar lavage was consistent with diffuse alveolar hemorrhage (DAH). Renal function rapidly declined and lupus pneumonitis and nephritis were suspected; renal biopsy showed class III lupus nephritis. Pulse dose steroids and rituximab were initiated. Despite this, patient developed recurrent hemoptysis, worsening renal failure, and purpuric rash, which did not improve with plasmapheresis. In setting of markedly elevated D-dimers and LDH, thrombocytopenia, low haptoglobin, and peripheral smear revealing schistocytes, thombotic microangiopathy was suspected. Furthermore, markedly depressed complement levels pointed towards complement activation, likely triggered by his previous infection, resulting in adult onset atypical hemolytic uremic syndrome. Eculizumab was initiated and patient was eventually discharged to rehabilitation unit. Genetic testing revealed he was positive for aHUS with thrombomodulin gene mutation.

Discussion: This is an unusual case of lupus associated aHUS, likely triggered by infection caused by cat bite which triggered alternate complement pathway causing DAH. Atypical HUS presenting as DAH is extremely rare, and this case pointed towards lung restricted TMA. It is imperative that aHUS remains on the differential for patients with AKI and suspected TMA, as recognition of this diagnosis drastically alters management. Timely management lowers morbidity and mortality in aHUS.

SA-PO802

Diagnostic Utility of Whole Exome Sequencing in Adults with CKD and Biological Markers of Thrombotic Microangiopathy

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Background: Chronic kidney disease (CKD) in adults may be associated with biological markers of thrombotic microangiopathy (TMA), defined as a mechanical hemolytic anemia with a decreased platelet count. In a number of cases, even after an extensive investigation including the search for variants in genes regulating the complement pathway, a definitive diagnosis cannot not be achieved. Whole Exome Sequencing (WES), which examines the entire coding regions of the genome, could be of interest in these clinical forms.

Methods: We included all consecutive adult patients who underwent WES for CKD of unknown origin between 10/10/17 and 31/12/22 in the Nephrology Department of Sorbonne University (Tenon and Pitié-Salpêtrière hospitals). The collection of clinical characteristics, including the presence of biological markers of TMA, is prospectively done by the prescribing physician. We retrospectively assessed whether patients had been accurately classified (Figure 1). All diagnoses were made according to the guidelines of the American College of Medical Genetics and Genomics.

Results: During the study period, 1410 patients underwent WES, and 193/1410 (14%) exhibited biological markers of TMA. Among them, WES identified a variant consistent with the renal phenotype in 31/193 (16%) cases. 22/31 (71%) did not involve genes regulating the alternative complement pathway: type 4 collagens (*COL4A3*, *COL4A4*, *COL4A5*) (n=7); nephronophthisis-associated genes (*TTC21B*, *NPHP3*, *NPHP4*) (n=5); *IFT140* (n=2); *TRPC6*, *PAX2*, *SOX18*, *HNF1A*, *MMACHC*, *SPTB*, and *MT-TL1* (n=1 each). Complement-related disorders involved *CFH* (n=4), *CFI* (n=3), *CD46* and *C2* (n=1 each).

Conclusions: Whole Exome Sequencing of 193 patients with CKD associated with TMA resulted in a diagnosis in 31/193 (16%) of the cases, and 22/31 (71%) diagnoses did not involve the alternative complement pathway.

Characteristic	N	No TMA, N = 1,217[1]	TMA, N = 193[1]	p-value[2]
Platelets, G/L	925	188 (139, 244)	141 (91, 200)	<0.001
Hemoglobin, g/dL	925	10.40 (7.50, 12.60)	8.00 (6.50, 10.30)	<0.001
Lactate dehydrogenase, U/L	783	297 (224, 417)	455 (330, 650)	<0.001
Haptoglobin, g/L	619	1.10 (0.58, 1.74)	0.43 (0.00, 1.08)	<0.001
Schizocytes, presence	381	32 (13%)	60 (47%)	<0.001
Schizocytes, %	208	0.00 (0.00, 0.00)	1.00 (0.00, 2.15)	<0.001
C3, g/l	474	1.02 (0.83, 1.21)	0.94 (0.77, 1.16)	0.022
C4, g/l	465	0.28 (0.22, 0.36)	0.27 (0.22, 0.35)	0.3
Anti-beta 2 glycoprotein 1, presence	280	22 (11%)	10 (11%)	>0.9
Anti-cardiolipin, presence	315	6 (2.7%)	3 (3.2%)	0.7
Pathological rosner index	101	14 (19%)	5 (18%)	>0.9

[1] Median (IQR); n (%)
[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

SA-PO803

The Value of Advanced Cardiac Magnetic Resonance Imaging Technologies in Detecting the Characteristics of Cardiac Involvement in Anderson-Fabry Disease

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Background: Anderson-Fabry disease (AFD) is a genetic disorder associated with cardiac involvement. Advanced cardiac magnetic resonance (CMR) technologies, including T1 mapping and gadolinium-enhanced CMR, have been used to detect and evaluate cardiac involvement in AFD patients. However, there is limited information on the characteristic CMR manifestations in Chinese AFD patients.

Methods: In this cross-sectional study, data were collected from patients with AFD diagnosed at this center from January 2022 to March 2023. Compared with echocardiography, CMR was used to evaluate cardiac function, the degree of cardiac structural lesions, and to analyze characteristic CMR findings in AFD.

Results: 20 patients with AFD from nine families were included. This study showed that left ventricular hypertrophy (LVH) was detected in 85% of patients (18.41 ± 4.56 mm) by CMR, whereas echocardiography identified LVH in only 65% of patients (16.86 ± 2.74 mm), suggesting that echocardiography may underestimate the severity of LVH in AFD patients (P=0.001). Moreover, all patients exhibited characteristic CMR findings of cardiac involvement in AFD (Fig.1, Fig.2), including decreased T1 values (95% of patients) and late gadolinium enhancement (LGE) associated with myocardial fibrosis (55% of patients).

Conclusions: This study demonstrated that CMR is a valuable tool for detecting and assessing cardiac involvement in AFD patients, providing characteristic CMR findings, including LVH, decreased T1 values, and LGE associated with myocardial fibrosis. Moreover, this study highlighted the diagnostic superiority of CMR over echocardiography in assessing LVH in AFD patients.

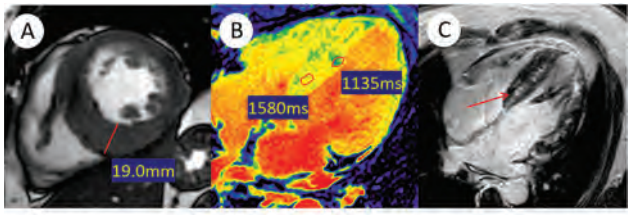

Fig.1. A: End-diastolic frames from cine in AFD patient (F1f): The myocardium is extensively thickened, the ventricular septal myocardium is significantly thickened, and the thickest myocardium is 19mm; B: T1Mapping(3.0T) in AFD patient (F1f): T1 values was uneven, the T1 value in the corresponding area of LGE was increased, the T1 value of non LGE zone is about 1100-1200ms; C: Gadolinium-enhanced cardiac magnetic resonance (10-15min) in AFD patient (F1f): Decreased subendocardial perfusion and LGE (indicated by the red arrow) were observed in the apical segment.

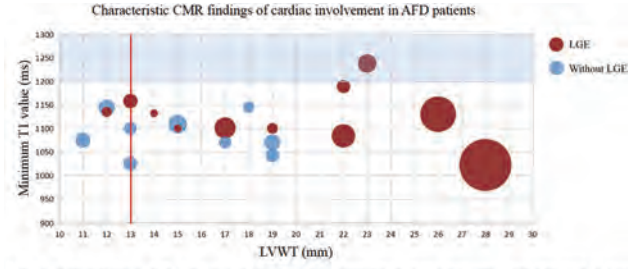

Fig.2 Characteristic CMR findings of cardiac involvement in AFD patients. The abscissa is the LVWT (mm) of each patient; The ordinate is the minimum T1 value (ms) of each patient; The bubble width is the LVMI of each patient. The red bubble represents that the patient has LGE, the blue bubble represents that the patient has no LGE. The red line is the critical line for the diagnosis of left ventricular hypertrophy (LVWT≥13mm), and the blue rectangle is the normal T1 value (1200--1300ms) in this center. LVWT: left ventricular wall thickness, LVMI: left ventricular mass index.

SA-PO804

FollowME Fabry Pathfinders Registry: Renal Effectiveness in a Cohort of Patients on Migalastat Treatment for at Least Three Years

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Background: The followME Fabry Pathfinders registry (EUPAS20599) is evaluating real-world safety, effectiveness and patient-reported outcomes for patients with Fabry disease who were enrolled into one of three groups: migalastat-amenable *GLA* variants receiving migalastat, any *GLA* variant receiving enzyme replacement therapy and migalastat-amenable *GLA* variants not receiving Fabry disease-specific therapy (untreated).

Methods: We present effectiveness data across categories of kidney function at enrollment in a cohort of patients who had received ≥3 years of migalastat treatment. Enrolled patients were ≥12 years old with an estimated glomerular filtration rate (eGFR) >30 mL/min/1.73 m2.

Results: As of August 2022, 125 patients (60.0% males; median age, 58.0 years) with amenable *GLA* variants had a mean migalastat exposure of 3.9 years. At enrollment, mean±SD eGFR was 83.7 ± 22.5 mL/min/1.73 m^2, and overall, 17 (14.7%) patients had an eGFR <60 mL/min/1.73 m^2. Median urine albumin: creatinine ratio was 19.0 mg/g (range 0–1124, n=40). Mean (SD) eGFR annualized rate of change (mL/min/1.73 m^2/year) in the overall cohort was –0.9 (4.9). When analyzed by eGFR category at enrollment annualized change was –1.0 (3.9) in patients with eGFR ≥90 (33.6%), –1.0 (5.9) in patients with eGFR ≥60–90 (43.2%), and –0.4 (3.5) in patients with eGFR ≥30–60 (12.8%). Overall, 94.4% of patients did not experience a renal Fabry-associated clinical event (FACE: doubling of serum creatinine level from the start of analysis [two consecutive values]; end-stage renal disease requiring long term dialysis or transplantation). Seven patients each experienced one renal FACE for an incidence of 14.2/1000 patient-years. When excluding patients with the mostly cardiac variant p.N215S (69.6%, n=87) mean eGFR rate of change was –1.4 (4.6) mL/min/1.73 m^2/year, n=81) and renal FACEs incidence was 20.9/1000 patient-years.

Conclusions: These data support sustained effectiveness with migalastat, regardless of kidney function at enrollment, in an amenable real-world cohort of patients with Fabry disease.

Funding: Commercial Support - Amicus Therapeutics

SA-PO805

Evaluation of Long-Term Renal Outcomes in Fabry Disease: A Single-Centre Prospective Cohort Study in North-West England

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Background: Fabry disease (FD) is a rare X-linked lysosomal storage disorder whereby deficiency of α-galactosidase-A results in progressive renal impairment and end-stage renal failure (ESRF). International recommendations suggest enzyme replacement therapy (ERT) in those with early signs of renal dysfunction, yet limited data exist on long-term outcomes.

Methods: 395 patients were included from a national FD database from conception to 1 February 2022. Baseline data include FD mutation, diagnosis and ERT initiation dates, renal biochemical values, co-morbidities and medications. Those on renal replacement therapy (RRT) were excluded. Rapidly progressive renal dysfunction was defined as eGFR decline of > 1 ml/min/year. Primary outcomes include ESRF requiring RRT, all-cause mortality, and non-fatal cardiovascular events (NFCVE).

Results: 395 patients (M=172;F=223) with median follow-up of 6.4 years were analysed. Males received more treatment (147 v 92, p<0.001), had RRT (12 v 1, p<0.001), experienced NFCVE (75 v 42, p<0.001) and all-cause mortality (21 v 8, p<0.001). Sub-cohort analysis (n=260) showed faster eGFR decline was not predictive of RRT, but associated with higher rates of NFCVE (52 v 50, p=0.01) and all-cause mortality (17 v 8, p=0.004;fig.1). Multivariate regression demonstrated only advancing age associated with faster renal disease progression (OR:1.05; 95% CI: 1.02-1.07; p<0.001). 33 developed CKD during median follow-up of 10.9 years. Genetic analysis showed highest prevalence of the commonest late-onset variant *c.644A>G/p.N215S.* 18(55%) started ERT, and 6 discontinued due to gastrointestinal intolerance or tiredness. 15(45%) experienced NFCVE, with stroke/TIA being commonest (n=6).

Conclusions: Our study supports early initiation of ERT, prior to onset of any renal decline, and advanced age a predictor of adverse outcomes.

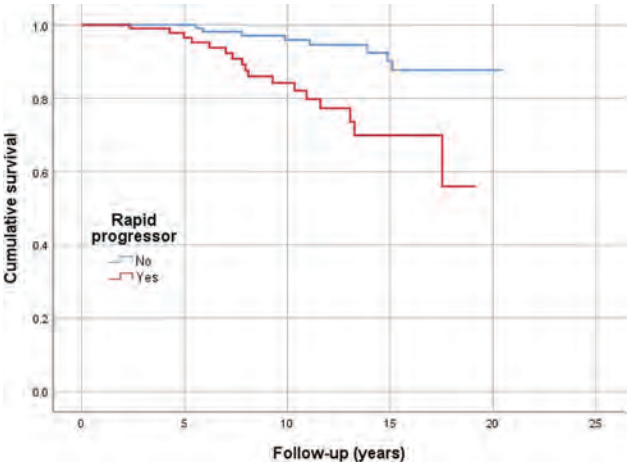

Figure 1: Rate of survival (all-cause mortality) of faster/slower eGFR progressors. Log-rank p<0.001

SA-PO806

Multidisciplinary Approach to Assessment and Management of Children with Fabry Disease: A Multicentre Study

Liu Jialu, Hong Xu, Qian Shen. Internet Plus Nephrology Alliance of the National Center for Children's Care. *Children's Hospital of Fudan University, Shanghai, China.*

Background: Considering the diversity manifestations of Fabry disease (FD) in chlidren, methods to improve screening and management of the suspects are needed. In April 2020, our hospital established China's first multidisciplinary diagnosis and treatment team (MDT) for children with FD, from July 2021 to January 2022, the MDT promoted to 15 centers in China.

Methods: This study summarizes characteristics and treatment of 45 children diagnosed with FD before January 1, 2023 by pediatric MDT teams of 21 centers in China. Data were derived from a multicenter network (Chinese Children Genetic Kidney Disease Database). A questionnaire specifically designed.

Results: Diagnostic median age was 10.9 year in males and 9.8 year in females, 26.4% in males and 81.8% in females were diagnosed by family screening, 11.8% in males were diagnosed by genetic test for other genetic disorders. At enrollment (median age 12.0 year), 29 (85.3%) of males and 5 (45.0%) of females reported symptoms (Fig1, 2). The median age of symptom onset was 6.7 year in males and 8.0 year in females. The most frequent symptom, neuropathic pain, was reported by 79.4% of males (median age 8 year) and 45.0% of females (median age 9 year). Anhidrosis or hypohidrosis were reported by 48.9%. 50% of males underwent lung function evaluation indicated obstructive respiratory diseases. 4 Of the 6 males developed Low bone mineral density. A few patients had serious manifestations, stage 5 chronic kidney disease (n=1), arrhythmia (n=4), and left ventricular hypertrophy (n=3). 22 had received agalsidase (start at median age 13.7 year in males and 13.5 year in females).

Conclusions: We provide an overview of the multicenter network of MDT for children with FD in China.

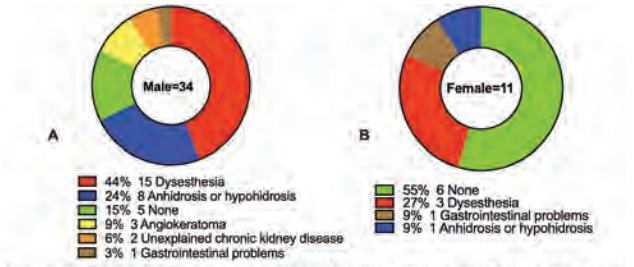

Figure 1. The first symptoms in male (A) and female (B) patinets diagnosed with Fabry disease

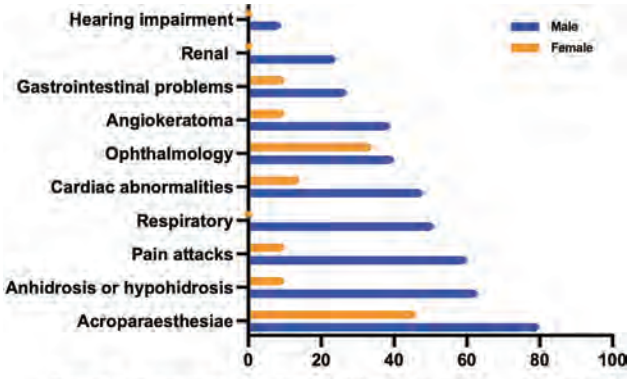

Figure 2. Proportion of male (n = 34) and female (n = 11) patients with Fabry disease showing different clinical manifestations.

SA-PO807

New Biomarkers to Quantify Fabry Disease Activity

Seyda G. Ozcan,[1] Necmi Eren,[2] Mevlut T. Dincer,[1] Metin Ergul,[2] Hakan Özer,[3] Kultigin Turkmen,[3] Sinan Trabulus,[1] Nurhan Seyahi.[1] *[1]Istanbul Universitesi-Cerrahpasa, Istanbul, Turkey; [2]Kocaeli Universitesi Tip Fakultesi, Izmit, Turkey; [3]Necmettin Erbakan Universitesi Meram Tip Fakultesi Hastanesi, Konya, Turkey*.

Background: Fabry disease (FD) is a rare, genetic lysosomal storage disease. Kidney and cardiac involvement are the leading causes of morbidity and mortality. Slow progression, genotypic and phenotypic heterogeneity prevents accurate prediction of the disease progression. We aimed to investigate the association of different biomarkers with FD activity for this unmet need.

Methods: In this case-control study, we examined 87 Fabry patients (FP), 46 CKD patients and 41 healthy controls (HC). Study subjects were recruited according to inclusion and exclusion criteria. We studied KIM-1, MCP-1, YKL-40, TNFR-1, TNFR-2, CysC with ELISA and eGFR was calculated based on cr and cr-Cys-C in all subjects. Statistical analysis was carried out using log transformed values of biomarker levels adjusted for age, sex and BMI.

Results: Box plots of biomarker levels are shown in Figure 1. While there was no difference between FP and HC regarding eGFR(cr); eGFR(cr-CysC) was significantly lower in FP. KIM-1 was significantly higher in FP compared to HC. MCP-1 was significantly lower in FP compared to CKD patients, and it was significantly higher in FP with cardiac involvement than in those without cardiac involvement as in renal involvement. YKL-40 was significantly lower in FP without kidney involvement compared to both control groups, probably reflecting the effect of enzyme replacement therapy (ERT). KIM-1 and YKL-40 were correlated with Lyso Gb3 while MCP-1 was not.

Conclusions: MCP-1, KIM-1, YKL-40 and CysC seem to be useful markers for the management of FP, each associated with a different aspect of the disease. While KIM-1 appears to be independent of organ involvement, MCP-1 seems to be associated with kidney and cardiac involvement independent of Lyso Gb3. YKL-40 might be associated with response to ERT. Identification of new pathogenic pathways associated with those biomarkers, might contribute to new treatment approaches.

Funding: Government Support - Non-U.S.

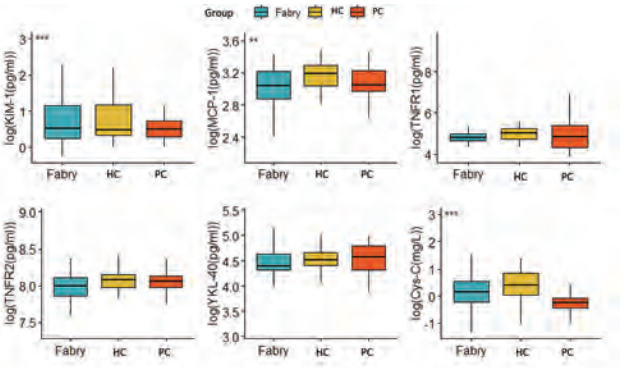

Figure 1. Biomarker levels in Fabry patients, patient controls and healthy controls
HC: Healthy control PC: Patient control
** MCP-1 p:0,025[2] ***KIM-1 p:<0,001[3] ***Sistatin C p:<0,001[1,3]
[1]HC-PC, [2]PC-Fabry, [3]HC-Fabry

SA-PO808

The Utility of Obtaining Kidney Biopsy in Female Patients with Fabry Disease

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Background: Fabry Disease (FD) is an X-linked inherited disorder caused by alpha-galactosidase-A enzyme deficiency resulting in the accumulation of the large fatty substrate Globotriaosylceramide (GL-3) in different cell types and organs. FD affects both males and females, but males usually develop symptoms at an earlier age and have more severe manifestations. Male patients with FD should be started on treatment at time of diagnosis. The decision to treat female patients with FD has been mostly determined by the severity of manifestations. Obtaining kidney biopsies in female patients with FD to support the decision to start treatment with enzyme replacement therapy or chaperone-based therapy remains controversial.

Methods: 14 female patients with FD underwent kidney biopsy at the University of Kansas Hospital shortly after being diagnosed with FD between 2011 and 2023. The age range was from 10 to 55 years. Serum creatinine, urine protein quantification, genetic mutation and clinical manifestations were recorded at the time of biopsy.

Results: Only one kidney biopsy revealed normal findings. 11 kidney biopsies revealed Fabry nephropathy as the sole pathology with light microscopy showing vacuolation in podocytes, glomeruli and tubular epithelial cells and electron microscopy showing lamellated inclusions. 6 of the 11 patients with Fabry nephropathy had microalbuminuria, 2 of which had abnormal kidney function. One kidney biopsy revealed crescentic glomerulonephritis coexisting with Fabry nephropathy in a patient with abnormal kidney function and non-nephrotic range proteinuria. Another kidney biopsy revealed IgA glomerulonephritis coexisting with Fabry nephropathy in a patient with abnormal kidney function and nephrotic range proteinuria.

Conclusions: This case series shows that Fabry nephropathy in female patients with FD is common despite most patients presenting with normal kidney function and no or minimal microalbuminuria. These findings suggest a beneficial role for kidney biopsy in female patients with FD to help guide treatment plan and to rule out coexisting conditions.

SA-PO809

Advanced Disease Modeling of the Fabry Disease Cardiorenal Phenotype with Organoids from Patient-Derived Human-Induced Pluripotent Stem Cells

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Background: Fabry disease is a multi-systemic lysosomal storage disorder resulting from mutations in the *GLA* gene. This complex lysosomal storage disorder can currently not be modelled accurately in animal models. Our project, therefore, aims at establishing advanced human in vitro systems to further our molecular understanding of the disease's pathology. To establish these informative systems, we employ human induced pluripotent stem cells (hiPSC) of Fabry patients and differentiate them into disease-relevant organoid systems.

Methods: We reprogrammed hiPSC from primary urinary cells (PUCs) collected from Fabry patients with different mutations (classical, classical and chaperone amenable, late onset, unclear significance). Isogenic control lines were created by CRISPR Cas9 gene editing. Using published protocols, we differentiated these cell lines into kidney and heart organoids as well as engineered heart tissue (EHTs) using published protocols.

Results: We confirmed the loss of alpha-galactosiade A protein, enzyme activity and the accumulation of globotriaosylceramide in patient-derived hiPSC lines and organoids

This phenotype did not impair the differentiation into organoids and EHTs. We established the treatment with enzyme replacement and, where applicable, chaperone therapy. Kidney organoids contained different nephron segments and confirmed the recently published pathologic accumulation of synuclein alpha in Fabry nephropathy. Heart organoids contracted and depicted several cardiac cell types including cardiomyocytes with sarcomeres and Z-Disc formation. Fabry EHTs contracted with reduced force and were prone to arrhythmias mirroring the clinical phenotype seen in Fabry patients.

Conclusions: We have established a novel unique discovery platform for human *in vitro* disease modelling to study Fabry disease. Ongoing experiments focus on single cell analyses of the established systems in combination with deep proteomic and spatial phenotyping combined with the application of available therapies.

SA-PO810

Exome Sequencing in Individuals with CAKUT Identifies De Novo Variants in Novel Candidate Genes in 15.5%

Caroline M. Kolvenbach,[1] Lea M. Merz,[1] Chunyan Wang,[1] Nils D. Mertens,[1] Steve Seltzsam,[1] Bshara Mansour,[1] Selina Hölzel,[1] Nina Mann,[1] Katharina Lemberg,[1] Ken Saida,[1] Florian Buerger,[1] Camille H. Nicolas Frank,[1] Kirollos Yousef,[1] Daanya Salmanullah,[1] Seyoung Yu,[1] Alina Hilger,[3] Velibor Tasic,[2] Shirlee Shril,[1] Friedhelm Hildebrandt.[1] *[1]Boston Children's Hospital, Boston, MA; [2]Medical Faculty of Skopje, Skopje, Macedonia (the former Yugoslav Republic of); [3]University of Erlangen, Erlangen, Germany*.

Background: Congenital anomalies of the kidney and urinary tract (CAKUT) represents the most frequent birth defect and encompasses a large variety of malformations arising from defective nephrogenesis. To date, mutations in 50 monogenic genes are known to cause CAKUT. However, in only 15-20% of CAKUT cases a causative mutation in a known monogenic CAKUT gene can be identified. Recent studies show the impact of *de novo* variants in *FOXP1* and *ZMYM2* in individuals with CAKUT, suggesting that *de novo* variants contribute to the genetic disease etiology.

Methods: In this study, we performed exome sequencing (ES) in 731 families out of which 264 were trio families in order to detect novel CAKUT candidate genes.

Results: i) Through proband-parent based evaluation, a variant in a single candidate gene was detected in 79 of 264 families (29.9%). **ii)** In 41 of 264 trio families (15.5%), we identified strong *de novo* variants in 43 potential novel CAKUT candidate genes. **a)** Of these 43 *de novo* variants, truncating or splice site *de novo* variants were found in nine genes (*ASPHD1, COPS7A, DUSP23, FBXW7, GRHL1, MTHFD1, PLA2G4A, SLTM, SOX13*). **b)** Four *de novo* variants were detected in murine CAKUT genes (*AGRN, COPS7A, PDE1A, PDS5A*). **c)** Interestingly, a relatively high percentage of *de novo* variants (25.6%, 11 out of 43) occurred in genes that are involved in transcription (*BRPF1, BSX, COPS7A, DLX3, FBXW7, GRHL1, IRX6, PROX1, SLTM, SOX13, TLK2*). **d)** Four *de novo* variants were found in genes that are paralogs of known disease causing CAKUT genes (*AGRN, HSP90AB1, PTPRZ1, SOX13*). Scoring variants in identified genes based on these categories (**a-d**), identified *COPS7A* and *SOX13* as the most promising new candidate genes for CAKUT.

Conclusions: Our findings suggest that *de novo* variants in novel candidate genes may contribute to the CAKUT pathogenesis. Here, we propose two novel candidate genes for CAKUT.

SA-PO811

GEN1 Is a Likely Candidate Gene for Human Congenital Anomalies of the Kidney and Urinary Tract

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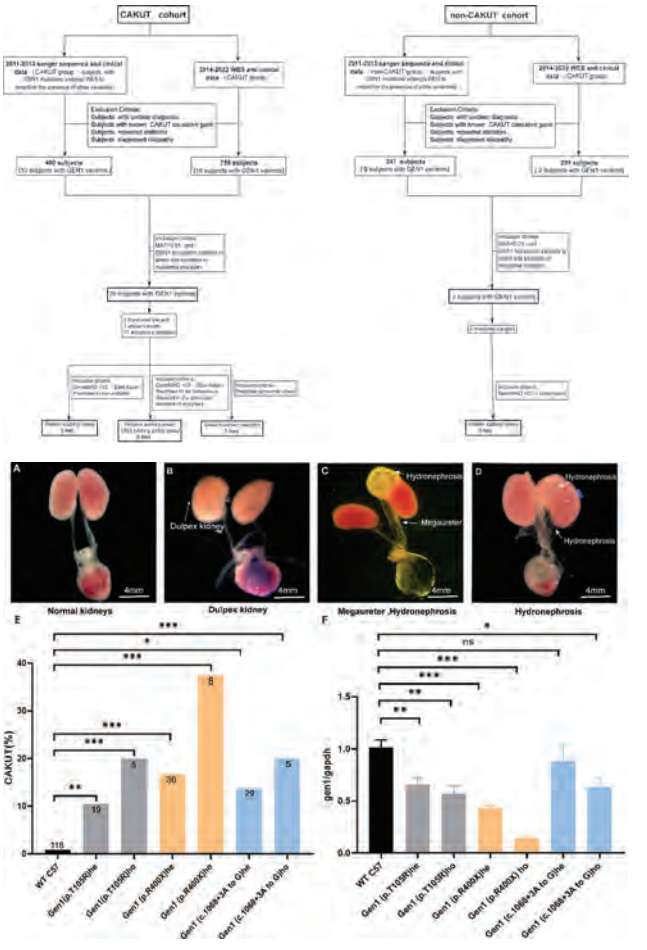
Background: Congenital anomalies of the kidneys and urinary tract (CAKUT) are among the most prevalent birth defects. Although many pathogenic genes of CAKUT have been discovered, they are far from enough to reveal the causes of all CAKUT patients. Previous studies suggest that *Gen1* is a mouse CAKUT gene.

Methods: There are three main parts, population data collection, in vitro function verification, and point mutation mouse construction and phenotypic observation (Fig1).

Results: DNA from 910 individuals with CAKUT were collected, among which 26 *GEN1* variants were identified, and two *GEN1* (missense) variants in a non-CAKUT group were found. In vitro, 10 variants (eight in the CAKUT group and two in the non-CAKUT group) were selected to verify mutant protein stability and protein stability changed in six variants in the CAKUT group. Using an electrophoretic mobility shift assay on eight variants (six in the CAKUT group and two in the non-CAKUT group) the enzymatic hydrolysis and DNA-binding abilities of mutant proteins were found to be impaired to varying degrees in CAKUT group, among which the most serious functional damage was observed in the *Gen1* variant that produced a truncated protein. Moreover, a mini-gene splicing assay showed that the c.1071+3 A>G variant in CAKUT group significantly affected splicing function. Three point mutant mouse strains were constructed and CAKUT phenotypes were replicated (Fig2).

Conclusions: Our findings promoted that *GEN1* is likely a human CAKUT candidate gene.

Funding: Government Support - Non-U.S.



SA-PO812

A Case Report of Functional Renal Impairment in Adult Patient with Townes-Brocks Syndrome

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Introduction: A late presentation of functional renal impairment without structural changes in a patients with Townes-Brocks Syndrome (TBS).

Case Description: A 48-year-old male patient with no significant past medical history presented to Nephrology clinic with incidental diagnosis of abnormal renal function on routine blood work. He does not endorse any other concomitant clinical symptoms including genito-urinary symptoms, denies regular use of NSAIDs, history of drug abuse or any history of hepatitis or HIV. Lab works showed elevated serum creatinine at 1.81 mg/dL and GFR of 46, urine albumin 1+, protein/creatinine ratio of 192 mg/g (in 24 hours), positive ANA (homogenous; 1:160) with normal C3, C4, C-ANCA and P-ANCA. Other CKD labs were reviewed and found to be within normal range. Serum protein electrophoresis and immunofixation did not reveal any monoclonal paraproteinemia. Renal ultrasound showed normal sized kidneys with increased echogenicity bilaterally, but no structural changes or hydronephrosis. No specific aetiology for CKD was identified. Coincidently, his son was born with one kidney as a part of congenital Townes-Brocks syndrome with chromosome analysis showing abnormality in chromosome 19, which is autosomal dominant and paternally inherited. Paternal chromosome analysis revealed similar diagnosis with heterozygous genotype.

Discussion: Towne-Brock's syndrome (TBS) is a rare autosomal dominant condition resulting from heterozygous variant in SALL1 gene and characterized by triad of imperforate anus, dysplastic ears and hand malformation. Renal impairment occurs in 42% of cases including ESRD with or without structural abnormalities and malformations. However, data on long term prognosis of renal involvement, slope of declining renal function and risk of developing renal failure is lacking. Thus, yearly renal function assessment throughout the life is indicated for patients with TBS as well as those with first degree relatives with TBS. Also, there is a need to determine the evidence of SALL1 mutation in patients with late-onset functional kidney disease without structural changes as well as in those with nephropathies of unknown origin in adulthood.

SA-PO813

Large-Scale Exome Sequencing Analysis Implicates FOXQ1, FOXI2, EXOSC2, and MMP15 as Candidate Genes for Human Congenital Obstructive Uropathy

Juntao Ke,[1] Tze Yin Lim,[1] Yask Gupta,[1] Gundula Povysil,[1] Gina Jin,[1] Jeremiah Martino,[1] Francesco Scolari,[2] Velibor Tasic,[3] Cathy L. Mendelsohn,[4] Ali G. Gharavi,[1] Simone Sanna-Cherchi.[1] *[1]Columbia University, New York City, NY; [2]Universita degli Studi di Brescia, Brescia, Italy; [3]Medical Faculty of Skopje, University Children's Hospital, Skopje, Macedonia (the former Yugoslav Republic of); [4]Columbia University Irving Medical Center, New York, NY.*

Background: Congenital obstructive uropathy (COU) is the most frequent urinary tract anomaly occurring in up to 2% of pregnancies, constituting a leading cause of pediatric chronic kidney disease. The genetic causes of COU are not well understood and remain to be deciphered.

Methods: We conducted an exome sequencing (ES) study on 880 COU cases, encompassing three main classes of congenital urinary obstructions: a) Ureteropelvic Junction Obstruction (UPJO; N=331), b) Ureterovesical Junction Obstruction / megaloureter (UVJO; N=188), and c) COU not otherwise specified (COU-NOS; N=361). To investigate the excess burden of rare coding variants on COU, we performed exome-wide collapsing analysis comparing the above 880 cases and 16,135 population controls with ES data using 4 main genetic models (3 dominant and one recessive). Analyses were conducted on the entire dataset and then again after removal of cases harboring diagnostic/pathogenic Mendelian mutations and structural variants. Study-wise exome-wide significant threshold was set at 1.25×10^{-6}.

Results: In the analysis on the entire cohort of 880 COU cases, the top signal was for *FOXQ1* in the dominant ultrarare model from European population ($P = 8.49 \times 10^{-6}$; OR= infinite). The signal improved after removal of solved cases, exceeding exome-wide significance ($P = 7.64 \times 10^{-7}$; OR= infinite), and supporting candidacy for this gene. Moreover, *Foxq1* is specially expressed in the mouse developing ureteric buds, ureteric epithelium cells of fetal mouse and human urinary tracts. From the subtype analysis, we found the following suggestive signals: *EXOSC2* ($P = 2.96 \times 10^{-5}$; OR= infinite) and *FOXI2* ($P = 5.52 \times 10^{-5}$; OR= 82.63) for UPJO; *MMP15* ($P = 2.56 \times 10^{-5}$; OR= 21.93) for UVJO.

Conclusions: These findings expand and deepen our understanding of the genetic underpinning of COU, identify novel candidate genes, and highlight the high genetic heterogeneity of disease. We are currently pursuing these findings using human and mouse derived urinary tract enriched organoid systems.

Funding: Other NIH Support - R01 DK103184, R01 DK115574 and P20 DK116191

SA-PO814

Unraveling the Role of TET2 Gene Variants in Kidney Disease Development: A Multi-Omics Approach

Xiujie Liang, Hongbo Liu, Jianfu Zhou, Amin Abedini, Hailong Hu, Andrea Sanchez Navarro, Konstantin A. Kloetzer, Katalin Susztak. Susztak Lab. *University of Pennsylvania, Philadelphia, PA.*

Background: In the quest to understand the genetic causes of kidney disease, Genome-wide association studies (GWAS) have recognized hundreds of sites, yet the precise genes, variants, and pathways remain ambiguous.

Methods: To pinpoint the genes linked to kidney disease, we combined kidney function GWAS, human kidney expression quantitative trait analysis (eQTL), and methylation quantitative trait analysis (meQTL). To discover the variants that modify gene expression in kidney cells, we utilized single-cell chromatin accessibility (snATACseq) and (Crispr-based) genome editing. We created kidney-specific Tet2 knockout mice and manipulated gene expression in human kidney cells using CRISPR to study its role in kidney disease progression. We performed single-nucleus multiomics studies in knock-out mice to delve into the role of Tet2.

Results: We identified the ten–eleven translocation (Tet) DNA demethylase TET2, and the variants that change its expression in kidney tubule cells as a novel kidney disease risk gene, risk loci and target cell type. Experiments with kidney-specific Tet2 knockout mouse models confirmed its protective roles in cisplatin-induced acute kidney disease and UUO/adenine-induced chronic kidney disease and kidney fibrosis development. Single-nucleus profiling of Tet2 knock-out mice indicated changed expression in genes related to cellular differentiation in the absence of Tet2. Further cellular studies suggested that Tet2 might be vital for tubule cell differentiation and could instigate kidney disease development by altering the cytosine hydroxymethylation level of associated differentiation genes.

Conclusions: Our findings underscore the crucial role of Tet2-mediated active cytosine hydroxymethylation on genes associated with differentiation in tubule cells in the onset of kidney disease.

Funding: NIDDK Support

SA-PO815

Genetic Contributions to Lower Urinary Tract Dysfunction

Nina Mann, Lily Hiltebeitel, Steve Seltzsam, Chunyan Wang, Shirlee Shril, Friedhelm Hildebrandt. *Boston Children's Hospital, Boston, MA.*

Background: Proper bladder function requires coordinated interactions between the urothelium, detrusor smooth muscle, urethral sphincter, and neuronal circuitry. Historically, severe voiding dysfunction, or the so-called non-neurogenic neurogenic bladder, was attributed to urinary withholding and behavioral maladaptation. However, several monogenic causes of lower urinary tract dysfunction have been identified, leading to a paradigm shift in our understanding of this disease. The aim of this study is to better understand the genetic landscape of voiding dysfunction in children.

Methods: We performed exome sequencing (ES) in 16 individuals with non-neurogenic neurogenic bladder or voiding dysfunction. Individuals with obstructive uropathy, spinal cord lesions, or a known neurological cause for their disease were excluded. In addition, we reviewed ES results from 24 individuals with non-neurogenic neurogenic bladder who have been described in our prior studies (van der Ven *JASN* 2018; Seltzsam *Genet Med* 2022) and analyzed data for variants in 76 candidate genes purported to play a role in urothelial signaling, detrusor function, or neuronal innervation of the bladder.

Results: We identified a pathogenic variant in 3/16 (18%) individuals with lower urinary tract dysfunction. Two individuals had homozygous variants in *HPSE2* (c.1099-2A>G, essential splice; exon9 deletion) and one individual had a homozygous variant in a phenocopy gene *ARL6* (c. 500_502delGAG, p.Gly67del), which causes a renal-retinal ciliopathy. Of the 24 individuals described in our prior publications, four had known pathogenic variants, of which three were homozygous pathogenic variants in *HPSE2* (c.457C>T, p.Arg153*; c.1099-2A>G, essential splice; exon 9 deletion). In total, 7/40 (17%) of our cohort were found to have a monogenic cause for their disease. Notably, two individuals in this cohort had homozygous deletions in exon 9 in *HPSE2*, which were identified only through manual inspection of ES data.

Conclusions: Variants in *HPSE2* are a common cause of non-neurogenic neurogenic bladder in our consanguineous cohort. Structural variants in *HPSE2* were identified in our cohort and have been described previously (Beaman *Front Genet* 13:896125, 2022), underscoring the importance of incorporating CNV analyses into genetic testing for individuals with lower urinary tract or voiding dysfunction.

Funding: NIDDK Support

SA-PO816

Phenotypic Quantification of an Hnf1b Knockout Mouse Model

Selina Hölzel, Caroline M. Kolvenbach, Florian Buerger, Katharina Lemberg, Ken Saida, Seyoung Yu, Daanya Salmanullah, Bshara Mansour, Izzeldin Elmubarak, Nils D. Mertens, Shirlee Shril, Friedhelm Hildebrandt. *Boston Children's Hospital, Boston, MA.*

Background: Congenital Anomalies of the Kidney and Urinary Tract (CAKUT) constitute the most frequent birth defect and are the leading cause of chronic kidney disease in the first three decades of life. Approximately 50 monogenic genes, if mutated, are known to cause CAKUT, explaining 5–20% of disease origin. Mutations in the transcription factor HNF1B represent the most common monogenic cause of CAKUT in 5% up to 30% of affected patients. To date, prevention and treatment options for patients with CAKUT are limited. To enable gene replacement therapy (GRT) for CAKUT, we re-phenotyped a published conditional *Hnf1b* knockout mouse model (Gresh *EMBO* J 7:1657-68, 2004) and developed an additional quantifiable phenotyping method to generate reproducible reference for evaluation of future GRT effects.

Methods: Kidney specific *Hnf1b* inactivation is achieved by usage of the Cre-LoxP technology under a kidney specific promoter (KspCre). We utilized a colony of heterozygous breeder pairs ($Hnf1b^{flox/+}$, KspCre+, C57BL/6J) and phenotypically evaluated mutant animals ($Hnf1b^{flox/flox}$, KspCre+) compared to heterozygous littermate controls starting at P0. For quantitative analyses we focused on the following independent parameters, adapted to Gresh et al.: Kaplan-Meier survival, weight gain over time, macroscopic and light microscopic examination of kidney and urinary tract.

Results: 83.3% (n=6) of mutant mice died before weaning with survival rates ranging from 1-12 days (median 9 days). Mutant mice living past P5 (n=2) showed growth retardation and an average weight reduction of 41% compared to controls. Macroscopically, we observed ureteral dilatation in 100% and hydronephrosis in 33.3% of mutant animals (n=3). Upon light microscopy we detected and quantified renal tubular cysts in equatorial kidney sections with an average of 129 cysts in mutant animals (n=3) and 0 cysts in controls (n=3).

Conclusions: We performed quantitative phenotype evaluation of a kidney specific *Hnf1b* knockout mouse model (Gresh et al.) providing reference for future *in vivo* mouse studies aiming for treatment of CAKUT.

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

SA-PO817

A Causal Relationship Between Body Mass Index and AKI Is Mediated by the Metabolome

Jefferson L. Triozzi,[1] Claire Lo,[1] Cassianne Robinson-Cohen,[1] Edward D. Siew,[1,2] Adriana Hung.[2,1] Million Veteran Program. *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

Background: Obesity is a known risk factor for chronic kidney disease, but its association with acute kidney injury is unclear. We investigated the causal relationship between body mass index (BMI), the metabolome, and acute kidney injury (AKI) using a Mendelian randomization (MR) experiment.

Methods: We performed MR using genome-wide association summary statistics of BMI as the exposure (GIANT Consortium, n = 681,275), the metabolome as a mediator (MuTHER Consortium, n = 7,822), and AKI as the outcome (FinnGen Consortium, n = 2,383 cases, n = 212,841 controls). First, a two-sample MR tested the association of AKI on BMI using the inverse variance weighted (IVW) primary analysis, and the weighted median, weighted mode, and MR-Egger regression sensitivity analyses. We then applied

multi-step and multivariable MR to integrate the role of the metabolome. In the first step, metabolome-wide MR identified causal relationships between BMI and metabolites. In the second step, univariable MR identified causal relationships between metabolites and acute kidney injury. Finally, multivariable MR assessed the indirect effect of BMI on AKI as mediated by metabolites.

Results: BMI demonstrated a causal relationship with AKI in the IVW (β= 0.56, SE = 0.097, p < 5.85E-09), weighted median (β= 0.55, SE = 0.17, p < 1.17E-03), weighted mode (β= 0.58, SE = 0.28, p = 0.03), and MR-Egger regression analyses (β= 0.617, SE=0.26, p=0.01). There were 14 significant BMI-metabolite relationships (p < 1.11E-04), of which there was 1 suggestive metabolite-AKI relationship (p < 0.05). This yielded a putative pathway between BMI, metabolonic lactone sulfate, and AKI. In the multivariable MR analysis, the indirect effect of BMI on AKI via the metabolome was 0.52925.

Conclusions: The causal relationship between BMI and AKI may be partially mediated by the metabolome, particularly metabolonic lactone sulfate. This metabolite has known associations with cardiometabolic health, with possible influence on blood pressure, lipid metabolism, and insulin resistance. This is the first report connecting this metabolite with AKI. The MR methodology supports a causal relationship and is less susceptible to confounding and reverse causation biases. Mechanisms linking obesity, the metabolome, and kidney outcomes deserve further investigation.

Funding: Veterans Affairs Support

SA-PO818

Decreased Kidney Volume Is Associated with AKI

Piera A. Sosa,[1] Jefferson L. Triozzi,[1] Cassianne Robinson-Cohen,[1] Edward D. Siew,[1,2] Adriana Hung.[2,1] *[1]Vanderbilt University Medical Center, Nashville, TN; [2]VA Tennessee Valley Healthcare System, Nashville, TN.*

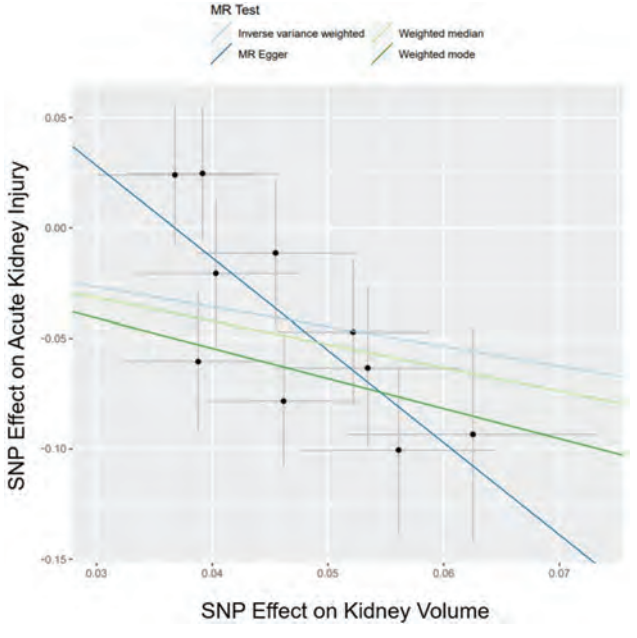
Background: Decreased kidney volume may increase glomerular filtration and nephron workload, potentially increasing the risk of acute kidney injury (AKI). However, the mechanisms of this relationship are unclear. In this study, we investigated the relationship between kidney volume, as measured by MRI, and AKI using Mendelian randomization (MR).

Methods: We performed a two-sample MR experiment using genome-wide summary statistics for kidney volume as the exposure from the UK Biobank (n = 32,860) and AKI as the outcome from the FinnGen Consortium (n = 2,383 cases, n = 212,841 controls). The inverse variance weighted (IVW) analysis was the primary outcome, and the weighted median, weighted mode, and MR-Egger regression were sensitivity analyses. Heterogeneity and pleiotropy were tested.

Results: An association between kidney volume and acute kidney injury was observed in the IVW analysis (β = -0.89, SE = 0.28, p = 0.0012) and supported in the weighted median (β = -1.054, SE = 0.30, p = 0.00055), weighted mode (β = -1.36, SE = 0.53, p = 0.031), and MR Egger regression analyses (β = -4.18, SE = 1.44, p = 0.020). There was no heterogeneity (IVW Q-statistic p = 0.16, MR Egger Q-statistic p = 0.47) but possible horizontal pleiotropy (MR Egger regression intercept p = 0.049). Ten SNPs were analyzed, of which six are related with anthropomorphic features, including body height and waist-hip ratio.

Conclusions: Kidney volume may have a causal effect on acute kidney injury. Larger kidney volume may protect against acute kidney injury. Some of the involved genes relate to anthropomorphic features, such as *PTCH1*. Further investigation is warranted to understand the mechanisms of this relationship and the role of the genes involved.

Funding: Veterans Affairs Support



Mendelian Randomization of Kidney Volume and Acute Kidney Injury

SA-PO819

Identifying Somatic Mosaicism for Tuberous Sclerosis Complex by Targeted Next-Generation Sequencing

Sol M. Carriazo Julio,[1] Ryan R. Ting,[1] Amirreza Haghighi,[1] Xuewen Song,[1] Andrew Paterson,[2] York P. Pei.[1] *[1]University Health Network, Toronto, ON, Canada; [2]SickKids Research Institute, Toronto, ON, Canada.*

Background: Tuberous sclerosis complex (TSC) is a rare disease typically manifested with hamartomas affecting the skin, heart, brain, liver, and kidney. However, 15-20% of patients display mild clinical features suggestive but not diagnostic of TSC, and often they have no pathogenic *TSC1* and *TSC2* mutation detected (NMD). Here, we report our study of a cohort of patients with mild clinical features suspicious of TSC somatic mosaicism (SM) using Next Generation Sequencing (NGS).

Methods: We performed targeted gene panel screen by NGS using DNA samples from blood, buccal mucosa, and urinary epithelial cells (when available) and a minor allele frequency of 1% cut-off to detect mosaicism. Standard algorithms for sequence alignment, base calling, and QC filtering were applied to identify rare (MAF ≤1%) deleterious variants of high and moderate impact as predicted by multiple predictive algorithms. All potential pathogenic mosaic *TSC1* and *TSC2* variants were validated by a novel in-house assay (Mosaic Detection by Enrichment of Mutant Allele; MODEMA) or droplet digital PCR.

Results: From a clinical review of 80 pts with confirmed or possible TSC, 18 patients with mild disease suspicious of TSC SM were sequenced. We found germline missense *TSC1/TSC2* mutations in 5 patients, mosaic *TSC1/TSC2* mutations in 9 patients in whom 7 were validated by MODEMA and/or digital PCR, and 4 with NMD. Patients with confirmed TSC SM were predominantly young female; all had multiple renal angiomyolipomas and few extra-renal clinical features.

Conclusions: Patients with mild clinical features suggestive but not diagnostic of TSC can be caused by missense or mosaic *TSC1/TSC2* mutations. The diagnosis of TSC SM has important implications for genetic counselling and clinical prognostication, and can be improved by NGS.

SA-PO820

Renal Transplantation in a Recipient with Birt-Hogg-Dube Syndrome

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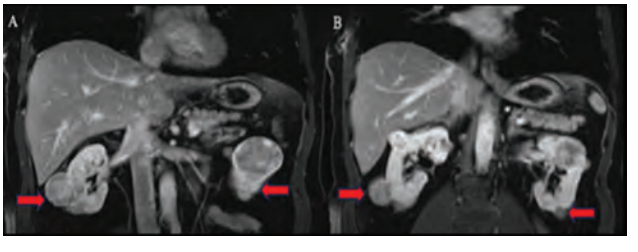
Introduction: Birt-Hogg-Dube Syndrome (BHDS) is a rare autosomal dominant disorder caused by folliculin (FLCN) germline mutations. Renal cell carcinoma (RCC) is the most serious manifestation of this condition occurring at a rate of 30%. Unlike other inherited renal cancers, BHDS is associated with a wide range of histologies. Although preserving renal function remains the central goal of management, the risk of end stage renal disease remains high. Patients with other inherited renal carcinomas (e.g. Von Hippel Lindau) have been successfully transplanted in the past. Herein, we have demonstrated how renal transplant can also be a viable treatment course for some patients with BHDS related RCC.

Case Description: A 48-year-old male presented to our facility for evaluation of recurrent pneumothorax. CT chest revealed bilateral pulmonary cysts and multiple bilateral renal masses. Given the coexisting pulmonary cysts and renal masses, he was evaluated and diagnosed with BHDS. After discussion with the patient, bilateral radical nephrectomy was performed due to the presence of multifocal tumors measuring up to 5 cm. Tumor pathology was consistent with oncocytoma and chromophobe RCC, pT1bN0M0. After two years of hemodialysis and surveillance, the patient was deemed a candidate for kidney transplant. Induction therapy consisted of thymoglobulin and solumedrol and the patient was discharged with mycophenolate mofetil, prednisone, and tacrolimus as maintenance.

Discussion: Tumor aggressiveness, metastasis risk, and time in remission are important factors when evaluating a patient with history of BHDS associated RCC for renal transplant. BHDS associated chromophobe and hybrid chromophobe/oncocytic tumors are less aggressive and it has been observed that the metastasis associated with these cancers tends to be more indolent in nature. Therefore, these patients are suitable candidates for transplant after a minimum waiting period. Post-transplant, immunosuppression with mTOR inhibitors can be considered since mutation of tumor suppressor FLCN in the mTOR pathway is central to BHDS pathogenesis.



CT scan showing bilateral renal tumors

SA-PO821

The Progressive Decline of Kidney Function: Can We Have an Answer?

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Introduction: With the field of nephrology moving towards personalized medicine, genetics is taking its lead in providing patient care. Tuberous sclerosis complex (TSC) is an inherited disorder with lesions involving multiple organs, including the kidneys. While TSC is often diagnosed during childhood, some cases might not be recognized until adulthood.

Case Description: Here we present a 58 y.o. female with a history of breast cancer, seizures, parathyroid adenoma, strictures of the esophagus, dental pitting, oral fibromas, and hyperpigmented macules in the mouth, who was referred due to abnormal results: Creatinine 1.6 mg/dL, eGFR 33 mL/min/1.73. Her family history was positive for cancer in her father of unknown origin. Her kidney ultrasound showed multiple fat-density tumors within both kidneys and a left renal cortical cyst. CT abdomen demonstrated bilaterally enlarged kidneys with innumerable fat-containing lesions consistent with angiomyolipomas. CT head revealed intracranial calcifications with MRI positive for cortical and subcortical glioneuronal tumors and giant cell gliocytoma. On CT lungs, there were numerous scattered thin-walled cysts throughout both lungs with numerous scattered nodules. Recently, the patient underwent surgery to remove a 4.4 cm invasive adenocarcinoma of the rectum with negative margins and lymph nodes for malignancy on biopsy. Genetic testing was performed that showed heterozygous pathogenic missense mutation in the TSC2 gene with AD inheritance mode: c.1832G>A (p. Arg611Gln), NM_000548.5 supporting the diagnosis of TSC. Multiple laboratories in the Clinvar Database predict this variant as pathogenic and absent in the gnomAD dataset, which tells about the rarity of this mutation. Silico's analysis supports the idea that this missense variant disrupts protein structure/function. Inactivation of the tuberin-hamartin complex leads to cell proliferation and size discoordination, which explains the pathophysiologic mechanism of our patient's phenotype.

Discussion: Currently, the patient continues to have progressive worsening of kidney function with a creatinine of 3.5-3.7 mg/dL. However, knowing the exact diagnosis helped with the appropriate management, prognosis and offered potential screening and diagnosing opportunities for family members.

SA-PO822

Investigation of T Cells Contributing to the Production of IgA-Type Autoantibodies Against Mesangial Cells in IgA Nephropathy

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Background: In IgA nephropathy (IgAN), the mechanism by which IgA antibodies (Abs) are selectively deposited in the glomerular mesangial region has not been elucidated. However, we have recently uncovered its mechanism by identifying IgA type auto-Ab against mesangial antigens, βII-spectrin, in gddY mice, a spontaneous IgAN animal model and IgAN patients (*Y. Nihei, H. Iwasaki and Y. Suzuki et al, Sci. Adv 2023*). We also found that a significant number of IgA+ plasmablasts (PBs) accumulated in the kidneys of gddY mice and these PBs produced IgA auto-Abs that bind to βII-spectrin and the surface of mesangial cells. We cloned cDNAs encoding IgA heavy and light chains from single IgA+ PB isolated from the kidney of gddY mice and found that most of the heavy- and light-chain V region genes of these PBs contained significant numbers of somatic mutations, indicating that they were generated in a T-cell-dependent manner through the germinal center. However, the detailed mechanisms of IgA auto-Abs production, such as which types of T cells are responsible for the induction of auto-Abs, are not clear. In the present study, we analyzed CD4+T cells in the kidney of gddY.

Methods: GddY mice were generated through selectively mating individuals within an early-disease onset group of ddY mice for more than 20 generations. All individual gddY mice exhibit proteinuria and glomerular IgA deposition by 8 weeks of age, followed by obvious renal failure and the pathology being similar to human IgAN. Isolated leukocytes from kidney of gddY or BALB/c mice at age of 8 weeks were analyzed by flow cytometry.

Results: We found that a significant number of CD4+ T cells accumulated in the kidneys of gddY mice compared to BALB/c. In details, Th1(CD4+ IFN-γ+), Th17(CD4+ IL-17+) and Treg(CD4+ Foxp3+) cells were significantly accumulated in the kidney of gddY compared to BALB/c. No significant differences were seen in the number of Th2(CD4+ IL-4+) accumulated in the kidney of gddY and BALB/c.

Conclusions: Present findings revealed that a significant number of CD4+ T cells, especially Th1, Th17 and Treg, but not Th2 cells accumulated in kidney of gddY. We will clarify the role of these CD4+ T cells in the induction of IgA auto-Abs in IgAN.

SA-PO823

Molecular Classification of Lupus Nephritis Based on Immune Pathway Profiling: Correlations with Histological Class and Clinical Manifestations

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Background: LN (lupus nephritis) ISN/RPS histopathological classification is the gold standard for assessment, however, does not inform the underlying immunological aberrations. A classification based on molecular typing of immune-related pathways may better stratify LN patients.

Methods: The expression matrix and clinical data were extracted from GEO and Nephroseq databases. ssGSEA method was used to derive immune phenotype with gene expression data. Hierarchical clustering with ssGSEA scores of selected gene sets classified LN tissues. Functional characterization and PPI of the DEGs were analyzed with Metascape. Kruskal-Walli test and chi-square test were performed to compare the clinical parameters.

Results: We calculated ssGESA scores of 96 immune-related gene sets in the glomerular and tubulointerstitial regions of LN kidney biopsy samples. Samples were then categorized into three clusters (Immune-Mild, Immune-Moderate, and Immune-Severe). Interferon-stimulated genes are a hallmark of LN. When compared to other groups, the Immune-Mild cluster from the glomerular region showed no T-cell activation pathway. The Immune-Mild (tubulointerstitial) showed minimal lymphocyte activation. PPI networks with MOCDE components further suggested that STAT1 and ISG15 are the core DEGs in different subgroups. The immune-Mild (Glomerular) showed a high prevalence of Class II and V LN, and Immune-Mild (Tubulointerstitial) showed more Class V LN. Immune-Severe group showed a higher degree of proteinuria and blood pressure but lower eGFR compared to the Immune Mild/Moderate groups.

Conclusions: A new molecular classification of LN based on the degree of immune pathway activation shows correlation with clinical manifestations, and may potentially guide personalized therapy in LN patients.

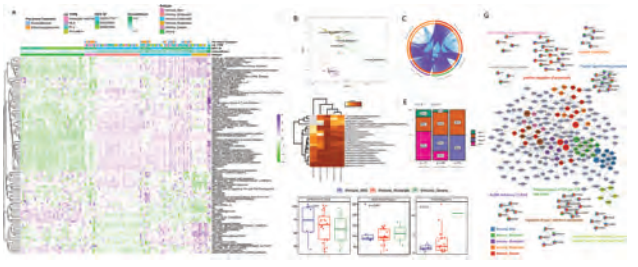

Figure 1. Features of Glomerular clusters.

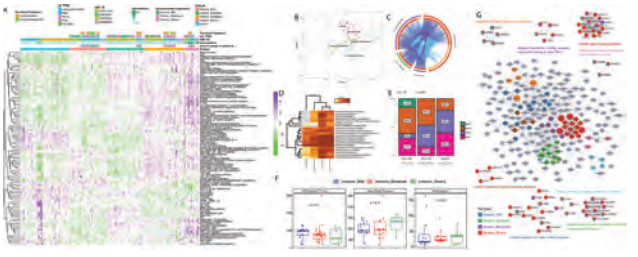

Figure 2. Features of Tubulointerstitium clusters.

SA-PO824

Proximal Tubular Sirt6 Has a Protective Role in the Murine Lupus Nephritis Model by Regulating Tubulointerstitial Inflammation

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Background: Systemic lupus erythematosus (SLE), an autoimmune disease, involves tissue inflammation of multiple organs, including the kidney. *Lupus nephritis* is an autoimmune complex glomerulonephritis that develops as a complication of SLE. Dysregulation of intrarenal immune tolerance to nuclear autoantigens produces autoantibody and immune disorders. Sirt6 is the NAD+-dependent deacetylase and mono-ADP ribosyltransferase and is involved in genome maintenance and metabolism. This study investigates the effect of proximal tubule-specific Sirt6 knockdown on murine lupus nephritis.

Methods: To investigate the role of Sirt6 specifically in proximal renal tubules, we crossed *gGt1*-cre mice and *Sirt6*flox/flox mice to generate Sirt6 conditional knock-out mice. The back area's skin was shaved and treated topically three times per week, with 100 μg of resiquimod in 100 μl of acetone for eight weeks. After murine kidney sample collection, we evaluated renal histology and immunofluorescent study for inflammatory cells and lymphatic vessels. We also assessed inflammatory cytokines and chemokines, lymphangiogenic factors by qRT-PCR.

Results: The loss of Sirt6 in proximal tubules aggravates glomerular mesangial cell proliferation and tubulointerstitial inflammation, and there also increases glomerular deposition of IgG, IgM, and C3 in immunofluorescence staining. LYVE-1(+) lymphatic vessels have increased expression and infiltration of F4/80, CD11c, and B220 (+) inflammatory cells in proximal tubule-specific Sirt6 knock-out mice. The pro-inflammatory cytokines and chemokines such as ICAM-1, VCAM-1, MCP-1, BAFF, LTβ, and CXCL13 mRNA levels were increased compared with wild-type mice.

Conclusions: Our data suggest that proximal tubule Sirt6 is important in resiquimod-induced lupus nephritis, especially in regulating tubulointerstitial inflammation.

Funding: Government Support - Non-U.S.

SA-PO825

Analysis of Galnt14-Null Mice Links O-Glycosylation Defects to Elevated Circulating IgA Levels and Altered IgA+ B Cell Tissue Distribution

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Background: Defects in *O*-glycosylation of IgA1 are a characteristic finding in IgA nephropathy. It is not known if aberrant *O*-glycosylation can impact IgA homeostasis, such as B-cell residence, homing, and migration. At least 17 distinct *N*-acetylgalactosami nyltransferases (GalNAc-T1-17*)* can initiate *O*-glycosylation of proteins.

Methods: We studied the circulating IgA, and the mucosal and non-mucosal tissue resident IgA+ B-cells in *Galnt14-/-* and WT mice using ELISA and flow cytometry.

Results: *GALNT14* is expressed in human and murine lymphoid tissue, specifically within germinal centers which is the major site for B-cell maturation, antibody class switching and proliferation. Serum IgA levels were significantly elevated in the *Galnt14-/-* mice compared to the WT mice (1.31±0.4 mg/ml and 0.75±0.1 mg/ml, respectively, $P < 0.01$). IgA+ B-cells in mucosal and non-mucosal tissues were examined to determine if there was an abnormal distribution of IgA+ B-cells. An increase in the percentage of IgA+ B-cells was observed in non-mucosal tissues of *Galnt14-/-* mice compared to WT mice (PMBC: 3.9±0.7% and 2.6±0.4%, respectively, $P < 0.01$; spleen: 4.2±0.9% and 3.0±0.7%, respectively, $P < 0.01$; and peritoneal cavity: 6.1±2.3% and 3.8±0.9%, respectively, $P < 0.01$). In addition, a significant decrease in the percentage of IgA+ B-cells was observed in the Peyer's patches of *Galnt14-/-* mice compared to WT mice (20.2±3.7% and 24.4±3.8%, respectively, $P < 0.01$). No differences in the percentage of IgA+ B-cells was observed in non-mucosal lymph nodes. The increased IgA in the circulation in *Galnt14-/-* mice correlated with the increased IgA+ B-cells in the circulation ($P < 0.01$) and the reduced IgA+ B-cells in the Peyer's patches ($P < 0.01$). Finally, reciprocal adoptive transfer experiments demonstrated that splenic derived B-cells isolated from *Galnt14-/-* mice have a reduced ability to home to the spleen, regardless of the recipient genotype.

Conclusions: *Galnt14-/-* mice have an altered distribution of IgA+ B-cells in mucosal and non-mucosal tissues, partially explaining the elevated levels of circulating IgA. We are currently exploring the mechanisms of the alterations observed in IgA+ B-cell recruitment and residence in mucosal and lymphoid tissues of *Galnt14-/-* mice.

Funding: NIDDK Support

SA-PO826

Spatial Transcriptomic Profiling to Understand Organ Cross-Talk: Insight into Environment-Linked Pulmonary-Renal Disease

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Background: Environmental inhalational exposures are implicated in etiopathogenesis of autoimmune pulmonary-renal diseases and CKDu. Underlying mechanisms of disrupted immune control and cross-organ injury are poorly understood. To gain insight into this under-studied field, we leveraged a tractable preclinical model dependent on mouse lung exposure to crystalline silica (cSi) dust. Inhalation of cSi is linked to SLE and ANCA vasculitis in humans and exposure to cSi generated from burned crops is suspected in pathogenesis of CKDu. In mice cSi exposure induces lung inflammation and lymphoid aggregates and promotes autoimmunity. To gain insight into molecular pathways dysregulated by inhaled cSi, we used spatial gene expression (GE) profiling.

Methods: Transcriptome analysis was performed using a 10X Genomics Visium platform with CytAssist at the Molecular Genomics Core of the Duke Molecular Physiology Institute. An FFPE section of lung harvested 3 months after cSi exposure was H&E stained, imaged, hybridized using a mouse transcriptome barcoded probe set, transferred, probes extended, and libraries constructed and paired-end sequenced on a NextSeq 1000 (Illumina). Raw data were preprocessed using Space Ranger, mapped to the mm10 genome, and aligned to the tissue image. Data filtering, normalization, and analysis were performed with the Seurat R package.

Results: Spatial sequencing yielded mean ~57K reads/spot, with median 2,041 genes/spot and total >19K genes detected. After dimensionality reduction, unsupervised spot clustering based on differential GE yielded 8 clusters. Overlay of molecular and image data showed spatial localization of clusters to lymphoid aggregates, granulomas, peribronchiolar loci, and minimal injury areas, supported by marker gene identification, as well as unexpected regional heterogeneity. Two clusters had strong Ig signals, consistent with distinct local adaptive immune niches. Upregulated genes with spatial restriction include a subset linked to immune control and two genes encoding soluble proteins implicated as circulating mediators of cardiopulmonary crosstalk in acute kidney injury.

Conclusions: Spatial transcriptome analysis in cSi-injured lung provides novel insight into the molecular framework of dysregulated tissue niches as well as potential biological pathways engaged in pulmonary-renal crosstalk.

Funding: Other NIH Support - National Institute of Environmental Health Sciences (NIEHS)

SA-PO827

A Role for Lung Foxp3+ T-Regulatory (Treg) Cells in Modulating Lupus Autoantibody Production Exacerbated by Silica Dust Exposure

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Background: Gene-environment (GxE) interactions promote systemic autoimmunity and induction of autoantibodies (autoAb) that destroy kidneys in SLE and ANCA vasculitis. In mice, inhalation of crystalline silica (cSi) dust, an exposure compellingly linked to human autoimmune diseases, induces local tertiary lymphoid structures (TLS) enriched in T and B cells. In lupus and other autoimmune-prone strains, cSi inhalation increases local and systemic autoAb and accelerates nephritis. To test the hypothesis that immune control is defective in GxE-influenced tissue microenvironments in lupus, we measured cells expressing transcription factor forkhead box protein 3 (Foxp3), a key marker of regulatory T cells (Treg), in cSi-exposed lupus BXSB and non-autoimmune C57BL/6J (B6) mice.

Methods: Lungs harvested from female mice 7-9 weeks after cSi exposure were sectioned and stained with anti-Foxp3 and anti-B220 (B cell) antibodies and visualized using a Zeiss Axio Imager. TLS-associated Foxp3+ nuclei were enumerated in n=16 TLS per mouse using Zeiss Zen software, with TLS identified as loci of densely packed nuclei overlapping B220+ clusters. In situ hybridization was performed using RNAScope on FFPE tissue sections from cSi and vehicle (V) exposed autoAb transgenic (Tg) B6 mice, using Foxp3 and control probes.

Results: Foxp3+ nuclei were identified within TLS in lung tissue of all cSi-exposed mice. In one of three BXSB mice, a single TLS had an exceptionally high Foxp3+ cell count, highlighting the potential for microniche heterogeneity. Exclusion of this outlier revealed significantly fewer Foxp3+ cells/TLS in BXSB vs B6 mice: 4.6±0.2 in BXSB vs 8.1±4.6 in B6 (mean±SD), $p<0.05$. Immunofluorescence and RNAScope imaging showed that Foxp3+ cells also localized to TLS regions in cSi-exposed autoAb Tg mice, whereas only a few scattered Foxp3+ cells were identified in V-exposed lung.

Conclusions: Foxp3+ Treg are recruited to lungs after cSi inhalation and localize to lymphocyte-rich TLS, suggesting a role in regulation of local autoimmune responses. The relative paucity of Foxp3+ cells in BXSB TLS may contribute to autoimmunity in this lupus-prone strain. Understanding the composition and contribution of local tissue immune niches in GxE-influenced pulmonary-renal diseases such as lupus may identify novel approaches to therapy.

Funding: Other NIH Support - National Institute of Environmental Health Sciences (NIEHS)

SA-PO828

Targeting Sphingosine-1-Phosphate Receptor 4 in a Mouse Model of Alport Syndrome

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Background: Alport syndome is a genetic condition in which the ability to produce the heterotrimer collagen 4a345 is disrupted. Alport syndrome results in glomerular disease and eventually renal failure. Sphingosine-1-phosphate (S1P) is a bioactive sphingolipid that exerts its effects by interacting with one of its five receptors (S1PR1-5). S1P signaling has a wide range of effects depending on the receptor and the cell type. S1P siganling plays a large role in the immune system as lymphocyte migration is dependent on it. However the role of S1P siganling in podocytes and the kidney is largely unknown.

Methods: S1P was measured through liquid-chromatography mass spectrometry. Col4a3 -/- mice were treated with either vehicle or 25mg/kg CYM50358 (S1PR4 antagonist) every other day starting at 4 weeks of age until sacrifice at 8 weeks of age. Albumin to creatinine ratio was determined through ELISA. Mesangial expansion was determined by PAS staining. Lipid accumulation was determined by oil red o staining. Fibrosis was determined by picro-sirius red staining.

Results: Col4a3 -/- mice have elevated S1P in the kidneys compared to control mice. We see higher kidney cortex expression of S1PR4 in Col4a3 -/- mice compared to control mice. We see that treatment with a S1PR4 antagonist is sufficent to lower proteinuria, lipid accumulation in the kidney, mesangial expansion and fibrosis.

Conclusions: Our results suggest that S1P may drive progression of renal failure in alport syndrome. We see that reducing S1PR4 signaling through pharmacological treatment is beneficial to renal outcomes in col4a3 -/- mice. Targeting other S1PR may be beneficial as well for slowing the progression of renal failure.

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

SA-PO829

The High-Throughput Approach Identifies Compounds that Block PLA2R and Anti-PLA2R Antibody Interaction

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Background: The pathogenicity of anti-phospholipase A2 receptor (PLA2R) antibodies has been elucidated in primary membranous nephropathy (MN).

Methods: Small-molecule compounds were screened for their inhibition effects to the binding between PLA2R and its antibodies by ELISA. The affinity of anti-PLA2R

antibodies from MN patients to the full-length extracellular PLA2R was determined by surface plasmon resonance (SPR). The blocking ability of each compound was tested by SPR competition study. The affinity of each compound was determined by SPR.

Results: 15 candidate compounds were selected from a library of over 4,000 small-molecule compounds for their inhibition rates > 20% to the binding between PLA2R and its antibodies. The affinity of anti-PLA2R antibodies and PLA2R antigens was similar among patients as approximately 1.0nM. The inhibitory potential of the 15 candidates was assessed by SPR and three compounds, Macrocarpal B, Doramectin, and Hypocrellin exhibit reproducible inhibitory ability, with Macrocarpal B being the most significant one. Macrocarpal B could eliminate nearly 30% of the antigen-antibody interaction in a dose-dependent manner, which was similar to the performance of the 31-mer peptide in SPR competitive inhibition assay. The competing Macrocarpal B bound to the immobilized PLA2R with an affinity of approximately 1.1Mm, whereas no interaction was detected between it and anti-PLA2R antibody/IgG.

Conclusions: We found a small molecular compound, Macrocarpal B, which could efficiently abrogate the binding between PLA2R and anti-PLA2R antibodies. These findings may have potential clinical value.

SA-PO830

Potency Assessment of a Recombinant IgA Protease: Toward the Treatment of IgA Nephropathy

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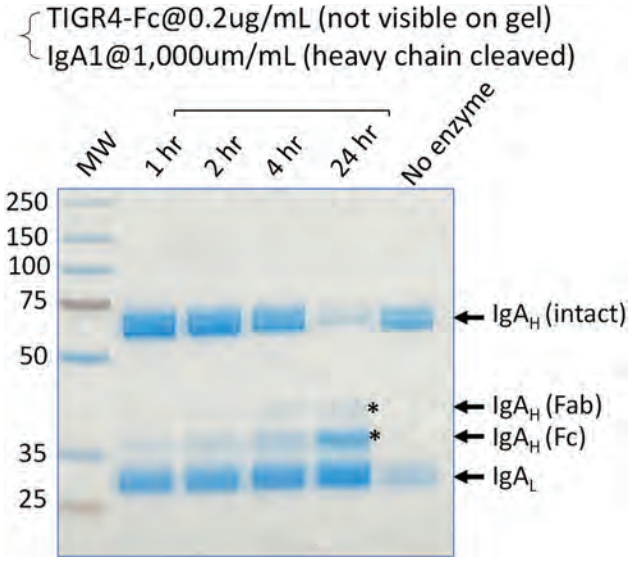
Background: Microbial IgA proteases represent a structurally heterogenous group of proteins. Despite their structural diversity, IgA proteases are highly specific to cleave the hinge region of human IgA1 heavy chain. Here we explore the potential use of an IgA protease derived from *Streptococcus* strain TIGR4 for the treatment of IgA nephropathy by the clearance of IgA deposits in the glomerular mesangial area.

Methods: We designed a TIGR4 with a truncation at its N-terminus in a fusion configuration with Fc for extending its plasma half-life. We then expressed this TIGR4-Fc fusion in *E. coli* strain BL21 under a Tac promoter, purified through MabSelect PrismA™ columns, and assessed its purity, stability, and potency.

Results: Recombinant TIGR4-Fc was expressed as a ~350 kDa dimer attributable to dimeric Fc in its native fold. The purity is estimated to be >90% on an SDS PAGE. At 10 mg/mL, it remains stable in pbs at 20°C for over a week without visible precipitation. When subjecting TIGR4-Fc to pbs of human IgA1, enzymatic cleavage of the heavy chain occurs. With TIGR4-Fc at 2 and 20 μg/mL, and the substrate at 1,000 μg/mL, all IgA was cleaved by the enzyme. When TIGR4-Fc is at 0.2 μg/mL, a partial cleavage of IgA was observed with an incremental of cleavage over a period of 24 hours.

Conclusions: These results demonstrated the feasibility of constructing a recombinant IgA protease in fusion with Fc. The resulting biologic exhibited stability in solution and showed an exceptional enzymatic potency for human IgA1. Based on the calculated EC90 of 0.2 μg/mL, a therapeutic dose of TIGR4-Fc of as little as 1 mg is sufficient to clear 90% of IgA contents in an adult patient. The Fc fusion may further extend the *in vivo* efficacy to 10-15 days in clearing IgA in both circulation and existing kidney deposits.



Fab and Fc of IgA$_H$ are cleavage fragments.

SA-PO831

Type 2 Innate Lymphoid Cells Are Activated in Steroid-Resistant Nephrotic Syndrome

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Background: 15% of children with nephrotic syndrome (INS) have steroid-resistant disease, which portends a poor renal prognosis. Approximately half of these patients are able to achieve remission, but only with intensive immunosuppression including calcineurin inhibitors and/or Rituximab. Given the demonstrated role of Type 2 innate lymphoid cells (ILC2) in steroid-resistant allergic asthma, and the association between INS and atopic disease, this study aimed to examine ILC2 populations in steroid-resistant (SRNS) compared to steroid-dependent INS (SDNS).

Methods: We recruited 18 patients (age: 15.7±1.9 years) with SDNS or SRNS, 9 of whom were in partial/complete relapse (urine protein:creatinine ratio>0.1g/mmol). ILCs were identified as CD45+Lin-CD127+ cells. Of these, ILC2 were CRTH2+, and inflammatory ILC2 were CRTH2+ CD45RO+.

Results: Patients with SRNS had a higher proportion of ILC2 compared to SDNS patients (28.6±4.4% vs 11.7±2.4%, p=0.003), including inflammatory ILC2 (19.7±3.5% vs 7.9±2.1%, p=0.01). Similar findings were observed even if ILC2 was defined with greater stringency as CRTH2+CD127^{hi} (p=0.02), while no concomitant changes were noted in ILC1 (p=0.61), ILC3 NCR+ (p=0.88) or ILC3 NCR- (p=0.45) populations. This elevation of ILC2 in SRNS compared to SDNS patients was more marked in relapse (35.4±2.4% vs 10.6±3.5%, p=0.002) compared to in remission (18.3±0.7% vs 12.7±3.6%, p=0.46). Correspondingly, ILC2 increased in relapse for SRNS patients (p=0.01) but not SDNS patients (p=0.99) (Figure).

Conclusions: ILC2s are activated in SRNS during relapse, but not in SDNS. If validated, ILC2s can be a potential target for therapy in SRNS.

Funding: Government Support - Non-U.S.

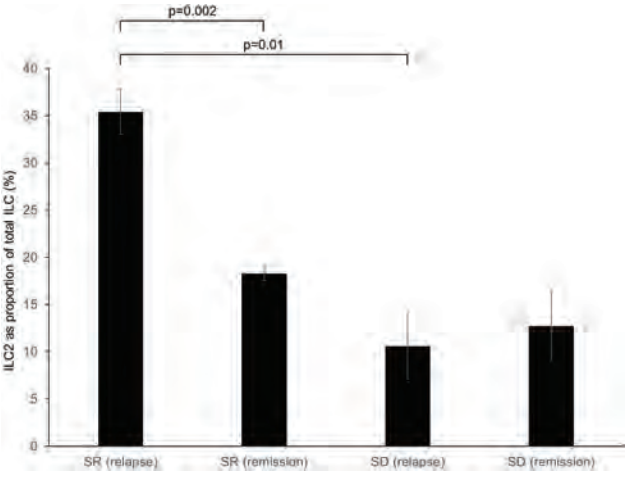

Figure: ILC2 in patients with steroid-resistant (SR) and steroid-dependent (SD) nephrotic syndrome, in relapse and remission.

SA-PO832

Neutrophil Reactive Oxygen Species Generation and Association with Clinical Disease Markers in Lupus Nephritis

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Background: There is growing evidence for neutrophil involvement in lupus nephritis (LN). Neutrophils infiltrate the glomerulus and mediate cellular injury via granular release of toxic and immunologic molecules including reactive oxygen species (ROS). We aim to determine if LN neutrophils are more primed to produce ROS than controls and if ROS generation is associated with clinical disease features.

Methods: Neutrophils were isolated from whole blood of 16 LN patients and 6 healthy controls for use in superoxide assay. Cells were untreated, treated with fMLF, or treated with fMLF plus TNF-α. fMLF is a positive activator and TNF-α primes the response. Clinical data were obtained from Epic: UPCR, C3, C4, anti-dsDNA, and creatinine. eGFR was calculated using the 2021 CKD-EPI creatinine equation. Control data were not available.

Results: ROS generation was compared by treatment group and patient status using mixed-effects analysis with Šídák multiple comparisons test. For fMLF alone, LN neutrophils produced more ROS than controls (p=0.0028). Fold change in ROS was calculated for untreated to fMLF as well as untreated to fMLF plus TNF-α priming, and the difference was compared using unpaired T-tests. For LN, fold change from untreated did not differ between fMLF and fMLF plus TNF-α (p=0.6221). However, fold change

from untreated to fMLF plus TNF-α was greater in controls (p=0.0041). Multiple linear regression was used to determine if clinical data is associated with ROS generation in LN. For untreated, anti-dsDNA (p=0.0439) and eGFR (p=0.0318) were associated. For fMLF, C4 (p=0.0286) was associated. For fMLF plus TNF-α, UPCR (p=0.0210), C3 (p=0.0199), C4 (p=0.0025), creatinine (p=0.0325), and eGFR (p=0.0130) were associated. Finally, anti-dsDNA was associated with fold change in ROS for untreated to fMLF (p=0.0136) and untreated to fMLF plus TNF-α (p=0.0152).

Conclusions: LN neutrophils had a greater response to fMLF than controls. This suggests the possibility of endogenous primers in LN serum, which may play a role in LN pathogenesis and affect neutrophils beyond ROS generation. Discussion and investigation are ongoing regarding the utility of clinical markers in LN as well as potential new markers. Using clinical data to predict underlying disease may improve future treatments.

Funding: NIDDK Support

SA-PO833

Dapagliflozin vs. Ramipril Therapy in Mice with Alport Syndrome

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Background: Angiotensin-converting enzyme inhibitors (ACEi) have been the best studied treatment for Alport syndrome with established benefits for renal function and survival in animals and humans. Recent clinical trials have shown that sodium glucose cotransporter 2 inhibitors (SGLT2i) are a key disease-modifying therapy to prevent the progression of chronic kidney disease when used on a background of renin-angiotensin-aldosterone system (RAAS) blockade. The objective of this study is to investigate whether SGLT2i exerts renoprotection as much as ACEi in Alport syndrome.

Methods: We studied male Col4α3 knockout mice, an Alport syndrome model, on a 129S1/SvImJ background. Dapagliflozin (1.5 mg/kg/day) or Ramipril (10 mg/kg/day) were orally administered via drinking water, starting at 4 weeks of age to 10 weeks of age (N=6-8/group). Wild-type (WT) and Alport littermates received vehicle for the same duration and served as controls. Glomerular filtration rate (GFR) was measured by inulin-FITC clearance in conscious mice, and kidneys were processed for histology (PAS, Sirius Red staining).

Results: Alport mice treated with Dapagliflozin had enhanced glucose excretion in urine, but blood glucose level was not changed. At 10 weeks of age, Alport mice developed a significant weight loss, decreased GFR/body weight, and elevated BUN. These were attenuated by Ramipril, but not by Dapagliflozin. Histological analysis of Alport mouse kidneys showed global and segmental glomerulosclerosis, tubular casts and tubulointerstitial fibrosis, which were more consistently improved by Ramipril than by Dapagliflozin.

Conclusions: Ramipril had more favorable effects on preservation of renal function and renal architecture in Col43 knockout Alport mice than Dapagliflozin. Our head-to-head comparison indicates that SGLT2i may not be an alternative option for ACEi in glomerular diseases. Further studies are currently ongoing to investigate the effects of a higher dose of Dapagliflozin and of combined treatment of SGLT2i with RAASi.

Funding: Private Foundation Support

SA-PO834

Plasma TET2 as Potential Noninvasive Biomarker for Type IV Lupus Nephritis

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Background: Therapeutic regimen of lupus nephritis (LN) should be based on the pathological classification by renal biopsy. The class IV is the most common type and has the worst prognosis in LN patients. However, some patients are contraindicated to renal biopsy. A non-invasive biomarker that can mirror to renal classification will help clinical decision-making. Ten-eleven translocation methylcytosine dioxygenase 2 (TET2) has been reported to involve in the pathogenesis of systemic lupus erythematosus and kidney diseases. We aim to verify whether plasma TET2 can reflect renal classification in LN patients.

Methods: Plasma samples were collected from 49 patients diagnosed as LN approved by renal biopsy in our department from January 2019 to January 2023 and 27 age-and -sex matched healthy volunteers (NC). Class IV (n=14) and class III + V/IV +V/ V (n=31) were included in LN patients. Plasma levels of TET2 were analyzed by enzyme-linked immunosorbent assay. Student's t test or one-way ANOVA test and receiver operating characteristic curve (ROC) were used for the data analysis.

Results: Plasma TET2 levels were increased in LN patients compared to NC. Plasma TET2 differentiated LN from NC with a high diagnostic accuracy with area under the curve (AUC=0.77, p<0.001, n=76). The sensitivity for diagnosing LN was 65.30%, and the specificity was 85.20%. Further more, plasma TET2 levels in class IV were decreased compared to that in class III+V/IV+V/V inside LN patients. Plasma TET2 also differentiated class IV from class III+V/IV+V/V (AUC=0.73, p<0.001, n=45) with the sensitivity 78.6%, and the specificity 71%. Serum albumin (sAlb) differentiated class IV from the other classes with 0.684 of AUC (p=0.047). With combination of blood TET2 and sAlb, AUC was increased to 0.83 (p<0.001) to differentiate class IV from class III+V/IV+V/V. The sensitivity was 85.7%, and the specificity was 80.6% with TET2 cutoff as 350 pg/ml.

Conclusions: Plasma TET2 level differentiated LN class IV from class III+V/IV+V/V. Combination with sAlb increased the differentiation efficiency. A panel of blood TET2 and sAlb might help on diagnosing LN class IV for those patients with contraindication of renal biopsy and benefiting to therapeutic decision. This study needs to be validated in large cohort of LN patients.

Funding: Government Support - Non-U.S.

SA-PO835

Identification of Anti-Peroxidasin Antibodies in Human and Experimental Glomerulonephritis

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Background: Peroxidasin (Pxdn) is an extracellular matrix (ECM) haem peroxidase critical for forming sulfilimine bonds which crosslink type 4 collagen. Sulfilimine bonds contribute to structural integrity and stability of the ECM and act to sequester the Goodpasture antigen giving it immune privilege. Autoantibodies to peroxidasin have previously been identified in patients with anti-glomerular basement (GBM) disease and MPO-ANCA associated vasculitis (MPO-AAV).

Methods: Circulating anti-Pxdn IgG was measured by ELISA in serum from patients (anti-GBM disease, AAV, and healthy volunteers) and rats with experimental autoimmune glomerulonephritis (EAG), an autoimmune model of anti-GBM disease. For coating, recombinant rat peroxidasin was expressed in HEK293 cells and purified; human peroxidasin was from a commercial source (Origene). Antibody specificity was confirmed using immunoblotting. Expression of Pxdn, deposited IgG, and smooth muscle actin (SMA) in kidney tissue was assessed by indirect immunofluorescence (IF).

Results: Circulating anti-Pxdn IgG antibodies were detected in 29.4% of (15/51) patients with anti-GBM disease, 14.2% (2/14) of patients with active MPO-AAV, and 0% (0/6) patients with active PR3-AAV (Fig 1A). Circulating anti-Pxdn IgG antibodies were detectable at day 28 after induction of EAG (peak glomerular injury) in 86.7% (13/15) of rats (Fig 1B). Anti-PXDN antibodies were detectable at low titre from day 18 suggesting they may arise later than anti-α3(IV)NC1 antibodies which are detected from day 7. IF staining of kidney tissue in EAG identified Pxdn at areas of glomerular injury and crescent formation. Pxdn co-localised with SMA but not with deposited rat IgG (Fig 1C).

Conclusions: We confirm the presence of anti-Pxdn antibodies in patients with glomerular disease. In EAG, anti-Pxdn antibodies were evident after the development of antibodies against α3(IV)NC1 and glomerular Pxdn expression was only detected after disease onset: thus we suggest anti-Pxdn antibodies may arise by a process of inter-molecular epitope spreading in the diseased glomerulus.

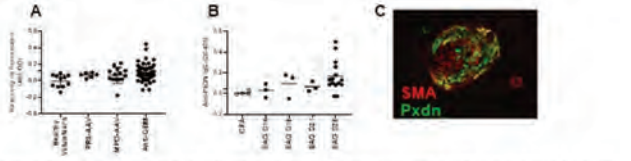

Figure 1(A). Circulating anti-PXDN antibodies in patients with anti-GBM disease and AAV. (B) Circulating anti-PXDN antibodies in rats at 28 days after induction of EAG. (C) Glomerular expression of PXDN co-localises with SMA 28 days after induction of EAG. (A+B) Dotted lines represent mean+2sd for HV and CFA respectively.

SA-PO836

Glomerular Parietal Epithelial Cell Expression of Cathepsin C Increases in Tg26 Mouse Model of HIV-Associated Nephropathy (HIVAN)

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Background: Collapsing glomerulopathy (CG) is a feature of human immunodeficiency virus-associated nephropathy (HIVAN). Previous studies in kidney biopsies of patients with primary, collapsing variant of focal segmental glomerulosclerosis (cFSGS) demonstrated activated glomerular parietal epithelial cells (PEC) expressing cathepsin C protease, migrating into glomerular tufts. Similar results were found with preliminary lab studies in biopsies of HIVAN patients. Cathepsin C is normally absent in the glomerular tuft, suggesting that PEC introduction of this protease may contribute to extracellular matrix (ECM) remodeling in cFSGS. For this study, we addressed the hypothesis that cathepsin C expression increases in PECs lining Bowman's capsule and PECs migrating onto glomerular tufts in Tg26 mouse model of HIVAN.

Methods: Kidneys from 8 week old male and female Tg26 transgenic and FVB wt mice used for this study were provided by Klotman lab, baylor college of medicine. Formalin-fixed paraffin-embedded kidney sections were subject to co-immunofluorescence staining for claudin-1, a marker of PECs, and cathepsin C. Images were acquired by confocal microscopy.

Results: claudin-1 and cathepsin C were localized to glomerular parietal epithelial cells lining Bowman's capsule in wt mice. In glomeruli of Tg26 mice, PECs lining Bowman's capsule showed increased expression of cathepsin C and had hypertrophied morphology, suggesting PEC activation. Glomeruli of Tg26 mice also showed migration of Claudin-1-positive PECs onto the glomerular tuft and these cells also expressed cathepsin C.

Conclusions: Glomerular PECs exhibit increased expression of cathepsin C in Tg26 mouse model of HIVAN CG. These findings are similar to our findings from human primary cFSGS and HIVAN, demonstrating utility of this mouse model to define the role of PEC induction of cathepsin C in the pathogenesis of CG. Defining the cellular and molecular basis for abnormal ECM remodeling in cFSGS offers the potential of interrupting disease progression.

SA-PO837

Interstitial Fibrosis in ANCA-Associated Vasculitis: Myeloperoxidase (MPO) vs. PR3

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Background: Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a necrotizing vasculitis characterized by inflammation of small blood vessels, being the kidney one of the most frequently affected organs. AAV has a high morbidity and mortality rate, leading to rapidly progressive renal failure that may lead to end-stage kidney disease. Its pathogenesis is a complex and multifactorial process involving inflammation and fibrosis. PR3-AAV and MPO-AAV have clinical-demographic differences and different renal phenotypes observed in kidney biopsy. The histopathological subgrouping into four classes (focal, crescentic, mixed, and sclerotic) is useful for predicting long-term renal survival, the worst being sclerotic class. Our aim is to determine whether interstitial fibrosis in AAV is at least as important as glomerular sclerosis in prognosis.

Methods: Retrospective single-center study of 95 AAV patients (78 MPO-AAV and 17 PR3-AAV) diagnosed by renal biopsy, with at least 1-year follow-up. Type of ANCA, immunosuppressant therapy and renal/patient survival were evaluated. Histomorphometric quantification using MetaMorph® software on trichrome-stained biopsies slides to measure the degree of fibrosis. Data analysis performed under standard conditions.

Results: PR3-AAV population was predominantly male (70%, mean age=62, mean follow-up=54 months), while MPO-AAV population was mainly female (65.8%, mean age=66, follow-up=65 months). There were no statistically significant differences in renal function between MPO and PR3-AAV at diagnosis. Albeit renal function improved throughout follow-up in MPO ($p<0.01$) and PR3-AAV ($p=0.05$), MPO-AAV showed worse renal function than PR3-AAV ($p=0.01$) at the end of follow-up. MPO-AAV showed more interstitial fibrosis at diagnosis than PR3-AAV ($p=0.01$). However, there were no significant differences in the incidence of glomerulosclerosis ($p=0.26$). PR3-AAV showed more crescentic proliferation ($p=0.03$) but less fibrotic crescents than MPO-AAV at diagnosis.

Conclusions: The method we used allows a quantitative assessment of renal fibrosis. Our data confirm that renal prognosis is better in PR3-AAV than in MPO-AAV. This could be explained by a greater interstitial fibrosis, as well as more fibrotic crescentic in MPO-AAV at diagnosis.

SA-PO838

The Protein/Creatinine Ratio Is a Reliable Indicator of 24-Hour Urine Protein, Regardless of the Level of Renal Function in Patients with Glomerulopathies

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Background: We aimed to determine the accuracy of the urine isolated protein/creatinine ratio (PCR) test, against the gold standard 24-hour urine protein (24hUP) measurement in patients with glomerulopathies, and according to the levels of renal function.

Methods: This prospective study of patients with glomerulopathies was developed at Professor Edgard Santos University Hospital in Salvador, Bahia-Brazil. The PCR and 24hUP measurements were performed using conventional methods within a maximum interval of 24 hours between the measurements. The patients were classified into three groups according to their renal function, group 1= <30 ml/min/1.73m^2, group 2= 30-60 ml/min/1.73m^2 and group 3= >60 ml/min/1.73m^2. Spearman correlation coefficient (r_s) and ROC curves were employed to compare PCR with 24hUP.

Results: The total was 167 urinary samples from 134 patients. The mean age was 42 ± 16 yrs, 68% were female and 91% non-white. A good correlation was observed between PCR and 24hUP total sample (r_s= 0.7, p= <0.000), as well as in comparison with the different levels of renal function (r_s= 0.8 for group 1, r_s= 0.9 for group 2 and r_s= 0.8 for group 3). The ROC between PCR and 24hUP total sample yield an AUC of 0.94 (CI= 0.89, 0.97), high sensitivity of 91% and specificity of 83%, at the optimal cut-off point was 0.7. The groups representing three levels of renal function showed high sensitivity and specificity in comparisons of both methods (group 1= 82%, 100%, group 2= 97%, 89% and group 3= 88%, 92%) with an AUC of 0.92, 0.96 and 0.96, respectively.

Conclusions: PCR shows high sensitivity and specificity for monitoring patients with glomerulopathies compared to 24hUP. Our findings suggest that PCR is a useful parameter to evaluate and monitor patients with different glomerulopathies regardless of the level of renal function.

Results in the total sample and by degree of renal function comparing protein/creatinine ratio with 24-hour urine protein

Variables	Total N=167	Spearman Correlation	Cut-off by Youden Index	Sensitivity (%)	Specificity (%)	Area under ROC curve (95%CI)
PCR vs 24hUP total sample	167	0.8	0.7	91	83	0.94 (0.8;0.9)
Degree of kidney function						
<30 ml/min/1,73 m2	35	0.7	0.8	82	100	0.92 (0.8;0.9)
30-60 ml/min/1,73 m2	42	0.8	0.9	97	89	0.96 (0.9;1.0)
>60 ml/min/1,73 m2	90	0.8	0.8	88	92	0.96 (0.9;1.0)

SA-PO839

Association of Neuroblastoma Suppressor of Tumorigenicity 1 (NBL1) with Interstitial Fibrosis Severity and Kidney Function Decline in IgA Nephropathy

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Background: We recently showed that the presence of neuroblastoma suppressor of tumorigenicity 1 (NBL1) in circulation is closely linked to the progression of kidney disease and histological abnormalities in individuals with diabetic kidney disease. This research aimed to investigate the potential association between serum NBL1 levels and kidney function, as well as renal histological leisons, in patients with IgA nephropathy (IgAN).

Methods: In this study, we assessed the NBL1 levels in 109 individuals with IgAN by using serum samples collected immediately before renal biopsy. We also evaluated the significance of serum NBL1 in relation to kidney function and renal histological findings based on the Oxford Classification (MEST score). Moreover, we examined the correlation between serum NBL1 and the long-term decline in kidney function among IgAN patients who had follow-up data on their estimated glomerular filtration rate (eGFR) (n=76).

Results: In early-stage IgAN patients, serum NBL1 levels were found to be higher compared to healthy individuals (n=93). Logistic regression analysis revealed a significant and independent association between serum NBL1 levels and tubular atrophy/interstitial fibrosis. Through immunohistochemical staining, NBL1 was highly expressed in the tubulointerstitium during the early stages of IgAN. Additionally, a significant correlation between serum NBL1 levels and the eGFR slope was identified on Spearman's rank correlation.

Conclusions: The serum NBL1 level was significantly associated with the severity of renal interstitial fibrosis and future kidney disease progression in patients with IgAN. Thus, circulating NBL1 may serve as a good biomarker for evaluating renal interstitial fibrosis and the risk of kidney disease progression.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO840

Longitudinal Changes in IgA1 O- and N-Glycoforms in IgA Nephropathy

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Background: An increased level of circulating aberrantly glycosylated IgA1 has been considered a significant initial step in the pathogenesis of IgAN. Recently, the molecular features of IgA1 *O*- and *N*-glycoforms in patients with IgAN have been reported using high-resolution mass spectrometry (HRMS). While specific glycopeptides have been reported to be a possible predictor of IgAN and glomerular function, it is still largely unclear how the glycosylation of IgA1 changes according to treatment. In this study, we aimed to determine the difference in IgA1 *O*- and *N*-glycoform changes between different treatment groups at two time points: at diagnosis and post-treatment, using a prospective cohort enrolled at Fujita Health University Hospital.

Methods: We registered patients diagnosed with primary IgAN by renal biopsy during 2017–2019. Ten patients who received tonsillectomy and corticosteroid therapy (T-CST group), eight patients who received conservative therapy (CO group), and five patients with other renal diseases who were treated with corticosteroid therapy (ORD group) were enrolled. IgA was purified from the serum of patients at two time points (at diagnosis and post-treatment). After neuraminidase treatment, *O*-glycoforms of the hinge region (HR) and *N*-glycoforms of the Fc region were analyzed using online liquid chromatography-HRMS.

Results: The mass spectrometry analysis of *O*-glycoforms of IgA1 HR showed that the number of *N*-acetylgalactosamine in the IgA1 HR was significantly increased only in the T-CST group from diagnosis to post-treatment (P = 0.0325), while the number of galactose in the IgA1 HR remained unchanged in all groups. The mass spectrometry analysis of *N*-glycoforms also showed several changes only in the T-CST group. In asparagine $(Asn)^{340}$, at post-treatment, there was a significant increase in the relative abundance of the oligomannose-type (P = 0.0020) and a significant decrease in the galactosylation of the tri-antennary-type (P = 0.0098); whereas in Asn^{144}, there was a significant decrease in the relative abundance of fucosylated glycan (P = 0.0195).

Conclusions: This study found that some glycoforms previously reported to be characteristics of IgAN were altered only in the T-CST group of IgAN but not in the CO group of IgAN or the ORD group. The detection of *O*- and *N*-glycoform alterations may be IgAN-specific biomarkers of disease activity.

Funding: Government Support - Non-U.S.

SA-PO841

Integrin β1 Mediates Interactions of IgA1-Containing Circulating Immune Complexes from IgA Nephropathy Patients with Cultured Primary Human Mesangial Cells

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Background: Biopsy features of IgA nephropathy include proliferation of mesangial cells and glomerular IgA1 that probably originates from deposition of circulating immune complexes (CIC) with variable amounts of IgA1, IgG, complement C3, and other proteins, e.g., fibronectin (FN). C-terminal segment of FN may bind IgA, and serum levels of IgA-FN complexes may have diagnostic value for IgA nephropathy. The mechanism by which CIC induce proliferation of the mesangial cells is not well understood. We explored interactions between CIC, mesangial cells, FN, and FN's receptors (integrin α1β1 and α5β1).

Methods: Cultured quiescent human mesangial cells were incubated for 15 min at 37°C with CIC from sera of patients with IgA nephropathy, without or with integrin α1β1 inhibitor obtustatin or integrin α5β1 inhibitor RGD. The integrins were immunoprecipitated (IP) from cell lysates using specific antibodies. Cell lysates and IP products were analyzed by SDS-PAGE/immunoblotting with antibodies specific for IgA, IgG, IgM, FN, and selected phosphoproteins. To assess effects of FN on CIC association with mesangial cells, CIC were incubated 15 min at 37°C with the cells and purified FN, with or without obtustatin.

Results: Variable amounts of IgA and IgG were detected in the lysates of cells incubated with CIC. CIC induced phosphorylation of several proteins, including PDGFR-β, Axl, ERK, and integrin β1. Obtustatin reduced the amounts of IgA and IgG in the lysates and decreased CIC-induced phosphorylation of ERK, Axl, integrin β1, and PDGFR-β. IgA, IgG, and FN were detected in the IP with antibodies specific for integrin α1β1 and α5β1. Obtustatin reduced amounts of IgA and IgG in the IP. Addition of FN to the cells with CIC enhanced the amounts of IgA, IgG, and IgM in lysates about 1.2-4.7-fold. Obtustatin decreased the FN-enhanced amounts of IgA, IgG, and IgM in lysates by about 10-25%.

Conclusions: CIC from patients with IgA nephropathy added to cultured mesangial cells induced cellular signaling and variable association of IgA/IgG/IgM in the cell lysates. Addition of FN enhanced the association of IgA/IgG/IgM with the cells. Future studies are needed to define mechanisms of integrin β1 and CIC interactions and a possible role of FN in these processes.

Funding: NIDDK Support

SA-PO842

Characterization of IgA1-Containing Circulating Immune Complexes in Patients with IgA Nephropathy with Progressive vs. Nonprogressive Disease

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Background: IgA nephropathy (IgAN) is an autoimmune disease wherein circulating immune complexes (CIC) deposit in the glomeruli and induce mesangioproliferative injury. These CIC contain IgA1 with some *O*-glycans deficient in galactose (Gd-IgA1) bound by IgG autoantibodies (AuAb) specific for Gd-IgA1. Serum levels of Gd-IgA1 and IgG AuAb predict disease progression, but little is known about characteristics of the CIC. Here, we analyzed the mesangioproliferative capacity and composition of CIC from patients with progressive vs. non-progressive IgAN.

Methods: CIC from sera of IgAN patients with progressive (IgAN-P; n=3) or non-progressive (IgAN-Np; n=2) disease were isolated by size-exclusion chromatography (SEC). IgAN-P were defined as having eGFR loss (2021 CKD Epi formula) >2 ml/min/1.73 m^2 per year. Median follow up was 13 years. Mesangioproliferative activity of CIC was assessed by using cultured primary human mesangial cells (MC). Jacalin affinity chromatography was used to deplete total serum IgA1 before SEC. Serum levels of IgA, Gd-IgA1, and IgG AuAb were determined by ELISA and CIC composition was assessed by SDS-PAGE/immunoblotting with antibodies specific for IgA, IgG, or complement C3.

Results: CIC of molecular mass (Mr) >700 kDa stimulated proliferation of MC. These CIC contained IgA, IgG, and C3. Most of C3 in these CIC was covalently associated with IgG and IgA, presumably through a thioester bond. Immunoblotting of CIC electrophoretically separated under reducing conditions revealed C3, C3b, and iC3b. CIC from IgAN-P exhibited greater mesangioproliferative activity compared to CIC from IgAN-Np. Jacalin removed these stimulatory CIC from serum, and the corresponding SEC fractions were devoid of IgA, IgG, and C3.

Conclusions: IgAN CIC with Mr >700 kDa that stimulated cellular proliferation of MC contained IgA1 with IgG and covalently attached C3. Jacalin affinity chromatography confirmed association of IgA1 with C3 and IgG. Moreover, IgAN-P had more active CIC compared to IgAN-Np CIC. Future studies will determine similarities and differences in the composition and amounts of these CIC associated with disease severity and/or progression.

Funding: NIDDK Support, Private Foundation Support

SA-PO843

Therapeutic Effect of Nanoparticle-Mediated shRNA Delivery in Lupus Nephritis Mice

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Background: Lupus nephritis (LN) is the most common and severe manifestation of systemic lupus erythematosus (SLE). LN pathogenesis is complex and incomplete understood. Therapy approach are predominantly nonspecific immunosuppressive medications. More effective drugs with favorable safety profiles are urgently needed. MRL/lpr mice develop lupus nephritis that mostly assemble disease manifestation in lupus patients. WD repeats and FYVEdomain-containing protein 1 (WDFY1) is an adaptor protein involving in inflammatory pathways in LN.

Methods: Protein levels of WDFY1 were analyzed by Western blot and immunofluorescent staining in the kidney of nephritic MRL/lpr mice and lupus nephritis patients. Lupus-like disease was first induced in C57BL/6 mice by ip administration with 1 X 10^8 splenocytes from bm12 mice. Serum autoantibody levels were measured by ELISA. Germinal center reaction and cell subtypes were analyzed. Twelve-week old MRL/lpr mice were treated with nanoparticle encapsuled WDFY1-shRNA for 5 weeks. Renal pathology, immune complex deposition, and complement activation were examined.

Results: Significantly enhanced WDFY1 expression was detected in the kidney of MRL/lpr mice compared to the age/sex-matched MRL/MpJ mice. The expression levels also correlated with the nephritis disease activity. Kidney sections from LN patients also showed increased WDFY1 expression compared to kidney samples from healthy controls. B6.WT mice developed increased levels of anti-dsDNA and anti-chromatin autoAbs after receiving bm12 splenocytes. AutoAb production was significantly diminished in B6.WDFY1-KO mice receiving the same dose of bm12 splenocytes. Most importantly, MRL/lpr mice treated with nanoparticle encapsuled WDFY1-shRNA showed improved kidney function with significantly decreased BUN and proteinuria.

Conclusions: Observations made here support the usefulness of WDFY1 for the treatment of lupus and lupus nephritis. Results may lead to more effective and safer molecule-specific approaches.

Funding: NIDDK Support

SA-PO844

Humoral Immune Responses Primed by the Alteration of Gut Microbiota Were Associated with Galactose-Deficient IgA1 Production in IgA Nephropathy

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Background: Galactose-deficient IgA1 (GdIgA1) is critical in the formation of immunodeposits in IgA nephropathy (IgAN), whereas the origin of GdIgA1 is unknown. We focused on the immune response to fecal microbiota in IgAN patients.

Methods: By running 16S rRNA gene sequencing, we compared IgAN samples to the control samples from household-matched or nonrelated individuals. Levels of plasma GdIgA1 and poly-IgA complexes were measured, and candidate microbes that can either incite IgA-directed antibody response or degrade IgA through specific IgA protease activities were identified.

Results: The IgAN group showed distinct composition of fecal microbiota as compared to healthy controls. Particularly, high abundance of Escherichia-Shigella was associated with the disease group based on analyses using Receiver-operating Characteristic (AUC 0.837, 95% CI 0.738-0.914), Principe Coordinates, and the LEfSe algorithm (LDA score: 4.56, $p<0.001$). Accordingly, the bacterial levels directly correlated with high titers of plasma GdIgA1($r=0.36$, $p<0.001$), and patients had higher IgA1 against stx2(2.88±0.46 IU/ml *vs*. 1.34±0.35 IU/ml, $p=0.03$), the main antigen of Escherichia-Shigella. Conversely, the healthy controls showed relatively higher abundance of the commensal bacteria that produce IgA-degrading proteases. Particularly, the abundance of some intestinal bacteria expressing IgA proteases showed an inverse correlation with the levels of plasma GdIgA1 in IgAN.

Conclusions: Our data suggest that mucosal IgA production, including those of GdIgA1, is potentially linked to the immune reactivities against gut Escherichia-Shigella, and conversely, the IgA protease-producing microbiota in the gut are suppressed in IgAN patients.

SA-PO845

Neutrophil Degranulation in Lupus Nephritis

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Background: There is accumulating evidence for neutrophil involvement in lupus nephritis (LN). Neutrophils are recruited into glomeruli following immune complex deposition, where they release toxic antimicrobial agents and immune regulatory molecules from preformed granules. Our previous reports with mice and cultured

cells show that neutrophil granule proteins contribute to immune complex-mediated glomerular injury and directly injure podocytes and glomerular endothelial cells. The aim of this study is to investigate the contribution of neutrophil degranulation in human LN.

Methods: Levels of twelve neutrophil granule proteins were measured in urine and serum from 10 LN patients with active disease and 8 healthy controls (HC) using an antibody-based array and ELISA validations. Flow cytometry was used to measure markers of secretory, specific, and azurophilic granule release in untreated neutrophils from LN patients and HC and in HC neutrophils in response to LN patient or HC serum.

Results: Six of the targeted granule proteins (neutrophil elastase, olfactomedin-4, lactoferrin, a-1AG, MMP-9, and cathelicidin) were significantly elevated in urine from LN patients, and neutrophil elastase was the only protein higher in LN serum. Degranulation of all granule subsets were significantly enhanced in untreated neutrophils from LN patients compared to HC. Serum from active LN patients, but not HC serum, significantly activated granule release in HC neutrophils.

Conclusions: Our findings suggest that enhanced neutrophil degranulation could play a role in LN pathology and that urine measurement of neutrophil granule proteins could serve as markers of kidney inflammation.

Funding: NIDDK Support

SA-PO846

The C-Terminal Region of HTRA1 Is the Predominant Target for Autoimmunity in HTRA1-Associated Membranous Nephropathy (MN)

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Background: We previously identified HTRA1 as a novel antigen in 4.2% of uncharacterized MN patients. This secreted serine protease is expressed in various tissues with high homology across human and rodent species (~92%). The trypsin-like serine protease domain in HTRA1 is responsible for its proteolytic activity whereas its PDZ domain facilitates protein-protein interactions by tethering HTRA1 to specific sites in the extracellular matrix.

Methods: Immunoblotting/cyclic constrained epitope mapping of patient serum from two independent cohorts with various truncated recombinant HTRA1 proteins. WT and HTRA1 KO mice were immunized with full-length human HTRA1.

Results: Sera from patients with HTRA1-associated MN is known to recognize native and recombinant human HTRA1 even under reducing conditions, which are expected to disrupt the conformation of the highly disulfide bonded N-terminal region of HTRA1. Accordingly, both circulating and glomerulus-eluted antibodies from patients with HTRA1-associated MN recognize the HTRA1 C-terminus, which encompasses its PDZ and protease domains. Immunization of WT or HTRA1 KO mice with human HTRA1 generates mouse Ab against HTRA1. Importantly, these mouse autoantibodies recognized the HTRA1 C-terminus (similar to what is seen with patient-derived autoantibodies). To further approximate the location of the targeted epitopes of HTRA1 autoantibodies, immunoblotting of reactive sera with various truncated recombinant HTRA1 proteins showed that HTRA1 autoantibody-containing human sera recognized full length HTRA1 and HTRA lacking AA 1-158 (referred to as DeltaMac25)**.** To identify any outliers or conformation-specific epitopes, the commercially available PEPperMAP Cyclic assay was performed. This analysis revealed the top three antibody responses were against non-conformational peptides with the consensus motifs AIINYGNS**GGPL** (AA 312-332, which encompasses the AA 328 site known to be required for HTRA1 protease function), and **GGPL**VNLDGEV (AA 329-339) in the protease domain, and IEVIPD (AA 415-420, required for HTRA binding activity) in the PDZ domain.

Conclusions: Together, these findings suggest that the targeted epitope in HTRA1 is non-conformational and located within the C-terminus which raises the possibility that anti-HTRA1 antibodies may interfere with biological function and/or binding.

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SA-PO847

Oxford Kidney Pathology Atlas: Single Cellular Profiling of Renal Biopsy Tissue

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Background: Glomerular damage is central to many kidney diseases, thus a better understanding of glomerular cell pathology is essential for developing more targeted therapeutics. Transcriptomic and proteomic profiling of human renal tissue may address this challenge. Many studies utilize nephrectomy sections, with limited samples, technical glomerular dissociation bias, and non-standardized methodology restricting the research application of biopsies. As part of the Oxford Kidney Pathology Atlas study, we developed experimental protocols for processing standard human renal biopsy samples for single-nuclei RNA sequencing (snRNA-Seq) and glomerular proteomics and generated pilot data from healthy donors and an early primary idiopathic nephrotic syndrome (iNS) case.

Methods: Biopsy cores from diseased patients and pre-transplantation controls were processed for clinical histology, snRNA-Seq and targeted glomerular proteomics. SnRNA-Seq libraries were analyzed using the R package Seurat. Glomerular regions from formalin-fixed paraffin-embedded (FFPE) renal biopsy sections were isolated via targeted laser capture microdissection coupled with mass spectrometry (MS). MS results were analyzed using DI-ANN and Perseus software to assess relative protein abundance.

Results: We conducted a targeted proteomics titration experiment with varying numbers of isolated glomeruli from healthy donors to establish the minimum material required for proteomics. We isolated glomerular proteins from FFPE-embedded renal section, quantifying over 4.5k unique proteins from a single glomerulus and over 5k proteins from 6-10 human glomeruli. By snRNA-Seq, libraries were generated per single biopsy core, with glomerular and tubular populations represented. Despite normal histology, iNS patient-derived nuclei enriched in select proximal tubule and glomerular cell clusters, with altered gene signatures including increased cellular transport function and extracellular matrix accumulation, and reduced podocyte function.

Conclusions: We demonstrate that glomerular proteomic markers can be captured from 6 glomeruli from a human FFPE biopsy section. Key renal cell types are detectable by snRNA-Seq from standard clinical biopsy core, sufficient to detect differential cell composition and gene expression in disease tissue. This platform will be applied to identify novel therapeutic targets in kidney disease.

Funding: Commercial Support - Novo Nordisk

SA-PO848

C5b-9 Deposition on Cultured Endothelial Cells in Patients with Thrombotic Microangiopathy of Different Etiology

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Background: Thrombotic microangiopathies (TMAs) are a group of diseases linked by endothelial injury for different mechanisms, one of which is deregulation of the complement system. The differential diagnosis of TMAs is challenging due to the etiological overlap and the absence of specific biomarkers, hence complement assessment may be a useful tool to improve the management of these patients.

Methods: Complement terminal pathway was assessed by analyzing deposition of C5b-9 (C5b-9d) on cultured endothelial cells (CEC), by immunofluorescence, after exposing them to the plasma of patients with TMA from different etiology, obtained between June-2021 and April-2023. C5b-9 deposits were calculated as percentage of labeled area over the total area analyzed. An increase ≥ 2x was considered significant.

Results: 120 samples were included (95 patients, 51(53.7%) men, 49±15 years), of which 58(48.3%) had a positive result (C5b-9d ≥ 2x;Figure 1). Of these, 40(69.0%) presented renal function impairment at diagnosis: 6(10.3%) AKI-1, 7(12.1%) AKI-2, 17(29.3%) AKI-3 and 10(10.7%) required dialysis. Regarding the evolution of renal function, 33(56.9%) patients presented complete remission, 9(15.5%) partial remission, 2(3.4%) started long-term dialysis program and 6(10.3%) died.

Conclusions: Our series shows that TMA is a frequent condition, with high morbi-mortality. The analysis of C5b-9d on CEC could be a useful biomarker to differentiate those cases in which there is a complement overactivation, which may allow to individualize the treatment and follow-up of these patients. In addition to aHUS, C5b-9d was mainly observed in TMA associated with hematological diseases, drugs, and infections.

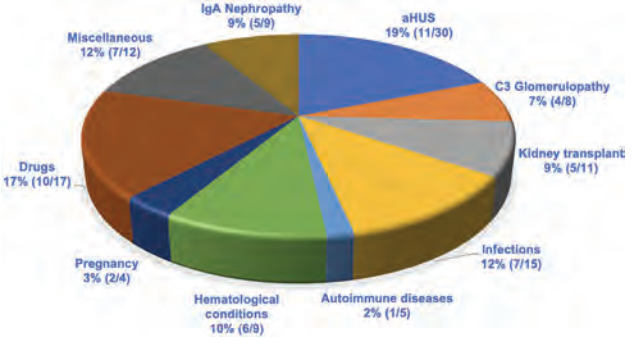

Figure 1. Etiology of TMA in patients with positive dC5b-9. The percentage expresses the positive cases of each etiology over the total number of positive cases. In parentheses, positive cases are shown over the total number of cases analyzed for each etiology.

SA-PO849

Late Renal Recovery in a Patient with Solitary Kidney and ANCA-Positive Glomerulonephritis (GN) Treated with Rituximab

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Introduction: ANCA vasculitis is the most common form of new-onset GN in adults >50. It is often associated with high rate of morbidity and mortality, especially when it causes significant renal injury requiring RRT. These patients often do not come off RRT, primarily when they have known CKD.

Case Description: 82yoF with CKD stage IIIa baseline SCr 0.9-1.1 with solitary right kidney due to renal cell cancer s/p left nephrectomy was found to have rapidly progressive AKI with SCr rising from 2.2 to 3.7 in a span of 2 weeks with associated dyspnea, leg edema, and fatigue. She was found to have focal necrotizing and crescentic pauci-immune GN with vascular findings consistent with vasculitis on her kidney biopsy. The crescents were limited to 4 of 46 glomeruli but had 13 globally sclerosed glomeruli with moderate interstitial fibrosis and 40-50% tubular atrophy. Along with positive c-ANCA and anti-MPO antibodies, she was confirmed to have ANCA vasculitis. Although she remained non-oliguric, her SCr continued to rise at 4.6 requiring hemodialysis (HD), which was continued even after hospital discharge. She was pulsed with steroids and was started on rituximab infusion after discharge. She was continued on rituximab and was able to come off HD after 8 months due to improvement in her SCr to 2.0-2.2 range. She remains off HD with last SCr of 2.1 from earlier this month.

Discussion: ANCA vasculitis remains a rare yet lethal disease that is yet to be fully understood as it is still unknown how ANCA antibodies develop. One study has shown that only 43% of patients who required RRT at the time of diagnosis were able to come off at 1 year. The prognosis is even poorer when they have known CKD with much lower rates of meaningful kidney recovery after initiating RRT at around 5%. Xu et al. emphasize how pathologic severity may determine renal recovery for ANCA vasculitis requiring RRT at disease onset with high proportion of fibrous crescent and global glomerulosclerosis being a predictor of dialysis dependence. Our patient's renal recovery indicates that even with advanced age, baseline CKD, and moderate tubulointerstitial involvement, it is worth treating the active vasculitis in the form of crescentic glomerular lesions with rituximab. We also make a case for biopsy of a solitary kidney when absolutely indicated despite the risks involved.

SA-PO850

Paraneoplastic IgA Nephropathy Associated with Renal Cell Carcinoma

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Introduction: Malignancy is a rare and underrecognized cause of secondary IgA nephropathy, particularly in elderly patients. We present a case of IgA nephropathy likely paraneoplastic to renal cell carcinoma (RCC) that resolved after tumor resection.

Case Description: A 71-year-old previously healthy woman presented to the nephrology clinic with an elevated serum creatinine. Although asymptomatic, the patient noted her son had IgA nephropathy requiring kidney transplant. On examination, she was hypertensive to 158/88 mm Hg but had a normal cardiopulmonary examination with no peripheral edema. Laboratory studies showed a serum creatinine elevated to 2.7 mg/dL from normal baseline. Urinalysis showed 100 mg/dL protein, large blood, 68 WBC/HPF, and 83 RBC/HPF. Serologic workup was unremarkable. A kidney ultrasound and subsequent MRI showed a mixed solid cystic mass measuring 4.6 x 4.1 x 3.8 cm involving the lower pole of the right kidney. A biopsy of the left kidney demonstrated IgA dominant immune complex glomerulonephritis with necrosis and crescents, for which she was treated with high dose prednisone. A biopsy of the right kidney mass identified clear-cell renal cell carcinoma, for which she underwent uncomplicated partial nephrectomy. Her kidney function subsequently stabilized allowing for discontinuation of steroids.

Discussion: IgA nephropathy can be associated with infection, autoimmune conditions, liver disease, and malignancies—such as lung cancers, lymphomas, IgA myeloma, and RCC. This case represents a paraneoplastic IgA nephropathy associated with clear cell RCC that resolved post-nephrectomy. Although fewer than ten cases related to RCC are reported in the literature, multiple studies have identified pathologic evidence of IgA nephropathy in RCC nephrectomy specimens. This suggests that IgA nephropathy may result from tumor-induced antigen-antibody response. The primary goal of treatment is to address the underlying malignancy to minimize the risk of further kidney damage and allow for recovery. The role of steroids or other immunosuppressive therapies is unclear. In this case, removing the tumor led to significant improvement possibly due to elimination of tumor-induced immune interactions.

SA-PO851

Peripheral Neuropathy Leading to Diagnosis of ANCA-Associated Glomerulonephritis

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Introduction: ANCA-associated glomerulonephritis (GN) rarely presents with concomitant neurologic symptoms.

Case Description: A man in his seventies with type 2 diabetes mellitus and hypertension was admitted with 6-months of worsening extremity weakness and gait instability leading to a fall. Electromyelogram demonstrated diffuse demyelinating polyneuropathy. On admission, he had acute kidney injury (AKI) with serum creatinine 1.86 mg/dL (0.9 mg/dL at baseline). Urine microscopy showed acanthocytes, red blood cell casts, and dense granular casts. Renal biopsy demonstrated crescentic GN, acute interstitial nephritis with tubular necrosis, and a medium-sized artery occluded by thrombus. Direct immunofluorescence was positive for C3 and negative for IgG, IgM, IgA, C1q, fibrinogen, albumin, or kappa/lambda light chains. Perinuclear ANCA titer was elevated at 1:320. Anti-MPO antibodies were >8 units; anti-PR3 antibodies were elevated at 2.7 units. Diagnoses of ANCA-associated GN and microscopic polyangiitis (MPA) were made. He was treated with induction methylprednisolone and rituximab followed by prednisone taper. After treatment, renal function and extremity neuropathy symptoms improved. Serum creatinine improved from 2.42 mg/dL pre-treatment to 2.0 mg/dL at hospital discharge.

Discussion: The initial presentation of weakness and polyneuropathy is an unusual dominant symptom for MPA, which may have delayed recognition of renal involvement. He lacked other symptoms, including rash or sinusitis, that are often associated with systemic small-vessel vasculitis. C3 positivity on direct immunofluorescence does not rule out ANCA-associated GN despite its classic "pauci-immune" appearance. Plasmapheresis was considered due to concurrent AKI and autoimmune-mediated demyelinating polyneuropathy but was deferred due to lack of rapid renal failure or pulmonary hemorrhage. Immunosuppressive therapy directed at preserving kidney function also improved the neuropathy suggesting that these were both due to MPA. Recognition of unusual features of MPA-associated GN as demonstrated in this case aided diagnosis and should be considered in AKI cases with neurologic derangements. *The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

SA-PO852

SLEeping in the Cold

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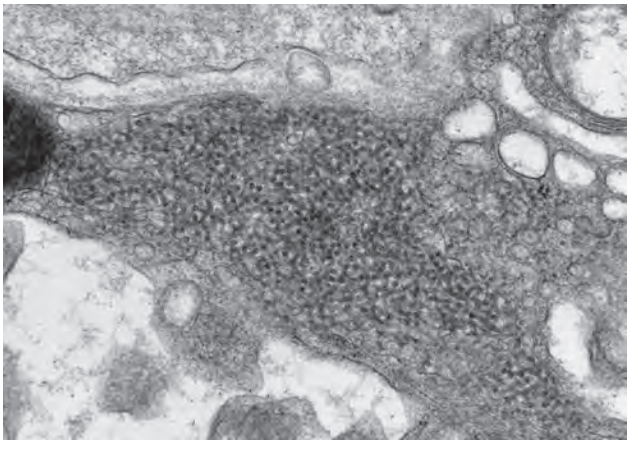
Introduction: Glomerular diseases in patients with systemic lupus erythematosus (SLE) can take many forms, however the classification of lupus nephritis by ISN/RPS does not include cryoglobulinemic vasculitis. We describe a patient evaluated for lupus nephritis who was found to have SLE-induced mixed cryoglobulinemic vasculitis.

Case Description: A 68-year-old woman with SLE and no prior kidney involvement was referred to the nephrology clinic for suspected lupus nephritis. Two months prior to evaluation, she developed edema and exercise intolerance, with workup notable for new proteinuria with urine protein-to-creatinine ratio (UPCR) of 3.8 g/g, mildly elevated serum creatinine (0.75 mg/dL) from baseline (0.60 mg/dL), low C4, and normal C3. There was no evidence of SLE or vasculitis on history or physical exam. Urine sediment microscopy was notable for many acanthocytes. Kidney biopsy was consistent with membranoproliferative glomerulonephritis and noted cryoglobulin deposits on electron microscopy. Further workup was notable for the presence of type II cryoglobulins (2%), elevated rheumatoid factor (140 IU/mL), negative hepatitis C virus antibodies, and normal serum free light chains. She was diagnosed with cryoglobulinemic vasculitis. Treatment with oral prednisone and mycophenolate mofetil resulted in improved proteinuria (UPCR 0.375 g/g) and decline in rheumatoid factor titers (59 IU/mL), however during her steroid taper the patient developed a purpuric leukocytoclastic rash, prompting the addition of rituximab. Her symptoms have markedly improved since receiving rituximab.

Discussion: While the most common glomerular disease affecting patients with lupus is lupus nephritis, many glomerular diseases are associated with SLE, including lupus podocytopathy, thrombotic microangiopathy, antiphospholipid antibody syndrome, and cryoglobulinemic vasculitis. Treatment of cryoglobulinemic vasculitis due to SLE is initially focused on treating the SLE itself, however with progressive or persistent disease, rituximab may be added.



SA-PO853

First Reported Association of Subcutaneous Panniculitis-Like T-Cell Lymphoma (SPTCL) and C3 Glomerulopathy with Renal-Limited Thrombotic Microangiopathy (TMA)

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Introduction: SPTCL constitutes <1% of peripheral T-cell lymphomas, with a 5-year survival of >80%. We report the first case of C3 glomerulopathy (C3G) with renal-limited TMA associated with SPTCL.

Case Description: A 71-year-old African American woman with history of hypertension, presented for a gradually spreading, hyperpigmented indurated plaque on the right thigh for 2 months, punch biopsy demonstrated SPTCL. In three weeks she developed similar lesions on both calves and right forearm. She was admitted for an elevated creatinine (2.74mg/dl; 0.82mg/dl baseline), lactate dehydrogenase (1471U/L), and uric acid (8.3mg/dl). Hemoglobin was stable, platelets and renal imaging were normal and urine protein-to-creatinine ratio showed new proteinuria (1410mg/g). She developed progressive renal injury requiring hemodialysis. Infectious and autoimmune work up remained negative except ANA of 1:320. Hemophagocytic lymphohistiocytosis and lupus were ruled out. Pulse dose steroids (250mg for 3 days) was given due to concerns for rapidly progressive glomerulonephritis. Kidney biopsy showed TMA with global glomerulosclerosis, 65% IFTA, without endocapillary hypercellularity, sclerosis or crescent formation. Immunofluorescence showed glomerular capillary wall and mesangium staining for C3 (4+). She completed 1.8g/m2 of fractionated cyclophosphamide (CYC) and 1.5mg/kg orally for 6 months. She received eculizumab, with a plan to continue pending complement work up. Despite therapy and improvement in urine output, she continued to be dialysis dependent.

Discussion: Direct association of complement activation with SPTCL is not reported, but there is growing evidence on complement dysregulation with tumorigenesis. As complement plays a role in immune surveillance against malignant cells, modified expression of complement proteins and regulators by tumor microenvironment can lead to over activation of complement pathways (1). We propose that SPTCL may contribute to complement dysregulation and resulted in renal-limited TMA in our patient. CYC was used to treat SPTCL and eculizumab for C3G and renal-limited TMA findings with success (2). Further understanding of mechanisms driving complement dysregulation with specific tumors are needed to explore potential treatment options.

SA-PO854

"Tag - You're It!" Use of Tagged Red Blood Cell (RBC) Scan to Localize Gross Hematuria

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Introduction: Tagged red blood cell (RBC) scan performed with technetium-99m-labeled autologous erythrocytes has proven to be a clinically useful tool for localizing bleeding in the gastrointestinal (GI) tract. However, it has never been used to identify a bleed in the kidneys or genitourinary tract (GU). We hereby present the first known case in which a tagged RBC scan was utilized to detect an occult GU source of bleeding.

Case Description: A 58-year-old African American female with an extensive history of gross hematuria and chronic severe anemia requiring monthly blood transfusions presented to the emergency department with complains of extreme fatigue. She has been having hematuria with the passage of blood clots for at least 25 years. She has had extensive hematological work up including bone marrow biopsy, angiograms and cystoscopies with no clear source of bleeding identified. She even underwent radical left nephrectomy with pathology revealing papillary necrosis and thin basement membrane disease. She was hypotensive and appeared extremely pale on presentation. Initial labs revealed a hemoglobin of 1.1 g/dl with surprisingly normal renal chemistry. After initial stabilization with multiple blood transfusions, the patient underwent CT angio abdomen and pelvis which did not show any evidence of active bleeding followed by an unremarkable cystoscopy. Patient was recommended to have the right nephrectomy as well which would have guaranteed lifelong dialysis dependency. In an attempt to identify the source of bleeding before any surgical intervention, she subsequently underwent a tagged RBC scan with technetium that did not show any evidence of renal bleeding, but instead showed increased radio tracer uptake in the urinary bladder wall representing the likely source of bleeding. This was followed by the placement of a percutaneous nephrostomy tube which drained clear urine versus the persistently bloody urine draining in the urinary bag further ruling out a renal source of bleeding and in turn salvaging her kidney.

Discussion: Tagged RBC scans are recommended to confirm gastrointestinal (GI) bleeding. We suggest this modality could be an alternative tool to localize bleeding in the kidneys and the GU tract, especially in difficult cases like ours, where there was no identifiable source of chronic hematuria. It proved to be an organ saver in her case.

SA-PO855

AA Amyloid Masquerading as C3 Glomerulonephritis

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Introduction: C3 glomerulopathies are a group of rare kidney disorders characterized by complement dysregulation. We present a case of AA amyloidosis presenting as C3 glomerulonephritis.

Case Description: 55-year-old woman with a history of metastatic vulvar squamous cell carcinoma, presented with right lower extremity pain, right groin abscess and acute kidney injury (AKI). Baseline creatinine was 0.46 mg/dL and peaked at 6.9. No nephrotoxins were reported on history or review of medical records. Urinalysis was significant for WBC 21-50/hpf, RBC 0-2/hpf, protein 300 mg/dL, small blood and Urine protein to creatinine ratio was 9g/g. Hep C was positive with HCV RNA PCR-657,000. Complements were normal. Serological and paraproteinemia workup was negative. Kidney biopsy showed MPGN pattern with lesions suggestive of thrombotic microangiopathy (TMA) in 80% of capillary loops on light microscopy (LM) and immunofluorescence (IF) was positive for diffuse 3 + mesangial and capillary loop reaction for C3. No reaction to IgG, IgA, IgM, C1q, kappa, lambda or fibrin. Based on LM and IF findings, diagnosis of C3GN and TMA was made, although TMA itself is very uncommon. It was presumed that activation of alternate complement pathway was due to infection. There was minimal endocapillary proliferation which did not fit with typical C3GN with such high serum creatinine level. Electron microscopy (EM) eventually cleared the final diagnosis. EM revealed thin delicate randomly arrayed fibrils within the mesangial matrix and Congo Red and Thioflavin-T staining was positive in the mesangium and capillary loops. What was read as TMA were actually amyloid deposits. Mass spectrography revealed AA Amyloid.

Discussion: This patient presented with multiple challenges in terms of diagnosis. Hepatitis C related MPGN, Infection related glomerulonephritis and paraneoplastic related GN were all considerations. Light microscopy and IF were suggestive of C3GN with TMA which fit clinical picture (and all can present in a similar fashion). Eventually EM clinched the diagnosis. It proved to be a case of mistaken identity. EM is invaluable in making management decisions especially when LM and IF are not corroborating with clinical and pathological findings. Patient deterioration was rapid and did not pursue active treatment and chose hospice care.

SA-PO856

Collapsing Focal Segmental Glomerulosclerosis (FSGS) with APOL1 Gene Mutation in Adult-Onset Still Disease (AOSD)

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Introduction: Collapsing FSGS is a distinct variant characterized by hypertrophy and hyperplasia of podocytes with glomerular tuft collapse. Collapsing FSGS is mostly seen with HIV or COVID-19 and cases not attributed to HIV are often idiopathic. Amongst the other secondary causes are autoimmune diseases such as AOSD. We present a case of collapsing FSGS attributed to AOSD in a high risk patient with APOL1 gene mutation.

Case Description: Our patient is a 24-year-old incarcerated African-American male with history of left nephrectomy who presented with orbital and facial swelling. He reported subjective fevers for 4 to 5 months, 40 pound weight loss; pain, stiffness, and swelling in bilateral hands. On exam, patient was febrile to 101 Fahrenheit, tachycardic to 110 beats/minute with periorbital edema, swelling and tenderness of bilateral second-fourth proximal interphalangeal joints. Skin examination revealed a rash over his right eyelid and bilateral knuckles. Lab investigations revealed WBCs 13.1 with 82% neutrophils, creatinine 4.3 mg/dL, albumin 2.1 g/dL, AST 206 IU/L, ALT 292 IU/L, ALP 130 IU/L, total bilirubin 0.5, ferritin 1737 ng/mL, ESR 104, CRP 7.3, urine protein/creatinine ratio (UPCR) 14,450. Other than ANA positivity 1:80, his additional work up, including hepatitis profile, TB, COVID, HIV, syphilis, CMV, EBV, C3/C4, and Anti-CCP, was negative. Renal biopsy was consistent with collapsing FSGS with mild-moderate interstitial fibrosis. Malignancy screening was negative. Genetic testing for APOL1(G1 & G2) was positive.

Discussion: AOSD displays renal manifestations in 25% of cases including mesoangioproliferative glomerulonephritis. Collapsing FSGS secondary to AOSD is extremely rare. To the best of our knowledge, there have been four previously reported cases. In our reported case, the renal biopsy provided a histological diagnosis of collapsing FSGS. Serologic and infectious workup were negative and a diagnosis of AOSD was established after fulfilling the Yamaguchi criteria. Our case is the first reported case to describe collapsing FSGS attributed to AOSD in a high risk patient with APOL1 gene mutation. Further studies are needed to determine treatment options. Our patient was treated with losartan and prednisone 60mg daily with symptom improvement and UPCR downtrended to 8,153 within 2 months.

SA-PO857

Carfilzomib-Associated Thrombotic Microangiopathy with Kidney Infarction Treated with Eculizumab

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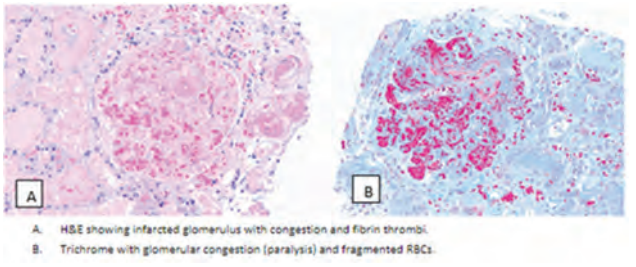
Introduction: Thrombotic microangiopathy (TMA) results from endothelial cell injury that can lead to kidney injury. Drug-induced TMA (DITMA) is a rare but serious adverse effect of certain medications, including carfilzomib, a proteasome inhibitor used for multiple myeloma (MM). Parenchymal kidney infarction is a rare and severe complication of TMA, which can lead to significant acute kidney injury (AKI). We report a case of kidney infarction with anuric AKI associated with carfilzomib use.

Case Description: A 66 yo White woman with refractory IgG lambda MM began carfilzomib-based therapy. Kidney function was stable until 6 months after starting carfilzomib, when she experienced rapid decline in urine output and AKI with a creatinine of 7.4 mg/dL (baseline 0.6 two weeks prior), with thrombocytopenia and anemia. Within 2 days she was anuric and required hemodialysis (HD). Labs showed low haptoglobin and high lactate dehydrogenase, suggesting microangiopathic hemolytic anemia. ADAMTS-13, C3, C4, E. coli Shiga-like toxins were normal. A kidney biopsy confirmed TMA with fibrin thrombi affecting glomeruli and arterioles, plus parenchymal kidney

infarction. (Fig 1) Carfilzomib was discontinued. Despite a negative complement genetic panel, eculizumab was started for severe TMA. Kidney function slowly improved, and HD was discontinued after 3 months.

Discussion: DITMA can be a rare but life-threatening complication of anti-cancer therapies. Carfilzomib has been associated with TMA. Although the exact mechanism is not fully understood, it is thought that Carfilzomib causes endothelial injury leading to TMA. Management of carfilzomib- associated TMA with kidney infarction involves prompt discontinuation of the drug. In severe cases, anti-complement therapy can be considered. A high index of suspicion is needed when caring for patients on this agent, as prompt recognition and management are essential for optimal patient outcomes.



A. H&E showing infarcted glomerulus with congestion and fibrin thrombi.
B. Trichrome with glomerular congestion (paralysis) and fragmented RBCs.

SA-PO858

Monoclonal Gammopathy of Renal Significance Presenting as Cryoglobulinemic Glomerulonephritis

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Introduction: Monoclonal gammopathy of undetermined significance (MGUS) is a premalignant plasma cell disorder characterized by serum monoclonal protein <3g/dL, clonal plasma cells <10% on bone marrow biopsy, and absence of end-organ damage. Treatment is not recommended. When monoclonal immunoglobulin causes kidney damage, monoclonal gammopathy of renal significance (MGRS) is diagnosed and treatment involves chemotherapy. We describe a patient with known MGUS presenting with AKI and cryoglobulinemic glomerulonephritis (CG) secondary to development of MGRS.

Case Description: A 73 year-old-man with CKD stage 3, type 2 DM, chronic microscopic hematuria, and MGUS presented with AKI. Previous CKD workup showed 0.5g/day proteinuria, positive ANA, low C4, positive rheumatoid factor, and negative dsDNA and ANCAs. He had elevated free kappa light chains on SPEP and bone marrow biopsy confirmed IgM MGUS. CKD and proteinuria were attributed to diabetic kidney disease. Work-up of chronic hematuria was unrevealing. He presented 8 month later with fatigue, dyspnea, epistaxis, lower extremity rash, and hematuria with Cr 2.2 mg/dL (baseline 1.7) and 24 hour urine protein 3.5g. Serology was positive for cryoglobulin and negative for Hepatitis B, C, and HIV. Kidney biopsy showed diffuse, focally crescentic mixed cryoglobulinemic glomerulonephritis, likely type II, with focal leukocytoclastic vasculitis, focal severe arteriosclerosis, and moderate to severe interstitial fibrosis and tubular atrophy. He underwent 5 sessions of plasmapheresis, IV rituximab, and induction with oral steroids. Symptoms resolved and Cr improved to 1.9 mg/dL at discharge. He continued steroid taper, rituximab, and started IVIG. At last follow-up, he had full resolution of symptoms with stable Cr of 1.8 mg/dL.

Discussion: This case describes a patient with known MGUS presenting with AKI and CG secondary to MGRS. Treatment was rapidly initiated with improvement in kidney function. CG can be caused by a variety of infections, autoimmune diseases, and hematologic malignancies. Identification of the underlying cause is important and guides treatment. Prompt nephrology referral and biopsy in MGUS patients with elevated creatinine, proteinuria, and hematuria allows for diagnosis of MGRS and initiation of therapy to preserve kidney function, avoid long term dialysis, and reduce mortality.

SA-PO859

A Unique Presentation of AA Amyloidosis

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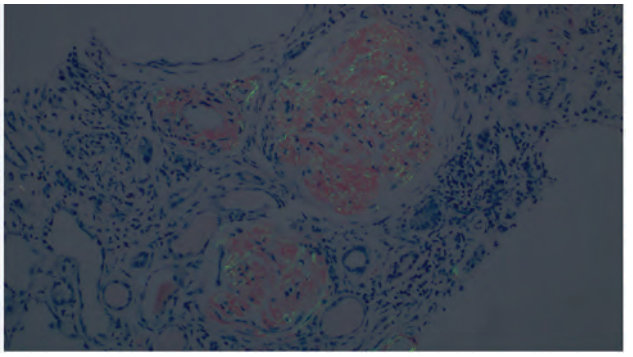
Introduction: While the overall prevalence of kidney amyloidosis in native kidney biopsies performed globally is 1.6%, in the United States, only 7% of these cases are due to AA amyloidosis. We describe a unique multisystem presentation of AA amyloidosis.

Case Description: A 64 year-old Pakistani woman with hypertension and goiter presented to the hospital for five days of abdominal pain and watery diarrhea, in addition to several weeks of worsening fatigue. She had goiter and tachycardia on exam, and laboratory studies demonstrated hyperthyroidism and non-oliguric kidney failure with 8.8 g protein in a 24 hour urine collection. Thyroid ultrasound showed diffuse fatty infiltration; kidney and urinary tract ultrasound was unremarkable. Kidney histology showed glomerular mesangial expansion with eosinophilic matrix and substantial fibrosis. Congo red stain revealed amyloid deposition in glomeruli, vessels, and the tubulointerstitium, identified as amyloid A with immunohistochemistry. Thyroid histology showed adipocytes with entrapped benign thyroid follicles (diffuse lipomatosis) and amyloid deposits in vessel walls by Congo red stain.

Discussion: AA amyloidosis is caused by extracellular deposition of serum amyloid A protein—a hepatic acute phase reactant—in tissues, and can occur in many chronic inflammatory conditions. Proteinuric kidney disease is a common presentation of AA amyloidosis; amyloid goiter is an uncommon presentation and associated hyperthyroidism is rare. Our patient's presentation with amyloid goiter, hyperthyroidism, and kidney failure has not previously been reported to our knowledge. Treatment of AA amyloidosis largely depends on identification of an inciting chronic inflammatory disease; however, extensive workup did not reveal a cause in our patient. She was initiated on hemodialysis for kidney failure and treated with beta blockade and methimazole for hyperthyroidism.



SA-PO860

Membranoproliferative Glomerulonephritis: A Rare Presentation in Systemic Sclerosis

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Introduction: Systemic sclerosis (SSc) is a chronic autoimmune condition that can affect multiple organ systems. Renal involvement in SSc can range from asymptomatic reduction of GFR to life-threatening scleroderma renal crisis (SRC). Membranoproliferative glomerulonephritis (MPGN) is a rare and under-investigated renal manifestation of SSc. MPGN is a histological pattern of glomerular injury consisting of mesangial hypercellularity and proliferation of glomerular capillary walls with subsequent formation of new basement membrane. Although MPGN can be caused by a variety of primary and secondary conditions, descriptions of its association with SSc are limited. We present a unique case of MPGN as a manifestation of systemic sclerosis in an adult patient, highlighting the challenges of diagnosis and management of MPGN in the context of SSc.

Case Description: A 64-year-old woman with a history of SSc, controlled hypertension, Raynaud's syndrome, and chronic kidney disease presented to our hospital with acute kidney injury and elevated blood pressure. Laboratory tests showed AKI, proteinuria, microscopic hematuria, and low complement levels. He did not meet the Scleroderma Clinical Trials Consortium Scleroderma Renal Crisis Working Group diagnostic criteria for SRC. Serologies were unrevealing for SLE and hepatitis B and C. No paraprotein was detected. A renal biopsy revealed immune complex-mediated glomerulonephritis (ICGN) with an MPGN pattern. The patient was started on mycophenolate mofetil (MMF) and showed improvement in renal function and complement levels.

Discussion: This case represents, to our knowledge, the second reported case of MPGN associated with SSc. It emphasizes the importance of understanding the various renal manifestations of SSc in patients with this condition and AKI, and the importance of considering diagnoses other than SRC. MPGN can be immune complex-mediated or complement-mediated, with specific complement levels indicating the pathway involved. Treatment depends on the underlying cause and may involve immunosuppressive agents for underlying autoimmune disease, chemotherapy for hematologic malignancies, or antimicrobials for systemic infection. In this case, the patient showed improvement with MMF therapy. Prompt evaluation and intervention are crucial to prevent permanent kidney damage in SSc patients with renal involvement.

SA-PO861

A Rare Case of ANCA-Negative Pauci-Immune Necrotizing Glomerulonephritis

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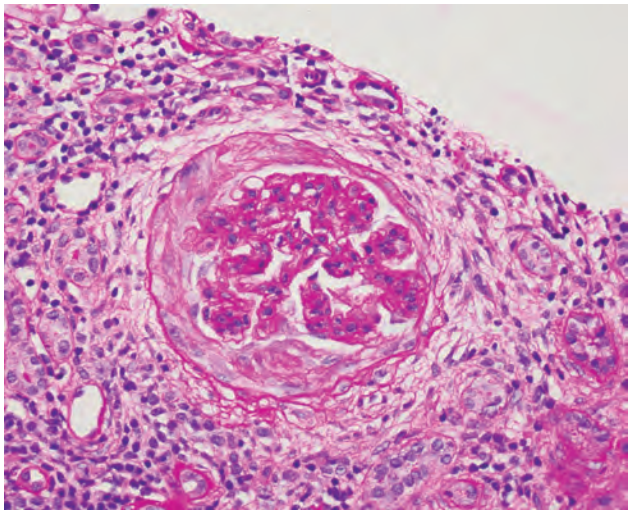
Introduction: Pauci-immune necrotizing glomerulonephritis (PING) is the most common subtype of crescentic glomerulonephritis accounting for 80% of cases. Among these, 90% have an association with ANCA antibodies. However, 2-3% of patients can have PING in the absence of ANCA Antibodies. Thus far, data on this clinical entity has been limited to few case reports and series. Herein we present a rare case of ANCA-negative Pauci-Immune Glomerulonephritis (AN-PING).

Case Description: 47 year old undomiciled male with past medical history of CKD3B, polysubstance use disorder, untreated hepatitis C, presented with lower back pain. Recently had MRSA bacteremia complicated by diskitis/vertebral osteomyelitis and epidural abscess treated non-operatively with daptomycin. Unfortunately patient later left AMA without antibiotics or outpatient follow-up. On this admission patient's imaging showed stable vertebral osteomyelitis/diskitis with interval decrease in epidural abscess size. Treated non-operatively with ceftaroline and pain management. During

hospitalization patient developed an AKI with Cr 1.65 mg/dL on presentation (recent baseline Cr 1.3-1.5 mg/dL) which rapidly peaked to Cr 3.6 mg/dL over the next 7 days. Initial concern was for acute interstitial nephritis from antibiotics vs infection-related GN. Notable labs include 24 hour UPCR 282 mg; UA: >50 RBCs, 0-5 WBCs. On urine microscopy, numerous isomorphic RBCs seen with few acanthocytes, no RBC/WBC or granular casts. Immunologic workup revealed normal complement levels (C3 94 mg/dL, C4 26 mg/dL), negative ANA, ANCA, Anti-GBM, cryoglobulin levels. Renal biopsy performed revealed pauci-immune focal crescentic glomerulonephritis. There was consideration to starting immunosuppression with corticosteroids; however, patient's Cr spontaneously down trended on supportive management with IV antibiotics (ceftaroline). On discharge patient's creatinine was 1.6 and 1.2 on follow-up 3 months later.

Discussion: AN-PING is rare, poorly recognized clinical entity among crescentic glomerulonephritis. Primarily related to its negative serology, AN-PING is often diagnosed late on renal biopsy. This delayed diagnosis has resulted in AN-PING patients having a worse prognosis and higher mortality relative to ANCA-positive GN. Treatment of AN-PING is challenging due to its association with Infection and malignancy (20%), and must be approached on a case-by-case basis.



SA-PO862

Secondary IgA Nephropathy as Red Herring in a Case of AKI

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Introduction: Liver disease, and particularly alcoholic cirrhosis, is the most common cause of secondary IgA Nephropathy (IgAN), with 50-90% of cirrhotic patients exhibiting glomerular IgA deposition. Despite this, <10% of adult patients show clinical evidence of glomerular kidney disease. We report a case of ATN with underlying diabetic kidney disease and microscopic hematuria due to cirrhotic IgAN.

Case Description: A 65-year-old man with history of type-2 diabetes mellitus and hypertension presented to our hospital after outpatient lab work showed elevated creatinine. His diabetes was managed with insulin. He had been prescribed metformin 6 months earlier but discontinued it 3 weeks before presentation due to severe diarrhea, which had partially resolved after cessation. He denied any known history of kidney disease and did not use NSAIDs. He did report heavy alcohol use for many years. Serum creatinine level was 3.7mg/dL with unknown baseline. UA was active with 3+ protein, 50-100 RBCs/HPF, and 0-5 coarse granular casts/HPF. He had ascites with nodular contour of the liver and an atrophic left kidney on imaging. Paracentesis revealed SAAG >1.1 and ascites total protein 1.6g/dL. Creatinine remained stable. ANA, dsDNA, C3, C4, cryoglobulins, ANCAs, and hepatitis panel were all negative. Serum immunofixation revealed no paraprotein. Right kidney biopsy was performed and showed ATN, significant mesangioproliferative IgA deposition, diabetic and hypertensive nephropathy with severe arteriosclerosis and arteriolar hyalinosis, and secondary FSGS. His acute rise in creatinine was attributed to ATN, hematuria and proteinuria were explained by glomerular accumulation of IgA, while FSGS was attributed to diabetic Kimmelstein-Wilson nodule formation and segmental scarring due to immune complex deposition. Kidney function slowly worsened with development of uremic symptoms, requiring initiation of hemodialysis.

Discussion: Decreased hepatic clearance of IgA complexes is the suspected etiology of secondary IgAN in patient with liver cirrhosis. Despite its infrequent presentation, this diagnosis should be suspected in cirrhotic patients presenting with AKI and active UA, with the decision to perform kidney biopsy based on the clinical presentation. Regretfully, our patient's biopsy showed advanced chronic changes due to DM, HTN, and secondary FSGS, and progression to ESRD was inevitable.

SA-PO863

Complex Clinical Interplay: A Case of Systemic Lupus Erythematosus Coexisting with Type II Cryoglobulinemia

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Introduction: The coexistence of Systemic Lupus Erythematosus (SLE) and cryoglobulinemia, characterized by the presence of cryoglobulins in the serum, represents a rare and challenging clinical scenario. This report highlights a case of a 32-year-old female with both conditions, presenting with acute kidney injury.

Case Description: A 32-year-old African American female with SLE and Type II cryoglobulinemia presented with severe shortness of breath, kidney failure, and pericardial effusion. Initial lab work revealed acute kidney injury (creatinine: 0.6 mg/dL to 2 mg/dL in 3 weeks). Treatment included azathioprine, prednisone, and hydroxychloroquine (methotrexate discontinued due to transaminitis). Her condition deteriorated with increased shortness of breath and hemoptysis. Lab findings: positive antinuclear antibodies, kappa-restricted IgM monoclonal protein (Type II cryoglobulin with monoclonal IgM kappa and polyclonal IgG), negative hepatitis panel, and red blood cells in urine. Kidney biopsy showed hyaline pseudo-thrombi and subendothelial/mesangial deposits on electron microscopy. Subsequently treated with therapeutic plasma exchange and cyclophosphamide infusions. Discharged with a stable creatinine level (0.9 mg/dL) on rituximab, hydroxychloroquine, and prednisone.

Discussion: The intersection of SLE and Type II Cryoglobulinemia presents a complex clinical picture with multiple implications. While studies suggest that cryoglobulinemia in SLE patients does not necessarily correlate with severe complications unless coupled with cryoglobulinemic vasculitis, our patient developed biopsy-proven lupus cryoglobulinemic glomerulonephritis, indicating systemic involvement. This case underscores the critical need for kidney biopsy in lupus management to target therapy for optimal outcomes.

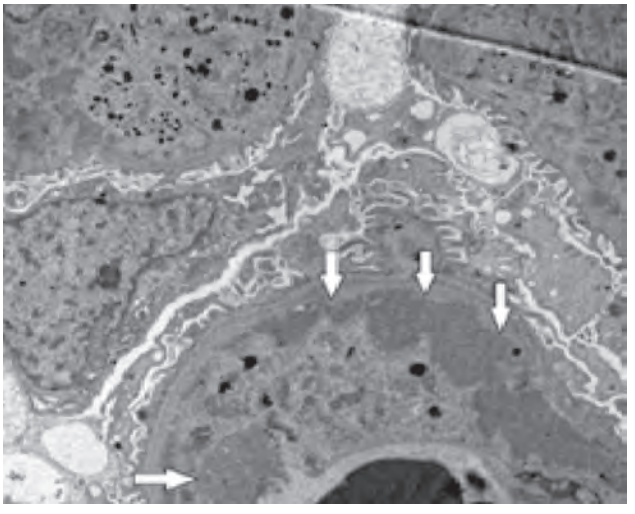

Figure 1: Electron Microscopy of glomeruli notable for subendothelial and mesangial deposits.

SA-PO864

Renal Riddles: Acute Interstitial Nephritis in Newly Diagnosed HIV

Amulya Rajagopal, Ruchi J. Sahota, James Hanna, Vivek Soi, Mark D. Faber, Lalathaksha Murthy Kumbar. *Henry Ford Hospital, Detroit, MI.*

Introduction: Acute interstitial nephritis (AIN) is an inflammatory process often triggered by medications, infections, autoimmune diseases, or idiopathic factors. Interstitial nephritis can occur as a direct consequence of HIV infection, but cases demonstrating this through exclusion of other etiologies are rare. We present a case of acute interstitial nephritis overlying non-collapsing focal segmental glomerulosclerosis (FSGS) in a patient with newly diagnosed HIV.

Case Description: A 51 year old African American male presented with hypertensive emergency along with 3 days of lower extremity edema, cough, dyspnea, and fatigue. Significant labs included: Cr 4.80 mg/dl (unclear baseline), UA with blood and > 500 protein, UPCR 9.9 g/g. Serology workup of nephrotic syndrome revealed ANA 1:640, ds-DNA 1:20, C3 low. Hepatitis panel was negative. HIV-1 positive, with viral load < 30 copies/mL, CD4 547, and Treponemal IgG with nonreactive RPR. Renal ultrasound showed bilateral increased renal echogenicity. Renal biopsy revealed primary FSGS non-collapsing variant and AIN with plasma cell rich infiltrate. Treatment with highly active antiretroviral therapy (HAART) was initiated. One month later, patient was readmitted with right cranial nerve (CN) III and VI palsy. MRI brain revealed possible new meningioma or inflammatory process. Repeat serology showed C3 improved, elevated IgG4, normal SSA/Ro and SSB/La, elevated rheumatoid factor, cerebrospinal fluid pleocytosis of mononuclear cells, and elevated IgG index and oligoclonal bands. Restaining of prior renal biopsy was negative for IgG4-related disease. Patient was started on corticosteroids for possible inflammatory neurologic process. Follow-up visits noted improvement in Cr < 1.0 mg/dl with continued nephrotic range proteinuria despite treatment.

Discussion: This case underscores the complexity of diagnosis in the presence of, autoimmune markers, HIV infection, and overlapping clinical features. The diagnosis of AIN occurred prior to initiation of HAART or any other medications. The patient's renal function showed initial improvement with HAART, but a more significant improvement was observed upon the initiation of corticosteroid treatment. The recommended treatment for HIV-associated interstitial nephritis involves initiating HAART, while the efficacy of corticosteroids in this condition remains uncertain.

SA-PO865

Human Immunodeficiency Virus-Associated Lupus-Like Nephritis: An Undetectable Viral Load and Negative Lupus Serology

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Introduction: HIV is a common cause of a wide array of kidney abnormalities including both glomerular and tubular disorders. HIV associated immune complex kidney disease (HIVICK) is a unique entity which includes lupus like nephritis which presents without classic serologic findings of lupus. We describe the case of a 29year old man with HIV who was diagnosed with lupus like nephritis without a diagnosis of lupus.

Case Description: A 29year old man with a history of HIV on anti-retroviral therapy (ART) and chronic kidney disease stage 4 presented with dyspnea and acute kidney injury. Pertinent labs included serum creatinine of 3.7 mg/dl up from 2.7 mg/dl and urine dipstick positive for hematuria and proteinuria. Urine microscopy had acanthocytes. Spot urine protein creatinine ratio was 0.7 g/g. A broad serologic workup was performed which was unremarkable (Table). HIV viral load was undetectable. A kidney biopsy was performed. Mesangial expansion and hypercellularity was noted without crescents. There was patchy tubular atrophy and interstitial fibrosis. Immunofluorescence staining pattern was positive for Ig (Immunoglobulin) A, IgG, IgM, C (complement)1q, and C3. Electron microscopy showed multiple subepithelial and mesangial electron dense deposits. A diagnosis of lupus like glomerulonephritis was made. Given the undetectable viral load kidney function was monitored closely without any active pharmacologic intervention.

Discussion: We present the case of HIV related immune complex glomerulonephritis. This case is unique because lupus like nephritis developed despite an undetectable HIV viral load and negative lupus serologies. The pharmacologic therapy in such cases is a subject for research. The optimal treatment remains unknown as of yet.

Pertinent serologic markers

Anti nuclear antibody (ANA)	-	cryoglobulin	-
C3	136 mg/dl (80-200)	rheumatoid factor	-
C4	30 mg/dl (10-50)	kappa/lamba	1.2 (0.2-1.6)
Anti double stranded-DNA, Phospholipase A 2 receptor Antibody, anti-histone Ab	-	Hepatitis B surface antigen	-
Anti neutrophil cytoplasmic antibody	-	hepatitis C antibody	-

SA-PO866

Efficacy of ANCA Autoantibody Clearance by High-Dose Immunoglobulins Prior to Plasma Exchange in Severe Pulmonary Renal Syndrome

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Introduction: Plasma exchange rapidly depletes pathogenic anti-neutrophil cytoplasmic autoantibodies (ANCAs) and is considered for induction therapy in severe ANCA-associated vasculitis. The aim of plasma exchange is to remove putative disease mediators from the circulation, such as toxic macromolecules and pathogenic ANCAs.

Case Description: To our knowledge, we here provide the first report of applying high-dose IVIGs prior to plasma exchange and assessment of ANCA autoantibody elimination in a patient with severe pulmonary renal syndrome due to ANCA associated vasculitis. After high-dose application of intravenous immunoglobulins (IVIGs) prior to plasma exchange treatment, efficacy of myeloperoxidase (MPO)-ANCA autoantibody elimination was substantially increased, associated with rapid clearance of MPO-ANCA autoantibodies. High-dose IVIGs resulted in marked reduction of MPO-ANCA autoantibody levels and did not directly affect autoantibody clearance by plasma exchange itself, as also confirmed by comparable MPO-ANCAs in the exchange fluid relative to serum levels. Moreover, measurements of serum creatinine and albuminuria confirmed that high-dose IVIGs were well tolerated and did not exacerbate kidney injury.

Discussion: We are aware that our observations require validation in larger study populations, that kinetics may have also been affected by previous induction therapy, pretreatment time of IVIGs or ANCA autoantibody subtypes, and that the exact mechanisms contributing to our observations require further investigation. Furthermore, the immunoassay is not fully accurate due to values higher than the manufacturer's reference range. Nevertheless, this ANCA level-driven approach might contribute to novel therapeutical strategies to increase efficacy of pathogenic ANCA autoantibody clearance in severe AAV.

SA-PO867

Extreme Fatigue as the Only Complaint in Double-Positive Anti-Glomerular Basement Membrane (GBM) and ANCA Disease: An Unusual Presentation

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Introduction: Acute glomerulonephritis (GN) due to anti-glomerular basement membrane (GBM) disease is extremely rare with reported incidence of one per million. Double positive disease with anti-GBM phenotype on kidney biopsy and ANCA positive titers on serology is reported to present in older population with high relapse rates compared to anti-GBM disease alone. Extreme fatigue as the only presenting complaint is uncommon, here we present one such case.

Case Description: 76 year old female who leads an active life-style presents to her PCP's office with extreme fatigue of 3 weeks duration. Initial work-up revealed AKI with serum creatinine of 4.19 mg/dL. She was admitted for further evaluation. Urinalysis was +ve for large blood, >10 RBC/HPF, and protein. She received IV fluids, serology for GN work up was sent and discharged home. She was re-admitted later as myeloperoxidase (MPO)-ANCA titers were reported positive. Kidney biopsy revealed cresenteric GN with 85% glomerular involvement. Treatment was initiated with pulse steroids, rituximab and plasma exchange for ANCA vasculitis till kidney biopsy findings confirmed anti GBM disease (Figure 1), anti-GBM titer results following a few days after kidney biopsy. Response to treatment is shown in Figure 2.

Discussion: Double-positive vasculitis with anti-GBM and ANCA is rare. Our patient did not have any lung involvement. While Rituximab alone for induction is not commonly reported in double positive disease, our patient was extremely frail and hence did not receive cyclophosphamide. A high degree of clinical suspicion for acute GN is needed when elderly patients present with AKI and an abnormal UA, extreme fatigue could be the only complaint.

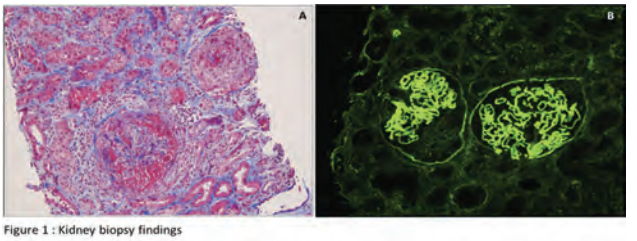

Figure 1 : Kidney biopsy findings

A - Trichome stain showing glomeruli with crescents and fibrinoid necrosis (85% cellular crescents noted).

B - Diffuse linear IgG GBM deposition by immunofluorescence.

Figure 1

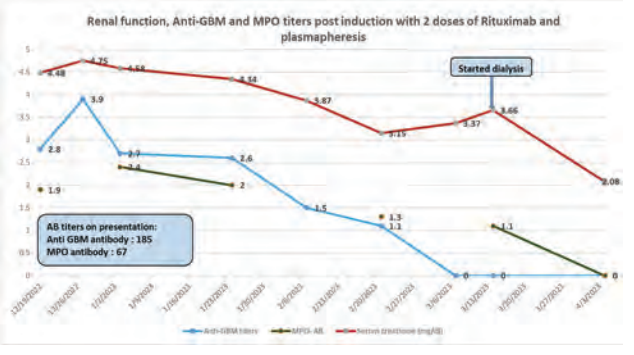

Figure 2

SA-PO868

The Effects of the Intensified B Cell Depletion Therapy in ANCA Vasculitis with Extremely Severe Renal Impairment Compared with Conventional Immunosuppression

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Background: Rituximab (RTX) has shown to be an effective induction treatment for ANCA associated vasculitides (AAV) in both newly diagnosed and relapsing patients. However, the role of RTX in the management of the most severe cases of AAV remains to be fully elucidated. The aim of this study was to assess both safety and efficacy of an intensified B-cell depletion therapy (IBCDT) protocol, including RTX, cyclophosphamide (CYC), and methylprednisolone pulses without additional maintenance immunosuppressive therapy in a cohort of 15 AAV patients with the most

severe features of AVV renal involvement (as <15 ml/min GFR and histological findings of paucimmune necrotizing glomerulonephritis with more than 50% crescents of non-sclerotic glomeruli at the renal biopsy)

Methods: Results of the IBCDT regimen have been compared to those obtained in a control cohort of 10 patients with AAV treated with a conventional therapy regimen based on oral CYC and steroids followed by a prolonged maintenance therapy with azathioprine (AZA). Plasma exchange was equally employed in the study and the control group.

Results: Complete clinical remission (BVAS 0) was observed at 6 months in 14 of 15 patients treated with IBCDT (93%). All cases who achieved a complete clinical remission experienced a depletion of peripheral blood B cells at the end of therapy. Of the 10 dialysis dependent patients at onset, 6 subjects (60%) experienced a functional recovery allowing the suspension of dialysis treatment. When compared to the control group, no statistically significant difference was observed in patients treated with IBCDT in terms of overall survival, 6-month therapeutic response rate, and 6-, and 12-month functional renal recovery. The cumulative total dose of CYC in the case group was on average 1 g/patient while in the control group on average 8.5 g/patient ($p = 0.00008$).

Conclusions: Despite the retrospective design and relative limited sample size, IBCDT appeared to be safe and had the same efficacy profile when compared to the conventional therapy with CYC plus AZA in the management of the most severe patients with AAV. Additionally, this avoided the need of prolonged maintenance therapy for long, and limited the exposure to CYC with consequent reduced toxicity and drug-related side effect rates.

SA-PO869

Non-Hepatitis C Virus (HCV)-Related Mixed Cryoglobulinemic Vasculitis with Biopsy-Proven Renal Involvement: The Effects of Rituximab

Roberta Fenoglio, Savino Sciascia, Dario Roccatello. *University Center of Excellence on Nephrologic, Rheumatologic and Rare Diseases, Coordinating Center of the Interregional Network for Rare Diseases of Piedmont and Aosta Valley, San Giovanni Bosco Hub Hospital, University of Turin, Turin, Italy*.

Background: Remarkable results in severe HCV-related cryoglobulinemic vasculitis have been obtained with Rituximab. Details of the clinical characteristics and effective treatment of non HCV-related cryogloulinemic syndromes are presently lacking.

Methods: This paper reports on a prospective single-Center open study aimed at evaluating the clinical presentation and effects of Rituximab administered alone in patients with severe non HCV-related cryoglobulinemic syndrome.

Results: The study group included 11 patients followed for at least 6 months. Three patients had type I cryoglobulinemia, 6 had type II and the remaining 2 patients had type III. Mean cryocrit was 2.5%. Four out of 11 patients had symptomatic sicca complex with anti-SSA (Ro)/anti SSB (La) antibodies. All 11 patients presented with biopsy-proven renal involvement, 4 out of 11 with leukocytoclastic vasculitis, and 8 with involvement of the peripheral nervous system. Renal biopsy revealed diffuse membranoproliferative glomerulonephritis (MPGN) in 9 out of 11 patients. Extracapillary proliferation and necrosis of the glomerular tuft was observed in 1 of these 9 cases. Interstitial nephritis together with mesangial expansion and capillary immune deposits were observed in 1 patient. Prevalent interstitial fibrosis and glomerular sclerosis were detected in the remaining case. Patients underwent treatment with rituximab alone. After 6 months we observed a remarkable improvement in the necrotizing skin ulcers and a substantial amelioration of the electrophysiological parameters of motor and sensory peripheral neuropathy. Improvement in both renal function (from 2.8 to 1.4 mg/dl, $p < 0.001$) and proteinuria (from 4.2 g/24 to 0.4 g/24 h, $p < 0.001$) was found in 10 out of 11 patients, while 1 could not be fully treated because of a severe infusion reaction and sudden development of anti-Rituximab antibodies. Good renal response was confirmed at the end of follow-up (38.4 months). Three patients had a relapse at 6, 12, and 48 months, respectively.

Conclusions: In our cohort the administration of 4 once-weekly infusions of Rituximab followed by 2 more infusions after 1 and 2 months proved to be effective in the management of these rare patients.

SA-PO870

Safety and Efficacy of Avacopan in Patients 65 Years and Older with ANCA-Associated Vasculitis

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Background: Older adults are at increased risk of glucocorticoid (GC)-related toxicity; minimization of GCs is a major focus for treatment of patients with ANCA-associated vasculitis (AAV). Although AAV especially affects older adults, many studies have excluded patients >75 years (y). In the Phase 3 ADVOCATE trial of avacopan, there was no exclusion criterion for maximum participant age.

Methods: This post hoc analysis reports safety and efficacy of avacopan compared to a prednisone taper in the subgroups of patients 65-74y (N=109) and ≥75y (N=51).

Results: In both studied age and treatment groups, a similar proportion of patients (69.4-73.1%) achieved remission at week 26 (**Table 1**). In the 65-74y age group, sustained remission rates at week 52 were 55.1% in the prednisone arm and 65.0% in the avacopan arm. Relapse rates were 18.8% in the prednisone arm and 12.3% in the avacopan arm. The total all-source median GC dose was 5.3x higher in the prednisone vs avacopan arm. Serious adverse events (SAEs) occurred in 22/49 patients (45%) in the prednisone arm (2 deaths) and 25/60 patients (42%) in the avacopan arm (2 deaths). In the ≥75y age group, sustained remission rates at week 52 were 56.0% in the prednisone arm and 65.4% in the avacopan arm. Relapse rates were 20.8% in the prednisone arm and 3.8% in the avacopan arm. Median GC dose was 4.8x higher in the prednisone vs avacopan arm. SAEs occurred in 14/25 patients (56%) in the prednisone arm and 17/26 patients (65%) in the avacopan arm. Other results including renal and quality of life outcomes are in **Table 1**.

Conclusions: A subgroup analysis of patients ≥65y demonstrated similar trends of efficacy and safety of avacopan as in the overall ADVOCATE trial, including reductions in GC-related toxicities, supporting a role for avacopan in the treatment of older patients with AAV.

Funding: Commercial Support - Amgen

Table 1: Safety and Efficacy Outcomes in Patients with ANCA-Associated Vasculitis Aged 65 to 74 Years and 75 Years and Older in the ADVOCATE Trial of Avacopan

	Age 65-74 (N=109)		Age ≥75 (N=51)	
Outcome	Prednisone taper (n=49)	Avacopan (n=60)	Prednisone taper (n=25)	Avacopan (n=26)
Remission at Week 26, n (%)	34 (69.4)	43 (71.7)	18 (72.0)	19 (73.1)
Sustained remission at Week 52, n (%)	27 (55.1)	39 (65.0)	14 (56.0)	17 (65.4)
Relapse rate[a], n (%)	9 (18.8)	7 (12.3)	5 (20.8)	1 (3.8)
eGFR change at Week 52[c], LSM ± SEM	5.4 ± 1.6	4.6 ± 1.5	7.8 ± 1.7	10.7 ± 1.7
UACR percent change at Week 4[d], LSM ± SEM	-19 ± 1.2	-34 ± 1.2	-8 ± 1.2	-33 ± 1.3
SF-36 PCS change at Week 52, LSM ± SEM	1.3 ± 1.3	3.0 ± 1.2	0.7 ± 2.5	3.2 ± 2.2
SF-36 MCS change at Week 52, LSM ± SEM	5.4 ± 1.6	6.9 ± 1.4	7.4 ± 3.0	7.0 ± 2.6
EQ-5D-5L VAS change at Week 52, LSM ± SEM	6.0 ± 2.5	13.0 ± 2.2	2.4 ± 5.5	13.7 ± 4.7
EQ-5D-5L Index change at Week 52, LSM ± SEM	0.020 ± 0.03	0.032 ± 0.02	0.021 ± 0.06	0.040 ± 0.05
GTI-CWS at Week 26, LSM ± SEM	53.6 ± 7.2	43.4 ± 6.3	51.4 ± 10.1	33.1 ± 8.8
GTI-AIS at Week 26, LSM ± SEM	15.1 ± 6.8	13.6 ± 5.9	15.1 ± 9.7	0.4 ± 8.5
Total all-source GC dose, mg (mean / median)	3579 / 3055	1410 / 575	3382 / 2840	1718 / 588
Total AEs, n (%) patients, n events	48 (98.0) 681 events	59 (98.3) 623 events	25 (100.0) 318 events	26 (100.0) 273 events
AEs of Infections, n (%) patients, n events	38 (77.6) 88 events	40 (66.7) 86 events	20 (80.0) 40 events	20 (76.9) 42 events
AEs possibly related to GCs, n (%) patients	41 (83.7)	30 (50.0)	20 (80.0)	24 (92.3)
Total SAEs, n patients, %	22 (44.9) 51 events	25 (41.7) 43 events	14 (56.0) 34 events	17 (65.4) 22 events
SAEs of Infections, n (%) patients, n events	5 (10.2) 6 events	11 (18.3) 13 events	6 (24.0) 8 events	4 (15.4) 4 events
SAEs possibly related to GCs, n patients, %	4 (8.2)	7 (11.7)	7 (28.0)	5 (19.2)
Deaths, n (%)	2 (4.1)	2 (3.3)	0 (0.0)	0 (0.0)

[a] Relapse rate are based on the number of patients who achieved a Birmingham Vasculitis Activity Score (BVAS) of 0 during the 52-week treatment period

[c] eGFR assessed only in patients with renal involvement (based on BVAS) at baseline

[d] UACR assessed only in patients with renal involvement (based on BVAS) at baseline and baseline UACR≥10 mg/g creatinine

AE, adverse event; AIS, aggregate improvement score; CWS, cumulative worsening score; eGFR, estimated glomerular filtration rate; GC, glucocorticoid; GTI, glucocorticoid toxicity index; LSM, least squares mean; MCS, mental component summary; PCS, physical component summary; SAE, serious adverse event; SEM, standard error of the mean; SF-36, Short Form-36; UACR, urine albumin:creatinine ratio; VAS, visual analogue scale

SA-PO871

Efficacy and Safety Experience with Avacopan Beyond 52 Weeks in the Early Access Program (EAP)

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Background: Avacopan, a selective C5aR1 inhibitor, has demonstrated efficacy and safety over 52 weeks in patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis. However, efficacy and safety data on avacopan beyond 52 weeks are limited. Here, we describe the experience with avacopan beyond 52 weeks from the EAP.

Methods: Safety data in patients with severe, active granulomatosis with polyangiitis (GPA) or microscopic polyangiitis (MPA) within the EAP were recorded in a global safety database from Feb 2019 – Apr 2023. Adverse events (AE) included a lack of effect and other events (i.e., relapse or worsening of disease).

Results: A total of 19 patients were treated with avacopan beyond 52 weeks within the EAP. Average age was 47 years, with 13 patients (68%) diagnosed with GPA and 6 (32%) with MPA. The median duration of therapy was 17 months (range 12–45). A total of 9 AEs were recorded in 2 patients (10.6%) (Table 1). One vasculitis flare was recorded 6 months after avacopan initiation and coincided with an unintended dose reduction to 20 mg BID, due to a product supply issue during COVID. The event was well-managed with rituximab, with no additional use of glucocorticoids, and avacopan 30 mg BID was reinstated. No further cases of a lack of effect, worsening of disease, or disease relapse were reported. Data regarding concomitant medications did not indicate a decline in the patients' status during treatment. No treatment discontinuations due to AEs were recorded.

Conclusions: These results suggest that continuation of avacopan beyond 52 weeks is generally well-tolerated in patients with GPA and MPA and may be effective in terms of disease control. Limitations of this program include low patient number, potential underreporting, and incomplete data.

Funding: Commercial Support - CSL Vifor sponsored early access program

Table 1. **Overview of Safety Events Reported in 2 of 19 Patients Receiving Avacopan Beyond 52 Weeks in the Early Access Program**

System Organ Class (*Preferred term*)	No. of events
Patient 1	
General disorders and administration site conditions *Malaise*	1
Infections and infestations *COVID-19*	1
Injury, poisoning, and procedural complications *Product dose omission issue*	1
Product issues *Product supply issue*	1
Patient 2	
General disorders and administration site conditions *Pain*	1
Musculoskeletal and connective tissue disorders *Psoriatic arthropathy* *Arthritis*	2
Surgical and medical procedures *Therapy interrupted*	1
Vascular disorders *Vasculitis*	1
Total	9

SA-PO872

Avacopan in Combination with Rituximab and Low-Dose Cyclophosphamide for Treatment of Severe ANCA-Associated Glomerulonephritis

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Background: Avacopan is approved in the USA and Europe as a novel treatment for ANCA-associated vasculitis. There are limited data regarding avacopan use in those with severe renal disease, and of 'real-world' experience using avacopan in combination remission-induction regimens.

Methods: Prospective cohort study of patients with ANCA-associated glomerulonephritis (ANCA-GN) treated at a single centre in London, UK from December 2022. Data presented as median (+/- IQR) unless otherwise stated.

Results: To date, 27 patients with ANCA-GN have received avacopan (median age 58 years [range 24-90]; 22 *de novo* disease, 5 relapsing). *Baseline parameters*: BVAS 16 (IQR 12-19), CRP 61mg/dL (21-174), creatinine 258µmol/L (149-391), eGFR 19ml/min/1.73m^2 (12-39), uPCR 164mg/mmol (6-216). 21 patients had confirmatory kidney biopsy, with no predominant Berden class. *Immunosuppressive treatment*: 23 patients received combination induction treatment with rituximab (2g) and low-dose IV cyclophosphamide (median dose 2.2g [1.0-2.5]); 4 were treated with rituximab alone; 8 received adjunctive plasma exchange. *Glucocorticoid (GC) use*: The median dose of IV methylprednisolone was 0mg (0-500). 25/27 patients received oral prednisolone with median dose and duration of 270mg (210-420) and 8 days (7-16), respectively. *Outcomes*: The median duration of follow up is currently 2 months: 26/27 have achieved disease remission (BVAS =0; 1 patient had progressive eGFR decline). Improvements in renal parameters were as follows: creatinine 152µmol/L (125-257), eGFR 37ml/min/1.73m^2 (23-48), uPCR 42mg/mmol (15-281). In those who presented with eGFR ≤20ml/min/1.73m^2 (n=15), median eGFR improved from 13 (9-18) to 27 (12-39). *Adverse Events*: 2 infections occurred (uncomplicated UTI treated with oral antibiotics; LRTI requiring IV antibiotics). 1 patient developed transaminitis requiring drug cessation.

Conclusions: This early series suggests that avacopan is well-tolerated and facilitates GC minimisation in patients with active ANCA-GN, in a non-trial setting, and in combination with rituximab and low-dose cyclophosphamide. Renal recovery was favourable in those presenting with eGFR ≤20ml/min/1.73m^2. Ongoing analysis will examine long-term renal recovery in this subgroup.

SA-PO873

Avacopan in ANCA Vasculitis: A Real-World Experience

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Background: Avacopan (AVP) is a recently approved adjunct therapy for remission induction of ANCA-associated vasculitis (AAV). Data on real-world use of AVP in AAV are lacking.

Methods: We performed a multi-center retrospective observational study of adult patients with AAV treated with AVP and collected clinical, treatment and outcome data. Data are presented as mean (±SD), median (IQR), or number (percent).

Results: Eighty patients were included. Mean age was 59 (17) years, 65% were female, 74% had MPO ANCA, and 95% had kidney involvement. AVP was used with rituximab ± cyclophosphamide in 95% of patients. AVP was started 8.8 (19.6) weeks after glucocorticoid initiation with 58 (73%) patients discontinuing prednisone 7.5 (18) weeks after starting AVP. At diagnosis, 19 (24%) patients had eGFR <15 with 8 dialysis dependent. Outcomes are summarized in Table 1. Among the 60 (75%) patients with hematuria at diagnosis, 70% had resolution of hematuria 14 (14) weeks after AVP initiation. Nadir proteinuria of 0.3 (0.1 – 0.7) g/g was achieved 10 (21) weeks after AVP initiation. The cumulative dose of IV methylprednisolone was 2.4 (1.4) g, and 12-week oral prednisone was 1.8 (1.1) g. At week 26, 5 of 39 (13%) patients remained on prednisone. AVP was stopped in 25 patients: 11 after 52 weeks, and 14 before 52 weeks due to adverse events. At a mean follow-up time of 8 (6) months, 5 had disease relapse, 7 had infections requiring hospitalization, 3 remained dialysis-dependent, and 3 died.

Conclusions: AAV patients treated with AVP have high clinical remission rates at weeks 26 and 52 and sustained improvement in eGFR.

Table 1. Outcomes of AAV patients treated with Avacopan

	Diagnosis	AVP initiation	Follow-up	
	T = 0 | N = 80	T = 8.8 (20) | N = 80	T = 26 | N = 59	T = 52 | N = 32
BVAS	13 (10 – 19)	6 (3 – 12)	0 (0 – 0)	0 (0 – 0)
uPCR, g/g	1.5 (0.3 – 2.7)	1.3 (0.3 – 2.3)	0.4 (0.2 – 1.1)	0.3 (0.1 – 0.7)
Hematuria	60 (75%)	37 (46%)	11 of 30 (37%)	3 of 10 (30%)
eGFR, mL/min/1.73m^2	47 (34)	42 (32)	59 (34)	62 (38)
ΔeGFR from baseline	-	-4.4 (19)	+8.3 (28)	+14 (29)
Clinical remission	-	-	54 (92%)	29 (91%)

Data are presented as mean (SD), median (IQR), or number (percent)Abbreviations: T = time in weeks; N = Number; BVAS, Birmingham Vasculitis Activity Score; eGFR, estimated glomerular filtration rate; uPCR, urine protein-to-creatinine ratio.

SA-PO874

Pneumocystis jirovecii Pneumonia Prophylaxis in Patients with ANCA Vasculitis on Rituximab Maintenance Therapy

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Background: Although an increased risk of Pneumocystis jirovecii pneumonia (PJP) has been reported in adults receiving rituximab, current evidence is lacking on the utility of PJP prophylaxis in AAV patients on maintenance rituximab therapy.

Methods: We performed an observational, single-center, retrospective study examining outcomes of patients with AAV on rituximab maintenance therapy with and without PJP prophylaxis. We included patients that were followed in our center from 6/1/2009-4/1/2023. Outcomes included PJP prophylaxis use, PJP infections, infections requiring hospitalizations, death, and end-stage kidney disease (ESKD). Outcomes were analyzed using T test, Fisher exact test, univariate, and multivariate logistic regression as appropriate.

Results: A total of 129 patients were included. The mean (SD) age was 62.5 (±16) years old and the mean (SD) follow-up was 7.2 (±5.4) years. 44% of patients received PJP prophylaxis, whereas 56% of patients did not. Trimethoprim-Sulfamethoxazole was used in 31% of patients, followed by Dapsone (7%), and Atovaquone (6%). In the PJP prophylaxis group, the mean (SD) duration of rituximab therapy was 3.6 (±2.5) years, and the mean (SD) prednisone dose was 0.66 mg (±1.87). In patients who did not receive PJP prophylaxis, the mean (SD) duration of rituximab therapy was 3.1 (±2.1) years, and the mean (SD) prednisone dose was 1.13 mg (±2.47). There were no PJP infections in the entire cohort. Lung involvement was associated with increased odds of PJP prophylaxis prescription (OR 4.09 [95% CI 1.8-9.82]). CD4 count <200 cells/mm^3 (n=5) and serum IgG level <500 mg/dL (n=32) were not associated with higher odds of PJP prophylaxis prescription (p=0.99 and p=0.08, respectively). PJP prophylaxis did not decrease infection rates requiring hospitalizations, ESKD, or death. Corticosteroid use was associated with increased rates of infections requiring hospitalizations (OR 5.75 [95% CI 2.00-16.92]) and death (OR 4.49 [95% CI 1.26-15.82]) even after adjustment for age, gender, and PJP prophylaxis use.

Conclusions: Regardless of use of PJP prophylaxis, PJP pneumonia was not observed in AAV patients receiving maintenance rituximab therapy. AAV patients with lung involvement were more likely to be on PJP prophylaxis. Additional studies are needed to confirm these findings to guide PJP prophylaxis use in AAV patients.

SA-PO875

EQUALISE Type B: Clinical Results of Itolizumab, a Novel Anti-CD6 Therapy, in Subjects with Lupus Nephritis

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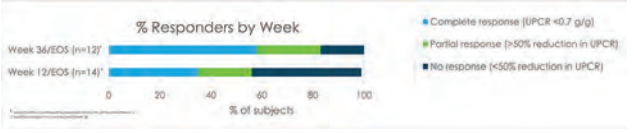
Background: Itolizumab is a first-in-class, non-depleting, monoclonal antibody against the co-stimulatory receptor CD6 that blocks its interaction with ALCAM, to inhibit T_{eff} cell activity and trafficking. It is being evaluated to treat immuno-inflammatory diseases where T cells play a central role, including active proliferative lupus nephritis (apLN). We present results from EQUALISE (Type B; NCT04128579), a Phase 1b study of itolizumab in subjects with apLN.

Methods: 17 adult subjects with apLN (ISN/RPS class III or IV with or without class V) were enrolled. All were treated with open-label itolizumab 1.6 mg/kg SC Q2W for up to 13 doses in combination with MMF (2-3g/d) and systemic corticosteroids (rapid taper to <prednisone 10mg/day by W10). Subjects had 12 weeks follow-up post dosing. Safety and efficacy were assessed.

Results: The median subject age was 34 years; 94% were female with 82% Asian; most subjects had class IV+V disease (47%). Mean duration of LN was 5.4 years with Baseline mean 24 hour urine protein of 4.9 g and eGFR of 104 ml/min/1.73m2. Treatment was completed in 11 subjects with 4 discontinuing early (3 due to adverse event (AE) and 1 due to physician decision) and 2 are still dosing. 88% of subjects experienced at least 1 AE, most common were peripheral edema and lymphopenia. At least 1 low lymphocyte count was reported by 7 subjects (41%). Serious AEs occurred in 2 subjects (12%), including dehydration and COVID-19, with none deemed related to study treatment. Based on the 14 subjects that completed/terminated the study and had a post-baseline measure, there was a median 72% reduction in spot urine protein creatinine ratio (UPCR), resulting in high partial and complete response (PR and CR) rates (FIGURE). These responses occurred as early as prior to Week 4 on study.

Conclusions: EQUALISE Type B demonstrates that subjects with proteinuric apLN had high CR and PR rates with rapid and deep reduction in UPCR when itolizumab was added to MMF and steroids. Further controlled studies are warranted in this population at high risk of disease progression and end stage kidney disease.

Funding: Commercial Support - Equillium



Equalise Type B: % of responders at Weeks 12 & 36

SA-PO876

Long-Term Safety and Efficacy of Voclosporin in Black Patients with Lupus Nephritis

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Background: Black patients with lupus nephritis (LN) are reported to have more severe disease, are often refractory to treatment, and have worse long-term outcomes. Voclosporin in conjunction with low-dose glucocorticoids and mycophenolate mofetil (MMF) has shown significant benefit across ancestries and classes of LN. Here we report outcomes on up to three years of follow-up in patients identifying as Black and treated with voclosporin during the global Phase 3 AURORA studies.

Methods: Key inclusion criteria for the parent AURORA 1 study included biopsy-proven LN, urine protein creatinine ratio (UPCR) ≥1.5 g/g (≥2 g/g for Class V) and estimated glomerular filtration rate (eGFR) >45 mL/min/1.73 m^2. Patients completing AURORA 1 were eligible to enter the AURORA 2 continuation study on the same blinded therapy of voclosporin or placebo in combination with MMF and glucocorticoids for an additional two years. Programmed complete renal response (CRR; UPCR ≤0.5 g/g, stable eGFR, low-dose steroids, and no rescue medication), partial renal response (PRR; reduction in UPCR of ≥50% from baseline) and safety were assessed in patients self-identifying as Black or mixed Black.

Results: Twenty-six of 179 (14.5%) and 19 of 178 (10.6%) patients identified as Black or mixed Black in the voclosporin and control arms of AURORA 1. Baseline characteristics were similar between arms. CRR rates at one year numerically favored voclosporin (46.2% vs 15.8%, OR 3.92 [CI 0.95, >9.99] p=0.0597) as did PRR rates (69.2% vs 47.4%, OR 2.62 [CI 0.72, 9.45] p=0.1422). Eighteen voclosporin-treated patients and seven control-treated patients in the Black subgroup continued into AURORA 2. Response rates at three years continued to numerically favor voclosporin (CRR, 44.4% vs. 14.3%, OR 4.17 [CI 0.41, >9.99] p=0.2276; PRR, 66.7% vs. 42.9%; OR 1.67 [CI 0.23, >9.99] p=0.6094). Greater reductions in mean UPCR were observed over the three-year period in the voclosporin arm (change from baseline -3.4 vs -1.5 g/g, p=0.0349). Mean eGFR levels remained stable and in the normal range over three years of treatment.

Conclusions: Black patients treated with a voclosporin-based regimen achieved higher rates of renal response than patients treated with MMF and glucocorticoids alone. For patients entering the continuation study, the response was largely durable for up to 3 years.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

SA-PO877

Comparison of Dual-Immunosuppressive Therapy and a Voclosporin-Based, Triple-Immunosuppressive Regimen for Lupus Nephritis: A Propensity Analysis of ALMS and AURORA 1

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Background: To understand the safety and efficacy of a voclosporin-based, MMF and glucocorticoid-sparing, triple immunosuppressive regimen as an initial approach to therapy in active lupus nephritis (LN) compared to conventional high-dose MMF and glucocorticoid regimens, we compared and analyzed clinical data in propensity-matched patients from ALMS and AURORA 1. We hypothesized that a voclosporin-based, triple immunotherapy approach would reduce exposure to toxicities associated with glucocorticoids and MMF, resulting in an improved safety profile without compromising efficacy.

Methods: Both studies enrolled participants with active LN. In ALMS, MMF was dosed to a target of 3 g/day with oral glucocorticoids initiated at a maximum dose of 60 mg/day and tapered every 2 weeks to 10 mg/day. In AURORA 1, participants received voclosporin 23.7 mg BID in combination with MMF at a target dose 2 g/day and oral glucocorticoids started at 25 mg/day and tapered to 2.5 mg/day by Week 16. Propensity matching generated 2 groups of matched patients based on demographic and disease characteristics. Safety and efficacy outcomes were assessed at 3 and 6 months.

Results: Propensity matching identified 96 pairs of participants with similar demographics and baseline disease characteristics. At 3 and 6 months, MMF and glucocorticoid exposure was more than 2-fold higher in ALMS than AURORA 1. Overall, fewer adverse events (AE) were observed in AURORA 1 across the majority of organ systems, including gastrointestinal, skin and subcutaneous tissues, endocrine, and psychiatric disorders, although more patients in AURORA 1 were reported to experience eGFR decrease; most reductions in eGFR were manageable by dose modification. The incidence of serious AEs was similar in both groups at 3 and 6 months. In the first 3 months, significantly more patients in AURORA 1 achieved >25% UPCR reduction from baseline (81.3% AURORA 1, 65.6% ALMS; p=0.011); the proportions of patients achieving UPCR ≤0.5 mg/mg and >50% UPCR reduction from baseline were numerically greater in the voclosporin arm; the differences were not statistically significant.

Conclusions: The above findings affirm the KDIGO 2023 recommendation that a voclosporin-based, triple-immunotherapy regimen should be considered as initial therapy in active LN.

Funding: Commercial Support - Aurinia Pharmaceuticals Inc.

SA-PO878

Results of Single-Arm, Phase 1b Study of Anti-C1q Treatment (ANX009) Show that the Classical Pathway Is a Key Driver of Complement Activation and Consumption in Patients with Active Lupus Nephritis

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Background: Lupus nephritis (LN) is an autoantibody-mediated disease involving glomerular deposition of immune complexes containing pathogenic anti-C1q antibodies, leading to C1q binding and activation of the classical complement pathway. ANX009 is a subcutaneously administered antigen-binding fragment of a humanized antibody that inhibits C1q interaction with immune complexes. Plasma measures of classical complement activation (C4d/C4 ratio) strongly correlate with disease activity in LN patients, suggesting that these patients may benefit from anti-C1q therapy.

Methods: LN-01 is an ongoing, single-arm, phase 1b study evaluating safety and tolerability of ANX009 in patients (N≤8) with class III or IV LN, high plasma C4d/C4 ratio, and urine protein/creatinine ratio >0.5 g/g at study enrollment. Patients undergo an 8-week screening period, a 3-week treatment period, and an 11-week off-treatment follow-up period. Primary and secondary endpoints are the percentage of patients with treatment-emergent adverse events (TEAEs) and change in complement biomarkers, respectively.

Results: To date, 4 patients completed treatment, one patient discontinued treatment, and screening is ongoing. Among 3/5 patients, 29 TEAEs occurred. All AEs were non-serious, except fever of unknown diagnosis in one patient. Injection site reactions arose in 3/5 patients—mild, mostly erythema. C4d/C4 ratio decreased with treatment in all 5 patients and returned to baseline after treatment cessation. Inhibition of C1q also resulted in normalization of downstream complement markers of activation and consumption for the entire pathway.

Conclusions: In this interim analysis, ANX009 administered subcutaneously was well tolerated and demonstrated C1q target engagement and complement inhibition in 5/5 patients. Normalization of all downstream activation markers and primary components, notably C3 and C5b-9, suggests the classical pathway, not the alternative pathway, is a key driver of complement activation in these LN patients. These interim results support further study of anti-C1q therapy in LN patients.

Funding: Commercial Support - Annexon Biosciences

SA-PO879

Long-Term Efficacy and Relapse in Lupus Nephritis Treated with Mycophenolate Mofetil and Tacrolimus Combination Therapy

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Background: Although recent research has shown the effectiveness of combination therapy with mycophenolate mofetil (MMF) and a calcineurin inhibitor for the initial treatment of active lupus nephritis (LN), its long-term outcomes still need to be explored.

Methods: We reviewed the medical records of 27 LN patients (4 males, 23 females) who underwent combination therapy with MMF and tacrolimus as an induction treatment from October 2009 to November 2018 in our department. Complete remission (CR) was defined by two criteria: 1) a urine protein to creatinine ratio (UPCR) of less than 0.5 g/gCr, and 2) a serum creatinine level (S-Cr) either normal or no more than 15% higher than the baseline. Both these criteria had to be met on two consecutive visits. A relapse was defined as a doubling of UPCR and ≥1.0 g/gCr on two consecutive visits or an intensification of immunosuppressive therapy after CR. Data are presented as median (IQR) or number (%).

Results: The median age was 38 (30-45) years, with 17 patients having new LN onset. Pre-treatment UPCR and eGFR were 4.21 (2.19-5.99) g/gCr and 62.6 (45.1-89.0) mL/min/1.73m^2, respectively. Renal histology (ISN/RPS 2003) showed: Class III in 1, III+V in 4, IV in 13, IV+V in 8, and V in 1. CR rates at 6 and 12 months were 59% and 74%, respectively. The combination regimen was administered for 25 (5.5-37.0) months, and the total observation period was 94.0 (63.0-111.5) months. During this period, one patient died from heart failure. No patient reached end-stage kidney disease or experienced a doubling of S-Cr. Although 26 (96.3%) patients achieved CR in total, 16 (59.3%) patients experienced a relapse. Kaplan-Meier analysis revealed that chronic lesions (A/C) in renal biopsy and the absence of a low C4 level were associated with relapse (P=0.006 and P=0.0007, respectively, by Log-rank test).

Conclusions: Combination therapy for LN was effective in inducing CR and preserving renal function over a long-term period. However, patients with chronic histological lesions or the absence of a low C4 level were more likely to relapse.

SA-PO880

Efficacy of Rituximab in Long-Term Maintenance of Remission in Lupus Nephritis

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Background: Rituximab(RTX) is known to be effective in inducing remission in patients (pts) with refractory lupus nephritis (LN). However, utility of RTX as maintenance therapy remains unclear.

Methods: We analyzed clinical data of 19 pts with LN treated at MGH who received RTX as maintenance therapy for >=12 months(mos) after achieving complete/partial remission. Pts were followed from the date of first RTX infusion after remission(baseline) to 6 mos after their last dose of RTX or development of ESKD. Renal relapse, renal survival and effect of oral immunosuppression reduction were described.

Results: Among the 19 pts, the main indication for RTX maintenance therapy was prior treatment failure with mycophenolate(n=13). Mean age was 36 (IQR 25-43),18/19 pts were female, 13/19 were white. Median creatinine(Cr) was 0.8mg/dL (IQR 0.7-1.4) and median proteinuria was 0.5g/g (IQR 0.3-1.0) at baseline.17 pts had class III/IV±V LN, 2 had pure class V LN. 6 renal relapses occurred in 5 pts during a median follow-up of 36 mos (IQR 24-71). All but 1 had B cell repopulation during relapse (Figure 1). 3 pts developed ESKD: all had advanced CKD at baseline(Cr >2mg/dL). 9/19(47%) pts were on RTX monotherapy at baseline, 11/19(58%) at 12 mos, 8/12(67%) at 24 mos. Median prednisone dose was 5mg/day (IQR 0-7.5) at baseline and 0 at 12 and 24 mos (Figure 2). 2 pts discontinued RTX due to infection.

Conclusions: RTX may be an effective alternative for long-term maintenance of remission in LN.

Figure 1

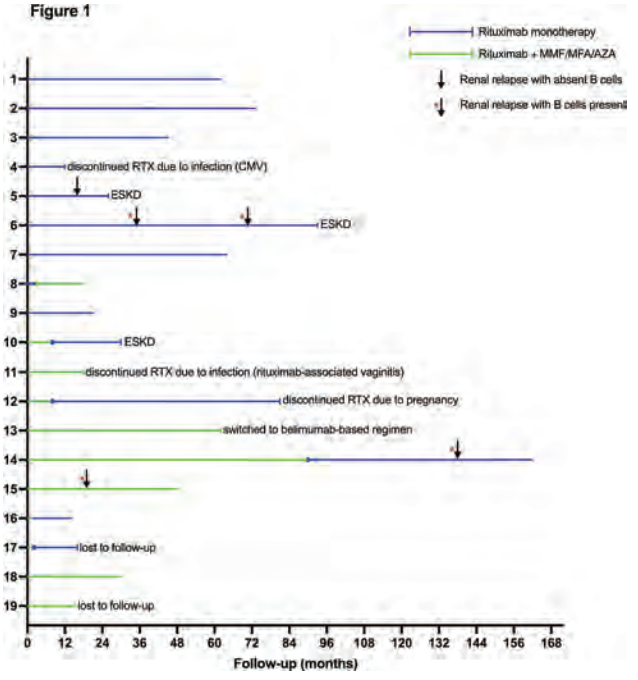
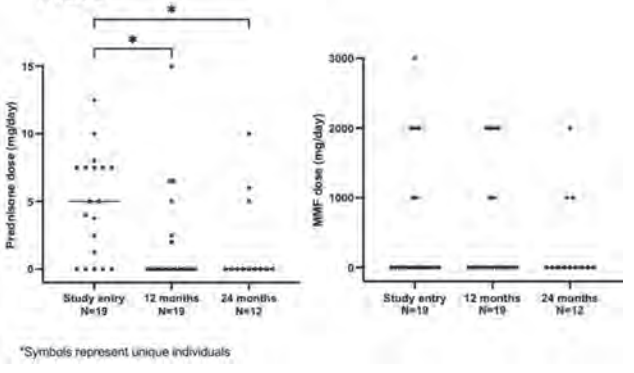


Figure 2



SA-PO881

Post Hoc Analyses of Biomarkers Predictive of a Renal Response to Intravenous (IV) Belimumab (BEL) Plus Standard Therapy (ST) in Patients with Lupus Nephritis (LN)

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Background: In BLISS-LN (GSK BEL114054), a Phase 3 trial of adults with LN treated with BEL 10 mg/kg/month IV or placebo (PBO), + ST, BEL resulted in significantly more kidney responses (Primary Efficacy Renal Response [PERR] and Complete Renal Response [CRR]), and greater improvements in anti-dsDNA and anti-C1q autoantibodies and complement C3 and C4 levels than PBO over 104 weeks (wks). This post hoc analysis of BLISS-LN assessed the characteristics of patients with LN most likely to benefit from the addition of BEL to ST.

Methods: Post hoc logistic regression models tested the ability of potential baseline (BL) biomarker levels and biomarker level changes in the first 12 months of treatment to predict PERR and/or CRR at Wk 104.

Results: Overall, 446 patients were evaluated. High BL anti-C1q predicted a PERR with BEL and a CRR with PBO (**Table**). High BL levels of immunoglobulin (Ig)A and a decrease in IgA at Wk 8 with BEL were predictive of PERR, and high BL levels of naïve B cells were predictive of PERR and CRR to BEL. Low BL plasmablasts, and a decrease in IgA or IgM at Wk 24 predicted a PERR in both groups and a decrease in IgA at Wk 24 predicted CRR to BEL. A reduction in anti-C1q at Wk 52 and of uPCR at Wk 12 also predicted PERR and CRR in both groups. Changes in B-cell subsets were not predictive of a response in the BEL group.

Conclusions: High levels of IgA and naïve B cells at BEL initiation, as well as early reductions in IgA, predicted attainment of PERR and/or CRR for BEL but not PBO. Early reductions in uPCR predicted responses regardless of whether patients received BEL or PBO.

Funding: Commercial Support - GSK (GSK BEL114054; NCT01639339)

Table. Significant BL biomarker and percentage change from BL to stated wks biomarker prediction of kidney response at Wk 104 (treatment policy*; post hoc analysis)

Predictor	PERR at Wk 104		CRR at Wk 104	
	PBO (n=223)	BEL (n=223)	PBO (n=223)	BEL (n=223)
IgA (g/l) at BL				
Parameter estimate†	-	0.3341	-	-
Odds ratio‡	ns	1.40, p=0.0173	ns	ns
IgM (g/l) at BL				
Parameter estimate†	0.6674	-	-	-
Odds ratio‡	1.95, p=0.0120	ns	ns	ns
Anti-C1q (U/ml) at BL				
Parameter estimate†	-	0.002391	0.001615	-
Odds ratio‡	ns	1.0024, p=0.0148	1.0016, p=0.0192	ns
Naive B cells (count/µl) at BL				
Parameter estimate†	-	0.001730	-	0.001688
Odds ratio‡	ns	1.0017, p=0.0433	ns	1.0017, p=0.0446
Plasmablasts (count/ml) at BL				
Parameter estimate†	−0.000166	−0.000111	−0.000193	-
Odds ratio‡	0.9998, p=0.0124	0.9999, p=0.0398	0.9998, p=0.0268	ns
Change in IgA (g/l) at 8 wks				
Parameter estimate†	-	−0.0199	-	-
Odds ratio‡	ns	0.98, p=0.0482	ns	ns
Change in IgA (g/l) at 24 wks				
Parameter estimate†	−0.0155	−0.0332	-	−0.0171
Odds ratio‡	0.98, p=0.0471	0.97, p=0.0003	ns	0.98, p=0.0456
Change in IgM (g/l) at 24 wks				
Parameter estimate†	−0.0132	−0.0152	-	-
Odds ratio‡	0.99, p=0.0174	0.98, p=0.0171	ns	ns
Change in anti-dsDNA (IU/ml) at 24 wks				
Parameter estimate†	−0.004507	-	-	-
Odds ratio‡	0.9955, p=0.0204	ns	ns	ns
Change in anti-C1q (U/ml) at 24 wks				
Parameter estimate†	−0.018157	-	−0.011071	-
Odds ratio‡	0.9820, p=0.0002	ns	0.9890, p=0.0190	ns
Change in anti-C1q (U/ml) at 52 wks				
Parameter estimate†	−0.012990	−0.016034	−0.011426	−0.013112
Odds ratio‡	0.9871, p=0.0020	0.9841, p=0.0055	0.9886, p=0.0190	0.9870, p=0.0219
Change in memory B cells (count/µl) at 24 wks				
Parameter estimate†	0.004601	-	-	-
Odds ratio‡	1.0046, p=0.0466	ns	ns	ns
Change in uPCR (g/g) at 12 wks				
Parameter estimate†	−0.5611	−0.3763	−0.8469	−0.3696
Odds ratio‡	0.57, p<0.0001	0.69, p=0.0018	0.43, p<0.0001	0.69, p=0.0094

*Treatment policy population included all available data, ignoring whether the patient had discontinued study treatment or started a prohibited medication; †estimates are from a post hoc logistic regression model for the parameter with covariates induction regimen (CYC vs MMF), race (Black African ancestry vs other), baseline uPCR, and baseline eGFR. Positive parameter estimates indicate that higher BL values or an increase from BL to stated wks lead to better response. Conversely, negative parameter estimates indicate that lower BL values or a decrease from BL to stated wks lead to better response. Parameter estimates with non-significant odds ratios are not displayed; ‡odds ratios are for a one unit change in the lab parameter, and due to this small scale, the odds ratios appear close to 1. Odds ratios that were not statistically significant predictors of response are not displayed.

PERR at Wk 104 (Wk 100, confirmed at Wk 104) = uPCR ≤0.7, eGFR no more than 20% below pre-flare value or ≥60 ml/min/1.73 m², no rescue therapy.
CRR at Wk 104 (Wk 100, confirmed at Wk 104) = uPCR <0.5, eGFR no more than 10% below pre-flare value or ≥90 ml/min/1.73 m², no rescue therapy.

BEL, belimumab; BL, baseline; CYC, cyclophosphamide; MMF, mycophenolate mofetil; CRR, Complete Renal Response; eGFR, estimated glomerular filtration rate; Ig, immunoglobulin; PBO, placebo; PERR, Primary Efficacy Renal Response; ns, not significant; uPCR, urine protein/creatinine ratio.

SA-PO882

Outcome of Lupus Nephritis Patients Treated with a New Anti-CD40 Monoclonal Antibody According to Kidney Biopsy Features

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Background: Lupus Nephritis (LN) is responsible for SLE-related mortality and morbidity. A phase II trial tested different doses of the anti-CD40 monoclonal antibody BI655064 as add-on therapy to the standard of care in class III or IV LN patients with active renal disease. A post-hoc analysis showed a potential benefit of the higher tested dosages (180mg/240mg) versus low dosage (120mg) and placebo. Monocytes constitutively express CD40. We investigated whether the efficacy of BI655064 was predicted by the presence of monocytes in the kidney biopsy.

Methods: 101 renal biopsies of LN patients enrolled in the BI 655064 trial were scored centrally. eGFR and spot urine protein/urine creatinine ratio (UP/UC) were evaluated at every visit. Through a linear regression model (last available value vs. baseline), patients were divided according to their ″Better'' or ″Worse'' performance compared to the average. Biopsy parameters which differed between the two groups in the univariate analyses ($p<0.1$) were entered into a multivariate logistic regression model, and a routine model selection procedure ($p<0.2$) used to identify parameters predictive for proteinuria reduction or increase in eGFR (LN class IV vs III, Mesangial sclerosis, Lymphocytes, Microthrombi, Modified Chronicity index for UP/UC; Adhesions, Modified Activity index, Modified Chronicity index for eGFR). A logistic regression model adjusted for the same parameters was used to investigate whether the efficacy of BI655064 associated with the presence of renal monocytes.

Results: A lower modified chronicity index was predictive of UP/UC improvement (P=0.032); eGFR tended to be higher with a lower modified chronicity and a higher modified activity index. A higher treatment dose (BI655064 180/240mg vs Placebo/ BI655064 120mg) was associated with a greater proteinuria reduction when kidney biopsies contained glomerular monocytes (OR 3.72 (1.07–12.9), P=0.039). No substantial association between monocytes and eGFR change was detected.

Conclusions: In this post-hoc analysis, we showed that BI 655064 treatment in LN may improve the rate of proteinuria over time when monocytes are present in the biopsy, suggesting that specific renal biopsy characteristics could direct the choice of treatment for individual LN patients.

Funding: Commercial Support - Boehringer Ingelheim International GmbH, Biberach, Germany

SA-PO883

Abstract Withdrawn

SA-PO884

Atacicept in IgA Nephropathy (IgAN): Continued Protective Titers to Diphtheria and Tetanus and Balanced Infections vs. Placebo with a Focus on COVID-19

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Background: Atacicept is a dual anti-BLyS/APRIL fusion protein currently in clinical development for IgA nephropathy (IgAN) treatment. Better understanding vaccine response and immunity with atacicept, especially to COVID-19, may help assess atacicept's benefit risk profile. Atacicept has been studied in IgAN in the Ph2a JANUS study which measured tetanus and diphtheria vaccine titers up to 72w, and the Ph2b ORIGIN study where impact of atacicept on COVID-19 infection rates and severity could be assessed.

Methods: JANUS and ORIGIN were double-blind placebo (PBO) controlled studies that enrolled adults with biopsy-proven IgAN and UPCR >0.75g/g who were on stable doses of renin-angiotensin system inhibitors. Patients (pts) were randomized 1:1:1 to PBO, atacicept 25, or 75mg SC qw for 72w in JANUS (n=16) and 2:1:2:2 to PBO, atacicept 25, 75, or 150mg SC qw for 36w in ORIGIN (n=116). In JANUS, tetanus and diphtheria titers were measured at 1, 48 and 72w in addition to safety assessments. In ORIGIN, safety data on infections were analyzed by treatment arm up to 36w.

Results: The JANUS population was 50% male with baseline (BL) median age 44; the ORIGIN population was 59% male, median age 37. No JANUS pts changed from protective to nonprotective status for diphtheria or tetanus toxin; overall infections were balanced between atacicept and PBO. ORIGIN pts across atacicept and PBO arms had similar rates of overall and COVID-19 infections (Table). All pts with COVID-19 had ≥1 COVID-19 vaccine dose prior to infection. No COVID-19 infection was serious; most were mild. Median duration of COVID-19 infection was 7.5 (IQR 7, 9) days. There were no permanent discontinuations although some COVID-19 infections led to temporary study drug interruption. No COVID-19 infection was reported as study drug related.

Conclusions: Atacicept treatment was associated with continued protective immunity to tetanus and diphtheria in the Ph2a JANUS study. In JANUS and ORIGIN, infections were balanced between atacicept and PBO with no increase in incidence or severity of COVID-19 infections in the Ph2b ORIGIN study.

Funding: Commercial Support - Vera Therapeutics

Table. Summary of COVID-19 Infections in the Ph2b ORIGIN Study (36 Week Double Blind Period)

n (%) or Median (IQR)		Atacicept 25 mg, n=12	Atacicept 75 mg, n=33	Atacicept 150 mg, n=33	Placebo, n=34
Infections overall		6 (38)	16 (48)	12 (36)	11 (32)
COVID-19 infections		4 (25)	9 (27)	8 (24)	6 (18)
COVID-19 vaccine prior to infection		4 (100)	9 (100)	8 (100)	6 (100)
Severity	Mild	3 (75)	8 (88.9)	7 (87.5)	6 (100)
	Moderate	1 (25)	1 (11.1)	1 (12.5)	0
	Severe	0	0	0	0
Outcome	Recovered	4 (100)	9 (100)	7 (87.5)	6 (100)
	Recovering	0	0	1 (12.5)	0
Action taken	No dose change	2 (50)	4 (44.4)	5 (62.5)	3 (50)
	Drug interrupted	2 (50)	5 (55.6)	3 (37.5)	3 (50)
Duration of COVID-19 infection, days*		11.5 (8.5, 14)	8 (7, 9)	8 (6, 8)	6.5 (6, 7)

*Duration of AE reported as median and interquartile range in days for 25 out of 27 participants who had outcome of AE as recovered/resolved.

SA-PO885

IMAGINATION: A Global Phase 3 Trial of RO7434656, an Antisense Oligonucleotide Inhibitor of Complement Factor B, in IgA Nephropathy

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Background: RO7434656 (IONIS-FB-L_{Rx}, ISIS 696844), a ligand-conjugated antisense oligonucleotide targeting complement factor B mRNA, was engineered for enhanced delivery to the liver as the primary site of factor B production. In a Phase 2 trial (NCT04014335), RO7434656 inhibited alternative complement pathway activation and demonstrated a clinically meaningful reduction in UPCR resulting in a stable eGFR in patients with IgA nephropathy (IgAN; **Fig 1**).

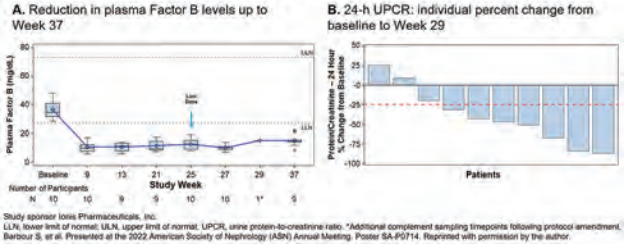
Methods: IMAGINATION (NCT05797610), a Phase 3, randomized, double-blind, placebo-controlled trial will evaluate the efficacy and safety of RO7434656 in adults with biopsy-confirmed primary IgAN (**Fig 2**). 428 patients will be divided into 2 cohorts: a primary cohort with eGFR ≥30 mL/min/1.73m^2 and an exploratory cohort with eGFR 20-29 mL/min/1.73m^2. Patients on maximally tolerated doses of ACEi/ARB will be randomized 1:1 to receive RO7434656 or placebo subcutaneously (SC) on Days 1, 15 and 29 and every 4 weeks (Q4W) thereafter for 105 weeks, with the option to continue double-blind or open-label treatment. The primary endpoint is change from baseline in 24h UPCR at Week 37. Key secondary endpoints include eGFR slope from baseline at Week 105, time to the composite kidney failure endpoint and patient-reported outcomes. Blood, urine and optional kidney biopsies will be collected throughout the study to assess biomarkers.

Results: Expected upon study completion.

Conclusions: The unique antisense modality and long tissue half-life of RO7434656 enables Q4W SC administration to inhibit the alternative complement pathway. IMAGINATION aims to evaluate the efficacy and safety of RO7434656 in adults with IgAN using a broad range of assessments over 105 weeks.

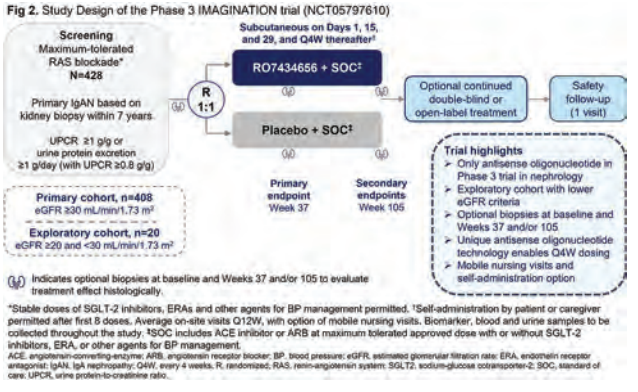
Funding: Commercial Support - Funded by F. Hoffmann-La Roche Ltd. Writing and editorial assistance was provided by Nicola Gillespie, DVM, CMPP, of Health Interactions, Inc. and funded by F. Hoffmann-La Roche Ltd.

Fig 1. Change in (A) UPCR and (B) Factor B in the Phase 2 Trial of RO7434656 (NCT04014335)



Study sponsor Ionis Pharmaceuticals, Inc.
LLN, lower limit of normal; ULN, upper limit of normal; UPCR, urine protein-to-creatinine ratio. *Additional complement sampling timepoints following protocol amendment.
Barbour S, et al. Presented at the 2022 American Society of Nephrology (ASN) Annual Meeting. Poster SA-P0714. Reprinted with permission by the author.

Fig 2. Study Design of the Phase 3 IMAGINATION trial (NCT05797610)



*Stable doses of SGLT-2 inhibitors, ERAs and other agents for BP management permitted. ‡Self-administration by patient or caregiver permitted after first 8 doses. Average on-site visits Q12W, with option of mobile nursing visits. Biomarker, blood and urine samples to be collected throughout the study. ‡SOC includes ACE inhibitor or ARB at maximum tolerated approved dose with or without SGLT-2 inhibitors, ERA, or other agents for BP management.
ACE, angiotensin-converting-enzyme; ARB, angiotensin receptor blocker; BP, blood pressure; eGFR, estimated glomerular filtration rate; ERA, endothelin receptor antagonist; IgAN, IgA nephropathy; Q4W, every 4 weeks; R, randomized; RAS, renin-angiotensin system; SGLT2, sodium-glucose cotransporter-2; SOC, standard of care; UPCR, urine protein-to-creatinine ratio.

SA-PO886

Modeling Based on NefIgArd Two-Year eGFR Total Slope Predicts Long-Term Clinical Benefit of Nefecon in a Real-World IgA Nephropathy (IgAN) Population

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Background: Nefecon, a targeted-release budesonide formulation, is approved for the treatment of patients (pts) with immunoglobulin A nephropathy (IgAN). Data from the full Phase 3 NefIgArd trial showed that 9 months of Nefecon 16 mg/d preserved estimated glomerular filtration rate (eGFR) and reduced urine protein–creatinine ratio (UPCR) vs placebo. These effects were maintained during the 15-month off-drug follow-up period, indicating that Nefecon is disease-modifying. We conducted a modeling analysis to predict the potential long-term benefit of Nefecon on clinical outcome (i.e., a composite endpoint of end stage renal disease, eGFR <15 mL/min/1.73m^2, or sustained doubling of serum creatinine) in a real-world IgAN population.

Methods: In the final analysis of the NefIgArd trial, there was a treatment benefit in 2-year eGFR total slope of 2.78 mL/min/1.73m^2 per year (95% confidence interval [CI] 1.39–4.17) with Nefecon vs placebo (linear spline mixed-effect model). This difference was applied to a published linear regression between treatment effects for the change in 2-year eGFR total slope and the log hazard ratio (HR) of clinical outcome, based on a meta-analysis involving >60K CKD pts (Inker et al. *JASN* 2019;30:1735-45). Median time to clinical outcome for a reference group receiving supportive standard of care (SoC) only was estimated by modeling long-term registry data from pts at Leicester General Hospital (LGH), UK, matching NefIgArd-recruited pts to individual LGH pt records based on their baseline UPCR and eGFR. Time to clinical outcome for SoC pts was estimated using a Weibull model.

Results: 352/364 NefIgArd pts were matched with 886 unique records from 192 LGH pts, which contained 287 clinical outcome event-times from 68 LGH pts. The NefIgArd 2-year eGFR total slope translated to a log HR for clinical outcome of 0.38 (95% CI 0.21–0.63), a 62% risk reduction vs placebo. Median time to clinical outcome was estimated at 9.6 years in SoC pts and 22.4 years in Nefecon-treated pts (median delay 12.8 [95% CI 4.8–27.9] years). 52% of SoC pts were predicted to have a clinical outcome within 10 years vs 24% of Nefecon-treated pts.

Conclusions: Modeling analyses indicate that the clinical benefit seen with Nefecon predicts a substantial delay in progression to kidney failure.

Funding: Commercial Support - Calliditas Therapeutics

SA-PO887

Atacicept 150 mg Reduces Serum Gd-IgA1, a Biomarker Associated with Long-Term Outcomes in IgA Nephropathy (IgAN): 36W Results from the Ph2b ORIGIN Study

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Background: IgA nephropathy (IgAN), the most common primary glomerulonephritis and a significant contributor to ESRD worldwide, is characterized by elevated serum levels of galactose-deficient immunoglobulin A1 (Gd-IgA1). High Gd-IgA1 levels are associated with greater risk of renal function deterioration. Gd-IgA1 production is driven by the B Lymphocyte Stimulator (BLyS)–A PRoliferation-Inducing Ligand (APRIL) signaling

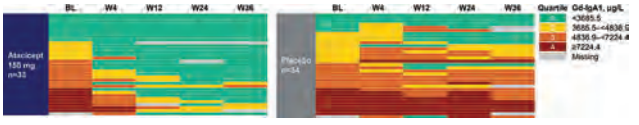
pathway's effect on B cells and plasma cells. Atacicept is a dual anti-BLyS/APRIL fusion protein in clinical development for IgAN treatment. The Ph2b ORIGIN study of atacicept in IgAN met its primary endpoint. The objective of this analysis is to evaluate change in serum Gd-IgA1 quartiles over 36 weeks (w) with atacicept 150mg, the dose being evaluated in a pivotal Ph3 study, vs placebo (PBO).

Methods: The randomized, double-blind, PBO controlled Ph2b ORIGIN study included 116 patients (pts) with biopsy-proven IgAN, eGFR ≥30mL/min/1.73m², and urine protein >0.75g/24h or UPCR >0.75g/g despite optimized renin–angiotensin system blockade. Pts were randomized 2:2:1:2 to atacicept 150, 75, or 25 mg vs PBO SC qw for 36w. At baseline (BL), 4, 12, 24, and 36w, Gd-IgA1 values were assessed and classified into quartiles using cutoffs derived from BL Gd-IgA1 values.

Results: Atacicept 150mg (n=30) achieved 64% mean Gd-IgA1 reduction vs 7% for PBO (n=29) at 36w (p<0.001) in pts with BL and 36w data. Atacicept 150mg led to steady Gd-IgA1 reduction to the lowest quartile 1 at 36w in 27/33 pts while most PBO pts transiently increased or decreased by 1 quartile (Figure). In the atacicept 150mg arm, 5/8 pts with BL quartile 4 had reductions to quartile 1 at 36w, while in the PBO arm 8/9 with BL quartile 4 remained in quartile 3 or 4 at 36w.

Conclusions: Atacicept 150mg achieved a durable and significant Gd-IgA1 reduction over 36w. Regardless of BL quartile, the vast majority of pts receiving atacicept 150mg for 36w had Gd-IgA1 reductions to the lowest quartiles, which has been associated with greater renal survival. These results provide further evidence supporting atacicept as a potential disease-modifying treatment for IgAN.

Funding: Commercial Support - Vera Therapeutics, Inc.



SA-PO888

Utilization of Corticosteroid Therapy in Patients with IgA Nephropathy and C1 Lesion

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Background: IgA nephropathy (IgAN) frequently leads to chronic kidney disease and progressive kidney failure. Among the prognostic factors is the presence of crescents on kidney biopsy, as a component of the MEST-C score, leading many to consider steroid treatment when crescents are found, even when seen in mild to moderate numbers (1-25%, C1 lesion). We wanted to assess if steroid treatment does indeed impact the outcome of IgAN patients with crescents.

Methods: Retrospective review of patient records from 2017-2022 who had biopsy proven IgAN with C1 lesions and adequate follow up was undertaken to assess patient characteristics, treatment and longitudinal follow up of outcomes of changes in eGFR and proteinuria. A multivariate model was created to relate steroid therapy to short to moderate term changes in kidney function (by eGFR slope).

Results: 68 of 176 consecutive patients met the study criteria, they had an average age of 41 years, 57% were women, mostly Asian, variable activity and chronicity in MEST score. Median (IQR) of crescent percent was 8.5(4.8-14.2%), UPCR median was 1.78g/g, eGFR mean (SD) was 63±36 ml/min/1.73m². Average follow up was 2 years. Most patients (75%) had been treated with renin-angiotensin system inhibitors. 37 of the patients underwent steroid therapy shortly after biopsy. There were differences in age, gender and MESTC score between treated and untreated patients. There were variable impacts on proteinuria. Utilizing linear mixed effects modeling, there was no significant difference between treated and untreated patients in their annual decline in eGFR, which averaged 2.13 ml/min/year (difference in slopes [treated v. untreated] of 0.70 ml/min/year, p=0.35).

Conclusions: Patients with IgAN and C1 lesions are frequently treated with corticosteroid therapy after kidney biopsy. In this predefined cohort, steroid therapy provided a non-significant trend for less disease progression over this follow up. Larger cohorts should be followed for longer periods of time, but presently, it does not appear prudent to choose steroid therapy based on C1 lesions seen on the biopsy.

Funding: Private Foundation Support

SA-PO889

Kidney Outcomes with Corticosteroid Treatment in IgA Nephropathy According to the Oxford-MEST-C Classification

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Background: Despite optimization of renin-angiotensin-aldosterone system (RAAS) inhibition, patients with IgA nephropathy remain at risk for kidney failure. The effect of steroids on kidney outcomes in IgA nephropathy with different renal pathologic lesions has been uncertain.

Methods: We retrospectively studied 67 patients with biopsy-proven IgA nephropathy who were receiving optimized RAAS inhibitor therapy and persistent proteinuria > 1 g/day between January 2016 and December 2020. Clinical parameters including estimated glomerular filtration rate (GFR) decline were compared between corticosteroids and supportive treatment.

Results: Overall, 68.7% of patients received treatment with corticosteroids. Median estimated GFR decline was significantly lower in the steroids than in the controls (-0.65 (IQR 7 to -3.45) vs - 5.75 (IQR -0.7 to -10.65) mL/min/1.73 m2/year, P=0.025, respectively). Slope of estimated GFR were also significantly different between the steroids and the controls in subgroup of patients with baseline GFR >50 mL/min/1.73 m2 (3.90±11.42 vs -9.31±5.08 mL/min/1.73 m2/year, P=0.011, respectively), mesangial hypercellularity M0 score (4.69±11.37 vs -2.63±6.42 mL/min/1.73 m2/year, P=0.049, respectively), and C0 score (2.48±12.63 vs -5.58±8.4 mL/min/1.73 m2/year, P=0.026, respectively). In additionally, the rapid GFR decline >5 mL/min/1.73 m2/year occurred in 9 (19.6%) in the steroids compared with 11 participants (52.4%) in the controls (P=0.006).

Conclusions: Corticosteroids therapy in addition to optimized RAAS inhibition has lower the risks of kidney disease progression in patients with IgA nephropathy especially baseline GFR >50 mL/min/1.73 m², Oxford classification M0 and C0 score.

SA-PO890

Targeted Release Formulation (TRF) Budesonide (Nefecon) Reduces Serum Biomarkers of Lymphocyte Activation in IgA Nephropathy, Which Correlates with Changes in Serum B Cell-Activating Factor (BAFF) Levels

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Background: The targeted-release formulation of budesonide, Nefecon, is designed to deliver budesonide to the gut-associated lymphoid tissue of the terminal ileum, a major site of immunoglobulin A (IgA) production. In the phase 2b NEFIGAN trial, treatment with Nefecon significantly reduced serum levels of galactose-deficient IgA1IgA/IgG immune complexes and cytokines involved in B-cell activation. This study investigates the effect of Nefecon on biomarkers of lymphocyte activation in the Part A population of the phase 3 double-blind, randomized controlled NefIgArd trial in which 9 months' treatment with Nefecon led to a reduction in proteinuria at 9 months (p=0.0005), and a reduction in loss of estimated glomerular filtration rate at 24 months (p<0.0001) compared with placebo.

Methods: Levels of the soluble cluster of differentiation (CD)23, CD27, and CD30 were measured using Luminex technology in 160 NefIgArd Part A participants using serum samples collected at baseline and 3, 6, and 9 months post randomization. Comparisons between placebo and Nefecon treated groups were made at each time point using unpaired t-tests, with a significance level of p<0.05.

Results: Treatment with Nefecon 16 mg/day resulted in a significant reduction in the levels of sCD23, sCD27, and sCD30 at 3 months (all p values <0.0001), 6 months (all p values <0.0001), and 9 months (all p values <0.0001), confirming the findings from the NEFIGAN trial. The extent of sCD23, sCD27, and sCD30 suppression correlated with the magnitude of B-cell activating factor (BAFF) reductions at each timepoint. sCD30 reductions at 6 months and 9 months correlated with the magnitude of reductions in IgA/IgG immune complexes.

Conclusions: These data validate the findings from the phase 2b study and further support a disease-modifying action of Nefecon, specifically an action on the BAFF-lymphocyte interactome and immune complex formation in immunoglobulin A nephropathy.

Funding: Commercial Support - Calliditas Therapeutics

SA-PO891

An Open-Label Trial Evaluating the Safety and Efficacy of Budesonide in Patients with IgA Nephropathy at High Risk of Progression

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Background: We sought to evaluate the efficacy and safety of budesonide (Budenofalk®) in the treatment of patients with IgA Nephropathy (IgAN).

Methods: The BUDIGAN trial (ISRCTN47722295) is a prospective, interventional, open-label, non-randomized study that enrolled 32 patients with IgAN, at high risk of progression defined as persistent proteinuria over 1 g/day despite adequate RAAS blockade for at least 3 months or patients with proteinuria between 0.5 and 1 g/day after RAAS blockade if they had additional risk factors for progression (eGFR<60 ml/min/1.73m2, presence of proliferative lesions). Patients were treated with Budenofalk® at a dose of 9 mg/day for the first 12 months, subsequently tapered to 3 mg/day for another 12 months. The primary endpoints were change of eGFR, proteinuria and hematuria at 36 months.

Results: The study cohort had a mean age of 41.7 ± 9.4 years (72% were males), while the mean eGFR and median 24-h proteinuria were 59 ± 24 ml/min/1.73m2 and 1.5 g/d (IQR:1.05-2.4), respectively. 25% and 12.5% of patients had a proteinuria level of 2-3.5 g/d and over 3.5 g/d, respectively. Treatment with budesonide determined a reduction in proteinuria at 12, 24 and 36 months by -42.3% (95%CI, -52.2 to -1.24), -61.5% (95%CI, -72.2 to -35.9) and -74.3% (95%CI, -80.6 to -55.7). The proteinuria at last follow-up was 0.34 g/d (IQR:0.12-0.86), significantly lower than the study baseline (p<0.001). The improvement in hematuria was similar to proteinuria with a reduction at 36 months by -92.6% (95%CI, -95 to -58.6). Budesonide treatment determined an eGFR preservation corresponding to a 12, 24 and 36 month change of +6.1% (95%CI, -9.5 to 21.7), +7.1% (95%CI, -10.2 to 24.3) and +4.7% (95%CI, -13.5 to 23), respectively.

The overall eGFR change/year was +0.61 ml/min/y (95%CI, -1.37 to 2.59). Budesonide (Budenofalk®) was well-tolerated, and treatment emergent adverse events were mostly mild in severity and reversible.

Conclusions: Budesonide (Budenofalk) was effective in the treatment of patients with IgAN at high-risk of progression in terms of reducing proteinuria, hematuria and preserving renal function over 36 months of therapy.

SA-PO892

Analysis of the NefIgArd Part A Study Population Confirms Nefecon Reduces Levels of Dietary Antigen-Specific IgA in Patients with IgA Nephropathy

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Background: Nefecon, the targeted-release formulation of budesonide, is delivered to the gut-associated lymphoid tissue (GALT) of the terminal ileum, a major site of immunoglobulin A (IgA) production. The Phase 3, double-blind, randomized controlled clinical trial NefIgArd tested the efficacy of Nefecon in patients with IgA nephropathy (IgAN) at high risk of progressive kidney disease despite optimized supportive care. The trial comprised 9 months of treatment with either placebo or Nefecon 16 mg/day, and a 3-month (Part A) or 15-month (Part B) off-drug observational follow-up period. Treatment with Nefecon 16 mg/day significantly reduced proteinuria after 9 months of treatment compared with placebo (p=0.0003) and this effect was maintained, along with preservation of estimated glomerular filtration rate (p<0.0001), over the 15-month off-drug observational follow-up period. The aim of this study was to determine the effect of Nefecon treatment on circulating levels of dietary antigen-specific IgA, secretory IgA, and a marker of gut permeability, fatty acid-binding protein 2 (FABP2).

Methods: Circulating levels of anti-gliadin IgA, anti-casein IgA, secretory IgA and FABP2 were measured in baseline serum samples and 3, 6, and 9 months after randomization during Part A of the NefIgArd trial using enzyme-based immunosorbent assays. Comparisons between placebo and Nefecon-treated groups were made at each study time point using unpaired t-tests, with a significance level of p<0.05.

Results: Treatment with Nefecon 16 mg/day significantly reduced levels of anti-gliadin IgA at 3 months (p=0.044), 6 months (p=0.029), and 9 months (p=0.027), and levels of anti-casein IgA at 9 months (p=0.023), compared with antibody levels at baseline. These data are consistent with Nefecon 16 mg/day results obtained in the Phase 2b NEFIGAN clinical trial. No significant changes were seen in levels of secretory IgA or FABP2.

Conclusions: Reductions in IgA antibodies against mucosally encountered antibodies confirm a local mucosal effect of Nefecon in IgAN. This effect is likely mediated by a direct action on GALT B cell IgA production rather than an effect on gut permeability and increased antigen exclusion.

SA-PO893

Analysis of the NefIgArd Part A Study Confirms Nefecon Modulates Proteins Involved in the Intestinal Immune Network for IgA Production

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Background: Nefecon, the targeted release formulation of budesonide, is delivered to the gut-associated lymphoid tissue (GALT) of the terminal ileum, a major site of immunoglobulin A (IgA) production. Results from the Phase 2b NEFIGAN and Phase 3 NefIgArd trials demonstrated that treatment with 16 mg/day Nefecon significantly reduces proteinuria and loss of estimated glomerular filtration rate compared with placebo. A number of serum biomarkers have been measured in the 2 trials and many of those identified to be modulated by Nefecon in the Phase 2b study have now been validated in Part A of the NefIgArd study. The aim of this study was to determine biological pathways modulated by Nefecon treatment using the data currently available from the Part A biomarker analysis program.

Methods: NefIgArd is a Phase 3 double-blind, randomized, controlled clinical trial designed to determine the efficacy of Nefecon in patients with immunoglobulin A nephropathy (IgAN) at high risk of progressive kidney disease despite optimized supportive care. The trial comprised 9 months of treatment with placebo or Nefecon 16 mg/day, and a 3-month (Part A) or 15-month (Part B) off-drug observational follow-up period. An interactome analysis was performed incorporating all serum proteins significantly modulated by treatment with Nefecon 16 mg/day in Part A of the NefIgArd study using the STRING protein-protein interactions database, which contains known and predicted protein interactions, to determine which biological processes and pathways are modulated by Nefecon treatment.

Results: Consistent with the Phase 2b findings, functional analysis demonstrated that serum biomarkers significantly modulated by Nefecon treatment in Part A of the NefIgArd trial are enriched for proteins involved in the KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway database for intestinal immune network for IgA production, and biological processes involved in B cell activation control, indicating the mechanism of action of Nefecon is, at least in part, driven by an effect within the GALT.

Conclusions: These findings support a disease modifying effect of Nefecon at the ileal mucosal surface and a direct effect on the ileal GALT, further strengthening the link between the gut and the kidneys in IgAN.

Funding: Commercial Support - Calliditas

SA-PO894

Mycophenolate Mofetil and Steroid for Treatment of Patients with IgA Nephropathy

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Background: The efficacy of steroids and mycophenolate mofetil (MMF) treatment in patients with IgA nephropathy (IgAN) is the subject of ongoing debate. We retrospectively evaluated the effects of MMF+steroid treatment compared to steroid alone or conservative therapy on incident kidney failure in adults with biopsy proven IgAN.

Methods: The study population was derived from biopsy proven adult IgAN patients seen at Mayo Clinic Rochester from 1/1/2008 to 12/31/2018. Patients were categorized into treatment groups based on which therapy they received within the first 3 months following kidney biopsy. The association between treatment group and risk of incident kidney failure was evaluated using Cox proportional hazards regression models using inverse probability of treatment weighted (IPTW) estimation with propensity scores to control for pre-treatment imbalances on observed variables.

Results: A total of 166 patients were included in the final analysis, with 30 (18%) patients developing incident kidney failure during a mean follow-up of 6.2 years. The conservative group exhibited lower levels of serum creatinine, degree of hematuria, and histopathological M, E, and C scores when compared to the treated groups. Conversely, the conservative group demonstrated higher eGFR compared to the treated patients (**Table 1**). The incidence of kidney failure was significantly reduced by 88% in patients who received MMF+steroid therapy compared to those who underwent conservative therapy (HR 0.12, 95% CI 0.02, 0.95, p=0.04). Although patients who received steroids alone were also less likely to experience kidney failure compared to conservative therapy, the results did not reach statistical significance (HR 0.50, 95% CI 0.19, 1.36, p=0.17).

Conclusions: Our data suggests that combined therapy of MMF+steroid could be a promising treatment strategy for white IgAN patients, particularly those with active inflammatory lesions on kidney biopsy.

Table 1. Baseline characteristics of patients with IgA nephropathy, overall and by treatment group

Baseline	Total (N=166)	Conservative (N=105)	Steroid alone (N=39)	MMF+steroid (N=22)	P
Age (years)	44 [33, 57]	44 [31, 57]	47 [38, 55]	40 [33, 58]	0.47
Male Sex	112 (67.5)	73 (69.5)	24 (61.5)	15 (68.2)	0.66
Race					0.30
Missing	5	3	2	0	
Non-white	24 (14.9)	16 (15.7)	7 (18.9)	1 (4.5)	
White	137 (85.1)	86 (84.3)	30 (81.1)	21 (95.5)	
Serum Creatinine (mg/dL)	1.6 [1.2, 2.1]	1.5 [1.1, 2.0]	1.9 [1.4, 2.3]	1.8 [1.3, 2.3]	**0.01**
Estimated Proteinuria (g/24hr)	1.7 [0.8, 3.5]	1.6 [0.8, 3.5]	2.3 [0.9, 3.5]	1.7 [1.3, 3.6]	0.50
eGFR (mL/min/1.73m^2)	43 [31, 62]	48 [33, 69]	32 [29, 48]	43 [26, 70]	**0.01**
Degree of hematuria [#]	4 [3, 6]	3 [3, 5]	4 [3, 8]	7 [4, 8]	**0.002**
MEST-C Scores (≥1)					
M	134 (80.7)	78 (74.3)	36 (92.3)	20 (90.9)	**0.02**
E	42 (25.3)	17 (16.2)	13 (33.3)	12 (54.5)	**<0.001**
S	104 (62.7)	64 (61.0)	24 (61.5)	16 (72.7)	0.58
T	62 (37.3)	38 (36.2)	16 (41)	8 (36.4)	0.86
C	41 (24.7)	13 (12.4)	16 (41)	12 (54.5)	**<0.001**

Baseline refers to the time of biopsy. Results are presented as median [IQR] for continuous variables and as n (%) for categorical variables. P-values for continuous variables were derived using the Kruskal-Wallis test; P-values for categorical variables were derived using the Chi-Square test. MMF: mycophenolate mofetil. [#] Degree of hematuria was categorized by the number of red blood cells in urine per high power field under microscopy into D1=0, D2=1-3, D3=3-10, D4=11-20, D5=21-30, D6=31-40, D7=41-50, D8=51-100, and D9≥100 at the time of biopsy.

SA-PO895

Efficacy of Therapeutic Apheresis for Cryoglobulinemic Vasculitis Patients with Renal Involvement

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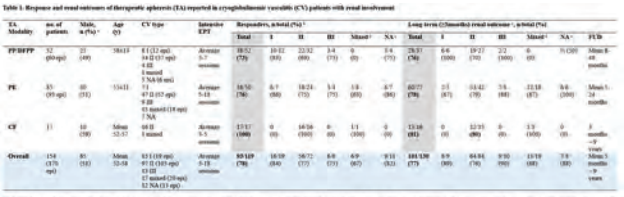
Background: The administration of therapeutic apheresis (TA) to eliminate excessive abnormal immunoglobulins in patients with cryoglobulinemic vasculitis (CV) is a frequently employed approach; however, its efficacy has not been firmly established. This systematic review aimed to evaluate the efficacy of various TA modalities such as plasma exchange (PE), plasmapheresis (PP), and cryofiltration (CF) in patients with renal involvement suffering from CV.

Methods: A literature search was conducted using MEDLINE, EMBASE and Cochrane Databases through December 2022. Studies that reported outcomes of TA in adult CV with renal involvement were assessed.

Results: A total of 154 patients from 76 studies (comprising 13 case series and 63 case reports) were evaluated, with 51% males and a mean age of 49 to 58 years. There were 15 type I, 97 type II, and 13 type III; the remaining patients were either mixed (n=17) or their CV type was undetermined (n=12). Hematologic malignancy and HCV were the common causes of type I (53%) and type II (27%), respectively. PE, PP and CF were performed in 85 (56%), 52 (34%), and 17 (11%) patients, respectively. The overall response rate for TA was 78%, with type I, II, and III patients experiencing response rates of 84%, 77%, and 75%, respectively. The overall response rates of PE and PP were similar (76% vs 73%), but lower than CF (100%). Most patients received steroids, immunosuppressants, and treatment targeting the causative disease during TA and follow-up period. The overall long-term renal outcome rate was 77%, with type I, II and III patients experiencing response rate of 89%, 76% and 90%, respectively. The renal outcome in patients receiving PE, PP and CF were similar (78%, 76% and 81%, respectively).

Conclusions: This systematic review demonstrates that incorporating TA in conjunction with other treatments, such as immunosuppressive therapy, is a successful strategy for managing severe renal involvement in CV patients. While PE, PP, and CF were all effective TA modalities, PE was the most commonly used approach.



SA-PO896

Mycophenolate Mofetil in Steroid Nonresponsive IgA Nephropathy

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Background: Immunosuppression use is suggested in patients of primary IgA nephropathy (IgAN) with persistent proteinuria≥1 g/day. We examined the role of mycophenolate mofetil (MMF) in steroid non-responsive IgAN.

Methods: In a retrospective study (2012-21) we included patients with primary IgAN who had received MMF for persistent proteinuria(≥1g/day) despite treatment with oral steroids(1mg/kg/day) for at-least 8 weeks. All patients had received MMF 1-2g/day for at-least 3 months. Patients with C2 lesions were excluded. Primary outcome was deterioration of renal function defined as sustained decline in estimated glomerular filtration rate(eGFR) by > 50% documented during at-least 2 consecutive clinic visits with no recovery or progression to end stage kidney disease. Complete remission (CR) was defined as proteinuria <500 mg/d with stable eGFR and partial remission (PR) as proteinuria<1g/day, at-least 50% reduction in proteinuria and decline of proteinuria to <3.5g/day with stable eGFR.

Results: 81 patients were included. Median age at presentation was 32(IQR 25-42) years and 67.9% were males. 67.9% had hypertension. 68(84%) had M1, 12(14.8%) had E1, 58(71.6%) had S1, 37(45.7%) had T1, 5(6.2%) had T2 and 16(19.8%) had C1 lesions. Median eGFR was 46.3(IQR 37.6-67.0) ml/min/173m2, median serum albumin was 3.9(IQR 3.4-4.3) g/dl and median proteinuria was 3.5(IQR 2.1-4.4) g/day at time of initiating MMF treatment. 70(90.1%) cases received renin angiotensin system (RAS) blockade therapy. 44(54.3%) patients achieved remission with MMF therapy (CR:24, PR:20) of whom 12/44(27.3%) relapsed. During a median follow up of 52.2 (IQR 30.8 to 69.1) months after diagnosis, 35(43.2%) patients had progressed to primary outcome. 35(43.2%) patients had adverse effects, 4 had diarrhea and 31 had infections.7 patients developed tuberculosis.

Conclusions: MMF has limited efficacy in steroid non-responsive IgAN but with significant adverse effects.

SA-PO897

Mycophenolate Mofetil (MMF) and Corticosteroids in Crescentic IgA Nephropathy (IgAN)

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Background: There is no gold standard for the treatment of crescentic IgAN.

Methods: Biopsy-proven crescentic IgAN patients treated with MMF plus corticosteroids 2000-2022(Figure1). Renal outcomes analyzed: hematuria, proteinuria, estimated glomerular filtration rate(eGFR), and end-stage kidney disease(ESKD) after one year.

Results: A total of 22 patients, 72.7% male, 86.4% white, age 38.9±15.3 years. Follow-up 3.9±2 years. Baseline serum creatinine(sCr)2.0±0.78mg/dl, and 100% had hematuria. Kidney biopsy showed(MEST, M1 [90.9%], E1 [59.1%], S1[86.4%], T0[59.1%], T1[27.3%], T2[13.6%], C1[72.7%], C2[27.3%]).95.4% no previous immunosuppression, 77.3% Intravenous methylprednisolone, and 100% received oral corticosteroids, time biopsy to MFF 19 [IQR3.5-69.5] days. At one-year, kidney survival 100%, hematuria disappeared in 68.4%, eGFR(CKD-EPI) increased from 35.6[IQR24.7-71.5] to 51.3[IQR36.4-87]ml/min/1.73m^2(p=0.003), proteinuria g/24h decreased from 1.8[IQR 1.2-4.0] to 0.55 [IQR0.2-1.3](p=0.003). The renal survival with IFTA≥40% was 40% vs. 88.2%with IFTA<40%. Persistent hematuria(PH) had a renal survival of 50% vs. 92.3% with no PH. Most common adverse event was infection(n=6), with temporary treatment discontinuation.22.7% developed ESKD.

Conclusions: MMF plus corticosteroids is associated with 100% kidney survival at one year and 77.3% at the end of follow-up. Advanced interstitial fibrosis and PH seem to be associated with worse prognosis in crescentic IgAN.

Figure 1 Flowchart for the selection of the patients with IgA Nephropathy (IgAN)

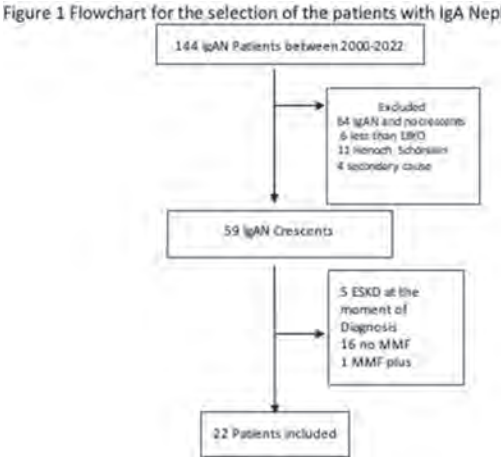
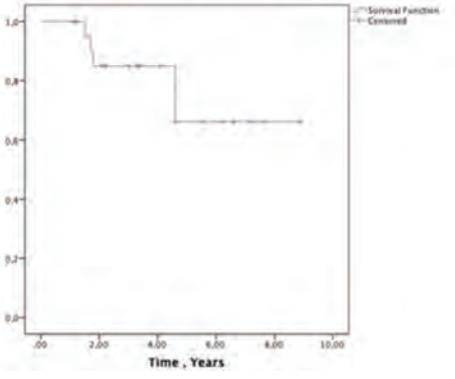


Figure2 Cumulative probability of survival without ESKD in patients with crescentic IgAN during the follow-up.



SA-PO898

Mycophenolate Mofetil in Immunoglobulin A Nephropathy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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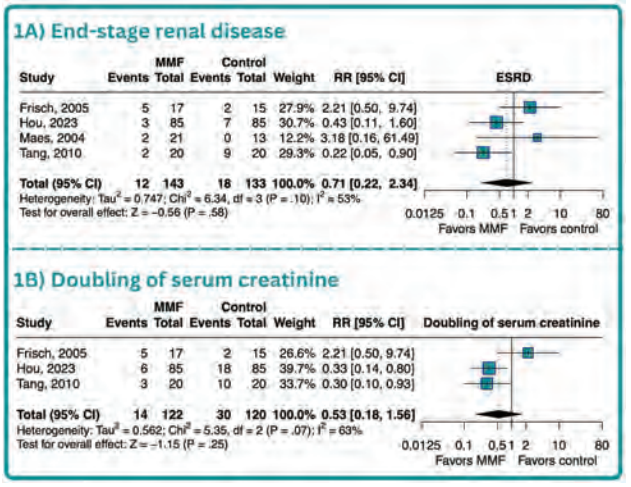
Background: Immunoglobulin A nephropathy (IgAN) is a prevalent primary glomerular disease worldwide. The efficacy of mycophenolate mofetil (MMF) for treating IgAN has yielded inconsistent findings in randomized controlled trials (RCTs).

Methods: In accordance with PRISMA guidelines, we systematically searched PubMed, Embase, Cochrane, and Web of Science in May 2023 for RCTs with long-term follow-up comparing MMF versus placebo or standard of care for IgAN with persistent proteinuria. Statistical analyses were performed using R software version 4.2.2.

Results: We included four RCTs comprising 276 patients with IgAN, of whom 51.81% were randomized to MMF. Average follow-up ranged from 24 to 72 months. MMF did not significantly reduce the incidences of end-stage renal disease (ESRD; RR 0.71; 95% CI 0.22-2.34; p=0.58; I2=53%; Fig. 1A) or doubling of serum creatinine (RR 0.53; 95% CI 0.18-1.56; p=0.25; I2=63%; Fig. 1B) as compared with placebo or standard of care in patients with IgAN.

Conclusions: In this meta-analysis of RCTs, there was no significant difference between MMF and placebo or standard of care in terms of ESRD and doubling of serum creatinine in patients with IgAN.



There was no significant difference between groups in terms of ESRD and doubling of serum creatinine.

SA-PO899

Long-Term Follow-Up of Methylprednisolone (MP) Pulse and Mesenchymal Stem Cell (MSC) Therapy in Severe IgA Nephropathy

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Background: Up to date there is no specific treatment method for severe IgA nephropathy, but giving ARB, MRA, omega-3, antiplatelet therapy, complement inhibitors, Nefecon, endothelin inhibitors, SGLT2 inhibitor etc. and eventually fall into ESRD and need dialysis or KTP. Cell based therapy especially autologous adipose derived stromal vascular fraction (SVF)/mesenchymal stem cells (MSC) is an emerging field in intractable immune-mediated disorders such as GVHD, multiple sclerosis, Crohn's disease, osteoarthritis and even immune dysregulating infectious diseases, however reports in nephrology field are very rare. We firstly reported 2 years follow up results of MP pulse and MSC in severe IgAN in 2015 (ASN) with promising results. We tried MP pulse therapy followed by autologous MSC and follow up for 7 to 9 years in severe IgA nephropathy.

Methods: We selected severe IgA nephropathy as two groups, first group by clinical CKD stage 3b or more (A) and second group by pathologically severe group as Lee's classification grade IV or V (B), and tried methylprednisolone pulse therapy followed by SVF/MSC. One cycle of methyl PD pulse is (20-30mg/kg/day, max 1g/day) for 3 consecutive days. We tried 3 to 17 cycles depends on the renal pathology, followed by autologous adipose derived SVF/MSC intravenously. Mean cell count was 3x10(7)/injection. Depends on the amount of harvested fat we tried 2-4 times.

Results: Seven patients were group A. Mean age 60 years old. Mean initial eGFR before therapy was 28 ml/min and after therapy 39 ml/min. Mean follow up period was 6.8 years. Control patient (eGFR 33 ml/min) without treatment started hemodialysis in 2 years. Three patients were group B. Mean age 25 years old. Mean initial eGFR before therapy was 85 ml/min and after therapy 106 ml/min. Mean follow up period was 9.3 years. No significan side-effects were noted. Follow up renal biopsy showed disapperance of mesangisl deposits, reduced mesangial proliferation, improved epthelial foot process fusion and disappearance of IgA depositon by immunofluorecent microscopy.

Conclusions: Follow up renal biopsy after MP pulse and SVF/MSC showed disappearance of immune deposits and improved subepthelial foot process fusion. Longterm follow up of MP-pulse and MSC/SVF therapy in severe IgA nephropathy showed a promising results and could be a lifesaving therapeutic strategies, although further studies are mandatory

SA-PO900

Treatment of IgA Nephropathy in Chinese Patients: Evidence from Real-World Data

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Background: Immunoglobulin A nephropathy (IgAN) accounts for more than 50% of primary glomerulonephritis in China[1]. The aim of this real-world study was to describe and compare the treatment strategy of Chinese nephrologist with nephrologists across the world for patients with IgAN.

Methods: A point-in-time, cross-sectional survey utilizing data from Adelphi Real-world IgAN Disease-Specific Programme was conducted in China, Japan, United States (US) and Europe (EU5: France, Germany, Italy, Spain, United Kingdom), from June to October 2021. 60 nephrologists from China completed a structured online record for successive 587 IgAN patients, including treatment regimens and patient clinical characteristics.

Results: The proportion of different lines of treatments with ACEi/ARB, SGLT2i, corticosteroids and other therapy was analyzed and shown (Figure 1). Compared with EU5 and US, the proportion of ACEi/ARB use at first line was lower in Asia (EU5 84%, US 86%, China 74%, Japan 59%), while the use of corticosteroids in Asia as first line was higher (EU5 36%, US 44%, China 47%, Japan 63%). Main reasons to stop corticosteroids was when patient's condition improved, treatment course completed, or side effects, of which weight gain (51%), acne (43%) and insomnia (30%) were most reported by Chinese nephrologists. Despite different lines of treatment, the proteinuria and eGFR levels were not well controlled (Table 1).

Conclusions: Despite attempts to alter various therapeutic regimens, IgAN remained poorly controlled. These data highlight an unmet need for the development of more effective drugs to treat and mitigate disease progression.

Funding: Commercial Support - Novartis Pharma AG

Figure 1 Treatment strategies adopted by nephrologists between different line treatments

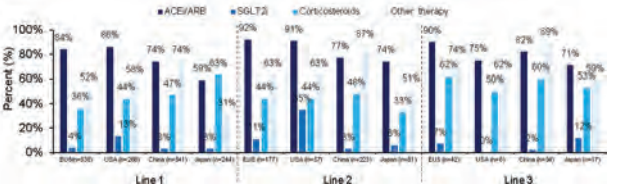


Figure 1 Treatment strategies adopted by nephrologists between different line treatments

Table 1 Mean Proteinuria and eGFR levels in patients with different line* treatments

	Number	*Levels of proteinuria* (g/day)	Number	*eGFR* (mL/min/1.73m²/year)
Line 1	430	2.1	402	85.1
Line 2	177	1.8	170	77.4
Line 3	75	1.8	73	71.8
Line 4	24	1.9	23	59.1
Line 5	6	1.4	6	43.3

*Line: A line change was determined by a change in treatment (add/stop/switch of a drug), defined by the nephrologists.

Table 1 Mean Proteinuria and eGFR levels in patients with different line* treatments

SA-PO901

Sparsentan as First-Line Treatment of Incident Patients with IgA Nephropathy: Preliminary Findings from the SPARTAN Trial

Chee Kay Cheung,[1] Colleen Burns,[2] Neeraj Dhaun,[3] Sian V. Griffin,[4] Alexandra L. Howson,[1] Radko Komers,[2] Alex Mercer,[5] Matthew Sayer,[3] Smeeta Sinha,[6] Lisa C. Willcocks,[7] Jonathan Barratt.[1] *[1]University of Leicester & Leicester General Hospital, Leicester, United Kingdom; [2]Travere Therapeutics Inc, San Diego, CA; [3]Royal Infirmary of Edinburgh, Edinburgh, United Kingdom; [4]University Hospital of Wales, Cardiff, United Kingdom; [5]JAMCO Pharma Consulting, Stockholm, Sweden; [6]Salford Royal Hospital Northern Care Alliance NHS Foundation Trust, Salford, United Kingdom; [7]Addenbrooke's Hospital, Cambridge University Hospitals, Cambridge, United Kingdom.*

Background: Sparsentan (SPAR) is a novel, non-immunosuppressive, single molecule Dual Endothelin Angiotensin Receptor Antagonist (DEARA) approved by the US FDA for treatment of adults with IgA nephropathy (IgAN). SPARTAN is an open-label, single-arm, multi-center, exploratory trial, investigating the safety and efficacy of SPAR as first-line therapy in newly diagnosed IgAN patients. We report preliminary findings.

Methods: Patients were aged ≥18 yrs with biopsy-proven IgAN diagnosed within 6 months before enrollment, proteinuria ≥0.5 g/d, and eGFR ≥30 ml/min/1.73m² at screening. No previous treatment with ACEis/ARBs within the past 12 months was permitted. Patients receive SPAR for 110 wks with 4-wk safety follow-up. In addition to safety monitoring, assessments include proteinuria, estimated and measured GFR, 24h ambulatory blood pressure (BP), and total body water assessment (TBW, bioimpedance). Renal and cardiac MRIs are performed at pre-defined time-points and repeat kidney biopsy at Wk 24.

Results: At data cutoff (4May2023) 6 patients had received ≥1 dose of SPAR with 12 wks follow-up. Mean (SD) age at enrolment was 42 (14) yrs (n=4 female). At baseline, median (IQR) proteinuria was 1.4 (0.6-2.0) g/d, mean (SD) eGFR 67 (27) ml/min/1.73m² and systolic/diastolic BP 122/80 (7/6) mmHg. **Table 1** and **Figure 1** summarize data over the first 12 wks. One patient discontinued due to hypotension.

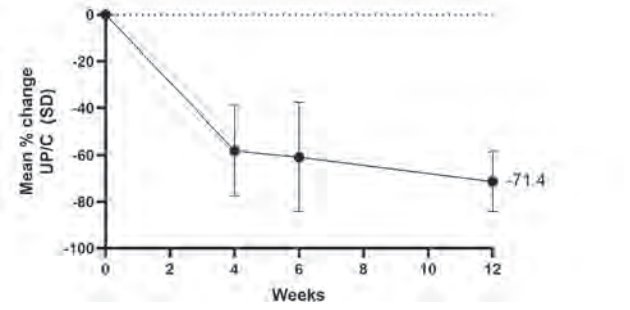
Conclusions: As first-line treatment in newly diagnosed IgAN patients, preliminary findings show SPAR was safe and generally well-tolerated and reduced proteinuria >70% over 12 wks, with reduced total body water over time.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table 1: Summary data over the first 12 wks (n=6)

	Baseline	Wk 2	Wk 4	Wk 6	Wk 12
Body weight, kg, mean (SD)	83 (29)	83 (29)	83 (29)	83 (29)	83 (29)
Total body water, l, mean (SD)	47 (4)	-	-	44 (10)	44 (9)
Achievement of complete remission of proteinuria (<0.3 g/d), n (%)	0 (0)	0 (0)	2 (33)	3 (50)	2 (33)

Figure 1: Mean percent change from baseline in proteinuria (urine protein-creatinine ratio on 24-hour collection) for patients on treatment over 12 wks



SA-PO902

Sparsentan and Sodium-Glucose Cotransporter 2 Inhibitors (SGLT2i) in the PROTECT Open-Label Extension (OLE) Substudy and SPARTACUS: Trials in Progress

Isabelle Ayoub,[1] Radko Komers,[2] Alex Mercer,[3] Priscila Preciado,[2] Sydney C. Tang,[4] Brad H. Rovin.[1] *[1]The Ohio State University Wexner Medical Center, Columbus, OH; [2]Travere Therapeutics Inc, San Diego, CA; [3]JAMCO Pharma Consulting, Stockholm, Sweden; [4]The University of Hong Kong, Queen Mary Hospital, Pok Fu Lam, Hong Kong.*

Background: Sparsentan (SPAR) is a nonimmunosuppressive, single-molecule, dual endothelin and angiotensin II receptor antagonist (DEARA). In the phase 3 PROTECT study, SPAR is compared to active control irbesartan in patients with immunoglobulin A nephropathy (IgAN). Subgroup analyses from the DAPA-CKD and EMPA-KIDNEY studies indicate SGLT2i reduce the risk of progression to kidney failure in patients with IgAN. The combination of SGLT2i and DEARA may provide therapeutic benefit due to potentially additive kidney protection. The double-blind period of PROTECT did not permit SGLT2i; however, an OLE substudy has been initiated which randomizes patients on stable SPAR to SGLT2i or no SGLT2i. The ongoing SPARTACUS study allows patients on stable SGLT2i to receive SPAR. These studies will evaluate the safety and effect of concomitant SPAR and SGLT2i in patients with IgAN.

Methods: The PROTECT OLE substudy is investigating the safety and effect of SGLT2i add-on with SPAR as compared to SPAR alone in patients with IgAN. SPARTACUS is a phase 2 study of SPAR safety and effect in IgAN patients on a stable dose of an SGLT2i. The **Figure** reports study designs and relevant inclusion criteria.

Results: The PROTECT OLE substudy and SPARTACUS safety and effect endpoints are reported in the **Table**, and results from these studies may be expected by late 2024 and early 2025, respectively.

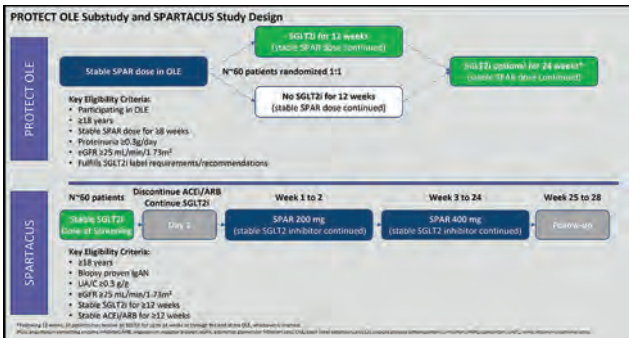
Conclusions: The PROTECT OLE substudy and SPARTACUS study will evaluate the safety and effect of concomitant SPAR and SGLT2i in patients with IgAN.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table. PROTECT OLE Substudy and SPARTACUS Endpoints

Endpoints	PROTECT OLE Substudy	SPARTACUS
Safety endpoints	TEAEs	TEAEs SAEs AEs leading to treatment discontinuation AEs of interest
Primary effect endpoints	Mean change from baseline in UP/C and UA/C at Week 12 Achievement of urinary protein excretion <0.3 g/day at Week 12 Change in absolute and percent change from baseline in eGFR at Week 12	Change from baseline in UA/C at Week 24
Secondary effect endpoint	-	Achievement of UA/C <0.2 g/g at Week 24

AE, adverse event; BP, blood pressure; eGFR, estimated glomerular filtration rate; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UA/C, urine albumin to creatinine ratio; UP/C, urine protein to creatinine ratio.



SA-PO903

Concomitant Sparsentan and Sodium-Glucose Cotransporter-2 Inhibitors (SGLT2i) in Patients with IgA Nephropathy (IgAN) in the PROTECT Open-Label Extension (OLE)

Laura Kooienga,[1] Robert Malecki,[2] Priscila Preciado,[3] Ping He,[3] Alex Mercer.[4] On Behalf of the DUPRO Steering Committee. *[1]Colorado Kidney Care, Denver, CO; [2]Nephrology Department of MSS, Warsaw, Poland; [3]Travere Therapeutics Inc, San Diego, CA; [4]JAMCO Pharma Consulting, Stockholm, Sweden.*

Background: Sparsentan (SPAR) is a non-immunosuppressive, single-molecule dual endothelin and angiotensin II receptor antagonist (DEARA). In the ongoing PROTECT trial SPAR is compared to irbesartan in patients with IgAN. SGLT2i may slow disease progression in IgAN as suggested in subgroup analyses from DAPA-CKD and EMPA-KIDNEY. Combined DEARA and SGLT2i therapy may provide additional kidney-protective effects with unknown adverse events. Concomitant treatment with SGLT2i was prohibited during the PROTECT double-blind period (DB); however, SGLT2i are allowed in the OLE. We report the early clinical experience of SGLT2i added to ongoing SPAR treatment in patients with IgAN enrolled in the PROTECT OLE.

Methods: Patients who completed the PROTECT DB and met eligibility criteria were enrolled in the PROTECT OLE. All patients received SPAR with a target dose of 400 mg/day. Investigators, at their discretion, could initiate concomitant SGLT2i treatment at any time during the OLE. Body weight, systolic and diastolic blood pressure, and urine protein/creatinine ratio (UP/C; based on 24-hour urine sample) were evaluated at baseline and at weeks 12, 24, and 36 after baseline. Baseline was defined as the OLE visit closest to SGLT2i start (ie, before or <14 days after). Treatment-emergent adverse events (TEAEs) were examined.

Results: At data cutoff, 21 patients (7 female) had received SPAR and add-on SGLT2i in the OLE. Mean (SD) age was 42 (11) years. Median (IQR) time from OLE start to SGLT2i start was 25 (11, 48) weeks. Summary data for selected variables are shown in **Table.** Eleven (52%) patients had TEAEs; most common were COVID-19, headache, hyperkalemia and hypotension in 2 patients (10%) each. Two patients discontinued SGLT2i and no patients discontinued SPAR.

Conclusions: Early clinical experience during the PROTECT OLE shows that SGLT2i added to a stable dose of SPAR appears to be generally well-tolerated. Data are consistent with an additive benefit on proteinuria. A randomized sub-study within the OLE is further investigating SPAR+SGLT2i combined treatment.

Funding: Commercial Support - Travere Therapeutics, Inc.

Table. Summary data for clinical variables at each timepoint during the PROTECT OLE

	Pre-SGLT2i Treatment Baseline[b] n=19	Week 12 n=18	Week 24 n=16	Week 36 n=12
Body weight, kg, mean (SD)	81.8 (19.47)	81.2 (18.68)	80.6 (20.03)	77.8 (18.95)
Systolic blood pressure, mmHg, mean (SD)	125.3 (11.89)	126.3 (13.43)	125.3 (13.71)	127.8 (17.75)
Diastolic blood pressure, mmHg, mean (SD)	82.4 (7.66)	83.3 (8.39)	81.8 (9.26)	82.1 (9.38)
UP/C, g/g, median (IQR)[a]	1.5 (1.1, 3.1)	1.1 (0.8, 2.7)	1.0 (0.6, 2.8)	0.9 (0.8, 2.9)

[a]UP/C n values = 21, 17, 14, and 8, respectively. [b]Baseline is before or <14 days after start of SGLT2i.

SA-PO904

Treatment Patterns and Outcomes in Crescentic IgA Nephropathy and Vasculitis

Manish K. Saha, Lauren N. Blazek, Duy Vu, Ronald Falk, George Terinte-Balcan, Susan L. Hogan, Vanessa Moreno, Vimal K. Derebail, Yichun Hu, Amy K. Mottl. *The University of North Carolina at Chapel Hill, Chapel Hill, NC.*

Background: Treatment patterns and consequent outcomes in crescentic IgA Nephropathy (IgAN-C) and IgA vasculitis (IgAV-C) are unknown.

Methods: We conducted a retrospective chart review of adults with biopsy proven IgAN-C/IgAV-C registered in the Glomerular Disease Collaborative Network from 1996 to 2018. Treatments were categorized as: IV cyclophosphamide (CYC) + steroids OR mycophenolate (MMF) + steroids, steroids alone or conservative therapy (CT). Minimal treatment included 2 months of CYC and 4 months of MMF or steroids. Azathioprine or MMF were used in all cases for maintenance treatment following CYC and MMF

induction therapy. MEST-C scoring was performed by a single nephropathologist. The composite kidney endpoint was a 40% decline in eGFR, ESKD or eGFR < 15ml/min/1.73m^2.

Results: The baseline demographics, clinical characteristics and endpoints are shown in Table 1. Median duration of follow-up was 46 months (95% CI 20-84) in the full cohort and was statistically similar across treatment groups (p=0.8). The only baseline difference between groups was in the severity of mesangial hypercellularity (MH) and crescentic involvement. MH was numerically lowest in the CT group and ≥25% crescents was numerically greatest in CYC group. The composite kidney endpoint was common, occurring in 60 (65%) of the total sample. Outcomes were similar across treatment groups, though there was a numerically lower risk for the composite kidney endpoint in the CYC group.

Conclusions: CYC may be superior for treatment of IgAN-C/IgAV-C. A randomized clinical trial is indicated to inform optimal therapy for this high-risk population.

Demographics and Clinical Characteristics	Cyclophosphamide (N=31) Median (95% CI)	Mycophenolate (N=15) Median (95% CI)	Steroids Alone (N=30) Median (95% CI)	Conservative Treatment (N=17) Median (95% CI)	p-value
Age, years	37 (27-55)	40 (26-42)	35 (27-55)	51 (22-65)	0.3
Female, N (%)	13(41.94%)	9(60%)	9(30%)	8(47.06%)	0.3
White race, N (%)	13(41.94%)	9(60%)	9(30%)	8(47.06%)	0.2
SBP, mmHg	132 (120, 140)	127 (121, 155)	133 (118, 149)	135 (118, 142)	0.9
DBP, mmHg	80 (68, 86)	90 (75, 86)	80 (77, 90)	79 (68, 84)	0.6
UPCR, g/g	3.3 (1.7, 5.2)	1.8 (1.2, 3.4)	1.5 (1.2, 4.0)	1.7 (1.4, 4.3)	0.4
eGFR, ml/min/1.73m^2	48 (27, 82)	69 (44, 89)	65 (36, 91)	61 (24, 102)	0.6
Rapid eGFR decline N (%)	13 (42%)	2 (13%)	9 (30%)	4 (24%)	0.2
MEST-C Scoring					
>50% Mesangial Hypercellularity, N (%)	16 (52%)	8 (53%)	13 (43%)	1 (6%)	0.006
Endocapillary Hypercellularity present, N (%)	25 (81%)	11 (73%)	24 (80%)	13 (76%)	0.9
Segmental Glomerulosclerosis present, N (%)	14 (82%)	4 (100%)	5 (83%)	1 (100%)	0.5
IFTA, N (%)					
26-50%	10 (32%)	1 (7%)	6 (20%)	6 (35%)	0.2
>50%	6 (19%)	1 (7%)	4 (13%)	1 (6%)	
≥25% Cellular or Fibrocellular Crescents, N (%)	13 (41.94%)	0 (0.00%)	5 (16.67%)	1 (5.88%)	0.007
Fibrinoid Necrosis present, N (%)	12 (40%)	1 (21%)	8 (30%)	3 (23%)	0.1
Clinical Endpoints					
eGFR slope, ml/min/1.73m^2/yr	0.5 (0.1, 1.5)	0.5 (-0.6, 0.9)	0.8 (0.1, 1.8)	-0.1 (-0.6, 1.7)	0.4
ESKD, N (%)	10 (32%)	2 (13%)	5 (17%)	4 (24%)	0.4
Death, N (%)	2 (6%)	0 (0%)	0 (0%)	3 (18%)	0.06
Composite kidney endpoint*, N (%)	14 (45%)	10 (67%)	22 (73%)	13 (76%)	0.1

Comparisons for continuous variables were made using Wilcoxon two-sample test and Fisher's exact test for categorical values; Composite kidney endpoint = 40% decline in eGFR, ESKD or eGFR < 15ml/min/1.73m^2

Table 1 Demographic features, laboratory characteristics, MEST-C score, and clinical endpoints among different treatment groups

SA-PO905

From Famine to Feast in IgA Nephropathy: New Treatments Present New Opportunities for Patients

Chris Dudzenski, Meghan Weiss, Stephen Regan. *Spherix Global Insights, Exton, PA.*

Background: As of only a few years ago, IgA nephropathy (IgAN), a common form of glomerulonephritis worldwide, had few treatment options beyond RAAS inhibitors and corticosteroids. The approval of SGLT2 inhibitors to treat non-diabetic CKD patients, along with accelerated approvals for targeted budesonide and sparsentan over the past three years have created new options. This analysis explores the evolution of IgAN treatment in the US.

Methods: Data from 1,359 patient charts were collected in partnership with 496 US nephrologists via HIPAA compliant online surveys annually from 2021 to 2023. Additionally, launch metrics have been collected on a monthly basis via an online survey of ~75 nephrologists each wave, beginning with the launch of targeted budesonide in February 2022.

Results: Audited chart data reveals US nephrologists are embracing new options, with exponential growth in the use of SGLT2is in IgAN patients (6% in 2021, 21% in 2022, and 43% in 2023) and steady growth in the adoption of newly approved agents. Correspondingly, as use of targeted budesonide grew from 2022 to 2023, corticosteroid use in IgAN patients dropped (14% in 2021 and 2022 to 7% in 2023). As of May 2023, 53% of US nephrologists reported they had prescribed targeted budesonide, having grown from 18% six months post-launch and 39% after 12 months on the market. In May 2023, after only a few months on the market, 87% of US nephrologists were aware of sparsentan's approval and 43% considered it an advance over other treatment options; a minority of physicians had written a prescription for the agent (21%). Sparsentan's REMs monitoring requirements may impact overall use as the product continues its launch. Despite newer options, 66% of nephrologists still perceive there to be a high unmet need for new IgAN treatments. The pipeline of potential disease-targeting mechanisms is robust, including complement inhibitors, anti-APRIL agents, and anti-BLyS agents. Notably, 68% of nephrologists believe the complement system plays an active role in the pathogenesis of IgAN as they seek non-immunosuppressive options that target the cause of the disease.

Conclusions: Within a short timeframe, nephrologists have gone from few treatment options for IgAN patients to having a more substantial arsenal. As more disease-targeting agents potentially come to market, care for IgAN patients is likely to continue to evolve.

SA-PO906

Low-Density Lipoprotein (LDL) Apheresis Removes Atherogenic Mediators in Focal Segmental Glomerulosclerosis

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Background: Focal Segmental Glomerulosclerosis (FSGS) is the most common cause of end stage kidney disease in adolescents. Lipid dysregulation causes cardiovascular morbidity and disease progression in FSGS. Unregulated lipoprotein associated phospholipase A2 (Lp-PLA2) activity causes increased oxidation of low-density lipoprotein (oxLDL) and production of inflammatory cytokines, leading to atherosclerosis and poor cardiovascular outcomes. However, this has not been explored in children with FSGS. We hypothesize that LDL apheresis can improve cardiovascular outcomes by removal of atherogenic mediators in patients with FSGS.

Methods: We enrolled 10 patients with FSGS from 4 centers (mean age 15.3 years, M/F: 6/4). Five patients had post-transplant FSGS recurrence. Patients received 12 LDL apheresis treatments via the Liposorber in addition to standard immune therapies. Atherogenic lipid metabolites (Lp-PLA2, oxLDL) and cytokines (TNFα, IL-6, IL-1β) were collected pre and post-treatment at set intervals and measured via ELISA. Proteinuria was measured by urine protein to creatinine ratio (UPC) and cystatin C GFR was monitored pre and at the completion of LDL apheresis treatment. Results expressed as mean±SEM.

Results: OxLDL was reduced from 94.7 ± 15.3 to 78.6 ± 11.4 u/L (p=0.019) at the completion of LDL apheresis. Lp-PLA2 showed a trend of reduction from 173.6 ± 36.8 to 117.9 ± 15.7 ng/mL (p=0.07). Interestingly, the mean baseline ox-LDL levels were significantly elevated, comparable to patients with extreme obesity. UPC was reduced from 10.3 ± 2.5 to 5.7 ± 1.8 mg/mg (p=0.005). Mean cystatin C GFR was 57mL/min at baseline and was unchanged over the study period.

Conclusions: We demonstrated that children and adolescents with FSGS have elevated levels OxLDL and Lp-PLA2, increasing the risk for long term atherogenesis and cardiovascular morbidity. We propose that monitoring and normalizing these lipid metabolites will promote cardiovascular health in patients with FSGS. LDL apheresis remains a safe and effective method of reducing oxLDL and Lp-PLA2 in patients with FSGS. This was accompanied by a significant reduction in proteinuria inducing disease remission. Larger studies are needed to further assess the effects of LDL apheresis and antilipidemic treatments on cardiovascular outcomes in this patient population.

Funding: Commercial Support - Kaneka Medical America LLC

SA-PO907

Obinutuzumab in Treatment-Resistant Primary Focal Segmental Glomerulosclerosis (FSGS): A Report of Four Cases

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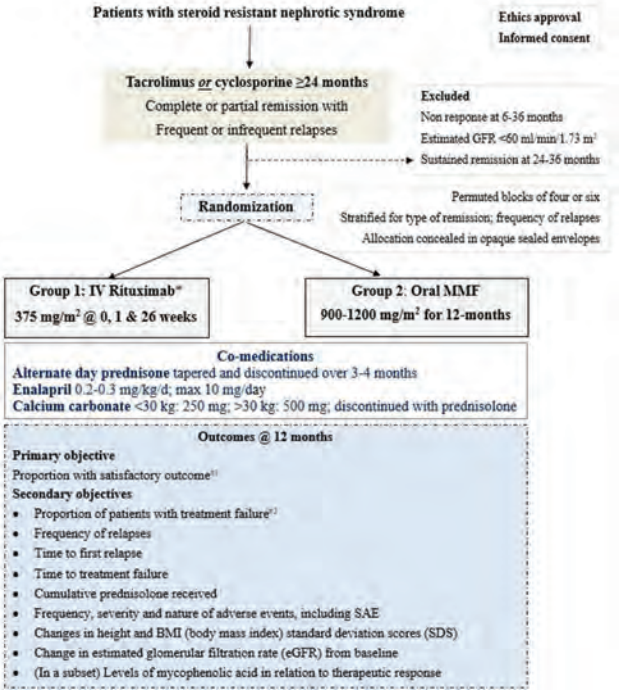
Background: There is no definite approach in treating patients with primary FSGS who fail to respond to immunosuppressive (IS) therapy including corticosteroids and calcineurin inhibitors. Other IS therapy such as rituximab (RTX), Acthar gel and mycophenolate have been use with sub-optimal response. Obinutuzumab is type II anti-CD20 monoclonal antibody that has been shown to be effective in treating patients who have been resistant to RTX in diseases such as ANCA associated vasculitis or membranous nephropathy.

Methods: We report 4 patients with treatment-resistant primary FSGS with negative genetic testing who were treated successfully with obinutuzumab. They were treated with an average of 4 other IS with sub-optimal response as shown in Table 1.

Results: The mean age was 48 years and 50% were males. The mean serum creatinine and mean serum albumin at the time of presentation was 2.2 mg/dL and 2.0 g/dL respectively. The mean proteinuria at the time of diagnosis and before initiation of obinutuzumab was 10.7 g/24 hours and 7.6 g/24 hours respectively. The mean proteinuria at 6 and 12 months after the infusion was 1.6 g/24 hours and 1.7 g/24 hours respectively. Mean serum albumin improved to a mean of 4.0 g/dL and 4.3 g/dL at 6 months and 12 months respectively. None of the patients experienced any adverse effects or infusion reactions. CD20+ B cells remained depleted over an average of 10.5 months.

Conclusions: We report 4 cases of treatment-resistant primary FSGS that were treated successfully with obinutuzumab infusions with 1 complete remission and 3 partial remissions. The efficacy of Obinutuzumab on treatment-resistant FSGS should be evaluated through a randomized clinical trial to determine short- and long-term outcomes and adverse effects.

Characteristics	Case 1	Case 2	Case 3	Case 4
Age	65	24	42	61
Sex	F	M	F	M
Initial Presentation				
Serum Creatinine (mg/dL)	1.27	4.1	0.56	3.1
Serum Albumin (g/dL)	1.4	1.5	2.5	2.9
Urine Protein (g/24 hours)	14	9.4	10.9	8.8
Initial Treatment	Prednisone, cyclosporine, Tacrolimus, mycophenolate mofetil, rituximab, ACTH gel	Prednisone, Cyclosporine, Tacrolimus, mycophenolate mofetil, rituximab	Prednisone, mycophenolate mofetil, Tacrolimus, rituximab	Prednisone, mycophenolate mofetil
Prior to Obinutuzumab				
Serum Creatinine (mg/dL)	1.33	1.7	1.7	1.24
Serum Albumin (g/dL)	3.5	3.6	3.0	2.5
Urine Protein (g/ 24 hours)	3	9.4	6.5	11.8
6 months after Initial Obinutuzumab Infusion				
Serum Creatinine (mg/dL)	2.01	1.3	1.03	1.26
Serum Albumin (g/dL)	3.8	4.6	3.6	4.3
Urine protein (g/ 24 hours)	1.6	2.2	2.6	0.33
12 months after Initial Obinutuzumab Infusion				
Serum Creatinine (mg/dL)	1.2	1.26	1.2	NA
Serum Albumin (g/dL)	4.0	4.9	4.0	NA
Urine protein (g/ 24 hours)	1.9	1.4	1.9	NA



SA-PO908

Intravenous Rituximab vs. Oral Mycophenolate Mofetil in Sustaining Remission in Calcineurin Inhibitor-Dependent Steroid-Resistant Nephrotic Syndrome: An Open-Label Randomized Controlled Trial

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Background: Retrospective unicenter studies in patients with steroid-resistant nephrotic syndrome (NS) show that switching of calcineurin inhibitors (CNI) to oral mycophenolate mofetil (MMF) or IV rituximab enables remission and is corticosteroid- and CNI-sparing, while avoiding therapy-associated adverse effects (AE). However, prospective controlled studies are lacking.

Methods: This open-label multicenter RCT will examine the superiority of IV rituximab *versus* oral MMF in maintaining satisfactory remission in patients with steroid-resistant NS who were in complete or partial remission while on therapy with tacrolimus or cyclosporine for over 2-yrs, but continued to show steroid-sensitive relapses. Eligible consenting patients with steroid-resistant NS, 1-18 yr-old, with complete or partial remission and steroid sensitive relapses while on ≥2-yr therapy with CNI, will be randomized to switch therapy to either oral MMF for 1-yr or IV rituximab (2 doses a week apart; 1 dose 6-months later). The primary outcome, on intention-to-treat analysis, will be the proportion of patients with satisfactory remission (sustained remission or infrequent relapses) at 1-yr (Fig. 1). Secondary outcomes are the proportions of patients with frequent relapses, steroid resistance & serious AE, incidence of relapses, prednisolone exposure, and changes in anthropometry & biochemistry (CTRI/2022/10/046890).

Results: The study began enrolment in October 2022 and will close enrolment in February 2025.

Conclusions: Findings from the study shall have important implications for guiding the choice of non-nephrotoxic therapies following induction and maintenance of remission with CNI for childhood idiopathic steroid-resistant NS.

Funding: Government Support - Non-U.S.

SA-PO909

Monthly Mini-Dose Rituximab for Primary Membranous Nephropathy: A Different Approach

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Background: The currently recommended dose of rituximab for primary membranous nephropathy is as high as that for lymphoma. This study assessed the efficacy of monthly 100 mg rituximab monotherapy in patients with primary membranous nephropathy.

Methods: This retrospective study included 32 patients with primary membranous nephropathy treated at Peking University Third Hospital between March 2019 and January 2023. All patients were anti-phospholipase A2 receptor (PLA2R) antibody-positive and received rituximab 100 mg intravenously monthly for at least 3 months without other immunosuppressive therapy.

Results: The baseline parameters included: proteinuria, 8.5±3.6 g/day; serum albumin, 24.8±3.4 g/L; and anti-PLA2R antibody, 160 (20-2659) RU/mL. B-cell depletion was achieved in 87.5% patients after the first dose of rituximab 100 mg and in 100% after the second equivalent dose. The median follow-up was 24 months (range 18-38). Twenty-seven (84%) patients achieved remission, with 11 (34%) patients achieving complete remission by last follow-up. The relapse-free survival from the last infusion was 13.5 months (range 3-27). Patients were stratified into the low-titer (<150 RU/mL, n=17) and high-titer groups (≥150 RU/mL, n=15) based on the anti-PLA2R titer. Sex, age, urinary proteins, serum albumin, and estimated glomerular filtration rate at baseline did not differ significantly between the two groups. At 18 months, compared to the low-titer group, the rituximab dose (960±387 vs 694±270 mg, p=0.030) was higher, while serum albumin (37.0±5.4 vs 41.3±5.4 g/L, p=0.033) and the complete remission rate (13% vs 53%, p=0.000) were lower in the high-titer group.

Conclusions: Monthly rituximab 100 mg appeared as a potential effective regimen for treating anti-PLA2R-associated primary membranous nephropathy with a low anti-PLA2R titer.

Funding: Government Support - Non-U.S.

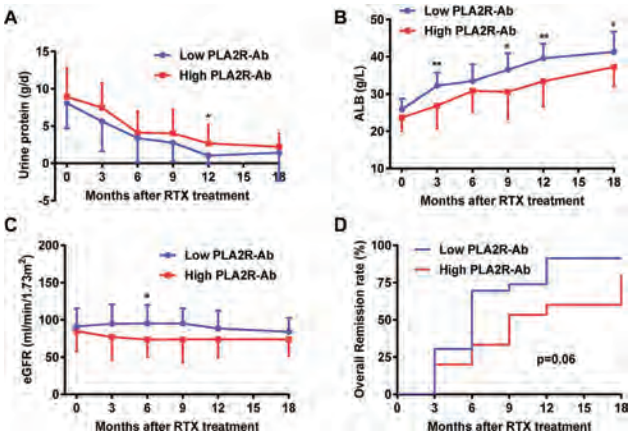

Figure 2. clinical data between different anti-PLA2R titer groups before and after monthly mini-dose rituximab treatment.

SA-PO910

Felzartamab Reduces aPLA2R Ab by Selectively Depleting CD38+ Plasma Cells and Plasmablasts, the Main Pathogenic Cellular Drivers of Disease in Primary Membranous Nephropathy (PMN)

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Background: Felzartamab (felza) is a fully human monoclonal antibody that binds to CD38 with high affinity and depletes CD38+ antibody-producing cells such as plasma cells/plasmablasts primarily via antibody-dependent cellular cytotoxicity & phagocytosis. In studies of high-risk PMN patients, felza substantially reduced aPLA2R with associated improvements in UPCR and serum albumin. To further characterize felza with respect to efficacy biomarkers and preservation of protective immunity, we analyzed samples collected prospectively during the M-PLACE (NCT04145440) and NewPLACE (NCT04733040) trials.

Methods: Serum and whole blood were collected pre/post- felza treatment in patients with aPLA2R+ PMN. Biomarker analyses were performed for aPLA2R (ELISA), total IgG (turbidimetry), anti-Tetanus Toxoid (TT) (ELISA), and B cell populations (flow cytometry).

Results: Felza reduced aPLA2R comparably in patients with baseline levels <150 and ≥150 RU/mL (Table 1). A dose-dependent effect on aPLA2R reduction at 6 months was observed across both M-PLACE (9 infusions) and NewPLACE (5 or 2 infusions). Depletion of detectable CD38+ plasmablasts was observed 1 wk after felza treatment. Treatment did not impact other B cell populations, as absolute counts of total, naïve, and memory B cells were unchanged. Total IgG decreased on treatment then recovered above baseline by end of study. Anti-TT titers decreased on treatment, however levels were maintained above the protective threshold (0.1 IU/mL).

Conclusions: Felza selectively depleted CD38+ plasmablasts and plasma cells, reducing pathogenic aPLA2R to a greater extent than protective anti-TT titers and total IgG, which was dose-dependent and durable. Treatment of PMN with Felza suggests an efficient and selective treatment concept with preservation of vaccine response compared to conventional immunosuppressive therapies.

Funding: Commercial Support - Human Immunology Biosciences Inc, MorphoSys AG

	Baseline Values			6 mo % Change from Baseline		
	Median	IQR	n	Median (% change)	IQR	n
aPLA2RAb (RU/mL)						
2 dose arm NewPLACE	200	(83, 211)	9	+15	(-29, 16)	9
5 dose arm NewPLACE	291	(114, 478)	6	-31	(-65, 23)	6
9 dose M-PLACE C1	182	(119, 262)	18	-67	(-85, -33)	15
<150 RU/mL	115	(77, 123)	7	-76	(-88, -66)	6
≥150 RU/mL	256	(210, 291)	11	-66	(-83, -21)	9
Immunoglobulins (M-PLACE C1)						
Total IgG (g/L)	5.1	(4.6, 6.5)	12	-20.6	(-26.7, -13.0)	12
Anti-TT (IU/mL)	0.4	(0.1, 1.1)	18	-4.1	(-30.3, 25.5)	17

Table 1. Median baseline values and % change in key biomarkers in M-Place and NewPlace trials

SA-PO911

Combined Rituximab and Cyclophosphamide Therapy in PLA2Rab-Associated Membranous Nephropathy (MN)

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Background: Optimal treatment of MN is debated: oral high-dose cyclophosphamide (CP) is effective (>90% immunological remission (IR)), but associated with toxicity. Rituximab (RTX) is less toxic, but also less effective (IR 65%). We evaluated the "McAdoo" treatment regimen (RTX 2*1000mg; CP 1.5mg/kg/day * 8weeks and prednisone (iv 2* 1gr + 3 weeks oral starting at 1mg/kg) in high risk MN. In this preliminary analysis, we evaluated PLA2Rab kinetics and immunological remission, a surrogate biomarker for later onset clinical remission.

Methods: We analysed data of incident patients with MN, at high risk for progression, treated according the prescribed protocol. aPLA2Rab levels were measured by ELISA in available samples collected at baseline (n=26), and 2 (n=18), 4 (n=20), 8 (n=20) and 12 (n=23) weeks after start of therapy.

Results: We included 26 patients (M/F 15/11, age 60 [47-68] years, Screatinine 128 µmol/l [102-136], Salbumin 18 g/l [14-21] and UPCR 7.1 gram/10 mmol [5.7-10.0]). Baseline PLA2Rab levels were 176 RU/ml [115-460]. Overall, there was a very fast decrease of PLA2Rab levels, with a decrease > 50% within 2 weeks in all but two patients. Within 8 weeks complete IR (ELISA < 2RU/ml) was 83 %. IR was associated with baseline PLA2Rab tertile (Table). The lower IR rate at 8weeks in patients in the highest tertile was not merely explained by the high baseline PLA2Rab levels, but more likely the consequence of a prolonged PLA2Rab half-life (Table). Most patients with high baseline PLA2Rab levels have received additional therapy (mostly RTX 2 gr).

Conclusions: Our study showed early and high immunological response rate in patients with PLA2Rab associated MN. The longer T1/2 in patients with very high PLA2Rab levels suggest immunological differences (increased B cell proliferation, presence of long-lived plasmacells). Assessment of PLA2Rab levels within 2-4 weeks after start of therapy may enable to identify patients who need more intensive therapy.

Tertiles of baseline PLA2Rab and outcome

PLA2Rab tertile	Low	Middle	High
PLA2Rab (RU/ml)	16-131	151-273	280-1500
IR after 8 weeks	100 %	100 %	43 %
PLA2Rab T1/2 > 7 days	0 %	0 %	71 %
Additional therapy	0 %	11 %	75 %

SA-PO912

Analysis of the Efficacy and Influencing Factors of Rituximab in the Treatment of Primary Membranous Nephropathy

Jiawei Cheng, Zhangzhe Peng. *Xiangya Hospital Central South University, Changsha, China.*

Background: Membrane nephropathy (MN) is the most common primary glomerular disease that causes adult nephrotic syndrome in the world. Primary membranous nephropathy (pMN) can progress to end-stage renal disease. Rituximab (RTX) has been listed as the first-line treatment for patients with medium and high risk pMN.

Methods: This study retrospectively analyzed 83 patients with pMN in XX Hospital who were confirmed by renal biopsy and received RTX treatment. According to the clinical outcome, the patients were divided into complete remission (CR), partial remission (PR) and no response (NR). CR, PR were considered effective in treatment while NR was considered ineffective in treatment. The baseline values of patients with different clinical outcomes were compared to explore the influencing factors that affect the efficacy of RTX in the treatment of pMN patients.

Results: After a follow-up of 10.66 (7.25, 16.46) months, 65.1% of those pMN patients achieved clinical remission, of which 27.7% had complete remission and 37.3% had partial remission. Patients with effective treatment (CR, PR) showed a significant decrease in urinary protein creatinine ratio after RTX treatment, while creatinine and eGFR remained stable. Patients with ineffective treatment (NR) showed no decrease in urinary protein creatinine ratio after RTX treatment, while creatinine significantly increased and eGFR significantly decreased. During follow-up, 9 patients (10.8%) experienced infection related adverse reactions. Multivariate Cox regression analysis showed that the combined use of glucocorticoids (p=0.027, HR=2.05), serum albumin (p=0.006, HR=1.10), and urinary light chain LAMBDA/KAPPA ratio (>0.622)(p=0.011, HR=0.33) were independent influencing factors on the effectiveness of RTX in treating pMN. Patients with lower serum albumin and higher urinary LAMBDA/KAPPA ratio may be more likely to have ineffective treatment, and the combined use of glucocorticoids may promote RTX induced disease remission.

Conclusions: RTX has a good therapeutic effect on pMN, which can reduce urinary protein and increase albumin in patients, maintain the stability of blood creatinine and eGFR, and have a low incidence of adverse reactions. The combined use of glucocorticoids, serum albumin and urinary LAMBDA/KAPPA ratio are independent factors affecting the effectiveness of RTX in the treatment of pMN.

Funding: Clinical Revenue Support

SA-PO913

Personalized and Standard Treatment of Rituximab in Primary Membranous Nephropathy: A Prospective Multi-Center Trial in the East Coastal Region of China

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Background: Guidelines recommend standard rituximab therapy (1000mg*2 or 375mg/m²*3-4) for patients with idiopathic membranous nephropathy (IMN) at high risk of progression to ESRD. This study assessed the safety and efficacy of B cell and anti-PLA2R antibody targeted low-dose rituximab therapy in patients with IMN.

Methods: In this prospective study, we compared the partial and complete remission, serious and non-serious events between the personalized treatment group and standardized protocols group. Patients were followed once every 2 months for 12 months. The primary outcome was a composite of complete or partial remission of proteinuria. In addition, laboratory indexes and safety were assessed.

Results: A total of 101 were available for statistical analysis out of 140 participants at inclusion. At 12 months, 34 out of 55 patients (61.8%) in the personalized group and 29 of 46 (63.04%) in the standardized group had complete or partial remission. Kaplan–Meier curves indicated no difference for the cumulative incidence of participants with IMN who progressed to the end point according to the two arms (Figure 2). The median (quartile) of total RTX dose at one year was 700 (600,1100) mg per patient with a total cost of RMB (yuan) 18786 (17388, 24378) per unit utility in the personalized group, which was markedly lower than that in the standardized group. Anti-PLA2R autoantibody depletion 6 months post-treatment could predict a higher probability of remission. There were statistically significant differences in the frequency of adverse events between groups (P=0.02).

Conclusions: B cell and anti-PLA2R antibody targeted rituximab therapy was as effective as standard protocols. It was a more economical and safer strategy for IMN patients.

Funding: Government Support - Non-U.S.

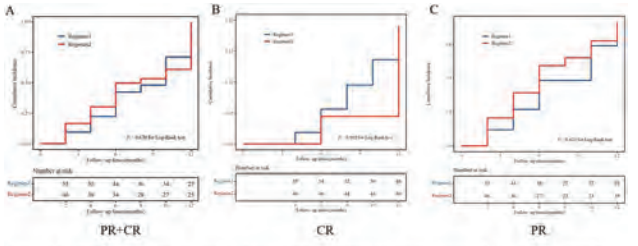

Figure 2. Kaplan–Meier curves for the cumulative incidence of participants with primary MN who progressed to the combined end point of complete or partial remission according to treatment with the B cell and anti-PLA2R antibody–driven regimen or standard regimen.

SA-PO914

Impact of Time to Treatment on Outcomes in Primary Membranous Nephropathy

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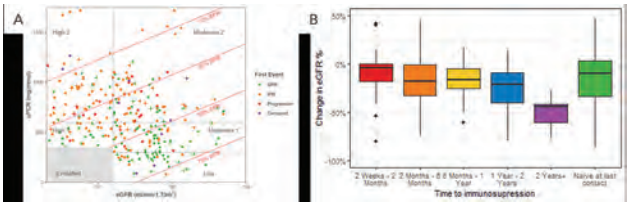
Background: Despite treatment, progression of renal dysfunction remains a significant burden globally in patients with primary MN (pMN). Clinicians use individualized risk assessment to choose immunosuppression therapy after '*watchful wait*' to help avoid side-effects in those who could otherwise have achieved remission spontaneously. Here we describe features of renal disease during the *'watchful wait'* period and its association with longer term outcomes.

Methods: Retrospective longitudinal cohort study of patients with pMN (biopsy-proven or positive serology in the absence of secondary causes). Data collected from three specialist centres in the North of England, with patients presenting as proteinuric kidney disease from Jan 2003 to July 2019, with follow-up data to Sept 2021. Risk markers included uPCR, eGFR and baseline demographic factors. Primary outcomes were CKD5 and Partial Remission (PR). Secondary outcomes were Progression (composite of doubling of creatinine, CKD5, and death). Analysis investigated the change in eGFR based on risk categorisation. Cox proportional hazard models were used to assess the association of outcomes with risk markers.

Results: 312 patients were included. Using eGFR and uPCR, patients in the low and moderate risk groups were more likely to achieve spontaneous PR (Fig 1A). The strongest predictor of renal outcome was eGFR at the start of immunosuppression (IS), irrespective of baseline function, and the longer patients waited to start treatment, the worse the renal decline (Fig 1B).

Conclusions: Combined eGFR and uPCR can be used to predict patients who are more likely to attain SR and that in patients who require IS, the longer it takes to initiate treatment, the worse their renal outcomes. This has significant implications for future guidelines in the management of pMN.



A) eGFR & uPCR at baseline and first key outcome B) Percent change in eGFR between baseline and start of IS **Low:***uPCR<350 & eGFR>60*; **Mod 1:***350≤uPCR<600 & eGFR>60*; **Mod 2:***uPCR≥600 & eGFR≥60*; **High 1:***300≤uPCR<600 & eGFR<60*; **High 2:**uPCR≥600 & eGFR<60; **SPR:** *Spontaneous PR;* **IPR:** *PR with IS; uPCR - mg/mmol; eGFR - ml/min*

SA-PO915

Anticoagulation Thromboprophylaxis Is More Effective than Antiplatelet Thromboprophylaxis for Individuals with High-Risk Membranous Nephropathy

Ayman Al Jurdi,[1] Christopher El Mouhayyar,[1] Karim Yatim,[1] Orhan Efe,[1] Saif A. Muhsin,[2] Leonardo V. Riella,[1] Reza Zonozi,[1] Karen A. Laliberte,[1] John Niles,[1] Anushya Jeyabalan.[1] *[1]Massachusetts General Hospital, Boston, MA; [2]Brigham and Women's Hospital, Boston, MA.*

Background: Data on the use of apixaban and antiplatelet therapies for thromboprophylaxis in MN are limited.

Methods: We conducted a multicenter retrospective cohort study of all individuals with high-risk MN, defined as having a serum albumin nadir < 2.5 g/dL in the setting of nephrotic-range proteinuria. The primary outcome was the incidence of thrombotic events within 12 months, stratified by thromboprophylaxis strategy.

Results: 66 individuals met the study's inclusion criteria. Median serum creatinine was 1.2 mg/dL (IQR 0.9-1.5), median UPCR was 12.2 g/g (IQR 8.5-16.6), and mean nadir serum albumin level was 1.9 ± 0.4 g/dL. 23 (35%) received no thromboprophylaxis, 20 (30%) received antiplatelet [AP] prophylaxis, and 23 (35%) received anticoagulant [AC] prophylaxis. Thrombotic events occurred in 11 subjects (17%): 1 in the AC group, 4 in the AP group, and 6 in the no prophylaxis group. No thrombotic events occurred in individuals who received apixaban (n = 11), while one individual in the warfarin group (n = 7) developed a recurrent ischemic stroke. The incidence of thrombotic events was lower in the AC group compared to both AP and no prophylaxis groups (log-rank P = 0.041, Fig 1A). In individuals with anti-PLA2R antibody-associated MN, higher anti-PLA2R antibody levels were associated with a higher risk of thrombotic events (Fig 1B) at various levels of serum albumin (Fig 1C). Three subjects had significant bleeding events, 1 in the AP group and 2 in the AC group.

Conclusions: AC prophylaxis, including apixaban, is associated with a lower risk of thrombotic events compared to AP or no prophylaxis in individuals with high-risk MN.

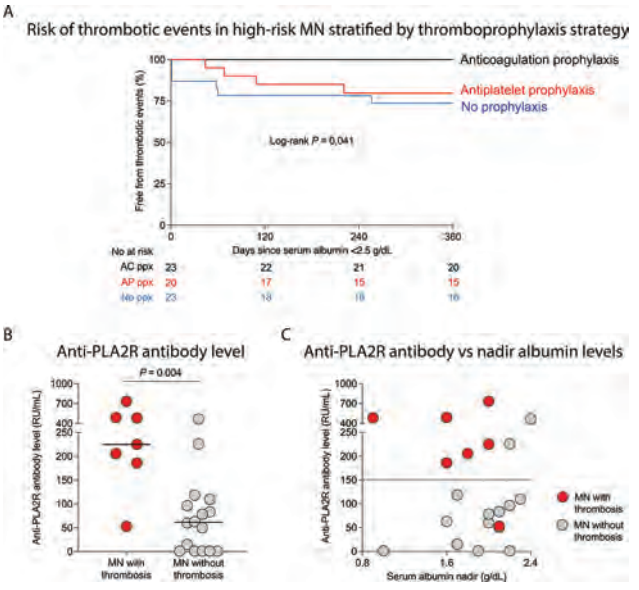


Figure 1. Thrombotic risk in individuals with high-risk Membranous nephropathy (MN).

Treatment status at time of survey	All (n=385)	EU5 (n=189)	US (n=100)	CN (n=60)	IP (n=36)
Currently treated for C3G	321 (83%)	161 (85%)	79 (79%)	53 (88%)	28 (78%)
Not currently treated for C3G, but they have been in the past	34 (9%)	15 (8%)	11 (11%)	2 (3%)	6 (17%)
Have never received treatment for their C3G	30 (8%)	13 (7%)	10 (10%)	5 (8%)	2 (6%)
Treatment of all patients receiving treatment at time of survey	**All (n=321)**	**EU5 (n=161)**	**US (n=79)**	**CN (n=53)**	**IP (n=28)**
ACEi and/or ARB	226 (70%)	116 (72%)	49 (62%)	42 (79%)	19 (68%)
ARB	118 (37%)	46 (29%)	22 (28%)	31 (58%)	19 (68%)
ACE inhibitor	115 (36%)	75 (47%)	27 (34%)	13 (25%)	0 (0%)
Immunosuppressant	250 (78%)	126 (78%)	67 (85%)	39 (74%)	18 (64%)
Corticosteroid	156 (49%)	71 (44%)	38 (48%)	29 (55%)	18 (64%)
Non-steroidal immunosuppressants	111 (35%)	65 (40%)	26 (33%)	14 (26%)	6 (21%)
Mycophenolate mofetil/ mycophenolate sodium	87 (27%)	55 (34%)	23 (29%)	5 (9%)	4 (14%)
Biologics (Eculizumab, Ravulizumab & Rituximab)	97 (30%)	52 (32%)	30 (38%)	14 (26%)	1 (4%)
Eculizumab	54 (17%)	35 (22%)	13 (16%)	6 (11%)	0 (0%)
Time between diagnosis and treatment initiation (Days)	**All (n=291)**	**EU5 (n=152)**	**US (n=61)**	**CN (n=52)**	**IP (n=26)**
Median	1.0	2.5	5.0	0.0	30.0
Proteinuria at time of survey	**All (n=281)**	**EU5 (n=149)**	**US (n=60)**	**CN (n=48)**	**IP (n=24)**
≥ 1 g/24hr	178 (63%)	98 (66%)	40 (67%)	32 (67%)	8 (33%)
Mean (standard deviation)	2.0 (2.5)	2.2 (2.8)	1.9 (2.0)	2.2 (2.5)	0.6 (0.7)
Median	1.3	1.4	1.4	1.3	0.0

Table 1: Current therapy and proteinuria levels by region

SA-PO916

C3 Glomerulopathy Current Treatment Options and Real-World Management: Results from a Multi-Country Study

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G is associated with a high risk of disease progression, approximately 50% of patients reach kidney failure within 10 years of diagnosis. KDIGO guidelines recommend treating with renin-angiotensin-aldosterone system inhibitors (RAASi) and in some patients, corticosteroids (CS) or mycophenolate mofetil (MMF), or eculizumab. This analysis aimed to better understand the treatment of C3G in the US, Europe, and Asia.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a real-world cross-sectional survey of C3G-treating nephrologists in US, France, Germany, Italy, Spain, UK (EU5), China and Japan from August 2022 to April 2023. Nephrologists completed forms via online links for consecutive patients presenting with C3G. Forms included patients' demographics, clinical characteristics and C3G treatments.

Results: 111 nephrologists completed records for 385 C3G patients (US 100, EU5 189, China 60, Japan 36). 321 (83%) patients were receiving treatment at time of survey. Of these, median patient age was 41 years, and 60% were male. Median proteinuria was 1.3 g/day. 63% of patients had proteinuria ≥1 g/day (Table 1). 70% were receiving RAASi, 49% CS, 27% MMF, and 30% biologics.

Conclusions: C3G is a rapidly progressing disease with no approved therapy. Most patients in this study were treated with both conventional immunosuppressants and biologics frequently added to RAASi. Despite this, proteinuria remained high, in most patients ≥1 g/day. This highlights the need for targeted therapies to treat the root cause of C3G.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO917

Change in GFR and UPC (Urinary Protein:Creatinine Ratio) Before and After Eculizumab in C3 Glomerulopathy

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Background: C3 Glomerulopathy (C3G) is an ultra-rare kidney disease characterized by alternative complement pathway dysregulation. Most patients reach end-stage renal disease (ESRD) within 10 years of diagnosis. The complement inhibitor, eculizumab, has been used to treat C3G with mixed results. In this study, we compared differences in GFR and UPC trends in a cohort of C3G patients before and after eculizumab treatment.

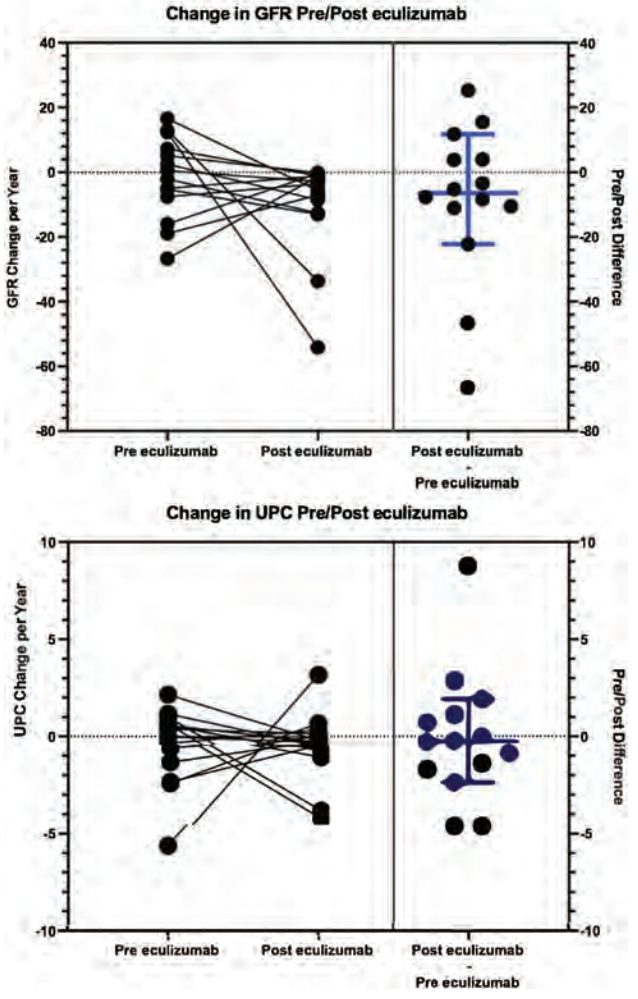
Methods: 14 patients from the University of Iowa's C3G Natural History Study were included in the cohort. Inclusion criteria: baseline native biopsy diagnosis of C3G and ≥1 year of clinical data (C3, GFR, UPC) prior to and after starting eculizumab. Exclusion criteria: teatment with other complement inhibitors, dialysis, and kidney transplant. Simple linear regression of the change in GFR and UPC before and after eculizumab initiation was measured. Paired t-test with p values were used to evaluate the significance of GFR and UPC change pre/post treatment; $p < 0.05$.

Results: GFR changes per year pre/post eculizumab were insignificant ($p = 0.201$). Trends showed a pattern of GFR decline with a median difference from pre- to post-eculizumab of -6.47. UPC change per year was also not significant ($p = 0.981$). General patterns showed improvement with a median difference in UPC change per year pre/post eculizumab of -0.26.

Conclusions: Most patients showed no significant change in disease trajectory with eculizumab therapy. There was a general trend towards worsening kidney function following eculizumab, though with a slight decrease in UPC. Limitations include sample size and gross slope estimation with only simple linear regression. Future directions include examining the baseline C3G histology, complement biomarkers, and other clinical markers to determine if outcome may be predicted.

Funding: NIDDK Support, Private Foundation Support

Figure 1: Change in GFR and UPC Pre/Post eculizumab



SA-PO918

CPV-104, a Recombinant Variant of Human Complement Factor H Produced in Moss, to Be Studied in a Phase 1/2 Clinical Trial in Patients with C3 Glomerulopathy (C3G)

Karin Heidenreich,[1] Björn Cochlovius,[1] Martin Bauer,[1] Andreas Busch,[1] Paulina Dabrowska-Schlepp,[1] Andreas Schaaf,[1] Fabienne C. Zeitter,[1] Karsten Häffner,[2] Joerg Koehl,[3] Tilman Schmidt,[6] Thorsten Wiech,[4] Peter F. Zipfel.[5] Eleva Clinical Trial Group. *[1]eleva GmbH, Freiburg, Germany; [2]Albert-Ludwigs-Universitat Freiburg Medizinische Fakultat, Freiburg, Germany; [3]Universitat zu Lubeck Sektion Medizin, Lubeck, Germany; [4]University Hospital Hamburg, Hamburg, Germany; [5]Leibniz-Institute for Natural Product Research and Infection Biology, Jena, Germany; [6]Universitat Greifswald, Greifswald, Germany*.

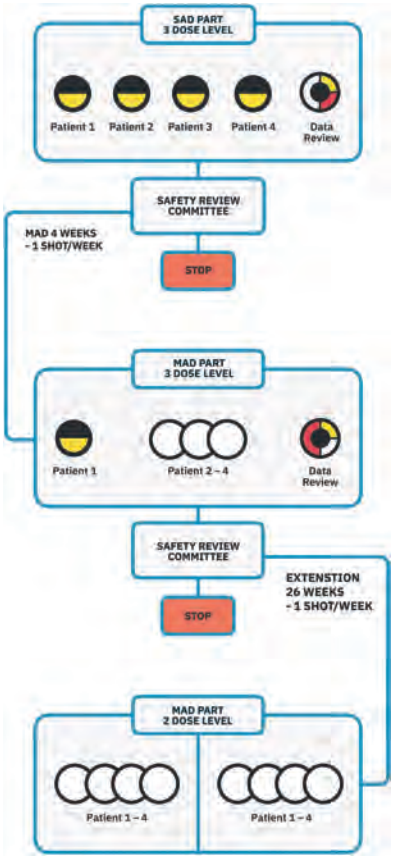
Background: Human complement factor H (CFH) is the main regulator of the alternative pathway (AP). CFH deficiency is associated with several complement-mediated diseases, such as C3 Glomerulopathy (C3G) or atypical hemolytic uremic syndrome (aHUS). C3G is caused by an uncontrolled overactivation of AP in fluid phase and on cell surfaces with overlapping clinical and pathophysiological features. AP dysregulation leads to predominant C3 fragment deposition within the glomeruli. C3G appears with proteinuria, microhematuria, acute kidney injury, and chronic kidney failure. About 50% of patients develop end-stage renal disease within 10 years. Recurrence of C3G after kidney transplantation is common. Currently there is no established disease-modifying treatment available. CPV-104 is produced in the suspension culture of moss *Physcomitrium patens* in 500L single-use bioreactors.

Methods: The current clinical program aims to develop CPV-104 for treatment of C3G.

Results: Preclinical in vivo (FH (-/-) knockout mice) and in vitro studies with CPV-104 demonstrated comparable or superior efficacy to that achieved with serum-derived CFH.

Conclusions: CPV-104 is a promising candidate for the 1st disease modifying treatment option in C3G. In preclinical studies CPV-104 demonstrated a strong potential to rebalance the dysregulated complement pathway, simultaneously maintaining its natural defense potential against infectious agents and pathogens. Following successful phase 1 and a proof-of-concept clinical trial in C3G, CPV-104 may also become a new treatment option for a broader spectrum of complement mediated diseases.

Funding: Commercial Support - eleva GmbH



Clinical Trial Design

SA-PO919

Outcome of Kidney Transplantation in Atypical Hemolytic Uremic Syndrome (aHUS): Eculizumab Prophylaxis vs. Rescue Therapy

Caroline Duineveld,[1] Emily Glover,[2] Romy N. Bouwmeester,[1] Nicole Van De Kar,[1] David Kavanagh,[2] Jack F. Wetzels,[1] Neil S. Sheerin.[2] *[1]Radboudumc, Nijmegen, Netherlands; [2]Newcastle Upon Tyne Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom*.

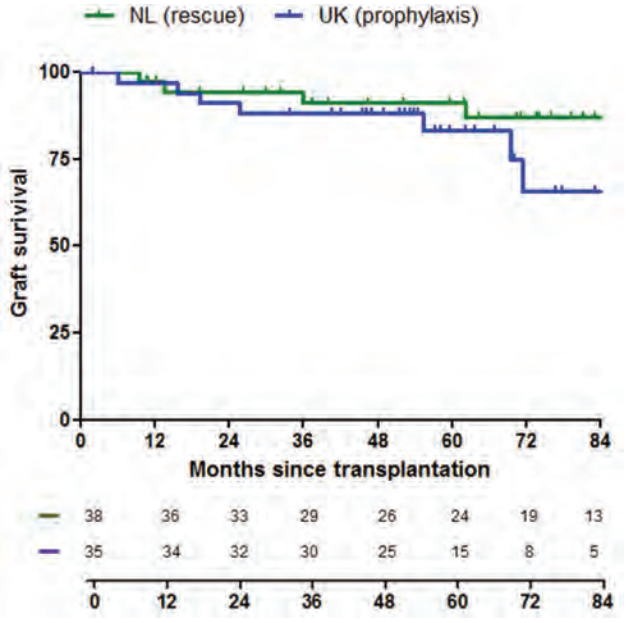
Background: Prophylactic eculizumab therapy is advised in aHUS kidney transplant recipients in view of high risk of recurrence. However, historical recurrence rates may be overrated and early start of eculizumab therapy at relapse ("rescue") may prevent graft loss. The efficacy, safety, and costs of different treatment strategies have not been compared in RCT's. We performed a comparative cohort study, including patients from a previously described Dutch cohort (NL) treated with eculizumab rescue therapy [PMID 37069997] and a UK aHUS cohort using eculizumab prophylaxis [PMID 36413152].

Methods: NL: we selected all adult aHUS patients who received a kidney transplantation between 2010-2021 in the Radboudumc (n=30) and enriched this cohort with 8 patients who received rescue therapy in other centers. UK: all adult aHUS patients transplanted between 2013 and 2017 were included.

Results: We included 38 NL patients (29 F, median age 45y, range 22-68) and 35 UK patients (24 F, median age 42y, range 17-64). Overall characteristics were comparable, although the UK cohort included more patients with a mutation in CFH SCR 20 / hybrid gene (31% versus 5%; $p<0.01$), whereas NL patients more often received a living donor kidney (66% versus 20%; $p<0.001$). The majority of the NL patients (74%) was transplanted using low dose tacrolimus (TAC). Eighteen (47%) NL patients were treated with eculizumab rescue therapy. Follow-up was comparable, NL 70.8m (range 10-134), and UK 55.4m (range 2-95). There were no significant differences in death-censored graft survival between the two cohorts (Figure).

Conclusions: Eculizumab rescue therapy was not inferior to eculizumab prophylaxis with respect to death-censored graft survival. **Limitation**: this conclusion holds for use of rescue therapy in a population characterized by low prevalence of "very high risk" genes, low TAC levels, and predominant use of living donor kidneys.

Funding: Commercial Support - This work was supported by research grants from the Dutch Board of Health Insurance Companies (Zorgverzekeraars Nederland)., Government Support - Non-U.S.



SA-PO920

Ravulizumab Is Associated with Positive Clinical and Quality-of-Life Outcomes in Patients with Atypical Hemolytic Uremic Syndrome in a Real-World Setting

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Background: Ravulizumab (RAV) is a complement C5 inhibitor first approved in 2019 for the treatment of atypical hemolytic uremic syndrome (aHUS), a rare disease characterized by hemolytic anemia, thrombocytopenia and organ damage. This study assessed real-world clinical and quality of life (QoL) outcomes in patients with aHUS treated with RAV.

Methods: Data were drawn from the Adelphi aHUS Disease Specific Programme™, a cross-sectional survey of physicians reporting on their consulting patients with aHUS (data collected August–December 2022). This analysis included physician-reported, patient data from Germany, Italy, Spain, the UK, and the USA. Patients included had physician-diagnosed aHUS and were treated with RAV at time of survey.

Results: Overall, 65 patients were included: 31 had switched from eculizumab (ECU; switch cohort) and 34 had not received ECU before RAV initiation (naive cohort). Median (range) age at time of survey was 34 (15–75) and 39 (14–66) years in the switch and naive cohorts, respectively; 10% (n = 29) and 16% (n = 32) had family history of kidney disease. For switch and naive cohorts, respectively, median (interquartile range) time from aHUS diagnosis was 531 (233–1043) and 257 (152–456) days and RAV treatment duration was 163 (93–293) and 201 (106–476) days; prior ECU treatment duration was 150 (62–440) days (switch cohort only; n = 24). Two patients (6%) in the switch cohort had had a kidney transplantation before switching. Clinical outcomes are shown in the **Table**. Physician-reported overall QoL was rated 'good' to 'excellent' in 97% (overall physical/mental health: 97%/93%) and 82% (overall physical/mental health: 82%/85%) of patients in the switch and naive cohorts, respectively.

Conclusions: After initiation of RAV, the majority of patients had better clinical outcomes (compared with before RAV initiation) and a favorable QoL.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease. The DSP is an Adelphi Real World product. Alexion were a subscriber to the DSP and did not influence the original survey through either contribution to the design of questionnaires or data collection.

Clinical outcomes	Switch cohort (n = 31)	Naive cohort (n = 34)
Patients undergoing dialysis, n (%)		
Before RAV	5 (16)	8 (24)
Most recent/at time of survey	1 (3)	1 (3)
Platelet counts, n		
Patients with counts within normal range ($150x10^9$–$400x10^9$ cells/L), n (%)	23	27
Before RAV	10 (44)	3 (11)
Most recent/at time of survey	16 (70)	11 (41)
Lactate dehydrogenase levels, n		
Patients with levels below 1.5x upper limit of normal range, n (%)	11	17
Before RAV	6 (55)	4 (24)
Most recent/at time of survey	11 (100)	11 (65)
Serum creatinine levels, n	19	17
Serum creatinine, mean, mg/dL		
Before RAV	2.1	3.4
Most recent/at time of survey	1.5	1.7

SA-PO921

Treatment Satisfaction with Ravulizumab in Patients with Atypical Hemolytic Uremic Syndrome in a Real-World Setting

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Background: Atypical hemolytic uremic syndrome (aHUS) is a rare disease characterized by hemolytic anemia, thrombocytopenia, and organ damage. Ravulizumab (RAV) is a complement C5 inhibitor approved for the treatment of aHUS in 2019. Our study assessed real-world RAV treatment satisfaction.

Methods: Data were drawn from the Adelphi aHUS Disease Specific Programme™, a cross-sectional survey of physicians and their patients with aHUS (Aug–Dec 2022) in Europe and the USA. Physicians reported broad attitudinal data and demographics, treatment history, and treatment satisfaction for their patients with aHUS. Patients could report their treatment satisfaction in a separate survey.

Results: Overall, 53 physicians who completed the survey had experience with RAV (EU5 [58%], USA [42%]), most were nephrologists (53%) practicing in urban areas/major city centers (66%) with a median of 11 (range: 1–22) years of experience treating patients with aHUS. Of the surveyed physicians, 87% were 'completely satisfied' or 'satisfied' with RAV; no physicians were 'dissatisfied' or 'completely dissatisfied'. In total, 65 patients currently treated with RAV were included: 31 switched from eculizumab (ECU; switch cohort) and 34 did not receive ECU prior to RAV initiation (naive cohort). In the switch and naive cohorts, respectively, median RAV treatment duration was 163 (interquartile range: 93–293) and 201 (106–476) days; and time since aHUS diagnosis was 531 (233–1043) and 257 (152–456) days. Data from patient records showed high physician satisfaction with RAV (**Table**). In 84% of patients in the switch cohort, physicians reported higher satisfaction with RAV vs ECU (n=26; top reasons were fewer infusions required [92%] and less burdensome to patient/caregiver [54%]); no physicians reported higher satisfaction with ECU. From the patient survey, RAV satisfaction was 100% (switch cohort; n=8) and 83% (naive cohort; n=11).

Conclusions: There was concordance in high satisfaction with RAV between physicians and patients, regardless of prior ECU treatment. No dissatisfaction with RAV was reported.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease. The Disease Specific ProgrammeTM is an Adelphi Real World product. Alexion was a subscriber to the Disease Specific ProgrammeTM and did not influence the original survey through either contribution to the design of questionnaires or data collection.

	Switch cohort (n=30) [a]	Naive cohort (n=34)
Physician satisfaction with RAV from patient records [b], n (%)		
'Completely satisfied'	10 (33)	13 (38)
'Satisfied'	19 (63)	19 (56)
'Neither satisfied or dissatisfied'	1 (3)	2 (6)
'Dissatisfied'	0	0
'Completely dissatisfied'	0	0

[a] n=1 patient excluded as RAV initiation was on the same day as the survey; [b] Physycians were asked to rate their satisfaction with RAV regarding the treatment of specific patients with aHUS based on patient records.

SA-PO922

Characteristics and Outcomes of Patients with Atypical Hemolytic Uremic Syndrome Switching to Ravulizumab from Eculizumab: A Global Registry Analysis

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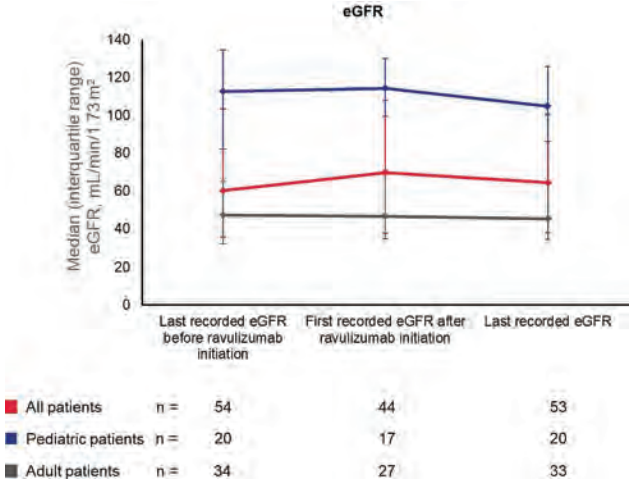
Background: There are currently no real-world cohort data on clinical characteristics and outcomes in patients with atypical hemolytic uremic syndrome (aHUS) who switched to ravulizumab (RAV) from eculizumab (ECU). This study aimed to address this need.

Methods: This was a post-marketing, observational, non-interventional, multinational registry study of patients diagnosed with aHUS who switched to RAV from ECU up to 27-Mar-23 (NCT01522183).

Results: Overall, 60 patients (24 pediatric) were included from Germany (45%), UK (18%), USA (18%), Denmark (10%), Spain (5%), and Israel (3%). Median (range) age at RAV initiation was 34 (2–72) years and 70% of patients were female. Overall, 58% of patients had a pathogenic variant or anti-complement factor H antibodies. Median (range) time on treatment was 21 (2–40) months for RAV and 62 (11–155) months for ECU. No new events of dialysis, kidney transplant, or thrombotic microangiopathy (TMA) relapse were reported during RAV treatment. Estimated glomerular filtration rates (eGFR) remained stable during the evaluation period (**Figure**).

Conclusions: Switching to RAV from ECU resulted in sustained maintenance of kidney function without evidence of new events of dialysis, kidney transplant, or TMA relapse over the median treatment period of 21 months. These results support the real-world effectiveness of RAV in patients with aHUS who switched from ECU.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease, Boston, MA, USA.



SA-PO923

Efficacy of 12-Week Pegcetacoplan in Kidney Transplant Recipients with Recurrent C3 Glomerulopathy (C3G) or Immune Complex Membranoproliferative Glomerulonephritis (IC-MPGN)

Andrew S. Bomback,[1] Erica Daina,[2] John Kanellis,[3] David Kavanagh,[4] Matthew C. Pickering,[5] Gere Sunder-Plassmann,[6] Patrick D. Walker,[7] Zhongshen Wang,[8] Zurish Ahmad,[8] Fadi Fakhouri.[9] *[1]Columbia University Irving Medical Center, New York, NY; [2]Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy; [3]Monash Medical Centre Clayton, Clayton, VIC, Australia; [4]National Renal Complement Therapeutics Centre, Newcastle University, Newcastle upon Tyne, United Kingdom; [5]Imperial College London, London, United Kingdom; [6]Medizinische Universitat Wien, Wien, Austria; [7]Arkana Laboratories, Little Rock, AR; [8]Apellis Pharmaceuticals Inc, Waltham, MA; [9]Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.*

Background: Pegcetacoplan (PEG; C3 inhibitor) may prevent C3G or IC-MPGN progression. NOBLE (NCT04572854) is the first prospective randomized controlled trial of PEG vs standard of care (SOC) in kidney transplant recipients (KTRs) with primary C3G or IC-MPGN recurrence.

Methods: Adult patients (pts) were randomized 3:1 to subcutaneous PEG 1080 mg twice weekly plus SOC (n=10) or SOC only (n=3). Primary endpoint: reduction in renal biopsy C3c staining (≥2 orders of magnitude [OOM]) from baseline to Week 12 (W12). Additional W12 endpoints: changes in eGFR, uPCR, C3G activity score, serum C3, and serum sC5b-9.

Results: 9 (69.2%) pts had C3G and 4 (30.8%) had IC-MPGN. At W12, 5 (50%) PEG pts had ≥2 OOM reduction in C3c staining (4 had 0 intensity); 8 (80%) had ≥1 OOM reduction (**Figure**). 9 (90%) PEG pts had reduced C3G activity score at W12. In subgroup (≥1000 mg/g), uPCR decreased with PEG (–39.2%) at W12. eGFR remained stable, serum C3 increased, and sC5b-9 decreased with PEG (**Table**). There were no discontinuations/deaths due to treatment-emergent adverse events.

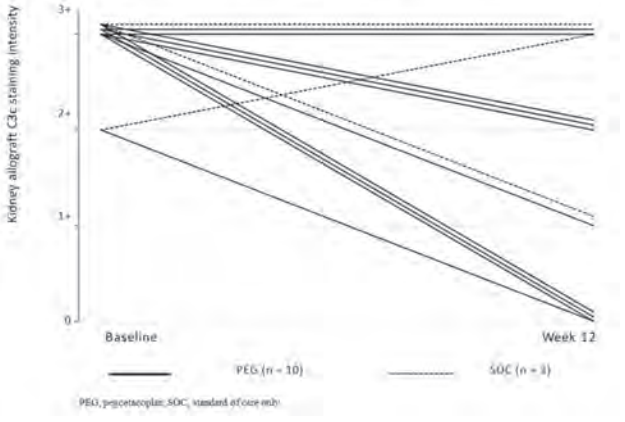
Conclusions: As early as W12, pegcetacoplan reduced C3c staining and proteinuria with stable eGFR, targeted the pathophysiology of C3 dysregulation, and was well tolerated in KTRs with recurrent C3G or IC-MPGN.

Table. Clinical and biomarker changes in C3G and IC-MPGN

		uPCR (mg/g)		uPCR (mg/g) [a] (Patients with ≥1000 mg/g at Baseline)		Serum C3 (mg/dL)		Serum sC5b-9 (ng/mL)		eGFR (mL/min/1.73m²)	
		PEG [b] (n=9)	SOC [c] (n=3)	PEG [b] (n=5)	SOC [c] (n=2)	PEG [b] (n=9)	SOC [c] (n=2)	PEG [b] (n=10)	SOC [c] (n=3)	PEG [b] (n=9)	SOC [c] (n=3)
Baseline	Mean [d] (SD)	1506.7 (1097.23)	2314.8 (2170.68)	2349.3 (595.15)	3217.3 (2129.81)	56.1 (33.83)	103.0 (67.88)	651.4 (1024.68)	145.3 (41.28)	51.8 (13.18)	53.3 (11.37)
Week 12	Mean [d] (SD)	1048.7 (1293.10)	2412.9 (1980.32)	1582.9 (1559.20)	3150.3 (2140.18)	291.1 (92.11)	89.5 (53.03)	123.4 (82.26)	228.7 (162.54)	53.7 (23.11)	47.3 (11.85)
Change from baseline	Mean [d] (SD)	–458.0 (956.06)	98.1 (286.08)	–766.4 (1182.82)	–67.0 (10.37)	235.0 (83.71)	–13.5 (14.85)	–528.0 (955.19)	83.3 (121.33)	1.9 (21.74)	–6.0 (2.65)

C3G, C3 glomerulopathy; eGFR, estimated glomerular filtration rate; IC-MPGN, immune complex membranoproliferative glomerulonephritis; PEG, pegcetacoplan; SD, standard deviation; SOC, standard of care; uPCR, urinary protein-to-creatinine ratio.
[a] Measured by triplicate first-morning spot urine.
[b] Patients received subcutaneous pegcetacoplan 1080 mg twice weekly plus standard of care. Of 10 patients, 8 (80%) had C3G, and 2 (20%) had IC-MPGN. The mean (SD) age of the patients was 39.8 (12.59) years.
[c] Patients received standard of care only (SOC). Of 3 patients, 1 (33%) had C3G and 2 (67%) had IC-MPGN. The mean (SD) age of the patients was 44.3 (24.03) years.
[d] Means were calculated only using non-missing values.

Figure. Individual changes in C3c biopsy staining



SA-PO924

Efficacy of Combined Rituximab (Anti-CD20) and Daratumumab (Anti-CD38) in Steroid-Resistant Nephrotic Syndrome and in Post-Transplant Recurrent FSGS

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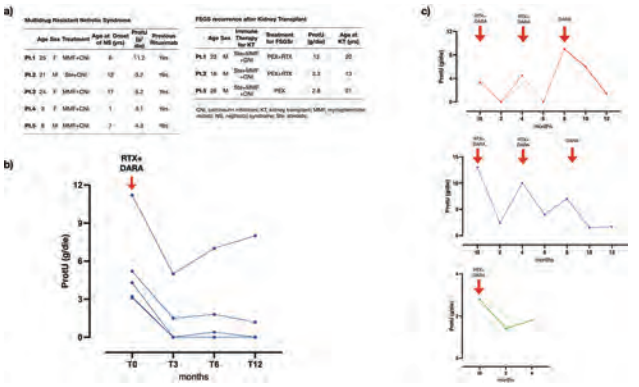
Background: Multidrug-resistant nephrotic syndrome (MRNS) accounts for 15% of overall cases of nephrotic syndrome (NS) in childhood. MRNS is associated with high risk of kidney failure and recurrence after kidney transplant (KT). Common treatments, including rituximab and plasma exchange (PEX), are poorly effective.

Methods: We ran a phase II proof-of concept clinical study (NCT05704400) including patients with MRNS (lack of antiproteinuric effect of therapy based on steroid plus CNI and MMF for at least 12 months before enrolment) and post-transplant FSGS recurrence (FSGSr) resistant to rituximab and PEX. We administered rituximab (single infusion 350mg/m², i.v.) + daratumumab (single 16mg/kg infusion). Primary outcome was complete (CR) or partial remission (PR defined as >50% proteinuria reduction).

Results: We enrolled 8 patients: 5 with MRNS and 3 FSGSr (**Fig.1a**). MRNS resulted resistant to previous infusion of rituximab alone (last infusion at least 9 months before enrollment). Combined rituximab + daratumumab therapy induced CR or PR in 3 and 2 subjects with MRNS, respectively (**Fig.1b**). In one patient with older history of MRNS (5yrs), proteinuria remission was transient, but she refused a second treatment. All 3 FSGSr achieved CR/PR and PEX was stopped. Relapse occurred after 4 months in all pts. We repeated the combined treatment in 2 pts that after initial reduction, had a second relapse after 4 months. Thereafter, administration of daratumumab alone obtained remission as well (**Fig.1c**). Treatment was well tolerated and all patients are in active follow-up.

Conclusions: Combined treatment with rituximab and daratumumab is effective in inducing proteinuria remission in MRNS and FSGS recurrence. In KT, relapse-free time was 4 months and repeated infusions were needed. Therefore, targeting CD20 and CD38 may represent a valid therapeutic strategy in MRNS and FSGS recurrence.



SA-PO925

The Type II Glycoengineered Anti-CD20 Antibody MIL62 or Cyclosporine in Chinese Primary Membranous Nephropathy: Updated Results of an Ongoing, Multicenter, Randomized, Open-Label Phase 1b/2 Trial

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Background: A novel glycoengineered type II anti-CD20 antibody, MIL62 with a nearly completely afucosylated N-glycans in Fc region, has demonstrated superior activity compared with rituximab and obinutuzumab in vitro and in vivo, respectively. We have many clinical data of MIL62 in lymphoma, so we chose two doses to evaluate the safety, tolerability, and efficacy of MIL62 in pMN.

Methods: Eligible pts with pMN diagnosed by kidney biopsy, proteinuria of at least 3.5 g per 24 hours received intravenous MIL62 (two infusions, 600 or 1000 mg each, administered 14 days apart; repeated at 6 months) or Cyclosporine (CsA, starting at a dose of 3.5 mg per kilogram of body weight per day for 12 months). Patients were followed up for up to 104 weeks. The primary outcome were immunological remission (iR) at 12 weeks and a composite of complete or partial remission of proteinuria with stable eGFR at 24 weeks.

Results: From Feb. 23th, 2022 to Dec. 21th, 2022, 86 patients (pts) were randomly enrolled. As of Mar. 23th, 2023, median follow up time was 24 weeks. 22/35 (62.9%) pts in the MIL62 group and 6/18 (33.3%) pts in the CsA group achieved remission at 24 weeks (P< 0.05). In the 69 pts positive for anti-PLA2R Abs (≥14RU/mL) at baseline, 41/47 (87.2%) pts in the MIL62 group achieved iR, which was superior to the CsA group [12/22 (54.5%), P< 0.05] at 12 weeks. The remission to MIL62 in our study was faster than Rituximab because 62.9% (22/35) of patients achieved complete or partial remission at 24 weeks compared with the 35% (23/65) 6-month response rate reported in the Mentor study. Treatment-related adverse events occurred in 73.3%, 77.1% and 88.5% pts in the MIL62 600mg, MIL62 1000mg and CsA group respectively; No treatment-related deaths occurred.

Conclusions: The 12-week iR and 24-week overall remmision of MIL62 was significantly higher than CsA, and had a manageable safety profile. A phase III clinical trial of MIL62 in pMN is ongoing (NCT05862233).

	Immunological Remission at 12 weeks		Overall Remission at 24 weeks	
	MIL62 (N=47)	Cyclosporine (N=22)	MIL62 (N=35)	Cyclosporine (N=18)
Remission rate n (%), 95%CI	42 (87.2) (74.3, 95.2)	12 (54.5) (32.2, 75.6)	22 (62.9) (44.9, 78.5)	6 (33.3) (13.3, 59)
P value	p=0.003		p=0.041	

SA-PO926

An Exploratory Trial of an Investigational RNA Therapeutic, IONIS-FB-LRx, for Treatment of IgA Nephropathy: New Interim Results

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Background: Overactivity of the complement Alternative Pathway (AP) has been proposed to contribute to pathogenesis of IgA nephropathy (IgAN). An antisense oligonucleotide to complement factor B (FB), IONIS-FB-L_{Rx} (ISIS696844, RO7434656) targets FB mRNA in the liver. IONIS-FB-L_{Rx} treatment led to inhibition of AP and reduction in proteinuria in IgAN patients (2022 ASN Abstract#SA-PO714).

Methods: An exploratory, single-arm, multi-national open-label Ph2 study (NCT04014335) recruited patients with biopsy-confirmed IgAN, proteinuria>1.5 g/d, eGFR>40mL/min/1.73m^2, and hematuria despite maximum tolerated RAAS blockade. Patients received monthly SC administration of IONIS-FB-L_{Rx} for 24 weeks. Primary outcome was change in 24-hr proteinuria at Wk29 (4 weeks after last dose) compared to baseline (BL).

Results: 13 subjects have completed study to date, 25-62 yr, 40% Female, 7 Asian, and 6 White. There was a selective reduction of plasma complement FB levels, serum AP activity, urinary Ba and urinary sC5b-9 (mean % change of -69%, -36%, -92%, and -26% respectively). Median 24-hr proteinuria at BL was 1.80 g/g (IQR 1.23, 2.33 g/g). At Wk29, a 47% geometric mean ratio reduction was observed. There was no change in eGFR at Wk29 compared to BL (mean±SD; BL 70±25; Wk29 72±22 mL/min/1.73m2). One subject opted to extend treatment and continued to receive treatment through Wk61, demonstrating a sustained reduction in proteinuria. One subject discontinued study drug after 4 months of treatment (last dose Wk17) to initiate SGLT-2 inhibitors. 24-hr urine samples collected 3 weeks after the last dose of IONIS-FB-L_{Rx}, but prior to use of SGLT-2 inhibitors (Wk27), demonstrated a 41% reduction in proteinuria. IONIS-FB-L_{Rx} demonstrated an acceptable safety profile with no Treatment Emergent SAE. The only clinically meaningful safety signal (moderate TEAE) was a reversible ALT elevation without a change in bilirubin in 1 subject.

Conclusions: This Ph2 open-label study provides continuing clinical evidence that IONIS-FB-L_{Rx} reduces complement levels and proteinuria in patients with IgAN, supporting Ph3 development (NCT05797610) to determine the potential of IONIS-FB-L_{Rx} to reduce the progression of IgAN.

Funding: Commercial Support - Ionis Pharmaceuticals

SA-PO927

Plasma Osteopontin Differentiates Active and Inactive Lupus Nephritis and Is Associated with Response to Therapy

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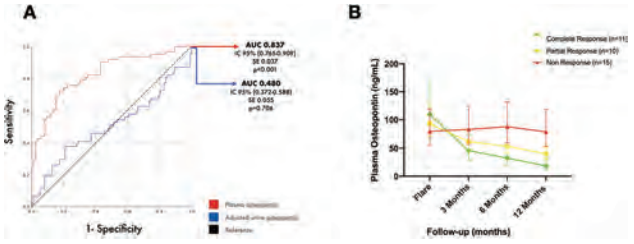
Background: New biomarkers are needed to differentiate activity from chronic damage in Lupus nephritis (LN) & to monitor response to treatment. Osteopontin (OPN) is an N-linked glycoprotein with integrin-binding ligands that has been identified as a potential biomarker of activity in systemic lupus erythematosus (SLE).

Methods: This is a diagnostic study with a cross-sectional and a longitudinal phase to describe the course of plasma (pOPN) & urinary OPN (uOPN) in a LN cohort. We recruited 62 patients with biopsy-proven active LN. As disease controls, we included 88 patients with non-renal activity, chronic LN on kidney biopsy, & inactive SLE. To evaluate the diagnostic yield of OPN we built ROC curves from the cross-sectional data. In the longitudinal phase, we included 36 active LN patients with prospective follow-up and plasma/urine samples collected at 3, 6, & 12 months. Response to therapy was evaluated at 6 & 12 months. Linear mixed models were fitted to evaluate the association between pOPN, uOPN, and response to therapy.

Results: Active LN patients had the highest levels of pOPN (81.18 ng/mL, IQR 53.75-169.46). Elevated pOPN levels correlated with SLEDAI-2K activity score (r= 0.51, p<0.001), SLICC/ACR damage index (r=0.24, p=0.003), ISN/RPS class IV LN (r=0.24, p=0.03), histologic activity index (r=0.46, p<0.001) and eGFR <60 mL/min/1.73m2 (r=0.35, p<0.001). There were no differences in uOPN between the groups. pOPN >58 ng/mL had 72% (95%CI 0.60-0.82) sensitivity and 81% (95%CI 0.71-0.88) specificity to differentiate active LN from inactive patients. The course of pOPN in response to therapy was associated with the type of response, with continuous reduction in complete responders and persistent elevation in non-responders. There was no association between uOPN and response to therapy.

Conclusions: Plasma OPN correlates with LN activity, it has a fast reduction within the first 3 months of therapy and is associated with response to therapy.



OPN ROC curves (A) & course of pOPN in response to therapy (B)

SA-PO928

Identification of New Therapeutic Targets of Arsenic Trioxide for Lupus Nephritis: Machine Learning Bioinformatics and In Vitro Studies

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Background: Lupus nephritis (LN) is a serious complication of systemic lupus nephritis (SLE). Preliminary study suggested that low-dose ATO treatment in active SLE patients was associated with reduced flare rates, but the underlying mechanisms have not well characterized.

Methods: The potential targets of differentially expressed genes (DEGs) from human SLE and LN PBMCs datasets were identified by bioinformatic analysis and network pharmacology. Characteristic hub genes were further selected using machine learning method. The relationship between the potential targets and immune cells was also examined.

Results: Twelve predicting immune related intersection DEGs in SLE were identified. KEGG pathway analysis indicated that ATO could attenuate IL-17 signaling pathway (p=1.67E-18), and TNF signaling pathway (p=5.77E-11) in SLE. Five genes of features importance were selected by three machine learning models, in which MMP9 showed the highest performance in predicting SLE development (ROC AUC: 0.942). MMP9 also showed positive correlations with macrophages and neutrophils in ssGSEA analysis (r=0.88 and 0.66 respectively). Our in vitro studies further demonstrated that ATO treatment downregulated MMP9 expression in PBMCs obtained from LN patients during disease remission (n=5).

Conclusions: ATO can attenuate LN via reduction of MMP9 expression in PBMCs and different inflammatory pathways.

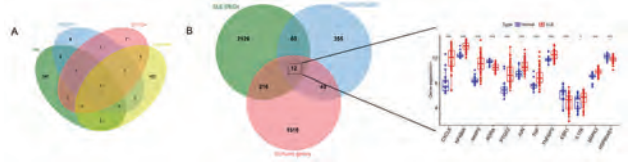

Figure 1. Intersection immune associated genes of arsenic trioxide in systemic lupus erythematosus (SLE).

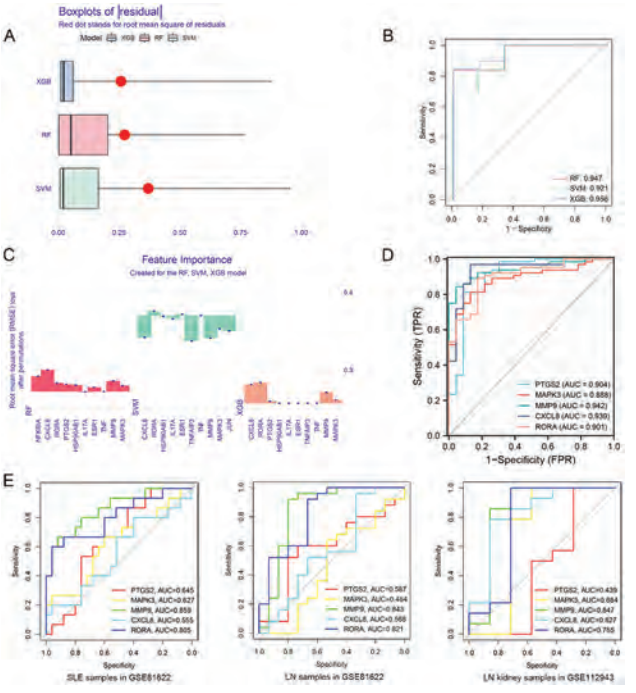

Figure 2. MMP9 was selected as the hub target in systemic lupus erythematosus (SLE).

SA-PO929

Genetic Determinants of Lupus Nephritis and Kidney Function in Systemic Lupus Erythematosus

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Background: Lupus nephritis (LN) is one of the most common and severe manifestations of SLE. We completed an LN genome wide association study (GWAS) in a multi-ethnic cohort of children and adults with SLE.

Methods: We included SLE patients from dedicated Lupus clinics and the SLICC cohort. All patients met ACR and/or SLICC SLE classification criteria and were genotyped on a multi-ethnic Illumina array. LN was defined by SLE criteria. Kidney function (eGFR) was estimated using the Schwartz Bedside formula for measures <18 years and CKD-EPI (without ancestry) for >18 years of age, collected longitudinally over time. Wilcoxon rank sum or Chi-square test were used for significance between LN and Non-LN patients. We completed GWAS of LN in marginal and multivariable adjusted regression models with principal components for ancestry, sex and cohort site.

Results: We included 2981 patients with SLE, 88% female, 46% of European ancestry, 27% childhood-onset SLE. LN was present in 45%. People at time of LN diagnosis were younger and more likely of African American or East Asian ancestry. People with LN had significantly lower within-person mean eGFR, greater eGFR variability and slope over time compared to those without LN (Table). GWAS of LN demonstrated a peak on chromosome 8, yet did not reach a genome-wide significance ($p < 5x10^{-8}$).

Conclusions: Our GWAS did not identify a significant locus for LN. We plan to repeat GWAS of repeated eGFR measures, as it is a more informative outcome that may improve power for detecting genetic loci for LN.

Funding: Government Support - Non-U.S.

Characteristics of LN and Non-LN patients

Patient Characteristics	All SLE Patients (n=2981)	LN SLE Patients (n=1351)	Non-LN SLE Patients (n=1630)	P-value
Sex, Female	2628 (88.2)	1138 (84.2)	1490 (91.4)	1.6e-09
Age at SLE diagnosis (years)	25.6 [16.4, 37.8]	22.6 [15.7, 33.0]	28.3 [17.3, 41.3]	2.2e-16
cSLE diagnosis	814 (27.3)	484 (35.8)	440 (27.0)	2.1e-07
Inferred Ancestry European East Asian African American South Asian Admixed	 1367 (45.9) 459 (15.4) 555 (18.6) 151 (5.1) 131 (4.4) 317 (10.6)	 493 (36.5) 252 (18.6) 316 (23.3) 80 (5.9) 68 (5.0) 141 (10.4)	 874 (53.6) 207 (12.7) 239 (14.7) 71 (4.4) 63 (3.9) 176 (10.8)	 2.2e-16
Hypertension*	1017 (37.1)	659 (52.6)	358 (23.8)	2.2e-16
Kidney failure (chronic dialysis or transplant)*	25 (0.9)	25 (2.0)	0 (0.0)	3.0e-08
Time from diagnosis to 1st eGFR (years)* Time from 1st eGFR measurement to last (years)*	0.6 [0.06, 3.4] 8.9 [4.1, 14.8]	0.6 [0.08, 3.8] 10.0 [5.1, 16.1]	0.5 [0.04, 3.0] 7.8 [3.4, 13.7]	3.3e-01 4.4e-13
Within-Person No. eGFR Measures*	16 [8, 35]	21 [10, 45]	13 [6, 29]	2.2e-16
Within-Person mean* Within-Person eGFR Variance* eGFR slope ml/min/1.73m2/y*	100.8 [86.0, 113.1] 106.6 [51.4, 198.7] -0.53 [-2.00, 0.48]	100.2 [81.3, 113.4] 137.2 [69.6, 268.6] -0.67 [-2.26, 0.36]	101.2 [88.6, 112.7] 87.2 [43.1, 156.4] -0.53 [-1.83, 0.67]	7.7e-02 2.2e-16 2.3e-02

* data available for N= 2740

SA-PO930

Discovery and Validation of Novel Circulating Auto-Antibodies in Lupus Nephritis Using Peptide Array Technology

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Background: Systemic Lupus Erythematosus (SLE) and Lupus Nephritis (LN) are prototypes of autoimmunity. Autoantibodies determining the first hit in LN have been identified; autoantibodies involved in renal progression remain an open issue.

Methods: We investigated sera of SLE, LN, rheumatologic and normal controls (20/20/60/40) using a high-density peptide array (17,402 peptides) covering the coding sequences of 464 proteins involved in rheumatologic/immunologic processes. The immune-fluorescence intensity was calculated by repeating incubation of sera with peptides 20 times to reduce variability for an overall of 348,040 peptide spots. The noise cutoff was set at IF>50. Validation of results was done by either specific assays (ELISAs) in many more patients (130 SLE, 91 LN) and by renal immuno-histochemistry (12 LN).

Results: Overall, 133 proteins reactive with SLE and LN sera were identified by the peptide array. Annexin A1 (ANXA1) and Formin-like 1 Protein (FMNL1) had the highest probability to be true antigens. Anti-ANXA1 antibodies have been already associated with LN and SLE, FMNL1 is a new identified antigen. Anti-ANXA1 and anti-FMNL1 IgG2 (ELISAs) were high in serum of LN and SLE patients (LN >SLE); FMNL1 co-stained with macrophage markers (CD68) in glomeruli, high expression being associated with proliferative LN (stage IV). FMNL1 was recognized in macrophage cell lysates 'in vitro' by sera of LN patients with high anti-FMNL1 IgG2.

Conclusions: Overall, these findings show many potential antigens in SLE and LN based on an innovative peptide array technology. Circulating anti-ANXA1 and anti-FMNL1 IgG2 were high in both conditions. Anti-FMNL1 antibodies target a protein of macrophages associated with proliferative LN, suggesting that targeting cells potentially involved in tissue damage and/or repair might have a definite role in determining the disease outcome.

Funding: Government Support - Non-U.S.

SA-PO931

Classical Complement Activation in Lupus Nephritis Correlates with Disease Biomarkers: Results from Two Observational Studies

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Background: Lupus nephritis (LN) is an autoantibody-mediated disease that can activate C1q and the classical complement pathway. Pathogenic anti-C1q antibodies (PACAs) are often present, amplifying classical pathway inflammation and contributing to progressive kidney damage. Elevated C4d and reduced C4 are markers of classical complement activation and consumption, respectively. For LN patients in the CLUES/UCSF Study, C4d/C4 ratio positively correlated with PACAs and urine protein-creatinine ratio (UPCR). To validate this correlation, the Sanguine Bio study was conducted.

Methods: Samples were collected from 40 LN patients (plus 20 healthy controls) from the CLUES/UCSF Study and 24 LN patients (plus 10 healthy controls) from Sanguine Bio. Complement activation and consumption (C4d, C4), exploratory biomarkers in plasma and urine, and UPCR were evaluated.

Results: Sanguine Bio samples from a subset of LN patients demonstrated elevated C4d/C4 compared to healthy controls indicating classical complement pathway activation (**Figure**). Urinary biomarkers of LN correlated with C4d/C4 ratio in these patients.

Conclusions: In these LN patients, C4d/C4 ratios were elevated and correlated with LN biomarkers in blood and urine, supporting classical complement activity. These data support an ongoing, phase 1b study of ANX009 with the goal of assessing safety, tolerability, and pharmacodynamics of repeat-doses of subcutaneous ANX009 with standard of care in adults with LN. ANX009 is an anti-C1q antigen binding fragment targeting LN patients with evidence of classical complement activity (elevated C4d/C4).

Funding: Commercial Support - Annexon Biosciences

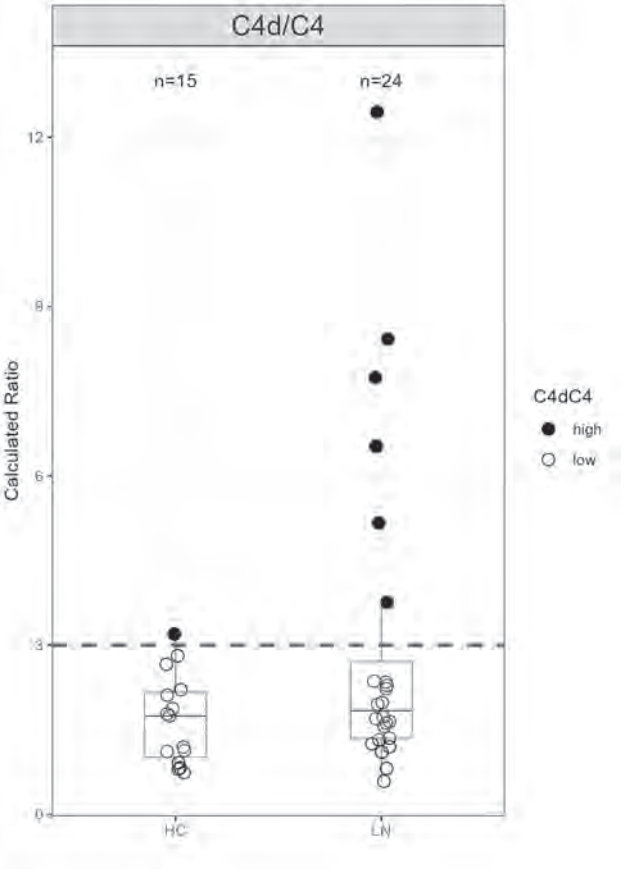

Figure. A Subset of Patients with LN Demonstrated Elevated C4d/C4 Over Healthy Controls

SA-PO932

EXT-1/EXT-2 and NCAM-1 Expression in Taiwan Patients with Lupus Membranous Nephropathy

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Background: Lupus nephropathy could be divided into 6 categories according to WHO classification. Class V lupus nephropathy have similar histologic features with primary membranous nephropathy. There are several autoantibodies and autoantigens demonstrated in primary membranous nephropathy, since the discovery of anti-PLA2R. Similarly, there are also some novel autoantigens found in lupus membranous nephropathy. EXT-1/EXT-2 and NCAM-1 were postulated recently in lupus membranous nephropathy. Therefore, we conducted a prospective study to evaluate the prevalence of EXT-1/EXT-2 and NCAM-1 expression in patients with lupus membranous nephropathy.

Methods: This prospective invesitgation is conducted at a tertiary medical center in Taiwan. During the study period, there are totally 55 patients with pathologic diagnosis of lupus membranous nephropathy. In addition to routine histologic examination by experienced renal pathologist, the investigators completed the immunohistochesmistry (IHC) stain of PLA2R, EXT-1 and NCAM-1. Demographic datas and clinical informations were also collected and evaluated.

Results: Among the 55 subjects, there are 52 subjects with successful IHC stain for EXT-1 and 49 subjects with successful IHC stain for NCAM-1. All the subjects are negative of IHC stain for PLA2R. EXT-1 and NCAM-1 expression could be found with ratio of 26.9% (14/52) and 2.0% (1/49), respectively. Comparing with other group, the prevalence of EXT-1 and NCAM-1 in this investigation is relatively lower.

Conclusions: In this prospective investigation, we first demonstrate the prevalance of EXT-1 and NCAM-1 expression in Taiwan patients of lupus membranous nephropathy. The prevalence of these 2 autoantigen is lower than former studies. The role of these autoantigen is not clarified yet. Further studies are needed.

SA-PO933

Urine sCD163/Creatinine Ratio Is a Potential Biomarker of Disease Severity in Patients with IgA Nephropathy

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Background: IgA nephropathy is the most common glomerular disease in adults. There are several prediction model postulated for IgAN but no one could be validated successfully. In addition, no any one biomarker was proved to predict severity and survival for patients with IgA nephropathy. Recently, one urinary metabolite from macrophage, soluble CD163 (usCD163) was found remarkably elevated in patients with IgA nephropathy. Gong et al demonstrate urine sCD163/creatine ratio seems correlated to disease severity of IgA nephropathy. Thus, the investigator conducted a prospective study to elucidate the role of urine sCD163/creatinine in IgA nephropathy.

Methods: The investigators initiated a prospective cohort of glomerular disease at a tertiary medical center in Taiwan. Mid-stream spot urine sample was prospectively obtained before renal biopsy. During the study period, there are 150 subjects with pathologic diagnosis of IgA nephropathy. After exclusion as criteria, there are totally 70 subjects believed as primary IgA nephropathy was studied. Pre-stored urine sample were used to check the level of soluble CD163 and creatinine.

Results: The level of urine soluble CD163/creatinine could be devided into 3 tertiles. Between these tertiles, there are no remarkable difference in serum creatinine and GFR. Greater tertiles of usCD163/Cr have greater severitiy of hypoalbuminemia, proteinuria, hypercholesterolemia and hypertension. Greater tertiles of usCD163/Cr have also more obsoleted glomeruli, greater severity of tubulointerstitial fibrosis, and more crescents formation. ≥ 50% decline of estmitaed glomerular filtration rate (eGFR) and entering dialysis during study period didn't achieve stastistical difference between 3 tertiles of usCD163/Cr. Survival analysis toward ≥ 50% eGFR deline and entering dialysis, however, revealed lower survival probability in tertile 3 compared to tertile 1+2.

Conclusions: Urine sCD163/creatinine ratio seems correlated to proteinuria and the symptoms associated with nephrosis. It also correlated to histologic injury of glomerular sclerosis and tubulointerstitial fibrosis. Although there are no stastistical significance of ≥ 50% eGFR decline and entering dialysis between these tertiles, survival analysis proved that lower survival probability in tertile 3 compared to tertile 1+2.

SA-PO934

Urinary Proteomics Identifying Novel Biomarkers for Predicting the Activity of ANCA-Associated Nephritis

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Background: Despite the pathogenic role of ANCA in ANCA-associated glomerular nephritis (AAGN), it's still challenging to determine the active stage. Urinary proteomics, specifically data-independent acquisition (DIA) proteomics, might be the non-invasive and efficient method to find potential biomarkers to identify the active AAGN.

Methods: The urine samples used for proteomic analysis were from patients diagnosed as AAV at Peking Union Medical College Hospital from May 2022 to April 2023. We performed LC-MS/MS analysis with quality control and identified differentially expressed genes (DEGs). Weighted gene co-expression network analysis (WCGNA), Least Absolute Shrinkage and Selection Operator (LASSO), and Random Forest analysis were used to figure out the target molecule and validated in the validation cohort by ELISA.

Results: In this study, 40 patients performed the urine DIA analysis, and the other 50 patients were in the validation group, with 56.7% female, with an average age of 58±15 years old. In the 358 DEGs identified between AAV with and without renal involvement, the top pathways were the complement, coagulation cascade, and cholesteryl mechanism. After WGCNA, Lasso, and Random forest analysis, four urine proteins, marked complement factor D (CFD), coagulation factor II (F2), fibrinogen Alpha Chain (FGA), and plasminogen (PLG) were highly associated with AAGN in the active stage and confirmed by ELISA (Figure 1). The receiver operating characteristic curve (ROC) values of F2 combined CFD in AAV patients with active renal involvement was 0.922 (P<0.001) with a sensitivity of 75% and a specificity of 97.1%.

Conclusions: Several biomarkers from the complement and coagulation cascade might be potential urine biomarkers for AAGN in the active stage.

Funding: NIDDK Support

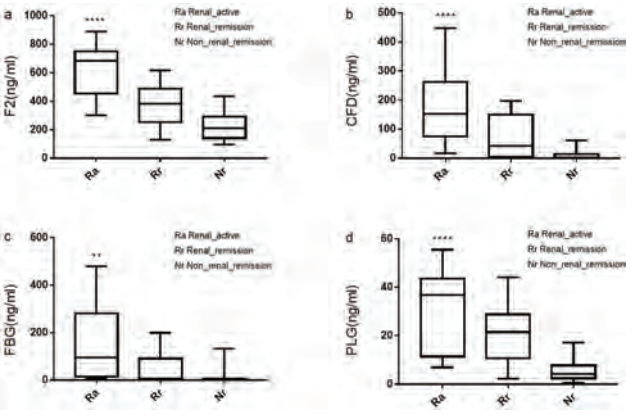

Figure 1. ELSIA analysis of F2, CFD, FBG and PLG.

SA-PO935

Citrullinated Histone H3-Positive Neutrophils May Be Associated with Disease Activity in ANCA-Associated Vasculitis

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Background: Neutrophil extracellular traps (NETs) formation is reportedly involved in the onset of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Citrullinated histone H3 (H3Cit) is an important component of NETs. Previously, we reported that the presence of H3Cit (+) neutrophils is more specific in AAV than in other glomerular diseases and H3Cit staining is useful for identifying activated neutrophils. However, there were no detailed analysis of association between H3Cit neutrophils and AAV disease activity.

Methods: We selected kidney biopsy cases with AAV at Nippon Medical School Hospital during 2011 to 2022. Clinical findings included age, gender, serum creatinine (sCr) level, CRP, MPO/PR3-ANCA titer, and urinary findings (urinary protein (U-P) level, urinary β2-microglobulin (uβ2-MG)). Histological findings were assessed as follows: rates of global sclerotic glomeruli, crescent formation, interstitial fibrosis, and atherosclerosis score). MPO (neutrophil marker) and H3Cit (NETs marker) staining were performed.

Results: A total of 49 cases with AAV were selected and were divided into two groups : H3Cit (+) group (n=44) and H3Cit (-) group (n=5) according to the presence or absence of H3Cit+ neutrophils in renal tissues. Clinically, sCr level and uβ2-MG level were significantly higher in the H3Cit (+) group although there were no significant differences in age, CRP, ANCA titer and U-P level. Histologically, H3Cit (+) neutrophils were observed in tubulointerstitial lesions in 43 cases, and in both tubulointerstitial lesions and glomeruli in 13 cases. Only one case showed glomerular involvement. H3Cit (+) neutrophils were observed mainly in peritubular capillaries, and around necrotic lesions of arteries and glomeruli. The rates of crescent formation and interstitial fibrosis were significantly higher in the H3Cit (+) group while there was no differences in rates of global sclerotic glomeruli and atherosclerosis score.

Conclusions: The H3Cit (+) group exhibited significantly worse renal function and urinary findings, as well as higher tissue activity. The presence of H3Cit+ neutrophils serves not only a disease-specific marker but also a potential indicator of disease activity in AAV.

SA-PO936

Clinical Implication of Platelets and Complement C3 as Link Between Innate Immunity and the Coagulation System in ANCA-Associated Renal Vasculitis with Myeloperoxidase (MPO) ANCA Seropositivity

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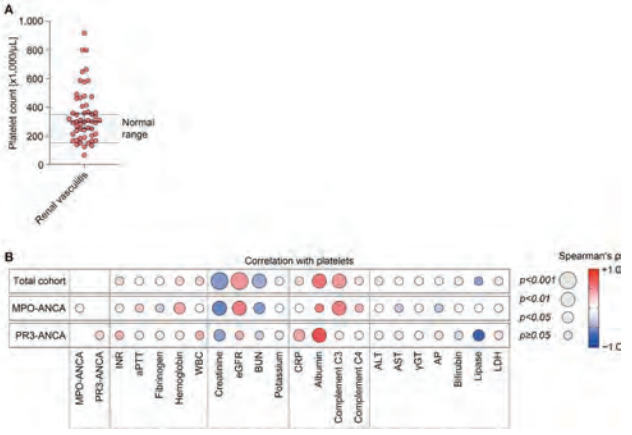
Background: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a potentially life-threatening systemic small vessel vasculitis (SVV). It is well established that AAV patients feature an increased risk of developing thrombotic events, and platelets are activated in AAV patients being triggered by the alternative complement pathway. We here aimed to systematically assess the relevance of platelet counts and systemic complement system activation regarding distinct histopathological lesions in ANCA associated renal vasculitis (AARV).

Methods: A total of 53 patients with biopsy proven AARV were retrospectively enrolled in a single center observational study. Multivariate regression analysis was performed to identify parameters associated with platelet counts in AARV compared to disease controls. Finally, the relevance of platelets for disease course and recovery was assessed by survival analysis.

Results: Lower platelet counts correlated with markers of kidney injury including eGFR loss (*p=0.0004*) and lower complement C3 levels (*p=0.0037*). Multivariate and subgroup analysis revealed that this association was only present in the MPO ANCA subgroup (eGFR loss: *p=0.0009*, lower C3: *p=0.0032*). Lower platelet counts correlated with interstitial fibrosis (*p=0.0313*), and tubulitis in areas of interstitial fibrosis and

tubular atrophy (*p=0.0033*). Finally, we observed significant differences with increased requirement of kidney replacement therapy or death in the subgroup below median platelet counts (HR: 4.1, 95% CI: 1.6-10, *p=0.0047*), associated with a prolonged hospitalization in this subgroup (HR: 0.5, 95% CI: 0.3-0.9, *p=0.0113*).

Conclusions: Based on our observed association between platelets and complement system activation in the MPO ANCA subgroup, we here show an impact on disease course and histopathological lesions implying distinct damage modes in different subtypes of AARV.



SA-PO937

Clinical Application of IgA-Type Autoantibodies Against Mesangial Autoantigen, βII-Spectrin, in IgA Nephropathy

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Background: Half a century has passed since the first report of patients with IgA nephropathy (IgAN), however, the whole pathogenesis of IgAN remains elusive. In particular, the important question why IgA antibodies (Abs) are selectively deposited in the mesangial region, a hallmark of IgAN, remains unanswered. Recently, we have uncovered the answer to this critical question by identifying IgA type autoantibodies directed against mesangial autoantigen, βII-spectrin, in sera of patients with IgAN (Y. nihei et al. *Science Advances* 9, eadd6734, 2023). We confirmed that serum anti-βII-spectrin IgA was positive in 60% of patients with IgAN by Western blot. In present study, we aim to elucidate the specificity of serum levels of anti βII-spectrin in patients with IgAN and to clarify clinical aspects of serum anti βII-spectrin IgA.

Methods: To evaluate the specificity of anti-βII-spectrin IgA, serum anti-βII-spectrin IgA were measured by enzyme-linked immuno sorbent assay (ELISA) in patients with biopsy-proven IgAN (N=70) or other kidney diseases (N=32). The clinical parameters were compared between patients with IgAN who were positive for anti-βII-spectrin IgA and those who were negative. To test whether serum anti-βII-spectrin IgA titers correlate with disease activity, we compared the titers before and after steroid treatment in IgAN patients with positive for anti-βII-spectrin IgA.

Results: We found that 24 of 70 patients with IgAN have serum anti-βII-spectrin IgA while only two of 32 were positive for anti-βII-spectrin IgA in patients with other kidney diseases. No differences in eGFR, proteinuria, or histopathological findings were found between IgAN patients with positive and negative for serum anti-βII-spectrin IgA at the time of renal biopsy. The titer of anti-βII-spectrin IgA in patients with IgAN decreased after treatment with improvement in hematuria and proteinuria.

Conclusions: We found that anti-βII-spectrin IgA were detected in patients with IgAN with high specificity (specificity, 93.8%), suggesting that serum anti-βII-spectrin IgA may be useful for the diagnosis of IgAN. The decrease in serum anti-βII-spectrin IgA titers with improvement in hematuria and proteinuria after treatment indicated that serum anti-βII-spectrin IgA can be also used as a biomarker for monitoring disease activity.

SA-PO938

GalD: An Available and High-Performing Lectin-Based Test for Serum Galactose-Deficient IgA1

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Background: Quantitative lectin-based assay for serum galactose-deficient immunoglobin A1 (Gd-IgA1) has been established as leading biomarker for kidney outcomes of patients with IgA nephropathy (IgAN) since 2007. This Gd-IgA1 analysis has been included in multiple landmark papers and been used as the quantitative phenotypic basis for genome-wide association studies of IgAN and serum Gd-IgA1. Initially, the lectin-based Gd-IgA1 analysis was not amenable for broad use due to lack of scalability, long sample-analysis timeframe, and user-to-user variation. Here, we report our development of the GalD biomarker test, a highly reproducible, fast, and newly available lectin-based assay for Gd-IgA1.

Methods: We used a 24-serum-sample quality-control set that spans the Gd-IgA1 concentrations reported in the literature in a 5-hour detection protocol to perform standard validation analysis. This approach included intra- and inter-assay performance and serial measurements to assess serum freeze-thaw stability. Additionally, multiple batches of key reagents were evaluated over time to ensure assay consistency.

Results: Our validation analysis demonstrated high-quality assay performance, with less than 10% plate-to-plate error. Furthermore, the assay demonstrated six-month stability of the components. The entire range of the calibrated assay was 29-2000 ng/mL. The lower limit of detection was determined to be 0.425 ng/mL. The lower limit of quantitation was 29 ng/mL. The GalD test is fully scalable to enable testing across multiple sample plates, dates, or users, and with same-day readout.

Conclusions: Our GalD test now brings the ability to measure serum Gd-IgA1 concentration to any laboratory while assessing the full spectrum of galactose-deficient IgA1 present in serum samples.

Funding: NIDDK Support

SA-PO939

Single-Cell RNA Sequencing Reveals Immune Cell-Specific Genes and Pathways Associated with IgA Nephropathy

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Background: IgA nephropathy (IgAN) is one of the most common primary glomerulonephritis globally. Increasing evidence suggests the importance of host immunity in the development of IgAN, but its dynamics during the early stage of IgAN pathogenesis are still largely unclear. Single-cell RNA-sequencing is a high-throughput sequencing technology with cells as minimal units, which could be applied to explore the pathogenesis of IgAN.

Methods: Peripheral venous blood samples were collected from 6 healthy controls and 10 newly diagnosed IgAN patients. Peripheral blood mononuclear cells (PBMCs) were isolated by FACS sorting with above 80% cell viability. Then single cell RNA-sequencing was performed using the BD Rhapsody platform. Downstream analysis was performed with the Seurat V3.0. Meanwhile, the clinical data of the IgAN patients were co-analyzed with single-cell RNA-sequencing results. Experimental and research procedures were approved by and in accordance with the internal review board and human subject guidelines of the Sun Yat-sen Memorial Hospital and Sun Yat-sen University.

Results: First, we generated an single immune cell landscape of early IgAN. The differentially expressed genes (DEGs) between the control and IgAN groups were mainly related to the NK cell-mediated cytotoxicity and NK cell killing pathways. We found that significant decreases in the NK cell numbers and cytotoxicity genes. Interestingly, we discovered that NK cell numbers and marker genes were negatively correlated with many clinical parameters, including urinary protein creatinine ratio (UPCR) and serum galactose-deficient IgA1 and IgA. In contrast, DEGs of B cells were enriched in different viral infection pathways, and one specific B cell subgroup exhibiting the inhibition of NFκB signaling, was positively correlated with IgAN clinical parameters. In addition, a subpopulation of monocytes expressing interferon-inducing genes was positively associated with clinical severity of IgAN. Finally, we identified vast dynamics in intercellular communications of NK cells and monocytes in IgAN.

Conclusions: We constructed a landscape of peripheral blood mononuclear cells from early IgAN patients by using scRNA-seq and found significant alterations in the number and gene expression pattern of immune cells, some of which are closely related to clinical manifestations.

SA-PO940

Low eGFRcys/eGFRcreat Ratio Indicates Glomerular Filtration Impairment in the Patients with IgA Nephropathy

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Background: Most glomerular diseases are characterised by disruption of the glomerular filtration barrier (GFB). The reduced pore size of GFBs as a result of endothelial damage is thought to result in lower clearance of medium-sized molecules (5000-3000 Da) such as cystatin C (cys) compared to small molecules (<900Da) such as creatinine (creat). Recently, the Shrunken pore syndrome (SPS) has been highlighted as a new phenotype of renal dysfunction characterised by an eGFRcys/eGFRcreat ratio < 60-70%. However, no reports examined the pathological association between the eGFRcys/eGFRcreat ratio and glomerular capillary wall. In the present study, we analyzed the clinical and pathological features associated with eGFRcys/eGFRcreat ratio in the patients with IgA nephropathy (IgAN).

Methods: 62 patients diagnosed with IgAN by kidney biopsy were analyzed. Thickness of capillary wall was determined by measuring the distance from endothelial to podocyte plasma membrane according to the past study. To evaluate the effect of muscle mass to creatinine, we measured surface of iliopsoas using CT images.

Results: Subjects with low eGFRcys/eGFRcreat ratio had more iliopsoas muscle mass, higher creatinine, thinner capillary wall, more severe microscopic hematuria (Table 1). The eGFRcys/eGFRcreat ratio was correlated with iliopsoas muscle mass (r=0.36, p=0.012), thickness of capillary wall (r=0.44, p<0.001) and severity of microscopic hematuria (r=-0.47, p<0.001). On multiple regression analysis, only capillary wall and microscopic hematuria contributed to eGFRcys/eGFRcreat ratio.

Conclusions: Present study showed for the first time the IgAN patients with low eGFRcys/eGFRcreat ratio had thinner glomerular capillary wall and more severe microscopic hematuria. Although their renal function was preserved, they might have

filtration impairment according to the concept of SPS. Therefore, it was suggested that it could also be a useful biomarker for impaired GFB in IgAN.

Table 1. Clinicopathological characteristics in 62 subjects.

	eGFRcys/eGFRcreat tertile			
	Low N=21	Intermediate N=21	High N=20	p for trend
eGFRcys/eGFRcreat	0.97 [0.92, 1.00]	1.11 [1.09, 1.13]	1.42 [1.30, 1.55]	
Age, (years)	44 [29, 62]	48 [38, 63]	46 [40, 49]	0.747
Male	42.8% (9)	47.6% (10)	55.0% (11)	0.736
Iliopsoas (cm^2)	1214 [1083, 1436]	1400 [1144, 1930]	1689 [1288, 2054]	0.035
Creatinine (mg/dL)	0.75 [0.60, 1.00]	0.93 [0.78, 1.17]	1.06 [0.84, 1.59]	0.023
Cystatin C (mg/dL)	0.98 [0.89, 1.47]	1.19 [0.85, 1.40]	1.00 [0.77, 1.29]	0.419
Urinary Protein (g/day)	0.72 [0.38, 1.20]	0.41 [0.21, 0.83]	0.57 [0.41, 2.26]	0.974
Urinary RBC				0.004
grade 1 (<10/HPF)	4.7% (1)	4.7% (1)	45.0% (9)	
grade 2 (10-30/HPF)	28.6% (6)	47.7% (10)	35.0% (7)	
grade 3 (30-60/HPF)	28.6% (6)	19.0% (4)	15.0% (3)	
grade 4 (>60/HPF)	38.1% (8)	28.6% (6)	5.0% (1)	
Capillary wall (nm)	368 [333, 423]	410 [392, 442]	480 [428, 524]	<0.001
Foot process effacement (%)	20 [20, 40]	30 [20, 40]	30 [20, 40]	0.590

Median [IQR] or % (N) shown in the table.

SA-PO941

Exploring Differentially Expressed Proteins in Plasma Extracellular Vesicles for Early Detection of IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most common primary glomerulonephritis and may develop end stage renal disease. The overproduction of galactose-deficient IgA1 (Gd-IgA1) leads to the production of autoantibodies, resulting in the formation of nephritogenic immune complexes. Extracellular vesicles (EVs) are cell-derived membranous vesicles encapsulating various proteins, lipids, and mRNAs. We aimed to develop EV-biomarkers for the early diagnosis of IgAN.

Methods: Size exclusion chromatography was used for isolating plasma EVs. A total of 60 plasma samples from individuals with IgAN, chronic kidney injury (CKD), and control group were utilized in this study. Each plasma had been reduced by dithiothreitol (DTT), alkylated by Iodoacetamide (IAA), and digested by trypsin. Tryptic peptides were analyzed using nano-liquid chromatography-mass spectrometry. PEAKS Proteomics, Reactome Pathway Database, FunRich, and Kyoto Encyclopedia of Genes and Genomes (KEGG) analyses were performed to identify differentially expressed proteins in IgAN patients.

Results: There were 86 differentially expressed proteins between the three groups. Of these, 92.9% of the cellular component was associated with the extracellular protein. After analyzing by Reactome Pathway Database, our results showed that the main functional pathways of the EVs from clinical plasma samples were the immune system pathway and the vesicle-mediated transport. We also compared the protein components of plasma-EVs from clinical samples. 12 out of 19 proteins showed significant differences, which may be served as EV markers for IgAN.

Conclusions: We have developed and validated a workflow to isolate plasma-EVs for proteomics analysis, and proteins that showed statistical differences among the three groups were identified. Potential EV biomarkers were discovered in this study and are under validation as well.

SA-PO942

Gut Microbiota Profiles Representing Pathogenic Severity in IgA Nephropathy Patients

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Background: Although immunoglobulin A nephropathy (IgAN) is not a definite genetic disease, it has an autoimmune trait of complex architecture with a solid genetic predisposition. Herein, we aimed to evaluate the difference in microbiota profile among patients with IgAN and healthy controls. In addition, we tried to evaluate the microbiome representing the disease severity.

Methods: We prospectively recruited subjects with IgAN and healthy control between July 2019 and December 2021. Gut microbiota was analyzed using the Illumina MiSeq system based on the 16S rRNA gene. We compared the abundance of the microbiome in each level of phylum, class, order, family, and genus between the groups using Mann–Whitney U test. Also, we tried to find a specific genus representing the disease severity based on the Oxford classification.

Results: A total of 87 subjects (IgAN 59, healthy control 24) were finally included in the study. The mean age was 40.3 and 38.1 years old in IgAN and healthy controls, respectively. The mean eGFR was 89.2 and 107.6 mL/min/1.73 m^2, respectively. At the genus level, there were 32 microbiomes that indicated a detection rate of more than 70% in all of the individuals. In comparing between two groups, the abundance of *Blautia*, *Anaerobutyricum*, *Dorea*, *Romboutsia*, and *Clostridium* was higher in IgAN patients. In contrast, *Prevotella* and *Lachnospira* were significantly lower in IgAN patients. According to the Oxford classification, the microbiome responsible for the difference in the T score was discovered the most, while the microbiome responsible for the difference in the E and S score was discovered the least. The abundance of *Blautia* was higher in T1, but *Prevotella*, *Lachnospiraceae*, *Escherichia*, *Kineothrix*, *Lachnospira*, and *Veillonella* were lower in T1 compared to T0. In contrast, only Coprococcus was detected at a higher level in E1, while Parabacteroides was detected at a lower level in S1.

Conclusions: The gut microbiota was well discriminated in subjects with IgAN from healthy controls. In addition, it was also differently observed according to the status of the pathologic findings of IgAN. These results may provide a basis for further metagenomics analysis of IgAN.

SA-PO943

Urinary Exosomal miRNA Signature of IgA Nephropathy: A Case-Control Study

Mythri Shankar. *Institute of Nephro Urology, Bangalore, India.*

Background: IgAN is a progressive disease. The current gold standard for diagnoses is kidney biopsy-invasive procedure with life-threatening complications. The hour needs a non-invasive, reliable, stable & accurate biomarker.miRNAs are small, non-coding endogenous RNA. Urinary exosomes are rich in miRNA and can be used as novel non-invasive biomarkers. We aim to study the urinary exosomal miRNA signature of pts with IgAN.

Methods: 50 biopsy-proven IgAN pts & 50 healthy controls were recruited in India. Urinary exosomes were isolated & miRNA extracted. Analysis was done with digital multiplexed nCounter® human miRNA Expression Assay which contains 799 unique miRNA barcodes. Lasso regression & consensus clustering were performed to discover significant miRNA.

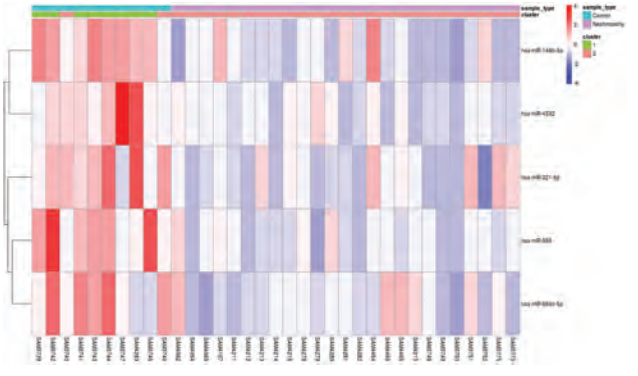
Results: Mean age:36.8yrs. Male:Female=3:1. Mean creatinine & proteinuria : 2.2 mg/dl and 2.9 gms/day respectively. Majority miRNAs were significantly downregulated. A group of 5 candidate miRNAs hsa.miR.146b.3p+hsa.miR.599+hsa.miR.4532+hsa.miR.664b.5p+hsa.miR.221.5p which could successfully differentiate between IgAN cases and healthy controls with very high sensitivity and specificity.

Conclusions: The group of five candidate urinary exosomal miRNAshsa.miR.146b.3p+hsa.miR.599+hsa.miR.4532+hsa.miR.664b.5p+hsa.miR.221.5p has the potential to serve as novel non-invasive biomarkers for IgA nephropathy.

Funding: Government Support - Non-U.S.

Model using the group of 5 miRNAs for diagnosis

Accuracy (95% CI)	1 (0.7151, 1)
Sensitivity	1
Specificity	1
Positive Predictive Value	1
Negative Predictive Value	1
Prevalence	0.18
Detection Rate	0.18
Detection Prevalence	0.18
AUC	1
Number of misclassified samples	0
Wrongly classified samples	NA
Kappa	1



Heat map showing the 5 miRNAs with biomarker potential giving a accuracy of 99%

SA-PO944

Relevance of Serum A Proliferation-Inducing Ligand (APRIL) as a Biomarker in South Asian Prospective Longitudinal Observational IgA Nephropathy Cohort (GRACE-IgANI)

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Background: The role of serum APRIL as a biomarker in a prospective longitudinal South Asian IgAN cohort (GRACE-IgANI) and the impact of immunosuppression (IS) is not known.

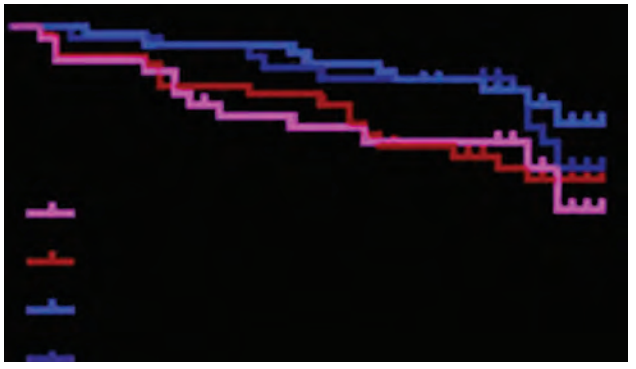
Methods: Serum APRIL levels were measured in baseline and longitudinal sera (1year, 2year & 3year) in IgAN patients, and at baseline in disease controls and healthy controls by ELISA (R&D Systems; Catalog No: DY884B). Short course IS was

given to patients with proteinuria ≥1g/day and/or renal impairment (73%). Composite outcome (CO) was defined as ≥50% fall in eGFR (CKD EPI) from baseline and/or eGFR <15ml/min/1.73m^2 or RRT/death.

Results: Lower baseline serum APRIL levels were diagnostic of IgAN in our cohort compared to disease controls and healthy controls (398 vs. 550 vs. 516 pg/mL, p=0.002). Serum APRIL levels had significant but weak positive correlation with baseline eGFR. MEST-C T1/T2 scores were significantly associated with lower baseline serum APRIL levels (T0: 490 vs. T1/T2: 372 pg/mL, p=0.007). In the treatment group I (low-risk group without IS), there was no significant association with CO at 3year. In the treatment group II (high-risk group with IS), there was significant association between lower serum APRIL levels at 1year, 2year, 3year and CO at 3year (1Y: 590 vs. 356 pg/mL, p<0.001; 2Y: 508 vs. 314 pg/mL, p=0.003; 3Y; 519 vs. 271, p<0.001) and the ROC curve of serum APRIL level at 1year showed good discrimination (AUC 0.75) for CO. There was a significant longitudinal increase in serum APRIL levels from baseline to 1year and which was sustained at 3year (Baseline: 414 vs. 1Y: 590 vs. 2Y: 508 vs. 3Y: 519 pg/mL, p<0.0001) in patients with favorable renal outcome.

Conclusions: Serum APRIL levels were an indepenpendent risk factor for progressive kidney disese in this cohort.

Funding: Government Support - Non-U.S.



SA-PO945

The Level of Poly-IgA Immune Complexes in the Short-Term Efficacy Evaluation and Disease Activity Monitoring of IgA Nephropathy (IgAN)

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Background: The formation of Poly-IgA immune complexes play a key role in IgAN. The levels of poly-IgA in IgAN were higher than those in healthy controls or in controls with non-IgAN disease. The changes of Poly-IgA in patients with IgAN are related to the severity of the disease. Whether Poly-IgA changes after treatment can evaluate the therapeutic effect, whether Poly-IgA level is an independent risk factor for non-remission, and whether it can be combined with other indicators to achieve a more accurate individual evaluation of IgAN patients still needs research.

Methods: 74 IgAN patients in Department of Nephrology, The Third Affiliated Hospital of Southern Medical University from March 17, 2022 to March 28, 2023 were recorded. 54 individuals had been treated with corticosteroids or immunosuppressants. Paired-samples T test was used to compare the levels of Poly-IgA before and after treatment. 39 of them with proteinuria > 0.5g/ day at the beginning or after treatment were selected for short-term efficacy Evaluations. They were divided into two groups based on changes in urinary protein(UP) levels before and after treatment. Patients with UP level less than 0.5g/ d after treatment were classified as remission group, otherwise as non-remission group. Risk factors for its short-term efficacy were analyzed using logistic regression.

Results: 54 IgAN patients were enrolled to compare the levels of Poly-IgA before and after treatment. We found out that the levels of Poly-IgA before treatment (Mean=18.91, SD=3.73) was significantly higher than that after treatment (Mean=14.24, SD=10.49), (P=0.01). The multivariate logistic regression identified that for every 0.306 increase in levels of Poly-IgA after treatment, the risk of disease progression in IgAN patients increased by 35.8%(P=0.022).

Conclusions: The findings suggest that elevated Poly-IgA levels after treatment are associated with an increased risk of non-remission in IgAN patients. Therefore, monitoring Poly-IgA level can be used as a valuable biomarker to evaluate the efficacy of IgAN. Further studies are needed in the future to validate these findings and to explore the potential of combining Poly-IgA with other measures to construct and optimize models for evaluating short - and long-term outcomes in IgAN patients to more accurately personalize the assessment of IgAN patients.

SA-PO946

Correlation of Immunoglobulin A/Complement Factor 3 (IgA/C3) Ratio with the Clinico-Histological Characteristics and Outcome in IgA Nephropathy

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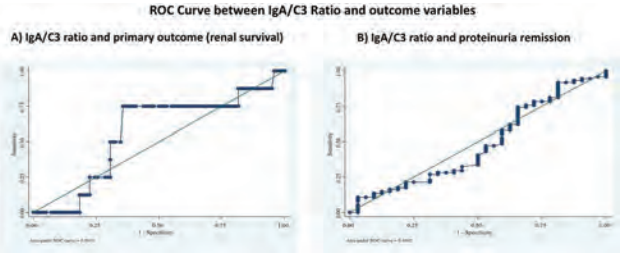
Background: IgAN is a heterogenous disease and has an aggressive clinical course in Asians. The serum IgA/C3 ratio at biopsy has been shown to correlate well with the prognosis of IgAN in few studies. We conducted this study to evaluate this non-invasive biomarker in our patients.

Methods: In an ambispective study we evaluated the baseline serum IgA and C3 levels, and IgA/C3 ratio in patients with biopsy proven primary IgAN and eGFR ≥ 30 ml/min/1.73m^2. For the patients recruited retrospectively, the same was determined from serum samples stored in a biorepository at the time of kidney biopsy. The ratio was evaluated in relation to the clinical severity at the time of presentation in terms of eGFR and proteinuria and histological severity assessed using the Oxford classification. We also assessed the role of the baseline IgA/C3 ratio as a prognostic biomarker in this cohort. The primary outcome assessed was renal survival which was defined as absence of > 40% decline in eGFR and/or progression to end stge renal disease. Remission of proteinuria was defined as urinary protein creatinine ratio(UPCR) <1g/g with stable renal function (≤ 25% decline in eGFR).

Results: 106 patients with a median follow-up period of 17.3 months with a median serum creatinine of 1.3 (0.4-2.6) mg/dl at presentation were analyzed. 46 patients (43.4%) had a baseline eGFR < 60 ml/min/1.73m^2. The mean UPCR at baseline was 2.1 ±1.6 g/g with 18 patients (17.0%) having nephrotic range proteinuria. The median IgA/C3 ratio in the population was 2.5 (0.79-4.75). The serum IgA/C3 ratio at baseline did not corelate with the baseline eGFR, proteinuria and the MEST-C characteristics. The ratio did not predict the primary outcome or the remission of proteinuria.

Conclusions: Future studies with larger sample size, milder cases, longer follow up period and a serial measurement of IgA/C3 are warranted for better clarification of any possible role of this biomarker in IgAN in our population.



SA-PO947

Association of Anti-EPOR Antibodies with Clinicopathological Findings in Patients with IgA Nephropathy

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Background: Disease severity in immunoglobulin A nephropathy (IgAN) is mainly determined by pathological findings. Noninvasive and more convenient biomarkers are thus required for evaluating its activity. In previous studies, the presence of autoantibodies to the erythropoietin receptor (anti-EPOR antibodies) has been shown to be associated with high disease activity and kidney function decline in patients with various kidney diseases including lupus nephritis, type 2 diabetes, and anti-neutrophil cytoplasmic antibody-associated vasculitis. In this study, we therefore investigated the association of anti-EPOR antibodies with clinical and pathological findings in patients with IgAN.

Methods: This retrospective cohort study included 56 patients with biopsy-proven IgAN between 2006 and 2016 at Kanazawa University Hospital. Serum anti-EPOR antibodies at kidney biopsy were measured by using enzyme-linked immunosorbent assays. We then evaluated the associations of anti-EPOR antibodies with clinical and pathological characteristics.

Results: The presence of anti-EPOR antibodies was detected in 12 (21%) patients. Mean age, eGFR, and hemoglobin were comparable at baseline between the patients with and without anti-EPOR antibodies. Serum IgA/C3 ratio was higher in patients with anti-EPOR antibodies than those without (4.33 versus 3.19, p = 0.001). For pathological findings, patients with anti-EPOR antibodies were more likely to have active glomerular lesions, such as crescents or adhesions, compared to those without (91.7% versus 66.7%). During mean follow-up of 7.6 years, no statistical differences were found in annual eGFR declines between the patients with and without anti-EPOR antibodies (Mean±SD: 1.4±3.8 vs. 3.0±3.8 ml/min/1.73 m^2/year).

Conclusions: The presence of anti-EPOR antibodies may reflect disease activity in patients with IgAN.

Funding: Government Support - Non-U.S.

SA-PO948

Rate of Loss of eGFR and Time-Averaged Proteinuria in IgA Nephropathy (IgAN) Patients Progressing from Early-Stage Disease to Kidney Failure

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Background: Cohort studies in IgAN have analyzed time-averaged proteinuria (TA-PU) and eGFR decline over long-term follow-up (f/u), and randomized controlled trials typically measure proteinuria and eGFR over 1-2 years, but none compare disease progression in early vs later stages of disease. In this study of patients enrolled into the UK National Registry of Rare Kidney Diseases (RaDaR) with biopsy-proven IgAN and f/u data spanning early-to-late CKD stages, we present preliminary findings comparing the extent of proteinuria (PU) and eGFR decline prior to and after entering CKD stage 3B.

Methods: Linear regression of eGFR values from baseline (first PU value ≥6mo after diagnosis) until kidney replacement therapy initiation or end of f/u was used to define patient's Time0 as the estimated date their eGFR passed 45. Longitudinal PU was assessed as TA-PU. Differences in eGFR slope and TA-PU before and after Time0 were analyzed using multilevel models and paired t-test; patients were required to have ≥3 eGFR and ≥2 PU values before and after Time0.

Results: eGFR decline was rapid and comparable in the 2 periods, either unadjusted or adjusted for age and sex (Table 1A; Figure). TA-PU was 41.4% greater in patients after progressing through the 45 ml/min/1.73m^2 threshold than before reaching this mark (Table 1B).

Conclusions: Given the comparability of eGFR decline prior to and after passing an eGFR of 45ml/min/1.73m^2, slope measurements in early disease stages may be useful in estimating future eGFR loss. Comparability of eGFR slopes but differences in TA-PU suggest patients with stable rates of eGFR loss suffer increasing damage to the glomerular filtration barrier.

Funding: Commercial Support - Travere Therapeutics, Inc.

Figure 1: Mean annualized eGFR slopes (95% CI) pre and post an eGFR threshold of 45 ml/min/1.73m^2

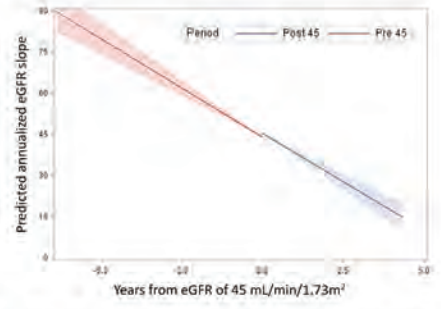

Table 1: Mean annualized eGFR slopes (95% CI) pre and post an eGFR threshold of 45 ml/min/1.73m^2 (A) and TA-PU prior to and after the eGFR threshold (B)

A (n=184)	Annualized mean slope (95% CI) pre eGFR 45 threshold	Annualized mean slope (95% CI) post eGFR 45 threshold	Difference (95% CI) after threshold
Unadjusted	-7.2 (-8.4, -6.0)	-7.0 (-8.2, -5.8)	0.13 (-0.19, 0.45)
Age-sex adjusted	-7.2 (-8.4, -6.0)	-7.0 (-8.2, -5.8)	0.14 (-0.18, 0.46)
B (n=195)	**TA-PU prior to eGFR 45 threshold**	**TA-PU after eGFR 45 threshold**	**Mean (95% CI) difference**
Median, g/g (IQR)	1.11 (0.64, 1.89)	1.57 (0.95, 2.67)	0.416 (0.077, 0.756)

SA-PO949

Comparative Analysis of Clinical and Pathological Traits in IgA Nephropathy with Nephrotic Range Proteinuria Based on Serum Albumin Level

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Background: Presently, the clinical outcomes associated with IgA nephropathy exhibiting heavy proteinuria and the potential correlation between decreasing serum albumin levels and adverse prognosis have not been conclusively established. The present study was designed to elucidate the clinical and pathological characteristics of IgA nephropathy patients who present with nephrotic-range proteinuria, particularly in relation to serum albumin levels.

Methods: This retrospective study was conducted using data from biopsy-confirmed IgA nephropathy patients presenting with nephrotic-range proteinuria between 2017 and 2022 from eight university-affiliated hospitals in South Korea. Patients were stratified into two groups based on a serum albumin level of 2.5g/dl. The study involved a comparative assessment of clinical and pathological characteristics across these two groups, as well as an evaluation of clinical prognosis with respect to the end-stage kidney disease (ESKD).

Results: The analysis included a total of 105 patients. Of these, 86 patients had a serum albumin level above 2.5g/dl (designated as the preserved albumin group, or PA group), while 19 patients had levels below 2.5g/dl (designated as the decreased albumin group, or DA group). The baseline characteristics of the two groups were found to be statistically similar. The mean age of the patients was 46.25 years, and 45.71% were male. Serum erythrocyte sedimentation rate, total cholesterol and low-density lipoprotein-cholesterol levels were significantly higher in the DA group. Pathological findings revealed more pronounced global sclerosis, interstitial fibrosis, and tubular atrophy in the PA group. Diffuse foot process effacement was more prominent in the DA group. During a median follow-up period of 23.64 months (range 0.03-69.53 months), 22 patients (25.58%) in the PA group progressed to ESKD, compared with 1 patient (5.26%) in the DA group. There was no statistically significant difference between the two groups in terms of progression to ESKD (P = 0.055).

Conclusions: In patients with IgA nephropathy presenting with nephrotic-range proteinuria, a decline in serum albumin levels was associated with less chronic lesions, and it was not found to be associated with adverse prognosis.

SA-PO950

Application of Prediction Tools in Patients with IgA Nephropathy: A Single-Center Cohort

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Background: IgA nephropathy (IgAN) is the most common glomerular disease. Despite the development of prognostic scores, such as then IgAN Prediction Tool (IgAN-PT), long-term clinical course is difficult to predict. The Kidney Risk Failure Equation (KFRE) is a four-variable equacionar which allows to predict the two and five-year probability of requiring kidney replacement therapy (KRT), but its accuracy on IgAN has not been established. The aim of this study was to assess the discriminative ability of the KFRE compared to the IgAN-PT to predict KRT in patients with IgAN.

Methods: We conducted a retrospective analysis of patients with IgAN followed by the Nephrology and Kidney Transplantation Department in Centro Hospitalar Universitário Lisboa Norte for five years. The primary outcome was the need for KRT within five years after kidney biopsy. The IgAN-PT and the four-variable KFRE were calculated for multiple follow-up points.

Results: Twenty-nine patients were included and 58.6% were male. At presentation, mean age was 41.3 ± 13.6 years, serum creatinine was 1.60 ± 1.17 mg/dL, and proteinuria was 1360 ± 1120 mg/g. At biopsy, the five-year KFRE score was 13.9 ± 25.6% and the five-year IgAN-PT score was 14.7 ± 15.9%. Three patients started KRT (10.3%) during follow-up. Proteinuria at presentation (3032 mg/g vs. 1159 mg/g, p=0.004) and serum creatinine on kidney biopsy (2.81 mg/dL vs. 1.35 mg/dL, p=0.003) were associated with need for KRT. Both the IgAN-PT and the KFRE correctly identified patients with higher risk for KRT, with the KFRE equation at clinical presentation exhibiting a slight superiority over the IgAN-PT (AUC 0.885 vs. 0.846).

Conclusions: The KFRE score at five-years after clinical presentation in patients with IgAN has shown excellent discriminative ability for identifying patients at risk of KRT. Moreover, it has demonstrated equivalent accuracy compared to the more specific IgAN-PT, being easier to apply and allowing for longer-term prognosis.

SA-PO951

Cnm-Positive Streptococcus mutans, a Major Pathogen of Dental Caries, May Cause IgA Nephropathy via Tonsils

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Background: The presence of *Streptococcus mutans*, a major pathogen of dental caries, expressing Cnm protein encoded by *cnm* in the oral cavity has been associated with the pathogenesis of IgA nephropathy (IgAN). Although tonsillectomy is applied for the treatment of IgAN, its effectiveness in the patients harboring *cnm*-positive *S. mutans* in the oral cavity is not clear. This study aimed to investigate the effects of tonsillectomy on patients with IgAN who harbor *cnm*-positive *S. mutans* in the oral cavity.

Methods: The presence of *cnm*-positive *S. mutans* was analysed by polymerase chain reaction in saliva specimens from 117 patients with IgAN. The patient's history of tonsillectomy was examined, and they were divided into four groups based on the results of *cnm*-positive *S. mutans* detection and tonsillectomy history: group A (n=52) (tonsillectomy (-), *cnm*-positive *S. mutans* (-)); group B (n=35) (tonsillectomy (+), *cnm*-positive *S. mutans* (-)); group C (n=16) (tonsillectomy (-), *cnm*-positive *S. mutans* (+)), and group D (n=14) (tonsillectomy (+), *cnm*-positive *S. mutans* (+)). The subjects' clinical parameters were analysed.

Results: The proportion of patients with an estimated glomerular filtration rate <60 mL/min was significantly higher in group C than the other groups ($p < 0.0083$). The proportion of proteinuria 2+ or higher was significantly higher in group C than the other groups ($p < 0.0083$). In the *cnm*-positive *S. mutans* (+) groups, serum IgA was significantly lower in tonsillectomy group than in non-tonsillectomy group (266.9mg/dl vs 358.9mg/dl, $p < 0.05$).

Conclusions: These results suggest that the exacerbation of IgAN by *cnm*-positive *S. mutans* may be mediated by the tonsils and tonsillectomy may be effective in patients with IgAN who harbor *cnm*-positive *S. mutans* in the oral cavity.

SA-PO952

Porphyromonas gingivalis Infection in Oral Cavity Is Associated with Elevated Galactose-Deficient IgA1 in IgA Nephropathy

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Background: The association between Porphyromonas gingivalis, a major periodontal bacteria, and the pathogenesis of IgA nephropathy (IgAN), with a focus on galactose-deficient IgA1 (Gd-IgA1), has not been fully understood.

Methods: Saliva samples were obtained from 30 IgAN patients and 44 patients with chronic kidney disease (CKD) to analyze the presence of P. gingivalis using PCR with a specific set of primers. The association between P. gingivalis detection and clinical parameters, including plasma Gd-IgA1, was analyzed for each group.

Results: IgAN group showed a significantly higher serum Gd-IgA1 level than CKD group ($p < 0.05$). *P. gingivalis*-positive group had a significantly higher serum Gd-IgA1 level than *P. gingivalis*-negative group in IgAN and CKD patients ($p < 0.05$). *P. gingivalis*-positive group in IgAN patients also showed a significantly higher serum Gd-IgA1 level than *P. gingivalis*-negative group in IgAN patients ($p < 0.05$). As for kidney biopsy findings, *P. gingivalis*-positive group exhibited a significantly higher frequency of the existence of segmental glomerulosclerosis than *P. gingivalis*-negative group when evaluating by the Oxford classification of IgAN ($p < 0.05$).

Conclusions: Our results suggest that *P. gingivalis* presence in oral cavity may be associated with IgAN pathogenesis due to induction of elevated level of Gd-IgA1.

SA-PO953

Validation of the International Immunoglobulin A (IgA) Risk Prediction Tool in American Indians and Hispanics

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Background: The International IgA risk prediction equation performance has not been studied in the Hispanic and American Indian population. Studies have reported a higher frequency of IgAN in American Indians. Therefore, we conducted this single-center study based in New Mexico to assess the performance of the International IgA risk prediction tool without race/ethnicity.

Methods: We searched the University of New Mexico kidney biopsy registry - a repository of kidney biopsies from 2002 -2016 - for instances of IgA nephropathy. We calculated the 5-year risk of developing kidney failure and assessed the equation performance using the metrics of calibration, discrimination, and overall prediction error in patients with primary IgA nephropathy on whom the predictions variables were available.

Results: Thirty-four patients were included, most of whom identified as of Hispanic race/ethnicity (44.1%), or as American Indians (26.5%). At biopsy, the median (IQR) age, serum creatinine, and spot urine protein to creatinine ratio were 38 years (27-45), 2.15 mg/dl (1.51-3.04), and 2.7 g/g (1.5-5.8), respectively. The equation identified patients at high risk of developing kidney failure early with a concordance statistic of 0.79 (95% CI 0.68 – 0.89). The agreement between observed and predicted outcomes at 5 years was marginal, with over-estimation of risk for patients with low observed risk and vice versa. Overall prediction error was suboptimal in this cohort [index of prediction accuracy 0.34 (0.03 -0.51)].

Conclusions: The International IgAN risk prediction equation without race accurately identified patients at elevated risk of developing kidney failure. At 5 years, the agreement between the observed and predicted outcomes was sub-optimal, possibly due to advanced kidney disease in this cohort. A diverse development population may improve the risk prediction.

Performance measures of the International IgAN Risk Prediction Tool without race in the study cohort

Metric	Value
Discrimination	
C-Statistics at 5 years	0.79 (0.64 – 0.79)
Area Under the Curve at 5 years	0.79 (0.68 – 0.89)
Calibration	
Observed/Estimated Risk at 5 years (O/E)	0.88 (0.51 – 1.25)
Calibration Intercept	0.10 (-0.37 – 0.58)
Calibration Slope	3.03 (0.43 – 5.64)
Overall Prediction Error	
Index of Prediction Accuracy (IPA)	0.33 (0.02 – 0.50)

SA-PO954

Challenges and Lessons Learnt Learned from Industry-Driven Multi-Centre Global Clinical Trials in IgA Nephropathy (IgAN): Site Investigators' Perspective

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Background: IgA nephropathy (IgAN) is the most common glomerulonephritis worldwide. Recently, many promising bio-molecules are being studied in clinical trials which are industry sponsored, multi-centre and global. Does the uniform protocol across the centers really reflect the regional practices or standard of care in a geographically varied disease like IgAN?

Methods: This was the site investigators' perspective after being involved in 5 ongoing industry driven phase 2/3/OLE multi-centre clinical trials in IgAN. More than 20 eligible patients were enrolled from one of the largest not-for profit quaternary medical centre in South India over a span of 3 years. We are highlighting some of the best practices and some of the regional challenges for participants.

Results: Consent process- The entire process of providing trial related information, informal consultations with relatives and family doctors before providing an informed written consent could take 3-4 months. The strength of this long-drawn pre-consenting phase is improved overall retention and minimal drop-outs. **Screening phase-** In India, it is common to test positive for latent tuberculosis using IGRA tests due to community exposure. This is one of the major impediments for recruitment as otherwise they would have received immunosuppression in the absence of active disease. Another major road block was the anti-hepatitis B core antigen testing in the absence of hepatitis B surface antigen or hepatitis B viral DNA positivity. **Recruitment and Retention phase-** Flexible appointment times, frequent reminders and good rapport with the clinical trial team gained the participants' trust and helped in retention. Reimbursement of actual expenses is vital to ensure proper visits and compliance to treatment. Investigators meetings and regular newsletters helped us to track recruitment and SAEs at a global scale. **Post trial access-** Indian regulatory approval for open label extension is long drawn which has directly affected the post-trial access to potentially valuable bio-molecules for participants in phase 2/3 clinical trials.

Conclusions: Industry driven global clinical trials are indispensable but sponsors could consider some regional modifications in the entry criteria and post-trial access. This also highlights the need for academic trials that repurpose the already available molecules.

SA-PO955

A Multi-Targeted Serologic Approach for Antigen-Specific Diagnosis of Membranous Nephropathy (MN) in the Clinical Routine

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Background: MN is caused by circulating antibodies (ab) targeting PLA2R1 or THSD7A in 70-80% of cases. Over the last years a diverse repertoire of other potential antigens has been identified, however, it remains unclear how an autoantibody-specific diagnostic workflow in patients with MN can be implemented in clinical routine.

Methods: We implemented a multi-targeted serologic screening procedure, which allows detection of ab directed against sensitive, conformational epitopes of multiple antigens within one experiment. Results were validated using ELISA, Western blot and immunohistochemistry of kidney biopsies. The clinical applicability of this system was tested in 410 patients with biopsy-proven MN.

Results: A PLA2R1-induced MN was diagnosed in 307 (74.9%) of 410 patients. Using our multi-targeted serology screening approach, we identified 17 (4.2%) NELL1-ab positive patients, 10 (2.4%) THSD7A-ab positive patients and 12 (2.9%) patients with circulating ab against one of the other antigens (PCDH7, HTRA1, NTNG1, CNTN1, or SEMA3B). Interestingly, 5 of these 12 patients showed ab against two different antigens simultaneously. Every ab result was validated using Western Blot showing concordance of results in 95% of cases. 20 (31.2%) of the remaining 64 sera showed reactivity to different preparations of human glomerular extract (HGE), indicating that for each antigen, ab detectability is strongly dependent on the experimental protocols used to extract the HGE antigens. 83% of patients with no reactivity to any antigen or the HGE in any experimental condition, had a remission of proteinuria, in 66% of them it was a spontaneous remission without use of immunosuppression.

Conclusions: We report a multi-targeted serologic approach, which allows an antigen-specific diagnosis of MN within days and is therefore applicable in clinical routine. To fully accomplish an antigen-specific MN diagnosis in every patient, sera with reactivity to HGE are used for antigen identification via immunoprecipitation. The 10% of cases with no serologic activity show a good prognosis, while antigen identification is performed by tissue-based mass spectrometry. For the implementation of the later two steps into clinical routine further adjustments are required, especially concerning the turn-around time for antigen identification.

Funding: Government Support - Non-U.S.

SA-PO956

Monoclonal Characterization of Autoreactive PLA2R1 Antibody Responses in Membranous Nephropathy (MN)

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Background: Membranous nephropathy (MN) is caused by circulating antibodies, which in 70-80% of cases are directed against PLA_2R1. The CysR domain of the PLA_2R1 is the immune dominant domain and all patients with PLA_2R1-induced MN exhibit antibodies against this domain of the protein. Today, all treatment options for MN are unspecific concerning the molecular disease pathogenesis.

Methods: We isolated PBMCs from patients with PLA_2R1-induced MN. Using tagged PLA_2R1, PLA_2R1-specific B cells were isolated and the corresponding B cell receptors were cloned, in order to produce monoclonal human PLA_2R1-antibodies (PLA_2R1-mAb) corresponding to autoantibodies from patients with MN. The inhibitory potential of these PLA_2R1-mAb for human PLA_2R1-antibody binding to PLA_2R1 was tested *in vitro* by competition ELISA using 60 sera from patients with PLA_2R1-induced MN and *in vivo* in a rat model, which expresses the human PLA_2R1 ($hPLA_2R1$) specifically on podocytes.

Results: In total, four PLA_2R1-mAb were cloned from PLA_2R1-specific B cells from patients with MN and bound epitopes on the CysR domain. Every PLA_2R1-mAb was tested for its inhibitory capability using 60 PLA_2R1-antibody positive sera from patients with PLA_2R1-induced MN. The PLA_2R1-mAb inhibited the PLA_2R1-antibody binding capacity of the patient sera by 45% - 96%. The inhibitory effect of each PLA_2R1-mAb was independent of the PLA_2R1-antibody level of the sera; i.e. the PLA_2R1-mAb with the highest inhibition of 96% exhibited a PLA_2R1-antibody inhibition of 95%, 96% and 96%, when sera with PLA_2R1-anitbody level of 40-79 U/ml, 80-250 U/ml and > 250 U/ml were used, respectively. PLA_2R1-mAb were injected into a rat with podocyte-specific $hPLA_2R1$-expression prior to passive transfer of human PLA_2R1-antibodies from patients with MN. This PLA_2R1-mAb led to an inhibition of PLA_2R1-antibody binding by 80% *in vivo*.

Conclusions: We report for the first time the characterization of human monoclonal antibodies specific for PLA_2R1 derived from memory B cells of MN patients. Cloned autoantibodies showed strong inhibition of PLA_2R1 autoantibody binding both *in vitro* and *in vivo*, opening the possibility of a potential PLA_2R1 epitope specific treatment.

Funding: Commercial Support - Novartis, Basel, Switzerland, Government Support - Non-U.S.

SA-PO957

Utility of Anti-PLA2R and Anti-THSD7A Antibodies in Predicting Membranous Nephropathy Recurrence: A Multi-Center Retrospective Cohort Study

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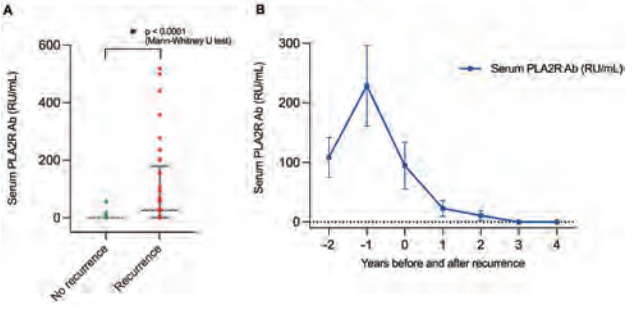
Background: Membranous nephropathy (MN) is a leading cause of nephrotic syndrome, frequently leading to kidney failure. The discovery of autoantibodies against podocyte antigens, including PLA2R and THSD7A, is a major advancement in our understanding of disease pathophysiology. The predictive value of PLA2R and THSD7A serum Abs in detecting recurrent MN remains undefined.

Methods: Through the Post-Transplant Glomerular Disease (TANGO) Consortium, we initiated a multi-center retrospective cohort study, investigating MN post-Tx, using clinical data and serum samples. Adults with biopsy-proven MN, transplanted between 2005-2021, were identified to study the predictive value of PLA2R and THSD7A in detecting recurrence.

Results: 22,921 patients were screened by 16 Tx centers across 3 continents. 86 kidney Tx recipients with biopsy-proven MN were included for anti-PLA2R Abs assessment. 46 patients were also screened for anti-THSD7A Abs. 37 patients (43%) developed recurrence at a median of 3.5 years (IQR: 1.5-6.1). Of these, 22 (59%) tested positive for anti-PLA2R Abs prior to recurrence. All 46 patients tested negative for anti-THSD7A Abs. The mean anti-PLA2R Abs for samples collected prior to recurrence was 136.9 RU/mL (95 CI: 55.7-218.2). These were taken with a median of 2.7 months (IQR: 12.9 – 0.1) before recurrence. Patients with recurrence had higher anti-PLA2R Ab than patients without (Figure 1A). Therapy consisted of RAAS inhibition for 30 patients (81%) and/or rituximab in 21 (56%) of the cases. After treatment, anti-PLA2R Abs notably decreased, with a mean of 13.9 RU/mL (95 CI: 3.7-24.1). These were taken with a median of 25.1 months (IQR: 4.0 – 54.6) after recurrence (Figure 1B).

Conclusions: The presence of anti-PLA2R antibodies may have predictive value in detecting recurrent MN post-transplant. Monitoring anti-PLA2R antibody levels and implementing appropriate therapies, in particular rituximab, could potentially aid in the management of recurrent MN.

Figure 1 | Comparison of anti-PLA2R Ab levels between patients with and without MN recurrence (A) and (B) serial anti-PLA2R Ab levels before and after MN recurrence.



SA-PO958

Effects of Rituximab on T Lymphocyte Subsets in the Treatment of Idiopathic Membranous Nephropathy and Its Significance

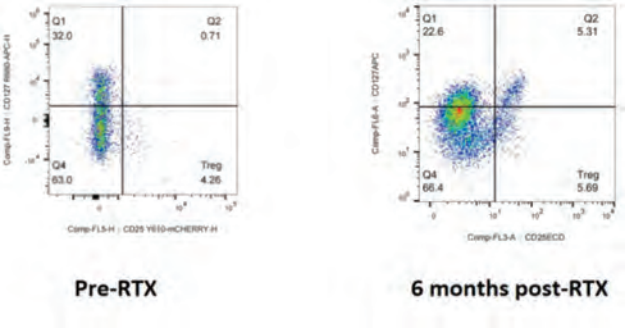
Lei Shen,[1] Yuanyuan Zhang,[2] Jingjing Yang,[1] Jiani Sun,[1] Jianzhong Li.[1] *[1]The First Affiliated Hospital of Soochow University, Suzhou, China; [2]Suzhou Hospital, Affiliated Hospital of Medical school, Nanjing Universtiy, Suzhou, China.*

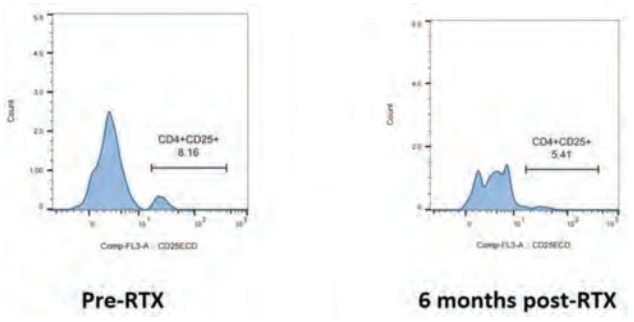
Background: We studied T lymphocyte subsets in patients with idiopathic membranous nephropathy (IMN) and examined the impact and significance of rituximab (RTX) on these subsets.

Methods: We examined peripheral blood lymphocyte subsets in 58 patients with IMN and 25 normal controls by flow cytometry. We followed up the above indicators in 33 patients for 6 months after RTX administration. We also evaluated the changes of anti-PLA2R antibody titers and 24-hour urinary protein before and after treatment.

Results: 1. Compared to the control group, peripheral blood CD3-CD19+B cells, CD3+ T cells, CD3+CD4+T cells, CD4+/CD8+, CD4+CD25+ T cells were significantly higher in IMN group before treatment($P<0.05$). The levels of peripheral blood Treg cells ($CD4+CD25+CD127^{lo}$), CD3+CD8+ T cells in IMN group were lower($P<0.05$). 2. After 6 months of RTX treatment, all the above abnormal indicators were reversed,especially Treg and CD4+CD25+ T cells($P<0.05$) 3. Before and after RTX treatment, the changes of peripheral blood CD4+ T lymphocyte subsets of IMN patients were not correlated with B lymphocyte counts and anti-PLA2R antibody titers.

Conclusions: IMN patients exhibit an abnormality in T lymphocyte subsets, particularly in CD4+ T cell subsets. RTX could restore the balance of CD4+ T lymphocyte subsets and enhance the levels of Treg cells. Importantly, this effect is not solely dependent on B lymphocyte depletion or changes in anti-PLA2R antibody titers. These findings suggest that RTX may have a beneficial impact on cellular immunity in IMN patients.





SA-PO959

Anti-PLA2R Antibody Levels and Treatment Response in Primary Membranous Nephropathy (MN)

Anne-Els van de Logt, Coralien Vink-van Setten, Jack F. Wetzels. *Radboudumc, Nijmegen, Netherlands*.

Background: We introduced individualized therapy in patients with MN and positive anti-PLA2R antibodies (PLA2Rab) by IIFT test (*Vink et al. Kidney International Reports 2023*). Treatment (cyclophosphamide combined with steroids) was stopped when the IIFT test (measured at 8, 16, or 24 weeks) became negative. After 8 weeks, 71% of patients were in immunological remission. Unfortunately, 30% of these latter patients needed renewed therapy within 12 months because of immunological and/or clinical relapse. We questioned if quantitative PLA2Rab measurement would predict treatment response.

Methods: Available, stored serum samples were retrieved, and PLA2Rab levels were measured by ELISA in available samples collected at baseline, and 8, 16, and 24 weeks after start of therapy. (EUROIMMUN Lübeck, Germany).

Results: The analysis included 46 incident patients (M/F 35/11, age 59 ± 12 years, serum creatinine 127 µmol/l [98-164], serum albumin 20 g/l [16-25] and urine protein-creatinine ratio 8.2 gram/10 mmol [6.0-11.7]). Baseline PLA2Rab levels were 145 RU/ml [IQR 97-381]. Thirty patients (65%) developed IIFT remission after 8 weeks, and of these 18 developed persistent clinical remission (group A1), while 12 patients received renewed therapy during follow-up (group A2; no clinical remission). Sixteen patients received initial treatment ≥ 16 weeks (group B), with 7 patients needing continued therapy beyond 6 months. PLA2Rab titer was numerically lower in group A compared to Group B (median 120 RU/mL [IQR 91-261] vs 267 RU/mL [142-436], p = 0.059). Patients with baseline ELISA <80 RU/mL (n =7) developed persistent immunological and clinical remission after only 8 weeks of cyclophosphamide. In patients with baseline PLA2Rab > 80 RU/ml neither baseline PLA2Rab levels, nor absolute or percentage change of PLA2Rab levels from baseline to 8 weeks predicted response or duration of therapy. All patients with at 8 weeks PLA2Rab levels > 20 RU/ml required treatment beyond 6 months (n=4).

Conclusions: Changes in PLA2Rab levels after start of therapy are not helpful in guiding treatment decisions. Still, for a limited number of patients quantitative analysis of PLA2Rab levels at baseline and at 8 weeks after start of therapy provides information that can be used in counseling and treatment planning.

SA-PO960

The Genetics of Idiopathic Nephrotic Syndrome at the Population Level

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Background: Genetics play an important role in idiopathic nephrotic syndrome (NS), but our current understanding of clinical-genetic correlations is drawn from small or highly selected studies, with limited representation of different ancestries, ages of onset, and responses to therapy. Here, we present results from a large and broadly-representative cohort of patients with INS who underwent whole exome sequencing.

Methods: 2,009 patients were enrolled and sequenced. The cohort included patients with proteinuric kidney disease with a biopsy showing FSGS or minimal change disease, or NS without biopsy. Patients with a known secondary cause were excluded. The cohort included children and adults of different genetic ancestries, irrespective of family history of NS or prior response to immunosuppression.

Results: Overall, 10.6% of patients were found to have a monogenic variant known to be associated with inherited NS. Across genetic ancestries, the rates of monogenic variant discovery were largely similar, with the notable exception being patients of African ancestry, in whom non-APOL1 Mendelian variants were much less common. Overall, the highest rate of discovery was in steroid-resistant pediatric patients. In adult-onset disease, there was also a significant rate of monogenic variant discovery, including in steroid-sensitive patients -- most of this group featured heterozygous COL4A variants. Pathway analysis showed that GBM-related variants were most common in adult-onset cases, while podocyte genes predominated in pediatric disease. APOL1 high-risk genotypes were associated with risk of ESKD within individuals of African ancestry, as well as faster eGFR decline even in steroid sensitive cases.

Conclusions: In this large cohort of patients with idiopathic NS, exome sequencing analyses provide a diagnostic roadmap for clinical-genetic correlations across the lifespan, ancestry, phenotype, and response to immunosuppression.

SA-PO961

B-Cell Lymphocyte Profiling Identifies Steroid-Dependent Forms of Idiopathic Nephrotic Syndrome Since Disease Onset

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Background: The clinical evolution of steroid-sensitive forms of idiopathic nephrotic syndrome (SSNS) is highly heterogeneous, ranging from non-relapsing or infrequently relapsing patients (NRNS/IRNS), treated only with standard courses of glucocorticoids (GC), to patients who present frequent relapses (FRNS) and lastly to severe patients showing a steroid-dependent course of disease (SDNS). This last group invariably require second-line steroid-sparing agents. Recently, the therapeutic benefit of anti-CD20 monoclonal antibodies in treating SSNS and the discovery of anti-nephrin antibodies in patients with minimal change disease have pointed to a role of B cells in disease pathogenesis. In particular, we and others have shown that memory B cells predict relapse following and before receiving anti-CD20 (rituximab) infusion in patients with mainly SDNS forms of disease. However, a prospective characterization of B cell subsets from disease onset, before GC and other immunosuppressive treatment, is lacking.

Methods: In this study, we characterized by flow cytometry the profile of circulating B-cell subsets in 19 SSNS children (11 males) at disease onset, before starting GC treatment. All patients were then followed for 12 months in order to define the clinical subtype of their form of SSNS based on the frequency of relapses in relation to GC treatment in the subsequent months.

Results: During follow-up, 6 patients never relapsed (NRNS), 3 were classified as FRNS and 10 as SDNS. Mean (SD) age was higher in NRNS patients (8.5±4.1 years) compared to FRNS patients (4.7±2.3 years, p=0.07) or SDNS patients (4.1±1.8 years, p<0.01). When compared with NRNS patients, FRNS patients showed similar amount of total CD19+ (p=0.66), transitional (p=0.43), mature-naive (p=0.25), and memory (p=0.62) B cells. In contrast, SDNS patients had significantly higher levels of all these B-cell subsets compared to NRNS patients (p<0.05). Moreover, they had similar levels of total CD19+ (p=0.16), transitional (p=0.31) and mature-naive B cells (p=0.77), but a significantly higher amount of memory B cells (p=0.04), when compared to FRNS patients.

Conclusions: Increased levels of circulating memory B cells may allow to discriminate SDNS from FRNS starting from disease onset.

Funding: Private Foundation Support

SA-PO962

Kidney Transcriptomics of Blood Pressure (BP) in Minimal Change Disease (MCD) and Focal Segmental Glomerulosclerosis (FSGS)

Christine B. Sethna,[1] Sean Eddy,[2] Fadhl Alakwaa,[2] Markus Bitzer,[2] Patrick H. Nachman,[3] Katherine R. Tuttle,[4] Gentzon Hall,[5] Tarak Srivastava,[6] Daniel C. Cattran,[7] Dorey A. Glenn,[8] Agustin Gonzalez-Vicente,[9] John R. Hartman.[2] NEPTUNE. *[1]Cohen Children's Medical Center, Queens, NY; [2]University of Michigan, Ann Arbor, MI; [3]University of Minnesota Twin Cities, Minneapolis, MN; [4]University of Washington, Seattle, WA; [5]Duke University, Durham, NC; [6]Children's Mercy Kansas City, Kansas City, MO; [7]University of Toronto, Toronto, ON, Canada; [8]The University of North Carolina at Chapel Hill, Chapel Hill, NC; [9]Cleveland Clinic, Cleveland, OH*.

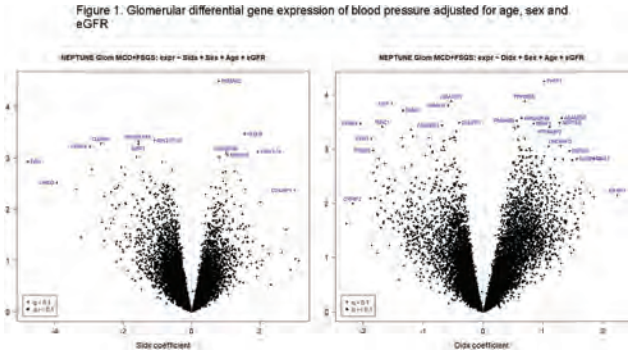
Background: Individuals with MCD and FSGS are at high risk for hypertension and cardiovascular disease, however molecular markers of BP in this population are unknown. The objective was to investigate kidney tissue differential gene expression associated with BP in MCD/FSGS.

Methods: Participants with biopsy-proven MCD or FSGS from the Nephrotic Syndrome Study Network (NEPTUNE) with previously sequenced genome-wide mRNA expression profiling of kidney tissue were included. Glomerular and tubulointerstitial transcriptomics were assessed for differentially expressed (DE) genes in adjusted linear models for enrollment BP. Systolic and diastolic BP were indexed (SBPi/DBPi) to the 95th%ile for children <13 years and to 130 mmHg for those ≥13 years.

Results: Participants included 192 children (age 11 IQR 5-14 yr, 57.3% male) and 370 adults (age 45 IQR 32.8-58.3 yr, 60.8% male), with 28.7% FSGS. Median SBPi was 0.8 IQR 0.70-0.9 and DBPi was 0.87 IQR 0.78-1, with 47.3% on RAAS blockade. Adjusting for sex only, there were 865 genes at 5% and 1622 at 10% FDR associated with SBPi, but none for DBPi. Adjusting for sex, age, and glomerular filtration rate (eGFR) revealed no significant genes for either SBPi or DBPi at 10% FDR (Figure 1). By p-value, the top genes in the SBPi and DBPI models were PNMA8C (p=3.2e-5) and PHTF1 (p=5.6e-5), respectively. There were no DE genes from tubulointerstitial tissue associated with BP.

Conclusions: Though hypertension is an important risk factor for progression of kidney disease, BP was not associated with differential gene expression in kidney tissue after adjusting for common confounders in patients with MCD/FSGS enrolled in NEPTUNE.

Funding: NIDDK Support



SA-PO963

Proteinuria Trajectories Among Patients with Minimal Change Disease (MCD) and FSGS in NEPTUNE

Abigail R. Smith,[1] Margaret Helmuth,[1] Laura H. Mariani.[2] *[1]Arbor Research Collaborative for Health, Ann Arbor, MI; [2]University of Michigan, Ann Arbor, MI.*

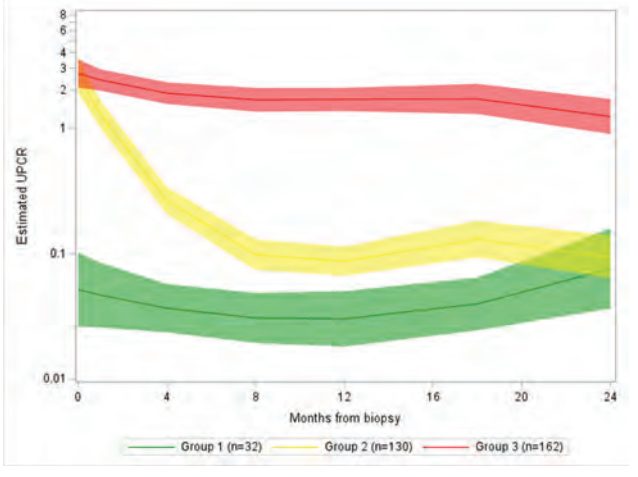
Background: Proteinuria is a primary symptom of nephrotic syndrome and known risk factor for disease progression. Our objective was to identify patient-groups based on longitudinal proteinuria trajectories.

Methods: Patients with minimal change disease (MCD, n=151) and focal segmental glomerular sclerosis (FSGS, n=173) enrolled at the time of biopsy in the Nephrotic Syndrome Study Network (NEPTUNE) were included. Group based trajectory modeling was applied to UPCR measurements from the first 2 years post-biopsy; groups were compared on demographics, clinical presentation, histopathologic features, and eGFR trajectories.

Results: Three groups were identified; Group 1 (n=32) had low proteinuria on average over the first 2 years post-biopsy; Group 2 (n=130) had nephrotic range proteinuria at biopsy that resolved within the first year; Group 3 (n=162) had nephrotic range proteinuria across the 2 years post-biopsy (Figure). Groups 1 and 2 were majority MCD (90% and 58%, respectively); Group 3 was 72% FSGS. Group 3 had more of glomeruli with global sclerosis/obsolescence, segmental obliteration, podocyte abnormalities, interstitial fibrosis/tubular atrophy, interstitial inflammation, and endothelial cell abnormalities. Group 1 was more likely to be treated with immunosuppression (IST, mostly glucocorticoids) prior to biopsy (63%) compared to Groups 2 and 3 (38% and 24%, respectively). By 2 years post-biopsy 92%, 85%, and 66% of Groups 1, 2, and 3, respectively had been exposed to IST. After 2 years post-biopsy eGFR increased by 3.8 ml/min/1.73m^2 per year on average in Group 1, and decreased by 2.2 and 4.6 ml/min/1.73m^2 per year on average in Groups 2 and 3, respectively ($p<0.001$).

Conclusions: Proteinuria trajectories identified patient phenotypes that did not completely align with traditional histopathologic diagnosis. These groups also differ on baseline clinical and histopathologic features that may help predict response to treatment.

Funding: NIDDK Support



Average proteinuria trajectories by group.

SA-PO964

Patients with Primary Focal Segmental Glomerulosclerosis with Detectable Urinary CD80 Are More Similar to Patients with Minimal Change Disease in Clinicopathological Features

Xiaojie Gong, Jing Huang, Zhao Cui. *Peking University First Hospital Department of Nephrology, Beijing, China.*

Background: Focal segmental glomerulosclerosis (FSGS) is an important cause of refractory nephrotic syndrome (NS) in children and adults. Urinary CD80 is elevated in some patients with primary FSGS, however, its clinical value is not fully clarified. This study aims to evaluate the clinical and pathological significance of urinary CD80 in patients with primary FSGS.

Methods: Sixty-one adult patients with biopsy-proven primary FSGS, with standard treatment and long-term follow up, were enrolled retrospectively. Urinary CD80, at the day of kidney biopsy, was measured using commercial ELISA kits and adjusted for urinary creatinine excretion. Their associations with clinical and pathological parameters were investigated.

Results: Urinary CD80 was detectable in 30/61 (49.2%) patients, who presented with a higher level of proteinuria (10.7 vs. 5.8 g/d; P=0.01), a lower level of serum albumin (19.3±3.9 vs. 24.2±8.2 g/L; P=0.005), a higher prevalence of hematuria (70.0 vs. 38.7 %; P=0.01), and showed lower percentage of segmental glomerulosclerosis lesion [4.8 (3.7-14.0) vs. 9.1 (5.6-21.1) %; P=0.06]. The cumulative relapse rate was remarkably high in these patients (log-rank, P=0.001). Multivariate analysis identified that the elevated urinary CD80 was an independent risk factor for steroid-dependent NS (OR 8.81, 95% CI 1.41-54.89; P=0.02) and relapse (HR, 2.87; 95% CI 1.29-6.38; P=0.01).

Conclusions: The elevated urinary CD80 is associated with mild pathological change and steroid-dependent cases of primary FSGS adults, which indicates these patients are more similar to minimal change disease (MCD).

SA-PO965

Clinical Significance of IgM and C3 Immunofluorescence Deposition Patterns in Patients with Focal Segmental Glomerulosclerosis

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Background: The presence of IgM and C3 deposits on immunofluorescence in some patients with Focal Segmental Glomerulosclerosis (FSGS) are considered to be a trapping of these molecules by mesangial sclerosis. However, there are studies that associate these deposits with a worse renal prognosis when compared to patients with negative immunofluorescence or only IgM deposit. We conducted this study aiming to evaluate the association of worse renal outcome with the presence of IgM and C3 deposits in glomeruli of patients from a Brazilian cohort with FSGS.

Methods: This is a retrospective study of clinical, laboratory, light microscopy histopathological and immunofluorescence (IF) data of patients diagnosed with FSGS, in the Nephrology Service of the Hospital das Clínicas of the School of Medicine of USP, from 2009-2017. Through immunofluorescence the patients were divided into four groups: with concomitant IgM + C3 deposition, IgM only, C3 only and without any deposition. These groups were compared to each other regarding data at diagnosis and at the end of follow-up.

Results: In the stipulated period, 114 patients were eligible for the study. The most commonly found IF patterns were concomitant IgM + C3 deposits in 46 patients (40.4%) and no deposits in 43 (37.7%). The other two patterns found were, exclusive IgM or C3 deposition, which occurred in seven (6.1%) and 18 patients (15.8%), respectively. When comparing these four groups, baseline creatinine, final creatinine and final proteinuria were significantly higher in the immunofluorescence groups with IgM + C3 and exclusive C3 deposition. The pattern of Collapsing Glomerulopathy was statistically significantly more frequent in the groups with IgM + C3 and exclusive C3 immunofluorescence (28.2 and 22.2% respectively) compared to those with negative immunofluorescence and exclusive IgM deposition (11.6 and 0% respectively) with $p<0.0001$. These first two groups also had the highest percentages of end-stage renal disease compared to the last two groups.

Conclusions: Our study showed that the presence of IgM and C3 on immunofluorescence is related to a worse renal prognosis. There is a need to return to the theme of a probable participation of the complement system in this disease.

SA-PO966

Identification of Biomarkers for Minimal Change Disease Based on LMD-DIA Technology Quantitative Proteomics

Fanna Liu, Sining Chen. *Nephrology, Guangzhou, China.*

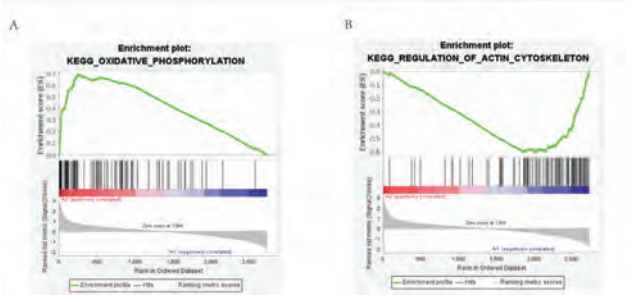
Background: Minimal change disease (MCD) accounts for 80%-90% of idiopathic nephrotic syndrome in children and 10%-15% in adults. There is no apparent pathological change in the kidney tissue under the light microscope, but the podocyte foot process is diffusely disappeared under the electron microscope.

Methods: The kidney tissues of 5 MCD patients and 5 normal patients were selected as the experimental and control group. The three regions of kidney: the glomerulus, renal tubule, and renal interstitium were sequentially cut by using a laser microdissection device. The fold change ≥1.5 was used as the criterion of significant difference to screen different proteins. GO enrichment analysis, KEGG pathway analysis, Gene Set Enrichment Analysis and PPI analysis were performed on the identified differential proteins to determine the target protein.

Results: We found that 552 differentially expressed proteins (DEPs) in the glomerulus group, 61 DEPs in renal interstitium group, 108 DEPs in renal tubular group. After bioinformatics analysis of the DEPs in the glomerular group, we found that the oxidative phosphorylation pathway and regulation of actin cytoskeleton pathway were play a significant role in MCD. In the renal interstitium group, Heterogeneous nuclear ribonucleoprotein K (hnRNP-K) were the most up-regulated DEPs and 4-hydroxyphenylpyruvate dioxygenase (HPD) were most down-regulated DEPs. In renal tubules group. Down-regulated HSP90AB1 have great influence in Akt to increase the apoptosis of renal tubule cell by PI3K–Akt signaling pathway.

Conclusions: ACTN4, ZYX, CSK and CAN1 are potential biomarkers for early diagnosis of MCD. COPD, HPRT, FIBG, HEMO, GTR1 and WBP2 may be the key proteins interacting with the immune compartment of the MCD kidney.

Funding: Government Support - Non-U.S.



SA-PO967

Differential Contributions of C5b-9 and C5a/C5aR1 Pathways to Thrombosis in Thrombotic Microangiopathy (TMA) Patients

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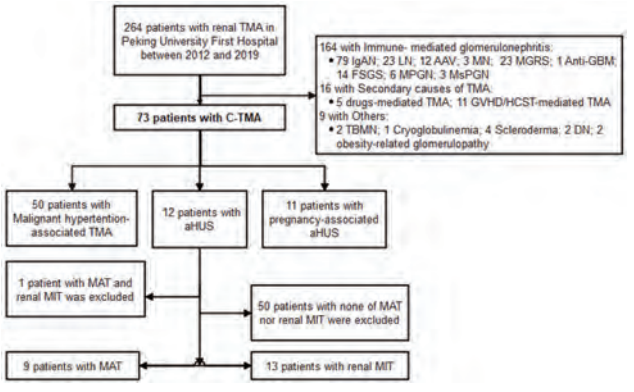
Background: This study aimed to clarify the critical role of C5a/C5aR and C5b-9 pathways in macrovascular thrombosis (MAT) and renal microthrombosis (MIT) formations based on a complement-mediated thrombotic microangiopathy (C-TMA) cohort.

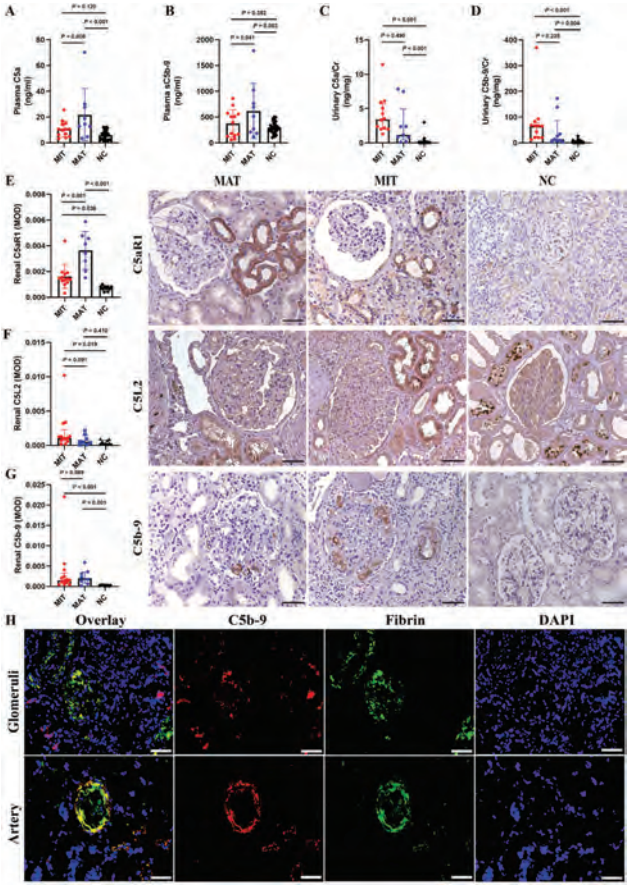
Methods: Seventy-three renal biopsy-proven C-TMA patients from 2012 to 2019 in Peking University First Hospital were collected. Amongst 73 C-TMA patients, 9 patients with pure MAT and 13 patients with pure MIT were selected. Their plasma and urinary C5a and soluble C5b-9 (sC5b-9) levels were evaluated, respectively. C5a receptors and C5b-9 depositions in renal biopsied specimens were assessed.

Results: Compared to patients with pure MAT, patients with pure MIT had lower levels of hemoglobin (P=0.008) and eGFR (P=0.049), and higher renal acute arterial scores (P=0.011). Plasma C5a and sC5b-9 levels were significantly higher in C-TMA patients with MAT than those with MIT (P=0.008, P=0.041, respectively). The mean optical density (MOD) of C5aR1 in the kidney was significantly higher in MAT patients than in those with MIT ($P < 0.001$). No significant difference was found in MOD of C5b-9 or C5L2 in the kidney or urinary C5a and C5b-9 levels between the two groups. However, urinary sC5b-9 level and renal depositions of C5b-9 were both associated with renal MIT formations (P=0.009; P=0.031, respectively).

Conclusions: MAT was not rare in C-TMA patients. The local C5b-9 and C5a/C5aR1 pathways might have differential contributions to MIT and MAT formations in the disease.

Funding: Government Support - Non-U.S.





SA-PO968

Ex Vivo Test of Complement Dysregulation in Atypical Hemolytic Uremic Syndrome Kidney Transplant Patients: A Pilot Study

Caroline Duineveld, Romy N. Bouwmeester, Nicole Van De Kar, Jack F. Wetzels. *Radboudumc, Nijmegen, Netherlands.*

Background: In 2014 the ex-vivo complement assay, which evaluated C5b-9 deposition on cultured endothelial cells, was proposed a possible biomarker for patients with aHUS. In our center eculizumab prophylaxis is not used in aHUS patients after kidney transplantation (Tx). A sensitive biomarker could improve management. The endothelial assay has not been studied in kidney transplant patients.

Methods: Pilot study. Serum samples of transplanted patients with aHUS who were in remission without eculizumab treatment, and transplanted patients with other primary kidney diseases (controls) were blindly evaluated in the complement assay (Noris lab).

Results: We included 13 patients (M 4; F 9) with aHUS, age 54 yrs (range 35-69), time after Tx 5.9 yrs (range 0.25-14.1), and 13 controls (M 7; F 6; age 42 yrs (27-60), time after Tx 5.8 yrs (1.6-11.7). All but 1 patient were treated with a calcineurin inhibitor. There were no significant differences in C5b9 deposits on resting (R) or activated (A) endothelial cells between aHUS patients (R 136%, range 93-382%, A 196%, range 99-388%) and controls (R 121%, range 75-200%; A 170%, range 113-260%, Figure 1). Three aHUS patients and 4 controls showed elevated C5b-9 deposits on resting cells, which should correspond to active aHUS or TMA. None of these patients has laboratory signs of TMA, and during follow-up of 15.8 m (range 6-21), eGFR has remained stable in all. Notably, in 5 aHUS patients with a genetic variant no increase in deposits were found on activated endothelial cells, which contrasts with literature suggesting that a positive test should identify carriers of a genetic variant.

Conclusions: Our data questions the accuracy of the ex-vivo complement assay in kidney transplant patients. We hypothesize that endothelial injury due to transplantation related factors may result in a positive test result. Further study is necessary before the test can be used in routine care for aHUS transplant patients.

Funding: Commercial Support - This work was supported by a research grant from the Dutch Board of Health Insurance Companies (Zorgverzekeraars Nederland)., Government Support - Non-U.S.

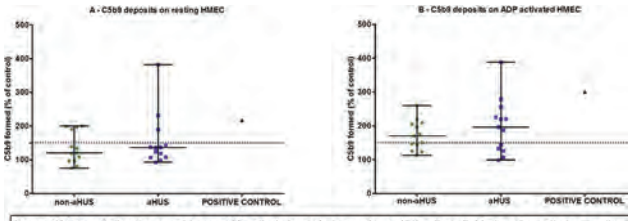


Figure: C5b9 deposits (median, range) in non-aHUS patients (controls, in green) and aHUS patients (in blue) and in a patient with active aHUS in native kidneys, in panel A deposits on resting cells, in panel B deposits on activated cells. C5b9 deposits of >150% is considered abnormal.

SA-PO969

Urinary Acanthocytes and Red Blood Cell Casts for the Diagnosis of Glomerulonephritis and Its Crescentic Forms

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Background: Identification of urinary acanthocytes (uAc) is fairly specific for the diagnosis of glomerulonephritis (GN), but it is perceived as having suboptimal sensitivity. We hypothesized that combining the finding of urinary red blood cell casts (uRBCC) with uAc for the diagnosis of GN, the sensitivity of urine microscopy (uMICRO) as a whole can be optimized. Furthermore, whether uAc provides diagnostic value for identification of more severe (ie, crescentic) forms of GN is unknown.

Methods: Records of patients seen in nephrology consultation who had a uMICRO over a 5-year period were reviewed. We identified cases in which a kidney biopsy was performed within 2 weeks of the uMICRO. We assessed the performance of uAc alone and that of uAc in combination with uRBCC for the diagnosis of biopsy-proven GN or for any glomerular disease (GD). In addition, we evaluated the performance of uAc for the identification of crescentic forms of GN.

Results: Of 747 patients who underwent uMICRO, 217 underwent kidney biopsy. Mean age was 56, 51% women, 47% White, 7% Hispanic, 41% Black. Mean serum creatinine was 3.5 mg/dL. Biopsy diagnosis was GD in 77%, GN in 54%, and others in 23%. The sensitivity (SENS), specificity (SPEC), positive predictive value (PPV) and negative predictive value (NPV) of uAc for diagnosing GN were 62%, 85%, 75% and 76%, respectively. Combining the presence of either uAc or uRBCC, the SENS, SPEC, PPV and NPV changed to 69%, 100%, 100% and 64%, respectively. When examining uAc to predict any form of GD, the SENS, SPEC, PPV and NPV were 45%, 100%, 100% and 35%, respectively. As for crescentic GN, either uAc or uRBCC were found in 29 out of 33 (88%). The SENS, SPEC, PPV and NPV of uAc for crescentic GN were 88%, 42%, 47% and 86%, respectively. Notably, uAc were comnon in IgA nephropathy (71%), pauci immune ANCA (81%), and infection-related GN (IRGN) (83%), but uncommon in lupus GN (29%).

Conclusions: With proficient examiners and well-equipped laboratory, identification of uAc and uRBCC by uMICRO aid in the diagnosis of GN. uAc are pathognomonic of GD. Crescentic forms of GN and certain pathologies (IgA nephropathy, pauci immune ANCA, IRGN) most commonly present with uAc and/or uRBCC.

SA-PO970

Clinical Picture and Outcome of SARS-CoV-2 Infection in Patients with Glomerular Diseases: A Multicenter Retrospective Study

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Background: This is a retrospective study exploring the clinical picture and outcome of sars-cov2 infection in patients with glomerular diseases (GD) and its impact in the probability of GD relapse.

Methods: Patients with biopsy-proven GD, who had been infected by sars-cov2 were studied. Patients who ended up in ESKD prior to infection or received the diagnosis of GD after the sars-cov2 infection were excluded. We recorded demographics, histopathological diagnosis, past medical history, immunosuppressive regimens, status of GD at the time of infection, clinical picture and outcome of the infection and the GD at end of follow up.

Results: 312 patients have been included in the study, of whom 214(68,5%) were diagnosed with sa, while the remaining 98 did not. Infected patients were younger compared with those not infected [44(28-59.75) versus 53(38-64) years, p<0.001]. The mean time from the diagnostic biopsy to Covid-19 was 67,6(±59,3) months. 82,5% of the infected patients were vaccinated against sars-cov2 and 49,1% were on immunosuppressive therapy at vaccination. 28(13%) of the infected patients required admission to hospital, which lasted 8,3(±5,1days. 84,2% of the infected patients experienced complete recovery of the infection, 4(1,9%) died due to Covid-19 and 24(11%) had symptoms for more than 3 months. Among patients who were in remission for the GD, the frequency of relapse of the primary disease was higher in patients with Covid-19 versus not infected patients (11.9% vs. 2.1 %, p=0.007).

Conclusions: According to the findings from this cohort, sars-cov2 infection appears to have a significant impact in patients with GD due to the related morbidity but also by increasing the probability of relapse of the primary disease when compared with patients who not infected with sars-cov2.

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SA-PO971

Anti-Nephrin Autoantibodies Broadly Detected in the General Population and in Non-Kidney Disease Patients

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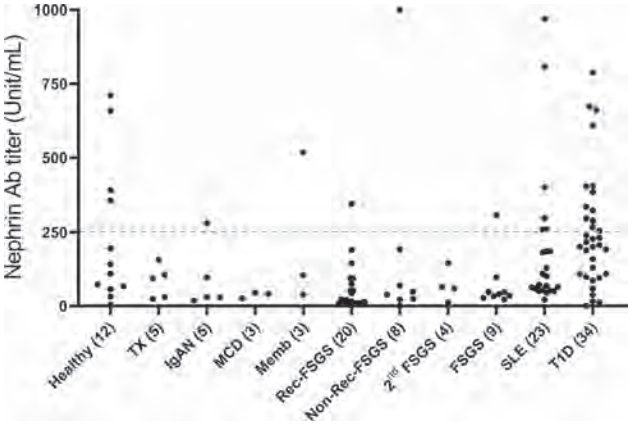
Background: Nephrin is the key structural component of the interpodocyte-spanning slit diaphragm, and mutations of *NPHS1* are associated with congenital nephrotic syndrome. Recently, Watts and colleagues discovered anti-nephrin autoantibodies in patients with MCD (*J Am Soc Nephrol*. 2022 Jan;33:238-252.), suggesting these autoantibodies may be directly attributable to the etiology of podocytopathy and also might play a role in primary FSGS. With our own focus on FSGS, we collected plasma samples from kidney and non-kidney diseases and had them examined for anti-nephrin antibodies.

Methods: We tested a total of 126 plasma samples of recurrent vs nonrecurrent FSGS, primary and 2nd FSGS, MCD, MN, LN, IgAN, TX, T1D with no kidney involvement, and health controls (Fig). Anti-nephrin antibody titers were measured using ELISA coated with recombinant Nephrin extracellular domain (R&D Systems, Cat:9399-NN-050). In addition, we performed Western blotting (WB) analyses of the antisera against nephrin (C-FLAG tagged full-length nephrin from CHO cell transfection with plasmid).

Results: Based on an arbitrary cutoff, a majority of samples were negative for anti-nephrin antibodies, whereas between 5% and 38% of the patients were tested positive for the antibody with varying titers. However, positive antibodies were broadly detected across the spectrum of the disease types, with the highest titer from a nonrecurrent FSGS

patient (post-renal transplant), and the highest percentage of antibody-positive cases in T1D. Consistently, high antibody titers detected by ELISA correlated well with high antibody signals in WB, confirming the robustness of our assays.

Conclusions: Admitting caveats, we were unable to find direct correlations between nephrin autoantibody titer and specific kidney or non-kidney disease types. Further studies are warranted to have a larger sample size, more balanced disease categories, and better methodologies for anti-nephrin autoantibody detection.



SA-PO972

Impact of Kidney Biopsy Findings Including Oxford MEST-C Scores on Kidney Outcomes in IgA Vasculitis Nephritis (IgAVN): A Study of the International IgA Nephropathy Network

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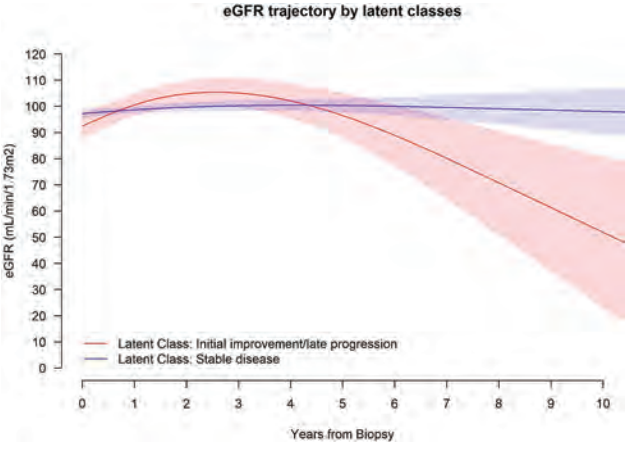
Background: Nephritis is a common manifestation of IgAV and is morphologically indistinguishable from IgA nephropathy (IgAN). However, while MEST-C scores are predictive of outcomes in IgAN, their value in IgAVN has not been widely studied.

Methods: Biopsies from 361 patients with IgAVN (262 children, 99 adults) from 17 centers in N. America, Europe and Asia were independently scored by 3 pathologists. Median time from clinical onset to biopsy was 2.0 mo, median post-biopsy follow-up was 2.7 y, 309 (85.6%) patients received immunosuppression (IS) during follow-up. As few patients developed ESKD or ≥30% eGFR decline, Latent Class Mixed Models (LCMM) were used to analyze eGFR trajectory post-biopsy in patients treated with IS. Association of clinical and histologic parameters with the different classes of eGFR trajectory was examined by logistic regression.

Results: Two classes were identified by LCMM (Figure), one with initial improvement in eGFR followed by a more notable decline (Class 1, n = 91) and one with stable disease (Class 2, n = 218). Among MEST-C scores, only E1 was predictive of Class 1 by multivariable analysis (OR 2.3; 95% CI 1.1,4.5); other scores were not although only 4.5% of patients had T>0. Other predictors of Class 1 were age ≤18 y, male sex, lower eGFR at biopsy, and extrarenal, non-cutaneous disease. Fibrous crescents were predictive of Class 2.

Conclusions: The clinical course of biopsied and treated patients with IgAVN is determined by active lesions, notably endocapillary hypercellularity (E1) which is not part of the ISKDC classification for IgAVN. The results support including MEST-C scores in biopsy reports of IgAVN. Patients with IgAVN, even those with initial therapeutic response, require long-term follow-up due to risk of late renal function decline.

Funding: Private Foundation Support



Classes of eGFR trajectory identified by LCMM. Shaded areas are confidence intervals.

SA-PO973

ANCA Renal Risk Score (ARRS) 2023: The Updated and Revised ARRS

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Background: Reliable prediction tools are needed to improve prognostication and personalisation of treatment in anti-neutrophil cytoplasmic antibody (ANCA) glomerulonephritides (GN). We aimed to update the ANCA Renal Risk Score (ARRS) prediction model.

Methods: We collated a retrospective multicentre international longitudinal cohort from referral centres and registries across the globe to revise the ARRS in a validation and recalibration study. The primary endpoint was end stage kidney disease (ESKD) and patients were censored at last follow-up. Cox proportional hazards models were used to reweight risk factors and develop a modified scoring system. Kaplan-Meier estimates, Harrell's C statistics and calibration plots were used to assess model performance.

Results: Of a total of 1591 patients, 1439 were included in the final analyses (959 in the development cohort, 52% male, median age 64 years). The ARRS demonstrated a discrimination of C=0.800, comparable to the original cohort. Updating the model found an additional useful cut-off for kidney function (K), and serum creatinine replaced glomerular filtration rate which provided higher reliability (K0: <250 μmol/l = 0 points, K1: 250-450 μmol/l = 4 points, K2: >450 μmol/l = 11 points). The risk points for the percentage of normal glomeruli (N) and interstitial fibrosis and tubular atrophy (T) were reweighted (N0: >25% = 0 points, N1: 10-25% = 4, N2: < 10% = 7, T0: none, mild or < 25% = 0 points, T1: ≥ mild-moderate or ≥ 25% = 3 points). We created four risk groups based on the sum of points: low (0 – 4 points), moderate (5 – 11), high (12 – 18) and an additional very high-risk (21). The model discrimination was C=0.831 and a supplemental continuous model was developed to supply a patient-specific annual risk. Three-year kidney survival was 96%, 79%, 54%, and 19%. The ARRS23 performed similarly well in the validation cohort with excellent calibration.

Conclusions: We demonstrated the out-of-sample validity of the ARRS and present the modified and improved score to optimise prognostication and risk stratification for clinical practice and trials.

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SA-PO974

The Use of Antimalarials in Lupus Nephritis Is Associated with Better Response to Therapy and Long-Term Kidney Survival

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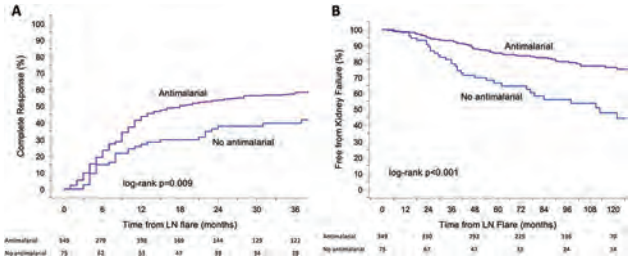
Background: The use of antimalarials (AM) in systemic lupus erythematosus (SLE) has been associated with lower disease flares and long-term damage accrual. Few studies have evaluated the effect of AM in lupus nephritis (LN) cohorts. We evaluated the association between AM use and response to therapy, LN flares, and long-term kidney survival in a large LN cohort.

Methods: The records of 424 patients with biopsy-proven LN were evaluated. We registered the dates of start and end of AM use, the type of AM (hydroxychloroquine [HCQ], chloroquine [CQ], or both), and the temporality of the AM initiation regarding the LN flare (previous and continued use, started at LN flare, or no use). The outcomes of complete response (CR), LN flare, kidney and patient survival were evaluated by uni and multivariable survival analyses.

Results: Out of 424 patients, 349 (82%) used an AM: 53 (13%) chloroquine, 282 (67%) hydroxychloroquine, and 36 (8%) used both AM at different times of follow-up. Of those taking AM, 195 (56%) had previous and continued use and in 154 (44%) the AM was started at flare. The time to CR was shorter in AM users than in non-users (log-rank p=0.009, Figure 1A). The incidence of LN relapses (p=0.017) and kidney failure (p<0.001) was lower in AM users (Figure 1B). The observations of better CR and lower incidence of LN flares and kidney failure with AM use were maintained when the data was analyzed according to the type of AM (HCQ or CQ) as well as the timing of use regarding the LN flare (previous and continued use or started at LN flare). The incidence of maculopathy was 1.2%, 5.9%, and 13.8% by 2-, 5-, and 10-years of AM use. There was no difference in the incidence of maculopathy between users of HCQ or CQ.

Conclusions: The use of AM in lupus nephritis is associated with better response to therapy, lower LN flares, and higher kidney survival. The rates of maculopathy are higher in LN cohorts than in general SLE cohorts.



Time to complete response (A) and kidney survival (B) according to the use of antimalarials.

SA-PO975

Voclosporin Ameliorates Both Proteinuria and Dyslipidemia in a Model of Noninflammatory Glomerular Disease

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Background: Idiopathic nephrotic syndrome (INS) is one of the most frequent glomerular diseases in children. There is a critical need for the development of more effective and less toxic INS treatments. Voclosporin (VCS) is a novel calcineurin inhibitor (CNI) approved in the USA, EU, Great Britain and Switzerland on a background of immunosuppressive therapy for the treatment of adults with active lupus nephritis. VCS does not require therapeutic drug monitoring due to an improved pharmacokinetic profile. We thus investigated whether VCS could reduce proteinuria in *non*-inflammatory glomerular disease using an animal model of nephrotic syndrome (NS).

Methods: Male Wistar rats received 50 mg/kg puromycin aminonucleoside (PAN) or saline via tail vein injection on day 0. Rats were gavaged twice daily with vehicle (VEH), VCS (4 mg/kg/dose), or cyclosporine (CsA, 10mg/kg/dose) at clinically relevant doses. Rats were euthanized on Day 11 and proteinuria, lipid profile, glomerular cell injury (TUNEL), and hypercoagulability (TGA) were measured.

Results: PAN induced proteinuria in all disease groups. VCS ameliorated proteinuria more effectively vs. CsA (mean reduction vs. disease control was 81% vs. 17%, respectively). Mean triglyceride (TG) levels increased by 74% vs. controls in the PAN + VEH group vs. 22% in the PAN + CsA group vs. -26% in the PAN + VCS group. Similarly, PAN induced increases in all other lipid levels vs. controls, while VCS reduced these lipid levels. Flow cytometry TUNEL positivity of isolated glomeruli revealed injury of 2.1% in control podocytes vs. 5.3% in PAN + VEH cells (152% increase) vs. 8.5% in PAN + CsA cells (305% increase) vs. 4.1% in PAN + VCS cells (95% increase). TGA assays revealed that VCS effectively improved PAN-induced hypercoagulopathy.

Conclusions: A clinically relevant dose of VCS ameliorated PAN-induced proteinuria, hypercoagulopathy, and *in situ* glomerular injury in a model of non-inflammatory glomerular disease, without apparent exacerbation of NS-associated dyslipidemia. Compared to CsA, VCS more effectively ameliorated proteinuria, hypercoagulopathy, and glomerular injury and led to a better lipid profile.

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SA-PO976

Altered Bone Marrow Myelopoiesis Contributes to Glomerular Dysfunction

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Background: Myeloid-biased hematopoiesis is observed in disease conditions associated with CKD, including infection, chronic inflammation, diabetes, CVD, and aging. Despite identifying immature myeloid cells (MCs) in the bone marrow (BM) as a significant contributor to renal injury in mice, the link between BM and kidney function in humans is not yet determined. Here, we tested if inflammatory signals alter BM myelopoiesis leading to glomerular dysfunction.

Methods: Flow cytometry (FC) was performed to evaluate the immunophenotyping of BM cells from CKD patients and healthy individuals, as well as human MCs differentiated in vitro. Bioenergetic and epigenetic changes in monocytes were assessed by Seahorse and ATAC-seq. Secretome analyses were performed using ELISA multiplex cytokine assay and FC staining. We assessed the impact of functionally altered MCs and their soluble factors to podocyte structure and filtration function by conducting an immunofluorescence assay on cultured podocyte and two different animal models.

Results: CKD patients exhibited increased levels of TNFα and suPAR in their BM and a myeloid-biased hematopoiesis, with an increase in inflammatory monocytes expressing uPAR. In vitro assays revealed that TNFα can alter myelopoiesis by skewing hematopoietic stem cell (HSC) differentiation towards monocytic lineage cells, leading to functional changes in the resultant monocytes. These TNFα-driven monocyte subsets exhibited increased uPAR expression and suPAR secretion, metabolic activity, and production of proinflammatory cytokines. Also, TNFα increased chromatin accessibility to genes for proinflammatory cytokines, metabolic activity, and those involved in inflammation signaling pathways, as evidenced by ATACseq. The soluble factors secreted by TNFα-driven MCs caused cytoskeletal rearrangement in cultured podocytes and filtration dysfunction in a transgenic zebrafish model. Mice injected with TNFα and IFNγ exhibited suPAR-associated glomerular dysfunction, demonstrated by albuminuria, and an increase in BUN levels, suPAR levels, and uPAR-expressing BM MCs.

Conclusions: This study reveals, for the first time, that TNFα contributes to renal injury by altering BM myelopoiesis and promoting the development of metabolically and epigenetically reprogrammed monocyte subsets that secrete soluble permeability factors and cytokines.

Funding: NIDDK Support

SA-PO977

Identification of a Podocyte-Derived Cytokine as a Potential Mediator of Injury in FSGS via Single-Cell RNA Sequencing of Human Kidney Tissue

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Background: Focal segmental glomerulosclerosis (FSGS) is a major cause of end stage kidney disease (ESKD) worldwide, and patients with primary and genetic forms of FSGS are frequently resistant to existing treatments. As such, there is a strong need for the development of new treatments for FSGS. There is evidence that cytokines may play a role in the pathogenesis of FSGS. Most of this evidence is based on immune cell-derived cytokines, and little is known about podocyte-derived cytokines in FSGS. The podocyte has been shown to produce cytokines and even act as an antigen presenting cell in other forms of kidney disease, but its role as an immune cell in FSGS has not yet been explored. That is the aim of our study.

Methods: Single cell RNA sequencing performed on kidney tissue from a patient with a genetic form of FSGS revealed increased expression of two different interleukins in the patient's podocytes versus podocytes from healthy kidneys. Because one of these interleukins, hereby referred to as interleukin (IL)-X, has also been shown to promote injury in other forms of kidney disease, we evaluated the expression of IL-X and NPHS2 in kidney tissue from patients with primary and genetic forms of FSGS via RNA scope.

Results: Baseline glomerular expression of IL-X was low to virtually undetectable in control kidneys. When IL-X was detected in control kidneys, it was seen in intercalated cells and immune cells that were negative for NPHS2 with only faint staining seen in the rare NPHS2+ podocyte. In kidneys with FSGS, both primary and genetic forms, IL-X was seen in NPHS2+ podocytes more frequently, and the IL-X signal in podocytes was consistently stronger in diseased kidneys than in control kidneys. Notably, single cell RNA sequencing data from the patient with genetic FSGS indicated that the receptor for IL-X was expressed primarily on lymphocytes.

Conclusions: Our findings indicate that IL-X expression is increased in podocytes in both primary and genetic forms of FSGS. Given that the receptor for IL-X is

expressed primarily on lymphocytes, we hypothesize that podocyte-derived IL-X recruits inflammatory cells to the glomerulus to propagate injury. We will use *in vivo* and *in vitro* models to define the role of IL-X in the pathogenesis of FSGS and to determine its utility as a therapeutic target in FSGS.

Funding: NIDDK Support, Private Foundation Support

SA-PO978

Podocytopathy with a Novel Variant in ARHGAP24 and an APOL1 Risk Allele

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Introduction: Genetic mutations cause up to 30% of steroid resistant nephrotic syndrome (SRNS) cases. A missense mutation responsible for hereditary podocytopathy was first described in ARHGAP24, a gene that encodes a GTPase activating protein (GAP) required for regulating podocyte motility, in 2011. We report a case of SRNS with an ARHGAP24 variant that has not been previously reported to our knowledge and a concurrent APOL1 risk allele.

Case Description: A 16-month-old male presented with anasarca, nephrotic range proteinuria, hypoalbuminemia, hypertension, microscopic hematuria, and severe anemia. Infectious work-up (hepatitis, HIV, COVID) was negative, and serum complement levels were within normal limits. Renal biopsy showed severe podocytopathy. Genetic testing showed a G1 APOL1 risk allele and a heterozygous missense mutation (c.584 A>C; p.K195T) in ARHGAP24. After a lack of response on 8 weeks of high dose steroids, the patient was transitioned to tacrolimus.

Discussion: Our patient's ARHGAP24 mutation is in the critical GAP domain that regulates podocyte motility. The ARHGAP24 mutation described in 2011 was also in the GAP domain, causing reduced GAP activity and increased podocyte motility with a dominant effect attributed to heterodimerization of the mutated and wildtype (WT) proteins. Our patient's mutation replaces lysine (positively charged) with threonine (neutral). This lysine residue, per Alphafold, is predicted to form a cation-pi interaction with a tyrosine residue in the GAP domain of the WT protein. Lysine is also highly conserved at this position across species. Therefore, we hypothesize that the positively charged lysine residue is required for preserving the GAP domain's integrity, and changing the residue to a neutral amino acid (threonine in our patient's case) disrupts the GAP domain. Despite the genetic findings, we opted to treat with tacrolimus, as the pathogenicity of this variant has not been confirmed. The patient also has a G1 APOL1 risk allele – while 1 allele is not expected to confer the risk associated with having 2 APOL1 risk alleles, the combination of 1 risk allele with a possibly pathogenic mutation in another gene has not been well-described. Thus, our patient presents multiple genetic findings that require further investigation to define their contribution to his podocytopathy and to determine if and how the two gene variants interact with each other.

SA-PO979

Circulating Hypo-Sialylated IgM by FSGS Subjects Induce Proteinuria and Podocyte Injury

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Background: Sialylation is an important regulator of protein function. Previous data showed that sialylation of total circulating IgM in Idiopathic Nephrotic Syndrome is significantly reduced compared to healthy subjects. The role of hiposialylated-IgM (hIgM) on podocytes in FSGS pathogenesis is unknown.

Methods: We characterized IgM derived by patients affected by multi-drug resistant FSGS (defined as lack of antiproteinuric effect of a double therapy based on steroid plus CNI and MMF for at least 12 months before enrolment). IgM were first analysed through two-dimensional electrophoresis. Sialylation levels were measured in total circulating IgM through incubation with biotinylated *Sambucus nigra* agglutinin (SNA). Then, sialylated and hyposialylated-IgM were put in culture with human podocytes. Incubation of podocytes with medium was used as control. IgM purified from serum of a patient were injected in rats.

Results: We enrolled 10 patients with resistant FSGS and 5 healthy controls, matched for age and sex (**Fig1a**). IgM derived from FSGS subjects induced significantly higher proteinuria than IgM from HC when injected in rats (**Fig1b**). IgM purified from serum of FSGS patients resulted significantly more cationic than IgM of HC (**Fig1c**), and as previously demonstrated, IgM cationic charge derived by hyposialylation (**Fig1d**). Co-incubation with hIgM, significantly induced human podocytes damage as opposed to sialylated IgM, which had no injurious effect (**Fig1e**).

Conclusions: Pathophysiology of FSGS is still largely unknown and common treatments often result poorly effective. We here reported that sialylation of IgM may be of relevance in this context, showing that hIgM induce *in vivo* proteinuria and *in vitro* podocytes structural damage. Therefore, hIgM may represent a promising therapeutic target for FSGS.

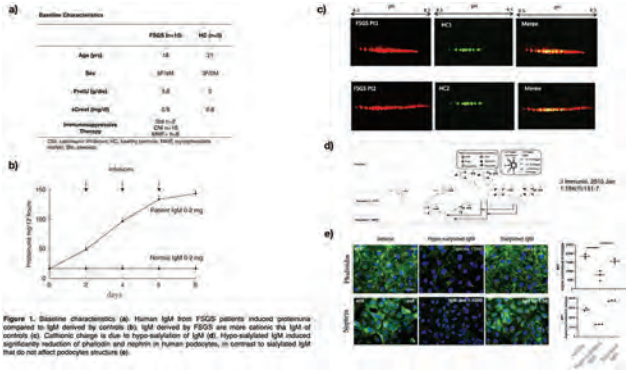

Figure 1. Baseline characteristics (a). Human IgM from FSGS patients induced proteinuria compared to IgM derived by controls (b). IgM derived by FSGS are more cationic than IgM of controls (c). Cationic charge is due to hypo-sialylation of IgM (d). Hypo-sialylated IgM induced significantly reduction of phalloidin and nephrin in human podocytes, in contrast to sialylated IgM that do not affect podocytes structure (e).

SA-PO980

Potential Roles of Autoantibodies Targeting the Podocyte in the Idiopathic Nephrotic Syndrome

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Background: The idiopathic nephrotic syndrome (INS) is characterized by heavy proteinuria, hypoalbuminemia, and edema. In both forms of INS, minimal change disease (MCD) and focal segmental glomerulosclerosis (FSGS), podocytes are injured by mechanisms that are still mostly unknown. This injury causes changes in their actin cytoskeleton, leading to the effacement of their foot processes. Recent evidence suggests that autoantibodies targeting the podocyte might play a role in this process. Our objective is to establish if such autoantibodies are implicated in the pathogenesis of INS and to understand how they contribute to podocyte injury and foot process effacement.

Methods: As previously published (Hada and al., *J Am Soc Nephrol*. 2022;33(11):2008-2025.), INS was induced in C3H/HeN mice by immunization with recombinant Crb2, a transmembrane protein expressed both at the murine and human podocyte's slit diaphragm. Immortalized podocytes expressing mouse Crb2 were incubated with serum from Crb2-immunized and control mice, then stained for phospho-ezrin, the phosphorylated form of ezrin, a protein that links Crb2 to the actin cytoskeleton. Sera from human INS patients in active disease and healthy controls were tested with quantitative ELISA specific for anti-Crb2 and anti-nephrin antibodies.

Results: C3H/HeN mice developed significant anti-Crb2 antibody titer and proteinuria 4 weeks after immunization. Podocytes incubated with Crb2-immunized mouse serum showed a significant increase in ezrin phosphorylation compared to podocytes incubated with control mouse serum (average staining intensity per cell of 1370 vs 68, $p<0.0001$). Among 67 INS patients in active disease, 22 (32%) had a positive anti-Crb2 antibody titer and 6 (9%) had a positive anti-nephrin antibody titer, while no healthy controls had a positive titer of either antibodies.

Conclusions: Mice immunized with the podocyte protein Crb2 develop an INS-like disease, and their anti-Crb2 antibodies induce phosphorylation of ezrin, which links Crb2 to the cytoskeleton. Such anti-Crb2 antibodies are also present in human INS patients in active disease, along with anti-nephrin antibodies, indicating that autoantibodies targeting podocyte proteins may contribute to the cytoskeletal changes and podocyte injury seen in INS.

SA-PO981

Prospective Study of B-Cell Subsets in New-Onset Primary Podocytopathy in Adults

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Background: Data on children suggests the involvement of an altered B-cell immunophenotype in the pathogenesis of nephrotic syndrome (NS) due to primary podocytopathy. Characterization of the immune signature in NS patients will likely improve therapeutic strategies. We examined B-cell subsets in a cohort of adults with new-onset NS.

Methods: This was a prospective study at a tertiary care center in India. Adults with new-onset NS due to biopsy-proven primary minimal change disease or focal segmental glomerulosclerosis were included. Three sequential visits for blood sampling were: 1(on the day of starting prednisolone), 2 (2 weeks after visit 1), and 3 (6 months after visit 1 and 2 weeks after stopping prednisolone). B-cell subsets studied were: naïve B cells (CD19+27-), memory B-cells (CD19+27+), and transitional B-cells (CD19+27-38+24+). Patients were categorized based on steroid responsiveness as steroid resistant (SR), infrequently relapsing NS, and steroid-dependent NS; the latter two were grouped as steroid sensitive (SS).

Results: Of 67 patients, 87% were steroid-sensitive (SS) within four weeks of therapy. The transitional B-cell proportion was lower, and the total B-cell proportion was higher in patients at baseline than 35 healthy controls. The baseline naive B-cell proportion was lower, and the memory B-cell proportion was higher in steroid-resistant (SR) patients than in steroid-sensitive (SS) patients (Table). The naive B-cell proportion decreased at the second visit and was followed by a plateau at the third visit (p=0.003). Memory B-cell proportion increased at the second visit, followed by a plateau at the third visit (p=0.005). Transitional B-cell proportion remained similar across all three visits (p=0.18).

Conclusions: Memory B-cell proportion was higher, and naïve B-cell proportion was lower in SR patients than in SS patients. While naive B-cells decreased, memory B-cells increased initially during prednisone treatment in the whole cohort.

Funding: Government Support - Non-U.S.

Baseline B-cell percentage

	IFRNS (N=50)	SDNS (N=8)	SRNS (N=9)	P value
Total B-cells, % of total lymphocytes	18.2 (12.4-23.1)	18.2 (12.4-23.1)	11.4 (7.9-22.1)	0.31
Naive B-cells, % of total B-cells	83.5 (76.4-90.7)	83.9 (74.3-93.9)	72.8 (58.6-73.3)	0.004
Memory B-cells, % of total B-cells	15.6 (9-23.7)	15.8 (6.1-25.9)	27.5 (26.6-38.3)	0.008
Transitional B-cells, % of naive B-cells	3.8 (1.9-8.4)	4.3 (2-14.9)	6.5 (2.9-9.9)	0.68

IFRNS: infrequently relapsing nephrotic syndrome, SDNS: steroid-dependent nephrotic syndrome, SRNS: steroid-resistant nephrotic syndrome

SA-PO982

Cooperative Elicitation of Complement-Dependent Cytotoxicity by Anti-PLA2R Autoantibodies in Primary Membranous Nephropathy

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Background: Primary membranous nephropathy (pMN) is an autoimmune disease causing abnormalities in the glomerular basement membrane and podocytes, leading to proteinuria. These changes relate to autoantibodies and accumulated activated complement proteins on the glomerulus. Autoantibodies, primarily against phospholipase A2 receptor 1 (PLA2R) found in 80% of pMN patients, are thought to activate the complement system and contribute to pMN. Surprisingly, the predominant PLA2R autoantibodies in pMN patients are IgG4, which doesn't activate the complement, while the complement-activating IgG1 and IgG3 are less common, questioning the role of PLA2R autoantibodies in pMN pathogenesis.

Methods: We isolated monoclonal anti-PLA2R antibodies (mAbs) from pMN patients' PBMC using single B cell sorting, then amplified the IgG gene for cloning into F293 cell vectors. We confirmed the mAbs' characteristics via Western blot, ELISA, and a BLI system. These mAbs were found binding to the membrane-bound PLA2R on human podocyte cells through immunocytochemistry. By using a Lentivirus system, we created a PLA2R-overexpressing podocyte line for a disease model. We assessed the mAbs' ability to trigger complement-dependent cytotoxicity (CDC) using a CellTiter-Glo assay to measure cell viability and complement-induced lysis.

Results: We studied PLA2R-reactive IgGs' role in complement activation in pMN, using a single-cell method to generate 16 anti-PLA2R mAbs from five patients. Our analysis revealed variable binding affinity across mAb groups, independent of binding sites. Using a CDC assay on PLA2R-overexpressing podocytes, we discovered that the combination of CTLD1 with another mAb significantly boosted CDC activation. After modifying the mAbs to IgG4, we found that a single IgG1 mAb was critical for CDC activation, but IgG4 could enhance it. Intriguingly, polyclonal IgGs from pMN patients, not from healthy volunteers, induced CDC. Furthermore, some patients with only CysR-IgG3 showed increased CDC activation with added CTLD1-IgG1 mAb.

Conclusions: These results identify an essential role of complement-reactive IgGs, presumably IgG1 and IgG3 synergies between single-domain epitopes CysR and CTLD1, which underlies pMN.

Funding: Government Support - Non-U.S.

SA-PO983

ApoL1 in Podocyte-Derived Urinary Microparticles

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Background: ApoL1 variants contribute the the high risk of progressive kidney disease in people of African ancestry. Overexpression of ApoL1 in podocytes may drive disease in people with high risk genotypes; ability to assess podocyte ApoL1 expression in vivo could be useful. Microparticles are 100-1000 nm vesicles that represent a sample of plasma membrane of their cells of origin, and hence may reflect the level of expression of specific proteins. Cells lining the nephron shed microparticles into the urine, and may provide a non-invasive way to assess protein expression in vivo.

Methods: The study was approved by the St. Louis University IRB. Urine was collected from 10 people with proteinuric kidney disease (3 membranous GN, 4 with immune complex GN (2 SLE nephritis, 2 infection-related), 2 diabetic nephropathy, and 1 AL amyloidosis) and one control. Microparticle-enriched urine sediment from 1.4 ml of urine was prepared by differential centrifugation, resuspended in buffered saline and incubated with fluorescently labelled probes to define microparticles (Annexin V), to identify podocyte origin (antibody to podocalyxin) and with antibody to ApoL1. Microparticles were analyzed by flow cytometry. Matched negative controls for each probe were used to define signal thresholds. Size gate was determined using polystyrene reference beads. Total particle number was normalized to urine creatinine concentration.

Results: A size gate of 250 to 1000 nm was applied. Annexin V positive population identifies the urinary microparticles (UMPs). Podocalyxin positive UMPs define the podocyte-derived urinary microparticles (PDUMP), and PDUMPs which also stain for ApoL1 are the ApoL1-positive PDUMPs (A^+PDUMPs). Urine from the patients had much higher total UMPs, PDUMPs and A^+PDUMPs than did control urine. Number of PDUMPS and A^+PDUMPs seemed to correlate with cause and activity of kidney disease: number of both PDUMPs and A^+PDUMPS were greatest in two patients with active membranous GN. The number of A^+PDUMPS, the ratio of PDUMPs to total UMPs, and the ratio of A^+PDUMPS to total PDUMPs all correlated weakly with proteinuria.

Conclusions: We have demonstrated the presence of ApoL1 in podocyte derived urinary microparticles. In this small sample, the A^+PDUMPs seem to correlate with the type of glomerular disease, with the highest level in patients who would be expected to have direct podocyte injury driving the disease.

Funding: NIDDK Support

SA-PO984

Topology of Membrane-Inserted ApoL1

John C. Edwards, Jonathan M. Bruno. *Saint Louis University, Saint Louis, MO.*

Background: ApoL1 inserts into membranes at low pH where it functions as an anion permease. Titration of the cis compartment to neutral suppresses the anion permeablity and activates a cation channel activity. pH 6.0 is optimal for membrane association that leads to cation channel after titration; pH 5 is optimal for the anion permease activity. As pH is lowered from 6 to 5, the total amount of protein associated with membranes increases along with the anion pemease, but the potential for cation permease after titration is suppressed. We hypothesize that the structure of the membrane inserted ApoL1 is altered by the pH at which it encounters the membrane.

Methods: Single cysteine substitution mutant were generated at position 40, 80, 89, 149, 168, 178, 204, 226, 236, 247, 263, 300, 314, 330, and 365, expressed in bacteria and purified. Each protein was mixed with preformed lipid vesicles. Accessibility of the engineered cysteine was probed with AF488-maleimide (AF-Mal) from the cis or trans compartment. Lipid-protein vesicles were separated by chaotropic wash followed by sepharose 4B chromatography. Membrane associated protein was separated by SDS PAGE. AF-Mal modification was detected by in-gel fluorescence, total protein by western blot.

Results: Protein associated at pH 6 was accessible to trans-modification at positions 300, 314, and 330 only, and this was unchanged by subsequent titration to pH 7.5. Protein associated at pH 5 was accessible to trans-modification at the same sites, plus at 365.

Conclusions: ApoL1 associated with vesicles at pH 6 has only one trans-accessible segment detected by these methods, minimally including positions 300 through 330 and we detect no change in topology with transition to conditions that activate the cation channel, consistent with a previously published model (Schaub et al., JBC (2021) 297: 101009). However, association at pH 5 leads to a larger portion of the molecule accessible from the trans comparment, consistent with the entire C-terminal region from 330 to the end translocated across the membrane. This additional translocation would eliminate the transmembrane segment that has been proposed to form the cation selective pore and would explain the decrease in cation channel activity after association at lower pH, additionally predicting different ion permeability activities depending on where along the endocytic pathway ApoL1 inserts into membranes.

Funding: NIDDK Support

SA-PO985

APOL1 G1-Mediated Cation Transport Inhibits Amino Acid Transport and Increases Endoplasmic Reticulum Calcium Release, Causing Podocytopathy

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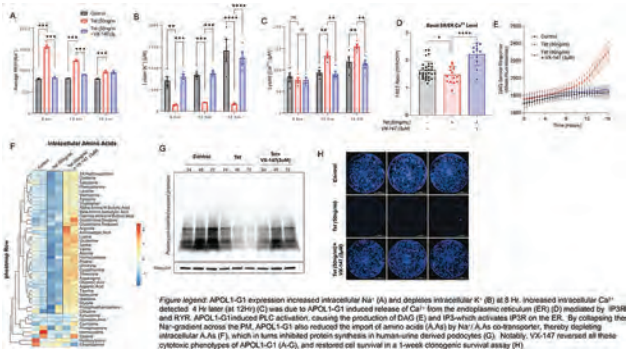
Background: How two coding variants of *APOL1* gene (G1 and G2) cause kidney disease is poorly understood. While experimental models have shown that these *APOL1* renal risk variants induce cytotoxicity, the causal mechanism underlying these effects is unknown. Previously, we reported that RRVs form cation pores that transport Na^+ and K^+ across the plasma membrane of mammalian cells.

Methods: We blocked APOL1 G1-cation channel function with a new small molecule inhibitor, VX-147 in inducible HEK293 cells and human-derived podocytes and measured cytotoxic phenotypes. We used Real-time cation sensors including genetically-encoded Ca^{2+} sensor to measure levels of cations in the cytoplasm and the endoplasmic reticulum (ER). We used inhibitor of IP3R and CRISPR-Cas9-mediated IP3R knockout to determine the impact of IP3R on APOL1-G1-induced increases in cytoplasmic Ca^{2+} and cell viability. Finally, using metabolomics and related methods, we measured APOL1-GI-mediated changes in amino acid transport, protein synthesis and ATP production, in the presence and absence of VX-147 treatment.

Results: We demonstrate for the first time that APOL1 G1-mediated transport of Na^+ and K^+ induces Ca^{2+} release from the ER via IP3R and ryanodine receptor (RyR), and that the liberated Ca^{2+} triggers a sequence of downstream cytotoxic events including mitochondrial dysfunction and inhibition of protein synthesis via AMPK-TSC2-mTORC1 and eIF2a signaling. We also discovered for the first time that APOL1 G1 cation function impedes amino acid uptake in kidney cells. All observed cytotoxic phenotypes are reversed by VX-147.

Conclusions: These findings established APOL1-mediated Na^+/K^+ transport as the proximal driver of podocyte injury, and that Ca^{2+} signaling and protein synthesis are potential therapeutic targets for APOL1 nephropathy.

Funding: Other NIH Support - NIH Common Fund; NIMHD



SA-PO986

Characterizing Roles of Reference and Haplotype FAT10 in APOL1-Related Kidney Diseases in Human Podocyte

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Background: FAT10 is a ubiquitin-like modifier, which can covalently link to target proteins or non-covalently interact with proteins, thereby altering protein function and/or stability. FAT10 is highly expressed in HIV-associated nephropathy (HIVAN) and is upregulated in glomeruli of nephrotic patients with APOL1 high-risk genotypes. FAT10 was also reported to interact with APOL1 and to accelerate degradation of APOL1 risk variants in vitro. A FAT10 haplotype with 4 missense mutations, referred to here as *FAT10b*, has a high allele frequency in persons of African ancestry. However, it is not known whether the *FAT10b* variant has altered effects on APOL1 compared to the *FAT10a* (reference) allele. Since expression of APOL1 risk alleles in podocytes promotes glomerular injury, we compared the effects of FAT10 variants upon APOL1 G0 and G1 proteins in human podocytes.

Methods: *APOL1G0/G0* (G0) and *APOL1G1/G1* (G1) podocytes were transfected with GFP-FAT10 variants using a Neon Transfection System. Immunoprecipitation (IP) was performed using anti-GFP antibody to pull down GFP-FAT10 and western blotting was performed to detect FAT10 and APOL1. Proteasome inhibitor MG132 (5 μM) was added 4 hours before IP.

Results: FAT10a increased endogenous APOL1-G0 and -G1 protein abundance, whereas FAT10b suppressed them. Both APOL1-G0 and G1 co-immunoprecipitated with FAT10a and FAT10b. 70kD and 110kD bands were observed only in *APOL1G1/G1* podocytes transfected with *FAT10b*, likely representing novel covalent FAT10 conjugates but western blotting revealed these FAT10 conjugates did not contain APOL1.

Conclusions: FAT10a and FAT10b interacted with APOL1-G0 and -G1, but FAT10a increased APOL1 G0 and G1 abundance whereas FAT10b increased APOL1 degradation. The emergence of high molecular weight FAT10 covalent conjugates only in podocytes co-expressing APOL1 G1 and FAT10b may indicate important new targets that contribute to podocyte injury in persons with high risk APOL1 and FAT10b genotypes. These data support the importance of further studies to elucidate mechanisms by which FAT10 variants modify APOL1-mediated kidney injury.

SA-PO987

RNAomics of APOL1 Risk and Non-Risk Allele Expressing Podocytes in HIV Milieu

Prabhjot K. Johal,[1] Vinod Kumar,[1] Karl Skorecki,[2] Raja Ramachandran,[1] Ashwani Malhotra,[3] Pravin C. Singhal.[3] *[1]Post Graduate Institute of Medical Education and Research, Chandigarh, India; [2]Bar-Ilan University, Ramat Gan, Israel; [3]Northwell Health Feinstein Institutes for Medical Research, Manhasset, NY.*

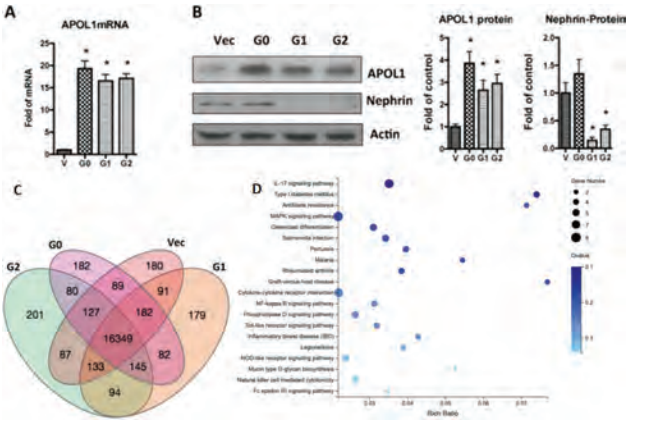
Background: African Americans (AAs) develop chronic kidney diseases (CKD) at 4-5 folds higher rates than European Americans (EAs), and this disparity is over 10 folds in the case of HIV-associated nephropathy (HIVAN), which is predominantly related to two risk alleles (G1 and G2) in APOL1 gene in AAs. To explore the underlying molecular mechanisms, we evaluated the gene expression profiles in podocytes expressing APOL1-G0 (wild-type), G1, and G2 in the HIV milieu.

Methods: Stably expressing APOL1-G0, G1, or G2 cell lines were transduced with HIV, followed by the extraction of RNAs and RNA-seq analysis.

Results: All cells expressed comparable RNA and protein expression of APOL1, but G1- and G2-podocytes displayed attenuated nephrin expression (a marker of podocyte health) in the HIV milieu. RNA-seq analysis showed similar gene expression alterations in G1- and G2-podocytes, their expression profiles differed from that in G0-podocytes. KEGG pathway enrichment analysis revealed predominant alterations in inflammation-regulating signaling pathways such as MAPK, NF-kappa B, phospholipase D, NOD-like receptor, and Fc epsilon RI in G-1 and G2- podocytes when compared with G0-podocytes.

Conclusions: These findings suggest that AAs may suffer from a higher occurrence of CKD due to enhanced inflammatory milieu in podocytes caused by APOL1 risk alleles. Our study provides insight into the underlying molecular mechanisms in developing APOL1-associated nephropathy.

Funding: NIDDK Support



All cells expressed comparable RNA (Figure A) and protein expression of APOL1 (Figure B), but G1- and G2-podocytes displayed downing of podocyte nephrin expression in HIV milieu. RNA-seq analysis showed that G1- and G2-podocyte expression profiles were disparate from that in G0-podocytes (Figure C). KEGG pathway enrichment analysis revealed that compared with APOL1-G0, the risk alleles G1 and G2 mainly altered inflammation regulating signaling pathways (Figure D).

SA-PO988

Microvesicular Passage of APOL1

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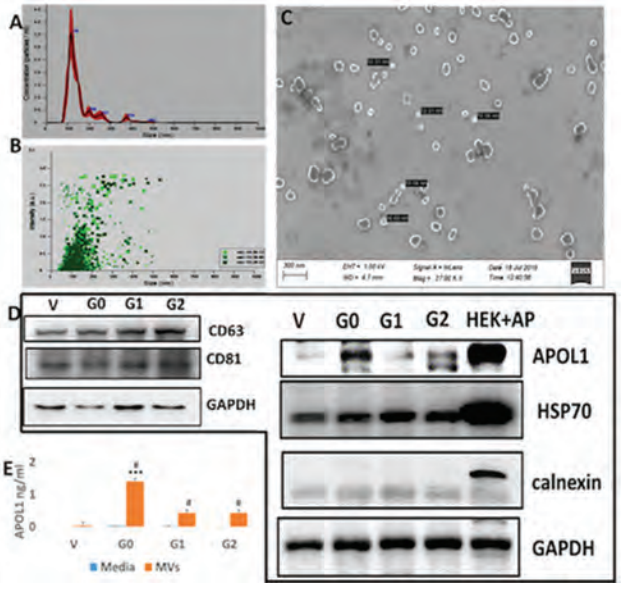
Background: Podocyte-APOL1 (pAPOL1) carry a signal peptide, but its secretion and paracrine/endocrine role are controversial. We propose that APOL1 secretion in podocytes use microvesicles (MVs) to get out of cells rather than direct secretion to the medium.

Methods: APOL1 (wild-type, G0) and its risk variants (G1 or G2) were over-expressed in human podocytes. After 48hr of incubation, the culture medium was collected and processed for MVs isolation by ultracentrifugation and MVs isolation kit. Isolated MVs were characterized by HSP70, CD81, and CD63 and the absence of Calnexin by Western Blot (WB) and FACS. The size was measured using the Nanosite system and Scanning Electron Microscopy (SEM). APOL1 was detected in the culture medium and lysed MVs using ELISA & WB. The isolated MVs were further incubated with non-APOL1 expressing Human Embryonic Kidney (HEK) cells, and after 48hr, HEK cell lysate was analyzed for APOL1 presence by WB.

Results: Nanosite & SEM measured the size of isolated MVs between 90-125nm. These MVs stained positive for the expression of CD63, CD81, and HSP70 but were negative for the expression of calnexin. Thereby confirming that there was no cytosolic contamination. We observed the presence of APOL1 protein only in the lysed MVs. However, the level of APOL1-G0 (intensity: 1.92±0.01) is much higher compared to Vector (0.11±0.01) G1 (0.12±0.01) and G2 (0.17±0.02) as shown in the figure.

Conclusions: This preliminary study shows that podocyte and HEK cells secrete APOL1 through the MVs pathway.

Funding: NIDDK Support



MVs size was measured using Nanosite system (A&B), and SEM (C). The expression of MVs protein marker and APOL1 are displayed (D). ELISA of APOL1 media was performed to detect MVs (E). ***p<0.001, #p<0.001 (*G0 Vs. V, G1 or G2; #media vs. MVs)

SA-PO989

HIV-Associated Nephropathy (HIVAN) Phenotype Is a Consequence of Compromised Parietal Epithelial Trans-Differentiation in the APOL1 Renal Risk Milieu

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Background: HIV-infected patients with African ancestry carrying APOL1 variants (ARRVs G1 and G2) have a several-fold higher risk of developing HIVAN than patients with APOL1 wild-type (G0). HIV enhances APOL1 expression in parietal epithelial cells (PECs). We hypothesized that HIV-mediated PECs' proliferation and transition are compromised in the ARRV milieu & result in PECs' accumulation in Bowman's space, manifesting HIVAN phenotype (a collapsing variant).

Methods: The cultured human parietal epithelial cells (PECs) were transduced with vector, G0, G1 & G2 & analyzed for their proliferative, fibrotic, & podocyte (PD)-specific differentiation phenotype (transition markers) using western blotting (WB). For phenotype-specific proliferative, profibrotic, and transition markers under the HIV milieu, V/G0/G1/G2-PECs were transduced with HIV(NL4-3) for 48hr(n=4) & analyzed by WB. The expression of mTOR signaling and PECs' transition markers was measured using Western blotting and miR193a expression by RT-PCR to evaluate the involved mechanisms. Renal tissues from control & Tg26 (a HIVAN model) mice were analyzed for miR193a & mTOR expression by FISH & IHC in PECs.

Results: In vitro studies, G1/G2-PECs displayed an increased expression of profibrotic (CD44, PERK, α-SMA, Fibronectin, Vimentin, MMP9, SNAIL) but an attenuated expression of transition markers in control and HIV milieus when compared to G0-PECs; in contrast, G0-PECs showed attenuated expression of profibrotic but an enhanced expression of transition markers in HIV milieu. These findings indicate that PEC to PD transition is compromised in G1/G2-PECs in the control and HIV milieu. G1/G2-PECs also displayed increased expression of p-mTOR, p-70S6K, p-4EBP, & p-eEF, indicating the activation of mTOR signaling. Renal cortical sections of Tg26 mice showed an increased accumulation of PECs in their Bowman's space and increased miR193a & mTOR expression by PECs compared to control mice.

Conclusions: HIVAN phenotype (collapsing variant) results from the compromised transition in profibrotic PECs to podocytes in APOL1 renal risk (G/G2) milieu in HIV-infected patients.

Funding: NIDDK Support

SA-PO990

Transcriptional Profiling of Induced Pluripotent Stem Cell (iPSC)-Derived Podocytes Comparing APOL1 Risk Variants

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Background: African Americans of sub-Saharan ancestry have a 3.5-fold increased risk for end-stage kidney disease compared to populations of European descent due to, in part, two high-risk variants G1 and G2 in the apolipoprotein L1 (*APOL1*) gene. Individuals with two high-risk alleles are predisposed to kidney disease through an undetermined mechanism. We sought to determine if *APOL1* expression in high-risk human induced pluripotent stem cell (iPSC)-derived podocytes causes transcriptional differences compared to reference APOL1 iPSC-derived podocytes.

Methods: We utilized iPSC-derived podocytes engineered with *APOL1* reference (G0) and high-risk (G1, G2) variant genotypes. Our lab has also developed a protocol to directly differentiate these iPSCs into podocyte populations that express *APOL1* with IFN-γ stimulation. To characterize the transcriptional impact of APOL1 variants, we performed mRNA-sequencing on G0/G0, G1/G1, and G2/G2 podocytes either untreated or treated with IFN-γ. EdgeR was used for differential gene expression and further analyzed by principal component analysis, gene ontology enrichment, and Gene Set Enrichment Analysis.

Results: Variant APOL1 iPSC lines differentiate into podocyte populations using our protocol, express *APOL1* with IFN-γ stimulation, and do not demonstrate differential cell death. Transcriptome principal component analysis shows both untreated (lacking *APOL1* expression) and, unexpectedly, IFN-γ treated (with *APOL1* expression) podocytes are not statistically different between reference and high-risk genotypes. The majority of variance (68%) results from IFN-γ treatment and the upregulation of more than 400 genes (2-fold change, FDR 0.05). Furthermore, the few differentially expressed genes between reference and high-risk podocytes could not be assigned a functional role using pathway analysis methods.

Conclusions: We were not able to identify an APOL1-specific transcriptome response between reference and high-risk APOL1 iPSC-derived podocytes. Variant-dependent differences may be overshadowed by the robust transcriptional response to INF-γ used for *APOL1* induction. This supports the need to induce *APOL1* expression without inflammatory stimulation in order to assess the effect of APOL1 variants on podocyte biology.

Funding: NIDDK Support

SA-PO991

FSGS Recurrence Modeling Using Induced Pluripotent Stem Cell (iPSC)-Derived Podocytes in Patients with Idiopathic Nephrotic Syndrome

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Background: Clinical outcome is highly variable, often resulting in renal failure, in patients with idiopathic Nephrotic syndrome and disease returns after transplantation (Tx) in about 50% of patients. Proposed circulating permeability factors (CPFs) are as of yet few and unvalidated in larger cohorts. *In vitro* assays to detect podocyte damage result in heterogeneous outcomes. Taken together, there are potential patient- and donor-specific characteristics that influence disease outcome after Tx. Here, we modelled FSGS recurrence using iPSC-derived podocytes.

Methods: We included 5 patient-donor couples with known outcomes of FSGS recurrence after Tx (3x recurrence, 2x non-recurrence) and generated iPSCs out of PBMCs. We subsequently exposed iPSC-derived podocytes to suspected CPF-containing plasmas and measured podocyte damage using various previously published *in vitro* damage assays.

Results: Using an optimized hybrid directed differentiation protocol, we successfully created iPSC-derived podocytes showing podocytes-specific markers. We were able to model primary FSGS using patients' iPSC-derived podocytes exposed to pre-Tx plasma (patient-specifically) mimicking the *in vivo* situation. We also modelled FSGS recurrence using donor iPSC-derived podocytes exposed to post-Tx plasma (patient-specifically) (Figure 1) again according to the *in vivo* situation. Differences in damage response between iPSC-derived podocyte cellines suggest we found proof for donor-specific characteristics that may influence disease recurrence after Tx using a crossmatching experiment.

Conclusions: iPSC-derived podocytes can be used to model primary FSGS and FSGS recurrence. Data suggests that currently unknown donor-specific characteristics may influence disease outcome after Tx in patients with idiopathic Nephrotic syndrome. We aim to further study these potential donor-specific characteristics.

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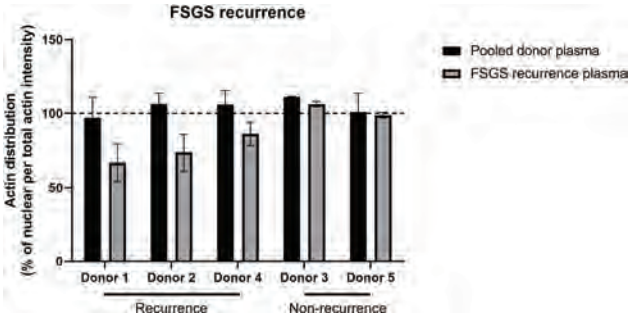

SA-PO992

Modeling Podocytopathies in Human Kidney Organoids

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Background: Podocytopathies include multiple kidney diseases such as Focal Segmental Glomerulosclerosis (FSGS) and Minimal Change Disease (MCD) in which podocyte injury results in albuminuria. Kidney organoids (KOrgs) derived from human pluripotent stem cells generate 3D architecture with multiple cell types seen in native kidneys more reflective of the human in vivo podocyte environment. The aim of this study was to assess KOrg podocyte (KOrg-podos) response to inflammatory stressors and hypoxia and to evaluate their ability to capture pathways relevant to human podocytopathies.

Methods: KOrgs were treated with recombinant TNFα or interferon-γ (IFNG) or subjected to 1% O_2 environment for 24 and 48h. Assessment of gene/protein expression in KOrgs included qRT-PCR, bulk and single cell (Sc) RNAseq, ELISA, IF and untargeted proteomics. Probability of ligand-target cell engagement was assessed by NicheNet based on differential protein expression. Organoid stressor-specific gene signatures were generated from bulk RNA-seq and/or proteomics data and used to assess summary gene expression in proteinuric human kidney tissue (NEPTUNE cohort).

Results: Proteomics analysis showed that baseline KOrgs expressed >90% proteins detected in human glomeruli; IF imaging confirmed anticipated localization of slit diaphragm proteins SYNPO and CD2AP in KOrg-podos. Further, NicheNet analysis confirmed that KOrg-podos responded to a host of ligands expressed by other cell types. Following treatment with TNFα, IFNG or hypoxia, Sc transcriptional profiling revealed that KOrg-podos lose expression of key podocyte markers (NPHS1, PODXL) and increase expression of genes observed in early glomerular epithelial cells (LYPD1, CDH6) as well as pathways associated with inflammatory response (NFkB) and mitochondrial stress. KOrgs stressor-specific gene signature expression segregated subgroups of individuals in a podocytopathic cohort.

Conclusions: Our multi-platform integrative analysis of KOrgs demonstrates that KOrg-podos functionally respond to multiple stimuli thought to contribute to podocytopathies. Further, KOrgs stressor-specific gene activity identified individuals with poor outcome in proteinuric kidney disease. These results confirm the relevance of KOrgs to studies of molecular mechanisms of podocytopathies.

Funding: NIDDK Support, Other NIH Support - National Center for Advancing Translational Sciences (NCATS), Commercial Support - Eli Lilly, Private Foundation Support

SA-PO993

Abstract Withdrawn

SA-PO994

Studying Organoid Phenotypes in CoQ10-Deficient Glomerulopathy

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Background: Monogenic causes of steroid resistant nephrotic syndrome (SRNS) account for 11-30% of childhood. Genes involved in coenzyme Q10 (CoQ_{10}) biosynthesis, such as *PDSS2, COQ2, COQ6 and ADCK4*, are well established causes of SRNS and focal segmental glomerulosclerosis (FSGS). CoQ_{10} is a component of the mitochondrial inner membrane which plays an important role in supporting electron transport of oxidative phosphorylation and protection from oxidative stress. ADCK4-deficient glomerulopathy can be partially treated by CoQ_{10} supplementation, but the therapeutic efficacy of this treatment is variable and has limitations. We here established a robust *in vitro* model system of CoQ_{10}-deficient glomerulopathies to study the therapeutic effects of drugs using elaborate manipulations, and to better understand the disease and thereby develop more effective treatment.

Methods: We generated CoQ_{10}-deficient kidney organoids from human induced pluripotent stem cells (iPSCs) using the well-established *in vitro* induction protocol (Taguchi et al). To establish CoQ_{10}-deficient human iPSCs, gRNAs targeting PDSS2, COQ2, COQ6 or ADCK4 were used with Cas9 protein individually. We performed immunostaining and light microscopy analysis to evaluate the extent of their differentiation and further test the mitochondrial dysfunction to observe the phenotypic characteristics due to CoQ_{10} deficiency.

Results: Gene ablation of the four genes in iPSCs was confirmed by sanger sequencing. CoQ_{10}-deficiency did not lead to failure of induction to nephron progenitors in organoids. CoQ_{10}-deficient kidney organoids were positive for NPHS1 (a podocyte marker), LTL (a proximal tubule marker), and ECAD (a distal tubule marker) expression, and no difference was observed when compared with control organoids. Further studies will assess mitochondrial dysfunction and ROS levels to quantify pathogenic characteristics

Conclusions: In conclusion, we have developed a modeling system of CoQ10-deficient glomerulopathy that can be used to further evaluate the efficacy of potential drugs for this disease.

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SA-PO995

Podocytopathy in Diabetic Nephropathy

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Introduction: Minimal change disease constitutes 15% of adult idiopathic nephrotic syndrome. The exact mechanism is unknown but is postulated to be due to T cell dysfunction and the production of glomerular permeability factor. With an underlying immune mechanism involved, minimal change disease responds to steroids and steroid-sparing agents. We present a case of diabetic kidney disease with overlying podocytopathy.

Case Description: A 47-year-old female with a past medical history of hypertension, and poorly controlled diabetes presented with complaints of worsening swelling of legs along with abdominal distension and reported weight gain of 40 pounds over a few weeks. She reported no improvement with oral furosemide 40 mg daily which she was prescribed for her edema and was not using her insulin for the past 9 months before admission. Her creatinine at presentation was 0.9. 24-hour urine protein revealed 6.4 grams/day. Autoimmune workup was negative. The patient was started on IV diuretics. She underwent a kidney biopsy which revealed moderate chronic kidney disease with podocyte foot effacement suggestive of minimal change disease. CT imaging was done to assess for any lymphoproliferative disease which found mildly enlarged inguinal lymph nodes. Oncology was consulted for the possibility of lymphoproliferative disease and believed that malignancy was unlikely. The patient was offered a steroid course versus immunosuppressive medications like mycophenolate mofetil. The patient chose to start mycophenolate mofetil to avoid steroids and their effect on diabetes. Proteinuria decreased and patient was discharged on mycophenolate mofetil 1000 mg twice daily with outpatient follow-up.

Discussion: Minimal change disease is often an idiopathic disease but has also been known to be associated with the use of certain drugs, infections, and hematological malignancies. The mainstay of diagnosis remains to be a kidney biopsy. In our patient, the most likely diagnosis at presentation was diabetic kidney disease from poorly controlled diabetes, the kidney biopsy proved vital in the assessment of the coexisting minimal change disease. Few case reports have been listed where patients with diabetes presented with sudden onset nephrotic syndrome and were found to have minimal change disease.

SA-PO996

DLBS3233 Reduces Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and Increases Peroxisome Proliferator-Activated Receptor Gamma and Nephrin in Diabetic Rat Podocytes

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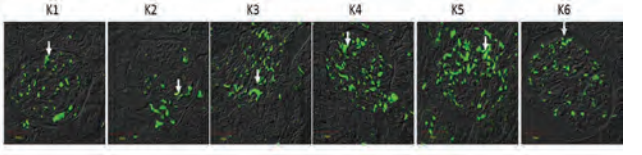
Background: DLBS3233 is a standardized extract derived from *Cinnamomum burmanii* and *Lagerstroaemia speciosa*, has shown antidiabetic effects. Here, we sought to explore the potential benefits of DLBS3233 to regulate insulin signaling in renal podocytes cell, represented by HOMA-IR, as well as podocytes PPAR gamma and Nephrin in diabetic rats with insulin resistance.

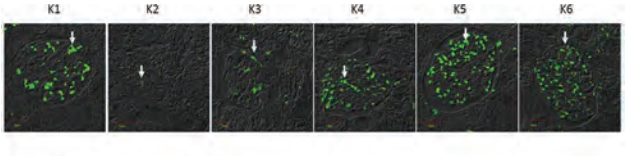
Methods: Thirty adult male Wistar rats were randomly divided into six groups (n=5 per group): nondiabetic rat group as a negative control (group I); untreated diabetic rats (group II), diabetic rats treated with DLBS3233 4,5mg/kgBB (group III); 9mg/kgBB (group IV); 18mg/kgBB (group V), and diabetic rats treated with pioglitazone (group VI). We checked HOMA-IR to confirm the occurrence of insulin resistance before and after administration of DLBS3233 in a group of rats with diabetes. Convocal examination was performed to examine the expression of PPARγ and Nephrin. The data were analyzed using paired t-test and ANOVA for pre and post DLBS3233 for HOMA IR.

Results: Administration of DLBS3233 showed work on improving insulin resistance from a significant decrease in HOMA-IR compared to the control group ($p < 0.05$). Increased expression of PPARg and Nephrin also confirmed the effect of a significant improvement in insulin resistance ($p<0.05$).

Conclusions: DLBS3233 was able to improve insulin sensitivity in diabetic rats with insulin resistance. The insulin sensitizing effect was projected from the reduction of HOMA-IR, increase of PPAR gamma and nephrin expression in renal podocytes cell. So further studies are needed to clinically test the efficacy of DLBS3233.



• Figure 5. Immunofluorescence overview of the effect of therapy on the expression of PPARγ between groups of rats



• Figure 7. Immunofluorescence overview of the effect of therapy on nephrin expression in podocytes between groups of rats

SA-PO997

Extracellular Vesicles of Podocytes Impact Intraglomerular Signaling and Parietal Epithelial Cell (PEC) Activation

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Background: Extracellular vesicles (EVs) have the ability to impact basic pathological processes such as malignant, metabolic and autoimmune diseases through intercellular signaling. However, we lack a concise knowledge about their role in kidney health and disease. Our study aims to characterize the intraglomerular signalling propagated by medium sized (mEVs) and small EVs (sEVs) shed by podocytes.

Methods: Using differential (ultra-) centrifugation we separated mEVs and sEVs from cell culture supernatants, kidney tissue and urine samples. Using Western Blot, immunofluorescence microscopy as well as image flow cytometry and cryo electron microscopy we investigated the release dynamics of podocyte-specific EVs in different models of murine podocyte damage *in vitro* and *in vivo*. Life microscopy and cross culture experiments were used to determine the effect of podocyte-specific EVs on parietal epithelial cells (PECs). To determine potential signaling factors we performed proteomic analysis of EV content.

Results: Podocytes shed medium-sized and small EVs detectable in culture supernatant, murine kidney tissue as well as the urine of healthy human volunteers. Upon podocyte damage *in vitro*, we detected an increase in EV release as a unified response with a size-shift in certain conditions revealed in Cryo-EM. Surprisingly, podocyte-specific EVs exerted different effects on the migratory behavior and proliferation of PECs depending on EV size and the initial insult to the podocyte. Proteomics revealed limited differences in the EV proteome in different stress conditions, with first candidate proteins potentially propagating the effect on PECs. *In vivo*, decreased EV release by podocytes resulted in reduced PEC activation and limited recruitment of macrophages in a model of crescentic nephritis.

Conclusions: Our study yields essential insights on podocyte-specific release of different sizes of extracellular vesicles, their protein contents and functional implications in health and upon podocyte damage. Ongoing experiments focus on further elucidating the impact of podocyte-specific release *in vivo* and the impact of knocking-out identified EV candidate proteins.

SA-PO998

PIK3CA Activation in Extracapillary Glomerulonephritis

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Background: Extracapillary glomerulonephritis are severe kidney disorders frequently associated with end stage kidney disease. Therapeutic options for these diseases are limited especially due to insufficient understanding of their pathophysiology.

Methods: Following the identification of a somatic *PIK3CA* gain-of-function mutation in podocytes of a patient, we used multiple genetically engineered mouse models, single cell RNA sequencing and spatial transcriptomics to unveil the role of PI3K-Akt mTOR pathway in podocyte biology of proliferative glomerulonephritis. Alpelisib, a pharmacological PI3Ka inhibitor, was used to inhibit the pathway.

Results: Podocyte-specific *PIK3CA* overactivation in mice developed progressive focal segmental glomerulosclerosis with podocyte proliferation, dedifferentiation and inflammation. Alpelisib treatment improved glomerular lesions and kidney function in different models of collapsing glomerulopathy and lupus nephritis by targeting podocytes. In addition, even more importantly and unexpectedly, we uncover that pharmacological inhibition of PI3Ka affects B and T lymphocyte population in lupus nephritis mouse models with reduction in proinflammatory cytokine and auto antibodies production, immunoglobulin and complement deposition. These findings were further confirmed in Human lymphocytes isolated from patients with lupus nephritis.

Conclusions: We demonstrate the crucial role played by PI3Ka for proliferative glomerular diseases and showed for the first time that alpelisib represents a promising therapeutic acting on both, podocytes and immune compartment.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO999

Podocytic and Endothelial Infolding in Focal Segmental Glomerulosclerosis with INF2 Mutation

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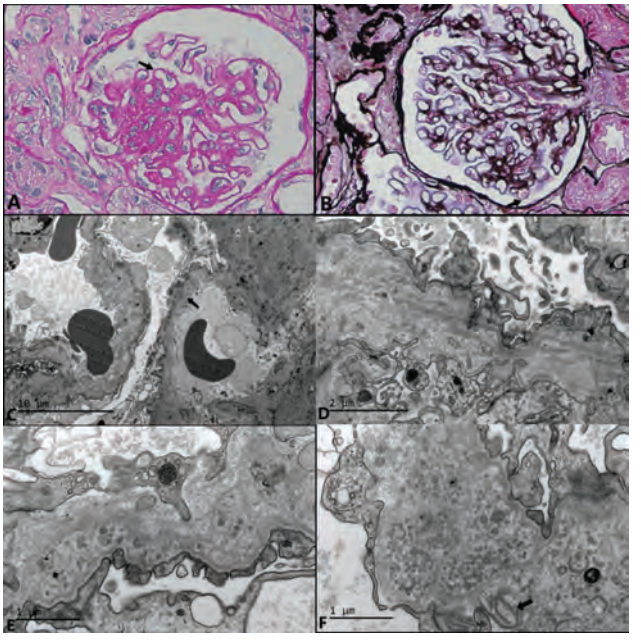
Introduction: Podocytic infolding glomerulopathy (PIG) is characterized by podocyte cell invading into the GBM and intra-GBM spherules with around 40 reports only. The invaginations of endothelial cells to the GBM were generally not described. We report the specific ultrastructure of endothelial cells evidently invading into the GBM besides podocytes of a 25-year-old woman with the inverted formin-2 (INF2) mutation.

Case Description: The patient presented as nephrotic syndrome whithout autoimmune disorders. Light microscopy of kidney biopsy showed the basement membrane was irregularly thickened (Figure 1(A-B)). Electron microscopy revealed diffuse irregular thickening of the basement membrane with podocyte foot-process infolding into and with many microspheres, some membrane like structures and a few electron-dense deposits inside (Figure 1(C-F)). Notably, villous cytoplasmic protrusion of endothelial cells were more conspicuous in the GBM. The gene sequencing showed novel heterozygous mutations in the INF2 gene (NM_022489.4). The c.395T>C mutation was classified as significance undetermined. The patient is stable with olmesartan and diuretics.

Discussion: The pathogenesis of PIG remains unclear. In particular, villous protrusions of endothelial cells were more remarkable in the GBM in our case, suggesting that endothelial cells may be related to PIG. When the GBM is injured, the disordered skeletal structure may also easily trap the decomposing podocyte or endothelial cell processes in and dissociate them. Genetic mutations may also be involved in PIG. Whether the c.395T>C mutation had connection with PIG remains unclear. To our knowledge, this is one of the minority reported cases of PIG with gene detection. The specific pathogenesis and genetic explanation of PIG still needs to be further explored.



LM and EM of kidney biopsy specimen

SA-PO1000

Laminin α2-Mediated Podocyte Damage Is a Dominant Driver of Glomerular Disease in Alport Mice

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Background: Earlier work showed that the progressive accumulation of laminin α2 in the GBM activates focal adhesion kinase and NF-kappa B, resulting in elevated expression of pro-inflammatory cytokines and metalloproteinases. The receptor(s) for laminin α2 were never identified, nor the functional consequences of activation of the laminin α2 receptors on podocytes.

Methods: Cultured podocytes were overlayed with recombinant laminin 211 (or not) then transfected with either scrambled SiRNA or SiRNA specific for α-dystroglycan (DAG) and RNA analyzed by RNA-seq. Cell signaling characterization was done using the Full Moon Biosystems (Sunnyvale, CA) *"cell signaling phospho Ab array"*. This platform has 312 antibodies representing the most common cell signaling pathways. We performed this analysis on podocytes transfected with scrambled Si RNA +/- and either α-dystroglycan or integrin α7 knockdown in podocytes treated (or not) with laminin 211.

Results: SiRNA studies show the genes that are most abundant and up regulated by laminin 211 that are normalized by DAG knockdown. This list includes profibrotic genes such as Acta2, Scube3, and TGF-Beta3, as well as genes that up-regulate ECM expression (Ccn2, which encodes CTGF) and Col4A1. KEGG analysis of this data implies important roles for laminin α2-mediated α-dystroglycan receptor activation in cell adhesion and cell migration. Full Moon cell signaling array studies demonstrate that laminin 211-mediated α-dystroglycan and α7β1 integrin signal by both shared and unique signaling pathways and are thus both functioning in laminin 211-mediated signaling in cultured podocytes. Both receptors showed significant activation of PI3K/AKT, Apoptosis, Cell cycle, Jak Stat, NFkappaB, p53, Ras and VEGF signaling pathways. mTor signaling was primarily influenced by integrin α7β1, and the TGF-beta signaling cascade was primarily activated by α-dystroglycan. Thus, the two receptors function both independently and more commonly through co-receptor signaling.

Conclusions: Laminin α2-mediated activation of integrin α7β1 and α-dystroglycan receptors is a major contributor to podocyte damage and glomerular disease progression in Alport mice.

Funding: Other NIH Support - NIDCD

SA-PO1001

EPAC1-Mediated cAMP Signaling Promotes Cellular Energy Adaptations and Glycolytic Metabolic Shift in Podocytes to Protect from Glomerulonephritis

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Background: Many efforts are made to identify new therapeutic targets to slow down, prevent Chronic Kidney Disease (CKD) progression. One of the therapeutic approaches is activating the renoprotective cAMP pathway. The exchange factor directly activated by cAMP 1 (EPAC1) has been identified as a novel, PKA-independent, mediator of cAMP signalling. EPAC1 is a guanidine exchange factor that regulates important cellular functions. Here we aim to determine the role of EPAC1 in CKD progression.

Methods: An immunostaining of EPAC1 is performed on biopsies of patients with glomerulonephritis. Nephrotoxic serum glomerulonephritis (NTS-GN) is induced in genetically modified mice with total and conditional EPAC1 deletion in podocytes. Then isolated glomeruli from the conditional mice are analysed by RNA-sequencing. The main metabolic energy pathways are studied in podocytes *in vitro* under oxidative stress exposure in the presence/absence of an EPAC1 agonist.

Results: EPAC1 is expressed in different GN disease and localized in glomeruli. Following the induction of NTS-GN, mice with genetic deletion of EPAC1 show aggravated renal disease, characterized by increased proteinuria, tissue inflammation and fibrosis compared to control mice. Conversely, pharmacological activation of EPAC1, with the agonist 8-pCPT-2-OMe-cAMP, delays NTS-GN progression. Since in human and mouse kidney tissues we observe EPAC1 expression in podocytes, mice with conditional deletion of EPAC1 in podocytes are generated. Similar to the whole-body knockout, conditional mice show worsened disease progression compared to control mice. RNA-sequencing analysis of glomeruli isolated from these mice show that gene expression of proteins linked to the pathway of glycolysis are abolished in early stage of NTS-GN. EPAC1 activation under oxidative stress in podocytes *In vitro*, promotes glycolysis with cellular energy production independently from mitochondrial respiration. The EPAC1-mediated glycolysis protected podocytes by increasing cell viability.

Conclusions: Podocytes-derived EPAC1 plays a protective role against the development of GN through cellular energetic adaptations based on metabolic shift to glycolysis. Activating the cAMP-EPAC1 signalling axis could represent a therapeutic option to delay CKD.

Funding: Government Support - Non-U.S.

SA-PO1002

Preliminary Renal Biopsy Registry: Dominican Republic

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Background: The rising incidence of renal diseases and the need to enhance their prevention, diagnosis, and treatment have prompted the establishment of national renal biopsy registries. These registries provide essential information about the epidemiology of renal diseases and can inform the design of clinical trials and the development of therapeutic strategies. With this premise, the Preliminary Renal Biopsy Registry was implemented in the Dominican Republic, aiming to compile and analyze renal biopsy data nationwide. This registry provides a valuable data source for studying renal diseases in this specific country, enabling the identification of risk factors and the evaluation of the effectiveness of public health interventions.

Methods: A retrospective database analysis was conducted, collecting national renal biopsy data. A call was made to nephrologists performing renal biopsies through the national society. Biopsies from 2002 to 2022 were included.

Results: A total of 929 biopsy were included of this study. Consisting of 814 (87.62%) non-transplanted and 115 (12.38%) transplanted patients. 455 (55.9%) were female, 604 (74.2%) biopsies were performed in northern part of the country and just 32 patients (3.9%) were re-biopsied. The five more common primary biopsy diagnosis in non-transplanted patient were the following: focal segmental glomerulosclerosis 174 (21.4%), lupus nephritis (14.3%), minimal change disease (10.3%), membranous nephropathy 73 (9%) and Alport syndrome/thin membrane disease 66 (8.1%). In transplanted patients however, the five more common were: acute rejection 45 (39.1%), no rejection 25 (21.7%), chronic rejection 22 (19.1%), acute tubular necrosis 5 (4.3%) and focal segmental glomerulosclerosis 4 (3.5%).

Conclusions: According to our study, FSGS was the most common type of glomerulonephritis in our population. Also, this study showed a high frequency of Lupic nephritis, ranking second among all the glomerulonephritis diagnoses, followed by minimal change disease. This pattern is similar to other studies in Latin America, revealing a higher frequency of lupus nephritis compared to European and American countries. This information is essential to realize and emphasize kidney diseases' importance, especially autoimmune glomerular disorders in Latin America.

SA-PO1003

Mechanisms of TMEM30A/NLRP3 Inflammasome Pathway-Mediated Podocyte Pyroptosis in FSGS

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Background: Primary Focal and Segmental Glomerulosclerosis (FSGS) is a renal histological disease characterized by podocyte injury. Transmembrane Protein 30A (TMEM30A) is involved in FSGS podocyte injury, but the underlying mechanism remains unclear.

Methods: Bioinformatics techniques were used to screen datasets related to FSGS in GEO database and search for keygenes. 20 FSGS patients and 20 normal control renal tissues were collected, and multispectral fluorescence staining was used to detect the expression levels of TMEM30A, Nephrin and NLRP3 in renal podocytes. In vivo study, adriamycin(ADR)-induced podocyte injury mice were constructed, and the expression levels of TMEM30A, Nephrin and NLRP3 were observed by multispectral fluorescence staining. Meanwhile, Podocyte specific *Tmem30a* knockout mice were constructed, and the expression levels of Nephrin and NLRP3 in renal podocytes were detected by multispectral fluorescence staining. In vitro study, ADR was used to induce mouse podocytes and *Tmem30a* knockdown mouse podocytes were constructed to observe the expression levels of podocyte protective marker and pyroptosis related proteins. After the intervention of NLRP3 inhibitor, the changes of podocyte marker protein and pyroptosis related protein were observed.

Results: In kidney tissues of FSGS patients and ADR-induced mice, We found that the level of TMEM30A and Nephrin significantly reduced and the level of NLRP3 significantly increased with obvious colocalization. In addition, multi-spectral fluorescence staining showed that NLRP3 was significantly increased in the kidney tissue of podocyte-specific *Tmem30a* knockout mice, colocalized with podocyte-related protein Nephrin. In vitro study, we successfully constructed adriamycin induce mouse podocytes and *Tmem30a* knockdown mouse podocytes with decreased podocyte marker WT1 and Nephrin. Then, We further found the expressions of pyroptosis-related proteins NLRP3, Caspase 1 and GSDMD were significantly increased. The NLRP3 inhibitor MCC950 could inhibit podocyte pyroptosis and improve podocyte injury.

Conclusions: TMEM30A could inhibit the activation of NLRP3 inflammasome, prevent the production of active Caspase 1 and the cleavage of GSDMD, reduce the podocytes pyroptosis, weaken the damage of podocytes, and improve FSGS.

SA-PO1004

Deletion of IRE1α Exacerbates Diabetic Nephropathy in Mice

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Background: Protein misfolding in the endoplasmic reticulum (ER) of podocytes is an important contributor to the pathogenesis of glomerular diseases. ER protein misfolding activates a compensatory signaling network called the unfolded protein response (UPR). Deletion of the UPR transducer, inositol-requiring enzyme 1α (IRE1α) in mouse podocytes leads to podocyte injury and albuminuria in aging, and exacerbates injury in glomerulonephritis. This study addresses the role of the UPR and IRE1α in diabetic nephropathy.

Methods: We studied mice with podocyte-specific deletion/knockout (KO) of IRE1α. Hyperglycemia was induced in male mice (age 3-4 months) with streptozotocin.

Results: Streptozotocin-treated control and IRE1α KO mice developed comparable hyperglycemia (diabetes). Diabetes caused progressive albuminuria in control mice (3.7 mg/mg creatinine at 6 months) that was exacerbated in IRE1α KO mice (8.5 mg/mg creatinine; $P<0.01$). Albuminuria was ~1 mg/mg creatinine in non-diabetic groups (4-13 mice/group). Compared to diabetic controls, diabetic IRE1α KO mice showed a reduction in podocytes (WT1-positive cells; $P<0.0001$) and synaptopodin ($P<0.05$). Both non-diabetic and diabetic IRE1α KO mice showed increased glomerular matrix expansion compared to their respective controls. Glomerular ultrastructure was altered only in diabetic IRE1α KO mice; changes included widening of foot processes and glomerular basement membrane, microvesiculation of podocyte plasma membranes, and markedly dilated ER and mitochondrial architectural damage in podocytes. Activation of the UPR (increased glomerular ER chaperones) and autophagy (increased LC3-II, decreased p62) was evident in diabetic control, but not diabetic IRE1α KO mice. Analysis of human glomerular gene expression in the JuCKD (Nephroseq) database demonstrated activation of pathways and gene ontology categories, as well as induction of genes associated with the ER, UPR and autophagy in diabetic nephropathy.

Conclusions: Mice with podocyte-specific deletion of IRE1α demonstrate more severe diabetic nephropathy. This was associated with an attenuation of the glomerular UPR and autophagy, implying a protective mechanism mediated via IRE1α. These results are consistent with data in human diabetic nephropathy and highlight the potential for therapeutically targeting these pathways.

Funding: Government Support - Non-U.S.

SA-PO1005

The miR-143/145 Cluster Induced by TGF-β1 Suppresses Wilms Tumor 1 Expression in Cultured Human Podocytes

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Background: Transforming growth factor (TGF)-β1 contributes to podocyte injury in various glomerular diseases, including diabetic kidney disease (DKD), probably in part by attenuating expression of Wilms' tumor 1 (WT1). We aimed to identify microRNAs associated with TGF-β1-induced podocyte injury.

Methods: miR-microarray studies were performed using total RNA extracted from differentiated human podocytes exposed to 5 ng/mL TGF-β1 for 24 h and control podocytes. db/db mice were used as animal models of type-2 diabetic nephropathy.

Results: Microarray analysis identified miR-143 as the miR with the greatest increase following exposure to TGF-β1 (2.3 fold increase as 2ΔLMR vs. control, p=0.0000077). We confirmed by reverse transcription-quantitative polymerase chain reaction that the miR-143/145 cluster expression significantly increased in a time-dependent manner for up to 48 hours after exposure to of TGF-β1 in cultured human podocytes (13.3 ± 3.7/ 17.4 ± 0.4 fold at 48 h vs. 0 h). We also observed upregulation of miR-143 in glomeruli of 16-week-old type 2 diabetic db/db obese mice compared to control mice, although miR-145 levels were comparable. Lentiviral ectopic expression of miR-143 and miR-145 in cultured human podocytes suppressed mRNA and protein expression of WT1 compared to ectopic expression of scramble allele as control, both with TGF-β1 exposure and non-exposure (0.37 ±0.057/ 0.49 ±0.084 fold vs. control for mRNA, 0.44 ± 0.093/ 0.38 ± 0.066 fold vs control for protein). Further, inhibition of SMAD signaling by shRNA targeting SMAD4 and inhibition of mammalian target of rapamycin (mTOR) signaling by exposure to rapamycin partially and significantly reversed the TGF-β1-induced increase in miR-143/145 and decrease in mRNA and protein expression of WT1.

Conclusions: In summary, in cultured human podocytes, TGF-β1 induces expression of the miR-143/145 cluster, in part through the classic SMAD and mTOR pathway, and miR-143/145 reduces expression of WT1. Thus, miR-143/145 may contribute to the TGF-β1-induced podocyte injury.

Funding: Commercial Support - Bayer Yakuhin, Ltd

SA-PO1006

Integrin α3β1 as a Potential Target for Diabetic Kidney Disease (DKD)

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Background: Integrin α3β1 is highly expressed in kidney and is critical for maintaining the glomerular filtration barrier integrity by mediating adhesion of podocytes to laminin on the glomerular basement membrane. In human, loss-of-function mutations of α3 or its ligand laminin cause congenital nephrotic syndrome. We hypothesized that α3β1 activity in DKD is reduced and that activating α3β1 should preserve podocyte adhesion and kidney function. Here, we tested this hypothesis in a *proof of mechanism* (POM) experiment using the integrin β1-agonistic antibody 9EG7 in translational mouse model of severe DKD.

Methods: Integrin α3β1 loss in DKD was measured by α3 expression in kidney tissues from DKD patients with increasing disease severity by immunofluorescence staining. Antibody 9EG7 was characterized *in vitro* using adhesion assay in cells overexpressing α3β1, as well as adhesion, binding and cell morphology in human and mouse podocytes. The *in vivo* POM experiment with 9EG7 was performed in hypertensive diabetic ReninAAV Unix db/db mice. End points were kidney function (albuminuria), biomarkers (podocytes markers in urinary shed cells (uSC) and exosomes-like vesicles (ELV)), AI-based assessment of podocytes counts and the analysis of podocyte foot process effacement (measured by super-resolution microscopy).

Results: We confirmed that in DKD there is a progressive loss and mis-localization of α3 with disease progression, supporting the notion of a potential beneficial effect of an agonistic mAb. *In vivo* efficacy studies with integrin β1-agonistic monoclonal antibody 9EG7 (2 weeks treatment) showed a dose dependent decrease in uACR ratio and reduction of podocyte markers in whole urine and isolated urinary ELV and uSC. AI-enabled quantification of podocyte marker WT1 showed increased podocytes counts per glomerulus. Quantitative analysis of podocyte foot process formation by super-resolution microscopy showed improved podocyte structure.

Conclusions: Integrin β1-activation with the monoclonal antibody 9EG7 ameliorated hypertension-and diabetes-induced albuminuria, increased podocyte counts in glomerulus and decreased urinary podocyte markers in a preclinical model of DKD. These findings suggest that α3β1 could be a potential target for DKD.

Funding: Commercial Support - Janssen Pharmaceuticals, Morphic Therapeutic

SA-PO1007

Nephrotic Syndrome-Associated TRIM8 Variants Impair the Proteasome-Dependent Turnover and Condensation of TRIM8 Protein

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Background: Nephrotic syndrome (NS) is the second leading cause of chronic kidney disease. *De novo* C-terminal truncating variants in *TRIM8* (tripartite motif containing 8) cause a novel form of NS. As N-terminal truncating *TRIM8* variants present in gnomAD controls precluded haploinsufficiency, we hypothesized that NS-associated *TRIM8* variants cause a podocytopathy through dominant-negative or gain-of-function mechanisms.

Methods: Protein-protein interactions were determined by co-immunoprecipitation (co-IP). The 26S proteasome inhibitor MG132 was used to modulate the levels of tagged wildtype (WT) and patient variant (PV) TRIM8 protein. The half-life of tagged TRIM8 protein was assessed by cycloheximide chase assay. Tagged WT and PV TRIM8 protein ubiquitination was measured by IP upon overexpression of HA-tagged *Ubiquitin*. GFP-tagged WT and PV TRIM8 protein cellular localization was evaluated by confocal microscopy.

Results: Wildtype and patient variant TRIM8 co-immunoprecipitated with WT TRIM8, indicating NS-associated *TRIM8* variants do not impair TRIM8-TRIM8 interactions. MG132 treatment increased WT TRIM8 but not PV TRIM8 protein levels, demonstrating disease-associated variants impair 26S proteasome-dependent TRIM8 degradation. PV TRIM8 exhibited increased stability (half-life > 5 hours) relative to WT TRIM8 protein (half-life 3 hours) by cycloheximide chase assay. Tagged TRIM8 WT protein underwent polyubiquitination, which was impaired by NS-associated *TRIM8* variants. GFP-tagged WT TRIM8 exhibited increased condensation to nuclear bodies upon proteasome inhibition, while PV TRIM8 maintained pan-nuclear localization in the presence or absence of MG132.

Conclusions: NS-associated variants in *TRIM8* cause increased TRIM8 protein stability but reduced protein condensation, suggesting these variants have hyper- or neomorphic effects.

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SA-PO1008

A Novel Frameshift Mutation in CLCN5 in a Family with Podocytopathy Phenotype

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Background: Steroid resistant nephrotic syndrome (SRNS) is a common cause of pediatric chronic kidney disease (CKD). However, the cause of approximately 80% of familial SRNS cases remain unknown. We hypothesized that additional genetic causes of disease can be discovered through next generation sequencing analysis of a large cohort of families with NS.

Methods: To identify the genetic cause of podocytopathy we performed whole genome sequencing, followed by direct sequencing and segregation analysis in over 300 patients from ~200 families.

Results: We identified a novel segregating hemizygote truncating mutation (c.1199del, p.Gly400ValfsTer29) in the gene encoding Chloride Voltage Gated Channel 5 (*CLCN5*) in a family with four affected boys with NS phenotypes including nephrotic range proteinuria and biopsy proven focal segmental glomerulosclerosis (FSGS). Segregation analysis revealed that the mother is heterozygous for the same variant, while the variant is absent in the father. Chloride Voltage Gated Channel 5 encodes a member of the chloride ion channels and ion transporters that regulate endosomal acidification and receptor mediated endocytosis in tubules. Mutations in *CLCN5* is a major cause of Dent Disease, a proximal tubulopathy characterized by hypercalciuria, nephrocalcinosis and nephrolithiasis. However, *CLCN5* is enriched in the podocyte at the mRNA and protein level. We also analyzed whole exome sequencing data from additional 200 patients with nephrotic syndrome and identified another family with a hemizygote variant of unknown significance (VUS).

Conclusions: Pathogenic variants in *CLCN5* represent a rare cause of secondary podocytopathy and should be included in the gene panel for SRNS. Analysis of iPSC-derived podocytes from this family will unravel the mechanisms by which *CLCN5* deficiency in podocyte can cause a podocytopathy-like phenotype.

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SA-PO1009

Gene Expression and Regulatory Activity Disruptions in Glomerular Disease Patients

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Background: The role of noncoding variants in glomerular disease is not well understood. In this work we use deep learning to analyze contributions of these variants to gene expression and regulatory activity disruptions in the CureGN cohort, which includes patients with minimal change disease (MCD), membranous nephropathy (MN), IgA nephropathy (IgAN) and focal segmental glomerulosclerosis (FSGS).

Methods: To systematically assess the functional impact of the variants, we used deep learning models to predict gene expression changes in primary human cell types and the underlying biochemical disruptions to chromatin regulators across millions of patient variants.

Results: Gene expression changes were predicted for over 3 million variants in 25 kidney cell types. Effects of rare variants were accumulated per gene. We found multiple genes and pathways (Reactome) that were significantly dysregulated across all patients. For example, a gene with significant gene expression disruption was RABGGTB (*p-val=1.42e-74*), which is prognostically unfavorable in renal cancer. Others include RREB1 (*p-val=1.178e-88*) and MAPK7 (*p-val=2.738e-220*). Top variants from each diagnosis group impacted distinct sets of partially overlapping genes and pathways. In addition to gene expression, we obtained predictions for regulatory activity disruption for over 25 million gene proximal patient variants. Predicted chromatin biochemical disruption was more severe for strongly conserved variants and variants associated with disease-related pathway genes. A subset of genes and pathways were significantly disrupted between and within patient groups. For example, within variants found in MCD patients, genes involved in PCSK9 reactions had stronger chromatin profiling disruptions (*p-val=6.36e-05*) than the other variants of MCD patients.

Conclusions: Through comprehensive analysis of the non-coding variants in the CureGN cohort, we discovered variants, genes, and biological pathways disproportionately perturbed across the CureGN patients. Gene expression predictions provided functional effects, while chromatin profiling predictions offered additional insight into disruption of molecular mechanisms. This analysis provides hypotheses for disease-contributing biology and a resource for the future experimental follow-up.

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SA-PO1010

Podocyte-Specific Deletion of MCP-1 Fails to Protect Against Angiotensin II- or Adriamycin-Induced Nephropathy

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Background: Investigating the role of podocytes in the pathophysiology of proteinuric disease is important to remedy the increasing global burden of chronic kidney disease (CKD). Monocyte chemoattractant protein-1 (MCP-1 or CCL2) is a chemokine upregulated in proteinuric CKD. Since podocytes can express both MCP-1 and its receptor (CCR2), we hypothesized that an autocrine MCP-1/CCR2 loop contributes to proteinuric CKD. To test this hypothesis, we generated podocyte-specific MCP-1 knockout mice (Podo-*Mcp-1*$^{fl/fl}$) and exposed them to proteinuric injuries.

Methods: Podo-*Mcp-1*$^{fl/fl}$ mice were generated by crossing MCP-1 floxed mice with mice harboring Cre recombinase under the transcriptional control of the podocin promoter. Podo-*Mcp-1*$^{fl/fl}$ mice and control littermates were subjected to either angiotensin II (Ang II; 1.5mg/kg/day x 28 days) or Adriamycin (Adr; 18mg/kg) to induce glomerular injury. Weekly spot urines were assessed for albuminuria. After 28 days, sera were collected to assess renal function while kidney tissues were used for histological, immunofluorescence, immunoblot, and quantitative PCR analyses. Unpaired Student's t-test (two-tailed) was performed for two group comparisons. Log-rank test was used to compare survival distributions. The threshold for significance was $P<0.05$.

Results: At baseline, there were no between-group differences in body weight, histology, albuminuria, and podocyte markers. After 28 days of injury with either Ang II or Adr, there were no between-group differences in survival, albuminuria, renal function, inflammatory mediators, histopathology, podocyte loss, nephrin expression, and fibrosis.

Conclusions: Due to the lack of protection in the knock-out mice, our findings suggest that podocyte-specific MCP-1 production is not a major contributor to either Ang II- or Adr-induced glomerular injury. MCP-1 signaling must originate from a non-podocyte cell type. Future studies will determine the source cell of MCP-1.

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SA-PO1011

Effect of Transglutaminase-Induced Stiffening of Glomerular Basement Membrane on Podocyte Function

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Background: Glomerular basement membrane (GBM) and podocytes are important components of the glomerular filtration barrier. Podocytes are terminally differentiated cells that develop an intricate 3D architecture in vivo that is difficult to maintain in vitro. New approaches to maintaining podocyte differentiation may improve in vitro studies. Matrix stiffening is closely related to cellular function and GBM stiffness is altered in chronic kidney disease. How GBM mechanical properties affect molecular permeability and podocyte function is not fully understood. This work aims to investigate podocyte differentiation on native and transglutaminase crosslinked GBM and evaluate its effects on molecular transport.

Methods: Glomeruli were isolated from pig kidneys by sieving. The stiffness of native and transglutaminase (TG) crosslinked glomeruli was evaluated by a customized compression system. Decellularized and lyophilized glomerular matrix was rehydrated in PBS and coated on a 12-well plate. Immortalized human podocytes were plated on sterilized native GBM, TG treated GBM, and Matrigel coated plates. Podocytes were proliferated at 33°C, followed by transferring to 37°C for 14 days differentiation. Podocyte specific markers (nephrin, WT-1, and synaptopodin) and tight junction markers (ZO-1) were evaluated by immunofluorescence. Glomerular matrix was pressure compacted to Transwell membranes under pressure in a stirred cell to evaluate barrier function.

Results: Crosslinking GBM with transglutaminase increases its stiffness. Podocytes express nephrin and WT-1 after 14 days differentiation in culture on native and crosslinked GBM, and Matrigel coated coverslips. There is no synaptopodin expression in undifferentiated podocytes, but it has strong expression in differentiated podocytes. Podocytes cultured on native GBM show clear ZO-1 staining but weak staining on the TG treated GBM. Diffusive permeability measured on GBM with cultured podocytes is significantly reduced after 14 days differentiation compared to 7 days differentiation. This suggests podocyte differentiation contributes to barrier permeability.

Conclusions: We provide an easy method to fabricate biomimetic GBM which can support podocyte differentiation during long-term culture. Stiffening of GBM affects podocyte differentiation and junction marker that may contribute to loss of filtration barrier integrity.

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SA-PO1012

A Novel Mutation in Podocyte-Specific Protease HtrA1 Is Associated with Glomerular Disease Progression

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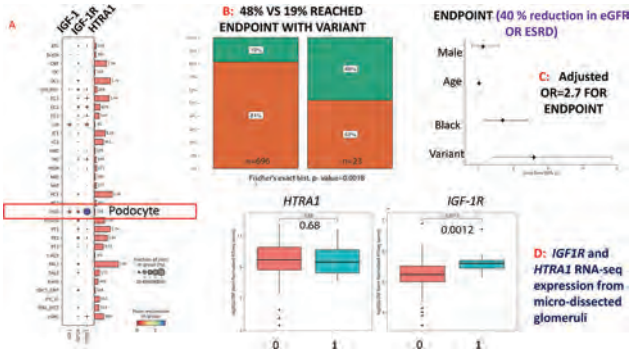
Background: In kidney allografts, IGF-1 signaling was associated with reduced expression of Integrin A3, a key podocyte adhesion protein, and accelerated podocyte detachment. Insulin-like growth factor binding protein 2 (*IGFBP2*) and the high-temperature requirement factor A1 (*HTRA1*) contributed to the observed IGF-1 signaling. Podocyte specificity of *HTRA1* was affirmed by single-cell RNA sequencing of healthy kidney tissue. The *HTRA1* encodes a protease and makes bound IGF-1 locally bioavailable(doi.org/10.1016/s0014-5793(96)01229-x). Since 99% IGF-1 is bound, functional mutations in the *HTRA1* gene could therefore perturb local IGF-1 signaling with functional consequences.

Methods: We searched for *HTRA1* coding variants in the NEPTUNE cohort (n=620). Six distinct variants passed QC filtering. Each variant was then examined for its association with negative outcome (ESRD or 40% reduction in GFR). Transcriptional consequences on IGF-1 signaling of these mutations were evaluated in glomerular RNA-sequencing data.

Results: One variant was associated with a 2.7-fold increased risk of negative outcome. This relatively rare SNP (rs369149111); allele frequency-0.0248 results in a missense mutation, leading to alanine to valine change within the conserved signaling peptide (Ala20Val) region. Corresponding higher expression of IGF-1R in glomeruli as observed in patients with this variant.

Conclusions: SNP (rs369149111) is associated with glomerular disease progression. This rare allele likely interacts with glomerular IGF-1 signaling that then contributes to podocyte loss observed in glomerular diseases and transplanted kidneys. Further studies are necessary to confirm the prevalence and mechanistic implications of this *HTRA1* variant

Funding: NIDDK Support



SA-PO1013

Novel Allosteric Agonists of Integrin a3b1 as Therapeutics for FSGS

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Background: Podocytes form the kidney filter that allows separation of urine and waste from blood. They attach to the extracellular basement membranes via cell surface integrin a3b1. Reduced podocyte adhesion, due to injury or mutations in a3b1, associated membrane proteins (CD151), or the integrin linked cytoskeleton, results in podocyte detachment and loss that weakens the kidney filter, resulting in progressive glomerular disease. Reinforcement of podocyte adhesion, via increased integrin-mediated cell adhesion and strengthened cytoskeleton is protective in various kidney diseases.

Methods: We used a human phage display library to identify a3b1 activating antibodies. K562 cells stably expressing a3b1, differentiated podocytes, and human SKOV cells were used in *in vitro* assays. K562 cells were used in flow-cytometry assays to characterize a3 agonists. Podocytes were used in High-Content Screening (HCS) based assays to quantify puromycin aminonucleoside (PAN) induced cell damage and integrin agonist mediated protection. Cells were also utilized in cell adhesion and cell migration based functional assays.

Results: Measurement of F-actin fibers, focal adhesions and active integrin levels in podocytes showed a quantifiable change due to PAN injury in podocytes, and protection from PAN-injury by b1 integrin agonists 9EG7 and pyrintegrin as well as by the novel antibodies. a3b1 agonists also showed increased cell adhesion and reduced cell migration *in vitro*. Mapping of the antibodies using various integrin chimeras showed that they selectively bound to the a3 head-domain, away from the ligand binding pocket.

Conclusions: We previously reported that activation of podocyte-expressed integrin a3b1 increases podocyte adhesion to matrix proteins and protects cells from damage. Here, we show that novel, integrin a3b1-directed allosteric agonist antibodies can be used to reinforce podocyte adhesion to the basement membrane. Data from our currently ongoing *in vivo* efficacy studies will provide further evidence of the therapeutic efficacy of this approach as a novel therapeutic strategy against a variety of glomerular diseases.

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SA-PO1014

Expression and Modulation of SGLT2 in Human Podocytes: Not All in Tubule

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Background: Inhibitors of the sodium-glucose cotransporter type 2 (iSGLT2) modify important non-glycemic pathways that lead to the protection of target organs. Its renoprotective pleiotropic effects in CKD, associated or not with diabetes, justifies further studies to elucidate the mechanisms of action (MoA) of these drugs. Although the co-transporter is mostly expressed in the proximal tubule, its location and function in other cells, potential therapeutic targets for inhibitor drugs, has not been well studied. We explored the presence of SGLT2 in human podocyte cells and whether it is modified in different situations of cellular stress.

Methods: Differentiated immortalized human podocytes were cultured under different experimental conditions for 24 or 48 h: Normoxia (Control); Normoxia + High concentration of glucose (HG); Hypoxia+2h Reoxygenation(H) and the combination H+HG. We also incubated with 0.1uM Dihydrotestosterone (DHT). SGLT2 gene expression was determined by quantitative PCR and SGLT2 protein was detected by Western Blot (WB) and immunofluorescence (IF).

Results: Sglt2 gene expression was detected with an increase after 24h of exposure to HG. Protein expression by WB showed a non-significant increase after 48h of exposure to HG and hypoxia, which was significant with co-incubation with DHT. The IF measured by intensity of area did not show an increase in the protein expression of the transporter under HG incubation. However, protein expression increased under all hypoxia conditions: Control 50.05±3, Hypoxia 140±16.3 ($p<0.05$ vs control) and HG+Hypoxia 253±21.29 ($p<0.001$ vs control).

Conclusions: Our data suggest that podocyte may be one of the therapeutic targets on which the iSGLT2 are acting. The experimental conditions described did not show differences in the expression of the transporter before the single stimulus of glucose, but they did under hypoxia and the combination Hypoxia-high glucose. In addition, co-incubation with testosterone seems to enhance the expression. Studying the MoA of iSGLT2 will open better comprehension of the kidney pathophysiology, particularly in the podocytopathies, regardless of diabetes.

SA-PO1015

A Case of Steroid Refractory Lupus Podocytopathy: Is Glucocorticoid Monotherapy Sufficient?

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Introduction: Lupus Podocytopathy (LP) is a rare, but clinically impactful, manifestation of Systemic Lupus Erythematous (SLE). Accepted management of LP, Minimal Change (MC) and FSGS - subtypes alike, utilizes glucocorticoid (GC) monotherapy for proteinuria suppression. We present a case of high-grade podocyte effacement LP with MC subtype refractory to conventional GC management requiring the addition of an immunosuppressive agent.

Case Description: 38 yo female with SLE and no chronic kidney disease presented with nephrotic syndrome and acute kidney injury. Creatine on presentation was 5.7mg/dL and urine protein:creatinine ratio 11g. Serologies demontrated +ANA > 1:640 and +dsDNA. Renal biopsy was performed and suggestive of LP - MC subtype. Electron Microscopy: diffuse (90%) visceral epithelial foot process effacement; no endothelial tubuloreticular inclusions or subendothelial immunocomplex deposits were noted (Figure 1). Light Microscopy and immunofluorescence were unremarkable for chronicity or proliferative nephritis. High-dose prednisone was initiated at 1mg/kg. No significant change in nephrotic syndrome was observed despite 4 months of prednisone monotherapy. Mycophenolate Mofetil (MMF) was subsequently incorporated achieving complete remission of proteinuria and return to baseline creatinine.

Discussion: Small retrospective studies evaluating LP have suggested GC monotherapy should be successful in achieving clinical remission, especially in MC subtypes. The case presented suggests the addition of a non-glucocorticoid agent may be required to mitigate the proposed pathogenic cytokine and T-cell dysfunctions. Factors such as high-grade podocyte effacement and heavy proteinuria should prompt consideration for empiric dual-agent immunosuppression. Larger-scale randomized studies are needed to demonstrate the clinical and pathologic criteria determining single vs. dual immunosuppressive therapy for LP.

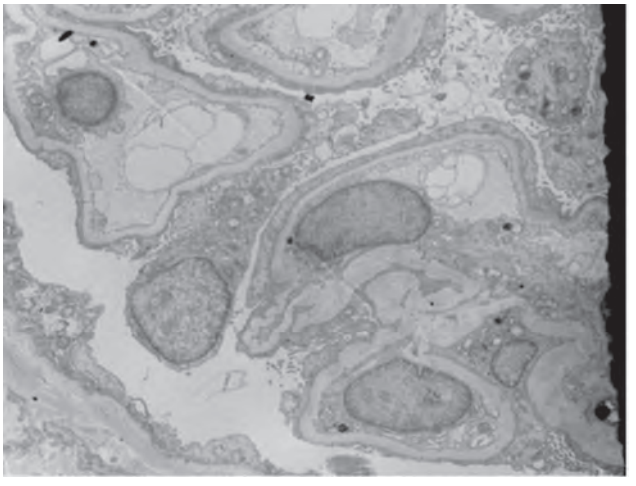

Figure 1 Electron Microscopy

SA-PO1016

A Case of Steroid-Resistant Focal Segmental Glomerulosclerosis in a Patient with a Heterozygous Mutation of COL4A3 Gene Variant of Uncertain Significance

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Introduction: Focal segmental glomerulosclerosis (FSGS) is a histopathological lesion that can manifest as severe hypertension, proteinuria, and nephrotic syndrome. FSGS can be a primary disorder or a secondary process related to medications, viruses, or genetic mutations. In this case, a 21-year-old patient presents with nephrotic syndrome secondary to collapsing FSGS with a heterozygous mutation of the COL4A3 gene.

Case Description: A 21-year-old black male presented with nephrotic syndrome. Labs revealed urine protein to creatinine ratio (UPCR) of 6.9 g/g, hematuria with 21-50 RBC/hpf, serum albumin of 1.1 g/dL, and serum creatinine of 1.2 mg/dL. A kidney biopsy showed minimal change disease. He was treated with high dose prednisone and tacrolimus. At 8 weeks, the patient had a UPCR of 14.5 g/g, serum albumin of 0.8 g/dL, and serum creatinine of 7.1 mg/dL. A second kidney biopsy was performed, showing collapsing FSGS with normal thickness of the glomerular basement membrane (Figure 1). Infectious work-up for HIV, hepatitis A, B, and C was negative. A Renasight kidney

genetic panel revealed a heterozygous mutation (p.Leu648Ile) of the COL4A3 gene with autosomal dominant and autosomal recessive inheritance patterns. It is a variant of uncertain significance, absent from the Broad gnomAD dataset. Patient was started on hemodialysis after failing immunosuppressive management.

Discussion: Heterozygous mutations of COL4A3 in patients with treatment-resistant FSGS with a normal glomerular basement membrane have been reported in the literature. Recognizing new genetic variants will help with developing future therapies and avoiding ineffective immunosuppression. More research will be necessary in this field.

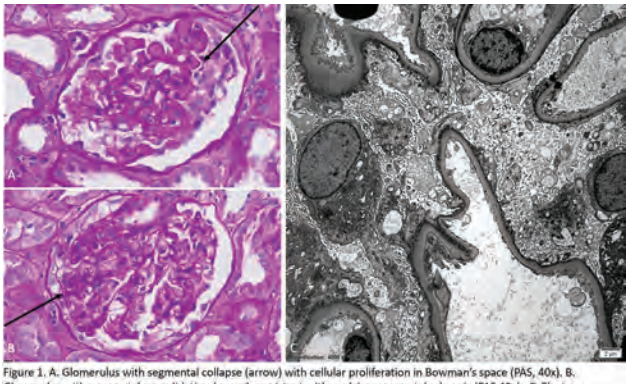

Figure 1. A. Glomerulus with segmental collapse (arrow) with cellular proliferation in Bowman's space (PAS, 40x). B. Glomerulus with segmental consolidation (arrow) consistent with evolving segmental sclerosis (PAS 40x). C. Electron microscopy showing global and diffuse effacement of the podocyte foot processes and microvillous changes in the podocytes

SA-PO1017

De Novo Relapsing Podocytopathies Following Novel COVID-19 Infection: A Case Series

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Introduction: COVID-19 Infection can result in significant multi-system disease, including pneumonia and renal pathologies. Thirty published articles have shown wide yet limited variety of underlying pathologies including collapsing FSGS, minimal change disease, and TMA following infection and vaccination. Our case series reintroduces discussion for unique podocytopathies following COVID-19 infection and vaccination, with relapsing MCD proteinuria, resistant MCD, and TIPS variant FSGS.

Case Description: Our first case is a 22 year old female, with no past medical history, who had an initial presentation of abdominal distension, extremity edema, nausea, and novel COVID-19 positivity, with a 24 urine protein of 5.3g, and secondary serologies negative. Her renal biopsy showed MCD phenotype. Her proteinuria initially responded to prednisone therapy, but relapsed secondary to a taper, requiring rituximab, with remission over 3 months. For this second case, a 36 year old male with a history of mast cell activation syndrome, thin basement membrane nephropathy, anabolic steroid use, presented with lower extremity edema and proteinuria of microalbumin to creatinine ratio of 4.5g, with kidney biopsy demonstrating TIPS variant FSGS, following COVID-19 infection positivity. Patient with poor tolerance to tacrolimus and prednisone due to adverse drug reactions, pending evaluation for sparsentan and rituximab. The third case is a 43 year old female with a history of APLS, presented with swelling, proteinturia, following COVID-19 infection, found to have a 24 hr urine protein of 10.7 grams. Patient initially responded to prednisone, however, had flare of proteinuria following taper, and COVID-19 vaccinations. Course unresponsive to cyclophosphamide treatment, with minimal responsiveness to rituximab, however given anticoagulation for APLS, repeat biopsy deferred.

Discussion: This case series reinforces an association between COVID-19 infection, vaccination and podocytopathy. However, it also provides groundwork for exploration of resistant and relapsing nephrotic syndromes, and the utility in early biopsies for early treatment. This raises the question whether there are long term effects of COVID-19 on renal health, and if COVID-19 induced nephrotic syndrome deserves its own treatment guidelines over traditional therapies.

SA-PO1018

Mapping the Molecular Atlas of Podocyte Response to Glucocorticoids Using Multi-Omics Analyses

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Background: Glucocorticoids are the mainstay of therapy for idiopathic nephrotic syndrome (iNS). Glucocorticoids have been found to directly influence podocyte behaviour and morphology, but the exact mechanism is unknown. Understanding this mechanism may help to identify targets for more effective treatment options with fewer side effects compared to glucocorticoids. We established an animal and kidney organoid model of steroid-sensitive NS to dissect the molecular mechanisms of glucocorticoids on podocytes using single-cell ATAC and RNA sequencing.

Methods: We used the puromycin aminonucleoside (PAN) rat model using one intravenous injection of PAN (10mg/100g) and daily intraperitoneal injections of prednisolone (1.5mg/100g). Human induced pluripotent stem cells were used to make kidney organoids, which were injured to various degrees using Adriamycin (ADR; ranging 0.5-2.5 ug/mL) or PAN (ranging 25-100ug/mL) and rescued with prednisolone (ranging 5-100 ug/mL). Single-cell sequencing was performed using the 10X genomics platform.

Results: Increased proteinuria, foot process effacement and increased podocyte specific desmin-protein expression were observed after PAN injection in rats. The injury was partially rescued by prednisolone treatment, whereas higher doses of prednisolone showed more proteinuria and desmin expression. Prednisolone treatment was not able to rescue more severe injury (by higher PAN injection). At the moment we are analysing single-cell ATAC and RNA sequencing data to identify responses in the podocytes to prednisolone. ADR and PAN can both be used to injure podocytes in kidney organoids, confirmed by western blot for autophagy markers and immunofluorescence for podocyte markers and caspase 3. Currently, rescue with prednisolone is tested before single-cell RNA sequencing is used to map molecular changes in the rescued podocytes.

Conclusions: We established a partially glucocorticoid-responsive *in vivo* model of NS and are currently performing single-cell sequencing to unravel mechanisms involved in prednisolone-induced podocyte recovery. Interestingly, high doses of prednisolone have adverse effects, and when the injury is too severe it cannot be rescued with prednisolone. In human kidney organoids, podocytes can be injured with ADR or PAN and recovery is being tested at the moment.

SA-PO1019

Nephrotic Syndrome from Primary Amyloidosis Can Be Linked with Multiple Myeloma: A Rare Presentation of a Case

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Introduction: Nephrotic syndrome from primary amyloidosis can co-exist with multiple myeloma on rare occasions. Early diagnosis and Appropriate management is crucial for the prognosis of these patients as the combination can reduce life expectancy.

Case Description: A 61-year-old female with PMH of Type 2 DM, HTN was seen for nephrotic range proteinuria detected by PCP screening. Her DM and HTN have been well-controlled for over 10 years. She had no complaints. Physical examination was unremarkable. She has had microalbuminuria since 2017 but developed significant proteinuria and hypoalbuminuria over the last year. A renal ultrasound was done which showed normal kidneys. Laboratory tests showed normal kidney function. Serum electrophoresis revealed monoclonal gammopathy and urine immunofixation showed monoclonal lambda plus IgG lambda fragments. Renal biopsy showed amyloidosis with randomly elevated fibrillary structure. Bone marrow biopsy showed mildly hypercellular marrow with 30% plasmacytosis. Flow cytometry showed lambda light chain. The patient was diagnosed with asymptomatic multiple myeloma and amyloidosis presenting as nephrotic syndrome. She was treated with daratumumab plus CyBorD, which includes cyclophosphamide, bortezomib, and dexamethasone. Over several months, her serum albumin levels have increased and the lambda light chain has decreased.

Discussion: Multiple myeloma (MM) is a malignant plasma cell disorder characterized by uncontrolled proliferation and infiltration of monoclonal plasma cells to the bone marrow. MM is observed concomitantly with amyloidosis in 12-15% of cases 1. Amyloidosis refers to the abnormal deposition of immunoglobulin light chains throughout body tissues. This case highlights a rare but possible scenario of asymptomatic multiple myeloma and amyloidosis that presented as nephrotic syndrome. Diagnosing asymptomatic multiple myeloma and amyloidosis can be challenging, as patients may have no significant symptoms. Further research is needed to investigate which types of patients are at risk. In this case, the patient was diagnosed following routine urine screening for diabetic nephropathy, emphasizing the importance of screening for these conditions. Treatment for asymptomatic multiple myeloma and amyloidosis largely overlaps, focusing on reducing abnormal proteins and managing complications such as renal damage.

SA-PO1020

Novel Anatomic and Macromolecular Models Define Realistic Glomerular Barrier

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Background: The glomerular barrier has been studied extensively using the polysaccharides dextran and Ficol, both modeled as rigid impervious spherical particles. Recent glomerular reconstructions reveal that afferent and efferent glomerular arterioles are joined by non-communicating branches; these parallel tubes are combined into a single uniform cylindrical filter composed of the two most restrictive layers of the glomerular capilary wall, basement membrane and visceral epithelial cells joined by slit diaphragm.

Methods: The classic matrix formulation is modified for flow dependent solute size because water penetrates partial draining polysaccharides such as dextran, but not non-draining proteins; linear regression yields fiber density from slope and transepithelial shunt from intercept. This model is introduced with the permeability of α1acidglycoprotein, albumin, transferrin, IgG, and α2macroglobulin in newly reported patients with primary glomerular disease and completed using appropriate hydrostatic pressures, vascular dimensions, and the permeability of dextran, Ficoll, albumin, and IgG in similar patients obtained from the literature.

Results: Fiber density was similar to fiber density reported for islolated basement membrane and was essentially the same in controls and patients; epithelial shunts

were proportional to total urinary protein excreted, fiber density was not. Effective polysaccharide size decreased when confined by fibers in basement membrane and when confined by streamlines in slit pore. Four-fold higher fiber density encountered by small polysaccharides compared to proteins and large polysaccharides reflect the stratified nature of the glomerular basement membrane and define two pathways through the glomerular capillary wall, a selective route direct through lamina densa and slit diaphragm, a non-selective indirect route through more lamina rara externa and infrequent widely spaced epithelial defects. Filtration area was similar to reported anatomic measurements in controls and was decreased in proportion to histologic abnormality in patients.

Conclusions: Dextran and Ficoll are more permeable than similar size proteins such as albumin and IgG because moving water penetrates, rearranges, and aligns chemically similar polysaccharides. In disease the basement membrane is preserved, but the visceral epithelium is not.

SA-PO1021

The Expression Profile of Complements in Human Renal Mesangial Cells, Endothelial Cells, Podocytes, and Proximal Tubular Epithelial Cells

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Background: More and more evidence indicated that the kidney was a notable source of complements. We aimed to explore the expression profile of complements in human renal mesangial cell (HRMC), glomerular endothelial cell (HRGEC), podocyte (HPC), and proximal tubular epithelial cell (PTEC) under physiological conditions.

Methods: Single-cell RNA sequencing (scRNA-seq) by a 10xGenomics Chromium system was used to identify the transcription of 30 complement genes in HRMCs, HRGECs, HPCs, and PTECs. RT-PCR was used to verify the expression of complement genes in cultured primary HRMC and HRGEC, and in HPC and PTEC cell lines. Immunofluorescence was used to confirm the protein expression of several key complements.

Results: By scRNA-seq, the transcription of nearly all complement genes was found in HRMCs, HRGECs, HPCs, and PTECs, and the expression of complement regulatory proteins was highest. RT-PCR confirmed the transcription of C1S, C1R, C4, CFD, MBL2, MASP1, MASP2, C3, C5, CFI, DAF, CD46, CD59, protein S, and C3AR1 in cultured cells. Immunofluorescence verified the expression of C3, DAF, CD46, C4BPB, and CD59.

Conclusions: Under physiological conditions, HRMCs, HRGECs, HPCs, and PTECs express multiple complements involved in three activation pathways.

Funding: Government Support - Non-U.S.

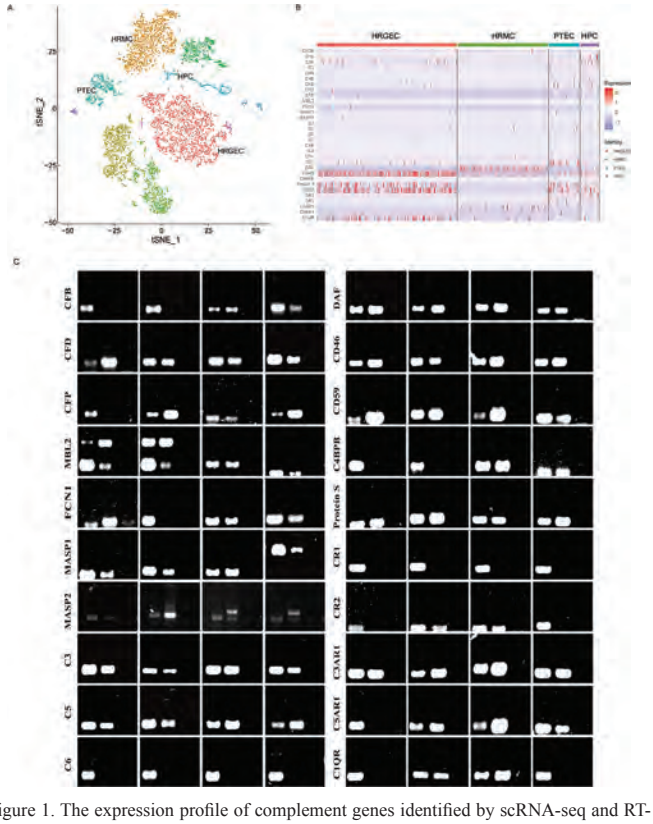

Figure 1. The expression profile of complement genes identified by scRNA-seq and RT-PCR

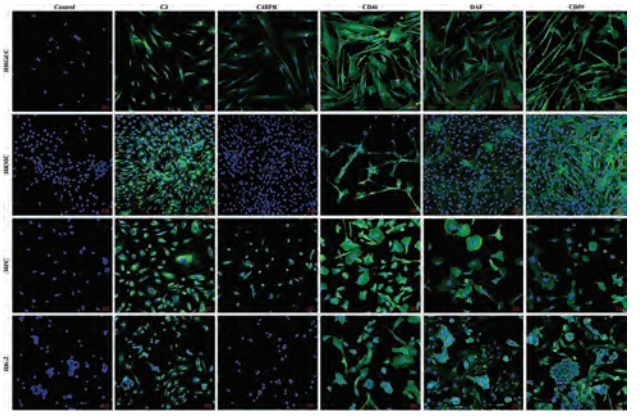

Figure 2. Complement protein expression in cultured human renal cells

SA-PO1022

Membranous-Like Glomerulopathy with Masked Monoclonal Deposits in a Patient with Class 5 Lupus Nephritis: A Case Report

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Introduction: Membranous-like glomerulopathy with masked IgG kappa (k) deposits is a pattern of immune complex deposition characterized by masked deposits that show IgG k restriction and are subepithelial and mesangial by electron microscopy. We present a case of a patient with SLE and biopsy-proven class 5 lupus nephritis whose repeat biopsy showed MMMD.

Case Description: A 26-year-old Hispanic female was admitted for the evaluation of persistent proteinuria. She was diagnosed with systemic lupus erythematosus (SLE) in 2015 and underwent a kidney biopsy in 2019 for proteinuria >1g that return with positive dsDNA, anticardiolipin antibody (IgG and IgM), and low C4. Initial biopsy was reported as "Membranous Glomerulonephritis consistent with class 5 Lupus Nephritis. The IgA was Glomeruli with focal segmental trace peripheral granular staining, IgG was Glomeruli with diffuse and global, peripheral granular staining 3+, IgM was Glomeruli with diffuse, segmental to global, mesangial, and peripheral granular staining 2+, C3 was Glomeruli with focal and segmental weak peripheral staining, arterioles +, C1q was Glomeruli with diffuse and global, peripheral granular staining 1+ to 2+. She volunteered to participate in a clinical trial for lupus nephritis in mid-2023, her labs were positive for dsDNA, low C4, and proteinuria >1g. FLC ratio indicates that Kappa and Lambda Glomeruli with diffuse and global, peripheral granular staining 3+, tubular protein droplets are positive, the second renal biopsy was done at this visit that reported as Membranous Glomerulonephritis, consistent with Lupus Class V Given the new finding of MMMD, a search for monoclonal gammopathy was initiated looking for flow cytometry, the serum protein electrophoresis (SPEP), and serum-free light chains, all of which were reported as negative (see table). Given the negative workup for Monoclonal gammopathy/MGRS, the MMMD was considered secondary to lupus nephritis, a rarely reported renal manifestation of Lupus Nephritis. She is currently on Mycophenolate, Hydroxychloroquine, Lisinopril, and Hydrochlorothiazide, based on recent lab results there is no significant improvement in her proteinuria.

Discussion: In conclusion, patients with SLE can develop Membranous glomerulonephritis with masked monoclonal deposits as a renal manifestation of the SLE in addition to classic class 5 lupus nephritis.

SA-PO1023

The Decrease of the Filtration Slit Density, Not Proteinuria, Is the Early Indication of Filtration Barrier Dysfunction

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Background: Intact podocyte foot processes (FP) are essential for a proper slize selective filtration. Changes in FP morphology are thought to be the first event leading to proteinuria, but this has yet to be proven. Since FP are below the optical resolution of a light microscope, changes are studied on ultrathin sections by electron microscopy. Here, we show the relationship between morphology and proteinuria using podocyte exact morphology measurement procedure (PEMP), which is a 3D-SIM-based procedure.

Methods: Mice were treated with NTS and sacrificed 24, 48, and 72 h after injection. 3D-SIM was done on podocin and integrin co-stained standard formalin-fixed and paraffin-embedded kidney sections (3 μm). The filtration slit density (FSD) was measured by PEMP (Siegerist, 2017). Electron microscopic analysis were done on glutaraldehyde fixed tissue and processed using standard procedures. Albumin to creatine ratios were also analyzed.

Results: We have found, that mice developed moderate proteinuria 48 h after NTS injection. Using PEMP, we found that the FSD was already significantly reduced in NTS-treated mice at 24 h compared to control-injected mice. Transmission electron microscopy analysis confirmed the presence of these structural alterations, indicating that effacement of the podocytes serves as the initial indication, followed by the onset of proteinuria.

Conclusions: PEMP analysis of standard histological sections from NTS-injected and control mice demonstrated that the first event in the functional loss of the size selectivity of the filtration barrier is the effacement of FP morphology, followed by detectable proteinuria. Therefore, the assessment of the FSD is a promising strategy for early and accurate detection of a loss of filtration barrier integrity, providing opportunities for faster and precise diagnostics.

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SA-PO1024

Expression Evaluation of CD2AP, ITGA3, and ITGB1 in Podocyte Cell Culture After Albumin Overload with and Without Puromycin-Aminoglycoside Damage

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Background: Proteinuria is considered a prognostic marker for kidney disease and one of the main symptoms of podocytopathies. Several molecules participate in the maintenance of glomerular filtration barrier, including the CD2-associated protein (CD2AP) present in the slit diaphragm and the α3β1 integrin in the basal membrane of podocytes. This study aimed to evaluate the relative expression of *CD2AP, ITGA3* and *ITGB1* genes after overload of albumin in podocytes *in vitro.*

Methods: Conditionally immortalized human podocytes were exposed to progressive concentrations of albumin (0, 3, 20 and 40 mg/ml) for 24 hours under two conditions: with or without 12 hours of 15 ug/uL of puromycin aminoglycoside (PAN) treatment. We evaluated *CD2AP, ITGA3* and *ITGB1* genes relative expression through qPCR (n=3). The Friedman test was used to compare the different albumin exposures with and without PAN ($p<0.05$).

Results: The fold change of *CD2AP, ITGA3* and *ITGB1* genes are presented in Table 1. No significant difference was found among the albumin exposures, neither with nor without PAN ($p>0.05$).

Conclusions: In the condition here studied, albumin overload have not modulated *CD2AP, ITGA3* and *ITGB1* genes.

Funding: Government Support - Non-U.S.

Fold change of CD2AP, ITGA3 and ITGB1 genes

PAN treatment	Albumin exposure (mg/mL)	Fold Change CD2AP	Fold Change ITGA3	Fold Change ITGB1
No	0	1	1	1
	3	0.017418	1.15284961	0.938208375
	20	0.044871	1.423730085	1.388398524
	40	0.02611	0.516405126	0.891691752
Yes	0	1	1	1
	3	1.386209	1.241183205	1.258075685
	20	1.776701	1.798257843	1.941487235
	40	1.896176	0.982406017	1.587184907

SA-PO1025

Significance of Single-Point Cystatin C Measurement

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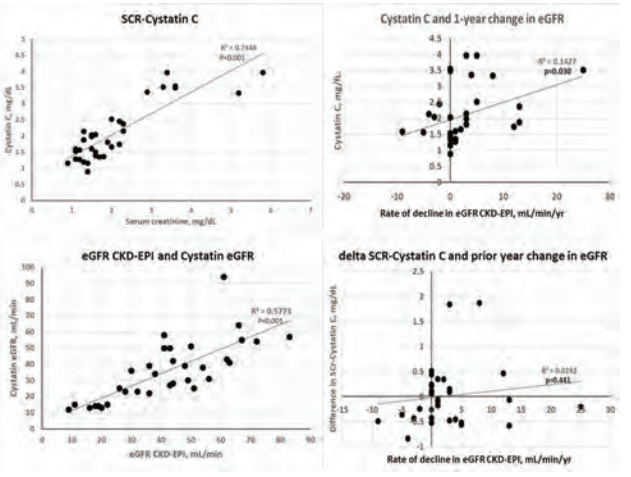
Background: Single-point serum Cystatin C in the absence of prior reference points has resulted in difficulties in interpretation of changes in kidney function. We investigated the correlation between Cystatin C and prior year change in creatinine (SCR) based eGFR for which multiple datapoints were available.

Methods: Simultaneously measured SCR and Cystatin C and their respective eGFRs were analyzed.

Results: 33 SCR-Cystatin C pairs were available for analysis. Patient characteristics included: mean age 72.1±8.7 years, 90.9% male gender, 84.8% African American race, prevalence of hypertension 90.9%, diabetes 48.4%, BMI 28.8±6.2, SCR 2.1±0.8mg/dL, eGFR CKD-EPI 41.8±14.9mL/min, Cystatin C 2.1±0.7mg/dL and Cystatin-eGFR 35.6±14.6mL/min. The mean difference in SCR-Cystatin was 0.00±0.41mg/dL. Mean rate of prior year eGFR decline was 2.4±4.1mL/min/year. SCR-Cystatin C demonstrated good correlation, as did eGFR CKD-EPI and Cystatin-eGFR. Although statistically significant, Cystatin C and prior year eGFR CKD-EPI changes demonstrated poor correlation. There were no significant correlation between delta SCR-Cystatin and delta eGFR CKD-EPI – Cystatin eGFR, Cystatin-BMI. Significant inverse correlation was observed between Cystatin C and eGFR CKD-EPI ($R^2=0.69$, $p<0.001$.

Conclusions: In a small sample of CKD patients, serum Cystatin C, while well correlated with simultaneously measured SCR and GFR, was a poor indicator of prior year change in GFR.

Funding: Veterans Affairs Support



Serum creatinine, Cystatin C and eGFRs

SA-PO1026

Evaluation of Plasma Oxalate Measurements

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Background: Oxalate is a uremic retention solute that accumulates in end-stage kidney disease since it is not efficiently removed by hemodialysis (HD). This increased plasma oxalate (POx) has been associated with higher cardiovascular (CV) mortality in HD patients. Oxalate is usually measured by oxalate oxidase methods, however, multiple large trials are now measuring metabolites using global metabolomics platforms allowing a great opportunity to mine data and identify associations between POx and CV outcomes. Our goal was to evaluate the congruence between targeted and untargeted methods.

Methods: We assessed oxalate in plasma samples previously collected during the pretreatment phase for a study evaluating inulin in HD patients (PMID: 35369018). In this post-hoc analysis, we measured POx in plasma samples for 12 HD patients, both at baseline and after 8 weeks. We first used the Trinity Oxalate Kit, with a protocol adapted for plasma samples. We then sent the same samples to the Broad Institute for HPLC coupled with Mass Spectrometry (MS). This metabolomics assessment was done in duplicate, and on thawed and non-thawed samples. Oxalate measurements were then calculated from a calibration curve using isotopically-labeled oxalic acid.

Results: First, based on the colorimetric output, POx ranged from 115 μM to 23 μM with a mean of 57.38 μM ± 27.94 μM. Based on the MS output, POx ranged from 17 to 31μM with a mean of 22.98 μM ± 3.17 μM, which is within the range described in the literature. POx levels were stable over 2 months for each patient. This low within-subjects variability highlights the stability of POx levels in the HD population. Regarding temperature effect, thawed sample values were 4% higher on average than non-thawed samples. Finally, a comparison of the colorimetric and the MS methods showed consistently higher colorimetric POx levels, on average 2.43-fold higher.

Conclusions: By quantifying oxalate in HD patients using a commercial metabolomics platform and an enzymatic bench assay, we identified a discrepancy between both measurements. Leaving the samples at room temperature did not majorly affect the MS output. Next steps will involve the optimization of the bench colorimetric assay.

Funding: Private Foundation Support

SA-PO1027

Purple Haze: An Uncommon Presentation of a Common Condition

Alexandra Schwarz, Ruchika Batwara. *Icahn School of Medicine at Mount Sinai, New York, NY.*

Introduction: Urine discoloration is a well-known clinical sign that often indicates an underlying pathology. However, purple-colored urine is a visually striking and rarely observed phenomenon that can cause great concern for patients and healthcare workers when encountered.

Case Description: An 80-year-old man with a chronic suprapubic urinary catheter presented with altered mental status following a fall. The patient's catheter was draining purple urine on arrival (as seen in Figure 1). Initial labs showed acute kidney injury (creatinine: 9.55 mg/dL) with previously normal creatinine at baseline, mild rhabdomyolysis (peak creatine phosphokinase: 2,734 U/L), and leukocytosis (white blood cells: 16.3 K/uL). Urinalysis revealed a large amount of leukocyte esterase and >182 white blood cells per high-power field. Renal and bladder imaging did not show any obstruction. The patient was managed as presumed urosepsis and promptly treated with meropenem and vancomycin, fluid resuscitation, and replacement of the suprapubic catheter. Antibiotics were started before sending cultures, so there was no growth observed in urine and blood cultures. The urinary catheter was draining yellow urine the following day and renal function returned to baseline during hospitalization.

Discussion: Purple Urinary Bag Syndrome (PUBS) is a rare phenomenon caused by certain bacteria that produce enzymes that metabolize tryptophan into indigo (blue)

and indirubin (red) pigments, resulting in purple urine color. Risk factors include old age, female gender, alkaline urine, constipation, and the use of plastic urinary bags. The discoloration itself is benign but timely recognition of this uncommon presentation of urinary tract infection is crucial to ensure prompt diagnosis and treatment while avoiding unnecessary investigations.

Figure 1

SA-PO1028

Melanuria: Black Urine as a Presenting Sign of Metastatic Melanoma

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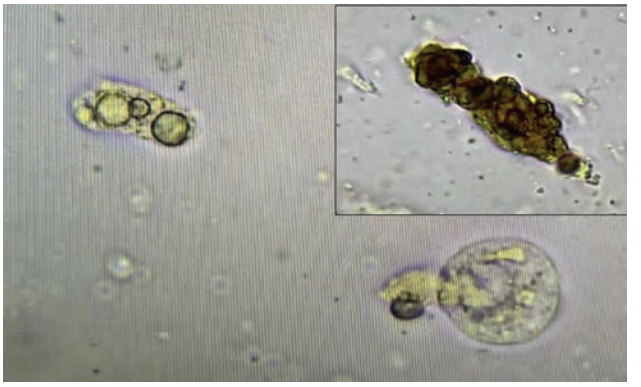
Introduction: The worldwide incidence of malignant melanoma has been increasing at an average annual rate of 5%.[1]We describe a case of melanuria as an initial sign of metastatic melanoma in a previously healthy young woman.

Case Description: A 24-year-old female with no medical history presented with two weeks of abdominal pain. On admission, she had mild tachycardia. Physical exam was notable for abdominal tenderness and lower extremity edema. Blood work showed creatinine of 1.5 mg/dL, lactate 19mmol/L, LDH 5000 IU/L. Amber urine that turned black upon exposure to air. Urine studies were negative for hemoglobin and bilirubin and microscopy showed dark brown casts and atypical cells with dense inclusions exhibiting a dark rim. Abdominal CT showed multiple hepatic and splenic lesions, suspicious for neoplasm. Liver biopsy showed BRAF-negative metastatic melanoma. Despite treatment, the patient expired on hospital day 13th.

Discussion: Melanuria is the urinary excretion of melanin precursors leading to black discoloration of the urine. It is present in up to 15% of cases of malignant melanoma and typically occurs with diffuse melanosis.[2,3]Urine sediment may show atypical pigment-laden cells and dark brown casts. Our patient had dark casts with atypical cells suggesting melanin-containing tubular epithelial cells and histiocytes. Although we did not test her urine for melanin precursors, we proposed the melanuria resulted from extensive tumor necrosis causing cytolysis of melanocytes and subsequent excretion in the urine. This case demonstrates that metastatic melanoma should be considered in the differential diagnosis of black urine.



SA-PO1029

No Need for Beef: A New Vegetarian Test to Measure Renal Functional Reserve

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Background: Renal functional reserve (RFR) corresponds to the physiologic increase in glomerular filtration rate (GFR) after a stimulus. It can be measured to evaluate living kidney donor candidates, risk and recovery of AKI in critical care situations and even risk of pre-eclampsia. The most frequently used test to measure RFR is by ingesting an oral load of protein from animal meat. We aimed to develop an alternative test to measure RFR without the need of meat consumption using L-arginine, a precursor of nitric oxide. Herein, we present the results of a pilot study.

Methods: A 4-hour creatinine clearance (ClCr) was measured in 7 healthy individuals in whom eGFR by CKD-EPI equation was 103.9 mL/min/1.73m^2 (range 92.3-113.4) after a day of plant-based diet and normal ingestion of fluids. The next day, at the same hour, a new 4-hour CrCl was measured, this time after the ingestion of 5 grs of L-Arginine 1 hour before the start of urine collection. RFR was calculated as the difference between indexed post-L-Arginine CrCl and indexed basal CrCl.

Results: Median basal CrCl was 124.6 mL/min/1.73m^2 (range 54.7-162). Post-L-Arginine CrCl was significantly augmented to 145.4 mL/min/1.73m^2 (range 81.1-179.7) ($p<0.05$). Median RFR was 20.8 mL/min/1.73m^2 (range -7.6-48.9). No adverse effects were reported.

Conclusions: Evaluation of RFR can be safely done using L-Arginine stimulation and could be considered as an alternative to meat consumption in vegetarian population. This preliminary data needs to be confirmed in a larger cohort. The optimal dosing of L-Arginine for this purpose should be determined in larger studies.

SA-PO1030

Augmented CD36 Stimulation by Fatty Acids Promotes Macrophage Activation and Endothelial Injury in ANCA-Associated Vasculitis

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Background: ANCA-associated vasculitis (AAV) is characterised by monocyte/macrophage activation and small blood vessel inflammation leading to organ damage. In some patients, macrophage activation leads to giant cell and granuloma formation, resulting in further tissue damage. CD36 is a transmembrane glycoprotein expressed on various cells, including macrophages and endothelial cells. CD36 is crucial in the modulation of inflammatory processes. However, the role of CD36 in AAV remains understudied.

Methods: Cellular expression of CD36 and endothelial cell activation markers was assessed by FACS and immunohistochemistry on tissue sections. ELISA was used to measure soluble(s) CD36 in serum and cell supernatants. Multinucleate Giant cell(MNGC) formation was investigated using established protocols following Palmitic acid (PA) stimulation of cells with or without CD36 knockdown. Macrophage activation markers were examined using qPCR.

Results: CD36 expression was found to be increased in AAV kidney biopsies on glomerular and tubular macrophages. Additionally, CD36 expression on classical and intermediate monocytes was significantly increased in AAV patients compared to healthy controls. Serum sCD36 was elevated in AAV patients, specifically in the PR3-ANCA subtype, in both remission and active disease. Stimulation of THP1-derived macrophages with PA resulted in an increase in CD36 expression, increased the expression of c-Myc and ATF-2, and generated M1 polarised macrophages with significant MIF production. In addition, there was an increase in MNGC formation. These findings were all attenuated by CD36 knockdown or MIF antagonism. Similarly, PA stimulation of endothelial cells increased CD36 and VCAM expression and promoted MIF production. Co-culture of endothelial cells and macrophages with PA resulted in increased migration of macrophages towards the activated endothelial cells.

Conclusions: AAV patients demonstrate elevated levels of monocyte and sCD36. Stimulation of CD36 by fatty acids promotes inflammatory responses in both macrophages and endothelial cells, potentially contributing to many of the features found in AAV. Targeting CD36 or its downstream effector MIF is a novel therapeutic strategy to be tested in AAV.

Funding: Government Support - Non-U.S.

SA-PO1031

Longitudinal Analysis of Urine Metabolomics of Preterm Infants Based on Ultra-High-Performance Liquid Chromatography-Tandem Mass Spectrometry (UHPLC-MS/MS) Technique

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Background: To explore the regular urinary metabolomic characteristics of preterm infants in the early postnatal period and find the association between early metabolic adaptation and urinary metabolism.

Methods: Between June 1, 2021 and September 31, 2022, 36 preterm infants were recruited from the Children's Hospital of Fudan University, urine samples were collected on postnatal day 1 (PND1), PND7) and PND14 respectively, for a longitudinal cohort self-control analysis. UHPLC-MS/MS was used to characterize urinary metabolomic changes at postnatal week 1 and week 2. Multivariate analyses were used to screen for differential metabolites and metabolic pathway.

Results: Widely targeted metabolomic analysis of urine from the first week of postnatal life in preterm infants identified 57 metabolites whose levels were upregulated and 18 metabolites that were downregulated from birth(Fig1). Widely targeted metabolomic analysis of urine from preterm infants at postnatal week 2 revealed that urine levels of 22 metabolites were upregulated and 7 metabolites were downregulated compared to week 1. Metabolic pathways significantly enriched in 29 urinary differential metabolites in the second postnatal week in preterm infants, the gluconeogenesis/glycolysis pathway was the metabolic pathway significantly associated with all urinary differential metabolites in the first 2 postnatal weeks (Fig2).

Conclusions: Urinary metabolic changes in preterm newborns were more pronounced in the 1st week after birth than in the 2nd week, suggesting metabolic adaptation in preterm newborns occurs mainly in the 1st week after birth. Glycometabolism is the key to the changes in urine metabolism in preterm infants during the first 2 weeks of life, and it is hypothesized that the regulation of glucose homeostasis in preterm infants is the focus of their early metabolism and development.

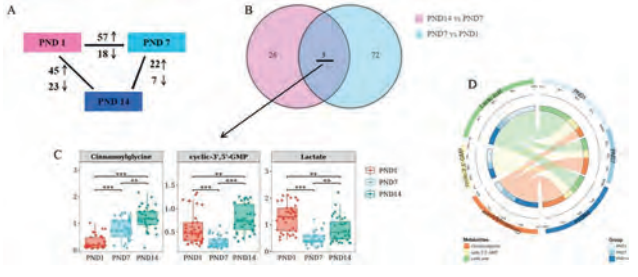

Fig1

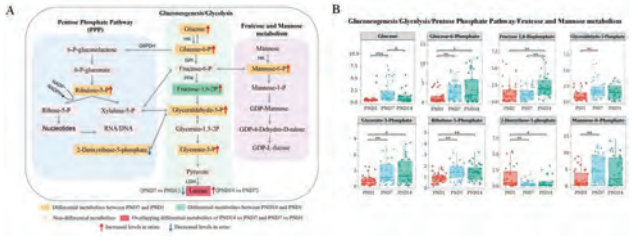

Fig2

SA-PO1032

Preservation of Slides of Fixed Urinary Sediment for Educational Purposes

Lauren Cohen,[1] Juan Carlos Q. Velez,[1] Jay R. Seltzer.[2] *[1]Ochsner Health, New Orleans, LA; [2]Missouri Baptist Medical Center, Saint Louis, MO.*

Background: Urine sediment slides for microscopy are best inspected promptly, as drying artifact, the result of evaporation, will occur and limit the time the slide is viable for viewing. Although teaching urine microscopy using stored images of cells, casts, and crystals is useful, there is no replacement for real-time microscopic examination of a urine sediment slide. Thus, we aimed to develop a reproducible method of preserving urine sediment slides.

Methods: Urine specimens from patients at Ochsner Medical Center (New Orleans) and Missouri Baptist Medical Center (St Louis) seen by the nephrology department were randomly chosen based on the presence of distinct urine sediment findings. Specimens were centrifuged and the supernatant discarded. Ten drops of 10% buffered formalin were added to resuspended pellets. After 30 minutes, samples were centrifuged for 2 minutes and remaining supernatant was discarded. The new pellet was resuspended in a solution of 1 drop of Sternheimer-Malbin stain, 2 drops of glycerol, and 1 drop of clear Elmer's® glue. One drop of this mixture was placed on the slide and a coverglass applied. CoverGrip® was painted around the perimeter of the coverglass as a sealant. Slides were examined at regular intervals (24, 48, 96 hours; 1, 2, 4, 8 weeks) and images were captured using SeBaCam®. Slide quality was evaluated for structure retention, stain intensity, and evaporation artifact.

Results: Various cast types (granular, waxy, cellular, vacuolated), acanthocytes, and crystals were captured in the preserved slides across all specimens (n = 12). The integrity of the structures identified on day 1 was preserved up to 8 weeks in all cases. No significant decay in quality was observed over time. Artifacts observed included evaporation artifact, cloudiness, and stain fading. However, none of those factors altered the overall interpretation of the slide. A library of preserved slides was successfully used by the authors in a recent hands-on educational workshop (KidneyCon).

Conclusions: Our novel method of urine sediment slide preservation was effective in preserving the quality and quantity of the findings revealed upon inspection immediately following urine collection. This technique can be implemented in academic centers for educational and clinical purposes. Further studies are required for optimization.

SA-PO1033

New Method of Immunophenotyping of Urinary Cells by Multicolour Flow Cytometry: A Pilot Study

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Background: Podocyturia, non-invasive option, was used to diagnose glomerulopathies(GN), namely fibrosis and glomerulosclerosis, previously detected only by renal histology(RB). Urinary sediment analysis after labelling with antibodies against podocalyxin and podocyte-specific transcription factor WT-1 was proven as clinically useful. Determination of mRNA was used, too, but hardly usable due to high instability.

Methods: Patients(pts) who underwent RB for nephrotic syndrome, regardless of its etiology, were examined before RB. First morning urine sample was collected. Urinary cell concentrates were prepared by ultrafiltration using strainers. Conventional staining protocol was used with panel of antibodies: anti-podocalyxin-PE, anti-CD86-FITC, anti-CD87-BV510, anti-CD24-Pe-Cy7, anti-CD10-PerCp, anti-CD133-APC, anti CD45-APC-Cy7. Heathy volunteers and isotype controls were used. The Hoechst33342 DNA dye was applied to identify cells. Gating strategy:only population of cells binding the DNA dye Hoechst33342 was selected to exclude non-nuclear elements, then exclusion of white blood cells, and then immunophenotypically specific rare cell populations could be observed in scatter plots.

Results: 13 pts with histology: DKD 5x, obesity-related glomerulopathy 2x, IgA nephropathy 5x, ANCA associated vasculitis 1x and 5 healthy controls were examined. Population of PCX+/CD10+/CD133+/CD24+ cells was detected in varying degrees of abundance, as well as a population of PCX-/CD10+/CD133+/CD24+ cells. The former population predominated mainly in patients where the histological findings were dominated by degenerative changes (interstitial fibrosis and glomerulosclerosis). In contrast, the latter population was more prevalent in active inflammatory changes, most notably in AAV and IgAN with the presence of fibroepithelial crescents. None of the above cell populations were present in healthy controls, both isotype controls.

Conclusions: The method significantly reduces the autofluorescence background of urine samples to remove noise that prevented multi-color analysis of urinary cells on flow cytometer and thus capture different rare populations of urine glomerular cells, which no published approach to urine flow cytometry has yet allowed. The method is inexpensive and offers the potential for non-invasive differential diagnosis and monitoring of therapy. *Supported by COOPERATIO 34.*

SA-PO1034

MUC1 on Urinary Extracellular Vesicles for Detection of Impaired Renal Function

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Background: The nephron's various cell types produce urinary extracellular vesicles (uEVs), which have the potential as a promising biomarker resource. Aiming to detect chronic kidney disease (CKD) in its early stage, we performed proteome analysis of uEVs from patients with a congenitally reduced number of functional nephrons and found that pediatric CKD can be detected accurately by the expression levels of molecules such as MUC1 in uEVs (iScience, 2022). In this study, we validated the diagnostic capacity of an ELISA-based test method analyzing uEVs to separate adult individuals with decreased renal function in a Japanese community cohort of the Tohoku Medical Megabank Project.

Methods: Two hundred eleven samples (male 109, female 102) provided were analyzed. The mean age ± SD was 51.2 ± 14.7 years. The expression levels of MUC1 and CD9, a classical exosomal marker, on the surface of uEVs (uEVs_MUC1 and uEVs_CD9) were measured using ELISA plates that enabled the isolation of uEVs and quantitation of expression of molecules. The correlation between the expression levels and clinical parameters was analyzed.

Results: uEVs_MUC1 showed a positive correlation with uEVs_CD9 but not with urinary albumin. As in pediatric patients with kidney diseases, the expression of uEVs_MUC1 was significantly decreased in adult individuals with reduced renal function (eGFR <60 ml/min/1.73m^2) ($P < 0.001$). uEVs_MUC1 had an AUC of 0.88 for separating individuals with eGFR <45 from those with eGFR ≥45 and 0.92 for separating those with eGFR <30 from those with eGFR ≥30. When combined with urinary albumin, the diagnostic accuracy was further enhanced. To further apply this ELISA to clinical testing, we generated a high-titer monoclonal antibody against MUC1, and established a protocol to quantify uEVs_MUC1 in clinical samples.

Conclusions: MUC1 expression in uEVs can be a biomarker of renal dysfunction independent from proteinuria, which was validated in childhood and adult cohorts. Future research will focus on elucidating the mechanism and conducting prospective investigations in order to advance with the development of the uEVs-based noninvasive test technique robustly diagnostic for CKD.

Funding: Other NIH Support - Grants-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (KAKENHI; grant number JP16K15523 to Y.H., and JP22K20847 to K.T.), by Japan Agency for Medical Research and Development (AMED; grant number JP20lm0203003 and JP21lm0203003, and JP22ym0126063h0001 to Y.H.), and by the University of Tokyo Gap Fund Program fifth period (to Y.H.)., Government Support - Non-U.S.

SA-PO1035

Findings in Urinary Sediment Inspected by Microscopy Several Days After Collection

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Background: Textbooks and clinical practice manuals recommend inspection of urinary sediment specimens immediately or within < 2 hours of collection because of presumed loss of specimen quality over time. However, there is no conclusive evidence supporting that recommendation. Based on anecdotal observations, we hypothesized that adequacy of urinary sediments can be maintained way beyond the 2-hour limit.

Methods: An experimental study was conducted utilizing urinary sediment specimens obtained from patients seen by the nephrology inpatient consultation service due to acute kidney injury. Aliquots of the specimens were stored at both room temperature (RT) and at 4^{o}C. Urine microscopy was performed at the time of collection, 24 hours, 48 hours, and 1 week post collection, and assessed for presence of granular casts (GC), waxy casts (WxC), renal tubular epithelial cell casts (RTECC), red blood cell casts (RBCC), acanthocytes, and lipids. Abundance of casts was assessed by an adaptation of the Perazella score (cast number/low power field).

Results: A total of 16 urine specimens were collected and divided into RT (n=16) and 4^{o}C (n=14). Overall, only 4.6% (3/65 data points) revealed a change in density of findings. By 48 hours, GC, WxC, RTECC and RBCC did not change in presence or abundance at either RT or 4^{o}C. By 1 week, 90% (9/10) did not change GC score for both RT and 4^{o}C, 75% (3/4) and 80% (4/5) did not change WxC score at RT and 4^{o}C, respectively, and 83.33% (5/6) and 100% (7/7) did not change RTECC score at RT and 4^{o}C, respectively. For samples with acanthocytes, at RT, 2 did not change in abundance for up to 1 week, whereas 1 changed from 40% to 25% at 48 hours. At 4^{o}C, 1 case did not change in acanthocyte abundance for up to 1 week, whereas 1 changed from 40% to 25% at 48 hours. For samples with lipids, 100% (5/5 at RT, 3/3 at 4^{o}C) maintained lipid presence for up to 1 week.

Conclusions: Our findings challenge the traditional knowledge and demonstrate that immediate inspection of the urinary sediment, although recommended, is not essential in clinical practice. Collected specimens can be kept for later examination in the event that an expert observer is required for corroboration of findings. Further research is necessary to precisely determine at which point urinary sediment quality begins to decay.

SA-PO1036

Urinary Sediment Podocin mRNA Excretion in Healthy Adults

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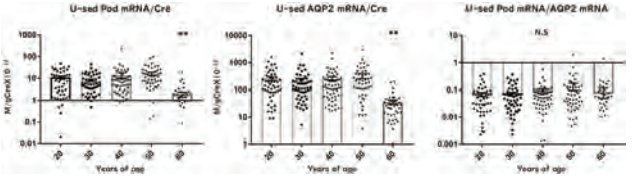
Background: We have previously reported that the excretion of urinary sediment podocin (U-sed Pod) mRNA is a useful biomarker for the early diagnosis and evaluation of various glomerular diseases. However, no study has been conducted on healthy adults. In this study, we investigated the excretion of U-sed Pod mRNA in healthy adults, including the effects of gender and age.

Methods: We studied 249 healthy individuals (48 in their 20s, 52 in their 30s, 58 in their 40s, 49 in their 50s, and 42 in their 60s or older, including 40 in their 60s and 2 in their 70s; a male-to-female ratio of approximately 1:1) who received health checkups from June 2018 to March 2019 and did not have hypertension (>140/90 mmHg), diabetes (fasting blood sugar >126 mg/dL), albuminuria (U-Alb/Cre >30 mg/gCre), or chronic kidney disease (eGFR > 60 ml/min/1.73m^2) and were not receiving medication. We measured the excretion of U-sed Pod mRNA in spot urine samples.

Results: No significant differences in U-sed Pod mRNA normalized to urinary creatinine (U-sed Pod mRNA/Cre) or U-sed Pod mRNA normalized to urinary sediment aquaporin 2 (U-sed AQP2) mRNA (U-sed Pod mRNA/AQP2 mRNA) were observed among the healthy adults less than 60 years of age. In addition, neither marker was significantly different between the genders. However, U-sed Pod mRNA/Cre excretion was significantly lower in subjects over 60 years of age compared to those less than 60 years (1.9 ± 0.5 M/gCre×10^{-12} vs. 12.4 ± 1.4 M/gCre×10^{-12}, p <0.001). Furthermore, U-sed Pod mRNA excretion was not detected in approximately 30% of subjects over 60 years of age. U-sed AQP2 mRNA excretion was also significantly lower in subjects over 60 years of age, similar to U-sed Pod mRNA excretion.

Conclusions: No age or gender differences were detected in U-sed Pod mRNA/Cre or U-sed Pod mRNA/AQP2 mRNA excretion in healthy adults less than 60 years of age who could be used as normal controls.

Funding: Government Support - Non-U.S.



Urinary sediment podocin mRNA/Cre, AQP2 mRNA/Cre and podocin mRNA/AQP2 mRNA

SA-PO1037

Rapid Diagnosis of Urinary Tract Infection by Flow Cytometry-Based Urine Analyser

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Background: Urinary tract infections (UTIs) are important healthcare problems for hospitalized and community patients. Various bacterial species can cause UTI, the most common of which is the Gram-negative bacilli Escherichia coli. The gold standard for UTI diagnosis remains urine culture, followed by antibiotic sensitivity testing. However, it takes around 48 hours for urine culture to be reported. Therefore, a rapid screening test for UTI is highly desirable to guide clinical decision-making. The Sysmex UF-5000 is a flow cytometry-based automated urine analyzer capable of providing WBC and bacterial counts and the Gram staining of the causative bacteria that positive impact on the rate of antimicrobial resistance. Our prospective cohort study aims to validate the automated flow cytometric analysis using Sysmex UF-5000 for rapid UTI screening and discrimination of gram-positive and gram-negative bacteria, compared to urine culture and conventional Gram staining.

Methods: Midstream urine samples from patients with suspected UTIs were collected in sterile containers. They were then subjected to analysis by Sysmex UF-5000 automated urine analyzer, conventional Gram staining, and urine culture. The correlation and agreement between the different methods were then determined and ROC curve analysis was performed where appropriate.

Results: A total of 285 urine samples were collected from 285 patients for analysis. An almost equal gender distribution was achieved. Out of the 285 patients included, 163 were outpatient, 104 were inpatient, 14 were wards in the ICU, and 4 presented to the emergency department). In total, 140 of 285 samples (49%) yielded ≥ 10^3 CFU/ml bacterial growth (73 with Gram-negative bacteria, 36 with Gram-positive bacteria, 27 with mixed cultures, and 4 with yeast). In comparison, 68 samples (23.9%) yielded ≥ 10^5 CFU/ml bacterial growth on urine cultures. We found that a UF-5000 bacterial count of ≥ 590.3 /uL predicted ≥ 10^5 CFU/ml bacterial growth on urine culture with a sensitivity of 86.8% and specificity of 81.1%. The bacterial discrimination performance of the UF-5000 for GN bacteria was superior to that for GP bacteria.

Conclusions: UF-5000 demonstrated a good potential utility for rapid UTI screening. The instrument's ability to predict Gram-negative bacterial infection is reasonable despite the need for further evaluation.

Funding: Commercial Support - Sysmex(Thailand) Co.,Ltd., Government Support - Non-U.S.

SA-PO1038

Urinary Immune Complex of V-Set Immunoglobulin Domain-Containing 4 as a Novel Biomarker of Lupus Nephritis

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Background: Lupus nephritis (LN) is a devastating chronic kidney disease (CKD) caused by Systemic lupus erythematosus (SLE). However, to monitor disease activity and predict the risk of LN flare is still challenging, and there is an urgent need to identify novel biomarkers of LN that have high diagnostic or predictive values. In our recent study, by using a quantitative proteome immunoarray, V-set Immunoglobulin-domain-containing 4 (VSIG4) was found siginifcantly elevated in the serum and kidneys of LN patients compared to healthy controls, and could reflect renal pathology of LN. We were interested to ask if VSIG4 was secreted into the urine in LN patients.

Methods: In an intial testing using ELISA, we simultaneously measured the free form, autoantibody, and immune complex levels of VSIG4 in the urine and serum samples from the same LN patients (N = 28), compared to other chronic kidney disease controls (CKD, N = 7) and healthy controls (N = 13).

Results: We found that the free form of VSIG4 was not detectable in the urine of LN or controls by using commercial sandwich ELISA kits. Interestingly, the urinary immune complex of VISG4 (VSIG4 ICx) was detectable in LN and controls. Importantly, the urinary VSIG4 ICx was significantly elevated in the LN patients, compared CKD controls (P-value = 0.031) and healthy controls (P-value = 3.05E-05). Urinary VSIG4 ICx was also significantly increased in the CKD patients compared to healthy controls (P-value = 2.58E-05). In the same patients, the free form of VISIG4 was significantly elevated in LN, compared to CKD contorls (P-value = 2.6E-05) and healthy controls (P-value = 1.14E-10); both serum autoantibody and serum ICx levels of VSIG4 were also significantly elevated in LN compared to healthy controls. By using a Spearman's paired test, the urinary VSIG4 ICx levels were positively correlated with the serum free-form VSIG4 levels ($r = 0.67$, $p < 0.001$). More interestingly, the urinary VSIG4 ICx levels were positively correlated with the following clinical parameters: SLEDAI (Spearman's Rank Correlation Coefficient $r_s = 0.49$, $p = 0.007$), rSLEDAI ($r_s = 0.44$, $p = 0.03$), urine protein/creatinine ($r_s = 0.4$, $p = 0.03$), and white blood cell counts ($r_s = 0.49$, $p = 0.04$).

Conclusions: Urinary VSIG4 immune complex may be a promising novel biomarker of SLE and LN.

Funding: Other NIH Support - R01AG062987

SA-PO1039

Profiling of Urinary RNA Biomarkers for CKD with Nanopore Sequencing

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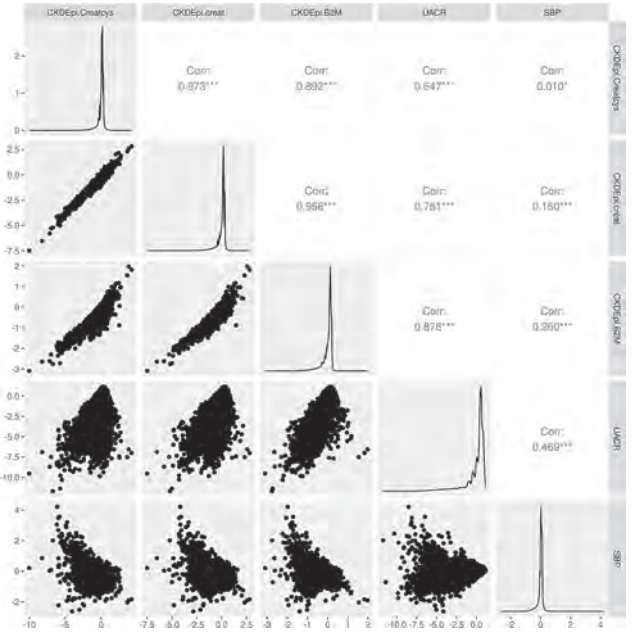
Background: There is a need to develop new biomarkers of kidney dysfunction & damage that are more informative than the estimated glomerular filtration rate (eGFR) & urine albumin to creatinine ratio (UACR). While RNAseq is increasingly being used for biomarker discovery, there are few reports of applications of 3rd generation sequencing platforms (Nanopore) to CKD.

Methods: Urinary RNA from participants in the COMPASS study (PMC5830321) with variable kidney function & UACR was isolated to make cDNA libraries with a novel pipeline for Nanopore sequencing (PALS-NS, https://www.biorxiv.org/content/10.1101/2022.12.16.520507v1). RNA counts were normalized via Analysis of Variance and analyzed via negative binomial mixed effects models (NBMEM, PMC5499834).

Results: 19 cDNA libraries were made from the initial and follow up (12 mo) samples of 7 pts (6F), aged 54 ± 22 yrs with SBP 132 ± 15 mmHg, UACR 48 ± 73 mg/g, eGFR was assessed via the 2021 CKD Epi formulas for Creat (74 ± 35), Beta 2 microglobulin (65.5 ± 30), Creat/Cystatin (86.53 ± 39). Protein coding and long non coding (lncRNA) RNAs were the most frequently encountered RNA species (14-20% and 8-9% respectively). Correlation of the counts between follow up & baseline samples was high (>0.89). NBME estimates of the effects of eGFR on counts were correlated highly with each other, correlated moderately with UACR and not correlated with SBP[fig]. Term analysis mapped the differentially expressed RNAs (>70% lncRNA) to trascriptional factors and the lysine degradation pathway (including several lysine methyltransferases) that has been recently implicated in the pathogenesis of CKD (PMC9283537) and podocyte injury (PMC9086358).

Conclusions: Nanopore sequencing provides a cheap, portable, platform for novel RNA biomarker discovery & quantification in CKD.

Funding: Other NIH Support - NCATS, UL1TR001449, Commercial Support - Dialysis Clinic Inc, #C-3765



SA-PO1040

Melatonin Increases Survival Through Upregulation of Clock NEAT1 and Enhancer-Associated Histone Modifications in Albumin-Injury Tubular Cells

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Background: Melatonin modulates circadian rhythm via the core clock genes, thereby regulating numerous physiological conditions in kidneys. The melatonin-regulated coding RNA is highly identified, it remains unknown whether long noncoding RNAs (lncRNAs) can be modulated by melatonin and exhibit the diurnal rhythm in renal tissue.

Methods: We identify melatonin-regulated clock lncRNAs including *NEAT1*, which are upregulated by melatonin and BMAL1/CLOCK heterodimer in human renal tubular epithelial cells (TECs).

Results: *Neat1* oscillations associated nocturnal change of core clock genes and endogenous melatonin in mouse TECs. Clock *NEAT1* promote TECs proliferation through an increased occupancy of histone 3 lysine 27 acetylation (H3K27ac) and histone 3 lysine 4 mono-methylation (H3K4me1) levels at MKI67 enhancer regions. Molecular studies showed that melatonin enhanced *NEAT1* expression via increasing BMAL1 stability and thereby enrichment on NEAT1 promoter. Treatment of albumin-injured TECs with melatonin alleviated cell death by transactivating clock *NEAT1* and restore the reduction levels of H3K4me1, H3K27ac, core clock genes and MKI67. Using an experimental membranous nephropathy (MN) model, exogenous melatonin treatment ameliorates the proteinuria and hypoalbuminaemia in experimental MN kidneys associated with the increased levels of core clock genes, H3K27ac, Mki67 and Neat1 in TECs.

Conclusions: Collectively, our results suggest that melatonin enhanced cell proliferation in albumin-injured TECs via upregulation of clock *NEAT1* and NEAT1 mediated-changes in histone modifications and MKI67 levels, which has the potential for therapeutic intervention.

Funding: Government Support - Non-U.S.

SA-PO1041

Single-Cell Transcriptome Atlas in C57BL/6 Mice Encodes Morphological Phenotypes in the Aging Kidneys

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Background: C57BL/6 mice are commonly used murine models with the desired genetic background for modification in different research settings. So far, there is still a lack of comprehensive kidney morphology and single-cell transcriptome atlas at various developmental stages of C57BL/6 mice. To provide an interactive set of reference standards for the scientific community, we designed the present study to dissect the kidney from the capillary-loop stage of development till senescence at 30 months of age.

Methods: Eight groups, with five to six mice each, represented embryonic (18.5 days), newborn (1 day), adolescent (1 month), young (3 months), adulthood (6 months), middle-aged (10 months), old (20 months), and senescent (30 months) animals, respectively. Periodic acid-Schiff and silver staining were used to examine the histology of the kidney. The ultrastructure features of the kidney were examined using transmission electron microscopy. Kidney single-cell transcriptome analysis was conducted in three and 30 month-old mice to reveal the gene expression profiles in glomerular cells. Unbiased sampling and quantitation method was used to analyze the glomerular structures.

Results: With age, there was an increase in the glomerular size, the percentage of podocyte foot process effacement, and the extent of mesangial expansion. The number

of Wilm's tumor 1 (WT1) positive podocytes remained stable from the young till 20 months of age. By age 20 months, the number of WT1 positive podocytes was reduced till 30 months of age. Of note, GBM knobs appeared at three months and became frequent with age. The level of urinary albumin to creatinine ratio (UACR) was increased in the senescent mice compared with the maturing and middle-aged mice. Using single-cell transcriptomic data, we assessed cell-type-specific manifestations of different hallmarks of aging, such as changes in the genes of intrinsic renal cells and biological alterations involved with age.

Conclusions: In conclusion, the availability of comprehensive kidney morphology and single-cell transcriptome atlas at various developmental stages of C57BL/6 mice would be a new and significant resource for mechanistic investigations and testing of potential therapeutic interventions.

Funding: Government Support - Non-U.S.

SA-PO1042

Investigation of Temporal Patterns of Biomarker Expression from Different Segments of the Kidneys in Healthy Subjects

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Background: Urinary extracellular vesicles (uEVs) may parallel physiologic and pathologic processes taking place in their kidney cell of origin. Combined with their ease of access, this makes uEVs excellent candidate biomarkers. It is known that kidney physiology and expression of some proteins follow a circadian pattern. Therefore, the normal daily variation in uEV excretion and the content of specific protein cargoes must be understood. The goal of this study is to examine changes over a 24 hour period of uEV markers of glomerula and tubular origin. In addition, we examined TSG101 (Tumor susceptibility gene protein 101) as an EV marker.

Methods: Each void during a 24-hour period for 13 healthy individuals (108 samples total) was collected. uEVs from each void was isolated by differential centrifugation at 20,000g, and washed with a low ionic strength buffer to remove uromodulin. uEV count and sizing was performed on each final pellet using Nanoparticle Tracking Analysis (ZetaView; Particle Metrix). Flow Cytometry using SpectralFlow was performed on uEVs stained with an antibody panel including CD35 (CR1), CD26 (DPP4), CD9 (Tetraspanin) and CD10 (Neprilysin). uEV protein lysates were immunoblotted for SLC12A3 and TSG101.

Results: TSG101 signal normalized to total protein has a positive linear correlation with creatinine ($r=0.62$, $p<0.001$); indicating it may be expressed steadily. Normalizing to creatinine or TSG101 expression of SLC12A3 vary over a day in a temporal pattern. The antibody panel of glomerular and tubular markers detected with single flow cytometry did not express a temporal pattern when normalized to TSG101.

Conclusions: uEV biomarker expression may be normalized to TSG101 signal as it correlates with creatinine. SLC12A3 has a critical role in kidney function with sodium reabsorption and has shown circadian pattern of expression previously in rodent models. Our results demonstrate a similar temporal pattern of a large range of uEVs carrying SLC12A3 in humans. This temporal variation of uEV markers needs to be further analyzed on other kidney markers in healthy individuals and disease. However, characterizing temporal protein expression patterns of uEVs has potential to accelerate uEV biomarker discovery for kidney diseases.

SA-PO1043

Nicotinamide Adenine Dinucleotide (NAD) Deficiency Contributes to Progressive Kidney Disease in HIV Nephropathy Mice

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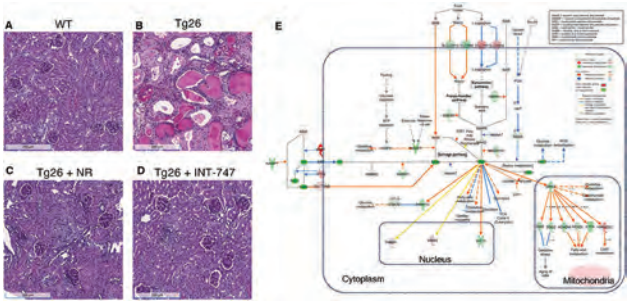
Background: HIV disease remains prevalent in the USA and is even more highly prevalent in sub-Saharan Africa. Recent investigations revealed that renal mitochondrial dysfunction contributes to HIV-associated nephropathy (HIVAN) in Tg26 transgenic mice. We hypothesized that nicotinamide adenine dinucleotide (NAD) deficiency contributes to energetic dysfunction and progressive tubular injury.

Methods: Tg26 and wild-type (WT) mice were treated with nicotinamide riboside (NR), 500 mg/kg body weight/day in drinking water or the farnesoid-X receptor agonist INT-747, 10 mg/kg body weight/day in the diet from 6 to 12 weeks of age. We used multi-omic characterization of kidney tissue transcriptomes and metabolomes to investigate metabolomic mechanisms of HIVAN tubulopathy and the effects of treatment with NR and INT-747.

Results: Treatment with NR and INT-747 ameliorated kidney tubular injury in Tg26 mice, as shown by serum creatinine, urine albumin and the tubular injury marker, urinary neutrophil-associated lipocalin (NGAL). NAD levels were significantly lower (2.86 [2.54-3.28, IQR] nmol/mg) in Tg26 kidney compared with WT mouse kidney (6.94 [5.48-8.72] nmol/mg) and levels were restored by either NR or INT-747 treatment. Integrated analysis of transcriptomic and metabolomic measurements showed that the NAD salvage pathway was downregulated in Tg26 mouse kidney. Sirtuin3 acetylation activity and mitochondrial oxidative phosphorylation activity were lower in *ex vivo* proximal tubules from Tg26 kidneys compared to those of WT mice. These activities were restored by supplementation with NR and with INT-747.

Conclusions: NAD deficiency contributes to HIVAN tubulopathy and mitochondrial dysfunction in Tg26 mice. Restoration of NAD levels in kidney improves these pathologies.

Funding: NIDDK Support



(**A-D**) Representative PAS staining images of mouse kidney, (**E**) NAD signaling pathway map overlaying transcriptomic and metabolomic results comparing Tg26 and WT mice.

SA-PO1044

Systemic Immune Dysregulation in a Mouse Model of Oxalate Nephropathy

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Background: Chronic kidney disease (CKD) is a leading cause of mortality and morbidity. Crystalline nephropathy induced by high oxalate is an established cause of CKD. CKD and crystal formation were shown to influence immune cell composition and gut microbiota. To investigate the impact of oxalate nephropathy on the immune system and the microbiome, high oxalate-fed mice were analyzed by flow cytometry and 16S sequencing.

Methods: To investigate the effects of oxalate we fed single housed C57BL6/N mice (n=7) a high oxalate diet for 10 days. Chow diet fed littermates served as healthy controls. Both groups were analyzed for immune cell composition (flow cytometry) of the spleen, kidney and small/large intestine (lamina propria immune cells [si/cLPL]) and bulk RNA sequencing of the kidney. Microbiota composition was analyzed by 16S sequencing.

Results: Mice fed a high oxalate diet demonstrated hyperoxaluria and increased kidney injury as measured by plasma creatinine concentration. Furthermore, we observed a significant reduction in body weight. Bulk RNA sequencing revealed a prominent inflammatory signature of the kidney, including increased classical damage markers (*Lcn2*, *Havcr1*), as well as genes enriched for Th17 differentiation pathway. Flow cytometry analysis identified more than 100 dysregulated immune subpopulations in the kidney. Furthermore, we detected a pronounced inflammatory response in the spleen and the intestine. Interestingly, type 17 T cells (IL-17A+ and RORgt+) within conventional T helper and regulatory T cells were the main and overlapping phenotypic drivers across different organs, namely the kidney, small and large intestine. Compared to the immune system, the microbiome only showed small scale taxonomic shifts (increase of 4 vs. decrease of 9 operational taxonomic units).

Conclusions: Our in-depth immune phenotyping uncovers a pronounced inflammatory signature across several organs (intestine, spleen and the kidney). Our study provides a comprehensive description of immune cell alterations and serves as a valuable resource for the scientific community.

SA-PO1045

Renal Medullary Macrophages Play a Pivotal Role in Cleaning off Intratubular Particles

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Background: During the passage of the glomerulus filtrates through the renal tubular system, various microscopic sediment particles, including mineral crystals resulting from urine concentration, are generated. Dislodging these particles in the intratubular compartment is critical to ensure free flow of filtrate and the final formation of urine. However, the underlying cellular mechanism for the clearance is unclear.

Methods: The interactions of macrophages and segments of renal tubules were analyzed by high-resolution confocal microscopy and scanning electron microscopy. Live movement of renal macrophages was monitored by two-photon microscopy. Bulk RNA-seq was performed to analyze the transcriptomic difference between cortical and medullary macrophages. Hyperoxaluria model was used to induce kidney stone formation.

Results: We uncovered that the juxtatubular macrophages in the renal medulla constitutively formed transepithelial protrusions and were "sampling" urine contents. This transepithelial protrusions were formed in a transcellular route instead of between epithelial cells, so that the overall junctional architecture of tubular epithelium was intact. In particular, juxtatubular macrophages were efficient in sequestering and phagocytosing intraluminal particles, and occasionally making transmigration to the tubule lumen to "escort" the excretion of sediment particles. As such, mice with underrepresentation

of renal macrophages were prone to developing various intratubular sediments. Mechanistically, integrin β1-mediated ligation to the tubular epithelium is crucial to the transepithelial behaviors of medullary macrophages.

Conclusions: This study unveils a previously unappreciated role of renal macrophages in keeping the tubular system unobstructed. In contrast to the traditional view that the renal epithelial barrier is insurmountable to cells, we found that these juxtatubular macrophages in the medulla constitutively formed transepithelial protrusions, and the underlying molecular mechanisms were provided as well. In addition, we demonstrated a divergence between medullary and cortical macrophages in transcriptomes and in behaviors. These findings may pave way for developing novel therapeutics for nephrolithiasis as well as renal infection caused by ascending microbes.

Funding: Government Support - Non-U.S.

SA-PO1046

Vascular Injury-Derived Exosomes Trigger Renal Tertiary Lymphoid Structures and Accelerate Lupus Nephritis

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Background: Microvascular damage is an emerging contributing factor to Lupus Nephritis (LN) leading to end stage renal disease. We have demonstrated that apoptotic exosomes derived from vascular injury (ApoExo) trigger the production of SLE-associated antibodies in wild-type mice. ApoExo infusion induces autantibody production and tertiary lymphoid structure (TLS) formation in a murine vascular allograft rejection model. We hypothesize that ApoExo induce an autoimmune response that accelerates the development of lupus nephritis.

Methods: 20 weeks old NZB/WF1 mice were infused with ApoExo or vehicle every second day for 3 weeks. Circulating anti-LG3 and ApoExo levels were measured by ELISA and hs-FCM respectively. Kidneys were collected and renal histology and 3D in vivo micro-computed tomography (MicroCT) analyses were performed.

Results: NZB/WF1 mice infused with ApoExo show higher levels of circulating anti-LG3 compared with the vehicle group ($p=0.0034$). MicroCT data suggest microvascular involution associated with LN development. In addition, ApoExo infused NZB/WF1 mice demonstrate significant renal inflammatory infiltration compared to mice infused with vehicle. ApoExo triggered the recruitment to the renal interstitium of $CD3^+$, $CD20^+$, and AID^+ lymphocytes into nodules reminiscent of TLS ($p=0.0342$) associated with increased Lyve 1+ suggesting lymphoangiogenisis. Finally, heightened renal tubular damage ($p<0.05$), blood urea nitrogen levels ($p<0.05$) and decreased survival ($p=0.0055$) were observed in ApoExo infused NZB/WF1 mice compared to the ones infused with vehicle.

Conclusions: ApoExo infusion increases renal nodular lymphocyte infiltration, autoantibody production increase renal damage in lupus prone mice. This project is, to our knowledge, the first to evaluate the contribution of vascular injury derived extracellular vesicles to LN.

Funding: Private Foundation Support, Government Support - Non-U.S.

SA-PO1047

Extracellular DNA Traps Are Induced by Medullary Range NaCl, but Not Urea, and Protect Against Bacterial Pyelonephritis In Vivo

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Background: Excessive NaCl and urea concentrations characterize the kidney medulla. Their effects on innate immune cell death, namely extracellular DNA trap (ET) formation were not known. A role for ET in response to renal bacterial infections had not been defined.

Methods: ET generation and myeloid cell death was studied in varying osmolyte concentrations and pharmacologic modulations of different cell death pathways. ET were studied in murine and human pyelonephritis and functions explored by pharmacologic PAD inhibition and modulation of the renal electrolyte gradient.

Results: Medullary-range NaCl, but not urea, dose-, time- and PAD4-dependently induced ET formation even in the absence of other stimuli. Moderately elevated NaCl promoted myeloid cell apoptosis. NaCl induced myeloid cell calcium influx. Modulation of Na-K ATPase and NCX channel were ineffective. Ca^{2+}-free media or Ca^{2+}-chelation reduced NaCl-induced apoptosis and ET formation. LPS amplified it. ET of granulocytic and monocytic origin were present in human pyelonephritis kidneys, predominantly in the renal medulla. Citrullinated histone levels were systemically elevated in patients suffering from acute pyelonephritis. PAD4 inhibition prevented renal ET formation and promoted pyelonephritis in mice. Depletion of the renal NaCl gradient by loop diuretic therapy diminished renal medullary ET formation and increased pyelonephritis severity.

Conclusions: Our data demonstrate that renal medullary range NaCl concentrations are novel inducers of programmed myeloid cell death, namely ET formation. PAD4-dependent extracellular DNA traps promote antibacterial host response in the kidney.

Funding: Government Support - Non-U.S.

SA-PO1048

Gadolinium Retention Is Modulated by Prior Magnetic Resonance Imaging Contrast Agent Exposures

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Background: Complications of magnetic resonance imaging (MRI) contrast agents include crippling systemic fibrosis, kidney injury, and fatal gadolinium encephalopathy. Gadolinium, a rare earth metal in the periodic table's lanthanide series, has been extensively used in modern diagnostic medicine to enhance MRI procedures. Gadolinium-based contrast agents (GBCAs) are grouped into two categories: linear (Omniscan) or macrocyclic (Dotarem). Patients are often exposed to multiple brands of contrast agents. The impact of this practice on gadolinium retention and pathology has never been examined.

Methods: In our study, 21 male mice were randomized to five experimental groups: (1) saline-treated controls; gadolinium-based contrast agent-treated (2) Omniscan (OMN), (3) Dotarem (DOT), or in combination (4) OMN (1 week) followed by DOT administration for 3 weeks or (5) DOT (1 week) followed by OMN treatment for 3 weeks. Saline or contrast agents were administered via intraperitoneal injections 5 days a week for 4 weeks according to our established protocols. Tissues were excised and snap-frozen in liquid nitrogen. On average, 15 mg of tissue were digested in nitric acid, and gadolinium concentrations were quantified using PerkinElmer NexION 300D inductively coupled plasma mass spectrometry (ICP/MS) with a detection limit of 0.01 ppb.

Results: Regardless of the mode of exposure, 4-week treatment of OMN or DOT only or in combination (OMN-DOT or DOT-OMN) resulted in a significant accumulation of gadolinium in the tested organs. Gadolinium accumulation in the liver was lower in animals treated with DOT alone or in combination with OMN (OMN-DOT) than in animals administered with OMN alone or with DOT (DOT-OMN). In the kidney, the lowest gadolinium accumulation was observed in the OMN-DOT group in comparison with other GBCA-treated groups. GBCA treatments did not influence calcium levels in the kidneys or livers.

Conclusions: Our data indicate that prior GBCA exposures influence gadolinium retention in the kidney or liver. Future studies are needed to determine if this factor is influential in the pathophysiology of NSF in humans.

SA-PO1049

Semiautomated Pipeline for Quantitative Analysis of Uremic Cardiomyopathy

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Background: Cardiac remodeling in patients with chronic kidney disease, also called uremic cardiomyopathy, is a leading cause of high mortality in these patients. The histological changes include cardiomyocyte hypertrophy and capillary rarefaction, the quantification of which is both technically challenging and highly time-consuming. Here we developed a semiautomated pipeline for quantification of the size of cardiomyocytes and capillary density in cardiac histology.

Methods: We generated macros in ImageJ, a broadly used, open-source, java-based software. We have used modified Gomori silver staining, which is easy to perform and digitize in high throughput, or Fluorescein-labeled lectin staining. The latter can be easily combined with other stainings, allowing additional quantitative analysis, e.g., of nuclei, capillary density, or single-cardiomyocyte protein expression. We validated the pipeline in a mouse model of cardiac hypertrophy induced by transverse aortic constriction, and in autopsy samples of patients with and without aortic stenosis.

Results: In both animals and humans, ImageJ-based histology quantification revealed significant hypertrophy of cardiomyocytes and enabled the analysis of protein expression in individual cardiomyocytes. The analysis also revealed that murine and human cardiomyocytes had similar diameters in health and extent of hypertrophy in disease. The number of capillaries relative to the size of the cardiomyocytes indicates a rarefaction of microvasculature.

Conclusions: The pipeline enables a rapid analysis not feasible by manual methods and facilitates quantitative histology analyses in preclinical and clinical samples. The software requires few hardware requirements and is freely available.

Funding: Government Support - Non-U.S.

SA-PO1050

DQB1 Mismatch in Living Donor Kidney Transplantation

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Background: Several studies have reported an association between HLA-DQ mismatch, and formation of dnDSA and ABMR. Given the notable linkage in inheritance of HLA- DR and -DQ, we sought to determine what additional benefit can be gained by adding DQB1 allele matching to predicting allograft outcome.

Methods: We included living donor kidney transplant recipients (N=3886) transplanted between 2010-2022. Clinical, demographic, and outcome data were obtained from SRTR. HLA DQB1 allele typing and DR antigen was provided by each center. Using multivariable Cox-proportional hazards models we evaluated the hazard (aHR) of graft failure with level of DR and DQB1 mismatching. We used AIC to evaluate which model provide the best fit.

Results: In an unadjusted model, DQB1 allele mismatching was not associated with an increased hazard of death-censored graft failure (DCGF). In adjusted models, both DQB1 and DR were independently associated with increased hazard of DCGF aHR per mismatch 1.2 (1.01, 1.44) and 1.21 (1.02, 1.45), respectively. When both DR and DQB1 are in the model, neither is statistically significant. The model with DQ+DR provided best fit, although the difference was not statistically significant (delta-AIC<2).

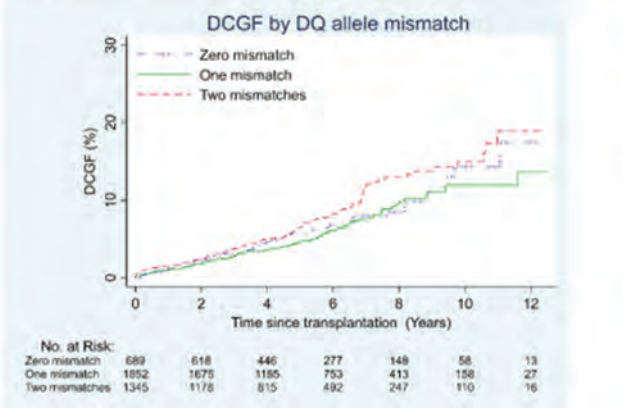
Conclusions: Despite a strong association between DQB1 mismatching and dnDSA/ABMR, its' addition to matching algorithms in living donor recipients when considering DCGF may not provide added benefit over DR matching, likely due to the strong linkage disequilibrium between these two loci.

Table 1. Association between death-censored graft failure and DQ allele mismatch/DR antigen mismatch.

	Hazard Ratios				
	Unadjusted	Model A	Model B	Model C	Model D
Zero mismatch	Ref	Ref	Ref	Ref	Ref
For each mismatch	1.16	1.20	1.21	1.11	1.12
AIC		4060.66	4060.47	4061.90	4059.91

All models adjusted for donor age per 10 years (splined at 50), sex, race (white, AA, Hispanic, others), recipients age per 10 years (splined at 50), sex, race (white, AA, Hispanic, others), Diagnosis (Glomerular disease, DMN, HTN, PCK, congenital/metabolic abnormalities, others), peak PRA (0,1-19,20-79,80-98,99-100) in addition to:
[i] Model A: DQB1 allele mismatch (per 1 mismatch)
[ii] Model B: DR antigen mismatch (per 1 mismatch)
[iii] Model C: DQB1 allele mismatch (per 1 mismatch) **[reported]** and DR antigen mismatch (per 1 mismatch)
[iv] Model D: Combined DQB1 allele + DR antigen mismatch (per 1 mismatch) [Range 0 – 4]

Figure 1. Death censored graft failure (DCGF) by DQB1 allele mismatch



SA-PO1051

Noninvasive Monitoring for Rejection: Need of the Hour, an In-Center Experience with Donor-Derived Cell-Free DNA (dd-cf-DNA) and Its Association with Antibody-Mediated Rejection (ABMR)

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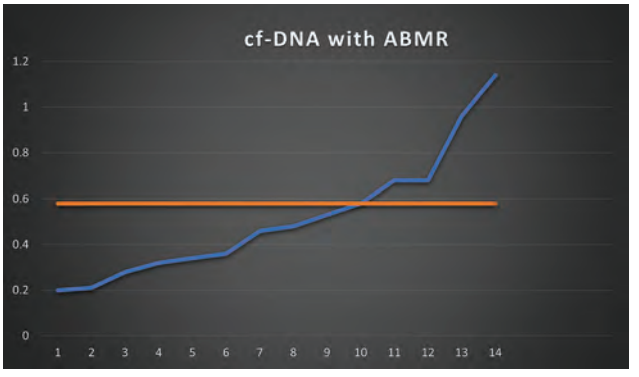
Background: Conventional modalities for detecting allograft rejection predominantly revolve around serial measurements of serum creatinine, and proteinuria. Serum creatinine, is a poor marker for detection of rejection as it lags considerably, and histologic analysis can be non-specific and operator dependent. Allograf biopsy remains the gold standard for detecting allograft rejection however biopsy is an expensive and invasive procedure by itself with risk of multiple complications. The quest for non-invasive tests for early rejection has been elusive. Recent advancements have shifted this paradigm towards newer diagnostic tests that independently provide an estimate into the injury state of the allograft kidney. Of these newer diagnostic modalities, dd-cf-DNA and gene expression, can be done regularly and can be used to complement traditional histological analysis.

Methods: We undertook a retrospective observational study in our renal transplant recipients to assess an association of dd-cf-DNA, gene expression, molecular tissue markers and histological analysis. We looked at the correlation of these variable with presence of antibody mediated rejection (ABMR) that was validated via protocol biopsy and molecular tissue marker analysis.

Results: We observed that dd-cf-DNA > 0.58% correlated with histological and molecular tissue marker proven antibody mediated rejection (ABMR). Furthermore, cf-DNA did not correlate with TCMR nor gene expression had any association with ABMR. With this study we report that a dd-cf-DNA of more than 0.58% is suggestive of ABMR which in the future can be used as a sole noninvasive test to diagnose ABMR and thereby avoiding the need for protocol biopsy.

Conclusions: Noninvasive monitoring for rejection is a need of the hour. Available literature along with our study supports the notion that cf-DNA is valuable in detecting ABMR.



Correlation of dd-cf-DNA with ABMR.

SA-PO1052

Blood Gene Expression Profile and dd-cfDNA for Diagnosis of Persistent Rejection

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Background: Persistent rejection (PRx) after treatment of BPAR is increasingly recognized and associated with worse outcomes. Repeat biopsies in the absence of clinical concern are rare.

Methods: This was a post hoc analysis performed on subjects with BPAR from the CTOT-08 study that had repeat biopsies available within 270 days after BPAR, and subanalysis of those within 90 days.

Results: Overall, 64 "index" BPAR with repeat biopsies were identified and 61% had PRx within 270 days. Rejection types are in Figure 2. Biomarker test characteristics for F/U biopsies within 270 days and 90 days are shown in Figure 1. PRx was in clinically stable patients in 67% within 270 and 71% within 90 days. Biomarker results and rejection type are shown in Figure 2. There was 2-year clinical F/U data available for 52 subjects showing 32 subjects (62%) met the composite endpoint of the CTOT-08 trial and subjects with PRx were more likely to meet the CCE (65% vs 34%, p=0.025).

Conclusions: Blood GEP and dd-cfDNA demonstrate excellent capability of identifying PRx, with high PPVs. PRx was associated with worse outcomes. GEP and dd-cfDNA may be tools to identify those in need of a F/U biopsy even when no clinical alterations are present (2/3 of subjects had stable function). The overlap of biomarker results shows that the 2 tests identify different rejections.

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Table 1.

Blood GEP Performance Characteristics on Follow-up Biopsies Within 270 Days of Rejection

	All Biopsies (n=64)	AMR/Mixed on Initial Biopsy (n=34)	TCMR/Borderline on Initial Biopsy (n=30)	TruGraf Positive on Initial Biopsy (n=33)
Sensitivity	59% (42-74)	73% (52-88)	31% (9-61)	85% (62-97)
Specificity	76% (55-91)	75% (35-97)	76% (50-93)	69% (39-91)
PPV	79% (60-92)	81% (59-95)	66% (27-93)	81% (58-94)
NPV	55% (38-72)	65% (35-88)	42% (22-65)	75% (43-95)
Accuracy	66% (53-77)	74% (56-87)	49% (30-68)	79% (61-91)

Blood GEP Performance Characteristics on Follow-up Biopsies Within 90 Days of Rejection

	All Biopsies (n=28)	AMR/Mixed on Initial Biopsy (n=12)	TCMR/Borderline on Initial Biopsy (n=16)	TruGraf Positive on Initial Biopsy (n=16)
Sensitivity	59% (33-82)	70% (35-93)	43% (10-82)	78% (40-97)
Specificity	82% (48-98)	100% (16-100)	78% (40-97)	71% (29-96)
PPV	83% (51-98)	100% (59-100)	74% (24-99%)	80% (43-98)
NPV	57% (31-81)	69% (20-97)	47% (18-78)	68% (26-95)
Accuracy	68% (48-84)	82% (50-97)	57% (31-81)	75% (48-93)

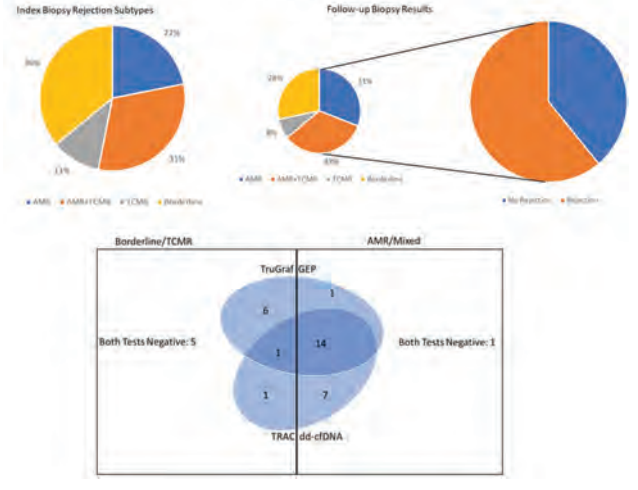
dd-cfDNA Performance Characteristics on Follow-up Biopsies Within 270 Days of Rejection

	All Biopsies (n=58)	AMR/Mixed on Initial Biopsy (n=32)	TCMR/Borderline on Initial Biopsy (n=26)	TRAC Positive on Initial Biopsy (n=21)
Sensitivity	62% (45-78)	72% (51-88)	42% (15-72)	84% (60-97)
Specificity	86% (64-97)	71% (29-96)	93% (66-100)	50% (1-99)
PPV	87% (67-97)	79% (55-94)	90% (42-100)	72% (45-90)
NPV	60% (41-77)	63% (32-88)	51% (28-74)	68% (15-98)
Accuracy	72% (58-83)	72% (53-86)	62% (41-80)	71% (47-88)

dd-cfDNA Performance Characteristics on Follow-up Biopsies Within 90 Days of Rejection

	All Biopsies (n=26)	AMR/Mixed on Initial Biopsy (n=12)	TCMR/Borderline on Initial Biopsy (n=14)	TRAC Positive on Initial Biopsy (n=10)
Sensitivity	50% (25-75)	60% (26-88)	33% (4-78)	71% (29-96)
Specificity	90% (56-100)	100% (16-100)	88% (47-100)	50% (1-99)
PPV	88% (51-100)	100% (54-100)	80% (16-100)	68% (23-96)
NPV	55% (29-78)	63% (19-94)	47% (18-78)	54% (5-97)
Accuracy	66% (45-83)	76% (44-95)	55% (27-81)	54% (5-97)

Figure 1. Biopsy Subtypes and Biomarker Overlap



SA-PO1053

Donor-Derived Cell-Free DNA in Biopsy-Proven Antibody-Mediated Rejection (ABMR) vs. Recurrent IgA Nephropathy After Kidney Transplantation

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Background: Antibody-mediated rejection (ABMR) and recurrent IgA nephropathy (IgAN) are major causes of graft loss and show comparable clinical features such as decline in renal function, proteinuria or worsening hypertension. Since ABMR and recurrent IgAN are indistinguishable using eGFR and urine albumin-creatinine-ratio (uACR) alone, we evaluated the ability of donor-derived cell-free DNA (dd-cfDNA) to discriminate both entities in consecutive cases from an ongoing prospective, observational trial.

Methods: At the time of clinically indicated biopsies, we collected venous blood samples and measured absolute (cp/mL) and relative (%) dd-cfDNA. We included 57 dd-cfDNA-matched biopsies, and assigned them to 3 groups based on histopathology: (1) active or chronic active ABMR (n=21), (2) recurrent IgAN (n=15), (3) no signs of rejection, infection or glomerulonephritis (n=21).

Results: Absolute and relative dd-cfDNA were lower in recurrent IgAN than in ABMR (median 11 cp/mL [IQR 7 - 13] vs. 76 cp/mL [IQR 57 - 103], p<0.001; median 0.32% [IQR 0.24 - 0.41] vs. 1.68% [IQR 1.1 - 2.7], p<0.001), but did not differ between recurrent IgAN and no rejection (median 11 cp/mL [IQR 7 - 13] vs. 12 cp/mL [IQR 7 - 16], p=0.995; median 0.32 % [IQR 0.24 - 0.41] vs. 0.30 % [IQR 0.26 - 0.54], p=0.983) (Figure 1). Using the prespecified cutoff of 50 cp/mL, no patient with recurrent IgAN, but 17/21 patients (81%) with ABMR had increased absolute dd-cfDNA levels. Four patients (27%) with crescent formation as a sign of severe recurrent IgAN had low absolute (min-max: 6 - 21 cp/mL) and relative dd-cfDNA (min-max 0.26 - 0.35%) as well.

Conclusions: Dd-cfDNA does not increase in recurrent IgAN after kidney transplantation.

Funding: Commercial Support - Oncocyte

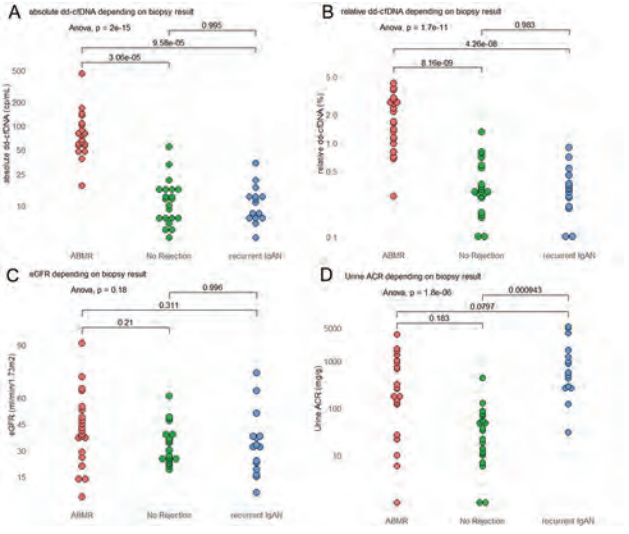

Figure 1. Dot plots showing biopsy-matched measurements of (A) absolute dd-cfDNA (B) relative dd-cfDNA (C) eGFR and (D) uACR in KTR with ABMR, no rejection, and recurrent IgAN.

SA-PO1054

Use of Donor-Derived Cell-Free DNA and Gene Expression Profiling to Facilitate Belatacept Monotherapy in Kidney Transplant Recipients

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Background: Studies have demonstrated that a donor-derived cell free DNA (dd-cfDNA; AlloSure) >1.0% can be used as a biomarker of allograft rejection. A gene expression profiling (AlloMap) threshold of 11.5 has shown to discriminate rejection from immune quiescence. We aimed to investigate their utility in weaning to Belatacept monotherapy immunosuppression.

Methods: Between December 2022 and April 2023, we enrolled adult kidney recipients on Belatacept immunosuppression with stable renal function (eGFR > 40 mL/min/1.73 m2) and negative Donor-Specific Antibodies (DSA) into a prospective, single-center, observational pilot study. Patients with acute rejection episodes were excluded. AlloSure, AlloMap, serum creatinine, urine protein, and DSA were measured at monthly Belatacept infusion visits. Patients deemed immune quiescent underwent immunosuppression tapering. Outcomes were: 1) Incidence of biopsy-proven acute rejection and 2) allograft and patient survival, change in eGFR, development of proteinuria or de-novo DSA.

Results: We analyzed the first 11 patients who completed 6 months of follow-up. Subjects were predominantly male (n=7), with a mean age of 57 years, mean eGFR of 65.1 mL/min/1.73m2 ± 14.7 SD on enrollment, and 67 mL/min/1.73m2 ± 15.0 SD at the 6 months follow up. The most common agents used with Belatacept were Prednisone and Mycophenolate (n = 9) followed by Prednisone and Everolimus (n = 2). Mean AlloSure and AlloMap values throughout follow up were 0.20% ± 0.05 and 11.5 ± 1.4 respectively. 5 patients (45%) were weaned off steroids; no subjects were weaned entirely off mycophenolate or everolimus due to an AlloMap over the threshold. There was 100% patient and graft survival, with no cases of biopsy-proven rejection, proteinuria or DSA development.

Conclusions: Despite having AlloSure <1%, the mean AlloMap score was above the reported treshold shown to discriminate rejection from quiescence. We hypothesize that patients on Belatacept-based immunosuppression regimen have a higher baseline AlloMap levels even if immune quiescent, as prior AlloMap studies primarily included patients treated with tacrolimus-based immunosuppression. Higher cutoffs may be necessary for these patients. Investigation is ongoing to assess this hypothesis in our cohort.

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SA-PO1055

Early Detection of Microvascular Injury in Renal Allografts Utilizing Donor-Derived Cell-Free DNA (cfDNA)

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Background: Early detection of allograft injury is critical in improving long-term allograft outcomes. Standard tests of renal function are insensitive, while renal biopsies are invasive and expensive. cfDNA allows sensitive surveillance of allograft injury. We present a series of patients where we identified microvascular injury (MVI) without evidence of alloantibody (DSA or donor directed non-HLA Ab) or C4d on biopsy based on elevatyed cfDNA.

Methods: We followed universal surveillance with cfDNA at month 1, 2, 3, then quarterly till 24 months. A biopsy was triggered if the surveillance value of cfDNA was >1%. Isolated MVI was diagnosed if their glomerulitis (g)+ peritubular capillaritis (ptc) score of >2 and C4d was negative. There were no other histopathological indicators of AMAR or CMR or infection based on Banff 2017 criteria. DSA and non-HLA antibodies (anti-AT1R, Anti-MICA) were negative.

Results: We followed 120 consequetive patients from 2/2022 till 2/2023. 5 patients with isolated MVI biopsied solely on elevated cfDNA signature. Their renal function was normal. C4d, DSA and non-HLA antibody panels were negative. None of these biopsies satisfied the Banff 2017 criteria for AMAR Patients were treated based on individual physician prerogative. Patients 1 & 2 received steroids only. Patients 3, 4 & 5 received steroids as well as 5 sessions of Plasmapharesis and IVIG. All five patients maintained renal function and showed decreased allograft injury based on reduced cfDNA signature (Table 1).

Conclusions: 1. Surveillance with cfDNA is an important tool to detect allograft injury. 2. Early detection of MVI by cfDNA provides an opportunity to treat it before allograft dysfunction becomes apparent 3. The exact nature of isolated MVI remains unclear. It can be postulated as an alloimmune response or allograft injury due to missing self class I antigens. 4. The exact treatment regimen remains unclear. In our series, there was stabilization in injury based on cfDNA signature by increasing immunosuppression.

Donor Derived Cell-free DNA Results in Patients with Micro-vascular Injury

Patient ID	Baseline Allosure %	Pre-Biopsy Allosure %	Post treatment Allosure %
1	0.31	1.8	0.95
2	0.18	1.7	0.41
3	0.79	7.6	0.5
4	2.9	6.6	3.0
5	3.9	5.4	1.8

SA-PO1056

Prospective Assessment of the Need, Discrepancies, and Added Value of Molecular Diagnostics of Kidney Allograft Biopsies: An Evaluation in Clinical Practice

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Background: The Molecular Microscope Diagnostic System (MMDx) may resolve inconclusive histology findings, as preserved biopsy material can be examined after histology findings have been obtained. The extent to which this proposed approach can be implemented in clinical practice remains an open question.

Methods: We prospectively analyzed 102 consecutive indication kidney allograft biopsies by histology and MMDx at the University Hospital Zurich from April to September 2022. Pathologists and clinicians with experience in MMDx assessed the need for MMDx by questionnaire when the histology report was available. Clinicians then assessed the discrepancy rate and assumed added value by questionnaire when the MMDx report was available.

Results: The need for MMDx was most frequently assessed for suspected ABMR (12/20) and mixed ABMR/TCMR (9/18) but less frequently for proven ABMR (1/11), TCMR/borderline (1/6), DSA only (1/20), and no ABMR/TCMR (3/28). Discrepancies were observed most frequently in cases with proven/suspected rejection (36/55) but rarely in the absence of histologic rejection (1/47). Clinicians considered an added value of molecular diagnostics mostly in suspected ABMR (3/20), mixed ABMR/TCMR (7/18), and TCMR/borderline (3/6). Classification into molecular ABMR occurred in 9 of 32 cases with suspected ABMR. However, classification into molecular TCMR was not observed in any of the 17 cases with suspected TCMR.

Conclusions: The need for MMDx in clinical practice goes beyond the recommendation for suspected ABMR. While discrepancies appear to be limited to cases with histologic rejection, an added value of MMDx is particularly suspected along the ABMR continuum. Because MMDx aims to overcome the inter-observer variability of histology, the potential added value of MMDx must be determined for each center individually.

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SA-PO1057

The Molecular Microscope Diagnostics System (MMDx) Does Not Identify Early Molecular Antibody-Mediated Rejection (ABMR) in the Presence of Donor-Specific Antibodies (DSA), but Absence of Microvascular Inflammation

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Background: The development of de novo donor-specific antibodies (DSA) or an increase in MFI values of preformed DSA are common indications for kidney allograft biopsies. If changes in transcript patterns analyzed by the Molecular Microscope Diagnostic System (MMDx) may precede histological antibody-mediated changes and identify early antibody-mediated rejection (ABMR), however, remains uncertain.

Methods: In this single-center cohort of 326 indication kidney transplant biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 138 cases with no glomerulitis (g0) and no ABMR (not meeting Banff 2019 ABMR criteria 1 and 2) concerning the presence (n=49) and absence (n=89) of DSA.

Results: Kidney allograft biopsies in the presence of DSA were performed later post-transplantation (median 37 months (IQR 5-170) compared to biopsies in the absence of DSA (median 13 months (IQR 3-93; p=0.03). Molecular ABMR was observed in 0/49 cases (0%) in the presence of DSA and 2/89 cases (2%) in the absence of DSA (2 cases of mixed molecular ABMR/TCMR with histological TCMR). 17/49 cases (35%) in the presence of DSA showed an all ABMR rejection phenotype score (sum of R4, R5, and R6) ≥0.20 compared to 22/89 cases (25%) in the absence of DSA (p=0.116). 13/49 cases (26%) with transplant glomerulopathy (cg) showed an all ABMR rejection phenotype score ≥0.20 compared to 26/89 cases (29%) without cg (p=0.1). Among cases with cg, the all ABMR rejection phenotype score did not differ between cases with DSA compared to cases without DSA (p=0.294). 1/4 cases with isolated C4d positivity ≥2 in the presence of DSA showed an all ABMR rejection phenotype score ≥0.20.

Conclusions: MMDx does not differentiate early molecular ABMR in the presence of DSA and/or transplant glomerulopathy but in the absence of histological antibody-mediated changes. If minor molecular changes are meaningful, at least in a subgroup of cases, needs to be assessed in the context of follow-up biopsies.

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SA-PO1058

Isolated Glomerulitis Is Associated with the Absence of Molecular Antibody-Mediated Rejection (ABMR) in Cases with Histologically Suspected and Confirmed ABMR

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Background: According to the 2018 Banff classification, the Molecular Microscope Diagnostic System (MMDx) is indicated in cases when histology is insufficient to diagnose antibody-mediated rejection (ABMR) due to an absence of diagnostic criteria groups 2 (antibody interaction with tissue) and/or 3 (DSA and equivalents). The impact of isolated glomerulitis (g>0, ptc0) on the likelihood of molecular ABMR appears critical to the implementation of this new biomarker.

Methods: We analyzed 326 kidney allograft biopsies by histology and MMDx at the University Hospital Zurich. Histologic findings were classified into: (1) 30 cases with suspected ABMR: isolated mild glomerulitis (g1), DSA-, (2) 32 cases with suspected ABMR: isolated mild glomerulitis (g1), DSA+, (3) 33 cases with suspected ABMR: MVI (g+ptc>1), DSA-, (4) 60 cases with confirmed ABMR: MVI (g+ptc>1), DSA+.

Results: MMDx diagnosed ABMR in 5/30 cases (17%) with isolated g1 without DSA, 12/32 cases (38%) with isolated g1 with DSA, 18/33 cases (55%) with MVI without DSA, and 30/60 cases (50%) with histologically proven ABMR. While only 17/65 cases (26%) with molecular ABMR showed isolated glomerulitis, 64/90 cases (71%) without molecular ABMR showed isolated glomerulitis (p<0.001). Among cases with isolated glomerulitis, molecular ABMR was detected more frequently in cases with proteinuria (p=0.011), the presence of DSA (p=0.033), and transplant glomerulopathy (cg; p=0.014).

Conclusions: MMDx confirms ABMR in a relevant proportion of cases with isolated mild glomerulitis. However, isolated glomerulitis is associated with the absence of molecular ABMR in cases with suspected and confirmed ABMR. Proteinuria, DSA, and transplant glomerulopathy are associated with molecular ABMR among cases with isolated glomerulitis.

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SA-PO1059

Impact of Donor-Specific Antibodies (DSA) with Low Median Fluorescent Intensity (MFI) on Allograft Outcomes in Kidney Transplant

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Background: Many factors are associated with allograft failure in kidney transplantation patients (KTs). Immune-mediated rejection is one of the most common causes of allograft failure. Many studies demonstrated that high level of donor specific antibody (DSA) correlated with complement binding capability and more severe tissue

injury. However, data on DSA with low MFI are scarce. We compared allograft outcomes in KT patients with low-MFI DSA in this study.

Methods: Post kidney transplant patients who were tested for DSA at Ramathibodi Hospital from January 2007 to December 2021 and had DSA with MFI < 1000, reported as negative, were evaluated. KTs were separated into two groups: those with very low DSA (VLL) (MFI 1-500) and those with low DSA (LL) (MFI 501-1000). The primary outcome was the incidence of acute rejection. One and 5-year serum creatinine, allograft and patient survival in KTs with and without antibody-mediated rejection (ABMR) were also studied. Univariate and multivariate analyses were used to analyze factors associated with rejection.

Results: Thirty-six KTs were identified (VLL n = 27, LL n = 11). Demographic characteristics were similar between the 2 groups except slightly higher use of ATG for induction in LL group. The LL group had significantly higher T-cell mediated rejection (TCMR) than the VLL group (45% vs. 12%, P = 0.04). Ten patients developed ABMR. Rate of ABMR, 5 years allograft survival and patient survival were comparable between groups. There was a trend toward higher MFI in KTs with ABMR than without ABMR (MFI 442 [74-684] vs. 198 [33-475]; P = 0.21). At 5 years, the median serum creatinine level among ABMR was significantly higher than in non-ABMR KTs (2.25 [2.00-2.98] mg/dl vs. 1.41 [1.11-1.87] mg/dl) (P = 0.03). Univariate and multivariate analyses revealed that LL was a risk factor for rejection.

Conclusions: DSA with low MFI is associated with higher incidence of rejection. DSA with low MFI should not be reported as negative and overlooked. All DSA should be reported regardless of MFI. These group of KTs should be monitored closely and have their immunosuppression intensified to reduce the incidence of rejection.

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SA-PO1060

Torque Teno Virus Load to Monitor Changes in Immunosuppression in Kidney Transplant Recipients with Indication Biopsy

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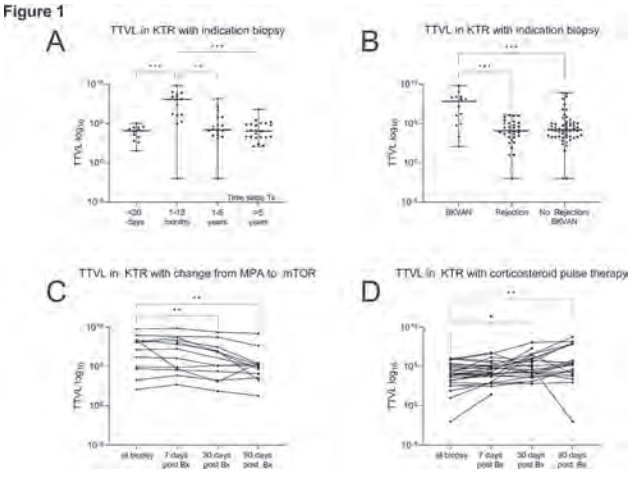
Background: Torque teno virus (TTV) is a potential surrogate parameter to monitor immunocompetence in kidney transplant recipients (KTR) early after transplantation. However, its use in monitoring changes in immunosuppression in KTR late after transplantation with different graft-associated pathologies requires further investigation.

Methods: In this post-hoc analysis we quantified TTV load in sera of 108 KTR with indication biopsy. TTV loads of 34 KTR with biopsy-proven acute rejection (BPAR) and 74 KTR with other pathologies, including 15 KTR with BKV-associated nephropathy (BKVAN), were quantified the day of biopsy, as well as 7, 30 and 90 days post-biopsy to identify changes in viral load related to adjustments in immunosuppressive therapy.

Results: In KTR with no BPAR or BKVAN, TTV load increased in the first month following transplantation and was highest in patients that received a graft biopsy between 1-12 months post-transplantation. Subsequently, with a reduction in immunosuppression, there is a gradual decline in TTV load across patients (Figure 1A). Patients with BKVAN had significantly higher TTV loads than patients with BPAR or other pathology (P<0.001 for both; Figure 1B). When converted from mycophenolic acid (MPA) to mTOR-inhibitors because of BKVAN, TTV loads decreased significantly in these patients (P<0.01, Figure 1C). In KTR with BPAR who received high-dose corticosteroid pulse therapy, a significant increase in TTV loads was observed between biopsy to 30d and 90d post-biopsy (P<0.05 and P<0.01, respectively; Figure 1D).

Conclusions: TTV load reflects changes in immunosuppressive therapy. Individual changes of TTV load appear to be of greater significance than universally defined cut-off values as TTV load varies depending on the time after transplantation.

Figure 1



SA-PO1061

Valacyclovir for Prevention of Cytomegalovirus Infection After Kidney Transplantation

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Background: Cytomegalovirus (CMV) infection is a frequent and devastating complication after kidney transplantation (KT). Although guidelines recommend anti-viral prophylaxis with ganciclovir or valganciclovir, there is a demand for alternative regimen for CMV prevention. We investigated the effects of valacyclovir-based prophylaxis for 3 months on CMV infection and clinical outcomes in KT recipients using a nationwide cohort.

Methods: 2,584 KT recipients from 20 transplant centers registered with the Korean Organ Transplantation Registry were analyzed in this study. The recipients were divided into two groups according to valacyclovir prophylaxis (valacyclovir prophylaxis group and non-prophylaxis group). The impact of valacyclovir-based prophylaxis on CMV infection and disease, and clinical outcomes including rejection, graft loss, cardiac events, and all-cause mortality were investigated. Risk factors for the development of CMV infection were also analyzed.

Results: Valaciclovir prophylaxis group showed significantly lower incidence of CMV infection and rejection compared to non-prophylaxis group (3.64 vs. 10.25 events per 100 person-years and 1.85 vs. 7.27 events per 100 person-years, respectively). The risk of CMV infection and rejection was significantly decreased in valaciclovir prophylaxis group compared to non-prophylaxis group. Valacyclovir prophylaxis, donor age, whether deceased donor or not, length of hospitalization after KT, anti-thymocyte globulin usage, and CMV serological mismatch between the donor and the recipient (donor+ and recipient–) were independent risk factors for the development of CMV infection.

Conclusions: Valacyclovir prophylaxis after KT significantly reduced CMV infection and rejection. Valacyclovir could be considered as an alternative strategy for CMV prophylaxis after KT. Well-designed randomized controlled trials with large sample size are needed.

SA-PO1062

Plasma Fibroblast Growth Factor 21 (FGF21) Concentration in Patients After Kidney Transplantation

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Background: Fibroblast growth factor 21 (FGF21) is a protein hormone involved in the regulation of metabolism and energy expenditure. Results of clinical studies suggest that plasma FGF21 concentration increases with the progression of chronic kidney disease (CKD). The aim of the present clinical study was to analyze the effect of successful kidney transplantation (KTx) on plasma FGF21 concentration and to study the factors related to plasma FGF21 concentration in patients long-term after KTx.

Methods: The first part of the study, i.e. the 6 months prospective observation**,** included 40 CKD patients directly before KTx [26 women and 14 men aged 47.0 (39.2 – 54.0) years]. In the second part of the study 184 patients long-term after KTx [72 women and 112 men aged 52.0 (48.0 – 54.0) years] and 50 healthy subjects (HS) [28 women and 22 men aged 52.0 (48.0 – 58.0) years] were enrolled. FGF21 plasma concentration was measured using Human FGF-21 ELISA (BioVendor R&D). Results were presented as median and 95% CI.

Results: In CKD patients directly before KTx plasma FGF21 concentration were significantly higher than in HS [1013.0 (689.6–1635.8) pg/ml *vs* 239.5 (219.0–294.5) pg/ml respectively; p<0.001]. At 14, 30 days and 6 months after KTx, a significant decrease of plasma FGF21 was observed [322.5 (197.3– 579.6) pg/ml; 355.0 (268.5–547.6) pg/ml; 344.0 (264.1–405.6) pg/ml (p<0.001), respectively]. In patients long-term after KTx, a negative correlation was found between plasma FGF21 concentration and estimated glomerular filtration rate and a positive correlations between plasma FGF21 concentration and BMI and serum concentration of triglycerides, insulin, interleukin 6, CRP and cystatin C.

Conclusions: 1. In CKD patients plasma FGF21 concentration measured directly before KTx is significantly higher than in HS. 2. Successful KTx leads to a significant decrease of plasma FGF21 concentration. 2. Plasma FGF21 concentration in patients long-term after KTx is related to the degree of graft function impairment and several metabolic abnormalities of these patients.

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SA-PO1063

Is Metabolic Acidosis a Risk Factor for Worse Long-Term Prognosis in Patients After Kidney Transplantation?

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Background: Metabolic acidosis (MA) frequently occurs in patients after kidney transplantation (KTx). Results of both experimental and clinical studies suggest that MA may contribute to faster progression of chronic kidney disease. Data on such relationship

in KTx patients is very limited. The aim of this clinical, single center, retrospective, observational study was to examine the relationship between MA and both mortality and renal outcomes in patients after KTx.

Methods: Blood bicarbonate concentration was measured in 486 patients (290 male; 196 female) aged 48.2 ± 12.0 years at least one year after KTx and subsequently all patients were observed during 11 years. MA was defined as the blood bicarbonate concentration lower than 22 mmol/L. The endpoints in Kaplan-Meier survival curves analysis were death, initiation of dialysis therapy or retransplantation as well as cumulative endpoint of the study i.e. death or initiation of dialysis therapy. Differences in survival curves were analyzed with log-rank test and were consider as significant when $p<0.05$. Relative risks (RR) were presented with 95% CI.

Results: Metabolic acidosis was diagnosed in 57 (12%) patients being long-term after KTx. The Kaplan-Meier curves analysis have shown that patients with MA reach endpoints of follow-up earlier (log-rank $p=0.002$ for death and $p<0.001$ for dialysis or retransplantation and for cumulative endpoint $p<0.001$). In patients with MA the risks of starting dialysis therapy or retransplantation was significantly higher than in patients without MA [RR=2.00 (1.42-2.82), $p<0.001$]. In patients with MA the risks of death was significantly higher than in patients without MA [RR=1.61 (1.01-2.55), $p=0.04$]. Risk of cumulative endpoint of the study (death and initiation of dialysis therapy or retransplantation) was also higher in patients with MA [RR=1.83 (1.49-2.23), $p<0.001$].

Conclusions: 1. Metabolic acidosis is an important risk factor for increased mortality and progression of graft failure in kidney transplant patients. 2. The prospective interventional studies with correction of MA in patients prone to allograft nephropathy progression will provide information whether treatment of MA improves the survival of both patients and transplanted kidneys.

Funding: Government Support - Non-U.S.

SA-PO1064

Application of Machine Learning for Repertoire Analysis in Antibody-Mediated Rejection (ABMR) of Kidney Transplantation

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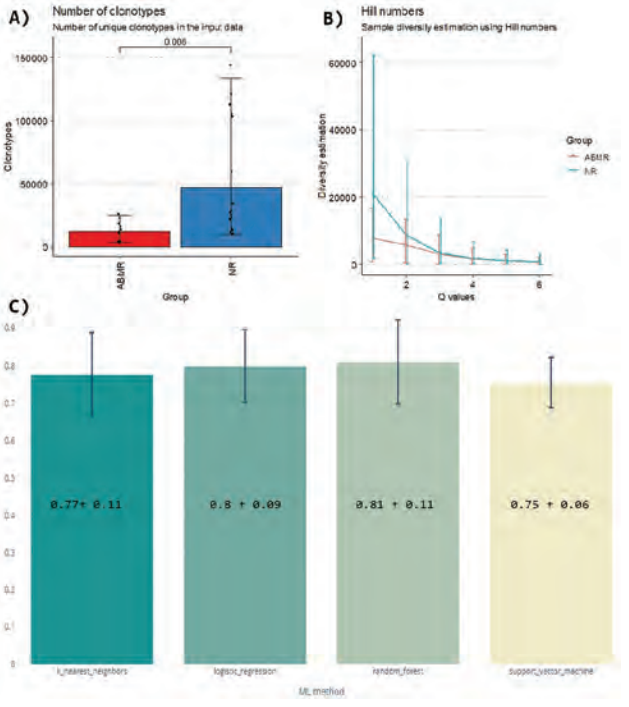
Background: The adaptive immune receptor repertoire (AIRR)-sequencing analyzes the individual repertoire at sequence level. Here we compare AIRRs of kidney transplant recipients using repertoire analyses and machine learning, regarding ABMR.

Methods: Total of 30 repertoires (9 ABMR and 21 No rejection) were analyzed. Bulk gDNA (2μg) was sequenced at 500,000 target read-depth (equivalent of 10,000 B lymphocytes). The MiXCR tool (v4.3.2) was used for preprocessing and normalization. Repertoire analysis using the immunarch R package (v1.0.0) included clonality, diversity and V(D)J gene usage analyses. Machine learning by ImmuneML (v2.2.4) used four algorithms of KNN, SVM, RF and logistic regression. Using 3-mer aminoacids encoding and ABMR status as classifiers, the performances of ML algorithms were assessed by AUC.

Results: From repertoire analyes, decreased number of clonotypes (P=0.008) and decreased diversity (P=0.02) were seen in ABMR. There were differences in V gene utilization, from which IGHV1-2 and IGHV1-8 were decreased in ABMR group, while IGHV3-30 usage was higher (P=0.026, 0.014 and 0.018). The AUC of ML algorithms KNN, LR, RF and SVM were 0.77±0.11, 0.8±0.09, 0.81±0.11 and 0.75±0.06. Analysis of 3mer correlated V gene usages, from which NEI, TEC, WAK and WAR were statistically significant 3mers after Bonferroni correction (P<0.00000625).

Conclusions: Reproducible and clinically applicable AIRR-seq workflow was implemented using IVD product. Repertoire analysis was capable of demonstrating differences from kidney transplant recipients. ML models using different algorithms generated overall favorable performances in classifying ABMR status, indicating that direct interpretation of AIRR-seq data is possible.



Differences in number of clonotypes (A), diversity (B) between ABMR and No rejection groups. The performances of ML algorithms (C).

SA-PO1065

Sodium Restriction Is Associated with Decreased Kidney Function Through TonEBP Downregulation in Calcineurin Inhibitor (CNI)-Treated Kidney Transplant Recipients

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Background: Tonicity responsive enhancer binding protein (TonEBP) protects kidney tubular cells against hypertonicity by adapting the osmolar gap across the membrane. Under hypertonic conditions, TonEBP shifts from the cytoplasm to the nucleus for the transactivation of tonicity responsive genes. Calcineurin inhibitors (CNI) are known to suppress TonEBP by hampering its nuclear translocation. We examined whether CNI induced nephrotoxicity in transplant recipients could be due to impaired TonEBP activity.

Methods: A total of 385 kidney transplant recipients at JCHO Sendai Hospital between 2000 to 2022 were enrolled. Data for these patients were extracted from medical records. TonEBP immunohistochemistry was performed by biopsy specimens from 144 patients. The decline of eGFR were described using Kaplan-Meier methods.

Results: By immunohistochemistry, TonEBP was predominantly located in the cytoplasm among CNI nephrotoxicity compared to nuclear-cytoplasmic staining in rejections, suggesting that TonEBP transactivation was restricted in CNI nephrotoxicity. Cytoplasmic TonEBP staining was observed regardless of acute or chronic CNI induced kidney injury. Next, we examined sodium intake, which is the primary TonEBP activator of the kidney. Patients diagnosed as CNI nephrotoxicity revealed significantly lower sodium chloride intake compared to rejections (7.5 vs 10.8g/day, $p<0.05$). A 10% decline of eGFR among transplant recipients without any history of rejection (nor pre/post renal injury events) was significantly faster in the low sodium intake group (<8g/day) compared to the higher intake group (≧8g/day) (Median follow up: 10 years, Log-Rank P=0.03).

Conclusions: 1) TonEBP transactivation of renal tubular cells could be impaired in CNI nephrotoxicity and sodium restriction may exacerbate its activity, which could fail the TonEBP-mediated cell protection from the hypertonicity. 2) Sodium intake of kidney transplant recipients should be reevaluated from the view of preventing CNI nephrotoxicity.

SA-PO1066

Recipient Obesity on Deceased Donor Kidney Transplant (DDKT) Outcomes: Overlooked Threats to Allograft Dysfunction and Delayed Graft Function (DGF)

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Background: As the prevalence of obesity increases globally, appreciating the effect of recipient obesity on graft outcomes is of increasing importance. However, the impact of recipient body mass index (BMI) on kidney transplant outcomes has been controversial. This study is designed to investigate the effect of recipient BMI on short and long-term outcomes of patients undergoing DDKT.

Methods: A total of 743 patients receiving deceased donor KT between 2005 and 2019 among 3 multi-centers were included in the study. Patients were divided according to their body mass index(BMI) into underweight (BMI<18.5,N=47), normal weight (BMI≧18.5 to BMI<25kg/m2,N=488), and obese (BMI≧25kg/m2,N=208) groups. Their clinicopathological characteristics, graft functions, graft survival rates and delayed graft function (DGF) were analyzed retrospectively.

Results: Obesity was associated with deterioration of allograft function. Kidney function was significantly lower in obese group compared with underweight and normal BMI groups after 3 months to 3 years follow up after DDKT(3 months follow up p= 0.005, 1year p=0.009, 3year p=0.034). Multivariate analysis showed that recipient obesity (BMI≧25) was an important prognostic factor for DGF (OR1.24, 95% CI, 1.011-1.438, P=0.042). Though statistically insignificant, the death-censored graft survival rate tends to be negatively associated with recipients' BMI level.

Conclusions: In conclusion, recipients' obesity increases the risk of allograft dysfunction and it is found to be statistically significant prognostic factor for DGF. Therefore, appropriate risk-adapted information concerning BMI should be provided to patients and efforts to improve recipients' obesity should be taken in advance to DDKT.

FIGURE1. ALLOGRAFT FUNCTION & RECIPIENTS' BMI

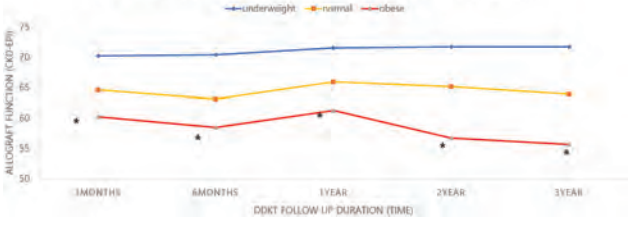

Figure 1. Allograft function & Recipients' BMI.

Table1. Risk factors for delayed graft function(DGF)

subordination variable	independent variable	B	S.E.	OR	95% CI	p
Delayed graft function (DGF)	Recipients age	0.027	0.010	1.027*	(1.007-1.048)	0.008
	Recipients sex	0.006	0.202	1.006	(0.678-1.494)	0.978
	Recipients BMI	0.014	0.017	1.240*	(1.011-1.438)	0.042
	Donor age	0.002	0.007	1.002	(0.988-1.016)	0.759
	Donor sex	0.003	0.216	1.001	(0.994-1.153)	0.193
	Donor BMI	0.014	0.028	1.014	(0.961-1.071)	0.605
	Cold ischemic time	0.001	0.001	1.050*	(1.000-1.086)	0.007
	Dialysis vintage	0.057	1.148	1.059	(0.112-10.042)	0.960

*$p<0.05$

Table1. Risk factors for delayed graft function(DGF)

SA-PO1067

Long-Term Evaluation of Coronary Calcifications in Kidney-Transplanted Patients: A Single Center Follow-Up of 15 Years

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Background: Few data are available on the long term behavior of coronary artery calcifications (CAC) in kidney transplantation (KTx). In a previous paper (Alfieri C et al. Sci Rep. 2019), we evaluated the factors implicated with CAC progression after 5 years of KTx. Here we present the preliminary data about CAC follow-up of the same population after 15 years of KTx (T15).

Methods: Previously 67 KTxps (2007-2008) were studied. At the present time, 19 of them were lost from the follow up: 8 died, 4 because of major cardiovascular event (MACE), 11 had a graft loss and 20 did not adhere to the control. Then, we evaluated 28 KTxps (M=18; age 60±9 yrs). Clinical, blood and urinary data were recorded for 15 years, considering the mean values in the analyses. At baseline and T15, using coronary TC, Agatson score was evaluated and patients were accordingly categorized in 4 groups: 1)0-10; 2)10-100; 3)100-400; 4)>400. The CAC progression was tested using the modification in CAC category (Cat-Prog+T15) and the formula proposed by Sevrukov (Prog+).

Results: At baseline and at T15, 46% and 18 % of pts were in the 1st grp, 14% and 25 % in the 2nd, 29% and 18% in the 3rd and 11 % and 39% in 4th, respectively. CAC at T15 were significantly higher than baseline (156±50 vs 334±71 p<0.0001). Both at baseline and at T15 CAC correlated directly with age and with each other. In the 79% Cat-Prog+T15 was found, in the 10,7% of more than 1 grp of CAC. 71% of KTxps were Prog+. They had higher systolic blood pressure levels, with no difference in specific therapy, lower mean Hb and Ca levels. Mean Ca Levels resulted the only independent factor inversely related with Prog+ (p=0.04). During the 15 years of KTx 25% of KTx had a MACE. No impact for CACs was found in MACE.

Conclusions: To the best of our knowledge, our study is the first one to evaluate CACs in KTxps for such a long time. According to the preliminary data obtained: 1) the prevalence of CAC in KTxps is high, and is related to age; 2) CAC worsening was observed in a consistent part of the cohort and was related to different parameters, especially to Ca levels. Future researches, possibly involving a higher number of KTxps could explain better these findings and explore more deeply the relation of CACs with MACE in the long term.

SA-PO1068

Association Between Pretransplant Dialysis Modality and Long-Term Graft Outcomes

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Background: previous systemic reviews have shown that peritoneal dialysis (PD) is associated with substantial improvements in patient survival and delayed graft function compared with hemodialysis (HD) treatment as a pretransplant modality, the association between pretransplant dialysis modalities and posttransplant outcomes remains controversial.

Methods: We retrospectively collected records from 773 kidney transplant recipients between January 2008 and October 2021 in 2 transplant centers. We excluded recipients under the age of 18, 2nd or 3rd transplant recipients, and preemptive recipients. The final analysis included 558 kidney transplant recipients(fig. 1)We examined graft survival across pretransplant modality.

Results: 558 kidney transplant recipients were 47.5 years old and included 42% females and 28% diabetes. 407 recipients underwent HD, and 151 recipients underwent PD before transplantation. The overall graft survival between pretransplant HD and PD showed no statistical difference (P=0.197)(Fig. 2). pretransplant HD seemed to be favorable for graft survival over a long-term follow-up period of over 10 years.

Conclusions: Pretransplant modalities during the transition to a kidney transplant are not associated with graft survival.

Table 1. baseline characteristics of 558 KT recipients

	All	HD	PD	P value
Characteristics, N (%)	558	407	151	
Age	47.5±11.8	48±11.5	46±12.5	0.214
Female	236 (42)	167 (41)	69 (46)	0.322
DM	158 (28)	127 (31)	31 (21)	0.02
HBP	82 (15)	59 (15)	23 (15)	
HBsAg	40 (7)	33 (8)	7 (5)	0.249
CKD cause				0.148
DM	132 (24)	103 (25)	29 (19)	
Hypertension	82 (15)	59 (15)	23 (15)	
GN	136 (24)	91 (22)	45 (30)	
PCKD	24 (4)	20 (5)	4 (3)	
Others	13 (2)	11 (3)	2 (1)	
Unknown	164 (29)	116 (29)	48 (32)	
Relations				0.609
LD	197 (35)	141 (35)	56 (37)	
DD	359 (64)	264 (65)	95 (63)	
ABOi tranplant	38 (7)	30 (7)	8 (5)	0.183
Waiting time, years	4.5 (1.5, 7.4)	4.5 (1.3, 7.7)	4.4 (2.0, 6.8)	<0.001
Rejection episode	445 (80)	330 (81)	115 (76)	0.021

LD, living donor; DD, deceased donor

SA-PO1069

The Effect of Kidney Transplantation on Biventricular Structure and Function Evaluated by Transthoracic Echocardiography

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Background: Kidney transplant (KT) recipients experience a higher risk of cardiovascular disease outcomes when compared with the general population. Due to the increasing number of patients requiring a transplant, better identification of cardiac risk is required to prevent premature death with a functioning graft.

Methods: We performed a single-center prospective and longitudinal study that included all transplant-eligible patients (living or deceased donors) from January-May 2022. The candidates underwent pre-transplant transthoracic echocardiography (TE) as per institutional protocol and a second one a year later. We excluded patients who were lost to follow-up or suffered a cardiovascular event during the studied period. The most representative cardiovascular structure and function values were evaluated.

Results: Seventeen patients were included a mean age of 50 years and 64.7% were men. The median time spent on dialysis was 2.6 years, 64.7% were on hemodialysis and 29.4% on peritoneal dialysis. Reverse remodeling of the left ventricular was observed following the KT as the LV mass decreased from 101 g to 82 g (p = 0.01). End-diastolic volume decreased from 124 to 100 ml (p=0.022), end-systolic volume from 52 to 30 mL (p= 0.031), and ejection fraction increased from 57% to 61% (p=0.06). E/e' did not significantly change (9 vs 7.65 p= 0.14). Additionally, there were no statistically significant differences in left and right ventricle strain (18.5 vs 19.4 p=0.191 and 24 vs 24 p=0.55).

Conclusions: Reverse cardiac remodeling following the KT was observed as a reduction in left ventricle mass and improvement in ejection fraction, left and right ventricle strain did not change. Further description and understanding of cardiovascular function modification before and after KT is needed to improve graft and overall survival.

Variable	Baseline	12 months	p
Structure	-		
LV end diastolic diameter (mm)	46 (39-51.5)	42 (36-48)	0.102
LV end systolic diameter (mm)	28 (26-36)	25 (20.5-31.5)	0.055
Interventricular septum (mm)	12 (10-13.5)	11 (8.5-13.5)	0.309
Posterior wall thickness (mm)	11 (10-13)	9 (8-11.4)	0.025
LV mass (g)	101 (86.5-150)	83 (75.5-105.8)	0.01
RV diastolic diameter (mm)	33 (28.5-41)	31 (75.5-105.8)	0.248
LA volume (mL)	36 (23-53.3)	31 (26-37)	0.107
RA area (m2)	16.8 (11.3-20)	15 (12.2-17)	0.469
Left Ventricle Systolic Function	-		
End diastolic volume (mL)	124 (90.5-167.5)	100 (74.5-123)	0.022
End systolic volume (mL)	52 (35.5-67.5)	36 (28.5-58.5)	0.031
Strain	*-18.5 (-20.5 a -15.7	*-19.4 (-20.9 a -17.9)	0.191
EF (%)	57 (53-61)	61 (58-64.5)	0.066
Right Ventricle Systolic Function	-		
Right ventricular shortening fraction %	45 (41.5-52.5)	50 (40.5-54.5)	0.569
TAPSE	23 (20.5-23.5)	20 (19-23.5)	0.169
S' (cm/s)	12 (10-13)	11 (10-13)	0.505
Strain	*-24 (-28 a -22)	*-24 (-29 a -22)	0.551
Diastolic Function	-		
E/A	1.1 (0.73-1.38)	1.2 (0.75-1.44)	0.755
E/E'	9 (6.95-12.3)	7.65 (6-9.32)	0.14
Other			
Pulmonary systolic pressure (mmHg)	35.5 (21.7-46)	14 (17-32)	0.05

SA-PO1070

Association Between Clinical Atherosclerotic Cardiovascular Disease and Some Kidney Transplant Outcomes: A Retrospective Study

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Background: Atherosclerotic cardiovascular disease (ASCVD) is a common comorbidity in patients with end stage renal disease that eventually get a kidney transplant. This study seeks to explore the association between clinical ASCVD and specific kidney transplant outcomes.

Methods: This study used the 2010-2022 data from the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, waitlisted candidates and transplant recipients in the US submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractor. Independent variables in our study include history of angina/coronary artery disease, history of peripheral vascular disease, history of cerebrovascular disease. Kidney transplant outcomes in this study include acute graft rejection, delayed graft function (measured in this study as failure of creatinine decline by 25% or more in the first 24hrs) and graft failure. Chi square was used to explore the association between atherosclerotic cardiovascular disease and kidney transplant outcomes.

Results: There were 108,927 kidney transplant recipients. 8,146 (7.5%) patients had clinical atherosclerotic cardiovascular disease. 2.5% of patients with clinical ASCVD vs 2.2% of patients without clinical ASCVD developed acute graft rejection (P-value=0.0401). 61.7% of patients with clinical ASCVD vs 52.5% of patients without clinical ASCVD developed delayed graft function (P-value=<0.0001). 1.7% of patients with clinical ASCVD vs 1.4% of patients without clinical ASCVD developed graft failure (P=0.0091).

Conclusions: Our study has shown that pretransplant atherosclerotic cardiovascular disease is a risk factor for acute graft rejection, delayed graft function and graft failure. This finding highlights the importance of both primary and secondary prevention of atherosclerotic cardiovascular disease in chronic kidney disease patients.

SA-PO1071

The Impact of Recipient's Pre-Transplant Viral Status on Acute Kidney Transplant Rejection in the United States: A Retrospective Study

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Background: Acute graft rejection is a feared complication of kidney transplant and some studies have suggested that certain viral infections could be a contributor to this feared outcome. This study therefore set out to identify the impact of some viruses on acute kidney transplant rejection in the United States.

Methods: This study used the 2010-2022 data from the Scientific Registry of Transplant Recipients. This data system includes data on all donors, waitlisted candidates and transplant recipients in the US submitted by the members of the Organ Procurement and Transplantation Network. The study included patients aged 18 years or older who had kidney transplants in the United States. Independent variables include age group of recipients, recipient's gender, recipient's race, donor gender, donor race, donor type, previous transplant in recipient, viral detection (HBV, HCV, HIV) in recipient at transplant time, number of HLA mismatches and pre-transplant malignancy. The dependent variable was acute rejection between transplant and discharge. Univariate, bivariate (Chi-square and t-test) and multivariable logistic regression (stepwise selection with P-value for entry and stay of a variable put at <=0.05) analyses were done using SAS 9.4.

Results: There were 207,732 kidney transplants. On multivariable logistic regression that adjusted for significant variables on bivariate analysis (age group of recipients, recipient's race, previous transplant in recipient, number of HLA mismatches prior to transplant), transplant patients who were positive for HBV surface antigen had 57% (AOR: 95% CI 1.21-2.02) higher odds of developing acute rejection compared to those negative for the antigen. Those who had HCV detected at transplant time had 27% (AOR: 95% CI 1.07-1.49) higher odds of acute rejection compared to those who had no HCV detected. HIV positive patients had 107% (AOR: 95% CI 1.61-2.66) higher odds of developing acute rejection compared to those negative for HIV.

Conclusions: Our study has shown that viral infections (HBV, HCV, HIV) increase the risk of acute rejection in kidney transplants. These findings suggest that treating these viruses to non-detectable levels prior to transplant could reduce the risk of acute graft rejection.

SA-PO1072

Successful Kidney Donation After Gastric Bypass Surgery Using Individualized Stone Risk Assessment

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Background: The effects of increased prevalence of morbid obesity in the general population is reflected in the population presenting for living kidney donation as well. Bariatric surgery is the most successful and longest-lasting treatment for morbid obesity. Some centers may exclude donors who have undergone Roux en Y gastric bypass due to the risk of hyperoxaluria and risk of stone events post donor nephrectomy. We describe four living donor candidates who underwent evaluation at our kidney stone prevention program that allowed an individualized risk assessment to assess their candidacy keeping donor safety as a priority.

Methods: Retrospective review of electronic medical records was used to identify four living kidney donor (LKD) candidates with history of Roux en Y gastric bypass between 2012 and 2022. Patients submitted paired 24 hour blood and urine samples for metabolic evaluation. We compared the characteristics of the LKDs who went on to donate and the ones who were declined.

Results: Table 1a and 1b summarize the demographics and urinary metabolic parameters. Patient 1 went on to donate kidney as she did not have any hyperoxaluria. Patient 2 had hyperoxaluria on her initial testing, which normalized on repeat testing after counseling (Table 1c). She went on to successfully donate. Both patients 3 and 4 were declined as candidates for living kidney donation due to significant hyperoxaluria. The patients who were approved for donation were 10 years and 14 years out from gastric bypass surgery versus the ones who were declined who were 1 and 2.5 years out respectively.

Conclusions: Successful living kidney donation after bariatric surgery is possible with careful individualized evaluation of metabolic stone risk paramatersat an experienced stone center prior to approving their candidacy.

	Age	Sex	Race	BMI	Years from gastric bypass surgery	Kidney donation approved
Patient 1	55	F	W	26.4	10	YES
Patient 2	54	F	H	33.8	14	YES
Patient 3	63	F	W	32.5	1	NO
Patient 4	42	F	W	31.0	2.5	NO

	Patient 1	Patient 2	Patient 3	Patient 4
Urine volume (L)	1.0	2.2	3.0	1.0
Urine calcium (mg/day)	143	41	111	100
Urine oxalate (mg/day)	31	77	158	49
Urine citrate (mg/day)	1143	314	411	469
Urine sodium (mg/day)	127	175	292	190
Supersaturation calcium oxalate	7.5	3.1	8.3	7.7

	Patient 2 Initial collection	Patient 2 After dietary counseling
Urine volume (L)	2.2	2.3
Urine calcium (mg/day)	41	58
Urine oxalate (mg/day)	77	44
Urine citrate (mg/day)	314	202
Urine sodium (mg/day)	175	103
Supersaturation calcium oxalate	3.1	2.8

Table 1a. Basic demographics. Table 1B. Urine studies from the 4 patients. Table 1C. Comparison of pre-post counseling urine studies for patient 2.

SA-PO1073

The Efficacy and Safety of SGLT2 Inhibitors and GLP1 Receptor Agonists in Kidney Transplant Recipients

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) and glucagon-like peptide-1 receptor agonists (GLP1RA) decrease adverse cardiorenal outcomes in the general population. We aimed to evaluate the efficacy and safety of SGLT2i and GLP1RA monotherapy and combination therapy in kidney transplant recipients (KTR).

Methods: This was a retrospective cohort study of all adult KTR started on SGLT2i and/or GLP1RA between January 1, 2000 and December 31, 2021. Baseline characteristics, drug safety/tolerability, estimated glomerular filtration rate (eGFR), and cardiorenal outcomes were collected.

Results: Of 227 patients analyzed, 78 were on SGLT2i, 79 on GLP1RA and 70 on combination therapy. 120 patients had pretransplant diabetes (DM) (53.6%) and 103 had post-transplant DM (46.0%). Compared to the period before drug initiation, there were no differences in rates of CV events and graft failure with either monotherapy or combination therapy. After one month, SGLT2 inhibition resulted in a median eGFR decline of 6 ml/min/1.73m^2 (interquartile range -11 to 3.5) (**Figure 1**). Drug discontinuation was high, with 19.2% of SGLT2i users, 28.7% of GLP1RA and 41.4% on combination therapy stopping therapy – 'hospitalization' with SGLT2i and 'intolerance' with GLP1RA and combination therapy were the most frequent causes of discontinuation. However, compared to the period before drug initiation, rates of urinary tract infections, ketoacidosis, acute kidney injury and hepato-pancreato-biliary complications were not significantly different.

Conclusions: SGLT2i, GLP-1RA and combination therapy appear to be safe in KTR, though drug discontinuation is relatively common. The acute eGFR 'dip' observed with SGLT2 inhibition suggests tubular-glomerular mechanisms are intact in this unique population.

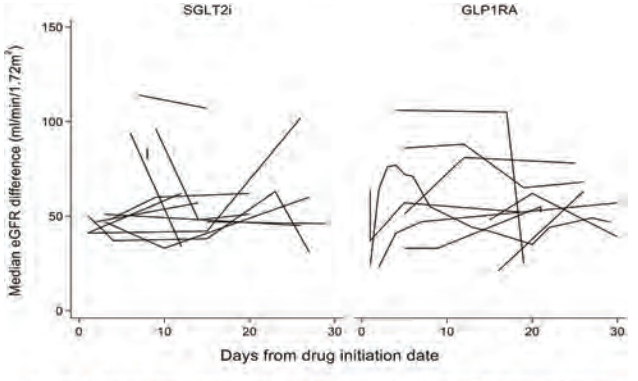

Figure 1: Individual patient trends in eGFR over 1 month after drug initiation

SA-PO1074

A Systematic Investigation on the Impact of Invasive Kidney Allograft Biopsy on Urinary Cell mRNA Profiles

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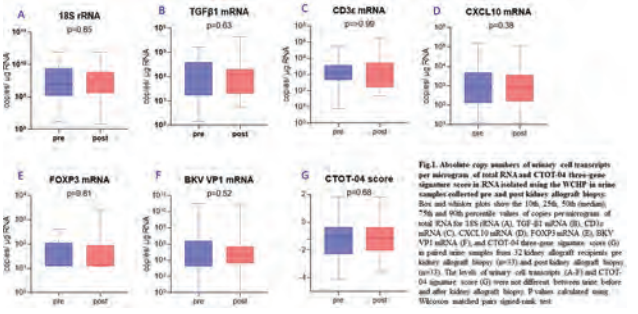
Background: Liquid biopsies offer an unprecedented window into intragraft events. It is preferred that biospecimens are collected prior to biopsy since mechanical injury from this invasive procedure may alter circulating levels of biomarkers of interest, (Kyeso Y et al. Transplantation Direct 2021). In the Clinical Trials in Organ Transplantation (CTOT)-04 study consisting of 485 kidney transplant recipients (KTR), 298 biopsy-matched urine specimens were used to develop and validate a urinary cell 3-gene signature consisting of 18S rRNA normalized CD3ε mRNA and CXCL10 mRNA (CTOT-04 signature) and all but 10 specimens were collected at the time of biopsy or ≤3 days prior (Suthanthiran M et al. N Engl J Med 2013). There were no paired pre and post biopsy specimens to investigate the impact of kidney allograft biopsy on absolute copy numbers of the transcripts or CTOT-04 signature. The current study was designed to fill this gap in knowledge.

Methods: We collected urine from KTR before and after kidney allograft biopsy, both ≤6 hours of biopsy. We used the Weill Cornell Hybrid Protocol consisting of urine filtration to collect eluate with stable RNA and mRNA enrichment during RNA isolation using a silica-membrane-based cartridge (Salinas T et al. J Immunol Methods 2022). We measured absolute copy numbers of CD3ε mRNA, CXCL10 mRNA, and 18S rRNA (CTOT-04 signature), and mRNAs for TGFβ1, FOXP3, and BKV VP1 in urine samples collected pre and post kidney allograft biopsy.

Results: Box and whisker plots show that the various urinary cell mRNA levels and CTOT-04 signature score are not different between urine samples collected before and urine samples collected after kidney allograft biopsy (**Fig. 1 A-G**, All P values >0.05, Wilcoxon matched pairs signed-rank test).

Conclusions: Urinary cell mRNA levels and CTOT-04 signature score are not impacted by the kidney allograft biopsy and yield indistinguishable results irrespective of whether the urine was collected prior to or after the invasive kidney allograft biopsy procedure.

Funding: Other NIH Support - NIH/NCATS Grant #2KL2TR2385



SA-PO1075

Effect of Different Treatment Regimens on Kidney Graft Function and Mortality in Patients with a Diagnosis of Antibody-Mediated Rejection

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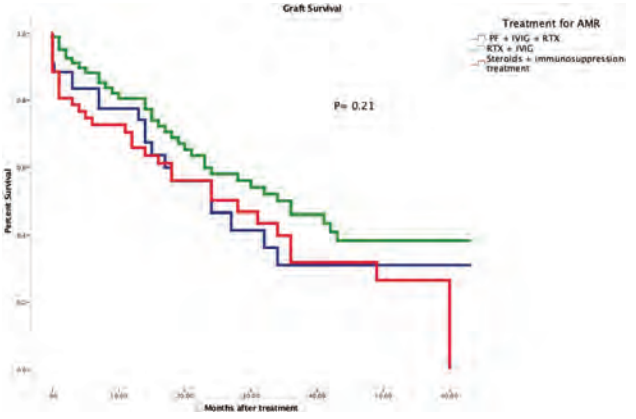
Background: The optimal treatment for Antibody mediated rejection (AMR) remains uncertain, and its presence causes up to 60% of kidney grafts loss.

Methods: A retrospective cohort from May-2016 to June 2022, that included 176 patients ≥18 years old, hospitalized with graft dysfunction and histopathological diagnosis of AMR to receive treatment. Were categorized into 3 groups; 1. Plasmapheresis (PF) + Intravenous immunoglobulin (IVIG), 2. IVIG + Rituximab (RTX) 3. Steroids and immunosuppression treatment optimization.

Results: On average, 63% of patients were men, and a majority were transplanted with a living donor kidney (89%), showing a median of age 32 ± 9; baseline serum creatinine (CrS) was 1.15 and during the rejection, 2.75 mg/dL; timing of biopsy 6 ± 5 years; C4d positive (68%) comparing groups of treatments there were no significant difference by CrS at the end of the follow up, episodes of infections was 27%, 20% and 10% (P=0.61), mortality was 6.8%, 2.5% and 5.8% each group (P=0.47).

Conclusions: There was no significant difference in graft function and mortality between treatment groups, but in a logistic regression analysis, predictive variables of poor graft prognosis were: CrS greater than 2.5 mg/dl at the beginning of treatment, using steroids and immunosuppression optimization treatment; greater chronicity and being younger at the time of diagnosis.

Table 1: Results N:176	Plasmapheresis + IVIG + Rituximab (44)	IVIG + Rituximab (80)	Steroids + immunosuppression treatment optimization (52)	p Value
Final serum Creatinine (mg/dL)	5.10	4.6	6.3	0.04
Functional graft mg/dL (%)	2.0 (50)	2.41 (56)	2.45 (42)	0.43
Lost graft mg/dL (%)	8.49 (50)	7.39 (44)	9.27 (58)	0.87
Infections N (%)	12 (27)	16 (20)	3 (10)	0.61
Death from all causes N (%)	3 (6.8)	2 (2.5)	3 (5.8)	0.47
Linear proportion table X^2 3.76 P < 0.0001				
Variable	RR	CI	p Value	
Creatinine > 2.5 mg/dl	1.95	[1.16-3.289]	0.01	
Steroids + immunosuppression treatment optimization	1.60	[1.10-2.31]	0.01	
GBM Double contours > 2	0.36	[0.23-0.62]	0.00	
Age	0.95	[0.92-0.98]	0.00	
Covariate: pertubular capilaritis, cAd, creatinine > 2.5 mg/dl , steroids + immunosuppression treatment optimization , GBM double contours = 2 , interstitial fibrosis tubular atrophy, age				



SA-PO1076

Relationship of Serum Procalcitonin (PCT) Levels with Kidney Graft Function in the Immediate Post-transplantation Period in Kidney Transplant Recipients

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Background: Renal function is one of the major determinants of PCT levels, which is why its relationship as a marker of acute kidney injury not associated with sepsis has previously been described. In kidney transplantation (KT) the persistently high levels of PCT seem to show a relationship with the function of the kidney graft because its levels increase after the elevation of other inflammatory cytokines in events of exaggerated inflammatory response and it is poorly cleared in patients with delayed graft function. This study seeks to find the relationship of serum PCT levels as well as their association with kidney graft function in the immediate period.

Methods: We conducted a retrospective cohort study from February 2016 to May 2022 of Nephrology and Transplant patients. A number of 82 KT recipient patients with PCT determination in the immediate postransplant period were obtained. Statistical analysis: Descriptive statistics, interferential statistics were performed by comparing groups and intragroup for categorical variables with x2 and Fisher's exact test; for non-parametric continuous variables Mann-Whitney U.

Results: They were classified as normal graft function (NGF), slow graft function (SGF) and delayed graft function (DGF). Within the baseline characteristics, no statistically significant differences were found for age, type of transplant, leukocytes, and hemoglobin at admission. Finding that a level > 3 ng/dl of procalcitonin conferred a greater risk of DGF, as well as higher levels in this group compared to patients with NGF.

Conclusions: Procalcitonin is an early marker to identify patients who develop delayed kidney graft function.

Characteristics

Variable	NGF n = 23	DGF n = 45	SGF n = 14	P value
Age (years)	37 ± 12	43 ± 15	46 ± 16	0.155
Male (%)	10 (43)	26	13	0.310
Deceased Donor (%)	16	35	12	0.556
Cold ischemia (Hrs)	11.5 (1-14.25)	16 (12-18)	13.25 (10.25-15.25)	0.0145
Leukocytes (miles/mm3)	7.5 (5.5-8.6)	7.9 (5.8-12.3)	8.6 (4.7-13.1)	0.562
Procalcitonin (ng/ml)	1.41 (0.23 – 3.97)	5.6 (0.79 – 29)	2.55 (0.37 – 6.77)	0.0230
PCT > 3 ng/dL	6	26	4	0.0203

NGF: Normal Graft Function; DGF: Delayed Graft Function; SGF: Slow Graft Function; Hrs: Hours; Min: Minutes.

SA-PO1077

Characteristics of Renal Allograft Survivors of More than 15 Years: A Single-Center Experience

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Background: We studied the characteristics and the predictors of graft and patient survival in Bahraini renal transplant recipients with an allograft that functioned for more than 15 years.

Methods: Out of 185, underwent renal transplantation between 1982 and 2007, 52 patients (28.1%) maintained functioning allografts for more than 15 years (range 15-41 years). Characteristics of the surviving patients, data on graft survival, and determinants of outcome were obtained by reviewing all medical records.

Results: The mean age at time of renal transplantation was 43.1 ± 11.3 years and 75% were males. The cause of end-stage renal disease was diabetic nephropathy in 28.5% and 86% received dialysis therapy before transplantation. The source of the graft in 39 (75%) recipients was from living related donors with a mean age of 31.7 ± 6.6 years, and it was the first graft in 50 recipients. The primary immunosuppression regimen was cyclosporine (CsA) based in 29 patients (29.1%), tacrolimus (Tac) based in 21 patients (40.4%) while three patients (5.6%) received steroids and azathioprine only. Induction therapy was administered to 58 patients. Acute rejection episodes occurred in 10 patients (19.2%), of whom two experienced two episodes. During the last follow-up, the mean serum creatinine was 123 ±36 µmol/L. Two patient were successfully treated for Covid-19 viral infection. A history of hypertension was encountered in 66% and posttransplant diabetes mellitus in 21%. We compared the graft functioning group with the graft failure group and found that the independent determinants of long-term graft survival included age of the recipient, time of late acute rejection episodes, use of induction therapy, histopathologic findings of chronic allograft damage, and serum creatinine at one year.

Conclusions: We conclude that renal transplantation in its earliest years and despite the associated numerous complications has provided a fifteen-year or more of near-normal life to patients with end-stage renal disease.

SA-PO1078

Navigating the Crossroads: Cytomegalovirus (CMV), Neutropenia, and Kidney Transplant Survival in High-Risk Patients

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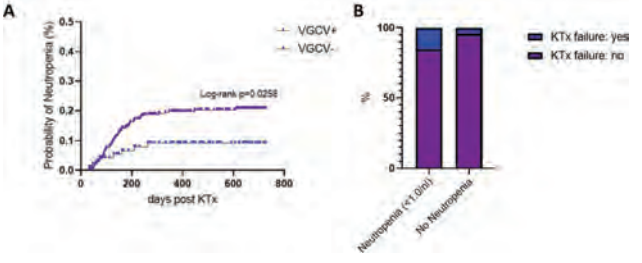
Background: Cytomegalovirus (CMV) infections constitute a significant condition in kidney transplant (KT) recipients with a major impact on morbidity, mortality and graft survival, with CMV negative recipients (R-) transplanted from a CMV positive donor (D+) at highest risk. The prevention of CMV disease in KT recipients mainly relies on antiviral prophylaxis and preemptive therapy with virostatics, e.g., valganciclovir (VGCV). Although these strategies proved to be efficient, their use is limited due to substance related toxicities. This study aims to evaluate the effects of VGCV administration on the development of neutropenia and graft survival in CMV high risk KT.

Methods: A retrospective data analysis was used to analyze KT recipients with CMV high risk constellation, transplanted at Charité Berlin (Germany) between 2003-2019. The incidence of neutropenia (<1/nl), severe neutropenia (<0.5/nl) and KT survival within the first 2 years after KT was assessed for recipients with and without a VGCV prophylaxis during day 0-200.

Results: 556 patients with CMV high risk constellation received a KT, including 437 (78.6%) and 119 (22.4%) with and without prophylactic VGCV administration, respectively. The likelihood of developing (severe) neutropenia was elevated in KT recipients with VGCV administration (log-rank 0.0289, **Fig.A**). The time to onset of neutropenia was 145±96 days for recipients with VGCV prophylaxis and 122±84 days for those without VGCV (p=0.062). The development of neutropenia was associated with an increased risk of graft failure within the first 2 years (p<0.01, **Fig.B**). However, VGCV administration was not linked to reduced graft survival (p=0.482).

Conclusions: Our results show that VGCV prophylaxis in CMV high-risk KT recipients is linked to an increased likelihood of developing neutropenia. However, the timing of the onset of neutropenia is not significantly altered by VGCV. Given the potential negative impact of neutropenia on KT outcomes, it is crucial to closely monitor neutropenic KT recipients. Further research may elucidate if targeting neutropenia could improve KT outcomes.

Funding: Commercial Support - MSD



SA-PO1079

Time-to-Graft Loss Prediction in Kidney Transplant Recipients

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Background: Several predictions models have been proposed which estimate graft failure risk in kidney transplant recipients (KTR). However, the risk resulting from the model is challenging to interpret. Therefore, this study aims to propose a machine learning model which predicts time to kidney graft loss.

Methods: Data were derived from the transplant registry of the University Medical Center Groningen, including KTR transplanted after 1-1-1995. Data for model training was obtained 1 year after transplantation. KTR with missing data <5 years after transplantation were excluded. Graft loss was defined as death or graft failure. To predict the time to graft loss, extreme gradient boosting (XGBoost) with the accelerated failure time objective was utilized. The model was trained using a bootstrap aggregating (bagging) approach. Variables included in the model were selected by feature selection. The performance of the machine learning model was internally evaluated using the C-index on 20% of the dataset which was not used for training.

Results: From the 2195 included patients (age 52 [41-61] years, 42% female), 1225 (56%) developed graft loss during median follow-up of 8.1 [5.1-13.0] years. The final model was trained using 45 commonly determined clinical variables, including eGFR, hemoglobin, age, and several feature-engineered variables. Feature engineered variables are new variables created from existing ones to improve the performance of the model. Hematocrit*eGFR, recipient age and gamma-glutamyltransferase were identified as the most important variables driving time to kidney graft loss. Internal validation showed a C-index of 0.74.

Conclusions: The machine learning model developed predicts time to graft loss with a reasonable accuracy.

SA-PO1080

Association Between Early State of Volume Overload with Delayed Graft Function in Kidney Transplantation

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Background: Delayed graft function (DGF) following kidney transplantation (KT) is a common problem and has been associated with decreased graft survival and increased risk of acute rejection. One of the factors that has been poorly studied so far is the state of volume overload as a risk factor for DGF. The aim is to associate the state of volume overload estimated by the daily accumulated fluid balance and measured through bioimpedance vectors, ultrasonographic parameters, serum B-type natriuretic peptide (sBNP), and Ca-125 with the development of DGF.

Methods: All patients over 18 years undergoing KT were included. Fluid balance was recorded, sBNP and Ca-125 were measured. Electrical bioimpedance and ultrasound measurements were also performed such as diameter of the inferior vena cava (IVC) and the portal vein pulsatility fraction (PVPF). Measurements were taken before KT and then every 24 hours for 3 days after KT. The primary outcome was the development of DGF, defined as the need for renal replacement therapy within the first 7 days post-transplantation.

Results: A total of 34 patients with KT were included, with an average age of 31 (26-42) years, and the main type of renal transplant was deceased donor (68%). Eight patients (23.5%) developed DGF. Analysis of the volume status revealed that the accumulated balance at 72 h was -79.7 mL (-3648 to -1875 mL) in the non-DGF group and 5596 mL (5126 to 7232 mL) in those who developed DGF (p<0.001). Pretransplant sBNP levels were 100.1 pg/mL (38-248) without DGF vs 525 pg/mL (74-1815) with DGF; p=0.045. Pretransplant Ca-125 levels were 12.1 U/mL (7.9-19) without DGF vs 10.1 U/mL (9-13) with DGF; p=0.92. Pretransplant IVC diameter was 1.6 cm (1.4-1.7) without DGF vs 2.3 cm (range 1.7-2.4) with DGF; p=0.1. Pretransplant PVPF was 23% (17-31) without DGF vs 37% (25-71) with DGF; p=0.09. Pretransplant total body water was 35.8 L (32.1-38.6) without DGF vs 39.5 L (35.9-42.7) with DGF; p=0.31. Univariate analysis revealed that only pretransplant BNP levels were associated with the development of DGF (OR: 1.002, 95% CI:1.001-1.003; p=0.04).

Conclusions: Volume overload, estimated by accumulated fluid balance, was associated with the development of DGF. However, the use of different volume status biomarkers only revealed that sBNP at baseline were associated with the development of DGF.

SA-PO1081

Drug-Drug Interaction of Potassium Competitive Acid Blocker with Tacrolimus and Mycophenolate in Kidney Transplant Recipients: A Randomized Controlled Trial Using Smart Clinical Trial Platform

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Background: Potassium competitive acid blocker (P-CAB) is a newly developed gastric acid inhibitor exhibiting faster action and lower drug toxicity than proton pump inhibitor (PPI). However, the drug-drug interaction of P-CAB with tacrolimus and mycophenolate is not investigated in kidney transplant recipients (KTRs). The study aimed to compare the changes in the blood concentration of immunosuppressants after the administration of P-CAB.

Methods: A total of 62 KTRs were randomized to either P-CAB (Tegoprazan®) or PPI group. A smart clinical trial platform monitored the enrolled patients with remote monitoring and safety management systems. Remote monitoring system transmitted data about adherence to the study drug, blood pressure, body temperature, and electrocardiogram. Questionnaires for general and gastrointestinal (GI) symptoms were surveyed using a self-developed app installed on the patient's phone. One non-face-to-face video visit was scheduled during the study period. Trough levels of tacrolimus and mycophenolate were checked monthly for 3 months.

Results: Baseline characteristics including trough levels did not differ between groups. The adherence to the study medication was 100% in both groups. A total of 13,726 biometric information and 5,031 questionnaire answers were collected. We conducted 5,704 feedback messages and 56 non-face-to-face video visits. Mean trough levels of tacrolimus and mycophenolate did not differ between P-CAB and PPI groups at 3 months (5.5 ± 2.5 vs. 5.8 ± 3.8 ng/dL, P = 0.50 and 2.7 ± 2.0 vs. 2.6 ± 2.0 ng/dL, P = 0.66, respectively). The intragroup difference of the trough levels between baseline and 3 months was not significant in both groups. The average questionnaire scores of GI symptoms were comparable between groups. The vital signs and allograft function maintained stably without significant difference during the study period.

Conclusions: P-CAB does not affect the serum trough levels of tacrolimus and mycophenolate in KTRs. P-CAB showed a similar effect on the patient-reported GI symptoms compared to PPI. Our smart clinical trial system with non-face-to-face video visits demonstrated the efficacy and safety in performing randomized trials.

SA-PO1082

Use of an LCP Tacrolimus (LCPT) in Kidney Transplantation: A Delphi Consensus Survey of Expert Clinicians

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Background: LCPT (Envarsus XR®) is a common once-daily, extended-release oral tacrolimus formulation used in kidney transplantation. Variations in real-world use mean uncertainty remains on how best to use LCPT in kidney transplantation in de novo and conversion populations. The objective of this study was to address the gaps in published data by developing consensus statements on the use of LCPT in kidney transplantation using the Delphi process with a panel of expert clinicians.

Methods: A panel of 12 clinicians with expertise in nephrology and kidney transplantation reviewed available clinical evidence on LCPT. The Delphi panel survey consisted of three rounds of an online survey. Consensus was achieved when ≥75% agreed strongly or with reservation to a statement.

Results: Twenty-three statements were evaluated: 14 on de novo and nine on general or conversion use. After two rounds, consensus was achieved for 20 statements (Figure 1). De novo, LCPT was recognized as a first-line option based on its safety and efficacy compared to immediate-release tacrolimus. In a conversion setting, full consensus was achieved for converting to LCPT to address neurological side effects related to immediate-release tacrolimus and for the time required (~7 days) for steady state LCPT trough levels to be reached.

Conclusions: The consensus statements generated in this study provide a real-world guide to using LCPT in kidney transplantation, especially in a de novo setting, for which guidance is currently lacking.

Funding: Commercial Support - Veloxis, Inc.

Final Recommendation	Consensus
De novo setting	
In the de novo setting, Envarsus XR® can be used as first-line therapy considering its efficacy and safety are equivalent to BID tacrolimus. A. Envarsus XR® has a similar efficacy profile as tacrolimus IR B. Envarsus XR® has a similar safety profile as tacrolimus IR	92%
Compared to twice-daily tacrolimus... When considering safety and efficacy, Envarsus XR® is preferred as first-line therapy for African American patient population in the de novo setting.	83%
Compared to twice-daily tacrolimus... When considering safety and efficacy, Envarsus XR® is preferred as first-line therapy in known rapid metabolizers in the de novo setting.	83%
In the de novo setting, the first assessment of trough levels of Envarsus XR® can be after the third dose although steady state is not expected until after 7 days on a stable dose.	92%
In the de novo setting, the Envarsus XR® dosing should begin with 0.14 mg/kg/day and should be calculated for ideal body weight in the setting of obesity, except in the following scenarios: A. The initial dosing of Envarsus XR® may be reduced in the setting of depleting antibody therapy when using induction therapy B. The dose may be increased in known rapid metabolizers. C. The dose may be adjusted in the presence of known drug interactions that influence tacrolimus metabolism.	92%
In the de novo setting, ideal body weight should be used as the preferred initial dosing weight for Envarsus XR® in obese recipients.	100%
In the de novo setting, Envarsus XR® should be initiated on the morning of POD1 for all kidney transplant recipients, regardless of initial kidney function.	83%
In the de novo setting, initial dosing of Envarsus XR® can be reduced in the setting of depleting antibody therapy when using induction therapy.	83%
In the de novo setting, initial dosing of Envarsus XR® can be adjusted in patients for whom the risk of supratherapeutic levels outweighs the benefit of rapid achievement of therapeutic levels.	100%
During the first week post-transplant the dose of Envarsus XR® should only be adjusted in circumstances of a supratherapeutic level or circumstances of a significantly subtherapeutic trough level suggestive of rapid metabolism (e.g., tacrolimus trough <3 ng/ml after postoperative day 3).	75%
Conversion to Envarsus XR® is recommended to address neurological side-effects related to BID Tacrolimus.	100%
Steady state is achieved after Envarsus XR® dose 7 and therefore, on a stable dose, dose adjustments can be made per clinical practice protocols following the seventh dose.	75%
Further evidence of clinical long-term outcomes (graft survival, renal function) would help support the use of Envarsus XR® in current clinical practice, in both the de novo setting and conversion setting	92%
Conversion setting	
Patients should consistently take Envarsus XR® on an empty stomach, rather than consistently with or without food.	92%
Trough level assessment of Envarsus XR® should take into account the time to achieve steady state (approximately 7 days).	100%
When available, pharmacogenomic screening is recommended for initial dosing considerations for Envarsus XR®.	83%
Additional cost and formulary considerations pose barriers to the use of Envarsus XR® as first line therapy in the de novo setting.	75%
Additional costs and staff time required pose barriers to conversion to Envarsus XR®.	92%
Intrapatient variability has been shown with tacrolimus preparations. There are no specific recommendations for utilization of Envarsus XR® related to intrapatient variability.	83%
Further evidence of clinical long-term outcomes (graft survival, renal function) would help support the use of Envarsus XR® in current clinical practice, in both the de novo setting and conversion setting.	92%

SA-PO1083

Effect of Prolonged-Release vs. Immediate-Release Tacrolimus on Neurocognition in Kidney Transplant Recipients: A Pilot Randomized Controlled Trial (RCT)

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Background: Tacrolimus is known to cause neurological side effects and elderly individuals seem particularly vulnerable. It is unknown if the prolonged-release (PR) tacrolimus (Envarsus XR) formulation minimizes neurocognitive side effects compared to immediate release (IR) tacrolimus due to lower peak serum levels. We aimed to compare the neurocognitive side effects of PR and IR tacrolimus in elderly kidney transplant recipients within the first months post-transplantation.

Methods: In this single center, prospective, open-label, randomized trial, 64 kidney transplant recipients aged 60 or above were randomized to PR tacrolimus or IR tacrolimus between 4 and 8 weeks post-transplantation and followed for 6 weeks. Neurocognitive performance was assessed by the Montreal Cognitive Assessment (MOCA) and Digit Symbol Substitution Test (DSST). Secondary outcomes of tremor and quality of life were assessed through the Quality of Life in Essential Tremor Questionnaire (QUEST) and Organ Transplant Symptom and Wellbeing Instrument (OTSWI).

Results: 32 patients were randomized to the IR tacrolimus arm and 31 into the PR tacrolimus arm. Mean age was 69 in both arms and 37% were women. Table 1 shows the assessment scores for the primary and secondary outcomes. There was no statistically significant difference between groups in the change in MOCA or DSST scores from baseline to 6 weeks or in tremor or quality of life measures.

Conclusions: Although prior studies indicated improvement in neurological side effects in PR tacrolimus compared with IR tacrolimus, the improvement does not appear to extend to neurocognitive side effects as assessed by the MOCA or DSST tests in this cohort.

Funding: Commercial Support - Veloxis Pharmaceuticals, Inc

	IR Tacrolimus (n=32)	ER Tacrolimus (n= 31)	p
Primary Outcomes			
Baseline MOCA score	23 (3.8)	22 (5.3)	
Baseline corrected MOCA score	23.3 (3.7)	22 (7)	
6-week MOCA score	22.8 (7)	22 (6.3)	
6-week corrected MOCA score	24.7 (3.6)	23 (5)	
MOCA (corrected) score difference	1.2 (2.1)	0.2 (2.9)	0.08
Baseline DSST score	35.1 (13)	32.5 (14)	
6-week DSST score	35.7 (11.5)	34.3 (16)	
DSST score difference	1.0 (7.8)	1.26 (7.5)	0.96
Secondary Outcomes			
Baseline Quest Summary Score	8.2 (14.4)	7.7 (12.3)	
6-week Quest Summary Score	7.4 (11.4)	4.3 (5.8)	
Quest Summary Score difference	-1.0 (10.4)	-2.9 (10.0)	0.15
Baseline OTSWI	25.5 (18.3)	25 (18)	
6 Week OTSWI	23.5 (19.2)	19 (13)	
OTSWI Score difference	-2.1 (9.7)	-6.2 (12.0)	0.1

Table 1. Neurocognitive Testing and Tremor Results. *P*-values were computed from ANCOVA adjusting baseline value and without adjusting for multiplicity. Values shown are mean and (standard deviation).

SA-PO1084

The Association Between 25-Hydroxyvitamin D and Recurrence of Glomerulonephritis in Kidney Transplant Recipients

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Background: Disease recurrence contributes significantly to allograft failure in kidney transplant recipients (KTR) with kidney failure due to glomerulonephritis (GN). Accumulating evidence has revealed a role of vitamin D in innate and adaptive immunity. While vitamin D deficiency is common among KTRs, the association between 25-hydroxyvitamin D [25(OH)D] and GN recurrence in KTRs remains unclear.

Methods: Data from KTRs with GN (focal segmental glomerulosclerosis, IgA nephropathy, membranous nephropathy, membranoproliferative GN, or lupus nephritis) transplanted at our center from 2000-2019 were analyzed. All post-transplant serum 25(OH)D measurements were included as a time-varying covariate. Disease recurrence was identified via allograft biopsy following abnormal clinical signs or laboratory measures. Survival models considered other causes of allograft loss, including death, as competing risk events. Disease recurrence within one year after each 25(OH)D measurement was considered as the event of interest. Models were adjusted for age at transplant, sex, race, donor status, prior transplant, and time of 25(OH)D measurement.

Results: A total of 63 cases of GN recurrence (median: 4.6 years) were identified in 823 KTRs followed for a median of 7.6 years after transplant. Each 1 ng/ml lower serum 25(OH)D was associated with a 5% higher incidence of recurrence (adjusted hazard ratio [aHR] = 1.05; 95% CI, 1.02-1.07). Vitamin D deficiency (≤ 20 ng/ml) was associated with a 3.04-fold (aHR = 3.04; 95% CI, 1.60-5.78) higher incidence of recurrence compared with vitamin D sufficiency (≥ 30 ng/ml). Similar results were found after further adjusting for concurrent urinary protein:creatinine ratio and excluding events within 30 days after 25(OH)D measurement (Table).

Conclusions: Vitamin D deficiency is associated with a higher incidence of GN recurrence in KTRs independently of proteinuria. Additional research is needed to explore the utility of vitamin D surveillance and management in KTRs with GN.

Models	Sample size		Serum 25(OH)D	Adjusted hazard ratio (95% CI)	P-value
Model A [a]	823 KTRs (63 events)	Continuous	Per ng/ml decrease	1.05 (1.02, 1.07)	<0.01
		Categories	Sufficiency (≥ 30 ng/ml)	Reference	
			Insufficiency (20 – 29 ng/ml)	1.26 (0.68, 2.36)	0.46
			Deficiency (≤ 20ng/ml)	3.04 (1.60, 5.78)	<0.01
Model B [b]	679 KTRs (51 events)	Continuous	Per ng/ml decrease	1.05 (1.02, 1.08)	<0.01
		Categories	Sufficiency (≥ 30 ng/ml)	Reference	
			Insufficiency (20 – 29 ng/ml)	1.07 (0.53, 2.14)	0.86
			Deficiency (≤ 20ng/ml)	3.33 (1.54, 6.34)	<0.01
Model C [c]	672 KTRs (39 events)	Continuous	Per ng/ml decrease	1.04 (1.01, 1.07)	0.02
		Categories	Sufficiency (≥ 30 ng/ml)	Reference	
			Insufficiency (20 – 29 ng/ml)	0.60 (0.34, 1.86)	0.60
			Deficiency (≤ 20ng/ml)	2.54 (1.14, 5.66)	0.02

25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; KTR, kidney transplant recipients
a. Adjust for age at transplant, sex, race, donor status, prior transplant, and time of 25(OH)D measurement.
b. Adjust for age at transplant, sex, race, donor status, prior transplant, time of 25(OH)D measurement, and urinary protein:creatinine ratio within one week of 25(OH)D measurement.
c. Adjust for age at transplant, sex, race, donor status, prior transplant, time of 25(OH)D measurement, and urinary protein:creatinine ratio within one week of 25(OH)D measurement. Events within 30 days after 25(OH)D measurement were excluded.

Table. Association between serum 25(OH)D and GN recurrence.

SA-PO1085

Cryptococcosis in Kidney Transplant Recipients

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Background: Cryptococcosis is the third most common invasive fungal infection in solid organ transplant recipients. Clinical management and disease prognosis have already been previously scrutinized in this setting but had yet to be investigated specifically in kidney transplant recipients(KTr).

Methods: We carried out a cohort study of patients diagnosed with cryptococcosis after KT in France. Cases were matched with controls derived from a multicenter KT database. Our main objective was to describe course of graft function and patient survival. Secondary endpoints consisted in investigating practices pertaining to immunosuppressive treatment adjustments, identifying risk factors. Multivariable analysis was performed using conditional logistic regression to identify risk factors for cryptococcosis.

Results: Eighty-eight patients were included, matched with 79 controls. During induction treatment of cryptococcosis, 37.5% of patients presented with acute kidney injury (AKI) with 13.3% warranting renal replacement therapy. 35.5% of AKI were caused by drug toxicity. 34% of the patients experienced 1 side effect :amphotericin B-related nephrotoxicity predominated (39%) and was characterized by AKI in every case. All surviving patients were exposed to azole treatment. Of these, 41.8% experienced an overdose of tacrolimus, half of which were complicated by AKI. Twelve months after diagnosis of cryptococcosis or equivalent period for controls, 22.4% of KTr experienced loss of graft function compared with 1.4% for control KTr ($p<0.001$). In 61.4% of patients on mycofenolate mofetil, drug was stopped whereas it was continued at unchanged doses in 12.3%. Dose of calcineurin inhibitors was not modified in 42.4% and reduced in 37.9% Upon multivariable analysis, patient's age (OR 1.04 p=0.004) and history of rejection (OR 2.32 p=0.04) were significantly associated with the development of cryptococcosis.

Conclusions: Cryptococcosis is associated with a highly impact on overall and kidney graft survival in KTr. Risk of acute graft dysfunction followed a threefold temporal sequence characterized by amphotericin-related tubular injury, tacrolimus overdose due to fluconazole/tacrolimus interaction through CYP competition and acute graft rejection in the setting of immunosuppression tapering.

Funding: Clinical Revenue Support

SA-PO1086

Chronic Lymphocytic Leukemia in Solid-Organ Transplant Recipients: A Single-Center Experience

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Background: To date, only two case series on chronic lymphocytic leukemia (CLL) in solid-organ transplants (SOT) has been published which showed an increased risk for severe infections and mortality. The aim of our study was to add to the limited literature on this topic, by evaluating the overall safety of transplanting such patients.

Methods: A 10 year retrospective chart review was performed to identify patients with a diagnosis of CLL who had undergone SOT at a large transplant center. Post-transplant outcomes including infectious complications, graft loss, and mortality were reviewed.

Results: A total of 10 CLL patients were studied: 5 had a CLL diagnosis pre-SOT, and 5 were diagnosed with CLL post-SOT (table 1). All kidney transplant recipients received anti-thymocyte globulin for induction, while liver transplant recipients received either Basiliximab or steroids. Maintenance immunosuppression (IS) therapy amongst the SOT recipients was similar, with 8 out of 10 patients receiving a calcineurin-inhibitor and mycophenolate derivative. Average follow up for pre-SOT CLL patients was 2.9 years (min 1, max 6) with 1 out of 2 deaths attributed to an infectious complication (COVID). Post-SOT CLL patients had a mean of 9 years between transplantation and CLL diagnosis. On an average follow up of 2.8 (min 0, max 7) years after CLL diagnosis, 3 out of 5 post-SOT CLL patients had death as an outcome.

Conclusions: Short-term outcomes in SOT recipients with a diagnosis of CLL prior to transplantation appear acceptable. However, SOT recipients who developed CLL post-transplantation seem to have an increased mortality risk. Infectious complications are a known cause for increased morbidity and mortality in CLL patients. As such, reduction in maintenance IS therapy in patients who are years out from transplantation may allow for improved outcomes.

Outcomes of patients with CLL diagnosis

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5	Patient 6	Patient 7	Patient 8	Patient 9	Patient 10
Type of transplant	Living kidney	Living kidney	DBD kidney	DCD liver	DBD liver	DBD kidney-pancreas	DBD kidney-pancreas	Living kidney	DBD liver	DBD liver
Demographics	52 y.o., male, white	63 y.o., male, white	71 y.o., female, white	66 y.o., male, white	59 y.o., female, white	37 y.o., male, white	59 y.o., male, white	42 y.o., female, black	64 y.o., male, black	63 y.o., female, white
Years from CLL diagnosis to transplant (if pre-SOT)	0	5	17	3	4	N/A	N/A	N/A	N/A	N/A
Years from transplant to CLL diagnosis (if post-SOT)	N/A	N/A	N/A	N/A	N/A	25	2	2	7	9
Years since transplant	6	4	1.5	2	1	27	9	6	7	10
Infectious complications	COVID pneumonia	No	Septic arthritis, recurrent UTIs	No	CMV viremia, COVID, chronic foot wound	No	Sepsis, C. diff colitis, recurrent UTIs	Sepsis, C. diff colitis, recurrent UTIs	No	Sepsis due to strep bacteremia
Death-censored graft loss	No	No	No	No	No	No	Yes, pancreas only	Yes	No	No
Death (cause)	Yes (COVID)	No	Yes (PEA arrest)	No	No	Yes (malignancy	No	No	Yes (unknown)	Yes (sepsis)

SA-PO1087

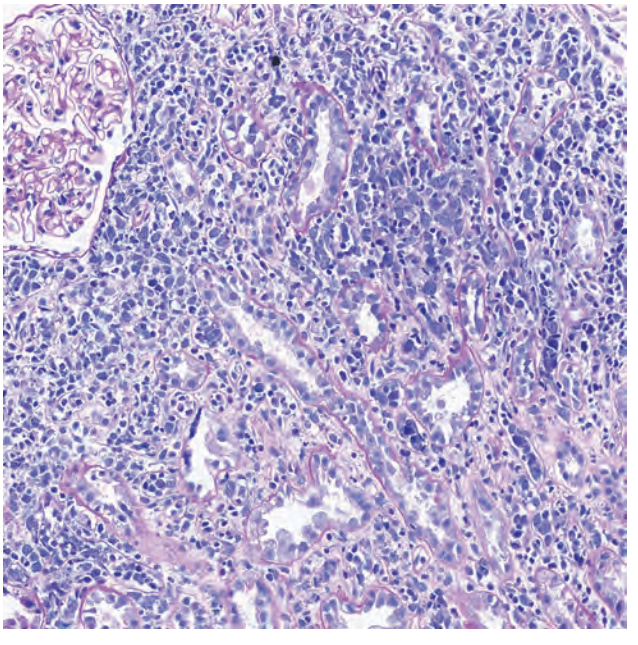
Donor-Derived Large B-Cell Lymphoma After SPK

Akshay Athreya, Gaurav Gupta, Ambreen Azhar, Layla Kamal, Selvaraj Muthusamy, Muhammad I. Saeed, Aamir Khan. *Virginia Commonwealth University, Richmond, VA.*

Introduction: Absolute risk of lymphoma transmission with SOT is unknown. In this unique case, DLBCL was detected after SPK with delayed renal allograft dysfunction with functional pancreas & mate kidney.

Case Description: Recipient was nonsensitized 42-year-old EBV IgG+ type 1 diabetic male. Donor was 39-year-old female with paraplegia due to multiple sclerosis on no treatment. No history of cancer at time of death, no leukocytosis & preprocurement CT abd/chest was normal. Cause of death was cerebellar bleeding. Donor was EBV IgG+, KDPI 31% with negative XM. Before implantation, a core needle biopsy was performed. LM showed CD20+ atypical lymphocytic infiltrate. The recipient received rATG induction & maintenance FK, MMF & steroids per protocol. A creatinine rise prompted biopsy 2 weeks post transplant. It showed diffuse mononuclear inflammatory tubulointerstitial infiltrate with clusters of atypical cells in interstitium & peritubular capillaries staining diffusely for CD20, Ki67(~50%) & variably for BCL2 & MUM1 indicating DLBCL. Atypical cells in procurement biopsy showed similar pattern. Simultaneous tissue gene expression testing (MMDx) showed AbMR, possibly indicating host vs tumor response. Immunosuppression was withdrawn except steroids. PET scan & peripheral flow cytometry were negative. Patient underwent allograft pancreatectomy & nephrectomy. Explant pathology showed DLBCL invasion of renal graft & portion of small bowel. Due to risk of microinvasion of tumor, rituximab (weekly *4) was given with serial PET scans & R-CHOP. No other donor derived lymphomas were reported to UNOS from heart, liver, lungs & mate kidney from this donor.

Discussion: Early allograft removal, immunosuppression withdrawal & cancer therapy was offered to the patient to maximize treatment efficacy & confer the best chance of survival in this high risk disease.



SA-PO1088

Post-Transplant Lymphoproliferative Disorders in Kidney Transplant Recipients: A Retrospective Single-Center Cohort Analysis

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Background: To characterize the posttransplant lymphoproliferative disorders(PTLD) including the Epstein-Barr virus (EBV) status, histological subgroups, site of occurrence and the clinical outcomes of kidney transplant recipients at our institution.

Methods: A retrospective cohort study of all kidney transplant recipients who developed PTLD and were followed up at our transplant centers from 1999 through 2021.

Results: 44 patients developed PTLD, with majority 86.4% being kidney alone transplants, while 13.6% were Kidney-Pancreas recipients. Heme-Oncology were primarily responsible for the treatments which was tailored to their individual type and stage and site of PTLD. Immunosuppression was lowered on an individualized basis.

Conclusions: We describe a large series of PTLD cases, with their outcomes with reasonable outcomes. The time-line to PTLD was not limited to early post-transplant course as seen in other series, and EBV-ve PTLD was more common. Careful adjustment of immunosuppression, early detection, and aggressive treatment can lead to acceptable outcomes.

Demographics	
Mean age at transplant	42.8+/-20.5 ; Median 44 (range 3.1-76.9)
Race	88.6% Whites; 9.1% AA
Gender	Males 77.3%; Females 22.7%
Transplant Type	Living Donor 27.3%; Deceased 70.5%
Cause of ESRD:	DM 34.1%; HTN 15.9%; GN 11.3% ; Congenital/Obstructive 13.6%, Others 18.1%
Mean age at PTLD Diagnosis	49.4+/-20; Median 52 (range 4.6-83.2)
Kidney Transplant Induction Immunosuppression	ATG 81.8% ; Others 18.2%
Maintenance Immunosuppression	Tac+MMF 86.4%; others 13.6%

Survival		
	Graft	Patient
Overall During Study Period	45.5%	54.5%
Graft Survival Time from Time of Transplant	11.5+/-7.6; Median 9.7 (range 0.6-35.7) years	12.7+/-7.8; Median 12.6 (range 0.6-35.7) years
Graft survival Time from PTLD Diagnosis	4.9+/-4.5 ; Median 3.3 (0.1-14.7) years	6.1+/-5.5 ; Median 5.0 (range 0.1-23) years
1 yr, 3yr, 5yr, 10yr Overall Graft Survival	93% , 89%, 89%, 59%	93%, 89%, 89%, 69%
1yr, 3yr, 5yr, 10yr Graft Survival from time of PTLD Diagnosis	81%, 65%, 57%, 46%	81%, 71%, 63%, 57%

PTLD Characteristics	
Rejection Pre-diagnosis of PTLD	11.4%
Time from Transplant to PTLD Dx	Mean 6.6+/-5.4 ; Median 6.3 (0.4-25) years ; 13.6% within 1 year, 25% within 2 years ;25% after 10 years
Type of PTLD:	DLBCL Monomorphic 75% (EBV+18.2%, EBV-ve 36.4%, EBV unknown 20.5%); CNS 6.8%; Polymorphic EBV+ (9.1%) ; Others 13.6%
Primary Site of PTLD	LN alone 29.5%; Small Bowel 18.2%; Liver 11.3%; CNS 11.3%; Colon 11.3%; Tonsil 9.1%; Others 9.3%
Treatment :	Rituximab alone 22.7%; All other a combination of Ritux with +/- Chemo, Surgery, radiation.
Response to Treatment	Complete Response 72.7% ; Partial Response 11.4%; Failed Response 13.7%;

SA-PO1089

Kidney MR Elastography on Controls and Patients with Kidney Transplant

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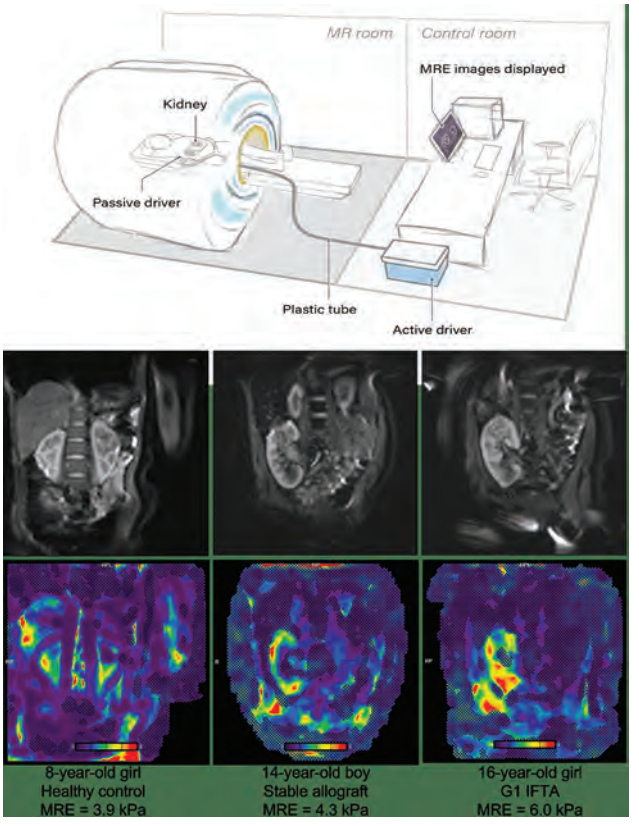
Background: To compare the diagnostic performance of MR elastography in controls and in pediatric patients with transplant kidneys.

Methods: A prospective study of pediatric kidney transplants undergoing clinically indicated biopsy & healthy controls, was performed. MRE was performed on a 3T MRI scanner equipped with MRE hardware consisting of an active-passive driver system. A 2D & 3D spin-echo planar MRE sequence were used to acquire coronal wave images and mean kidney stiffness (in kPa) were measured. For each patient, one to three needle biopsy cores of the lower pole were obtained and fixed in formalin. Three micron sections were stained with hematoxylin & eosin, and Masson trichrome. The severity of interstitial fibrosis and tubular atrophy (IFTA) was graded according to Banff 2017. A comparative analysis was performed using one-way ANOVA.

Results: A prototype hardware, software and acquisition sequence for Kidney MRE was developed and implemented. 10 pediatric controls were enrolled (Median age: 14.5 years). Mean kidney stiffness was 3.8 kPa. We also enrolled 4 healthy adults (Median age: 28 years). Mean stiffness measured by MRE was 4.2 kPa. Significantly higher mean baseline stiffness was observed in adult controls as compared to children. 12 kidney transplant recipients were enrolled (Median age: 15.5 years). Mean stiffness measured was 5.3 kPa. We found the mean stiffness of kidneys in children with allografts was significantly higher than controls. MRE showed significant differences among the allograft groups when evaluating IFTA.

Conclusions: Our study has shown that MRE has the potential to be utilized as non-invasive tools for quantitative measurement of fibrosis in renal allografts with a correlation with histopathology. MRE technology has the potential of detecting IFTA in patients with kidney transplant.

Funding: NIDDK Support



SA-PO1090

Noninvasive Evaluation of Renal Allograft Fibrosis Using Magnetization Transfer Imaging

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Background: Fibrosis negatively affects kidney allograft survival, but the options for early noninvasive diagnosis are limited. Magnetic transfer imaging (MTI) magnetic resonance imaging (MRI) assesses tissue macromolecule accumulation (like collagen), a characteristic of fibrosis. We tested the hypothesis that MTI non-invasively detects allograft fibrosis in patients with KT.

Methods: Multiparametric MRI was performed in 13 (M9/F4) KT recipients with stable kidney function prior to the protocol allograft biopsy (Table 1). Cortical and medullary magnetization transfer ratio (MTR) at 1.5T MRI, oxygenation (blood oxygen level-dependent MRI), perfusion (arterial spin labeling), and microstructure (diffusion-weighted imaging) were compared with interstitial fibrosis (IF) on the kidney biopsy (trichrome staining) and with albumin-to-creatinine ratio (ACR). Glomerular filtration rate (GFR) was measured using iothalamate clearance.

Results: MTR correlated directly with both cortical and medullary histological IF and with ACR (Figure-1) but not with GFR. No other imaging-derived index correlated with any renal parameter.

Conclusions: Both the % of IF on kidney biopsy and ACR correlated significantly with MTR-MRI but not with any other MRI indices. Hence, MTR may provide a noninvasive tool for the detection and assessment of IF in renal allografts, pending confirmation in a larger number of patients.

Funding: NIDDK Support, Other NIH Support - AG62104 (National Institute on Aging) and DK122734 (NIDDK)

Patient demographics (mean±standard deviation or median (min, max))

Parameter	Total
Post-transplant, Yrs.	4 (4,7)
Age, Yrs,	58 ± 12
MRI-kidney biopsy interval, days	1 (1,41)
Cortical fibrosis (%)	9.9 (6.3,41.8)
Medullary fibrosis (%)	17.3 ± 9.7
Mean arterial pressure, mmHg	100 ± 12
Serum creatinine, mg/dl	2 ± 1
Iothalamate clearance, ml/min/BSA	53 ± 18
Albumin/creatinine ratio, mg/g	14 (3,102)

MRI=magnetic resonance imaging; BSA=body surface area.

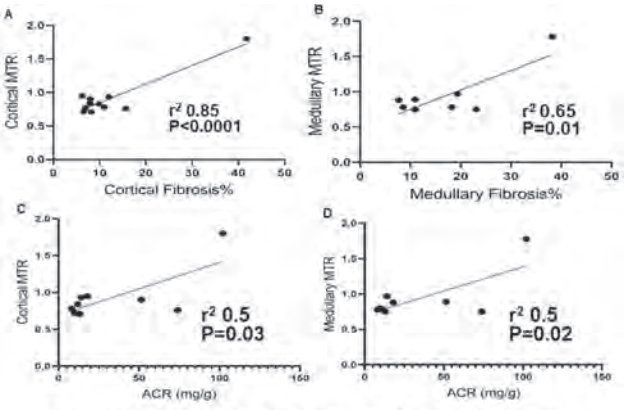

Figure-1 Correlation of cortical and medullary 1.5T MTR with histology measured fibrosis% and ACR

SA-PO1091

Prognostic Implications of Chronic Active T-Cell-Mediated Rejection Diagnosed on Renal Allograft Protocol Biopsies

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Background: Banff 2017 introduced Chronic Active TCMR(CA-TCMR) into the classification of rejection. However, the significance of this finding on early protocol biopsies has not been explored.

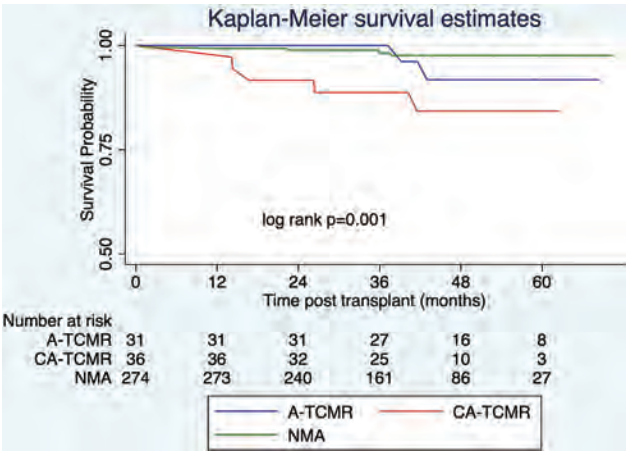
Methods: We identified a cohort of patients with serial protocol biopsies performed between Oct 2018-Jan 2022. Biopsies were done at 3- and 12- months. We chose the protocol biopsy closest to the 1-year time point. We included both living and deceased donor kidney transplants. De-novo and repeat kidney transplants were included. We excluded biopsies with borderline rejection, antibody mediated rejection or BK virus nephritis. Biopsies that qualified for TCMR were further divided into acute TCMR(n=31) and CA-TCMR(n=36). Biopsies with no major abnormalities (NMA) were used as control. The maximum follow up period was 5.5 y with a median follow up of 3.5 y. All patients received induction therapy with anti-thymocyte globulin and maintenance immunosuppression with tacrolimus and MMF. Patients with cPRA>90% also received maintenance steroids.

Results: See below

Conclusions: CA-TCMR is common in early protocol biopsies and is more common in deceased donor kidney transplants. Allograft survival was lower in biopsies with CA-TCMR. Finding of CA-TCMR on early protocol biopsies prognosticates long term allograft outcome.

Demographics

	ALL (n=341)	NMA (n=274)	A-TCMR (n=31)	CA-TCMR (n=36)	p-value
Age Median (Q range)	56 (42-66)	55(41-65)	58(45-70)	59.5(46.5-68.5)	0.1808
Race - Black	274(80.4)	225(82.1)	24(77.4)	25(69.4)	0.1807
Donor Type- DBD	125(36.7)	95(34.7)	13(41.9)	17(47.2)	0.0593
Donor type - DCD	65(19.1)	49(17.9)	5(16.1)	11(30.6)	
Donor type - Living	151(44.3)	130(47.5)	13(41.9)	8(22.2)	
Gender - Male	222(65.1)	182(66.4)	19(61.3)	21(58.3)	0.5670
PRA I >50	27(8.0)	17(6.3)	5(16.1)	5(13.9)	0.0598
PRA II >50	39(11.5)	27(9.9)	6(19.4)	6(16.7)	0.1752



SA-PO1092

Leveraging Machine Learning Methods and Novel Data Sources to Develop Race-Free Algorithms to Predict Deceased Donor Kidney Quality

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Background: To help transplant professionals choose appropriate kidneys for patients, the national transplant organization uses the Kidney Donor Risk Index (KDRI) that predicts the risk of graft failure. Unfortunately, the KDRI has modest predictive accuracy (C-statistic 0.6). The KDRI has been criticized for penalizing hepatitis C virus (HCV), given recent therapies, and race, given ethics concerns. We aimed to develop machine learning based, race-free models and longitudinal organ donor lab data to predict 3-year all-cause kidney (graft) survival and delayed graft function (DGF, dialysis in the first week post-transplant).

Methods: Using registry data, we assembled a cohort of adult (≥18 years) recipients of deceased donor kidneys between 5/1/07-12/31/21. We developed models with different combinations of donor and recipient characteristics using standard regression (Cox and logistic regressions) and machine learning algorithms (Random Forest, Ridge, Lasso, Elastic Net).

Results: The final cohort included 162,905 recipients of kidneys from 95,811 donors. Median donor age was 39.5 years (IQR 27-51) and 38% were female. For 3-year kidney survival, the C-statistic of KDRI was 0.59. Removal of donor race and HCV covariates, or inclusion of donor longitudinal data, made little difference, but inclusion of recipient covariates improved the C-statistic to 0.63-0.64 across different algorithms (Figure). For DGF, the KDRI had a C-statistic of 0.60. Refitting models with or without donor race had similar C-statistics of 0.68-0.69. The inclusion of recipient covariates improved the C-statistics for DGF to 0.74-0.75.

Conclusions: These models demonstrated the feasibility of eliminating donor HCV and race without a meaningful decrement in predictive accuracy for kidney survival and DGF outcomes. The addition of recipient characteristics substantially improves prediction of both outcomes.

Figure 1. Comparison of C-Statistics for 3-year Deceased Donor Kidney Survival

Model	Model 1	Model 2	Model 3	Model 4
Variables	Variables in KDRI (includes race and HCV)	Model 1 + excluding race and HCV	Model 2 + recipient variables & donor-recipient interactions	Model 3 + restricted to April 2016 and later (new antivirals available)
KDRI (Reference)	0.592	0.592	0.592	0.545
Lasso	0.592	0.589	0.631	0.646
Ridge	0.592	0.589	0.631	0.646
Elastic net	0.592	0.589	0.631	0.646
Random forest	0.592	0.589	0.632	0.638

SA-PO1093

Inflammation Alters Relationship Between High-Density Lipoprotein Cholesterol and Risk of CKD: Results from UK Biobank Study

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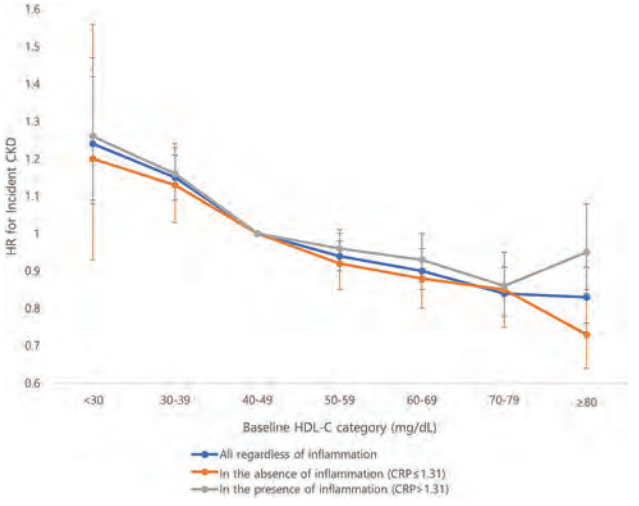
Background: Under inflammatory condition, the functional changes of high-density lipoprotein-cholesterol (HDL-C) can transition from a protective role to a proatherosclerotic direction. We aimed to investigate whether inflammation could modify the relationship between HDL-C and risk of incident chronic kidney disease (CKD).

Methods: We conducted an observational study in 342,204 European adults, aged 38 to 73 years, who were free of CKD at recruitment between Mar 13, 2006, and Oct 1,

2010, from the UK Biobank study. The main exposure was HDL-C level. The presence of inflammation was defined when high sensitivity C-reactive protein (hs-CRP) level was above the median (>1.31 mg/L). The primary outcome was incident CKD.

Results: During a follow-up period of 3,983,553 person-years (median, 11.9 years), the primary outcome occurred in 13,950 (4.1%) participants. Overall, a higher HDL-C level was associated with a decreased risk of incident CKD in multivariable Cox analysis after adjustment of confounders. There was a significant interaction between HDL-C and the presence of inflammation on the risk of incident CKD (*P*-for-interaction=0.019). In patients without inflammation, the protective association of a higher HDL level remained similar. The hazard ratios (HRs) (95% CIs) for HDL-C of <30, 30-39, 50-59, 60-69, 70-79, ≥80 mg/dL were 1.20 (0.93-1.56), 1.13 (1.03-1.24), 0.92 (0.85-1.00), 0.88 (0.80-0.96), 0.85 (0.75-0.95), 0.73 (0.64-0.85), respectively, compared with HDL-C of 40-49 mg/dL. However, this association was attenuated in patients with inflammation, particularly for HDL-C ≥80 mg/dL. Notably, a lower HDL level was associated with a higher risk of CKD in all patients with a stronger increased risk observed in patients with inflammation.

Conclusions: A higher HDL-C level is associated with decreased risk of incident CKD, but this association was weak under inflammatory condition. These findings suggests that inflammation may modify the relationship between HDL-C and the development of CKD.



SA-PO1094

The Association Between Higher Serum Triglyceride Level and Poor Kidney Outcome Among Patients with CKD: The Fukuoka Kidney Disease Registry (FKR) Study

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Background: Dyslipidemia, especially hypertriglyceridemia, is a very common complication in patients with chronic kidney disease (CKD). Although hypertriglyceridemia is known to be a risk factor for the development of CKD in the general population, it is unclear whether there is a relationship between higher serum triglyceride levels and the progression of kidney failure in patients with CKD. The aim of this study was to investigate the relationship between serum triglyceride levels and the progression of kidney failure.

Methods: A total of 4,101 Japanese outpatients aged ≥16 years were prospectively followed for 5 years. Patients were divided into four groups based on quartiles of serum triglyceride levels at baseline (<87, 87-120, 121-170, >170 mg/dL). The primary outcome was the progression of kidney failure, defined by a 1.5-fold increase in serum creatinine from baseline or the development of end-stage kidney disease. We estimated the relationship between serum triglyceride and the outcome using a multivariable-adjusted Cox proportional hazards model.

Results: During the 5-year observation period, 1410 patients developed the progression of kidney failure. The incidence rate of the progression of kidney failure increased linearly with the increase in serum triglyceride levels (*P* for trend <0.05). In the multivariable-adjusted analysis, the hazard ratio (HR) for the progression of kidney failure in the highest serum triglyceride quartile (Q4) was 1.22 (95% CI, 1.02-1.45; *P* <0.05) compared with the lowest serum triglyceride quartile (Q1). This association was increased in patients with higher baseline BMI (≥ 25 kg/m^2) (*P* for heterogeneity <0.05).

Conclusions: The current study shows that higher serum triglyceride level is associated with the progression of kidney failure in patients with CKD. It also highlighted that this relationship was more pronounced in individuals with a higher BMI.

SA-PO1095

Incidence of CKD in Prediabetes

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Background: Diabetes complications may occur in persons with prediabetes mellitus (PDM) defined by hyperglycemia below the threshold for diabetes diagnosis. The study aim was to assess the incidence of chronic kidney disease (CKD) in PDM in a real-world population.

Methods: The study population was derived from the Center for Kidney Disease Research, Education, and Hope (CURE-CKD) Registry of electronic health records from Providence and UCLA Health systems. PDM was defined by HbA1c 5.7-6.4%, 2 measures of fasting (100-125 mg/dL) or random (140-199 mg/dL) blood glucose at least 1 day apart, or ICD-9/10 codes. CKD was defined by estimated CKD-EPI 2021 glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, urine albumin/creatinine ratio ≥30 mg/g, or urine protein/creatinine ratio ≥0.15 g/g ≥90 days apart, or ICD-9/10 codes. Incidence of CKD was estimated in persons ≥18 years old with PDM and without CKD in the previous 6 months. Estimates for 2015-2020 were standardized to the 2020 US population. Incidence rate ratios (IRR) compared CKD incidence within age, race/ethnicity, and sex groups.

Results: Persons with PDM (N=256,829) were 55% women and 56±15 years old. At baseline, mean eGFR was 93±16 mL/min/1.73 m^2; mean HbA1c and systolic blood pressure were 5.8±0.3% and 127±16 mmHg. After a median follow-up of 2.6 years (interquartile range 1.5-3.8), CKD was identified in 7%. Of these, 43% had an eGFR <60 mL/min/1.73 m^2. Standardized incidence rate of CKD was 30.4 cases/1,000 person-years (95% CI 29.8-31.0). IRRs are presented in the Figure.

Conclusions: CKD developed among 1 in 14 persons with PDM in a short period of time. Older age and non-White race groups with PDM, except the Asian patient group, had higher incidence of CKD compared to the White group, whereas women had lower risk than men. These results suggest that certain demographic groups may benefit from targeted awareness, detection, and strategies to prevent CKD progression.

Funding: Other U.S. Government Support

Incidence of CKD in Prediabetes: Incidence Rate Ratios (IRR) by demographic group

	Person-Years	CKD Cases	IRR (95% CI)	P-value
Sex				
Men	268,066	9,537	1 (Reference)	
Women	338,560	9,442	0.82 (0.79-0.86)	<.001
Race/Ethnicity				
White	424,977	14,294	1 (Reference)	
American Indian/Alaska Native	3,894	146	1.33 (1.10-1.61)	0.004
Asian	87,760	1,260	0.72 (0.68-0.77)	<.001
Black	26,023	933	1.35 (1.22-1.49)	<.001
Hispanic	58,597	1,745	1.10 (1.04-1.16)	<.001
Native Hawaiian/Pacific Islander	3,260	120	1.88 (1.26-2.80)	0.002
Age				
18-39	93,746	1,769	1 (Reference)	
40-59	258,401	5,097	1.21 (1.15-1.29)	<.001
60-79	227,726	9,326	2.27 (2.14-2.40)	<.001
80+	24,753	2,187	4.86 (4.44-5.33)	<.001

SA-PO1096

Impact of Hyperglycemia on Renal Prognosis in Lean Individuals

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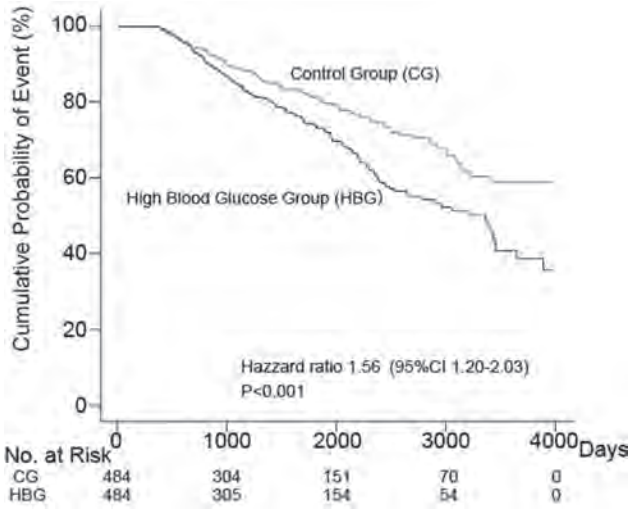
Background: Obesity not only affects blood glucose but also influences haemodynamics and adipocytokines, making it unclear to what extent hyperglycemia alone contributes to organ damage. Therefore, our aim was to investigate the specific impact of hyperglycemia on renal prognosis in lean individuals with elevated blood glucose levels.

Methods: In this single-center study from 2012 to 2022, we analyzed body mass index (BMI), estimated glomerular filtration rate (eGFR), and hemoglobin A1c (HbA1C) data. Individuals with a BMI <18.5 at any time were selected, excluding those under 18 years old, on dialysis, or with one year of data. Participants with HbA1C >6.5% were assigned to the hyperglycemic group (HBG), while the rest formed the control group (CG). Propensity score matching adjusted for background factors, and both groups underwent time-to-event analysis for a 40% eGFR decline. A 12-month landmark analysis minimized guarantee time bias.

Results: Among individuals with recorded BMI, 14.2% experienced a BMI below 18.5 during the study. Out of the initial 3149 individuals, 516 were classified as HBG, having a significantly higher average age than CG (74.3 vs. 63.7 years). Among those who did not reach a renal function endpoint within one year of enrollment, we selected a final sample of 484 patients in each group after adjusting for background factors including gender, age, first-year eGFR, duration of observation, and minimum BMI. The selected participants had a mean age of 74.9 years, mean duration of observation of 1755.4 days, and mean minimum BMI of 16.5. Survival time analysis showed that HBG reached the endpoint significantly more often than CG (Hazard ratio: 1.56 (95%CI 1.20-2.03), P < 0.001).

Conclusions: Lean individuals with hyperglycemia, who were more likely to be elderly, exhibited a significantly higher prevalence of impaired renal function compared to background-matched controls.



SA-PO1097

Changes in the Thyroid, Pituitary, and Gonadal Hormones in CKD Patients During One-Year Follow-Up

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Background: Hormonal disorders are common complications of chronic kidney disease (CKD). Endocrine disturbances interplay with nutritional status and both are associated with kidney function and influence long term outcomes. The aim of the study was to examine changes of serum levels of chosen hormones, changes in kidney function and nutritional parameters in CKD patients during one-year follow-up.

Methods: Male CKD patients with eGFR lower than 45 ml/min/1.73m^2 on conservative treatment formed cCKD group and male patients treated with hemodialysis for more than three months formed HD group. In both groups serum levels of total (TT), free testosterone (FT), dehydroepiandrosterone sulfate (DHEA-S), sex hormone binding globulin (SHBG), luteinizing hormone (LH), prolactin (PL), thyroid-stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), creatinine (Cr), albumin (A) were measured at the moment of inclusion and after one year.

Results: 21 men aged 67±7 were included to cCKD group and 20 aged 63±8 to HD group. Over one-year follow-up in cCKD group serum levels of LH, PL and TSH increased significantly whereas DHEA-S decreased. Serum levels of TT, FT, SHBG, fT3, fT4 as well as Cr, A and levels did not change significantly. In HD group over one year follow-up serum levels of fT3 and fT4 significantly decreased. Whereas the rest of parameters did not change significantly.

Conclusions: In male with CKD on conservative treatment significant changes of DHEA, LH, prolactin and TSH were observed during one-year follow-up whereas at the same time Cr, eGFR and nutritional markers did not change significantly. In HD group only fT3 and fT4 decreased significantly. We can suspect that hormonal changes can precede decline in kidney function and deterioration of nutritional status in CKD patients.

	cCKD inclusion	cCKD after one year	p	HD inclusion	HD after one year	p
TT (ng/ml)	3.9±1.6	3.9±1.5	0.835	2.8±0.9	3.0±1.1	0.332
FT (pg/ml)	9.6±4.5	10.4±4.5	0.205	11.6±6.5	10.7±4.8	0.737
DHEA-S (ug/dl)	145±89	130.2±87.1	0.014	120±93	107.3±85.2	0.277
SHBG (ug/ml)	4.7±1.4	4.9±1.4	0.532	4.6±3.8	4.5±2.7	0.455
LH (IU/l)	10.7±8.0	13.2±9.3	0.019	17.8±20	17.6±19.2	0.411
PRL (ng/ml)	10.2±3.9	13.2±5.6	<0.001	32.5±32.5	35.2±28.4	0.681
TSH (uIU/ml)	1.9±1.5	2.7±2.8	0.042	1.7±1.0	1.7±1.1	0.970
fT3 (pmol/l)	4.7±0.6	4.7±0.8	0.808	4.0±0.6	3.5±0.7	<0.001
fT4 (pmol/l)	16.3±3.5	17.1±3.7	0.085	14.6±2.2	13.6±2.5	0.009
eGFR	32.9±10.7	35.7±19.3	0.498			

SA-PO1098

Impact of Lifestyle Changes on Quality of Life in Patients with CKD: Results from a Real-World Study

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Background: Lifestyle changes can slow progression of chronic kidney disease (CKD) but can be difficult for patients to implement. We assessed the impact of lifestyle changes on quality of life in patients with CKD.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a cross-sectional survey of physicians and patients conducted in the USA from Jan-June 2022. Non-dialysis patients completed the Short Form Health Survey 12-item (SF-12) and provided information on the successes in implementing recommended lifestyle changes. Two groups were formed, 'successfully implemented' and 'unsuccessfully implemented'. T-tests were used to compare groups.

Results: Overall 221 patients provided data, the mean [SD] age was 63.2 [12.58], 55% were male, and 66% were white. Lifestyle changes were recommended to 74%, and 95% of these patients reported difficulty implementing the change(s), of which 20% found it very/extremely difficult. In the SF-12 physical health domain, stopping/reducing alcohol consumption, improving sleep pattern, starting/increasing exercise and reaching/maintaining a healthy weight had the largest difference in composite scores between successful vs unsuccessful (p <0.001) [Table 1]. In the SF-12 mental health domain, stopping/reducing alcohol consumption, stopping/reducing smoking, reaching/maintaining a healthy weight, reducing potassium intake, and consulting a nutritionist had the largest difference in composite scores between successful vs unsuccessful (p <0.05) [Table 1].

Conclusions: High numbers of patients describe difficulty implementing lifestyle changes recommended by their physician. Unsuccessful implementation can lead to a greater impact on physical and mental quality of life. Support is needed to help patients with these changes, provide optimal care and better patient outcomes.

Table 1 - Mean patient reported SF-12 scores, shown per recommended lifestyle change

Recommended lifestyle change	SF-12 Physical Health Composite			SF-12 Mental Health Composite		
	Unsuccessfully implemented mean (n)	Successfully implemented mean (n)	P-value	Unsuccessfully implemented mean (n)	Successfully implemented mean (n)	P-value
Reduce dietary sodium intake	41.84 (106)	44.48 (70)	0.0808	47.21 (106)	50.45 (70)	0.0342
Reduce intake of foods high in sugar	41.28 (101)	45.89 (55)	0.0052	47.43 (101)	51.60 (55)	0.0084
Start/increase exercise	40.84 (107)	51.70 (28)	<0.0001	48.72 (107)	53.27 (28)	0.0264
Other dietary changes (i.e. eat healthier)	39.44 (69)	46.56 (42)	0.0002	47.00 (69)	51.51 (42)	0.0312
Reduce dietary potassium intake	39.74 (53)	45.64 (49)	0.0027	44.55 (53)	52.35 (49)	0.0001
Reach/maintain a healthy weight	39.88 (55)	50.22 (25)	<0.0001	45.24 (55)	53.63 (25)	0.0015
Consult a dietician/nutritionist/health coach	43.24 (24)	47.89 (29)	0.0785	44.87 (24)	52.18 (29)	0.0166
Reduce intake of fizzy/carbonated drinks	40.80 (43)	43.50 (24)	0.2896	46.60 (43)	46.81 (24)	0.9357
Increase fluid intake	42.02 (41)	50.74 (25)	<0.0001	48.76 (41)	53.92 (25)	0.0095
Reduce dietary phosphrous intake	41.40 (34)	44.28 (20)	0.3108	44.59 (34)	51.07 (20)	0.031
Improve sleep pattern	38.73 (38)	50.64 (20)	<0.0001	45.92 (38)	52.38 (20)	0.0344
Stop/reduce alcohol consumption	38.13 (17)	52.23 (14)	<0.0001	41.31 (17)	56.53 (14)	<0.0001
Stop/reduce smoking	36.16 (9)	45.70 (11)	0.0715	41.04 (9)	54.65 (11)	0.0122

Green highlighted cells indicate significant results; SF-12, Short form health survey 12-item

SA-PO1099

Factors Influencing Quality of Life in Moderate to Severe CKD

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Background: Improving quality of life is one of the targets of CKD management which are involved in several factors including physical, mental and social factors. In addition to factors in general population, evaluation tools for health related QoL (HRQoL) in CKD patients should include kidney related parameters. KDQOL-SF1.3 is a tool developed and established to demonstrate QoL in ESRD, but data in non-dialysis CKD is scarce. Therefore, this study is to present factors contributing to HRQoL in stage 3-5 CKD.

Methods: There were 94 stage 3-5 CKD patients followed up at Siriraj CKD Clinic, Faculty of Medicine Siriraj Hospital, included into the study from November 2021 and August 2022. The data were collected at the baseline for age, gender, comorbidities, CKD etiology, household incomes and education, current medications and pill numbers, blood pressure, nutritional status, physical activity, muscle mass, handgrip strength, and physical performance. Laboratory data included serum creatinine based estimated CKD-EPI GFR, hemoglobin, serum albumin, calcium, phosphate and intact parathyroid hormone (PTH). HRQoL was assessed by KDQOL-SF1.3.

Results: Demographic data were demonstrated in table 1. There was no difference of overall scores of HRQoL in each stage of CKD (stage 3; 70.0 ± 15.3, stage 4; 69.0 ± 18.3 and stage 5; 73.5 ± 16.2; p = 0.545). However, lower HRQoL scores were associated with poor physical capacity parameters and PTH. Mean 6-minute walk test was 184.9 ± 79.7 m vs. 259.1 ± 89.4 m; p=0.002, median 5-times chair stand test was19.9 (7.9) vs. 13.2 (6.9) seconds; p=0.004 and metabolic equivalent of task (MET) was 100 (420) vs. 480 (2200) MET-min/week; p=0.009, among the patients with HRQoL <60 and ≥60, respectively. PTH was associated with lower physical component summary (PCS) scores [median PTH 149 (106) vs. 90.4 (94.0) pg/ml in PCS <38 vs. PCS >38, respectively; p=0.025].

Conclusions: Lower physical capacity is strongly associated with poor QoL in moderate to severe CKD. Factors associated with physical activity and skeletal health in CKD should be further evaluated to intervene for improving the outcomes.

Funding: Government Support - Non-U.S.

Table 1. Demographic data

Parameters	CKD stage 3 (n=33)	CKD stage 4 (n=30)	CKD stage 5 (n=31)	P value
Male, n (%)	20 (60.6)	16 (53.3)	12 (38.7)	0.21
Age; median (IQR)	68 (11)	68 (11)	65 (12)	0.80
Household incomes (USD/months)				
< 455	9 (27.3)	10 (33.3)	8 (25.8)	0.61
455 -3,000	24 (72.7)	17 (56.7)	22 (71.0)	
>3,000	0	3 (10)	1 (3.2)	
DM, n (%)	23 (69.7)	20 (66.7)	19 (61.3)	0.77
CAD, n (%)	2 (6.1)	3 (10)	3 (9.7)	0.81
History of PCI or CABG, n (%)	2 (6.1)	3 (10)	3 (9.7)	0.81
CHF, n (%)	0	1 (3.3)	2 (6.5)	0.31
Vitamin D deficiency, n(%)	11 (33.3)	6 (20)	7 (22.6)	0.048
Hb <10 g/dl, n(%)	2 (6)	4 (13.3)	15 (48.4)	<0.0001

SA-PO1100

An Investigation into the Relationship Between Frailty and Health-Related Quality of Life in Patients with CKD and Heart Failure

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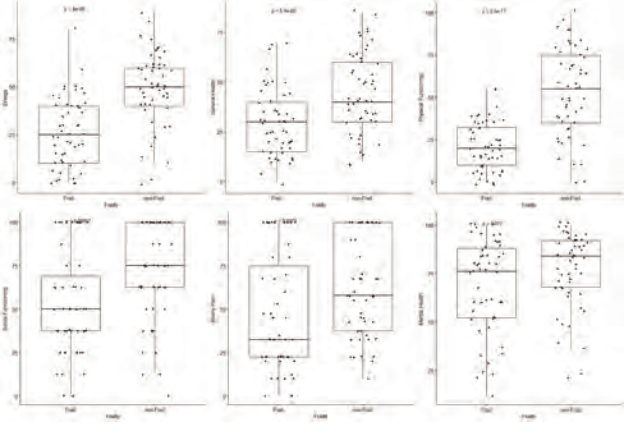
Background: An increasing number of patients have comorbid Chronic Kidney Disease (CKD) and Heart Failure (HF); CKD-HF. Patients with CKD and HF have high frailty levels. Frailty is a predictor of morbidity; however, its association with health-related quality of life (HRQOL) is poorly understood. The aim of this study was to investigate the relationship between frailty and HR-QOL in patients with CKD-HF.

Methods: This was a single centre, cross-sectional study of adults with CKD stage 3-5 with HF. Frailty was defined as Modified Frailty Phenotype (MFP) score >=3. HRQOL was assessed using the validated Short Form (SF-36) Health Survey. All data was collected at one point in time.

Results: The characteristics of the 103 included participants were: median age 76 years (IQR 13), 62% (64/103) male, mean BMI was 28.7 (SD 6.3) and median eGFR 30 (IQR 17). Fifty-one (50%) of participants were frail, and 52 (51%) were non-frail according to the MFP. Compared to non-frail patients, frail patients had significantly worse physical functioning scores (frail 20.88+/-14.48, non-frail 53.24+/-25.94, p-value <0.001), general health scores (frail 29.51+/- 16.86, non-frail 45.00(+/-20.05, p-value <0.001), bodily pain scores (frail 46.29+/-33.60, non-frail 63.27+/-29.22, p-value 0.008), social functioning scores (frail 52.23+/-29.65, non-frail 72.58+/-28.05, p-value 0.001) and energy levels (frail 26.37+/-18.31, non-frail 49.71+/-19.22, p-value<0.001). Most respondents cited 'better quality of life' as their healthcare priority.

Conclusions: Better quality of life is a priority for patients with CKD-HF. Frailty is negatively associated with quality of life. Early detection and intervention of frailty should be a priority for healthcare professionals.

Funding: Other NIH Support - This study received £1,000 from St George's University Academic Training (GAT) Faculty 'Small Grant Fund'- St George's University, GAT office, Crammer Terrace, London, SW17 0RE.



Graphs representing the relationship between frailty and several parameters of HR-QOL; energy, general health, physical functioning, social functioning, bodily pain and mental health.

SA-PO1101

Sleep Duration and Kidney: Does Weekend Sleep Matter?

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Background: Weekend sleep duration is linked to health issues, including mortality. However, how weekend sleep duration can impact chronic kidney disease (CKD) still needs to be understood. Therefore, we aimed to analyze how weekend sleep duration is associated with kidney function.

Methods: Data were obtained from the 2017-2018 National Health and Nutrition Examination Survey. We included 5,362 study participants and categorized them into nine subgroups by sleep duration (≤6 hours, 6–9 hours, and ≥9 hours) on weekdays and weekends and analyzed for the respective association with renal function using multivariable linear regression.

Results: Weekend sleep duration for 9 hours or more was associated with decreasing estimated glomerular filtration rate (eGFR) levels by 2.8 to 6.4 ml/min/1.73 m^2 among people with long to short weekday sleep duration compared with short weekday and weekend sleep durations (control group) after adjusting for demographic characteristics, body measurement, sleep quality, smoking, and comorbidities. The study population with short weekday sleep duration (sWK) and long weekend sleep duration (lWKD) had the most significant decline in eGFR. For the study population with sWK, eGFR level significantly decreased by 1.1 ml/min/1.73 m^2 as sleep duration on weekends increased by one hour. Therefore, weekday and weekend sleep duration should both be considered when investigating the relationship between sleep duration and CKD.

Conclusions: Longer weekend sleep duration was linked to a decrease in eGFR levels. It warrants further study to confirm the causal association and clarify the mediators

Funding: Government Support - Non-U.S.

SA-PO1102

Depressive Symptoms Do Not Worsen over Time in Individuals with CKD: The BRINK Study

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Background: The prevalence of depression is high in the chronic kidney disease (CKD) (20-40%) and dialysis (30-50%) populations. It is unclear how depression symptoms change over time in patients with CKD.

Methods: Participants in the Brain in Kidney Disease (BRINK) cohort completed a Patient Health Questionnaire (PHQ-9) and an eGFR annually. We completed a retrospective longitudinal analysis of this cohort using a mixed linear effects model to examine the mean change in PHQ-9 score by CKD stage compared with the changes among people without CKD. We also compared changes in depression scores among those who initiated dialysis and those with CKD5.

Results: We followed 571 participants for up to five years, of whom 31% reported a diagnosis of depression at baseline. Baseline PHQ-9 scores were 3.5, 4.4, 4.3, 4.7, and 4.8 for participants without CKD (n=147) and those with CKD3a (n=98), 3b (n=190), 4 (n=112), and 5 (n=24), respectively. After adjustment for baseline PHQ-9 score and covariates, mean PHQ-9 scores improved by 0.20 points per year (95% confidence interval [CI] 0.08-0.33) for people who remained without CKD, and improved by 0.30 points (95% CI 0.14-0.47) and 0.19 points (95% CI 0.07-0.32) for people with CKD 3a and 3b (figure), while annual mean PHQ-9 scores among patients with CKD 4 or 5 and dialysis-dependent CKD did not change significantly. Compared with participants who did not develop CKD, no differences in changes in PHQ-9 scores for any CKD subgroup were observed, nor when comparing change in PHQ-9 scores between people with dialysis-dependent CKD and CKD 5. Results were similar in a sensitivity analysis that excluded 141 individuals reporting anti-depressant use.

Conclusions: We found that mean PHQ-9 scores improved slightly over time in people without CKD and those with stage 3 CKD, but not among those with later stage CKD. However, when we directly compared changes in PHQ-9 scores between those with any stage of CKD and those without CKD, we did not observe significant differences. Our study suggests that progression of CKD may not result in worsening depressive symptoms.

Funding: Other NIH Support - National Institute on Aging Grants #R01AG03755 and 1R01AG058729, Private Foundation Support

Changes in PHQ-9 scores in BRINK participants, n=571	Yearly mean PHQ-9 score change, adjusted model		Difference in slope vs eGFR≥60 mL/min/1.73 m^2, adjusted model	
eGFR Range	Estimate (95% CI)	P-value	Estimate (95% CI)	P-value
eGFR ≥60 mL/min/1.73 m^2	-0.20 (-0.33, -0.08)	0.001	0 (Ref)	
eGFR 45 to <60 mL/min/1.73 m^2	-0.30 (-0.47, -0.14)	<.001	-0.10 (-0.29, 0.09)	0.319
eGFR 30 to <45 mL/min/1.73 m^2	-0.19 (-0.32, -0.07)	0.003	0.01 (-0.16, 0.18)	0.893
eGFR 15 to <30 mL/min/1.73 m^2	-0.04 (-0.21, 0.14)	0.686	0.17 (-0.04, 0.38)	0.122
eGFR <15 mL/min/1.73 m^2	0.03 (-0.33, 0.39)	0.866	0.23 (-0.14, 0.61)	0.223
Dialysis-dependent	-0.22 (-0.54, 0.10)	0.181	-0.01 (-0.36, 0.33)	0.935

SA-PO1103

CKD-Associated Pruritus (CKD-aP): Associations with Cardiovascular and Infection Events in Non-Dialysis CKD Patients

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Background: Chronic kidney disease associated pruritus (CKD-aP) is a disturbing symptom of CKD. We describe the prevalence of CKD-aP in non-dialysis CKD, treatment patterns, and associations with clinical outcomes.

Methods: We analyzed 4410 patients from 91 clinics in Brazil, France, and US enrolled in the CKDopps (2013-2021), a prospective cohort of adults not on dialysis with an eGFR <60 mL/min/1.73m^2. CKD-aP was self-reported by response to the question*: During the past 4 weeks, to what extent were you bothered by itchy skin?* Associations with time-to-event outcomes were investigated using Cox regression models adjusted for potential confounders.

Results: The proportion of patients not at all, somewhat, moderately, very much, and extremely bothered by itchy skin was 49%, 27%, 13%, 7%, and 3%, respectively. Among patients at least moderately bothered, 23% were prescribed at least one pharmacotherapy – 35% in the US, 19% in France, 4% in Brazil – including antihistamine (10%), gabapentin (6%), topical corticosteroids (4%), pregabalin (3%), or sedating antihistamine (3%). The hazard ratio (95% CI) for patients extremely (vs. not at all) bothered was 1.84 (1.22, 2.75) for cardiovascular events and 1.36 (0.80, 2.31) for infection events.

Conclusions: CKD-aP can cause significant discomfort for individuals, however we found less than a quarter impacted in our cohort received treatment, and medications chosen can have significant side effects. We also found an increased risk of adverse clinical events with worsening CKD-aP. These results highlight the need for further investigation and education about CKD-aP.

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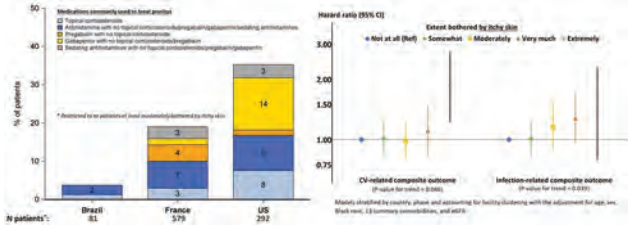

SA-PO1104

The Association of the Influenza Vaccination with CKD Progression to ESKD in a High-Risk Patient Population

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Background: Individuals with CKD who received influenza vaccination have lower risk of infection-related hospitalizations, cardiovascular events, and mortality compared to unvaccinated. However, the association between influenza vaccination status and risk of progression to ESKD has not been studied.

Methods: We describe a cohort of 4,020 adult patients with CKD stage 3b or 4 (eGFR < 45 mL/min/1.73 m^2) identified through ATLAS and FluSurv-Net database from 9/2008 to 9/2010 (index dates) at risk for progression to ESKD. Primary exposure was receipt of influenza vaccine during the index period. Patient were followed to ESKD (primary outcome) or administratively censored at 12/31/2019. Multivariable Cox proportional hazards models were used to determine the association between influenza vaccination status and progression to ESKD.

Results: In this cohort, 46% were unvaccinated and 54% vaccinated. Vaccinated patients mean age was 71 years (SD 13.2), were predominantly Black (45.7%) and Hispanic (27.5%). Compared to unvaccinated patients, vaccinated patients were significantly older, more likely to be female, White or Hispanic, have higher baseline eGFR and comorbidities like hypertension, diabetes, congestive heart failure, peripheral vascular disease, malignancy, and neurologic disease (Table 1). In the unadjusted Cox model, risk of progression to ESKD in unvaccinated vs. vaccinated patients was 24% higher [HR 0.76 (95% CI: 0.67, 0.86)]. However, this risk attenuated [HR 0.92 (95% CI 0.81, 1.03)] after adjusting for age, sex, race/ethnicity, and comorbidities.

Conclusions: Influenza vaccination was associated with a lower risk of progression from CKD to ESKD; however, significance of risk reduction was attenuated by concomitant comorbidities and sociodemographic factors.

Table 1. Clinical Characteristics of CKD Stage 3b/4 Patients by Flu Vaccination Status

	Unvaccinated (N=1852)	Vaccinated (N=2168)	P value
Age, years, mean (SD)	66.3 (14.8)	71.1 (13.2)	<0.0001
Sex, n(%)			
Female	863 (50.7)	1305 (56.3)	<0.0001
Male	839 (49.3)	1013 (43.7)	
Race/ethnicity, n(%)			
Non-Hispanic Black	909 (49.1)	991 (45.7)	
Non-Hispanic White	233 (12.6)	321 (14.8)	0.001
Hispanic	437 (23.6)	596 (27.5)	
Other	273 (14.7)	260 (12.0)	
SES, median (IQR)	-2.5 (-6.1, -1.1)	-2.4 (-5.9, -1.0)	0.45
Comorbidities, n(%)			
Hypertension	1668 (44.3)	2101 (55.7)	<0.0001
Diabetes	865 (42.0)	1192 (58.0)	<0.0001
CHF	271 (37.7)	447 (62.3)	<0.0001
PVD	239 (37.5)	398 (62.5)	<0.0001
Malignancy	176 (36.9)	301 (63.1)	<0.0001
Liver disease	153 (42.3)	209 (57.7)	0.13
Neurologic disease	206 (38.2)	333 (61.8)	<0.0001
Rheumatologic disease	38 (37.6)	63 (62.4)	0.09
Hepatitis	66 (42.9)	88 (57.1)	0.42
Baseline eGFR, mL/min/1.73m^2, median (IQR)	34.1 (26.9, 40.2)	35.4 (29.4, 40.5)	<0.0001

SA-PO1105

PCV13 and PPSV23 Effectiveness in Individuals with and Without Reduced Kidney Function

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Background: Individuals with chronic kidney disease have increased risk of infection and decreased serologic response to pneumococcal vaccination. The comparative effectiveness of pneumococcal vaccination in individuals with and without CKD is unknown.

Methods: Test negative design of all hospitalized adults at Geisinger Health System with a pneumococcal urine antigen test from 2016 – 2021. Cases were defined by a composite of positive urine test, body fluid culture, or diagnostic code for pneumococcal disease. Controls were those who tested negative. We used doubly robust estimation by controlling for the probability of receiving a pneumococcal vaccine using inverse probability of treatment weighting as well as multivariable logistic regression to estimate the odds ratios (ORs) of receiving vaccination between cases and controls. VE was calculated as 1-OR*100.

Results: We identified a total of 180 cases and 3,889 controls (mean age 69 years, female 48%, White 97%, mean eGFR 71 mL/min/1.73 m^2). The receipt of PCV13, PPSV23, and both was seen in 42%, 76%, and 39% among cases, and 51%, 78%, and 48% among controls. In the overall population, the adjusted PCV13 VE was 36% (95% CI 2.6 – 58%), and combination PCV13 & PPSV23 was 40% (13 - 59%); but not evident for PPSV23 (VE -16% [95% CI -93 – 31%]). When stratified by eGFR, the adjusted PCV13 VE was consistent in eGFR ≥60 (VE 38% [95% CI -5.2 - 64%]) and 30-59 ml/min/1.73m^2 (VE 57% [95% CI 11 – 79%]) without significant interaction; but not calculable for eGFR <30 due to small sample size.

Conclusions: Receipt of PCV13 was associated with reduced risk of pneumococcal diseases in individuals with reduced kidney function.

Table. Vaccine Effectiveness against Streptococcal Pneumonia by CKD Status in a Test-Negative Design[a]

PCV13	Vaccinated Cases		Vaccinated Controls		Unadjusted VE	Adjusted VE
All cases	75/180	(42%)	1,982/3,887	(51%)	31 (7.2 – 49)*	36 (2.6 – 58)*
eGFR[b] ≥60	44/117	(38%)	1,113/2,495	(45%)	25 (-9.2 – 49)	38 (-5.2 – 64)
eGFR 30 – 59	26/55	(47%)	709/1,127	(63%)	47 (9.0 – 70)*	57 (11 – 79)*
eGFR <30	5/8	(62%)	160/265	(60%)	–	–
PPSV23						
All cases	136/180	(76%)	3,018/3,887	(78%)	11 (-27 – 37)	-16 (-93 – 31)
eGFR ≥60	85/117	(73%)	1,853/2,495	(74%)	8.0 (-41 – 39)	-47 (-144 – 11)
eGFR 30 – 59	43/55	(78%)	947/1,127	(84%)	32 (-37 – 64)	36 (-32 – 69)
eGFR <30	8/8	(100%)	218/265	(82%)	–	–
PCV13 & PPSV23						
All cases	70/180	(39%)	1,858/3,887	(48%)	31 (5.9 – 49)*	40 (13 – 59)**
eGFR ≥60	41/117	(35%)	1,043/2,495	(42%)	25 (-10 – 50)	38 (1.6 – 61)*
eGFR 30 – 59	24/55	(44%)	664/1,127	(59%)	46 (7.1 – 69)*	59 (25 – 78)**
eGFR <30	5/8	(62%)	151/265	(57%)	–	–

[a] Adjusted VE calculated by combining logistic regression for vaccine receipt among Test Negative Cases/Controls with IPTW of vaccine receipt (doubly robust estimation). Covariates for both models included demographics, medical comorbidities, eGFR, immunosuppression use, and relevant vaccination history (PPSV23 in the PCV13 model; PCV13 in the PPSV23 model). VE calculated as 1-OR x 100%.
[b] Race-free 2021 eGFR$_{Cr}$ (mL/min/1.73 m^2); * P-value < 0.05; ** P-value ≤ 0.01

Abbreviations: VE, vaccine effectiveness; PCV13, Pneumococcal conjugate vaccine 13; PPSV23, Pneumococcal polysaccharide vaccine 23; eGFR, estimated glomerular function; ICD10, International Classification of Disease; IPTW, inverse probability of treatment weighting

SA-PO1106

Progress Against Progression? CKD Management in the Age of Telenephrology

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Background: Nephrology has seen an uptick in transition to remote care delivery, but there has been limited direction for optimal selection of patients appropriate for this method of care. Furthermore, there is limited literature to show which profile of patients utilize the telenephrology platform. In this study, we report the baseline population differences between telenephrology and in-person care groups that are naturally selected when this option is available.

Methods: Single center retrospective cohort analysis involving 1,305 patients seen across 4,230 visits over a 3-year period at a well-established nephrology clinic within the Veterans Affairs health system. Baseline characteristics and health profile data were assessed based on grouping of individuals to the telenephrology group (>50% virtual visits) or in-person group (≤50% virtual visits).

Results: Baseline characteristics including demographic information and comorbid conditions were similar between the two groups. A higher preponderance of those living in rurally defined areas, as compared to those in urban settings, were found to receive in-person care. Individuals who received in-person care were noted to have twice as many emergency department (ED) visits and hospitalizations throughout the course of the study. Similarly, those seen in-person were significantly more likely to be referred for hospice/palliative services.

Conclusions: Understanding the health profiles of those who receive telenephrology versus in-person care can inform future decision-making for appropriate utilization. It was surprising to see a higher degree of telemedicine visits occurring with individuals residing in urban locations. Discomfort with aspects of technology and/or lack of reliable internet for those living in rural areas are possible factors implicated in this. More surprising was the increase in ED visits, hospital admissions, and palliative care by those seen in-person. It could be that those seen in-person were more ill, this was a use of convenience due to proximity, or that care is being missed with telenephrology. These finding makes future research on the cause of these differences, as well as the impact of telenephrology on CKD progression, imperative.

SA-PO1107

Exploring the Implementation of Telenephrology in the Iowa City Veterans Affairs Health Care System: A Qualitative Study

Melissa L. Swee,[1,2] Bradley S. Dixon,[2] Mary V. Sarrazin,[2] Qianyi Shi,[1] Benjamin R. Griffin,[1] Masaaki Yamada,[1,2] Meenakshi Sambharia,[1] Diana I. Jalal.[1,2] [1]*University of Iowa Hospitals and Clinics, Iowa City, IA;* [2]*Iowa City VA Medical Center, Iowa City, IA.*

Background: Telenephrology has emerged as a promising approach to improve access to nephrology care, particularly for Veterans residing in rural areas. This qualitative study aimed to explore the implementation process and identify key factors influencing the adoption and utilization of telenephrology in the Iowa City Veterans Affairs Health Care System.

Methods: A multidisciplinary team collaborated to create a scalable and flexible dashboard system in the Iowa City Veterans Affairs healthcare system. Using iterative Plan-Do-Study-Act cycles and employing thematic analysis, nephrologists, primary care physicians, and case managers actively contributed to dashboard design. The Kano Model was utilized to prioritize features based on user needs. The project was initially piloted in four rural clinics, and subsequent cycles focused on refining parameters and enhancing efficiency as telenephrology was implemented in additional rural clinics.

Results: Findings from the semi-structured interviews revealed several important themes. Participants expressed appreciation for the potential of telenephrology to improve access to specialized nephrology care, particularly for Veterans living in remote areas. The convenience and reduced travel burden were highlighted as major advantages. However, concerns were raised regarding the coordination of care and potential increases in workload for primary care practitioners. Autonomy and the need for clear guidelines in integrating telenephrology into existing care processes were also discussed.

Conclusions: This qualitative study sheds light on the experiences and perspectives of key stakeholders involved in the implementation of telenephrology in the Iowa City Veterans Affairs Health Care System. The findings underscore the potential benefits of telenephrology in improving access to nephrology care for Veterans in remote areas. Addressing concerns related to care coordination, workload, and autonomy is crucial for successful adoption and integration of telenephrology. The insights gained from this study can inform future initiatives to optimize the implementation and utilization of telenephrology in similar healthcare settings.

SA-PO1108

Telenephrology Dashboard for Active Surveillance of Kidney Disease in Primary Care: A Quality Improvement Initiative

Melissa L. Swee,[1,2] Bradley S. Dixon,[2] Mary V. Sarrazin,[1,2] Qianyi Shi,[1] Benjamin R. Griffin,[1] Meenakshi Sambharia,[1] Masaaki Yamada,[1,2] Diana I. Jalal.[1,2] [1]*University of Iowa Hospitals and Clinics, Iowa City, IA;* [2]*Iowa City VA Medical Center, Iowa City, IA.*

Background: Early detection and management of kidney disease are essential for optimal care and cost savings. We implemented a quality improvement project to develop a telenephrology dashboard for active surveillance of kidney disease in primary care clinics.

Methods: A multidisciplinary team collaborated to create a scalable and flexible dashboard system in the Iowa City Veterans Affairs healthcare system. Using iterative Plan-Do-Study-Act cycles and employing thematic analysis, nephrologists, primary care physicians, and case managers actively contributed to dashboard design. The Kano Model was utilized to prioritize features based on user needs. The project was initially piloted in four rural clinics, and subsequent cycles focused on refining parameters and enhancing efficiency as telenephrology was implemented in additional rural clinics.

Results: Findings from the semi-structured interviews revealed several important themes. Participants expressed appreciation for the potential of telenephrology to improve access to specialized nephrology care, particularly for Veterans living in remote areas. The convenience and reduced travel burden were highlighted as major advantages. However, concerns were raised regarding the coordination of care and potential increases in workload for primary care practitioners. Autonomy and the need for clear guidelines in integrating telenephrology into existing care processes were also discussed.

Conclusions: This qualitative study sheds light on the experiences and perspectives of key stakeholders involved in the implementation of telenephrology in the Iowa City Veterans Affairs Health Care System. The findings underscore the potential benefits of telenephrology in improving access to nephrology care for Veterans in remote areas. Addressing concerns related to care coordination, workload, and autonomy is crucial for successful adoption and integration of telenephrology. The insights gained from this study can inform future initiatives to optimize the implementation and utilization of telenephrology in similar healthcare settings.

Funding: Private Foundation Support

SA-PO1109

Initiatives to Enhance the Quality of Referrals from Primary Care to Nephrology: A Systematic Review

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Background: Excessive referrals to nephrology are major determinants for prolonged wait times to access specialist kidney care. We conducted a systematic review of initiatives aimed at improving the quality of referrals to the nephrology service.

Methods: Studies published from inception to April 1, 2021, that were designed to increase guideline concordant (GC) referrals or to reduce wait times and/or total referrals of adult patients with chronic kidney disease from primary care (PCP) to nephrology services were included. The primary outcomes of interest were changes to wait times, changes in the total number of referrals, and changes in the proportion of guideline-concordant referrals. The review was performed using a pre-specified protocol and reported using the PRISMA model. The results are reported based on taxonomy of interventions (provider education, provider reminder system, audit and feedback, multiple interventions, and other).

Results: 27 studies met eligibility criteria, including 16 pre-post designs, 5 observational studies, 3 interrupted time series studies, and 2 randomized control trials. Among 6 studies that provided information on the relative change in total referrals after an intervention was applied, the proportionate change in total referrals was 15.3% [IQR: -16.7-80.6%]. 8 studies showed an increased trend in absolute number of referrals for the study periods with a median 23.2 [IQR, 22.0-56.2]. Among four pre-post design studies that reported the mean change in wait times, a significant reduction in the overall wait time was noted (median -26.3 [IQR, -104.2-1.6] days). Three studies used multiple interventions per each initiative, and two of these studies showed a relative increase by 11-fold in GC referrals pre and post intervention.

Conclusions: Practice-based initiatives designed to improve the quality of referrals from PCP to nephrology services had different effects on their outcomes of interest. It appears that multifaceted interventions are more appropriate for a greater impact as no single intervention in our study showed a greater effect over another on reducing wait times, absolute number of referrals, or proportion of GC referrals.

SA-PO1110

Identifying Opportunities to Improve Early Referral for Hematuria with Concomitant Proteinuria in a Large Health System

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Background: Hematuria is a common problem encountered in primary care though limited data exists on appropriate referral patterns. The purpose of this study was to examine opportunities to improve workup of hematuria for early diagnosis of important associated conditions such as glomerulonephritis and urologic malignancy.

Methods: The study cohort included adults 18+ years of age, with hematuria (defined as 1+ or greater blood on dipstick), who received care at Geisinger, a large regional health system in Central and Northeast PA from 01/01/2022 to 9/30/2022. The proportion of patients with hematuria who were referred to nephrology or urology within 3 months were examined. Characteristics of patients who were referred vs. not referred were compared using descriptive statistics and non-parametric tests as appropriate.

Results: Out of 507,423 patients who had at least 1 outpatient visit during the study period, 63,895 underwent urinalysis; of these, 8,790 patients had 1+ or greater hematuria. After excluding 3,102 who had a prior nephrology or urology appointment, 419 of 5,688 (7.4%) had a nephrology or urology appointment within 3 months and 483 (8.5%) had a nephrology or urology appointment within 6 months. Completion of nephrology or urology appointments at 3 months was higher for patients with greater hematuria (1+: 5.7% vs. 2+: 9.9%; p<0.001) and for patients with concomitant proteinuria (no proteinuria: 5.1%, trace: 8.3%, 1+: 7.7%, 2+: 7.3%, 3+: 9.3%; p=0.01). In a sensitivity analysis excluding patients with positive nitrite and leukocyte esterase (surrogate for possible infection risk), rates of completed nephrology or urology appointments were similarly low (3 months: 234/2,968 [7.9%]; 6 months: 265/2,968 [8.9%]; p<0.001 for chi-square test). Other factors associated with higher completed nephrology or urology appointments included male sex, White race, having a Geisinger primary care provider, and having concomitant proteinuria.

Conclusions: In a regional health system, we identify low referral rates to nephrology and urology after hematuria diagnosis, even among patients with concomitant proteinuria. Future studies are needed to determine optimal strategies to improve follow-up and management of hematuria.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

SA-PO1111

Palliative and Hospice Care Utilization Among a National Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis

Yoko Narasaki,[1] Kamyar Kalantar-Zadeh,[2] Ji Hoon Yoon,[1] Csaba P. Kovesdy,[3] Dana B. Mukamel,[1] Susan T. Crowley,[4] Lisa Le,[1] Seungsook You,[1] Danh V. Nguyen,[1] Connie Rhee.[1] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]Harbor-UCLA Medical Center, Torrance, CA; [3]The University of Tennessee Health Science Center, Memphis, TN; [4]Yale University, New Haven, CT.*

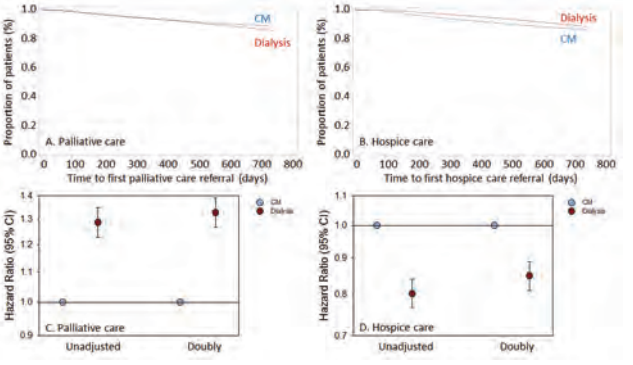
Background: Given the high symptom burden of the aging and ailing advanced CKD population, there is compelling need for palliative or hospice care in routine nephrology management to optimize quality of life. Little is known about the comparative utilization of palliative/hospice care in advanced CKD patients treated with conservative management (CM) vs. dialysis.

Methods: We examined a national cohort of advanced CKD patients (≥2 eGFRs <25 separated by ≥90 days) treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of 1st eGFR <25) over 1/1/07-6/30/20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. We compared time to 1st referral to palliative care (primary outcome) or hospice (secondary outcome) among CM vs. dialysis patients who were matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 to address confounding using Cox models.

Results: Among 28,740 CM patients PS-matched to 28,740 patients who transitioned to dialysis, baseline characteristics were well-balanced. In the PS-matched model, compared to CM, dialysis was associated with higher likelihood of palliative care referral: HR (95%CI) 1.29 (1.23-1.35). In contrast, dialysis was associated with lower likelihood of hospice referral vs. CM: HR (95%CI) 0.80 (0.77-0.84). Similar findings were observed in analyses doubly-adjusted for PS covariates.

Conclusions: In a national advanced CKD cohort, compared to patients treated with CM, those who transitioned to dialysis had higher palliative care referral yet lower hospice utilization. Further studies are needed to determine the underlying factors contributing to the differential utilization of palliative care vs. hospice among advanced CKD patients transitioning to CM vs. dialysis.

Funding: NIDDK Support



SA-PO1112

Hospitalization Outcomes in a National Cohort of Advanced CKD Patients Treated with Conservative Management vs. Dialysis

Connie Rhee,[1] Ji Hoon Yoon,[1] Yoko Narasaki,[1] Seungsook You,[1] Csaba P. Kovesdy,[2] Dana B. Mukamel,[1] Susan T. Crowley,[3] Matthew D. Nguyen,[1] Danh V. Nguyen,[1] Kamyar Kalantar-Zadeh.[4] *[1]University of California Irvine School of Medicine, Irvine, CA; [2]The University of Tennessee Health Science Center, Memphis, TN; [3]Yale University, New Haven, CT; [4]Harbor-UCLA Medical Center, Torrance, CA.*

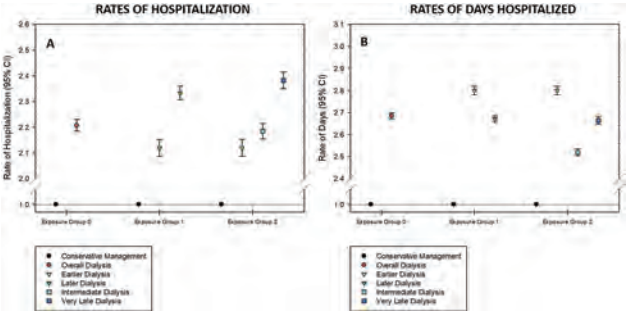
Background: Dialysis has been the default treatment strategy in advanced CKD patients progressing to ESKD, yet may be associated with higher healthcare utilization in certain subgroups. We compared hospitalization outcomes in a national cohort of advanced CKD patients treated with conservative management (CM) vs. dialysis.

Methods: We examined advanced CKD patients treated with CM vs. dialysis (defined as non-receipt vs. receipt of dialysis within 2-years of the 1st eGFR <25) over 1/1/07-6/30/20 from the Optum Labs Data Warehouse, which contains de-identified administrative claims, including medical/pharmacy claims and enrollment records for commercial/Medicare Advantage enrollees, and EHR data. In secondary analyses, we examined finer gradations of dialysis timing, defined as earlier dialysis (ED) vs. later dialysis (LD) (eGFRs ≥15 vs. <15 at dialysis transition); in tertiary analyses we compared ED, intermediate dialysis (ID), vs. very-late dialysis (VLD) (eGFRs ≥15, 10-<15, vs. <10 at dialysis transition). We compared rates of hospitalization (primary outcome) and days hospitalized (secondary outcome) in CM vs. dialysis patients matched by propensity score (PS) in a 1:1 ratio with a caliper distance of ≤0.2 using Poisson regression.

Results: Among 28,850 CM patients PS-matched to 28,850 dialysis patients, dialysis transition was associated with higher rates of hospitalization and days hospitalized vs. CM: IRRs (95%CIs) 2.21 (2.19, 2.23) (Fig A) and 2.80 (2.75, 2.86) (Fig B), respectively. In secondary and tertiary analyses, compared to CM patients, those who transitioned to dialysis had higher rates of hospitalization and days hospitalized vs. CM, irrespective of timing of dialysis initiation.

Conclusions: Patients treated with CM had lower rates of hospitalization and days hospitalized vs. those who transitioned to dialysis. Further studies are needed to determine the downstream sequelae of the differential hospitalization patterns in CM vs. dialysis patients.

Funding: NIDDK Support



SA-PO1113

QI Project: Identify Modifiable Risk Factors and Improve the Safety of Performing Kidney Biopsies

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Background: Bleeding events are the most feared complication in patients undergoing kidney biopsies (KB). Certain factors have consistently shown to carry an increased risk such as CKD. Not assessed in all prior studies was whether KBs done under real-time CT vs ultrasound (USG) guidance or whether transplanted kidneys (TK)

versus native kidneys (NK), or whether the use of automated trocar-guided biopsy guns (ATGBG) or the use of non-trocar guided biopsy guns (NTGBG) of various sizes carried any differential risk.

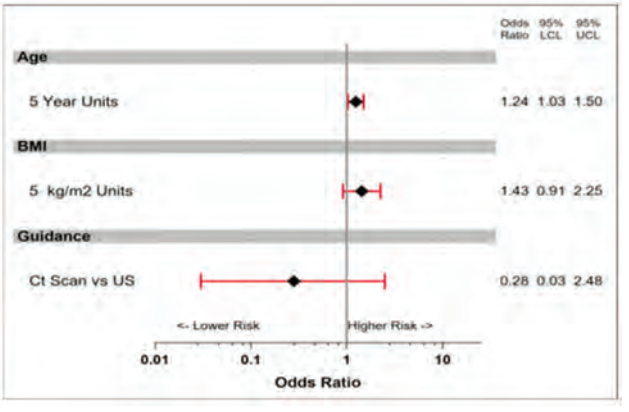
Methods: All KBs performed at our hospital between 2015 to 2022 were included. Two independent physicians reviewed the charts to acquire the data. Quantitative variables were presented as means +/- SDs using the Wilcoxon test, while qualitative variables as frequencies or %s and compared using the chi-square or Fisher's exact test. Only factors with p-value <0.3 were included for logistic regression.

Results: Overall, information on 174 biopsies performed was collected, of which native was 83% and 17% in a transplanted kidney. Blacks constituted 90% of cases. The median age was 42 Years [7-78 years]. Detailed descriptive results are in Table 1. Univariate analysis showed bleeding risk statistically higher in >65 years and lower in CT-guided KB. In multivariable analysis, age was the most influential risk factor with every 5 years increased bleeding by 24%. Every 5-unit increase in BMI increased bleeding by 43% but not statistically. Fig 1

Conclusions: Our study found that additional safety measures needed to be considered when performing biopsies in the elderly. Using CT instead of USG guidance might be warranted for additional safety. We did not find any additional differential in risk of bleeding between NK versus TK or by the use of ATGBG versus NTGBG as far as some real time procedures were utilized.

Demographic

Total Biopsy 174	Blacks 156 (90%)	Native kidney 144 (83%)	Transplant 30 (17%)	Automated trocar 132 (76%)	Non trocar guided 42% (24%)	USG guide 144 (83%)	CT guided 30 (17%)	Median age 42 [7-78]	Bleeding 17 (9.7%)



Multivariate analysis of bleeding

SA-PO1114

A Comparison of Standard Survival Analysis and Recurrent Event Analysis in the KNOW-CKD Study

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Background: Recurrent events are typically defined as events that occur repeatedly. While many clinical studies primarily focus on identifying risk factors for the first occurrence of an event, known as incident events, there is also interest in investigating the risk factors associated with recurrent events and examining whether there are differences compared to a conventional method.

Methods: We conducted a recurrent event analysis on cardiovascular(CV) events using data from the KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease(KNOW-CKD). Statistical models employed in the analysis included Poisson regression, proportional intensity model, Prentice-Williams-and Peterson total time and gap time models, and frailty model. Furthermore, we compared the results of these models with those from Cox proportional hazards model.

Results: During a median follow-up period of 7.205 years, a total of 2,238 participants were included in the analysis. Among these participants, 155 experienced a CV event for the first time, while 35 experienced a second recurrent event, and 4 experienced a third recurrent event. Using Poisson regression model, we further identified associations between recurrent CV events and sex, mean blood pressure, alcohol consumption, hemoglobin levels, and urine protein-creatinine ratio. However, we found that BMI was only associated with incident events and not with recurrent events. Other models did not yield any significant differences compared to the results obtained from Cox proportional hazards model.

Conclusions: Our analysis of recurrent event data provided us with valuable insights that were not attainable through a conventional survival analysis focused solely on the time to the first event.

Funding: Government Support - Non-U.S.

	Odds ratio	95%lower	95%upper	p value
Age	1.659	1.418	1.950	**<0.001**
Sex	0.395	0.240	0.655	**<0.001**
DM	2.308	1.643	3.241	**<0.001**
mBP	0.986	0.972	1.000	**0.049**
history of CV event	2.851	1.876	4.244	**<0.001**
Smoking	1.168	0.770	1.809	0.476
Drinking	0.516	0.341	0.794	**0.002**
Stage of CKD	0.745	0.648	0.857	**<0.001**
BMI	0.959	0.909	1.009	0.110
Pulse pressure	0.988	0.975	1.002	0.083
Hemoglobin	0.853	0.760	0.956	**0.007**
Ln(CRP)	1.176	1.063	1.298	**0.001**
LDL	0.996	0.990	1.001	0.114
Triglyceride	1.001	0.999	1.002	0.328
Ca*P	0.999	0.972	1.028	0.961
1,25-Vit D3	1.014	0.992	1.034	0.191
UPCR	1.083	1.004	1.155	**0.024**

Table 1. Poisson regression analysis for CV events among KNOW-CKD participants.

SA-PO1115

Kidney Outcomes Associated with Adherence to Recommendation from Evidence-Based Clinical Practice Guidelines for CKD 2018 in Japanese Real-World Clinical Practice

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Background: Adherence to recommended treatment is critical in chronic kidney disease (CKD) to prevent complications and progression to kidney failure. The purpose of this study was to explore the adherence to recommendation of patients with CKD, using the Japan Chronic Kidney Disease Database (J-CKD-DB-Ex).

Methods: We developed clinical questions (CQ) recommendation scoring from Clinical Practice Guidelines for CKD 2018 (see Table). We quantified adherence to each of the 8 component metrics, with metric scores ranging from 0 points (poor adherence to recommendation) to 8 points (meeting recommendation). Kidney failure defined estimated glomerular filtration rates (eGFR) <15 mL/min/1.73m^2 or eGFR ≥30% reduction. We evaluated the adherence of CQ recommendations and the decline of eGFR and composite kidney outcomes by the Cox proportional hazards models adjusted for age, sex, and eGFR baseline.

Results: Among 4,455 CKD patients, mean age was 67.2 years, mean eGFR was 54.6 mL/min per 1.73 m^2, and women was 46.5 % at baseline. Scores of CQ recommendation of 0-5 points group was 12.0%, 6 points group was 29.3%, 7 points group was 41.1%, 8 points group was 17.6%. 838 composite kidney outcomes occurred, more than 6 points groups were at significantly lower risk (6 points: HR 0.67, 95% CI 0.54–0.83).

Conclusions: Great adherence of CQ recommendations was associated with prevention of complications and progression to kidney failure.

Funding: Other U.S. Government Support

Clinical questions scoring from Clinical Practice Guidelines for CKD 2018

Variables	1 point	0 point
(A) Serum Potassium (mmol/L)	≤5.4	>5.4
(B) Sodium - Chlorine (mmol/L)	≥33	<33
(C) Administration of RAS inhibitors	Yes	No
(D) Serum Calcium (mg/dL)	≥8.4	<8.4
(E) Serum Phosphorus (mg/dL)	≤6.0	>6.0
(F) Uric acid (mg/dL)	<7.0	≥7.0
(G) Low-density lipoprotein cholesterol (mg/dL)	<120	≥120
(H) Hemoglobin (g/dL)	≥11.0	<11.0

SA-PO1116

Fatty Kidney: A Meaningful Diagnosis?

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Background: Fatty kidney has been proposed as a detrimental metabolic condition akin to fatty liver, related to obesity and metabolic syndrome. It has primarily been recognized as an increase in fat within the renal sinus which purportedly exacerbates hypertension and CKD. Whether this condition truly exists and can be diagnosed based on

the amount of sinus fat remains unclear because the parameters that normally determine the amount of sinus fat are unknown. This was explored retrospectively in patients who underwent renal sonography in an outpatient nephrology clinic.

Methods: 137 sonograms performed in an outpatient nephrology clinic over a 5 month period were reviewed. Kidneys with cysts or hydronephrosis or that were inadequately visualized were excluded Both kidneys were excluded in 49 studies and one kidney was excluded in 20. Total kidney and sinus fat volumes were estimated by measuring areas on longitudinal images using Image J software. Data are presented as means, standard errors, and ranges.

Results: Patient age was 59 ± 2 (39-89), weight 84 ± 2.3 kg (37-142), height 67 ± 0.5 in (59-76), eGFR 46 ± 2 ml/min/1.73 m^2 (5-70), and body mass index (BMI) 29 ± 0.7 kg/m^2 (12-45). Diabetes was present in 44%, and 77% had hypertension. Sinus fat area per kidney was 13 ± 0.6 cm^2 (4-34), kidney area was 40 ± 1.1 cm^2, and ratio of sinus fat to total kidney area was 0.33 ± 0.01 (0.10-0.53). Sinus fat was strongly correlated with total kidney area (r=0.86), weakly with age (r=0.22), height (r=0.40), weight (r=0.44), BMI (r=0.29), serum triglycerides (r=0.24, and high density lipoprotein (r=0.33), but not with diabetes (p=0.30), hypertension (p=0.77), fasting blood sugar (r=0.14), hemoglobin A1C (r=0.12) or eGFR (r=0.07). After normalization to kidney size to provide a measure of excess sinus fat, only age remained as a significant determinant (r=0.45). In a multivariate model including age, diabetes, triglycerides, HDL, and BMI, only age was a significant determinant (p=0.003).

Conclusions: In this cohort comprising mostly patients with CKD, the amount of sinus fat was determined almost entirely by kidney size and did not correlate with the degree of CKD or with any metabolic parameters after adjustment for kidney size. Correlations with sinus fat volume previously reported are likely explained by the renal enlargement that occurs with obesity or hyperglycemia.

Funding: Clinical Revenue Support

SA-PO1117

Monocyte to High-Density Lipoprotein Cholesterol Ratio (MHR) and Carotid Intima-Media Thickness (cIMT) in Patients with CKD: Secondary Analysis of Pooled Clinical Study Data

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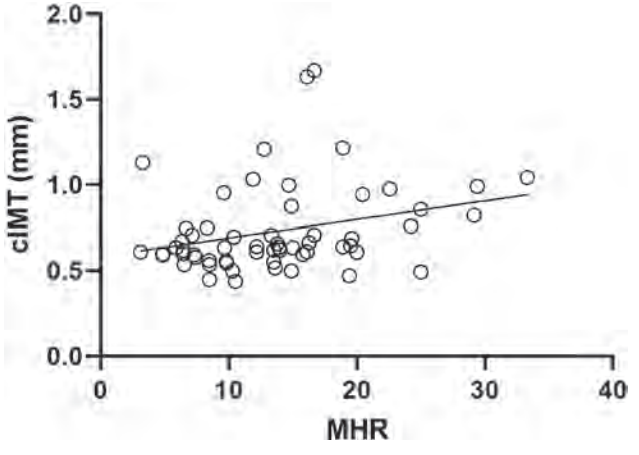
Background: Monocyte to high-density lipoprotein cholesterol ratio (MHR) is an emerging prognostic marker of cardiovascular diseases, including atherosclerosis. Circulating monocytes contribute to plaque development, whereas, high-density lipoprotein (HDL) cholesterol neutralizes the pro-inflammatory and pro-oxidative properties of monocytes, resulting in an atheroprotective effect. Indeed, in the general population, MHR is associated with carotid intima-media thickness (cIMT; a measure of subclinical atherosclerosis). However, this association has not been assessed in a cohort with chronic kidney disease (CKD), a population with atherosclerotic risk. The current study aimed to examine whether MHR is associated with cIMT in patients with stage 3-4 CKD.

Methods: This pooled analysis included baseline data from four clinical studies (2 published [PMID: 27647856; 36636757] and 2 unpublished [NCT Number: NCT04911491; NCT05471518]) that measured monocyte number, serum HDL cholesterol levels, and cIMT in patients with stage 3-4 CKD. Univariate and multivariate regression models were used to evaluate associations of MHR with cIMT and to further adjust for clinically relevant covariates.

Results: A total of 59 participants (39% female; 76% white; mean±SD age 65±10 years; eGFR 41±13 mL/min/1.73m^2; MHR 14±7; cIMT 0.73±0.26 mm) were included. There was an association between MHR and cIMT (β=0.286; P=0.03) in the unadjusted model (Figure). The association between MHR and cIMT was slightly attenuated after fully adjusting for age, sex, body mass index, and low-density lipoprotein cholesterol (β=0.266; P=0.06).

Conclusions: MHR may be associated with cIMT in patients with CKD; this observation should be explored further in a larger cohort.

Funding: NIDDK Support, Veterans Affairs Support, Private Foundation Support



Scatter plot of the association between monocyte to high-density lipoprotein cholesterol ratio (MHR) and carotid intima-media thickness (cIMT)

SA-PO1118

Concordance Between Laboratory- and ICD-10 Code-Defined Stages of CKD Among Patients Hospitalized with Heart Failure in a Large US Integrated Health System

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Background: The presence of chronic kidney disease (CKD) in patients with heart failure (HF) conveys increased cardiovascular risk, while informing use of some forms of guideline-directed medical therapy. Accordingly, we sought to better understand the level of concordance between laboratory-and ICD-10 code-defined stages of non-dialysis-dependent CKD in this population.

Methods: We performed a retrospective cross-sectional analysis of patients admitted to a large integrated health system within the western US between January 1, 2018 and October 1, 2022 with a principal diagnosis of HF (defined by ICD-10 codes: I50.2, systolic heart failure; I50.3, diastolic heart failure; I50.4, combined systolic and diastolic heart failure; I11.0, hypertensive heart disease with heart failure; and I13.0 and I13.2, hypertensive heart disease with heart failure and CKD). CKD was assessed using pre-discharge laboratory data (based on the 2021 CKD-EPI equation) as well as ICD-10 codes.

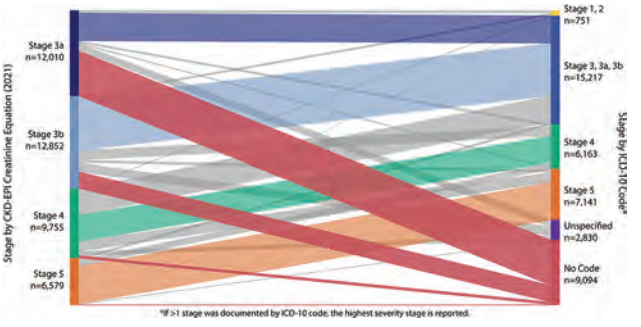
Results: Over nearly 5 years, 61,238 HF hospitalizations occurred, involving 43,234 patients, with 94% having a serum creatinine available. Stage 3a, 3b, 4, and 5 CKD was noted in 21%, 22%, 17%, and 11% of hospitalized patients, respectively, based on laboratory data (Table). Among patients with an ICD-10 code for stage 3-5 CKD, rates of concordance with laboratory-defined CKD rose from 6% to 80% (Table and Figure) as renal function worsened.

Conclusions: Concordance between laboratory- and ICD-10 code defined stages of CKD rose as CKD severity increased.

Funding: Commercial Support - Lexicon Pharmaceuticals, Inc.

CKD Stage by Laboratory Data	CKD Stage by Highest Severity ICD-10 Code									
	1	2	3	3a	3b	3, 3a, 3b Combined	4	5	Unspecified	No code
3a (n=12,010)	0.4%	3%	23%	6%	3%	32%	2%	1%	8%	53%
3b (n=12,852)	0.2%	2%	40%	8%	9%	57%	10%	3%	9%	18%
4 (n=9755)	0.1%	0.6%	26%	3%	9%	38%	38%	14%	6%	4%
5 (n=6579)	0.02%	0.1%	3%	0.4%	1%	5%	13%	80%	1%	1%

Relationship between CKD severity by laboratory data and ICD-10 codes



Relationship between CKD severity by laboratory data and ICD-10 codes

SA-PO1119

Association Between Longitudinal eGFR and Sudden Cardiac Death Among CKD Patients

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Background: The risk of sudden cardiac death (SCD) is high among dialysis dependent patients, but is poorly characterized in earlier chronic kidney disease (CKD) stages. We aimed at analyzing the relation between longitudinal eGFR and the risk of SCD in patients with moderate to severe CKD.

Methods: We analyzed data from the CKD-REIN cohort study, which enrolled adult patients with CKD stage 3 to 5 from 40 nationally representative outpatient nephrology clinics in France. All cardiovascular (CV) deaths were reviewed, and causes were adjudicated by two cardiologists. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) of SCD and other CV deaths associated with current eGFR value and slope were estimated with shared frailty joint models. Non-CV death and kidney replacement therapy were competing events. Models were adjusted for age, gender, urine albumin-creatinine ratio, diabetes, systolic blood pressure, body mass index, smoking, alcohol consumption and education.

Results: We included 3020 patients: 65% men, mean age 67±13 years, eGFR 34±13 mL/min/1.73m2, 30% with history of heart failure or coronary heart disease. Over a median follow-up of 5 years (interquartile range 4.6-5.2), patients underwent 12 (8-17) eGFR measurements, and the mean eGFR slope was -2 mL/min/1.73m2/year. Forty-four SCD and 102 CV deaths from other causes occurred; incidence rates were 3.7 (95% CI 2.7-5.0) and 8.7 (7.1-10.6) per 1000 person-years, respectively. Lower current eGFR value was similarly associated with the risks of SCD and other CV deaths (40 to 60% higher event hazard per 10mL/min/1.73m2 eGFR decrease, with overlapping 95% CI), whereas current eGFR slope was only associated with the risk of other CV deaths (Table).

Conclusions: Patients with more advanced CKD had higher risks of both SCD and CV deaths from other causes, but steeper eGFR decline seemed more closely related with CV deaths other than SCD.

Funding: Commercial Support - Fresenius Medical Care; GlaxoSmithKline; Vifor France; Sanofi-Genzyme; Baxter and Merck Sharp & Dohme-Chibret; Amgen; Lilly France; Otsuka Pharmaceutical; and AstraZeneca., Government Support - Non-U.S.

	Model including only current eGFR value and slope		Fully-adjusted model	
	HR	95% CI	HR	95% CI
Sudden cardiac death				
- Current eGFR value*	1.53	1.03 - 2.27	1.42	1.04 - 1.94
- Current eGFR slope**	0.95	0.67 - 1.36	0.97	0.69 - 1.36
Other CV deaths				
- Current eGFR value*	1.61	1.33 - 1.95	1.58	1.27 - 1.97
- Current eGFR slope**	1.31	1.08 - 1.6	1.44	1.21 - 1.72

*per -10 mL/min/1.73m2

**per -2 mL/min/1.73m2/year

SA-PO1120

The Relationship Between Smoking Cessation and Atherosclerotic Cardiovascular Disease Development Among Patients with CKD

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Background: Previous studies evidenced that smoking is associated with higher atherosclerotic cardiovascular disease (ASCVD) and mortality risk. However, whether quitting smoking is associated with reduced ASCVD risk compared to maintaining smoking in patients with chronic kidney disease (CKD) is unclear. Here we evaluated the association between smoking cessation and ASCVD in patients with CKD.

Methods: We analyzed 1698 participants with non-dialysis dependent CKD from the KoreaN cohort study for Outcome in patients With Chronic Kidney Disease (KNOW-CKD). Key exclusion criteria were 1) kidney failure requiring renal replacement therapy, 2) history of ASCVD at enrollment, and 3) missing data for smoking history. We categorized participants according to smoking history and compared the risk of ASCVD and all-cause mortality. The ASCVD event was defined as a composite of myocardial infarction, stroke, or cardiovascular mortality.

Results: During 12,168 person-years of follow-up (median 8.0 years), the ASCVD event occurred in 52 (3.06%) participants, and 111 (6.26%) participants died among the KNOW-CKD participants. There were 19 (2.03%), 18 (4.09%), and 15 (4.64%) ASCVD events in never (n=935), former (n=440), and current smokers (n=323), respectively. The incidence of ASCVD was higher in current smokers (6.6 per 1000 person-years) than in former (5.7 per 1000 person-years) and never-smokers (2.8 per 1000 person-years) (P=0.02). A multivariable Cox regression showed that continuing smoking is significantly associated with ASCVD even after adjustment of age, sex, diabetes mellitus, estimated glomerular filtration ratio, and proteinuria. However, the risk of ASCVD events in former smokers was comparable to never smokers (Hazard ratio, 1.83; 95% confidence interval, 0.95-3.52).

Conclusions: In the present analysis, quitting smoking was associated with reduced risk for ASCVD compared to continuing smoking in CKD patients.

Funding: Government Support - Non-U.S.

SA-PO1121

Association Between CKD and Venous Thromboembolism Post-Hospitalization

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Background: Chronic kidney disease (CKD) has been implicated as a risk factor for venous thromboembolism (VTE), but the evidence is limited to relatively healthy populations. The objective of the current study is to discern whether parameters of kidney function and damage are associated with the occurrence of VTE after hospitalization.

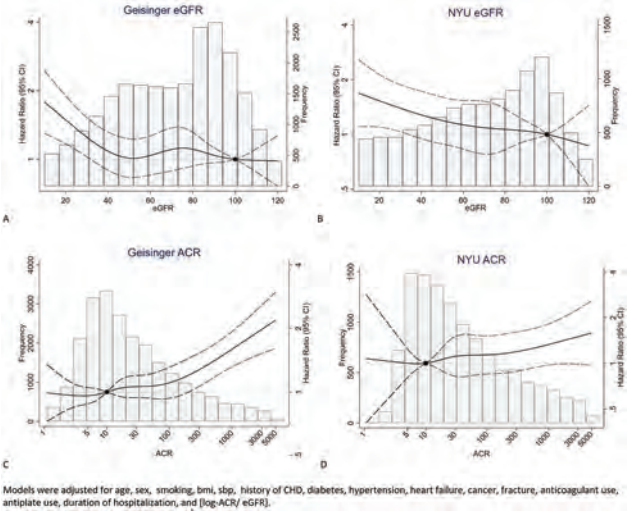
Methods: We conducted a retrospective study including 24,048 and 11,737 adult individuals hospitalized within Geisinger Health and NYU Langone Health from 2004 to 2019 and 2012 to 2022, respectively. A Poisson model was used to evaluate adjusted incidence rates of post-hospitalization VTE according to estimated glomerular filtration rate (eGFR) and albuminuria stages of CKD in each cohort. Cox proportional hazards models were used to analyze associations of eGFR and urine albumin to creatinine ratio (ACR) with VTE.

Results: In the Geisinger cohort, the incidence of VTE after hospital discharge increased from 10.7 (95% CI 9.2 – 12.6) events per 1000 person-years in individuals in G1A1 (eGFR>90 mL/min/1.73 m^2 and ACR <30 mg/g) to 27.7 (95% CI 20.7 – 37.3) events per 1000 person-years in individuals with G4-5A3 (eGFR<30 mL/min/1.73 m^2 and ACR >300 mg/g), with similar findings in the NYU cohort. Meta-analysis of the two cohorts showed that every 10 mL/min/1.73m^2 reduction in eGFR below 60 mL/min/1.73m^2 and each two-fold increase in ACR were associated with a higher risk of VTE (HR 1.08, 95% CI [1.02 – 1.15] and HR 1.05, 95% CI [1.03 - 1.08]) respectively.

Conclusions: Both eGFR and ACR are independently associated with increased risk of VTE after hospitalization. The incidence rate increases with the severity of CKD. This suggests the potential need for targeted strategies of VTE prophylaxis after hospitalization in individuals with CKD.

Funding: Other NIH Support - K24HL155861 and R01DK115534

Figure. Adjusted hazard ratios of post-hospitalization VTE with eGFR and (log) ACR modeled as cubic splines



Models were adjusted for age, sex, smoking, bmi, sbp, history of CHD, diabetes, hypertension, heart failure, cancer, fracture, anticoagulant use, antiplate use, duration of hospitalization, and (log-ACR/ eGFR).

SA-PO1122

Longitudinal Trajectory Triglyceride-Glucose (TyG) Index Associated with Adverse Renal Outcome in Metabolic Dysfunction-Associated Fatty Liver Disease

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Background: Nonalcoholic fatty liver disease (NAFLD) is considered a multisystem disease that is significantly associated with an increased risk of chronic kidney disease (CKD), cardiovascular disease and extrahepatic malignancies. Recent study demonstrated that the metabolic dysfunction-associated fatty liver disease (MAFLD) definition identified a higher proportion of individuals at risk of developing incident CKD than the NAFLD definition. Triglyceride-glucose (TyG) index is a marker for predicting metabolic syndrome and also shows an insulin resistance state. This study aimed to evaluate the association between the longitudinal trajectory TyG index and CKD progression in patients with MAFLD.

Methods: In the data from the medical records database in Gangnam Severance Hospital from 2006 through 2020, a longitudinal analysis included participants with CKD. MAFLD was diagnosed in patients with was diagnosed in individuals with hepatic steatosis and at least one of the conditions as follows: 1) overweight or obese (defined as body mass index [BMI] ≥ 23 kg/m2), 2) type 2 diabetes mellitus, or 3) two or more

metabolic abnormalities. Adverse renal outcome was defined by a reduction in the estimated glomerular filtrations rate (eGFR) ≥30% of baseline. The changing trend of TyG index over time was classified using latent variable mixture modeling with TyG index during the exposure period. Logistic regression analyses were used to determine the association between TyG index and progression of CKD by adjusting for the influence of confounders.

Results: The study included 4,286 patients, of whom 1287 had MAFLD. Mean age was 52.3 ± 10.9 years. Two distinct groups of TyG index trajectories were identified during the exposure period: decreasing (n= 649) and increasing (n=638). During the event accrual period, 136 patients (10.57 %) developed adverse renal outcomes, and the risk was higher in the increasing TyG trajectory group than in the decreasing TyG trajectory group (hazard ratio 2.265, 95% CI (1.114-4.608), P=0.024). The results were similar after adjustment for baseline clinical characteristics, comorbidities, anthropometric and laboratory findings, and eGFR.

Conclusions: An increasing tendency of TyG index was associated with a higher risk of adverse renal outcomes in patient with MAFLD.

SA-PO1123

Exploratory Study on Renal Dysfunction and Its Risk Factors in Patients with Inflammatory Bowel Disease

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Background: Many studies have consistently demonstrated a higher incidence of renal function decline and progression to chronic kidney disease in patients with inflammatory bowel disease (IBD), primarily attributed to factors such as dehydration, malnutrition, medication side effects, and the impact of the underlying inflammatory bowel disease. However, there is a scarcity of data regarding the precise association between IBD and impaired renal function, as well as the specific risk factors involved. This study aims to investigate the frequency of renal function decline and identify the associated risk factors among patients diagnosed with IBD.

Methods: We performed a retrospective observational cohort study of patients at Yokohama City University Medical Center in Japan. We enrolled patients diagnosed with ulcerative colitis (UC) and Crohn's disease (CD) between 2016 and 2021 who had an eGFR of 60mL/min/1.73m^2 or higher at the time of diagnosis. We collected data, including eGFR and other blood test results, from patients over a period of two years. The participants were divided into two groups: a group that experienced a decline of 30% or more compared to baseline eGFR, and a group that did not experience a decline based on eGFR two years later. The study then evaluated the differences in baseline values between these two groups. Risk factors for renal dysfunction were assessed by univariate and multivariate analysis.

Results: A total of 351 eligible patients with UC and 184 with CD were included. The mean age at the time of diagnosis was 41.9 years with UC and 36.1 years with CD. The frequency of eGFR decline of 30% or more was 19.0% (67 patients) with UC and 17.3% (32 patients) with CD. Univariable analysis demonstrated several possible risk factors, including albumin with UC and hemoglobin with CD at the time of diagnosis. Multivariate regression analysis demonstrated albumin was an independent determinant factor with UC (95% confidence interval(CI): 0.22-0.60, *P*<0.01) and hemoglobin was an independent determinant factor with CD (95% CI: 0.53-0.87, *P*<0.01).

Conclusions: Patients with IBD have a high incidence of concurrent renal impairment, as previously reported, and in UC, albumin levels at diagnosis and in CD, hemoglobin levels at diagnosis were found to be significantly associated with decreased renal function at 2 years.

SA-PO1124

Fibrotic Burden in Patients with Hepatitis B Virus-Related Cirrhosis Is Independently Associated with Poorer Kidney Outcomes

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Background: Liver cirrhosis and chronic kidney disease (CKD) are chronic conditions that share cardiometabolic risk factors and pathogenic mechanisms. We investigated whether higher fibrotic burden was independently associated with poorer kidney outcomes in patients with hepatitis B virus (HBV)-related cirrhosis.

Methods: A total of 1,691 patients with HBV-related cirrhosis without baseline CKD who underwent transient elastography (TE) between March 2012 and August 2018 were selected. The study outcome was the composite of development of incident CKD, defined as the occurrence of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 or proteinuria (≥1+ on dipstick) on two consecutive measurements during follow-up, 50% decline in eGFR or onset of end-stage kidney disease, or all-cause mortality.

Results: The mean age was 53.4 years and 1,030 (60.9%) patients were male. During 8,379 person-years of follow-up (median 5.2 years), 60 (3.5%) patients experienced study outcomes. When stratified according to TE-defined fibrotic burden, multivariable Cox models revealed that risk of poorer kidney outcomes was 2.77-fold (95% CI, 1.16-6.63, *P*<0.001) higher in patients with cirrhotic range liver stiffness (≥11.7 kPa), compared to those without significant liver fibrosis (<7.9 kPa).

Conclusions: Higher fibrotic burden assessed using TE was independently associated with poorer kidney outcomes in patients with HBV-related cirrhosis.

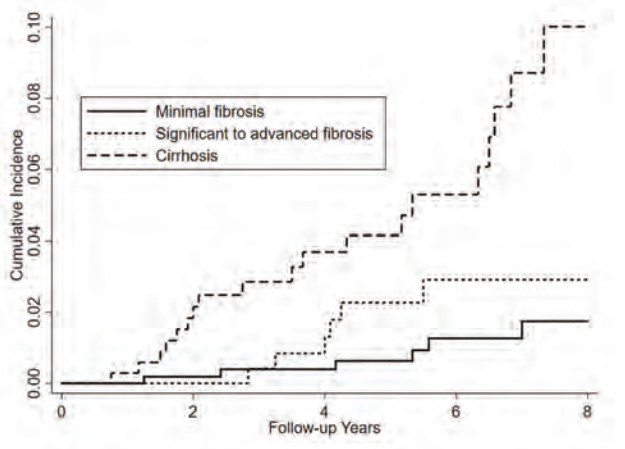

Figure 1. Cumulative incidence of adverse kidney events by fibrotic burden. Log-rank test *P* < 0.001. *Abbreviations:* TE, transient elastography.

SA-PO1125

Risk of Incident CKD Among Patients with Urolithiasis: A Nationwide Longitudinal Cohort Study

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Background: Urolithiasis has been infrequently implicated to have a causal association with chronic kidney disease (CKD). Recently, several studies have demonstrated the relationship between urolithiasis and CKD. However, the generalizability of their results is limited. We aimed to examine the association between the long-term effects of urolithiasis and the risk of incident CKD.

Methods: From the longitudinal National Health Insurance Service data, this nationwide population-based cohort study identified 219,570 Korean adults with incident urolithiasis requiring procedural interventions and without prior kidney disease and 219,570 controls without urolithiasis matched by age and sex. The primary outcome of interest was the de novo development of CKD, defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 for at least two consecutive measurements at least 90 days apart. In the sensitivity analyses, the risk of incident CKD was further examined using the outcome defined by the newly occurring diagnostic codes indicating CKD.

Results: Over a mean follow-up of 6.0 years, 12,338 (2.8%) primary outcome events of CKD were observed, with an incidence rate of 4.6 per 1,000 person-years. Multivariable Cox analysis revealed that patients with urolithiasis were associated with a higher risk of incident CKD compared with controls, with an adjusted hazard ratio of 1.41 (95% confidence interval, 1.36–1.46). This association remained consistent across all clinically relevant subgroups and when the CKD outcome was defined based on the diagnostic codes in the sensitivity analysis.

Conclusions: In this large national cohort study, patients with urolithiasis were associated with a higher risk of incident CKD than those without urolithiasis. Further studies are warranted to establish the benefits of preventing urolithiasis in reducing CKD development.

SA-PO1126

The Association of Kidney Function with Disposition After Inpatient Noncardiac Surgery: A Population-Based Cohort Study

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Background: People with advanced kidney disease have more non-cardiac surgeries compared to the general population and a higher risk of postoperative cardiac events and death. However, whether post-operative length of hospitalization and discharge disposition vary with kidney function is not known. In this population-based cohort study from Alberta, Canada, we explored differences in postoperative length of stay (LOS), the number of days spent at home after surgery within 30 days (home time), and the discharge disposition according to preoperative kidney function.

Methods: We identified adults undergoing inpatient surgery between April 2005 and February 2019, and categorized them by preoperative outpatient kidney function based on eGFR in mL/min/1.73m^2: ≥ 60 (G1-2), 45-59 (G3a), 30-44 (G3b), 15-29 (G4), < 15 not receiving dialysis (G5ND) and receiving dialysis (G5D), and kidney transplant recipients (G1T-5T). Outcomes of interest were LOS, home time, and discharge disposition. We estimated associations between eGFR category and outcomes with multivariable generalized estimating equation (GEE) models to account for multiple surgeries clustered at the patient level.

Results: We identified 927,560 inpatient surgeries in 666,770 people, with 55.9% of patients being female and median age of 57.4 years. People receiving dialysis (G5D) had the longest adjusted LOS at 17.9 days (95%CI 17.0, 18.7), more than 2 times greater

than people with G1-2 kidney function (Adjusted Rate Ratio [ARR] of 2.21 [95%CI 2.10, 2.32]). This group also had the lowest home time, with an ARR of 0.69 (95%CI 0.67, 0.70) compared to people with G1-2 function. Most people were discharged home without support after surgery (82.8%), though people with G5D function were discharged to a facility with 24-hour nursing care nearly 4 times more often than the G1-2 group. There were graded increases in risks of these outcomes among adults with G3-G5ND kidney function.

Conclusions: Patients with advanced kidney disease spend significantly more time in hospital after surgery, and less time at home. They are also more likely to be discharged with additional support at home or to a facility with nursing support. These findings may help inform perioperative resource planning and shared-decision making.

SA-PO1127

Association of Albuminuria with Interstitial Lung Abnormalities

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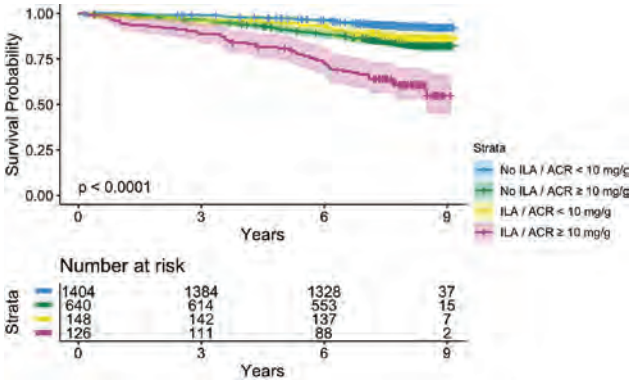
Background: Pulmonary microvascular dysfunction has been implicated in the pathogenesis of pulmonary fibrosis. Albuminuria, a marker of endothelial dysfunction, may be a risk factor in the early development of interstitial lung disease (ILD). We hypothesized that higher UACR would be associated with interstitial lung abnormalities (ILA), which may represent early stages of pulmonary fibrosis.

Methods: A subset of the U.S. population-based Multi-Ethnic Study of Atherosclerosis cohort (n = 2,260) had spot UACR and full-lung CT measurements at Exam 5 (2010–2012). The association between UACR and ILA was examined cross-sectionally using a generalized linear mixed model accounting for clustering by study site. Due to potential differential associations by age, we performed a stratified analysis with an age cutoff of 65 years. Kaplan-Meier estimation was used to examine whether UACR modified the association of ILA with all-cause mortality (2010–2019).

Results: Compared to participants without ILA, those with ILA (11.8%) were older (74.2±9.1 vs. 68.2±9.0 years), had higher UACR levels (8.4 [IQR, 4.0–20.3] vs. 5.8 [3.5–12.6] mg/g creatinine), and a higher prevalence of smoking history. After adjustment for covariates, UACR was not associated with ILA in the overall group (P=0.71). An association was observed in the age≥65 (OR=1.17, 95% CI: 1.06–1.29; P=0.002) but not in the age<65 group (P=0.88). Adjustment for age in stratified analysis did not change the estimates considerably. The presence of both ILA and higher UACR (≥10 mg/g) was associated with greater risk of death when compared with fulfilling only one or none of the two criteria (Figure; log-rank P<0.001).

Conclusions: Albuminuria was associated with more ILA and worse survival in older community-dwelling adults. Albuminuria may be a risk factor in early ILD and requires further investigation.

Funding: Other NIH Support - NHLBI (NIH) grants R01-HLO77612, R01-HLO93081, and RC1-HL100542 and contracts (HHSN268201500003I, N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169).



SA-PO1128

Impact of CKD on Incidence of Visual Impairment: The Singapore Epidemiology of Eye Diseases Study

Charumathi Sabanayagam,[1,2] Joanna Chiok,[1] Feng He,[1] Cynthia C. Lim,[3] Gavin Tan,[1,2] Ching-Yu Cheng.[1,2] *[1]Singapore Eye Research Institute, Singapore, Singapore; [2]Duke-NUS Medical School, Singapore, Singapore; [3]Singapore General Hospital, Singapore, Singapore.*

Background: To examine the impact of chronic kidney disease (CKD) on the incidence and severity of visual impairment (VI) in a population-based sample of Asian adults.

Methods: We analysed data from 4732 Chinese, Malay and Indian adults who participated in the baseline (2004-2011, aged 40-80 years) and 6-year (2011-2017) follow-up visit of the Singapore Epidemiology of Eye Diseases and were free of VI at baseline. CKD (n=447, 9.4%) was defined as an estimated glomerular filtration rate (eGFR)<60 ml/min/1.73 m2 and severity of CKD was categorized into stages G1-5. Participants underwent comprehensive eye examinations including refraction and slit-lamp examinations. Incident VI was defined as best-corrected visual acuity (BCVA) <20/40 in the better eye. Severity of VI was defined as normal, low vision and blindness (≥20/40, <20/40 to >20/200 and ≤20/200). Associations between CKD and VI were examined using Logistic regression models adjusted for age, gender, ethnicity, diabetes, and hypertension status.

Results: The incidence of VI was significantly higher in individuals with CKD compared to those without (14.3% vs. 3.3%, p<0.001). In severity analyses, incidence of low vision and blindness were also higher in those with CKD (13.4% and 0.9%) compared to those without (3.3% and 0%, p<0.001). There was a clear trend of increasing incidence of VI with the progression of CKD stages, with rates of 3.3%, 13.5%, and 16.3% in stage G1-2, G3a, and G3b-G5 (p-trend <0.001, Figure 1). After adjusting for other factors, CKD was independently associated with an increased risk of any VI, with an odds ratio of 1.47 (95% confidence interval: 1.03 -2.10).

Conclusions: Our results suggests that the presence of CKD increased the risk and severity of VI in Asian adults. Given the increasing prevalence of CKD worldwide, these findings highlight the importance of regular ocular examinations for individuals with CKD to reduce the risk of VI.

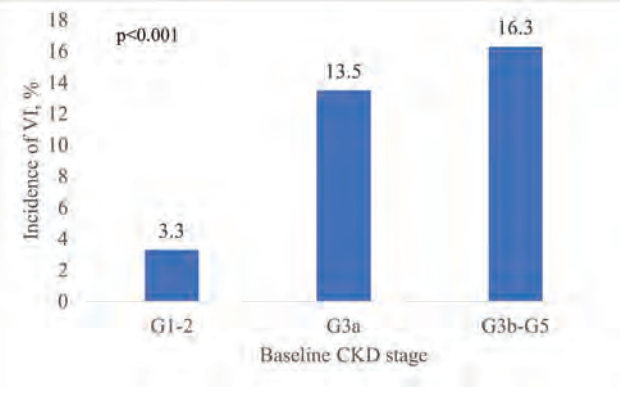


Figure 1: Incidence of VI by baseline CKD stage

SA-PO1129

Time Is Nephron: Chronic Urinary Bladder Herniation Resulting in ESKD

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Introduction: Inguinal hernias involving the urinary bladder occur in 0.4-3% of cases. They are often asymptomatic but can result in lower abdominal discomfort, urinary tract infections, and kidney complications. We present a patient with an inguinal urinary bladder hernia presenting with end-stage kidney disease.

Case Description: 43-year-old class 3 obese male was admitted for an enlarging right inguinal hernia. The surgeon advised him to return to the specialty clinic for his 8 month-long-lump after seeking urological assistance and deciding on his choice of surgical option offered. 3 weeks before admission, he was noted to be uremic and oliguric. On admission, his vital signs were stable, and physical examination revealed bilateral inguinal hernia, and lab results showed S. Cr 14.07mg/dL, BUN 226mg/dL, S. K 6.1mmol/L, and S. Bicarb 7mmol/L. The CT scan revealed a grossly distended urinary bladder herniating into the right inguinal canal and bilateral hydronephrosis. The patient declined kidney replacement therapy due to concerns about his quality of life. He was managed medically and discharged home on hospice care at his request. His S. Cr levels stabilized(in the high 7s), and he passed away one month after hospitalization.

Discussion: Urinary bladder herniation(UBH) can occur as direct inguinal hernia and, less commonly, as indirect inguinal or femoral hernia. Male gender, advanced age, obesity, bladder obstruction, and abdominal wall weakness are contributing factors. Most cases are asymptomatic, but some experience groin pain, urinary retention, hematuria, flank pain, or lower urinary tract symptoms. If left untreated, long-standing urinary bladder hernias cause renal failure, bladder perforation, recurrent stones, or hydronephrosis.

Symptomatic UBH usually require emergency management, initial drainage using a Foley catheter before definitive surgery. Ultrasound, computed tomography scan, or MRI can aid in diagnosis and surgical planning. Open repair of urinary bladder herniation involving reduction of the bladder, followed by a standard herniorrhaphy technique, is the typical approach; however, conventional and robotic-assisted laparoscopic repairs have also been reported. UBH is a rare and overlooked condition more prevalent in high-risk populations such as overweight men. Timely diagnosis and surgical repair are crucial to prevent irreversible kidney damage and fatal outcomes.

SA-PO1130

Dynamic Bayesian Networks (DBN) Predicted ≥40% Decline in eGFR over Six Years

Panayiotis Petousis,[1] David Gordon,[1] Kenn B. Daratha,[2] Keith C. Norris,[1] Katherine R. Tuttle,[2] Susanne B. Nicholas,[1] Alex Bui.[1] Center for Kidney Disease Research, Education, and Hope (CURE-CKD). *[1]University of California Los Angeles, Los Angeles, CA; [2]Providence Medical Research Center, Spokane, WA.*

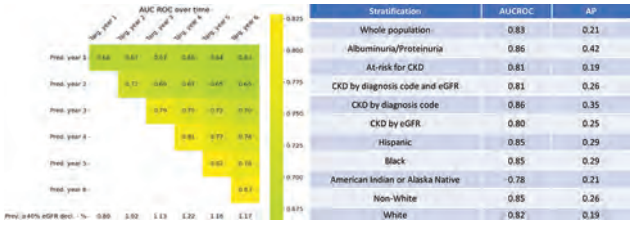
Background: A ≥40% decline in eGFR over two years is associated with an adjusted hazard ratio of ~10 for progression to kidney failure in patients with chronic kidney disease (CKD). Here, we predicted ≥40% eGFR decline at least one year in advance and simulated missing values along a patient's CKD trajectory.

Methods: Electronic health records from patients with and at-risk (diabetes, prediabetes, hypertension) for CKD (by diagnosis code and eGFR <60 mL/min/1.73 m^2) from the CURE-CKD Registry (1/1/2006-12/31/2020; N=2,250,806) at Providence (N=1,917,619) and UCLA (N=333,187) Health were used. A DBN for CURE-CKD was created using the Ranking Approaches for Unknown Structures software. The DBN was trained, tuned, and validated on a blind test set. We included demographics, comorbidities, lab values, medications, and vitals over 6 years. The primary outcome was an annual ≥40% decline in eGFR from baseline.

Results: Using observations before the prediction year, the DBN predicted the outcome of the target year despite an average rate of 29% missing values across most variables. Model performance improved over time, suggesting that longer follow-up improved the simulation of missing values and the prediction of ≥40% eGFR decline. By the 6th year, the model achieved an area under the receiver operating characteristic curve (AUCROC) of 0.83 and an average precision (AP) of 0.21 (Figure). When stratified, patients with albuminuria/proteinuria had the highest prevalence of ≥40% eGFR decline and were most accurately predicted (Table), and higher performance was observed in Hispanic and Black groups, who had a higher prevalence of ≥40% eGFR decline versus the whole population.

Conclusions: DBNs can simulate missing data to predict ≥40% eGFR decline in patients with CKD and in racial and ethnic minority groups. Model performance dramatically improved with longer follow-up.

Funding: Other NIH Support - NIMHD



Stratification	AUCROC	AP
Whole population	0.83	0.21
Albuminuria/Proteinuria	0.86	0.42
At-risk for CKD	0.81	0.19
CKD by diagnosis code and eGFR	0.81	0.26
CKD by diagnosis code	0.86	0.35
CKD by eGFR	0.80	0.25
Hispanic	0.85	0.29
Black	0.85	0.29
American Indian or Alaska Native	0.78	0.21
Non-White	0.85	0.26
White	0.82	0.19

Model performance for >=40% eGFR decline in the 6th year

PUB001

Characterization of Acid-Base Status of Critically Ill COVID-19 Patients by Stewart's Methodology

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Background: SARS-CoV-2 infection is associated with unfavorable outcomes and high costs. Although the occurrence of electrolyte derangements in the affected patients is expected to have significative clinical impact, more detailed description and associations to outcomes remains scarce, and limited to the traditional approach of Hendelsson-Hasselbach.

Methods: We conducted a cohort of adult patients with ICU stay of more than 4 days that had blood gas analysis and a typical chest CT involvement at admission. SARS-COV-2 infection was diagnosed by a positive PCR from nasal swab. Data was analyzed in the PSPP statistical package, version 1.2.1.

Results: A total of 799 patients had a COVID-19 diagnosis in our hospital, and 456 were admitted to an intensive care unit. From these, 211 patients had at least a 4 day ICU hospital and were analyzed; the mortality rate of this group was 13,7%. Overall, 149 patients (70,6%) presented alkalemia, 28 acidemia (13.3%) and the remaining 34 patients (16.2%) had a normal arterial pH. From those presenting acidemia, most had a low aSID (20 patients, 9,5%); within the group with alkalemia, 128 (61% of all patients) had respiratory origin. The non-survivors were older, had more co-morbidities and a higher Charlson's and SAPS 3 scores. Bacterial infections were also more common in this group. Blood gas variables were similar in both groups; overall, we did not find severe acid-base derangements in this population. Stewart 's variables analyzed - SID eff, SID app, SIG, and the albumin, lactate, phosphorus and chloride effect were not different between both groups.

Conclusions: The description of acid-base variables in SARS-COV-2 infected patients remains scarce, and limited to the traditional approach. Alkalemia was the most prevalent acid base disturbance in this population, and mainly of respiratory origin. Although we did not found association between acid-base variables by Stewart's methodology and mortality, dialysis and respiratory failure, the use of this innovative methodology may provide valuable insights in the description of this severe disease.

PUB002

COVID-19 Is Associated with Hyponatremia up to 90 Days, but Long COVID Is Not Associated with Chronic Hyponatremia

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Background: Hyponatremia has also been reported with high frequency (25% to 45%) and to predict mortality among patients hospitalized with COVID–19. There are no studies that address hyponatremia at longer periods after COVID - 19 diagnosis.

Methods: This is a retrospective cohort studying using data from TriNetX research network containing 93 million unique EMR records. **Exposure**: COVID-19 diagnosis. **Outcomes:** serum sodium levels, mild (130-134 mmol/L), moderate (125-129 mmol/L), or severe (<124mmol/L) hyponatremia. Differences in outcomes between the respective cases and control cohorts were evaluated after propensity score matching with student t-test for the continuous variables and chi-squared test for dichotomous variables. We report risk differences and differences in mean sodium level.

Results: In high-risk patients, COVID - 19 cases had lower sodium values up to 30 days after COVID-19 and had higher risk of hyponatremia up to 90 days following COVID-19 than the controls. In low-risk patients, COVID-19 cases had lower sodium values up to 14 days after COVID-19 and had a higher risk of mild or moderate hyponatremia up to 30 days following the COVID-19 diagnosis than the controls and higher risk of severe hyponatremia up to 7 days after COVID-19 than the controls; whereas at all greater time points, there were no differences in rates of hyponatremia between the cases and controls.

Conclusions: COVID – 19 is associated with the development of mild, moderate and severe hyponatremia that persists for durations longer the acute time frame. COVID – 19 during the sub-acute phase can be complicated by hyponatremia, but that durations > 90 days (long COVID), are not associated with hyponatremia.

Figure 2. High risk

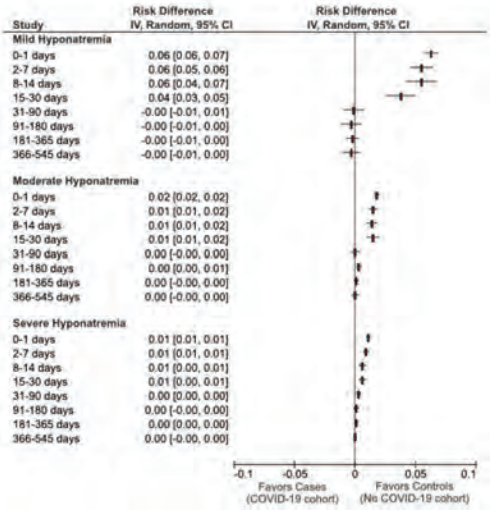
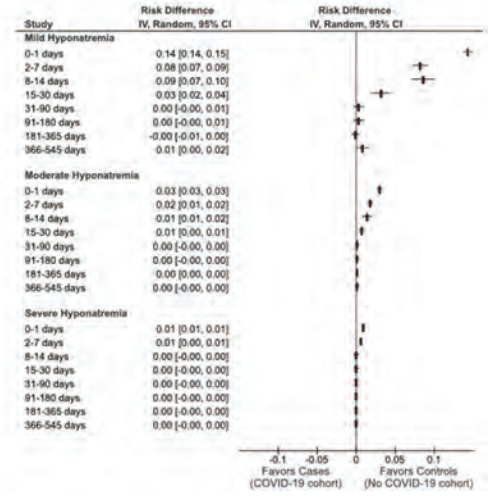


Figure 3. Low risk



PUB003

New-Onset Severe Eosinophilic Granulomatosis with Polyangiitis (EGPA) Following the Third Dose of COVID-19 Vaccine

Samia Ait Faqih, Krishnamoorthy Sundara Raman, Alaedin Shurrab. *Hamad Medical Corporation, Doha, Qatar.*

Introduction: Vaccines against SARS-CoV-2 represent a pivotal and effective countermeasure to contain the COVID-19 pandemic by stimulating both humoral and cellular immunity. Although anti-SARS-CoV-2 vaccines are highly safe, there are reports suggesting that they might be able to trigger de-novo or exacerbate pre-existing immune-mediated diseases. This case report suggests association between COVID-19 vaccination and new-onset EGPA.

Case Description: A 53-year-old patient presented with a history of asymmetrical hand clumsiness associated with difficulty in walking. He also reported a history of fatigue, myalgia and nonpruritic skin rash over the back and both lower limbs since he received the third dose of COVID-19 vaccine. The first two doses COVID-19 vaccines were given eight months ago, three-week apart, and he was not diagnosed to have COVID-19 disease before. The neurological assessment showed distal muscle weakness of both upper limbs. Lower limb examination revealed non-blanchable violaceous skin rash over both shins. The autoimmune panel was positive for p-ANCA. Nerve Conduction study is consistent with acute mononeuritis multiplex. A skin biopsy showed leucocytoclastic vasculitis, the kidney biopsy confirmed the presence of pauci-immune necrotizing and crescentic glomerulonephritis. He received induction therapy of methylprednisolone and Rituximab with a repeated dose two weeks later. Then maintained on a tapering dose of prednisolone and Rituximab infusion every 6 months. One year later, the patient was still having left wrist drop with significant wasting of the small muscles of both hands, his renal function was stable with undetectable ANCA antibody level. Repeat EMG and NCS showed worsening electrophysiological features of mononeuritis multiplex. He has since been started on cyclophosphamide and IV Ig.

Discussion: We present a case of new-onset multisystemic EGPA following a booster dose of covid 19 vaccine in a patient with no personal or family history of auto immunity. Since there is no temporal association between vaccine administration and disease onset, it is difficult to establish a causal relationship. Nevertheless, our report may suggest that caution should be paid during the administration of Covid 19 vaccines. However, these events are extremely rare and further studies are required to draw reliable conclusions.

PUB004

A Retrospective Cohort Study on the Duration of Dexamethasone and Clinical Outcomes of CKD Patients on Dialysis with Severe to Critical COVID-19

Marie Kathleen R. Uy-Huang Chih Chang. *National Kidney and Transplant Institute, Quezon City, Philippines.*

Background: Chronic kidney disease [CKD] is considered an important comorbidity associated with adverse outcomes in patients with COVID-19. There is no current studies on corticosteroids on dialysis patients. Hence, this study aimed to compare the clinical outcomes of patients who received a short course and a longer course. The results and analysis from this study will help treat CKD patients with severe to critical COVID-19.

Methods: A retrospective review of patients with CKD on dialysis, with a diagnosis of severe or critical COVID-19, received intravenous dexamethasone, and was admitted at the NKTI from July 1, 2020 to December 31, 2021. This study included all adult patients who, before COVID-19 infection, were diagnosed with CKD V and on dialysis and tested positive on COVID RT-PCR. Excluded are patients who had been on steroid therapy before COVID-19 infection or admitted as reinfection or readmission for COVID-19.

Results: The analysis showed no significant difference in the baseline measurements of oxygen saturation, ejection fraction, hemoglobin, WBC, platelets, inflammatory markers between groups. The median number of days of dexamethasone was 3 days and 10 days for shorter and longer course, respectively. Patients in the longer course group had lower 30-day mortality (54%). The 30-day mortality rates were 67.44 (95% CI 61.83–72.71) % overall. The numbers needed to treat to prevent 1 death was 3.33 and 3.45 among severely-ill and critically-ill COVID-19 patients, respectively. A longer dexamethasone course showed lower 30-day mortality. In addition, patients in the longer course group had a prolonged duration of confinement and days on oxygen support.

Conclusions: Our data shows that 6 mg dexamethasone for more than 5 days, with a median of 10 days, lowers the risk of death in patients with severe to critical COVID-19 with CKD Stage V on dialysis. In addition, patients' period of hospitalization and need for oxygen support was directly proportional to the duration of dexamethasone. Therefore, appropriate dosage and duration of dexamethasone after onset are essential in treating patients with severe and critical COVID-19.

PUB005

An Unusual Presentation of Acquired Thrombotic Thrombocytopenic Purpura in a Young Patient with COVID-19

Leonardo R. Ramirez Botana. *Hospital de la Concepcion, San German, Puerto Rico.*

Introduction: Acquired thrombotic thrombocytopenic purpura (aTTP) is a medical emergency. Untreated thrombotic thrombocytopenic purpura is usually fatal, but with proper treatment, survival rates are over 90 %. Cases of aTTP have been described in a population greater than 55-year-old. Very few cases after COVID- 19 infection in a population between 20 and 30 years old.

Case Description: We describe a 36-year-old man, no past medical history, who developed a progressive worsening shortness of breath during active COVID-19 infection. He had positive COVID-19 Ag test 6 days ago before admission. These symptoms were associated with moderate abdominal pain, 7/10 intensity, localized upper and left side of the abdomen, non radiated, constant, that worsening any time the patient breath. Patient has 38.6 C of temperature at ER, and after 2 hours of this episode he started to had numbness and weakness in left arm, one episode of left arm involuntary movement, fatigue and general weakness. Labs shows anemia, profound thrombocytopenia with schistocytes on peripheral smear, acute renal failure and normal coagulation profile, Direct Coombs Test negative and was order Adams13 test Antibody.

Discussion: The association of this episode of aTTP with COVID-19 infection, with no other discernible cause in this patient, made COVID-19 infection the most likely the trigger to produce this disase. Circulating SARS-CoV-2 attaches and enters into the cytoplasm of monocytes, platelets, and endothelial cells; causing their activation and release of pro-inflammatory and pro-coagulant activators leading to a hypercoagulable state. In four of six reported cases reviewed, aTTP was present at the time of the COVID-19 diagnosis or within 10 days. Four out of six COVID-19 infected patients who developed aTTP had a mild course of COVID-19 infection. All patients reported had recovered after treatment, however, three patients had a prolonged and complicated recover. This case highlights the fact that TTP may occur with days after be diagnosed of COVID-19 infection. Clinicians should be aware of this association for prompt recognition and timely treatment. There is a significant increase in acquired thrombotic thrombocytopenic purpura in patients with COVID 19 infection, however, with the correct treatment, the severity of acquired thrombotic thrombocytopenic purpura may have short-term prognostic significance.

PUB006

Prevalence and Risk factors of AKI in Hospitalized Patients with COVID-19

Reem J. Hashem, Hanaa O. Okda, Nashwa M. Elgharbwy, Kamal M. Okasha. *Tanta University, Tanta, Egypt.*

Background: Acute kidney injury (AKI) has been frequently described in Covid-19 patients with reports confirming its negative impact on Covid outcomes.

Methods: This prospective cross-sectional study focused on all admitted Covid19 patients between September and December 2020. A total of 480 patients were enrolled. Patient demographics, medical records, and laboratory data were gathered. Patients were split into two groups: AKI and non-AKI. Comparisons comprised demographics, labs, ICU transfer, need for ventilation and oxygen therapy, medications, hospital stay, and deaths. Patients COVID - 19 positive patient diagnosis based on Clinical symptoms and signs (Fever, Cough, Breathing difficulties, Organ failure). Laboratory findings as elevation of inflammatory biomarkers (CRP, Ferritin, D-dimer, INR, Lactate dehydrogenase), decrease in lymphocyte and hypokalaemia. and Polymerise chain reaction (PCR).

Results: Showed incidence rate of 40.83% of AKI. The prevalence of HTN was 57.1% in the AKI group which was statistically significantly higher as compared with the non-AKI cases, as well as the prevalence of DM was 67.3% in the AKI group which was significantly higher. Fever was the most common clinical presentation (93.3%) followed by fatigue (70.8%), cough (65.8%) and headache (60%). The prevalence of critical Covid19 disease severity was 44.9% in the AKI group which was significantly higher as compared with the non- AKI (19.7%) (p= 0.005). The duration of hospital admission was statistically significantly longer in the AKI cases. In terms of ICU transfer, 55.1% of patients with AKI were transferred to the ICU and 33.8% of the non-AKI group (P<0.001%). Regarding overall mortality11.7% died in hospital. Among AKI patients, 16.3% died compared to 8.5% among non-AKI group (P=0.008). Also severity of the disease was 44.9% in AkI group and 19.7% in non AKI patients (P=0.005).

Conclusions: Acute kidney injury in patients infected with Covid-19 is associated with a significant increase in patients' morbidity and mortality. Identification of the risk factors is crucial for early anticipation and management of this dreadful complication. This study should make risk stratification of clinical-based scoring systems for the prediction of AKI in Covid patients in order to early manage the problem in high-risk cases by protective measures.

Funding: Other NIH Support - Tanta university

PUB007

Analysis of Reasons for Refusing COVID Vaccination or Boosters in Central Washington Patient Populations with CKD

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Background: Numerous studies have demonstrated improved hospitalization outcomes and reduced mortality rates in COVID-vaccinated patients with CKD, including those who have received a booster. The Nephrology Associates of Yakima (NAY), located in rural Central Washington manages a diverse patient population who are on dialysis, are immunosuppressed with kidney transplants, and are diagnosed with early CKD. These patients are associated with high mortality rates with COVID infections. Despite all the public health emphasis, it is concerning that vulnerable high risk populations, such as patients with CKD, continue to exhibit vaccine hesitancy.

Methods: We screened 345 patients in central Washington area to identify individuals who either refused all COVID vaccines or refused the COVID booster after receiving the initial Covid vaccine series during the encounter period of December 2022 to March 2023. Of the 40 patients who were identified during the screening process, 36 individuals (52% women and 48% men) agreed to participate. Surveys were conducted during appointments at the NAY clinic and the 5 DaVita Dialysis Centers located in Yakima and Kittitas County. In total 4 patients refused to fill the survey.

Results: Of the total 36 pts identified, 23 patients had ESKD and were on dialysis, 2 pts had Kidney Transplant and remaining 11 had Other CKD issues. The Age spread : 6 pts were less than 40 yrs old, age group 40 to 60 yrs included 7 pts and Age group More than 60 yrs included 23 total pts. The Race/Ethnicity data : Caucasian pts total included 25, Hispanic pts total included 10, Asian pt was total only 1. Native American pts and African American pts were none in the Covid vaccine refusal group. Our Results showed 36.11% of the 36 patients indicated, "worried about new mRNA vaccine technology" as the primary reason for refusal, followed by, "worried about side effects" at 22.22%, and "unsure of vaccine effectiveness" at 16.66%. Other reasons given were "patient believes in natural immunity" at 13.88%, "patient usually does not take any vaccines" in 8.33% and "Religious reasons" in 2.77% of patients.

Conclusions: This pilot study highlights the critical need for further patient education, especially in high-risk population. We need to improve the general public's understanding of mRNA technology for better Covid vaccine acceptance.

Funding: Clinical Revenue Support

PUB008

SARS-CoV-2 Nucleocapsid Antibodies in Kidney Transplant Recipients Are Common After Reinfection

Matthew R. D'Costa, Hersharan K. Sran, Emmett Tsz Yeung Wong, Zi Yun Chang, Anantharaman Vathsala. *National University Hospital, Singapore, Singapore.*

Background: There remains limited data on SARS-COV-2 immunity after COVID-19 infection in kidney transplant recipients (KTR), and the severity of COVID-19 reinfection (RI) in KTR is uncertain.

Methods: We performed a retrospective, single-centre study of all SARS-CoV-2-infected KTR confirmed by PCR during the Delta (09/17-12/28/21) and Omicron BA.1, BA.2, BA.4, BA.5 and XBB (12/29/21-12/31/22) waves. SARS-CoV-2 spike antibody (SpAb) levels were assessed at diagnosis. RI was defined as a new infection confirmed by PCR >90 days after recovery of first infection including symptom resolution and repeat surveillance PCR cycle threshold (CT) >25. Post-infection immunity was assessed including SpAb and SARS-COV-2 nucleocapsid (NAb) antibody >42 days post-infection.

Results: In all, 276 KTR had ≥ 1 COVID-19 infection. They were a mean 53±12 years old, 52% male, 65% ethnic Chinese, 19% obese, 36% diabetic, 91% vaccinated with ≥3 mRNA SARS-COV-2 vaccines; 56% living kidney transplant, vintage 9±7 years, 9% eGFR ≤ 30 ml/min, and 87% maintained on calcineurin-inhibitor + anti-metabolite + prednisolone. RI occurred in 25 (9%) KTR at 210 (range 103-436) days after the infection – all with Omicron variants. RI had higher SpAb at diagnosis; characteristics were otherwise similar. Severe disease (supplemental oxygen, ICU stay) occurred in 22 KTR and 3 died; no KTR with RI had severe disease. Post-infection SpAb was similar but NAb were more likely to be reactive in RI (Table 1).

Conclusions: RI in KTR was relatively mild in our well-vaccinated cohort. NAb is common in KTR with RI likely due to a memory response from prior infection. More studies are needed on the longevity and efficacy of NAb on future RI in KTR.

Table 1: Humoral immunity of kidney transplant recipients after COVID-19 infection

Table 1a: SARS-COV-2 Spike antibody and Nucleocapsid antibody pre and post-infection

N (%) or mean +/- SD	First infection (N=276)	Re-infection (N=25)	p-value
At diagnosis			
-Spike Ab, U/mL[1]	2123±3381	5500±4489	<0.001
-Spike Ab >250 U/mL	183 (66%)	24 (96%)	<0.001
-Spike Ab > 500 U/mL	158 (57%)	23 (92%)	<0.001
Post-infection			
-Spike Ab, U/mL	9267±4650	9225±4135	0.96
-Nucleocapsid antibody, reactive[2]	105 (38%)	22 (88%)	<0.001

Table 1b: Predictors of reactive nucleocapsid antibody after COVID-19 infection

	Univariate analysis Odds ratio (95%CI)	Multivariable analysis[5] Odds ratio (95%CI)
Reinfection	**17.4 (4.0-75.4)**	**18.7 (4.31-81.37)**
Age, per year	0.99 (0.98-1.02)	-
Vintage post-transplant, per year	1.00 (0.97-1.03)	-
Obesity, BMI >30 Kg/m2	1.41 (0.77-2.6)	-
COVID-19 disease variant – Omicron vs Delta	0.39 (0.14-1.09)	**0.32 (0.12-0.90)**
PCR cycle threshold	0.99 (0.99-1.00)	-
ISARIC-4C Score at Admission	1.08 (0.98-1.18)	-
Spike Ab <500 U/mL	1.03 (0.64-1.65)	-
Calcineurin inhibitor use	0.96 (0.25-3.67)	-
Mycophenolate mofetil or Mycophenolic acid vs Azathioprine/no anti-metabolite	1.65 (0.60-4.53)	-
Any mAb[3]	0.72 (0.43-1.20)	-
Early remdesivir therapy[4]	0.84 (0.51-1.39)	-
Severe disease (supplemental O2 or worse)	1.56 (0.24-9.91)	-

1.Roche® Cobas SARS-CoV-2-S assay (Spike antibody) range: non-reactive (<0.4) to >12,5000 U/mL (upper limit of assay). Non-reactive = 0 and >12,500 = 12,500 for purposes of analysis.
2. Roche® Cobas SARS-CoV-2-N assay (Nucleocapsid antibody); reactive = cut-off value ≥1.0 U/L. 8/25 (32%) of KTR with RI had reactive nucleocapsid antibody after their first infection.
3.Monoclonal antibody (mAb) treatment – sotrovimab for Delta if SpAb <100 U/mL and Ba.1 if SpAb <250 U/mL; tixagevimab/cilgavimab for BA.2 onwards –and not on oxygen/severe disease (Supp02). Tixagevimab/cilgavimab was also given for pre-exposure was given as pre-exposure prophylaxis if no prior history of infection or post-exposure prophylaxis if exposed to a household contact with COVID-19.
4.Remdesivir was given at ≤7 days of illness for BA.2 onwards if SpAb >500.
5.Adjusting for reinfection and COVID-19 disease variant as KTR with Delta variant did not have reinfection with Delta.

PUB009

Effect of CKD on the Severity of COVID-19 in Hypertensive Subjects

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Background: Comorbidities such as hypertension (HTN) or chronic kidney disease (CKD) may worsen the prognosis of subjects infected by SARS-Cov-2 and hypertensives are at greater risk of suffering renal dysfunction. The purpose of this study is to assess the effect of CKD on the progression of COVID-19 in hypertensive patients.

Methods: Multicenter, observational, cross-sectional, retrospective and analytical study. Patients, over 18y, were selected by random sampling in 10 autonomous regions of Spain, among subjects with treated HTN, infected by SARS-Cov-2 under Primary Care Health. CKD was defined as GFR<60 mL/min/1.73m^2 and/or UACR>30 mg/g creatinine. The Pearsons test and multivariate logistic regression analysis adjusted for age, sex, smoking, and obesity were used to assess the association between the severity of COVID-19 and the presence of CKD in our hypertensive population.

Results: 1372 patients were recruited, mean age 67y, women 51%, smoking 13%, obesity 44%, diabetes 28%, controlled HTN 56% (BP<140/ 90mmHg). The severity of the progression of COVID-19 was defined as mild-asymptomatic 971 (71%), hospital admission 401 (29%), ICU admission 74 (5.4%), death 48 (rate of lethality 4%). 63% had CKD with a worse prognosis, since of total hospitalizations we found 69% with CKD vs 31% without it (p=0.0064). 18% of patients with GFR<60 (77y, 54% women) also progressed worse, with 44% hospitalizations, 8% in the ICU, and mortality11%. Comparing mild-asymptomatic subjects with hospitalizated patients, those with reduced GFR had an unfavorable course (OR=2.4; 95%CI:1.6-3.7; p<0.001), without significant differences in BP. There was also greater severity of COVID-19 in smoking patients with CKD (OR=6.8; 95%CI:2.4-19.5; p<0.001) for hospitalization and (OR=6.0; 95%CI:1.7-21.6; p<0.05) for ICU admission. We did not found any effect of RAS inhibitors, statins or antidiabetic drugs.

Conclusions: The prevalence of CKD among hipertensive subjects infected by SARS-Cov-2, in our Primare Care environment is very high. CKD, even without a reduced GFR, is related to a greater severity in the progression of COVID-19. Smoking seems to exert a deleterious modulatory effect associated to CKD for the disease outcomes.

PUB010

Detailed Analysis of Kidney Transplant Recipients Admitted to a Tertiary Care Transplant Center with SARS-CoV-2

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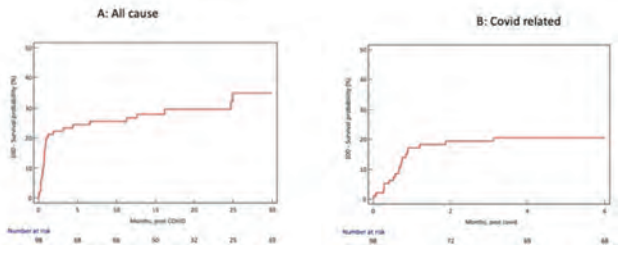
Background: Kidney transplant recipients (KTR) are a vulnerable immunocompromised population at risk of severe disease and mortality from COVID-19.

Methods: We retrospectively describe all adult KTRs who were hospitalized at our center during their first episode of COVID-19 between 04/2020 and 04/2022 and had at least 12 months follow-up (unless they experienced graft failure or death). Outcomes of interest included length of hospitalization, intensive care unit admission, respiratory symptoms at admission, uncensored graft failure at the last follow up, and death related to COVID-19.

Results: 98 KTRs were hospitalized at our center due to their first episode of COVID-19 between 04/2020 and 04/2022. The mean age at COVID-19 diagnosis was 57± 14.2 yrs. 57% of the cohort received at least one vaccine dose against SARS-CoV-2. Of those unvaccinated, 33% (14) had death at last follow-up compared to 26.7% (15) of those vaccinated. The most common cause of end stage kidney disease was diabetes mellitus (29%). The average length of hospitalization was 11.5 days, with 66% of KTRs presenting with respiratory symptoms on admission and 21% requiring intensive care unit admission. 30% died during the study period, of which 19% were COVID-19-related (Figure 1). Mortality was highest within a month of COVID-19 diagnosis.

Conclusions: In this single-center descriptive retrospective study of 98 KTRs, one fifth of those hospitalized at our center died related to COVID-19. KTRs still have high COVID-19-related morbidity and mortality.

Figure 1: Mortality



PUB011

Trajectory of Kidney Function in Patients with AKI and COVID-19 in a Reference Center in Mexico

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Background: Kidney disease due to COVID-19 is clear, however, there are few data on kidney function (KF) evolution.

Methods: Retrospective cohort conducted at the National Medical Center "La Raza" in Mexico City, Mexico. 252 patients hospitalized from March to June 2020 due to COVID-19 were included. Quantitative variables are expressed as mean ± standard deviation. Odds ratios were calculated to identify associated factors, with a 95% confidence interval.

Results: The mean age was 57.87±15.27 years. The incidence of acute kidney injury (AKI) and acute kidney disease (AKD) were 42.06% (106 cases), 18.87% (20 cases) respectively. A follow-up of at least 12 months of 9 cases was completed, of which 100% developed some stage of chronic kidney disease (CKD). The reason why it was not possible to obtain more data on KF in the rest of the patients was due to loss of follow-up. In the multivariate analysis, the factors associated with AKI were vasopressor (OR: 1.51; CI: 1.44 – 1.59 p <0.001), use of mechanical ventilation (MV) (OR: 1.35; CI: 1.27 – 1.44 p < 0.001), a high value of lactate dehydrogenase P-isoenzyme (OR: 1.32; CI: 1.22 – 1.41 p <0.001) and leukocytosis (OR: 1.23; CI: 1.14 – 1.43 p < 0.001). In the univariate analysis, the factors associated with AKD were coronary artery disease (OR: 5.55; CI: 1.56 - 19.67), use of MV (OR: 4.90; CI: 1.72 - 13.97), mild thrombocytopenia (OR: 4.19; CI: 1.36 – 12.94), use of lopinavir/ritonavir in hospitalization (OR: 3.34; CI: 1.10 – 10.13) and use of angiotensin II receptor antagonist in hospitalization (OR: 3.03; CI: 1.13 – 8.12). In the univariate analysis, the factors associated with CKD were type 2 diabetes (OR: 4.23; CI: 1.03 – 17.34) and the use of lopinavir/ritonavir (OR: 1.13, CI: 1.06 – 1.22). In patients with AKI and AKD associated with COVID-19, a mortality of 64.15% (68 cases, OR: 5.46; CI: 3.16 - 9.44), 80% (16 cases, OR: 4.62; CI: 1.75) was observed. – 12.17).

Conclusions: AKI is a frequent complication in patients with COVID-19, with risk factors involved in its development, as well as in its evolution to AKD or CKD.

PUB012

Serum Electrolyte Profile Among COVID-19 Patients in a Tertiary Health Facility from April to September 2020

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Background: Around December of 2019, an outbreak of unknown epidemic was noted in the province of Hubei in Wuhan China. This infectious agent was identified from the SARS family and was termed as 2019-nCoV, the causative agent associated with the COVID 19 disease. The disease was then considered pandemic after it has infected a number of countries across the globe. The aim of this study was to determine the serum electrolyte profile among COVID 19 patients admitted in a tertiary hospital in Cebu City from April to September 2020.

Methods: Retrospective research design was used in the study. The charts of moderate severe and critical cases of COVID 19 admitted at Vicente Sotto Memorial Medical Center from April to September 2020 were reviewed. The investigator collected the patients' age, sex, and co-morbid conditions. Once these data have been collected, the researcher determined the patients' baseline serum electrolytes upon admission. In particular, the serum Sodium, Potassium, and Calcium were obtained. This were classified either as low, normal, or high. This was compared as regards the severity of cases of COVID 19 patients.

Results: Most patients had moderate and critical COVID 19 infections wherein most of these patients were in their late 50s (58.8±15.2). The largest number of patients was male (54.7%). The most prevailing underlying comorbidities, which are more prevalent in men are Hypertension (50.0%) and Diabetes Mellitus (27.7%). Hyponatremia had the largest number of patients (63.9%) common among moderate COVID 19 infection (132.7±5.4). Hyperkalemia was found to develop critical COVID 19 infection (4.4±1.2). Hypocalcemia was common in moderate and critical COVID 19 infection (1.2±0.1 and 1.2±0.2) respectively.

Conclusions: Hyponatremia was observed in the largest number of patients where the largest number of cases of patients had moderate COVID 19 infection. Patients who developed hypernatremia were found to have developed critical COVID 19 infection. There was significant difference in serum potassium when patients were grouped according to severity of COVID 19 infection. Patients with hyperkalemia were found to develop critical COVID 19 infection. Patients with lower serum calcium was found to be at higher risk for developing critical COVID 19 infection. This indicates that serum calcium is a potential biomarker for severe COVID-19 infection.

PUB013

Effect of the Paxlovid on Glomerular Disease Patients

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Background: The reported efficacy of nirmatrelvir-ritonavir (Paxlovid®) in reducing the risk of severe COVID-19 progression in high-risk patients is well-known. However, there is limited evidence regarding its effects on glomerular disease patients (GDP).

Methods: We retrospectively assessed the influence of nirmatrelvir-ritonavir on the risk of death and hospitalization in GDP. We also examined the changes in estimated glomerular filtration rate (eGFR) before and after COVID-19 infection. Proteinuria was defined as urine protein/creatinine ratio > 0.2 mg/mg. Nine patients were included. The mean age of 46 years. Six patients were female. The mean follow-up was 10 months (ranging from 9 to 11). The etiology of glomerulonephritis included ANCA-associated vasculitis (n=2), atypical hemolytic uremic syndrome (n=1), lupus nephritis(n=1), membranous proliferative (n=1) glomerulonephritis, IgA nephropathy (n=2), membranous nephropathy (n=1), and minimal change disease (n=1). Our COVID-19 management protocol involved discontinuing immunosuppression and administering Paxlovid according to the datasheet: nirmatrelvir (2 tables) and ritonavir (1 table) twice a day for 5 days. Weekly oropharyngeal samples were collected for COVID-19 PCR testing to confirm viral negativization, following which immunosuppressants were reintroduced. Four patients had proteinuria before infection.

Results: None of the patients died or required hospitalization. At the time of infection, eGFR decreased by 8.9 mL/min/1.73m2 (P = 0.021); however, it recovered at month six. The presence of proteinuria prior to infection did not significantly affect the trend of eGFR. Furthermore, neither proteinuria levels nor hematuria changed after infection. One patient with lupus nephritis developed long-COVID syndrome and a rapid decline in eGFR. Medication was well tolerated, with only one patient reporting gastrointestinal symptoms.

Conclusions: Paxlovid demonstrated effectiveness in GDP, as no deaths or hospitalizations were required. Importantly, the evolution of eGFR did not show a significant change at the end of the follow-up period, even among patients with pre-existing proteinuria.

PUB014

Ethical Analysis on Mandating COVID-19 Vaccination Prior to Kidney Transplantation in Brazil

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Background: With the advent of the COVID-19 pandemic, we saw the debate on the best social protection strategy. In what extent can the principle of individual autonomy be limited by the need for social protection? Would it be licit to limit access to health measures, such as kidney transplantation? The cost of refusing the vaccine has an impact on society, on the transplant program and on other patients admitted to the transplant unit. In kidney transplantation, we have the possibility of analysis and investigation regarding the guiding principles of bioethical decisions, discussing how we should proceed when candidates for transplantation object to vaccination.

Methods: Primary bibliographical research of indexed scientific articles, by the search tools "Google Scholar" and "Pubmed", with the keys of "renal transplantation" and "COVID-19 vaccine refusal". Bibliographical research on technical norms for kidney transplantation and in bioethics books related philosophical and ethical foundations.

Results: The false opposition between autonomy and beneficence is secondary to a market and principialism vision. However, autonomy must be exercised responsibly, in a relational way. It requires a qualified choice, based on an individual's narrative identity with: coherence component and socially shared reality. Several countries have different approaches to conduct. Some with severe restrictions or punishments, some with financial punishments, others discretionary. The reasons for vaccine objection are multiple, we can summarize three main ones: the presence of religious or philosophical motives, medical and willingness to benefit without sharing risks.

Conclusions: Although the authors have different bioethical views, we can draw common points in the construction of a minimum ethics. Most understand the application of coercive measures as a mistake, but that we should value specific situations. To create objective criteria on organ allocation we should acknowledge that the autonomy of the individual is not opposed to social beneficence. The vaccination requirement for deceased donor kidney transplantation is ethically valid. It should be illicit in urgent transplantation, pediatric transplants or related living donor. In the above cases, the patient must accept the universal protection measures determined by the transplant service.

PUB015

A Comparative Study of COVID-19 and Viral Hemorrhagic Fevers

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Background: Coagulation and platelet dysfunction are hallmarks of covid-19 and viral hemorrhagic fevers (VHF). Agents of VHF have the potential to cause the next pandemic. Examining the differences between the two will help prepare for the next pandemic and efficiently meet the healthcare resources.

Methods: Patients admitted to a community hospital formed the study group between February 2020 and April 2020. A published cohort of viral hemorrhagic fevers formed the historical cohort. The historical VHF cohort case reports were reviewed for comparison. Descriptive statistics were applied. First, the groups were compared using independent t-tests. A p-value of <0.05 was considered significant. Proportions of patients with Lung infiltrates, AKI, and who required MV, ICU, and RRT were then compared using student t-tests. Finally, the proportion of patients who died in the two groups was compared. A P-value of less than 0.05 was considered significant.

Results: COVID-19 group (Covid19 SG) had 51 patients. The control group had 79 cases, of which 61 were selected. The COVID-19 SG had 51 patients. The VHF-CG had 61 patients. Comorbidities included were diabetes, hypertension, and chronic disorders. See Table 1. Diabetes and hypertension were present in 58.8% of patients in the study group. There was no difference in the sex distribution among the groups. The need for mechanical ventilators is five times greater in the COVID-19-SG compared to VHF-CG. See table 2.

Conclusions: The odss ratio of a patient dying becayse of covid-19 alpha variant was six times greater compared to viral hemorragic fever. The need for RRT increases as the ICU stay increases.

TABLE NO.1

COVID-19 SG	N=51	VHF – CG	N = 51	P value
Demographic data				
Mean Age	54.2 (IQR 15)	Mean Age	41.9 (IQR 24)	
Sex M/F	33/18 (Chi square test)	Sex M/F	47/14	0.15
With Comorbidities	32/19 (Chi Square test)	With Comorbidities	4/57	<0.00001

TABLE NO.2

Study Parameters	Proportion Covid19-SG	Proportion VHF-CG	Odds Ratio (Covid19 SG / VHF-CG)	[Confident Interval 95%]	P value
CXR infiltrates	51/51	33/61	27.27	[3.47, 214.215]	0.000834
Mechanical Ventilation	38/51	23/61	4.829	[2.139, 10.914]	0.000077
Intensive Care Units	51/51	41/61	24.88	[24.39,193.25189.533]	0.00113
AKI	16/51	61/61	0.0076	[0.001, 0.06]	0.000002
Renal Replacement therapy	11/51	41/61	0.134	0.057, 0.315]	0.000002
Outcome: Death	36/51	18/61	5.73	[2.536, 12.963]	(0.000014)

PUB016

Effect of Phase Angle by Electrical Bioimpedance on the Incidence and Severity of AKI Following Cardiac Surgery

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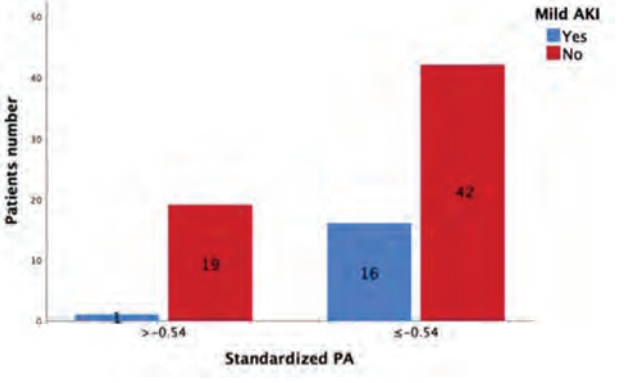
Background: Bioimpedance (BE) measures the electrical characteristics of the body to evaluate the patient's fluid, nutritional, and pathological condition by measuring resistance, reactance, and phase angle (PA). Low preoperative PA is related to greater morbidity and mortality, although the exact relationship with the development of acute kidney injury (AKI) is unclear. Our objective was to determine whether or not preoperative PA increased the risk for AKI following cardiac surgery.

Methods: Prospective Cohort from Aug-2022-Apr-2023 that included 78 patients ≥18 years old, undergoing elective valve replacement, coronary bypass surgery, or both, in a single surgical procedure. PA was measured 24 hours before surgery and standardized PA was calculated using data from the Mexican population. Serum creatinine was assessed, and the occurrence and severity of AKI were confirmed 7 days following surgery.

Results: The mortality rate was 15% (12 patients) and the incidence of AKI was 30% (23 Pt); 22% (17 Pt) experienced mild AKI, whereas 8% (6 Pt) developed moderate-severe AKI. A PA ≤4.5 was not associated with postoperative AKI and mortality. A standardized PA >-0.54 was related to a lower incidence of mild AKI, 5% (1/20 Pt) vs 28% (16/58 Pt) (p=0.035), with a RR 0.18 (95%CI:0.03-1.16), with no difference in the incidence of moderate-severe AKI and mortality.

Conclusions: PA ≤ 4.5° did not increase the risk of AKI and mortality while a standardized PA >-0.54 could be protective for mild AKI.

	PA ≤ 4.5° = 10	PA >4.5° = 68	p
Age (years)	69 (IQR, 62-76)	63 (IQR, 56-67)	0.028
Male-gender n (%)	40	65	0.134
Weight n (Kg)	61±10	74±15	0.007
Grip stength n (Kg)	18±8	26±8	0.004
AKI n (%)	30%	29%	0.970
Mortality at 7-days n (%)	20%	15%	0.665



PUB017

Comparison of 4 Predictive Scoring Methods as Assessment Tools for Cardiac Surgery Associated-Acute Kidney Injury in Post Coronary Artery Bypass Surgery Patients: A Single-Center Retrospective Study

Cathleen B. Iway, Hariett Torres. *Perpetual Succour Hospital, Cebu City, Philippines.*

Background: Cardiac surgery associated acute kidney injury (CSA-AKI) is a common cause of hospital acquired-AKI precipitated by perioperative factors. The surgery itself is a renal stressor and post operative kidney function is an important predictor of morbidity and mortality. Various objective, bedside predictive models were developed to risks stratify patients who would likely develop CSA-AKI. This study is to determine the most sufficient scoring system to be utilized by comparing 4 predictive models that may help facilitate clinical decision making, early preventive strategies and patient counselling.

Methods: A chart review was done to all patients who underwent open heart surgery last January 2010 to January 2019. Patients who developed AKI after cardiac surgery were identified and binary logistic regression was used to describe the relationship between the development of CSA-AKI and the four scoring methods as its predictors. Confidence interval is set at 95%, comparison significant at <0.05, hypotheses tested at 0.05 level of significance. Therefore, if the p-value is less than or equal to the significance level, it can be concluded that there is a statistically significant association between the response variable and the predictor.

Results: There were a total of 114 cases of open heart surgeries. A sample size population of 86 were reviewed. There were 43 patients (50%) who developed CSA-AKI wherein 5 patients (5.81%) eventually progressed to renal replacement therapy. The p-values for the Cleveland Clinical Score and Simplified Renal Index are greater than the significance level. With the p-values less than the significance level, there is statistically significant association between the Mehta (p value 0.019) and AKICS score (p value 0.011) and the development of CSA- AKI. The odds ratios for both Mehta Score (1.10) and AKICS Score (1.19) are also greater than 1, indicating that AKI is more likely to occur if the Mehta score or the AKICS Score increases.

Conclusions: In this single-center study, AKI was more likely if the scores for both Mehta and AKICS scoring system methods increase. This supports that either Mehta or the AKICS scoring systems are useful methods that can be employed to predict CSA-AKI among patients who underwent coronary artery bypass.

PUB018

Incidence, Risk Factors, and Outcomes of Postoperative AKI in China: A Multicenter Retrospective Analysis

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Background: Postoperative acute kidney injury (AKI) is a common condition after surgery, however, the available data about nationwide epidemiology of postoperative AKI in China from the large and high-quality studies is limited. This study was aimed to determine the incidence, risk factors, and outcomes of postoperative AKI among patients undergoing surgery in China.

Methods: This was a large, multicenter, retrospective study performed in 16 tertiary medical centers in China. Adult (at least 18 years old) patients who undergoing surgical procedures from January 1, 2013 to December 31, 2019 were included. Postoperative AKI was defined by the Kidney Disease: Improving Global Outcomes creatinine criteria. The associations of AKI and in-hospital outcomes were investigated using logistic regression models adjusted for potential confounders.

Results: Among 520707 patients included in our study, 25830 (5.0%) patients developed postoperative AKI. The incidence of postoperative AKI varied by surgery type, which was highest in cardiac (34.6%) surgery, followed by urologic (8.7%), and general (4.2%) surgeries. 89.2% postoperative AKI cases were detected in the first 2 postoperative days. However, only 584 (2.3%) patients with postoperative AKI were diagnosed with AKI on discharge. Risk factors for postoperative AKI included advanced age, male sex, lower baseline kidney function, pre-surgery hospital stay≤3 days or > 7 days, hypertension, diabetes mellitus, and use of PPIs or diuretics. The risk of in-hospital death increased with the stage of AKI. In addition, patients with postoperative AKI had longer length of hospital stay (12 vs 19 days), were more likely to require intensive unit care (13.1% vs 45.0%) and renal replacement therapy (0.4% vs 7.7%).

Conclusions: Postoperative AKI was common across surgery type in China, particularly for patients undergoing cardiac surgery. Raising the awareness and development of an alarm system is important for the battle against postoperative AKI.

PUB019

Outcomes of AKI Hospitalizations Among Patients with Heart Failure and Atrial Fibrillation: A Nationwide Analysis

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Background: Acute Kidney Injury (AKI) has a high incidence among patients with heart failure (HF) and atrial fibrillation (AF). The primary aim of our study is to compare rates of in-hospital mortality and morbidity for patients admitted with AKI only, AKI with AF, AKI with HF, and AKI with both HF & AF.

Methods: This is a retrospective study with data obtained from the National Inpatient Sample database. We included all adults who were admitted with a principal diagnosis of AKI between 2018 & 2020. The cohort was stratified into patients with AKI only, AKI with AF, AKI with HF, and AKI with both HF and AF. The primary outcome was inpatient mortality. Secondary outcomes included acute coronary syndrome, cardiogenic shock, STEMI, length of stay (LOS), average hospital cost, average patient charge, and acute respiratory failure. Univariate and Multivariate Logistic, Linear & Poisson regression model were used for analysis.

Results: Patients with AKI alone had the lowest rates of in-hospital mortality (1.45%). Compared to the AKI only group, patients with AKI and AF had higher rates of in-hospital mortality (2.90%), acute coronary syndrome (3.64%), STEMI (0.92%), cardiac arrests (0.68%), cardiogenic shock (0.20%), acute respiratory failure (7.31%), and septic shock (1.27%), with an average LOS of 4.93 days and an average patient charge of $43,564. Compared to the AKI only group, patients with AKI and CHF had even higher rates of in-hospital mortality (2.77%), cardiac arrests (0.32%), cardiogenic shock (0.064%), acute respiratory failure (15.95%) and septic shock (1.29%), with an average length of stay of 5.39 days and an average patient charge of $49,126. AKI patients with both AF and CHF had the poorest outcomes, with higher rates of in-hospital mortality (4.38%), acute coronary syndrome (4.54%), STEMI (1.16%), cardiac arrests (0.96%), cardiogenic shock (1.21%), acute respiratory failure (17.67%), septic shock (1.40%), with an average length of stay of 5.51 days and an average patient charge of $49,153.

Conclusions: In conclusion, our study demonstrated that mortality and morbidity is significantly higher in patients with concurrent cardiac co-morbidities, compared to AKI alone. There was an incremental increase in poorer outcomes with AF, CHF, and combined CHF with AF, respectively.

PUB020

Racial Disparities Following Severe AKI

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Background: Acute kidney injury requiring dialysis (AKI-D) is a severe complication during acute hospitalizations. AKI survivors remain at risk for adverse outcomes and follow-up care has been shown to be suboptimal. The goal of this study was to identify any racial disparities in post-AKI follow-up care and outcomes, laying the groundwork for future interventions to reduce racial disparities.

Methods: Single-center retrospective analysis of consecutive patients with AKI-D in 2021 who were discharged alive and off dialysis. Patients discharged to hospice or with a history of ESRD or kidney transplant were excluded. Patient demographics, labs, documented education, follow-up recommendations, and 12m post-discharge outcomes were collected.

Results: A total of 78 patients were included: mean age 57y, 71% male, mean baseline eGFR 64. Mean duration of dialysis was 12d and hospital length of stay 41d. Most patients self-identified as White (55, 70%) or Black (18, 23%), so analyses were limited to comparing these groups. 72% of Black patients had a documented recommendation for post-discharge nephrology follow-up compared to 31% of White patients (p = 0.002). Among these patients, 54% of Black patients completed follow-up compared to 94% of White patients. Overall, 39% of Black patients and 29% of White patients followed up with a nephrologist. 12-month mortality was over four times higher for African American patients than Caucasian patients (p = 0.036).

Conclusions: Compared to White patients, Black patients were more likely to have a nephrology follow-up visit recommended as well as completed. Despite this, Black patients had lower survival compared to Caucasian patients. These findings suggest the need to explore additional, modifiable factors to reduce excess mortality experienced by this population.

	Race	
	Black (N = 18)	White (N = 55)
Baseline Characteristics		
Age (mean)	52.4	58.8
Male	15 (83%)	36 (65%)
Female	3 (17%)	19 (35%)
Baseline eGFR (mean)	63.9	63.6
LOS (mean)	35.7	42.3
Process Metrics		
Recommended Neph Follow-Up	13 (72%)*	17 (31%)*
Completed Neph Follow-Up	7 (39%)	16 (29%)
Outcome Metrics		
Recurrent Hospitalization within 12mo	11 (61%)	37 (67%)
AKI Recurrence within 12mo	3 (17%)	19 (35%)
Needing Dialysis within 12mo	2 (11%)	6 (11%)
12-month mortality	4 (22%)*	3 (5%)*

*Indicates statistical significance (p<0.05)

PUB021

Evaluating the Consequences of Delirium on Patient Outcomes During Hospitalizations for AKI

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Background: Delirium frequently accompanies acute kidney injury (AKI) during hospitalizations and can lead to increased healthcare usage and poorer outcomes. This study delves into the specific impact of delirium on AKI hospitalizations.

Methods: We conducted a cohort study using the National Inpatient Sample (NIS) database from 2019-2020. The International Classification of Disease-10 codes were used to identify hospitalizations with AKI as the principal diagnosis and then stratified them based on whether they had delirium. The outcomes that were measured included in-patient mortality, length of stay, total hospital charges, and complications during the hospitalization. We used multivariate regression analysis to adjust for confounders.

Results: Of 9,121,794 AKI hospitalizations, delirium was present in 198,664. The delirium group had a higher average age (74 vs. 67, p <0.001), with a majority being male (56%, p=0.003) and Caucasian (66%, p<0.001). After adjusting for patient demographics, comorbidities, and hospital characteristics, delirium-associated hospitalizations demonstrated significantly higher odds of mortality (aOR=1.19, p<0.001, CI: 1.14 - 1.25), acute ischemic stroke (aOR= 1.4, p<0.001, CI: 1.34 - 1.46), acute respiratory failure (aOR= 1.18, p<0.001, CI: 1.09 - 1.28) and acute coronary syndrome (aOR= 1.06, p=0.003, CI: 1.02 - 1.1). Length of stay (coefficient=6.85, p<0.001, CI: 6.62 - 7.12) and total hospital charges (coefficient=96,303, p<0.001, CI: 86976 - 105629) were also increased in the delirium group.

Conclusions: AKI hospitalizations with concurrent delirium exhibited worse outcomes in terms of mortality, length of stay, total hospital charges, acute ischemic stroke, acute respiratory failure, and acute coronary syndrome. This highlights the critical need for early identification and management of delirium in AKI hospitalizations.

PUB022

The Influence of AKI on Patient Outcomes in SARS-CoV-2 Pneumonia Hospitalizations

Anish Surapaneni,[1] Akil S. Kavcar,[2] Meghana Vallabhaneni,[2] Cameron T. Lawson,[2] Chadi Y. Saad.[1] *[1]Garden City Hospital, Garden City, MI; [2]ECU Health, Greenville, NC.*

Background: Acute Kidney Injury (AKI) is a recurrent complication in patients with SARS-CoV-2 pneumonia, often leading to adverse outcomes and inflated healthcare costs. The aim of this study was to elucidate the effects of AKI on mortality and other in-hospital outcomes in SARS-CoV-2 pneumonia hospitalizations.

Methods: We conducted this study using the National Inpatient Sample (NIS) database from 2020. SARS-CoV-2 pneumonia hospitalizations were identified, classified, and stratified by AKI presence using International Classification of Diseases-10 codes. Mortality served as the primary outcome, with in-hospital complications as secondary outcomes. Confounding factors were adjusted through multivariate regression analysis.

Results: Out of 1,058,815 hospitalizations with SARS-CoV-2 pneumonia, 265,925 involved AKI. Patients with AKI were typically older (median age 70 vs 62, P<0.001), predominantly male (51%, P<0.001), and Caucasian (53%, P<0.001). Total hospital charges and average length of stay were significantly higher in the AKI group by $53,132 (P<0.001) and 2.67 days (P<0.001), respectively. Figure 1 illustrates the adjusted odds ratios for complications and mortality.

Conclusions: AKI presence in SARS-CoV-2 pneumonia hospitalizations is associated with increased mortality risk, in-hospital complications, length of stay, and total hospital charges. These findings underscore the necessity of prompt AKI detection and management in this patient population.

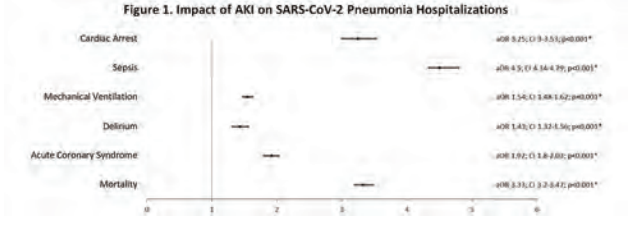

Figure 1.

PUB023

Development and Validation of a Least Absolute Shrinkage and Selection Operator (LASSO) Prediction Model for Cisplatin-Induced Nephrotoxicity: A Case-Control Study in China

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Background: Early identification of high-risk individuals with cisplatin-induced nephrotoxicity (CIN) is crucial for avoiding CIN and improving prognosis. In this study, we developed and validated a CIN prediction model based on general clinical data, laboratory indications, and genetic features of lung cancer patients before chemotherapy.

Methods: We retrospectively included 696 lung cancer patients using platinum chemotherapy regimens from June 2019 to June 2021 as the test set to construct a predictive model using Absolute shrinkage and selection operator (LASSO) regression, cross validation, and Akaike's information criterion (AIC) to select important variables. We prospectively selected 283 independent lung cancer patients from July 2021 to December 2022 as the validation set to evaluate the model's performance.

Results: The prediction model showed good discrimination and calibration, with AUCs of 0.9217 and 0.8288, sensitivity of 79.89% and 45.07%, specificity of 94.48% and 94.81%, in the test and validation sets respectively. Clinical decision curve analysis suggested that the model has value for clinical use when the risk threshold ranges between 0.1 and 0.9.

Conclusions: Predictive models based on laboratory and demographic variables can serve as a beneficial complementary tool for identifying high-risk populations with CIN.

PUB024

Association Between Serum Osmolality and AKI in Critically ill Patients: Prospective Observational Study

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Background: AKI is common in hospitalised patients and especially in critically ill patients. There has been growing research on AKI concerning biomarkers of renal injury to predict AKI. These markers are not readily available and cost constraints have limited their use in Indian settings. There have been limited studies that have used serum osmolality as a tool to determine the volume status and predict AKI. We wanted to study whether low or high serum osmolality was associated with new-onset AKI and mortality during the ICU stay.

Methods: The study was a prospective observational study conducted on patients admitted to the ICU of tertiary care hospital in India. From April 2022 to Jan 2023, 1300 patients were recruited. Patients having abnormal creatinine at baseline were excluded at time of admission. Serum osmolality was calculated at the time of admission. Serum osmolality of 280-295 mmol/l was considered normal. Patients were followed up for the development of AKI and mortality during their stay in ICU. Univariate and Multivariate analysis was done for various cofactors and AKI and Mortality in ICU.

Results: Incidence of AKI was 26%**.** Abnormal serum osmolality showed a significant association with AKI. Abnormal serum osmolality had an OR 12.97 (CI 9.24-18.2)**.** On sub-analysis of patients with abnormal serum osmolality, there was an incidence of AKI was 44.25% (OR:11.14 CI 7.9 -15.70) in the group with low serum osmolality and 81.97% (OR: 63.8 CI 31.13-130.88) in the group with high osmolality as compared with 6.65% in patients with normal osmolality (p<0.0001). AKI had a significant association with mortality in ICU with a prevalence of 78.6% (p < 0.0001). High or low serum osmolality was independently associated with an increased risk of mortality with low osmolality < 280 having an odds ratio of 3.1056 (CI 1.63-5.88) and high serum osmolality > 295 having an odds ratio of 13.11 (CI 5.83-29.47).

Conclusions: Both high and low serum osmolality at the time of admission were independently associated with an increased risk of development of AKI compared with normal serum osmolality. Low and high serum osmolality was associated with an increased risk of mortality during the stay in the ICU.

PUB025

Incidence, Etiology, and Outcome of AKI in the Coronary Care Unit: A Retrospective Study from a Single Center in Thailand

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Background: AKI can lead to complications such as fluid overload, uremic symptoms, electrolyte disturbance, and metabolic acidosis. It is associated with increased morbidity, mortality, and incidence in critically ill patients. However, data on AKI in the CCU in the low to middle income countries are limited. This study aims to assess AKI incidence, etiology, risk factors, survival rate, and occurrence of ESKD and KRT in CCU patients in Thailand.

Methods: A retrospective cohort study was undertaken on patients admitted to the CCU at Vajira Hospital, a tertiary care facility located in Bangkok, Thailand, from January 2019 to September 2020. The analysis encompassed various factors including baseline characteristics, comorbidities, CKD stage, medications, volume of contrast media, hypotension upon admission, use of inotropes, mechanical ventilator utilization, as well as EKG and CXR characteristics.

Results: Of 209 eligible patients admitted to CCU in Vajira hospital, AKI has occurred in 64 (31%) patients. The most common diagnosis of AKI was an acute tubular injury (ATI) which occurred in 27 (42%) patients. At both 30 and 90 days, it was found that AKI was associated with higher rates of all-cause mortality Patients with AKI had an overall mortality rate of 36% (23/64 patients) at 30-days compared to 1% (5/145 patients) in those without AKI, p <0.001 and a 90-days mortality rate of 44% (28/64 patients) compared to 7% (10/145 patients) in those without AKI, p <0.001. Mortality also increased with AKI severity. There were significant differences in survival (log-rank, p <0.001) in the Kaplan–Meier survival analysis between non-AKI and AKI groups. Multivariate analysis shows risk factors associated with AKI were CKD stage 3 and CKD stage 5, inotropic use, reduced left ventricular ejection fraction, and on a mechanical ventilator, respectively. Furthermore, an increase in age, CKD stage 5, atrial fibrillation, and inotrope use are associated with kidney replacement therapy.

Conclusions: AKI is common in patients admitted to the CCU. Patients with AKI are associated with higher mortality and progression to ESKD compared to non-AKI patients. Inotropic use, reduced Left ventricular ejection fraction, on a mechanical ventilator, and CKD were the risk factors associated with AKI.

PUB026

Atypical Hemolytic Uremic Syndrome Secondary to Transcatheter Aortic Valve Replacement (TAVR)

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a rare subtype of TMA mediated by complement dysregulation with an incidence of 0.23-0.43 cases per million population. It can manifest in a diverse range of conditions and presentations, but acute kidney injury is a common prominent feature because of the apparent propensity of the glomerular circulation to endothelial damage and occlusion. We present a case of aHUS developed after an elective TAVR.

Case Description: An 86-year-old man with PMH of aortic stenosis who presented for an elective TAVR which was successfully done. However, post-operative day 1, he developed new onset hematuria [dark brown to tea colored urine] and elevated BUN/ Creatinine [Baseline serum creatinine of 0.9 to 1 mg/dL. He continued to have hematuria and worsening renal function. Laboratory studies were remarkable for thrombocytopenia, low haptoglobin, and low fibrinogen. Normocytic anemia. Schistocytes on peripheral smear. Elevated D-dimer, CK, LDH, total bilirubin, direct bilirubin, AST. ADAMS 13 activity was greater than 5%. UA showed trace blood and 4-5 RBC. Complements, vasculitis panel, hepatitis panel, coagulation panel, cryoglobulinemia, and direct antiglobulin test were all negative. The patient remained asymptomatic throughout the hospital stay. He was managed symptomatically with antihypertensives for blood pressure control, intravenous hydration with normal saline, and platelet transfusion for thrombocytopenia. With the improvement of renal function, thrombocytopenia, and resolution hematuria. The patient was discharged home to follow-up with Nephrology and hematology.

Discussion: Atypical hemolytic uremic syndrome is most commonly due to a loss of function of a regulatory protein either by genetic mutation or autoantibody. The most common triggers include infections, autoimmune conditions, drugs, malignancies, or pregnancy. Treatment can be supportive, plasma exchange and anticomplement therapy. Although aHUS are associated with significant mortality and morbidity, including end-stage renal disease [ESRD], prompt diagnosis and initiation of supportive and specific management can transform outcome.

PUB027

External Validation of a Simple Prediction Model for AKI After Noncardiac Surgeries

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Background: The Simple Postoperative AKI Risk (SPARK) index is a practical prediction model for postoperative acute kidney injury (PO-AKI) in patients undergoing non-cardiac surgery. Its universality needs more verification.

Methods: This single-center retrospective cohort included adults who had surgery under general anesthesia from 2018 to 2020 at Peking University First Hospital **(Figure 1).** PO-AKI was defined according to KDIGO-Scr criteria. Critical AKI was defined as AKI stage 2 or greater or requiring dialysis. The area under the receiver operating characteristic curves (AUC) and the Hosmer-Lemeshow test were assessed.

Results: Among 8484 participants, 4710 (55.52%) were male, 183 (2.16%) developed PO-AKI stage 1, and 55 (0.65%) developed critical AKI. Compared with the SPARK cohort, participants in our cohort were older (median [IQR] age, 61 [49-69] years vs 56 [44-66] years) and had a higher prevalence of dipstick albuminuria (urine albumin ≥1+) (37.61% vs 9.3%)**.** The incidence of PO-AKI and critical AKI increased as the scores on the SPARK index increased **(Figure 2a)**. The SPARK index showed fair discrimination and calibration power for both the PO-AKI and the critical AKI **(Figure 2b,c,d,e).**

Conclusions: SPARK index can be a reliable tool for predicting PO-AKI and identifying high-risk patients in Chinese population.

Funding: Government Support - Non-U.S.

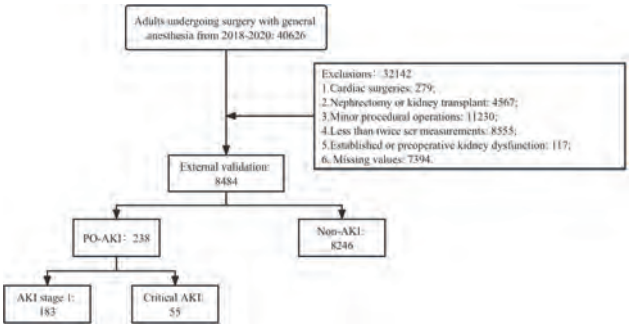

Figure 1. Study Flowchart

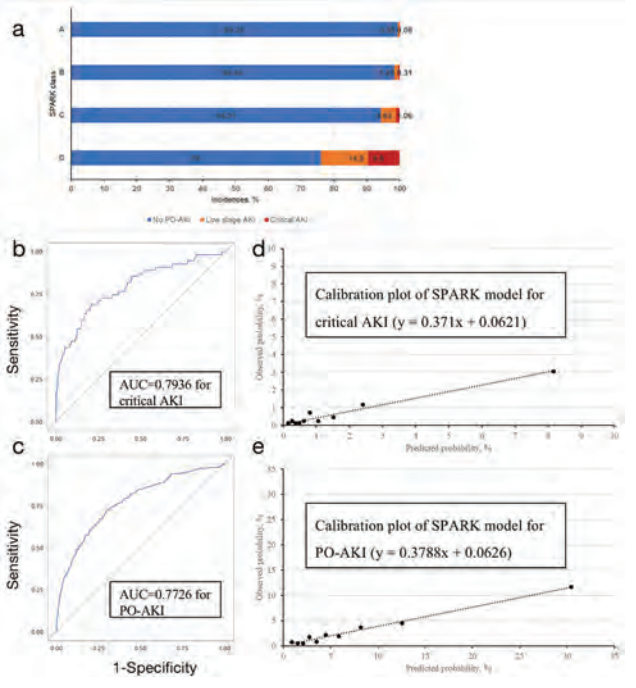

Figure 2. Discrimination and calibration ability of the SPARK model in the external validation cohort

PUB028

Diffuse Alveolar Hemorrhage in ANCA-Associated Vasculitis with Renal Involvement

Stella O. Ogbonna. *Novant Health New Hanover Regional Medical Center, Wilmington, NC.*

Introduction: Diffuse alveolar haemorrhage (DAH) is a potentially life-threatening feature of ANCA-associated vasculitis (AAV) which is caused by disseminated injury of pulmonary capillaries with an incidence of 1 in 20,000 annually in the United States. Though plasmapheresis (PLEX) is part of the recommended treatment, our case highlights that the early diagnosis and initiation of steroids and Rituximab even without PLEX is paramount for survival.

Case Description: A 79-year-old hispanic male with prior history of renal disease, recent ANCA positive with indeterminate results on renal biopsy was admitted with several days of dyspnea on exertion associated with hemoptysis. Chest x-ray consistent with pneumonia, physical examination was remarkable for coarse respiratory sounds. Required intubation and mechanical ventilation due to worsening of respiratory failure. Underwent renal failure, and dialysis was initiated. After intubation, he underwent emergent bronchoscopy and was noted to have sequential in all liquids with diffuse alveolar haemorrhage, receiving 1 pRBC for acute blood loss anaemia. Repeat chest x-ray showed worsening bilateral pulmonary edema vs haemorrhage. CT chest without contrast revealed extensive alveolar consolidation. ANA, C3, C4, Anti GBM Ab, acid fast bacilli, pneumonia and respiratory panel were unremarkable. He immediately received pulse dose steroids on arrival to the ICU and Rituximab once daignosis was made. He was successfully extubated on day 4 and discharged on steroid taper, followed up with Rheumatology and Nephrology for Rituximab treatment on day 15.

Discussion: Though the MEPEX trial strongly supports PLEX treatment in our case, the PEXIVAS trial showed that the use of PLEX did not improve survival. Our case challenges the use of PLEX and also showed complete recovery with treatment with prednisone and rituximab. The role of plasmapheresis as adjunctive therapy remains to be established. The role of plasmapheresis is unclear, and based on data review it didn't show

superiority when compared to treatment with high doses of steroids and Rituximab. Early treatment in DAH is fundamental for survival. More studies need to be done to prove the benefits of PLEX in DAH and to support treatment without it, especially in facilities where plasmapheresis access is limited. This case supports the theory of early treatment with good outcomes despite no PLEX.

PUB029

AKI and Its Outcome in Filipinos 100 Days After Hematopoietic Stem Cell Transplantation: A Single-Center Retrospective Study

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Background: Hematopoetic stem cell transplantation (HSCT) is a complex life-saving procedure that had significantly made an impact in the management of various hematologic disorders. However, it exposes patients to several complications such as infusion reactions, medication side effects, infections, graft rejection, kidney injury, and cardiovascular events. Acute kidney injury (AKI), in particular, is a common complication linked to higher morbidity and mortality affecting the overall outcome of HSCT. Locally, data focusing on HSCT is very limited due to the modest increase in transplant procedures recording only 207 cases until the year 2018. Hence the study aimed to determine the incidence of AKI and its outcomes in Filipinos who underwent HSCT in a single tertiary hospital.

Methods: The study included Filipino patients aged 18 years and above, and excluded those who were maintained on dialysis during the time of transplantation. Data were collected retrospectively by chart review from July 2016 to June 2022, consisting of patients' demographics and medical history, laboratory results, HSCT details and the reported complications.

Results: A total of 49 patients were included, with a mean age of 47 years, 42% were male, 36% were hypertensive, 12% were diabetic and 12% had chronic kidney disease. Baseline creatinine showed a mean of 0.83 ± 0.27mg/dL and a mean eGFR of 95.7 ± 21.84mL/min/1.73m^2. AKI was documented in 14% of patients, with a median of 28 days (18 to 44) from the day of transplant, median creatinine of 1.22mg/dL (1.07 to 1.29) and a median peak creatinine of 1.32mg/dL (1.23 to 1.48). The study showed that AKI was statistically higher in allogeneic transplants (p <0.001) and in those who had an acute graft versus host disease (aGHVD) (p 0.001). Infections (p 0.012) and exposure to carbapenems (p 0.041) were also associated with increased risk of AKI after HSCT. Clinical outcomes such as length of hospital stay (p 0.003), readmissions (p 0.031) and mortality (p 0.016) were all statistically significant in patients with AKI.

Conclusions: AKI is a common complication in Filipinos following HSCT and is associated with increased mortality, longer hospital stay and higher rate of readmissions. The presence of factors such as allogeneic HSCT, infections, and aGVHD predisposes patients to higher risk of AKI 100 days after HSCT.

PUB030

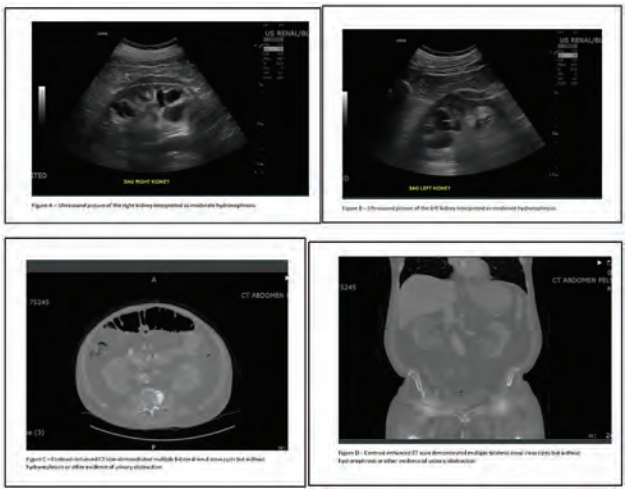
No, It's Not Bilateral Hydronephrosis: It's Pseudohydronephrosis!

Macaulay A. Onuigbo, Jessica Okrant. *University of Vermont Larner College of Medicine, Burlington, VT.*

Introduction: Bilateral hydronephrosis remains the sine qua non diagnostic criterion for clinically relevant obstructive uropathy. Therefore, renal sonograms are often utilized for this diagnostic step. Conversely, pseudohydronephrosis, renal imaging characteristics that mimic obstructive uropathy without obstructive pathology has only been very scantily reported.

Case Description: An 80-year-old male with coronary artery stent in 2005 was diagnosed in November 2022 with biopsy-proven pure red cell aplasia. He started cyclosporine 3mg/kg BID and prednisone 25mg/day. He was admitted two months later with HSV1-positive facial and oral lesions and started Valacyclovir 1000mg BID. He had no urinary or other systemic symptoms except weight loss from reduced food intake. Vital signs were stable. Serum creatinine was 1.58 mg/dL in October 2022, 1.81 mg/dL on admission, with hyperkalemia, 5.7 mmol/L. Trough cyclosporine was 169 ng/mL. Bactrim, lisinopril, and atorvastatin were held. Renal sonogram showed bilateral moderate hydronephrosis (A,B). Follow-up contrast- enhanced-CT demonstrated cortical atrophy, multiple renal sinus cysts but otherwise no urinary obstruction (C,D). Serum creatinine, one week later improved to 1.61 mg/dL, and potassium was 5.1 mmol/L. The discharge diagnosis was pseudohydronephrosis.

Discussion: Pseudohydronephrosis, very rarely reported, was first described in 1953. Unnecessary expensive, invasive, and potentially dangerous investigations and procedures must be avoided. Clearly, the absence of hydroureters concurrent with bilateral hydronephrosis on the sonogram should have triggered thoughts about pseudohydronephrosis. Kidney function improved without any additional surgical intervention. It is not obstructive uropathy – it is pseudohydronephrosis!



Composite labeled figures

PUB031

Safe and Effective Implementation of a Regional Citrate Anticoagulation Protocol in an Emergency Use Situation

David Catanzaro,[1] Stephen J. Amerson,[2] Matthew Jacques,[1] Fadi Abouzahr,[3] Mohammed Ahmad,[4] Rachel Sterling,[2] Hitesh V. Gidwani,[5] Linda E. Sousse,[2] Kevin K. Chung,[1] Sai Prasad N. Iyer,[1] H. David Humes.[6] *[1]SeaStar Medical, Cincinnati, OH; [2]Methodist Healthcare System of San Antonio Ltd, San Antonio, TX; [3]Renal Associates PA, San Antonio, TX; [4]San Antonio Kidney Disease Center, San Antonio, TX; [5]Texas IPS, San Antonio, TX; [6]University of Michigan, Ann Arbor, MI.*

Introduction: Despite the fact the KDIGO guidelines recommend using regional citrate anticoagulation (RCA) over heparins in CRRT, unfractionated heparin remains the most widely used anticoagulant worldwide. Advantages include: wide availability, large body of experience, short half-life, an available antagonist and low costs. Disadvantages include: a narrow therapeutic index (bleeding risk), unpredictable kinetics and heparin resistance. At our institution, standard practice for anticoagulation in CRRT utilizes two separate heparin boluses prior to initiation and again after start of therapy. RCA is only used at our site if the patient is on plasmapharesis and allergic to heparin or for physician preference.

Case Description: We recently employed the emergency use of the investigational selective cytopheretic device (SCD) in saving the life of a 28 year old woman (5 days post cesarean-section) who developed streptococcal toxic shock syndrome and multi-organ failure. The SCD is a cell-directed extracorporeal therapy that promotes an immunomodulatory effect of the host septic response when the CRRT circuit ionized calcium is maintained at <0.40 mmol/L with regional citrate anticoagulation. As the SCD is an investigational device, our institution obtained the device via an emergency use request directly with the device company. Within 3 days of our request, we were able to initiate therapy in the patient. The device company sent a nurse educator to our institution to oversee staff training on device implementation and RCA anticoagulation protocol. This report will summarize our experience initiating this protocol in an urgent setting with staff who had limited experience with RCA.

Discussion: Potential hesitations with implementing an RCA protocol at other sites might include costs, access and complexity of use. Best practices we can share from our experience include proper communication with pharmacy and our lab. This ensures we have the correct 1L bags for infusion and the proper identification of iCa collection site. Protocol complexities can be addressed with proper staff training for ordering the infusion rate based on the algorithm in the protocol shared with our site.

PUB032

AKI Induced by Cryptosporidium in a Patient with Acquired Immunodeficiency Syndrome

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Introduction: Cryptosporidiosis is a global disease that causes infectious enteritis in immunocompromised patients, which results in volume reduction, loss of sodium, potassium, as well as bicarbonate. It has not been previously published that cryptosporidiosis can bring about kidney disease in Human Immunodeficiency Virus(HIV) infected adults. Here, we present a patient with acute kidney injury induced by Cryptosporidium.

Case Description: A 33-year-old man presented with general weakness and watery diarrhea for several days. He was diagnosed of AIDS three months ago but did not take any antiviral agents afterward. He had dry oral mucosa, dry skin turgor, mild diffuse abdominal tenderness, and symmetrically decreased proximal muscles strength. Laboratory exams

revealed serum sodium(Na) 128 mmol/L, potassium(K) 1.6 mmol/L, chloride(Cl) 107 mmol/L, bicarbonate 10 mmol/L, pCO2 24.1 mmHg, blood urea nitrogen 100 mg/dL, creatinine 4.2 mg/dL, serum pH 7.23, CD4 count 47/uL (Table). Urinalysis unveiled creatinine 106.7 mg/dL, Na 5 mmol/L, K 5.1 mmol/L, Cl 15 mmol/L. He was treated with saline infusion, intravenous potassium chloride, and oral potassium gluconate. Watery diarrhea persisted. His stool PCR was detected positive for Cryptosporidium parvum. Triumeq tablet was prescribed on the fourth day. Diarrhea subsided gradually, and no more potassium supplement was needed.

Discussion: Kidney injury and hypokalemia can be attributed to significant loss from diarrhea in our case. It reminds us that Cryptosporidium may be a crucial origin of kidney disease in HIV patients with poor compliance to anti-viral treatment. Hypokalemia, azotemia and metabolic acidosis implies intestinal loss of potassium and bicarbonate. Aggressive fluid supplement, close monitor and rapid replenish of electrolytes imbalance assist renal function full recovery. Antiretroviral therapy remains the most important treatment.

Level of kidney function, sodium, potassium and stool amount.

Hospital day	BUN (mg/dL)	Creatinine (mg/dL)	Sodium (mmol/L)	Potassium (mmol/L)	Stool amount (g)
1	100	4.2	128	1.6	1420
2	99	3.2	127	1.4	1400
3	84	2.0	137	1.4	3400
4	-	-	137	1.5	1800
5	30	1.0	138	2.1	810
6	-	-	138	2.5	770
7	9	0.8	138	3.0	550
12	8	0.8	139	3.3	0

PUB033

Kinetic Formula (KeGFR) for the Estimation of Glomerular Filtration Rate in a Mexican Population with AKI

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Hospital General Tacuba, Mexico City, Mexico.

Background: Acute kidney injury (AKI) management requires drug dosage adjudgment based on glomerular filtration rate (GFR). Commonly used calculators like MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) estimate glomerular filtration rate based on a steady-state creatinine. The KeGFR (Kinetic Estimated Glomerular Filtration Rate) calculator has been used to better estimate the GFR in states of rapidly changing creatinine. The following study aimed to identify the usefulness of KeGFR in Mexican patients with AKI and calculate the concordance between this calculator and commonly used MDRD and CKD-EPI.

Methods: Prospective trial, 60 patients with AKI hospitalized in December 2022. Patients with chronic kidney disease were excluded. GFR was estimated with digital calculators. Three categories were established (<30, 30-49 and >50 mL/min) based on need for drug dosage adjustment. Distribution of episodes was calculated for every category, as was mean and concordance coefficient. A $p<0.05$ was considered significant. STATA® 14.0 was used.

Results: KeGFR found a greater number of episodes and had the smallest mean in the lowest GFR category <30 ml/min (Table 1-2). Also, calculators became less concordant as the GFR declined (table 3).

Conclusions: KeGFR could be a useful tool in Mexican patients with rapidly changing creatinine values since it results in a lower GFR which in turn would lead to more drug dosage adjustments, protecting patients from nephrotoxic effects. To complement this trial, the glomerular filtration rate should be measured with an exact method like cystatin c to determine the concordance with the calculators.

Distribution of patient episodes in the eGFR categories by the 3 estimation methods

eGFR category	KeGFR	MDRD	CKD-EPI
>50	17	17	20
30-49	14	19	15
<30	29	24	25

Table 1

Mean between eGFR categories by the 3 estimation methods

eGFR category	KeGFR	MDRD	CKD-EPI
>50	68 ± 19	70 ± 20	71 ± 20
30-49	40 ± 5	39 ± 5	40 ± 3
<30	14 ± 8	16 ± 6	17 ± 7

Table 2

Agreement between GFR categories by concordance correlation coefficient (CCC)

eGFR category	KeGFR vs MDRD	KeGFR vs CKD-EPI	MDRD vs CKD-EPI
>50	0.856 (0.718 - 0.994)	0.795 (0.618 - 0.973)	0.945 (0.896 - 0.994)
30-49	0.850 (0.543 - 0.947)	0.519 (0.066 - 0.972)	0.725 (0.542 - 0.907)
<30	0.479 (0.194 - 0.764)	0.502 (0.232 - 0.772)	0.985 (0.975 - 0.996)

Table 3

PUB034

Blood Urea Nitrogen and Urinary Output as Renal Recovery Factors After Continuous Renal Replacement Therapy (CRRT) in Critically Ill Patients with AKI

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Background: Due to the lack of standardization for continuous renal replacement therapy (CRRT) cessation and predictive factors that help determine renal recovery, the need for new research about this topic is essential. The aim of our study is to assess renal recovery capacity based on predictive factors such as urine output (UO), albumin, creatinine, and blood urea nitrogen (BUN). This study was carried out with patients admitted to the intensive care unit (ICU) in a hospital in northern Mexico, with acute kidney injury (AKI) that required CRRT.

Methods: A retrospective, observational and descriptive study from January 2019 to 2023 in ICU. Patients with AKI requiring CRRT. The population was divided into two groups: I) patients who recovered renal function as prior to therapy; and II) patients who did not recover renal function.

Results: A total of 39 subjects were analyzed, 29 (74.4%) were men; mean (SD) age 66 (14). 16 (41.1%) patients are overweight, and 8 (20.5%) have diabetes. The dependent variable was renal recovery. The independent variables significantly positive were UO and BUN 24 hours after the start of CRRT. In the inferential statistics, a linear regression model was performed, which showed that UO (p 0.030) and BUN 24 hours after CRRT initiation (p 0.028) help us to predict renal recovery.

Conclusions: There is an association between UO and BUN 24 hours after the start of CRRT with renal recovery. We can compare the results with other studies which take urine output as the indicator for cessation CRRT therapy and possible renal recovery. It is important to continue searching for predictors of renal recovery. Lately the proenkephalin (PENK) has been studied as a biomarker and predictive factor of renal, damage and recovery.

Image 1. CRRT

PUB035

Severe Obstructive Uropathy due to Mycobacterium avium Complex in an HIV Patient

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Introduction: Tuberculosis is a well-known cause of genitourinary (GU) tract infection and obstructive uropathy, however, non-tuberculosis (non-TB) mycobacterium has not been commonly reported as a cause for kidney injury. Here, we present an HIV patient presenting with severe acute kidney injury (AKI) from bilateral obstructive uropathy that improved with treating Mycobacterium Avian Complex (MAC).

Case Description: 32yo with HIV on HAART therapy and CKD III (Cr 1.5 mg/dL six months prior) presented with back pain and AKI. Prior cystoscopy for gross hematuria months before showed erythematous bladder mucosa due to chronic active cystitis. Admission Cr was 4.2. Urinalysis detected large esterase with WBC and RBC >100/hpf despite two negative urine cultures. CT imaging revealed severe bilateral hydronephrosis with diffuse uroepithelial thickening. Cr worsened to 6.2, so bilateral nephrostomy tubes were placed. Chest CT showed small tree-in-bud nodularities in a bronchovascular distribution of the RLL consistent with granulomatous disease. Kidney biopsy specimen showed mild tubular atrophy and interstitial fibrosis with scant interstitial infiltrates of lymphocytes and no detectable acid-fast organisms. Renal cores sent for viral, bacterial, and fungal/AFB cultures were negative at 6 weeks. Of 4 serial early morning voided urine specimens sent for culture, only one grew MAC at week 8. She was treated with Azithromycin, Ethambutol, and Rifabutin. Nephrostomy tubes were removed without worsening obstruction. Six months post discharge Cr improved to 1.2.

Discussion: Ascending TB and non-TB GU infections are rare and difficult to diagnose. Susceptible patients presenting with kidney failure and sterile pyuria require thorough work up. Infections can cause obstructive uropathy via ascending tract inflammation and subsequent kidney injury. In our case, kidney biopsy and serial urine AFBs were necessary to identify a pathogen and rule out other HIV related renal pathology. Remarkably, only 1 of 4 serial urine AFBs were positive for non-Tb MAC, detectable only at week 8, demonstrating that physicians should remain vigilant to rule out infectious pathogens with close coordination with pathology and microbiology colleagues. Prompt treatment allowed for improvement of the inflammatory obstructive process and renal function.

PUB036

Can Quality Indicators in Continuous Renal Replacement Therapy (CRRT) Be Achieved in Middle Income Countries? A Comparison Between a Public and Private Hospital

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Background: As mentioned in ADQI 22nd, there are few studies that have been examined the Quality of Care (QoC) provided to patients with AKI that require RRT. As proposed by the experts, QoC is suboptimal, and substantial knowledge-to-care gaps that need to be addressed so that we can provide an adequate care and safety therapy for those who require.

Methods: We performed a dual - center retrospective analysis chart review of adults who required CRRT during the last year in the Hospital Universitario of Monterrey Dr. Jose Eleuterio Gonzalez (public hospital) and the Hospital Christus Muguerza Alta Especialidad (private hospital) in Nuevo Leon, Mexico. The quality assessments were: Patients prescribed dose, fluid management, filter life and small solute clearance which was compared to the ADQI QoC. Data was extracted from clinical records, all the patients that received CRRT in that period of time given were included; patients with incomplete clinical records were excluded. The analysis was performed with R version 4.0.

Results: A total of 22 patients were included, 11 in each cohort, overall results were as followed: 68.2% (15) were men, in 95.5% (21) patients the modality used was CVVHDF and 4.5% (1) received SCUF, the mean prescribed dose was 2450 ml/min, the ultrafiltrate was 75.5 ml/hr, the initial serum creatinine was 3.07 mg/dL, and in the day 2 the mean serum creatine was 2.18 mg/d the mean life of the filter was 64 hrs, in 59.1%. In the overall accomplishment of the goals, 77.3% accomplished the filter life > 60 hours, 68.2% accomplished goal for ultrafiltrate for at least 80%, and 90.9% accomplished the clearance goal. In comparison between hospitals, in the public hospital the filter life > than 60 hours was accomplished in 72.7% of the therapies, while in the private one in 81.8%, the ultrafiltrate goal was accomplished in 54.5% and 81.8% respectively, and the clearance goal in a 90.9% in both hospitals.

Conclusions: This comparison helped us to discern between what we can improve in both hospitals and what QoC and security measures we have accomplish already. It is important to mention that the quality indicators are not in order of importance as they should be and we must change this concept.

PUB037

Severe Hypercalcemia with Parathyroid Crisis Results in Acute Renal Failure Ending in Fatal Acute Respiratory Distress Syndrome (ARDS)

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Introduction: We present a remarkable case of severe hypercalcemia resulting in a catastrophic outcome.

Case Description: A 52-year-old male with past medical history of obesity, hyperlipidemia, and BPH presented with fatigue, abdominal pain, constipation, and confusion. Medications included atorvastatin and tamsulosin. At the presentation vital signs and exam were unremarkable. Initial workup revealed: serum Ca 34.2, ionized Ca 7.0, Bun/Cr 58/6.60, iPTH 1180, PTHrP 2.2, and 1,25 Dihydroxy Vitamin D <0.5. CVVHDF with citrate regional anticoagulation was initiated. Imaging suggested an underlying parathyroid adenoma and/or carcinoma. Parathyroidectomy was recommended by Endocrine Surgery. On hospital day 2, the patient developed acute hypoxemic respiratory failure attributed to aspiration pneumonia. Chest X-ray revealed bilateral interstitial infiltrates. Echocardiogram showed normal LV function. The patient was diagnosed with ARDS and septic shock requiring multiple pressors. Due to persistent critical illness, the patient never became sufficiently stable to undergo parathyroidectomy, and the family opted for comfort measures.

Discussion: In addition to infectious causes, there are additional potential mechanisms for the development of ARDS. Severe hypercalcemia can lead to calciphylaxis affecting small and medium vessel walls, leading to intimal proliferation, fibrosis, and necrosis. It has been suggested that hypercalcemia may also produce sepsis-like syndrome and acute lung injury by increasing plasma nitrate/nitrite, free radicals, proinflammatory cytokines, and procalcitonin. There have only been 4 cases reported since 1974 linking hypercalcemia to ARDS. In some cases, autopsy findings revealed metastatic calcification of the alveolar surface and the destruction of the alveolar-capillary barrier in the setting of serum calcium levels > 20. Malignant hypercalcemia with multiorgan failure is known to increase mortality in the setting of CKD and CAD. Malignant hypercalcemia resulting in metastatic calcification is expected, but accompanying ARDS is seen less frequently. More study is needed to clarify a mechanistic link between malignant hypercalcemia and ARDS if one does indeed exist.

PUB038

Hypertriglyceridemia-Induced Acute Pancreatitis and Renal Failure Requiring Plasma Exchange and Continuous Veno-Venous Hemofiltration

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Introduction: Severe hypertriglyceridemia is defined at a level of greater than 1000 mg/dL and accounts for 1-4% of patients with acute pancreatitis. Rapid lowering of triglyceride levels is achieved with plasmapheresis (PLEX), and when there is concomitant renal failure and shock, continuous veno-venous hemofiltration (CVVH) is the treatment of choice. We describe a case of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) and renal failure where triglyceride levels were > 5300 mg/dL.

Case Description: A 48-year-old male with history of CKD stage 3a, T2DM, HTN and hyperlipidemia presented to the hospital with an altered mental status. Vital signs: T 100.9 °F, HR 111 beats/min, RR 29 breaths/min, and BP 73/56 mm/Hg. The patient was in acute respiratory distress requiring intubation. Complete blood count: WBC 11,300, hemoglobin 12.8 g/dL, hematocrit 37.3% and platelet count 69,000. Complete metabolic panel: creatinine 6.60 mg/dL, BUN 62 mg/dL, glucose 1,422 mg/dL, CO2 16 mEq/L, anion gap 30 mmol/L, serum osmolality 431 mOsm/kg, AST 267 U/L, ALT of 112 U/L, CK 5,542 U/L, lipase >3,000 U/L, and triglycerides >5,376 mg/dL. He was admitted to the ICU for HTG-AP and hyperosmolar hyperglycemic state requiring vasopressors and insulin infusion. Given his severe hypertriglyceridemia and acute kidney injury, PLEX was immediately initiated followed by CVVH. After two sessions of PLEX, triglyceride levels decreased to <500. Images were negative for necrotizing pancreatitis. However, the patient had worsening rhabdomyolysis with CK > 20,337 U/L, requiring CVVH for 7 days. Once hemodynamic and metabolic parameters improved, the patient was transitioned to intermittent dialysis. Serum creatinine had peaked at 7.4 mg/dL and was 3.9 mg/dL with GFR of 18 when he came off dialysis at the time of hospital discharge. On outpatient follow up, creatinine had further improved to 2.26 mg/dL.

Discussion: This is a complicated case of HTG-AP and renal failure that was highly responsive to both PLEX and CVVH, resulting in meaningful renal recovery. More than one observational study shows that the combination of PLEX and CVVH for the management of HTG-AP with organ dysfunction has better outcomes than CVVH alone. Our case supports the benefit of combination therapy in the setting of severe cases of HTG-AP.

PUB039

Combined Extracorporeal CO2 Removal and Renal Replacement Therapy in a Patient with Acute Respiratory Distress Syndrome (ARDS)

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Introduction: In critically ill patients, concomitant lung and kidney damage can determine unfavorable outcomes. With recent technological advances, patients with acute respiratory distress syndrome (ARDS) and hypercapnia can benefit from extracorporeal

CO2 removal (ECCO2R). ECCO2R in ARDS allows lung-protective ventilation (LPV) with low tidal volumes. We describe the case of a patient with severe hypercapnia, threatening acidemia and acute kidney injury treated with ECCO2R membrane combined with continuous renal replacement therapy (CRRT).

Case Description: A 69-year-old man with a history of systemic arterial hypertension, diabetes and rheumatoid arthritis was admitted to the intensive care unit with severe pneumonia, septic shock and ARDS, also evolving with severe AKI. Chest tomography showing inflammatory infiltrate involving more than 80% of the parenchyma. Initial treatment involved ventilatory and circulatory support. Even after adjustments and ventilatory strategies, blood gas data showed persistent hypercapnia, PaCO2 reached 92 mmHg with resulting respiratory acidosis (arterial pH 7.03). He evolved with oliguria and severe hyperkalemia (K = 5.7 mEq/L) and was treated with an ECCO2R membrane inserted in series after a hemofilter in a CRRT platform. Nitric oxide and reverse prone were additional strategies used to rescue refractory hypoxemia. After 18 hours of therapy there was an improvement in hypercapenia with PaCO2 37mmHg and pH 7.41. After 72 hours maintaining metabolic balance, the use of ECCO2R was discontinued. The patient was extubated on the sixth day. He was discharged after 27 days of hospitalization without the need for supplemental oxygen and with normal renal function (sCr: 0.7mg/dl).

Discussion: We describe a case of success with the use of ECCO2R associated with CRRT in a critically ill patient. This combined therapy ensured an efficient metabolic balance and favored a substantial clearance of carbon dioxide, allowing LPV and greater lung protection, minimizing future.

PUB040

Continuous Urine Output Monitoring to Guide De-Escalation of Continuous Renal Replacement Therapy

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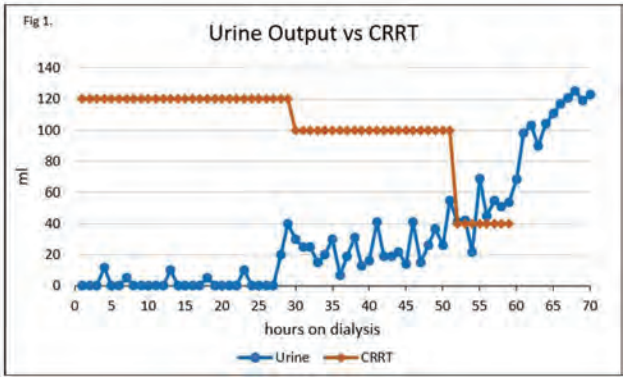
Introduction: Of heart failure patients with acute kidney injury (AKI), 20% progress to dialysis (AKI-D). We present a case of acute decompensated heart failure (ADHF) with severe AKI needing continuous renal replacement therapy (CRRT). Continuous electronic urine output (UO) monitoring was used to guide CRRT de-escalation until successful withdrawal.

Case Description: A 68y/o male was admitted to the cardiac intensive care unit with ADHF, recent myocardial infarction (MI), and severe left ventricular heart failure. Comorbidities: type 2 diabetes mellitus, hypertension, past MI, and chronic kidney disease. Baseline serum creatinine (SCr) was 1.98 mg/dl. On admission, a Foley catheter was inserted and connected to the RenalSense Clarity RMS electronic UO monitoring system. In the following 3 hours, he was non-responsive to 80 mg of IV furosemide. Furosemide dose was increased to 250 mg/day continuous IV, with severe oliguria (UO of 0.1-0.2 ml/kg/h) persisting over 24 hours. SCr increased to 2.8 mg/dl within 12 hours of admission and 3.9 mg/dl by 24 hours. CRRT was initiated due to AKI, fluid accumulation, and pulmonary congestion. Initial fluid removal was 120 ml/h. After 36 hours of CRRT, a gradual persistent increase of 0.2-0.4 ml/kg/h in UO was recorded. Consequently, CRRT fluid removal was reduced to 100 ml/h (Fig 1). Successful withdrawal of CRRT was followed by a polyuric stage over 36 hours gradually decreasing to 1-1.3 ml/kg/h until Foley removal four days later. Concurrently, SCr decreased to 1.82 mg/dl.

Discussion: Heart failure patients with AKI-D have increased risk of dialysis dependence and higher mortality. Optimal timing for CRRT initiation has been more widely studied than that for withdrawal. Predictive factors for successful CRRT cessation include UO, SCr, and time on CRRT. In this study, changes in UO guided CRRT fluid removal leading to gradual withdrawal of CRRT 60 hours after initiation, and UO increase to 120 ml/h. This case study suggests using continuous electronic UO monitoring to guide de-escalation from CRRT.



PUB041

Development of Risk Model to Predict the Cause of Death due to Kidney Disease: A Need of the Hour

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Background: Death attributable to a particular condition is a major quantifier of disease burden and any error in this data could lead to significant health-care inequities. We hypothesized that cross-comparison of COD (cause of death) due to kidney disease in death certificates with chart review of hospital records would highlight this error. We aimed at developing a risk prediction score for accurately documenting COD due to kidney disease and to validate this model internally.

Methods: A retrospective chart review was conducted in a tertiary care hospital on randomly selected death cases from medical ICUs. A risk prediction model for COD attributable to renal disease was developed using multivariable logistic regression. Discrimination and calibration measures for the model were calculated and model presentation was done using an e-calculator.

Results: A total of 365 patient charts were scrutinized. Our study findings showed that there was underreporting of COD attributed to kidney disease in the death certificate after verification of hospital source documents. Clinical characteristics that accurately predicted COD due to kidney disease in our model included documentation of- Oliguria, and hemodialysis, followed by sepsis, dehydration or volume depletion, cardiovascular disease, circulatory shock, anemia, and advanced age. The final model had good discriminant scores/c-statistics of 0.87 for threshold probability >50% and good calibration by the goodness of fit test statistic 4.571(df=8,p=0.8022).

Conclusions: There was under-reporting of COD due to kidney disease in death certification. A validated risk prediction model was developed for accurately documenting COD due to kidney disease. Future research includes multi-centric external validation of the risk model.

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PUB042

An Unusual Presentation of Atypical Hemolytic Uremic Syndrome: Acute Disease Without Platelet Consumption

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Introduction: Atypical hemolytic uremic syndrome (aHUS) is a thrombotic microangiopathy (TMA) in which platelet consumption is a key diagnostic element, together with hemolysis and kidney damage.

Case Description: Herein, we described a peculiar case of aHUS due to complement factor H mutation (c.238T>A/p.Cys80Ser) that repeatedly occurred without evidence of platelet consumption. The patient was 39 years-old when she first experienced aHUS following uneventful pregnancy and delivery. The diagnosis was confirmed by renal biopsy and the patient was successfully treated with eculizumab, discontinued after full recovery. Five years later, without an evident trigger, the patient experienced an aHUS relapse with AKI, hemolytic anemia but still no evidence of platelet consumption. Eculizumab treatment was re-started and remission was obtained with full recovery of renal function. Laboratory data are reported in the table. The patient has always suffered from frequent mild bleeding episodes (epistaxis, gingival bleeding, menorrhagia, ecchymosis following mild trauma). Platelet functional tests (aggregation, secretion, nucleotide and serotonin) only showed a granule secretion and an intra-platelet serotonin at the lower normal limit. Platelet procoagulant activity is being investigated.

Discussion: The episodes of aHUS experienced by this patient were all characterized by a mild course and the patient never required dialysis, suggesting a critical role of platelet consumption in determining the severity of the disease. Our data suggest future studies to evaluate a possible role of antiplatelet therapy in the prophylaxis of patients at risk of aHUS.

	PLT (k/mmc)	Kapt (mg/dL	Cr (mg/dL)	Hb (mg/dL)	UPr/Ucr	LDH (UI/L)	JN (mg/	Alb (g/dL)	C3 (mg/dL)
Remission	257	9,1	42	291	1,12	68	0,53	4	56
Acute phase	286	8,7	0	417	1,3	70	5,2	3,9	57
Remission with ES	276	10	183	252	0.84	38	0.16	4	66

PUB043

A Rare Case of Vancomycin-Induced Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) Syndrome, Eosinophilic Pneumonitis, and Steroid-Resistant Acute Interstitial Nephritis Requiring Additional Immunosuppression: A Case Report

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Introduction: Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) syndrome is a severe hypersensitivity reaction characterized by a skin rash, fever, hematological abnormalities, and multiorgan involvement. Acute Interstitial Nephritis (AIN) can occur in 10%-30% of cases. We describe the case of a patient with DRESS syndrome due to vancomycin, with widespread rash, eosinophilic pneumonitis, and steroid-resistant AIN, leading to successful resolution with immunosuppression.

Case Description: A 73-year-old female with a history of breast cancer on exemestane, GERD, and hypothyroidism who presented to the emergency department with a pruritic, erythematous rash spreading from the chest to the extremities and face over two days. She had a vertebral fusion complicated with MRSA-vertebral osteomyelitis, treated with prolonged IV vancomycin. Physical examination was unremarkable except for diffuse erythematous macules and papules on the trunk and extremities. Laboratory data showed peripheral eosinophilia, elevated liver enzymes, and acute kidney injury with an initial creatinine 0.9 mg/dL. Her clinical condition deteriorated despite high-dose prednisone, with new onset hypoxemic respiratory failure, pleural effusions, and worsening kidney function (peak serum creatinine 2.9 mg/dL). A skin biopsy confirmed DRESS syndrome, and subsequent evaluations revealed eosinophilic pneumonitis, with a kidney biopsy consistent with severe acute interstitial nephritis. Given the steroid-resistant AIN and pulmonary involvement, cyclosporine, and mycophenolate mofetil were initiated. Her overall clinical condition gradually improved with serum creatinine down to 1.4 mg/dL.

Discussion: This case emphasizes the importance of promptly diagnosing AIN through renal biopsy in patients with worsening acute kidney injury despite discontinuation of the offending agent. Aggressive follow-up and consideration of additional immunosuppressive measures may be necessary if steroids fail. Although the specific impact of each medication is difficult to discern, mycophenolate has shown promise as a therapeutic option for steroid-resistant AIN, warranting further investigation.

PUB044

Shiga Toxin-Directed Complement-Mediated Hemolytic Uremic Syndrome Treated with Eculizumab

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Introduction: Hemolytic uremic syndrome (HUS) has classically been used to refer to Thrombotic Microangiopathies that occur with acute kidney injury. The terminology has evolved and is now typically divided into ST-HUS (formerly diarrhea associated HUS) and CM-TMA (formerly atypical HUS). ST infections are typically acquired through consumption of contaminated food or water, or through contact with infected animals or their environment. Kidney injury occurs as a result of the shiga toxin causing native cells to undergo apoptosis. Shiga toxin is also prothrombotic through intracellular pathways contributing to the injury of normal cells. CM-TMA formerly referred to as atypical HUS occurs when there is unrestrained activation of the alternative pathway of complement causing injury of normal cells.

Case Description: We report a case of a 43-year-old female that presented with 3 days of nausea, vomiting, epigastric pain and bloody diarrhea. Family reported patient had eaten undercooked boiled eggs. Lab work notable for an anion gap metabolic acidosis with concomitant non anion gap metabolic acidosis in setting of mild lactic acidosis, acute kidney injury, acute bloody diarrhea and thrombocytopenia. Hospital course complicated by worsening renal function and mental status requiring initiation of dialysis. HUS secondary to shiga toxin and other thrombotic microangiopathy (TMA) were considered. ADAMTS-13 was 29% and O157:H7 grew on chromogenic agar with testing positive for Shiga toxin. Case discussed among transfusion medicine and nephrology team; patient was managed as atypical HUS with monoclonal anti-C5 inhibitor, Eculizumab. The TMA panel equivocal, but showed heterozygous missense mutation on PLG, three polymorphisms on CFH gene, and negative for C5 polymorphisms. Patient improved and two weeks later, in clinic, patient noted to have complete renal recovery.

Discussion: This case highlights the importance of considering anticomplement therapy for select cases of ST-HUS. An interesting point was the patient's TMA genetic profile and how it helped direct her care. Our case illustrates the difficulty definitive diagnosis, but the importance for early consideration of aHUS in patients presenting with TMA. More importantly, we highlight that near-normal renal recovery may be attained with eculizumab in adults even after a dependence on dialysis.

PUB045

A Curious Case of ANCA Glomerulonephritis and Membranous Nephropathy: A Rare Double Hit

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Introduction: Membranous glomerulonephritis (MGN) is typically diagnosed in patients with preserved renal function. Hematuria is common in these cases. Subepithelial immune complex deposits are the pathologic finding on biopsy and result in spike formation of the glomerular basement membrane. Secondary causes of MGN, about 25% of cases, can be attributed to infection, malignancy as well as several drugs. However, ANCA-associated necrotizing and crescentic glomerulonephritis (GN) appears more rapidly progressive than MGN and can have active urine sediment with RBC casts. Rarely are these two conditions seen together.

Case Description: Patient is a 62-year-old man with HTN, atrial fibrillation and COPD who presented with shortness of breath. During the initial workup he was found to have a large pulmonary mass with liver metastasis as well as renal failure with a creatinine of 7 mg/dL. This patient had no known baseline renal function. He was subsequently started on dialysis. Urinalysis would show proteinuria, hematuria and several granular casts, a protein to creatinine ratio would result 7.3 mg/mg. Serologies were obtained and a positive p-ANCA and MPO >8.0 were found. A renal biopsy was done on the 5th day of admission and confirmed ANCA-associated necrotizing and crescentic GN as well as MGN. The overwhelming finding on the biopsy was the necrotizing crescentic GN. Staining for PLA2R, Exostosin and NELL 1 was negative. Pulse dose steroids were given for 3 days as well as oral cyclophosphamide initially. A biopsy of the liver metastasis would reveal that this patient had metastatic small cell lung cancer. In this setting, the use of immunosuppressive treatments would pose a significant challenge. Ultimately, the patient chose to go home and declined any further treatments.

Discussion: Rarely, ANCA-associated GN and MGN are seen together. In this case it was thought to be in the setting of two distinct disease processes. The MGN was thought to be secondary to the recently diagnosed malignancy with the ANCA-GN being a separate entity. Renal prognosis in this situation was guarded as treatment of ANCA-GN is very challenging in the setting of malignancy with associated secondary MGN. It is important to be aware of this possible coexistence when ANCA-GN is associated with nephrotic range proteinuria.

PUB046

A Rare Case of ANCA-Mediated Acute Interstitial Nephritis Without Glomerulonephritis

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Introduction: Acute interstitial nephritis (AIN) is characterized by an inflammatory infiltrate in the kidney interstitium which is most commonly caused by drugs, with less common contributors being infections and systemic diseases, and generally leading to acute kidney injury. Here we present a case of an 80-year-old female patient with AIN thought to be caused by non-myeloperoxidase (MPO), non-proteinase-3 (PR-3) antineutrophil cytoplasmic antibody (ANCA) without glomerular involvement.

Case Description: An 80-year-old female was referred to the renal clinic with acute kidney injury and a one-month history of worsening fatigue, nausea, and poor appetite. Her medical history was notable for resistant hypertension, maintained in seven anti-hypertensives for over 40 years. Her creatinine was 4.2 mg/dL, with a baseline creatinine of 0.7 mg/dL about six months prior to presentation. Blood pressure was 132/68 mm Hg. Urine sediment showed several WBCs and WBC casts with no evidence of infection. She had minimal proteinuria and serologic work-up revealed positive c-ANCA with titers >1:640, but negative PR3 and MPO antibodies. A renal biopsy showed markedly active tubulointerstitial nephritis, predominantly composed of lymphocytes and plasma cells and minimal eosinophils, along with mild granular immune complex deposition (1+ IgG, IgA, and C1q) in some tubular basement membranes and interstitium suggestive of an autoimmune etiology. All 33 glomeruli were unremarkable, with no crescents, immune complexes, or inflammation. She was treated with prednisone 1 mg/kg with a slow taper, and her creatinine continued to improve drastically along with a concurrent decline in c-ANCA titers.

Discussion: ANCA-associated vasculitides (AAV) are a group of disorders that typically cause pauci-immune glomerulonephritis, including granulomatosis with polyangiitis, microscopic polyangiitis, renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis. ANCA-associated AIN especially without glomerular involvement is rarely seen. Moreover, non-MPO and non-PR3 ANCAs are infrequent and could be pathologic in nature. Our case is suggestive of non-PR3 and non-MPO ANCA-associated AIN without glomerular involvement, which improved drastically with corticosteroid therapy. In cases of AIN without obvious causative drugs, serological work-up including ANCA screen should be considered.

PUB047

AKI and Spontaneous Rupture of the Urinary Collecting System

Alaaeldin Mustafa, Muhammad U. Jahngir, Sumithra Nalla, Jean Lee. *Temple University, Philadelphia, PA.*

Introduction: Obstructive uropathy is an uncommon cause of AKI and usually associated with bladder neck dysfunction. Rupture of the renal calyx with bilateral(B/L) hydronephrosis in the absence of bladder neck dysfunction is even rare. We are reporting a case of bilateral hydronephrosis causing rupture of left collecting system.

Case Description: An 81-year-old man was admitted with altered mental status, hyperkalemia and metabolic acidosis due to AKI with creatinine of 16mg/dl (BL 1mg/dl). Several weeks prior to admission while traveling abroad, he had developed left flank pain, painful urination and hematuria. CT scan abdomen revealed B/L hydronephrosis and a collection around the left kidney consistent with calyceal rupture of the renal pelvis. Prostatomegaly was observed but the bladder was not distended. Despite the insertion of a Foley catheter, the patient remained anuric and required hemodialysis for altered mental status and severe metabolic acidosis. He then had a percutaneous nephrostomy tube placed in right kidney and a drainage tube into the left sided collection, which resulted in rapid improvement of renal function. Cystoscopy revealed a necrotic partially calcified mass which engulfed the right lateral wall of the bladder, extended to the bladder neck, and was accompanied by a few small satellite lesions on the posterior bladder wall with distortion of the trigone region of bladder. The bladder mass was revealed to be a papillary urothelial carcinoma. He was sent home with bilateral ureteral stents and a percutaneous drain on the left. The patient's SCr down trended to a nadir of 0.91mg/dl prior to discharge.

Discussion: Spontaneous rupture of the collecting system is rare and is typically unilateral with the most plausible mechanism being, gradual increase of intraluminal pressures up to 75mmHg. About half of the cases of spontaneous urinary extravasation are caused by ureteral stones, while occurrences related to tumors are rare. Interestingly, when extravasation is associated with a tumor, it tends to occur more frequently on the left side rather than the right side. The exact reason for this asymmetry is not known, but it is hypothesized that the direct extension of tumor cells may be easier on the left side, creating weak points along the path of extension, leading to leakage and rupture.

PUB048

A Case of Terbinafine-Associated Rhabdomyolysis and Drug-Induced Liver Injury (DILI) That Progressed to Acute Renal and Liver Failure

Gabriela S. Mosquera Cordero. *Novant Health New Hanover Regional Medical Center, Wilmington, NC.*

Introduction: Terbinafine is commonly prescribed for the treatment of onychomycosis. Has been associated with acute hepatic injury and rarely associated with rhabdomyolysis, acute renal failure (ARF) and liver failure (LF). Here we present a case of a patient presenting with general muscle weakness with elevated CK, abnormal renal and hepatic function. Notably, the only new medication reported was terbinafine 3 weeks prior to hospital admission.

Case Description: A 72 year-old female presented to the hospital for worsening of general muscle weakness. Patient completed treatment for onychomycosis with terbinafine 3 weeks prior. The patient denied any other new medications for the past few years. Lower extremity weakness was initially attributed to worsening of spinal stenosis. Lumbosacral MRI was performed, and it showed progression of spinal stenosis but no cord compression. Neurosurgery consult advised against surgical intervention. Chemistry was relevant for CK >9000; Cr 5.78; BUN 117; with a mixed hepatocellular and cholestatic pattern. Autoimmune and infectious etiology were investigated but all were negative. USG and MRI showed CBD dilation correlated with age and post cholecystectomy status. Patient's CK continued upward with minimal urine output. Patient rapidly decompensated, requiring transfer to ICU, and dialysis. Unfortunately, the patient passed away hours later.

Discussion: Terbinafine is a common antifungal drug used for onychomycosis that may cause hepatic or renal toxicity. The side effects are usually self-limiting, but can rarely progress to rhabdomyolysis, ARF, DILI and LF. Few cases of rhabdomyolysis and ARF associated with Terbinafine have been reported, and even less cases were associated with DILI leading to LF. There are limitations with the definitive diagnosis due the patient passed away before perfforming liver or renal biopsy. Treatment primarily consists of stopping the causative agent and NAC for DILI, but some cases with liver failure will require liver transplantation, and dialysis for worsening of renal failure. There is a lack of guidelines and cases associating Terbinafine with rhabdomyolysis, ARF, or LF. Nevertheless, physicians need to be aware and carefully monitor patients when prescribing this medication, especially with prior history of chronic renal or liver conditions or any chemistry abnormalities related to its use.

PUB049

Calciphylaxis in a Patient with Lupus Nephritis and Recent AKI

Zohreh Gholizadeh Ghozloujeh, Roy O. Mathew, Amir Abdi Pour, Sayna Norouzi. *Loma Linda University Medical Center, Loma Linda, CA.*

Introduction: Calciphylaxis is a rare and severe disease characterized by calcification, fibrosis, and thrombosis of small blood vessels. While it primarily affects patients with end-stage renal disease (ESRD) on dialysis, limited cases of calciphylaxis in patients with acute kidney injury (AKI) and lupus have been reported.

Case Description: This case report describes the occurrence of calciphylaxis in a 35-year-old Hispanic female recently diagnosed with lupus nephritis class IV and acute kidney injury requiring dialysis for two months. AKI was resolved, and the patient was off dialysis when she presented with new-onset skin lesions on her thighs, which progressively enlarged and were associated with pain and itching. Physical examination revealed stellate-shaped purpuric patches and plaques on the thighs, which were painful, firm, and indurated, with focal overlying necrosis. The serum phosphate was 1.4 mmol/L, and the parathyroid hormone was 177 pg/mL. Dermatology was consulted. A CT scan revealed mottled foci of calcifications in the pelvic area and subcutaneous soft tissues. Skin biopsy was suggestive of possible CUA with dermal necrosis and dilated blood vessels. Sodium thiosulfate was initiated with mild improvement in lesion appearance and symptoms.

Discussion: This case report highlights the importance of the possibility of CUA in the setting of lupus nephritis. It also emphasizes the importance of a multidisciplinary approach to optimize the management of calciphylaxis.

PUB050

Prdx1 Aggravates Hypoxia-Induced Renal Injury

Yuanyuan Han, Zhangzhe Peng. *Xiangya Hospital Central South University, Changsha, China.*

Background: Hypoxia refers to a condition in which oxygen is limited. Hypoxia can trigger a renal injury response and may stimulate inflammation of proximal tubular cells by damage-associated molecular patterns (DAMPs). Extracellular Prdx1 can play the role of DMAPs by activating the pro-inflammatory response. Previous studies have demonstrated that Prdx1-mediated activation of TLR4/NF-κB contributes to neuroinflammatory responses in intracerebral hemorrhage and acute liver injury. However, the role of extracellular Prxd1 after hypoxia-induced renal injury has not been clarified.

Methods: 1.A 3d and 7d hypoxia model was established in wild-type mice to observe renal function, kidney injury and Prdx1 expression. 2.Hypoxia model was established in Prdx1 knockout mice, and renal function, kidney injury, inflammation and MAPK/NF-κB expression were observed.

Results: 1.Hypoxia can induce kidney injury in mice, and Prdx1 content in serum and kidney tissue increases in the mice model of hypoxia for 3d and 7d. 2.After Prdx1 knockout, hypoxia-induced kidney injury, inflammation and phosphorylation of MAPK and IκB of mice were alleviated.

Conclusions: 1.In the mouse model of hypoxia, the expression of Prdx1 in serum and kidney is increased; 2.Circulating Prdx1 aggravates hypoxia-induced kidney injury by activating MAPK/NF-κB mediated inflammation.

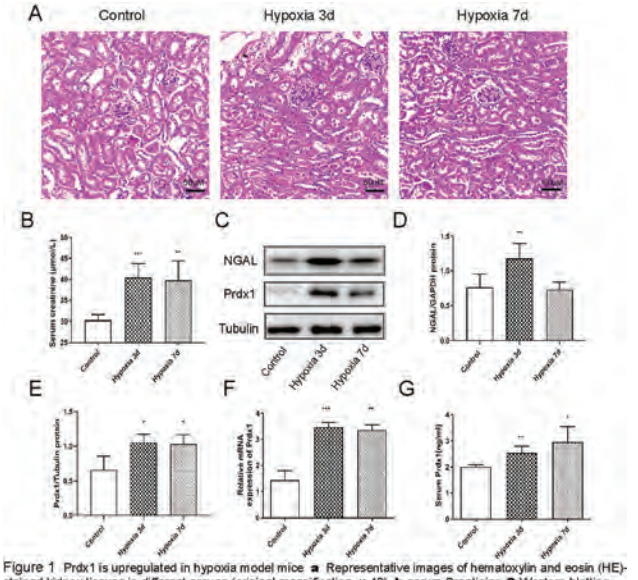

Figure 1 Prdx1 is upregulated in hypoxia model mice **a** Representative images of hematoxylin and eosin (HE)-stained kidney tissues in different groups (original magnification, × 40). **b** serum Creatinine **C** Western blotting and quantitative analysis of NGAL(**D**) and Prdx1(**E**) in mice kidney tissues. **F** The mRNA levels of *prdx1* in kidney tissues of mice **G** Serum Prdx1.*p < 0.05, **p < 0.01,p ***< 0.001 vs. control group

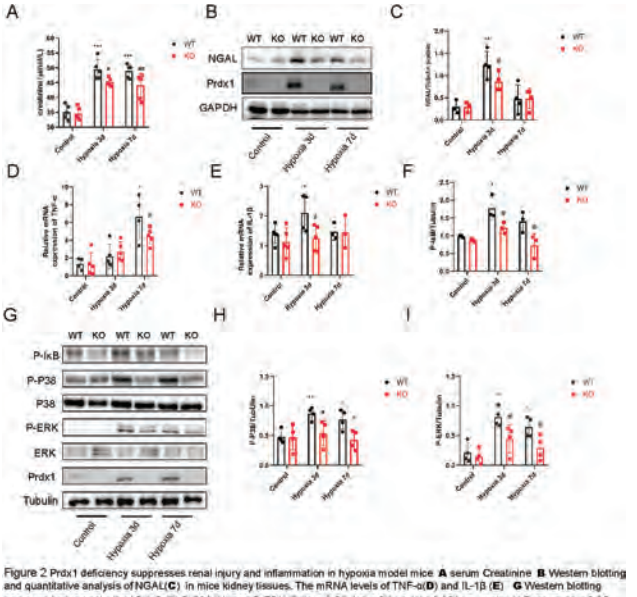

Figure 2 Prdx1 deficiency suppresses renal injury and inflammation in hypoxia model mice **A** serum Creatinine **B** Western blotting and quantitative analysis of NGAL(**C**) in mice kidney tissues. The mRNA levels of TNF-α(**D**) and IL-1β (**E**) **G** Western blotting and quantitative analysis of P-IκB (**F**),P-P38 (H) and P-ERK (**I**).*p < 0.05, **p < 0.01,p ***< 0.001 vs. control WT group. *p < 0.05, **p < 0.01 vs.WT group

PUB051

Lymphadenopathy with AKI

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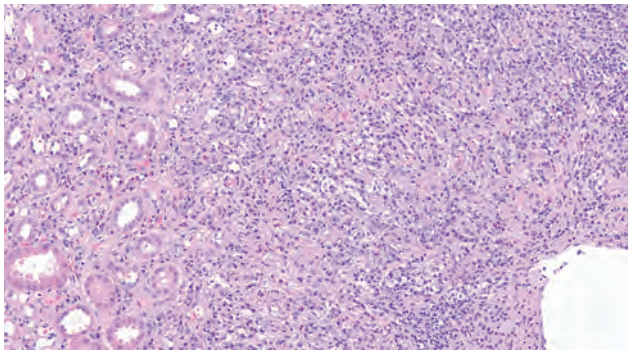
Introduction: Immunoglobulin G4-related disease (IgG4-RD) can present with different manifestations simultaneously. We present a case of bilateral inguinal lymphadenopathy with AKI found to have IgG4-RD.

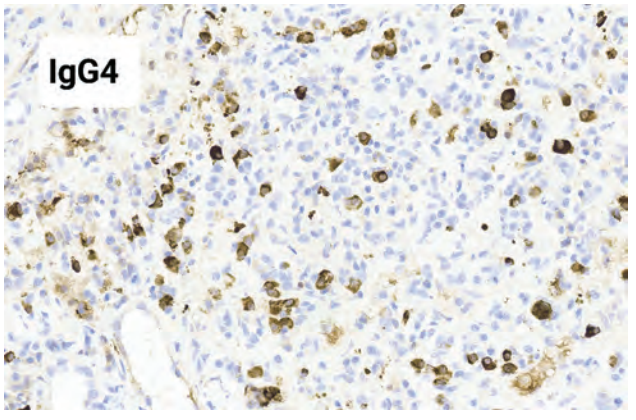
Case Description: A 77-year-old female with history of bladder cancer s/p resection and urostomy, DM-2, COPD, HTN and HLD presented with 2 week history of right sided flank pain after being treated for urinary tract infection. She endorsed poor oral intake, shortness of breath and persistent abdominal pain. On physical examination, bilateral inguinal lymphadenopathy was found. In the laboratory evaluation, serum creatinine was 2.57 mg/dL (reference range 0.8-1.5 mg/dL). Two months prior, it was 0.83 mg/dL. Immunological data revealed elevated IgG level at 3,994 mg/dL (reference range 700-1000 mg/dL). IgG4 level was 773.2 mg/dL (reference range 3.9-86.4 mg/dL). C3 and C4 complements were low at 32 mg/dL (reference range 90-180 mg/dL) and < 2 mg/dL (reference range 10-40 mg/dL). Computed Tomography showed mild pelvocaliectasis and ureterectasis. The biopsy of inguinal lymph node showed plasma cells with storiform pattern. A renal biopsy showed marked plasma cell rich interstitial chronic inflammation with a high fraction of IgG4-restricted plasma cells, proliferative fibrosis, and both

tubulointerstitial and glomerular immune complex deposits, consistent with IgG4-related kidney disease. The patient was treated with pulse steroids followed by steroid taper and IV Rituximab. Two months later, her IgG4 level has decreased. The creatinine has trended down to 1.17 mg/dL.

Discussion: We present a case of IgG4-RD diagnosed with renal biopsy with response to steroids and Rituximab.



Light Microscopy



IgG4 staining

PUB052

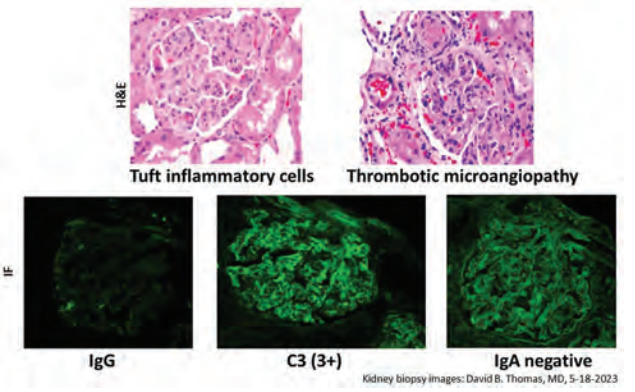
Atypical Hemolytic Uremic Syndrome Induced by Inflammatory Bowel Disease

Fausto R. Cabezas, Charlie Spell, Sandeep R. Sasidharan, Sonalika Agarwal, Mary C. Mallappallil, Isha Puri. *SUNY Downstate Health Sciences University, New York City, NY.*

Introduction: Atypical hemolytic uremic syndrome (aHUS) is a congenital or acquired dysregulation of the complement alternative pathway that leads to thrombotic microangiopathy (TMA) and acute kidney injury (AKI). The prevalence of aHUS ranges from 2 to 10 cases per million. There have been few reports of aHUS associated with Inflammatory bowel disease (IBD). We present a case of a young man with IBD and biopsy proven TMA associated AKI.

Case Description: A 26-year-old male presented with 4 weeks of hematochezia. Laboratory data showed severe hemolytic anemia (hemoglobin 2.9 gr/L, schistocytes on smear; LDH 1,415 U/L, haptoglobin <10 mg/dL, Coombs test), leukocytosis (52.87 k/uL), thrombocytopenia (107 k/uL); severe AKI (SCr 8.32 mg/dL from previous normal eGFR), urinalysis showed 10 WBCs/HPF, RBC 9/HPF, protein 100 mg/dL. Kidney ultrasound was unrevealing. ADAMTS-13 activity was 43% with decreased complement levels (C3 40, C4 25, CH50 17). Negative Shiga toxin. Sigmoidoscopy showed diffuse mucosa inflammation throughout rectum, descending and transverse colon. Biopsies demonstrated chronic colitis. He received multiple transfusions and empiric antibiotics with no improvement. Intravenous methylprednisolone (0.5 mg/kg/day) was started. AKI started to improve before complement blockade therapy with Eculizumab. Kidney biopsy showed acute TMA with immune mediated C3 dominant diffuse proliferative glomerulonephritis (figures). Genetic panel testing for aHUS associated mutations showed no pathological variants.

Discussion: This patient presented with one month of gastrointestinal symptoms preceding the AKI and hemolytic anemia. Overlap of symptoms and laboratory markers pose a challenge when identifying aHUS. In contrast to our case, previous reports have shown remission of AKI and chronic relapsing IBD only after Eculizumab is started. This is a rare case of IBD induced aHUS which responded to a course of steroids and Eculizimab.



PUB053

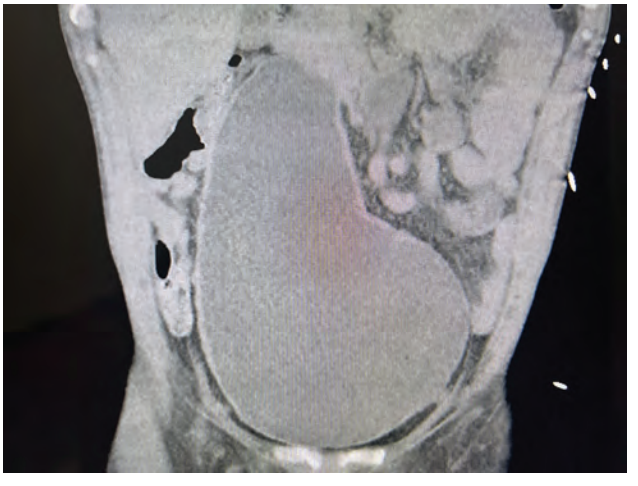
Giant Urinary Bladder Causing Massive Hydronephrosis

Esosa U. Ukponmwan. *Michigan State University, East Lansing, MI.*

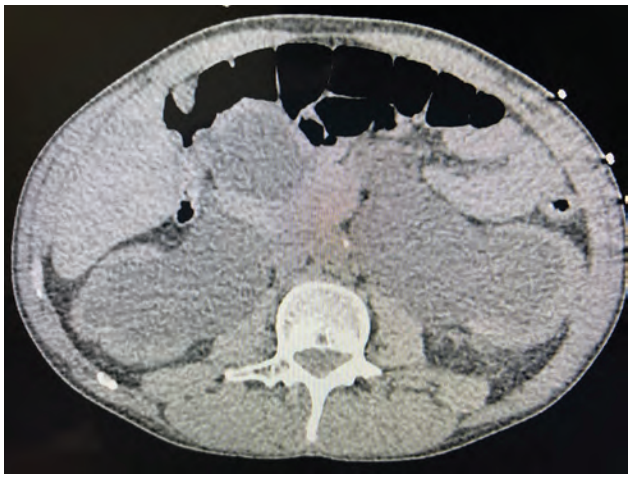
Introduction: Obstructive uropathy is caused by a structural or functional impairment in urinary flow. It is a potentially reversible cause of acute and chronic kidney disease, accounting for 10 percent of acute and chronic kidney disease.

Case Description: A 58-year-old man presented with fatigue, shortness of breath and dyspnea on exertion for eight months, worse over the previous week. He also complained of urinary frequency, urgency, hesitancy, feeling of incomplete urinary bladder emptying, terminal dribbling, abdominal pain and swelling. He was pale, dyspneic, diaphoretic and in respiratory distress. Rales present bilaterally, heart sounds were normal. Abdomen was tender and distended. No pedal edema. He had an elevated blood urea nitrogen of 126mg/dl and creatinine of 9.24mg/dl, high anion gap metabolic acidosis, hyperkalemia and hyperphosphatemia. CT-scan chest, abdomen and pelvis revealed pulmonary edema, severe bilateral hydronephrosis and hydroureter down to the urinary bladder. Marked distention of the urinary bladder causing bowel obstruction. Cortical atrophy of the kidneys suggesting chronic obstruction. Foley catheter was placed with 3500mls of urine drained. Hemodialysis was started due to symptoms of pulmonary edema and uremia. Overall clinical status improved. He was placed on long-term foley catheter and tamsulosin started, with nephrology and urology follow up.

Discussion: Early recognition of obstructive uropathy is important in management of acute and chronic kidney disease. There is an inverse relationship between duration of obstruction and recovery.



Giant urinary bladder



Massive hydronephrosis

PUB054

Long-Term Safety/Outcome of a Novel Half-and-Half (Darbepoetin/ Epoetin) Combination Therapy in Hemodialysis Patients: A Comparison with Epoetin-Monotherapy Period

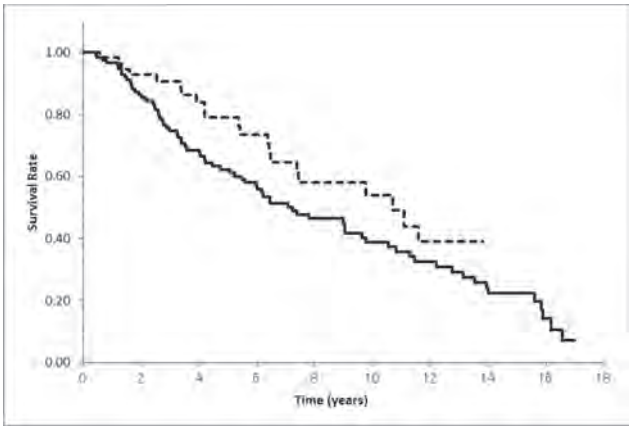
Kazumasa Shimamatsu, Yoshihiro Mimura. *Shimamatsu Naika Iin, Chikushino, Japan.*

Background: Long-acting erythropoiesis-stimulating agent (ESA), darbepoetin (DA) has a longer terminal half-life and a reduced dose frequency than short-acting epoetin (EPO). However, DA might be associated with increased mortality. To lower mortality risk concerned, we reported a novel *half-and-half* (DA/EPO) combination therapy consisting of a stable dose of DA occasionally assisted by EPO having resulted in reduced hemoglobin fluctuation, reduced ESA doses, and lower costs. Long-term safety/ outcome of the *half-and-half* therapy was evaluated.

Methods: All the 280 patients on maintenance hemodialysis (HD) during 31 years are subject to this study. Out of 280 patients 189 belonged to EPO monotherapy period (EPO period), and 91 belonged DA/EPO combination therapy period (*half-and-half* period). For retrospective analysis, we selected 120 patients who had been transferred to our clinic within one year after the initiation of HD in EPO period and 64 patients in *half-and-half* period. The Kaplan-Meier survival curve of the *half-and-half* period was compared with that of the EPO period.

Results: The age of the HD patients in *half-and-half* period was significantly older than that of the HD patients in EPO period (66.6±11.8 vs. 60.1±14.9 yrs, p<.005). The gender, HD vintages at the time of transference to the clinic and original renal diseases were not significantly different between the EPO period and *the half-and-half* period. The Kaplan-Meier survival curve of the *half-and-half* period was significantly superior to that of the EPO period despite the older ages (Figure).

Conclusions: A novel *half-and-half* therapy may be safely feasible with rather better survival and also might be a way to avoid a potential risk on mortality of long-acting ESAs.



Kaplan-Meier survival curves of EPO period (solid line) and *half-and-half* period (dotted line). There is significant difference between the two survival curves (generalized Wilcoxon test, p<0.05).

PUB055

Therapeutic Effect of Originator Erythropoiesis Stimulating Agents (ESAs) vs. Biosimilar ESAs on Hemoglobin Level in Hemodialysis Patients: A Single-Center Study

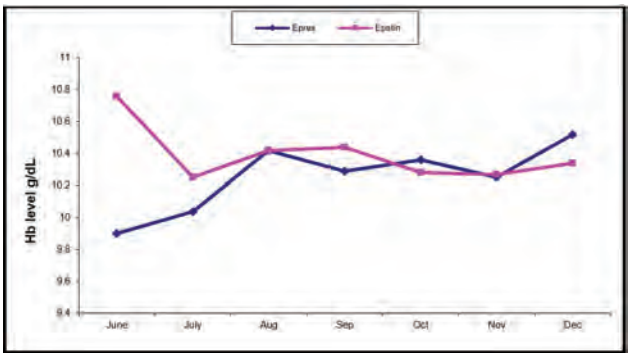
Ahmed Emara,[1,2] Osama I. Azab,[3,2] Goodluck R. Maro,[2] Ahmed Y. Ali.[4,2]
[1]Ain Shams University Faculty of Medicine, Cairo, Egypt; [2]Armed Forces College of Medicine, Cairo, Egypt; [3]Maadi Military Hospital, Cairo, Egypt; [4]Cairo University Kasr Alainy Faculty of Medicine, Cairo, Egypt.

Background: The use of ESAs and IV iron is the main line of treatment of renal anemia. There are few studies done to compare efficacy & cost benifit of originator vs. biosimilar ESAs. The aim of this study was to compare the therapeutic effect of originator ESA (Eprex®) vs biosimilar (Epoetin®) on mainataing Hb to the target level among ESRD patients on Hemodialysis (HD).

Methods: Prospective cohort study involved 81 prevalent HD patients in Maadi Military Hospital, Cairo. patients were randomised into two cohorts, Originator ESA (Eprex®) (27 subjects) and biosimilar Epoetin® (54 subjects). Baseline data including Hb, ESAs (dose & cost) and dialysis specifications and adequacy parameters were recorded at the time of enrollment, then monthly for 6 months for all patients. Iron studies were done at baseline & every 3 months.

Results: A total of 81 patients completed the study. both groups were age & gender matched. Eprex group (27 subjects) had more males (18 '66.7%') and Epoetin group (54 subjects) had more female (29 ' 3.7%') *(p = 0.083).* Baseline Hb was *lower* in Eprex vs. Epotin group (9.9±1.3 g/dL vs. 10.8±1.3g/dL respectively) *(p = 0.006).* The absolute Hb change relative to baseline for six months of follow up in Eprex vs. Epotin was ranging between 0.1 – 0.5g/dL vs. 0.4 – 0.1 g/dL respectively *(p = 0.007).* The median dose used in Eprex vs. Epotin were comparable, ranged between, 6-10 vs. 4-8 ampules per month, respectively *(p >0.05).* in both groups, no significant difference in the % of patients attained target Hb in Eprex vs. Epotin (66.7% vs. 61.1% respectively *"p >0.05").* The total cost in the 6 months study period was *significantly lower* in Epotin vs Eprex group, it ranged between 472-630 LE vs 2131-2648 LE respectively *(p =* <0.001).

Conclusions: Biosimilar epoetin® showed therapeutic equivalence with lower cost compared to originator drug (Eprex®) in maintaining Hb to target level in ESRD patients on HD.



Trend of mean Hb level in both groups over the study (6 months)

PUB056

Exploring the Potential of ChatGPT as an Artificial Intelligence (AI)-Powered Resource for Patient Education on a Renal Diet

Ahmad A. Qarajeh,[1] Supawit Tangpanithandee,[2] Pajaree Krisanapan,[3] Oscar A. Garcia Valencia,[2] Maria Lourdes Gonzalez Suarez,[2] Charat Thongprayoon,[2] Wisit Cheungpasitporn.[2] *[1]The University of Jordan, Amman, Jordan; [2]Mayo Clinic Minnesota, Rochester, MN; [3]Thammasat University Hospital, Khlong Nueng, Thailand.*

Background: Patients with chronic kidney disease (CKD) require a customized renal diet to avoid complications such as hyperkalemia and hyperphosphatemia. However, managing the nutrition of CKD patients requires careful time-consuming analysis of food composition. ChatGPT, an AI language model, has the potential to serve as a patient education resource.

Methods: To assess ChatGPT's accuracy in determining the potassium and phosphate content of food items, we presented 240 food items to ChatGPT in two separate sessions with a two-week interval between them. We selected the food items based on their potassium (149 items) and phosphate (91 items) content using the Mayo Clinic's renal diet book for patients with CKD. We asked ChatGPT to categorize each food item as having high or low potassium and high phosphate content. We compared the results with those from the Mayo Clinic Renal Diet book and computed the overall concordance to determine ChatGPT's accuracy and reliability.

Results: Our results showed that ChatGPT demonstrated moderate to high accuracy in identifying food items with high or low potassium and phosphate content in a renal diet. ChatGPT correctly classified 98 out of 149 (66%) food items as having high or low potassium content. Among the 81 food items with high potassium content, ChatGPT correctly identified 72 (89%), while it classified 26/68 (38%) of low potassium foods correctly. ChatGPT correctly classified 77 (85%) out of the 91 food items with high phosphate content. The concordance between the two ChatGPT sessions was 121/149

(81%) for potassium-containing food items, with 54/68 (79%) and 67/81 (83%) for low and high potassium food items, respectively. The concordance between the two ChatGPT sessions was 82/91 (90%) for phosphate-containing food items.

Conclusions: ChatGPT exhibited moderate to high accuracy in identifying food items with high or low potassium and phosphate content in a renal diet. ChatGPT's precision was higher for identifying food items with high potassium or phosphate content than those with low content. The overall concordance between two ChatGPT sessions was high, indicating ChatGPT's consistency in producing results. Further research is required to optimize its performance and maximize its potential as a clinical tool.

PUB057

Exploring the Use of Artificial Intelligence (AI) and Machine Learning in Nephrology Research: A Bibliometric Analysis

Pajaree Krisanapan,[1,2] Yuh-Shan Ho,[3] Tibor Fulop,[4,5] Wisit Cheungpasitporn.[1]
[1]Mayo Clinic Minnesota, Rochester, MN; [2]Thammasat University Hospital, Khlong Nueng, Thailand; [3]Asia University, Taichung, Taiwan; [4]Medical Services, Ralph H. Johnson VA Medical Center, Charleston, SC; [5]Medical University of South Carolina, Charleston, SC.

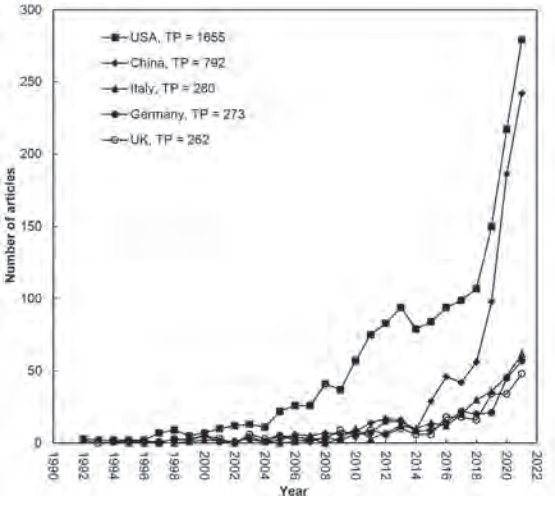
Background: Artificial intelligence (AI) and machine learning (ML) have increasingly been integrated into the field of nephrology in recent years. This study aimed to identify the most productive authors, institutions, and countries in this field, examine publication trends and patterns, and investigate the impact of collaboration on citations.

Methods: The study utilized the Science Citation Index Expanded (SCI-EXPANDED) of Clarivate Analytics Web of Science Core Collection to search for AI and machine learning publications related to nephrology from 1992 to 2021. The authors used quotation marks and Boolean operator "or" to search for keywords in the title, abstract, author keywords, and Keywords Plus. The 'front page' filter was applied to exclude non-research articles. A total of 5,425 documents were identified and analyzed.

Results: The results showed that articles represent 75% of the analyzed documents, with an average authorship ratio of 7.4 and an average number of citations per publication in 2021 of 18. English articles had a higher citation rate than non-English articles. The USA was preeminent in all publication indicators, followed by China (**Figure**). Collaborative research was found to enhance citations in the field.

Conclusions: This study provides a comprehensive analysis of the use of AI and ML in nephrology research publications from 1992 to 2021. Collaborative research was found to be important in advancing the field, and the study highlights research foci and frequently used author keywords. These results can guide researchers and practitioners in identifying key areas of research and advancing the use of AI and ML in nephrology research.

Figure. Development trends of the top five productive countries. TP: number of articles contain the keywords



PUB058

Is Shared Decision-Making for Hemodialysis Adequate? The Rationale and Design of a Clinical Trial to Evaluate Video-Assisted Electronic Consent for Hemodialysis

Pedro H. Gois,[1,2] Rebecca Saunderson,[3] Marina Wainstein,[1,4] Kelly C. Li,[5] Matthew J. Damasiewicz,[6] Vera Y. Miao,[7] Kirsten S. Hepburn,[8] Martin Wolley,[8,1] Ann Bonner,[9] Helen G. Healy.[8,1] *[1]The University of Queensland Faculty of Medicine, Brisbane, QLD, Australia; [2]John Hunter Hospital, New Lambton Heights, NSW, Australia; [3]The University of Sydney Faculty of Medicine and Health, Sydney, NSW, Australia; [4]West Moreton Hospital and Health Service, Ipswich, QLD, Australia; [5]Saint George Hospital, Kogarah, NSW, Australia; [6]Monash Medical Centre Clayton, Clayton, VIC, Australia; [7]Hornsby and Ku-ring-gai Hospital, Hornsby, NSW, Australia; [8]Royal Brisbane and Women's Hospital, Herston, QLD, Australia; [9]Griffith University, Nathan, QLD, Australia.*

Background: Current methods of informed consent have repeatedly been demonstrated to be inconsistent and inadequate. We hypothesise that quality informed consent improves decision-making and is key to preparing patients for hemodialysis (HD). Study aims: To demonstrate that video-assisted electronic consent (eConsent) (intervention) compared to standard paper-based consent (control) improves patient experience, with better comprehension, reduced anxiety, increased satisfaction, less decisional regret, and improved adherence.

Methods: This is a multi-center, open label, randomized controlled trial (RCT). Participants: Incident and prevalent adult HD patients randomised 1:1 to either the intervention or the control groups. Intervention group: Participants will be coached to an online platform that delivers a simple-to-understand video animation followed by a knowledge questionnaire prior to signing an eConsent form to receive HD. The animation, co-designed with consumers, will consist of human figures role-playing a patient-doctor interaction. Control group: Participants will be consented by a clinician and sign a paper form. All groups will have any questions answered by a clinician prior to consent. Figure 1 depicts the RCT design and outcomes of interest.

Results: This RCT outcomes directly address patient experiences in the decision-making processes for HD. It will also standardize the content of complex HD health information, which may impact in decision-making and patient satisfaction.

Conclusions: If video-assisted eConsent is proven superior to the existing consent process, this RCT will serve as a proof-of-concept for changes in nephrology.

Funding: Government Support - Non-U.S.

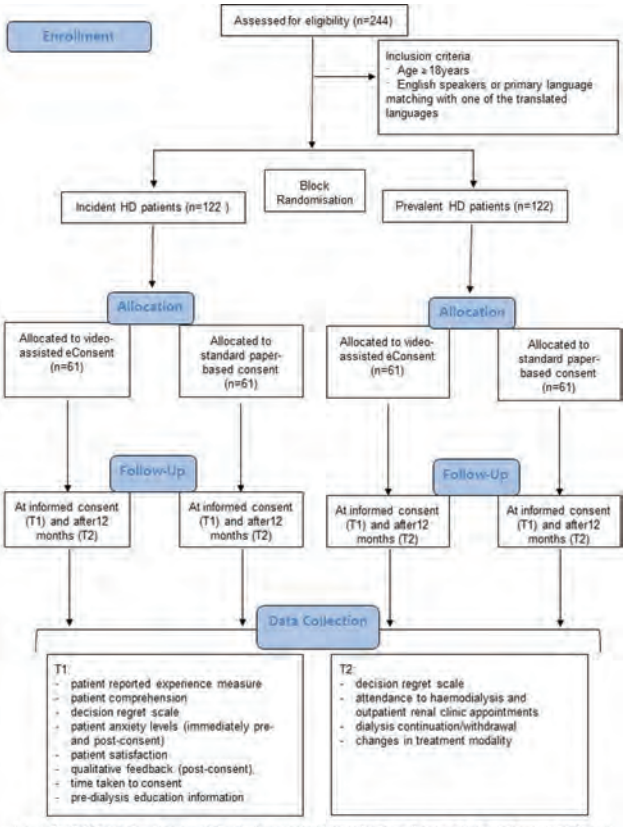


Figure 1: CONSORT flow diagram of the study protocol. Data collection will occur at informed consent (T1) and after 12 months (T2). Primary outcomes: Patient reported experience measure (modified Kidney PREM) and patient comprehension measured using an 18-point questionnaire previously published. Secondary outcomes: Validated decision regret scale, patient anxiety levels (six-item short form of the Spielberger State-Trait Anxiety Inventory), patient satisfaction (five-point Likert scale), compliance to renal care (attendance to HD and outpatient clinic appointments), dialysis continuation/withdrawal, changes in treatment modality, time taken to consent and participants' qualitative feedback.

PUB059

Impact of Behavioral Health on Kidney Disease Progression and Cost: Retrospective Analysis

Saravanan Balamuthusamy.[1,2] [1]*Texas Christian University Anne Burnett Marion School of Medicine, Fort Worth, TX;* [2]*PPG Heath, Fort Worth, TX.*

Background: Kidney disease can be impacted by other chronic conditions like cardiovascular disease and Diabetes. However, the impact of mental health on the progression of kidney disease and its impact on cost is unclear.

Methods: Retrospective analysis of 538,009 patients from a health analytics database was utilized for the analysis. Patients were stratified with and without behavioral health diagnosis. Patients with BHD were identified using relevant ICD-1, CPT codes and BH drug utilization for at least 3 months. Patients at risk for progression to high and ultra-high risk kidney disease were assessed using three different ML models (XG Boost, SVP and Random Forrest). Cost prediction across patients with and without behavioral health for risk or kidney disease progression was assessed from claims records.

Results: The mean age of the analyzed cohort is 55+/- 22, and 59% were males. The prevalence of kidney disease was 16.4% in patients with BHD. The risk of progression to high and ultrahigh risk kidney disease was 1.05 (1.03-1.06, $p < 0.001$) in patients with BH diagnosis. The average cost per member amongst patients with BHD at risk for progression to high-risk kidney disease is $54,989.97 vs $87,797.

Conclusions: There is a significant impact of BHD on kidney disease progression and its cost consequences. Risk stratification based on BHD is necessary while predicting disease to understand the true impact of disease progression so that appropriate case management and behavioral therapy strategies can be utilized to bend the cost and disease curve.

Impact of Behavioral Health on Kidney disease progression and cost: Retrospective Analysis

Table 1: Demographics

	BHD	No BHD
No.	14734	73498
men	8693	40,423
women	6041	33075
AA	2652	13964
Hispanic	3241	15434
Caucasian	8103	43363
CKD 3 and less	2357	9554
CKD4,5	144	492

PUB060

Image Segmentation Model Detects Abdominal Aortic Calcification in Dialysis Patients

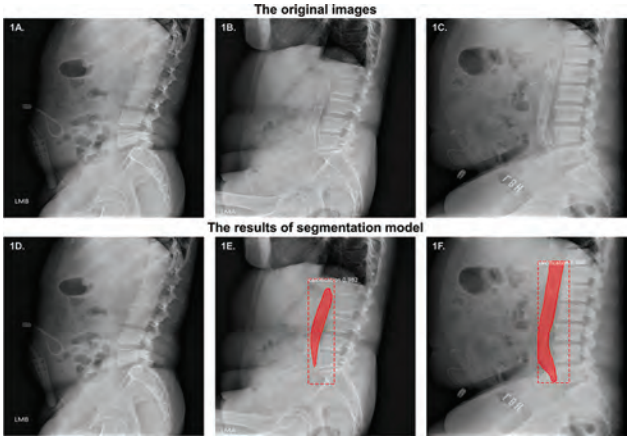
Chia-Tien Hsu,[1,2] Cheng-Hsu Chen,[1] Chin-yin Huang.[2] [1]*Taichung Veterans General Hospital, Taichung, Taiwan;* [2]*Tunghai University, Taichung, Taiwan.*

Background: Cardiovascular events remain the leading cause of death in patients with end-stage renal disease. Previous studies have established the considerable predictive value of the abdominal aortic calcification score in predicting cardiovascular morbidity and mortality. Our preliminary study aims to develop an artificial intelligence (AI) model using image segmentation to automatically detect abdominal aortic calcification.

Methods: This study analyzed 200 lateral view of abdominal X-ray images from patients who underwent dialysis. All included images were de-identified to protect patient privacy. We annotated the abdominal aortic calcification in the images using the "Labelme" marking tool and then split them into training and validation sets. For this image segmentation problem, we utilized the Mask-RCNN deep learning model. Furthermore, we randomly selected three extra abdominal X-ray images, separate from the initial dataset, for testing purposes. These three images consisted of one without calcification and two with calcification.

Results: After 30 training epochs, the loss was reduced to 0.1940, while the "val_loss" decreased to 0.2319. Subsequently, we tested our detection model on three extra images (Figure 1A~1C), and the results showed its ability to accurately predict the presence of abdominal aortic calcification. Figure 1D displayed the correct identification of an image without calcification, while Figure 1E and 1F demonstrated accurate detections of images with calcification. However, the model's boundary outlining didn't align precisely with the actual boundary. Improvement in this aspect of the model is needed.

Conclusions: AI has the potential to improve the accuracy and efficiency of healthcare delivery. The results of our preliminary study revealed that the AI assistant model successfully detected abdominal aortic calcification in the test images. Further investigation with a larger dataset and comparisons to other AI models are needed.



PUB061

Bone and Vascular Changes in CKD-MBD over 2 to 3 Years Analyzed by Artificial Intelligence

Hartmut H. Malluche,[1] Amr E. Mohamed,[1] Florence Lima,[1] Jin Chen,[1] Qi Qiao,[1] David Pienkowski.[2] [1]*University of Kentucky College of Medicine, Lexington, KY;* [2]*University of Kentucky, Lexington, KY.*

Background: Bone abnormalities and vascular calcifications occur with reduced GFR, but their relationships and progression are unclear.

Methods: Bone markers in serum and vascular calcifications were measured. Bone histology, Fourier transform infra-red spectroscopy of bone, and dual photon x-ray absorptiometry of hip and spine was done at baseline and after 2-3 years observation in 23 subjects with GFR 18-70 ml/min. Data were analyzed using artificial intelligence.

Results: Bone quality and quantity declined with early loss of GFR and were predicted by serum activin, FGF-23 and klotho. 18 subjects had baseline coronary or aortic calcifications: 52% and 65% rsp progressed. 5 subjects had no coronary calcifications at any time. Vascular calcifications were related to serum phosphorus levels. Increases in serum began at 4.0 mg/dl.

Conclusions: Serum markers offer promise as indicators of structural and cellular bone abnormalities accompanying early reduced kidney function. These include reduced bone quantity, quality and turnover abnormalities which are associated with coronary and aortic calcifications. Calcifications occur and progress in most studied subjects. Serum phosphorus levels ≥ 4.0 mg/dl predict vascular calcification progression.

Funding: NIDDK Support, Private Foundation Support

PUB062

Prospective, Randomized Controlled Pilot Trial to Investigate the Impact of Artificial Intelligence (AI) on Shared Decision Making in Post-Kidney Transplant Care (PRIMA-AI): Study Protocol for a Randomized Controlled Trial

Bilgin Osmanodja, Klemens Budde. *Charite Universitatsmedizin Berlin, Berlin, Germany.*

Background: Risk prediction models in kidney transplantation are ever increasing. Translation from good metrics to clinical benefit is the upcoming challenge. Another open question is how implementation of AI-based decision support systems (AI-DSS) affects physician-patient relationship in general and shared decision making (SDM) in particular.

Methods: In previous work, we developed risk prediction models for the prediction of infection, rejection and graft loss in kidney transplant recipients (KTR) and showed its superior performance in comparison to experienced physicians in a case-based reader study. Based on these models, we developed an AI-DSS that is implemented into the institutional electronic health record (EHR), and is studied in the PRIMA-AI trial.

Results: A 2-year, prospective, randomized, 2-armed, parallel group, single-center trial. KTR will be recruited in a German transplant center. All patients will receive the same routine care with clinical visits every 3 months. For patients in the interventional arm, physicians will be assisted by an AI-DSS that estimates 1-year risk for rejection, graft loss, or urinary tract infection (UTI). Based on the patients' risk scores, medical and SDM interventions will be suggested to the physicians per protocol. As primary endpoint, two scores for SDM, the CollaboRATE mean score, and the Control Preference Scale are compared between both groups at baseline and 12 months after randomization. Secondary endpoints address differences in patient and graft survival, rejection episodes, time from suspected rejection to biopsy, hospitalization for UTI, outpatient treatment of UTI, dialysis initiation via catheter or shunt, and patient-reported outcome measures. Qualitative semi-structured interviews with patients, support persons and physicians to study communication experiences and preferences as well as barriers and enablers of the implementation of AI-DSS in routine care and help interpret the quantitative data.

Conclusions: First, we investigate the potential benefit of an AI-DSS for the prediction of graft loss, rejection, and UTI in KTR. Additionally, using a mixed-methods approach, we aim to study the influence of AI-DSS on SDM, which can be relevant beyond the use case of kidney transplantation.

Funding: Government Support - Non-U.S.

PUB063

A Systematic Review of Externally Validated Machine Learning Models for Predicting AKI in General Hospital Patients

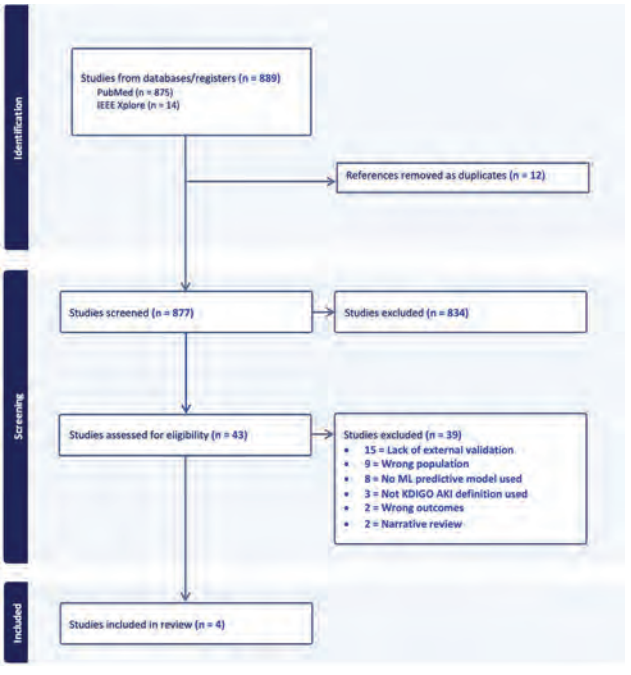
Marina Wainstein,[1,2] Emily K. Flanagan,[1] David W. Johnson,[3,1] Sally Shrapnel.[1]
[1]The University of Queensland, Brisbane, QLD, Australia; [2]West Moreton Hospital and Health Service, Ipswich, QLD, Australia; [3]Princess Alexandra Hospital, Woolloongabba, QLD, Australia.

Background: Acute kidney injury (AKI) is one of the most common and consequential complications among hospitalized patients. Timely AKI risk prediction may allow simple interventions that can minimize or avoid the harm associated with its development. Given the multifactorial and complex etiology of AKI, machine learning (ML) models may be best placed to process the available health data to generate accurate and timely predictions.

Methods: We searched the literature for externally validated ML models developed from general hospital populations using the KDIGO AKI definition. Data extraction was done using the CHARMS and TRIPOD checklist and risk of bias was assessed using PROBAST.

Results: Of 889 studies screened, only four were retrieved that fit these criteria (Fig 1). While most models performed well and had a sound methodological approach, the main concerns relate to their development and validation in populations with limited diversity, comparable digital ecosystems, use of a vast number of predictor variables and over-reliance on an easily accessible biomarker of kidney injury.

Conclusions: These are potentially critical limitations to the applicability of ML models in diverse socioeconomic and cultural settings, prompting a need for simpler, more transportable prediction models which can offer a competitive advantage over the current tools used to predict and diagnose AKI.



PRISMA flowchart

PUB064

Implementation of Risk-Stratified CKD Screening Among Patients with Type 2 Diabetes

Camilla Sammut-Powell,[1] Rose Sisk,[1] Susana Goncalves,[2] Shreyash Jain,[2] Luong Nguyen Cong,[2] Mark P. Edge,[1] Thomas D. Moitié,[1] Claudia S. Federico,[1] Ahmed Hadaoui,[2] Rory S. Cameron.[1] *[1]Gendius Limited, Alderley Edge, United Kingdom; [2]AstraZeneca PLC, Cambridge, United Kingdom.*

Background: A minimal-resource model to risk-stratify patients with type 2 diabetes for CKD screening has been developed and globally validated. However, it remains to understand how it can be best utilised in practice to support earlier identification of CKD. The CKD Screening Prioritizer (CSP) is risk-stratification tool powered by the minimal-resource model that can be integrated directly into existing systems or accessed via a user interface. This study aims to describe the implementation of the CSP within different technology systems with the goal of ensuring it is accessible to a broad spectrum of users.

Methods: Two core objectives of implementation were identified: 1. To determine the market need of the tool and 2. To determine the suitability and acceptance of implementation across several channels. Patients that were determined high risk by the CSP were recommended for serum creatinine testing. The total number of patients processed by the CSP and the proportion identified as high risk were measured across each implementation.

Results: The CSP was implemented across several countries via healthcare professional (HCP)-facing systems and direct to patients. HCPs were able to use the tool during face-to-face consultations on a per-patient basis or by processing entire clinic populations using historic patient records. Using a custom application-programming interface (API) we integrated with electronic health records. Chatbots within healthcare websites allowed direct-to-patient implementation: patients identified as high risk from this method were recommended to consult a healthcare professional on evaluating the next best course of action.

Conclusions: The CSP is a well-accepted and easily integrated risk-stratification tool that can be adopted across several settings. With the large and growing burden of type 2 diabetes, universal annual screening becomes an unrealistic target, particularly in lower resource healthcare systems. The CSP offers a novel solution to targeted CKD screening, enabling strategic allocation of healthcare resources, directing care to those who need it most and reducing system waste.

Funding: Commercial Support - Gendius Limited, AstraZeneca

PUB065

Construction of a Prediction Equation for the Progression and Worsening of CKD Using Artificial Intelligence

Koki Ogawa,[1] Yasushi Takahashi,[2] Seiko Oana,[2] Hiroaki Hara,[1] Tsukasa Odo,[2] Kento Soma,[2] Akito Maeshima,[1] Hajime Hasegawa.[1] *[1]Saitama Medical Center, Saitama Medical University, Kawagoe, Japan; [2]NEC Solution Innovators, Ltd., Koutouku, Japan.*

Background: Clinical studies in the past have focused on specific clinical characteristics (blood pressure, body mass index, renal function, urinary protein, various biochemical test parameters and specific markers, etc.) and analyzed their association with disease severity assessment, prognosis, and prediction of treatment responsiveness, mainly through statistical methods for specific populations. However, there are a wide variety of factors that can influence the above analysis, including age, gender, body size, presence and severity of comorbidities, and presence and type of medications, and so on. To conduct a more accurate and effective analysis, it is necessary to comprehensively consider the various data above for each individual. Against this backdrop, attempts to use various Ai(Artificial intelligence) algorithms to evaluate overall severity and predict future risk have been reported in certain fields in recent years. However, reports in the field of renal disease are limited. To develop a model to predict the risk of CKD progression and exacerbation using Ai, and to identify factors that have a significant impact on this exacerbation.

Methods: Data was collected from patients treated in our department from April 1 2006 to May 31 2021 with examination intervals of at least one year (3098 cases). The groups with the Green, Yellow and Orange stages of the CKD heatmap were analyzed at one year using Ai (rule discovery inference engine) to create a prediction equation. In addition to blood and biochemical test results, 209 factors were used in the analysis, including the name of the disease and drugs administered. A prediction equation was established using 85% of the cases in the population, and the accuracy of the prediction equation was verified by applying the obtained equation to the remaining 15% of cases. The final number of subjects for analysis was 1786 for Green, 824 for Yellow, and 488 for Orange.

Results: When the prediction formula was verified by the above method, the correct answer rate for each group was 76.8% for Green, 75.6% for Yellow, and 70.8% for Orange. Factors influential in CKD exacerbation at each stage were different.

Conclusions: The results of this analysis suggest that the relevant factors may have different priorities for each CKD stage.

PUB066

A New Deep-Learning Analysis Pipeline to Analyze and Quantify Renal Atrophy

Giuseppe L. Spatoliatore,[1] Alberto Rosati,[1] Guido Garosi,[2] Noemi La Francesca,[3] Clarissa Gambina,[4] Simone Cancelli,[4] Sergio A. Tripodi.[2] *[1]Ospedale di San Giovanni di Dio Firenze, Florence, Italy; [2]Azienda Ospedaliera Senese, Siena, Italy; [3]University of Siena, Department of Medical Biotechnology, Siena, Italy; [4]University of Siena, Department of Information Engineering and Mathematical Sciences, Siena, Italy.*

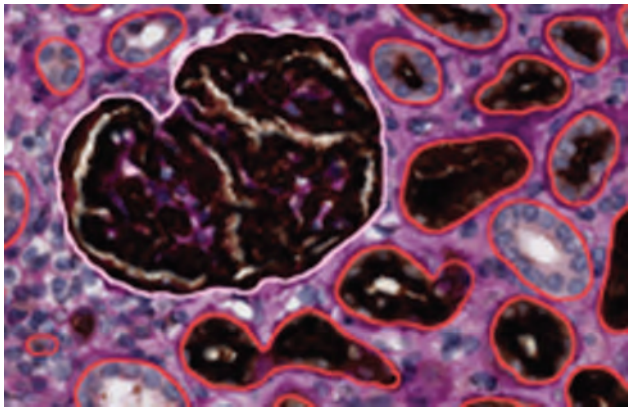
Background: atrophy represents a prognostic factor in many renal diseases and in kidney graft evaluation. Up to date the evaluation of atrophy is made using eyeball method and has low interobserver agreement. So, there is an urgent need to introduce user-friendly and affordable tools. Digital pathology coupled with AI represents the solution but is challenged by the need of long training of nets through large, annotated datasets. Annotations are manual, time-consuming and need skilled pathologists. Herein we propose a new method to annotate fast and well.

Methods: we have developed two new strategies to perform fast and accurate annotations. The first was the employment of immunostaining with CD10/PAS. CD10 brown decorates podocytes and the brush border of proximal tubules, Pas counterstain membranes pink. CD10 is under expressed in atrophic proximal tubules and absent in the distal nephron. Thus, it represents not only a morphological but also a functional marker. The second strategy was to speed up the annotation step using a new workflow (fig1).

Results: using our pipeline colours are well separated and the contours of the structures well delineated (fig2). Annotation time was dramatically shortened, and more than 10000 tubules were annotated in less than an hour compared with a mean of 24 hours of manual annotation and with a high variability depending on the skill of the operator.

Conclusions: we developed an easy fast method, based on AI, that combines morphology and immunophenotype. We wish to improve and standardize the morphofunctional evaluation of kidneys in nepropathology as well as in transplantation.

Funding: Government Support - Non-U.S.



PUB067

Improving Outcomes of Patients with CKD by Employing Chronic Care Management Machine Learning Technology

Leigh J. Mack. *Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom.*

Introduction: Many patients today struggle with treatment plan adherence due to not understanding the plan or how prescriptions, diet, and exercise are all integral to improved outcomes. By employing personalized messages, two-way communications along with patient education, patients with chronic kidney disease take more interest and ownership in improving their condition. Patient follow-up after a clinical visit is key to improved outcomes. Many times patients do not fully understand the treatment plan and therefore do not follow it as prescribed. Initial contact is made by SMS text that is personalized to the patient from the physician. Patients were then asked to engage in a digitized questionnaire to measure prescription adherence, treatment plan compliance, and lifestyle choices along with specifics on diet and exercise.

Case Description: A total of 521 Medicare patients were enrolled in the service and followed up after 7 days after the last clinical appointment with the physician. Patients had a diagnosis of chronic kidney disease stage 3 through 5. Patients were contacted by SMS text and asked to call in to a service, employing the physician's digitized voice, asking the patient specific questions related to their condition. Patients were asked 20 questions every two weeks related to observable conditions, prescription adherence, treatment planned adherence, diet, exercise, overall health, and quality of care experience from the provider. Conversations were reviewed by a medical technician for the quality of responses and sentiment. The sentiment was measured using validated machine learning software. Cases were reviewed for 90 days, after which data was compiled with machine learning analytics software to analyze correlations. Specific data shall be presented as it relates to patient engagement and data analysis of all 20 questions.

Discussion: At the time of this submission data is still being gathered and expected to be completed by the beginning of September, 2023. Even though this was a large population, next steps might include lengthening the study to 6 months and enroll a population of over 10,000. A repository might be upwards of 50,000 and might include the patient's full EMR. As we explore more machine learning processes, we might expect the software systems to detect multifaceted clinical relationships.

PUB068

Application and Improvement of Interpretable Artificial Intelligence (AI) Algorithms Using Global Permutation Importance for Intradialytic Hypotension

Jian-An Wang,[1] Hsiang Wei Hu,[1] Kuanyu Chen,[2] Chi Hin Un.[1] *[1]National Cheng Kung University, Tainan, Taiwan; [2]AcuSense Biomedical Technology, Tainan, Taiwan.*

Background: In recent years, machine learning has made significant breakthroughs in the field of smart healthcare. Dialysis has also become part of smart healthcare. In Taiwan, it's 3,679 people per million undergoing dialysis, whereas the global average prevalence rate of intradialytic hypotension is 11.6% in the past study. Therefore, intradialytic hypotension makes the application of smart healthcare in blood dialysis an important topic. Several articles have used various machine learning algorithms to predict the occurrence of hypotension during dialysis. However, these prediction results often lack proper explanations or are too complex to understand. Therefore, this study aims to improve interpretable AI algorithms and proposes the Global Permutation Importance method as an example, which is the simplest and most interpretable algorithm.

Methods: The core of this method lies in "changing the object of explanation to achieve high interpretability." Due to the complex feature engineering and mathematical operations, some features in the dataset may have lost readability, and their explanatory results cannot be directly applied to the real world. Therefore, this study transfers the object of explanation to the raw data, namely the dataset without feature engineering. By randomly shuffling the features of this dataset and utilizing the established feature engineering and model, the impact of each feature on the prediction process is evaluated.

Results: The bar plots are used to interpret the results of feature importance. There are some features that are difficult to understand, such as time-related features and difference-related features. For example, the mean and median of the blood flow sequence cannot identify the differences in the world. It's difficult to interpret how these features impact the prediction. However, all of the features become useful and meaningful using global permutation importance, such as blood flow and body temperature. Additionally, feature engineering can evaluate whether the feature engineering has an effect on the prediction.

Conclusions: Through the aforementioned techniques, our explanatory results not only cover the model training and feature engineering processes but also enable healthcare professionals to fully understand the explanations, thereby increasing trust in the model and prediction results.

PUB069

In Vitro Iohexol Adsorption in Cartridges with Mesoporous Styrene-Divinylbenzene Sorbent

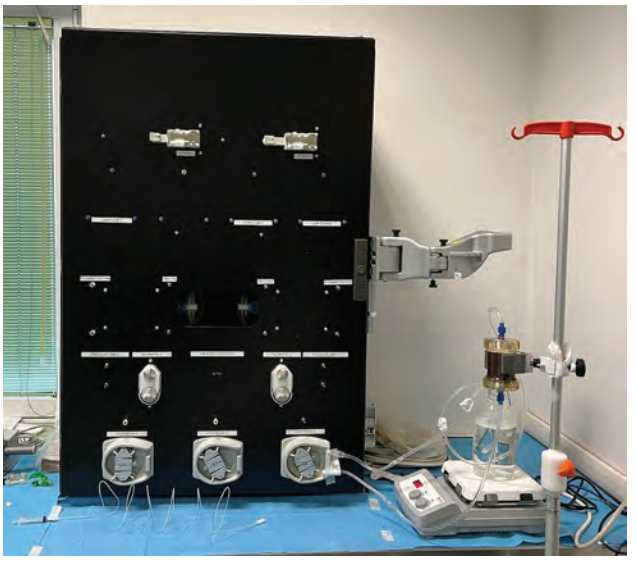
Thiago A. Reis,[1,2] Gonzalo Ramirez Guerrero,[3] Valentina Corradi,[3] Massimo de Cal,[3] Anna Lorenzin,[3] Claudio Ronco,[3] Monica Zanella.[3] *[1]D'Or Institute for Research and Education (IDOR). São Luiz Itaim Hospital, São Paulo, Brazil; [2]Laboratory of Molecular Pharmacology, University of Brasília, Brasília, Brazil; [3]International Renal Research Institute of Vicenza, Vicenza, Italy.*

Background: A strong rationale supports the removal of iodinated contrast media because of its nephrotoxicity. In this experiment, we aimed to investigate the efficacy of iohexol (molecular weight 821 Da) adsorption with a mesoporous styrene-divinylbenzene sorbent using an in vitro model.

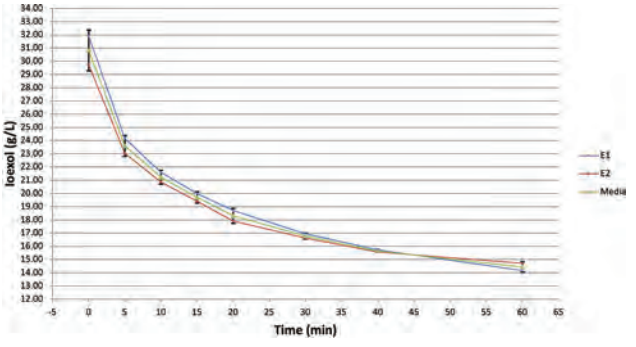
Methods: We used a 0.9% NaCl solution spiked with iohexol in a closed-loop circuit. The circuit had a cartridge with adsorbing resin interposed downstream of a peristaltic pump. A glass reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with iohexol. The cartridge was filled with 75 g sorbent resin beads. The concentration of iohexol was assessed by high-performance liquid chromatography with ultraviolet (HPLC-UV) detection. The collection of 2 mL aliquots occurred at eight-time points (0, 5, 10, 15, 20, 30, 40, and 60 minutes).

Results: The reduction ratios after 5, 30, and 60 minutes were 24,5%, 47,5%, and 56,1%, respectively. In the second experiment, the reduction ratios after 5, 30, and 60 minutes were 22,5%, 44,1%, and 50,5%, respectively. After 30 minutes, the adsorption curved plateaued, indicating cartridge saturation.

Conclusions: Removing iohexol via adsorption was effective, with each gram of sorbent removing roughly 105 mg of iohexol (i.e., equilibrium load of 105 mg/g). The use of adsorption has the clinical potential to reduce exposure to nephrotoxic contrast agents.



Closed-loop circuit



Iohexol concentration during the experiment

PUB070

Vancomycin Adsorption in Cartridges with Mesoporous Styrene-Divinylbenzene Sorbent Enhanced by Vibration

Gonzalo Ramirez Guerrero, Thiago A. Reis, Anna Lorenzin, Massimo de Cal, Claudio Ronco, Monica Zanella. *International Renal Research Institute, Vicenza, Italy*.

Background: Flow distribution inside the cartridge is one of the main issues concerning the performance of the sorbent. The packed beads can be approximated as a bundle of capillary tubes with some wide-diameter channels and gaps in the structure resulting in "channeling of the flow," avoiding complete contact with the beads. Fluid dynamics studies have shown different local velocities in the cartridge, determining the production of vortices; these may enhance contact time between blood and beads. Transverse vibration induces a substantial amount of radial mixing in the fluid. It creates a swirling or spiraling motion in the fluid, represented by vorticity contours with the potential beneficial effects of increasing contact time.

Methods: The circuit had a cartridge with adsorbing resin interposed downstream of a peristaltic pump. A reservoir in which the inlet and outlet lines were placed contained 1,000 mL of the saline solution with 10 g of vancomycin. The resin originated from HA380 cartridge. The GALILEO machine propelled the solution via a peristaltic pump for human hemoadsorption therapy. For each study point, a sample was drawn at 5, 10, 15, 20, 25, 30, 40, 60, 80, 100, and 120 minutes. Vibration was implemented with a speed at 1800 percussion per minute, amplitude of 10 mm, and frequency of 30 Hz. The device was installed in front of the cartridge, specifying the middle segment of the cartridge as the contact area. The reduction ratio was calculated using the formula: *[Initial concentration - Final concentration]/Initial concentration*

Results: Reduction ratios after 5, 10, 15, 20, 25, 30, 40, 60, 80, 100 and 120 minutes were 12,5%, 26.3%, 27.6%, 25.8%, 20.4%, 31.4%, 33.1%, 42.1%, 43%, 47.4% and 50%, respectively. A higher vancomycin reduction rate was observed in the first 20 minutes. Subsequently, the obtained curve was similar to a previous experiment without vibration after 20, 40, 60, 80, 100 and 120 minutes.

Conclusions: In this in vitro model, removing vancomycin via adsorption appears to be greater in the first 20 minutes when using vibration to accentuate this technique. Vibration in adsorption to increase performance warrants further investigation.

Funding: Private Foundation Support

PUB071

Ion Chromatography Study of Ca/Mg Phosphate Binders

Deanna J. Nelson.[1,2] *[1]BioLink Life Sciences Inc, Cary, NC; [2]NC State University, Raleigh, NC.*

Background: Ca and Mg are each well-known phosphate-binding cations. However, combinations of these cations provide unique clinical benefits in addition to phosphate (Pi) binding. Both in clinical studies and long-term use, increases in serum Mg were small and self-limiting, an unusual finding. To rationalize these reports, an *in vitro* Pi-binding study was completed using combinations of soluble Ca & Mg salts.

Methods: In a typical Pi-binding experiment, known quantities of Ca salt and Mg salt were incubated at 37 °C with a second, known quantity of Pi in buffer solution (0.1 N acetate, pH 4.5; or 0.1 N borate, pH 6.8). The solution pH was not adjusted after mixing. Aliquots were removed and filtered. Portions of the filtrate were diluted before analysis in triplicate for Ca and Mg using a validated ion chromatography method.

Results: Experimental data showed that combinations of Ca & Mg salts (110 mg Ca, 60 mg Mg) failed to bind Pi in acetate buffer, pH 4.5. (Ca acetate binds about 60% of available Pi under these conditions.) In contrast, in pH 6.8 borate buffer, rapid & extensive Pi binding was observed. Most of the Ca was bound to Pi & precipitated, but 65% of Mg remained in solution, even after extended lengths of time.

Conclusions: These observations strongly suggest combinations of soluble Ca and Mg salts react with Pi differently from Ca or Mg alone. At values of pH characteristic of the small intestine, the two cations rapidly precipitated Pi. However, over half of the Mg ion remained in solution under these conditions. The data suggest that residual Mg ion remains in solution after Pi-binding takes place in the upper intestine. If residual Mg is not absorbed, it acts beneficially in the colon. Conversely, if Mg is absorbed, it acts beneficially in the systemic circulation and intracellularly. Normalization of systemic Mg self-limits further absorption of the ion.

Funding: Commercial Support - BioLink Life Sciences Inc

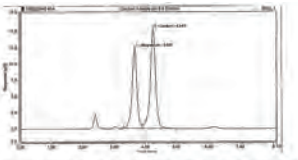


Figure 1. Representative chromatogram of calcium and magnesium solutions before addition of phosphate.

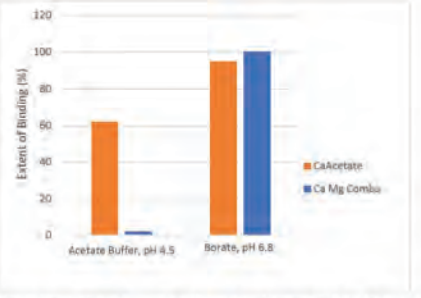


Figure 2. Phosphate binding in buffer solutions by Ca or any of several combinations of Ca and Mg in a 1:1 molar ratio.

PUB072

Prevalence and Factors Associated with Renal Hyperparathyroidism Among Dialysis-Requiring Patients

Bai Ramlyn G. Solaiman, Jennifer Ivy Togonon-Leaño, Jose Paolo P. Panuda. *Southern Philippines Medical Center, Davao City, Philippines*.

Background: Renal hyperparathyroidism, a CKD complication, is associated with increased parathyroid hormone levels from calcium, phosphate, and Vitamin D imbalances. It is 12-54% prevalent worldwide and associated with significant mortality and morbidity. This study aimed to determine the local prevalence and the factors associated with it among dialysis patients.

Methods: A cross-sectional study was conducted wherein all ESRD patients aged 19-75 years old and on maintenance dialysis ≥3months were included. The mean intact parathyroid hormone (iPTH), Vitamin D, ionized calcium, phosphorus and alkaline phosphatase were recorded. Correlation of age, gender, pre-dialysis co-morbidities, dialysis vintage and frequency were determined using spearman rank correlation coefficient, chi-square test and regression analysis.

Results: A total of 240 chronic dialysis patients in our unit were identified. Out of the 240 patients, 168 patients were included. There were 147 patients with elevated iPTH, giving an 87.5% prevalence. Age was negatively correlated with iPTH (r=-0.212, p=0.006, 95%CI-0.352,-0.062) and as they age, their iPTH is predicted to decrease by 15.195pg/mL (p=<0.01). Dialysis vintage had positive correlation with iPTH (r=0.369, p=<0.01, 95%CI0.227,0.512) and the longer they were on dialysis, their predicted iPTH will be higher by 93.637pg/mL (p=<0.01). Dialysis frequency was positively correlated with iPTH (r=0.19, p=0.016, 95%CI 0.036,0.344) and the more frequent their sessions were, their predicted iPTH will increase by 353.508 pg/mL (p=<0.012). Three pre-dialysis co-morbidities showed positive correlation with iPTH and their presence can

increase the iPTH significantly {hypertensive nephrosclerosis: x^2=9.44; p=0.024, diabetic kidney disease: x^2=19; p=<0.01, chronic glomerulonephritis: x^2=12.680; p=<0.01}.

Conclusions: The 87% prevalence rate supported the high prevalence world-wide. Factors identified were age, presence of pre-dialysis co-morbidities, longer dialysis vintage, and frequent dialysis sessions (3x a week). Shorter dialysis interval stimulates parathyroid gland from increased blood flow triggered during dialysis and altered calcium handling by the kidneys, subsequently leading to hormone secretion.

PUB073

Hypercalcemia as a Solitary Feature of Sarcoidosis

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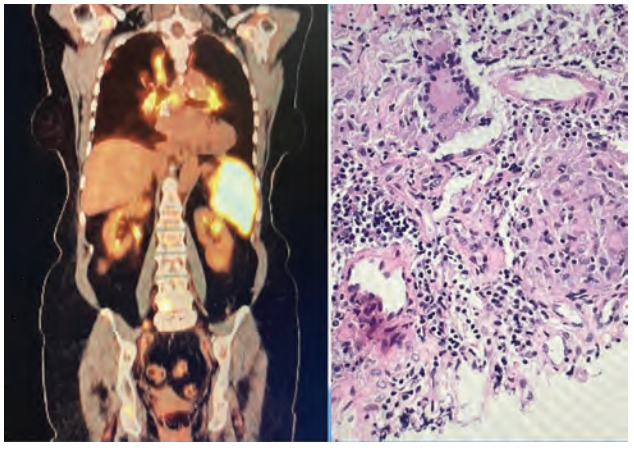
Introduction: In over 90% of cases, sarcoidosis typically manifests initially in the intra-thoracic region, characterized by mediastinal or hilar lymphadenopathy (LAD). It is rare for sarcoidosis to present solely as extra-thoracic, and even rarer for hypercalcemia to be the only initial sign.

Case Description: A 70-year-old Caucasian female with history of childhood histoplasmosis, presented with hypercalcemia of 12.2 mg/dl and elevated 1,25 dihydroxy vitamin D3 (1,25(OH)2 D) of 123 pg/ml. A chest CT revealed calcified lymph nodes (LN) in the mediastinum, indicating a previous histoplasmosis. PET-CT showed extensive generalized LAD with increased FDG uptake in the enlarged spleen. Additionally, myocardium showed no abnormal metabolic activity. An inguinal LN biopsy demonstrated non-necrotizing granulomatous inflammation. Staining with Grocott Methenamine Silver (GMS) and AFB was negative for organisms. Histopathology was negative for malignancy or lymphoma. Results of Fungitell, QuantiFERON TB gold, antibodies against Histoplasmosis, Blastomycosis, and Coccidiomycosis were all negative. Treatment with prednisone at 0.5 mg per kg led to the normalization of calcium and 1,25(OH)2 D levels within three weeks.

Discussion: The measurement of vitamin D metabolites is crucial for diagnosing hypercalcemia mediated by 1,25(OH)2 D. Granulomatous disease can lead to hypercalcemia and elevated 1,25(OH)2 D, therefore, should be considered in the differential diagnosis of hypercalcemia. When diagnosing sarcoidosis, other potential causes of granulomatous inflammation are typically ruled out by clinical features, laboratory findings, imaging, and tissue histopathology (as described under case description). A PET-CT scan is an essential tool in determining an appropriate biopsy site and excluding potential cardiac involvement of sarcoidosis.1,25(OH)2 D mediated hypercalcemia is responsive to glucocorticoid therapy.



High FDG uptake in spleen. H&E slide demonstrate non-necrotizing granuloma in the lymph node tissue.

PUB074

Giant Bladder Stone in a Young Male: When Surgery Complements Medicine for Better Outcomes

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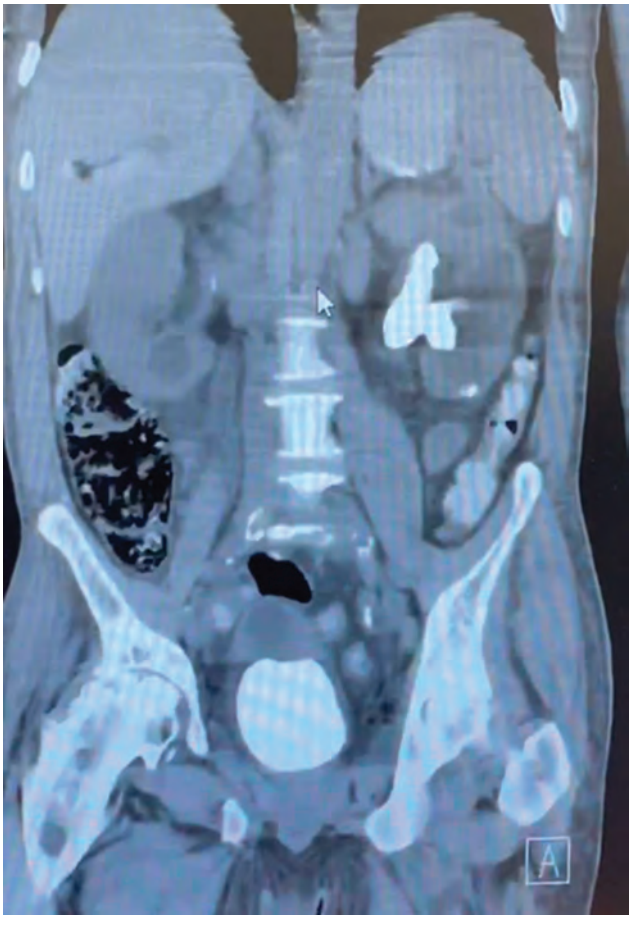
Introduction: Bladder stones are extremely rare especially more than 100 grams. This is a case of giant bladder stone in 49 years old male with recurrent UTI and foreign body retention leading to open cystolithotomy.

Case Description: 49-year-old male with PMH of recurrent UTI and recurrent nephrolithiasis (lost follow-up with double J stents and nephrostomy tube) evaluated for symptomatic UTI. He denied family history of nephrolithiasis, Crohn's disease, or consumption of supplements. Blood workup revealed leucocytosis and hyperchloremic normal anion gap metabolic acidosis with normal potassium. Urinalysis showed turbidity with pH of 8.5, moderate triphosphate crystals, and positive for nitrite and LE. Radiology showed large urinary bladder calculus, bilateral hydroureteronephrosis with encrusted ureteral stents and staghorn calculus in left kidney. ESBL proteus mirabilis grew in blood and urine cultures. General urology and interventional radiology stepped out as extremely encrusted stents made high-risk with usual procedures. As an end resort surgical urology stepped in for multi-modal endourological approach starting with open cystolithotomy. Cystoscopy during surgery was performed which ruled out intravesical obstruction. Stone biochemical showed mixture of struvite and calcium apatite.

Discussion: Open cystolithotomy is preferred over transurethral cystolitholapaxy for large stones.



PUB075

Novel Markers of Early CKD-MBD Pathophysiology That Predict CKD Progression and All-Cause Mortality in Patients with Predialysis CKD

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Background: CKD-MBD develops in the early stages of CKD and contributes to the increased risk of end-stage kidney disease and mortality. Thus, it is critical to identify new indicators that reflect early events of CKD-MBD and can predict mortality in the pre-dialysis stage of CKD.

Methods: We examined 4,308 patients enrolled in the FKR study, a prospective observational study of patients with pre-dialysis CKD stages G1–G5. We focused on fractional excretion of phosphate (FEP) and estimated phosphate concentration in proximal tubular fluid (ePTFp) as indicators of early CKD-MBD pathogenesis. We compared the onset of change in each indicator with the serum PTH, calcium, and phosphorus levels using baseline data. Additionally, we determined the association of FEP or ePTFp with the risk of all-cause mortality and composite renal event using longitudinal data. The composite renal event was defined as the development of end-stage renal failure and/or 1.5-fold increase in serum creatinine concentrations.

Results: Over 5 years, 1,488 patients developed a composite renal event and 423 died. FEP and ePTFp were elevated as early as an eGFR of 70 mL/min/1.73m^2 and preceded the changes in serum PTH, calcium, and phosphorus concentrations. Multivariate-adjusted Cox proportional hazard regression analyses revealed a significant association between FEP and ePTFp increase and a heightened risk of developing a composite renal event and all-cause mortality. The hazard ratio (95% confidence interval) for a 1 standard deviation increase in log FEP and log ePTFp was 1.36 (1.20–1.54) and 1.39 (1.21–1.59), respectively. This association was independent of the serum PTH, calcium, and phosphorus concentrations and remained almost unchanged on application of competing risk regression analysis.

Conclusions: FEP and ePTFp may serve as indicators of early CKD-MBD pathophysiology that predict CKD progression and all-cause mortality in patients with pre-dialysis CKD.

PUB076

Beyond Bones: Examining Vascular Calcification in Hemodialysis Patients and Its Association with Bone and Mineral Metabolism

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Background: Patients on dialysis are at an increased risk of cardiovascular disease (CVD). The presence of vascular calcification (VC) is predictive of CVD and mortality. This study aimed to evaluate the possible relationship between VC and bone and mineral metabolism (BMD) in patients on dialysis.

Methods: This study was conducted in all ambulatory dialysis centers in Qatar from January to December 2022. We retrospectively reviewed dialysis patients' charts, including patient demographics, comorbidities, BMD parameters (corrected calcium, phosphorus, PTH, and Vitamin D3), and average medication doses per week. In addition, VC was assessed by echocardiography, abdominal and chest X-ray, and abdominal CT.

Results: 842 HD patients were included during the study period. VC was detected in 52.6% of patients (most commonly in the mitral valve with 55.5%). Patients with VC were older age (61.6±14.2 vs. 58.0±16.3 years, p 0.001), had diabetes mellitus (DM) (75% vs. 29%, p 0.006), Higher vitamin D levels (39.0±18.0 vs. 32.1±17.2 p=0.003), and higher 1α-hydroxyvitamin D3 and cinacalcet doses (p<0.001) compared to patients without VC. All other parameters were not different. Regression analysis (univariate and multivariate) for risk factors associated with VC is shown in Table 1. In multivariate analysis, age and diabetes were significantly associated with risk of VC (OR 1.049, p< 0.0001 and OR 1.768, P<0001) respectively). In addition, higher vitamin D levels and higher doses of 1α-hydroxyvitamin D3 were significant risk factors for calcifications (OR 1.017, p 0. 007 and OR 1.178, p <0.0001 respectively).

Conclusions: We found a high prevalence of vascular calcification among our hemodialysis cohort. Risk factors for VC were identified, including old age, DM, high vitamin D level, and high 1α-hydroxyvitamin D3 dose.

Funding: Government Support - Non-U.S.

Table 1: Regression analysis of risk factors for vascular calcifications in hemodialysis patients

	Univariate Analysis			Multivariate Analysis		
	OR	95%CI	P- Value	OR	95%CI	P- Value
Age	1.054	1.042-1.065	<0.001	1.049	1.033-1.065	<0.001
Diabetes	2.653	1.958-3.595	<0.001	1.768	1.128-2.772	0.013
Vitamin D Level	1.013	1.004-1.021	0.002	1.017	1.005-1.030	0.007
Oral Cinacalcet Dose	1.002	1.002-1.004	<0.001	1.002	1.000-1.003	0.051
1α-hydroxyvitamin D3	1.172	1.096-1.252	<0.001	1.178	1.092-1.270	<0.001

PUB077

Symptomatic Hypercalcemia Secondary to Hyperthyroidism

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Introduction: Hypercalcemia is often encountered in clinical medicine. The most common causes of hypercalcemia include primary hyperparathyroidism, iatrogenic causes (medications) and malignancy, while a rare cause is hyperthyroidism. This case highlights a nursing home resident presenting with severe hypercalcemia and undiagnosed thyroiditis.

Case Description: A 58-year-old AA woman with PMHX of CVA on PEG tube feedings presented with sudden onset non-exertional chest pain. The emergency department consulted the Nephrology service for evaluation of severe hypercalcemia and AKI. Medication list included aspirin, statin and citalopram. On exam, her PEG tube was in place, reflexes and vital signs were normal but was hypovolemic. Initial serum chemistries showed a BUN 67 mg/dl, serum Cr was 1.4 mg/dl, (SCr baseline <1 mg/dl). ALP 317 U/L, AST 283 and ALT 317 U/L respectively. CK was normal. Calcium was 13.4 mg/dl, albumin 3.5 g/dl. PTH was suppressed at 17 pg/ml, ionized calcium was 1.67 mmol/L. PTHrP was 5 pmol/L. Vitamin D 25-OH Vitamin D 1,25-OH were normal. SPEP and UPEP had no signs of monoclonality. TSH was extremely suppressed at <0.02 ulU/ml. T4 was high at 4.12 ng/dl and T3 was 5.13 pg/ml respectively. Thyrotropin receptor antibody was 3.23 IU/L and thyroid peroxidase antibodies titer was 278.2 IU/ml. U/A was normal. Urine drug screen was negative. Renal U/S had normal kidneys. A thyroid ultrasound showed a diffusely heterogenous in echogenicity with abnormal increased vascularity throughout. EKG had sinus tachycardia. The patient was treated with volume expansion with normal saline, pamidronate and calcitonin. Her serum calcium on discharge decreased to 10.7 mg/dl. She was treated with methimazole and propranolol for newly diagnosed Grave's thyroiditis. Her symptoms resolved and she returned to her nursing home.

Discussion: causes increased osteoclastic activity leading to bone resorption. Prompt recognition and early treatment of the hyperthyroid state is essential.

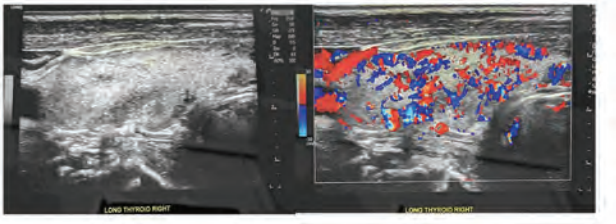


Figure 1. Transverse (a) sonographic and (b) Doppler ultrasound images of the thyroid gland showing diffuse echogenicity with increased vascularity, respectively.

PUB078

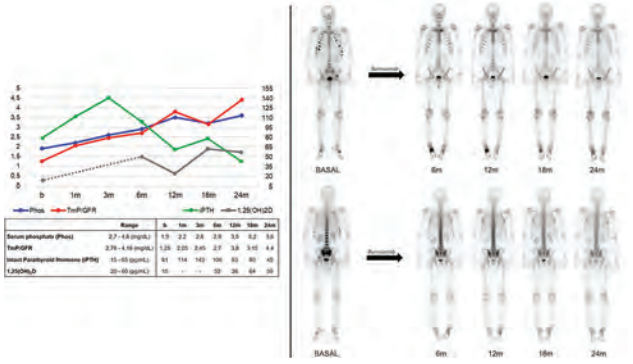
Burosumab Effects on Osteomalacia: A Tumor-Induced Osteomalacia (TIO) Case Report

Nadia Edvige Foligno,[1] Hajime Kato,[2] Yoshitomo Hoshino,[2] Soichiro Kimura,[2] Naoko Hidaka,[2] Takashi Sunouchi,[2] So Watanabe,[2] Teresa Arcidiacono,[1] Arianna Bologna,[1] Federica Giambò,[1] Giuseppe Vezzoli,[1] Nobuaki Ito.[2] *[1]Nephrology and Dialysis Unit, IRCCS San Raffaele Hospital, Milan, Italy; [2]Division of Nephrology and Endocrinology, The University of Tokyo Hospital, Tokyo, Japan.*

Introduction: Tumor-Induced Osteomalacia (TIO) is a rare paraneoplastic disorder caused by a tumor (PMT), usually of small size and benign, secreting FGF23. FGF23 suppresses the reabsorption of phosphate and the synthesis of 1,25$(OH)_2$vitD in the renal proximal tubule; consequently, affected patients develop hypophosphatemia and osteomalacia, resulting in bone pain and pathological fractures. The treatment of choice is the surgical resection of PMT, but when the latter is not detected or cannot be removed, phosphate salts and active vitD can be employed to improve symptoms. Burosumab, a monoclonal antibody directed against FGF23 introduced for XLH, has recently been tested for the treatment of TIO non-surgical patients, with encouraging results.

Case Description: Starting from January 2021, a 56M patient affected by TIO without identified PMT has been treated with burosumab 1mg/kg s.c./4w. Before the introduction of burosumab, his blood exams showed hypophosphatemia, low 1,25$(OH)_2$vitD levels and hyperparathyroidism secondary to previous administrations of phosphate salts. He also reported widespread bone pain, suspect of multiple fractures and pseudofractures, confirmed by whole skeleton bone scintigraphy (BS) as numerous areas of pathological accumulation in the ribs, sacrum, bilateral femur, right proximal tibia, sternoclavicular joint and vertebral bodies. After the initiation of burosumab, serum phosphate, PTH and 1,25$(OH)_2$vitD levels gradually normalized. The patient also reported an improvement in bone pain, and later BS described a notable and continuous reduction in pathological accumulations, which almost completely disappeared after 24m, confirming the absence of new fractures and the improvement of the existing ones.

Discussion: Therefore, burosumab is suggested as an alternative treatment for non-surgical TIO patients, especially since, unlike phosphate salts and active vitD, its therapeutic action seems to contribute to the further improvement of osteomalacia.



PUB079

Effect of Magnesium Supplementation on Serum Matrix Gamma-Carboxyglutamate Protein as Biomarkers of Vascular Calcification in Patients with CKD

Bancha Satirapoj, Pavitra Charoensrisakkul, Peeraya Permkarnjaroen, Narittaya Varothai, Narongrit Siriwattanasit, Naowanit Nata, Theerasak Tangwonglert, Amnart Chaiprasert, Ouppatham Supasyndh. *Phramongkutklao College of Medicine, Bangkok, Thailand*.

Background: Vascular calcification is a major risk factor of cardiovascular disease and cardiovascular mortality in patients with chronic kidney disease (CKD). Magnesium has pleiotropic potential for interfering with progression of vascular calcification by modulating the expression of anti-calcification proteins including matrix gamma-carboxyglutamate protein (MGP).

Methods: This study is double-blinded, randomized, placebo-controlled trial in CKD patients with high risk of vascular calcification. The subjects were randomly assigned (1:1) to receive oral magnesium dioxide (MgO2) 200 mg/day or matching placebo for 12 weeks. The primary end point was the between-groups difference in serum MGP level after 12 weeks.

Results: A total of 31 CKD patients (19 males and 12 females) were enrolled in the study. At baseline, mean serum magnesiumwas 2.05±0.23 mg/dL and baseline serum MGP levels did not differ significantly between the two groups. After 12 weeks, the mean MGP concentrations significantly increased in the MgO2 group (mean change, 90.45±102.06 ng/mL; 95%CI 209.45 to 219.80) and also significantly increased in the placebo group (mean change, 73.47±117.73 ng/mL; 95%CI 208.05 to 227.05). However, absolute MGP change was not significantly different between groups (P=0.682). There was no report of serious side effect or hypermagnesemia during the study.

Conclusions: Among CKD patients, magnesium supplementation for 12 weeks did not improve serum MGP level as biomarkers for preventing vascular calcification compared with placebo. Larger-scale trials are warranted to confirm these findings.

PUB080

Breaking Bad Calcium: The Role of Hemodialysis for Severe Hypercalcemia

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Introduction: Hypercalcemic crisis is an emergent medical condition that may lead to serious complications such as acute kidney injury (AKI), muscle flaccidity, neurologic changes including obtundation and coma and cardiac arrhythmias leading to cardiac arrest. Standard treatment for hypercalcaemia includes saline hydration, bisphosphonates, steroids, calcitonin and in refractory cases, hemodialysis (HD). HD can effectively lower serum calcium levels but its use is not commonly reported by literature.

Case Description: A 48-year-old man with a right thigh mass as recently diagnosed with high grade sarcoma and bilateral pulmonary lesions was admitted for inpatient chemotherapy with cisplatin and doxorubicin was consulted to Nephrology service due to hypercalcemia. Patient was not taking any medications or had a prior history of renal disease. Vital signs with blood pressure 167/90 mmHg, heart rate 100 beats per minute, respiratory rate 20 breaths per minute, oxygen saturation 99% at room air and temperature 37°C. EKG showed QT shortening. Physical exam was remarkable for a critically ill patient oriented to person, dry mucous membranes, icteric sclera, large right thigh soft tissue mass with associated leg pitting edema +4 and palpable pulses. Laboratory results were significant for BUN 114 mg/dL, creatinine 3.69 mg/dL, bicarbonate 22.5 mmol/L, corrected calcium 19.4 mg/dL and intact PTH 40.86 pg/mL. Despite aggressive intravenous isotonic fluids, bisphosphonate and calcitonin administration, patient persisted with severe hypercalcemia. In view of altered mental status, EKG changes, worsening renal function and poor response to medical management, the patient was started on kidney replacement therapy with low calcium dialysate concentration. After 3 sessions of intermittent HD, serum calcium levels improved and treatment was discontinued.

Discussion: Hypercalcemia remains a medical emergency and the prompt diagnosis and management of underlying pathology are essential for adequate patient outcomes. Although not commonly used, HD is an efficient treatment for severe refractory hypercalcaemia as in our case or in whom aggressive fluid treatment is contraindicated. Along with conservative treatment, low calcium HD should be considered in patients with or without AKI, as severe hypercalcaemia is an indication for HD.

PUB081

Is There a Link Between Mineral Bone Disease, Ethnicity, and Kidney Transplantation?

Francisco Montero,[1] Thomas B. Coupe,[1] Rouven Calayag,[1] Rosa M. Montero.[1,2] *[1]St George's University Hospitals NHS Foundation Trust, London, United Kingdom; [2]King's College London, London, United Kingdom*.

Background: Health inequalities have been reported internationally to affect access to transplantation in ethnic minorities. It is unclear whether mineral bone disease treatments are also affected by this. Several studies have shown that there are ethnic differences in bone mineral metabolism that may further predispose kidney transplant recipients (KTR) to increased fracture risk, morbidity and mortality. Our centre serves a multi-ethnic population in South West London. This cross-sectional observational study looks at the current distribution of mineral bone disease medications and whether this is influenced by ethnicity.

Methods: All KTR active in the transplant programme in 2021-2022 were included. Data was collected from the electronic patient record. All those with a documented ethnicity were analysed together with biochemical markers and medications used for mineral bone disease. T-test and ANOVA statistical tests were used with significance $p<0.05$.

Results: 509 KTR with 40(8%) patients with unknown ethnicity were excluded. 469 KRT analysed: 45% White, 18% Black, 19% Asian, 2% Chinese, 8% other. 257 Male, 212 Female with a median age of 56yrs(21-87yrs). PTH levels were higher in Black people(18.8umol/L) and significantly decreased in all ethnicities($p<0.05$) between 2021-2022. Adjusted calcium levels were significantly increased in all ethnicities ($p<0.05$) except Chinese. Phosphate levels significantly decreased in all ethnicities($p<0.01$) and were higher in Asians. Creatinine was significantly raised in Whites compared to Asian and Other populations($p<0.05$) in 2021 but not seen in 2022. All ethnicities on Cinacalcet had significantly lower Creatinine in 2021($p<0.01$) and 2022($p<0.05$). All treatments were given to White persons with higher numbers on Cinacalcet+Alfacalcidol+VitaminD3 combination. Black persons were predominantly on Cinacalcet+Alfacalcidol, Asians on Alfacalcidol+VitaminD3 and Chinese on Cinacalcet. There was a significantly lower intake of Vitamin D3 in KTR($p<0.05$) in all ethnic groups.

Conclusions: There is a disparity in transplantation of ethnic minority groups with White persons predominantly being transplanted despite our multi-ethnic population. Treatment variations are seen between ethnic groups that can be multifactorial. These findings could suggest health inequalities and we are currently investigating potential drivers behind this.

PUB082

Bone Mineral Disorder in Patients with CKD Undergoing Hemodialysis Replacement Therapy at a Reference Center

Juan D. Diaz Garcia, Diana Maldonado Tapia, Enrique F. Morales Lopez, Francisco J. Hernandez Copca, Jose L. Ortega, Irving G. Ramirez, Julio C. Nieto, Beatriz R. Cerezo Samperio, Abel Humberto V. Compean, Mario Alamilla-Sanchez. *Centro Medico Nacional 20 de Noviembre, Mexico City, Mexico*.

Background: Bone mineral disorder - conical renal disease is a syndrome that includes one or more alterations of: calcium, phosphorus, parathormone, vitamin D; remodeling, bone mineralization or volume, vascular or soft tissue calcifications. Generating high cardiovascular risk and fractures. Objective: To determine the prevalence of bone mineral disorder - chronic kidney disease in hemodialysis patients in a reference center.

Methods: Descriptive and association study, observational, cross-sectional, prolective, which included patients with chronic kidney disease on hemodialysis older than 18 years who agreed to participate. Sample size for prevalence of 60%, with alpha probability of 0.05 and precision factor of 0.1 was 93 patients, however, only 27 patients agreed to participate. Serum values of PTH, calcium, phosphorus, calcidiol, time on hemodialysis, age, sex, and presence of diabetes were obtained. Data processing analyzed with SPSS 22, ORP calculation with 95% CI, Chi square and logistic regression $p<0.05$.

Results: 90% prevalence of bone mineral disorder, prevalence of high turnover bone disease 81.2%. The association of vascular calcifications with age OR 1.324 IC (1.003 to 1.7) p 0.04, with PTH OR 1.001 IC (0.9 to 1.04) p 0.3 and with time on hemodialysis 3.4 (0.2-46.4) p 0.04.

Conclusions: In our population, the prevalence of bone mineral disorder is consistent with that reported in the literature. Our patients present a high frequency of vascular calcifications and a predominance of high turnover bone disease. The underdiagnosis of this disorder generates complications that have an impact on cardiovascular morbidity and mortality.

PUB083

Investigating Mesenchymal Stem Cell Sources for VEGFA mRNA Transfection and In Vivo Protein Exposure

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Background: Cell based therapies offer promising avenues for the treatment of kidney diseases. Among these, mesenchymal stem cells (MSCs) have shown potential due to their immunomodulatory properties. Recent advances in RNA-based technologies have opened up new avenues to enhance MSC functionality. Here we investigate the function of MSCs transfected with RNA encoding vascular endothelial growth factor-a (VEGFA), an important angiogenic protein in the kidney and other organs that is diminished in ischemic diseases.

Methods: Pig (adipose) and human (bone marrow, umbilical, adipose, or induced pluripotent) MSC sources were investigated for reproducible production of VEGFA protein following RNA transfection. VEGFA protein production from MSCs was then investigated *in vivo* in a mouse pharmacokinetic model and a pig model of renal artery stenosis.

Results: Reproducible and similar post-transfection expression patterns of VEGFA (6-8x10^6 pg/mL) were achieved in human bone marrow MSCs and porcine adipose tissue derived MSCs *in vitro*, with the prior demonstrating greater expansion potential. Healthy mice injected with VEGFA-MSCs showed transiently increased VEGFA protein levels in kidney. In renal artery stenosis pigs, injection of porcine VEGFA-MSCs produced a peak of VEGFA (3.95 pg/mg renal tissue; 6hrs post injection) which resolved by 10 hours. RNA transfection did not change the immunomodulatory capacity of MSCs nor their capacity for trilineage differentiation.

Conclusions: These data confirm a transient burst in VEGFA protein is achievable through RNA transfection of MSCs, delivered in a relevant disease setting. The pharmacokinetic parameterisation of MSC-based VEGFA protein production *in vivo* will inform future cell therapy development.

Funding: Commercial Support - AstraZeneca

PUB084

Hypoxic Preconditioning Alters Micro-RNAs Expression in Mesenchymal Stem Cells from Patients with Hypertensive Kidney Disease

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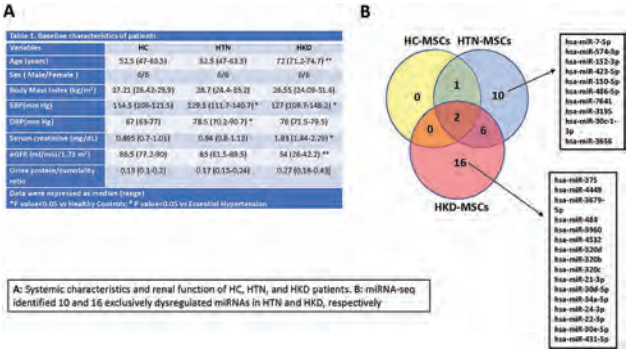
Background: Hypertensive kidney disease (HKD) is a common cause of end-stage kidney disease. Autologous mesenchymal stem cells (MSCs) emerge as a therapeutic option for many kidney diseases, but HKD might alter their regenerative ability. Hypoxic preconditioning (HPC) enhances MSC functionality by modulating global gene expression. We hypothesize that HPC can promote MSCs function by altering their miRNAs expression.

Methods: MSCs were collected from abdominal subcutaneous fat biopsies of healthy controls (HC), hypertensive (HTN), and HKD patients (n=12 each, **Fig. 1A**). miRNA sequencing (seq) was performed on MSC cultured in normoxic (20% O_2) or hypoxic (1% O_2) conditions for 24-72h. Differentially expressed (DE) miRNAs (log fold>1.5 or <1.5; p<0.05) were identified followed by target predictions and gene ontology analysis.

Results: miRNA-seq identified 10 and 16 miRNAs altered by HPC exclusively in HTN and HKD, respectively (**Fig. 1B**). In HPC MSCs, the upregulated HTN miRNAs target genes were involved in telomere maintenance, DNA damage, and FGFR signaling, whereas downregulated ones were implicated in blood vessel development and growth regulation. Contrarily, upregulated HKD miRNAs target genes participate in TNF-α signaling and response to hormones, whereas downregulated ones were involved in VEGFA-VEGFR2 pathways and regulation of embryonic development.

Conclusions: HPC differentially influences the expression of miRNAs implicated in vascular development and cell senescence in human HKD- and HTN-MSCs and may thereby enhance angiogenesis and MSC regenerative capacity and blunt inflammation. Further studies are needed to explore the unique role of HPC in miRNAs expression and MSCs functionality in HKD.



A: Systemic characteristics and renal function of HC, HTN, and HKD patients. B: miRNA-seq identified 10 and 16 exclusively dysregulated miRNAs in HTN and HKD, respectively

PUB085

Osteopontin-Associated Reparative Effects of Selected Renal Cells

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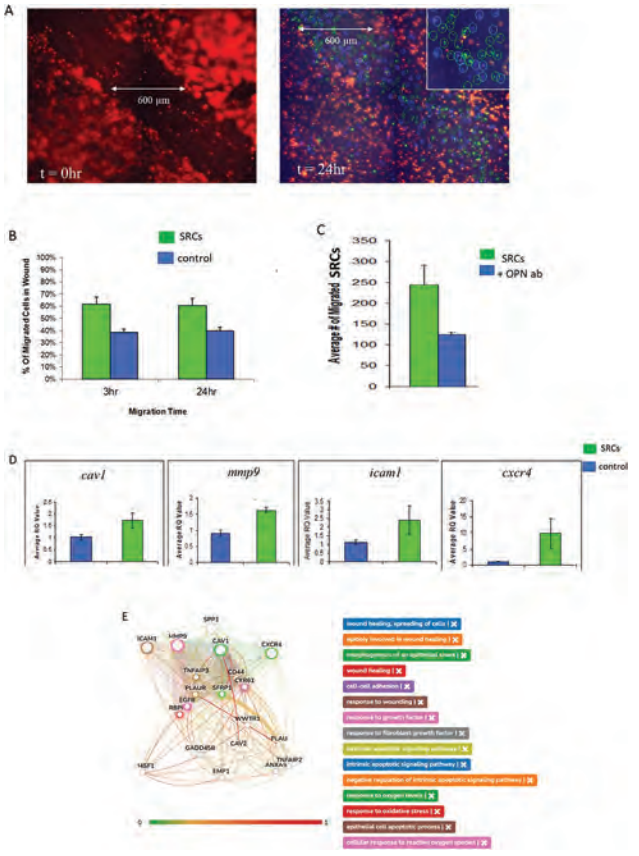
Background: Osteopontin (OPN) conveys renal reparative effects. Selected renal cells (SRCs), a glomerular- and tubular epithelial cell-enriched platform, exhibit reparative and restorative effects in models of CKD. In the present study, we tested the hypothesis that OPN mediates SRC reparative activity.

Methods: Human SRC (National Disease Research Interchange) and renal cortical biopsy (control) monolayers were submitted to a scratch assay in the absence/presence of an OPN neutralizing antibody (ab). Reparative activity was evaluated by imaging (blinded) the number of cells migrating to bridge the wound. Expression of *cav1*, *mmp9*, *icam1* and *cxcr4* was evaluated using qPCR. Genes were seeded into HumanBase for visualization of transcriptome function.

Results: Compared to control, SRCs exhibited increased migration into the wound (p<0.05), an effect reduced by the OPN ab (p<0.05). Expression of migratory markers *cav1*, *mmp9*, *icam1* and *cxcr4* was upregulated in SRCs (p<0.05). Gene ontology confirms that the *opn*/ssp1-*cav1*-*mmp9*-*icam1*-*cxcr4* axis regulates migration, adhesion, and wound healing in the kidney.

Conclusions: These data suggest that SRC associated preservation of renal microarchitecture and maintenance of the renal filtration function, including creatinine clearance, electrolyte balance, fluid homeostasis, urine concentration and Cystatin C metabolism, may be mediated, in part, by an OPN-associated wound healing cascade.

Funding: Commercial Support - ProKidney LLC.



(A) Renal wound healing assay. (B, C) SRCs exhibit increased migration into the wound, an effect reduced with OPN ab pretreatment. (D) SRCs exhibit upregulation of migratory genes *cav1, mmp9, icam1* and *cxcr4*. (E) The *opn*/ssp1-*cav1-mmp9-icam1-cxcr4* axis regulates renal migration, cell-cell adhesion, and wound healing.

PUB086

Selected Renal Cells Express Cell Adhesion Markers and Form Renal Tubules

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ProKidney, Winston-Salem, NC.

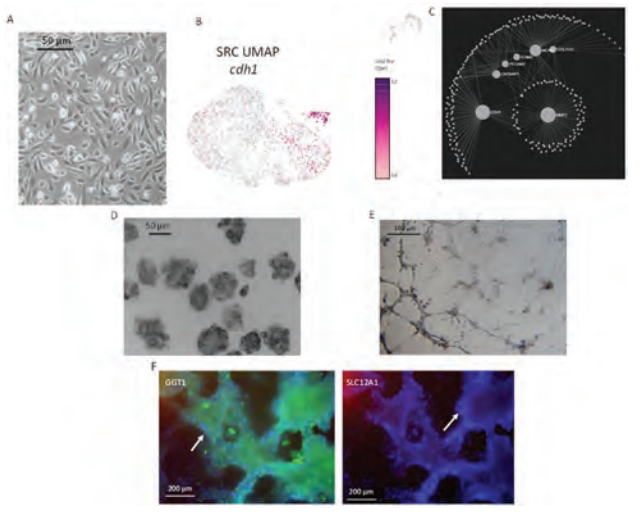
Background: Selected renal cells (SRCs) express podocyte, ureteric bud and cap mesenchyme markers and demonstrate renal reparative and restorative activity potentially by recapitulating events associated with embryologic kidney development. We tested the hypothesis that SRCs express cell-cell adhesion markers and form renal tubules.

Methods: Human SRCs (National Disease Research Interchange) were submitted to mRNA-seq for identification of differentially expressed genes (DEGs vs. source biopsy; P_{adj} <0.05), to scRNA-seq to map gene expression, and to flow cytometry for phenotypic marker identification. SRC cell-cell adhesion markers were identified using KEGG pathway analysis and their network visualized using miRNet.ca. SRCs were placed in culture±hydrogel for evaluation of renal tubule formation with antibody staining for epithelial markers GGT1 and SCL12A1.

Results: SRCs (A) exhibited upregulation (Log2FC) of cell-cell adhesion genes *icam5* (2.5), *mcam* (1.5), *cntnap1* (1.65), *col11a1* (3.1) and *mmp2* (2.1) and expression of PECAM1 and CDH1 (B). Gene ontology confirmed an interactome comprising these cell-cell adhesion markers (C). Placed in culture, SRCs assembled into organoids (D) which in the presence of hydrogel united to form renal tubules (E) expressing GGT1 and SCL12A1 (F).

Conclusions: These data suggest that the potential therapeutic activity of SRCs may be mediated in part via formation of renal tubules and therefore, maintenance of electrolyte balance, fluid homeostasis, reabsorption of essential nutrients, urine concentration and Cystatin C metabolism.

Funding: Commercial Support - ProKidney



SRCs (A) express cell-cell adhesion markers including CDH1 (B) that form an interactome (C). Placed in culture, SRCs form organoids (D) which, in the presence of hydrogel integrate into renal tubules (E) expressing GGT1 and SCL12A1 (F, arrows).

PUB087

Chronic Exposure of Melamine Accelerates the Progression of Kidney Injury in High-Fat Diet-Induced Obese C57BL/6 Mice and db/db Diabetic Mice

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Background: Diabetes mellitus (DM) is the major cause of chronic kidney disease (CKD). Our previous studies have found that environmental melamine exposure is significantly associated with kidney function deterioration in patients with early-stage CKD. However, the underlining molecular mechanism is unclear yet. Whether melamine could promote the progression of CKD in DM remains to be clarified. In this study, we aimed to investigate whether chronic exposure of melamine could promote progression of kidney injury in DM.

Methods: We conducted two type 2 diabetic animal models, high-fat diet (HFD) induced model in C57BL/6 mice and db/db diabetic mice, with exposure of melamine at the mimic human tolerable daily intake (TDI) levels (2.5, 6.3 and 50 mg/kg body weight/day). Urine albumin-creatinine ratio (uACR) was used to monitor kidney function. We applied Periodic Acid-Schiff (PAS) staining, Masson trichrome staining, TUNEL assay and Western blotting to observe kidney injury, fibrosis, apoptosis and related protein expression.

Results: We observed an increased trend of urinary albumin levels in chow-diet (CD) and HFD with melamine exposure, indicating an early sign of kidney injury in the mice with hyperglycemia after 22-week exposure to melamine at the mimic human TDI levels. Even though serum BUN and creatinine levels remained normal, changes in kidney morphology were seen. According to the result of PAS staining, many renal tubular cells were damaged and formed vacuolation morphology. Tubulointerstitial fibrosis and apoptotic cells were more frequently to be seen the HFD mice coexposed with melamine. The protein biomarkers of inflammation (CD68, NF-kB phosphorylation), apoptosis (cleaved caspase 3) and fibrosis (active form of TGFb) were also increased. In db/db diabetic mice, we observed that serum creatinine and urinary total protein were significantly increased in the melamine exposure group. Tubulointerstitial fibrosis and urinary NAG (N-acetyl-β-D-glucosaminidase) level were significantly increased in the db/db mice exposed to melamine for 10 weeks.

Conclusions: Taken together, these results suggest that chronic melamine exposure may increase risk to accelerate the development of diabetic nephropathy.

Funding: Government Support - Non-U.S.

PUB088

Transmembrane Protein 72, Expressed in the Distal Convoluted Tubule, May Play a Potential Role in Diabetic Kidney Disease

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Background: Transmembrane protein 72 (TMEM72) is highly expressed in tubules of the kidney. This study is designed to explore the role and the potential mechanism of TMEM72 in the development of diabetic tubulopathy.

Methods: Serum TMEM72 concentration was tested in health control, patients with diabetes mellitus (DM) and diabetic kidney disease (DKD). The variation trend of TMEM72 was determined by immunohistochemistry on kidney tissues from patients in different stage of DKD. Immunofluorescence staining was performed with TMEM72, SGLT2, NKCC2 and AQP2 to identify the expression site of TMEM72 in mice renal

tubules. To investigate the potential cellular pathway that TMEM72 was involved, an immunofluorescence test was performed with TMEM72, LAMP1, Mito-tracker and Calnexin in cultured distal convoluted tubule (DCT) epithelial cells. Western blot was used to detect the activity of TMEM72 in HK2 cells following HG treatment.

Results: The concentration of serum TMEM72 was lower down in DM and DKD group when compared to the health control (P<0.001). The expression of TMEM72 also decreased gradually in human kidney tissue of different stage of DKD following the progression of disease. Co-localization of TMEM72 and NKCC2 in immunofluorescence staining indicated that TMEM72 was mainly expressed in DCT. Stimulated by different glucose concentrations, cell culture study (mouse DCT cell; human kidney-2 cell, HK-2 cell) in vitro showed that TMEM72 was down-regulated as the glucose concentration gradient rised. In immunofluorescence, the co-localization of TMEM72 and LAMP1 suggested that TMEM72 might be involved in lysosomal metabolic pathways and participate in the progression of DKD.

Conclusions: Our current study has revealed that TMEM72 may act as a novel participator in DKD by being involved in the renal tubular injury.

Funding: Government Support - Non-U.S.

PUB089

Anti-Fibrotic Gene Protects Kidney and Muscle Through Myokine-Mediated Organ Cross-Talk in Diabetic Kidney Disease Mice

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Background: The muscle-kidney crosstalk is emerging as a treatment strategy for kidney disease. Irisin is a beneficial myokine that improves kidney function and inhibits renal fibrosis via TGF-b1. This study investigated whether the anti-fibrosis gene (anti-F) as a negative regulator of TGF-b1, could demonstrate renoprotective effects through myokine modulation in db/db mice.

Methods: The db/db mice (5 weeks, male) were employed for a type 2 diabetic kidney damage. Mice were injected intraperitoneally with 40 μg of anti-F plasmid with TGF-ß promoter once a week for 16 weeks from 9 weeks, euthanized, and serum, muscles, and kidneys from all mice were harvested for analysis.

Results: The db/db mice showed worse kidney function parameters than db/m+ mice (Fig 1). In db/db mice, mRNA expression of irisin was downregulated in the muscle and kidney tissue. However, anti-F administration counteracted downregulation of irisin mRNA. Anti-F is involved in the reduction of muscle atrophy reflected by mRNA level for MuRF1 and in rising of muscle regeneration reflected by mRNA level for Myf1 in diabetic circumstances (Fig 2).

Conclusions: This study provides that anti-F could be a candidate that links "muscle-kidney crosstalk" related to the recovery of kidney damage from diabetes, and anti-F gene therapy might be one of options for treating patients with diabetic kidney disease.

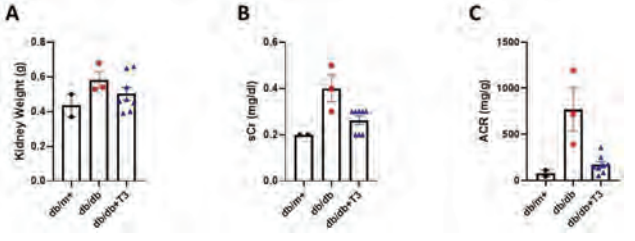

Figure1. Anti-F alleviated kidney dysfunction in db/db mice**A** kidney weight; **B** serum creatinine; **C** urinary albumin to creatinine ratio

(T3, anti-F plasmid)

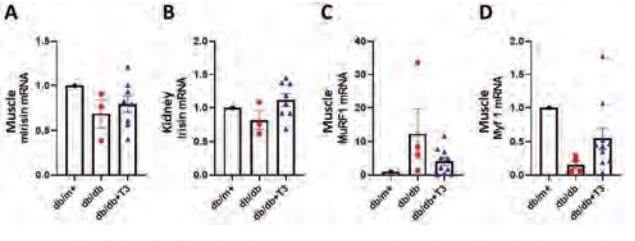

Figure2. Anti-F is involved in changing mRNA expression of myokines in the muscle and kidney in diabetic circumstances**A** Irisin mRNA expression in muscle; **B** Irisin mRNA expression in kidney; **C** muscle RING-finger protein-1 mRNA expression in muscle; **D** Metal Regulatory Transcription Factor 1 mRNA expression in muscle.

(T3, anti-F plasmid)

PUB090

Finerenone in Chinese Patients with Type 2 Diabetes and CKD: A FIDELITY Analysis

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Background: Finerenone significantly reduced the risk of cardiorenal outcomes in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) in the FIDELITY prespecified pooled analysis of the phase III FIDELIO-DKD and FIGARO-DKD trials. This FIDELITY subanalysis explored the efficacy and safety of finerenone in Chinese patients.

Methods: Of 13,026 patients, 697 from sites in China were self-identified as Chinese and were randomized 1:1 to finerenone or placebo. Eligible patients had T2D and CKD (urine albumin-to-creatinine ratio [UACR] ≥30–<300 mg/g and estimated glomerular filtration rate [eGFR] 25–≤90 mL/min/1.73 m^2, or UACR ≥300–≤5000 mg/g and eGFR ≥25 mL/min/1.73 m^2), and were on optimized renin-angiotensin system inhibition. Key outcomes were a kidney composite (kidney failure, sustained ≥57% eGFR decrease from baseline over ≥4 weeks, or renal death) and a cardiovascular (CV) composite (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure). A secondary kidney composite was kidney failure, sustained ≥40% eGFR decrease from baseline over ≥4 weeks, or renal death. Safety outcomes were assessed by treatment-emergent adverse events and laboratory evaluations (e.g. serum potassium).

Results: Finerenone reduced the risk of the primary and secondary kidney composite in the Chinese subgroup (hazard ratio [HR] 0.57; 95% confidence interval [CI] 0.38–0.86; p=0.0066 and HR=0.54; 95% CI 0.40–0.74; p<0.0001, respectively) vs placebo, with consistent effects on components such as kidney failure (HR=0.53; 95% CI 0.33–0.86; p=0.0094). The HR of the CV composite was 0.82 (95% CI 0.52–1.29) for finerenone vs placebo, consistent with that in the overall FIDELITY population. Overall safety outcomes were similar between treatment arms. Hyperkalemia leading to treatment discontinuation was low for finerenone (2.6%) and placebo (0.9%); the difference in mean serum potassium increase from baseline between finerenone and placebo was ~0.13 mmol/L from month 1 to 20.

Conclusions: Finerenone had cardiorenal benefits and a favorable safety profile in the FIDELITY Chinese subgroup.

Funding: Commercial Support - Bayer AG

PUB091

Association Between Neutrophil-Lymphocyte Ratio (NLR) and Clinical Outcomes Among Filipino Patients with ESRD Secondary to Diabetic Nephropathy on Maintenance Hemodialysis

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Background: Evidence on the usefulness of neutrophil-to-lymphocyte ratio (NLR) as a prognostic biomarker in diabetes patients with chronic kidney disease is still scarce to date. This study aimed to determine the association between NLR and morbidity among Filipino patients with end-stage renal disease (ESRD) secondary to diabetic nephropathy on maintenance hemodialysis.

Methods: This was an observational descriptive, prospective cohort study that evaluated outpatient Filipino citizens aged >18 years diagnosed with ESRD secondary to type 2 diabetes mellitus (T2DM). All patients had good compliance to their hemodialysis regimen (i.e., at least twice weekly dialysis within the past 3 months). The patients were divided into two groups according to the baseline NLR value at a cut-off of 3.5 as the high NLR group (NLR ≥3.5) and the low NLR group (<3.5). The cutoff was based on data that a high NLR of ≥3.5 was correlated with increased inflammatory states leading to higher morbidity. Patients were followed up after 6 months, and data on the primary outcome measure of disease occurrence were collected.

Results: Of the 63 patients evaluated, majority (n=39, 61.9%) had a baseline NLR value of <3.5. The high NLR group included 24 (38.1%) patients; among them, 9 developed disease. In the low NLR group (n=39), only 2 patients developed disease. NLR was significantly correlated with clinical disease outcomes (p=<0.05).

Conclusions: A baseline NLR of ≥3.5 was associated with disease occurrence. In conclusion, patients with a high baseline NLR have increased inflammatory state and a higher risk of developing disease conditions than patients with an NLR <3.5. Thus, the baseline NLR value can be used to predict prognosis in T2DM patients with ESRD.

PUB092

Dapagliflozin in CKD Patients with Diabetes from a Real-World Study

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Background: Diabetes is one of main causes of chronic kidney disease (CKD), and it increases the risk of adverse outcomes including cardiovascular events, end stage renal disease and mortality. Dapagliflozin (DAPA), as a selective sodium glucose cotransporter 2 inhibitor, has been reported to be beneficial for CKD patients with diabetes in previous clinical trials, however, real-word evidence is limited, especially among Chinese population.

Methods: A total of 803 CKD patients with type 2 diabetes were included in China from January 2011 to December 2021. Eligible participants were adults with estimated glomerular filtration rate (eGFR) ≥20 ml/min/1.73m^2 and 24-hour urinary protein (24h-UP) of 300 to 3500 mg/24h. Both groups received a stable dose of RASi without immunosuppression therapy or >10 mg prednisolone daily. DAPA group received 10 mg DAPA once daily. Propensity score matching was applied to balance the baseline characteristics, including age, sex, eGFR, 24-UP, and hypertension history. The primary outcome was the change in 24h-UP from baseline at 6 months. Nonparametric tests were used to compare differences between groups.

Results: Of the 803 patients, 276 were in the DAPA group (mean age 55.6 yrs, male 66.3%, median eGFR 69.2ml/min/1.73m^2, median 24h-UP 1214.0mg/24h) and 527 in the control group (mean age 57.4 yrs, male 64.9%, median eGFR 72.1 ml/min/1.73m^2, median 24h-UP 858.0 mg/24h). After 6 months, DAPA significantly reduced 24-UP compared to the control group (-23.0% vs -4.51%, P<0.05). The reduction in uric acid was significantly greater in the DAPA group than in the control group at 6 months (-6.78% vs 0.51%, P<0.001). eGFR decreased significantly in the DAPA group compared to the control group at 3 months (-2.50% vs -0.02%, P<0.05), but no significant between-group differences were observed at 6 months (-2.14% vs -1.89%, P=0.90). Changes in glucose and lipid metabolism during the study did not differ significantly between groups.

Conclusions: In CKD patients with type 2 diabetes, dapagliflozin significantly improves proteinuria with short-term eGFR changes as previously reported. The effectiveness of DAPA in reducing uric acid in the real-world experience was observed, while the underlying mechanisms remain to be investigated.

PUB093

Congestive Hepatopathy Caused by Cardiorenal Syndrome Causing Severe Elevations

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Introduction: 80 year old female presenting with a TIA and heart failure exacerbation with AKI on CKD requiring to be started on ionotrope assisted diuresis to prevent further renal failure. She does not respond to the therapy and also develops sepsis from hospital acquired pneumonia and UTI requiring continuous renal replacement therapy, pressors and intubation for further optimization. The severity of her cardio renal syndrome and cardiogenic shock leads her to develop concomittant congestive hepatopathy leading her to develop severe elevations in her liver enzymes to the level to shock liver or ischemic hepatitis which is a unusual finding.

Case Description: 80 year old female presenting with slurred speech and exertional dyspnea. Admitted for TIA with negative workup of stroke. Patient found to be in a heart failure exacerbation. She has a known medical history of heart failure with reduced ejection fraction with an EF of 20-25% secondary to Takotsubo cardiomyopathy and a clean cardiac cath. She has a CRT-D placed. Patient started on dobutamine assisted diuresis due to severe AKI on CKD III with poor urinary output. Transferred to ICU due to acute metabolic encephalopathy secondary to septic and cardiogenic shock requiring intubation for severe HCAP and a E coli urinary infection. She was required to be placed on a bicarbonate infusion and got CRRT. Due to ongoing cardiogenic shock she developed severe congestive hepatopathy with liver enzymes peaking at AST / ALT of 945/ 590. These levels usually seen in shock liver and unusual in congestive hepatopathy. Pateint also noted to have lupus workup positive. Renal biopsy to rule out SLE nephritis remarkable for findings of diabetic nephropathy and ATN. Patient's renal functions subsequently improved and she was discharged with improved renal outcomes and resolution of her aminotransferases.

Discussion: The takeaway from this unique case of cardiorenal syndrome is the severity of congestive hepatopathy causing significant elevations in aminotransferases. It is very unusual to see such elevations unless it is drug induced, autoimmune or ischemia induced which tells us the severity of her heart failure and her perfusion status. The reason why this happened remains a mystery but it is important to know that it can cause significant elevations in the liver enzymes.

PUB094

Effect of Volume Removal by Hemodialysis on Elevated N-Terminal Pro Brain-Type Natriuretic Peptide (NT-ProBNP) Level

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Background: N-Terminal pro brain-type natriuretic peptide (NT-proBNP) is highly sensitive and specific for the diagnosis of congestive heart failure (CHF). Nearly all end-stage kidney disease (ESKD) patients on renal replacement therapy have an elevated NT- proBNP plasma level. Measurements of NT-proBNP before and after hemodialysis (HD) in patients who are hospitalized with volume expansion is a common practice. The purpose of this study is to determine the clinical value of repeated NT-proBNP measurements in patients with ESKD or acute kidney injury (AKI) requiring HD, and to study the effect of volume removal via HD on NT-proBNP level.

Methods: We conducted a retrospective analysis of patients admitted to two community hospitals over a 3-year period (Jan/2020-Dec/2022). Patients with AKI requiring HD or ESKD were screened if they had an admission diagnosis of volume expansion including acute CHF or pulmonary edema that was verified radiographically and by physical examination. Patients with an admission NT-proBNP level and a repeat level 2 to 12 hours after HD were included. Over the 3-year period, 36 patients with ESKD and 5 patients with AKI requiring HD fulfilled the inclusion criteria.

Results: Volume removal via HD had no impact on NT-proBNP levels in ESKD or AKI patients (ESKD P= 0.7858; AKI P=0.6903). Our patients had significantly elevated NT-proBNP due to renal dysfunction and volume expansion. The table below summarizes our main findings.

Conclusions: While identifying acute or chronic HD patients with volume expansion and significant elevation in NT-proBNP to intensify their cardiovascular management may be beneficial, measuring NT-proBNP level after a single HD session to document a positive effect of volume removal is of no clinical value. Our data suggest that NT-proBNP is a useful cardiac biomarker for volume expansion and its elevated level predict high cardiovascular mortality and recurrent hospitalizations in acute and chronic HD patients.

	ESKD (n=36)	AKI (n=5)
Duration of HD in hours (Mean, range)	3.3 (2.5-4)	2.8 (2.5-3)
Volume removal in liters (Mean, range)	2.5 (1-5)	1.3 (1-2)
Number of hospitalizations post initial presentation during the study period (Median, range)	3.0 (0-14)	1 (0-3)
Mortality over the study period (%)	30	60
Pre-HD NT-Pro BNP (pg/ml) (Mean ± SD, range) NT-proBNP calibration range 5 to 35,000 pg/mL	29,151±10,039 (4,113-35,000)	25,823±12,271 (4,270-35,000)
Post-HD NT-Pro BNP (pg/ml) (Mean ± SD, range)	28,980±9,815 (4,440-35,000)	26,523±11,339 (4,736-35,000)

PUB095

Cardiac Dysrhythmia Characterization by Intradialytic Holter Monitoring in Patients with Chronic ESRD

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Background: Cardiac dysrhythmias are a common complication in patients with end-stage chronic renal disease undergoing hemodialysis. The intradialytic period, during which patients undergo hemodialysis, is particularly vulnerable to developing cardiac dysrhythmias. Intradialytic Holter monitoring is a non-invasive technique that continuously monitors the heart's electrical activity during hemodialysis. The study aims to characterize the different types and frequencies of cardiac dysrhythmias during hemodialysis using intradialytic Holter monitoring. This information could help improve the management and treatment of cardiac dysrhythmias in patients with end-stage chronic renal disease.

Methods: This research corresponds to a descriptive, observational, cross-sectional, primary source study from October 2020 to January 2021. The analysis was conducted using a form divided into four sections corresponding to demographic data, clinical data, laboratory tests, and Holter study reports. The same happens after the participant's agreement and signature of the informed consent.

Results: The results showed that 37.5% of the patients had dysrhythmias recorded on a 24-hour Holter, 55% were between 45 and 64 years of age, and the majority were female, represented by 66.7%. Furthermore, although there was no statistically significant relationship between the duration of dialysis sessions and the number of sessions received per week, it is evident that 88.9% of the patients whose Holter recorded dysrhythmia attended three times per week. The most frequent dysrhythmias recorded were tachyarrhythmias in 41.6%, of which 44% were ventricular.

Conclusions: Although no statistically significant differences were observed, age, sex, and the number of hemodialysis sessions per week are regarded as the group with a predisposition for the presence of dysrhythmias in patients on hemodialysis therapy.

PUB096

Methemoglobinemia in Hemodialysis Patients due to Acute Chlorine Intoxication

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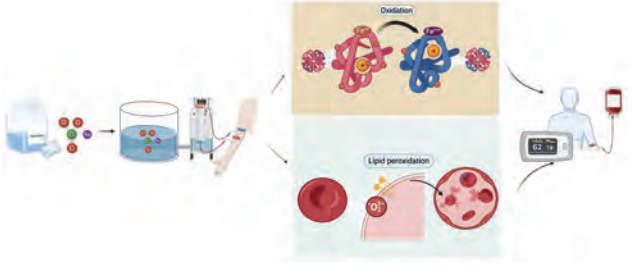
Background: Hemodialysis uses municipal water that must be strictly purified and sterilized to be used for that procedure. Large amounts of decontaminants are often used, such as chlorine, and if these compounds are not subsequently removed they can be transferred to the blood of patients causing complications including methemoglobinemia.

Methods: In this case series study dialysis patients in one unit were evaluated. We reviewed clinical characteristics and laboratory findings obtained on the day when the water supply was disinfected with chlorine, with the aim to quantify methemoglobin concentrations. Our objective was to characterize the clinical presentation and management of patients who presented with methemoglobinemia on a specific index day. We also reviewed reported cases in the literature regarding this underreported complication.

Results: Eight patients who presented with chlorine intoxication were evaluated. The methemoglobin concentrations were between 1.3% and 7.9% (reference value 0-1%). We believe this to be caused by water containing 0.78 mg/L of total chlorine. Seven patients presented with cyanosis, 4 with dizziness, 6 with dark brown blood, 4 with dyspnea and 4 with headache and hemolytic anemia. Subjects were treated with supplemental oxygen, methylene blue, intravenous vitamin C, blood transfusions, and increased doses of erythropoietin. No patient died, and all continued with their usual hemodialysis sessions.

Conclusions: Acute chlorine intoxication transferred by the water used during hemodialysis sessions can present with methemoglobinemia accompanied by cyanosis, oxygen desaturation, and hemolytic anemia. Chlorine levels should be carefully monitored in the water used for hemodialysis treatment.



PUB097

Hyperkalemia Prevalence and Recurrence in Chinese Patients on Hemodialysis: A Prospective Multicenter Cohort Study (PRECEDE-K)

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Background: Hyperkalemia (HK) is a risk factor for cardiac arrhythmia and death in patients with end-stage renal disease (ESRD) on hemodialysis (HD). PRECEDE-K (NCT04799067) was a prospective cohort study that investigated HK burden in Chinese patients on HD.

Methods: Patients aged ≥18 years on HD (≥2 sessions/week) were consecutively enrolled from 15 centers in China and followed up for 24 weeks. Primary and secondary endpoints were the occurrence and recurrence of HK (serum potassium [sK] >5.0 mmol/L), respectively. Risk factors associated with HK occurrence and recurrence were exploratory endpoints.

Results: A total of 600 patients were enrolled (median age: 55 years; 67% male). Most had adequate dialysis at baseline (65% had urea reduction ratio >65%; 75% had Kt/V >1.2). Yet, 453 (76%) patients experienced HK (297 [50%] had sK >5.5 mmol/L and 171 [29%] had sK >6.0 mmol/L; Figure). At 6 months, 356 (79%) of these 453 patients had HK recurrence; 203 (45%) recurred in 1 month and 300 (66%) in 3 months (Figure). HK recurred ≥3 times in 306 (68%) patients and ≥6 times in 161 (36%) patients (Figure). Risk factors for HK occurrence were history of HK, female sex, lower dialysis frequency, and longer dialysis vintage. Risk factors for HK recurrence were history of HK, history of diabetes, and lower dialysis frequency.

Conclusions: HK is common in Chinese patients with ESRD despite standard adequate HD. The high frequency of and short time to recurrence allude to the chronic nature of HK. Effective potassium control on non-dialysis days is recommended in patients on HD, especially those with risk factors, for long-term management of chronic HK.

Funding: Commercial Support - AstraZeneca, Clinical Revenue Support, Government Support - Non-U.S.

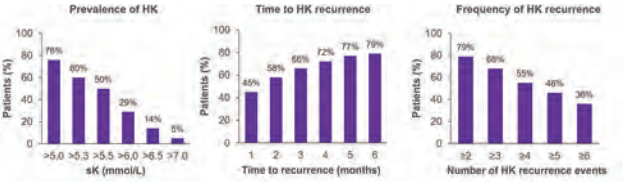

Figure: The prevalence and recurrence of hyperkalemia in Chinese patients with end-stage renal disease on hemodialysis

PUB098

A Cross-Sectional Study on Outcome of Pro-Brain Natriuretic Peptide (PRO BNP) Levels in Patients on Hemodialysis and Peritoneal Dialysis in a Tertiary Care Hospital

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Background: Mean amino-terminal pro-brain natriuretic peptide (NT-proBNP) level has not been studied well in Saudi hemodialysis population and the effect of high flux hemodialysis membrane in comparison to Peritoneal dialysis patients. We aimed to study the significance of NT-pro BNP level in both hemodialysis and peritoneal dialysis subjects.

Methods: This cross-sectional study looked at NT proBNP levels in 50 hemodialysis (HD) patients and 50 patients on Peritoneal dialysis (PD) group in November 2022. Patients in both groups were categorized according to age above and below 70 years. Patients on HD or PD with history of ischemic heart disease or valvular heart disease were excluded from the study.

Results: Among PD patients, 12 patients were above 70 years with mean age of 77.1, while PD patients younger than 70 years comprised of mean age of 41.2 years. We found NT-proBNP 26000 pg/ml in Male patients above 70 years and >12500pg/ml in Females respectively. Similarly those with age less than 70 years had an average NT-proBNP of >17000pg/ml and 25000 pg/ml in male and female subjects respectively. In HD population 26 patients were above 70 years with mean age 73.5 and remaining 24 patients were younger than 70 years of age, with mean age of 50.8. We observed the NT-proBNP levels >5000pg/ml and > 640 pg/ml in Male and female subjects doing PD and HD respectively in older (Above 70) age group. While, younger age group (less than 70 years) had NT-proBNP levels >11000 pg/ml and 8500pg/ml on PD and HD respectively. We found that on average NT-proBNP levels were significantly higher in peritoneal dialysis patients in comparison to hemodialysis patients. No significant difference was found across either gender in both groups.

Conclusions: We hereby conclude that NT-proBNP levels in peritoneal dialysis patients in older age group without any ischemic heart disease, volume overload is high and low in hemodialysis patients due to membrane adsorption effect.

PUB099

Adaptive Dialysis: A New Way of Care in Post-Open-Heart Patients

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Background: Automated adaptive dialysis (AAD) is a system shown to improve tolerance, adherence, clinical versatility and is the backbone of our in-house dialysis machine. The purpose of this quality improvement project is to showcase the performance of the AAD system in post open heart patients.

Methods: A retrospective-observational, chart review study. Database was queried from January 01, 2016, thru December 31, 2022, to include post open heart patients undergoing dialysis via the AAD system in the post-operative stage. Patients undergoing Coronary Artery Bypass Surgery (CABG) and Aortic Valve Replacement (AVR), Mitral Valve Replacement (MVR) and Tricuspid Valve Replacement (TVR) were included.

Results: A total of 30 patients between 42 and 79 years of age, were treated with the AAD system: 73% underwent strict intermittent hemodialysis (IHD) and 27% received a combination therapy (CmT) of either continuous renal replacement therapy, sustained low-efficiency dialysis or slow continuous ultrafiltration. Average body max index was 28.9 and hundred percentage of patients received mechanical ventilation and vasopressor support during the post operative stage. Only patients who received IHD were included in the main analysis since patients on combination therapy had insufficient data recorded and had significant critical illness. Patient characteristics per type of surgery in the main

analysis group consisted of 18 patients post CABG, 1 patient post AVR, 2 patients post MVR and 1 patient with combined CABG/AVR. Ninety percentage of the cohort had history of ESRD and intradialytic complications like clotting only occurred in the CmT group (n:3). Average time of vasopressor support in the main analysis group was less than 24hrs. Key performance indicators are shown on Table 1, while dialysate and blood flow rates ranged between 200-300ml/min and 200-400ml/min respectively. System clotting was prevented by frequent saline flushes instead of heparin flushes except on those patients with complications.

Conclusions: Treatment adequacy with the AAD system in this subset of patients was a safe intervention with adequate performance indicators.

Key Performance Indicators

Ultrafiltration per Treatment(L/tx)	Avg: 2.08 / SD 0.747
Ultrafiltration per Hours on Therapy (L/hr)	Avg: 0.564 / SD 0.184
Hours on Therapy per Treatment (hr/tx)	Avg: 3.65 / SD 0.417
UF/Hours on Therapy per Treatment (L/Ttx)	Avg: 1.09 / SD 0.677
ICU LOS (days)	Avg: 2.97 / SD 1.19

PUB100

Oral Manifestations, Periodontal Disease, and Need for Dental Treatment in Our Hemodialysis Unit

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Background: CKD is associated with specific oral signs and symptoms. Periodontal disease (PDD) is very prevalent in HD individuals, it in turn is related to malnutrition, inflammation, and cardiovascular risk. We evaluated the prevalence of oral manifestations, PDD and need for dental interventions in our HD patients.

Methods: Cross-sectional study of individuals in a HD unit. We analyzed dental features, described the prevalence of oral manifestations, PPD and need for odontological interventions. A dentist performed the dental history and examination. According to his assessment suggested the need for and kind of treatment. All included patients signed an informed consent.

Results: We included 34 individuals, age 62±15, ♂ 77%, HD vintage 48m (6-281). 88% showed absence of dental pieces, 62% had prosthesis. Most frequent oral manifestations were xerostomia 70%, mucosal pallor, whitish tongue, dysgeusia gingival recession (~40%), least frequent bruxism, dental erosion, halitosis, hypersensitivity 6-15% **Table1**. We found 64% of EPD (manifested as calculi and dental pockets) **Table2** and 24% dental caries. The frequency of brushing per day was sometimes 12%, 1x 41%, 2x 32%, 3x 15% **Table3**. 24% were active smokers **Table4**. 65% of patients required some type of treatment, the most frequent being periodontal scaling and dental fillings, >40% required repair or a new prosthesis **Table5**. The frequency of brushing was not positively nor negatively associated with any parameter of PDD or oral signs.

Conclusions: We found a high prevalence of PDD in our HD unit, in accordance with international studies. ~65% of patients require some kind of dental intervention or any action on their prostheses. For this reason, we believe that dental evaluation and treatment should be an integral part of the care of patients in HD. Performing these interventions could improve the parameters of nutrition and inflammation and the quality of life of our patients? Prospective and Interventional studies will be needed to answer this question.

Oral Signs (%) (T1)	
Xerostomia	24 (70)
Mucous Pallor	14 (41)
Saburral Tongue	14 (41)
Gingival Recession	13 (38)
Dysgeusia	12 (35)
Bruxism	5 (15)
Dental Erosion	4 (12)
Halitosis	2 (6)
Hypersensitivity	1 (3)
Aphthous Ulcers	0

Periodontal Status (%) (T2)	
Periodontal Pockets	9 (27)
Dental Calculi	13 (38)
Normal	12 (35)

Brushing Frecuency (%) (T3)	
Sometimes	4 (12)
1 time/d	14 (41)
2 times/d	11 (32)
3 times/d	5 (15)

Smoking Status (%) (T4)	
Currently smoking	8 (24)
Ex-smoking	10 (29)
Never Smoked	16 (47)

Suggested Treatment (%) (T5)	
Tartrectomy	12 (36)
Radicular Scaling	9 (27)
Fillings 1 or more	7 (21)
Extractions	4 (12)
Multiunit Prosthesis	7 (21)
Single unit Prosthesis	4 (12)
Partial Prosthesis	2 (6)

PUB101

Prevalence of Amputations in Hemodialysis Patients: Dialysis Program Without Socks

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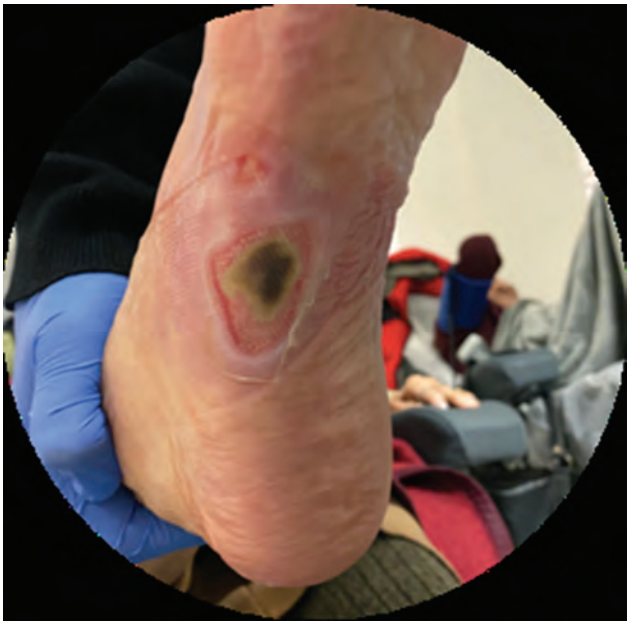
Background: Dialysis patients are at high risk of ischemia and foot ulcers (14.4%) that frequently precede severe complications, including amputations (5.9%), hospitalizations, and mortality. Critical ischemia in this location accounts for 20% of the annual causes of death in hemodialysis, produces pain that is difficult to control and greatly reduces the quality of life. The aim of this work was to analyze the prevalence and factors associated with amputations in hemodialysis patients, and to assess the evolution after amputation.

Methods: Carrying out a survey by email sent by the SEN (Spanish Society of Nephrology) and SOMANE (Madrid Society of Nephrology). Retrospective, cross-sectional, multicenter study. The survey sent to all hemodialysis units nationwide. Answered by 47 Centers. The exclusion criteria were oncological-traumatic amputations.

Results: 50% of the Units have more than 70 patients 40% diabetics In most Units only 5% of dialysis patients have ulcers 70% of the centers answer that 5% have minor amputations and 5% have more serious amputations 63% of the centers answer that 5% of the patients have more than one amputation Risk factors for amputation: > 60 years, male, diabetes, smoking, hyperphosphatemia, malnutrition, ischemic heart disease In most Units <10% of amputees have been prosthetized Annual mortality in patients with chronic ischemia is 20%. Most of the Units use some diagnostic measure to screen for ulcers and/or chronic ischemia of lower limbs.

Conclusions: Most dialysis units have patients with ulcers in the lower limbs that precede amputations, mortality and dependency. Having amputee patients in the Unit entails reorganization of work and an effort of human and material resources.



PUB102

Not Every ESRD-Hypertension (HTN) Is Missed Dialysis

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Introduction: ESRD is defined as eGFR < 15ml/min/1.73m2, along with signs and symptoms of uremia. In US > 500,000 people have ESRD and the number is increasing yearly. One of the common presentations for ESRD in an ED is elevated BP.

Case Description: A 39-year-old AA woman with history of ESRD, uncontrolled HTN with vitreous hemorrhage, MI and CVA with family history of early MI and CVA presented with severe headache and palpitations for two days and had 6 similar admissions for the last one year. Her post-HD BP were noted to be >160/110 and with four antihypertensives. Normal physical exam with vitals stable except for BP of 210/125 without discrepancy in both arms, confirmed with repeat. EKG unchanged with T Inversion in a few leads. Secondary HTN work up initiated for resistant HTN. Labs showed low Dexamethasone <30 mg/ml, Urinary Dopamine <30 mcg, and elevated Aldosterone 42.6 ng/dl, Renin 34.9 ng/ml/hr, normetanephrine 534 nmol/L. Elevated urinary Epinephrine 67 mcg/24 hour, Norepinephrine 436 mcg/24 hour, 24-hour normetanephrine 1041 mcg/24 hour and plasma. CT abdomen showed a 1.4 cm left adrenal mass. Genetic testing revealed paraganglioma with SDHAF2 mutation. 123I-MIBG scan was negative. She is scheduled to go to NIH to have a DOTATE 68 gallium Pet scan for localization and paraganglioma surgery. She continues to be on HD with multiple antihypertensives.

Discussion: Hereditary Paraganglioma Pheochromocytoma Syndrome was diagnosed in our case based on urinary metanephrines and catecholamine levels > thrice the normal value and SDHAF2 mutation. Four distinct syndromes are described with mutation of Succinate Dehydrogenase gene. Our case had PGL type 2 with SDHAF2 mutation. This mutation results in about 95% decrease in flavination of the SDHA and significantly decreases SDH activity. Only few cases of families with SDHAF2 mutation are reported with all the individuals have head and neck paragangliomas only. Pheochromocytomas and paragangliomas are rare neuroendocrine tumors with an estimated prevalence of 1:4500 and 1:1700 and with an annual incidence of 3 to 8 cases per 1 million/year in the general population. Treatment primarily is surgical removal with alpha adrenergic blockade. We present the first reported case of PGL2 with SDHAF2. More studies are needed to find its true prevalence in ESRD population and to be aware not every HTN in ESRD is missed dialysis.

PUB103

Polysulfone Dialyzer Allergy in a Patient on Aquadex Hemofiltration

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Introduction: Polysulfone dialyzer allergy is a cause of intractable hypotension, usually occurring within the first 20 minutes of hemodialysis. The treament is to change to a dialyzer made from a different materiel, such as cellulose triacetate. Hemofiltration membranes for the Aquadex system are made of polysulfone. Here we present a case of polysulfone dialyser allergy with Aquadex hemofiltration, preventing the use of this system.

Case Description: An 82 y/o man with CHF, complete heart block, DM, dementia and ESRD was admitted in the CCU for MRSA bacteremia with aortic valve endocarditis and pacemaker lead infection. He was treated with Daptomycin and his pacemaker leads were replaced. He received hemodialysis via a new tunneled catheter. On subsequent treatments his BP was noted to be soft, the next treatment he did not tolerate ultrafiltration and then his dialysis had to be stopped after 50 minutes because of hypotension. The patient was started on Aquadex hemofiltration which was complicated by hypotension with SBP in 80 range with Levophed and Dopamine. The rapid response team was called for itching, facial swelling and dyspnea which was treated with epinephrine, Benadryl and Solumedrol. Aquadex hemofiltration was stopped and BP recovered with albumin. The next day an attempt at hemodialysis was aborted because of hypotension with SBP drop from 120 to 70 range within 20 minutes. A clinical diagnosis of polysulfone dialyzer allergy was made and the following day hemodialysis was performed using a cellulose triacetate dialysis. The proedure and UF were tolerated wthout incident. Subsequent treatments were uneventful and the patient eventually recovered and was discharged.

Discussion: This case shows that polysulfone dialyzer allergy can occur with the Aquadex system, making ultrafiltration impossible despite treatment with steroids, H2-antagonist, epinephrine and vasopressor support. Polysulfone dialyzer allergy is difficult to detect in the critically ill and in patients with heart failure who have multiple possible causes of severe hypotension. This case shows that despite a simpler design, dialysis expertise is valuable for patients using hemofiltration systems.

PUB104

Magnesium in Dialysate: Is Less More?

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Background: Lower Mg++ levels are associated with increased risk of cardiovascular events in CKD. Higher dialysate Mg of 1 mmol has shown 22% increase in T50 which indicates a higher potency of the serum to inhibit calcification. Recently published study with Magnesium supplementation in CKD did not show slower progression of vascular calcification despite increase in plasma magnesium. It would be helpful to know if patients are at higher risk of low Magnesium level with standard dialysate magnesium of 0.5 mmol/L (1 mEq/L).

Methods: To know the impact of currently used dialysate magnesium on serum Magnesium level in haemodialysis patients predialysis Mg was measured in February 2020, October 2021, November 2022 and May 2023 on all prevalent and incident patients. Dialysate Magnesium was 0.5 mmols/L (1 mEq/L) in all patients. We also measured serum potassium, PTH and phosphate and reviewed medicine intake as Proton pump inhibitors, Calcineurin inhibitors and phosphate binders.

Results: In the years 2020, 2021, 2022 and 2023, Mg level was measured in 124, 93, 99 and 96 patients respectively. Mg level average and range in mmols was 0.944 (0.5-1.4), 0.977 (0.7-1.7),1.004 (0.6-2.1), 1.003 (0.6-2.2) in those consecutive years. Number of patients with Mg level 0.7 or below was 13 (10.4%),3 (3.2%), 3 (3.0%) and 3 (3.1%) in the respective years.

Conclusions: With the current use of standard dialysate magnesium a small number of patients were found to have low Mg, 22 out of 412 (5.3%) on data for 4 consecutive years during measurement of predialysis magnesium in single dialysis unit. After first measurement of serum Mg++ 22.5 % of dialysis patient had died within a year of measurement of Mg level of whom more than half died with COVID-19 in 2020 thus it was difficult to ascertain the impact of serum magnesium on their survival. In following years we found less patients with lower magnesium level. Comaparitively more patients on Proton Pump Inhibitors PPI or Calcineurin inhibitors CNI had lower Mg 14/22 (63%) but the numbers were too small to come to a definite conclusion. In general we did not find a significant impact of dialysate magnesium of 0.5 mmol to increase the risk of hypomagnesimia. Whether increasing dialysate magnesium to increase serum magnesium level have a survival benefit will need to be ascertained by larger and longer term studies. In the mean time standard dialysate magnesium on 0.5 mmol continues to be a safe and acceptable option.

PUB105

Evolution of Clinical Characteristics and Prognosis of Maintenance Hemodialysis Population: A Single-Center Retrospective Study

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Background: To analyze the trends of clinical characteristics of the maintenance hemodialysis (MHD) population in a single center, and to explore the risk factors affecting the survival of MHD patients.

Methods: An epidemiological survey of MHD was carried out in a center of a tertiary hospital from January 1,2009 to December 31, 2018. The original medical records were checked through the HIS and LIS systems. The follow-up endpoints were death, replacement of renal replacement therapy, and transfer to other centers. The trend of clinical characteristics of this population for ten years was observed, and the the risk factors of survival were analyzed using univariate and multivariate COX regression.

Results: A total of 1,509 MHD patients were included. The average age was 63.66±15.21 years old, including 914 males (60.6%) and 595 females (39.4%), and the median vintage of dialysis was 23 months. With the progress of time, the annual number of MHD patients increased from 200 to 915. Diabetic nephropathy has gradually become the primary cause of end stage renal disease. The annual mortality rate decreased from 51.9/1000 person-years to 38.2/1000 person-years, the main cause of death was cardiovascular events, followed by infection. Hospitalization rate was 302/1000 person-years to 405/1000 person-years. The main cause of hospitalization was cardiovascular complications, followed by vascular access-related complications. The COX univariate study indicated that increasing age, DN, hyperphosphatemia, hyperlipidemia, hypoalbuminemia, and central venous catheter were risk factors for death in MHD patients ($p < 0.05$). The COX multivariate study analyzed that increasing age, DN, and TCC use were still risk factors ($p < 0.05$).

Conclusions: The prevalence rate of maintenance hemodialysis in our center increased year by year, and the mortality rate decreased year by year. Aging, diabetic nephropathy, and long-term central venous catheter use were independent risk factors for dialysis patient death.

Funding: Government Support - Non-U.S.

PUB106

Not the Usual Pericarditis: A Life-Threatening Complication

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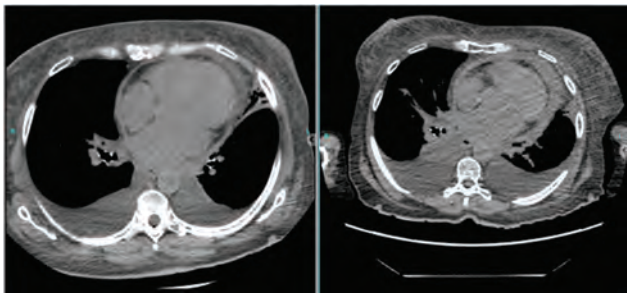
Introduction: Uremia can cause multiple systemic manifestations, including pericardial effusion and pericarditis. Its prevalence ranges from 3%-41%, but in recent decades due to improved treatment, less than 5% develop uremic pericarditis. Below we present a case of a patient with CKD with a rare, life-threatening complication of uremia.

Case Description: Case of a 60-year-old female with stage 4 CKD who presented with shortness of breath, decreased urine output, and chest discomfort. On examination the patient had jugular venous distention, distant heart sounds, tachycardia, decreasing mean arterial pressure, and bilateral lung crackles. Findings were remarkable for anemia, worsening renal function, and azotemia. The patient never developed pulsus-paradoxus or stigmata of cardiac tamponade. Nevertheless, on the serial 2D-ECHO patient had plethoric IVC and evidence of worsening pericardial effusion from small to moderate-large. CT remarkable for pericardial effusion with attenuation indicative of blood products in the space. Findings on echocardiography are presumed to be secondary to uremia. The patient was managed with continuous hemodialysis therapy and blood transfusion. After seven sessions of hemodialysis back-to-back, the patient's clinical condition improved, and the pericardial effusion resolved completely without the need for pericardiocentesis or pericardial window.

Discussion: Hemorrhagic pericarditis is a rare but serious complication of pericarditis and occurs in less than 5% of all cases of pericarditis and confers significant mortality. There is limited specific data available regarding the mortality rate exclusively for hemorrhagic pericarditis in CKD patients but the patient can experience cardiac tamponade, myocardial infarction, and shock. This case highlights the importance of intensive back-to-back hemodialysis therapy along with intensive blood transfusions to the improvement of this life-threatening condition and serial echocardiograms to ensure the resolution of the disease.



PUB107

Efficacy and Safety of Difelikefalin in Treating CKD-Associated Pruritis: A Case Series

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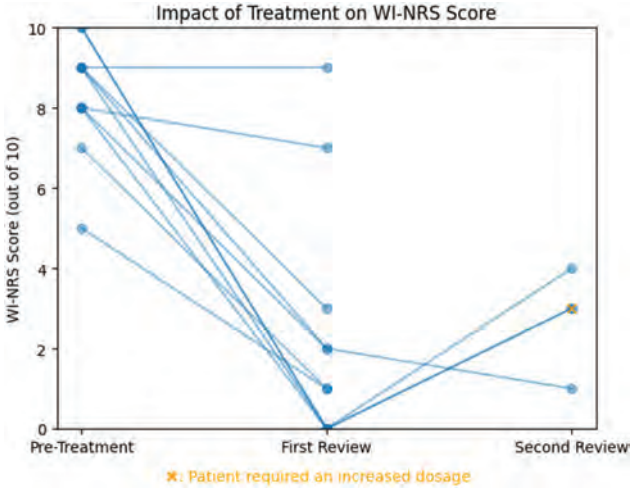
Introduction: Chronic kidney disease-associated pruritus (CKD-aP) is a prevalent and debilitating condition characterized by moderate to severe itching specifically linked to kidney disease in patients with end-stage renal disease (ESRD). The pathophysiology of CKD-aP remains incompletely understood, but accumulating evidence suggests that it may result from a combination of uremic toxins and instability in the opioid receptor system, particularly antagonistic peripheral kappa opioid receptors. This case series aims to evaluate the efficacy and safety of difelikefalin in treating CKD-aP.

Case Description: We assessed the level of itching in 11 ESRD patients, using the Worst Itching Intensity Numerical Rating Scale (WI-NRS) before and after the administration of difelikefalin (0.5 mcg/kg dry wt.). We recorded patients' baseline characteristics, including age, sex, BMI, time on dialysis, dialysis sessions per week, dialysis duration, and continuation of anti-pruritic treatment. We also documented the quantities of any administered antihistamines, gabapentinoids, topical treatments, narcotics, sedatives, and phosphorus binders and CaXP, Kt/V Urea, PTH and K levels before and during the treatment period. **Results:** Difelikefalin injection significantly reduced the level of itching as measured by WI-NRS scores in 9 out of 11 patients. No serious adverse events were observed, and the known side effects of difelikefalin injection were recorded with consideration to patients' pre-existing health conditions.

Discussion: Our findings suggest that difelikefalin is a safe and effective treatment for CKD-aP in ESRD patients, with no significant adverse effects. However, limitations include relatively small sample size, lack of a control group and short duration of follow-up. Further large scale studies are needed to confirm our results and to determine the optimal dosing and duration of treatment.



DFK

PUB108

Association Between Modified Simple Protein-Energy Wasting (PEW) Score and All-Cause Mortality in Patients Receiving Maintenance Hemodialysis in Phramongkutklao Hospital

Narongrit Siriwattanasit. *Phramongkutklao Hospital, Bangkok, Thailand.*

Background: Protein-energy wasting (PEW) is a frequently observed complication that leads to increased mortality in hemodialysis patients. Many nutritional indexes may be correlated with mortality in these patients. However, a multifaceted assessment of PEW by combined objective nutritional parameters inn Thai population has not yet been established.

Methods: We conducted a single-centered, analytical retrospective study that included 28 ESRD patients receiving maintenance hemodialysis at Phramongkutklao Hospital from January 2020 to December 2021. We calculated modified simple protein-energy wasting (mPEW) from four parameters: Serum albumin and Creatinine level, normalised protein catabolic rate and body mass index. The cutoff values of the modified simple PEW score components were based on receiver operating characteristics curves determined by the Youden index. The sensitivity, specificity, accuracy of mPEW were calculated by independent t-test.

Results: During the 2-year follow-up period, 11 patients died of any cause. The optimal cutoff values of mPEW score to predict mortality in Thai patients is 2, which provided 100% sensitivity, 58.8% specificity and 75% accuracy.

Conclusions: The modified simple PEW score is a useful composite indicator of nutritional status that stratified the risk of all-cause mortality in Thai patients undergoing maintenance hemodialysis.

Funding: Private Foundation Support, Clinical Revenue Support

PUB109

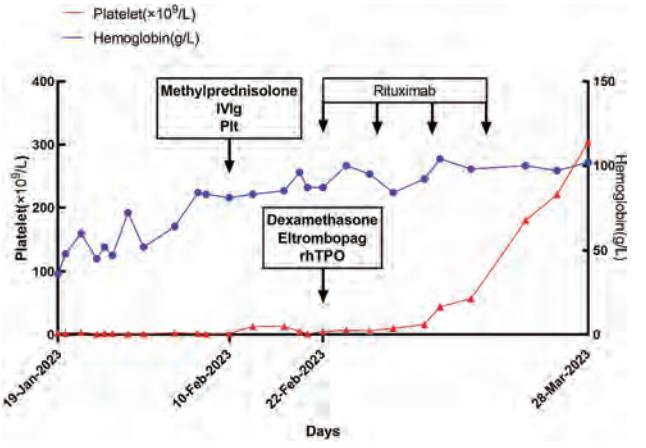
Severe Thrombocytopenic Purpura in a Patient Undergoing Hemodialysis

Shuqin Mei. *Shanghai Changzheng Hospital, Shanghai, China.*

Introduction: Severe acute respiratory syndrome coronavirus (SARS-CoV-2) infection has been a global threat since the end of 2019. Although the main clinical manifestation of coronavirus disease 2019 (COVID-19) are respiratory, its range of clinical manifestation is extensive and may include various systems, including hematological disorders, such as lymphopenia, thrombotic events, thrombocytopenia and immune thrombocytopenic purpura (ITP). A recent meta-analysis and systematic review reported that most of the patients that had developed COVID-19-associated ITP were male and elderly patients. The present paper was the first one that aimed to raise awareness of ITP induced by COVID-19 in patients undergoing maintenance hemodialysis.

Case Description: This is the case of a 75-year-old Asian woman who was diagnosed of COVID-19 positive 15 days before attending to our Emergency Department on January 19th, 2023, with a three-day history of severe bleeding symptoms, including gastrointestinal, mucosal bleeding, epistaxis, and a nadir platelet count of 5×109/L. She had a preexisting medical history of chronic kidney disease for 30 years and treated with maintenance hemodialysis (MHD) 3 times a week since 2012. Platelet count recovery was observed after 45 days of combined treatment with corticosteroids, intravenous immunoglobulin (IVIG), thrombopoietin receptor agonists (TPO-RAs) and rituximab.

Discussion: Hematological consequences of COVID-19 are not uncommon. The mechanism of this manifestation could be changes in bone marrow environment, changes in megakaryocytic differentiation and maturation resulting from infection of hematopoietic stem cells and megakaryocytes, decline in TPO production by liver cells and by the lung damage caused by COVID-19 infection.



PUB110

Epidemiology and Outcomes of Endophthalmitis in Maintenance Hemodialysis Patients: A 5-Year Experience

Srilakshmi Gaddam,[1] Lakshmi Aishwarya Pavuluri,[1] Darshini Kattula,[1] Shaik S. Heera,[1] Jagritee Gupta,[1] Venkata A. Yalamanchili,[2] Siva K. Vishnubotla,[1] Ram Rapur.[1] *[1]Sri Venkateswara Institute of Medical Sciences, Tirupati, India; [2]Dallas Nephrology Associates, Dallas, TX.*

Background: Endophthalmitis is a severe eye infection leading to severe impairment of vision. We would like to present the epidemiology and clinical features of endophthalmitis in maintenance hemodialysis patients in a tertiary referral centre.

Methods: Our institute is a government run tertiary care centre. The department of nephrology conducts more than 72000 dialysis sessions per annum. The demographic features, clinical manifestations, infection focus and visual outcome of the maintenance hemodialysis patients who suffered endopthalmitis from 2017 to April 2023 were recorded.

Results: We observed endopthalmitis in nine patients (0.28%) out of 3206 maintenance hemodialysis patients dialysed at our institute from 2017 to April 2023. The age range was 17 to 74 years (median: 51 years). Most patients presented with ophthalmalgia, periorbital swelling and redness (n = 9, 100%). Blurred vision was reported by seven patients (77.7%) at admission. There were five diabetics and two patients received immunosuppression in the past. The vascular accesses were: untunneled internal jugular catheter in three, arteriovenous fistula in three, tunnelled internal jugular catheter in two and arteriovenous graft in one. Staphylococcus aureus, Klebsiella pneumoniae, Pseudomonas aeruginosa and Acinetobacter were the most frequent causes of bacteremia. Intravenous and intravitreal injections of antibiotics and vitrectomy were performed in all. Only one patient had final vision of 6/20.

Conclusions: This is a large series of patients of endophthalmitis in maintenance hemodialysis patients. Our study showed different pathogen spectrum, different vascular accesses as source of infection and worse visual outcome.

PUB111

Dialysis Disequilibrium Syndrome: A Case of Rapid Overcorrection

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Introduction: Dialysis disequilibrium syndrome (DDS) is a rare, but potentially life-threatening, complication of hemodialysis (HD). It presents as an assortment of neurologic signs with varying severity. It may result in seizures, coma, and even death. Major risk factors include severe azotemia and metabolic acidosis.

Case Description: A 72-year-old male, with no known past medical history, presented with bilateral leg swelling and mild shortness of breath. On presentation he was alert and oriented, examination was remarkable for some asterixis and lower extremity edema. His creatinine level was 24.53 mg/dL, blood urea nitrogen (BUN) 167 mg/dL, and bicarbonate (HCO3) 14 mmol/L. Given metabolic acidosis and volume overload resulting in respiratory compromise, HD was initiated 48 hours after admission. The prescription consisted of blood flow rate of 300 ml/min and dialysis filtration rate of 600 ml/min during 2 hours with no complications during the procedure. Upon completion of his first session, BUN dropped by 50%. He subsequently became encephalopathic. 12 hours later he underwent his second session of HD with same prescription lasting 2.5 hours where

his BUN dropped another 50% and his acidosis was further corrected. Afterwards he developed progressively worsening encephalopathy requiring evaluation for higher level of care. After extensive work up with imaging and laboratory testing for other causes, the diagnosis of DDS was made.

Discussion: DDS is a rare complication of HD occurring secondary to an osmotic gradient that is created by rapid removal of BUN. Other theories include rapid correction of metabolic acidosis and idiogenic osmoles creation. Our case highlights the changes induced by chronic azotemia facilitate the formation of this osmotic gradient. These include increasing aquaporin channels and decreasing urea transporters, which limits the removal of urea even further than its baseline of its normal coefficient of reflection of 0.45 that the urea has (1). Rapid overcorrection of metabolic acidosis, producing a "paradoxical brain acidosis" may also contribute to the genesis of DDS, as this case highlights(2). Management is supportive until homeostasis is restored. Preventative measures include gentle initiation of HD, gradual clearance of urea, and slow correction of acidosis. Adding active osmoles to the dialysate may reduce gradient formation (3).

PUB112

Indications and Complications Associated with Centrifuge-Based Therapeutic Plasma Exchange: A Nephrologist's Perspective

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Background: Therapeutic Plasma Exchange (TPE) is an extracorporeal treatment modality used to treat certain diseases, many of which are managed by nephrologists. To investigate the indications and safety of TPE, a retrospective review was conducted to identify the indications and complications of TPE.

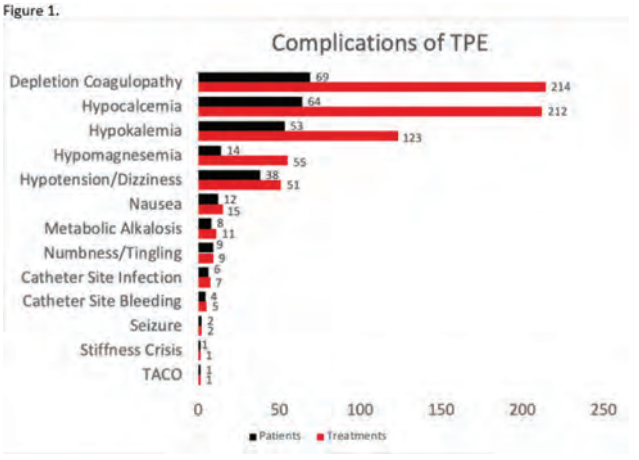
Methods: This is a single center retrospective review of centrifuge based TPE managed by the division of nephrology at a tertiary care academic center from June 2018 to July 2022. A total of 1219 TPE treatments in 145 patients were reviewed.

Results: In total, there were 25 diagnostic indications for TPE as outlined in Table 1 with their category of indication as defined by the American Society for Apheresis (ASFA) 2022 guidelines. There were 14 complications associated with TPE which are documented in Figure 1.

Conclusions: Most common being antibody-mediated rejection in kidney transplant recipients (20%), autoimmune encephalitis (16%), and Neuromyelitis optica (11%). 21% of procedures were performed for a condition classified as Category III by the ASFA or not classified. Depletion coagulopathy (48%), hypocalcemia (44%), and hypokalemia (37%) were the most common complications. This study exemplifies the utility of having a systematic audit to review the practice patterns of TPE and supports the inclusion of education on TPE management in nephrology training programs.

Diagnosis	ASFA Category	# of Patients	# of Treatments
AMR, kidney transplant	I	29	166
Autoimmune encephalitis	I	23	132
Myasthenia gravis	I	14	111
AIDP	I	7	37
ANCA Vasculitis	I	4	13
CIDP	I	2	208
Recurrent FSGS, post-transplant	I	2	119
Catastrophic APS	I	1	5
TTP	I	1	14
Neuromyelitis optica	II	16	94
Multiple sclerosis	II	12	65
TMA, secondary to SLE	II	1	14
Hashimoto's Encephalitis	II	1	7
Lambert-Eaton Syndrome	II	1	23
AMR, heart/liver transplant	III	9	51
Paraneoplastic neurological syndromes	III	7	35
FSGS	III	4	73
Stiff Person Syndrome	III	3	17
Medication overdose	III	2	3
Multiple myeloma	III	1	4
Central Pontine Myelinolysis	N/A	1	5
CRION	N/A	1	5
AMR, pancreas transplant	N/A	1	4
Belatacept removal, COVID-19	N/A	1	2
Unexplained transverse myelitis	N/A	1	5

Figure 1.



PUB113

Mortality After Gastrointestinal Bleeding Among Dialysis Patients

Belen Alejos,[1] Yue Jiao,[2] Melanie Wolf,[1] John W. Larkin,[2] Anke Winter,[1] Sheetal Chaudhuri,[2] Manuela Stauss-Grabo,[1] Len A. Usvyat,[2] Jeffrey L. Hymes,[2] Franklin W. Maddux,[3] David C. Wheeler,[4] Peter Stenvinkel,[5] Jürgen Floege.[6] On Behalf of the INSPIRE Core Group. *[1]Fresenius Medical Care, Bad Homburg, Germany; [2]Fresenius Medical Care, Waltham, MA; [3]Fresenius Medical Care AG & Co KGaA, Bad Homburg, Germany; [4]University College London, London, United Kingdom; [5]Dept of Renal Medicine Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [6]University Hospital RWTH Aachen, Division of Nephrology and Clinical Immunology, Aachen, Germany.*

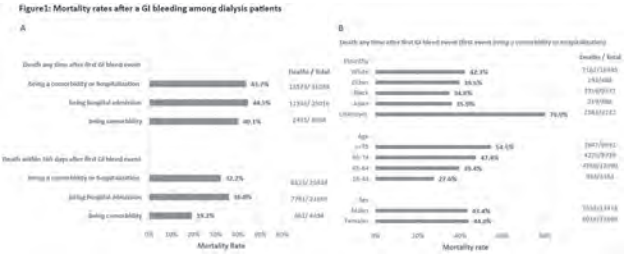
Background: Gastrointestinal bleeding (GIB) is common in patients on chronic dialysis, yet associated outcomes are uncertain. The INSPIRE group used data on a nationally representative sample of dialysis patients to characterize the mortality rate after a GIB episode.

Methods: We used data on adult dialysis patients treated at a provider network in the United States during Jan-2018 to Mar-2021 who had ≥1 GIB episode. GIB episodes were identified from ICD diagnosis codes recorded as a comorbid condition during dialysis care, or as a discharge reason for hospitalization (Zhao et al., AHRQ 2006). Crude mortality rate was calculated considering death anytime, or 365 days, after the first GIB.

Results: Among a population of 405,530 patients, 31,084 (7.7%) had ≥1 GIB episode. Crude mortality rate any time after the first GIB was 43.7% (n=13,573; **Figure 1A**). Mortality rate after the first GIB comorbidity (40.1%, n=2,435/6,068) was slightly lower than after the first GIB hospitalization (44.5%, n=11,138/25,016). Mortality rate increased with older age and appeared to be highest among patients with an unknown race, followed by a white race (42.3%; **Figure 1B**). Limiting the analysis to the 365 days after the first GIB, mortality rate was 32.2% after any GIB, 19.2% after a GIB comorbidity, and 36.0% after a GIB hospitalization.

Conclusions: Mortality rate after a GIB is high in dialysis patients, with 30% dying within a year and 40% dying anytime during follow-up. Mortality rates were higher after GIB hospitalization versus comorbidity, albeit exceedingly high in both cases. Further analyses are needed and should consider adjustments for age, race, and modality, and comparison to patients who never had a GIB.

Funding: Commercial Support - Fresenius Medical Care



PUB114

Exploring the Management of CKD-Associated Pruritus in Routine Haemodialysis Practice: A Qualitative Content Analysis

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Background: CKD associated pruritus (CKD-aP) is an extremely common symptom affecting up to 68% of patients receiving haemodialysis (HD), and associates with poor outcomes such as reduced quality of life, increased hospitalisation and mortality. However, it is under recognised and undertreated. This study explores current approaches to CKD-aP assessment and management.

Methods: Out-patient letters of prevalent HD patients from the Leicester Renal Network between January 1st and December 31st 2022 were considered. Searches were conducted using terms 'itch', 'pruritis' and 'scratch' plus all derivatives. Qualitative content analysis was conducted (NVivo v1.6.1).

Results: Of the 1085 clinic letters from 389 prevalent HD patients, only 55 mentioned CKD-aP. Braun and Clarke's thematic analysis identified three main themes: responsibility, role of treatment and complexity of CKD-aP. Within the responsibility theme, clinicians were predominantly responsible for management *decisions;* patients, their relatives, and HD staff were responsible for *identifying and monitoring* itch. Treatment was a significant theme throughout. Clinician discussions were almost entirely treatment based. Heterogeneity in approaches between clinicians in managing itch was apparent. Itch is a complex symptom, difficulties in communication were directly linked to non-adherence to treatment. Complexity of CKD-aP was characterised by the interplay of itch with other symptoms. As well as non-adherence, letters often identified the symptom was discussed but then no management plan produced or enacted. Cross cutting all the themes was the significant variability in how itch was identified, addressed, managed, and discussed amongst health care professionals, patients and carers.

Conclusions: There is considerable variation in the assessment and management of CKD-aP. The role of the clinician goes beyond management. Pro-active identification and ongoing monitoring of itch is crucial to successful management and a shared responsibility of all staff, especially as new treatments become available.

PUB115

A Red Herring: Two Simultaneous Cases of Dialysis Effluent Discoloration

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Introduction: Hydroxocobalamin is a synthetic injectable form of vitamin B12, approved for treatment of cyanide toxicity. A favorable side effect of hydroxocobalamin is a transient elevation in blood pressure, utilized in the setting of vasoplegic syndrome during cardiac surgery. Vasoplegic syndrome manifests with hypotension, increased cardiac index, and decreased systemic vascular resistance. Hydroxocobalamin depletes nitric oxide in vascular endothelium, which helps to reverse vasoplegic syndrome. Hydroxocobalamin, however, can cause reddish discoloration of body fluids interfering with lab colorimetric assays. This can persist for 7-35 days. Hydroxocobalamin's deep red color penetrates the dialysis filter and discolors the dialysis effluent causing false blood leak alarms in the hemodialysis (HD) machines via the machine's photometric sensor. This automatically shuts down the HD machine. An alternative treatment option is continuous renal replacement therapy (CRRT). Blood leak detectors on CRRT machines typically use a single optical emitter which detects light scatter. Therefore, it will not alarm with discolored effluent.

Case Description: Here, we present 2 patients who received Hydroxocobalamin and subsequently developed red effluent. Patient 1 is a 75 yo M with cardiogenic shock having severe mitral regurgitation, and aortic insufficiency (AI). He underwent aortic valve replacement (AVR) and mitral valve replacement. Post-op course was significant for AKI. He was initiated on HD. However, HD was interrupted multiple times due to blood leak alarms that persisted despite changes in the dialysis machine and filter. HD was discontinued, and he was placed on CRRT. Hours later, pt. 2, a 67 yo M with severe AI and severe TR, underwent AVR and TVR. The post-op course was significant for cardiogenic shock with fluid overload. HD was attempted but was terminated due to multiple blood leak alarms. He was also placed on CRRT. On further chart review, pt. 1 received hydroxocobalamin 3 days prior to HD, and pt. 2 received it the day prior to HD.

Discussion: Hydroxocobalamin administration can cause dialysis effluent discoloration. This can lead to the inability to receive HD treatment. Clinicians should be aware of this potential complication and discontinue hydroxocobalamin in HD patients whenever possible. Nephrologists should also be aware of alternative treatment options such as CRRT.

PUB116

Pulmonary Hypertension in Hemodialysis (HD) Patients and Associated HD-Specific Factors: A Retrospective Cohort Study

Firoozeh Farahmand. *Saint Louis University, Saint Louis, MO.*

Background: Pulmonary hypertension (PH) is associated with increased mortality and morbidity in hemodialysis (HD) patients. The high incidence of PH in HD patients is not only due to left sided heart disease and HD-specific factors are involved. Mechanisms of PH in HD patients have not been fully understood. This study aimed to evaluate HD-specific factors in PH.

Methods: In a university affiliated dialysis center, a retrospective cohort of ESRD patient under maintenance hemodialysis for at least 3 months followed in dialysis unit. Patients with previous pulmonary embolism, collagen vascular disease, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), severe mitral or aortic valve diseases, liver failure and heart failure were excluded from the study. A total of 47 patients were included in the study. Echocardiography, Cr and BUN, CBC and electrolyte parameters amd B-type natriuretic peptide (BNP) and proximal and distal AVF in PH group and and non-PH group were examined and their correlation with PASP (Pulmonary arterial systolic pressure) were analyzed. Univariate and adjusted logistic regression analysis were performed to identify the independent associated factors.

Results: Following adjustments in the regression analysis, internal diameters of the left atrium, right atrium, and LVEF were independently associated with PH. There was a positive correlation between access blood flow and PASP. PASP in patients with proximal AVF was significantly higher compared with those with distal AVF. The only laboratory parameter associated was PH was B-type natriuretic peptide (BNP).

Conclusions: PH has a high incidence in ESRD patients under maintenance hemodialysis. The higher level of inflammatory marker BNP suggests a microinflammatory state as an independent risk factor for PH. Left and right atria diameter and LVEF were also independently associated with PH. PASP in patients with proximal AVF was significantly higher compared with those with distal AVF. This study found differences in HD-related factros beween the groups with and without PH.

PUB117

Acute Hemodialysis Rapidly Reverses Cefepime Neurotoxicity

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Introduction: Cefepime-induced neurotoxicity (CIN) is a rare but potentially serious adverse event thought to be due to alterations in γ-aminobutyric acid (GABA) neurotransmission, neurotoxic metabolites, & impaired renal function (S. Lee J of Neurocritical care Vol 12; pp75). Clinical presentation of CIN can range from mild symptoms such as confusion and delirium to more severe symptoms such as seizures and encephalopathy. The best treatment for CIN may be renal replacement therapy (RRT). Herein, we report two cases of severe CIN that were successfully treated with hemodialysis (HD).

Case Description: Case 1 A 65-year-old male with a history of ESRD on iHD, and gram-negative bacteremia due to AV graft infection on cefepime (2gm post HD), developed obtundation, somnolence and unresponsiveness. Entire work for metabolic encephalopathy was negative. Presumed diagnosis of CIN was made and emergent HD resulted in complete resolution of symptoms within 2.5 hours of dialysis. **Case 2** An 85-year-old woman with ESRD and pseudomonas bacteremia on cefepime (2g post HD), was admitted for myoclonus, somnolence and obtundation. Encephalopathy work up was negative. An electroencephalogram (EEG) showed findings consistent with non-convulsive status epilepticus (NCSE). She was started on anti-epileptics and benzodiazepine, however with minimal improvement. NCSE was presumed due to cefepime neurotoxicity and patient underwent emergent HD with improvement in mentation in 3 hours of dialysis. A repeat EEG at 6 hour post HD showed resolution of NCSE.

Discussion: CIN should always be suspected in patients receiving high dose cefepime in the setting of renal failure and encephalopathy. Treatment for CIN primarily involves drug cessation and supportive measures however RRT remains a curative intervention for severe CIN symptoms (seizures, encephalopathy). Hemodialysis removes cefepime from blood rapidly and hastens recovery, especially in life-threatening situations. A single 3-hour HD session efficiently removes 70% - 80% of a given dose (S. Lee J of Neurocritical care Vol 12; pp79). Clinicians should maintain a high index of suspicion in individuals receiving cefepime with diminished renal function. Our cases show that acute hemodialysis effectively reverses CIN. With this we also propose the recommendation for weight based dosing for cefepime to reduce risk of CIN.

PUB118

Membrane Filtration Plasma Exchange Therapy in Nonrenal Diseases and the Participation of the Nephrologist as an Expert in Extracorporeal Therapies

Claudia B. López,[1,2] Pedro Morales Molina,[1,2] Diana Maldonado Tapia,[1,2] Monica Lopez Mendoza,[1,2] Juan D. Diaz Garcia,[1,2] Abel Humberto V. Compean,[1,2] Beatriz R. Cerezo Samperio,[1,2] Julio C. Nieto,[1,2] Pamela Prado,[1,2] Irving G. Ramirez.[1,2] *[1]Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico; [2]Universidad Nacional Autonoma de Mexico, Ciudad de Mexico, Mexico.*

Background: Therapeutic plasma exchange (TPE) is a treatment indicated in multiple diseases with the objective of eliminating high molecular weight plasmatic components that has had favorable results, but in some the benefit is questionable.

Methods: Descriptive, observational and retrospective study of patients with pathologies of non-renal etiology with indication of plasma exchange performed with membrane filtration in a reference medical center from 2016 to 2023.

Results: Data were collected from 16 patients, 50% women, with a mean age of 26.7 years. The indications for performing TPR were 4 due to alveolar hemorrhage, 4 due to thrombotic microangiopathy, 3 due to acute inflammatory demyelinating disease, 2 due to humoral liver rejection, 2 due to acute immune-mediated liver failure, and 1 due to thyroid storm. Systemic autoimmune etiologies were 68.7%, two patients with active humoral

liver rejection, one patient with transverse myelitis, one with multiple sclerosis and one with Guillain-Barré syndrome, 56% presented acute renal failure, of these 77 % required renal supportive therapy. Regarding the prescription, all were performed by membrane filtration (Prismaflex 2000 filter), with replacement fluid with 3% albumin, with a replacement volume of 1.5 in relation to the patient's plasma. Among the complications, the most frequent was hypocalcemia. As outcomes we found that 62% presented complete clinical response.

Conclusions: We found in plasma exchange therapy a safe and effective tool, with main benefit in alveolar hemorrhage and acute inflammatory demyelizing disease since they presented 100% recovery, no favorable response was found in liver disease, among the most serious complications were the infectious processes. The prognosis was good in patients who received plasma exchange.

Variable	N: 16 (Total) Media ± DE*	N:10 (Response)	N: 6 (No response)	p
Age	26.7± 15.9	29.7±17.6	21.8±12.6	**0.09**
Male / Female	8/8	6/4	2/4	**0.04**
Systemic autoimmune (%)	11 (68.7)	7 (63)	4 (37)	**0.08**
Lung affection (%)	4 (25)	4 (100)	0	**0.03**
Liver disease(%)	4 (25)	0	4 (100)	**0.04**
Neurological condition(%)	3 (18.7)	3 (100)	0	**0.03**
Acute kidney injury (%)	9 (56.2)	5 (55)	4 (45)	**0.09**
Complication (%)	13 (81.2)	8 (61.5)	5 (38.5)	**0.06**

Table 1: Demographic characteristics
***standard deviation**

PUB119

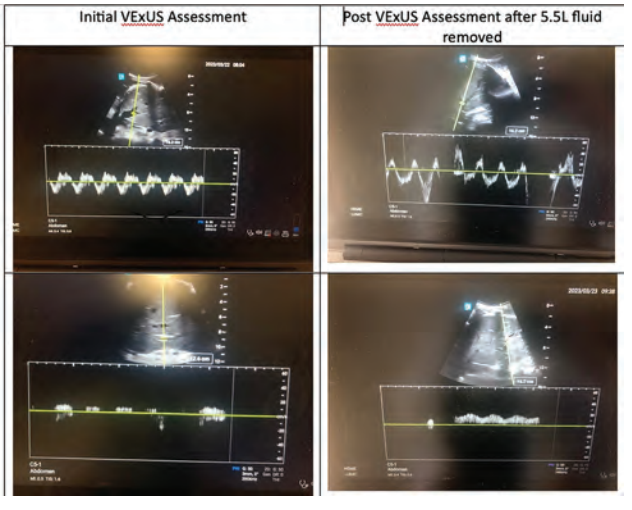
Point-of-Care Ultrasound (POCUS) Venous Excess Ultrasound (VExUS) Score Used for Ultrafiltration Titration in a Patient with Fluid Overload

Sylvester Barnes IV.[1,2] *[1]Loyola University Chicago Stritch School of Medicine, Maywood, IL; [2]Edward Hines Junior VA Hospital, Hines, IL.*

Introduction: The patient is a 82YOM with a history of ESRD on MWF renal cell carcinoma with metastasis admitted to hospital after a planned bronchoscopy for biopsy of a lung mass complicated by acute hypoxic and hypercapnic respiratory failure post procedure. The patient required NIV PPV and eventual intubation, with extubation one day afterwards. He received regular HD after extubation with an UF of 1.5L. On hospital day 4 the patient was examined at the end of dialysis with UF of 2.5L performed. The patient still complained of feeling short of breath and "not himself".

Case Description: POCUS was performed at the bedside showing B lines present in all lung fields, and a very dilated plethoric IVC. The significant dilation lead to further examination of the patient's hepatic veins and portal vein. Venus excess ultrasound score provides a sonographic way to evaluate a person for significant venous overload. In this patient he had reversal of his S and D waves in the hepatic veins along loss of continuous portal venous flow resulting in only systolic flow (figure 1). Due to the patients ESRD statues renal vein examination was not performed. Based on his high VExUS score IUF was planned for the following day and had increased UF with HD following this. In total an additional 5.5L were removed over two days with repeat VExUS performed showing less dilated hepatic veins, no longer S and D wave reversal and much some pulsatile portal vein flow remaining but flow that is now continuous. The patient felt significantly less short of breath and felt better overall.

Discussion: In this case POCUS, specifically VExUS, examine along with patient symptoms lead to targeted fluid removal not only until his symptoms improved but also corresponding to sonographic improvement as well. VExUS is an easy tool that can quickly be incorporated for examination of ESRD patients when there is concern for fluid overload and help target more accurate and more accurate UF goal.



PUB120

Predictors and Outcomes of Unplanned Emergency Department Visits of ESRD Patients on Maintenance Hemodialysis in a Tertiary Hospital in Davao City

Phillip Jaynard P. Gatmaitan. *Davao de Oro Provincial Hospital, Montevista, Philippines.*

Background: The incidence of End Stage Renal Disease (ESRD) is high, with Diabetes Mellitus and Hypertension as the leading causes. Statistics showed that it is the seventh leading cause of death among Filipinos with a 10 to 15 percent increase per year and more than 5,000 on renal replacement therapy. ESRD patients on hemodialysis account for 5%-7% of health care expenditures in developed countries. In this study, we aim to determine the factors influencing emergency department (ED) visits among patients with ESRD on maintenance hemodialysis.

Methods: This prospective study included the following: >18 years old and diagnosed ESRD patients on Maintenance hemodialysis.

Results: There were 156 patients included; the mean age was 48.42±14.06, most were males (51.93%) and from Davao City, and have their maintenance hemodialysis in a non-hospital based institution (66.66%). Outcome of this study showed that admission rates were at 87.17%. Odds ratio showed that those that are located outside of Davao city (OR=1.685, P=0.471) and those with Economic status Class D (OR=1.914, P=0.573) got the highest risk associated for admission. For the comorbidities, strongest factor is the presence of Diabetes (OR=5.059, P=0.085) and Hypertension (OR=4.972, P=0.099) and number of resident physician visit of at least a year (OR=2.809, P=0.734) and nephrologists visits of more than eight in a year (OR=1.025, P=0.590) also showed to be a risk factor.

Conclusions: Overall, among the predictors, the strongest risk factors associated with increased risk of admission are patient related factors. These include those that are not from Davao City, Class D socio economic status, comorbidities such as diabetes, hypertension, and congestive heart failure, and lastly nephrologists visit > 8/year and resident physician visit at least 1/year were all identified to have an increased risk for admission. Considering those risk factors, this study showed that admission rates were high and none resulted to death.

PUB121

Evaluation of Triglyceride (TG)/High-Density Lipoprotein Cholesterol (HDL-C) and Non-HDL-C/HDL-C ratios as Mortality Predictors in Hemodialysis Patients of National Medical Center XXI Century

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Background: The efficacy of triglyceride/high-density lipoprotein cholesterol (TG/HDL- C) and non-high-density lipoprotein cholesterol/ high-density lipoprotein cholesterol (non-HDL-C/HDL-C) ratios had been demonstrated as predictor of adverse cardiovascular events and mortality predictors on healthy patients. However, limited studies have been performed to evaluate the efficacy of TG/HDL-C and non-HDL-C/HDL-C ratios as mortality predictors in hemodialysis patients.

Methods: A longitudinal, retrospective, case-control study was developed. A total of 386 patients with treatment of end stage kidney disease on hemodialysis therapy in Hemodialysis Unit of National Medical Center XXI Century from January of 2019 to December of 2022 were enrolled. The medical records, albumin levels, calcium, hemoglobin, parathyroid hormone (PTH), total cholesterol, HDL-C, LDL-C, triglyceride, TG/HDL- C and non-HDL-C/HDL-C were registered. The odds ratio was calculated using chi-square and student's t-test, considering a $p > 0.05$ as a statiscally significant value. The prognostic values were accessed by univariate and multivariate COX regression analysis.

Results: A total of 386 patients were enrolled. They were distributed as 288 control patients (living) and 98 case patients (dead). The multivariate Cox regression analysis showed that patients over 60 years old (2.19, CI 95%, 1.52-3.17 p <0.001), and a TG/HDL- C index >3.29 were strongly correlated with increased risk of death (1.648, CI 95%, 1.029-2.638, p 0.038). In contrast, the treatment of dyslipidemia was associated with reduction on the risk of death (0.298, CI 95%, 0.160-0.553, p <0.001).

Conclusions: The TG/HDL-C ratio have potential as predictor of mortality in hemodialysis patients. The non-HDL-C/HDL-C ratio failed as prognostic tool, with no statistically significant results in the analysis.

Table 1. Baseline characteristics according to outcome

	Total	Living	Dead	p
Patients (n)	386	288	98	
Age (years)	50 (39-63)	49 (36-62)	55 (46-66)	<0.001
Sex				0.686
Men (n. %)	198 (51.30)	146 (50.70)	52 (53.10)	
Women (n. %)	188 (48.70)	142 (49.30)	46 (46.90)	
Time on HD (meses)	24 (12-48)	24 (12-48)	24 (12-36)	0.205
DMT2 (n. %)	157 (40.70)	111 (38.50)	46 (46.90)	0.144
HAS (n. %)	339 (87.80)	259 (89.90)	80 (81.60)	0.030
BMI (kg/m^2)	24.03 (21.22-27.21)	24.16 (21.11-27.33)	23.38 (20.87-26.76)	0.410
ACE	51 (13.20)	35 (12.20)	16 (16.30)	0.292
RI EPO	17.90 (8.21-27.57)	16.93 (8.25-26.42)	17.75 (5.79-29.45)	0.898
Tx SRAA (n. %)	187 (48.40)	139 (48.30)	48 (49.00)	0.903
Tx dyslipidemia (n. %)	56 (14.50)	49 (17.00)	7 (7.10)	0.017
Albumin (g/dL)	3.70 (3.10-4.10)	3.70 (3.20-4.12)	3.40 (2.70-3.84)	<0.001
Calcium (mg/dL)	9.68 (9.04-10.12)	9.65 (9.06-10.11)	9.70 (8.22-9.70)	0.953
PTH (ng/dL)	190.00 (78-376)	196.00 (81.80-407.00)	171.00 (73.23-305.25)	0.023
Hb (g/dL)	9.80 (8.40-11.10)	9.80 (8.50-11.20)	9.70 (8.18-10.63)	0.052
Col-T (mg/dL)	147.00 (123.00-177.00)	149.50 (127.00-181.00)	134.00 (108.75-169.25)	0.002
HDL-Col (mg/dL)	41.00 (33.00-52.50)	41.00 (33.42-52.00)	36.60 (29.00-51.77)	0.014
LDL-Col (mg/dL)	76.90 (56.90 - 100.40)	78.00 (57.45-101.40)	67.60 (48.35-94.30)	0.004
TG (mg/dL)	117.00 (86.00 - 163.00)	118.50 (89.00-173.00)	119.50 (83.00-165.25)	0.764
TG/HDL-Col	2.90 (1.75 - 4.58)	2.83 (1.92-4.49)	3.75 (1.69-5.57)	0.043
Col No-HDL / HDL-Col	2.49 (1.70 - 3.51)	2.52 (1.77-3.49)	2.60 (1.68-3.62)	0.378

ACE: Adverse cardiovascular events, BMI: body mass index, HAS: Hypertension, HD: hemodialysis, HDL-C: high-density lipoprotein cholesterol, PTH: parathyroid hormone, RI EPO: Erythropoietin resistance index, TG: triglyceride, Tx SRRA: renin angiotensin aldosterone system treatment. TG/HDL-C: triglyceride/high-density lipoprotein cholesterol , Col no-HDL/HDL-C: non-high-density lipoprotein cholesterol/ high-density lipoprotein cholesterol

PUB122

Prevalence of Sarcopenia in a UK Haemodialysis Population

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Background: Sarcopenia is a characterised by a loss of muscle wasting, reduced muscle strength and low physical performance. Although often associated with ageing, it is now recognised as a complication of other long term health conditions and is associated with worse clinical outcomes including poor quality of life, higher hospitalisation rates and increased mortality. Sarcoenia is cited as a frequent complication of CKD, especially common in people with more advanced disease, but the true prevalence of sarcopenia is unknown. The aim of this study was to determine the prevalence of 'confirmed' and 'severe' sarcopenia in a cohort of UK haemodialysis patients.

Methods: This is a secondary analysis of the CYCLE-HD study cohort, which was a randomised controlled trial assessing the effects of a 6-month intradialytic cycling intervention on cardiovascular health. Presence of sarcopenia was determined using the criteria established by the European Working Group of Sarcopenia in Old People (EWSOP) definition. Sit to stand 5 was used to determine muscle strength, fat free mass index was used ato determine muscle mass and the short physical performance battery to determine physical function. Individuals were classified as either having no evidence of sarcopenia, probable sarcopenia, confirmed sarcopenia, or severe sarcopenia based on the specified cut-offs.

Results: 117 patients (56 ±15 years, 82 [78%] male) were included in the analysis. n=12 patients had probable (10%), n=46 had confirmed (39%) and n=19 (15%) had severe sarcopenia, demonstrating that 63% of our population had some degree of sarcopenia.

Conclusions: The prevalence of sarcopenia that we report here is high. Given the association with poor outcomes and reduced quality of life, it is important to be able to identify those patients with, or at risk of developing sarcopenia to be able to implement effective treatment strategies. Unfortunately, the process of diagnosing this disease is multi-factorial and requires the use of tests that can be expensive and require training. This means that patients are rarely screened, and their sarcopenia status is not recorded. Furthermore, there are currently no validated treatments for sarcopenia. Given the high prevalence in our end-stage renal failure population, there is a clear an urgent need for both better detection and treatment strategies.

PUB123

Improving Transition onto Haemodialysis: A Novel Trainee-Led Clinic

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Background: Starting haemodialysis (HD) is a precarious time with high mortality and worse outcomes in unplanned starts. An audit of our unit demonstrated median time to first consultant clinic review after HD start was 51 days. Two patients died before review and there were 31 emergency admissions within 60 days of HD start. Running an HD unit is in the UK training curriculum. A 2018 survey of nephrology trainees revealed only 40% within 2 years of completion felt, "somewhat/very confident to run an HD unit".

Methods: A trainee led clinic with 1 hour slots 2-3 weeks following in or outpatient HD start was co-designed with patients and the renal MDT. Consultations focused on background, route onto HD, modality choice, vascular access, transplant prospect, medication review, HD adequacy and fluid status exam. Pre-specified data were collected from hospital records and compared with patients starting HD prior to the clinic start using Mann Whitney U tests.

Results: Between Nov 2022 and May 2023 all patients commencing HD (n=47) were seen in the clinic. Patient characteristics (age, gender, ESKD aetiology), route onto HD (planned vs unplanned), modality prior to HD start and dialysis access in use at start were similar to the baseline audit. Time to first review reduced from 51 to 19 days (p=<0.001).

Conclusions: Earlier formal medical review of patients improved time to target weight review, earlier opportunities for referrals to the wider MDT and earlier tailoring of immunosuppression and stop of medications no longer indicated. Trainees gained experience of managing HD patients outside a pager-based, trouble-shooting setting. Future data collection is ongoing to explore reduction in hospital admissions and improvements in trainee confidence in managing HD patients.

	Baseline audit 1/10/21 – 31/3/22 (n=50)	New starter clinic 1/11/22 – 12/5/23 (n=47)
Time to clinic review (median, 1st-3rd IQR)	51 days (30-69)	19 days (14-27)
Trainee ad hoc reviews before 1st clinic	47 (0.94 per patient)	28 (0.6 per patient)
Routine HD care	28 (60%)	6 (21%)
Acute medical issue	12 (26%)	22 (79%)
General non-acute medical issue	7 (15%)	0
Time to first TW (Mean, range)	13 days (0-42)	11 days (0-37)
First ever TW in new starter clinic	N/A	5 (11%)
TW alteration in new starter clinic	N/A	19 (40%)
Time to UO (Median, 1st – 3rd IQR)	7 days (4-20)	11 days (5-24)
Time to dietician(Median, 1st – 3rd IQR)	6 days (2-11)	5 days (1-15)
Referrals		
Vascular access team	N/A	9 (19%)
Transplant team	N/A	8 (17%)
Home therapies	N/A	10 (21%)
Counsellor	N/A	5 (11%)
Welfare Advisor	N/A	9 (19%)
Medication review at 1st clinic		
CKD medications	N/A	15 (32%)
Transplant immunosuppression wean	N/A	4 (57% of failed transplants)

TW=target weight; UO=urine output measurement.

PUB124

Disaster Preparedness for Climate-Driven Atlantic Hurricanes for Patients Diagnosed with ESKD

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Background: Customized disaster preparedness is a critical unmet need for patients diagnosed with end stage kidney disease (ESKD) who need in-center dialysis. In this current era of compounding disasters, climate change is making Atlantic hurricanes stronger and wetter, with a tendency to stall at the time of landfall, resulting in more powerful, prolonged, and damaging impacts that disrupt in-center dialysis and clinical services for ESKD patients. Surges of airborne diseases complicate hurricane evacuation and sheltering. This complex risk landscape requires tailored approaches to disaster preparedness for patients, clinicians, and dialysis providers.

Methods: We are conducting a literature review on the intersection of ESKD, climate change, hurricane hazards, and disaster preparedness. We devised a qualitative study involving focus groups of ESKD patients and key informant interviews with dialysis providers and nephrologists. We interviewed dialysis providers about their 2022 Hurricane Ian experience. We developed a survey that examines ESKD patients' hurricane threat appraisal, adaptation appraisal, and past hurricane experience. Adaptation appraisal focuses on disaster preparedness, including preparing the household, stockpiling supplies, taking airborne disease precautions, and adding on ESKD-specific preparedness. Patient demographics, assessment of disability, and mental health scales are included.

Results: Based on our interviews, the dialysis center experience during Hurricane Ian was exemplary: among 232 dialysis centers closed for Hurricane Ian, half were operational 2 days post-storm and 230 (99%) were operational 5 days post-storm. We will present key findings from the literature review and the qualitative study, and initial findings from the ESKD patient survey.

Conclusions: Patients living with ESKD who require in-center dialysis have special needs during disasters yet are underprepared for extreme events striking their communities. Layered risks leading to compounding disaster scenarios are increasing in frequency and severity. Compounding disaster risks amplify the urgency for developing effective approaches for safeguarding patients with ESKD, their caregivers, their providers, and their care systems.

PUB125

Lung Ultrasound to Assess Volume Status in Hemodialysis Patients: One-Center Experience

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Background: Assessing volume status in hemodialysis (HD) is challenging. Misleading dry weight adjustments contribute to intradialytic hypotension or volume overload, with avoidable morbidity and unnecessary expenditure for the healthcare

system. Our objective was to compare lung ultrasound (LUS), bioimpedance analysis (BIA) and physical examination (PE) in volume assessment status in HD patients.

Methods: This is a unicentric, prospective, longitudinal descriptive study. We evaluated volume status by LUS, BIA and PE after the long interdialytic period, predialysis and postdialysis. Data regarding demographics, clinical information, lab tests and HD sessions were recorded.

Results: 9 patients (77.7% male) were included with an average 37±15 months on HD, median age 65±13 years old. Residual renal function was present in 44% of them (> 400 ml only in one), urea-creatinine mean clearance was 3±2.6 ml/min/1,73m2 and 89% had an arterio-venous fistula. Arterial hypertension was present in 78%, diabetes in 33%, ischemic heart disease in 33%, reduced left ventricle ejection fraction in 22% (transthoracic heart ultrasound <6 months) and previous stroke in 22%. Predialysis: 33% showed volume overload signs on PE. Lab test (average): Hemoglobin 11.0 ±0.6 g/dL, urea: 159.4 ±39.8 mg/dL, serum sodium: 139.9 ±1.5 mEq/L and serum potassium: 5.0 ±0.6 mEq/L. BIA: 2.0 ±1.6 L mean volume overload. LUS: mean Frassi Score was 1.7 ±1.0 (normal = 0). Postdialysis: After a mean ultrafiltration of 3.1 ±1.0 L (which represents 4.3 ±1.1 % of the patients' dry weight) with a sodium conductivity of 139.9 ± 1.0 mEq/L, only 2 patients presented transitory intradialytic hypotension. These 2 patients were the ones that presented higher number of B lines in LUS, with no correlation with BIA. 0% showed volume overload signs on PE. Mean Frassi Score was reduced to 0.7±0.7. No dry weight adjustments were needed.

Conclusions: PE showed poor sensitivity for volume status in these patients. LUS was a better predictor of intradialytic hypotension than BIA/PE and constitutes a useful, cheap, innocuous and readily available tool to use in HD patients.

PUB126

Skin Biopsy (SB) in Calciphylaxis: A Must?

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Background: Calciphylaxis is defined by calcification of cutaneous small blood vessels, resulting in ischemic necrotic lesions. It's associated with high mortality, being more common in dialysis patients. Although its diagnosis is mainly clinical, SB the gold standard. However, it has limited sensitivity and is associated with complications such as infection. Imaging tests have been suggested as an alternative diagnostic method, without great success.

Methods: Patients with calciphylaxis between January 2001-February 2023 were included. We evaluated the performance of SB, SB timing, its diagnostic accuracy and complications.

Results: 25 patients were diagnosed, 48% males, mean age of 63.7±14.2 years (range 31-87, median 68). 12 were on hemodialysis, 8 on peritoneal dialysis, 3 were transplanted with functioning grafts and 2 were predialysis. Dermatologists performed 21 SB: 18 first biopsies and 3 rebiopsies (one patient underwent 2 initial biopsies at the same time). The mean time from symptoms onset to SB was 23.8±16.5 days (median 20). In 8 patients, diagnosis was clinical based on characteristic lesions and risk factors. 17 SB were performed on the lower extremities, 3 on upper extremities, and 1 on the abdomen. 76.2% (16) were punch biopsies and 5 were deep spindle-shaped. From first biopsies, 10 (55.5%) were diagnostic, as were the 3 rebiopsies, giving an 61.9% overall diagnostic yield. Time to biopsy was longer in cases where the initial SB was diagnostic (25 vs 22.14 days, p=0.722). All post-SB lesions required wound care, along with calciphylaxis ulcers. Topical sodium thiosulfate, with or without intravenous administration, was used in 4 patients and surgical debridement was performed in 1 patient. Mean wound treatment time was 16.41±13.56 weeks (median 12.14), which was longer in patients with a favorable outcome compared to those who died (21.28 vs 8.48 weeks, p=0.051). Twelve patients developed infectious complications in calciphylaxis lesions (48%), with 8 of them having undergone previous SB (47%). One-year survival rate was 47.8%.

Conclusions: SB is the confirmatory test for calciphylaxis, although it can be inconclusive and associated with complications. Further research is needed to expand our knowledge on the usefulness of imaging techniques, particularly ultrasound considering its availability.

PUB127

Low Parathyroid Hormone (PTH) Is a Risk Factor for Mortality in Incident Patients on Hemodialysis

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Background: CKD-MBD is a major complication in patients on hemodialysis, contributing to high mortality. We evaluated the role of PTH as a risk factor for mortality in a large cohort of incident patients on hemodialysis.

Methods: 4,317 individuals starting therapy between February 1, 2012, and December 31, 2016, were included. Data evaluated included age, sex, race, diabetes mellitus, body mass index (BMI), paying source (Public Health System or private), place of first dialysis (clinic or hospital), calcium, phosphorus, albumin, urea, alkaline phosphatase and PTH. Patients were divided into 3 groups according to PTH values (<150, 150-600 and >600 pg/mL). Survival analysis was performed using competing risk (kidney transplantation) and censorship for dialysis withdrawal (clinic transfer, change of method or recovery of renal function).

Results: The mean age was 58 ± 16 years, 58.4% men, 43.7% white, 39.7% with diabetes mellitus, 70.9% had their first dialysis session in a hospital, and 59% were financed by the Unified Health System. Median PTH levels were 252 (118-479) pg/ml. The percentage of patients with PTH <150, 150-600 and >600 pg/mL was 32%, 51% and 17%, respectively. Patients with PTH <150 pg/mL were significantly older, mostly white, 47.5% financed by Public Health System, 74% started dialysis in a hospital, had lower BMI, albumin, urea, potassium, phosphorus and alkaline phosphatase, and higher calcium. There were 1,613 deaths in 5 years, of which 423 occurred in the first year. Competing risk analysis revealed that PTH < 150pg/mL was an independent risk factor for mortality (HR 1.14, 95% CI 1.0-1.30, p=0.044) in a multiple-adjusted model in five years but not in a 1-year follow-up (p=0.418).

Conclusions: One-third of patients initiate dialysis PTH <150pg/ml, a population characterized by a lack of private health insurance and laboratory markers suggesting malnutrition. Developing public health policies are needed to minimize the risk of mortality.

PUB128

Holistic Design Philosophy in Dialysis

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Background: Medical care is increasingly being pushed to new settings. As dialysis treatments are increasingly conducted at home, in skilled nursing facilities and transitional care units, the requirements on dialysis machines are changing to meet these needs. A more holistic design philosophy is required to balance sometimes competing or conflicting requirements.

Methods: The creation of a design framework starts with a list of the important categories of information. These categories structure information around the challenges we face during product design. For example, how do we think about the tradeoffs between ease of use and flexibility in therapy? The broad categories capture the main design elements we are trying to optimize. Within the broader categories there are more specific attributes or features that make up the major user needs the final device should embody. Once we have created the categories, we organize them in a way that helps highlight how the categories relate to each other; are they opposed or do the overlap? This emerging framework is then used to describe the problems we face and focus ideation on those difficult places where our priorities conflict with each other.

Results: A simple version of the framework that we developed is outlined in Figure 1. The benefit of this framework was to focus early design exploration on the areas that were most in conflict with each other. An iterative process of design, build, test was able to better show the tradeoffs we would need to make to balance our priorities and optimize the design. We know that we can't create something that is all things to all people, so properly exposing and evaluating the tradeoffs between desired attributes allows for a design the holistically meets our requirements.

Conclusions: A framework for understanding conflicting design elements and guiding design at a high level is the best way to balance the many needs and requirements of a complex device.

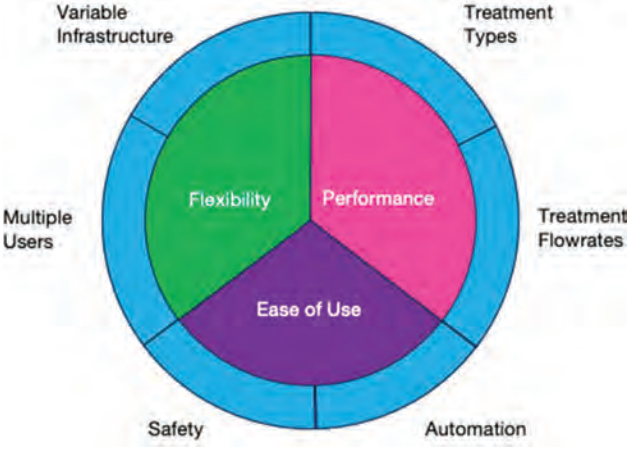


Figure 1: Framework for Design

PUB129

Preliminary Results of Effective Response to Long-Acting Erythropoiesis-Stimulating Agent (ESA) vs. Short-Acting ESA via IV Route of Administration in Anemia Management

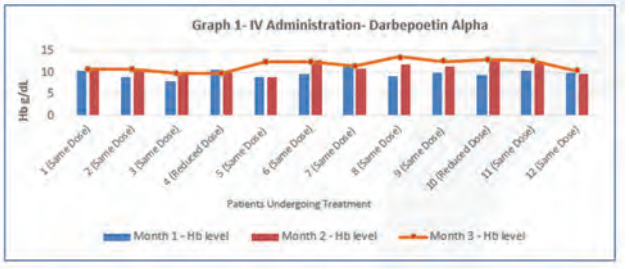
Mercy Chandrabose, Satarupa Gogoi. *HHD Home Healthcare LLC, Dubai, United Arab Emirates.*

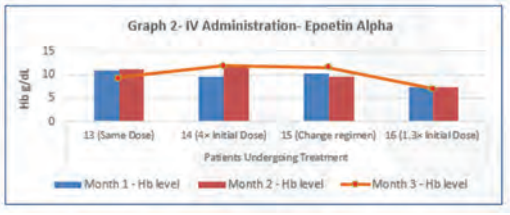
Introduction: The anemia of chronic kidney disease (CKD) is primarily due to insufficient production of the hormone erythropoietin (EPO). Agents that replace EPO plays primary role in treatment of anemia. The subcutaneous route improves the efficiency of therapy, result in reduced dosing requirement (of about 25%) for short acting ESAs, despite patients undergoing hemodialysis in our HHD facility preferred to be treated via IV route, as primary reason is the discomfort with subcutaneous injections. Replacing

short acting ESAs with a longer acting agents provide extended time in circulation to allow the drug to bind to erythropoietin receptors, IV administration of agents with long serum half-life are better choice than Epoetin Alfa.

Case Description: This is a prospective comparative 3 month study on random 16 adult CKD 5D HD patients, treated by Darbepoetin alfa, Epoetin beta (long-acting ESA) & Epoetin alfa (Short acting ESA) weekly to avoid having the Hb concentration fall below (9.0 g/L) were included in this study, average age 58.4 (55-85yr, 70.5% male. Etiology of ESRD was DM in 70%, 60% are Anemic. The serum concentration time profile of medication Aranesp (Darbepoetin alpha) following IV route in CRF patients receiving dialysis were biphasic with a mean terminal half- life of 21 hours which was approx. 3-fold longer than that of Epoetin alfa. Another eg. of Mircera – Epoetin Beta, which has long serum half-life of approx. 5.5 days. The preliminary results of treating anemia by Darbepoetin alfa & Epoetin Beta vs Epoetin alfa via IV route in a special cohort of HD patients shown in Graph 1 & 2.

Discussion: This short study showed, Darbepoetin alfa & Epoetin Beta with long serum half-life via IV route is more efficient in the treatment of anemia than Epoetin alfa thereby eliminating the need for Subcutaneous administration of the drug or increased dose requirement of the medication.





PUB130

Longest Case of Inotropic Support for Cardiorenal Syndrome and Dialysis

James R. Sterrett. *NCH Healthcare System, Naples, FL.*

Introduction: Chronic inotropic use for advanced heart failure and cardiorenal syndrome has been used as an adjunctive therapy at home for those patients. We present an interesting case of a male in his 80s with advanced cardiorenal disease, end-stage cardiomyopathy and advanced chronic kidney disease who survived with a relative quality of life for more than 5 years on continuous infusion of inotropic therapy with dobutamine with hemodialysis TIW.

Case Description: A male in his late 80s with a past medical history of hypertension, diabetes, multifactorial chronic kidney disease, myocardial infarction due to severe obstructive coronary artery disease with subsequent drug-eluting stent placement. This resulted in severe left ventricular dysfunction with an estimated average ejection fraction (EF) 19%. His functional class was III. He underwent cardiac resynchronization therapy and a defibrillator (CRT-D). He was admitted several times for acute decompensated heart failure and on further evaluation he was deemed too tenuous for transplant or destination left ventricular assisted device for mechanical circulatory support. He was recommended to undergo hospice and He was sent home on palliative inotropes with dobutamine at 4 mcg/kg/hr via Peripherally Inserted Central Catheter (PICC) line. Due to advanced chronic kidney disease that failed several diuretic regimens. He continued in outpatient dialysis clinic without significant exacerbations for almost 6 years.

Discussion: Home intravenous inotropic support for palliative reasons has been described in patients with advanced cardiorenal syndrome and end-stage cardiomyopathy not suitable for either transplant or destination therapy such as LVAD. This is to our knowledge, the first reported case of home inotropic use for advanced heart failure that efficiently lasted for more than 5 years. A potential explanation for these long-lasting effects without decompensation is that this patient had a close follow-up with nursing services available throughout the day. During subsequent follow-ups, He did not exert ventricular arrhythmias or required shocks from his defibrillator. Ultimately, he had couple of PICC line infections and sepsis that improved with intravenous antibiotics.

PUB131

Survey of Peritoneal Dialysis Patients' Challenges and Experiences During the COVID-19 Pandemic: A Multicenter Study in the United States

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Background: During the COVID-19 pandemic adjustments were made to peritoneal dialysis (PD) practices in the outpatient units. These unilateral decisions were made by dialysis providers, clinical staff, and governments. The patient perspective regarding these changes during the pandemic has not been explored. We sought to evaluate patient experiences and perceptions of the challenges they faced, institutional adjustments, as well as their mental health during the height of the COVID-19 pandemic in the United States.

Methods: We conducted a cross-sectional survey of PD patients across four home dialysis units affiliated with four large academic centers who were on PD between March 2020 and March 2021.

Results: 98 participants completed the survey across the 4 outpatient PD clinics. Most PD patients did not have to change their home accommodations during the pandemic or have issues getting their dialysis supplies and medications delivered. Most patients felt comfortable coming to the dialysis unit if they needed to during the pandemic. The majority of patients felt supported by their dialysis staff during the peak of the COVID-19 and had modified PHQ-2 and GAD-2 scores not consistent with depression or anxiety. Less than 10% of patients considered changing their dialysis modality.

Conclusions: The adjustments made by the dialysis units during the peak of the pandemic were effective in maneuvering the challenges facing our patients during the COVID-19 pandemic, while providing high quality medical care.

PUB132

Human Factors Testing of the Quanta Dialysis System for Self-Care Hemodialysis in the United States

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Background: Most hemodialysis (HD) treatments are delivered by healthcare professionals within a facility (in-center HD) but HD is increasingly performed at home via self-care. Uptake of home hemodialysis (HHD) in the United States (US) remains low despite potential improvements in quality of life, health outcomes and cost savings compared to in-center HD. This may be because patients fear they are unable to manage complex treatments at home. With this in mind, the Quanta™ Dialysis System (Quanta Dialysis System) was designed to be more user-friendly. Human factors testing demonstrated the usability of the Quanta Dialysis System in the United Kingdom but has yet to be validated in a US cohort. Using a human factors testing process, we sought to assess how two lay user groups, patients with kidney failure and caregivers, use the Quanta Dialysis System within a representative, simulated use environment in the US.

Methods: We recruited patients with kidney failure and caregivers from a dialysis center in California between June and November 2022. Adults who were a patient on dialysis, or a caregiver for a patient on dialysis, within the last 4 years (including the present) were eligible. Participants trained on the Quanta Dialysis System for 4-5 sessions with a Qualified Nurse Trainer followed by a competency sign off session. After a 48-hour decay period, those deemed competent proceeded to 2 test sessions to perform tasks independently. During testing, independent human factors moderators scored patient performance on 111 critical tasks required to effectively set up, operate, and shut down the Quanta Dialysis System. We assessed the number of participants who passed each task.

Results: A total of 31 individuals (16 patients, 15 caregivers) participated. The mean age was 49 years and 16 (51.6%) participants were female. Of the 16 patients, 9 (56.3%) were from in-center HD. There were 7,200 tasks were tested across all participants. Of these, 96.4% were completed without difficulty, error or assistance.

Conclusions: The Quanta Dialysis System was easy to use after a small number of training sessions and a 48-hour decay period. These results indicate the Quanta Dialysis System has demonstrated a high level of usability in the US and may help improve HHD penetration by using a state of the art, compact, easy to use device.

Funding: Commercial Support - Quanta Dialysis Technologies

PUB133

Low Albumin May Be a Predictor of Mortality in Patients Transferred from Peritoneal Dialysis to Haemodialysis

Pranesh Jain, Hari Dukka. *University Hospitals of Derby and Burton NHS Foundation Trust, Derby, United Kingdom.*

Background: Peritoneal dialysis(PD) is a preferred modality for many patients needing dialysis treatment. Most patients on PD either get transplanted, switch to haemodialysis(HD) or die. We did a retrospective, observational study to ascertain the outcomes in patients transferred from PD to HD over a 5-year period and determine variables which may predict poor outcomes.

Methods: Electronic data base was used to obtain data for all patients transferred from PD to HD from 2014-2018. Variables noted were gender, serum albumin, reason for transfer, PD vintage, whether the transfer was expected (commencement of Haemodialysis using arterio venous fistula), as well as Stoke co-morbidity index score(SCI) at the time of transfer. Observed events were infection(pneumonia, cellulitis, line sepsis, tunnel infection or foot infection), morbidity due to vascular disease(peripheral vascular disease, cardiovascular or cerebrovascular accidents) and mortality, within 1 year of transfer to HD. COX regression analysis was used to determine the predictor value for each of the variables for these events.

Results: 95 patients (63 male/32 Female) were transferred from PD to HD in the study period. The mean age was 57.03 +/- 14.22 years, mean serum albumin 24.41+/-6.46 g/dl, mean PD vintage 1.55+/-1.95 years, mean SCI 1.05+/-0.63. The events noted within one year of transfer from PD to HD were death(n=11), vascular events(n=28), infection(n=44). The reasons for switch from PD to HD were infection(62.4%) mechanical causes(12.9%), inadequate dialysis(9.68%), patient's choice(8.6%) and not coping on PD(6.45%).32.3% transfers were expected. COX regression analysis (Table) indicated low albumin was better predictor of mortality post transfer to HD within 1 year of transfer. None of the variables were statistically significant in predicting cardiovascular morbidity or infections.

Conclusions: Patients with low albumin on PD may have adverse outcomes, when transferred to HD**.** Further studies with larger patient numbers are needed to determine outcomes.

Cox regression analysis- predictors for mortality

	HR	Lower 95% CI	Upper 95% CI
Albumin	0.88	0.79	0.99
Stoke co-morbidity Index	1.6	0.66	4.63
Transfer expected	2.58	0.62	10.82
PD Vintage(years)	1.14	0.9	1.44
Age	1.02	0.97	1.07

PUB134

Who Has a Better Kidney-Related Quality of Life: Peritoneal Dialysis or Hemodialysis Patients? A Cross-Sectional Study from Saudi Arabia

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Background: ESKD substantially impacts different aspects of patients' lives, including mental and physical health and overall quality of life. The aim of our study is to assess the quality of life (QoL) and the associated predictors in ESKD Saudi Arabian patients receiving either hemodialysis (HD) or peritoneal dialysis (PD). Saudi Ministry of health (MOH) is advancing dialysis care in the country with more focus on patients' satisfaction and QoL. However, the data regarding QoL in Saudi Arabian dialysis patients is limited.

Methods: A cross sectional study was carried out using Kidney Disease Quality of Life scale (KDQOL-36) to assess the QoL. We disturbed a validated formal arabic version of the questionnaire. Patients older than 18-year-old and attending dialysis clinics in Aseer region, Saudi Arabia, were invited to participate in the study.

Results: A total of 152 responses were analyzed, which were separated into two primary groups: the HD group (98 patients) and the PD group (54 patients). Our results showed no significant differences between the two groups except for the physical composite score at which the PD group had a higher mean than the HD group 37.84 vs 44.75, respectively (p <0.001). However, more PD patients reported feeling depressed compared to HD patients.

Conclusions: KDQOL-36 cores were comparable between HD and PD groups except for the physical composite score. On the other hand, PD patients tend to suffer from depression more than HD patients. Interventions to attenuate the physical deconditioning and depressive symptoms in HD and PD patients, respectively, are crucial. Future prospective studies with larger sample sizes are warranted.

Table 1: Comparing Scores Between Hemodialysis and Peritoneal Dialysis

n = 152	Hemodialysis = 98 Mean (SD)	Peritoneal Dialysis = 54 Mean (SD)	p-value
Symptom/ problem list (I1-I12)	64.63 (21.91)	70.8 (18.98)	0.082 a
Effects of kidney disease on the daily life	64.19 (23.52)	67.48 (18.93)	0.380 a
Burden of kidney disease	48.66 [Median: 50.00] (25.98)	47.45 [Median: 46.88] (24.81)	0.657 b
SF-12 Physical Composite #	37.84 [Median: 37.17] (10.21)	44.75 [Median: 41.69] (9.60)	<0.001* b
SF-12 Mental Composite #	45.03 (11.05)	43.07 (10.47)	0.287a

n: Sample size, Normality was tested using Kolmogorov-Smirnov test of normality, a - Compared using independent samples t-test to compare 2 means, b- Compared using Mann-Whitney U test

PUB135

A Review of the Risk Factors and Rates of Peritoneal Dialysis (PD) Peritonitis: A Single-Centre, Retrospective Cohort Study

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Background: PD Peritonitis is a frequent and important outcome which contributes to the longevity of the peritoneal membrane and the burden of patient co-morbidities. The existing risk factor data relates to a pool of cohort analyses which are hindered by small numbers of patients included in final analyses. As such, evidence-based indicators against Peritoneal dialysis have not been established.

Methods: This single centre retrospective study pooled all patients who accessed peritoneal dialysis from January 2013 to January 2021 and into two separate groups; those who had microbiological evidence of PD peritonitis vs. those with no evidence of PD peritonitis. Demographic and baseline clinical information was compared between the two groups to provide indicators of peritonitis risk.

Results: A total of 631 patients were included in the final analysis, which included 80 patients with a history of PD peritonitis. A total number of 129 infections were reported in the time frame. The organism most commonly reported was staphylococcus aureus, with 37 infections. The mean age of patients at the time of infection was 60, compared to 55, in their non-infected counterparts (mean difference 4.9 years p = 0.0008). The relative risk of male gender resulting in PD peritonitis was 1.03 (CI 0.75-1.14). Within the infected cohort, the relative risk of Asian and Caucasian ethnicity were reported as 0.62 and 0.56 respectively (CI 0.33-1.8 and CI 0.4-0.77). A total of 28 patients reported recurrent infections. The average age for multiple infections was 63, compared to 57 amongst those with a single infection episode (mean difference 5.8 years CI 0.1). An assessment of the role of diabetes status, serum albumin levels, difficulty rating and method of PD catheter insertion, body mass index along with nasal Staphylococcal Aureus Nasal carriage and patient kt/V, as risk factors for PD peritonitis, is currently underway.

Conclusions: This data demonstrates that in a retrospectively assessed cohort of 631 patients, age was a statistically significant determinant of risk of PD peritonitis, with a predominant staphylococcal organism. Caucasian and Asian ethnicities appeared to have a lower risk of PD peritonitis, but gender was non-significant. Given the retrospective nature of the available data, further investigation is required.

PUB136

Effective Removal of Methylurea by Peritoneal Dialysis

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Background: Peritoneal dialysis (PD) clears different uremic solutes at different rates. The highest peritoneal clearance known to date is that for urea. Because urea is partially reabsorbed in the native kidney as well as rapidly cleared across the peritoneal membrane, PD can control plasma urea levels as residual function is lost. This study examined whether another low molecular weight uremic solute, methylurea, has clearance characteristics similar to those of urea.

Methods: Measurements were made in 9 patients recieving maintenance PD with a weekly stdKt/Vurea of 1.86 ± 0.55 and with variable residual native kidney function (average residual GFR 4.0 ± 3.1 ml/min; range 0 to 9 ml/min). Methylurea, urea, and creatinine were measured in plasma, dialysate, and urine with a new LC/MS/MS assay for methylurea and clearances were calculated using standard formulas.

Results: The time-averaged peritoneal dialytic clearance of methlyurea was the same as that of urea and significantly greater than that of creatinine. The residual native kidney clearance of methylurea was also the same as that of urea with both solutes having residual clearance values less than that of creatinine. This reflected similar native kidney tubular reabsorption of methylurea and urea (fractional residual clearance < 1) in contrast to native kidney secretion of creatinine (fractional residual clearance > 1). The total clearances of the three solutes were similar but peritoneal clearance accounted for a larger portion of the total clearance of methylurea and urea. Mathematical modeling showed that for methylurea and urea current standard PD can provide a time-average clearance of close to 7 ml/min and, presuming no change in solute generation, maintain plasma levels below those seen at the initiation of dialysis as patients become anuric.

Conclusions: The uremic solute methylurea is cleared as rapidly as urea across the peritoneal membrane and its plasma level can be effectively controlled by PD. Other small uremic solutes which share these characteristics remain to be discovered.

Funding: NIDDK Support

	Dialytic Clearance (ml/min)	Residual Clearance (ml/min)	Fractional Residual Clearance	Total Clearance (ml/min)
Methylurea	4.4 ± 1.6	2.3 ± 2.0	0.60 ± 0.23	6.6 ± 1.5
Urea	4.2 ± 1.5	2.6 ± 2.2	0.65 ± 0.14	6.8 ± 1.4
Creatinine	2.0 ± 1.4 *	5.4 ± 4.2 *	1.35 ± 0.14 *	7.4 ± 4.1

*, p<0.01 vs methylurea and urea

PUB137

Trends and Outcomes in Open vs. Laparoscopic Peritoneal Dialysis Catheter Placement from 2013 to 2018

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Background: Patients receiving dialysis require a durable access to the bloodstream for hemodialysis or peritoneal cavity for peritoneal dialysis. In peritoneal dialysis, the catheter can be placed via a percutaneous or surgical approach, With the surgical approach being open or laparoscopic. The purpose of our study is to demonstrate in the modern era in a nationwide, US cohort the trends and outcomes associated with laparoscopic versus open PD catheter insertion.

Methods: We conducted a retrospective analysis using NSQIP database from January 1, 2013, to December 31, 2018. Patients undergoing peritoneal dialysis catheter placement were identified using relevant Current Procedural Terminology (CPT) codes. Data on patient characteristics, surgical approach and operative characteristics, and perioperative outcomes were extracted. Trends in the proportion of open versus laparoscopic techniques were analyzed over the study period.

Results: A total of 11,732 patients who underwent peritoneal dialysis catheter placement were included in the analysis. The proportion of laparoscopic techniques increased steadily from 76.1% in 2013 to 86.8% in 2018, while the proportion of open techniques showed a corresponding decline. Statistical analysis revealed a significant temporal trend towards a higher utilization of laparoscopic catheter placement ($p<0.001$). Mortality was greater for open insertion compared to laparoscopic (odds ratio (OR) 1.56, 95% Confidence Interval (CI) 1.03 – 2.36, p = 0.04). There was no difference in surgical site infection (OR 1.25, 95% CI .97 – 1.73, p = 0.18), transfusion (OR .89, 95% CI .6 – 1.31, p = 0.55), or sepsis (OR 1.04, 95% CI .67 – 1.6, p = 0.87).

Conclusions: This study provides insights into the temporal trends in open versus laparoscopic peritoneal dialysis catheter placement using a large national database. Our findings indicate a substantial shift towards laparoscopic techniques over the study period. While we found open catheter placement to be associated with higher mortality, we believe this is due to confounding by indication and residual confounding. These findings contribute to the growing body of evidence on the evolving trends in peritoneal dialysis catheter placement and have implications for surgical decision-making and healthcare resource planning.

Funding: Clinical Revenue Support

PUB138

On Growing Home: A Single-Centre Experience with a Dedicated Peritoneal Dialysis Access Clinic

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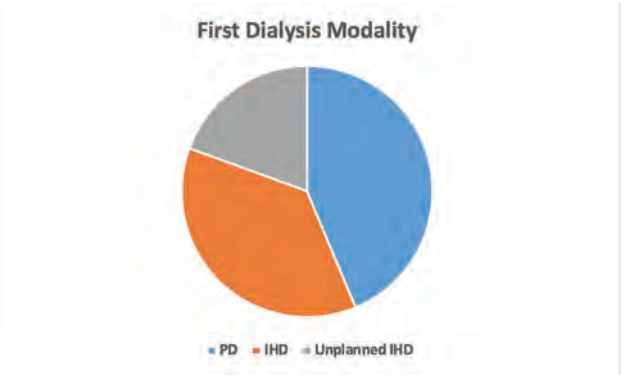
Background: Growing home dialysis programs has been a priority across Canada over the last decade. Initially a rise in home dialysis rates was observed across the country with initiatives targeting predialysis modality education, the use of transitional care units and increased utilization of assisted home dialysis programs. However, this growth has been challenging to sustain with observed attrition during the COVID-19 pandemic. In 2018, our center established a peritoneal dialysis (PD) access clinic as a means to streamline the process of establishing PD access for patients who had chosen PD as their modality of choice. Herein we describe our center's experience with this dedicated access clinic.

Methods: We reviewed the charts of 29 prevalent predialysis patients who selected PD as their dialysis modality of choice and had an appointment with our PD Access Clinic (PDAC) between March 2021 and November 2022. We collected baseline data including eGFR (mL/min) and risk of progression to ESKD at 2 years' time (as measured by the Kidney Failure Risk Equation) at the time of their appointment, time to PD catheter access and first dialysis modality. We also collected information on unplanned dialysis starts, defined as hemodialysis access placed during hospital admission.

Results: The mean (SD) patient age was 67 (14) years. Patients had an average eGFR of 10 mL/min and KFRE of 64% at the time of their initial PDAC appointment. There were a median of 3 months to PD catheter insertion from their access clinic appointment. Less than half of patients (45%) ended up on PD as their first dialysis modality and 20% of patients had an unplanned dialysis start. 17% remained predialysis at the time of our review.

Conclusions: Dedicated PD access clinics do not ensure preferred dialysis modality. Unplanned dialysis starts occur with a high degree of frequency despite predialysis clinics. Earlier referral for PD access at higher eGFR may increase likelihood of peritoneal dialysis as the initial modality and would be a future area of study.



PUB139

Comprehensive Peritoneal Dialysis Care Model in a Renal Transplant Program

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Background: Pretransplant peritoneal dialysis (PD) has shown potential benefits, including a reduced incidence of delayed graft function and improved patient survival after kidney transplant. While existing literature does not highlight any significant disadvantages of PD compared to hemodialysis (HD) in the context of transplantation, this study aims to demonstrate the impact of an integral model of care in PD as part of a kidney transplant program for a group of economically disadvantaged patients lacking social security in a third-level hospital in Mexico City.

Methods: An incident cohort of peritoneal dialysis patients was analyzed, who were treated under an integral management model from the beginning of dialytic therapy until kidney transplantation. The integral care model consists of a monthly evaluation by a multidisciplinary team of experts in peritoneal dialysis, who analyze the nutritional, psychological, social, and familial aspects, as well as health education, therapeutic adherence, self-care, hygiene, and aspects related to home therapy. Additionally, nephrological evaluation is included, along with remote monitoring system support for dialytic therapy. Patients over 18 years of age, diagnosed with end-stage renal disease, requiring initiation of renal replacement therapy, and candidates to start a kidney transplant protocol, were included. They were treated at the Nephrology Department of Hospital Juárez de México between June 1, 2022, and March 31, 2023. Descriptive statistics were employed.

Results: A total of 51 patients were included in the comprehensive care model. The characteristics of these patients are presented in Table 1.

Conclusions: The integral model of peritoneal dialysis is a good option for incident patients with the possibility of kidney transplantation.

Funding: Commercial Support - Macrotech

Table 1	Cohort		Non-transplanted		Transplanted	
	n	Value	n	Value	n	Value
Age (average SD)	51	40.01 ± 13.38	39	41.37 ± 13.12	12	35.60 ± 13.84
Female	15	29.40%	11	28.20%	4	33.30%
Diabetes mellitus	11	21.60%	11	28.20%	0	0.00%
High blood pressure	30	58.80%	25	64.10%	5	41.70%
Glucose last follow-up (mg/dL) (median, minimum and maximum)	44	85 (39 – 233)	33	84 (61 – 233)	11	86 (39 – 93)
Systolic blood pressure (mmHg) (median, low and maximum)	46	120 (100 – 200)	34	126.5 (100 – 200)	12	120 (100 – 130)
Diastolic blood pressure (mmHg) (median, minimum, and maximum)	46	80 (60 – 120)	34	80 (60 – 120)	12	80 (70 – 90)
Residual urine volume (mL/24h) (median, minimum and maximum)	50	800 (39 – 5,000)	38	800 (61 – 5,000)	12	900 (139 – 2,000)
Follow-up days (median, minimum and maximum)	51	108 (1 – 837)	39	108 (1 – 837)	12	108 (39 – 283)

Table 1

Table 2 Kidney transplantation	n	SCr Pre-KT	n	SCr Pos-KT 1m	n	SCr Pos-KT 3m
General	12	12.91 ± 4.59	12	1.15 ± 0.36	9	1.01 ± 0.22
Deceased donor	5	15.36 ± 5.53	5	1.36 ± 0.37	3	0.96 ± 0.28
Living donor	7	11.16 ± 3.10	7	1.01 ± 0.28	6	1.03 ± 0.21
Average ± standard deviation shown						

Table 2

PUB140

Effects of Thrice Weekly vs. Home Dialysis on Cardiovascular Functional Capacity (ELDEN) Feasibility Study

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Background: Conventional in-center thrice weekly hemodialysis (ConHD) regimens are associated with unacceptably high cardiovascular (CV) risk. Given the persistently poor prognosis with ConHD, emerging evidence supports an overarching hypothesis that a more physiological approach to administering dialysis through peritoneal dialysis (PD) or Home Hemodialysis (HHD) may improve outcomes. Our preliminary work has demonstrated that cardiopulmonary exercise testing (CPET) can be used as a robust quantitative probe of impaired CV functional capacity in dialysis patients. The present ELDEN feasibility study sought to assess the feasibility of recruiting PD and HHD patients for comprehensive CPET.

Methods: The ELDEN feasibility study is an ongoing single-center, nonrandomized 3-arm prospective controlled trial comparing HHD, ConHD and PD. Patients in each group were matched by age, gender, and dialysis vintage. All patients underwent breath-by-breath CPET, physical function testing, echocardiography and bioimpedance testing at baseline and 1-year.

Results: A total of n=84 patients to-date (ConHD n=12; HHD n=24 and PD n=48) were screened to-date. N=48 patients met eligibility criteria (ConHD n=8; HHD n=14 and PD n=26), n=28 were have been enrolled to-date (n=7 ConHD, n=8 HHD and n= 13) and n=14 have completed testing (n=6 ConHD, n=8 HHD and n=8 PD patients) to-date(Table 1). There was no difference in age (p=0.7), gender (p=1.0) or dialysis vintage (p=0.2). For CPET, all participants reached a respiratory exchange ratio (RER) > 1.1. No participants experienced an adverse event. Although the study was not powered to detect differences in VO2Peak, there was a trend toward higher VO2Peak in patients on PD (14.5 (12.2, 19.5) ml/min/kg) and HHD (14.6 (12.5, 15.8) compared to ConHD (10.6 (10.0, 14.2) ml/min/kg, P=0.29), Furthermore, VE/VCO2 was highest in patients on HHD compared to PD and ConHD (P<0.01). Additionally, patients on ConHD exhibited reduced peak heart rate compared to those on PD and HHD (P<0.01).

Conclusions: The present study depicts the feasibility of recruitment and performance of CPET in home dialysis patients. Patients on HHD exhibited impaired ventilatory efficiency while ConHD patients demonstrated chronotropic incompetence compared to the other groups.

Funding: Private Foundation Support

PUB141

Significant Association of Shared Decision Making on Predialysis Patients with Satisfied Modality Selection and Increased Quality of Life (QOL) After Dialysis

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Background: As the prevalence of kidney failure continues to increase and various patients bear the burden of dialysis, the importance of shared-decision making (SDM) processes is increasing, where health care providers and patients work together to make individualised decisions. Impaired quality of life (QOL) is a serious issue for the patients with kidney failure, but it is unclear whether modality selection and QOL is associated with appropriate shared decision-making.

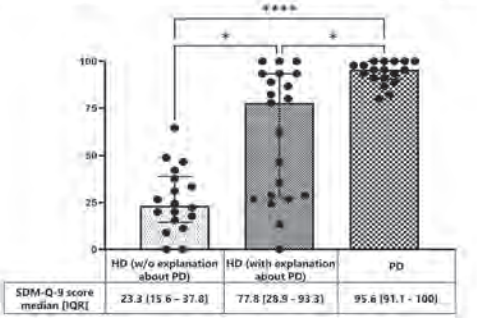
Methods: We recruited the patients undergoing hemodialysis (HD) or peritonial dialysis (PD) in two dialysis centers between June and December 2022, and surveyed retrospectively regarding their reasons for modality selection, Kidney Disease Quality of Life 36 (KDQOL-36), and 9-item shared decision making questionnaires (SDM-Q-9); based on a 6-point Likert scale that can measure nine concepts related to SDM.

Results: Of 57 participants, with an average age 68.4 ± 14.8 years, 77.2% male and dialysis vintage 2.3 ± 1.7 years, PD patients were 18 (31.6%). The SDM-Q-9 score is significantly higher in PD patients compared with HD patients who received appropriate explanations before initiation of dialysis (Figure). The SDM-Q-9 at the initiation of dialysis in HD patients was positively associated with physical function, social function and role limitations caused by physical or emotional problems at the time of survey, and multiple regression analysis showed a significant association with role/social component summary (P=0.015).

Conclusions: This study has demonstrated that the utilization of SDM process on pre-dialysis patients is significantly associated with appropriate modality selection and better QOL after initiation of dialysis.

Funding: Private Foundation Support

Figure. The association between selection of dialysis modality and SDM-Q-9 score



	HD (w/o explanation about PD)	HD (with explanation about PD)	PD
SDM-Q-9 score median [IQR[	23.3 [15.6 – 37.8]	77.8 [28.9 – 93.3]	95.6 [91.1 – 100]

PUB142

Corynebacterium: Too Sticky to Treat Through Peritonitis?

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Introduction: Corynebacterium is an uncommon cause of peritonitis in peritoneal dialysis (PD) with a prevalence of 1.5%. It reportedly responds to antibiotics alone in 60-80% of cases, with a 15% rate of catheter removal (1). We report a case of recurrent Corynebacterium peritonitis ultimately requiring PD catheter removal and transition to hemodialysis.

Case Description: 41M with ESRD on PD developed severe abdominal pain and mild fever. PD catheter exit site and tunnel showed no evidence of infection. WBC was 11,000/uL and PD fluid cell count was 2500 PMN/uL. He was given 2 weeks of IP vancomycin and PD fluid culture was negative. Abdominal pain improved for 6 weeks. Routine post-peritonitis PD fluid WBC count was 143/uL and culture was positive for Corynebacterium species. He was treated with vancomycin for 4 weeks with adequate troughs, but his abdominal pain persisted. PD fluid WBC count was 478 PMN/uL and culture again grew Corynebacterium species. IP vancomycin was restarted but he developed worsening abdominal pain. WBC count rose to 12,300/uL and PD fluid WBC count was 665 PMN/uL. His PD catheter was removed and he began hemodialysis. He completed a 2-week course of IV vancomycin and was transplanted 4 months later.

Discussion: The cure rate of Corynebacterium peritonitis with antibiotics alone was more common compared with S. aureus, Pseudomonas and other gram negatives (2). However, other data suggests that catheter removal may be required more frequently. C amycolatum causes relapsing and refractory peritonitis in children (3), notoriously refractory to antibiotic therapy. Repeat episodes are common even after prolonged quiescence, likely due to biofilm formation, rather than antibiotic resistance. Corynebacterium causes infective endocarditis, mainly in prosthetic valves (4). Patients with C. jeikeium IE more frequently required valve replacement, again suggesting biofilm formation. The rate of biofilm formation in Corynebacterium bacteremia was 46-62% (5). Another study (6) showed the capacity of C.striatum to adhere to abiotic surfaces. Biofilms facilitate pathogen adhesion to foreign surfaces, impeding successful antibiotic therapy. Given the propensity of Corynebacterium species to form a biofilm, treatment may require PD catheter removal at a higher rate than previously recognized.

PUB143

Incidence and Risk Factors for Major Adverse Cardiovascular Events in Peritoneal Dialysis

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Background: The high prevalence of cardiovascular disease(CVD) in peritoneal dialysis(PD) is due to traditional cardiovascular risk factors(CVRF), nontraditional factors and dialysis itself. The aim of our study was to assess the incidence of major adverse cardiovascular events(MACE) in PD patients and evaluate risk factors for its occurrence.

Methods: We retrospectively studied PD patients in our unit between January 1st 2015 and April 30th 2022, with a minimum 3-years PD vintage, excluding patients with previous CVD. Data on CVRF, dialysis efficiency, bone mineral disease and PD-related infections was collected. MACE was defined as acute myocardial infarction(AMI), congestive heart failure(CHF), stroke and peripheral arterial disease(PAD).

Results: Of the 43 patients studied, 53.5% were male with a mean age of 56.4±11.8 years. About 98% were hypertensive, 21% diabetic, 19% obese and 54% had dyslipidemia. Twenty-one (48.8%) patients had a MACE after PD initiation. Sex, age, PD vintage and traditional CVRF were similar between patients with and without MACE. The overall incidence rate of MACE was 10.7 events per 100 person-years. Higher calcium level (p=0.028), need of phosphate binders (p=0.046), lower renal Kt/V_{urea} (p=0.034), renal and total creatinine clearance (p=0.038 and p=0.015) were associated with MACE. In logistic regression, higher calcium was an independent predictor of MACE (OR 4.510, CI 95%:1.048-19.415). Nine (20.9%) patients had an AMI with an incidence of 4.6 events per 100 person-years. Cumulative number of peritonitis was an independent predictor of AMI (OR 4.918, CI 95%:1.093-22.132). Eighteen (41.9%) patients developed CHF with an incidence of 9.2 events per 100 person-years. Higher calcium (OR 169.440, CI 95%:2.440-11765.297) and use of sevelamer (OR 54.130, CI 95%:1.272-2302.893) were independent predictors of CHF. Four (9.3%) patients developed PAD and one had

a stroke, with an incidence of 2.04 and 0.51 events per 100 person-years, respectively. There were no predictors for PAD or stroke.

Conclusions: Cardiovascular events rates were high in our PD cohort. Hypercalcemia and hyperphosphatemia, associated with vascular and valvular calcification, were risk factors for MACE and CHF. PD-related peritonitis was a predictor of AMI in our population, in line with previous studies.

PUB144

Partnering for Success: Exploring the Relationship Between Task Distribution and Adherence to Home Hemodialysis (HHD)

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Background: Despite several benefits of the more physiologic nature of frequent HHD when compared to in-center hemodialysis, patient and/or care-partner burnout and attrition remains high in HHD with 25 to 40% patients dropping out within the first year (1). Little is known about the degree of patient involvement with specific HHD-related tasks and adherence to therapy. This study aims to assess distribution of HHD-related task burden among patients and care-partners and whether this correlates with adherence to HHD.

Methods: All patients and their care-partners currently enrolled in a single center HHD program were surveyed using PATH-D (2), an instrument that lists 20 HHD related tasks and asks who performs them. We evaluated association between the proportion of tasks a patient reported self-performing with their age, sex, duration on HHD, depression score using patient health questionnaire-9 (PHQ-9) and the number of missed treatments per month.

Results: All 18 patients currently active in the HHD program were surveyed. 9 (50%) patients were female, mean age was 57.8 (range 30-79) and 17 patients did HHD with their spouses. Mean duration on HHD was 552 days (range 83-2058). 12 (66.7%) patients had no missed treatments while 5 had missed a mean of 4 (range 1.5-8) treatments per month. PHQ-9 scores were low (mean 1.3; range 0-3). The proportion of 20 PATH-D HHD related tasks that patients reported self-performing ranged from 0%-90% (mean 32.1%). 43% patients self-cannulated their arteriovenous fistulas. No association was found between proportion of self-performed tasks and demographic characteristics or PHQ-9 scores.

Conclusions: Whether there is an association regarding different patient and care partner task distribution, the type of task and adherence to HHD remains unclear. Even though our ongoing study and early data shows high adherence with nearly 70% patients having no missed treatments within the past three months as well as low depression scores, we observed significant variation in self-performed tasks. Understanding how HHD task distribution impacts adherence to therapy over time can provide a frontier of opportunity for patient empowerment, consideration for retraining to improve ability to self-care, and thereby reduce attrition and burnout.

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PUB145

Dialysis-Associated Peritonitis due to Serratia marcescens: A Case Report

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Introduction: Serratia marcescens (SM) is a Gram-negative, opportunistic, highly virulent bacterium and a rare pathogen that causes peritonitis Case reports, a Canadian case series, and a systematic review in Hong Kong suggested that peritonitis in PD due to SM was associated with high rates of treatment failure and catheter removal We present a clinical case of peritonitis due to SM that led to catheter loss.

Case Description: A 34-year-old man with a history of end-stage renal disease secondary to diabetes on continuous ambulatory PD for 5 years with a history of 2 previous cases of peritonitis with adequate resolution of these and with peritoneal fluid (PF) cultures without microorganism development Admitted for severe abdominal pain, nausea, vomiting and diarrhea in addition to cloudy PF cytology was requested where leukocytes were "uncountable", being 100% polymorphonuclear (PNL), empirically started intravenous ceftriaxone and vancomycin; PF culture was collected where SM was isolated, treatment was continued and cytology was taken again on the third day of treatment finding leukocytes of 1130, being 90% PNL, thinking in adequate response antibiotics were continued for 7 days, however, he presented fever, cytology reporting 3456 leukocytes with 90% of PNL and new culture with isolation of SM again, showing sensitivity to meropenem by meropenem, showing sensitivity to meropenem by meropenem, and the patient was treated with a new culture, She showed sensitivity to meropenem, so it was decided to change the antibiotic, which was effective for 3 days until she presented clinical deterioration and a referral to nephrology was requested, who decided to change to HD and remove the catheter, during the removal she presented purulent material and multiple adhesions, so it was decided that the cavity was not useful and definitive HD; She completed 14 days of treatment with meropenem, presenting improvement and it was decided to discharge her.

Discussion: Peritonitis due to SM is a serious complication, so its surveillance should be intensified and appropriate treatment compatible with the antibiogram should be offered. Low socioeconomic status, poor home environment and hygienic conditions increase the rates of peritonitis due to this pathogen, so more frequent and careful patient and family education in such conditions may improve patient care.

PUB146

Reduced Rate of Peritonitis in Incremental Peritoneal Dialysis (PD) vs. Standard-Dose PD

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Background: incremental PD associates with a reduced rates of infection as compared to standard dose PD. may be related to less manipulation of the PD system but there can be other causes like a better local peritoneal defense resulting from less exchanges. incremental PD is an aything different from standard dose PD:(4 exchanges manual, 2 6lts bags plus a daytime one for APD). **Objective:** to evaluate our results in a retrospective cohort of adult chronic PD patients in a single center analyzing results of peritonitis in both groups: incremental and standard dose PD.

Methods: Patients: 246 adults patients, 53% men, 71.1 % on manual PD and 34.5% incremental. **Study period:** December 1994 to December 2022. Inclusion criteria:chronic PD (3 months) in stable patients with a disconnect double bag system. Peritonitis is according ISPD guide 2016 and causative agents recovered as described previously# (standard culture plaques until 2010 followed by the BACTEC technique plus the Malditof analysis.

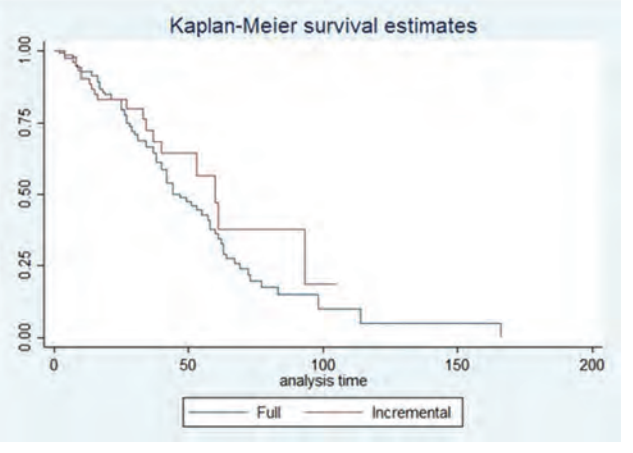
Results: See attached tables.

Conclusions: Incremental PD associates to a reduced ner of peritonitis episodes as compared to standard dose PD. Time of followup is significantly lower in Increnmental PD. Kaplan meier (time adjusted) although marking a positive tendency couldn't show a significant reduction in time to the first infection episode for incremental PD. Further prospective studies are needed to answer properly this important question.

Patients	all (n: 246)	Incremental (n: 85)	Full (n: 161)	P
Men Women	136 (55.3%) 110 (44.7%)	49 (57.6) 36 (42.4)	87 (54) 74 (46)	0.588
PD type: Manual Cycler Other: (IPD)	175 (71.1) 68 (27.6) 3 (1.2)	82 (94.5) 0 3 (3.5)	93 (57.8) 68 (42.2) 0	<0.001
Peritonitis (at least 1 epi)	96 (39)	20 (23.5)	76 (47.2)	<0.001
Time follow up months	22.5 (10-41)	17 (9-33)	27 (13-44)	0.003

RR for peritonitis incremental = 0.48 (IC 95%= 0.31-0.74; p=<0.001), compared with PD full dose

Patients	all (n: 246)	Incremental (n: 85)	Full (n: 161)	P
Men	136 (55.3%)	49 (57.6)	87 (54)	0.588
Women	110 (44.7%)	36 (42.4)	74 (46)	
PD type:				<0.001
Manual	175 (71.1)	82 (94.5)	93 (57.8)	
Cycler	68 (27.6)	0	68 (42.2)	
Other:(IPD)	3 (1.2)	3 (3.5)	0	
Peritonitis (at least 1 epi)	96 (39)	20 (23.5)	76 (47.2)	<0.001
Time follow up months	22.5 (10-41)	17 (9-33)	27 (13-44)	0.003



PUB147

Peritoneal Dialysis After Gadolinium-Based Contrast Agent (GBCA) Exposure: A Case Study

Ida A. Ayensu, Kara Kaplan, Khaled Boubes. *The Ohio State University, Columbus, OH.*

Introduction: Nephrogenic systemic fibrosis (NSF) is a disorder characterized by thickening and hardening of the skin overlaying extremities and trunk as well as the expansion of fibrosis of the dermis associated with CD34+ fibrocytes. This rare disorder is only seen in patients with advanced CKD. The most common risk factor of NSF is gadolinium-based contrast agent, (GBCAs). These finding were initially reported in early 2000s when unstable linear GBCAs were given to patients ESKD patients that were dialysis dependent or patients with AKI. Current guidelines recommend dialysis promptly after GBCAs clearance. There is insufficient data on gadolinium clearance with PD. We know that 73-78%, 92-95% and 98-99% of free gadolinium is removed after 1, 2, and

3 HD treatments, respectively. Very few case reports describe limited GBCA clearance with PD. There are no studies on hospitalized patients with high intensity CAPD for gadolinium clearance to guide appropriate therapy, as HD after gadolinium exposure may not be warranted and, thus, could prevent further unnecessary procedures.

Case Description: We had a 49 yo F, on PD for 5 years presented with SDH who had MRI with gadoterate meglumine. She had no other dialysis access other than PD catheter. We prescribed increase frequency of PD exchanges from 4 to 7 exchanges in 24 hours for duration of 48 hours after exposure to GBCA. Serum Gadolinium levels were measured at 0 hours, 24 hours, and 48 hours after exposure. There was a 58% reduction in serum gadolinium levels after 48 hrs. However, we noted that for a variety of reasons, the patient only received 11 (instead of 14) exchanges in 48 hours. Gadolinium level (ng/ml) was [78159] at 0 hrs, [54040] at 24 hrs and [32460] at 48 hrs.

Discussion: The continuous ambulatory PD (CAPD) in this case was less efficient than HD in clearing GBCA. However, this was with a reasonably regular prescription and one would argue that if patient was able to receive 16 exchanges in 48 hours, there is very high probability they could get close to 90% clearance. One study used Automated Peritoneal dialysis (APD) with 10-15 exchanges per day for 24 and 48 hours showed reduction of gadolinium by 90% at 48 hours (Murashima et al). Treatment of patients on PD getting MRI with gadolinium should be tailored to maximize the clearance of GBCA. Further studies on PD and GBCA clearance are needed to establish a better understanding of GBCA clearance.

PUB148

Impact of Dialysis Modality Selection Clinic

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Background: President Trump's Executive Order on Advancing American Kidney Health has led to ESRD Treatment Choices (ETC) Model taking effect on January 1, 2021, to promote greater use of home dialysis and kidney transplants for Medicare beneficiaries with ESRD in order to preserve or enhance their quality of care while reducing Medicare expenditures. ETC model and other related models have put tremendous pressure to grow home dialysis programs and Dallas Nephrology Associates (DNA) started 'CKD Modality Selection Clinic' in 2022 to address this. DNA is a single specialty nephrology practice having 110 nephrologists and 15 nephrology offices in Dallas Fort Worth area.

Methods: DNA's CKD Modality Selection Clinic involves a 40 minute visit offered to patients in late stage CKD 4 and CKD 5 before they commit to a dialysis modality. During the initial 20 minutes, they were given a dialysis modality education booklet and were shown a video on dialysis modality education. Subsequent 20 minutes were dedicated to a physician visit involving history taking, focused examination and discussion of certain key elements shown in the video using the demo manequins with PD catheters, demo PD cyclers and demo NxStage machines. An assessment was made regarding dialysis modality selection both by the nephrologist and the patient. Patients were asked to choose a dialysis modality before and after the clinic. Patients were followed by the primary nephrologist and the final ESRD treatment selection was noted when they went on dialysis.

Results: The clinic was started in May 2022 and as of April 2023, clinic has been started in 7 offices. 209 patients have attended this clinic so far. In the pre-clinic questionnaire, 47.8% were uncertain about their dialysis modality selection and post-clinic questionnaire showed that 15.8% were uncertain. As of May 2023, among those who attended the modality selection clinic, 12 patients started home dialysis and 3 started in center hemodialysis.

Conclusions: Modality selection helps people make decision about dialysis modality selection. Educated patients chose home dialysis more often than those who do not take advantage of education.

PUB149

The Technique Failure Frustrating the Road of Intermittent Dialysis to Continuous Ambulatory Peritoneal Dialysis

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Background: When starting peritoneal dialysis in patients with end-stage chronic kidney disease, the biggest challenge is the transition from a modality of intermittent peritoneal dialysis to continuous ambulatory peritoneal dialysis (CAPD).

Methods: A cohort study of patients who started PD in an intermittent modality from September 2022 to May 2023 in the Hospital General de México. Those patients were followed until they met one of the outcomes: starting ambulatory PD, migrating to hemodialysis, or death. We defined technique failure as any outcome that included suspending peritoneal dialysis (migrating to hemodialysis and death).

Results: We included 62 patients, 61% (38) were men, the average age was 49±14 years, 74% (46) had a basic educational level and only 21% (13) had a job. The most frequent comorbidities were hypertension in 92% (57) and diabetes in 58% (36). Urgent dialysis start was present in 68% (42) patients and 85% (49) are economically dependent on their families. Technique failure was presented in 42% (26) of the patients. We found an association between technique failure and unemployment (OR 5.2, 95%IC 1.05-26.3, p=0.04), and with presenting at least one event of peritonitis (OR 15.3, 95%IC 3.8-61.4, p=0.0001). Furthermore, patients with technique failure had a 58% reduction in residual urine output compared with 33% in those continuing dialysis.

Conclusions: There have been a few descriptions about the process faced by patients to achieve an ambulatory PD, especially those who do not have health insurance. In this cohort, we observed that more than 40% of the patients had a failure of the technique before being able to dialyze at home, reflecting a complex adaptation process in patients with limited family support. In addition, it is necessary to facility access to replacement therapy that really improves the quality of life and long-term prognosis.

PUB150

A Patient with a History of Renal Transplant and a Digit Infection was Found to Have Vascular Insufficiency: A Detailed History and Physical Exam Saved the Patient's Limb

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Introduction: Steal syndrome is an ischemic phenomenon that can occur as a complication of creating vascular access for hemodialysis. It occurs when blood flow is diverted from the venous side distal to the arterio-venous fistula, resulting in reduced blood supply to the distal tissues.

Case Description: A middle-aged patient who had received a renal transplant 13 years previously was found to have a digital ulcer and was admitted for amputation. After a thorough review and physical examination, the patient was discovered to have an arteriovenous fistula in the same limb; furthermore, there was evidence of steal syndrome. Instead of amputation, the arteriovenous fistula was closed, and the patient recovered spontaneously as blood supply improved.

Discussion: The literature describes some similar cases of ischemic steal syndrome. Our case is unique because the patient presented with ischemic steal syndrome many years after the arteriovenous fistula was no longer in use. In the past, practitioners often asked patients on dialysis about the method of access during the initial examination and immediately considered possible complications. However, when a patient presents with problems that are not located near the access point 13 years after a transplant, this issue can be missed. Furthermore, in our case, the area was covered as the patient had dressed the wound, and the patient did not mention her surgical history during the initial examination. In such cases, the treating practitioner should request consultations from colleagues, take a detailed patient history and ensure that a specialised team conducts a thorough physical examination. Multi-disciplinary team meetings are a cornerstone of patient care. In such meetings, teams cooperate to improve patient care, and every team member works to optimise patient management under the guidance of the leading physician (primary team). Official meetings should be held in all institutions, and meetings can also be called by the lead by the Primary attending Physician/Surgeon. A thorough history and clinical examination is necessary; today, these elements are often under-estimated due to the availability of advanced technology and complex laboratory and radiological investigations.

PUB151

Changes in Catheter Dependence at In-Center Hemodialysis Initiation and During the First Year After Initiation

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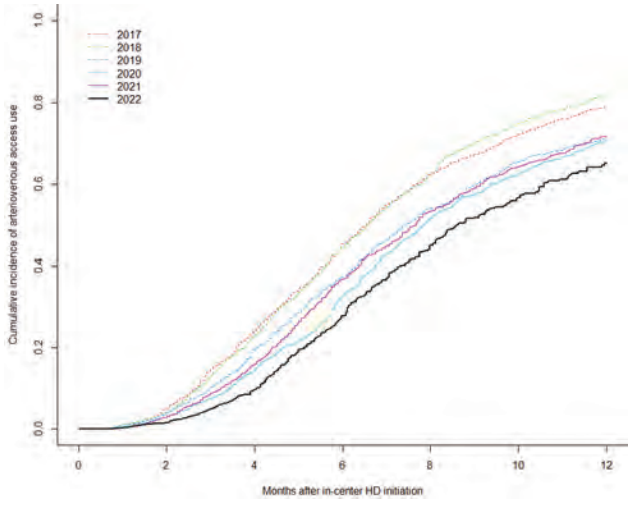
Background: The majority of in-center hemodialysis (HD) patients initiate treatment with a central venous catheter (CVC), despite the association of CVC use with poor outcomes, including bloodstream infection. During the coronavirus disease 2019 (COVID-19) pandemic, the prevalence of CVC dependence among HD patients in the US has increased. We investigated whether this trend reflects underlying changes in CVC dependence at initiation and the incidence of conversion from a CVC to an arteriovenous (AV) access.

Methods: We analyzed the electronic health records of Satellite Healthcare, a mid-sized, not-for-profit dialysis provider. From 2012 to 2022, we identified incident end stage kidney disease patients who initiated in-center HD. For each patient, we recorded age, sex, and state of initial dialysis facility. We used segmented linear regression and logistic regression to estimate trends in the prevalence of CVC dependence at first outpatient HD treatment. In the subgroup of patients who were CVC-dependent, we used Fine-Gray regression to estimate trends in the cumulative incidence of conversion to an AV access for ≥6 consecutive HD treatments.

Results: The cohort included 14,764 patients. The prevalence of CVC dependence at HD initiation decreased between 2012 and 2017, reaching a nadir of 79.0%, but increased thereafter, reaching a high of 85.4% in 2022 (adjusted odds ratio, relative to 2019, 1.44; 95% CI, 1.18-1.74). As displayed, the cumulative incidence of conversion from a CVC to an AV access fell initially in 2019, stabilized in 2020 and 2021, and fell again in 2022 (adjusted hazard ratio, relative to 2019, 0.69; 95% CI, 0.61-0.77).

Conclusions: Increasing prevalence of CVC dependence among in-center HD patients has its roots in worsening trends in CVC dependence at HD initiation and during the first year after initiation. These trends emerged before the pandemic, but strengthened in 2022.



PUB152

Nontunneled Hemodialysis Catheter Survival in Uninsured Population in Yucatan, Mexico

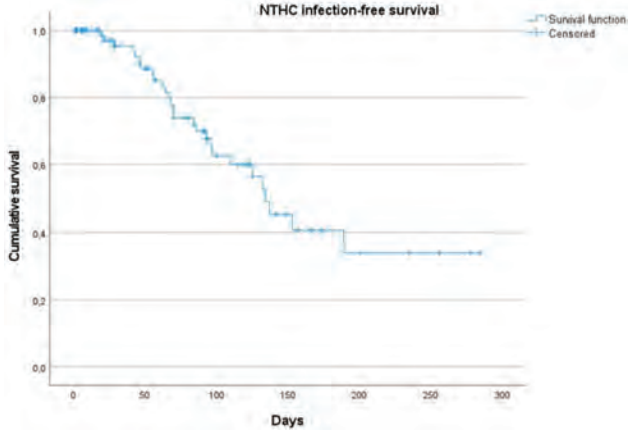
Julio I. Pech Cruz, Leticia M. Tapia Silva. *Hospital General Agustin O'Horan, Merida, Mexico.*

Background: In Mexico, the access to renal replacement therapy (RRT) is unequal, especially for the uninsured. Yucatan has a high prevalence of obesity, diabetes, hypertension, and nephrolithiasis which implies a high burden of chronic kidney disease (CKD). The Hospital Agustin O'Horán receives uninsured patients with CKD from southeast Mexico. In patients who are not candidates for peritoneal dialysis but require RRT with hemodialysis (HD), a non-tunneled hemodialysis catheter (NTHC) is placed. NTHC has a higher rate of infectious complications compared to tunneled hemodialysis catheter (THC) or arteriovenous fistulas (AVF). Our objective was to determine the infection-free survival of NTHC in a low resource setting.

Methods: This is an observational study in patients ≥ 18 years with CKD, who started HD with NTHC in our center from January to December 2022 and evaluated the survival rate of the NTHC related to catheter related bloodstream infections (CRBSI).

Results: 93 NTHC were placed, 63.4% in women, mean age was 49.5 years. Most of the NTHC were non-ultrasound guided (74.2%) and the internal jugular vein was the main insertion site (87.1%). The median survival time until the development of CRBSI was 134 days (95% CI 105.79-162.20). There were no significant differences in catheter survival with respect to sex, age, and insertion site. Compared to the first 30 days after catheter placement, the relative risk for CRBSI was 7.00 (95% CI 2.14-22.87, p= 0.001) within 31-60 days and 7.63 (95% CI 2.36-24.65, p= 0.0007) within 61-90 days.

Conclusions: Long-term catheterization with NTHC is a reality in our center despite the evidence that it poses a high risk for CRBSI. Unfortunately, the lack of a vascular access team for the creation of AVF and placement of THC prevents us to use a more permanent access with less complications. In that sense, we need to engage our policymakers in order to guarantee better vascular access care, especially for the uninsured population.



NTHC infection-free survival

PUB153

Mortality After Arterio-Venous Shunt Creation

Richard E. Wing, Nikhila S. Rao, Nilesh S. Rao, Matthew Wang, Eliane S. Grace, Thu H. Le. *University of Rochester Medical Center, Rochester, NY.*

Background: Arterio-venous shunt (AVS) is the preferred access for most chronic hemodialysis (HD) patients, although placement of AVS induces hemodynamic changes that may be adverse. It is uncertain if echocardiographic findings prior to AVS placement may predict outcomes.

Methods: We conducted a survival analysis on chronic HD patients who were followed by URMC nephrology faculty. We identified subjects who underwent an interpretable ambulatory echocardiogram (echo) <90 days prior to successful AVS creation. Subject characteristics were obtained from the EMR. Echos were re-read for measures of right heart function. Right Ventricular Dysfunction (RVD) is defined as abnormality in any of the following: Myocardial Systolic Excursion Velocity < 9.5 cm/s, Tricuspid annular plane systolic excursion < 17 mm, Right Ventricular Fractional Area Change < 35%, or Right Ventricular Free Wall Strain > -20%. Missing data were imputed as normal. Censoring occurred at transplantation or on 12/31/2022.

Results: Between 1/1/2010 and 12/31/2022, 1319 advanced CKD or ESRD patients under our care underwent at least one echo and/or underwent AVS construction. Thus far, we have identified 38 subjects who received maintenance hemodialysis with an interpretable ambulatory echo <90 days prior to successful AVS creation. Mean follow-up was 1872 ± 1112 days. We tested subject and echo characteristics using the log-rank procedure for association with survival. A multivariate model was constructed using a cox proportional hazards model (table).

Conclusions: In addition to age, abnormalities in right heart function may predict mortality in patients receiving HD who undergo AVS creation. Most subjects in this preliminary group were selected for a related study requiring a second echocardiogram, thus potentially biasing results. Further plans include identifying and adding all eligible subjects from our sampling frame to the cohort.

Table 1	Selected Subject Characteristics	
Selected Parameter	**Count (of 38)**	**Log-Rank p value**
Age over 65 at ESRD	10	0.0546
Male Sex	28	0.1045
Black Race	16	0.0654
Hispanic Ethnicity	6	0.2274
BMI > 30	16	
History of Coronary Artery Disease	9	0.1367
History of Peripheral Artery Disease	9	0.1299
History of Congestive Heart Failure	15	0.2565
History of Lung Disease	11	0.0462
E.F. <50% on Echocardiogram	8	0.2633
Grade 2 or 3 Diastolic Dysfunction on Echocardiogram	17	0.2799
RVD	16	0.1158
Received a kidney Transplant	11	
Died	15	
Multivariate Model Parameter	**Hazard Ratio**	**p**
Age over 65 at ESRD	3.3	0.0322
RVD	2.7	0.0665

PUB154

Arteriovenous Fistula Creation Affects the Von Willebrand Factor

Suzanne Laboyrie,[1] Laura M. van der Linden,[1] Roel Bijkerk,[1] Zhuotao Xiao,[1] Laisel Martinez,[2] Roberto I. Vazquez-Padron,[2] Joris I. Rotmans.[1] [1]*Leids Universitair Medisch Centrum, Leiden, Netherlands;* [2]*University of Miami School of Medicine, Miami, FL.*

Background: Von Willebrand Factor (vWF) is a glycoprotein secreted by endothelial cells as high molecular weight multimers (HMWM). VWF mediates hemostasis by platelet binding and factor VIII stabilization. When HMWMs are cleaved into low molecular weight multimers (LMWMs), the capacity to bind platelets is lost. Cleavage of HMWMs is dependent on shear stress and blood flow patterns, such as laminar to turbulent flow transition. Loss of HMWMs can result in increased bleeding tendencies. An arteriovenous fistula (AVF) is the gold standard for hemodialysis access, whereby there is a transition from laminar into turbulent flow at the anastomosis between the artery and vein. In this study, we investigated the effect of AVF flow on the composition of vWF multimers.

Methods: Patient matched plasma samples of two-stage brachiobasilic AVF surgeries were obtained from the Jackson Memorial Hospital and the University of Miami Hospital, according to the hospitals regulatory requirements. ELISAs were performed to determine total plasma vWF concentrations and vWF's collagen-binding capacity. VWF multimers were separated based on molecular weight in a multimer assay and quantified with

densitometric analysis. To eliminate the effect of comorbidities and medication and determine the direct effect of AVF flow on vWF, we used an *in vitro* AVF flow-model.

Results: Plasma samples from patients with end stage kidney failure showed a higher vWF concentration compared to control pooled plasma, and levels remained the same after AVF surgery. No significant reduction in the HMWM over total vWF ratio was observed in the total patient population after AVF creation. However, AVF surgery did result in a 26% reduced capability to bind collagen (p= 0.038). Preliminary data from our *in vitro* AVF flow model indicates a reduction in HMWMs with AVF-mimicking turbulent flow compared to laminar flow.

Conclusions: Decreased collagen binding capacity after AVF surgery indicates a reduction in vWF adherence to the vessel wall. Ongoing experiments in our in vitro AVF flow system will reveal if there is a causal relation between turbulent AVF flow patterns and the reduction in HMWM.

PUB155

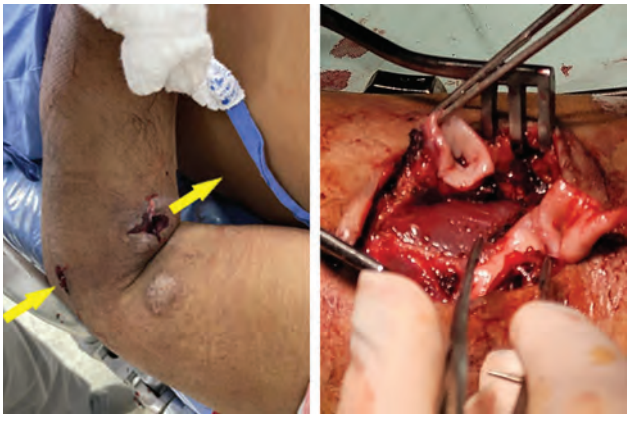
Gunshot Wound in an Arteriovenous Fistula in Hemodialysis Patient

Roberto Ramirez Marmolejo,[1,2] Angélica M. Delgado,[3] Sofia Ramirez Isaza,[4] Carlos Mejia.[2,1] Prevrenal Group. *[1]Universidad del Valle, Cali, Colombia; [2]Fundacion Prevrenal, Cali, Colombia; [3]Hospital Mario Correa Rengifo, Cali, Colombia; [4]Pontificia Universidad Javeriana Facultad de Medicina, Cali, Colombia.*

Introduction: The violence in Cali Colombia has put the medical team in interesting and difficult challenges. The city is in position #24 of the most dangerous in the world. A patient is presented who received an impact from a firearm projectile precisely in his left antebrachial arteriovenous fistula, he was immediately taken to vascular surgery. No articles were found in the literature that presented similar wounds.

Case Description: A 23-year-old male patient, on hemodialysis, was admitted to the emergency, after receiving the impact of a firearm projectile precisely in his left antebrachial arteriovenous fistula. He lost a lot of blood, which was controlled with a tourniquet. He was immediately taken to surgery, finding an aneurysmal degeneration and multiple endothelial lesions proximal to the anastomosis. consequence of the projectile. Image 1. A spindle incision is made over aneurysmal degeneration, Image 2. The fistula is closed and medium-caliber vessels are repaired using the Carrel technique.

Discussion: No articles were found that presented wounds in an arteriovenous fisutula for hemodialysis due to a firearm projectile and only one was found where a self-inflicted stab wound by the patient himself was described as a suicide attempt. the blood flow from an arteriovenous fistula for hemodialysis is greater than 600ml/min, any injury is potentially lethal if not handled properly.



PUB156

Epidemiology of Hemodialysis Vascular Catheter-Related Blood Stream Infections: A Clinical Audit

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Background: Central venous catheters (CVC) are commonly used as a temporary access method for hemodialysis among patients with End Stage Renal Disease (ESRD). Catheter related blood stream infections (CRBSI) are a frequent complication of CVCs. Acceptable incidence rate for CRBSI is <1.5/1000 catheter days according to KDOQI clinical practice guideline for vascular access :2019 update. Therefore, this clinical audit aimed to assess the incidence of CRBSI and associated risk factors.

Methods: Records of ESRD patients undergoing hemodialysis via a CVC at a tertiary care hemodialysis center in Sri Lanka from April 2022 to March 2023 were considered for this audit. Data regarding demographics, medical history, hemodialysis access type (tunneled or non-tunneled central venous catheter), access site (internal jugular or femoral vein), duration of CVC, co-morbidities, development of CRBSI and responsible microorganisms were collected. Age, gender, CVC type, access site, CVC duration and presence of Diabetes mellitus were analyzed to determine the association with CRBSIs.

Results: A total of 76 ESRD patients were analyzed. The mean age was 54.7 (±11.5) years. Majority were male (63.2%). Common co-morbidities were Diabetes mellitus (72.4%) and hypertension (73.8%). In most patients, (81.6%) diagnosis of chronic kidney disease was made after ESRD developed. No previous nephrology clinic follow up, before initiation of hemodialysis, was observed in 44 (57.9%) patients. Median catheter duration of non-tunneled CVCs (NTCVC) (n=49) was 16 days and tunneled CVCs (TCVC) (n=71) was 144 days. NTCVCs had a CRBSI incidence rate of 7.07/1000 catheter days while TCVCs had a considerably low-rate of 0.58/1000 catheter days. Causative microorganisms were *Staphylococcus aureus* (31.6%) including Methycillin resistant variant, Coagulase negative *Staphylococcus* (23.07%) and *Klebsiella pneumoniae* (15.3%). Age, gender, Diabetes mellitus, site of CVC and duration of CVC showed no significant associations with CRBSIs.

Conclusions: Tunneled CVCs CRBSI incidence is within the acceptable range despite having longer catheter durations, while NTCVCs show a higher CRBSI incidence than the target value. Our analysis did not discover any significant associations with CRBSI incidence. Therefore, we recommend changing access from NTCVC to TCVC or arteriovenous fistula at earliest convenience to prevent CRBSI.

PUB157

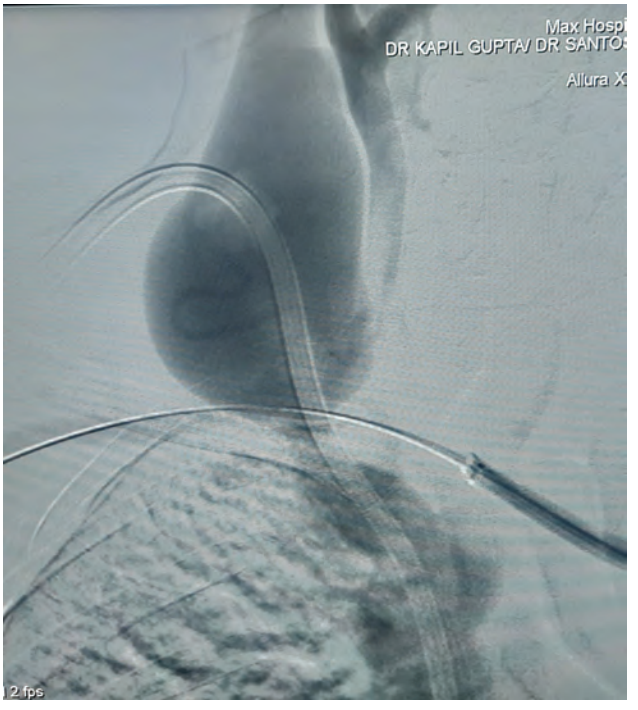
A Rare Complication of Traumatic Arteriovenous (AV) Fistula Creation Between Right Subclavian Artery (SCA) and Right Internal Jugular Vein (IJV) After Right IJV Permcath Insertion

Anil K. Jhajhria, Lovy Gaur, Manisha Dassi, Manoj Singhal. *Max Super Speciality Hospital Vaishali, Ghaziabad, India.*

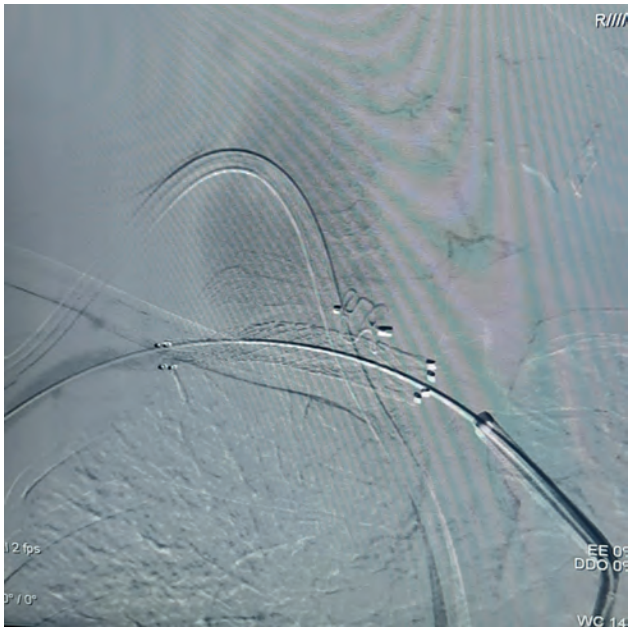
Introduction: Interventional Nephrology (IN) is emerging as a subspecialty which has a lot of potential to grow.

Case Description: 59 years female, case of chronic kidney disease stage 5 on maintainence haemodialysis (MHD) via right IJV permcath got admitted with fluid overload. On examination, a continous thrill was felt in the neck at the site of permcath insertion. After stabilisation, she was taken for peripheral angiography, angioshot from right femoral artery (RFA) showed large tract leading to AV fistula between right SCA & right IJV. In the same sitting, vascular plug through RFA long sheath passed & deployed in the tract. Covered stent deployed at the origin of right SCA & ballon expansion done. Two coils deployment done but due to high flow through AV fistula, coils were dislodged into pulmonary artery which were later snared out. Post procedure check angiogram showed drastically reduced flow through AV fistula & clinically thrill disappeared.

Discussion: This case showed successful treatment of traumatic AV fistula with angioplasty, highlighting the importance of IN in management of vascular access associated complications.



AV fistula



Post Angioplasty

PUB158

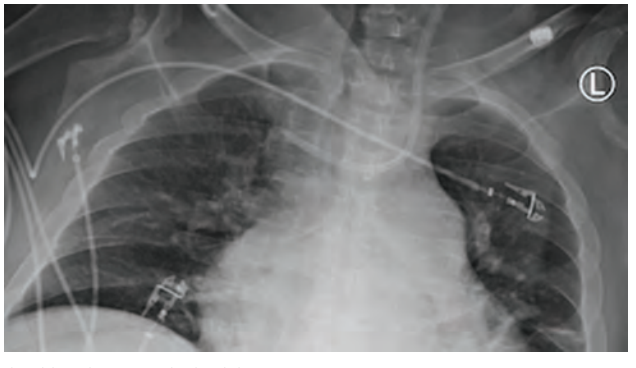
Unconventional Ultrasound (US)-Guided CVC Placement

Madeline S. Chung, Marie Fouad, Khaled Boubes. *The Ohio State University Wexner Medical Center, Columbus, OH.*

Introduction: Percutaneous canulation of central veins is used for both short and long-term vascular access (VA). VA is an area of difficulty among KRT patients who have had multiple procedures involving the central veins. These patients are prone to vascular calcification, stenosis and thrombosis related to their VA, complicating further VA planning and procedures. This is especially true in emergencies when expedient bedside placement of dialysis access is necessary, but difficult using conventional methods.

Case Description: 60 yo man with ESKD on HD via LUE AVF who presented with worsening dyspnea admitted for CHF and pulmonary hypertension management complicated by septic shock requiring initiation of CRRT via catheter. The left internal jugular vein was the only access option. Confirmatory CXR showed the catheter with the tip overlying the right brachiocephalic vein (BCV) near the superior vena cava (SVC) confluence. Two further attempts at placement in the LIJ vein resulted in similar positioning. He was unstable for transport to IR. We placed a guidewire into the malpositioned LIJ catheter and retracted it. The ultrasound (US) probe was placed at the base of the right neck to visualize the right subclavian arch (opposite the insertion site) and guidewire, which was retracted out of the right BCV. The wire was advanced without visualiztion in the right subclavian arch, leaving the SVC as the default location, since its location deep in the thoracic cavity, precludes visualization of the SVC by US.

Discussion: CVC can be a difficult procedure especially when approached via the LIJ vein due to its tortuous path. It is further complicated in patients with difficult anatomy. At most institutions, bedside resources for image guidance are still largely limited to US and CXR, and are generally the only option in patients too ill for transport to the radiology department where more advanced options are available. It is therefore important to utilize the bedside US to its full capacity and learn different windows to visualize VA options beyond the conventional approach.



Malpositioned LIJ CVC in the right BCV

PUB159

The Impact of the Infecting Organism on the Outcome of Tunneled Dialysis Catheter-Related Bloodstream Infections: A Single-Center Record

Petros Kalogeropoulos, Ourania Tsotsorou, Ioanna Tsoumpou, Konstantinos Gkiolas, Petros Nikolopoulos, Sophia Lionaki. *Department of Nephrology, 2nd Propaedeutic Internal Medicine, Medical School, National and Kapodistrian University of Athens, "Attikon" University Hospital, Athens, Greece.*

Background: Tunneled double-lumen catheters are increasingly used as permanent vascular access in hemodialysis patients. Catheter-related bloodstream infection (CRBSI) is a major cause of hospitalization with increased mortality and cost. The purpose is to study the effect of the pathogen on the clinical course of the hemodialysis patients with CRBSI.

Methods: Patients hospitalized in our department from 11/2021 to 12/2022 with established CRBSI were retrospectively studied. Their demographics, duration of hospitalization, microbiological data, central venous catheter management and hospital outcome were recorded.

Results: A total of 27 patients with median age (SD) 68,03 (16,93) years were treated, 12 (44.4%) were men. The following pathogens were isolated from the blood cultures: Staphylococcus aureus in 7 (25.9%) patients, coagulase-negative Staphylococcus in 10 (37%) patients, Gram-positive bacteria in 4 (14.8%) patients, Gram-negative bacteria in 3 (11.1 %) patients, candida in one (3.7%) patient, while 2 (7.4%) patients had negative cultures. Mean (SD) duration of hospitalization was 16,85 (13,15) days for all patients. Patients in whom Staphylococcus aureus and Candida were isolated had longer hospital stay than other infections with a mean (SD) 29 (18) days and 41 days respectively (p=0.014). Metastatic infections occurred in 4 (14,8%) patients, of whom 2 had endocarditis, one endocarditis and pulmonary abscess, and one endocarditis, lung abscess and brain abscess. All 4 patients isolated Staphylococcus aureus in blood culture out of a total of 7 (57,1%) patients with this pathogen (p=0.02). 3 of 7 (42,8%) patients with Staphylococcus aureus, 1 of 10 (10%) with coagulase-negative Staphylococcus, and 1 of 3 (33,3%) with Gram-negative bacteria died (p=0.385). In 26 of the 27 patients (96.3%) central venous catheter was removed.

Conclusions: The majority of patients in the present sample required central venous catheter removal. The type of pathogen seems to play an important role both in the duration of hospitalization and in the occurrence of metastatic infections.

PUB160

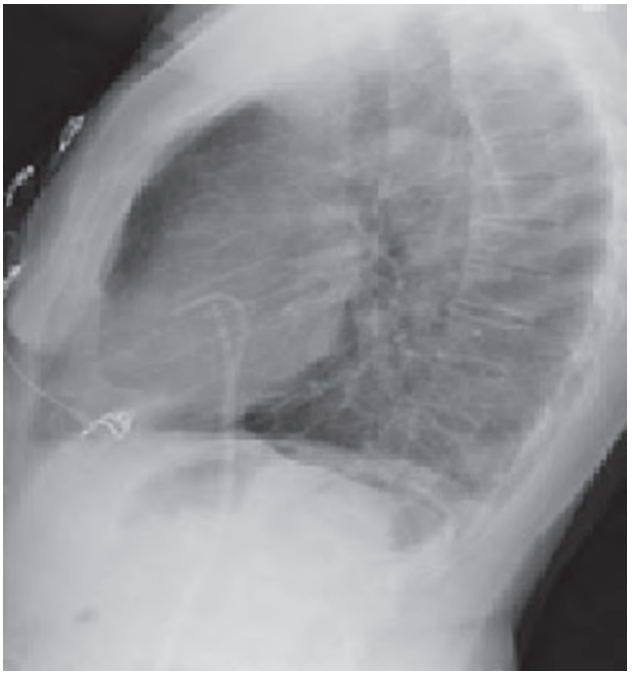
A Stormy Dialysis Catheter

Naeim G. Salah, Amit Kaushal. *University Health Network, Toronto, ON, Canada.*

Introduction: Central venous catheters (CVCs) are used to administer hemodialysis (HD) therapy. The CVC tip should be positioned in a central vein, with devices tips at the atriocaval junction (upper body CVC), and in the inferior vena cava (IVC, lower body CVC) [1]. Here we describe a case of life-threatening arrhythmia associated with CVC position.

Case Description: A 58-year-old female dialysis patient presented for cardiac testing for upcoming renal transplant. She was being dialyzed via a CVC due to failure of her arteriovenous fistula. Due to central venous stenosis, a 55cm tunneled right femoral CVC was placed in 2021. During her exercise stress echocardiogram, she developed ventricular arrhythmias 6.5 minutes into the test. The procedure was halted. She had 5 minutes of sustained ventricular tachycardia, with resolution of arrhythmias 8 minutes into recovery but was stable throughout. Coronary angiogram was negative. Chest x-ray demonstrated the CVC had a split-tip, both of which were in the right atrium. Cardiology determined the arrhythmia was related to irritation of the conduction system by a malpositioned CVC. The CVC was replaced with a new 31cm catheter resting in the IVC.

Discussion: Arrhythmias in HD patients are often attributed to ischemia, electrolyte abnormality, or systemic stresses [2]. Here, catheter position was considered the primary trigger. Though not documented, oscillation of the lumen tips during dialysis could also have precipitated intradialytic arrhythmia. While confirmation of CVC position by chest x-ray is standard for temporary upper body devices, it should be considered for any CVC where malposition could occur (e.g. small body size).



Lateral chest radiographs demonstrating deep position of CVC and split-tip catheter, respectively)

PUB161

Minimally Invasive Guidewire Exchange Technique for Tunneled Hemodialysis Catheters: Preservation of Venous Insertion Site in Chronic Hemodialysis Patients

Fernando A. Cuellar-Gonzalez,[1,2] Sebastian Consuegra-Flores,[1,2] Néstor H. Cruz Mendoza,[1] Mauricio Arvizu Hernández.[1,2] *[1]Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico; [2]Tecnologico de Monterrey - Campus Ciudad de Mexico, Ciudad de Mexico, Mexico*.

Background: Tunneled hemodialysis catheter (THC) has become an acceptable form of vascular access (VA) when an arterio-venous fistula is not feasible or available. Dysfunction of THC is associated with removal and replacement of THC. Few techniques of guidewire exchange of THC have been reported. We aim to present the experience of our center in guidewire exchange of THC, with preservation of the same venous insertion site with only one incision at the jugular site, without fluoroscopy and local anesthesia performed by interventional nephrologist.

Methods: Retrospective, single-center study conducted between Jan/2018-May/2023. Guidewire exchange of THC due to dysfunction in 15 pts on chronic HD with preservation of venous insertion site and creation of a new subcutaneous tunnel with local anesthesia without fluoroscopy. Successful exchange, complications, and catheter patency were reported at 3 months.

Results: 15 procedures were performed in same number of patients, mean age 41.2 +/- 13.6 years, 53% were female, mean duration of HD was 3.2 years; 12 (80%) have one previous VA, all THC were located in right internal jugular vein. The success rate of the procedure was 100%. At 3 months, 12 cases remained functional, two catheters had not completed three months of follow-up, one catheter was removed earlier due to infection. Only mild complications, such as bleeding requiring sutures, were reported in two cases, with no major complications recorded.

Conclusions: Our study shows that the guidewire exchange of THC, with preservation of the same venous insertion site with only one incision at the jugular site is a reliable method in patients with dysfunction of THC and with low risk of complications.

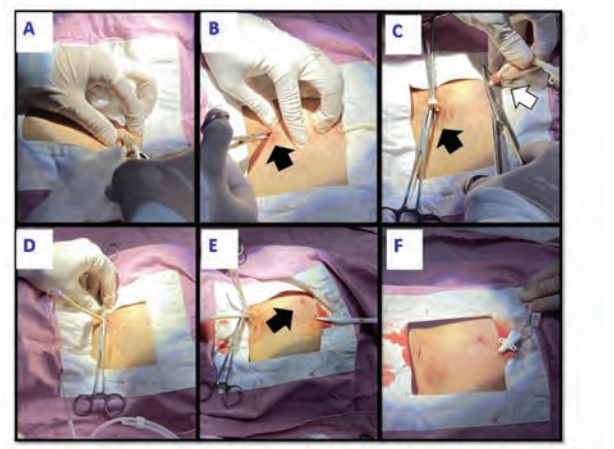


Figure 1. A) The cuff was released from the subcutaneous tissue, **with blunt disessection, without incision** B) An incision is made in the cervical region along the subcutaneous path of the catheter (arrow), and the tissue is dissected until the catheter is brought to the external surface. C) In the externalized portion, double clamping is performed proximal to the blood vessel (black arrow). A cut is then made in the region proximal to the clamping site (white arrow), and the distal portion of the catheter is removed. D) A guide is advanced through the distal end of the catheter to ensure venous access. E) A new tunnel is created laterally to the previous one (arrow).F) The procedure concludes with only one incision, which is sutured.

PUB162

Patient's Navigator for Lupus Nephritis: Pilot Evaluation

Patricia Nogueira De Sa, Faith Ryu, Mia Kim, Himanshi Verma, Michael Go, Pranav S. Kancherla, Aylin Ergin, Laura Liu, Abdallah Sassine Geara. *University of Pennsylvania, Philadelphia, PA.*

Background: Systemic Lupus Erythematosus(SLE) is an autoimmune condition that disproportionately affects women, racial and ethnic minorities, and individuals of lower socioeconomic status[1]. Patients with SLE often face social determinants of health challenges that are barriers to care and influence health outcomes[2]. To improve outcomes, we implemented a patient's navigator program focused on addressing the medical and social needs of patients with lupus nephritis (LN).

Methods: In this pilot phase, we included 13 patients with LN that were identified by their treating physician with high medical needs (newly diagnosed or flare of LN;recent hospitalization or emergency room visit;or transitioning from pediatric to adult care) and/or high social needs (food and economic insecurity, uninsured; complex family situation with childcare or elderly care needs, high no-show rate, limited health literacy, mental health challenges). Initial screening was performed by college volunteers connected to the medical team who reviewed the results and implemented interventions aiming patient's specific needs. Follow-up assessments were arranged to modify the social determinants of health that negatively affected patients.

Results: The demographic and screening results are summarized in Table 1. Financial help with medication and physician visit copays were reported as the most pressing need followed by transportation, disease education and assistance with medication compliance. Based on the initial screening, we started an intervention plan tailored to individual needs such as financial support for transportation, social services, blood pressure machine, pill box and lupus education.

Conclusions: The pilot phase of our patient navigator program successfully identified additional medical and social needs for patients with LN. We plan to expand this program by identifying more patients and arranging for follow-up assessments to modify social determinants of health that negatively affect our patients. Our program can serve as a model for other institutions to improve outcomes for patients with SLE.

Funding: Private Foundation Support

Table 1

Age: median (range)	36 (20-53)
Gender	Female: 11 Male: 2
Ethnicity	Black: 11 White: 1 Hispanic: 1
Lupus status	Acute flare: 8 Partial remission: 5
Identified needs	Transportation: 6/13 Mental health: 3/13 Disease education: 4/13 Referral to support group: 2/13 Medical supplies (BP machine; pill box): 7/13 Copay for medication or visit: 8/13 Assistance with compliance: 6/13 Social services: 3/13

BP: Blood pressure

PUB163

An International Public-Private Partnership Model for Renal Replacement Therapy in Uzbekistan: Lessons and Challenges

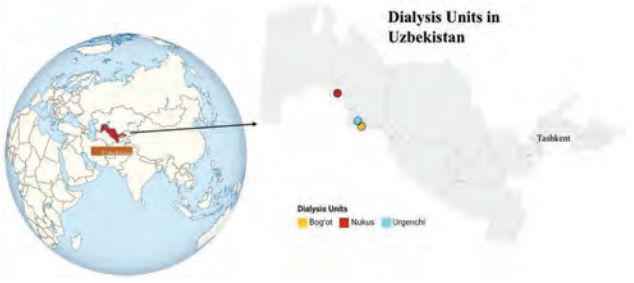
Suresh Sankarasubbaiyan, Botir Daminov, Savitha Kasiviswanathan, Dilshod Sobirov, Ravshanbek Raximov, Khurshid U. Dosimbergenovich, Shiva Chaudhary, Kamal D. Shah. *Nephrocare Health Services Pvt Ltd, Hyderabad, India*.

Background: Uzbekistan is part of New Independent States region in Europe with 35.6 million population and GDP/capita of 2254.9 dollars with an acute need for RRT availability and accessibility.

Methods: The Uzbekistan government chose a dialysis provider from India to initiate a public-private partnership model of RRT. Our objectives are 1. Describe the model for hemodialysis by roles, resources and service provided 2. Present demography, dialysis practice and clinical outcome from April-December 2022.

Results: Under the model, the government funded and governed while the private provider ensured leadership, human resources, technology, HD delivery and information capture (paper based & digital). HD facilites were at: Bogot (pop:10600), Nukus (pop:330,000) and Urgench (105,000) with machine capacity of 25, 34, and 31 respectively at 65% utlization (Image 1). B Braun dialog machines and Wego F18 Polysulfone 1.8m2 dialyzers were used. Staff patient raio of 1:3 with oversight by physicians with nephrology training. Image 2 presents patient, practice and outcome characteristics. Proximal public health facilites provided support for acute care and biochemical monitoring.

Conclusions: We demonstrate an emerging model of knowledge and skill transfer between LMIC in RRT with profound delivery challenges in acces to care, manpower and HD delivery in Uzbekistan.



No	Characteristics	Number(%)
1	Age	
	<18	1(0.23)
	18 - 40	123(28.6)
	41 - 60	219(50.93)
	61 - 80	86(20)
	>80	1(0.23)
2	Gender	
	Female	160(37.21)
	Male	270(62.79)
3	Education	
	< 10th	40(9.3)
	High school	332(77.21)
	College	40(9.3)
	Post Graduate	2(0.47)
	NA	16 (3.72)
4	CKD cause	
	DKD	118(27.44)
	GN	235(54.65)
	HTN	12(2.79)
	ADPKD	10(2.33)
	Pyelonephritis	30(6.98)
	Others	25(5.81)
5	Vascular access	
	AVF	321(74.65)
	IJVC	74(17.21)
	Single lumen	35(8.14)
6	Hb (g/dl) (N=283)	
	<8	109(38.52)
	8 - 9.9	81(28.62)
	10 to 12	60(21.2)
	>12	33(11.66)
7	Viral marker	
	HBsAg	12
	HCV	84 (19.53)
	HEP-B&C	10
	HIV	1
	Negative	323
8	Facility distance	
	<10	88(20.47)
	10 to 30	156(36.28)
	31 to 60	103(23.95)
	>60	83(19.3)
9	Outcome	
	Continue	326(75.81)
	Died	66(15.35)
	Unclear	2(0.47)
	Shifted elsewhere	12(2.79)
	Txp	24(5.58)

Patient characteristics N=430

PUB164

Language Barrier and Abdominal Compartment Syndrome with Renal Replacement Therapy (RRT) in the Intensive Care Unit (ICU)

Alvin G. Kwon, Melissa Baker, Hanny Sawaf. *Cleveland Clinic, Cleveland, OH.*

Introduction: In the US, using a primary language other than English is a known barrier to adequate healthcare utilization and patients' comprehension of diagnosis and treatment. Adverse events were more prominent in limited English-proficient patients at 46.8% compared to 24.4% in English-proficient patients. Abdominal compartment syndrome (ACS) is commonly diagnosed with intra-abdominal pressure over 20mmHg and related organ failure such as AKI. However, ACS has nonspecific symptoms and poor physical exam sensitivity as low as 40-50% making it challenging for physicians to diagnose it promptly. We present patient with intra-bladder pressure proven ACS complicated by AKI required hemodialysis.

Case Description: Patient is a 25-year-old Spanish-only speaking male diagnosed with necrotizing pancreatitis after being found with septic shock requiring two vasopressors for blood pressure support. Patient was also found to have generalized weakness, abdominal distension, hyponatremia, and jaundice. The patient tested positive

for Confusion Assessment Method and needed to rely on a landline interpreter service. He had no family or social support to assist with his history. After rigorous intravenous fluid resuscitation for pancreatitis, patient remained anuric with lower extremities edema and was initiated on continuous veno-venous hemodialysis. Given his severe abdominal distention and tenderness on physical examination, intra-bladder pressure was measured at 29 mmHg while patient was still systemically hypotensive. Surgical intervention was not performed, given comorbidities and concerns that it caused more harm than benefit. Decompression via nasogastric tube and scheduled enema were continued and bladder pressure was decreased at 5 mmHg three days later. Unfortunately remained dialysis-dependent and passed away from worsening septic shock.

Discussion: Poor socioeconomic status and language barriers and confusion from encephalopathy are previously unrevealed risk factors for ACS that may contribute to mortality in vulnerable populations; additional barriers to communication with providers may make reporting symptom changes difficult. Therefore, physicians should pay extra attention to vulnerable people. Future studies between language barriers, socioeconomic status, and ACS should be followed.

PUB165

What Does Justice Require of Us in Kidney Health?

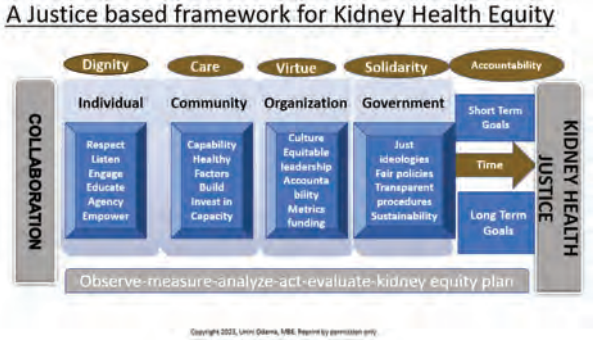
Unini Odama. *Harvard University, Cambridge, MA.*

Background: Thirty-seven million Americans live with chronic kidney disease, while over 800 000 have end-stage kidney disease (ESKD), a devastating life-altering condition. Unfortunately, kidney health disparities and inequities abound, and the current literature does not integrate a comprehensive view of justice in kidney health. Justice, the fair distribution of fundamental rights, duties, socio-economic, health, and healthcare opportunities, is linked to wellbeing. The overarching goal of this project was to demonstrate how kidney health, health equity, and justice are inextricably linked.

Methods: This work used a wide justice lens to explore the moral question of variances in kidney health metrics (disparities) and outcomes (inequities). Relevant peer-reviewed scientific journals and seminal justice articles were reviewed. Information was gleaned from discussion with Justice experts. Justice principles and relevant bioethical principles were linked to create a Kidney health justice-based framework.

Results: Findings unveiled widespread inequities in kidney disease risk, care, and outcomes. Common kidney disease risk factors- diabetes and hypertension- are 12-13 times more prevalent in Blacks; ESKD prevalence in Blacks (29.8 %) is quadruple that of Whites. Blacks and Hispanics are 53% and 65%, and 79% and 53%, less likely to receive home dialysis and kidney transplantation than Whites. Also, racism, poverty, and oppression are unique determinants of kidney health inequities.

Conclusions: This project illustrated the link between kidney health and justice with a novel justice-based kidney health framework, connecting normative justice theories to bioethical principles of dignity, care, virtue, and solidarity. An infographic highlighted the necessity for collaboration at the individual, community, organizational, and governmental socio-ecological levels. Justice requires policymakers and kidney care stakeholders to adopt a far-reaching, transparent, accountable, sustainable, and just kidney health plan.



PUB166

Use of Cell/Smartphone Technology in an Urban Free-Standing Hemodialysis Facility in the United States: A Single Center Study

Sujith K. Palleti,[1] Kavitha Vellanki,[1] Judith Beto,[2] Vinod K. Bansal.[1] *[1]Loyola University Medical Center Department of Nephrology, Maywood, IL; [2]Loyola University Health System, Maywood, IL.*

Background: Cell/smartphone has become a basic necessary commodity in the 21st century and a cornerstone for knowledge sharing. It can be a valuable resource for patient education when used appropriately. Data on cell/smartphone technology usage in the hemodialysis (HD) population is non-existent. We proposed to study the utilization of cell/smartphone technology in selected activities to better understand our patient population and identify the best means of communication.

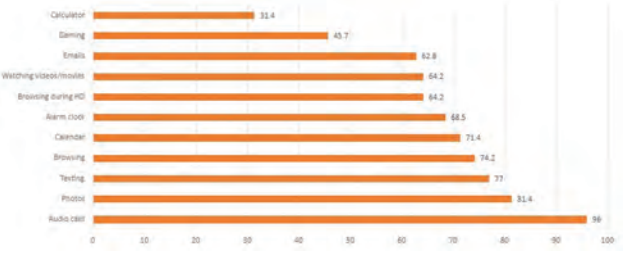
Methods: All patients receiving in-center dialysis were approached to complete a 2-page paper survey. Data collected included age, sex, self-reported ethnicity, presence of landline/internet at home, and ability to drive. The food security risk score was assessed using the USDA validated 2-question format.

Results: Of the 110 HD patients, 77 agreed to participate (70% response rate), and 70 of the 77 had a cell/smartphone. The baseline demographics of the study population are shown in Table 1. Image 1 demonstrates the various activities smartphone is used in our HD cohort. Interestingly, women used text messaging more frequently than men (82% vs. 68%), and those who used text messaging were found to be younger than those who did not (58.1 and 71.2; age in years). 64% reported active browsing on their phones while receiving HD. We did not find any association between the ability to drive and the food security risk score.

Conclusions: The use of social media platforms accessed by cell/smartphone technology should be explored to find better means of education and communication in HD patients.

Demographics of study population

Gender, N (%)	Male: Female 37 (52.9%): 33 (47%)
Mean Age, Years (SD)	61.7 (SD - 13.4)
Self-reported Ethnicity (N=70)	African American – 50% Hispanic, not white – 34% Caucasian, white – 13% Asian – 3%
Landline at home (%)	28.6%
Internet at home (%)	74.3%
Drove car in last 30 days	57.1%
Food security risk score (N=67)	High risk score – 6.8% Moderate risk score – 27.9% Low risk score – 70.6%
Dialysis access, N (%)	AVF - 39 (55.7%) AVG - 13 (18.5%) PC – 18 (25.7%)



Utilization of smart phone for various activities in our dialysis cohort

PUB167

Assessing the Current Evidence on Environmental Sustainability in Nephrology: Protocol for a Scoping Review by the International Society of Nephrology, Emerging Leaders Program Cohort 2022-2024

Isabelle Ethier,[1,2] Divya P. Bajpai,[4] Brendan Smyth,[5,6] Winston W. Fung,[7] Maria Pippias,[9,10] Peace Bagasha,[14,15] Letizia De Chiara,[13] Ehab Hafiz,[11] Dearbhla M. Kelly,[3] Ugochi C. Onu,[12] Shaifali Sandal,[8] Workagegnehu H. Bilchut.[16] International Society of Nephrology – Emerging Leaders Program Cohort 2022-2024. *[1]Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [2]Centre de Recherche du Centre Hospitalier de l'Universite de Montreal, Montreal, QC, Canada; [3]Mater Misericordiae University Hospital, Dublin, Ireland; [4]King Edward Memorial Hospital and Seth Gordhandas Sunderdas Medical College, Mumbai, India; [5]NHMRC Clinical Trials Centre, Camperdown, NSW, Australia; [6]St George Hospital, Kogarah, NSW, Australia; [7]The Chinese University of Hong Kong, Hong Kong, Hong Kong; [8]McGill University Health Centre, Montreal, QC, Canada; [9]University of Bristol Faculty of Health Sciences, Bristol, United Kingdom; [10]Southmead Hospital, Bristol, United Kingdom; [11]Theodor Bilharz Research Institute, Giza, Egypt; [12]University of Nigeria, Nsukka, Nigeria; [13]Universita degli Studi di Firenze, Firenze, Italy; [14]Mulago National Referral Hospital, Kampala, Uganda; [15]Makerere University, Kampala, Uganda; [16]University of Gondar, Gondar, Ethiopia.*

Background: Human-induced climate change is a significant threat to global public health. The healthcare sector contributes significantly to environmental damage through resource depletion and greenhouse gas emissions. Furthermore, nephrology practices have a disproportionately higher share in the carbon footprint produced by medical therapies (e.g. dialysis). This review aims to map the available evidence of green/sustainable nephrology in the literature to better understand the current lacunae in the evidence and challenges faced while adopting eco-friendly practices.

Methods: A search strategy, developed in collaboration with a medical librarian to be used in Medline, and adapted for other databases (PubMed, Embase, Cochrane Library, CINAHL), will be used to retrieve references. A secondary manual search of all references from included studies will be undertaken (snowballing approach). All publications (including original studies, case reports, editorials, review articles, editorial letters, positional statements from professional societies, and conference abstracts) addressing any environmental impact of activity in kidney care; current knowledge or awareness of environmental impact of kidney care impact; any activity, strategy or effort focused on environmental sustainability of kidney care activity; or any barrier or challenge faced in adopting environmentally sustainable kidney care activity will be included. A data extraction table will be used to record the key components and information from the retrieved papers. Extracted data will be analyzed qualitatively using preidentified and newly identified themes.

Results: Results will be summarized using descriptive statistics and narrative summaries around the identified themes, to explore the environmental impact of kidney care and the application of sustainability approaches.

Conclusions: Results from this scoping review, which should be available for presentation in the fall of 2023, will help facilitate the formulation of a planned toolkit by our group, based on relevant components identified, which can direct healthcare professionals to vital resources in sustainable nephrology.

PUB168

Renal School at Dubai Hospital: 15 Years of Predialysis Health Education Program

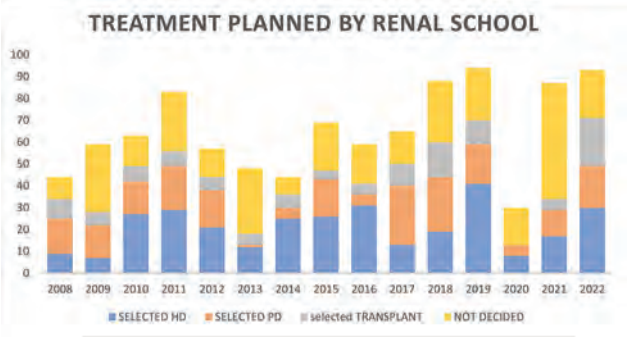
Hind H. Alnour, Fakhriya J. Alalawi. *DAHC, Dubai, United Arab Emirates*.

Background: For patients with end-stage renal disease (ESRD), renal replacement therapy (RRT) is necessary to sustain life. However, many pre-dialysis CKD patients lack the information to make wise healthcare decisions regarding their future management. We have a model program named Renal School, launched in 2008 and still working to date, and consists of a multispecialty team (including nephrologists, clinical dieticians, haemodialysis and PD nurses, psychologist, and social worker). We provide comprehensive education about various modalities of renal replacement therapy to patients with CKD stages 4 and 5 (eGFR<30 ml/min), aiming at reducing the need for emergency dialysis and catastrophic complications associated with delayed RRT.

Methods: Sine 2008 until date, 1021 patients attended renal school and were explained various modalities of RRT. Patients received a number of learning resources, and their preference for a particular modality was considered.

Results: Among 1021 patients, 315 selected haemodialyses, 217 opted for peritoneal dialysis, 119 were referred for pre-emptive kidney transplantation, and 332 remained undecided. Educated patients were prepared with access at the start of dialysis, which reduced complications associated with delayed dialysis therapy, had fewer hospital days of stay and had significant cost savings. Moreover, they received better care, enjoy better clinical outcomes, and cope better with the stresses of RRT. Although the majority (32.5%) could not decide regarding the type of RRT, yet they became more compliant with medication and dietary regimen, and they were able to plan healthy lifestyles and cope with their chronic illness.

Conclusions: By offering comprehensive information, fostering shared decision-making, providing psychosocial support, and addressing lifestyle management, these programs empower patients to actively participate in their healthcare decisions. Through their involvement, patients can select the most suitable RRT modality based on their preferences, leading to improved treatment outcomes and a higher quality of life.



PUB169

Reproductive Health Perceptions and Priorities of Males Living with CKD: A Survey Protocol

Nicole Larsen, Sofia B. Ahmed, Tessa A. Woodside, Victoria J. Riehl-Tonn, Shu Foong, Sandi M. Dumanski. *University of Calgary, Calgary, AB, Canada*.

Background: Chronic Kidney Disease (CKD) affects 1 in 10 Canadian males, and up to 80% of males living with CKD experience complications related to their reproductive health (sexual function and fertility). Despite its importance to overall health and quality of life, reproductive health is often overlooked during the management of CKD in males. This study aims to identify the reproductive health perceptions and priorities of males living with CKD.

Methods: An exploratory web-based survey will be designed through a comprehensive literature review and in consultation with experts in the field of nephrology, urology, and reproductive health. The survey will assess reproductive health perceptions and priorities of males living with CKD and will use both close- and open-ended questions. Survey pre-testing by patient partners will assess validity, usability, and functionality. Snowball sampling will be employed to recruit self-identified adult males living with CKD, with invitations disseminated through national and international CKD patient organizations, social media platforms, and CKD clinics in Calgary, Alberta, Canada.

Results: Descriptive statistics will be employed to analyze numeric and Likert-scale data, while conventional content analysis will be utilized to analyze open-ended data.

Conclusions: Reproductive health perceptions and priorities of males living with CKD are poorly understood. Our findings will guide future patient-directed research and encourage the development of targeted interventions to address the reproductive health needs of males living with CKD.

PUB170

Hemodialysis Dose as a Modifiable Sex-Specific Cardiovascular Risk Factor: A Systematic Review

Victoria J. Riehl-Tonn,[1] David D. Nicholl,[2] Sandi M. Dumanski,[1] Meghan J. Elliott,[1] Jennifer M. MacRae,[1] Colleen M. Norris,[3] Sofia B. Ahmed.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]The University of British Columbia, Vancouver, BC, Canada; [3]University of Alberta Faculty of Nursing, Edmonton, AB, Canada*.

Background: Cardiovascular (CV) mortality and morbidity may be reduced by increasing the hemodialysis (HD) dose above the current standard in females compared to males given sex-based differences in body composition and distribution of water. We sought to compare the associations between measures of HD dose and mortality (all-cause, CV-related) and CV morbidity between females and males receiving HD.

Methods: A systematic literature search of electronic databases (Medline, EMBASE, CENTRAL) was completed to identify articles including**:** 1) adult females and males on HD 2) measures of HD dose (Kt/V, urea reduction ratio, ultrafiltration rate) 3) all-cause and CV mortality and morbidity (coronary heart disease, myocardial infarction, ischemic or hemorrhagic stroke, venous thromboembolism, hypertension, heart failure, CV hospitalization) 4) original data (randomized controlled trial[RCT], quasi-RCT, cohort, case-control, cross-sectional study). All articles will undergo title and abstract screening before full-text review and data extraction and will be done independently by two investigators.

Results: Databases were systematically searched from inception to December 2022, which identified 24,051 articles eligible for title and abstract screening. Extracted data will include population characteristics, measures of HD dose, incidence of CV outcomes, study quality and risk of bias. Inter-reviewer reliability will be calculated at both phases. Data will be presented descriptively and meta-analysed using a random effects model. Heterogeneity will be explored and meta-regressed.

Conclusions: HD dose may be a modifiable sex-specific CV risk factor, with the potential to improve CV health in females on dialysis.

PUB171

Gender and Choice of Kidney Replacement Therapy: A Protocol

Victoria J. Riehl-Tonn,[1] Sandi M. Dumanski,[1] Meghan J. Elliott,[1] Jennifer M. MacRae,[1] Colleen M. Norris,[2] Sofia B. Ahmed.[1] *[1]University of Calgary, Calgary, AB, Canada; [2]University of Alberta Faculty of Nursing, Edmonton, AB, Canada*.

Background: The prevalence of dialysis, a life-sustaining kidney replacement therapy(KRT), is rising annually at significant economic cost. Compared to in-center dialysis, home-based dialysis is associated with improved outcomes and lower cost yet may be underutilized. Currently, patient education addressing dialysis modality options is gender-blind. Therefore, the objective is to determine if measures of gender, including identity, roles and relations, are associated with KRT choice.

Methods: Exploratory mixed-methods study with online survey and semi-structured interview. Using a convenience sample, individuals with chronic kidney disease (Stage4-5) who have not yet initiated dialysis will be recruited from Kidney Care Clinics in Calgary, Canada. The exposure, gender and gender-related factors, will be measured using the Genesis-PRAXY Gender questionnaire, which encompasses gender identity, roles and relations. The outcome, participant's choice of KRT, will be measured through a survey and a semi-structured interview. Questions for survey and interview will be developed through a thorough literature review and in consultation with experts in the field.

Results: Data will be reported descriptively with proportions and percentages, when applicable. Non-parametric statistical tests, such as Kruskal-Wallis and Mann-Whitney U test, will be utilized to assess the association between gender-related factors and participants choice of KRT. Semi-structured interviews will be analyzed using a deductive thematic analysis where two independent reviewers will identify common themes.

Conclusions: Understanding the gender-related factors associated with dialysis modality choice will influence delivery of care in a gender transformative person-centred manner.

PUB172

Clinical Practice Gap Analysis of Anemia Associated with CKD

Amy Larkin, Linda Ritter. *Medscape Education, New York, NY*.

Background: Understanding clinical practice gaps in the clinical understanding of screening, health outcomes, and emerging treatments for anemia of chronic kidney disease (CKD) can inform development of tools to improve physician practices.

Methods: A survey instrument of 25 multiple choice, knowledge- and case-based questions allowed participants to assess their clinical knowledge with regard to anemia of CKD. The survey was available online to physicians without monetary compensation or charge. Respondent confidentiality was maintained and responses were de-identified and aggregated prior to analyses. Initial data collection occurred from August 12, 2022 to October 10, 2022.

Results: In total, 66 nephrologists completed the full assessment within the data collection period. Physicians demonstrated gaps in the following areas:

Conclusions: This educational research on assessment of physicians' clinical practices yielded important insights into clinical gaps related to anemia of CKD screening, health outcomes, and emerging treatments. Further studies are planned to assess the effect of medical education on decreasing these clinical practice gaps.

Funding: Commercial Support - Developed through independent educational grant from GSK

Topic	Incorrect Responses to Knowledge and Clinical Decision-Making Questions (%)
Main Cause of Anemia in CKD	33%
Regulation of Iron Absorption in CKD	30%
Strategies for Measuring Severity of Anemia in CKD	29%
KDIGO Guidelines for Anemia Screening in CKD	74%
Complications of Anemia of CKD	59%
Effect of Anemia on Patient Health Outcomes	42%
Health Inequities in Anemia of CKD	29%
Clinical Trial Data Related to Clinical Use of ESAs	47%
MACE Outcomes for IV Iron	59%
Mechanism of Action of HIF-PHIs	73%
Mechanistic Differences Between HIF-PHIs and ESAs	64%
Dosing of HIF-PHIs	41%
Clinical Trial Data for HIF-PHIs	23%

PUB173

Online Continuing Medical Education (CME) Improves Knowledge of Gaps in CKD-Anemia Management in Practice

Amy Larkin, Linda Ritter. *Medscape Education, New York, NY.*

Background: We sought to determine if online continuing medical education (CME) could improve the clinical knowledge and confidence of nephrologists and hematologists related to current gaps in care for patients with CKD-anemia.

Methods: The CME intervention comprised a 30-min online video-based roundtable discussion among 3 expert faculty with downloadable slides. The effects of education were assessed for learners completing both knowledge pre- and post-assessment questions using a matched pre-/post-assessment design, with participants serving as their own controls. A paired samples t-test was conducted for significance testing on overall average number of correct responses and for confidence rating, and a McNemar test was conducted at the question level (5% significance level, $P < .05$). Confidence was assessed in a 4th question using a 5-point Likert scale. The activity posted September 16, 2022, and data were collected through December 21, 2022.

Results: In total, 59 nephrologists and 35 hematologists answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation: Overall, 39% of nephrologists and 29% of hematologists improved their knowledge 27% of nephrologists and 14% of hematologists demonstrated improvements at recognizing disparities in the management of CKD-anemia (P<.01 for nephrologists, P=NS for hematologists) 22% of nephrologists and 20% of hematologists demonstrated improvements at recognizing the burden of disease of CKD-anemia (P<.05 for nephrologists, P=NS for hematologists) 27% of nephrologists and 43% of hematologists had a measurable improvement in confidence in overcoming gaps in management of CKD-anemia (P<.01 for both groups) Continued educational gaps: 39% nephrologists and 40% of hematologists need additional education related to disparities in the management of CKD-anemia 59% nephrologists and 40% of hematologists need additional education related to the burden of disease of CKD-anemia

Conclusions: This study demonstrates the success of online CME in a roundtable format on improving clinical knowledge and confidence of ER physicians and nephrologists related to managing patients with hyperkalemia. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Developed through an independent educational grant from Glaxo Smith Kline

PUB174

Impact of Online Continuing Medical Education (CME) on Ability to Manage Patients with Dialysis-Dependent CKD-Associated Pruritus (DD-CKD-aP)

Amy Larkin, Donald Blatherwick. *Medscape Education, New York, NY.*

Background: We sought to determine if online continuing medical education (CME) could improve the clinical competence and confidence of nephrologists and primary care physicians (PCPs) related managing patients with dialysis dependent chronic kidney disease-associated pruritus (DD-CKD-aP).

Methods: Educational design included a "test, then teach" approach to elicit cognitive dissonance, with evidence-based feedback provided following each learner response. A repeated pairs pre-/post-assessment study design and a McNemar's test (P <.05 is considered significant) assessed educational effect, with Cohen's d being used to assess educational impact (<0.2 modest effect, 0.2-0.49 small effect, 0.5-0.79 moderate effect and >0.8 extensive effect). The activity launched November 4, 2022 and data were collected through January 24, 2023.

Results: In total, 108 nephrologists and 252 PCPs answered all pre-/post-assessment questions and were included in the study. Overall improvements were seen after participation: Overall, 85% of nephrologists and 81% of PCPs improved their competence (P<.01 for both groups). 55% of nephrologists and 52% of PCPs demonstrated improvements at screening for and diagnosing DD-CKD-aP (P<.01 for both groups). 42% of nephrologists and 63% of PCPs demonstrated improvements at managing DD-CKD-aP (P<.01 for both groups). 59% of nephrologists and 49% of PCPs demonstrated improvements at providing patient education related to DD-CKD-aP (P<.01 for both groups). 41% of nephrologists and 40% of PCPs had a measurable improvement in confidence in providing team-based management of CKD-aP (P<.01 for both groups). Continued educational gaps: 20% of nephrologists and 29% of PCPs need additional education related to screening and diagnosing DD-CKD-aP. 11% of nephrologists and 28% of PCPs need additional education related to managing DD-CKD-aP 8% of nephrologists and 30% of PCPs need additional education related to patient education for DD-CKD-aP.

Conclusions: This study demonstrates the success of online, text-based, interactive cases on improving clinical competence and confidence of nephrologists and PCPs related to managing patietns with DD-CKD-aP. Continued knowledge gaps were identified for future educational targets.

Funding: Commercial Support - Developed through an independent educational grant from CSL Vifor

PUB175

Online Patient Education Improves Understanding of CKD-Associated Pruritus

Amy Larkin, Donald Blatherwick. *Medscape Education, New York, NY.*

Background: This study assessed the impact of online patient education on knowledge, confidence and intent to act regarding chronic kidney disease-associated pruritus (CKD-aP).

Methods: The educational intervention consisted of 2 activities comprised of text, integrated visuals, and patient video commentary published on WebMD Education in 2022. Demographic questions were asked prior to each activity. Knowledge questions were asked both before and after to assess learning gains. Intent to change and confidence questions were asked at the end of each activity. Absolute improvements were calculated for pre/post questions.

Results: Activity 1: **Dialysis: Talking to Your Doctor About Your Skin** 9,355 learners; 327 completers of all questions 56% female; 53% white, non-Hispanic; 65% over 54 years of age After the education, 80 % intend to talk to HCP about CKD-aP; 81% confident in understanding changes that can happen to skin while on dialysis Activity 2: **Ways to Manage the Itch When You're On Dialysis** 938 learners; 213 completers of all questions 62% female; 64% white, non-Hispanic; 81% over 54 years of age 20% improvement in knowledge regarding ways to treat CKD-aP; 85% intend to talk to HCP about ways to help manage the itch while on dialysis; 80% confident in talking to HCPs about their skin and if itching happens [LA1]Data missing from dashboard, waiting on data

Conclusions: The metrics and outcomes gathered in this assessment are a strong indicator that online patient activities on WebMD Education improved knowledge and confidence and prompted intent to act related to CKD-aP.

Funding: Commercial Support - This education was supported by an independent educational grant from CSL Vifor.

PUB176

Virtual Nephron: A Qualitative Assessment of a Virtual Reality (VR) Educational Tool

Georges Nakhoul,[1] Jonathan J. Taliercio,[1] Elias Bassil,[1] Susana Arrigain,[2] Jesse D. Schold,[2] John F. O'Toole,[1] S. Beth Bierer,[1] Joseph V. Nally,[1] John R. Sedor,[1] Ali Mehdi.[1] *[1]Cleveland Clinic, Cleveland, OH; [2]University of Colorado Anschutz Medical Campus, Aurora, CO.*

Background: The proliferation of VR technology has led to the creation of innovative educational tools. Using funding from the ASN, we developed a 3D VR renal physiology course. We present a qualitative analysis of its perceived utility.

Methods: Internal medicine PGY1 residents were randomly assigned into 2 groups: a VR group (exposed to the VR session) and a conventional group (received a printed script of the VR learning course). The VR session consisted of a 3D review of water and electrolyte transport and on diuretic mechanism of action. Within a week of the intervention, both groups underwent a 2-hour seminar on physiology of solute/water transport and diuretics. The VR group was asked to rate their VR experience at the end of the seminar. This was performed using a RedCAP-based survey consisting of a 4-point Likert scale. Residents randomized to the VR group were also asked to participate in a focus group. Sessions were recorded and transcribed verbatim. Data was analyzed through the content analysis approach by two independent reviewers who met to compare coding and reach consensus on emerging themes.

Results: Of the 64 PGY1 residents who were randomized to VR group, sixty-two completed the platform assessment. Overall, > 90% of the residents rated the platform positively in all parameters, and 77% preferred it as a teaching method (Table 1A). Three focus groups met for one hour. Each group respectively comprised 9, 8, and 15 interns from each academic years 2020-2023. Several recurring themes emerged in our analysis (Table 1B).

Conclusions: The feedback of the VR course was overwhelmingly positive and was perceived to be a helpful educational adjunct. Educational institutions should consider supporting the development of interactive educational tools to enhance leaner experience.

Survey Question	Total (N=62)	
	N missing	N agree or strongly agree (%)
The program is user friendly	0	58(93.5)
The response time of the program is adequate	1	59(96.7)
I was absorbed in the activity of the simulation	0	61(98.4)
The delivered material was clear	0	59(95.2)
The delivered material appropriately covered the learning objectives	1	59(96.7)
The Oculus Quest made it easy to understand the learning objectives	0	57(91.9)
The Oculus Quest is a useful learning aid	0	57(91.9)
Oculus Quest enhanced my understanding of nephrology concepts	0	58(93.5)
I found the Oculus Quest enjoyable to use while learning	0	60(96.8)
I preferred using the Oculus Quest to the conventional teaching method	0	48(77.4)
I would like the Oculus Quest to be utilized for more topics in nephrology	0	58(93.5)

Table 1A. Survey evaluating the VR platform

POSITIVE THEMES	NEGATIVE THEMES
Recall: memory anchor with recall that was described as relevant to clinical practice	Lack of immediate clinical relevance
Attention span: great hook	More interaction: somewhat passive experience despite interactive format
Interaction: engaging and powerful	Organization: VR and lesson to be taught concurrently
Spatiality: improves understanding of structures	Environment control: ability to change the speed of the simulation
Enjoyable: cool / fun / graphically appealing	Logistical challenges: inability to take notes
Great supplemental resource	Technical challenges: motion sickness, lag, teleportation feature

Table 1B. Focus group themes

PUB177

Assessing ChatGPT's Reliability as a Novel Educational Resource for Interventional Nephrology

M. Salman Sheikh, Fawad Qureshi, Charat Thongprayoon, Iasmina Craici, Wisit Cheungpasitporn. *Mayo Clinic Minnesota, Rochester, MN.*

Background: Interventional Nephrology is a new subspeciality of Nephrology that focuses on ultrasound guided renal biopsy, insertion of peritoneal and tunneled dialysis catheters, and endovascular procedures for managing arteriovenous fistulas in dialysis patients. Additional educational resources are necessary to support its growth as a developing field. ChatGPT is an state-of-the-art language model with exceptional proficiency in natural language processing tasks, raising questions about its potential as an educational resource for interventional nephrology. However, its performance in this field has not yet been evaluated.

Methods: The Nephrology Self-Assessment Program (NephSAP) of the American Society of Nephrology (ASN) was utilized to evaluate the accuracy of ChatGPT in answering questions related to Interventional Nephrology. There was a total of 55 questions on NephSAP related to Interventional Nephrology. The question bank was executed twice using ChatGPT, and the level of concordance between the initial and subsequent runs was determined. Questions containing images were excluded from the assessment due to current limitations in ChatGPT's image processing capabilities.

Results: ChatGPT achieved an accuracy of 52% on the initial run and 60% on the subsequent run. The overall concordance between the initial and subsequent runs was 73%, with the same responses on 40 questions (73%) and different responses on 15 questions (27%). Correct concordance was 63%, while incorrect concordance was 38%. Among the 15 questions with different responses, ChatGPT revised 7 incorrect responses to correct responses on the subsequent run. Conversely, it also switched 5 correct responses to incorrect responses on the subsequent run. There were 3 questions on which ChatGPT's responses remained incorrect on both runs.

Conclusions: ChatGPT's accuracy in answering questions related to Interventional Nephrology was suboptimal with an overall accuracy of 56%. The concordance between the initial and subsequent runs also suggested that ChatGPT may be unreliable. Based on these findings, the current version of ChatGPT is not a dependable educational resource for nephrologists, nephrology professionals, or medical staff in this subspecialty. Further development would be necessary to enhance ChatGPT's performance in the field of Interventional Nephrology.

PUB178

Enhancing Patient Education Through Artificial Intelligence (AI): Evaluating ChatGPT's Accuracy in Providing Information on Living Kidney Donation

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Background: Living kidney donation is a complex process and individuals seeking reliable information often turn to Frequently Asked Questions (FAQs) websites, such as Donate Life America. ChatGPT is an AI language model with the potential to offer accurate information on various topics including living kidney donation. However, its effectiveness in addressing patient queries specific to this topic has not been assessed. We aimed to evaluate ChatGPT's performance in providing accurate information on living kidney donation by comparing its answers with those provided by nephrologists and a widely accessible FAQs website.

Methods: The study collected 27 questions on living kidney donation from the Donate Life America's website and divided into four steps: original questions, paraphrased questions with different interrogative adverbs, paraphrased questions with verbs and prepositions removed, and paraphrased questions with misspelled words. ChatGPT's answers to each question were compared with those provided by the FAQs website and nephrologists to evaluate its accuracy.

Results: ChatGPT's accuracy varied depending on the question type. ChatGPT provided correct answers for 85.2% of the original questions. Notably, when the questions were paraphrased with different interrogative adverbs or with verbs and prepositions removed, correct answers were provided by ChatGPT in 96.3% and 92.6% of the cases, respectively. The accuracy decreased to 85.2% when the questions contained misspelled words. The original questions were tested a 2nd time with an accuracy of 92.6%. The overall concordance in correct answers between the 1st and 2nd test of the original questions was 85.2%.

Conclusions: This study highlights ChatGPT's promising accuracy, in providing reliable information on living kidney donation. ChatGPT consistently demonstrated accuracy rates of >85% across a range of question formulations, including original questions and paraphrased versions. However, caution should be exercised when relying on ChatGPT's responses to questions with misspelled words. The study suggests that further advancements are needed to enhance ChatGPT's performance and ultimately improve patient education.

PUB179

Nephrology Program Director Protected Time for Training Program Administration: A Follow-Up Survey

Christina M. Yuan,[1] Brian Y. Young,[2] Maura A. Watson,[1] Amy N. Sussman.[3] *[1]Walter Reed National Military Medical Center, Bethesda, MD; [2]University of California Davis School of Medicine, Sacramento, CA; [3]The University of Arizona Health Sciences, Tucson, AZ.*

Background: In 2022-23, the Accreditation Council for Graduate Medical Education (ACGME) reduced minimum required program director (PD) protected time from 0.25 (10 hrs/week) to 0.2 FTE (8 hrs/week) for programs with <7 approved fellow positions. A survey of nephrology PDs in April 2022 found that 48% were not receiving the minimum 10 hrs/week.

Methods: A 22-question, anonymous follow-up survey was sent to all US adult nephrology PDs (March 2023) on how much protected time they received in 2022-23 and how much they needed to effectively administer their programs. We compared results with 2021-22, asked how PDs would use extra time if provided and assessed PD potential for burnout."

Results: Response was 62% (92/149) with 88% completion. Geographic distribution and number of approved positions was similar to the national profile. 61% had <7 approved fellow positions. Median protected time for 2022-23 was 10 hrs/week [IQR 6.25,12]; 8 hrs/week [IQR 4,10] for programs with <7 fellows. 40% of programs were not in compliance with protected time requirements, regardless of approved fellow number. 37% (30/81) of PDs agreed they had "enough protected time to effectively administer my program." PDs at smaller programs (≤ 4 and 5-6 fellows) estimated needing a minimum 10 hrs/week for effective program administration (16 hrs/week for >10 fellow programs). The top 3 tasks PDs would focus on if they had more time were 1) improve didactic curriculum (60%); 2) develope individualized fellow learning pathways (48%); 3) mentor fellow scholarly work (46%). 51% indicated they would prefer defined protected time in hrs/week for each program leadership member. Only 15% would prefer a block of time divided between faculty as they saw fit. 22% (18/81) were at high risk for emotional exhaustion, reporting feeling "burned out from my work" daily or a few times a week.

Conclusions: PDs report needing more protected time to complete necessary administrative and didactic tasks--a minimum 10 hrs/week regardless of program size. This would allow PDs to focus on improving fellow didactics and developing individualized fellow learning pathways, as recommended by the 2022 ASN Taskforce on the Future of Nephrology. *The views expressed in this abstract are those of the author(s) and do not necessarily reflect the official policy of the Department of Defense or the U.S. Government.*

PUB180

Surveying the Nephrology Landscape: A Targeted Needs Assessment Among Resident Learners

Christina L. Tamargo,[1] John Sperati,[1] Christiana M. Zhang,[1] Paul D. O'Rourke,[1] Stephen M. Sozio.[1,2] *[1]The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD.*

Background: Interest in a nephrology career has waned among residents. Knowledge gaps and lack of exposure may contribute to this. Survey-based needs assessments have identified educational needs among nephrology fellows, but research targeting internal medicine residents is limited.

Methods: We distributed an electronic survey to internal medicine and medicine-pediatrics residents at two academic teaching hospitals in Maryland in fall 2022. It included four sections: demographics, training, kidney disease topics, and educational resources. We analyzed responses using mixed methods including descriptive statistics, Spearman correlations, and inductive thematic analysis.

Results: Forty-nine of 208 residents completed the survey (24% completion rate). Those who had completed more time on nephrology rotations were more likely to have considered a nephrology career (P=0.006). The resources residents used most frequently and deemed most helpful are displayed in Figure 1. Residents felt most knowledgeable about hypertension (average 3.8 on a 5-point scale) and least knowledgeable

about transplant nephrology (1.5/5). They most desired additional instruction on tubulointerstitial disease (51%). Suggestions for improvement in nephrology education centered around increased exposure to nephrology faculty, additional clinical rotations in nephrology, more nephrology teaching, and greater availability of nephrology resources.

Conclusions: Residents are interested in learning about nephrology topics and having nephrology incorporated more consistently into the internal medicine residency curriculum. These findings will help guide the creation of educational interventions to increase residents' knowledge of and interest in nephrology.

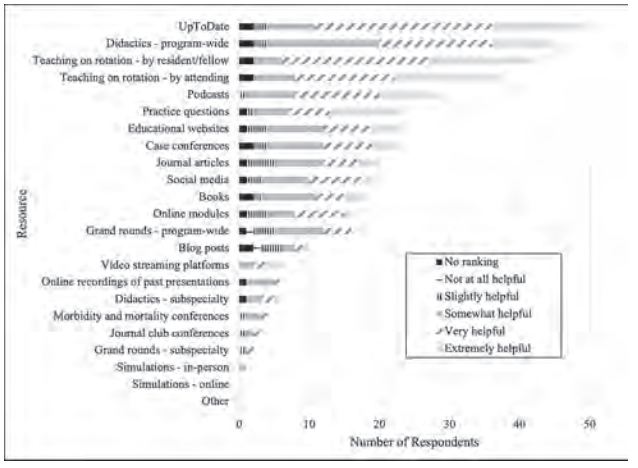

Figure 1. Value of educational resources reported by internal medicine residents.

PUB181

Does an Online Curriculum for Continuous Renal Replacement Therapy Affect Internal Medicine Trainee Knowledge?

Amol M. Patel,[1] Sarah F. Sanghavi.[1,2] *[1]University of Washington School of Medicine, Seattle, WA; [2]VA Puget Sound Health Care System Seattle Division, Seattle, WA.*

Background: Current online resources of continuous renal replacement therapy (CRRT) do not focus on its clinical application at the resident level. We developed an interactive, video-based online curriculum on CRRT with learning objectives specifically designed for internal medicine residents. We aimed to improve resident fluency with CRRT using a stand-alone educational resource.

Methods: We sent an online needs assessment survey to internal medicine residents at our institution. This was followed by voluntary study participation. Our study included two arms: The control arm completed a 10-question knowledge assessment. The intervention arm participated in an interactive 20-minute online curriculum module prior to completing the same knowledge assessment. Participants in the intervention arm also completed a post-curriculum survey.

Results: Our needs assessment showed that residents had minimal instruction on CRRT but were interested in learning. Baseline characteristics and results can be seen in Table 1. Participants in the intervention arm scored higher on the knowledge assessment than the control. There was no difference based on PGY level or prior nephrology rotation experience. All (100%) of those who completed the curriculum recommended the module to their peers and thought the length was appropriate. An important limitation was low participation rate: 188 participants were surveyed, and 36 (19%) responded.

Conclusions: This study demonstrates a stand-alone module can improve resident knowledge in CRRT. Participants in the intervention arm performed better on an assessment irrespective of PGY level and prior nephrology rotation experience. Further studies will aim to optimize trainee participation.

Results

	Performance
Control (28)	73 %
Intervention (8)	98 %
R1 (13)	84 %
R2 (12)	77 %
R3 (9)	73 %
R4 (2)	75 %
Completed Nephrology Rotation (15)	78 %
Did Not Complete Nephrology Rotation (21)	79 %
Future Career Plan is Nephrology (4)	95 %
Future Career Plan is Not Nephrology (32)	76 %

PUB182

Improving Dialysis Nursing Burnout with Innovative Technology Training

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Background: Nursing burnout is prevalent due to both rising shortages and increased workload. Studies cite dialysis nurses lack time and resources necessary for patient care. Furthermore, nurses in public hospitals are at higher risk for compassion fatigue, creating a greater need for change. Many owe the burnout to frequent complex patient interactions, high levels of depersonalization in poor work environments and complex technology. With respect to technology, a newer dialysis device, cleared in 2018 produces dialysate on demand for use in the acute, chronic, and home settings. The Tablo system offers a coordinator training program to ease implementation of this innovative technology. This reports findings from the training program.

Methods: An electronic survey was distributed to trainees enrolled in the Tablo coordinator program from May 2020-April 2023 (n=439). Questions included demographic hospital setting, dialysis experience, comfort with troubleshooting alarms and net promoter scores.

Results: Results from 399 respondents (90.88% overall response rate), from 187 unique facilities were analyzed. Most were dialysis or critical care nurses (24.56% and 25.81% respectively), worked in a hospital (82.20%) and greater than 5 years dialysis experience (53.38%). Many have never managed or managed less than 5 treatments on Tablo before training (58.16%), over 87% were extremely satisfied with the Tablo learning curve and 77.2% felt prepared for survey readiness. 88.97% of participants would highly recommend the Tablo Coordinator program to their friends and colleagues. 130 participants reported being either satisfied or very satisfied after training, see Table 1.

Conclusions: In summary, most nurses trained on this innovative technology feel they can perform tasks successfully and are looking forward to working with the device. This Tablo training program will help combat the stressors that dialysis nurses are faced with daily, leading to burnout. More research is needed to address the burnout issue in the dialysis sector.

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Results of survey after training program

	Can perform most tasks successfully	Can perform some tasks	Not comfortable performing most tasks
Training and coaching new nurses†	124 (95%)	5 (3.8%)	1 (0.7%)
Preparing for survey†	116 (89%)	13 (10%)	1 (0.7%)
Managing Tablo settings‡	127 (98.4%)	1 (0.7%)	1 (0.7%)
Managing prescriptions‡	126 (97.6%)	2 (1.5%)	1 (0.7%)
Troubleshooting†	121 (93%)	8 (6.1%)	1 (0.7%)

† n=130 & ‡ n=129

PUB183

Impact of the Preclinical Renal Block on Medical Students' Attitudes Toward Nephrology

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Background: Teaching during the medical students' (MS) clinical years is critical in deciding what specialty they pursue. Previous research in nephrology and other fields (e.g. psychiatry, general surgery) has explored the impact of clinical rotations on a medical student's attitudes and preference for that specialty as a future career. Per our literature review, this is the first study to evaluate the impact of education in the pre-clinical years on a medical student's preference towards nephrology. We present the impact of the Renal Block (4-week pre-clinical nephrology curriculum for first-year MS) on students' attitudes towards nephrology and their desires to pursue nephrology as a specialty.

Methods: We administered a survey to first-year MS at the University of North Carolina School of Medicine (Chapel Hill, NC) for the 2022-2023 academic year [n=194]. This survey was distributed before and after the Renal Block and consisted of attitude-based questions that aimed to evaluate students' perceptions and preferences.

Results: Pre-survey response rate was 51.5% (100/194) and post-survey response rate was 40.2% (78/194). Not all questions were answered by every student. 92% of the students found the field interesting after Renal Block as compared to 76% before the block. 90% felt that the block increased their interest in nephrology. Work-Life Balance, intellectual curiosity and long-term patient relationships were the top 3 factors affecting choice of specialty amongst MS (Table 1).

Conclusions: The three key findings were: 1) More students became interested in nephrology as a subject and/or career choice post-Renal Block; 2) Work-life harmony is an extremely important factor to students when choosing a specialty to pursue; and 3) Per students' responses on short answer, the individual teaching the Renal Block had a major impact on student experience. Thus, pre-clinical nephrology teaching has a huge impact on MS attitudes towards nephrology.

Table 1: Comparison of pre- and post-surveys including factors affecting specialty choice

	Pre-Survey		Post-Survey	
Survey Statement	Disagree	Agree (includes unsure)	Disagree	Agree (includes unsure)
"I find the field of nephrology interesting."	24.32% (18/74)	**75.68%** (56/74)	7.94% (5/63)	**92.06%** (58/63)
"I could see myself as a nephrologist in the future."	59.46% (44/74)	**40.54%** (30/74)	44.26% (27/61)	**55.74%** (34/61)
"The Renal Block increased my interest in nephrology."			10.29% (7/68)	**89.71%** (61/68)
"The Renal Block changed my perspective on nephrology."			1.49% (1/67)	**98.51%** (66/67)
Factors Affecting Choice of Specialty	**Number of times listed amongst top 3 factors (Pre-Survey)**		**Number of times listed amongst top 3 factors (Post-Survey)**	
Work-Life Balance	**81.33%** (61/75)		**85.71%** (54/63)	
Intellectual Curiosity	**54.67%** (41/75)		**60.32%** (38/63)	
Long-Term Relationship w/ Patients	**46.67%** (35/75)		**47.62%** (30/63)	

PUB184

Creation of a Comprehensive List of Interventional Nephrology Training Centers in the United States

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Background: Interventional Nephrology practice in the United States (US) began in the private sector in the 1990s. Unlike other nephrology sub-specialties, the training of Interventional Nephrology in the US is available in both academic and private practice centers. There needs to be a comprehensive resource that outlines the details of the Interventional Nephrology training programs in the US. This lack of resource has created a barrier for nephrology trainees interested in pursuing Interventional Nephrology training. The Training and Workforce Committee of the American Society of Diagnostic and Interventional Nephrology (ASDIN) aimed to develop a comprehensive list of Interventional Nephrology training programs in the US.

Methods: The Training and Workforce Committee of the ASDIN sent an electronic survey to all ASDIN members. The survey questionnaire focused on the type of Interventional Nephrology training center (academic/hospital-based or private practice), type of Interventional Nephrology procedure training, duration of training, and eligibility for Interventional Nephrology training for trainees on Visitors International Stay Admission (VISA).

Results: We received survey responses from the Medical Directors of 27 Interventional Nephrology training centers. Of these 27 centers, 14 were academic or hospital-based, and 13 were private practice centers. 17 of these centers were accredited by ASDIN. All centers provide hemodialysis vascular access procedure training, 10 centers provide peritoneal dialysis catheter placement training, and 13 centers provide endovascular arteriovenous fistula creation training. The duration of Interventional Nephrology training varied across the centers, and in majority of the centers, the training duration was either 3-6 months (9 centers) or 6-12 months (9 centers). Eligibility for Interventional Nephrology training based on the trainees' VISA status was variable, with 5 centers offering training to J-1 VISA holders.

Conclusions: To date, this is the most comprehensive list of the Interventional Nephrology training programs in the US. The list is available on the ASDIN website: https://www.asdin.org/page/trainingcenters. This list will be an invaluable resource for nephrology trainees interested in pursuing Interventional Nephrology training.

PUB185

Increasing Attitudes Toward the Field of Nephrology Using Interactive Dialysis Modules for Trainees

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Background: End-stage kidney disease and dialysis-dependent patients form a significant portion of the hospital population encountered by resident physicians. However, these trainees often lack formal education and confidence in managing dialysis-related care. Previous studies have indicated that trainees find kidney disease complex, contributing to decreased interest in nephrology. Additionally, there is a need for interactive educational tools to facilitate learning. This study aimed to assess the impact of interactive online modules on dialysis knowledge acquisition and attitudes towards nephrology.

Methods: We created five case-based interactive online modules, each focusing on an indication for acute dialysis initiation (acidosis, electrolyte abnormality, intoxication, volume overload, uremia) and linking these to fundamental dialysis principles (diffusion, convention, ultrafiltration, adsorption). The modules were designed to be completed within 10-20 minutes. Learner responses guided the progression of cases, providing detailed explanations for incorrect responses and concise synopses for correct responses. Modules were distributed among internal medicine resident physicians and medical students for voluntary completion. Pre- and post-module assessments included a 5-point knowledge questionnaire and a 4-point Likert scale survey measuring attitudes towards nephrology concepts and careers.

Results: 27 participants responded (16 pre-curriculum, 11 post-curriculum), including one medical student. Post-curriculum knowledge assessment scores showed improvement compared to pre-curriculum scores (3.3 vs. 4.5, $p < 0.01$), driven primarily by PGY-1 responses (2.9 vs. 4.5, $p < 0.01$). While attitudes towards the field of nephrology did not improve significantly, there was a decrease in participants who found dialysis intimidating (3.2 vs. 2.7, $p = 0.03$).

Conclusions: The study demonstrated that interactive online modules enhanced participants' knowledge of dialysis concepts and increased their comfort in managing dialysis patients, particularly among internal medicine trainees. Although attitudes towards nephrology careers were unchanged, this would not be expected from a single intervention. These modules could be combined with other strategies to improve nephrology knowledge and generate greater interest in the field.

PUB186

A Successful Resuscitation: Bedside Native Kidney Biopsies Performed by Nephrology Fellows at an Academic Tertiary Care Center

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Background: Biopsy is the gold standard for diagnosing renal pathology, and performance of percutaneous kidney biopsy is a core curriculum requirement for ACGME graduate medical education in nephrology. The growth of interventional radiology and COVID-19 pandemic-related department restructuring and staffing turnover significantly decreased fellows' opportunity to perform and gain clinical competency in kidney biopsies at our academic tertiary care center. Faculty and fellows developed a new protocol for performing low-risk ultrasound guided biopsies at bedside, resulting in a significant increase in kidney biopsies performed by nephrology.

Methods: A protocol for low-risk kidney biopsies performed at bedside by nephrology was developed and implemented. The protocol included indications and contraindications for biopsy, characteristics of low-risk biopsy patients, pre-biopsy clinical management guidelines, the biopsy procedure, standardized post-biopsy orders, and templates for related documentation. The protocol was revised to address institution-specific challenges as they arose. Data regarding the number of biopsies, complications, and diagnoses were recorded and analyzed.

Results: From June of 2020 through December 2021, two bedside kidney biopsies were performed by nephrology fellows (1.26 biopsies per year). The new protocol was implemented at the start of the 2022-2023 academic year. In the subsequent 11-month period, ten biopsies were performed at bedside by nephrology fellows (10.91 per year), an 864-percent increase. One of the ten biopsies (10%) was complicated by subcapsular hematoma; though our sample size is small, this rate comparable to that in a systemic review and meta-analysis of over 118,000 renal biopsies as published in CJASN in 2020 (11%). Data collection is ongoing, but an additional benefit at our institution has been that patients can be biopsied, and diagnosis obtained, earlier in the clinical course.

Conclusions: At our tertiary academic center, a protocolized approach to low-risk kidney biopsies at bedside has significantly increased the number of kidney biopsies performed by nephrology. An unanticipated benefit is that low-risk patients have had shorter wait-times for biopsy, allowing for tissue diagnoses and initiation of treatment earlier in the clinical course.

PUB187

Observations from the POCUS Precourse at the NKF 2023 Spring Clinical Meetings

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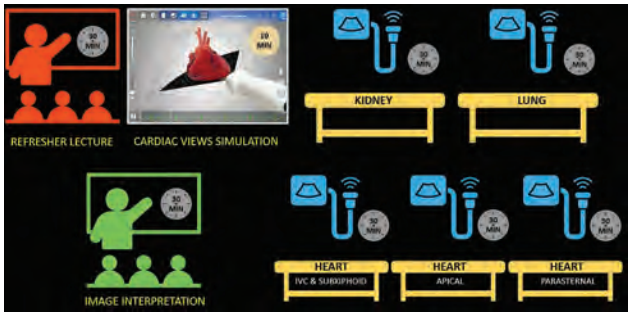
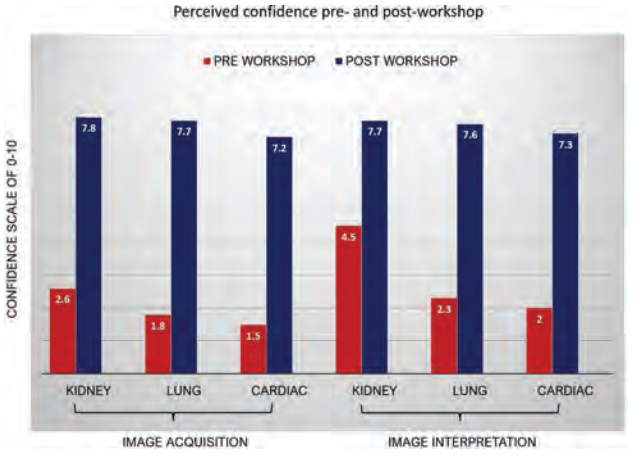
Background: In April 2023, a POCUS precourse was conducted at the National Kidney Foundation (NKF) Spring Clinical Meetings with the intent of providing foundational knowledge and practical skills necessary to perform basic scans pertinent to nephrology.

Methods: To maximize the time for hands-on learning, a set of 5 recorded lectures was provided to the registrants as pre-reading material. The workshop structure consisted of two identical 4-hour sessions (AM & PM) accommodating 16 and 23 learners respectively. See Figure 1 for the layout. An anonymous post-course survey was sent out, answered by 25 unique respondents (response rate 64.1%).

Results: The respondents were asked to rate their perceived confidence in acquiring and interpreting POCUS images on a scale of 0-10. The confidence in acquiring kidney images increased significantly from 2.6 ± 2.3 (mean ± SD) before to 7.8 ± 1.5 after the workshop ($p<0.001$). Confidence in acquiring lung and cardiac images showed a remarkable improvement (1.8 ± 2.4 to 7.7 ± 1.5 [$p<0.001$] and 1.5 ± 2.2 to 7.2 ± 1.3 [$p<0.001$] respectively). In addition, the respondents reported a substantial improvement in their confidence in interpreting kidney, lung, and cardiac ultrasound images (4.5 ± 2.2 to 7.7 ± 1.1 [$p<0.001$], 2.3 ± 2.4 to 7.6 ± 1.5 [$p<0.001$] and 2 ± 2 to 7.3 ± 1.5 [$p<0.001$] respectively) [Figure 2].

Conclusions: The NKF POCUS precourse was successful in improving confidence of the participants in acquiring and interpreting basic scans. While confidence does not necessarily imply competence, it serves as a motivating factor for continued practice. It is not realistic to expect improvement in competence via a half-day workshop.





PUB188

Nomophobia: Phone-Lessness Phobia Among Kidney Professionals

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Background: The nature of healthcare providers' work demands continuous connectivity and accessibility to digital resources eg. quick access to medical references, patient information and teleconsultations. Nomophobia, also known as "No Mobile Phone Phobia", refers to anxiety, or nervousness caused by not being in contact with a mobile phone. There is paucity of literature to explore the prevalence and severity of nomophobia among kidney professionals.

Methods: A cross-sectional pilot study was conducted among healthcare professionals from April-May 2023. This abstract includes responses from attending physicians, fellows, nurses, advanced care providers (APP) and dialysis technicians. A web-based validated survey was shared using emails and social media applications such as whatsapp, linkedin and twitter. The study was IRB-exempt.

Results: A total of 100 responses were recorded from 10 countries in this ongoing survey. There were 49% females, with the highest representation in the age (in years) between 35-45(35%) and 25-35(25%). Approximately 50% of the respondents were Asians, 36% were White, 5% were Hispanics, and 2% were Black. The kidney professionals included attending physicians (38%), nurses (23%), fellows (11%), and APP (8%). The majority years of experience was of 6-10 (28%). Nearly 50% kidney professionals reported using their smartphones for more than 2 hours at work, and 64% reported using them for personal activities for up to 4 hours (Fig. 1). A vast majority (74%) was an I-phone user. The nomophobia prevalence of mild, moderate, and severe nomophobia were 13%, 52%, and 34%, respectively.

Conclusions: This pilot study denotes that the 2/3rd kidney professionals have self-reported nomophobia. Early recognition and management of nomophobia are crucial for improving work-life balance, and ensuring their wellbeing in the evolving digital era.

PUB189

Provider Education to Improve AKI Outcomes and Awareness: A Scoping Review

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Background: Acute kidney injury (AKI) care is often fragmented due to lack of healthcare team member knowledge regarding AKI. The goal of the AKINow Initiative Education Subcommittee is to increase AKI awareness and establish best practices in AKI education to optimize outcomes. We sought to characterize the current state of provider-focused AKI education by reviewing available literature on this topic.

Methods: Ovid Medline and CINAHL searches identified literature on provider-focused AKI education and awareness. Search strategy included keywords and Medical Subject Headings related to AKI, education, information, specific educational materials, and purpose for information sharing. To increase sensitivity, adjacency searching was used in lieu of phrases for the provider education and information concepts. No limits were applied to the results. After screening for relevance based on inclusion criteria of: 1) AKI population, 2) provider-focused education, the characteristics of included abstracts were summarized.

Results: Search criteria identified 187 abstracts; 140 were excluded (55 non-AKI focus, 78 without focus on provider education, 7 other); 47 abstracts met inclusion criteria, 37/47 (79%) were published prior to 2019. Journal types included 30/47 (64%) biomedical, 16/47 (34%) non-physician provider, and 1/47 (2%) bioinformatics. Target learners were providers involved in AKI prevention 11/47 (23%), AKI treatment 21/47 (45%), and care for AKI at multiple stages 15/47 (32%). Study designs included 9 cross-sectional survey studies of provider AKI awareness and knowledge, 23 review articles published as educational resources, 1 editorial, and 14 prospective, non-randomized studies of educational interventions reporting the following Kirkpatrick level outcomes: Level 1 (learner reaction), 1/14 (7%); Level 2a (change in attitude), 3/14 (21%); Level 2b (change in knowledge) 3/14 (21%); Level 3 (behavior change), 5/14 (36%); Level 4a (organizational change), 3/14 (21%); Level 4b (patient benefit), 5/14 (36%).

Conclusions: There is a paucity of literature, particularly since 2019, on the AKI education of providers. High-level evidence exploring educational interventions to close AKI knowledge gaps amongst healthcare team members are needed to improve transitions of care and clinical outcomes for patients with AKI.

PUB190

Metformin-Associated Lactic Acidosis

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Introduction: Metformin increases plasma lactate levels in a plasma concentration-dependent manner by inhibiting mitochondrial respiration predominantly in the liver. The presence of an anion gap in a diabetic patient on Metformin, especially if associated with evidence of renal insufficiency should prompt clinicians to consider metformin as a contributing factor.

Case Description: Patient is a 49 F with a history of ICH 2/2 AVM, obstructive hydrocephalus with VP shunt, HfrEF (EF 15 to 20%), T2DM, HTN, who presented to the ER with AMS. Over the past few days, she had been feeling sick and had poor appetite, she, however, had been compliant with her medications which include, Metformin 1000mg BID, Lasix, spironolactone, and others. She had been on Metformin for 2 years. She was reported to have ventricular arrhythmia for which she got defibrillation and was given amiodarone. Her initial vital signs on arrival were BP 128/95, HR 123, RR 28, and SpO2 89% on room air. She was intubated in the ED due to respiratory distress and then transferred to the ICU. Physical exam showed dry oral mucosa, S1 S2 present, no added sound and lungs are clear, +2 pedal edema. Initial labs showed BUN 70, Cr 7.54, Na 138, K+ 8.1, Co2 4, Cl 95, Anion Gap 35, troponin 92 ng/l, Lactate 16.36, pH 6.85, WBC 19.2, no bands, CT head was negative, EKG sinus rhythm, wide QRS, no ST changes. Nephrology initiated emergent CVVHD. By day 2 in ICU, she was extubated, and on day 3, underwent a trial of Hemodialysis. She was discharged from the ICU on day 4.

Discussion: MALA is a rare but significant complication from metformin in the setting of renal insufficiency. A high index of suspicion is required to make the diagnosis. Lactic acidosis resulting from metformin toxicity should be suspected in any patient who has all of the following five criteria: a history of metformin administration, lactate level > 15, anion gap >20; pH 7.1or less, Co2 < 10, and a history of renal insufficiency GFR< 45 or cr > 2. It is well documented that acidosis leads to low contractility of the cardiac Myocytes. This coupled with HrEF in the patient led to Ventricular arrhythmia and cardiac arrest. Hemodialysis is the most preferred mode of therapy in hemodynamically

stable patients however CVVHD could be substituted in patients in shock. Education of both patients and providers to avoid metformin when there is a risk of renal failure, particularly with hypovolemia, is crucial to prevent MALA.

PUB191

Treatment of Severe Hyponatremia with Urea in Liver Cirrhosis

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Introduction: Treating severe hyponatremia in liver cirrhosis is challenging. Hypertonic saline and vaptans can be unsafe and cost prohibitive. It needs ICU for close monitoring. Urea given orally can be safe in treating patients with hyponatremia with SIADH. Its role in treating hyponatremia in liver cirrhosis is not established. We present our experience in treating one such patient successfully.

Case Description: A 58-yr-old female with liver cirrhosis from alcoholism and hepatitis C infection was admitted with hypotension, tense ascites and shortness of breath. Her chemistries revealed a sodium of 120 mmol/L, total protein 7g/dl and albumin 2.5 g/dl, BUN 3 mg/dl and creatinine of 0.4 mg/dl. AST 146 U/L, ALT 57 U/L and a bilirubin of 2.8 mg/dl. Urine sodium was <5 mmol/L and osmolality was 366 mOsm/kg. Therapeutic paracentesis of 6 liters performed on the day of admission and 4.25 L on 3rd day and was started on urea15 grams bid. Her sodium level was monitored frequently. On day 3 her sodium was 126 mmol/L and she was discharged on day 5 when it was 128 mmols/L.

Discussion: Hyponatremia can be caused by several conditions. The treatment in most conditions includes elimination of free water, free water restriction or deficient hormones replacement in adrenal insuficiency and hypothyroidism. Hyponatremia is frequently seen in patients with ascites secondary to advanced cirrhosis and portal hypertension. The development of ascites in patients with cirrhosis with portal hypertension and systemic vasodilation leads to activation of the sodium-retaining neurohumoral mechanisms, which include the renin-angiotensin- aldosterone system, sympathetic nervous system, and release of antidiuretic hormone (ADH). The net effect is the avid retention of sodium and water to compensate for the low effective circulatory volume resulting in worsening of ascites. Salt and water restriction alone may not be effective and hypertonic saline and vasopressin receptor (V2R) antagonists' use can be costly and potentially lethal from osmotic demyelination. We conclude that urea is a novel option for treating hyponatremia. It may eliminate the risk of osmotic demyelination unlike with hypertonic saline and V2R. It is an endogenous product of amino acid metabolism, is cost effective in treating hyponatremia of liver cirrhosis and hence should be utilized more frequently. Controlled trials are needed.

PUB192

An Intricate Balance: Co-Existing Types 1 and 4 Renal Tubular Acidosis (RTA)

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Introduction: Renal tubular acidosis (RTA) is a group of conditions that affect a kidney's ability to maintain acid-base balance despite unaltered glomerular function. As per studies, type I (distal) RTA and type IV (hyperkalemic) RTA are rare conditions in less than 1 per 10,000 people. We illustrate a unique case where type I and type IV RTA co-existed, and treatment of type IV RTA uncovered an underlying type I RTA.

Case Description: An 88-year-old male presented with fatigue and lightheadedness. His history included metastatic melanoma treated with nivolumab, polymyalgia rheumatica, Sjogren's syndrome on chronic steroids, and hypertension on lisinopril. He was admitted with hyponatremia and hyperkalemia. Labs showed normal anion gap metabolic acidosis (NAGMA), positive urinary anion gap (UAG), and acidic urinary pH. On questioning, he stated that he reduced his steroid dose to one-fourth. Low cortisol, a positive cosyntropin test, normal aldosterone, and high renin confirmed diagnosis of adrenal insufficiency provoked by acute steroid cessation. He was treated and discharged. Electrolyte abnormalities resolved, but NAGMA persisted. A few months later, he was readmitted with hypokalemia, contrasting labs, alkaline urine pH, and a positive UAG. NAGMA persistence suggested type I RTA. (Fig 1) Distal RTA was deemed secondary to his Sjogren's syndrome or nivolumab; it was treated with potassium citrate.

Discussion: Type I RTA, associated with autoimmunity, is caused by impaired distal convoluted tubule hydrogen ion excretion leading to high urine pH, a positive UAG, and hypokalemia. Type IV RTA is linked to hypoaldosteronism, aldosterone resistance, and renin-angiotensin-aldosterone blocking agents. It leads to low urine pH, hyperkalemia, and a positive UAG. Cortisol, like aldosterone, acts on mineralocorticoid receptors of the collecting ducts to activate the epithelial sodium channels (ENAC) and renal outer medullary potassium channels (ROMK) to facilitate electrolyte movement. We postulate that his type IV RTA was potentiated by exogenous steroid withdrawal while on lisinopril; once treated, the underlying baseline type I RTA was uncovered.

Table 1. Pertinent Laboratory Findings

		Baseline	First Admission Day 1	First Admission Day 2	Second Admission Day 1
Serum					
	Sodium (mmol/L)	127	123	129	126
	Potassium (mmol/L)	3.4	5.2	5.5	3.5
	Chloride (mmol/L)	104	112	106	109
	Bicarbonate (mmol/L)	20	19	21	13
	Anion Gap	10	8	9	9
	Glucose (mg/dL)	108	89	113	108
Urine					
	pH	None	<5	<5	>6.5
	Urine Anion Gap	None	Positive	Positive	Positive

PUB193

Severe Anion and Non-Anion Gap Metabolic Acidosis in a Patient with Hereditary Periodic Paralysis

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Introduction: Hypokalemic periodic paralysis (HPP) is a disorder of ion channels that may cause individuals to experience paralytic episodes. Treatment depends on the severity of the attacks. Patients are encouraged to increase potassium intake. Carbonic anhydrase inhibitors have been shown to be effective in reducing attacks in some patients.

Case Description: The patient is a 19-year-old female with a history of HPP (on Diamox, recently increased) who presented with a one-week history of increasing weakness with subjective fevers, night sweats, chills, dyspnea, wheezing, and diarrhea. On admission, the patient was hemodynamically stable with tachycardic. Labs included a respiratory viral panel positive for parainfluenza, high anion gap metabolic acidosis (HAGMA) (7.19/24/50/9, AG 21), and normal potassium (3.6). Laboratory studies suggested starvation ketosis with ketonuria and glucose of 68. Subsequent laboratory workup demonstrated alkaline urine (pH 8.0) and potassium drop to 2.3, indicating possible renal tubular acidosis type two (RTA2). HAGMA was secondary to ketoacidosis and non-anion gap metabolic acidosis (NAGMA) secondary to diarrhea and RTA2 due to chronic Diamox use. Treatment included potassium replacement progressively as a priority before normalizing her acidosis which had the potential to make her life-threatening hypokalemia worse. Therefore, a total of 200-270 per 24 hours mEq of KCL was given and a decision was made to give oral sodium bicarbonate since the bicarbonate drip at our hospital contains d5w which can make her hypokalemia worse. A renal function panel was ordered every four hours initially, observing for rebound hyperkalemia. EKGs were completed twice a day. Diamox was resumed at a lower dose once the patient stabilized. The patient's weakness continued to improve until back at baseline.

Discussion: This case underlines the complexity of managing a combined HAGMA/NAGMA in an HPP patient. The priority in managing similar patients should be carefully correcting hypokalemia in an ICU setting with EKG monitoring and immediately holding Diamox. Once the hypokalemia is corrected, start oral bicarbonate with IV fluids and oral feeding to reverse the ketosis. Careful correction of potassium and metabolic acidosis was necessary as the base defect was large, but treatment with bicarbonate could worsen hypokalemia.

PUB194

SLC34A3 Mutation: A "Non-Garden Variety" of Hypercalcemia

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Introduction: Hypercalcemia is a common reason for renal consultation. Measurements of parathyroid hormone (PTH), PTH-related peptide, 1,25$(OH)_2$ vitamin D (1,25D), and serum phosphorus are typically ordered. 1,25 hypervitaminosis prompts routine investigation for ingestion, granulomatous disease, or lymphoproliferative disorders. When a source is not obvious, further genetic testing should be considered.

Case Description: 60-year-old woman with diabetes mellitus type 2, hypertension, hyperlipidemia, chronic osteoarthritis, chronic pelvic pain, and history of rheumatic heart fever was referred for intermittent hypercalcemia, ranging between 9.9-11.2 mg/dL. Medications: amlodipine, atorvastatin, fenofibrate, glimerpiride, metformin, metoprolol, magnesium oxide, loratidine Vital signs: height 160 cm, weight 85.5 kg, blood pressure 145/62 mmHg, pulse 72 bpm, 36.2°C Physical exam: within normal limits Other laboratory findings: Serum phosphorus ranges between 2.6-3.8 mg/dL (2.4-4.7 mg/dL), albumin 4.1 g/dL (3.5-4.8 g/dL), PTHrp 16 pg/mL, (14-27 pg/mL), 1,25D_3 ranges between 67-82 pg/mL (18-72), PTH ranges between 28-49 pg/mL (15-65). 24-hour urine study: calcium 645 mg, creatinine 1.4 g, sodium 280 mmol, phosphorus pending. No bone abnormality of chest or hand radiographs Kidney ultrasound without stones or structural abnormality Genetic testing (Natera, Renasight) revealed heterozygous mutation of SLC34A3 gene.

Discussion: Genetic testing was positive for heterozous mutation of SLC34A3, a gene encoding the renal sodium-dependent phosphate cotransporter 2c (NaPi-IIc). In this condition, phosphaturia is thought to increase 1,25D synthesis to increase gastrointestinal (GI) absorption of phosphorus. The high 1,25D level simultaneously enhances GI aborption of calcium, causing hypercalcermia and corresponding hypercalciuria. At the time of this writing, urine studies for phosphaturia is pending. Presence of hyperphosphaturia would confirm the etiology of hypercalcemia as hereditary hypophosphatemic rickets with hypercalciuria, in which case, treatment would be phosphorus supplementation. In current heterozygous case, patient only develops abnormal calcium and phosphorus profile without associated bone involvement. Hypercalcemia has a wide differential diagnosis. A thorough search for its cause is warranted for direct and specific therapy.

PUB195

When History Repeats Itself: Metformin-Associated Lactic Acidosis

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Introduction: Metformin associated lactic acidosis (MALA) is a fatal phenomenon that clinicians often overlook. However, predisposing comorbidities such as CKD can make the patient more vulnerable to MALA, especially if the metformin dose is not appropriately adjusted. We present a patient with a suspected history of CKD, prior admission for suspected MALA, on high dose metformin who presented with severe lactic acidosis and acute kidney injury requiring dialysis.

Case Description: A 70-year old female with a history significant for diabetes and hypertension presented with nausea, vomiting, fatigue and confusion. Chart review showed that she had several hospitalizations before that were complicated by AKI requiring dialysis, including one in which MALA was suspected. Unfortunately, her home metformin dose (1000 mg BID) was never adjusted. Her GFR the previous year ranged from 30 to 60 ml/min per 1.73 meters squared, and creatinine remained around 1.1 mg/dL. Vitals on admission were 113/55 mmHg, heart rate of 111 bpm, respiratory rate of 28, and temperature of 97.1 F. On physical exam she was alert and oriented, appeared uncomfortable and had tachycardia. Creatinine was 6.2 mg/dl, with blood urea nitrogen of 40 mg/dL, lactic acid of 18 mmol/L, beta-hydroxybutyrate of 1.8 mmol/L, bicarbonate of 6 mmol/L, anion gap of 37 mmol/L, and initial pH of 6.63. She was initiated on maintenance fluids and sodium bicarbonate infusion, but continued to deteriorate, with lactic acid peaking at 40 mmol/L and she was intubated and transferred to the ICU. Her hospitalization was further complicated by shock requiring pressors and steroids. She was started on continuous renal replacement therapy. Within 24 hours her lactic acidosis resolved, her mentation improved, and she was liberated from the mechanical ventilator. Her home metformin was discontinued.

Discussion: While our patient was never officially diagnosed with CKD, there are several factors that raise suspicion for her having this chronic illness. Her average GFR the previous year, history of hypertension, diabetes, as well as prior episodes of AKI requiring hemodialysis warranted an evaluation for CKD. Patients who survive AKI have been shown to have an association with developing CKD. In the setting of recurrent admissions for AKI and CKD risk factors, providers should have a lower threshold for investigating potentially nephrotoxic medications.

PUB196

Drug-Induced Fanconi Syndrome Presenting as Chronic Constipation: A Well-Known but Forgotten Entity

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Introduction: Fanconi syndrome is a proximal renal tubular dysfunction characterized by renal wasting of electrolytes and solutes. Acquired Fanconi Syndrome is described in the context of various exogenous toxins, drugs, and systemic diseases. We present a case of long-standing constipation treated with a seemingly simple solution by identifying an often-ignored underlying etiology.

Case Description: This is a 59-year-old South Asian female with history of hypertension, diabetes, stage 3a chronic kidney disease, and chronic hepatitis B and C infection who presented to the hospital with complaint of persistent abdominal discomfort due to constipation for 3 weeks. She had prior hospitalizations for the same complaint. Her home medications included tenofovir disoproxil fumarate (TDF) which she had been taking for 10 years amongst others. Lisinopril and metformin were recently discontinued owing to a previous hospitalization for acute kidney injury. At presentation, labs were significant for severe hypokalemia (K 2.3), unresponsive to aggressive oral and intravenous potassium supplementation, mild hyponatremia (Na 131), hypophosphatemia (PO4 1.9), hyperchloremia (Cl 113), and acute on chronic renal dysfunction with BUN/Creatinine 20/2.17 mg/dL. Urinalysis showed a glucose of >1000 mg/dL and protein of 100 mg/dL. Further work-up of hypokalemia revealed a trans-tubular potassium gradient (TTG) of 5-6, indicating renal wasting. Tenofovir was suspected to be the culprit causing renal tubular acidosis and electrolyte derangements precipitating chronic constipation. Patient was switched to Entecavir after consultation with infectious disease. Follow-up during subsequent months showed correction of electrolyte abnormalities without the need for supplementation and resolution of constipation.

Discussion: Fanconi syndrome is a well-established entity, with a known association with Tenofovir. Clinicians often overlook the pathology leading to unnecessary work-up and prolongation of symptoms. In our case, simply discontinuing the drug helped correct the electrolyte derangements and prevent subsequent hospitalizations due to constipation. Physicians should closely monitor patients on medications known to induce Fanconi and keep this syndrome in the differential when dealing with multiple electrolyte imbalances and disproportionate glucosuria. Early identification can prevent progression of disease.

PUB197

Anion Gap Metabolic Acidosis in Chronic Acetaminophen Use: An Ongoing Conversation

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Introduction: In the inpatient setting high anion gap metabolic acidosis (HAGMA) is a common finding. Clinical approach to address HAGMA tends to focus on common etiologies such as lactic acidosis, diabetic ketoacidosis, uremia and others, usually overlooking acetaminophen toxicity as the underlying problem. Accumulation of 5-oxoproline has been described as causing HAGMA in chronic use of acetaminophen (APAP).

Case Description: 74yo female with medical hx of HTN, SLE, DM2, end-stage renal disease (ESRD) on hemodialysis (HD) Admitted for CABG and severe aortic stenosis repair. Last HD had been a day prior to surgery and resumed on POD1 as continuous veno-venous hemofiltration (CVVH). Scheduled medications included APAP, aspirin, heparin, hydroxychloroquine, pantoprazole, polyethylene glycol. On laboratory values Na 135 mEq/L, K 4.6 mEq/L, Cl 99 mEq/L, HCO_3 25 mmol/L, BUN 22 mg/dL, creatinine 3.02 mg/dL, glucose 88 mg/dL Ca 9.6 mg/dL and PO_4 4.5 mg/dL. Post-op complicated with altered mental preventing extubation, enterococcus bacteremia with septic shock requiring pressors. Started on ampicillin and cefepime antibiotic therapy, CVVH continued for 26 days. Transitioned to accelerated veno-venous hemofiltration (AVVH) thrice weekly. After AVVH was completed the patient developed metabolic acidosis with a bicarbonate of 16 mmol/L. Arterial blood gases pH 7.29, paO2 183 mmHg, pCO2 level 34 mmHg and bicarbonate level 16 mmol/L. Lactic acid level 0.8 mmol/L and D-lactic acid undetected. Due to acidosis CVVH was restarted on POD28. The following day bicarbonate was 24 mmol/L.

Discussion: Medication review showed scheduled APAP since prior to admission. There was low concern for ketones as the exogenous source of anions as insulin continued throughout the tube feedings. We inferred the increased HAGMA likely resulted from 5-oxoproline accumulation. APAP was discontinued on POD29, CVVH was discontinued the next day with intermittent HD provided on POD31on a thrice weekly schedule. Holding HD for greater than 48 hours, bicarbonate nadir was 21 mmol/L. Chronic acetaminophen use and 5-oxoproline should be considered in HAGMA when more common etiologies have been addressed. The use of RRT complicated the picture and delayed diagnosis. Most reported cases have been females with chronic medical conditions including renal insufficiency, malnourishment, sepsis.

PUB198

Unsettling Lactate Levels: A Hint Toward Metformin Toxicity

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Introduction: Metformin is a common and safe antidiabetic agent to treat diabetes mellitus (DM). Metformin-associated lactic acidosis (MALA) is a rare condition yet has high clinical deterioration and mortality rates. The following case illustrated a patient presenting with encephalopathy, found to have metabolic acidosis due to metformin toxicity.

Case Description: A 51-year-old male with a past medical history of atrial fibrillation, congestive heart failure, DM type II, hypertension, hyperlipidemia, and obesity presents with encephalopathy and respiratory distress. Physical exam was remarkable for somnolence, scleral icterus, bilateral lower limb edema and venous stasis dermatitis. His baseline serum creatinine levels were in the 1.10-1.20mg/dL range. Relevant labs at presentation revealed serum creatinine 2.77 mg/dL, blood urea nitrogen 34 mg/dL, potassium 8.3 mmol/L, bicarbonate 8 mmol/L, anion gap 39 mmol/L, and lactate 22.3 mmol/L. Metformin level was at 9.0 mcg/dL. Radiological workup was unremarkable. Patient went into circulatory shock requiring vasopressor support and mechanical ventilation. Continuous renal replacement therapy (CRRT) was initiated for severe hyperkalemia and acidosis. Sodium bicarbonate infusion was started to improve acid-base dyscrasia. He was transitioned to hemodialysis after hemodynamic stability was achieved. Hospital course was complicated with hospital aquired pneumonia and acute liver failure. After prolonged intubation, tracheostomy and percutaneous endoscopic gastrostomy were performed with no immediate complications. He continued to improve and remained stable, allowing discharge to a long term acute care hospital.

Discussion: According to the literature, therapeutic plasma metformin level ranges between 0.1 and 4 mg/ml, higher metformin levels are proposed to be a cause of lactic acidosis. Risk factors include individuals with decreased renal function, impaired hepatic metabolism and circulatory abnormality. Metformin stimulates lactate conversion and promotes substrates for lactate production, owing to unsettling lactate levels when it accumulates. MALA presents with nonspecific symptoms which can lead to delays in diagnosis. It is imperative that dialysis is promptly initiated for treatment, clearing metformin accumulation. Early suspicion and metformin levels in specific patients can lead to favorable outcomes.

PUB199

Hypokalemia-Induced Nephrogenic Diabetes Insipidus in an Adult with Severe Hyponatremia: A Case Report

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Introduction: Acquired nephrogenic diabetes insipidus (DI) can be due to kidney disease, medication adverse effects, or electrolyte derangements, such as hypokalemia. We report a case of acquired nephrogenic DI due to hypokalemia in the setting of severe hyponatremia.

Case Description: A 54-year-old man with hypertension and bipolar disorder on lithium therapy presented with nausea, vomiting, and fatigue for several days. Initial laboratory work showed metabolic alkalosis with venous blood pH of 7.61, serum bicarbonate of 41 mmol/L, serum sodium of 102 mmol/L, serum potassium of 2.0 mmol/L, and serum chloride of 60 mmol/L. Urinalysis showed low osmolality of 60 mOsm/kg and sodium of <20 mmol/L. The hyponatremia was attributed to a combination of psychogenic polydipsia and decreased solute intake and was treated

with fluid restriction. Subsequent hyponatremia overcorrection (>12mmol/L per day) with a continued urine output of 7-8 L/day was managed with dextrose 5% in water and desmopressin. Interestingly, urine osmolality remained at 63 mOsm/kg and did not increase after several doses of desmopressin, consistent with the diagnosis of nephrogenic DI, initially attributed to lithium use. However, after normalization of serum potassium, spontaneous urine concentration to 360 mOsm/kg was observed (Figure 1), suggesting hypokalemia-induced nephrogenic DI.

Discussion: This case illustrates the critical role that potassium plays in the urine concentrating ability of the kidney. Adequate serum potassium levels are necessary for the kidneys to respond to desmopressin, which is an essential tool in treating hyponatremia overcorrection. Rapid potassium repletion is often initially delayed to avoid hyponatremia overcorrection and its dramatic complications. However, hypokalemia can lead to acquired nephrogenic DI which can worsen hyponatremia overcorrection.

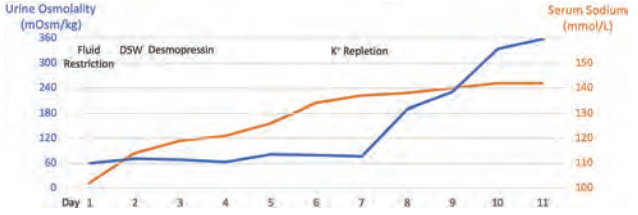

Figure 1. Serum sodium and urine osmolality trend over the course of the treatment. The urine osmolality did not increase with desmopressin administration. However, with potassium repletion, the urine osmolality started rising, suggesting a diagnosis of hypokalemia-induced nephrogenic diabetes insipidus.

PUB200

A Rare Case of Zonisamide-Induced Distal Renal Tubular Acidosis (RTA)

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Introduction: Zonisamide is a commonly used anti-epileptic drug which has been associated with side effects such as constipation and nausea. It has also been reported to cause distal renal tubular acidosis in the past but this is an exceedingly rare occurance. Upon review of literature, only one documented case report has been published showing the association between zonisamide use and RTA. In this case, we aim to further the knowledge of this seldom seen side effect.

Case Description: A 28 year old male with history of autoimmune limbic epilepsy and temporal lobectomy on zonisamide was admitted to our institution after being referred by PCP for hypokalemia and rhabdomyolysis. Prior to admission, he noted a myriad of symptoms such as myalgias, unsteady gait, and nausea. BMP on admission revealed potassium level of 1.6, serum chloride 115 and serum bicarbonate 2. EKG changes associated with severe hypokalemia were noted. He was started on continuous potassium replacement with IV as well as oral supplements. Despite adequate correction, his potassium level continued to drop and remained under 2 mmol/L. Workup showed normal serum aldosterone level. Serum and urine electrophoresis showed no evidence of monoclonal gammopathy. Renal ultrasound, CT abdomen and CT chest were all normal with no anatomical abnormalities or masses. Urine anion gap was inconclusive- neither significantly positive nor negative. Spot urine protein/creatinine ratio was 37.6 mg/g which was suggestive of urinary potassium losses. After ruling out other causes of potassium depletion, his medication list was reviewed and zonisamide was identified as a potential cause of hypokalemia. He was tapered off zonisamide and started on alternate therapy. He was eventually stablizied and discharged to home. Upon follow up labs in 6 weeks, his potassium had normalized and he was asymptomatic which further proved that zonisamide was the cause of distal RTA and severe hypokalemia.

Discussion: This case highlights the importance of thorough history and medication review which aids in diagnosing such challenging presentations. Although there is not much literature to support, zonisamide can cause RTA as shown in our case. Other anti epileptic agents have been studied such as topiramate which are implicated in RTAs, suggesting that agents previously which have not been studied might also have the potential for such side effects.

PUB201

Pseudonormokalemia

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Introduction: Thrombocytosis is a well known cause of "pseudohyperkalemia", whereby measured serum potassium is falsely elevated due to release from platelets after clotting once collected, which can be overcome by the addition of heparin. In clinical practice, heparinized tubes are used after identification of hyperkalemia to rule out pseudohyperkalemia. Rarely is this considered in the setting of normal serum potassium, but is still an important consideration in patients with thrombocytosis as a normal value may represent a total body deficit in potassium, known as "pseudonormokalemia". We present the case of a patient with thrombocytosis and normal measured serum potassium who developed metabolic alkalosis during diuresis, though found to have significant hypokalemia after heparinizing the collection tube.

Case Description: Our patient was a 53 yo man with HTN admitted to the cardiothoracic service for CABG after admission for STEMI. His course was complicated by AKI for which the nephrology consultation service was involved. His kidney function recovered during his admission, though with hypervolemia for which he was diuresed with IV furosemide. During his course he developed reactive thrombocytosis, and rising serum bicarbonate with apparent normal serum potassium (Figure1). After heparinizing potassium collection, significant hypokalemia (2.9 MEQ/L) was revealed in a patient with sensitive myocardium.

Discussion: We report the case of "pseudonormokalemia" in a patient diuresed with furosemide with concomitant reactive thrombocytosis. We believe this case highlights an important consideration in the evaluation of patients at risk for hypokalemia, and to consider use of heparinized collections in those with thrombocytosis regardless of their serum potassium level.

Laboratory test	T-3	T-2	T-1	T
Platelet Count (10^3/uL)	672	672	933	1,099
Sodium (MEQ/L)	131	131	133	135
Potassium (MEQ/L)	3.7	3.7	3.7	3.7
Heparinized Potassium (MEQ/L)	-	-	-	2.9
Chloride (MEQ/L)	88	88	84	85
Bicarbonate (MEQ/L)	29.7	28.0	35.1	33.7
Urea nitrogen (mg/dL)	87	85	83	76
Creatinine (mg/dL)	6.84	6.63	5.99	5.47

Figure 1-Trend in platelet count and basic metabolic profile during hospital admission. T represents day of heparinizing sample.

PUB202

Trimethoprim-Sulfamethoxazole-Associated Severe Hyponatremia

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Introduction: Trimethoprim-Sulfamethoxazole (TMP-SMX) is recommended as first line therapy for the treatment of *Pneumocystis Jirovecii* pneumonia. Although described in the literature, hyponatremia remains a rare complication of TMP-SMX treatment. Here, we present a case of severe hyponatremia in a hospitalized patient following treatment with high-dose intravenous TMP-SMX.

Case Description: 65-year-old female with metastatic lung cancer presented to our hospital for shortness of breath and fatigue. Pt. received a course of chemotherapy 4 days prior to presentation. Pt. was found to have *Pneumocystis Jirovecii* pneumonia and was initiated on high-dose intravenous TMP-SMX (430 mg trimethoprim and 86 mg SMX twice daily). SNa was 137 mmol/L (normal range 135-145 mmol/L) prior to initiation of TMP-SMX treatment. SNa subsequently decreased to 129 mmol/L the day after and decreased further to 118 mmol/L 3 days later. CT chest showed diffuse bilateral ground glass opacities concerning for infectious process vs pulmonary edema. Patient received intravenous furosemide therapy. SNa however decreased further to 114 mmol/ L. Hyponatremia work up revealed low serum osmolality of 250 mosm/kg, elevated urine osmolality of 481 mosm/kg, and inappropriately elevated urine sodium of 45 mmol/L. Patient was initiated on 3% hypertonic saline infusion. SNa improved but remained stable at 121 for the next 2 days. Intravenous TMP-SMX was subsequently discontinued. SNa gradually improved to 129 mmol/L, 2 days after discontinuation of TMP-SMX. Over the next few days, patient clinical condition worsened and died during the hospital stay.

Discussion: Patients receiving chemotherapy are at an increased risk for serious bacterial, fungal, and viral infections. Our patient was found to have *Pneumocystis Jirovecii* pneumonia. Treatment with high dose intravenous TMP-SMX resulted in severe acute hypo-osmolar hyponatremia. While the exact mechanism of hyponatremia secondary to TMP-SMX use remains unclear, inappropriate secretion of anti-diuretic hormone and renal salt wasting have been proposed in the past. Hyponatremia improved significantly in our patient soon following the discontinuation of TMP-SMX treatment. Clinicians should be aware of this potential and reversible adverse effect of this agent.

PUB203

Oxcarbazepine-Induced Hyponatremia

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Introduction: Antiepileptic medications are well known to induce hypoosmotic hyponatremia, however, the precise mechanism of action remains under debate, ranging from SIADH induction to psychogenic polydipsia. Unfortunately, these agents are often overlooked and continued upon hospital admission. We describe a patient who developed hypoosmotic hyponatremia in setting of recently started oxcarbazepine.

Case Description: 54F pmhx seizure disorder, hypertension, and COPD presented with the chief complaint of progressive shortness of breath and refractory nausea due to community acquired pneumonia and viral gastroenteritis, respectively. Chemistry panel

showed serum sodium 121 mmol/L (138 mmol/L one month prior), serum osmolality 262 mOsm/kg, potassium 4.1 mgl/dL, BUN 17 mg/dL, and serum creatinine 0.9 mg/dL. Vital signs showed blood pressure 128/73 mmHg and heart rate 72 BPM. Physical exam revealed euvolemic volume status with lack of altered mentation. Urine studies, obtained prior to fluid administration, revealed urine sodium 42 and urine osmolality 500 suggesting SIADH attributed to pneumonia and nausea. She was started on a 1.5L daily free water restriction and urea 15 mg BID and admitted to ICU for sodium monitoring. Home medications, including oxcarbazepine, were continued upon admission. The serum sodium failed to improve over the first 36 hours despite increasing urea powder to 30 mg BID and increasing fluid restriction to 1.2L. Medication review revealed continuation of home oxcarbazepine which, per patient history, was initiated three weeks prior to hospitalization. Oxcarbazepine, urea powder, and fluid restriction were stopped and neurology service consulted for implementing an alternative anti-epileptic agent. The serum sodium improved spontaneously, without additional intervention, from 121 mmol/L to 138 mmol/L, over the proceeding 72 hour time interval.

Discussion: Oxcarbazepine can result in hyponatremia refractory to the common therapeutic strategies used to treat SIADH. Our case illustrates the importance of reviewing the outpatient medication list as many pharmacologic agents can be continued upon admission, without discretion, ultimately contributing to refractory electrolyte abnormalities. Additionally, we must consider alternative etiologies, even in the setting of known SIADH stimuli, when common clinical practices fail to result in hyponatremia improvement as an unidentifiable etiology may be present.

PUB204

Salt Is Good: Correction of Hyponatremia in Heart Failure with Dietary Sodium

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Introduction: Hyponatremia is the most common electrolyte imbalance in patients with acute decompensated heart failure. It is associated with increased mortality, hospitalizations and can pose challenges with management of volume overload. The mechanisms of hyponatremia in heart failure are high levels of antidiuretic hormone coupled with low glomerular filtration rate and the use of loop and thiazide diuretics. We present a case highlighting the complexity of sodium balance in acute decompensated heart failure.

Case Description: A 65-year-old female with CHF with preserved EF (60-65%), pulmonary hypertension, CAD, Type II diabetes, atrial fibrillation, CKD, presented with acute decompensated heart failure and volume overload. Diuresis was started with bumetanide on day 1 of the hospitalization. Chlorthalidone was added on day 5. This was switched to Metolazone on Day 7. On admission, sodium was 134 mmol/L and down trended to a low of 121 mmol/L on hospital day 13. This was accompanied by significant nausea and vomiting. Despite strict free water restriction and a diuretic holiday, hyponatremia persisted. She was then encouraged to eat ramen (2167 mg Na per serving) and given salt tablets in addition. Free water restriction was continued as well and so were the loop diuretics. Thiazide diuretics were held. Serum sodium subsequently improved to 131 mmol/L with improvement in symptoms. She was discharged in a euvolemic state on a home regimen of bumetanide and oral salt.

Discussion: We present a case of hypotonic hyponatremia in acute decompensated heart failure. The first line management of hyponatremia in heart failure is diuresis and dietary sodium restriction. However, hyponatremia may be induced or worsened in these patients by multiple mechanisms including SIADH- like physiology and use of thiazide diuretics. In such cases, adherence to a sodium restricted diet while on diuretics may worsen hyponatremia. Increased access to dietary salt with concomitant free water restriction may correct this problem as demonstrated in our patient. Using dietary sources of sodium may work just as effectively as giving hypertonic saline (1770 mg Na per 150 ml bolus). Further studies are needed to elucidate the underlying mechanisms and reproduce similar results on a larger scale.

PUB205

Opening the Gates: Tolvaptan for Chronic Hyponatremia

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Introduction: Hyponatremia is a well-studied electrolyte imbalance, and despite established guidelines for its management, it is often difficult. In patients with CHF, hyponatremia is a predictor of death, which makes it important to treat promptly and effectively.

Case Description: A 63-year-old male with a past medical history of CKD stage 2, atrial fibrillation, heart failure, mitral valve replacement, aortic aneurysm repair, and hypothyroidism was admitted with a left hip fracture secondary to a ground-level fall, COVID-19 pneumonia, and severe hyponatremia with mild hypokalemia. Upon initial evaluation, the patient was disoriented with signs of volume depletion, including dry oral membranes, and decreased capillary refill. Laboratory evaluation was remarkable for a sodium level of 114 mEq/L, serum osmolarity of 251 mOsm, and urine sodium of less than 10 mEq/L, consistent with hyposmolar hypovolemic hyponatremia. After a 24-hour trial of isotonic fluid and potassium repletion, the serum sodium improved to 117 mEq/L, and potassium levels were corrected. 0.9% Normal saline was continued with improvement of sodium to 122 mEq/L in a 48-hour period. At this point, the patient's mental cognition improved, he was alert and oriented. Over the next 72 hours, sodium levels remained unchanged, and the patient started developing signs of volume overload. Isotonic fluids were discontinued, and a fluid restriction diet plus diuretic therapy was initiated. Volume status improved, but with only mild changes in sodium levels. To correct the sodium level to at least 130 mEq/L for the patient to undergo surgery for his fractures, a trial of tolvaptan 7.5 mg PO daily was initiated, resulting in a rise in serum sodium to 127 mEq/L in the first 24 hours, and a level of 130 mEq/L in 72 hours. Diuretic therapy was discontinued and tolvaptan was continued for the remainder of the hospitalization, with the sodium level reaching 134 mEq/L by day 26 of therapy. He was able to undergo surgery, tolvaptan was discontinued, and the patient was discharged home with normal sodium levels.

Discussion: Tolvaptan is a breakthrough in the treatment of hyponatremia, particularly in patients with SIADH, but its use in patients with HF has also been of great support. This case is an example of its effectiveness in this population.

PUB206

Hypo-Hypercalcemia of Rhabdomyolysis

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Introduction: Rhabdomyolysis (RD) is the breakdown of skeletal muscle, with release of intracellular contents including electrolytes and enzymes, which can result in AKI. Hypocalcemia is commonly associated; however, hypercalcemia after initial hypocalcemia has been reported. The pathogenesis of hypercalcemia remains unclear with multiple theories. We report a case of hypo-hypercalcemia associated with cocaine induced rhabdomyolysis.

Case Description: A 42-year-old male with a history of polysubstance abuse presented with septic shock along with cocaine intoxication leading to severe muscle damage, cardiac arrest, and oliguric AKI, requiring HD. On admission, CK level was 103510 U/L, BUN 28 mg/dL Creati 2.8 mg/dL, and Corrected Ca 6.7 mg/dL. 1 week after the admission, his Ca level started to normalize; However, after 20 days he developed hypercalcemia with Ca values ranging from 10.3 to 12.8 mg/dL with PTH 16.3 pg/mL and 1,25(OH)2 D <8.0 pg/dL. His AKI did not show any improvement with a GFR < 15 mL/min, still oliguric and eventually became HD dependent. The hypercalcemia was managed with intermittent doses of calcitonin when the level rose above 12.0 mg/dL. After 1 month, his clinical condition started to deteriorate, and he passed away.

Discussion: Disturbance in Ca homeostasis has been observed in cases of rhabdomyolysis-induced AKI. Initial Hypocalcemia is due to sequestration of Ca associated with hyperphosphatemia in the destroyed muscle. Subsequent hypercalcemia may occur during the recovery phase of AKI caused by RD. The pathophysiology of hypercalcemia has remained a subject of debate. Some believed that the pathophysiology of hypercalcemia occurring in the recovery phase of RD induced AKI, was from resorption of Ca from injured muscle and transient hyperpara. However, others believed that the mechanism of hypercalcemia is the dissolution of deposited CaPO4 from the damaged muscles, in which the deposits were shown in the technetium pyrophosphate scan. This case supports the hypothesis that remobilization of calcium deposits from damaged muscle is the main element of delayed hypercalcemia, as the PTH and 1,25(OH)2 D levels were suppressed during the period of hypercalcemia. However, our patient was unique in presentation as his hypercalcemia occurred while on HD as opposed to during renal recovery. We want to increase awareness of this phenomenon with our case report.

PUB207

Octreotide-Induced Hyperkalemia

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Introduction: Sulphonylurea agents are widely used in the treatment of type II diabetes. Hypoglycemia is a major side effect with renal impairment and long acting SUAs as risk factors. Octreotide is a synthetic somatostatin analog that is a potent inhibitor of growth hormone, glucagon, and insulin and used to treat relapsing or refractory hypoglycemia induced by SUAs.

Case Description: 43-year-old male with obesity, hypertension, diabetes, sleep apnea, heart failure, hyperlipidemia, recent hospitalization for hypoglycemia, CKD 5 nearing dialysis. Presents with asymptomatic hypoglycemia with BS ranging 20-50s for two days not resolved with oral glucose. He had discontinued Semaglutide since last admission and on Glipizide at admission. Vitals were BP 138/80mmHg, Pulse 93 bpm, Temp 97.8 F, Resp 21/min, sat 96% on 3L of NC(85% on RA), BMI 48 kg/m2. Labs significant for K 5.6 MeQ, BUN 52 mg/dl, Creat 8.06 mg/dl, Glucose 45mg/dl, Insulin 7.05mIU/L, Ph 7.24, PCo2 66mmHg, Lactate 1.3mmol/L, U/A had Protein 300, large blood, trace leucocyte esterase, RBC 73, Glucose, ketone, bilirubin, nitrite, WBC, cast were neg. U/S showed bilaterally increased echogenicity and simple renal cysts. After hypoglycemia did not resolve with D5W. He was transferred to ICU for D10 infusion and started on Octreotide SQ. His hypoglycemia resolved but he developed severe hyperkalemia at 7.3 MeQ without EKG changes, which did not resolve with medical therapy. He required HD. His potassium improved but continued HD for CKD5.

Discussion: Octreotide, similar to somatostatin, directly inhibits the release of insulin from the pancreas, preventing rebound hypoglycemia, as compared to dextrose infusions for SUAs overdoses. The mechanism of octreotide induced hyperkaliemia is most likely due to the suppression of insulin release, which impairs cellular potassium uptake resulting in an increased extracellular potassium concentration. While octreotide is primarily metabolized in the liver, some experts suggest that dosage modification may be necessary due to reduced clearance. Although there have only been a few reported cases in the literature, we suspect that hyperkalemia induced by octreotide may be more

prevalent and may be attributed to other factors. Therefore, our case report aims to raise awareness of this potential complication and contribute to a better understanding of octreotide-induced hyperkalemia.

PUB208

The Alkaline Tube: A Dangerous Tide

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Introduction: Metabolic alkalosis is the most common acid-base disorder in critically ill patients. When severe (pH>7.55) it is associated with significantly increased mortality. Here, we have a critically ill patient in the setting of severe metabolic alkalosis who was treated successfully with hemodialysis (HD). The case highlights the importance of recognizing nasogastric tube (NGT) suction as a source of severe metabolic alkalosis, as well as rapid intervention.

Case Description: An 83-year-old man with HTN, CAD, HFrEF, DM, and CKD IV (baseline Cr 2.6 mg/dL) presented with nausea, vomiting, and abdominal pain. He was found to have SBO and was treated with NGT decompression at an outside hospital. NGT output increased over 4 days up to 7L in 24 hours. Bicarbonate increased to >50mmol/L on day 4 with ABG showing pH 7.63; bicarbonate was estimated at 78mmol/L based on Henderson-Hasselbach equation. He only received NS at 100 mL/h for 4 days despite rising NGT output. He developed anuric AKI with a creatinine of 6.7mg/dL with fatigue, muscle twitching, and tremors. He was sent to the ICU due to recurrent ventricular arrhythmias, then was transferred to our institution for HD due to severe metabolic alkalosis and anuric AKI. Despite the ICU team's attempt to place a dialysis catheter, adequate blood flow for dialysis was not achieved. A new catheter was not placed until the following morning delaying HD for around 12h. Post-HD ABG showed a pH of 7.45 and bicarbonate 33mmol/L. The patient was eventually able to stop dialysis and was discharged.

Discussion: This patient developed severe metabolic alkalosis due to loss of gut HCl. The underlying physiology is a chloride-sensitive alkalosis that may be treated with NS and repletion of potassium, however in the setting of his oliguric AKI, he was unable to secrete adequate bicarbonate. His case illustrates a few important pitfalls; first, high NGT output should have prompted major adjustments to therapy; receiving NS at 100mL/h led to gross undertreatment of his chloride losses. Second was underestimating his acuity upon arrival in the ICU; he had been experiencing significant ventricular arrhythmias and was at high risk for seizures and death, however, the malfunctioning dialysis catheter took more than 12h to replace. This patient ultimately had a good outcome but illustrates common pitfalls that many providers could make in the management of severe metabolic alkalosis.

PUB209

Linezolid-Induced Lactic Acidosis

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Introduction: Linezolid is used to treat many gram-positive bacterial infections. Its use has increased with the emergence of many multi-drug resistance organisms. Lactic acidosis is a rare but potentially fatal adverse effect of linezolid. Here we discuss a case highlighting the importance of prompt recognition of Linezolid-induced severe lactic acidosis.

Case Description: A 41-year-old woman with ovarian cancer complicated by severe lower extremity lymphedema presented to the emergency department with worsening bilateral lower extremity swelling and pain after failed outpatient antibiotic therapy. Initial workup included a CT scan of the lower extremities concerning for necrotizing fasciitis. Her course was complicated by septic shock, temporarily requiring pressor support, eventually improving after surgical debridement and antibiotic initiation. She received a 4-week course of Ampicillin/Sulbactam, Minocycline, Linezolid, and Voriconazole based on wound culture results. She continued to have severe metabolic acidosis with elevated lactate levels of upwards of 16mmol/L despite clinical improvement and resolution of septic shock nearly 3 weeks following initial presentation. After other etiologies of continued metabolic acidosis were excluded, Linezolid was promptly discontinued. Hemodialysis was performed to enhance drug clearance. Her lactic acidosis improved after 3 days of renal replacement therapy.

Discussion: Linezolid is a bacteriostatic oxazolidinone that inhibits initiation of bacterial protein synthesis at the 50S ribosome demonstrating activity against multidrug-resistant gram-positive bacteria. Though very rare, type B lactic acidosis is a known (potentially fatal) complication that occurs following impairment of mitochondrial protein synthesis and reproduction. It can occur at any point during the course of linezolid use. Treatment is largely supportive and hemodialysis has been shown to assist in drug clearance in a few documented case reports. As described in the literature, it may take approximately 7-14 days for Linezolid to be eliminated even without evidence of renal dysfunction. Currently, no guidelines exist regarding timing of initiation of hemodialysis. However, we believe hemodialysis should be initiated following suspicion of linezolid toxicity along with prompt drug discontinuation in events of severe metabolic and lactate acidosis, acute renal failure or failure to improve despite supportive care.

PUB210

A Case of Uremic Optic Neuropathy

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Introduction: Uremia is the accumulation of urea in the blood; typically secondary to retention due to kidney dysfunction. Damage to the optic nerve due to its toxicity can lead to visual defects and eventual blindness. Initial management is treating the underlying cause but may require emergent hemodialysis to rapidly filter out the excess urea.

Case Description: 29 year old male with unknown past medical history presents with bilateral blurry vision. Initial labs confirmed BUN of 166 mg/dl, Creatinine of 27 mg/dl and e-GFR of 2 (ref range: 60-89). CT scan of the abdomen showed bilateral shrunken kidneys. Fundoscopy confirmed findings of optic neuropathy. Inflammatory and autoimmune work up was sent for his glomerulonephritis. Per his labs, he met criteria for CKD stage V and was started on peritoneal dialysis; vision improved after 3 sessions and was discharged in stable condition.

Discussion: Uremia can be caused by retention of waste products in the blood due to kidney dysfunction. Accumulation of uremic toxins in the optic nerve can lead to ischemia and optic nerve damage causing visual disturbances; from blurriness to complete loss. In one study, out of 278 patients studied with CKD, 4.7% were found to have uremic optic neuropathy with prevalence proportional to the extent of renal dysfunction [1]. Another study of 93 patients with end stage renal disease found that incidence of 7.5%; risk factors included age, longer duration of renal failure, and higher serum levels [2]. Cataracts are also common uremic patients. Retinopathy in uremic patients can be caused by various mechanisms including ischemia, hypertension, and diabetic nephropathy [3]. These studies highlight the importance of early recognition and treatment of uremic optic neuropathy in patients with renal dysfunction. Managing the underlying cause of renal dysfunction is the first step. As in our case, hemodialysis is often required to remove uremic toxins and prevent further optic nerve damage. 1. Greven CM, Slusher MM, Weaver RG. Uremic optic neuropathy. J Clin Neuroophthalmol. 1985;5(2):93-99. 2. Kim NR, Kim YH, Kim JH, et al. Optic neuropathy in patients with end-stage renal disease undergoing dialysis. Graefes Arch Clin Exp Ophthalmol. 2011;249(2):297-304. 3. Maconachie GDE, Renouf D, Downie LE. Ocular manifestations of systemic disease: uremia. Curr Opin Ophthalmol. 2018;29(6):556-562.

PUB211

Renal/Cerebral Salt Wasting in a Patient with COVID-19

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Introduction: Renal salt wasting (RSW), commonly known as cerebral salt wasting (CSW), a less recognized cause of hyponatremia, which has mostly been reported in patients with CNS disease, can also be associated with other medical conditions. Hyponatremia has been reported with COVID-19 infection, mostly multifactorial due to loss of sodium ions in the digestive tract, SIADH, and poor intake. It has only rarely been reported with COVID-19. We report a case of COVID-19 infection-associated hyponatremia due to renal/cerebral salt wasting.

Case Description: A 95-year-old male with a history of dementia, hypertension, hyperlipidemia, stage 3a chronic kidney disease, and prostate cancer presented to the emergency department with cough, sore throat, and a positive home COVID-19 test. Initial workup revealed normal chest X-ray, WBC count of 8.0, serum sodium of 121 mmol/L, potassium of 4.6 mmol/L, chloride of 87 mmol/L, BUN of 20 mg/dL, creatinine of 1.1 mg/dL, serum osmolality of 252 mOsm/kg, urine osmolality of 460 mOsm/kg, urine sodium of 32 mmol/L, cortisol of 14.7 mcg/dL, TSH of 3 uIU/mL, uric acid of 2.6 mg/dL, and fractional excretion of uric acid (FEUric acid) of 12.8%. He had no diarrhea but reported decreased oral intake. He remained mentally alert, had a mild cough, and maintained adequate oxygen saturation on room air. Intravenous fluids (IVF) were administered, improving sodium levels to 126 mmol/L. However, upon discontinuation of IVF, the sodium decreased to 115 mmol/L, eventually improving over several days with the re-initiation of IVF, reaching a level of 133 mmol/L. Repeat FEUric acid remained elevated at 11.97%, and serum uric acid remained low at 3.5 mg/dL. He was discharged with improved laboratory results and remained stable during follow-up visits.

Discussion: Differentiating RSW/CSW from other causes of hyponatremia is important due to different treatment approaches. Both RSW/CSW and SIADH have similar clinical parameters like high urine osmolality and sodium, low serum uric acid, and high FEuric acid initially. However, the FEuric acid improves in SIADH after an improvement in sodium levels but not in CSW. SIADH is usually treated with fluid restriction in addition to other measures. While RSW/CSW is treated with volume repletion as patients have intravascular volume depletion. This case signifies that RSW/CSW should be in the differential diagnosis of patients with COVID-19 and hyponatremia.

PUB212

Hyponatremia Causing Confusion, or Confusion Causing Hyponatremia?

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Introduction: Hyponatremia can present with vomiting, confusion and sezures. This case discusses hyponatremia caused by LGI1 Associated Limbic Encephalitis.

Case Description: 75 year old female presents after having tonic clonic movements of upper and lower extremities. Physical examination shows a laceration at her temple and alert to self only. Labs show WBC of 14.2 K/uL, Na of 117mmol/L, K of 2.8 mmol/L,

osmolality of 248 Osm/kg H_2O, Urine osmolality of 726 Osm/kg H_2O and urine Na of 74 mEq/L. CT head showed no acute intracranial abnormality. Seizures are attributed to hyponatremia; normal saline at 100 mL/hr was started and patient's Na decreased to 113 mmol/L and she had multiple seizures. Hypertonic saline is started but Na is unchanged. Lumbar puncture is normal. EEG monitoring showed numerous clinical episodes, and she has cognitive impairment, startle trigger, ocular dysfunction and gait dysfunction. MRI brain showed subtle right lentiform nucleus enhancement. CSF is sent out for viral and autoantibody screening and there is anti-leucine rich anti glioma 1 protein (anti-LGI1) present. Solumederol and plasmaphoresis for 5 days is started. Na increases from 113mmol/L to 130mmol/L and patient's neurological symptoms resolves.

Discussion: Limbic Encephalitis affects the amygdala, thalamus hypothalamus and medial temporal lobes of the brain causing behavioral disturbances, changes in personality and cognitive behavior; seizures, and psychiatric symptoms. It is a paraneoplastic syndrome associated with small cell lung cancers, germ cell tumors of the testis and tumors of the ovaries. It can be associated with infections, immunosuppression and autoimmune encephalitis. Auto-antibodies associated with the autoimmune encephalitis include N-methyl-D-Aspartate receptor, glutamate 1 and glutamate 2 receptors, and leucine rich anti glioma 1 protein (LGI1). The severe hyponatremia is because it is expressed in the hypothalamus and has excess release of ADH, which correlates with our patient leading to a picture of syndrome of inappropriate ADH. Additionally, LGI1 is also expressed in the tubules of the kidneys. Treatment is high dose steroids, IVIG, and plasmapheresis. Many develop malignancies and require frequent screening. In conclusion, although confusion and seizures are symptoms of hyponatremia, if it does not resolve with traditional fluids; the confusion can cause hyponatremia and encephalitis needs to be considered.

PUB213

Successful Treatment of a Rare Profound Lactic Acidosis and Anuric AKI due to Metformin-Associated Lactic Acidosis

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Introduction: Metformin therapy in patients with reduced kidney function can generate toxic levels since these drugs are almost entirely removed by kidney, resulting in lactic acidosis. We report a case of metformin induced lactic acidosis in a patient with AKI.

Case Description: A 73-year-old female with a past medical history of type 2 Diabetes, hypertension, seizure, cardiovascular disease sent from Nursing home for hypotension, hypoglycemia and altered mental status. Her medications included metformin 500mg bid, metoclopramide, risperidone, ondansetron. On exam, blood pressure 92/42mmHg, and O2 saturation 96% on 3L nasal cannula, respiratory 20 breaths/min, Heart rate 53 beats/min, and temperature 35.6 °C. Initial lab workup showed VBG PH 6.9 with Pco2 32mmHg HCO3 6 mmol/L lactic acid 21 mmol/L beta-hydroxybutyrate 6.9 mmol/L, Cr 2.6mg/dL (per family, no history of kidney disease) BUN 90 mg/dL, potassium 5.5 mmol/L, sodium 143 mmol/L, chloride 95mmol/L, glucose 30 mg/dL, WBC 10.86 K/uL which revealed high anion gap metabolic acidosis with compensated respiratory alkalosis and anuric AKI. Serum metformin level was collected and sent. Salicylate level and acetaminophen level is low. Patient was treated with intravenous hydration with NS, bicarbonate therapy and antibiotics for suspected pneumonia without improvement in acidosis hence emergency hemodialysis with minimal ultrafiltration was initiated for possible metformin associated lactic acidosis. After 1 hemodialysis session, bicarb improved to 18 mmol/L, lactic acid 5.2 mmol/L, ABG showed PH 7.24. We repeated hemodialysis next day, bicarb improved to 25 mmol/L without metabolic acidosis and lactic acid improved to 2.4 mmol/L. Patient started to make good urine and Cr improved from 2.6 to 1.2 and normalized 3d after second hemodialysis. Metformin level returned a week later to be elevated at 9.1 mcg/ml with therapeutic range of 1-2mcg/ml.

Discussion: This case illustrates complexity in interpretation of the cause of lactic acidosis in a patient with septic shock and metformin toxicity or a combination of both since there is no additional biomarkers, but also illustrates the need for aggressive treatment of septic shock and early initiation euvolemic hemodialysis support to reduce metformin levels and to correct metabolic acidosis.

PUB214

1,4-Butanediol Overdose: An Unrecognized Toxidrome

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Introduction: Butanediol (BD) is an industrial solvent, used for plastic manufacture. Illicit recreational use is associated with central nervous system (CNS) depressant effects ("date-rape drug") and euphoria. Overdose can be lethal, but often unrecognized. We present a case of possible toxic alcohol exposure, turned out to be BD overdose.

Case Description: 43yo man, found obtunded in a mechanical shop. Last seen normal 30 minutes prior, at same location. Field vitals unavailable. On admission: BP 146/97mmHg, HR 53, T33.9°C RR 20, obtunded, myotic pupils, no clonus. Unresponsive to naloxone and flumazenil, then intubated. Gastric aspirate showed a red sweet smelling liquid. Initial labs: Normal CBC Na 141 K 3.3 Cl 98 CO2 17 AG 26 BUN 13 Cr 0.98 Glu 115 Ca 9.0 Alk Phos 110 AST 207 ALT 319 TBili 0.46 Alb 4.3 Lactate 7.4 BHB (-). Vbg pH 7.35 pCO2 34. Acetaminophen, salicylate, EtOH and UDS(-). Labs 2h later were essentially unchanged & EtOH still (-). Measured serum Osm 312 with osmolal gap (OG) of 23. Nephrology consulted for ethylene glycol (EG) poisoning suspicion, fomepizole started. Labs 3h later had lower AG and OG (20 and 11, respectively), inconsistent with EG overdose. Patient extubated on the next day and endorsed ingesting 1,4-BD. EG and methanol levels were negative.

Discussion: *In vivo*, BD is quickly metabolized to gamma-hydroxybutyric acid (GHB), an inhibitory neurotransmitter (GABA B receptor agonist) that causes euphoria and sedation. BD poisoning mimics other toxic alcohols toxidromes, but is not detected on traditional drug screening tests. An increased OG is typically present, and supportive care is the mainstay therapy. No antidote is available. Concomitant ingestion of ethanol increases its toxicity, and the use of EtOH as a competitive substrate for alcohol dehydrogenase is contraindicated. The majority of patients can be managed without dialysis, as GHB has a rapid clearance and short duration of clinical effects (between 2-5h). **Take away lesson:** BD overdose can be lethal. The presence of an increased OG with negative tests for other toxic alcohols may be a diagnostic clue. Management is supportive care.

PUB215

Topiramate Causing a Mixed Renal Tubular Acidosis: A Case Report

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Introduction: Topiramate is an anti-seizure medication that gained popularity in use for migraine prophylaxis. We report a case of hyperchloremic non-anion gap metabolic acidosis in a patient on Topiramate for migraine prophylaxis for. With its growing utility it is crucial to be cognizant of it's adverse reactions for prompt management.

Case Description: A 43-year-old female with a medical history of CAD, CKD 3b secondary to HTN, COPD, and migraine headaches presented with progressive confusion of 3 days witnessed by family. She was hemodynamically stable but had expressive aphasia on neurological exam. CT head without contrast showed no acute process. UDS was negative, acetaminophen, salicylate level, and ethanol levels were unremarkable. pH: 7.27/CO2:42/HCO3:19 on VBG. Serum Na: 147/Cl:121/K+:4/HCO3:22/Cr:1.4(at baseline)/BUN:32. UA: no proteinuria, nitrites, leukocyte esterase, or blood. Urine Na:131/Ur Cl:147/Ur K:34.6/Ur Cr:109.7/Ur pH:6.0/Ur anion gap:18.6/Ur osmolal gap:345. CPK:71. D5W with 100mEq of sodium bicarbonate at 100cc/hr was initiated. Her mentation returned to baseline with follow-up VBG:7.22/49/20, hypernatremia resolved. Respiratory acidosis was due to underlying COPD and NAGMA due to RTA from topiramate use(100mg daily for migraine prophylaxis). The patient was discharged home on oral sodium bicarbonate supplements with a plan to discontinue topiramate outpatient after discussuion with neurology.

Discussion: Topiramate is known to cause RTA by inhibition of carbonic anhydraze in both proxomal and distal tubule. Once a NAGMA has been established, urine pH, urine bicarb excretion, urine anion gap/osmolal gap, urine citrate, and beta-2 microglobulin can be used to differentiate between Type 1 and Type 2 RTA in the absence of GI loss. Type 1 has urine pH >5.5, urine Na>25 mEq/L, low urine ammonium, and citrate excretion. Type 2 has urine pH <5.3, increase urinary HCO3 and beta 2 microglobulin excretion. Our patient had urinary studies showing mixed RTA with increased urinary pH, low ammonia excretion (positive anion gap), and no concern for Fanconi syndrome(seen with type 2). Metabolic acidosis may lead to hyperventilation, altered mentation, nausea, vomiting, nephrolithiasis, and osteoporosis. Checking serum bicarbonate levels before initiation and at regular intervals in patients on the medication can help prompt management. Adequate hydration and alkali therapy is the mainstay of treatment.

PUB216

Slow Supratherapeutic Tylenol: A Recipe for Acidosis

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Introduction: Acute acetaminophen (APAP) toxicity is the most common cause of liver transplantation in the US. However, its chronic ingestion can lead to depletion of the glutathione cycle, accumulation of 5-oxoproline (pyroglutamic acid), and development of severe high anion metabolic acidosis (HAGMA). Here we describe a case of a young woman admitted with severe persistent metabolic acidosis that required kidney replacement therapy after prolonged consumption of APAP.

Case Description: Briefly, a 37 y.o. female with a history of type II diabetes, heart failure, and recent left trans-metatarsal amputation due to gangrene was admitted due to shortness of breath and altered mental status. Her medications included metformin, spironolactone, sacubitril-valsartan, and hydrocodone-APAP. Her initial bicarbonate level was only 3 mEq/L, and her arterial pH was 7.01, BUN 17 mg/dL, creatinine 1.5 mg/dL, glucose 307 mg/dL, Na 129 mEq/L, K 5.6 mEq/L, Cl 101 mEq/L, Albumin 3.4 g/dL, anion gap 25 mmol/L (corrected 26.5), serum osmolality 305 mOsm/kg, alkaline phosphatase 249 U/L, ALT 70 U/L, AST 65 U/L. The beta-hydroxybutyrate level was only 0.32 mmol/L, and lactic acid 5.8 mmol/L. Urinalysis had no ketones, urine pH 5, and urine drug screen was negative. She was intubated and admitted to the intensive care unit. She was started on a bicarbonate drip and broad-spectrum antibiotics. Due to persistent acidosis, prolonged intermittent kidney replacement therapy (PIKRT) for 6 hours was started, followed by continuous kidney replacement therapy (CKRT). Sent-out tests were obtained: blood for metformin level showed a therapeutic range of 1.7 mcg/mL, and urine for pyroglutamic acid showed markedly increased excretion. Further history review with her husband revealed that the patient had been taking 3-4 tablets of APAP every 4-6 hours for the past 3 weeks for pain. The patient was diagnosed with severe HAGMA due to acquired pyroglutamic acidosis in the setting of chronic APAP toxicity. Eventually, she had adequate resolution of acidosis and was discharged to a long-term acute care facility.

Discussion: Pyroglutamic acidosis is under-recognized and can be a fatal cause of severe high anion gap metabolic acidosis. High clinical suspicion in the setting of risk factors and early recognition are paramount in improving outcomes. CKRT was beneficial in this situation to improve acidosis in the critical care setting.

PUB217

Symptomatic Uremia Without Significant Azotemia

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Introduction: Uremia is a clinical syndrome encompassing many non-specific symptoms such as anorexia, nausea, and fatigue. Typically, uremia occurs once the glomerular filtration rate (GFR) dips below 50% of average normal GFR, and overt uremia is not usually observed in patients with GFR greater than 10 ml/min and BUN lower than 100 mg/dL. In addition, the BUN represents one of many organic waste products that accumulate with decline in GFR and does not appear to contribute much to the uremic illness.

Case Description: A 61-year-old woman with CKD stage 3b secondary to diabetic nephropathy presented to the emergency department from nephrology clinic for acute kidney injury. Over the past year she had been losing weight due to intractable nausea, vomiting, diarrhea, and decreased appetite. During this time, she was at CKD stage 3b with blood urea nitrogen (BUN) ranging 28-39 mg/dL. Due to hyperbilirubinemia and elevated transaminases, she underwent extensive GI workup including gastric emptying study, abdominal CT and MRI, EGD, and liver biopsy. She was diagnosed with gastritis due to Helicobacter pylori infection which was treated without resolution of her symptoms. The liver biopsy showed hepatic steatosis and congestive hepatopathy. Nephrology was consulted and, though the BUN was only mildly elevated with a peak of 53 mg/dL, the patient was started on inpatient hemodialysis (HD) with marked improvement in her symptoms. After her second day of HD, she ate an entire personal pizza with no emesis when two days prior there were discussions regarding whether she should be started on total parenteral nutrition due to her prolonged anorexia and significant malnutrition.

Discussion: Uremia represents a constellation of symptoms related to accumulation of organic waste products as the GFR falls. The often-subjective nature of the diagnosis of uremia poses a great diagnostic challenge in patients such as this with rather unremarkable BUN levels. Diagnosis of uremia in the absence of significant azotemia represents an important gap in the extant literature because patients with symptoms impacting their overall quality of life would benefit from earlier initiation of renal replacement therapy (RRT) and may be spared expensive and invasive testing as a result. This case is an excellent reminder not to anchor on the BUN level when considering whether a patient has overt uremia requiring initiation of RRT.

PUB218

Drug-Induced Fanconi Syndrome with Hyperphosphatemia

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Introduction: Fanconi syndrome is characterised by proximal renal tubular dysfunction leading to hypophosphatemia, hypokalemia, hyperchloremic metabolic acidosis, glycosuria, and aminoaciduria. It is usually an inherited condition diagnosed in children, but can be acquired in adults as well, commonly due to drugs such as antimicrobials, antivirals, anticancer drugs, and valproate.

Case Description: An 81-year-old male presented from a nursing home with complaints of severe generalized weakness, and was found to have significant volume depletion, along with a potassium of 1.7, metabolic acidosis, acute kidney injury, and rhabdomyolysis. During the hospitalization, despite aggressive supplementation, he continued to have severe refractory hypokalemia and hyperchloremic metabolic acidosis. However, interestingly, the patient initially had hyperphosphatemia. Urine studies revealed glycosuria, proteinuria, and inappropriate sodium, potassium and phosphate wasting with increased fractional excretion of these electrolytes. After extensive work up ruled out other causes of these metabolic derangements, the leading differential was Fanconi syndrome. The patient had been recently started on valproate for bipolar disorder which is a known cause of Fanconi syndrome. However, one of the defining features of Fanconi syndrome is hypophosphatemia, whereas our patient had hyperphosphatemia. This was likely secondary to rhabdomyolysis, which might have been caused either by hypokalemia itself or prolonged immobility due to hypokalemia induced weakness. Another possible contributor was transcellular phosphate shift secondary to Fanconi syndrome induced metabolic acidosis. The patient's valproate was held and all electrolyte levels started improving. As expected in Fanconi syndrome, the initial hyperphosphatemia transitioned towards hypophosphatemia as the rhabdomyolysis and metabolic acidosis improved, and eventually normalized.

Discussion: Patients with Fanconi syndrome may have incongruous lab findings due to other causes, such as our patient with hyperphosphatemia due to rhabdomyolysis despite increased urinary phosphate excretion. It is thus important to critically examine every part of the clinical picture, in order to avoid erroneously ruling out the diagnosis. Urinalysis and electrolytes should be regularly checked in patients on valproate therapy as it is a known cause of Fanconi syndrome.

PUB219

Idiopathic Recurrent Serositis After Bilateral Nephrectomy in ADPKD

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Introduction: Nephrectomy in autosomal dominant polycystic kidney disease (ADPKD) is performed in up to 40% of patients being evaluated for renal transplant. Indications are recurrent or hemorrhagic cysts, urinary tract infections, large size of native kidneys or intractable pain. The most common complications are blood loss, iatrogenic bowel injury, and death due to sepsis. Few case reports have described recurrent ascites as a postoperative complication, usually of hepatic origin. This case describes recurrent serositis following bilateral nephrectomy with no apparent liver pathology.

Case Description: GP is a 72-year-old male with advanced CKD due to ADPKD. He underwent bilateral nephrectomy prior to a living unrelated donor transplant with hemodialysis planned as a bridge. In March 2022, he had open bilateral nephrectomy complicated by a liver laceration. Coagulation and liver function tests remained normal. He returned to the hospital 2 months later with complaints of worsening abdominal distention. CT showed new large bilateral pleural effusions, a pericardial effusion, and ascites. The pericardial effusion was drained, and pericardial biopsy showed no histologic abnormality or evidence of malignancy. Pleural fluid was transudative. Cytology and cultures were unremarkable. Initial ascitic fluid was indicative of portal hypertension, yet several repeats were not suggestive of portal hypertension. He was evaluated for tuberculosis, hepatitis B and C, lupus, and scleroderma, all of which were negative. An echocardiogram showed a newly reduced ejection fraction 30-35%, which recovered after CABG in June 2022. Transjugular liver biopsy in December 2022 was negative for cirrhosis or portal hypertension. He required biweekly paracentesis with removal of 6-8 L until the fluid tapered and resolved by January 2023. In February 2023 he received a deceased donor renal transplant. At 3 month follow up creatinine was 0.97 mg/dL with no further serositis.

Discussion: Bilateral nephrectomy for ADPKD has rarely been associated with recurrent ascites. Iatrogenic chylous ascites and ascites due to hepatic venous outflow obstruction or polycystic liver disease have been described. Neither non-iatrogenic pleural nor pericardial effusions following nephrectomy in ADPKD were seen on literature review. This case highlights serositis after nephrectomy, a yet undefined complication.

PUB220

Gitelman Syndrome: A 12-Year Diagnostic Challenge

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Introduction: Gitelman syndrome (GS), also known as familial hypomagnesemia-hypokalemia is an inherited salt-losing tubulopathy characterized by hypokalemic metabolic alkalosis with hypomagnesemia and hypocalciuria. Mutations in SLC12A3 gene is the underlying cause which results in defects in the apical sodium chloride cotransporter also known as the thiazide sensitive cotransporter in the distal convoluted tubule. GS is rare and inherited in autosomal recessive fashion with an estimated incidence of 1 in 40,000.

Case Description: We present a 26-year-old woman referred to the nephrology clinic for evaluation of chronic hypokalemia. It was first noticed at the age of 14, she reported several hospital admissions requiring treatment for hypokalemia. She was once admitted to the ICU after developing temporary paralysis which resolved with K+ replacement. She was subsequently prescribed 40mEq b.i.d of KCL. Her previous lab work showed K in range of 2.5-3 mmol/L and metabolic alkalosis. She denied any cramps, palpitations, weakness, polydipsia, salt cravings, vomiting, use of laxatives or diuretics. She reported taking OTC Mg supplements daily. Clinical examination was unremarkable. Her weight was 50kg with BMI 17.9 and BP was 116/79. Lab work showed aldosterone 24.7ng/dL and renin 14 ng/mL/h with a normal ARR of 1.76, other labs are shown in Table.1. She was counseled on likely diagnosis and informed consent was obtained to perform genetic testing which confirmed GS.

Discussion: The criteria for suspecting diagnosis of GS include; chronic hypokalemia with inappropriate renal K wasting (FeK > 9%); Metabolic alkalosis; Hypomagnesemia with inappropriate renal Mg wasting (FeMg > 4%); Hypocalciuria (spot urine Ca:Cr < 0.07mg/mg) 0.05mg/mg in this patient; High plasma renin activity (normal levels 0.6 – 4.3ng/mL/h); Fractional excretion of Cl > 0.5%; Low or normal-low BP and normal renal US. Clinical diagnosis can be challenging due to substantial number of mimics. Demonstrating biallelic mutations in SLC12A3 achieves a molecular genetic diagnosis of GS.

Table.1

Electrolyte	Serum value (unit)	Urine value (unit)	Fractional Excretion (FeX)
Potassium (K)	3.9 mmol/L	35 mmol/L	14.6%
Bicarbonate (HCO3)	25 mmol/L		
Magnesium (Mg)	1.6 mg/dL	5.74 mg/dL	5.8%
Calcium (Ca)	9.8 mg/dL	2.2 mg/dL	
Chloride (Cl)	104 mmol/L	82 mmol/L	1.3%
Creatinine (Cr)	0.7 mg/dL	43 mg/dL	

PUB221

Importance of Genetic Testing in APO L1 Nephropathy

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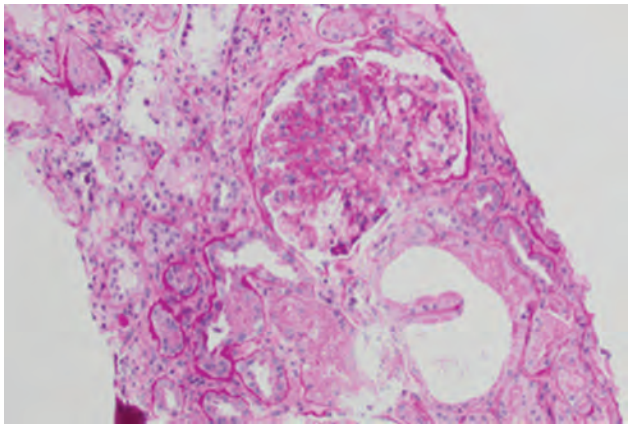
Introduction: A 28-year-old non-diabetic, non-hypertensive female from West Africa (Mali) with pertinent history of pulmonary embolism, latent TB, recently diagnosed with H pylori on triple therapy, came to nephrology office for evaluation of proteinuria. Pertinent family history of ESRD on dialysis in 2 first degree relatives. No h/o smoking or alcohol use. Physical exam grossly normal.

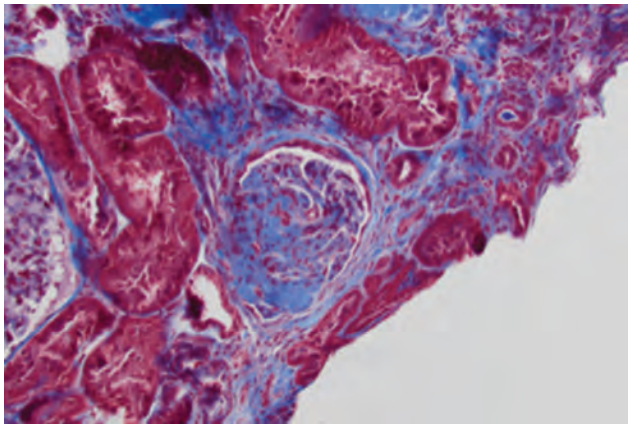
Case Description: Initial labs showed creatinine 1 mg/dl, GFR 58. UA 1+ protein. UPCR of 2.3 g. Renal ultrasound showed increased echogenicity, normal size and cortical thickness. Serological work up for proteinuria including hepatitis B/C, HIV, ANA, SPEP

and UPEP was negative. Renal biopsy was performed for proteinuria. Pathology showed FSGS. Genetic testing was performed remarkable for homozygous APOL1 gene. She was CKD stage 3b/4 at the time of diagnosis of APOL1 nephropathy. Then progressed to ESRD now on hemodialysis.

Discussion: In 2010, genetic variants were discovered in the apolipoprotein L1 [APOL1] gene that explained a surprisingly large fraction of this major health disparity. Understanding the biology of APOL1 gene risk variance has been advancing at a molecular level [1] [2]. APOL1 gene is 1 of the 6 members of the APOL gene family on human chromosome 22. It is a naturally occurring gene that can be found in many organs of the body, including the podocytes of the kidneys [1]. Approximately 13% of African-Americans carry two APOL1 risk alleles. These variants termed G1 and G2, are a frequent cause of kidney disease-termed APOL1 nephropathy [2]. Spectrum of APO L1 nephropathy include HIV associated nephropathy [HIVAN], primary focal segmental glomerulosclerosis (FSGS), Lupus collapsing glomerulopathy, sickle cell disease nephropathy, and hypertension-attributed arterionephrosclerosis [6]. KDIGO 2021 guidelines for the management of glomerular diseases updated classification of FSGS into 4 types. One of them is genetic cause which includes APOL1 nephropathy leading to ESRD [3]. APO L1 kidney disease tends to be progressive, and current standard therapies are generally ineffective [2]. Multiple studies have demonstrated that APOL1 high risk donor kidneys fail at higher rates than non-risk kidneys, whereas the recipient APOL1 genotype has not yet been shown to affect graft survival [1].



PAS stain showing focal and segmental sclerosis



Trichrome stain

PUB222

Genetic Testing in Hemodialysis Patients

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Background: There is currently little available knowledge on potentially pathogenic genes present in patients on dialysis. The purpose of this study is to describe the prevalence of positive findings as well as variants of undetermined significance in an actively treated hemodialysis patient population.

Methods: At a large suburban academic medical center dialysis unit, patients were consented for genetic testing during dialysis treatment. Massive parallel genetic sequencing was performed using a panel of 385 genes with testing through Renasight platform via Natera Inc.(Austin, Texas, USA) (TM). Clinical parameters, demographics and vintage on dialysis were collected. Clinical care was not impacted for any patient regardless of their decision to participate.

Results: 75 of the 122 HD patients consented to enrollment. Genetic testing results were received for 71 patients. At the time of this analysis, four patients' results are pending. 66 identified as non- Hispanic while 9 identified as Hispanic. 31 patients identified themselves as white, 21 as African American, 14 as Asian and 10 chose not to report. Results are summarized in Table 1. 11 (15.5%) patients were found to have a gene allele meeting criteria to cause kidney disease. 27 (38%) patients were found to be carriers of autosomal recessive gene alleles known to cause kidney disease. 32 (45%) patients were found to have genes of unknown significance only. We were especially interested in APOL1 risk gene alleles. Of the 11 patients found to have a kidney disease causing gene allele, 6 patients were found to be positive for APOL1. 3 patients were heterozygous for the APOL1 gene but had 2 allele copies, and 3 were homozygous positive.

Conclusions: In an academic suburban center HD unit, 15.5% of HD patients were positive for disease causing genes and 45% of the patients have variance of unknown significance genes. Further studies will be needed to better understand the genetic disease prevalence and relevance in the ESKD population.

Category	Number of Patients
Patients consented	75
Patients with testing results	71
Patients with at least one gene identified	70 (98.6%)
Positive pathogenic genes causing kidney disease	11 (15.5%)
Carrier of pathogenic genes only	27 (38%)
Variance of unknown significance	32 (45%)

PUB223

Genetic Analysis and Minigene Splicing Assay of a New Splicing Variant of the COL4A5 Gene Causing Alport Syndrome

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Background: The aim of this study is to examine the genetic characteristics of a patient with Alport syndrome (AS) and confirm the existence of splice variant.

Methods: The study focused on a patient with AS who received a diagnosis at the Department of Nephrology of the affiliated Hospital of Inner Mongolia Medical University. Whole exome sequencing and Sanger sequencing were performed to identify gene variation sites. Additionally, mRNA abnormal splicing was conducted to investigate the impact of the variation on transcripts. 3D structure of the variant protein was analyzed. Immunofluorescence and immunohistochemistry were performed on the renal tissues of the patient to confirm the presence of AS kidney injury.

Results: Gene sequencing revealed that the patient had a splice variant c.835-9T>A in the *COL4A5* gene, which was not observed in either of the patient's parents. The experiment conducted in vitro revealed that the mutation c.835-9T>A (p.279_297del) resulted in the deletion of 57bp in exon 15 of the *COL4A5* gene mRNA. This deletion caused the loss of amino acid residues from positions 279 to 297, which in turn, impacted the stability of the secondary structure of the α5 chain encoded by the *COL4A5* gene. These amino acids are conserved across various species and their damage can be observed through evolution. The results of homology modeling indicated that the trimerization of Col-IV with the mutated α5 chain could be achieved, however, the 3D structure was found to be severely distorted. The diagnosis of AS kidney damage was confirmed through immunofluorescence results. Following the variant rating guidelines of the American Society for Medical Genetics and Genomics, c.835-9T>A was rated as a probable pathogenic variant (PVS1_Moderate+PS3_Moderate+PM2_Supporting+PS2+PP3+PP4).

Conclusions: The c.835-9T>A mutation in the *COL4A5* gene has been identified as the cause of disease in AS patients. In vitro experiments have confirmed that this mutation leads to splicing variation. Additionally, histopathological examination of the kidneys has provided in vivo evidence for the pathogenicity of the mutation and has expanded the spectrum of mutations associated with the *COL4A5* gene.

Funding: Government Support - Non-U.S.

PUB224

Glomerulopathy with Fibronectin Deposits Caused by an FN1 Mutation in a Large Family with Variable Clinical Presentation

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Introduction: Glomerulopathy with fibronectin deposits is a rare hereditary kidney disease with autosomal dominant inheritance. Mutations in the FN1 gene encoding fibronectin have been identified as responsible and account for 40% of cases. Light microcopy findings are non-specific. Electron microscopy shows: subendothelial and mesangial electron dense deposits with a granular or fibril-like structure.

Case Description: We describe a family with a diagnosis of focal and segmental glomerulosclerosis (FSGS) in whom the genetic test was crucial for a correct etiological diagnosis. The index case was a 46-year-old female with FSGS. Her mother had chronic kidney disease (CKD) with proteinuria and microhematuria as well as two maternal aunts (one deceased and the other one with FSGS on hemodialysis since 37 years old). Her deceased maternal uncle started hemodialysis at 42 years old, she also had a dead brother with FSGS who was a kidney transplant recipient, two maternal male cousins with CKD (one dead with kidney allograft) and two maternal female cousins with CKD (one of them with advanced CKD). The index patient received prednisone for 6 months and developed adverse effects. Interestingly, the patient and relatives had traumatological complaints,

but with unremarkable neurologic findings. Electron microscopy was not available. We performed a massive parallel sequencing for 70 genes known to be associated with FSGS and detected a heterozygous *FN1* mutation: NM_212482:exon8:c.A1123G, p.(Thr375Ala) which segregated with the disease. This information motivated the performance of a kidney biopsy in one of the female cousins who presented with proteinuria 0.73 g/day and normal creatinine clearance. It showed absence of hypercellularity and discrete mesangial matrix expansion. Immunohistochemistry revealed mesangial and pericapillary fibronectin staining. Electron microscopy: 70% foot process effacement and mesangial and subendothelial electron dense deposits, some with fibrillar substructure and others finely granular.

Discussion: Here we emphasize the importance of genetic testing when a familial renal disease is suspected, encouraging the use of non-standard histopathologic techniques for a correct diagnosis, like fibronectin immunohistochemistry stain in this case.

PUB225

Renal ANCA+ Vasculitis Concurrent with Fabry Nephropathy: Coincidence or Complication?

Michael L. West, Laurette Geldenhuys. *Dalhousie University, Halifax, NS, Canada*.

Introduction: Fabry disease (FD in an X-linked disorder of glycosphingolipid metabolism with chronic inflammation triggered by Gb3 and lysoGb3 metabolites. Various forms of glomerulonephritis (GN) and inflammatory disease have been reported with FD. Immune complex GN has complicated enzyme replacement therapy (ERT). GN including antineutrophilic cytoplasmic antibody (ANCA) disease has also been reported in association with COVID19 vaccination and infection. We report the case of a 73 year-old woman with type 1 diabetes mellitus, Fabry disease and COVID19 vaccination on ERT who presented with acute ANCA+ GN. Was Einstein right, there is no such thing as coincidence?

Case Description: The patient had stable diabetes since age 27, normal kidney function and low grade proteinuria 1 year prior. ERT (agalsidase alfa 0.2 mg/kg i.v. q2 wks) was given for 3 years for Fabry hypertrophic cardiomyopathy with moderate diastolic dysfunction. COVID19 vaccination was given 4 months prior to development of dyspnea, and acute kidney injury with microscopic hematuria. There was no extra-renal disease. Anti-myeloperoxidase (MPO) ANCA was positive. Renal biopsy showed focal proliferative GN with crescents plus background diabetic and Fabry nephropathies. She required hemodialysis. Despite treatment with glucocorticoids and Rituximab, there was no renal recovery. ANCA measurement in 83 FD adults revealed and negative results in 24M, 59F; transient false positive anti-PR3 ANCA occurred in 1M in which renal biopsy showed Fabry nephropathy plus an immune complex GN.

Discussion: FD has been previously reported with with renal vasculitis ANCA+ (antiPR3) in 1 patient and ANCA- in 2 patients. This is the first such case in which FD was already diagnosed and ERT given. ANCA associated vasculitis and other forms of GN usually occur within 90 days of COVID19 vaccination, mean 19 days, which does not fit with the observed time course in this case. The chronic inflammation of FD plus increased circulating MPO, the association with other GNs and other inflammatory conditions including vasculitis, the presence of kidney and lysosomal ANCA antigens, all suggest that vasculitis with or without ANCA is a rare complication of Fabry disease and Einstein was right. While our case did not improve with immunosuppressive therapy, others have, which suggests that FD patients should be treated for this serious but rare complication.

PUB226

A Decentralized Registry for Adults and Children with Alport Syndrome: Alport Syndrome Foundation (ASF) Alport Patient Registry Design

Lisa Bonebrake,[1] B. A. Weinstock,[1] Joshua Henderson,[2] Femida Gwadry-Sridhar.[2] [1]*Alport Syndrome Foundation, Phoenix, AZ;* [2]*Pulse Infoframe, London, ON, Canada*.

Background: The ASF Alport Patient Registry is a retrospective and prospective longitudinal, web-based, decentralized registry of patients of all ages with Alport syndrome (AS) in the USA. Genetic testing has become the primary means by which AS patients are correctly diagnosed in the USA. As such, newly diagnosed and engaged AS patients and their caregivers – as opposed to medical record repositories – are in a unique position to populate an up-to-date registry. The registry's primary objective is to collect real-world data to improve understanding of the natural history of AS; characterize kidney and non-kidney symptom presentation and diagnosis in patients; understand treatment practices and outcomes; and understand the quality of life and burden of disease. The registry also provides patient education resources and facilitates patient-centric research and therapeutic development.

Methods: Eligible patients of all ages with a verified clinical diagnosis of AS will be invited to participate. Diagnosis will be verified by a certified genetic counsellor or treating physician based on genetic test results -or- familial history, clinical signs, and kidney biopsy pathology if genetic results are inconclusive. Via web-based portals, patients or their caregivers will complete an initial survey and periodic follow-up surveys for as long as the participant chooses to be enrolled. Data collected are based on AS patient and clinical researcher inputs and include disease profile; medical, familial, and treatment histories - in particular RAASi and/or SGLT2i treatments; and genetic variant(s), audiological, and kidney laboratory results. Demographics and lifestyle characteristics are collected at enrolment and participant surveys are included at follow-up.

Results: Registry enrolment opened in May 2023. Data are anticipated for presentation in 2023.

Conclusions: The registry will be the first longitudinal registry in adult and pediatric AS patients collecting key determinants of patient management and outcomes, including the patient experience from diagnosis and treatment. The registry is positioned to become the primary US platform for real-world AS data that will facilitate education of patients and caregivers, inform clinical decision-making, and contribute to the development of therapeutic strategies with a better understanding of patient impact.

Funding: Private Foundation Support

PUB227

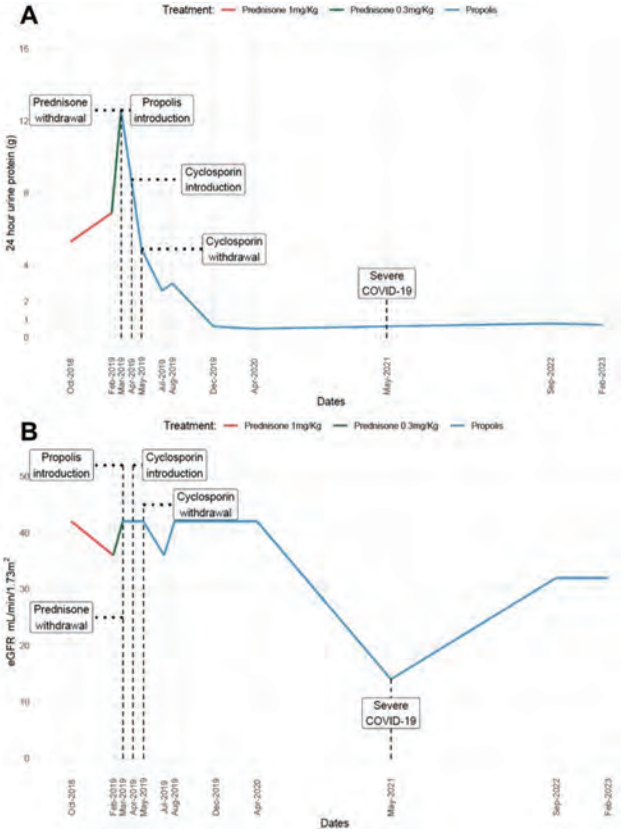
Collapsing Glomerulopathy (CG) in a Patient with High-Risk Apolipoprotein L1 (APOL1) Genotype: 4-Year Clinical Evolution of Use of Standardized Brazilian Green Propolis Extract (EPP-AF)

Marcelo D. Silveira, Sergio P. de Souza, Isadora G. Dultra, Ludmila B. Santos, Marcelo Lopes, Luis M. Conceição, Paulo benigno P. Batista, Rogerio Passos. *Hospital Sao Rafael, Salvador, Brazil*.

Introduction: Apolipoprotein L1 (APOL1) is expressed in podocytes and gene variants of high renal risk are associated with cell injury and glomerular damage. Collapsing glomerulopathy (CG) is one of the phenotypic expressions of these variants. Immune and inflammatory mechanisms may be related to its genesis, and specific treatments are not yet a reality. We hereby present data concerning the 4-year clinical evolution of a patient with APOL1 mutation of high renal risk in homozygosity and in use of standardized Brazilian green propolis extract (EPP-AF).

Case Description: A 41-year-old woman diagnosed with nephrotic syndrome in October, 2018, with proteinuria of 5.3 g/day at the time. Kidney biopsy revealed CG. The patient used prednisone 1 mg/kg for 12 weeks, showing no improvements and was found to have proteinuria of 12.6 g/day at the end of tapering in February, 2019. She did not tolerate ciclosporin. She has initiated the use of EPP-AF in March, 2019. Currently, four years later, the patient has proteinuria of 0.7 g/day. Glomerular filtration rate (GFR) was kept stable between 36-42 ml/min/1.73 m^2 for more than two years until the moment the patient had severe Covid-19 and GFR dropped and is currently at 32 ml/min/1.73m^2 .

Discussion: APOL1 mutation of high renal risk may be associated with CG with a poor prognosis. Covid-19 may be associated with more severe damages among these patients. Typical immunosuppression is oftentimes ineffective. The use of EPP-AF in this case was able to control nephrotic syndrome for four years.



PUB228

A 2-Year Analysis of Collagen IV Mutations in the Minho Region, Portugal

Sofia H. Marques, Maria Lopes-de-Almeida. *Hospital de Braga, Braga, Portugal*.

Background: Monogenic diseases represent 10-15% of chronic kidney diseases (CKD). More than 400 genes have been associated with hereditary nephropathies. However, genetic testing for kidney diseases remains scarce. Pathogenic mutations in COL4A3,

COL4A4 and COL4A5 may underlie different diseases such as isolated hematuria, Alport syndrome, diabetic kidney disease and focal segmental glomerulosclerosis (FSGS). In Portugal, there are regional diagnostic practices and patterns of genetic diseases. Our aim is to analyze the results of Braga Hospital concerning collagen IV mutations in the last 2 years.

Methods: We reviewed medical records and genetic test results of patients with variants in type IV collagen genes. A targeted panel covering 3 genes (COL4A3-5) using next generation sequencing (NGS) based on whole exome sequencing was applied. In certain cases, a larger panel covering genes implicated in FSGS was used.

Results: Approximately 1800 new patients attended our Nephrology department during 2021 and 2022. During this period, 62 patients underwent genetic testing to search for a hereditary cause of kidney diseases. In particular, 29 were tested for mutations in COL4A3-5 using the 3-gene (18 cases) or a larger FSGS NGS panel (11 cases). All patients were unrelated, 15 were women, mean age was 55±15 and 20 had a family history of CKD. Most were refered for CKD of unknown cause, microhematuria and proteinuria; 6 had hearing loss and 10 had a biopsy showing FSGS. Pathogenic variants were found in 4 patients and variants of uncertain significance (VOUS) in 5. The remainder had negative results. Of the 4 pathogenic mutations, all were heterozygous; 3 affected COL4A4 and the other COL4A3. These patients had a median creatinine of 1mg/dL (range 0.8 – 2.6mg/dL), median protein/creatinine urinary ratio of 1g/g (range 0.3-3.4g/g), 3 were women and 3 had kidney biopsies with FSGS. Of the 5 VOUS, 3 were in COL4A4, 1 in COL4A3 and 1 in COL4A5, in a female patient.

Conclusions: Despite probable underdiagnosis, genetic tests improved diagnostic accuracy even after renal biopsy. The clinical spectrum of heterozygous variants of COL4A3, COL4A4 or COL4A5 in female carriers varies: most likely they are disease modifiers for a range of kidney diseases, one of which, as occured in our series, is FSGS. Further research is needed to better understand their role in nephropathies other than Alport syndrome.

PUB229

Autosomal Dominant Tubulointerstitial Kidney Disease due to Uromodulin Mutation (ADTKD-UMOD)

Aarzoo Gupta, Anuroop Yekula, Susant O. Gurung, Ashish Verma. *Saint Vincent Hospital, Worcester, MA.*

Introduction: ADKTD-UMOD is a rare genetic disorder manifesting as a slowly progressive chronic kidney disease that usually leads to end-stage kidney disease (ESKD). Here we present a patient with a typical presentation of ADKTD-UMOD-related CKD.

Case Description: A 51-year-old white male with long-standing hypertension was evaluated a decade ago for slowly progressive CKD. He had 300-1000 mg/d proteinuria. Urine sediment was bland. Kidney imaging, hepatitis B & C titers, C3 & C4, ANA, SPEP, UPEP & IF were negative. CKD was attributed to hypertensive kidney disease and efforts were directed at suppressing proteinuria and keeping blood pressures consistently below 130/80 mmHg with ACEI/ARB. After relative stability for about 4 years, creatinine started to worsen rapidly. Sediment showed WBC casts and the patient mentioned he was taking a kidney health herbal supplement. This was stopped and a brief trial of steroids ensued with transient improvement of creatinine only to relapse a few months later. The above workup was repeated and was negative but a kidney biopsy showed tubulointerstitial nephritis besides with secondary adaptive FSGS, over 50% globally sclerosed glomeruli, and over 60% cortical atrophy with advanced arterial and arteriolar hyalinosis. A repeat course of steroids made no difference and was rapidly tapered off. A renal genetic panel was performed, and the patient tested positive for UMOD gene variant c.317 G>T which is known to be associated with ADTKD-UMOD. The patient was provided genetic counseling for the self and at-risk family. He is currently under evaluation for home dialysis and kidney transplantation.

Discussion: Uromodulin (UMOD), also known as Tamm-Horsfall protein is exclusively produced in the kidney. It regulates salt transport and protects against urinary tract infections, stones, and immune-mediated insults. Approximately 1% of patients with CKD stages 3–5 have UMOD gene mutations. ADTKD-UMOD is considered rare and mostly remains unrecognized due to the paucity of genetic testing. The disease is often insidious without characteristic hematuria or proteinuria. As no treatment options are as yet available for halting disease progression, dialysis and transplantation are often the primary therapy modalities. Full genome analysis might be helpful in identifying the etiology of CKD, prognostication, and family counseling.

PUB230

A Peculiar Case of Hypercalcemia

Aarzoo Gupta, Anuroop Yekula, Felipe Fernandez del Castillo. *Saint Vincent Hospital, Worcester, MA.*

Introduction: Hypercalcemia is common in adults and typically results from increased calcium and Vitamin D intake or from hyperparathyroidism. With the increased feasibility of genetic testing, various underlying gene defects have surfaced in previously idiopathic hypercalcemic cases. Here we present a scenario of a rare genetic cause for persistent hypercalcemia, complicated by recurrent kidney stones.

Case Description: A 23-year-old male with a history of hypertension presented with gross hematuria. Abdominal imaging revealed a 1 cm ureteral stone with bilateral medullary nephrocalcinosis. The retrieved stone fragments consisted of calcium oxalate. Metabolic testing showed hypercalcemia of 11 mg/dl, with low 25 OH D and PTH levels. Kidney function and other electrolytes were normal. A 24-hour urine collection revealed increased urinary calcium excretion of 260 mg/day and decreased urinary citrate of 236 mg/day. He was instructed to increase fluid intake, start potassium citrate supplements and adhere to his thiazide diuretic. In spite of adherence to these recommendations, he continued to have symptomatic nephrolithiasis, prompting additional workup. A SPEP with immunofixation, ACE levels, TB testing, and PTHrP were unremarkable. His 1,25 OH-D level was elevated at 90 pg/mL. Given a strong family history of nephrolithiasis, a comprehensive genetic analysis was sent demonstrating a homozygous loss-of-function defect in the CYP24A1 gene which has been previously reported as a cause of hypercalcemia.

Discussion: Genetic causes of hypercalcemia have been identified in recent years with the advent of clinically practical genetic testing. In our patient, a previously reported rare gene mutation of the CYP24A1 was noted as the source of hypercalcemia. CYP24A1 encodes the enzyme 24-hydroxylase, which is typically responsible for calcitriol breakdown. Homozygous inactivating mutations in this enzyme can cause PTH-independent hypercalcemia, hypercalciuria, and nephrolithiasis. Because the mechanism of hypercalcemia is from hypervitaminosis D due to deficiency of 24-hydroxylase, therapy should be directed at lowering vitamin D levels. Drugs like fluconazole inhibit the activity of 1-alpha hydroxylase and can be used to reduce active vitamin D levels, restoring normal calcium balance. Our patient was started on fluconazole 50 mg, with subsequent normalization of his serum calcium level and no further stone episodes.

PUB231

Extrarenal Manifestations of Atypical Hemolytic Uremic Syndrome: A Systematic Review and Meta-Analysis

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Background: Atypical Hemolytic Uremic Syndrome (aHUS) is a chronic thrombotic microangiopathy (TMA) resulting from abnormal alternative complement pathway activation. Although renal vasculature is commonly targeted, aHUS can involve many organ systems. Our review investigates the incidence and clinical outcomes of aHUS patients with extrarenal manifestations.

Methods: The literature search was conducted through PubMed/Medline, Embase, Web of Science Core Collection, and CINAHL. The search criteria comprised terms such as 'aHUS', 'extrarenal', and various individual organ systems. Clinical features specific to the patient were collected, including extrarenal involvement, laboratory values, genetic abnormalities, and adverse outcomes. The meta-analysis was completed using SPSS version 22.

Results: In total, 47 studies were included encompassing a sample size of 890 aHUS patients. The most widely reported genetic abnormalities were in factor H (CFH) mutations [12% (84/700 patients); n=19 studies] and anti-FH IgG antibodies [27.1% (102/376 patients); n=10 studies]. The most commonly occurring extrarenal manifestations across the included studies were related to the central nervous system [28% (240/858 patients), n=32 studies], with seizure being the most-common CNS symptom. This was followed by the gastrointestinal system [31% (230/741 patients); n=25 studies] and the cardiovascular system [16% (97/607); n=23]. The proportion of aHUS patients with end-stage renal disease was reported across 11 studies in 13.2% (61/463 patients) of this subpopulation, and the mortality rate was 8.9% (56/632 patients) across 27 studies.

Conclusions: Extrarenal manifestations were present in approximately 20-30% of aHUS patients, depending on age and organ system. Our findings indicate neurologic and gastrointestinal involvement to be the most incident. Studies infrequently report genetic findings and are limited in population size, warranting larger multi-centered cohort investigations.

PUB232

Hereditary Renal Amyloid and Kidney Transplantation

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Introduction: Lysozyme amyloid is a rare cause of end stage kidney disease which can present with a wide range of symptoms. We present a patient with this genetic condition with a positive family history, who has since undergone a successful transplant.

Case Description: Our patient presented at the age of 63 to the renal outpatient department with elevated creatinine; 185umol/L and a urine albumin-creatinine-ratio of 3.7mg/mmol after routine testing. She did not have a history of diabetes or hypertension. It was known that her son had the diagnosis of lysozyme amyloid, and she underwent genetic testing, along with a renal biopsy. The biopsy showed renal amyloidosis with deposits largely restricted to the interstitium and artery/arterioles. The glomeruli were preserved explaining her low proteinuria despite amyloid deposition. Within 3 years she had progressive kidney failure requiring consideration of kidney replacement therapy. During transplant work up, she had a positive faecal occult blood testing and colonoscopy showed gut mucosal involvement of amyloid with numerous irregular round eosinophilic acellular nodules in the lamina propria, also positive on the Congo red stain. There was no cardiac involvement. With careful consideration, she underwent a directed living transplant, at 3.5 years post diagnosis of this condition. 2 years post transplantation, our patient's graft has BK nephropathy, but of note, biopsy has not shown recurrence of amyloid deposition.

Discussion: Our patient's genetic test returned positive for variant LYZ:c.314A>T. Lysozyme is an amyloidogenic precursor protein and in lysozyme amyloid, it is a ubiquitous bacteriolytic enzyme synthesized by hepatocytes, polymorphs, and macrophages. Currently, there is no amyloid-specific therapy apart from supportive management. The National Amyloidosis Centre in UK published a case series of three patients who underwent kidney transplantation, and there was no recurrence at the time of publication (0.8, 1.8 and 6.6 years post transplantation). Our patient's type of amyloid is different to AA, AL amyloid where recurrence might be expected. There may be a role for genomic sequencing for patients with amyloid deposition in biopsy, with no notable family history, which may lead to identification of rare amyloid types.

PUB233

Using Ambulatory Genetic Testing to Improve the Evaluation of Kidney Diseases in Our Veterans

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Background: Chronic kidney disease (CKD) is a major public health issue in the United States, and also for our veterans. Monogenic causes are present in ~10% of cases of adult CKD. Identification of causes of CKD can impact prognosis and patient management. In our Nephrology clinic at the Miami VAMC, we evaluate patients with chronic kidney disease (CKD), and occasionally no clear etiology of CKD is identified. Broad genetic panels can provide an unbiased testing approach, which is advantageous in phenotypically heterogeneous diseases. However, the use and yield of broad genetic panels by VA Nephrologists in clinical practice is not yet well characterized.

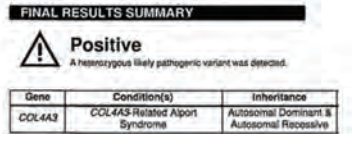
Methods: A total of eight patients were selected to have renal genetic testing. Seven patients had unclear causes for kidney disease, and one patient had a questionable genetic condition on imaging studies. Renal genetic testing was performed in 8 patients. Genetic testing was executed using Renasight and Fulgent, commercially available sequence-based tests for 385 genes associated with kidney disease. Renasight and Fulgent determine if there is a genetic cause for an individual's kidney disease, or if there is an increased hereditary risk due to family history. Results were available in 4 weeks.

Results: See image.

Conclusions: Use of broad panel genetic testing by our clinical Nephrologists had a high success rate in identifying etiologies of CKD in our veteran population. Establishing a genetic diagnosis is crucial to define the precise etiology of CKD. Accurate genetic testing allows improved genetic counselling and enhanced patient management. Implementation of various genomic strategies has resulted in a direct, demonstrable diagnostic and therapeutic benefit to affected patients.

Patient	Indications for Genetic Testing	Result
1	Hematuria, CKD unknown etiology	COL4A3 Heterozygous
2	Hematuria, CKD unknown etiology	Negative
3	Hematuria, CKD unknown etiology, CHF unknown etiology	APOL1 Heterozygous; Hereditary Transthyretin Amyloidosis (TTR) Heterozygous
4	CKD unknown etiology	Negative
5	CKD unknown etiology	RPGRIP1L carrier (Ciliopathy associated w/ Meckel/Joubert syndrome and COACH syndrome)
6	Kidney cyst evaluation, rule out PCKD	Negative
7	Elevated creatinine, unclear cause	Negative
8	Elevated creatinine, unclear cause	Negative

Example of result:



FINAL RESULTS SUMMARY

Positive

A heterozygous likely pathogenic variant was detected.

Gene	Condition(s)	Inheritance
COL4A3	*COL4A3*-Related Alport Syndrome	Autosomal Dominant & Autosomal Recessive

PUB234

Autosomal Dominant Alport Syndrome in a 62-Year-Old Hispanic Woman: A Clinical Case Report

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Introduction: Alport syndrome (AS) is a monogenic disease caused by mutations in the COL4A3/4/5 genes encoding collagen IV, often characterized by progressive kidney function decline, hearing loss, and vision loss. It has an autosomal dominant inheritance pattern in approximately 5% of cases. Autosomal dominant Alport syndrome (ADAS) may be underdiagnosed due later onset of disease.

Case Description: We present a case of a 62-year-old Hispanic woman who presented for evaluation in nephrology clinic with bilateral renal cysts, chronic microscopic hematuria, proteinuria (5.13 g/g), and secondary hypertension. She stated that she had been experiencing arthritis, otalgia, and noted a history of LASIK eye surgery. IgA nephropathy and thin basement membrane disease were highest on the differential diagnosis. A kidney biopsy was performed showing thin glomerular basement membranes with an average width of 130 nm, and focal segmental glomerulosclerosis. However, given her significant proteinuria and subtle GBM changes concerning for a collagen defect, genetic testing using next generation sequencing was performed and revealed a heterozygous pathogenic variant, c.2794A>T (p.Lys932) in the COL4A4 gene that is associated with ADAS. Her baseline creatinine was 0.76 mg/dL, increased at the time of diagnosis to 0.9 mg/dL with a downward trend most recently stabilizing at 0.71 mg/dL. Evaluation by ophthalmology and audiology excluded ocular findings or hearing impairment. She was subsequently started on Losartan and dapagliflozin, with the goal to slow kidney disease progression and prevent end-stage kidney disease (ESKD).

Discussion: ADAS is characterized by a later age of onset and rare extra-renal manifestations in contrast to autosomal recessive disease. Next generation sequencing has increased the frequency of ADAS diagnosis compared to pedigree analysis and Sanger sequencing and should be considered in suspected patients regardless of age. ADAS carries >20% risk of ESKD highlighting the importance of early recognition and multidisciplinary management for improving outcomes in affected individuals.

PUB235

Mortality Risk Factors in Elderly Patients Undergoing Hemodialysis in a Nursing Home

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Background: As patients undergoing hemodialysis (HD) advance in age, they often exhibit greater mental and physical frailty, resulting in an increased number of patients requiring nursing care. However, few studies have examined the risk factors contributing to mortality in this subpopulation. Our dialysis center is affiliated with a nursing home, and most residents are elderly patients undergoing HD. This setup enabled us to assess the nursing home residents during follow-ups in medical and nursing care aspects. We aimed to clarify the mortality risk factors in this subpopulation.

Methods: We included patients undergoing HD who were admitted to our affiliated nursing home between April 2014 and March 2022. Patients with dialysis duration of <3 months were excluded. All participants were followed up until March 2023 and their medical data were collected upon admission. The association between survival and patient demographics was analyzed.

Results: This study included 106 patients (81.3 ± 7.9 years old; 36.8% men; median dialysis vintage, 32.5 months). The most commonly reported cause of death was pneumonia (19.1%), followed by heart failure (16.0%) and infections (8.5%). The patients were stratified into two groups based on their body mass index (BMI), and Log-rank test analysis revealed a poorer prognosis for those with a lower BMI than those with a higher BMI (p=0.002). Multivariable Cox proportional hazards analysis demonstrated a significant association between BMI (hazard ratio, 0.87; 95% confidence interval [CI]: 0.82–0.94; p<0.001) and survival rate. Additionally, multivariable logistic regression indicated that dementia was significantly associated with a lower BMI (odds ratio: 2.89, 95% CI: 1.07–7.83, p=0.03).

Conclusions: Our findings revealed that low BMI is an important factor contributing to a lower survival rate. Furthermore, low BMI was also associated with dementia. Therefore, energy supplementation and management of dementia could be essential for nursing home residents undergoing HD to improve their survival rate.

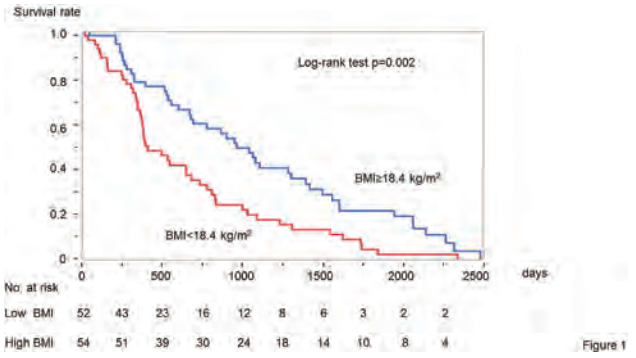


Figure 1

Figure 2 – Creatinine trend during hospital stay

PUB236

AKI in the Elderly: The Tip of an Iceberg

Lakshna Sankar, Pooja Sanghi. *Geisinger Health, Danville, PA.*

Introduction: Acute kidney injury (AKI) in the elderly is of multiple etiologies. Renal biopsy remains the gold standard for diagnosis.

Case Description: A 68-year-old male with history of rheumatoid arthritis on adalimumab was re-admitted with altered mental status, poor oral intake and AKI after a recent hospitalization for lumbar osteomyelitis requiring long term intravenous (IV) cefepime. Work up including infectious, autoimmune profile and renal imaging were unremarkable. Hemodialysis was contemplated due to worsening renal function with creatinine at 8.4 mg/dl (reference range: 0.5 - 1 mg/dl), hyperkalemia and concern for uremic encephalopathy, but he responded to supportive care with IV fluids and IV piperacillin tazobactam. A thorough history revealed intake of nabumetone for several years at doses as high as 1.5 gm daily. Renal biopsy was obtained due to unclear etiology of AKI in the setting of multiple confounding factors such as medications and recent infection. Biopsy showed features of acute interstitial nephritis (AIN) and few myoglobulin positive tubular casts of unclear significance (Figure 1). Antibiotics and nabumetone were discontinued. He was treated with steroids, had marked improvement in creatinine (Figure 2) and was discharged home with steroid taper over 6 weeks.

Discussion: Aging kidneys are more susceptible to AKI due to low renal reserves. AKI developed during hospitalization has high mortality. A thorough understanding of etiology, clinical course and having a low threshold for kidney biopsy aids in diagnosis of AKI with possibilities of better outcomes in the elderly population.

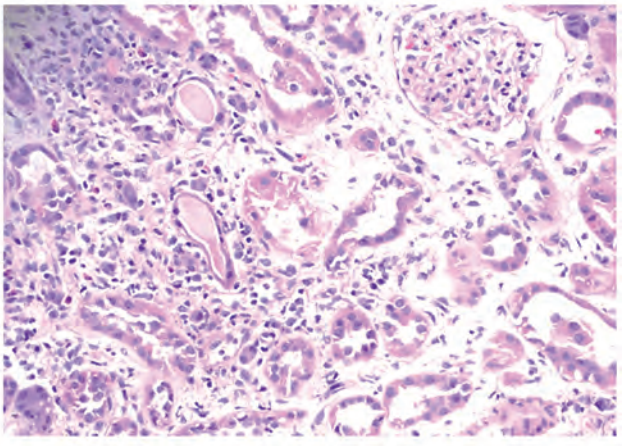


Figure 1 – Light microscopy shows patchy acute tubular injury and interstitial inflammation (hematoxylin and eosin, 40 X magnification)

PUB237

Trajectory of Physical Function and Resilience in Incident Dialysis Patients

Samantha F. Smoger, Derek M. Devine, Katharine L. Cheung. *University of Vermont, Burlington, VT.*

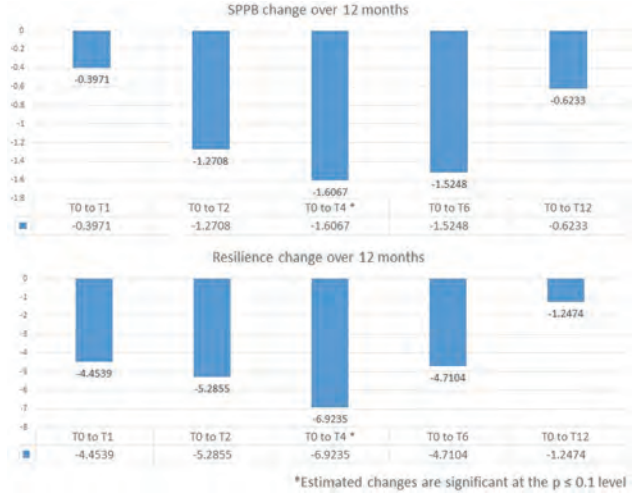
Background: Initiating dialysis is a stressor and associated with functional decline. Resilience is a protective factor that may help patients starting dialysis. We aimed to describe the correlation between and trajectories of resilience and function in the first year of dialysis.

Methods: Incident dialysis patients ≥ 50 years were recruited from 2016-19. The short physical performance battery (SPPB) and Resilience Scale were performed at baseline and 1, 2, 4, 6, and 12 months. Age, sex, income, education, eGFR, serum albumin, cognitive status and comorbidities were identified from EMR and surveys. Spearman's correlation coefficient was used to assess the relationship between resilience and function. Multivariable linear regression was used to identify predictors of resilience and function. Mixed model analyses were used to determine resilience and function trends over 12 months.

Results: 58 incident dialysis patients participated, mean age 68 years, 43% female. At baseline, median (IQR) resilience was 152/175 (135-159) and SPPB was 5.5/12 (1-8). Correlation of resilience and function was ρ -0.23. Serum albumin was independently associated with SPPB; no variables were predictive of resilience. Trajectories of function and resilience are shown in the Figure.

Conclusions: Resilience and function are inversely correlated and decrease in both after 4 months then improve to baseline at 1 year. Greater study is needed to understand predictors of resilience and whether it might improve function for this population.

Funding: Other NIH Support - Vermont Center for Cardiovascular and Brain Health P20GM135007-03, The University of Vermont Center on Aging, Private Foundation Support



Trajectories of function and resilience

PUB238

Medication-Induced Acute Encephalopathy in Severely Impaired Renal Function

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Introduction: Commonly we as providers understand the importance of renally dosing certain medications or avoiding others altogether when we encounter a patient with impaired renal function. More commonly we will avoid modalities of diagnostic testing fearing we will further damage the already injured kidneys. However almost just as frequently we don't consider renal impairment when prescribing other common medications due to lack of education, experience or alternatively over confidence in our knowledge of the drug.

Case Description: The patient is a 76 year old man with a history significant for end stage renal disease (on peritoneal dialysis), coronary artery disease and diabetes who presented to the ICU with altered mental status. He was recently admitted to a different hospital 3 days ago for right sided facial numbness, pain and dysgeusia for which he was given gabapentin, Percocet and acyclovir as it was suspected trigeminal neuralgia. On day 5 of this previous admission he became acutely encephalopathic while the neurological workup including MRI returned negative. He was transferred to our ICU for further management. He was given Narcan numerous times without improvement nor did a round of peritoneal dialysis improve his mental status. Upon arrival family stated he was normally very interactive and appropriate. After 2 days of withholding opiates, gabapentin and acyclovir his mental status finally began to improve.

Discussion: Upon further review, we believed the offending medication to be acyclovir (1) and this was suspicion confirmed by the nephrologist on the case. It is rare but certainly can happen especially in the elderly (2). For many of us this was the first time hearing that acyclovir could be the offending agent. How could a medication so commonly prescribed without consideration of renal function be overlooked as the cause of acute encephalopathy? It is clearly important to have a deep understanding of what medications are renally excreted which is typically information covered in medical school but not necessarily reinforced in the primary care and hospital medicine settings. Additional education and appreciation of this concept would most likely result in safer treatment and shorter hospital stays. Had this been realized in the above patient, he would have not required a transfer nor a 2 day ICU stay costing the medical system both resources and space.

PUB239

Impact of Body Mass Index on Mortality of Elderlies Requiring Acute Hemodialysis

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Background: The increasing life expectancy of the world population elicited the increasing numbers of elderly patients starting hemodialysis (HD), however little is known about the impact on those requiring acute hemodialysis. Malnutrition is alredy related with a higher risk of mortality in non elderly HD patients. The purpose of this study is to evaluate these factors in the elderly population who requiere acute hemodialysis.

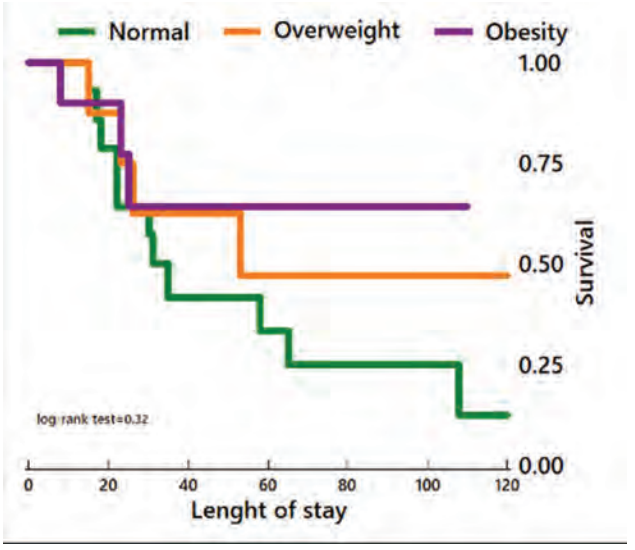
Methods: Retrospective cohort of 33 patients >70 years requiring Hemodialysis was categorized based on their Body Mass Index as normal (18.5-24.9 kg/m2), overweight (25-29.9 Kg/m2) and obesity (>30 kg/m2). Kaplan Meier survival analysis with log-rank test and the Cox proportional hazards model were performed to assess the association between BMI 120-day mortality. Multivariate regression analysis was performed to know the independent association with increased mortality.

Results: Differences in BMI were observed between survivors (15 patients) and non-survivors (18 patients) (p=0.02). Cox-Analysis shows a higher risk of mortality in normal BMI (HR 1.98, 95% CI 0.76-5.13, p value=0.15). A significant association was found between normal BMI and 120-day mortality (HR = 3.28,95% CI = 1.04 - 10.29;P value = 0.041).

Conclusions: A normal BMI was associated with higher risk of mortality in unplanned hemodialysis elderly patients.

Clinical and demographics characteristics

	Total (n=33)	Survivors (n=15)	Non-survivors (n=18)	p-value
Age	79.6 ± 5.0	79.7 ± 5.3	79.5 ± 5.0	0.89
BMI (kg/m2)	28.1 ± 6.5	30.9 ± 7.2	25.8 ± 4.8	0.02*
BMI (kg/m2) 18.5 - 24.9	43%	20%	61%	0.04*
BMI (kg/m2) 25 - 29.9	27%	33%	22%	
BMI (kg/m2) >30	30%	47%	17%	
Length of stay (days)	31 (22-65)	63 (28-105)	24 (18-35)	



PUB240

External Validation of a Risk Prediction Tool in Determining Early Death Among Elderly Patients Initiated on Dialysis

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Background: The increase in the senior population is one of the factors that has contributed to the rise in the number of dialysis patients in the Philippines. The elderly generally has an increased risk for poor dialysis-associated outcomes, and studies have been conflicting if they have better survival with dialysis as compared to conservative management. The Thamer Risk Scoring tool uses simple variables to predict early mortality in elderly patients after initiating dialysis, however this has not been validated in the Philippine setting.

Methods: A retrospective cohort research design was used. Patients ≥ 60 years old, diagnosed with end-stage renal disease, and initiated on dialysis from 2018 to 2021 in a tertiary institution in the Philippines were subjected to the tool to predict 3-month, 6-month, and over-all mortality after dialysis initiation. Patients with <90 days dialysis duration, recovery of kidney function, and with incomplete data to meet all the variables for the tool were excluded.

Results: Majority of the 181 patients included in the study were male (56.35%), and initiated on hemodialysis (97.24%). The mean age of the population was 67.34 years. All-cause mortality was 38.12% at 3 months, and 3.57% at 6 months after dialysis initiation. Patients with heart failure, cancer, asthma, and need for assistance in daily living had significantly higher mortality rates (p-values 0.007, 0.040, 0.040, 0.022 respectively). In comparison to the Thamer study with an AUROC = 0.691 for the tool in their validation cohort, this study showed an AUROC = 0.6245, 0.2847, and 0.5993 in the 3-month, 6-month, and over-all mortality groups respectively. As the score increased for the three groups, the tool became less sensitive and more specific with a concomitant increase in accuracy for predicting mortality.

Conclusions: Despite the poor performance of the Thamer risk scoring tool in predicting mortality in terms of AUROC in this study, the sensitivity, and specificity had a similar performance in the Thamer study. Furthermore, the consistent trend of accuracy of predicting mortality in these groups reflect that a higher score portends to a higher accuracy in predicting mortality.

PUB241

Kidney Biopsies in Elderly Patients: Analysis of a 7-Year Institutional Experience

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Background: Kidney biopsies are essential for diagnosing and guiding treatment decisions, but limited data exist on their utility and safety in older adults (> 60 years). This study aims to analyze kidney biopsies performed on patients aged 60 years and above at our institution from 2015 to 2022, considering age-related changes, comorbidities, and survival influences.

Methods: A retrospective analysis of 78 kidney biopsies in elderly pts. was conducted. Demographic data, comorbidities, and pathological findings were collected to evaluate indications, procedural characteristics, and complications associated. All biopsies were performed by Nephrologists and Interventional Nephrology fellows.

Results: Among the 78 biopsies, 53 were performed on pts. aged 60-70 years, and 25 on pts. above 70 years (only 3 pts. aged ≥ 80 years). The mean pts. age was 68±7.1 years, 56% were female. The primary indication for biopsy was Nephrotic Syndrome (58.9%), followed by Acute Kidney Injury (9%). All patients met institutional protocol criteria prior to biopsy. The most common diagnoses were Pauciimmune Glomerulonephritis (19.2%), Diabetic Nephropathy (15.3%), Acute Interstitial Nephritis (12.8%), Focal Segmental Glomerulosclerosis (10.2%), Amyloidosis (10%) and Membranous Nephropathy (8.9%). Frequency needle passes were 1 in 34% and 2 in 55%. Minimal complications were observed, only 3 pts. with small hematomas, were monitored by ultrasound; no blood transfusions or interventions for bleeding were required and no major complications were observed.

Conclusions: Kidney biopsies in elderly pts. offer valuable diagnostic information and aid in tailoring management strategies. Nephrotic Syndrome was the leading indication, and Pauciimmune Glomerulonephritis was the most common diagnosis. Understanding the diagnostic yield, prevalent etiologies, and potential complications associated with kidney biopsies in the elderly is crucial for personalized care in this vulnerable population.

PUB242

Diagnostic Impact and Safety of Percutaneous Kidney Biopsy in Adults Older Than 65 Years

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Background: Population older than 65 years has been increasing worldwide and the incidence of kidney disease. Currently, there are no consensus defining an age limit for percutaneous kidney biopsy (PKB). Some centers do not perform routinely this procedure in this population.

Methods: Retrospective cross sectional study spawning data from 2019-2022 of patients >65 years old that underwent a PKB at Interventional Nephrology Service of the National Institute of Cardiology "Dr. Ignacio Chávez". Sampling was performed in real time guided by ultrasound. We describe demographic data, comorbidities, kidney morphology and histological findings.

Results: 35 patients underwent a PKB were analyzed. 65.7% were women; the mean age was 71.8 years with a mean GFR of 50.2 ml/min/1.73 m2, and mean kidney length of 9.56 cm. 54.28% were performed as outpatients. Mean of needle passes was 1.6 and the mean number of glomeruli was 16.9. Complications occurred in 8 patients, 5 were minor (macroscopic hematuria or hematoma < 2cm), and just 3 were major (hematoma > 2cm). There was no need for blood transfusions, nephrectomies or deaths. The most frequent pathology diagnosis was AAV (17.14%); IC-MPGN, amyloidosis and NOS FSGS in 11.42% each; TIN and MN in 8.57%, each. Treatment was modified in 11 cases (31.4%) after obtaining a pathology diagnosis. (Fig. 1)

Conclusions: PKB in adults 65 years or older is a safe procedure, that provides a pathology diagnosis in most of the cases that may help modify treatment and prognosis in our patients. Advanced age should not be considered a contraindication for kidney biopsy.

Funding: Government Support - Non-U.S.

Table 1. Descriptive characteristics of study sample

Demographic data	n=35
Women (%)	23 (65.7)
Age (Years)	71.8 (69-77)
Outpatient setting (%)	19 (54.28)
Inpatient setting (%)	15 (42.85)
GFR, CKD-EPI (ml/min/.173 m²)	50.2 (28.89-113.89)
KDIGO G1 (%)	6 (17.14)
KDIGO G2 (%)	7 (20)
KDIGO G3 (%)	8 (22.8)
KDIGO G4 (%)	10 (28.57)
KDIGO G5 (%)	4 (11.42)
Kidney size (cm)	
Length	9.56 (8.95-12.1)
Width	5.04 (4.35-7.89)
Kidney borders	
Smooth (%)	22 (62.85)
Lobulated (%)	13 (37.14)
Corticomedullary ratio	
Preserved (%)	25 (71.42)
Decreased (%)	10 (28.57)
Pathology diagnosis (%)	n (%)
ANCA-associated vasculitis (AAV)	6 (17.14)
Immune complex-mediated membranoproliferative glomerulonephritis (IC-MPGN)	4 (11.42)
Glomerular amyloidosis	4 (11.42)
NOS FSGS	4 (11.42)
Secondary membranous nephropathy (MN)	3 (8.57)
Tubulointerstitial nephritis (TIN)	3 (8.57)
IgA nephropathy	2 (5.71)
Diabetic nephropathy	2 (5.71)
Collapsing FSGS	1 (2.85)
Thrombotic microangiopathy	1 (2.85)
Primary membranous nephropathy	2 (5.71)
Others	1 LN, 2 insufficient sample
Needle passes (%)	
1 pass	15 (42.85)
2 passes	20 (57.1)
Complications (%)	**8 (22.85)**
Minor	5 (14.2)
Major	3 (8.57)
Modifications in treatment after kidney biopsy (%)	
No modifications (Conservative)	24 (68.57)
With modifications (Immunosuppressors: CS, CYC, RTX, PLEX, MMF)	11 (31.4)
Sample quality	
Number of glomeruli	16.91 (+/- 7.2)

PUB243

Systemic Lupus Erythematosus and ANCA-Associated Vasculitis Presenting De Novo in the Puerperium

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Introduction: Overlap syndrome of systemic lupus erythematosus (SLE) and ANCA associated vasculitis (AAV) is uncommon. Most patients have a worse renal presentation and require more aggressive treatment.

Case Description: A 38-year-old woman with a history of preeclampsia in her first and only pregnancy underwent a cesarean section 5 months ago and presented with chronic arterial hypertension during the gestation period. She is referred to the nephrology clinic for presenting muscle pain, oral ulcers, dyspnea, and foamy urine for 3 months. She presented with blood pressure in 136/89 mmHg, basal crackles in both lung bases, and stage III edema with pitting in lower limbs. The test showed a nephrotic syndrome with ANA and ANCA-P positive (Table 1). A renal biopsy showed pauci-immune crescentic lupus nephritis with AAV (Figure 1). Management began with pulses of intravenous corticosteroids for 3 days followed by prednisone, hydroxychloroquine, cyclophosphamide (6 doses). For 10 months the patient has had a good evolution (Table 1). Although in the 3rd month of treatment he was diagnosed with herpes zoster, which made it necessary to stop for 2 months and manage with mycophenolate mofetil.

Discussion: Overlap of SLE and AAV has been described in less than 3%. The use of steroids at high doses and cyclophosphamide or rituximab is necessary. SLE during pregnancy is difficult to quickly diagnose and when symptoms of preeclampsia persist after delivery, SLE should be ruled out.

Months	Entry	2	3	4	6	8	10
Hematological study							
Hemoglobin (g/dL)	8	11.5	14	12.1	13.7	14.4	13.9
Hematocrit (%)	24.5	34.9	43	36.4	41	44	41.4
Leukocytes (cels/µL)	7.86	14.08	8.46	7.42	12.3	15.6	9.35
Neutrophils (%)	83	80	71	58.6	60	65	59.60
Platelets (mcL)	395	468	397	420	509	424	536
Renal function							
Creatinine (mg/dL)	3.32 (0.61 four months ago)	1.91	1.54	1.49	1.47	1.46	1.54
BUN (mg/dL)	41	51	27	16	24		24
Electrolytes							
Na (mEq/L)	137.77	140			140		140
K (mEq/L)	4.75	4.19		4.6	4.7		4.4
Cl (mEq/L)	102	100					
Ca (mEq/L)	8.67	8.2					
Lipid panel							
TC (mg/dL)	199	292	199	166	210	170	150
HDL (mg/dL)	53	109					78
LDL (mg/dL)	130	180	74	81	92	78	59
TG (mg/dL)	119	167	170	175		174	91
Others							
Albumin (g/dL)	2.5	2.7	2.8		4	4	4.1
Total proteins (g/dL)	6.2	5.4			6.2	6.2	6.5
CO2	24						
Thyroid panel	Normal						
Glucose (mg/dL)	75	71		77	76	64	71
Urinalysis	Protein 4+ Blood 4+ 60-80 rbcs 10% crenated, 30% dysmorphic, 60% normal						Prot 4+ Blood 3+ Glu 3+ 10-20 rbcs
24hr urine total protein (mg/dL)	10889	6349	3720	3924	3639	2127	1744
ANA	1/320						
Anti-dsDNA	562				106.8		
Anti-DNA	1/40					1/20	1/20
Anticardiolipin	IgA - IgG + IgM -						
ANCA-P	1/640						
Complement(mg/dL)	C3 58 C4 5	C3 82 C4 19		C3 128 C4 37	C3 107 C4 26	C3 99 C4 42	C3 101 C4 25
Infectious							
HIV	Nonreactive						
Anti-HCV	Negative		Neg				
HBsAg	Nonreactive		Neg				
Herpes zoster			IgM +		IgM -		

Table 1. Tests Results

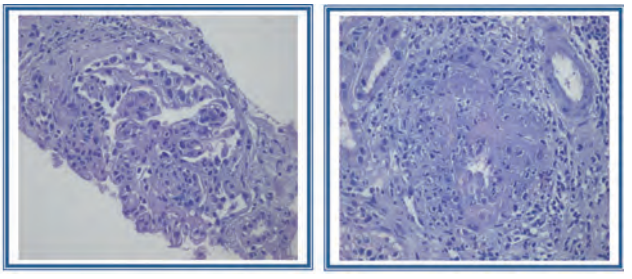

Figure 1. Kidney Biopsy

PUB244

Pauci-Immune Necrotizing Glomerulonephritis in Association with Chronic Hepatitis C

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Introduction: Necrotizing glomerulonephritis (GN) is a severe form of glomerular injury associated with crescent formation, characterized by rapidly progressive impairment of renal function. It is usually caused by small vessel vasculitis and presence of circulating antineutrophilic cytoplasmic antibodies (ANCA). Chronic hepatitis C (HepC) rarely leads to ANCA associated necrotizing GN. We present a case of likely MPO-ANCA associated necrotizing GN with chronic HepC.

Case Description: A 58-year-old male with a history of type 2 diabetes, hypertension and chronic HepC, presented with cough and blood tinged sputum of 1 month. On admission, covid-19 was positive and Chest X ray showed a small right basal density, creatinine 1.54mg/dl, (0.80mg/dl 1 year prior), microhematuria and proteinuria (urine protein creatinine ratio - 965.5mg/g), with HepC viral load of 5,680,533 IU/ml. Serologic tests showed positive MPO-ANCA (>133 U/ml), ANA (>1:1280) and anti–dsDNA (21 U/ml). PR3-ANCA, rheumatoid factor and cryoglobulins were negative, C3 and C4 were normal. Kidney biopsy revealed pauci-immune focal segmental necrotizing GN in less than 20% of the glomeruli, suggestive of microscopic vasculitis. Additional findings were mild tubulointerstitial involvement with acute tubular necrosis. In view of necrotizing GN, likely related to HepC and relatively stable renal function, he was started on treatment for HepC, using Glecaprevir/pibrentasvir, without immediate immunosuppressive therapy. Follow up in 6 weeks showed serum creatinine down to 1.21mg/dl and remained stable, undetectable viral load, decreasing MPO-ANCA titers (from >133 U/ml to 99 U/ml, to 79 U/ml), negative ANA and anti DsDNA, but with persistent hematuria and proteinuria.

Discussion: This patient with untreated HepC, positive MPO-ANCA, ANA and anti-dsDNA, presented with acute nephritic syndrome. Kidney biopsy showed pauci-immune focal segmental necrotizing GN features consistent with MPO-ANCA associated disease. Even though immediate immunosuppressive treatment of necrotizing GN is required for improved renal outcomes, in our case, treatment was withheld in view of 2 active viral infections. HepC therapy was initiated with improvement in renal function, progressive reduction in MPO-ANCA titers and disappearance of ANA and anti-dsDNA positivity.

PUB245

An Atypical Case of Immune Complex-Mediated Glomerulonephritis

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Introduction: Rapidly progressive crescentic glomerulonephritis is an aggressive clinical syndrome characterized by massive loss in kidney function in a relatively short period of time, days to weeks. The etiology of this disease is varied, with subtypes including anti-glomerular membrane disease, immune complex-mediated injury, or pauci-immune. We report a rare case of acute exudative and crescentic glomerulonephritis leading to end-stage renal disease due to an unknown infection.

Case Description: A 28-year-old African American male with a medical history only remarkable for asthma presents with nausea, vomiting, diarrhea, and severe abdominal pain for 3-4 days. On admission, the patient's lab data showed a serum creatinine level of 12.28 mg/dL, BUN of 71, and WBC of 23,000. Renal ultrasound showed increased echogenicity of bilateral kidneys suggestive of medical renal disease. Non-emergent HD and kidney biopsy were ordered. COVID-19, flu A/B, hepatitis panel, ANA, c-ANCA, p-ANCA, and anti-GBM were all negative. Serum protein electrophoresis showed mildly elevated IgG lambda. C3 was mildly decreased, and C4 was normal. Blood cultures were negative. The patient was initiated on vancomycin/Cefepime/Metronidazole. Kidney biopsy demonstrated 14/16 glomeruli with necrotizing crescents, C3 predominant mesangial and capillary loop staining, and numerous mesangial and segmental endothelial humps.

Discussion: Patients with postinfectious glomerulonephritis and <50% glomerular involvement have a higher chance of mild disease and potential recovery, with >80% glomerular involvement documented as severe disease requiring therapy. This case represents ~87% glomerular exudative crescents due to an unknown cause, likely post-infectious. The patient was treated with pulse steroids x3 days, but no other immunosuppression was started as data is lacking in severe post-infectious GN as well as idiopathic immune complex RPGN. Initiation of oral or IV cyclophosphamide or rituximab was considered, however, was deferred and the patient was treated with steroid monotherapy. The patient remains on hemodialysis with no evidence of renal recovery. This case highlights the need for further studies in immunosuppression guidelines for patients with this debilitating disease.

PUB246

From Low Hemoglobin to Chronic Renal Failure: An Unusual Presentation of Advanced IgA Nephropathy in a Young Patient with Anemia

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Introduction: IgA nephropathy is a leading cause of CKD and renal failure. The most common primary glomerulonephritis in the world among patients undergoing renal biopsy. Its diagnosis is associated with a reduction in life expectancy between 6 and 10 years.

Case Description: We describe a patient case presented to emergency room due to general weakness of 4 weeks evolution. Our patient, with a PMH of asthma, was diagnosis with severe anemia, and admitted due to progressive shortness of breath, moderate chest pain and severe acute renal failure. The patient was worsening clinically over a period of less than 1 hour at the emergency department, blood pressure was uncontrolled and renal failure worsening, for this reason an emergency renal replacement therapy was required. Laboratory tests showed anemia and severe renal failure with high anion gap metabolic acidosis. Urinalysis reported proteinuria, and moderate blood in urine. Testing for HIV, Hepatitis B, C, ANA, complements C3/C4, Anti Cyclic Citrullinated Peptides and serum free light chains were normal, except Glomerular Basement Membrane Ab that was out of range. A kidney biopsy was recommended and prednisone, plasmapheresis and therapy with Rituxan was started.

Discussion: Cases reviewed have been reported with IgA nephropathy associated with focal segmental glomerulosclerosis. Electron microscopy showed mesangial and subendothelial immune type electron dense deposit. Understanding the pathogenesis of IgA nephropathy reveals therapeutic targets. Mucosal IgA production by plasma cells occurs by T cell dependent and independent processes. B cell and plasma cell inhibitors such as rituximab, may result in decreased IgA production, using as part of the treatment in our patient. Complement inhibitors may prevent formation of immune complexes. This case will further contribute to the diagnosis and management of population of patients with Iga Nephropaty in Puerto Rico. Our patient was discharging home, to continue renal replacement therapy, and using a first line medication for aggressive blood pressure control and high-intensity statin therapy for hyperlipidemia and oral prednisone. She was set up for hemodialysis. There is a strong possibility of this patient is having a progressive course leading to ESRD, so early diagnosis and treatment are of key importance.

PUB247

A Case of Hydralazine, a Common Antihypertensive, Causing ANCA-Associated Vasculitis

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Introduction: Hydralazine is a vasodilator that is commonly used as an anti-hypertensive agent. Hydralazine induced ANCA vasculitis is a rare phenomena; with approximately < 100 cases reported.

Case Description: A 66-year-old male with significant PMHx of non-ischemic cardiomyopathy, HTN presented to the emergency department for hyperkalemia and worsening renal function. The patient otherwise had no complaints. It was noted that patient was on hydralazine 100mg twice daily. Initial vitals were BP 144/101, HR 86, Resp 16, O2 100% on RA, temperature 97.7F. The reminder of the examination revealed 2+ pitting edema in the lower extremities. Laboratory studies revealed BUN 89, Creatinine 5.95, K 6.0, Hgb 5.7, urinalysis was positive for large blood and >100 RBC cells. Of note it was found that the patient had worsening renal function for approximately two years with progressively worsening renal function from Cr 1.57 to present of 5.95. The patient had a CT abdomen pelvis w/o contrast performed which demonstrated edematous changes. The patient was started on a Lasix challenge and a glomerulonephritis work-up was sent out. The patient continued to have urine output; however due to progression of chronic kidney disease, was initiated on dialysis. The initial blood work sent out came back positive for MPO >8.0, ANA at 1:2560 and anti-histone antibodies >7. Vasculitis was high on the differential and hydralazine was held. The renal biopsy revealed crescentic GN, and diabetic/hypertensive changes with >50 % of IFTA, crescents in <50%. The immunofluorescence was consistent with pauci-immune disease. The patient received three days of pulsatile steroids, followed by Rituxan infusion. The remainder of the hospitalization was unremarkable.

Discussion: The mechanism of hydralazine induced ANCA vasculitis remains unknown- with multiple theories associated with MPO leading to neutrophil apoptosis. Typical symptoms include myalgia, petechiae. In cases of hydralazine-associated vasculitis- symptoms can include rapidly progressive renal dysfunction. Hydralazine associated vasculitis diagnosis is made via serologic measures including ANCA, MPO antibodies and anti-histone antibodies. Renal biopsy will demonstrate pauci-immune GN. Treatment would include cessation of hydralazine, pulsatile steroids, and immunosuppression with cyclophosphamide or rituximab.

PUB248

Proteomic Analysis of Lysine 2-Hydroxyisobutyryl in Systemic Lupus Erythematosus (SLE) Reveals Protein Modification Alteration in Complement and Coagulation Cascades and Platelet Activation Pathways

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Background: Post-translational modifications (PTMs) are considered to be an important factor in the pathogenesis of systemic lupus erythematosus (SLE). Lysine 2-hydroxyisobutyryl (Khib), as an emerging post-translational modification of proteins, is involved in some important biological metabolic activities. However, there are poor studies on its correlation with diseases, especially SLE.

Methods: Khib levels in SLE patients and healthy controls were compared based on liquid chromatography tandem mass spectrometry, then proteomic analysis was conducted.

Results: Compared with healthy controls, Khib in SLE patients was up-regulated at 865 sites of 416 proteins and down regulated at 630 sites of 349 proteins. The site abundance, distribution and function of Khib protein were investigated further. Bioinformatics analysis showed that 11 Khib differentially modified proteins (DMPs) were significantly enriched in the Complement and coagulation cascades pathway. 23 Khib DMPs on the Platelet activation pathway were significantly enriched.

Conclusions: Khib in PBMCs of SLE patients was significantly up- or down-regulated compared with healthy controls. Khib DMPs in the Complement and coagulation cascades and Platelet activation pathways affect platelet activation and aggregation, coagulation functions in SLE patients, and may play an important role in the pathogenesis of SLE. This result provides a new direction for the possible significance of Khib in the pathogenesis of SLE patients.

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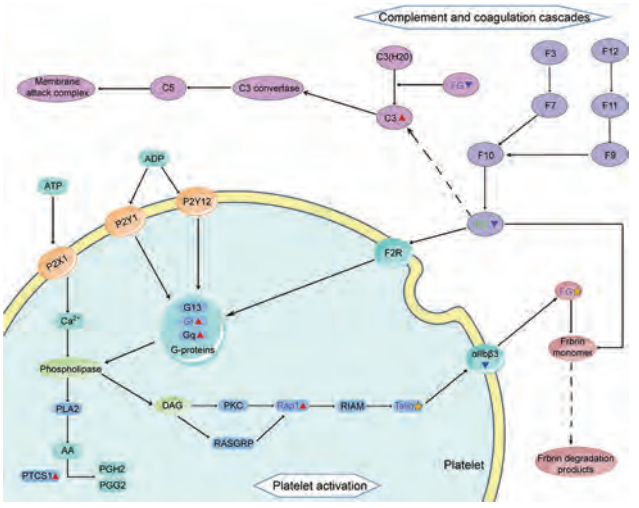

PUB249

Phenotypic Characteristics of Monocytes and Macrophages in Lupus Nephritis with Bacterial Antigen Induction

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Background: Monocytes and macrophages play crucial roles in the innate immune system. Systemic lupus erythematosus is an autoimmune disease with diverse manifestations, including lupus nephritis (LN), where monocyte and macrophages (M&M) are believed to be involved in the pathogenesis. Understanding their role in LN remains challenging. This study aimed to compare the phenotypic characteristics of M&M in patients with LN, specifically focusing on their response to bacterial antigens.

Methods: 12 patients with biopsy-proven LN and 3 healthy volunteers (HG) were enrolled. The LN group consisted of 11 females and 1 male, aged 28-67 years (mean:48). Disease activity was assessed using SLEDAI and SLAM-R scores, while serum creatinine and daily proteinuria were measured as markers of kidney involvement. Monocytes were magnetically isolated from PBMC and cultured under 3 conditions: without bacteria, with Escherichia coli or Enterococcus faecalis. The cells were evaluated at 4-time-points (4, 8, 10, 12 days). We examined monocytes (CD14+ and CD14+CD16+ phenotype) and macrophages (pro-inflammatory M1[CD68+CD80+] and anti-inflammatory M2[CD68+CD163+]).

Results: Our findings revealed consistent behavior of CD14+ cells in HG, where their percentage decreased over time. In LN patients, the decrease was more expressed in samples exposed to bacteria, particularly E. coli. CD14+CD16+ monocytes were significantly lower at each time-point in samples with bacterial exposure, indicating reduced reactivity in LN. M1&M2 macrophages increased over time in non-exposed groups, but LN M1 cells decreased from day 8 in samples with bacterial induction. LN M2 decrease was observed even earlier, especially with E.faecalis exposure. These results demonstrate differential behavior of M&M in LN patients compared to healthy individuals when exposed to bacterial antigens. The low percentage of M1 cells in LN samples with bacterial antigens suggests faster activation in LN patients, occurring as early as day 1-3 of incubation.

Conclusions: This study highlights the phenotypic differences in M&M in LN patients, particularly in response to bacterial antigens. Further investigation into the mechanisms underlying these differential responses could provide valuable insights into the pathogenesis of LN and potential therapeutic targets.

Funding: Government Support - Non-U.S.

PUB250

JAK/STAT Expression in Patients with IgA Nephropathy

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Background: The JAK/STAT signaling pathway is an intracellular signal transduction pathway, that is involved in diverse biological processes, including cell proliferation, differentiation, apoptosis and regulation of the immune system. Recent studies have explored abnormal receptor tyrosine kinase activation in the pathogenesis of IgA nephropathy(IgAN).

Methods: A retrospective analysis was performed on all IgAN patients diagnosed by kidney biopsy. Clinical and laboratory data were collected at baseline and at the end of follow up. Kidney tissue sections were stained with antibodies specific for components of JAK/STAT pathway. We included 63 patients with IgAN and compared with 6 controls.

Results: Staining for JAK3 was observed observed in the renal tubule and glomeruli. Staining for JAK3 was enhanced in patients with IgA nephropathy compared to controls. The expressions of JAK2, pSTAT and STAT3 were analyzed, but there was no significant

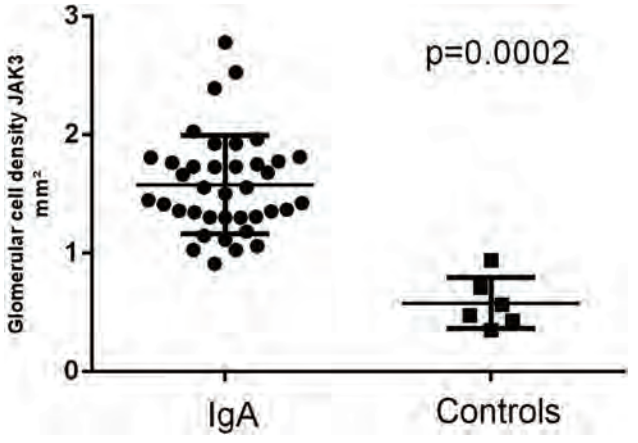
marking in the glomerulus. Correlations of JAK3 cell density with markers such as creatinine, proteinuria, as well as the MEST score were performed, but without significant results.

Conclusions: The presence of activation of the JAK/STAT signaling pathway has been demonstrated in patients with IgAN. This pathway may represent a therapeutic target in this pathology.

Clinical and laboratory data at the time of biopsy and at the end of follow-up

Age	33.00 [24.50-46.00]
Women(%)	35 (55.6)
CKD-EPI baseline mL/min/1,73 m2	58.00 [31.00, 95.00]
Remission (n/%)	31 (54.4)
Outcome (n/%)	19 (31.1)

The primary outcome was defined as end-stage renal disease (ESRD) or doubling of baseline creatinine. Remission has been defined as 50% reduction in baseline proteinuria and <3.5 g/day.



Comparison of JAK3 cell density in patients with IgA and controls

PUB251

Diffuse Alveolar Hemorrhage Presenting in IgA Nephropathy

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Introduction: Immunoglobulin A nephropathy (IgAN) is the most common glomerulopathy worldwide. Clinical presentation of IgAN ranges from isolated hematuria to progressive glomerulonephritis and more rarely as pulmonary-renal syndrome. Here, we describe a case of diffuse alveolar hemorrhage (DAH) accompanying IgAN.

Case Description: A 38-year-old female with a history of end-stage liver disease secondary to alcohol-related cirrhosis, presented with oliguria and abdominal distention. Labs showed creatinine of 2.7 mg/dL (baseline 1.2), red blood cells on urine microscopy, urine protein to creatinine ratio of 7.13 mg/mg and diagnostic paracentesis was negative. ANA was positive with titers of 1:40, low C3/C4, but other serologic markers were negative, including Anti-Smith, MPO, and PR3. During hospitalization, she developed hypoxemic respiratory failure with hemoptysis. Chest CT showed diffuse alveolar opacities concerning for DAH. She was electively intubated, and BAL confirmed DAH. She received pulse steroids for four days, followed by two days of 0.5 mg/kg steroids, and underwent an ultrasound-guided kidney biopsy confirming IgAN with acute tubular injury. Due to steroid-associated delirium, immunosuppression was switched to Mycophenolate Mofetil with marked improvement in pulmonary symptoms. The patient required temporary hemodialysis to manage AKI with electrolyte derangements and volume overload. Before discharge, she achieved renal recovery sufficient to discontinue hemodialysis. Creatinine has remained at 0.9-1.0 mg/dL four months after presentation.

Discussion: This case suggests that IgA nephropathy should be included in the differential diagnosis of DAH and emphasizes the importance of a timely renal biopsy in patients with pulmonary-renal syndrome. Although initial steroid treatment can be limited due to poor tolerance, quick transition to targeted immunosuppression, such as Mycophenolate Mofetil, can result in significant clinical response in individuals with progressive Ig A nephropathy.

PUB252

Active Components of Traditional Chinese Medicine for IgA Nephropathy, Shen Ping, Include Mixed-Linkage Glucans That Inhibit Cell Proliferation and Signaling in Human Mesangial Cells Induced by Platelet-Derived Growth Factor (PDGF)

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Background: Shen Ping (SP), a prescribed traditional Chinese medicine, has been used for decades to treat IgA nephropathy in China. Our prior studies showed that SP inhibits PDGF-induced cellular proliferation and signaling in primary human mesangial cells. However, identity of the active components in SP is unknown. We report the chemical nature of the SP components that inhibit PDGF-induced activation of mesangial cells.

Methods: Human mesangial cells in 96-well plates were serum-starved for 24 h and SP or SP-derived purified components were tested for capacity to inhibit PDGF-induced proliferation. Signaling tests used confluent serum-starved mesangial cells stimulated with PDGF-BB for 15 min in the presence or absence of SP or SP-derived components. Cell lysates were then analyzed with SDS-PAGE immunoblotting to assess changes in phosphorylation of selected proteins. Active SP compounds were isolated by chromatographic and physical-separation methods and then characterized by physical and enzymatic methods combined with the assessment of biological activity in mesangial cells.

Results: The active SP components, precipitated and concentrated using a 10-kDa cut-off ultrafilter, inhibited PDGF-induced cellular proliferation and phosphorylation of ERK, Axl, and Akt. These compounds were heat-resistant and likely consisted of polysaccharides. β1,3-exoglucanase removed β1,3-glucans without impacting the anti-PDGF activity. Conversely, an endoglucanase (lichenase) that cleaves mixed-linkage glucans inactivated most of the anti-PDGF activity. Thus, the active compounds in SP are mixed-linkage glucans. To further characterize them, we produced a β1,3-exoglucanase-digested SP sample and performed size-exclusion chromatography. Active fractions analyzed by high-performance anion-exchange chromatography coupled with pulsed amperometric detection identified a series of polysaccharides. Lichenase digestion removed most of the polysaccharide material while producing shorter oligosaccharides.

Conclusions: The active compounds in SP are mixed-linkage glucans. Future experiments will determine their detailed structures and mode of action.

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PUB253

A Case of Crohn Disease-Related Tubulointerstitial Nephritis

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Introduction: The prevalence of extraintestinal manifestations (EIM) in Crohn's disease (CD) varies and can involve almost every organ. Renal involvement in patients with IBD is not uncommon, with varied manifestations. Nephrolithiasis, tubulointerstitial nephritis (TIN), glomerulonephritis (GN), and amyloidosis are the most common manifestations. Although most cases of TIN have been associated with 5-ASA, and cyclosporin A agents underlying immune pathophysiology could directly involve the kidney as well. We describe a biopsy-proven case of TIN most likely secondary to CD and less likely to drug exposure.

Case Description: A 59-year-old woman with a background of hypertension (HTN) and stable CD on infliximab infusions for about 2 years was referred to Nephrology after a hospital admission for AKI originally thought to be due to uncontrolled HTN. On investigation, renal function drastically decreased over 9 months with a serum Cr increase from 0.8mg/dL to 2.7mg/dL. Urine Analysis was unremarkable without cells or proteinuria. A renal biopsy showed 4/15 glomeruli with global sclerosis. Focal lymphocytic inflammatory in the interstitial compartment associated with rare eosinophils and focal tubular injury confirmed TIN with 30-40% interstitial involvement. It also showed significant thickening of arterioles with ischemic changes in glomeruli, and no immune deposits on immunofluorescence or electron microscopy. TIN was treated with oral steroids for four weeks with tight BP control. No improvement after steroids was seen along with worsening of her CD. A week after resumption of Infliximab therapy her Cr stabilized to 2.4mg/dL followed by 2.1mg/dL a month later.

Discussion: It is difficult to establish whether renal dysfunction is secondary to CD itself or medical treatment. However, recent literature highlighted the link between TIN and IBD. Prompt and thorough evaluation of AKI in patients with IBD via a kidney biopsy with judicious use of therapeutic agents is warranted. Infliximab appears to have low risk of TIN. Even in absence of intestinal flare, kidney injury could have occurred as EIM of CD. Excluding other acute and chronic etiologies of TIN, and improvement in renal function after infliximab, Crohn's disease related TIN was likely the cause of interstitial kidney injury in our patient.

PUB254

Focal Segmental Glomerulosclerosis with Glomerulomegaly as a Rare Complication of Testosterone Replacement Therapy

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Introduction: Testosterone replacement therapy (TRT) is the mainstay of treatment for hypogonadism in male adults. Androgenic-anabolic steroids (AAS) are all synthetic derivatives of the hormone testosterone and include those used illegally as performance enhancing drugs. The main differences between TRT and illegal AAS abuse is the dosing, proper supervision by a health care provider and purity of the drugs, however the compounds used are often similar if not identical. Focal segmental glomerulosclerosis (FSGS) is a common cause of nephrotic syndrome, it accounts for about 40% of cases in adults and 20% in children. FSGS has been linked to long-term AAS abuse. There have not been any documented cases of the development of FSGS in adult male patients with hypogonadism on long term TRT.

Case Description: A 51-year-old man with a history of chronic kidney disease stage 3, hypogonadotropic hypogonadism on chronic TRT, hypertension and chronic hepatitis C was sent by his nephrologist to a local Emergency Department (ED) in January 2023 after lab work revealed a significant increase in creatinine from his baseline of 1.7 mg/dL to 3.19 mg/dL. On arrival his vital signs were stable. He denied any acute symptoms or changes in his health. Serological workup was unrevealing. He was taking testosterone propionate 25 mg daily intramuscularly for hypogonadism, somatropin 1.6 mg daily intramuscularly for growth hormone deficiency. Renal biopsy was obtained to determine the cause of the patient's renal failure. Pathology from renal biopsy showed focal segmental glomerulosclerosis with glomerulomegaly. The patient was instructed to speak with his endocrinologist about lowering the dose and even discontinuing testosterone therapy.

Discussion: The beneficial effects of TRT in the treatment of male hypogonadism are widely known, however the risks and complications of long-term use have not been as widely studied. Both FSGS and glomerulomegaly have been described among bodybuilders with long term AAS abuse. Our case highlights the need for further research on the renal complications of TRT.

PUB255

Unique Case of Fibrillary Glomerulonephritis

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Introduction: Fibrillary Glomerulonephritis (FGN) accounts for approximately 0.5-1% of all adult Glomerulonephritis cases on Renal Biopsy. FGN is characterized by the deposition of Microfibrils 10-30nm in diameter in the mesangial and Glomerular capillary walls and is often found in patients with a history of diseases, including Cancer, Autoimmune diseases, and Hepatitis C. The diagnosis of FGN is usually made with a Kidney biopsy with a pathognomonic finding of DNAJB9 staining.

Case Description: A 69-year-old white woman with a past medical history significant for morbid obesity (BMI-55), hypertension, and type 2 diabetes mellitus was referred by her PCP due to a decline in Renal function with a rise of her serum creatinine up to 2.6 mg/dl(baseline was 1.3 in 2021). Her rise was slow over six months, with a change in GFR from 55 to 19 with minimal proteinuria and no lower extremity edema. She had no history of NSAID, herbal, or Supplemental usage and had no Family history of Renal disease. Upon evaluation, her serum albumin was 3.6 gram/deciliter, and the protein creatinine ratio was 327mg/gram on random urine. Serological studies were negative for HIV and Hepatitis C. SPEP, UPEP, and serum-free light chains were nonrevealing. C3 and C4 complements were normal. Cryoglobulin was negative. Renal USG showed 12 x 5 cm bilateral kidneys with normal Echogenicity and Cortical thickness. Renal biopsy: Light Microscopy: Mesangial matrix expansion noted, no definite nodules, endocapillary hypercellularity, or crescent formation: no RBC or atypical casts. Immunofluorescence showed Smudgy, Mesangial reactivity in the glomerulus for Ig G 3+, C3(1+), Kappa light chain 3+, and lambda light chain 3+. Electron Microscopy: Segmental deposition of fibrillar material 12-25 nm in diameter. The immunohistochemical stain was positive for DNAJB9.

Discussion: We report a 69-year-old white woman well-controlled diabetes with minimal proteinuria. Unfortunately, the Kidney biopsy showed FGN. Although her loss of kidney function was gradual in the setting of minimal proteinuria, her diabetes could not explain decline in her renal function; a kidney biopsy changed the management of this patient. Kidney biopsy remains the gold standard for the diagnosis of kidney pathology. It is safe and allows us not to miss a major Glomerular disease. We plan to treat her with Rituximab Immunosuppressive therapy to prevent the disease's progression.

PUB256

Membranous Nephropathy Relapse After 26 Years

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Introduction: Membranous nephropathy (MN) is the most common cause of nephrotic syndrome in non-diabetic white males older than 40 years. Primary MN is diagnosed in 80% of all cases and is characterized by the presence of PLA2 R antibodies in 80% of cases. Relapse of MN after treatment is common however most relapses happen within the first 5 years. We present a rare case of MN relapse after 26 years of remission.

Case Description: A 68 years old male with past medical history of primary MN diagnosed on 1995, CKD stage II, hypothyroidism, T2DM, HTN and obesity was referred to the nephrology clinic for worsening albuminuria on May 2021. He had history of MN on 1995 that was treated with Prednisone and Cyclophosomide. He had been on remission since that time with regular nephrology follow ups. When he presented to the nephrology clinic he reported frothy urine for 3 months. **Physical exam:** Vitals, cardiovascular, lungs and abdominal exams were unremarkable. No lower extremities edema. **Investigations:** BUN 9 mg/dl Cr 0.9 mg/dl Albumin 3.2 HbA1c 10.2 Urine Albumin Creatinine Ratio 1470 mg/g **Clinical course:** He was started on Losartan with improvement in albuminuria from 1470 to 900mg/g. On September 2021, albuminuria worsened to 4g/g. Serology was remarkable for +ve anti PLA2 R. A kidney biopsy showed subepithelial immune complex-type dense deposits and moderately sclerotic arteries and severely hyalinized arterioles. His Cr was mildly elevated to 1.4 and albuminuria decreased from 4g/g to 2g/g however on December 2021 he started to have worsening edema with rise of Cr to 2.5 and albuminuria worsened to 13g/g. On March 2022 he was started on weekly Rituximab and completed 4 doses. His Cr peaked at 2.6 and then started to trend down after Rituximab to 1.2-1.4 however he continued to have persistent nephrotic range proteinuria.

Discussion: We report a patient with primary membranous nephropathy relapse after 26 years. MN relapse is rare after 5 years and cases of relapse after 20 years of remission are extremely rare. The biopsy showed features of MN and diabetic kidney disease. Despite maximally tolerated Losartan dose, he continued to have worsening Cr and proteinuria. His Cr improved after Rituximab however he had persistent proteinuria. The decision to use Rituximab rather than CNI was due to poorly controlled diabetes. Diabetic kidney disease is likely a factor in the failure of MN remission in our patient.

PUB257

Complement Dysregulation and Volume Excess Hyponatremia in Pre-Eclampsia

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Introduction: Complement abnormalities may occur in pre-eclampsia but their significance has not been completely elucidated. Hyponatremia occurs in severe pre-eclampsia but the mechanisms causing this are unknown. Some investigators suggest that SIADH is the cause but Hayslett suggests that volume excess hyponatremia is the most important cause. We describe a patient with pre-eclampsia who presented with severe nephrotic syndrome, edema and 14 g proteinuria & hyponatremia. She had a CFH variant but no complement deposition on renal biopsy.

Case Description: A 29-yo presented at 25+3 weeks gestation had hypertension and clinical volume overload. She had a BP of 150/90 with ankle swelling and hemoglobin 8.6 g/dL, platelets 174 k/mm3 & S. creatinine 1.3mg/dL. Urinalysis showed microscopic hematuria with Tp/cr ratio 14 g/dl. Labs showed: Na 132 meq/L, K 5.6 meq/L, Cl 105 mEq/dL, HCO3 21 meq/L, BUN 29 mg/dL & S.uric acid was normal at 6.4 mg/dL and urine specific gravity was 1.024 equivalent to urine osmolality to 700 Osm. LDH was 449 IU/ml, haptoglobin 69 g/dl, ADAMST13 was normal, ANA negative, anti-dsDNA positive at 14, and other auto immune workup was negative. C4 complement nadired at 5 mg/dL, with a C3 level of 107 mg/dL. Due to the low C4 complement, dsDNA and proteinuria, a diagnosis of lupus nephritis was made & she received pulse dose steroids for 3 days. Complement genetic testing showed a CFH variant. Factor H, factor I, factor B, CD46 expression were all normal. A renal biopsy showed glomerular endothelial swelling & no immune complexes by IF or EM. Findings showed thrombotic microangiopathy (TMA) consistent with pre-eclampsia. An urgent C-section was performed. Serum Na & edema rapidly corrected to normal without diuretics with resolving proteinuria & complete recovery of renal function.

Discussion: Complement dysregulation occurs in pre-eclampsia and eclampsia. In our case, despite a genetic study confirming a CFH variant, no complements were seen in the renal biopsy which was a surprise. This suggests serum complement dysregulation in pre-eclampsia may not be involved in intrarenal TMA. In addition, our case suggests that nephrotic syndrome extracellular fluid volume excess is the cause for hyponatremia in severe preeclampsia. Prompt delivery of hyponatremic patients with pre-eclampsia leads to rapid improvement of the serum Na without diuretics.

PUB258

A Rare Case of Renal-Limited Hydralazine-Induced Pauci-Immune Glomerulonephritis

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Introduction: RPGN is characterized by a rapid decline in renal function with significant hematuria and proteinuria. Pauci-immune GN predominantly presents as granulomatosis with polyangiitis, 90% have ANCA antibodies, hence the name ANCA-associated vasculitis. Hydralazine has been used since the 1950s for the management of hypertension. Evidence for hydralazine-associated vasculitis dates to the pre-ANCA era.

Case Description: A 58-year-old man with CKD IV, HTN, CVA, and polysubstance usage presented with chest pain, accelerated hypertension, cough, and SOB. Creatinine 6.75 mg/dl, bicarb 15 mmol/L, urine P/C ratio 5 gm/gm, procalcitonin 1.17 ng/mL, and hemoglobin of 5.7 gm/dl. Of note, the patient was recently started on hydralazine outpatient. The patient received antibiotics, blood, and was admitted to the step-down unit. The renal US revealed diffused renal echogenicity. Started on RRT, GN serologies revealed mildly positive RF, increased C-ANCA and MPO Abs, positive dsDNA, and negative Anti-PLA2R and complement, elevated SFLC and polyclonal gammopathy,

but no monoclonal spike. Anti-histone Abs was mildly positive, hydralazine was discontinued. Renal biopsy revealed total glomeruli 31, global glomerulosclerosis 18, moderate interstitial fibrosis with tubular atrophy, and severe arterial intimal fibrosis. One of four nonsclerotic glomeruli showed fibrin and small crescent formation. The patient was not placed on a pulsed dose steroid due to active infection and was started on prednisone 60 mg daily instead. Outpatient TRUXIMA (rituximab) was started.

Discussion: Pauci-immune GN accounts for up to 80% of RPGN occurrences, affecting 7–10 per million Americans per year. PICG has 80% 1-year mortality without therapy. 5-year survival is 75% with strong immunosuppression. Hydralazine-induced pauci-immune GN is rare; we present this case to highlight several critical aspects of drug-induced pauci-immune GN that can aid with early identification and improve patient outcomes. Early detection of MPO Abs helps diagnose the condition and timely kidney biopsy can guide adequate treatment. The offending agent must be discontinued early. Untreated RPGN evolves to ESRD in days to weeks. Prompt diagnosis and treatment enhance prognosis. We recommend serologies and, if inconclusive, a kidney biopsy. A patient with RPGN-suggestive symptoms needs a clear and urgent diagnosis and treatment.

PUB259

Unanticipated Cause of Minimal Change Disease: A Rare Case due to Hypothyroidism

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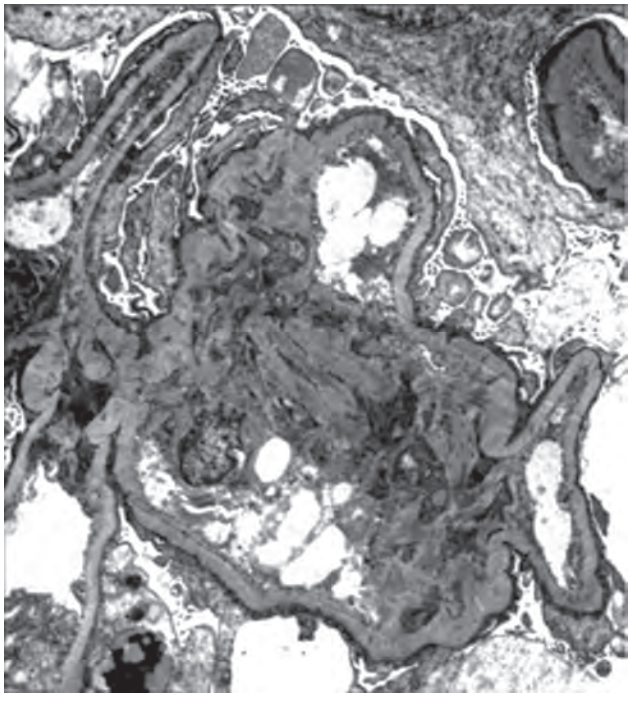
Introduction: Hypothyroidism, also called underactive thyroid, may affect renal physiology and impair kidney function, among other metabolic implications. In certain case studies, hypothyroidism was mentioned as a contributing factor to minimum change disorder, which we will be emphasizing here.

Case Description: An 82-year-old female with PMH of Graves' disease s/p thyroidectomy, non-compliant with Levothyroxine presents to the ED with a complaint of edema, mainly in the lower limbs, slowly worsening over 2 weeks, as well as foamy urine. Laboratory workup showed a high TSH of 65.2 uIU/ml, a normal FT4, and a low FT3 of 0.4 pg/ml, creatinine of 4.35 mg/dl, hypoalbuminemia, and hyperlipidemia, urinalysis showed >500 protein, urine P/C was 3. A Glomerulopathy workup was begun. After ruling out autoimmune kidney disorders, a renal biopsy was done, confirming Minimal Change disease. Prednisone 60 mg and Levothyroxine 125 mcg were prescribed. Three weeks later, he demonstrated a favorable response to treatment with an improvement in symptoms and a repeat creatinine of 3.8.

Discussion: Inadequate supply of thyroid hormone can impair kidney function by influencing vascular resistance, the re-absorptive process, and renal blood flow. It can also influence the RAAS system, beta-adrenergic receptors, and renal tubular cell's dopaminergic activity. Gradual deterioration of kidney function causes an increase in the loss of free and bound thyroid hormones, ultimately increasing thyroxine need. GFR is reversibly lowered (by roughly 40%) in more than 55% of hypothyroid people. Thyroxine therapy reduces edema, albumin capillary permeability, and plasma colloid osmotic pressure. Because just a few isolated incidences have been documented in the literature, more study is needed to identify the link between hypothyroidism and nephrotic syndrome.



PUB260

Unilateral Parotid Swelling as the Initial Manifestation for HIV-Associated PLA2R-Negative Membranous Nephropathy

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Introduction: There are two major types of HIV-associated renal disease: HIV-associated nephropathy, which is more common, and HIV-associated immune complex disease. Kidney biopsy is necessary to differentiate between these types as they appear different histologically and may be beneficial to determine overall prognosis. We present the case of a patient with unilateral, painless swelling of the parotid region, who not only had underlying HIV infection but also full-blown renal failure requiring hemodialysis.

Case Description: A 34-year-old African-American male with no medical history presented to the hospital for worsening right-sided parotid swelling at the mandibular angle for 1 week. He also endorsed generalized malaise, intermittent shortness of breath, subjective fevers, and unintentional weight loss. Physical exam showed a soft, non-tender, mobile right-sided parotid mass. Labs were remarkable for profound renal dysfunction (BUN/Cr 92/9.71 mg/dL) and significant hyperkalemia with non-anion gap metabolic acidosis. Urinalysis revealed a protein-creatinine ratio 931 mg/g and 24-hr urine protein of 862 mg/dL. Imaging of the neck showed a well-marginated 3.4x3.0x3.6 cm, hypo-attenuated structure in the right parotid tail. He tested positive for HIV and syphilis. Hemodialysis (HD) was initiated. Drainage of the parotid mass was consistent with a lymphoepithelial cyst with no evidence of malignancy on biopsy. Kidney biopsy revealed burnt-out phase of membranous nephropathy, PLA2R negative, with presence of tubular microcysts on light microscopy, podocyte foot process effacement and tubuloreticular inclusions on electron microscopy. The patient was initiated on treatment for HIV and syphilis. After 4 months of treatment, his HIV viral load was undetectable with improvement in renal function and urine output allowing us to hold HD. Patient is currently maintaining a stable creatinine off HD.

Discussion: HIV poses a threat for the development of both acute and chronic kidney disease. It is imperative to consider the possibility of undiagnosed HIV infection in a patient presenting with painless cysts of the head and neck region. Furthermore, in cases of suspected HIV-associated nephropathy, obtaining a biopsy is clinically significant to not only provide a histological diagnosis but also aid management and prognosis.

PUB261

Granulomatosis with Polyangiitis in a Diabetic Woman with Nephrotic Proteinurias: Case Report

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Introduction: Granulomatosis with polyangiitis (GPA) is an antineutrophil cytoplasmic autoantibody (ANCA)-associated vasculitides (AAV) is partof a group of disorders. All are associated with ANCA, affect predominantly small-sized arteries, in which it can present with pulmonary hemorrhage, deterioration of renal function, constitutional symptoms that can lead to death if not treated in time.

Case Description: A 71-year-old female with a known morbid history of Diabetes mellitus 2 + systemic arterial hypertension + grade II morbid obesity + hypothyroidism; which she was being investigated by hematology for approximately 3 two months for normochromic normocytic anemia + thrombocytosis + leukocytosis. She herself began to notice foamy urine and asthenia with normal kidney function and that is when she is referred to nephrology. Protein dosage is performed in 24-hour urine (5.2/24hrs) with C-Anca: weakly positive. It was decided to perform a renal biopsy and while waiting for it, the patient developed fever, cough, and respiratory distress that required CPAP 1 week later, and she was admitted to the intensive care unit. A diffuse pattern with opacities is evident on radiography with tomographic data suggestive of pulmonary hemorrhage and rapidly progressive deterioration of renal function. (Family members refused to perform bronchoalveolar lavage by bronchoscopy). A biopsy was received reporting granulomatosis with polyangeitis. Treatment with cyclophosphamide and rituximab plus steroids was started.

Discussion: After initiating pulses of steroids, cyclophosphamide, and rituximab, the patient remains in the intensive care unit for approximately 3 weeks due to impaired ventilatory mechanics. Subsequently, she is transferred to the clinical ward and her discharge is decided. Outpatient management continues. During the 3rd dose of cyclophosphamide, she presented severe neutropenia + fever + complicated urinary tract infection where she was in sepsis and required admission to the intensive care unit again and placement of colony stimulants. She is admitted in stable condition, treatment continues after her discharge. Until now, a patient with normal renal function, with a decrease in proteinuria by approximately 50%, with a significant improvement in its clinical picture.

PUB262

Infection-Related Pauci-Immune Golmerulonephritis: To Treat with Immunosuppression or Not, That Is the Question

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Introduction: Pauci-immune glomerulonephritis is a common cause of crescentic or rapidly progressive glomerulonephritis. Treatment typically consists of immunosuppression; however, we present a case of pauci-immune glomerulonephritis treated without immunosuppression.

Case Description: An 84-year-old female with medical history of breast cancer status post resection and chemoradiation, chronic lymphocytic leukemia with treatment-related myelodysplastic syndrome, and recent SARS-CoV-2 infection with central venous port-related coagulase negative staphylococcus bacteremia developed acute kidney injury. Urinalysis revealed proteinuria and hematuria. Urine sediment analysis showed dysmorphic red blood cells and red blood cell casts. Serologic studies were notable for hypocomplementemia, ANA, and c-ANCA; however, myeloperoxidase and proteinase 3 were negative. Kidney biopsy was performed. Light microscopy showed focal segmental glomerular necrosis with small crescent. Immunofluorescence performed on frozen sections showed a full house picture, but immunofluorescence performed on paraffin sections only showed 1-2+ mesangial staining for IgM. However, there were no electron dense deposits on electron microscopy which is most consistent with pauci-immune glomerulonephritis. Despite rising creatinine, immunosuppression was not started in the setting of persistent bacteremia and was planned to be started once blood cultures were negative for more than 48 hours. Once blood cultures became negative, creatinine started to stabilize. Creatinine peaked at 4.9mg/dL. Ultimately, steroids were not started given that creatinine continued to improve with antibiotics once blood cultures remained negative.

Discussion: Pauci-immune glomerulonephritis has been reported in cases of infective endocarditis and treated with antibiotics. This case highlights infection as a possible cause of pauci-immune glomerulonephritis with antibiotics being the mainstay of therapy in such cases.

PUB263

Methamphetamine-Associated Thrombotic Microangiopathy

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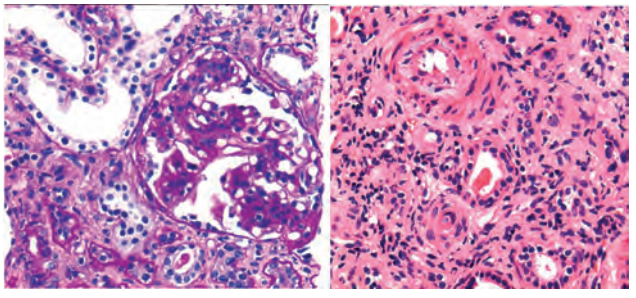
Introduction: Thrombotic microangiopathy (TMA) is characterized by clinical presentation with microangiopathic hemolytic anemia, thrombocytopenia, and target organ damage. It can present acute kidney injury with damage and occlusion of the glomerular circulation. The requirement of renal replacement therapy has a poor prognosis.

Case Description: 16-year-old male, with no known pathological history. He has a history of drug use such as crack and methamphetamine. Brought in due to a month-long condition with nausea, cough with expectoration, dyspnea, and edema of the lower limbs. Upon admission to the emergency room, a patient was received with blood pressure 190/80mmHg, HR112bpm, 35 rpm, temperature 36.9°, saturation 95%, hemoglobin 5.5gr, platelets 72,000, BUN 149mg/dL, Cr19.6mg/dL, and potassium 6.1mEq. In its gasometry with pH 7.31 HCO3 12.6. Urinary sediment was obtained with a leukocyte cast, without dysmorphic erythrocytes. In renal ultrasound with adequate renal measurements, it was decided to carry out a renal biopsy. Image 1: expansion of the mesangial matrix with segmental proliferation, folded and healed basement membranes, with duplicated segments, leukostasis, karyorrhexis, and fibrin thrombi, partially organized and incorporated into the walls. Image 2: preglomerular, interstitial, and small-caliber arteriolar vessels with obliterative concentric thickening, advanced fibromyxoid intima, endothelial edema, and fibrin debris adhered to the walls. The biopsy also showed grade III chronic interstitial damage, and chronic glomerular hypoperfusion with advanced sclerosis, so it was decided to start hemodialysis as renal replacement therapy.

Discussion: In this case, we are dealing with thrombotic microangiopathy with severe renal involvement. MAT can have primary and secondary causes. In this patient, primary causes were ruled out, and secondary causes could only be associated with the use of deoxyephedrine (methamphetamine), a cause of CKD in a small population group that, on occasion, cannot be diagnosed.



PUB264

C3 Glomerulopathy in Kidney Transplant: A Case Report

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Introduction: Membranoproliferative GN (MPGN) is glomerular injury with increased mesangial matrix, cellularity, and capillary wall thickening. It includes immune-complex MPGN and C3 glomerulopathy. Incidence is rare (1-4 cases per million). Dysregulated complement pathway plays a role. Prognosis is poor, with kidney failure expected within 10 years. Recurrence in transplanted kidney causes graft failure in 50%-90% of recipients.

Case Description: A 59-year-old female presented with lower extremity swelling and fatigue. Vital signs: BP 160/71 mm Hg, PR 65 bpm, RR 16 breaths/min. Lab results: Na-130, BUN-93, Sr.creatinine-3.71, Albumin-3.2. In 2002, she underwent renal transplant due to presumed transitional cell carcinoma of the right kidney with neoplasia in the bladder. Her end-stage renal disease potentially caused by herbal medicine (aristocholic acid) intake. August 2022 biopsy showed glomerular abnormalities: C3c deposits, matrix expansion, sclerosis in 2 out of 5 glomeruli. Cellcept dosage increased to 750mg twice daily, prednisone added. Baseline creatinine 1.0-1.2 mg/dl until 2019, recent value 3.71mg/dl. Worsening proteinuria (urine protein creatinine ratio 1.8g) despite RAAS blockade. Hypertension, chronic hyponatremia, acute anemia (hemoglobin 6.7 g/dl). Anemia treated with packed RBC and IV iron. Repeat biopsy deferred due to bleeding risk from elevated blood urea level. Medication: Cellcept 750mg BID, Cyclosporine 75mg BID, Prednisone 5mg OD. Hemodialysis twice a week, frequency adjusted based on blood urea levels.

Discussion: C3 glomerulopathy recurrence in transplant is not uncommon, but diagnosis of C3 GN on a transplanted kidney who has primary aristocholic acid nephropathy is rare. Diagnosis of C3 glomerulopathy relies on kidney biopsy. C3 predominance of at least two orders of magnitude by IF compared with other immunoreactants has been adopted as a diagnostic criterion. Our patient exhibited similar findings and commenced regular hemodialysis with close monitoring. Hence, native kidney biopsy is crucial in most cases.

Laboratory reports

	2/09/2023	2/10/2023	2/11/2023	2/12/2023	2/14/2023
Blood Sodium	132	132	130	131	128
Blood Urea Nitrogen	82	88	79	91	101
Blood Creatinine	3.8	3.7	3.5	3.5	3.8
Albumin	3.5	2.8	2.7	2.7	
Hemoglobin	7.7	6.7	7.5	7.5	7.5

PUB265

Henoch-Schoenlein Purpura (HSP) Nephritis in Adults

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Introduction: Henoch-Schoenlein purpura (HSP) is a small vessel vasculitis. It affects children more often than adults but renal involvement is more common & severe in adults. Few studies on HSP nephritis (HSN) in adults have been reported. Prompt evaluation & aggressive treatment in HSP nephritis can prevent progression of kidney disease.

Case Description: A 48-year-old non-diabetic, non-hypertensive & non-smoker Caucasian female with PMH of seizure disorder, morbid obesity (BMI 53.8), & asthma, presented with a lower extremity purpuric rash & arthralgia in knees, hip joints. Labs consistent with normal CBC, normal coagulation profile, normal renal function (creatinine 0.77 mg/dl). UA with microscopic hematuria (5 RBCs/HPF) & proteinuria (100 mg/dl). She was suspected to have Henoch-Schoenlein purpura (HSP) based on clinical findings of palpable purpura and arthralgia. Further investigation showed proteinuria of 1904 mg/day & elevated serum IgA level (526 mg/dl). Patient underwent a kidney biopsy that showed mesangial proliferation, mesangial immune complex deposits identified as IgA & C3 on immunofluorescence study and as dense deposits on electron microscopy. These findings were supportive for HSP nephritis. She was started on Lisinopril and prednisone. Repeat urine study showed improvement in proteinuria (189 mg/day) & hematuria (4 RBC/HPF) with 4 months of tapering prednisone therapy.

Discussion: HSP is a small vessel vasculitis. Renal involvement in HSP can cause hematuria, mild-to-moderate proteinuria, RBC cast, elevated serum creatinine, hypertension & nephrotic range proteinuria. Latter 3 presentations are associated with worse renal prognosis. ESRD may develop in 15-25%. Patients with proteinuria >1g/day should undergo kidney biopsy. Adult patients with limited kidney involvement (hematuria, proteinuria <1 g/day, and normal serum creatinine) require no immunosuppressive therapy. ACE inhibitor or ARB is used to reduce proteinuria. Patients with more severe kidney involvement (proteinuria ≥1 g/day, elevated serum creatinine, or crescentic glomerulonephritis on kidney biopsy) require immunosuppressive therapy with glucocorticoids. Our patient had evidence of severe disease (>1g/day proteinuria), therefore she underwent kidney biopsy & required glucocorticoid treatment resulting in almost complete resolution of proteinuria in 4 months. She did not require any further immunosuppressive therapy.

PUB266

Atypical Hypoproteinemia and Fluid Retention: AKI in an IgAκ Multiple Myeloma with Type 2 Diabetes

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Introduction: Diagnosis of multiple myeloma (MM) is usually evident when chronic bone pain, pathologic fractures, and hypercalcemia are complicated by proteinuria and kidney failure. Cast nephropathy is should be considered when proteinuria (often ≧3 g/day), particularly without concomitant hypoalbuminemia or significant albuminuria, is found in a patient who is ≧ 40 y/o 1).

Case Description: An Asian 75 y/o male had dysarthria as well as right upper limb weakness for 2 weeks. He was brought to ED due to unconsciousness and difficulty of moving by himself, then admitted to the nephrology with pleural effusion, ascites, and

hypoalbuminemia. Past medical history included well-controlled pancreatic diabetes, which basal-bolus insulin regimen was initiated 6 years ago. He had worsen for 6 years to serum Cr 2.33 mg/dL, eGFR 23.3 mL/min/1.73m^2, Alb 1.1 g/dL, TP 4.6 g/dL, Ca 10.4 mg/dL, IgA 645 mg/dL, Hb 8.1 g/dl; urine Alb 59 mg/gCr, TP 270 mg/gCr, and protein 0.2 g/day. Anemia was not improved by transfusions and ESA. Both GIS and CS did not detect active bleeding site, nor amyloid deposition with Congo-Red staining. No Bence Jones protein in urine. Alpha-antitrypsine clearance test excluded malabsorption syndrome. ^{99m}Tc-HSAD scintigraphy excluded protein-losing gastroenteropathy 2). During 2 weeks, he had worsen to Hb 7.7 g/dL, Cr 2.58 mg/dL. Serum free light chain (κ/λ) was 130/152 mg/L (=0.86). SPEP detected IgAκ M protein. Bone marrow show CD79a$^+$ in 30-40 % of eukaryocytes; diagnosed MM IgAκ type. The patient received bortezomib 1.0 mg/m^2/week for 4 weeks with DEX renalidomide. He discharged with no leg edema, UP(+/-), Cr 1.56 mg/dl, eGFR 34.5 ml/min/m^2, TP 6.4 g/dL, Alb 3.0 g/dL, Hb 8.8 g/dL, and IgA 406 mg/dL.

Discussion: It was atypical as main symptoms of MM that the patient had hypoproteinemia and fluid retension instead of acute kidney injury with hypercalcemia. We could not perform kidney biopsy; not confirm presence of cast nephropathy in the patient. Urine protein is within upper limit of normal range, therefore we estimate his acute kidney injury as presenting interstitial nepritis caused by M protein. This case was compatible with incidence that ≧60% reduction of free light chain M protein recovered kidney function in ~80 % case of myeloma kidney 3). Reeferences. 1) NKF primer on kidney diseases 7/e, pp.274-82. 2) PLoS ONE 2015;10(4):e0123036. 3) JASN 2011;22:1129-36.

PUB267

Epidemiology of FSGS over a 20-Year Period

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Background: This epidemiological study describes a renal centre's 20 year experience of patients with primary Focal segmental glomerulosclerosis (FSGS), one of the leading causes of nephrotic syndrome (NS) in adults.

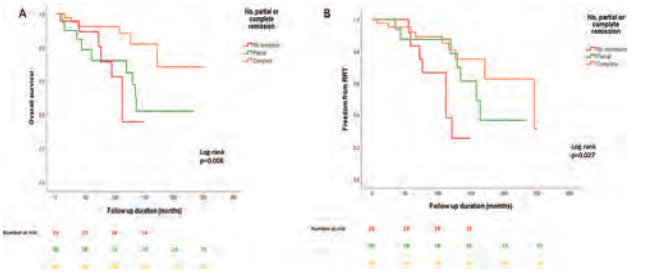
Methods: Retrospective longitudinal analysis of primary FSGS at a tertiary renal centre over 2 decades. Baseline demographics, labs and outcomes: Complete (CR) & partial (PR) remission, relapse, progression RRT and mortality were collected.

Results: 87 patients were identified with primary FSGS after exclusion of secondary causes. Mean age was 49.3 years, 60.9% male, 86.2% white with median eGFR 46ml/min, urine PCR 573mg/mmol, serum albumin 33g/l (Table 1). Rates of PR and CR were 23% & 49.4%, respectively. Progression to RRT occurred in 27.4%, death in 27.4%. 29 (33.3%) presented with NS. Those who presented with nephrotic syndrome were more likely to receive immunosuppression (IS) 86.2% vs 20.7% (P<0.001) and more likely to achieve CR 69% vs 39.7% (p 0.01) with no increased rates of relapse. Patients that achieved complete remission were less likely to die; patients that achieved either partial or complete remission were less likely to progress to ESKD (Figure 1).

Conclusions: This Retrospective longitudinal study of primary FSGS over a period of 2 decades provides important prognostic information for this understudied area. Despite the exclusion of secondary causes only 1/3 of patients presented with NS. Those who presented with NS were more likely to receive IS and achieve complete remission. Regardless of whether the patient had NS, complete or partial remission was protective of ESKD and CR was associated with reduced risk of death. Given 27.4% die or progress to RRT, this emphasises the importance of achieving remission, if even partial

Funding: Commercial Support - unrestricted project grant from Vifor

Variable		Total cohort (n=87)	Nephrotic (n= 29)	Non – Nephrotic (n= 58)	P- value
Age		49.3 (+/- 17.9)	54.8 (+/- 19.0)	46.8 (+/- 16.3)	0.043
Male gender		53 (60.9%)	18 (62.1)	35 (60.3)	0.877
Caucasian ethnicity		75 (86.2%)	26 (89.7)	49 (84.5)	0.510
Diabetes		8 (9.2%)	2 (6.9)	6 (10.3)	0.668
Hypertension		46 (52.9%)	13 (44.8)	33 (56.9)	0.400
Cardiovascular disease		13 (15.1%)	2 (6.9)	11 (19.0)	0.137
eGFR, ml/min/1.73m^2		46 (27 – 76)	39 (20.5 – 73.5)	46.5 (31.8 – 78.5)	0.39
Remission	Partial	20 (23%)	5 (17.2)	15 (25.9)	0.368
	Complete	43 (49.4%)	20 (69)	23 (39.7)	**0.01**
	Combined	63 (72.4%)	25 (86.2)	38 (65.5)	**0.042**
Time to remission (days)		523 (159-1231)	208 (97 – 613)	763 (204 – 1836)	**0.006**
Relapse		29 (33.7%)	14 (48.3)	15 (25.9)	0.096
ACEi/ ARB		67 (79%)	21 (72.4)	46 (79.3)	0.471
Immunosuppression		37 (42.5%)	25 (86.2)	12 (20.7)	**< 0.001**
RRT		24 (27.6%)	8 (27.6)	16 (27.6)	1
Mortality		24 (27.6%)	9 (31.0)	15 (25.9)	0.611



PUB268

Examining the Role of External Factors with Risk of ANCA Vasculitis Relapse

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Background: The role of patient-reported stressors, insect bites, and infections on disease relapse of ANCA vasculitis has yet to be well studied.

Methods: In a case-control study of subjects with ANCA vasculitis, we defined cases as those who relapsed (Relapse Cohort) and controls as those who did not relapse (Remission Cohort) during the study (2011-2022). Longitudinal surveys were collected every 3 to 6 months and included self-reported exposures, including stressors (defined as biological, environmental, cognitive, behavioral, and life events), insect bites, and infections. Exposures happening within 15 months before relapse were included in the Relapse Cohort, and exposures happening in the 15 months after achieving remission were included in the Remission Cohort. The two groups were compared using Fisher Exact, Wilcoxon 2-sample, and Cochran-Armitage Trend tests.

Results: The number of reported infections (Table) was higher in the Relapse Cohort than in the Remission Cohort (p=0.03). Upper respiratory infections were most common, and consistently reported more frequently between 6 and 15 months before relapse versus 15 months post-remission (p-trend=0.0017, Figure). There was no significant evidence for stressors and insect bites as external factors in disease relapse.

Conclusions: More frequent patient-reported infections, specifically upper respiratory infections, may contribute to patient vulnerability to relapse for up to 15 months after infection. Counseling and closely monitoring patients after infectious symptoms could aid in earlier detection of disease flares.

Funding: Other NIH Support - 5-R01-DK125350-01

Variables: n, % or Median (IQR)	Relapse Cohort N=66	Remission Cohort N=47	P value
Female	36(55%)	22(47%)	0.45
PR3 ANCA	37(56%)	19(40%)	0.13
Any Stressors	89%	77%	0.08
Number of Stressors	2(1,3)	2[1,3)	0.38
Insect Bites	32%	32%	1.00
Number of Insect Bites	0(0,1)	0(0,1)	0.99
Infections	71%	55%	0.11
Number of Infections	1(0,2)	1(0,1)	0.03

Table. Characterization of Cohorts

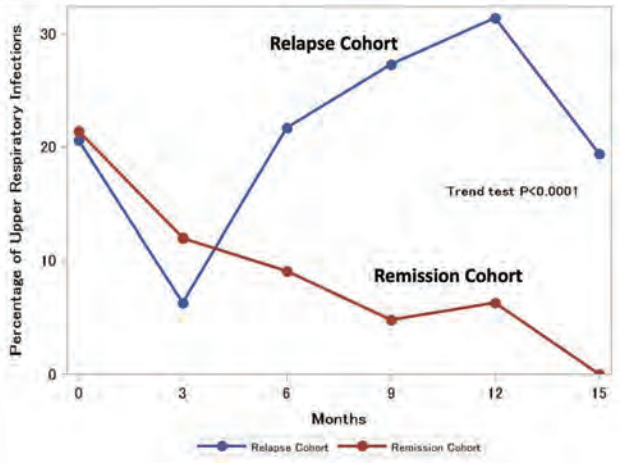

Figure. Distribution of URI

PUB269

IgA Nephropathy and Thrombotic Microangiopathy: A Rare Manifestation of Lupus After COVID-19 Infection

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Introduction: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease which may present with lupus nephritis (LN), lupus anticoagulant (LAC) and thrombotic microangiopathy (TMA). SLE is rarely described in association with non-lupus glomerulonephritis (GN). We present a case of SLE presenting with renal dysfunction, hypertension (HTN), proteinuria, and microscopic hematuria in a patient with LAC, shortly after COVID-19 infection, in which renal biopsy confirmed IgA nephropathy (IgAN) with TMA.

Case Description: A 37-year-old male with history of antiphospholipid syndrome (APLS) with LAC, right leg deep vein thrombosis in 2016, osteosarcoma of left distal femur in 2002, melanoma in 2022, HTN, and hyperlipidemia, was referred to Nephrology in December 2022 for elevated creatinine (Cr) and proteinuria. In September 2022, he developed right leg numbness/tingling and facial droop. He caught COVID-19 in late November 2022. In December 2022, he presented with severe HTN (SBP>200), Cr 1.6-1.7 mg/dL, urine protein/Cr ratio (UPCR) 7000 mg/g Cr, microscopic hematuria, low-normal C3, low C4, +ANA (1:1280), +dsDNA Ab, negative anti-GBM Ab, normal SPEP, and negative hepatitis. He was treated with methylprednisolone 500 mg IV daily x 3 days. Renal biopsy in late December 2022 revealed IgAN (Oxford Class M1 E1 S0 T0 C0) with concomitant TMA. After steroid therapy, his eGFR improved from 49 to 54 mL/min, Cr improved from 1.7 to 1.4 mg/dL, and proteinuria improved from 7000 to 3000 mg/g Cr in early January 2023. He was initiated on losartan, amlodipine, fish oil, atorvastatin, and hydroxychloroquine (HCQ). In February 2023, a rheumatologist diagnosed him with SLE. In April 2023, his UPCR improved to 300 mg/g Cr and Cr was stable.

Discussion: This is a rare case of SLE presenting with renal dysfunction, HTN, proteinuria, and microscopic hematuria found to be due to IgAN rather than LN, in conjunction with TMA in the setting of LAC. It underscores the importance of performing renal biopsy in patients suspected of having LN, as other GN's may coexist with SLE. This case is unique in that the onset of IgAN and SLE occurred after COVID-19 infection, which may increase risk of autoimmune disorders. Clinical response was like that of non-SLE associated IgAN. This case supports the utility of HCQ as a therapeutic option in IgAN, particularly in IgAN occurring in SLE.

PUB270

Use of Mycophenolate Mofetil (MMF) in IgA Nephropathy: When Steroids Induce Psychosis

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Introduction: IgA nephropathy (IgAN) is one of the most common glomerular diseases worldwide and up to 40 % can progress to ESKD. Current management of IgAN is focused on supportive care (SC), to slow the rate of progression. This includes BP management, low Na diet, ACE/ARB use if proteinuria >500mg/d, weight loss, exercise, smoking cessation, and CV optimization. KDIGO currently recommends that patients who remain at high risk of progressive CKD despite maximal SC, be considered for a 6-month course of glucocorticoid therapy.

Case Description: 66F history of SLE, HTN, HLD, depression presented to hospital with fatigue and anemia seen on outpatient labs, found to have symptomatic anemia (Hgb 5.8) requiring 2u pRBCs and complicated by AKI. Patient underwent EGD, which was normal and Hgb remained stable, so was placed on PPI and advised against NSAID use. On admission the patient's serum creatinine (SCr) was noted to be 3.49 mg/dL with gross hematuria and spot urine total protein/creatinine ratio of 2.4g. Baseline SCr was 1.0 three months prior, increased to 2.2 one month prior. A kidney biopsy was performed but was an inadequate sample. She was started on empiric steroid therapy for concern for RPGN, however had steroid induced psychosis and steroids were stopped. Patient was discharged with SCr of 2.73 and underwent repeat biopsy outpatient which showed focal proliferative IgAN with cellular crescents in 20 % of glomeruli, and moderate acute interstitial nephritis. Given patient's contraindication to steroids, she was started on MMF with stable kidney function and improving proteinuria (SCr 1.46 and urine protein/Cr ratio 0.7).

Discussion: The appropriate therapy for IgAN with crescents and proteinuria remains uncertain. The TESTING study showed use of steroids reduced kidney failure, however it increased serious adverse events (AE). Steroids were not well studied in patients with eGFR< 50 and not every patient can tolerate steroids. There has been mixed data regarding the use of MMF as a steroid sparing agent. MMF may be a reasonable alternative to reduce progression of IgA nephropathy.

MMF use in IgA Nephropathy

Date	Authors	Findings
2/2023	Hou FF, Xie D, Wang J, et al.	MMF reduced progression of CKD compared to SC
2/2017	Hou JH, Le WB, Chen N, et al.	MMF + steroids vs steroids did not reduce proteinuria but had less AEs
11/2015	Hogg RJ et al.	MMF had no change in proteinuria compared to placebo

PUB271

Clinical Characteristics, Histologic Patterns, and Disease Outcomes in C1q Nephropathy (C1qN): A Single-Center Experience

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Background: C1qN is a rare glomerulopathy associated with mesangial dominant C1q deposition on immunofluorescence staining. Clinical presentation and outcomes are heterogenous, ranging from asymptomatic proteinuria to nephrotic syndrome. We explore the demographic and clinical characteristics of a C1qN cohort stratified on nephrotic syndrome at diagnosis.

Methods: We searched the University of New Mexico Kidney Biopsy registry for instances of C1qN. We excluded transplant recipients, obtained the relevant demographic and clinical data from the electronic medical records, and summarized and compared data stratified on nephrotic syndrome at diagnosis.

Results: Of the 11 renal biopsies with C1qN, 8 were native and were included in this study. Patients with nephrotic syndrome were younger, had higher proteinuria and serum cholesterol, and lower albumin (table 1). Patients without nephrotic syndrome had greater microscopic hematuria. Apart from a greater degree of foot process effacement in patients with nephrotic syndrome, no other trends were evident on microscopy. Patients with nephrotic syndrome were likely to receive immunosuppressive therapy. Disease relapse was seen often in patients with nephrotic syndrome; however, immunosuppressive therapy led to proteinuria resolution in all patients.

Conclusions: C1qN is an immune-complex mediated rare diagnosis afflicting children. Nephrotic syndrome is associated with foot process effacement and a trend towards frequent relapses. Patients without nephrotic syndrome have microscopic hematuria and are less likely to relapse. Therefore, patients with C1qN - especially those with nephrotic syndrome at diagnosis - should have a long-term follow-up to identify disease relapse.

	No Nephrotic Syndrome, N = 4[a]	Nephrotic Syndrome, N = 4[a]	p-value[b]
Demographics and Laboratory data			
Age at biopsy (Years); Median (IQR)	15 (10 - 20)	3 (3 - 6)	0.3
Sex- Female; n (%)	3 (75%)	2 (50%)	>0.9
Urine Protein to Cr ratio (g/g); Median (IQR)	0 (0 - 2)	6 (0 - 16)	0.7
Red blood cells on urinalysis; n (%)	100 (75 - 100)	2 (1 - 28)	0.4
Cholesterol (mg/dl); Median (IQR)	230 (230 - 230)	381 (324 - 412)	0.5
Albumin (g/dl); Median (IQR)	3.60 (3.20 - 3.95)	2.70 (1.68 - 3.73)	0.7
Electron Microscopy			
Foot process effacement; n (%)	0 (0%)	3 (75%)	0.14
Treatments			
Steroid use at the time of diagnosis; n (%)	0 (0%)	4 (100%)	0.029
Immunosuppression use; n (%)			0.045
Cyclosporine	1 (8.3%)	4 (33%)	
Tacrolimus	0 (0%)	1 (8.3%)	
Prednisone	1 (8.3%)	4 (33%)	
None	10 (83%)	3 (25%)	
Outcomes			
Follow up duration (Years); Median (IQR)	1.4 (0.4 -3.6)	2.1 (0.7 – 4.6)	<0.001
Recurrent relapses	1 (25%)	3 (75%)	0.5
n (%); Median (IQR)			
Fisher's exact test; Wilcoxon rank sum exact test			

Demographic and clinical data at biopsy.

PUB272

Atypical Anti-Glomerular Basement Membrane Disease with IgA Nephropathy: A Rare Dual Pathology in Rapidly Progressive Glomerulonephritis

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Introduction: The anti-GBM disease is a rare small vessel vasculitis in which circulating antibodies are directed against an antigen intrinsic to the glomerular basement membrane (GBM) and/or alveolar basement membrane, resulting in rapidly progressive glomerulonephritis and/or alveolar hemorrhaging. A diagnosis of anti-GBM was obtained based on the identification of anti-GBM antibodies, either in serum or in tissue, along with pathological features of crescentic glomerulonephritis with or without evidence of alveolar hemorrhaging. The authors describe one such case with a dual pathology involving IgA nephropathy and atypical anti-GBM disease.

Case Description: A 48-year-old female with microscopic hematuria and proteinuria in the nephrotic range accompanied by a slight elevation in serum creatinine presented to our facility. The pathological results of a renal biopsy showed a crescentic glomerulonephritis and an immunofluorescence pattern, indicative of a dual pathology of IgA nephropathy and anti-GBM disease (Figure 1). Serum anti-GBM antibody titer was not detected. After treatment with pulse methylprednisolone, 10 plasma exchange therapy

sessions over two weeks, and oral cyclophosphamide, the patient's serum creatinine returned to relatively stable levels, and her hematuria and proteinuria improved over the subsequent six months.

Discussion: Atypical anti-GBM disease manifests milder kidney injury and minimal pulmonary hemorrhaging compared to classical cases. In this case, the patient's condition improved, and renal function remained relatively stable with corticosteroid, plasma exchange therapy, and oral cyclophosphamide treatment.

Figure 1:a dual pathology of IgA nephropathy and anti-GBM disease.

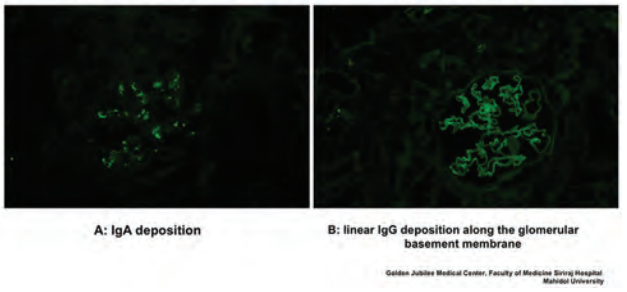

Figure 1

PUB273

Experience with Ravulizumab in Atypical Hemolytic Uremic Syndrome

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Background: The arrival of eculizumab revolutionized the treatment of Atypical Hemolytic Uremic Syndrome (aHUS). Ravulizumab also offers C5 inhibition but with longer half-life. We describe the experience with ravulizumab in two scenarios: switching from another C5 inhibitor in stable patients and direct therapy initiation (naïve).

Methods: We present 9 patients with 42±13years and 81±12.4kg. Switching to ravulizumab began 2 weeks after the last eculizumab dose while in naïve patients it started after excluding other causes of aHUS. Initial dose was 2700mg followed by 3300mg after 2 weeks and subsequently every 2 months. Analytical variables of renal function, hematological and complement parameters were collected.

Results: *Switch*: 6 patients (50%females), 4/6 transplant recipients (3 on prophylactic treatment). Regarding renal function, 5/6 had complete response with eculizumab (creatinine 1.33±0.32mg/dL, eGFR 59.5±34.3mL/min/1.73m2, proteinuria 115±91.5mg/g), and all had complete hematological response. After the switch, all maintained complete hematological response, renal function stability and serum complement levels. *Naïve*: 3 cases (2 males); 2/3 required hemodialysis (HD) at presentation. Renal response was complete in two patients and partial in the third (who discontinued HD after 90 days and currently remains with CKD-G3b). All had complete hematological response. Only 3 adverse effects were documented (arthralgia, headache, and rhinitis), no infection cases.

Conclusions: Ravulizumab use is effective both maintaining complete response after switching from eculizumab and as first-line therapy. The safety profile is comparable with the main difference being the posology, as ravulizumab requires fewer administrations and leads to a reduction in direct and indirect costs.

Status	Cr (pre)	eGFR (pre)	Cr (post)	eGFR (post)	$Prot_u$ (pre)	$Prot_u$ (post)	Alb_u (pre)	Alb_u (post)	Hem_u (pre)	Hem_u (post)
Switch	1.325 ± 0.315	59,5± 34.25	1,24± 0,55	64± 37,75	115± 91,5	153,5±161	7,5±23,5	7±27	1,5±3	3±2,25
Naïve	6,47± 2,46	8±8	1,14± 0,9	78± 30	3100± 929	129±276,5	1939± 1312,5	31±115	15±6,2 5	3±4
Status	**Hb (pre)**	**Hb (post)**	**Plt (pre)**	**Plt (post)**	**LDH (pre)**	**LDH (post)**	**Hapto (pre)**	**Hapto (post)**	**Esquist (pre)**	**Esquist (post)**
Switch	138,5 ± 15,5	142± 19	166,5 ± 33,75	164,5 ±41	169± 51,25	164,5± 28,25	1,165± 0,287	1,045± 0,207	0±0	0±0
Naïve	72 ±15,5	138 ±3,5	30 ±21,5	230 ±19	1431± 578	144±20	0,02±0,01	1,55± 0,43	5,5±3,5	2±2
Status	**C3 (pre)**	**C3 (post)**	**C4 (pre)**	**C4 (post)**	**CH50 (pre)**	**CH50 (post)**	**C5b9 (pre)**		**C5b9 (post)**	
Switch	0,798 ± 0,201	0,755 ± 0,108	0,24 ± 0,037	0,233 ± 0,009	12±12,2 5	13,5 ± 7,75	327±279		284±99,25	
Naïve	0,79 ± 0,243	0,974 ± 0,01	0,257 ± 0,102	0,411 ± 0,01	60±8,5	24±9	NA		281±12	

Table 1. Clinical evolution of patients with aHUS treated with ravulizumab.
(Median and interquartile range shown for: creatinine mg/dL [Cr]; estimated glomerular filtration rate mL/min/1.73m2 [eGFR] using the CKD-EPI formula; proteinuria mg/gCr [protu]; albuminuria mg/gCr [albu]; hematuria red blood cells/field [hemu]; hemoglobin g/L [Hb]; platelets x103/L [plt]; lactate dehydrogenase U/L [LDH]; haptoglobin g/L [hapto]; schistocytes number/field [esquist]; C3 g/L; C4 g/L; CH50 U/mL; soluble C5b9 ng/mL, non-available [NA]).

PUB274

Anti-Phospholipase A2 Receptor (Anti-PLA2R) Antibody in Diagnosis and Treatment of Idiopathic Membranous Nephropathy: A Single-Center Experience

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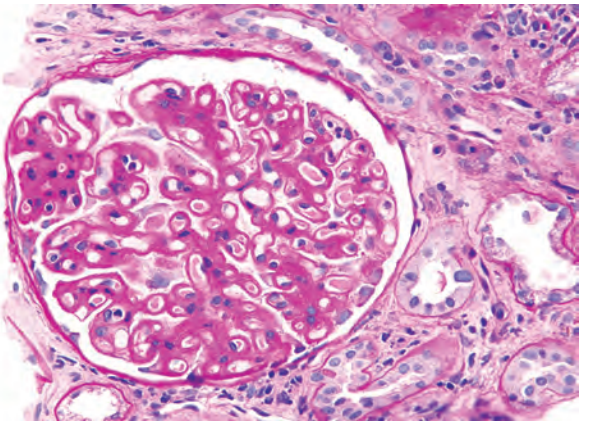
Background: The aim of this study was to observe the prevalence of serum Anti-Phospholipase A2 Receptor (Anti-PLA2R) in patients with idiopathic membranous nephropathy (IMN) and to observe its clinical and laboratory parameters in Pakistani population.

Methods: We enrolled 84 patients with idiopathic membranous nephropathy who were diagnosed on renal biopsy. Study group had nephrotic syndrome at the time of presentation. These patients further had testing for serum anti-PLA2R antibody, serum albumin, 24 hour urinary protein (24 U/P), serum creatinine and GFR estimation. Serum anti-PLA2R antibody was measured by enzyme-linked immunosorbent assay (ELISA). These patients were treated with combination therapy of low dose steroids and CNI(tacrolimus,CSA) and response was assessed at 6 months.

Results: Thirty seven 37 (44%) patients were positive for serum anti-PLA2R antibody while Forty seven 47 (55%) patients were negative among all patients with iMN. Patients who were positive for serum serum anti-PLA2R antibody had high level of 24 urinary protein, low level of serum albumin at the time of presentation in comparison with those who were negative for serum anti-PLA2R antibody (p : 0.05). In terms of response to treatment, in patients with serum anti-PLA2R antibody positive, at 6 months complete and partial repose was 38% and 45% respectively. In anti-PLA2R antibody negative group at 6 months complete and partial repose was 62% and 20% respectively.

Conclusions: Serum anti-PLA2R antibody is non-invasive technique, clinically helpful and specific biomarker for diagnosis of IMN. Our results suggest that serum anti-PLA2R antibody can help to diagnose, predict course of disease and response to therapy in IMN patients.

Funding: Private Foundation Support



PUB275

A Case of Severe Parvovirus B19 Infection with Glomerulonephritis Requiring Artificial Ventilation

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Introduction: Initial infection of parvovirus B19 (PVB19) is known to occasionally cause inflammation in systemic organ tissues such as myocarditis and glomerulonephritis (GN), and possibly result in severe outcomes including death. In the present case, we encountered a patient with severe PVB19 infection along with GN, requiring artificial ventilation.

Case Description: A 22-year-old female developed a fever along with rashes on her extremities. Antibiotic therapy was initiated at a previous hospital, with less effectiveness. One month later, she also complained about dyspnea and was referred to our hospital. She had no past history and had taken no medicines before the onset of her symptoms. Her blood pressure and heart rate were 127/105 mmHg and 94 /min, respectively. Her respiratory rate was 31 /min and required 4 L/min of oxygen. Chest CT revealed findings of severe pulmonary edema, and ultrasound cardiography found diffuse left ventricular hypokinesis as well. Due to her severe respiratory failure, artificial ventilation was initiated. Blood and urine tests at the admission found an increase in serum level of creatinine (1.1 mg/dL) and C-reactive protein (4.9 mg/dL), and the presence of glomerular hematuria and proteinuria (1.1 g/gCr). These findings indicated the involvement of GN-related diseases; therefore, a kidney biopsy was performed under artificial ventilation to aid in the diagnosis. It revealed the pathological findings of infection-related GN and following serum examination found the high titer of an IgM antibody for PVB19. Intravenous injection of methyl prednisone (1000 mg/day for 3 consecutive days) dramatically improved her respiratory failure and urine findings, and she was discharged without any sequelae. With these clinical presentations, we diagnosed her as having severe PVB19 infection accompanied by GN.

Discussion: PVB19 infection can be fatal due to the inflammation mediated by globoside, a receptor for PVB19 expressed in the heart, lung, and kidney. However, since the initial symptoms of PVB19 are complicated and present with various manifestations, it is difficult to detect systemic injury caused by PVB19 infection at an early stage. For patients who have systemic organ injuries with abnormal urine findings, PVB19 infection should be suspected, and a kidney biopsy needs to be taken into account.

PUB276

Immunoglobulin A Nephropathy Management Quality Improvement Initiative Project in China

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Background: In China, Immunoglobulin A nephropathy (IgAN) accounts for 45%-53% of biopsy-confirmed primary glomerulonephritis and individuals of Pacific Asian origin are 1.56 times more likely to develop end-stage renal disease compared with other origins. Currently, there is few nationwide data on the diagnosis and treatment patterns of IgAN in China. Immunoglobulin A Nephropathy Management Quality Improvement Initiative Project in China (IGAN-MIC) aims to establish an IgAN cohort collaboration network to learn about the real-world practice of IgAN management in China.

Methods: IGAN-MIC project will establish an IgAN Chinese expert committee consisting of 14 experts from 13 regions in China with geographical representativeness to assess differences between regions and ethnicities. These hospitals play leading roles in the nephrology development in their provinces and nearby areas. The first-stage of IGAN-MIC project is to establish a nationwide data platform to extract data on clinical characteristics, renal biopsies, diagnosis, comorbidities, laboratory results and medications from electronic medical records and hospital information systems. Biopsy date will be defined as the index date and follow-up data will also be recorded. The second-stage of the project focuses on physician education activities via presentations and handbooks based on the management gap on the data platform.

Results: IGAN-MIC is designed to focus on the pathologic classification, prognostic assessment, medication used and improvement of key laboratory results after IgAN management. The project is scheduled to start in July 2023 and end by December 2024. All hospitals with capabilities of performing renal biopsy and IgAN treatment can join the network. Over 100 healthcare institutions in China are expected to participate with a minimum of 5000 IgAN patients enrolled to develop a portrait of IgAN diagnosis and treatment in China, also to fill the gap in this area globally.

Conclusions: IgAN is the most common glomerular disease in China. The IGAN-MIC project aims to optimize the management of IgAN in China.

PUB277

Late-Onset Lupus Nephritis Presenting as Acute Decompensated Heart Failure

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Introduction: Lupus nephritis (LN) occurs in 20-50% of systemic lupus erythematosus (SLE) cases and usually develops within the first 5 years of SLE diagnosis, rarely occurring afterward. We describe a case of late-onset LN in a patient with known SLE who presented with acute systolic heart failure.

Case Description: A 64-year-old female with a history of SLE for 31 years without renal involvement, atrial fibrillation, prior right innominate artery occlusion, hypertension and type 2 diabetes presented to the hospital with worsening exertional shortness of breath. Physical exam was notable for stable vitals, bibasilar rales on lung auscultation and 3+ bilateral lower extremity pitting edema. Laboratory investigation was significant for serum creatinine (SCr) 2.9 mg/dL, with a baseline of 0.9-1.1 mg/dL, BUN 27 mg/dL, albumin 1.8 g/dL and BNP 110 pg/mL. Echocardiogram revealed a mildly reduced ejection fraction of 40-50% with a small pericardial effusion and a chest x-ray showed vascular congestion and a left pleural effusion. He was admitted for acute systolic heart failure and acute kidney injury. Further workup revealed a urine protein/creatinine ratio of 16.01. C3 and C4 complement levels were within normal range. Given the nephrotic-range proteinuria, the patient underwent a kidney biopsy which showed class V membranous nephropathy and acute tubular necrosis, consistent with LN. Along with diuresis, the patient was initiated on mycophenolate mofetil 1000 mg twice daily and pulse doses of IV methylprednisolone with taper. On discharge, SCr improved to 1.3 mg/dL and the patient had close follow-up for management of the newly diagnosed LN.

Discussion: This is a unique case of late-onset LN occurring 31 years after SLE diagnosis. The patient's chronic SLE symptoms of malar rash, fatigue and joint pain were managed with prednisone and hydroxychloroquine up until this presentation of acute systolic heart failure. There are few reported cases in literature of LN occurring 30 years after SLE diagnosis. With the increasing lifespan due to effective treatment options for SLE, late-onset LN may become more prevalent. As such, we recommend that physicians closely monitor signs and symptoms of LN even in patients without initial renal involvement.

PUB278

Hydralazine-Induced Vasculitis: A Case Report

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Introduction: Hydralazine-induced ANCA-Associated Vasculitis (AAV) is a rare condition in which there is an autoimmune mediated reaction leading to renal and pulmonary involvement and complications.

Case Description: A 37-year-old female with a history of hypertension, hyperlipidemia, DVTs, and multiple strokes who presented for anemia and elevated creatinine. Home medications consisted of Lipitor, Coreg, Xarelto, and Hydralazine. After admission, the patient developed fevers and orbital swelling. Hydralazine was stopped due to concerns of association with her periorbital edema. The patient was started on antibiotics for suspected orbital cellulitis. CT imaging showed a large pericardial effusion, as well as multiple pulmonary nodules. ECHO showed cardiac tamponade. The patient had an emergent pericardial window. Autoimmune workup for pericardial effusion and pulmonary nodules was started. The patient was found to be ANA, p-ANCA positive (MPO and PR3). The patient was worked up for ANCA vasculitis. Further testing revealed high levels of dsDNA and anti-histone antibodies. Renal biopsy was deferred in the setting of anticoagulation use. She was started on high dose steroids and discharged with improved renal indices.

Discussion: Hydralazine is a common anti-hypertensive medication. It is known to cause drug induced Lupus (DIL), but it is less commonly associated with ANCA-Associated Vasculitis (AAV). AAV has a predilection for renal and pulmonary vasculature. Inflammation is caused by autoantibodies against myeloperoxidase (MPO) and Proteinase 3 (PR3). Renal biopsy demonstrates pauci-immune glomerulonephritis. Hydralazine-induced AAV is dose and duration dependent. Risk factors include female gender, kidney disease, and old age. Complications of AAV include rapidly progressive glomerulonephritis, as well as pulmonary-renal syndrome. The incidence of Hydralazine-induced AAV is about 10-20 cases per million. Treatment consists of drug cessation and immune modulator therapy. It can be challenging to differentiate between DIL and Hydralazine-induced AAV. Anti-histone antibody positivity and hypocomplementemia are not independent between the two. DIL lacks antibodies to dsDNA, and ANCA levels are not elevated in DIL; ANCA positivity is diagnostic of AAV. Hydralazine-induced AAV can be challenging to recognize and diagnose. Immediate cessation of Hydralazine and prompt initiation of immune modulators mainstay treatment.

PUB279

Kicking a Glomerulus When It's Already Down

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Introduction: Hydralazine-associated ANCA vasculitis (HA-AV) can be a devastating complication, with a pathogenesis that is not well understood. Here, we present a patient with biopsy-proven membranous glomerulopathy and IgA nephropathy who developed HA-AV.

Case Description: A 74-year-old man with CKD IV from biopsy proven membranous glomerulopathy (negative PLA2R and THSD7A) and mild concurrent IgA nephropathy was transferred to our institution with acute kidney injury and acute hypoxemic respiratory failure. The prior biopsy also demonstrated severe interstitial fibrosis and tubular atrophy. CT Chest revealed extensive multifocal airspace disease in both lung fields. Bronchoscopy with bronchoalveolar lavage confirmed diffuse pulmonary hemorrhage with bloody aliquots. Hydralazine for hypertension was discontinued. Pulse dose steroid treatment was initiated along with apheresis. Initial work-up returned as follows: ANA titer 1:160, MPO-ANCA titer 990, normal complements, infectious workup negative, Anti-ds-DNA, SS-A, and SS-B antibodies were negative. Patient received IV Cytoxan once and was begun on Rituximab therapy with improvement in respiratory symptoms. Kidney function worsened requiring dialysis briefly with improvement to baseline kidney function.

Discussion: HA-AV can be a long-term complication of hydralazine treatment and can be quite serious. In this case, the patient was treated by discontinuing the medication. Due to the severity of this patient presentation, apheresis, pulse dose steroids, Cytoxan, and Rituximab therapy were utilized. Of the known risk factors, the patient did have a history of hypothyroidism. Hydralazine also was dosed in a range consistent with most cases on literature review that would put him at risk for developing hydralazine induced MPO ANCA. The patient did not undergo further kidney biopsy due to the degree of advanced kidney disease seen on imaging and previous biopsy. The patient responded well to treatment and was discharged after several weeks to rehab with close follow-up. The patient did quite well for many months. Subsequent medical complications after a cardiovascular procedure have led to progression of his renal disease and transition to ESRD on hemodialysis. We conclude that, given numerous anti-hypertensive alternatives, hydralazine should be avoided if at all possible, and if not, the duration of treatment should not be prolonged.

PUB280

A Rare Case of Anti-PLA2R-Negative Membranous Nephropathy and ANCA-Negative Crescentic Glomerulonephritis

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Introduction: It is reported that the sensitivity of PLA2R staining is 75% and specificity is 83%, for the detection of primary membranous nephropathy (MN); therefore, negative anti-PLA2R does not exclude primary MN. Also, it has been reported

that 10-30% of patients with pauci-immune crescentic glomerulonephritis (GN) are ANCA-negative. Here we have a case of combined PLA2R negative MN and ANCA negative pauci immune crescentic GN.

Case Description: A 59 year old man with a medical history of hypertension, chronic kidney disease stage 3A, and history of treated syphilis presents with shortness of breath, admitted for community acquired pneumonia management. Patient also diagnosed with an acute kidney injury. Labs showed serum creatine at 3.56, urinalysis with proteinuria (1g) and 2-5 RBC. Immunological studies showed positive SM/RNP antibody (ab) but negative Smith ab, ds-DNA ab, ANCA panel, anti-PLA2R ab, glomerular basement membrane (GBM) ab, and normal c3/c4. Infectious work-up showed positive RPR, negative quantiferon, negative hepatitis B surface ab and negative hepatitis C ab. Renal biopsy showed PLA2R antibody negative MN, pauci immune crescentic GN, and acute tubular injury.

Discussion: Our patient presents with findings that suggest an overlap of primary membranous nephropathy and pauci-immune crescentic GN. By renal biopsy, characteristic findings of primary MN such as fine spikes and holes along the GBM are present but PLA2R staining is negative. As well, three glomeruli show cellular crescents and additional fibrocellular and fibrous crescents were identified, and these findings are unusual in primary MN. A secondary MN is also unlikely in view of no endocapillary hypercellularity. Given lack of linear GBM staining and no autoimmune symptoms, the crescentic lesions can be suggestive of a pauci-immune mediated process, however, the patient had negative ANCA serologies checked twice. A recent study showed ANCA-negative pauci-immune crescent glomerulonephritis can be primary or secondary, especially if associated with infection or malignancy that requires prompt identification and specific treatments. It is important to realize that association of vasculitic GN with MN is estimated to be <5% of all membranous GN cases, thus this case can be used as future reference for clinical practice.

PUB281

The Utility of Kidney Biopsy in PLA2R-Positive Membranous Nephropathy

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Introduction: Primary membranous nephropathy (MN) is one of the major causes of nephrotic syndrome. In the last decade, studies have shown that anti-phospholipid A2 receptor (PLA2R) antibodies are positive in 70% to 80% of patients with a high specificity for MN. Traditionally, the diagnosis was made through kidney biopsy; however, testing for serum PLA2R antibodies has introduced the possibility of diagnosing patients non-invasively. We describe a case of MN that was complicated by a rapid decline in kidney function and discuss the value in obtaining a kidney biopsy even in the setting of a high serum PLA2R titer.

Case Description: A 67-year-old woman with a history of Type 2 DM and HTN presented due to a 20-pound weight gain and worsening dyspnea; exam was notable for 2+ bilateral lower extremity edema. Objective data showed a serum creatinine of 1.46 mg/dL (~1.0 mg/dL 3 months prior), 24-hour urine protein of 16.7 g/day, and a serum albumin of 2.0 g/dL. Immunologic testing showed an anti-PLA2R titer of 455 RU/mL, positive ANA in > 1:1280 titer, anti-dsDNA < 1 IU/mL, and normal complements levels. She was diuresed for her nephrotic syndrome and continued maximally tolerated Losartan. She was treated using a low dose Prednisone, Cyclophosphamide, and Rituximab regimen. However, her kidney function declined further prompting kidney biopsy 2 weeks after presentation. Serum creatinine at time of biopsy was 2.53 mg/dL. Her biopsy showed MN, diffuse and focal nodular diabetic glomerulosclerosis, moderate (20-30%) interstitial fibrosis and tubular atrophy, and severe arteriosclerosis. Her MN alone did not account for the significant decline in GFR and Losartan was discontinued due to concern for hypoperfusion in the setting of renin-angiotensin-aldosterone system blockade with underlying severe arteriosclerosis. Her course was complicated by severe cytopenias resulting in cessation of immunosuppression and she ultimately required dialysis.

Discussion: Although there are many cases of PLA2R positive MN where biopsy can be deferred, it was vital in revealing a secondary diagnosis of severe arteriosclerosis explaining her GFR decline and guiding decision making in our case. Even in the setting of high anti-PLA2R antibody titers, biopsy should be strongly considered for patients with declining kidney function to elucidate whether the decline is secondary to underlying MN or another etiology.

PUB282

Crescentic Glomerulonephritis in Immunoglobulin A-Associated Vasculitis Without Purpura in an Adult Patient

Caroline F. Carrera, Ricardo M. Borges, Washington A. Freire Filho, Felipe Carvalho Barros Sousa, Liliana M. Kassar, Livia B. Cavalcante, Lectícia Jorge, Cristiane B. Dias, Luis Yu. *Universidade de Sao Paulo Hospital das Clinicas, Sao Paulo, Brazil.*

Introduction: Immunoglobulin A (IgA) vasculitis, formerly called Henoch–Schönlein purpura, is a systemic, immune complex–mediated vasculitis affecting small vessels with dominant IgA deposits. Although rare in adults, it tends to be more severe than in children and is defined by a tetrad of clinical features: palpable purpura (leukocytoclastic vasculitis), arthralgia and/or arthritis, abdominal pain and kidney disease. Specific therapies are still controversial and their efficacy poorly known.

Case Description: A 35-year-old healthy male patient with a history of an isolated episode of macroscopic hematuria pending investigation was admitted at our service a few days after a low-intensity trauma, followed by unilateral visual loss. Brain MRI showed intraluminal thrombosis in the right internal carotid artery, not entirely compatilble with the trauma mechanism. On admission, acute kidney injury, hypertension, microscopic hematuria, subnephrotic proteinuria, bicytopenia, and daily fever were noted. Acute phase markers were elevated and viral serologies, ANCA, Anti-MPO, Anti-PR3, rheumatoid factor were negative. C3 and C4 were normal. Kidney biopsy showed IgA deposition with mesangial hypercellularity, focal crescents and podocyte hypertrophy/hyperplasia. Abdomen AngioCT showed parietal calcifications at infrarenal abdominal aorta and coronary arteries, suggesting the diagnosis of systemic vasculitis. Methylprednisolone and cyclophosphamide were initiated.

Discussion: Purpura has been postulated as a mandatory clinical criterion for IgA vasculitis diagnosis. In this case report, the patient presents with systemic, radiological and anatomopathological renal signs compatible with IgA vasculitis, lacking the typical purpura.

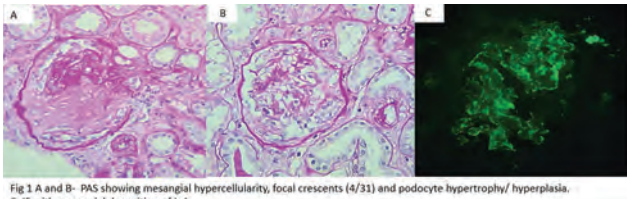

Fig 1 A and B- PAS showing mesangial hypercellularity, focal crescents (4/31) and podocyte hypertrophy/ hyperplasia. C: IF with mesangial deposition of IgA.

PUB283

Can Serum and Histologic Biomarkers Predict Kidney and Overall Survival in ANCA-Associated Vasculitis?

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Background: ANCA vasculitis (AAV) still have poor renal and overall survival. The role of prognostic factors is yet to be defined. Herein, we explored serum and pathological biomarkers as predictors of kidney and patient survival.

Methods: Retrospective analysis of AAV glomerulonephritis diagnosed between 2006-2023 was performed. Most significant markers as ANCA titer, C3 and CRP at admission (d), remission, relapse, and last follow-up (f) were associated to GFR, dialysis need, ESKD and mortality. Berden classes (BC), Brix renal risk score (BRS), IFTA and crescentic glomeruli percentages, C3-IF and interstitial hemorrhage (IH) were also associated with outcomes.

Results: A total of 62 patients 69±10 years old, 56,5% male and 82,3% MPO were included; in 46 biopsies 17.4% were sclerotic, 28.3% mixed, 39.1% crescentic, 15.2% focal; 2.2% with low, 28.3% medium and 58.7% high ESKD risk. dANCA didn't relate to dialysis requirement and titers didn't relate to GFR at any time point. fC3 predicted ESKD (p=0.028) and shorter time to dialysis (p=0.006), not confirmed by multivariate analysis (MA). Likewise, dCRP related to dialysis need (p=0.035) only in univariate analysis. ANCA titers didn't predict survival. dANCA did not relate to death. Lower dC3 (p=0.023) and higher fCRP (p=0.012) were markers of mortality. MA with age and gender lost dC3 significance for death. fCRP seems to remain significant (p=0,06, model p=0,05). C3, CRP and dANCA didn't relate to any histological variable. Higher fANCA predicted higher BRS (p=0.037), persisting on MA (p<0.001, model p<0.001). IH was an independent predictor of ESKD in a MA with gender, age, GFR and dialysis need at admission (HR 0.332, CI 0.114-0.968, p=0.043; model p=0.002). BC didn't predict ESKD. IFTA, BC and BRS didn't predict mortality.

Conclusions: In our cohort, serum biomarkers value remains uncertain. Higher ANCA at last follow-up related to ESKD and histologic chronicity. Nonetheless, didn't predict kidney survival. Last-CRP relation to death might translate infectious bias, although not analyzed. Initial C3 might be prognostic, in line with C3 deposition in other studies, but C3 deposition didn't predict ESKD. IH might be relevant in future broader studies. Further and larger studies might bring stronger data and we still need better predictive markers.

PUB284

Associations of sTNFR-1, sTNFR-2, and YKL-40 with Histopathologic Lesions in Individuals with Glomerular Disease

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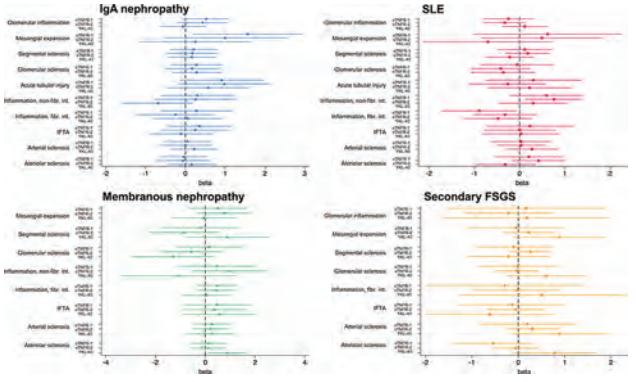
Background: Soluble tumor necrosis factor-1 (sTNFR-1), sTNFR-2, and YKL-40 may provide non-invasive assessments of histopathology, but there is limited data on their associations with histopathologic lesions in individuals with glomerulopathies.

Methods: We measured each plasma biomarker in 188 plasma samples from individuals with glomerulopathies, enrolled into the Boston Kidney Biopsy Cohort (BKBC), a cohort of individuals with semi-quantitative assessment of histopathologic lesions from clinically indicated native kidney biopsies. Multivariable linear regression models tested associations between biomarkers and histopathologic lesions in subgroups of individuals with glomerulopathies, including IgA nephropathy, systemic lupus erythematosus with lupus nephritis (SLE), membranous nephropathy (MN), and secondary focal segmental glomerulosclerosis (sec FSGS).

Results: The mean baseline eGFR was 70±35 ml/min/1.73m² and median proteinuria [IQR] was 1.8 [0.7, 3.7] g/g creatinine. Twenty-eight % of individuals with glomerulopathies had IgA nephropathy, 36% had SLE with lupus nephritis, 20% had MN, and 16% had sec FSGS. After multivariable adjustment for age, race, sex, and eGFR, higher plasma sTNFR-1 levels were associated with more severe mesangial expansion (beta=1.58, p=0.027) in individuals with IgA nephropathy. In individuals with SLE, higher sTNFR-2 levels were associated with the presence of inflammation in the non-fibrosed interstitium (beta=0.76, p=0.019) and lower levels of sTNFR-1 were associated with the presence of inflammation in the fibrosed interstitium (beta=-0.90, p=0.034). Higher levels of plasma YKL-40 associated with more severe arteriolar sclerosis (beta=0.87, p=0.028) in individuals with MN. There were no significant associations between biomarkers and histopathologic lesions in individuals with sec FSGS (**Figure 1**).

Conclusions: Plasma sTNFR-1, sTNFR-2, and YKL-40 may aid with the non-invasive assessment of histopathologic patterns of injury in individuals with IgA nephropathy, SLE with lupus nephritis, and MN.

Funding: NIDDK Support



PUB285

Prevalence and Trend of Biopsy-Proven IgA Nephropathy in China: A Systematic Review

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Background: IgA nephropathy (IgAN) is one of the most common primary glomerulonephritis worldwide, and its distribution varies significantly in different regions. The prevalence and trend in different regions of China remains unclear. Therefore, this study aims to analyze renal biopsy data from different regions in China to figure out the prevalence and trend of IgAN.

Methods: Through systematic electronic search of the PubMed, Embase, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Literature Database (SinoMed), Cochrane Library and Wanfang databases from inception to March 1, 2023. The search keywords included: "renal biopsy", "renal pathological diagnosis" and the names of the different provinces, municipalities and autonomous regions. After completed the electronic database search, we performed a manual search of professional medical journals and thesis.

Results: After collecting and analyzing literatures, we sorted out renal biopsy data of 143176 patients with primary glomerulonephritis from 34 provinces of China, of which 39.73% were IgAN (in total of 56886 cases). The proportions of male and female patients were 58.67% and 41.33%, respectively. The proportion of IgAN patients was higher in economically developed provinces and municipalities. The weighted average prevalence before 2010 and after 2010 was 40.45% and 37.74%, respectively.

Conclusions: IgAN remains the most common biopsy-proven primary glomerulonephritis in China. The prevalence of IgAN was 39.73% in China and was higher in developed provinces and municipalities than in other areas. The weighted average prevalence of IgAN in China decreased slightly after 2010 than before 2010.

PUB286

Low Levels of Hemoglobin Are Associated with Critical Illness and Predict Disease Course in Patients with ANCA-Associated Renal Vasculitis

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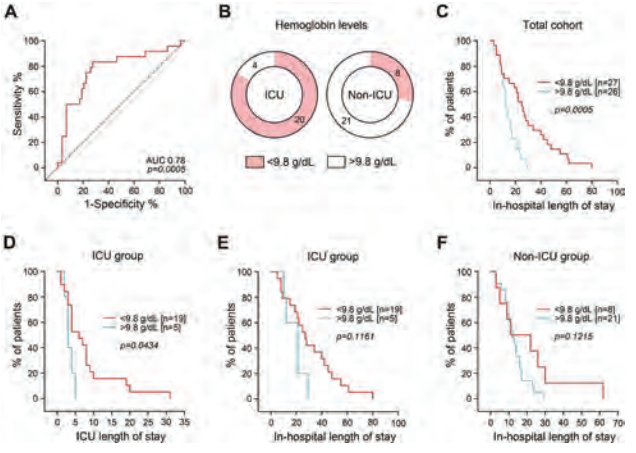
Background: Antineutrophil cytoplasmic antibody (ANCA) associated vasculitis (AAV) is a small vessel vasculitis (SVV) often leading to critical illness by multi organ failure. Data for patients with specifically ANCA associated renal vasculitis requiring intensive care unit (ICU) supportive care are limited and have mainly focused on long term renal and overall outcome. Particularly, data on critical illness during the initial course of disease are scarce and remain poorly determined. Therefore, the purpose of this retrospective study was to identify predictors of critical illness in a cohort of patients with ANCA associated renal vasculitis.

Methods: We retrospectively included a total number of 53 cases with biopsy-proven ANCA associated renal vasculitis between 2015 till 2020 in a single center cohort study. Clinical data assessment enclosed age, sex, date of admission, discharge, and ward transfer during hospitalization, parameters relevant for ICU treatment, such as initial heart rate, mean arterial pressure, body temperature, urine output, serum creatinine, eGFR, sodium, potassium, white blood cells, platelets, pH, and hemoglobin levels at admission. A nonICU (*n=29*) and an ICU group (*n=24*) was formed. Between group comparisons, correlative analyses by means of multiple logistic regression and survival curve analyses were conducted.

Results: We here identified an association between low hemoglobin levels and requirement of ICU supportive care in patients with ANCA associated renal vasculitis. Levels of hemoglobin below 9.8 g/dL at admission independently predicted prolonged requirement of ICU supportive care in critically ill patients with ANCA associated renal vasculitis.

Conclusions: We here expand our current knowledge that low levels of hemoglobin negatively affect short term outcome in ANCA associated renal vasculitis, further improving our current understanding for the role of anemia in autoimmune kidney diseases.



PUB287

Unexpected Biopsy Finding in a Hispanic Man

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Introduction: Fibrillary glomerulonephritis (FGN) is a rare primary glomerular disease with a very poor prognosis. Defined by the ultrastructural finding of haphazardly arranged, straight fibrils measuring 10 to 30 nm in thickness, deposited in the mesangium, glomerular basement membranes or both. On immunofluorescence, deposits typically stain for polyclonal IgG and complement. These changes are found in 0.5 to 1% of native kidney biopsies. FGN is more often seen in Caucasians compared to Hispanics, with a ratio of 100:1. We present a case of an Hispanic man with chronic proteinuria and progressive kidney disease with unforeseen biopsy findings.

Case Description: A 72 y/o Hispanic man was seen for the first time at nephrology clinics due to a progressive decrease in eGFR and nephrotic range proteinuria. Already a CKD IV, normal A1c and work up for causes of proteinuria (including C3, C4, UPEP, SPEP, HIV, Hep B/C) was non contributory. Age appropriate cancer screening was negative. ANA was positive at 1:320 with diffuse speckled pattern. Anti-PLA2R was also found normal. The patient eGFR and proteinuria remained stable, without nephrotic syndrome for 3 years. He presented to the ER due to elevated blood pressure and found with increase in creatinine to 3.5mg/dl from 2.7mg/dl. Proteinuria quantified at 5.2g/day and noted with glucosuria without hyperglycemia. ANA positive at 1:80 with speckled pattern, and DS-DNA negative. Biopsy showed changes suggestive of membranous glomerulopathy based on LM and IF as well as tubules with calcium oxalate casts. EM later reported fibrillary deposits consistent with fibrillary glomerulopathy. Kidney function improved and blood pressures were controlled, and he was discharged home for continued follow-up at clinics.

Discussion: FGN typically presents with proteinuria (usually nephrotic), hematuria, kidney insufficiency, and hypertension. It is typically associated to malignancies, autoimmune disorders, and dysproteinemias with only 7% being associated to membranous nephropathy. It is extremely rare in Hispanics. Renal prognosis is dire with average time to dialysis being 87 months. Although there is no available treatment, clinicians should be aware of this possibility of a diagnosis as planning and educating patient about the poor prognosis such diagnosis entails can lead to better outcomes with early preparedness.

PUB288

A Case of Dialysis-Dependent Rapidly Progressing C3 Glomerulonephritis

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Introduction: We present a case of dialysis-dependent rapidly progressing C3 glomerulonephritis (GN) without evidence of infection or paraproteinemia.

Case Description: Our patient (pt) is a 72-year-old male who presented with a subacute history of weight loss, fatigue, bilateral flank pain, and anasarca. Given his non-specific presentation, he initially went to an oncologist. Workup including bone marrow biopsy and serum protein electrophoresis was unremarkable aside from a creatinine elevation from a baseline of 0.8 (1 month prior) to 7.4 mg/dL. After admission to the hospital, he initiated hemodialysis for acute kidney injury. Autoimmune evaluation revealed negative anti-nuclear cytoplasmic antibody (ANCA), negative double-stranded DNA, low complement C3 (25 mg/dL), normal complement C4 (17 mg/dL), and anti-nuclear antibody testing (ANA) was weakly positive (1:160, speckled appearance). Repeat serum protein electrophoresis with immunofixation was negative. Infectious evaluation including urine culture, blood cultures, and a transthoracic echocardiogram was also negative. Renal biopsy revealed crescentic C3 GN. He was started on prednisone with plans to initiate cyclophosphamide pending insurance clearance. However, within 4 weeks, the pt recovered off of dialysis prior to the initiation of cyclophosphamide. The patient has continued on a steroid taper and was initiated on mycophenolate mofetil 1,500 mg twice daily. His most recent metabolic panel showed a creatinine of 0.78 mg/dL and persistent microscopic hematuria at approximately 5 months since diagnosis.

Discussion: To our knowledge, this is the first reported case of dialysis-dependent C3 GN which improved with steroid treatment alone. It remains unclear if the patient experienced post-infectious GN from an unidentified infection versus an idiopathic C3 GN with rapid progression.

PUB289

Porphyria Cutanea Tarda and Systemic Lupus Erythematosus: An Unusual Association in a Patient with Nephritic Syndrome

Caroline F. Carrera, Ricardo M. Borges, Washington A. Freire Filho, Felipe Carvalho Barros Sousa, Liliana M. Kassar, Livia B. Cavalcante, Lectícia Jorge, Cristiane B. Dias, Luis Yu. *Universidade de Sao Paulo Hospital das Clinicas, Sao Paulo, Brazil.*

Introduction: Porphyria Cutanea Tarda (PCT) is a metabolic disorder caused by reduced activity of enzyme uroporphyrinogen decarboxylase in the liver, generating accumulation of porphyrinogens. It is a rare photodermatosis that manifests as hemorrhagic blisters, hyperpigmentation and hypertrichosis. The most commonly found susceptibility factors are infection by C virus and HIV, alcohol abuse, smoking and exposure to estrogens. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by production of autoantibodies and systemic inflammation, in which lupus nephritis occurs in about 60% of cases.

Case Description: White male patient, 59 years, whose history of tense bullous lesions started in 2020 on the upper and lower limbs and thorax. Skin biopsy showed subepidermal cleavage, papillary dermis with scalloped appearance and vessel wall thickening suggestive of PCT, in addition to Elevated urinary porphyrins. In the last year, this patient started nephritic syndrome with hypertension, hematuria, mild proteinuria and creatinine elevation from 1.2 mg/dl to 2.0 mg/dl associated with positive ANA and complement consumption. The renal biopsy showed membranoproliferative and membranous pattern, an aspect suggestive of Class III+V Lupus Nephritis and signs of chronicity. Immunosuppressive treatment, photoprotective therapy and hydroxychloroquine were initiated.

Discussion: There are few reports in the literature of the simultaneity between PCT and SLE becoming a therapeutic challenge. Some studies suggest that chronic pro-inflammatory state generated by PCT could trigger an autoimmune response such as SLE in patients with mutual genetic susceptibility. Our patient showed good control of skin lesions using hydroxychloroquine. Considering signs of chronicity and little activity in renal biopsy, maintenance treatment for lupus nephritis was initiated with Mycophenolate and low doses of corticosteroids.

PUB290

A Case of Syphilis-Induced Secondary Membranous Nephropathy

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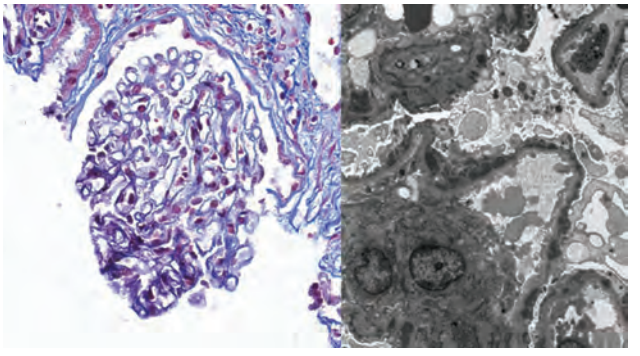
Introduction: Secondary membranous nephropathy (SMN) is typically caused by drugs, infections, autoimmune disorders, or malignancy. Although the association between syphilis and renal disease was first identified over 100 years ago, renal involvement has been infrequent especially in the US, but has been rising. This case elucidates SMN due to syphilis with dramatic resolution of proteinuria with antibiotics.

Case Description: A 41-year-old woman with history of intravenous drug use presented with acute onset of gross anasarca and frothy urine. She was found to have serum creatinine of 1.6 mg/dL, serum albumin of 2.0 mg/dL, and nephrotic range proteinuria of 25 g/g. Urine sediment was bland without casts or cells. A renal biopsy revealed an immune-complex mediated glomerulopathy with a membranous pattern of injury and "full house" immunoreactivity. Rheumatological workup for lupus was negative, with negative ANA, dsDNA, normal C3, and low C4. Anti-PLA2R was also negative. Of note, she had recently tested positive for chlamydia, gonorrhea, syphilis, and received appropriate antibiotic therapy. She did not follow up in clinic until 6 weeks later to discuss immunosuppression, which was not given as she was noted to have complete resolution of proteinuria, and her creatinine and serum albumin returned to baseline.

Discussion: Etiologies of SMN are diverse and differentials are broad, especially when clinical, morphological and immunostaining do not fit classic presentations. Possible renal manifestations of syphilis include membranous, glomerular, and non-glomerular conditions, with membranous nephropathy being the most common. Although the exact pathophysiology is unknown, renal biopsies have shown presence of immune complexes containing anti-treponemal antibodies. Immunofluorescence stains for IgG, C3, IgA, IgM and C1q, also known as "full-house" pattern. As in our patient, renal response to appropriate treatment of syphilis was dramatic, and possibility of syphilis should be considered in new diagnoses of MN with full-house immunoreactivity to avoid unnecessary immunosuppression.



PUB291

Successful Treatment of Co-Existing IgA Nephropathy and Collapsing FSGS with SGLT2i and Steroids

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Introduction: IgA nephropathy (IgAN) is the most common lesion to cause primary glomerulonephritis and occurs most commonly in Asian individuals. While focal segmental glomerulosclerosis (FSGS) has been reported to co-exist with IgAN, the co-existence of the collapsing subtype of FSGS (cFSGS) with IgAN is rarer and has notoriously few treatment options and poor renal prognosis. Here we report a case of IgAN and cFSGS with near 60% improvement in proteinuria after co-administration of prednisone and the sodium-glucose cotransportor-2 inhibitor (SGLT2i), dapagliflozin.

Case Description: A 50 year-old Asian male with history of CKD stage 3 (baseline creatinine 1.7 mg/dL), anti-phospholipid syndrome, and hypertension was noted on routine follow up to have increasing proteinuria, quantified at 5.9 g/day, which was up from 2.7 g/day two years previously (patient lost to follow up during COVID-19). Patient denied history of recent COVID infection or smoking. On examination he was normotensive on home BP meds of losartan 100 mg and metoprolol 50 mg daily. His BMI was 27 and he had no edema. Labs revealed an albumin of 3.5 g/dL, Cr 1.7 mg/dL and UA was negative for hematuria. Serologies including HIV, Hepatitis panel, ANA and PLA2R Ab were negative. Renal biopsy revealed IgAN and cFSGS with 25% tubular atrophy and interstitial fibrosis. His proteinuria continued to rise after renal biopsy to a peak of 6.3 g/day and decision was made to initiate Prednisone 80 mg daily and Dapagliflozin 5 mg daily. Prednisone was tapered after two months and by month three proteinuria improved to 2.7g/day, close to 60% reduction, while creatinine remained stable.

Discussion: Here we describe an interesting case of IgAN and cFSGS with successful partial remission achieved with the combination therapy of Prednisone and Dapagliflozin, on the background of Losartan. Generally, the co-existence of IgAN and cFSGS portends dismal prognosis with one report citing 90% ESRD rate. While dapagliflozin has been approved for treatment of IgAN, its use in cFSGS has not been clearly established. Further studies like this are necessary to determine management for either isolated or co-existing IgAN and cFSGS.

PUB292

Elevated Inflammatory Biomarkers Are Risk Factors for Composite Outcome in South Asian IgA Nephropathy (IgAN)

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GRACE-IgANI. *[1]Christian Medical College Vellore, Vellore, India; [2]University of Leicester, Leicester, United Kingdom.*

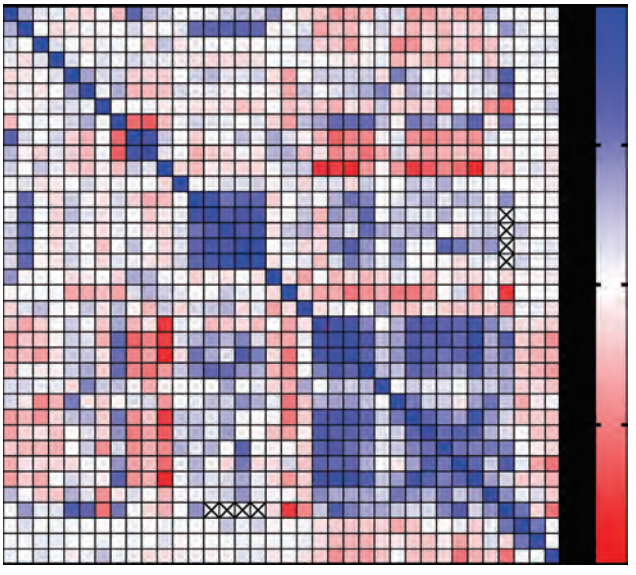
Background: The role of placebo controlled immunosuppression (IS) trial in high-risk South Asian IgAN is still controversial. The effect of IS on longitudinal biomarkers can be surrogate end-points for assessing its impact on CO.

Methods: Serum APRIL levels were measured in baseline and longitudinal sera (1year, 2year) by ELISA. Serum Gd-IgA1 levels were measured in baseline and longitudinal sera (1year, 2year) using KM55 ELISA. Serum levels of TNF-RI, CD27 & BCMA were quantified with a Luminex multiplex assay. CO was defined as ≥50% fall in eGFR (CKD EPI) from baseline and/or eGFR (CKD EPI) <15ml/min/1.73m² or RRT/death. Partial remission (PR) in proteinuria was defined as decrease of 24-hour urine protein by 50% from baseline and <3g/day if nephrotic at baseline OR proteinuria <1.5g/day if non-nephrotic at baseline for at-least three months.

Results: Out of 201 IgAN patients, 37% of patients reached composite outcome (CO) in 3 years in the GRACE-IgANI cohort. Treatment group II (high-risk group with IS) had 146 patients. The mean time to PR in proteinuria was significantly longer in the CO group (10 vs. 6months, p= 0.005). Achieving less than <1g/day at 6month significantly increased renal survival (36 vs. 22months, p<0.001). There was significant longitudinal increase in serum APRIL levels from baseline to 2year in patients with favourable renal outcome. The longitudinal decrease in serum Gd-IgA1 levels at 6month paralleled the serum IgA levels. There was significant association between baseline inflammatory markers (TNF-R1, CD27 & BCMA) and CO at 3 years whereas baseline elevated hsCRP levels showed a global decrease over time.

Conclusions: Placebo-controlled trial in this high-risk population entails ethical considerations hence assessing the known impact of IS on surrogate end-points can potentially guide rational therapy.

Funding: Government Support - Non-U.S.



PUB293

Outcomes of Inflammatory Bowel Disease-Related IgA Nephropathy

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Background: Case reports have linked IgA nephropathy (IgAN) and inflammatory bowel disease (IBD) but data remains sparse. We describe a patient cohort with IBD associated IgAN from the nationwide VA database.

Methods: We retrospectively studied patients with IBD who had kidney biopsy confirmed IgAN. We also conducted a systematic search of electronic databases through 2022 using the terms "IBD" and "IgAN" to synthesize the existing literature on this topic.

Results: 25 subjects were included: all men with age 64.2 ± 13 years (mean ± SD), eGFR 41 ± 28 mL/min and UPCR 3.1 ± 3.2 g/g. 74% received RAAS blockade and 55% required immunosuppression. 28% developed ESKD and 48% died during a follow-up period of 56 ± 49 months (Table 1). The literature search yielded only 3 series of patients with IBD-IgAN (Table 2), prohibiting any pooled analysis.

Conclusions: Our study adds to the limited data regarding IBD-IgAN and highlights the poor outcomes associated with this disease. Large, prospective, multicenter studies are needed to better characterize this association.

Clinical variables	Total n = 25
Age at kidney biopsy (years)	64.2 ± 13 (34 to 83)
Sex (Male %)	100%
Ethnicity (%)	
Caucasian	96
African American	4
IBD diagnosis type (%)	
Crohn's disease	64
Ulcerative Colitis	36
Time from IBD diagnosis to kidney biopsy (years)	22.1 ± 18.6 (-2.0 to 59.0)
Bowel surgery for IBD (%)	52
Smoking (%), n = 18	
Current	16.7
Former	66.7
Never	16.7
Serum Creatinine at biopsy (mg/dL), n = 24	2.6 ± 1.9 (0.8 to 7.6)
eGFR at biopsy (mL/min/1.73 m²), n = 24	40.9 ± 27.8 (8 to 118)
Urine Protein to Creatinine ratio (g/g), n = 22	3.1 ± 3.2 (0.2 to 10.8)
Hematuria at presentation (%)	88
MEST-C score reported (%)	20
IFTA (%), n = 21	
Absent or <25%	52
Moderate or 26-50%	24
Severe or >50%	24
ESKD (%)	28
KRT at biopsy (%)	8
Time to ESKD (months), n = 7	18 ± 12 (0 to 31)
Serum Creatinine Comparison[a] (mg/dL), n = 24	
Baseline	2.2 ± 1.1 (0.8 to 4.4)
Follow-up	1.8 ± 0.9 (0.8 to 3.7)
Mortality (%)	48
Time to mortality (months), n = 12	41 ± 29 (4 to 82)
Treatments (%)	
RAAS inhibitors	72.7
Prednisone	54.5
Mycophenolate	9.1
Cyclophosphamide	9.1
Fish Oil	27.3

Table 1. Patient characteristics. Categorical data presented as % and continuous as mean±SD (range).

[a]Excluding 7 patients who developed ESKD and 3 with missing data

Characteristic	Our study	Joher 2022	Review of case reports[a] (n = 19)	Akiyama 2021
Country	USA	France	Multiple	Japan
Age (years)	64 ± 13	37 ± 15	30 ± 15	35.1 ± 12.2
Male (%)	100	66.7	73.7	94.4
IBD diagnosis type (%)				
Crohn's disease	64	75	67	100
Ulcerative Colitis	36	25	33	0
Serum Creatinine (mg/dL)	2.6 ± 1.9	NR	NR	1.5 ± 0.8
eGFR (mL/min/1.73 m²)	40.9 ± 27.8	70.4 ± 29	63 ± 40	NR
Proteinuria	3.1 ± 3.2 (UPCR)	2.3 ± 2.1 (UPCR)	1.34 ± 1.6 (g/day)	1.39 ± 1.09 (test strip)
Histopathology (%)	N = 5	N = 21		N = 18
M0	80	42.9		55.6
M1	20	57.1		44.4
E0	60	52.4		94.4
E1	40	47.6		5.6
S0	60	23.8	NR	77.8
S1	40	76.2		22.2
T0	80	42.8		55.6
T1	20	47.6		33.3
T2	0	9.6		11.1
C0	80	61.9		66.7
C1	20	38.1		33.3
Treatment (%)				
RAAS inhibition	73	79	NR	11
Steroids	55	50	75	50
Follow-up (months)	56 ± 49	82 ± 70	22 ± 22	NR
ESKD (%)	28	13	0	
KRT at onset (%)	8	4	0	
Mortality (%)	48	8	0	

Table 2. Comparison of IBD-IgAN patient series.[a]Reviewed by Joher et al. 2022

PUB294

Bridging the Gap in Understanding Variations Between Indo-Asian and White Ethnicities in ANCA Vasculitis

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Background: ANCA associated vasculitis (AAV) is a rare autoimmune condition predominantly seen in white Caucasian populations. There are variations in AAV worldwide and little is known about outcomes in ethnic minority patients in particular Indo-Asian populations.

Methods: A multicentre, retrospective cohort study of patients with AAV and who self-identified as belonging to the following ethic groups; 'Indian, British Indian, Pakistani, British Pakistani, Asian or Asian British' was carried out. The study included patients from 2 regional centres in the North West, UK, between 2009 and 2023. A 2:1

ratio of consecutive white patients was included as a control cohort for comparison with Indo-Asian patients. Data collection included demographics, renal histology and clinical outcomes.

Results: The demographics of each cohort are presented in Fig.1. GPA was observed in 54% and MPA in 46%. There were significantly more diabetics (P=0.002) and history of TB (P=0.019) in the Indo-Asian group. There was similar distribution of organ involvement and baseline laboratory results including eGFR. Berden's classification was similar although there were higher rates of crescentic class in the Indo-Asian group (36% v 13%) and a greater number in the medium and high-risk groups of the RRS (71% v 52%). Similar rates of RRT at presentation, relapse, ESKD and mortality were observed.

Conclusions: Our findings suggest Indo-Asian patients tend to be younger and have a higher prevalence of diabetes, previous TB exposure and abnormal glomeruli on biopsy. Further research is required to comprehend the genetic contribution to AAV's pathogenesis and clinical phenotype, as well as establishing if disparities among ethnic minorities arise from genetic and / or environmental factors, so as to enhance patient outcomes.

		Total (n=66)	Indo-Asian (n=24)	White (n=42)	P-value
Demographics					
Age, yrs (IQR)		55 (45-75)	53 (38-65)	57.5 (48-70)	0.15
Female, %		36 (54.5)	14 (58.3)	22 (52.4)	0.64
eGFR at baseline, ml/min (IQR)		25 (16-68)	32.5 (17-68)	18.5 (11-48)	0.242
Diabetes, %		10 (15.2)	8 (33.3)	2 (4.8)	0.002
Previous TB, %		3 (4.5)	3 (12.5)	0 (0)	0.019
GPA, %		37 (56.1)	13 (54.2)	24 (57.1)	0.230
MPA, %		25 (37.9)	11 (45.8)	14 (33.3)	
Berden's classification and Renal Risk Score					
Focal, %		16 (24.2)	3 (21.4)	13 (41.9)	0.183
Mixed, %		9 (13.6)	4 (28.6)	5 (16.1)	0.334
Crescentic, %		9 (13.6)	5 (35.7)	4 (12.9)	0.077
Sclerotic, %		11 (16.7)	2 (14.3)	9 (29)	0.287
Renal Risk Score, %	Low	19 (28.8)	4 (28.6)	15 (48.4)	0.213
	Med	15 (22.7)	8 (57.1)	7 (22.6)	0.023
	High	11 (16.7)	2 (14.3)	9 (29)	0.287
Outcomes					
RRT at presentation, %		11 (16.7)	5 (20.8)	6 (14.3)	0.492
Relapse, %		11 (16.7)	4 (16.7)	7 (16.7)	0.382
Progression to ESKD, %		13 (19.7)	5 (20.8)	8 (19.0)	0.861
Mortality, %		17 (25.8)	7 (29.2)	10 (23.8)	0.632

A comparison of demographics, histological and clinical outcomes in Indo-Asian and white patients

PUB295

A Case of Relapsing Pauci-Immune Glomerulonephritis After Soft Tissue Infections

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Introduction: The association between infections and vasculitis relapses is well established, especially after airway infections and endocarditis. However, pauci-immune glomerulonephritis (PIGN) after infection is still poorly described, particularly after cutaneous infection, and the most appropriate management in this context is still unclear. We report a case of a recurrent PIGN after two episodes of soft tissue infections.

Case Description: A 51-year-old man was seen with erysipelas in left lower limb. He had a medical history of obesity and two episodes of thrombosis in the left femoral vein, with negative tests for thrombophilia. On the 7th day of treatment with amoxicillin/clavulanate, he had red urine and decreased urine output, with serum creatinine (sCr) 4.5 mg/dl; urinalysis with acanthocytes and traces of protein. He lost follow-up and was seen by a nephrologist 4 months later with sCr 1.2mg/dL (same as baseline), microscopic hematuria and urine albumin-creatinine ratio (uACR) 198 mg/g. A few days later, he was admitted with bullous lymphangitis and received piperacillin-tazobactam plus teicoplanin. Despite clinical improvement of infection and absence of other symptoms, he developed rapidly progressive glomerulonephritis (sCr 10.7, dysmorphic hematuria, red cell casts and uACR 1117 mg/g) and needed hemodialysis. Viral serologies were negative and complement levels were normal. Renal biopsy revealed 1/12 glomeruli globally sclerotic, 2 fibrous crescents and foci of rupture of the glomerular basement membrane with interstitial fibrosis and tubular atrophy of 35-45%, without deposits at immunofluorescence and electron microscopy, characterizing a PIGN with crescents in sclerosing phase. The patient recovered renal function until discharge with Cr 1.3 without immunosuppressive treatment. After 10 months, he remains in clinical and laboratory remission.

Discussion: There is evidence of association of bacterial infections with vasculitis relapses, however soft tissue infections are infrequently reported. Furthermore, recurrence of PIGN associated with infections in the same patient is also quite uncommon. The present case showed that PIGN associated with infection can have a favorable outcome after treating the infection without immunosupression.

PUB296

Cohort of Mexican Patients Diagnosed with IgA: Mortality and Requirement for Renal Support Therapy

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Background: IgA glomerulonephritis is the most frequent type among primary glomerulonephritis (GN), with highly uneven incidence due to population differences, biopsy indications, and variable outcomes. Mortality and the need for kidney replacement therapy (KRT) were determined in a cohort of renal biopsies conducted on Mexican population.

Methods: Retrospective cohort study on patients with a histological diagnosis of primary IgA nephropathy, from June 2017 to May 2022. The primary objective was mortality and the requirement for renal support therapy.

Results: 692 patients were followed up for 5 years, of which IgA glomerulonephritis accounted for 18% (33 cases), with 33% being female and 66% male. The average age of presentation was 17±1, and the average glomerular filtration rate (GFR) was 77 ml/min/m. 30% progressed to chronic kidney disease, none required renal support therapy, and there was a mortality rate of 6% (2 cases). Conclusions: IgA nephropathy remains one of the primary and most relevant glomerulonephritis in young patients, with a progression to end-stage renal disease within a short period. Therefore, timely diagnosis is of utmost importance for identification and treatment.

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PUB297

Exostosin 1- and 2-Associated Lupus-Like Membranous Nephropathy in Men

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Introduction: The detection of Exostosin (EXT) 1 and 2 through immunofluorescence (IF) has predominantly been linked to secondary forms of membranous nephropathy, often observed in autoimmune disorders. This report presents two cases of Caucasian males with no known autoimmune conditions who exhibited de novo lupus-like membranous nephropathy with Exostosin positivity.

Case Description: A 61-year-old man presented with subacute onset nephrotic syndrome a few weeks after a COVID-19 infection. His laboratory showed a creatinine (Cr) of 2.3 mg/dL (baseline 1.4 mg/dL), peak proteinuria 34 g/g by 24h uPCR, microscopic hematuria, albumin 2.3 g/dL. Serologic workup with strongly positive RF, low C4, ANA >1:1280, negative reflex, cryoglobulin, hepatitis B and C, and phospholipase A2 receptor antibodies (aPLA2R). His kidney biopsy showed subepithelial immune deposits, no tubuloreticular inclusions (TRI), and no cryoglobulinemic deposits on electron microscopy (EM), and full-house pattern by IF with EXT 1 positivity. He was treated with mycophenolate, tacrolimus, and steroid taper. One year later, he achieved remission: cr 1.6 mg/dL, albumin 4 g/dL, 24h uPCR 0.4 g/gCr. A 57-year-old man with a history of mantle cell NHL in remission and chronic VTE, presented for evaluation of nephrotic syndrome. He had a stable Cr of 1.1 mg/dL, proteinuria 12.5 g/24h, microscopic hematuria, albumin 2.4 g/dL. Serologic workup with ANA >1: 1280, dsDNA 1:40, +RNP, +SM Ab; and unremarkable aPLA2R, C3/C4, hepatitis B and C, syphilis, HIV, and parvovirus. Kidney biopsy showed subepithelial and subendothelial deposits and TRI on EM, with full-house pattern and EXT 2 positivity on IF. The patient was treated with tacrolimus and mycophenolate. At 2 months, his Cr is stable, proteinuria is persistent, but albumin improved to 3 mg/dL.

Discussion: Exostosin-associated membranous nephropathy (EMN) is a favorable kidney prognosis subgroup primarily found in young women with autoimmune conditions. Our report observed two males with lupus-like membranous nephropathy (MN) but no systemic lupus symptoms who met the SLICC criteria for standalone renal involvement. Triggers for EMN are unclear in an atypical age and gender presentation, but a high interferon state from prior chemotherapy or a recent COVID-19 infection may play a role. Further research is needed to understand mechanisms. Initial multitarget therapy shows promise in treatment.

PUB298

Unmasking Lupus: The Great Masquerader

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Introduction: Pyrexia of unknown origin (PUO) has always been a challenging condition that an internist comes across. Infections, inflammatory diseases and neoplasia are among the common etiologies of it. Systemic lupus erythematosus (SLE) is a chronic autoimmune disease that can virtually affect any organ and is a significant cause of morbidity and mortality. Here we present a case of SLE as the cause of PUO due to its rare occurrence in a young male and presentation as an infective endocarditis mimic.

Case Description: An 18 year old Asian male presented with fever and hematuria for 2 months. Examination revealed bilateral infrascapular pleural rub, a pansystolic

murmur in left parasternal area and tender hepato-splenomegaly. Initial lab reports showed anemia (Hb 6.9 gm/dl), neutrophilic leukocytosis with schistiocytes, urea 127 mg/dl, creatinine 3.1 mg/dl, deranged liver enzymes, hypoalbuminemia with hematuria 3+ and proteinuria 4+. HRCT chest showed multiple cavitatory nodules in bilateral peripheral lung fields with mild pleural and pericardial effusion. Blood and urine cultures were sterile, but inflammatory markers were persistently raised. Echocardiography was performed, which revealed vegetations along the tricuspid valve. Transesophageal echocardiography confirmed 1x1cm vegetation above the leaflet of tricuspid valve. A working diagnosis of infective endocarditis was kept, and treatment with ceftriaxone and vancomycin was started. As the patient was not improving, the possibility of autoimmune aetiology (although rare in males), was kept among differentials. An autoimmune workup showed ANA and anti-ds DNA antibodies positivity, low C3 and C4 and negative ANCA and APLA profiles. A renal biopsy confirmed class 3 focal lupus nephritis with acute tubular necrosis. Based on 2019 ACR/EULAR SLICC criteria, a diagnosis of SLE with class 3 lupus nephritis with isolated culture-negative tricuspid valve Libman- Sacks endocarditis was made. There was drastic improvement in patient's symptoms and kidney and liver functions post-methylprednisone and cyclophosphamide pulse.

Discussion: Our case is special since it highlights the diagnostic dilemma between infective endocarditis and SLE in a young male. Both diseases have totally different treatment algorithms and prognosis. Hence, SLE should be considered in the differentials of PUO for timely therapeutic intervention to control the progression of the disease.

PUB299

A Brief Clinical Course of Fibrillary Glomerulonephritis

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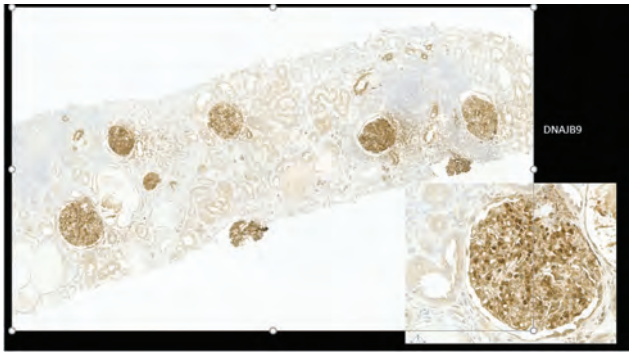
Introduction: Fibrillary Glomerulonephritis (FGN) can be primary or secondary as in cases, associated with malignancies. The presence of DNAJB9, a heat shock protein, in the glomeruli is > 98% sensitive and specific for FGN.

Case Description: 62-year-old man with history of long standing hypertension, CKD 3A, with baseline creatinie of 1.6 mg/dL, presented to emergency room with shortness of breath and edema in October 2020. He was on ibuprofen 600 mg three times daily for pain 3 months prior to that, and his creatinine was found to be 4.6 mg/dL. He had normal sodium, potassium, calcium and bicarbonate with low serum albumin of 2.2 mg/dL (3.5- 5). He was diuresed and his creatinine trended down to 2.6 mg/dL. He saw a nephrologist 6 months later and was found to have 15 grams of proteinuria on spot urine collection, with albumin of 3.2 (3.2- 5.2), but was lost to follow up. During that time, he was diagnosed with prostatic adenocarcinoma with extension to seminal vesicles, and involvement of iliac and obturator lymph nodes. He was started on anti androgen therapy with gonadotropin-releasing hormone (GnRH) antagonist degarelix, and GnRH analogue Leuprore, and also treated with brachytherapy. In July 2022 and was found to have a creatinine of 3.15 mg/dL, but with dereased protinuria of 4.5 on spot collection. Renal biopsy done showed Fibrillary GN, DNAJB9 positve with background moderate chronic interstitial nephritis with interstitial fibrosis and tubular atropy of about 30%. He was started on Lisinopril for his proteinuria, since the fibrillary GN was presumed secondary to his protate adenocarcinoma, and his creatiniene since then has remained stable at 3.33, and proteinuria of 4.5.

Discussion: This case illustrates the importance of renal biopsy in evaluating renal insufficiency, especially when there are confounding factors that can cause acute kidney injury. There is no specific treatment of FGN, but treating the underlying cancer seems to keep patient's renal function stable.



PUB300

Antineutrophil Cytoplasmic Antibody-Associated (ANCA) Vasculitis Associated with Hydralazine

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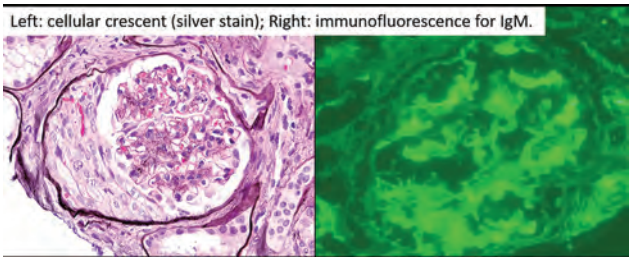
Introduction: Hydralazine is a commonly used antihypertensive agent, but its use has been associated with drug-induced autoimmune diseases such as lupus and ANCA vasculitis. We present a case of severe hydralazine-induced ANCA vasculitis.

Case Description: A 68-year-old man with hypertension treated with hydralazine for 18 months and chronic kidney disease (CKD) with baseline creatinine (Cr) 1.5 mg/dL is admitted with acute kidney injury. Exam was notable for lower extremity edema. Labs included Cr 13.4 mg/dL, urinalysis with >150 RBCs/HPF, and spot urine/protein creatinine ratio 1.54 g/g. This prompted serologic testing, including antinuclear antibody (ANA) titer 1:640, ANCA titer >2560, anti-proteinase 3 (PR3) 3.4 AI, and anti-myeloperoxidase (MPO) antibody >8.0 AI. C3 was low at 65 mg/dL with normal C4. We initiated hemodialysis (HD), pulse corticosteroids, and 5 sessions of plasmapheresis. Renal biopsy revealed focally crescentic glomerulonephritis (GN) with 2+ IgM and C3 staining. His course was complicated by post-biopsy perinephric hematoma requiring embolization and bowel perforation requiring laparotomy. Ultimately further immunosuppression was held. He remains on HD 6 months later.

Discussion: Hydralazine-induced ANCA vasculitis is uniquely characterized by frequent dual MPO and PR3 positivity, positive ANA, hypocomplementemia, and low-level glomerular immune complex deposition. Immunosuppression is usually required despite discontinuation of hydralazine, with outcomes similar to other forms of ANCA GN. Indeed, in the absence of immunosuppression which was preclude by other complications in this case, renal prognosis is poor.



PUB301

Pauci-Immune ANCA(-) Extracapillary Glomerulonephritis in a Patient with Systemic Lupus Erythematosus (SLE)

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Introduction: Although ANCA was first associated with primary vasculitides, it is now clear that 15-20% of lupus patients have ANCA+, in some cases, although negative, histological features are the cause for suspicion. in this entity.

Case Description: A 29-year-old female with SLE diagnosed in 2019 presented hematological and mucocutaneous disease, ANAs laboratories 1:160, with induction treatment for one year based on azathioprine, prednisone and hydroxychloroquine. In 2021 she presents with proteinuria of 672 mg and hematuria, creatinine of 0.9 mg/dl, treatment with mycophenolic acid. One year later, she had an increase in proteinuria of 703 mg/dl, ANCAs PR3 and MPO negative. She integrates hematuria proteinuria syndrome, without deterioration of renal function, eucomplementemic. Kidney biopsy active extracapillary hypercellularity, cellular crescents with active extracapillary lesion with fibrocellular crescents. Prominent and vacuolated podocytes, interstitium with patches of fibrosis with tubular atrophy, IFI with positive IGG, positive C3C, active and chronic extracapillary proliferative glomerulonephritis with scant deposits of immune complexes. By histopathology, ANCA (-) vasculitis is suspected. Therefore, treatment with cyclophosphamide was started, with subsequent improvement in proteinuria.

Discussion: Crescentic glomerulonephritis is a severe form of glomerular lesion characterized by Bowman's capsule proliferation and fibrinoid necrosis, which implies little or no Ig deposition at the glomerular level, which is why it is called pauciimmune. This type of lesions associated with SLE are very rare and even more so in the context of negative ANCA, we present the case to take this type of histological presentation into account.

PUB302

Signs and Symptoms at Diagnosis in Patients with C3 Glomerulopathy: Results from a Real-World Multi-Country Study

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Background: Complement 3 glomerulopathy (C3G) is a rare kidney disease, with an estimated incidence of 1-2/million/year. C3G associates with a high risk of disease progression, up to 50% of patients reach kidney failure within 10 years of diagnosis (Dx). Signs and symptoms include proteinuria, hematuria, edema, hypertension and fatigue. This analysis aimed to understand the signs and symptoms of C3G from patients in the US, Europe and Asia, at the time of Dx.

Methods: Data were drawn from the Adelphi C3G Disease Specific Programme, a cross-sectional survey with retrospective data, of C3G-treating nephrologists in US,

France, Germany, Italy, Spain, UK (EU5), China and Japan between August 2022 and April 2023. Nephrologists completed forms for consecutive patients presenting with C3G. The forms included demographic and clinical information including signs, symptoms and lab values.

Results: 111 nephrologists completed records for 385 C3G patients (US 100, EU5 189, China 60, Japan 36). Median patient age at Dx was 38.8 years, and 59% were men. Median eGFR at Dx was 49.0 ml/min/1.73m^2. Median proteinuria at Dx was 3.4 g/day and was ≥1 g/day in 85% of patients. The other most common signs and symptoms were hematuria, edema, hypertension and fatigue. Discolored urine, pain and appetite loss were also reported (**Table 1**). Physicians perceived disease severity at Dx as moderate in 50% and as severe in 34% of patients.

Conclusions: C3G patients experience symptomatic and clinical burden at Dx. This symptom burden, high proteinuria, and relatively low eGFR are consistent with physician assessment of moderate or severe disease at Dx. Effective Dx and treatment is an important goal to improve patient symptoms and disease.

Funding: Commercial Support - Novartis Pharmaceuticals Corporation

Table 1: Patient signs and symptoms at diagnosis by geographic region

Signs and symptoms present at diagnosis	All patients (n=385)	EU5 (n=189)	US (n=100)	CN (n=60)	JP (n=36)
Proteinuria	330 (86%)	163 (86%)	83 (83%)	48 (80%)	36 (100%)
Haematuria	232 (60%)	111 (59%)	56 (56%)	35 (58%)	30 (83%)
Edema	186 (48%)	102 (54%)	36 (36%)	35 (58%)	13 (36%)
Hypertension (140/90mmHg)	177 (46%)	107 (57%)	33 (33%)	27 (45%)	10 (28%)
Fatigue	147 (38%)	89 (47%)	35 (35%)	20 (33%)	3 (8%)
Discolored urine	68 (18%)	31 (16%)	16 (16%)	20 (33%)	1 (3%)
Pain in back/sides/abdomen	60 (16%)	32 (17%)	6 (6%)	20 (33%)	2 (6%)
Appetite loss	54 (14%)	31 (16%)	7 (7%)	15 (25%)	1 (3%)
High cholesterol	53 (14%)	27 (14%)	7 (7%)	12 (20%)	7 (19%)
Nausea	52 (14%)	30 (16%)	12 (12%)	10 (17%)	0 (0%)
Oliguria	50 (13%)	28 (15%)	8 (8%)	14 (23%)	0 (0%)
Sleep problems	47 (12%)	36 (19%)	5 (5%)	4 (7%)	2 (6%)
Proteinuria at diagnosis	**All patients with a known proteinuria value at Dx (n=310)**	**EU5 (n=159)**	**US (n=69)**	**CN (n=53)**	**JP (n=29)**
<1 g/24hr	47 (15%)	9 (6%)	8 (12%)	12 (23%)	18 (62%)
≥1 g/24hr	263 (85%)	150 (94%)	61 (88%)	41 (77%)	11 (38%)
Median	3.4	4.0	2.9	3.1	0.1
Interquartile range	1.8-5.0	2.1-6.0	1.7-5.0	1.1-6.0	0.0-2.2
Mean (standard deviation)	3.7 (3.0)	4.2 (2.7)	3.2 (2.1)	4.4 (4.6)	1.3 (1.8)
Range	0-20	0-19	0-10	0-20	0-7
(e)GFR at diagnosis	**All patients with a known (e)GFR value at Dx (n=325)**	**EU5 (n=172)**	**US (n=68)**	**CN (n=54)**	**JP (n=31)**
Median	49.0	40.0	50.0	66.5	50.0
Interquartile range	32.0-72.0	25.2-67.0	38.0-72.0	50.8-80.5	35.0-75.0
Mean (standard deviation)	52.8 (27.8)	46.7 (26.4)	53.2 (23.9)	69.6 (31.7)	56.7 (24.7)
Range	4-163	4-121	8-150	20-163	25-130

Table 1

PUB303

Morphology-Based Assay for Podocyte Damage In Vitro

Pavlos Pissios, Nikolay O. Bukanov, Maria Chiara Magnone. *Janssen Research and Development LLC, Boston, MA.*

Background: Podocyte foot processes are crucial components of the glomerular filtration barrier. Foot processes are effaced in genetic or acquired forms of podocytopathies resulting in increased albuminuria and eventual kidney failure. Molecular changes underlying foot process effacement include remodeling of actin cytoskeleton leading to the detachment of podocytes from the glomerular basement membrane. In this study, we developed an assay to quantify changes in podocyte shape induced by a known podocyte-damaging agent, puromycin aminonucleoside (PAN), and prevention of the changes in shape using integrin beta 1 agonistic antibody that enhances podocyte adhesion to laminin.

Methods: Immortalized (Tert) human podocytes isolated from human urine were obtained from Evercyte. Podocytes were cultured on laminin-coated plates and exposed to increasing doses of PAN in combination with integrin beta 1 agonistic antibody. Changes in podocyte area and eccentricity (a metric of elongation) were analyzed in Incucyte. Changes in actin cytoskeleton were assessed by phalloidin staining.

Results: Exposure of podocytes to PAN caused a dose-dependent increase in cell area and rounding of podocytes. Application of integrin beta 1 agonistic antibody prevented the effects of PAN on podocyte shape likely acting on alpha 3-beta 1 integrin, the main podocyte integrin mediating its adhesion to laminin.

Conclusions: We developed a functional assay to model changes in podocyte shape *in vitro* using a known podocyte toxin, puromycin aminonucleoside. The assay could find applicability to other podocyte toxins and for screening for podocyte protective agents.

Funding: Commercial Support - Janssen

PUB304

A Unique Presentation of Lupus Podocytopathy with Collapsing FSGS Variant

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Introduction: Lupus podocytopathy is a rare subset of lupus nephritis seen with nephrotic range proteinuria that presents with findings on kidney biopsy mimicking that of minimal change disease or focal segmental glomerular sclerosis (FSGS). A rare subset of collapsing glomerulopathy can also be seen. This condition has also been linked to the pathologic APOL-1 gene variant. We report a rare case of lupus podocytopathy with collapsing FSGS.

Case Description: A 42-year-old African American male with a history of hypertension and systemic lupus erythematosus (on mycophenolate mofetil (MMF) 1.5 g twice daily for non-renal manifestations) presented after outpatient labs showed dramatically increased serum creatinine and BUN. His only reported symptoms were shortness of breath and fatigue. In the ED, blood pressure was 148/84 mmHg. Labs showed serum creatinine of 10.23 mg/dL (baseline of 2.0 mg/dL), BUN of 111, bicarbonate of 9 mmol/L, and hemoglobin of 7.4 g/dL. The urine albumin to creatinine ratio was 1,463.5 mg/g with a urine protein to creatinine ratio of 2.91 g/g. COVID-19, flu A/B, hepatitis panel, EBV, CMV, HIV, blood cultures, and parvovirus were all negative. Kidney biopsy demonstrated acute tubular injury, WHO class II lupus nephritis, and collapsing FSGS in the setting of lupus podocytopathy. APOL-1 gene testing is pending. He was initiated on pulse dose steroids for 3 days, and hemodialysis was initiated due to worsening acidosis. He was continued on his home dose of MMF. He currently remains hemodialysis dependent (declared ESRD).

Discussion: Patients with SLE podocytopathy represent less than one percent of all SLE flares, with collapsing FSGS variant even more rare and associated with poor prognosis. In recent years the literature started defining non-HIV-related collapsing glomerulopathy, but no unified data regarding treatment guidelines exist. This patient was treated with a combination of steroids and MMF without success, highlighting a unique presentation of a rarely seen syndrome in lupus nephritis.

PUB305

Delaying Progression of Kidney Diseases in Patient with FSGS with Dietary Interventions

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Introduction: Plant-based diets along with lowering dietary protein intake can lower production of uremic toxins and may provide protection in advancing chronic kidney disease. Nutrition education should be provided via Registered Dietitian to optimize potassium and phosphorus intake in patients following plant-based diets in later stages of chronic kidney disease.

Case Description: 50-year-old male with histoy of chronic kidney disease stage V, hypertension, and cardiomyopathy. The etiology of his chronic kidney disease (CKD) is biopsy proven FSGS with IgA glomerulopathy. The patient was diagnosed with CKD in 2019 and had an AV fistula placed in 2022 in preparation for a dialysis start and is actively listed for kidney transplantation. On initial RD visit, patient voiced he follows a whole food and plant-based approach and reads food labels to limit inorganic phosphorus. Interventions to reduce serum phosphorus and potassium included: Continuance of lower protein diet by limiting animal-based protein portions to 3 oz., starting tums as a phosphate binder per nephrologist and double boiling potatoes and sweet potatoes. The patient had maintained GFR < 10 without start on dialysis as of April 2023. He reported no uremic symptoms and continued with good appetite. His proteinuria also improved from nephrotic range to non-nephrotic range with dietary interventions.

Discussion: High consumption of protein intake is associated with increased incidence and progression of kidney disease. Plant based diets have shown to slow down the progression of kidney disease by lowering intraglomerular pressure in patients with diabetes and hypertension however literature is lacking to support their use to delay progression in patients with glomerulopathies associated with proteinuria. Our patient has biopsy proven FSGS with Ig A nephropathy with rapid decline in kidney function which was stabilized after adopting plant-based diet and limiting protein intake. Additionally, proteinuria improved from nephrotic range to non-nephrotic range without the use of any antiproteinuric medication. Typically, normal recommendation for protein intake is 0.8-1.0g/kg body weight. CKD recommendations are 0.55-0.6 g/kg body weight non-diabetic and 0.6-0.8/kg body weight for diabetic patients. Side effects include elevated potassium and phosphorous levels, and early dietitian intervention can help mitigate these complications.

PUB306

Intradialytic Amino Acids Improved Malnutrition Markers in ESRD with Complex Congenital Heart Disease on Peritoneal Dialysis

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Introduction: Peritoneal dialysis (PD) is a cost-effective, home-based therapy for ESRD. The use of amino acid-based solutions resulted in better preservation of the ultra-structure of the peritoneal membrane when compared to glucose containing products. Malnutrition in the PD patient leads to poor outcomes. Intraperitoneal Nutrition (IPN), a nutrition intervention strategy designed specifically for the malnourished PD patient, is non-invasive, well tolerated, yet underutilized. A major obstacle is insurance

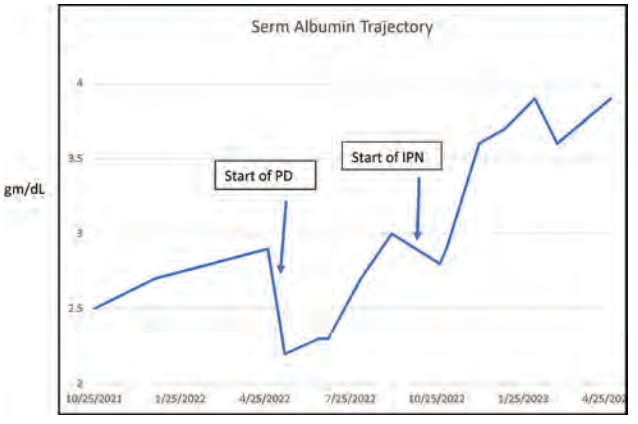
non-coverage. IPN with amino acid-based PD solutions induce anabolic response in malnourished PD patients and serve as source of proteins and calories.

Case Description: A 51-year-old male patient with complex congenital heart disease including Tetralogy of Fallot with Eisenmenger physiology, on starting PD for ESRD, had significant malnutrition with a high Malnutrition Inflammation Score (MIS) (Table). He had early satiety. Oral nutrition supplements failed. Albumin was low for many years prior to starting PD. Using one daily exchange (1500 mL) IPN (1% amino acid solution with 1.43% dextrose providing 12 gm amino acids), significant improvements in his MIS and albumin levels followed (Figure). Quality of life including energy level, improved.

Discussion: The management of any chronic disease must include ongoing nutritional assessment and the implementation of nutrition enhancing intervention therapies. Improving nutritional status improves outcomes. The use of IPN in a PD patient with complex congenital heart disease improved markers of inflammation and nutritional status. In conclusion, IPN contributes to long-term improvement of the nutritional status in malnourished PD patients.

Malnutrition Inflammation Score (Scores >8 = severe malnutrition)

Month	MIS Score
May 2022	14
January 2023	9
April 2023	8



Serum Albumin Trajectory

PUB307

Chyluria Presenting as Milky Urine with Nephrotic Range Proteinuria: A Case Report

Kiran Munir, Abhishek Nimkar, Susana Hong. *Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY.*

Introduction: The classical appearance of milky white urine is caused by a fistulous communication between the lymphatic system and the urinary tract resulting in chyle in the urine, known as chyluria. The etiology of chyluria can be divided into parasitic and non-parasitic causes including but not limited to malignancy, lymphatic malformation, and abscess. We present a case of a 67-year-old male who presented with chyluria and nephrotic range proteinuria.

Case Description: A 67-year-old male with history of longstanding diabetes mellitus came to the office for milky white urine and known proteinuria for the past one year associated with ~10lbs weight loss in the last six months. Previous workup included a spot urine protein-creatinine ratio (UPCR) of 7.3g and a urinalysis significant for glucosuria, hematuria, proteinuria but negative for leukocyte esterase. His lipid panel was within normal limits. Computerized tomography scan of the abdomen revealed non-obstructing bilateral renal calculi but was negative for mass effect or hydronephrosis. The patient had a thorough infectious disease workup which was unremarkable. Kidney biopsy revealed normal tubules and interstitium with mild arterial sclerosis. The immunofluorescence and electron microscopy were negative for immune complex and deposits. The patient was then evaluated by urology and a diagnostic lymphaticscintigraphy was negative for lymphatic-urinary fistula. Hence, cystoscopy was pursued which revealed chyluria from the left ureteral orifice. Patient had complete resolution of proteinuria and hematuria post laparoscopic nephrolysis.

Discussion: Chyluria generally indicates the presence of abnormal communication between intestinal lymphatics and urinary tract. Patients with chyluria typically present with milky white urine and the urine chemistry usually shows heavy protein and moderate blood but remains negative for leukocyte esterase. Further evaluation of such a patient includes a thorough history, physical exam, extensive infectious lab work, and further radiologic testing. Urologic intervention with cystoscopy can be useful to lateralize the chyluria. Nephrolysis may be indicated for complete resolution of chyluria.

PUB308

Relationship Between Sarcopenia and Decreased Oral Function in Japanese Patients Undergoing Hemodialysis

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Background: Dialysis patients are progressively aging in Japan. Sarcopenia is a systemic condition that leads to loss of muscle mass and strength with age; when exacerbated, it leads to frailty and death. The primary stage of frailty is also associated with a decline in oral functions; this is called oral frailty. In Japan, oral hypofunction has been covered by the public medical insurance system since 2018. However, there is limited research on oral hypofunction in patients undergoing dialysis. Therefore, the present study examined the relationship between sarcopenia, oral hypofunction, and nutritional status in patients undergoing hemodialysis.

Methods: A total of 112 patients (77 men and 35 women) who had undergone hemodialysis were included in the study. The patients were classified into sarcopenia and non-sarcopenia groups based on the Asian Working Group for Sarcopenia (AWGS) 2019 index and examine associated with oral function, nutritional status, and blood levels. The diagnosis of decreased oral function was based on the presence of three or more of seven diagnostic items. Nutritional assessment utilized the Protein Energy Wasting (PEW) index, the Nutritional Risk Index for Japanese Hemodialysis patients (NRI-JH), and the Geriatric Nutritional Risk Index (GNRI). This study was approved by the Institutional Ethics Committee of Kinjo Gakuin University, and was supported by JSPS KAKENHI.

Results: Thirty-nine patients (34.8%) were diagnosed with sarcopenia. The sarcopenia group was significantly older and had significantly lower blood urea nitrogen, creatinine, and dry weight ($p<0.05$). Nutritional risk indices (PEW, NRI-JH, and GNRI) were significantly lower in the sarcopenia group ($p<0.05$) than in the non-sarcopenia group. Furthermore, the sarcopenia group exhibited significantly lower scores in terms of oral dysfunction, specifically the number of remaining teeth, tongue and lip motor functions, and tongue pressure ($p<0.05$).

Conclusions: Blood biochemistry tests showed that the sarcopenia group had low levels of blood urea nitrogen and creatinine; the group was also older and showed low dry weight. The sarcopenia group also had a higher risk of malnutrition according to all assessment methods. Regarding oral function, diagnostic items related to muscle mass and strength showed significantly lower scores.

Funding: Government Support - Non-U.S.

PUB309

Phosphate Levels as Predictors of Muscle Strength Assessed by Handgrip Strength

Dror Ben Noach,[1] Dina Levy,[1] Michal A. Raz,[1,2] Hila Soetendorp,[1,2] Orit Kliuk Ben Bassat.[1,2] *[1]Tel Aviv Sourasky Medical Center, Tel Aviv, Israel; [2]Tel Aviv University Sackler Faculty of Medicine, Tel Aviv, Israel.*

Background: Hyperphosphatemia is common among dialysis patients. Although considered a major risk factor for cardiovascular mortality in patients with chronic kidney disease, the interaction between serum phosphate level and survival in dialysis patients has a U-shape configuration, with increased mortality either with low (less than 4.0 mg/dL) or high (above 5.5 mg/dL) phosphate level. Dietary phosphate restriction may result in undesirable protein restriction and malnutrition in dialysis patients. We aimed to assess the correlation between serum phosphate level and muscle strength, assessed by handgrip strength (HGS).

Methods: A single-center prospective observational study, comparing HGS to various biochemical parameters in chronic hemodialysis (HD) patients. Primary endpoint was the correlation between phosphate level and HGS, measured using a Handgrip Dynamometer in the dominant hand before dialysis session. To avoid bias of phosphate urinary loss, only patients with urinary output less than 200ml/24 hours were included. HGS cutoffs for low muscle strength were defined as <27 kg in men and <16 kg in women. Clinical and biochemical parameters, daily protein consumption assessed by protein catabolic rate (PCR) and dialysis adequacy were compared.

Results: Forty HD patients were recruited and included in the analysis. Median age 75.5 years (IQR 64-83), 15 females (37.5%), median dialysis vintage 43.5 months (IQR 27.25-80.25). Median HGS was 23 for men (IQR 20-29) and 16 for women (IQR 10.7-23). Overall, 17 patients (42.5%) had normal muscle strength while 23 (57.5%) were defined with low muscle strength. Spearman's test demonstrated a significant correlation between normal HGS and lower creatinine (p=0.017), and a trend with younger age (p=0.066) and lower phosphate level (p=0.058). There was no correlation between PCR to HGS or phosphate level. On logistic regression, only younger age predicted normal HGS (p=0.023).

Conclusions: Higher phosphate level did not correlate with higher HGS, nor with higher protein intake. Considering hyperphosphatemia may result from inadequate dialysis, low compliance to phosphate binders or dietary choices, it may not reflect protein intake reliably. Furthermore, it is plausible that high protein consumption is insufficient to enhance muscle strength in dialysis patients.

PUB310

A Classification of Lipids and Lipoproteins in Cardiovascular Diseases

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Background: With imbalances of lipids and lipoproteins being significant contributors to the development and advancement of cardiovascular disease (CVD), there is a growing recognition of the importance of categorizing them according to their mechanistic influence on CVD. This classification is crucial for the identification of novel approaches for predicting and treating CVD. Hence, there is a pressing requirement for a fresh lipid classification system that takes into account their specific impact on cardiovascular health.

Methods: To advance our understanding of the role of lipids and lipoproteins in cardiovascular disease (CVD), it is essential to reclassify them based on their specific mechanistic impact, rather than relying solely on their traditional classification according to biological functions. In light of this, we classified lipids and lipoproteins into three distinct groups: (i) those that enhance CVDs, (ii) those with a conditional impact on CVDs, and (iii) those with no known effect on CVDs due to insufficient evidence.

Results: Low density lipoprotein, very low density lipoprotein, lipoprotein (a), triglycerides, trans-fatty acids, phosphatidylcholine, and lysophosphatidic acid have a strong impact on thrombosis and atherosclerosis. High density lipoprotein, fatty acids, sphingolipids andphospholipids have a conditional impact on CVD progression based on based on factors such as oxidation, presence of cofactors, and plasma concentration of other lipids. Due to lack of evidence in existing literature proving their impact on CVD risk or events, biologically active lipids such as mono- and diglycerides, prenol lipids, stearic acids, galactolipids, sterols, glycolipids, and sulpholipids are placed in this category, implying that these lipids are essential for biological functions but do not have known impact on the onset or progression of CVD.

Conclusions: By this novel classification of lipids and lipoproteins we identify the intersecting mechanisms by which lipids that enhance CVDs cause genesis and progression of CVDs is important to discover new therapeutic avenues.

Funding: Government Support - Non-U.S.

PUB311

Pathophysiological Insights and Therapeutic Options for Cardiovascular Disease in CKD

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Background: Patients with chronic kidney disease (CKD) are at an increased risk of cardiovascular complications, including coronary artery disease, heart failure, arrhythmias, and sudden cardiac death. The incidence and prevalence of cardiovascular events are already higher in patients with early CKD stages (CKD stages 1-3) compared to the general population, but the risk significantly escalates in patients with advanced CKD stages (CKD stages 4-5). In fact, cardiovascular disease surpasses end-stage kidney disease (CKD stage 5) as the leading cause of death in this high-risk population. CKD induces a chronic proinflammatory state throughout the body, leading to vascular and myocardial remodeling processes.

Methods: The information presented in this article is based on a comprehensive review of existing literature related to cardiovascular disease in patients with CKD. Relevant studies, research articles, and clinical data were collected from various databases and sources. The selected information focuses on the pathophysiology, clinical consequences, and underlying mechanisms of cardiovascular disease in CKD.

Results: Patients with CKD face an elevated risk of cardiovascular complications, with cardiovascular disease being the leading cause of mortality in this population. CKD contributes to a systemic proinflammatory state that drives vascular and myocardial remodeling processes. These processes give rise to atherosclerotic lesions, vascular calcification, vascular senescence, myocardial fibrosis, and cardiac valve calcification. The cardiovascular manifestations in CKD resemble an accelerated aging process, further exacerbating the cardiovascular risk.

Conclusions: The understanding of cardiovascular disease in CKD is crucial due to its high prevalence and impact on patient outcomes. The systemic proinflammatory state induced by CKD contributes to significant vascular and myocardial alterations, leading to various cardiovascular complications. Recognizing the accelerated aging effect on the cardiovascular system in CKD patients is essential for effective management and the development of preventive strategies. Further research is warranted to explore novel therapeutic approaches and interventions targeting cardiovascular disease in CKD.

Funding: Government Support - Non-U.S.

PUB312

Systolic Blood Pressure in CKD Grades 4-5 and Risk of Kidney Replacement Therapy and Mortality

Jonathan Chavez,[1] Bladimir Diaz Villavicencio,[1] Clementina Elizabeth Calderon Garcia,[1] Manuel Arizaga Napoles,[1] Ana E. Oliva,[1] Frida Margarita de la Vega Méndez,[1] Francisco Gonzalo Rodríguez García,[1] Juan Gómez Fregoso,[1] Guillermo Navarro Blackaller,[1] Ramon Medina,[1] Maria de la Luz Alcantar Vallin,[1,2] José David G. Barajas.[1,2] [1]*Hospital Civil de Guadalajara, Guadalajara, Mexico;* [2]*Universidad de Guadalajara, Guadalajara, Mexico.*

Background: In patients with chronic kidney disease grade 4 and 5 (CKD G4-5) without dialysis and arterial hypertension, it is unknown if the values of systolic blood pressure (SBP) considered in control <120 mmHg are associated with kidney replacement therapy (KRT) and mortality.

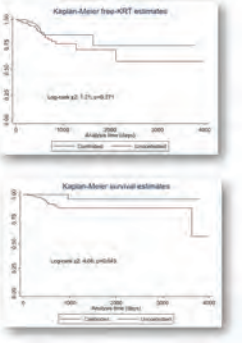
Methods: In a retrospective cohort study, hypertensive CKD G4-5 patients attending the Renal Health Clinic at the Hospital Civil de Guadalajara were enrolled. We divided them into those that achieved SBP < 120 mmHg (controlled) and those who did not (>120 mmHg), the uncontrolled. Our primary objective was to analyze the association between the controlled group and KRT; the secondary objective was the mortality risk, and if there were subgroups of patients that achieved more benefit.

Results: A total 275 hypertensive CKD G 4-5 patients were included, 62 in the controlled and 213 in the uncontrolled group; mean age 61 years, SBP was lower in the controlled group (111 mmHg) compared to the uncontrolled group (140 mmHg), eGFR was similar (20.41 ml/min/1.73m^2). There was a tendency to increase the mortality risk in the uncontrolled group (OR 6.4, p= 0.082) and an association by the Kaplan-Meir analysis (Log-rank p= 0.043). The subgroup analysis for risk of KRT in the controlled group revealed that patients ≥ 61 years had a lower risk of KRT (OR 0.87, p=0.03, p of interaction = 0.005), but no differences were found in the subgroup analysis for mortality. Before propensity score matching, no association was found in the risk of KRT in a multivariate analysis.

Conclusions: In a retrospective cohort of patients with CKD G4-5 and hypertension, SBP >120 mmHg was not associated with risk of KRT but could increase the risk of death.

Table 2. Incidence rate of kidney replacement therapy and death according to systolic blood pressure groups.

Group	Patient - year	Events	Rate (1000 patient - year)	LIC	UIC
Kidney replacement therapy					
Controlled	92.27	8	86.69	43.35	173.35
uncontrolled	295.87	26	87.87	59.83	129.06
Total	388.15	34	87.59	62.56	122.59
Mortality					
Controlled	109.44	1	9.13	1.28	64.86
uncontrolled	296.27	14	47.25	27.98	79.78
Total	405	15	36.97	22.28	61.32



PUB313

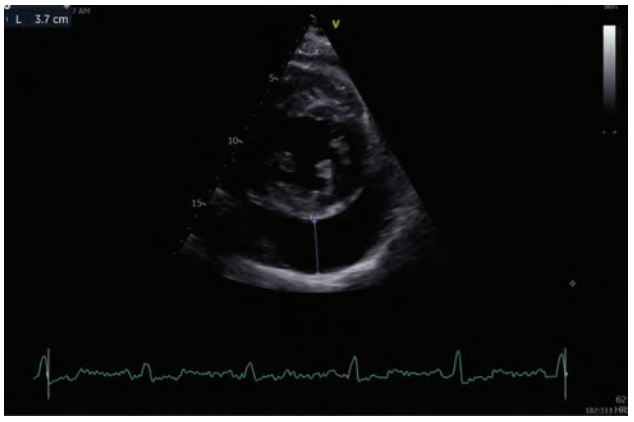
Minoxidil-Related Pericardial Effusion in a Renal Transplanted Patient

Bahram Hashemi Dam,[1,2] Joanna Delekta,[1] Laura Vakili Jensen,[2] Sam Riahi.[1,2] [1]*Aalborg Universitetshospital, Aalborg, Denmark;* [2]*Aalborg Universitet, Aalborg, Denmark.*

Introduction: Minoxidil is used in patients with inadequate response to conventional antihypertensive treatment. It causes vasodilation by opening adenosine triphosphate-sensitive potassium channels. A serious side effect of minoxidil is fluid retention. Multiple case reports have shown minoxidil-induced pericardial effusion in dialysis patients; yet none has been published in a kidney transplanted patient.

Case Description: A 49-year-old man with type 1 diabetes mellitus and renal transplantation in 2014, with stable renal allograft dysfunction (serum creatinine about 1.7 mg/dl) was treated for resistant hypertension with amlodipine, ramipril, furosemide, metoprolol and minoxidil. From March to July 2021, he was admitted four times at the Department of Cardiology due to exertional dyspnea and palpitations. Physical examinations revealed noticeable pericardial friction rub and subtle peripheral edema, otherwise he was hemodynamic stable. Echocardiography showed normal left ventricle ejection fraction, mild ventricular hypertrophy, no valvular dysfunction and nor pulmonal hypertension. Large pericardial effusion, up to 3.7 cm posterolateral to the left ventricle was visualized (Figure). There was no sign of tamponade; but due to large amount of fluid the patient underwent pericardiocentesis where 1700ml was drained. Analysis revealed a transudate fluid without infectious, malignant or inflammatory characteristics. His renal allograft function was stable and near normal. Attention was then paid towards minoxidil toxicity. It initiated 6 months before the first pericardial effusion. Minoxidil was discontinued upon the discharge from the hospital in July 2021. Total resolution of pericardial effusion was observed on control echocardiography after one month.

Discussion: Minoxidil-induced pericardial effusion occurs in about 3% of patients. It can also be idiosyncratic, such as our case with otherwise uneventful post-transplant period. Though, ruling out other causes is essential.



PUB314

Analysis of the Kidney-Heart Cross-Talk Using Computation Ecosystems

Vera Jankowski,[1] Shruti Bhargava,[1] Zhuojun Wu,[1] Joachim Jankowski.[1,2] *[1]Universitatsklinikum Aachen, Aachen, Germany; [2]Experimental Vascular Pathology, Cardiovascular Research Institute Maastricht (CARIM), University of Maastricht, Maastricht, Netherlands.*

Background: Over the past 50 years, there has been extensive research focused on identifying mediators and understanding molecular processes involved in physiological, pathophysiological, and correlation-based studies within individual organs like the kidney or heart. The organ-centered approaches are valuable for addressing specific research questions, but, they are insufficient, failing to provide a comprehensive understanding of disease progression. The interconnectedness and multidimensional correlations that exist within complex biological systems are often overlooked within the framework of these approaches. Therefore, there is a growing recognition of the need to adopt a more holistic and multilevel approach that integrates various factors and dimensions to gain a more accurate and complete understanding of disease processes.

Methods: Holistic approaches to understanding multimorbid diseases involve integrating, merging, and correlating extensive, diverse, and multidimensional data from various sources, including -omics and nonomics databases. The importance of holistic approaches has grown significantly in comprehending and revealing intricate interactions and molecular overlaps between diverse organ systems in the pathophysiology of systemic diseases such as cardiorenal syndrome. The objective of these approaches is to develop practical and applicable disease models through the utilization of mathematical, statistical, and computational tools, thus establishing initial computational ecosystems.

Results: Holistic approaches help gain deeper insights into complex diseases by considering multiple dimensions and facilitating the translation of findings into clinical applications. Effectively addressing the intricacies of multimodality and multimorbidity requires data-driven scientific approaches that extend beyond the existing capabilities and necessitate multiphased and cross-sectional methodologies. These approaches aim to deconstruct complexity by tackling smaller, more manageable challenges.

Conclusions: We provide an overview of the existing understanding regarding the interconnection between the kidney and heart, known as kidney-heart crosstalk. Additionally, we explore the methodologies and prospects that emerge from the innovative utilization of computational ecosystems, enabling a comprehensive analysis of this interplay between the kidney and heart.

Funding: Government Support - Non-U.S.

PUB315

Anti-Histone Antibodies Associated with a Hydralazine-Induced Rash

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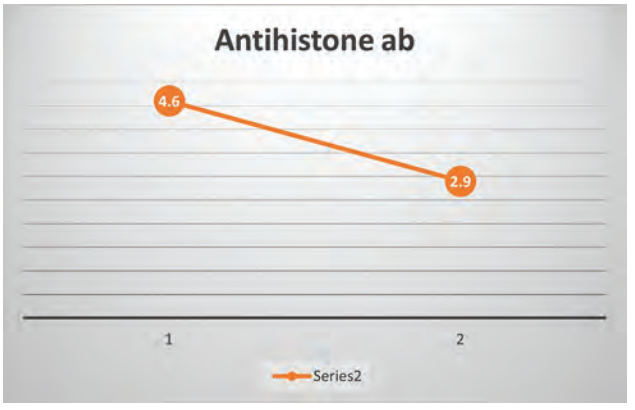
Introduction: Hydralazine is used in the treatment of hypertension and heart failure. It's side effect profile includes Hydralazine-Induced Lupus (HIL). Typical manifestation of HIL include arthralgias, serositis, myalgias, and a malar rash. It is serologically associated with anti-histone antibodies (Anti-HisAb) and a + antinuclear antibody (ANA).

Case Description: The patient is a 50yo male with a history of hypertension. Management of his hypertension has been complicated by many drug sensitivities. His regimen consisted of nifedipine, hydralazine, and carvedilol. It had been stable for over 2 years. The patient developed a new-onset rash consisting of diffuse erythematous papules with excoriations. He denied any new medications, lotions, clothing, or other new exposures. The patient underwent a punch biopsy which showed eczematous dermatitis with eosinophils. This was thought to be diagnostic of allergic contact dermatitis, spongiotic drug eruption, and atopic dermatitis. The rash improved with cotricosteroids but it returned after discontinuation of steroids. Serologies showed a +ANA but a negative anti-double stranded deoxyribonucleic acid antibody (Anti-dsDNA). Given the hydralazine and +ANA, an Anti-HsAb was checked, despite the lack of classic HIL symptoms (including the classic rash) and negative dsDNA. This returned positive. Because of the recurrent rash and the + Anti-HisAb, hydralazine was stopped. The patient experienced an improvement in his rash and a reduction in his Anti-HisAb titer (see figure).

Discussion: Drug rashes are very common in many drug classes. This case is unique in that the patient did not have the classic rash or other symptoms of HIL but had + Anti-HisAb. There are case of reports of lupus being associated with atopic dermatitis (which was noted on biopsy) but this is an atypical finding. This report supports the contention that patients on hydralazine should be serologically evaluated for HIL should evidence of drug reactions occur, despite a lack of classic symptoms.



PUB316

Efficacy of Cardiac Synchronization Therapy for Patients with ESRD and Chronic Heart Failure

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Background: To evaluate the efficacy and safety of cardiac resynchronization therapy (CRT) in CKD patients complicated with chronic heart failure.

Methods: 4 Patients who received CRT implantation from January 2019 to June 2022 in Center for Kidney Disease,2nd Affiliated Hospital of Nanjing Medical University were admitted. CRT is recommended for symptomatic patients with HF with Left ventricular ejection fraction (LVEF)≤40%, QRS duration≥150m, and LBBB QRS morphology despite OMT. The clinical data, electrocardiogram, echocardiography and cardiac function screening were collected.

Results: Patients (average age of 62.3±7.9 years) were followed up for 19.7±9.9 months. The dialysis age was 76.2 (27.3,79.0) months. Patients were implanted with CRT, the QRS duration (183.3±26.3 Vs 150.0±13.0ms), left ventricular end-diastolic diameter LVEDD (70.3±10.3 *vs* 64.0±11.1 mm), left ventricular end-systolic diameter LVESV (57.8±13.2 *vs* 48.8±15.7mm), and pro-BNP [167459.5 (59645.8, 231789.0) ng/ml *vs* 81773.0 (26151.3, 134313.0) ng/ml were decreased, the decline rates were respectively 18.2%, 9.0%, 15.6%, 25.1% and 51.2%. The LVEF (32.8±7.4 *vs* 42.3±15.3%) was improved by 30.0%. The cardiac function status was improved. None could tolerate 6 min walking test before operation. The average distance of 6min walking test in 3 patients was (328.3 ±138.2) meters one year after operation.

Conclusions: CRT improves left ventricular function and quality of life in uremic patients with chronic heart failure, and none of serious side effects were observed.

Funding: Government Support - Non-U.S.

PUB317

Beneficial Markers for Renal Prognosis in Hypertensive Emergencies with Severe Renal Dysfunction

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Background: Hypertensive emergencies are poor prognosis conditions associated with rapid blood pressure (BP) elevation and various organ damage. The frequency of dialysis induction due to nephrosclerosis is high and early detection and appropriate therapeutic intervention is important.

Methods: We selected 15 patients diagnosed as hypertensive emergencies with severe renal dysfunction (serum creatinine level > 2.5mg/dL) admitted to our hospital over the past 14 years. These were divided into two groups: those who received renal replacement therapy (RRT, n=9) after 3 years and those who were not received (non-RRT, n=6). The clinical features and laboratory data were reviewed and compared retrospectively.

Results: The median age was 48 years old and the male to female ratio was 3:1. All the patients lacked medical examination and regular checkups after diagnosis of hypertension. 33% of them were obese with a body mass index > 25. On admission, about 80% had elevated plasma renin activity and serum aldosterone levels, while there were no cases of renal artery stenosis. Between the two groups, there was no significant difference in serum creatinine levels. Serum LDH levels in the non-RRT group were higher than those in the RRT group. Serum potassium levels and platelet counts were lower, respectively. These data at post-antihypertensive treatment was improved significantly in

the non-RRT group. Serum values of LDH, potassium, and platelet in the comparison of pre-and post-treatment data of the two groups showed significantly improved by two-way analysis of variance.

Conclusions: In our study, there were young or middle-aged adults and some of them were obese. Therefore, taking health-checkup is helpful for the prevention of the risk of hypertension and appropriate treatment. Higher LDH levels and decreased platelet counts in the non-RRT group suggested the development of severe endothelial damage with rapid BP elevation in the short term. Severe renal dysfunction in these cases can be improved by appropriate antihypertensive therapy. Furthermore, the lower potassium level suggested the aggravation of the renin-angiotensin-aldosterone system (RAAS) and early induction of RAS inhibitors would be beneficial for the maintenance of BP and renal protection. In conclusion, serum LDH, platelet count, and serum potassium would be useful predictors of renal prognosis.

PUB318

A Case of Primary Hyperaldosteronism with Hypomagnesemia

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Introduction: Primary hyperaldosteronism classically involves a hypertensive patient with spontaneous or diuretic induced hypokalemia and metabolic alkalosis. We describe one such patient with hypomagnesemia and hypocalcemia along with the classic features.

Case Description: 51 year-old male, presented for management of 20-year history of hypertension (HTN). He has history of type 2 diabetes mellitus and coronary artery disease. Labs showed serum creatinine of 1.3 mg/dl, low serum potassium at 2.8 mmol/l, metabolic alkalosis with serum bicarbonate at 30 mmol/l, low serum magnesium at 1.2 mg/dl and low serum calcium at 7.9 mg/dl (serum albumin of 4.2 mg/dl). Fractional excretion of potassium (22.4%) and magnesium (4%) were high. Parathyroid hormone was appropriately elevated at 98.6 pg/ml and 25-O vitamin D level was mildly low at 16.2 ng/ml. Primary hyperaldosteronism was suspected due to hypokalemia and metabolic alkalosis. Random plasma renin activity was low at 0.10 ng/ml/hr (normal range- NR: 0.25-5.82 ng/ml/hr) and aldosterone was normal at 11 ng/dl (NR: <= 21 ng/dl) with elevated aldosterone: renin ratio at 110 (NR: 0.9-28.9). He was started on oral potassium and magnesium supplementation, and spironolactone was prescribed at 25 mg daily. Repeat laboratory values after 2 weeks showed normal serum potassium at 4 mmol/l. 24-hour urine electrolytes at this time showed sodium of 241 mmol, potassium of 78 mmol and a high calcium at 445 mg (NR: <300 mg). Plasma aldosterone: renin ratio remained elevated at 147 even after correcting the serum potassium. Computerised tomography scan of the abdomen with intravenous contrast showed a 1.2 cm right adrenal adenoma with normal left adrenal gland. Dose of spironolactone was increased to 50 mg daily. His home blood pressures remained controlled at 135/80 mm of Hg. A diagnosis of primary hyperaldosteronism secondary to unilateral adrenal adenoma was made with further plan to do adrenal vein sampling and adrenalectomy as appropriate.

Discussion: The case highlights a rare presentation of primary hyperaldosteronism with magnesium and calcium wasting, mimicking Gitelman's syndrome. Aldosterone escape could potentially decrease sodium reabsorption at the thick ascending limb of Henle, which in turn leads to poor magnesium reabsorption. Consequent hypomagnesemia leads to calcium wasting due to PTH resistance at the level of thick ascending limb.

PUB319

Anti-Müllerian Hormone and Cardiovascular Risk in Males with CKD: Preliminary Findings from a Cross-Sectional Study

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Background: Cardiovascular (CV) disease is the leading cause of death for people living with chronic kidney disease (CKD), and this risk is higher in males. Reduced Anti-Müllerian Hormone (AMH), a reproductive hormone involved in male fertility, is a common complication of CKD and is associated with increased CV risk in males in the general population. However, the relationship between AMH and CV risk in males living with CKD remains unknown. Our study aims to estimate the association between AMH and arterial stiffness, a validated predictor of CV risk, in males living with CKD.

Methods: A cross-sectional study was completed in males living with CKD recruited from Calgary, Alberta, Canada. We collected basic demographic and comorbidity data. Serum AMH levels were measured using a validated immunoassay. Using standardized protocols, we assessed pulse wave velocity (PWV) and aortic augmentation index (AIx) with applanation tonometry to determine arterial stiffness. Mean Arterial Pressure (MAP) was calculated using systolic and diastolic blood pressure measurements which were collected using standardized protocols. Multiple linear regression analyses were used to estimate the association between AMH and each measure of arterial stiffness, as well as MAP.

Results: Nine males living with CKD were included (age 42 ± 11 years, estimated glomerular filtration rate 76 ± 25 ml/min/1.73m^2). A trend towards a negative association between AMH and AIx was demonstrated ($R^2 = 0.41$, $p = 0.06$), though no association was observed between AMH and PWV ($R^2 = 0.05$, $p = 0.57$).

Conclusions: AMH levels are not significantly associated with increased arterial stiffness in males living with CKD, though it is likely that our sample is underpowered to detect a significant association. Given the high CV risk of males with CKD, further investigation into this potential CV risk factor is warranted.

Funding: Government Support - Non-U.S.

PUB320

Impact of Impaired Kidney Function in the Mortality of Patients with Chagas Disease Submitted to Cardioverter-Defibrillator Implant

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Background: Data on kidney disease impact in HFrEF due to Chagas Disease (CD) is limited in the current literature. Unlike other causes of HFrEF, CD may have such a high disease burden that it overshadows other comorbidities. We performed a prospective study to access if an impaired glomerular filtration rate (eGFR) had an association with mortality and survival rates in patients with CD submitted to cardioverter-defibrillators (ICD) implant.

Methods: We collected data on 141 patients with CD that implanted ICD between 2017 and 2020. An altered kidney function was considered with an eGFR < 60 mL/min. An analysis for the survival rate between the groups was made with the Log Rank test. Multivariable logistic regression was used to identify predictors of death. Statistical analysis was done through SPSS, v.25, and significance level was set in 5% ($p<0.05$).

Results: Baseline characteristics are reported on Table 1. The median follow-up was 563 days. Patients in both groups had similar prescriptions regarding use of triple therapy for HFrEF (p=0.77). During the study, 52 patients died; 47.7% patients had altered kidney function and 32% with normal eGFR. In a univariate analysis for the outcome of death, the presence of a lower eGFR was not statistically significant (p=0.07). In the analysis for the survival rates, there was no difference between them (p=0.06). In a binary logistic regression model, a greater chance of death was not associated with a change in eGFR in these patients [p=0.227 (OR 1.69; CI 95% 0.721-3.959)].

Conclusions: In our study, in a group of patients with HFrEF due to Chagas cardiomyopathy using ICD, with similar patterns of disease modifying drugs, there was no significant association between kidney function and mortality.

Table 1. Baseline characteristics of the patients

	eGFR < 60 ml/min (n = 44)	eGFR ≥ 60 ml/min (n = 97)	P value
Male (%)	19 (43.2)	63 (64.9)	0.015
Age (± SD)	62.7 (9.34)	57.3 (11.26)	0.006
Diabetes (%)	13 (29.5)	18 (18.6)	0.144
Atrial fibrillation (%)	19 (43.2)	29 (29.9)	0.123
Maggic SCORE (IQR)	17.5 (12.2-31.1)	12.2 (7.7-20.3)	0.001
Ejection fraction (IQR)	28 (23.2-33.7)	29 (23.5-35)	0.375
eGFR* (IQR)	47 (37.2-53.7)	83 (70-98)	< 0.001

eGFR - estimated by the CKD-EPI 2021 equation; IQR – interquartile range.

PUB321

Hyperfiltration, Metabolic Syndrome, and Risk of Adverse Clinical Outcomes

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Background: Glomerular hyperfiltration and metabolic syndrome increase the risk of cardiovascular disease and all-cause mortality. While hyperfiltration is strongly related to the metabolic risk, it is little known how the combined association of these two factors affects the risk of metabolic syndrome-related complication, CV disease and all-cause mortality.

Methods: We reviewed the National Health Insurance Service database of Korea for people who received national health screenings between 2009 and 2011. Hyperfiltration (n = 199,807) was defined as eGFR >95th percentile after stratification for age, sex, height and weight and normal filtration as eGFR 25-75th percentile (n = 2,376,489). Metabolic syndrome was considered as the presence of three or more of the metabolic risks. Individuals were compared based on the presence of hyperfiltration and metabolic syndrome

Results: Compared to normal filtration without metabolic syndrome, co-existence of glomerular hyperfiltration and metabolic syndrome was associated with the greatest risk of hypertension, diabetes and cardiovascular event. Hyperfiltration without metabolic syndrome also increased the risk of diabetes (HR 1.22, 95% CI 1.18-1.27) and hypertension (HR 1.06, 95% CI 1.04-1.07), but it was not associated with higher risk of cardiovascular event (HR 1.04, 95% CI 0.99-1.09). among four categorized individuals, the risk of all-cause mortality increased highest in those who had hyperfiltration without metabolic syndrome (HR 1.22, 95% CI 1.17-1.28) and there was a significant interaction between hyperfiltration and metabolic syndrome in association with all-cause mortality (P for interaction = 0.003).

Conclusions: Our findings indicate that glomerular hyperfiltration was significantly associated with higher risk of hypertension and diabetes, even in the absence of metabolic syndrome. Notably, hyperfiltration without metabolic syndrome was more detrimental to mortality than that with metabolic syndrome.

PUB322

Dapagliflozin in Patients with Low and High uACR

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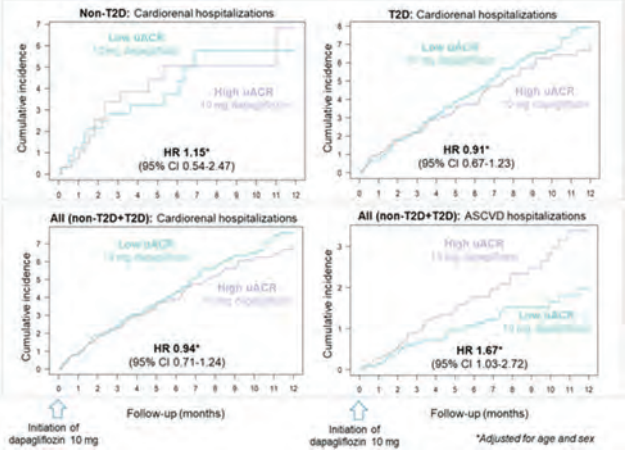
Background: We explored clinical outcomes in new users of dapagliflozin 10 mg with low urine albumin to creatinine ratio (uACR; 30–200 mg/g) and high uACR (≥ 200 mg/g) in patients with chronic kidney disease (CKD), with and without type 2 diabetes (T2D).

Methods: This study used claims data from the USA between 2021 and 2022. Patients with and without T2D who were new users of dapagliflozin 10 mg were indexed at treatment start and grouped according to baseline uACR (low or high). Patients on dialysis or immunosuppressive drugs or with polycystic kidney disease or stage 5 CKD were excluded. Incidence of hospitalization for cardiorenal events (CKD or heart failure) and atherosclerotic cardiovascular diseases (ASCVD) were compared separately within non-T2D and T2D populations using age- and sex-adjusted survival regression.

Results: In non-T2D patients, 332 (54%) new users of dapagliflozin had low uACR and 286 (46%) had high uACR. Corresponding numbers for patients with T2D were 1987 (53%) and 1741 (47%). New users of dapagliflozin with low and high uACR had similar baseline characteristics, both with and without T2D. In non-T2D patients, event rates for cardiorenal hospitalizations were similar in the low and high uACR groups (8.3 and 9.2 per 100 patient-years, respectively). There was no significant risk difference between low and high uACR (hazard ratio [HR] 1.16, 95% confidence interval [CI] 0.54–2.49; Figure). Similar results were seen in patients with T2D (HR 0.92, 95% CI 0.68–1.24). In contrast, the risk of ASCVD was significantly higher in patients with high uACR versus low uACR (HR 1.67, 95% CI 1.03–2.72).

Conclusions: Dapagliflozin's beneficial effect on cardiorenal risks appeared similar in patients with low and high uACR independent of T2D. ASCVD risk remained higher in high versus low uACR patients. These findings suggest cardiorenal effectiveness of dapagliflozin in patients with CKD and low uACR, without T2D.

Funding: Commercial Support - AstraZeneca



PUB323

Urinary Features Predict Cast Nephropathy

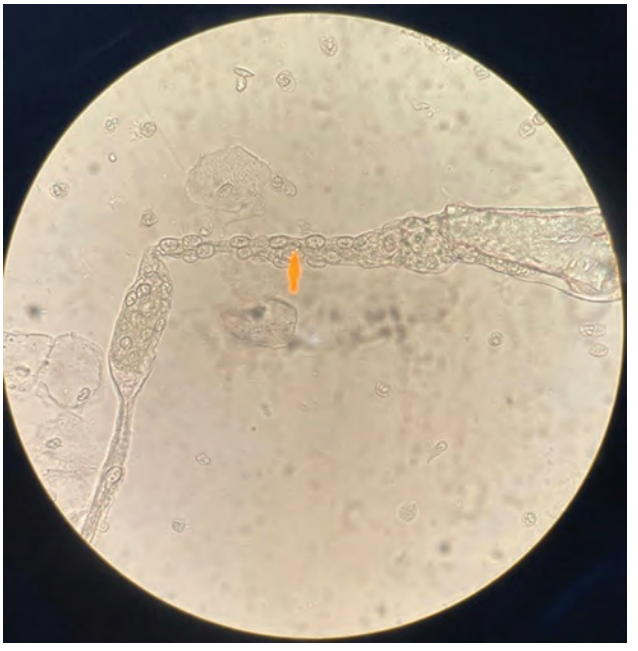
Richard E. Wing, Shamsul Hasan, Daniel Rechlin, Jerome L. Jean-Gilles. *University of Rochester Medical Center, Rochester, NY.*

Introduction: Multiple Myeloma may present with a constellation of features including back pain, anemia, hypercalcemia, renal failure, and bland urine sediment. A multitude of findings are possible on biopsy most commonly including cast nephropathy, al amyloidosis, monoclonal immunoglobulin deposition disease, and tubular injury. Urinary characteristics may predict biopsy findings.

Case Description: A 63 year old woman former smoker presented with two years of progressive backpain treated with NSAIDs. Plain films revealed thoracic compression fractures. Select laboratories are summarized in the table. Urine microscopy relevealed a largely intact tubulo-epthelial cast [Image]. A percutaneous renal biopsy was obtained. The light microscopy revealed angulated, fractured casts with associated cellular reaction and tubular injury. A Congo red stain was negative. A paraffin based immunofluorescence showed monoclonal Kappa positivity in the casts. Moderate atherosclerosis and severe interstitial fibrosis were noted. Bone marrow biopsy revealed plasma cell myeloma (90% of marrow cellularity).

Discussion: Urinary findings include a large intact tubular cast, high sodium:creatinine ratio, and large non-albumin proteinuria. All point to a biopsy finding of a cast nephropathy.

Hemoglobin (mg/dL)	9.7
Serum Bicarbonate (mmol/L)	19
Serum Creatinine (mg/dL)	5.5
Serum Calcium (mg/dL)	11.2
Serum Albumin (g/dL)	4.0
Serum Total Protein (g/dL)	6.9
Serum Paraprotein (g/dL)	0.2
Serum Kappa:Lambda ratio	3630
Urine Total Protein:Creatinine ratio	5.8
Urine Microalbumin (mg/dL)	<1.2
Urine Creatinine (mg/dL)	36
Urine Sodium (mmol/L)	44



PUB324

When You Hear Hoof Beats, It Can Be a Horse or a Zebra or Both Galloping Simultaneously!

Danish Waqar, Maria M. Picken, Ewa Borys, Kavitha Vellanki. *Loyola University Medical Center, Maywood, IL.*

Introduction: Multiple primary malignancies are defined as two or more malignancies arising independently of one another. While it is not uncommon to have multiple primary malignancies in a life time, simultaneous diagnosis is rare. Here, we present a case of acute kidney injury (AKI) and hypercalcemia, work up of which lead to simultaneous diagnosis of two different primary malignancies.

Case Description: A 74 year old male presented with 2 month duration of abdominal pain, weight loss and poor appetite. He had a large palpable abdominal mass, confirmed on CT imaging as a 13.8 x 13.4 cm mesenteric mass. Laboratory work up revealed AKI (serum creatinine of 5.6 mg/dL) and hypercalcemia (serum calcium of 14.2 mg/dL). Urinalysis was +ve for protein with 24 hour urine protein of 2.5 grams. Mesenteric mass biopsy confirmed our suspicion of lymphoma, final diagnosis being diffuse large B-cell lymphoma (DLBCL). Work of hypercalcemia is shown in Table 1 and kidney biopsy revealed lambda light chain proximal tubulopathy (Figure 1) with subsequent bone marrow biopsy confirming the diagnosis of Multiple Myeloma (MM).

Discussion: Simultaneous occurrence of DLBCL and MM is extremely rare. Our case illustrates the importance of a thorough workup of hypercalcemia despite an obvious cause as both malignancies can present with AKI, hypercalcemia and proteinuria. Workup of hypercalcemia (normal 1, 25 (OH)2 D which is usually elevated in lymphoproliferative disorders and markedly elevated serum lambda light chains) prompted us to a kidney biopsy and diagnose MM simultaneously. Conclusion: Even with a concurrent known cause of hypercalcemia, a full workup for hypercalcemia is always warranted. We like to think "When you hear hoof-beats, it can be a horse or a zebra or both".

Table 1 summarizing the hypercalcemia workup

Hypercalcemia workup	25-hydroxy vitamin D	1,25-Dihydroxy Vitamin D	Intact Parathyroid hormone (iPTH)	Parathyroid hormone related protein (PTHrp)	serum free light chain (kappa)	Serum Free light chain (lambda)	Serum Kappa/Lambda ratio
Result in units (reference range)	28 ng/ml (20-80 ng/ml)	<8 pg/ml (0-8 pg/ml)	7 pg/ml (14-67 pg/ml)	19 pg/ml (11-20 pg/ml)	31.8 mg/L (3.3-19.4 mg/L)	3,117 mg/L (5.7-26.3 mg/L)	0.01 (0.26-1.65)

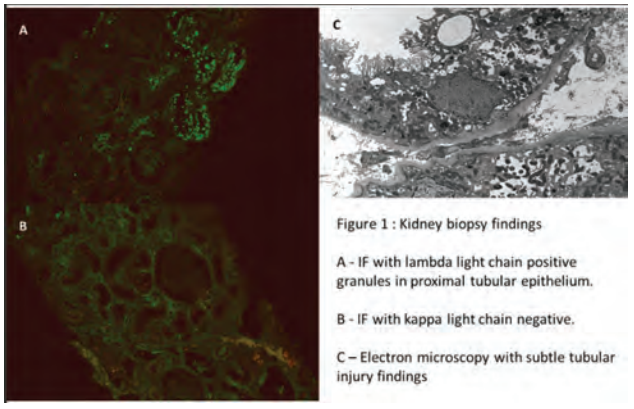


Figure 1

PUB325

Safety of Systemic Anticancer Treatment (ST) in Patients with ESKD and Metastatic Renal Cell Carcinoma (mRCC): A Single Institution Experience

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Background: ST for mRCC is linked to a variety of adverse events (AEs) including bleeding and infections. A significant number of patients with mRCC develop CKD that can progress to ESKD requiring renal replacement therapy. It is not known however whether these patients have an increased risk for bleeding and infections while receiving ST.

Methods: We identified 29 ESKD patients (21 male, 8 female) with mRCC who received ST that included VEFGR/TK inhibitors, immune check point inhibitors (ICI) or mTOR inhibitors alone or in combination at the Institute of Oncology Ljubljana in Slovenia between December 2009 and January 2023. By manual chart review, we determined the frequency and severity of bleeding and infectious AEs in this cohort while on active treatment for mRCC.

Results: The median age for the patients studied was 71 years (range 47-83). At the start of ST, 20 patients were already on chronic hemodialysis (HD). Six patients had eGFR ≤30 ml/min/1.73m^2 and three had a GFR >30 ml/min/1.73m^2 at the start of ST but all patients eventually developed ESKD and were started on chronic HD. Before ST, eight patients experienced a bleeding episode including three who had a gastrointestinal bleed (GIB). Grade 4 epistaxis was seen in three patients, including a patient that developed hemorrhagic shock during first-line treatment with sunitinib. Two patients experienced grade 4 anal hemorrhage, one due to hemorrhoids during first-line therapy with sunitinib. One patient underwent an urgent nephrectomy due to bleeding during treatment with sunitinib and a second patient during pazopanib treatment. In four patients, grade 4 GIB was observed during or after the ST. The cumulative incidence of grade 3/4 bleeding was 0.59 (17 events/29 pts), and 1.4 (40 events/29 pts) for all-grade bleeding. During ST, 10 patients experienced grade 4 infectious AEs. Six developed sepsis, and one, who was in the first cycle of first-line treatment with sunitinib and receiving HD, developed septic shock.

Conclusions: Serious AEs during ST, including bleedings and infections, may be more frequent in mRCC patients with ESKD as compared to the general mRCC population. Clinicians should be aware of this increased risk that may have a significant impact on the duration and selection of ST for these patients.

Funding: NIDDK Support, Other NIH Support - NCI

PUB326

Renal Cell Carcinoma Presenting as Jaw Pain

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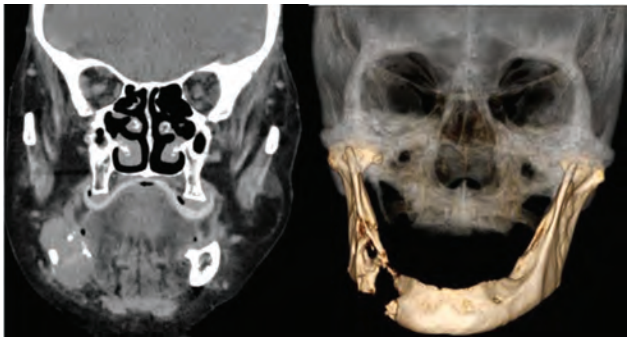
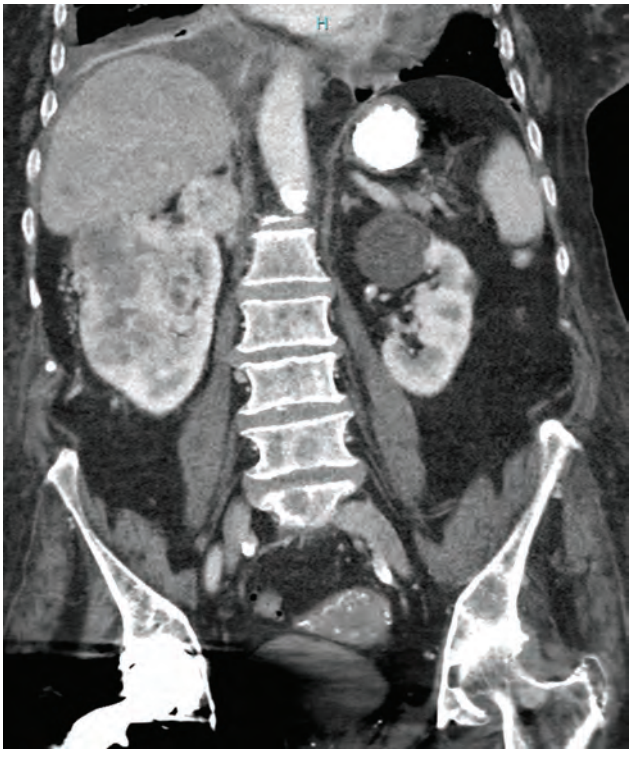
Introduction: Renal Cell Carcinoma (RCC) is the most common renal malignancy. Metastases to bone usually present as osteolytic lesions from T12-L5. This case demonstrates a mandibular mass as the initial presentation of RCC.

Case Description: A 91-year-old female presented with shortness of breath. Medical history was significant for chronic pain for which she took daily oxycodone. She did not smoke. Physical examination revealed a right mandibular jaw mass. No cervical lymphadenopathy, trismus or parotid gland swelling was found. Computed tomography (CT) of the maxillofacial structures demonstrated a 3.5 cm destructive lesion with a displaced pathologic fracture of the right mandibular body. It also showed a large destructive mass at the level of C3 extending into the spinal cord. Biopsy demonstrated renal cell carcinoma. Subsequent CT Abdomen/pelvis revealed a large 8.5 cm multilobulated mass replacing a majority of the right kidney.

Discussion: RCC is the most common solid tumor of the kidney. The classic presenting symptoms are the triad of hematuria, flank pain, and a palpable abdominal mass; however, this presentation only occurs in 10-15% of patients. 25-30% of patients will have metastatic disease at time of presentation. RCC commonly spreads to orofacial soft tissues and sinuses, however, only 1% of patients with RCC demonstrate isolated head and neck metastases. Oral metastases convey a worse clinical prognosis. When multiple osteolytic lesions present in the head and neck, it is strongly recommended that a search for the primary tumor be conducted.





PUB327

Single and Combination Immunotherapy with Chemotherapy and the Risk of AKI in Patients with Solid Cancer

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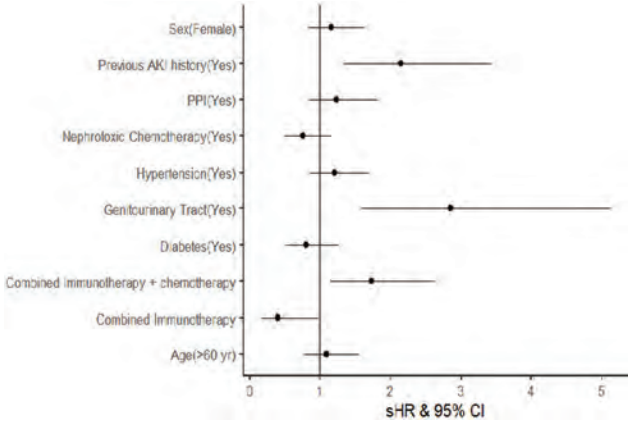
Background: Acute kidney injury (AKI) has emerged as an important toxicity among patients with advanced cancer treated with these drugs. The aim of this study was to describe the incidence, risk factors of AKI in patients receiving checkpoint inhibitors alone or in combination with another immunotherapy or chemotherapy.

Methods: We included all patients who received immune checkpoint inhibitors alone or combined with another immunotherapy or chemotherapy at AC Camargo Cancer Center from January 2015 to December 2019. AKI was defined as a increase 1.5 fold increase in creatinine from baseline within 12 months of checkpoint inhibitor initiation. We assessed the association between the baseline demographics, comorbidities, medications and risk of AKI using a competing risk model, considering death as a competing event.

Results: We included 614 patients in the analysis. The mean age was 58.4 ± 13.5 years, the mean baseline creatinine was 0.8 ± 0.18 mg/dL, and the baseline eGFR was 101.4 ± 33.2 ml/min. AKI occurred in 144 (23,5%) patients on average 14, 2 weeks after the beginning of treatment. The most frequent AKI etiologies were multifactorial (10,1%), hemodynamic (8,5%) and possibly related immunotherapy (3,6%). The likelihood of AKI was greater in the patients genitourinary cancer (sHR =2.84; 95% CI, 1.58-5.12, p < 0,01), with previous AKI history (sHR =2.1 95% CI, 1.34-3.42, p < 0,01) and taking anti-PD1/PD L1 combined with chemotherapy (sHR =1.73; 95% CI, 1.13–2.63, p < 0,01) (figure). An evaluation by a nephrologist occurred in 20,8% of the patients.

Conclusions: The patients receiving checkpoint inhibitors frequently developed AKI due to various etiologies. Genitourinary cancer, previous AKI and anti-PD1/PD-L1 combined with chemotherapy were associated with a higher likelihood of developing AKI.

Funding: Private Foundation Support



Fine–Gray model for AKI within 12 months of initiation of immune checkpoint inhibitor.

PUB328

Wunderlich Syndrome: Spontaneous Perinephric Hematoma in a Patient with Chronic Myelomonocytic Leukemia (CMML)

Nathaniel Klair, Sean Pickthorn, Salman B. Mahmood, Mark E. Rosenberg. *University of Minnesota Twin Cities School of Medicine, Minneapolis, MN.*

Introduction: Wunderlich syndrome describes the uncommon presentation of spontaneous perinephric hematoma that are most often caused by renal neoplasms. We present a case of bilateral spontaneous perinephric hematomas in a patient ultimately diagnosed with chronic myelomonocytic leukemia (CMML).

Case Description: A 62-year-old woman presented with acute onset right flank pain, hypotension, and anemia (Hgb 6.8 g/dL) requiring emergent transfusion. Workup showed WBC of 49x10^3/μL, platelets 380x10^3/μL, and Cr 0.9 mg/dL. CT revealed a large right perinephric hematoma, but no active extravasation was seen on angiography. The patient was stabilized with medical management and outpatient bone marrow biopsy was planned. Two days later she presented with acute onset left flank pain. CT showed a stable large right perinephric hematoma and a new left perinephric hematoma (Figure 1). Angiography revealed active extravasation from bilateral segmental renal arterial branches which were successfully embolized. Post embolization, the patient developed oliguric AKI (peak Cr 3.6 mg/dL), likely due to a combination of contrast exposure, ischemia from embolization and acute blood loss, and compression of the kidneys. She briefly required dialysis while her renal function recovered over a period of 2 weeks. During this time, a bone marrow biopsy was performed which revealed CMML. Treatment was initiated with hydroxyurea.

Discussion: The most frequent cause of spontaneous perinephric hematoma is primary renal malignancy or mass. CMML rarely has shown renal infiltration leading to renal failure but has no prior association with Wunderlich syndrome. While no biopsy was performed, we suspect this patient had leukemic infiltration of both kidneys which predisposed her to spontaneous bilateral perinephric hematomas in short succession.

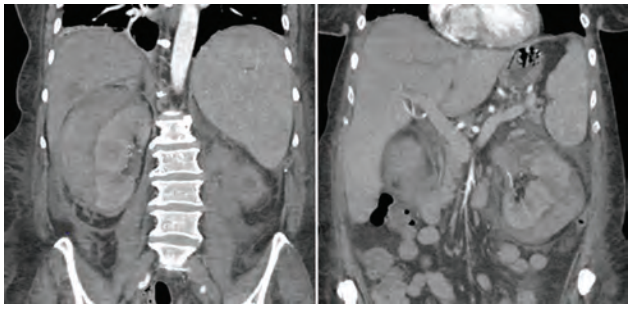


Figure 1: CT with contrast showing bilateral perinephric hematomas.

PUB329

Exploring Uncharted Territories: Unusual Distant Metastases in Renal Cell Carcinoma

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Introduction: Metastatic renal cell carcinoma (RCC) is known for its tendency to disseminate to the skeletal system, particularly as lytic lesions. The predilection of this metastasis primarily involves vascular regions within the axial skeleton (e.g., vertebral bodies and the pelvis). While rare, there have been scant reports documenting the manubrium as the primary site of metastasis. In this context, we present a case of metastatic RCC, wherein the patient's initial manifestation manifested as chest pain.

Case Description: A 50-year-old male with 50 pack-years of smoking history, presented to the emergency department (ED) with right-sided chest pain aggravated by recent hand trauma. The patient reported progressive difficulty with overhead movements and right-hand lifting. He had no alleviating factors and denied shortness of breath, diaphoresis, or recent weight loss. Further evaluation ruled out acute coronary syndrome (ACS). The chest x-ray was unremarkable. However, a commuted tomography (CT) of the abdomen and pelvis raised concern about a large left-sided renal mass. He was discharged with outpatient follow-up. Within three weeks, the patient returned to ED due to worsening chest pain and now, a growing mass in the sternum. ACS was ruled out again. A chest CT scan revealed a concerning lytic lesion in the manubrium. To establish a diagnosis and stage of a presumed metastatic renal cell carcinoma, the patient underwent a positron emission tomography scan and bone biopsy of the lesion. The subsequent pathology report confirmed metastatic RCC. Treatment was initiated with immunotherapy (nivolumab and ipilimumab) and palliative radiation therapy targeting the sternum. Left radical nephrectomy and adrenalectomy with clean margins were performed. Ongoing treatment involves immunotherapy aimed at reducing the burden of metastatic disease.

Discussion: RCC commonly metastasizes to the lungs and lymph nodes, with axial skeletal involvement being less frequent. Sternal metastases are rare, likely due to the limited vascularity in this region compared to sites like the pelvis or vertebrae. However, RCC is a treatable cancer, and both surgical intervention and immunotherapy have shown efficacy in improving metastatic disease outcomes. Timely treatment can enhance quality of life and potentially even lead to metastatic disease regression.

PUB330

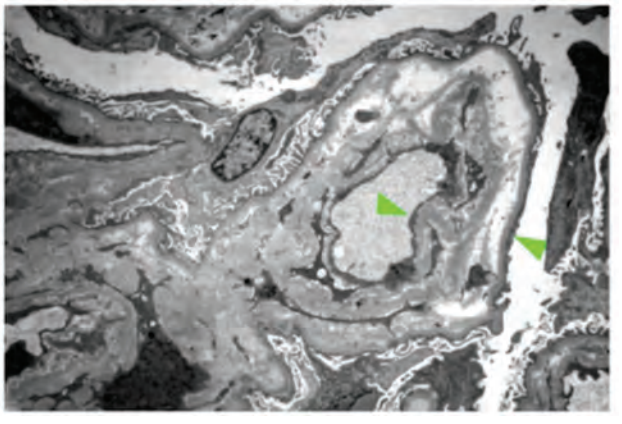
A Rare Case of Thrombotic Microangiopathy (TMA) with Lenvatinib

Chinnawat Arayangkool,[1,2] Thiratest Leesutipornchai,[1,2] Noppawit Aiumtrakul,[1,2] Manasawee Tanariyakul,[1,2] Titus David,[1,2] Chuong Dinh,[3] Lisa Kim.[3] *[1]University of Hawai'i at Manoa John A Burns School of Medicine, Honolulu, HI; [2]Hawaii Residency Programs Inc, Honolulu, HI; [3]The Queen's Health Systems, Honolulu, HI.*

Introduction: Lenvatinib is a rare cause of drug-induced TMA because its mechanism includes inhibition of VEGFR 1-3. The podocytes of the renal glomerulus produce VEGF, which is essential for the maintenance and proper function of adjacent endothelial cells. We report a patient on lenvatinib who developed TMA.

Case Description: A 65-year-old woman with recurrent endometrial carcinoma metastatic to the lung and liver, for which she received treatment with doxorubicin and bevacizumab. After completing eight cycles of this regimen, the patient developed whole-body swelling and was found to have uncontrolled hypertension and acute kidney injury with new-onset proteinuria attributed to the effects of bevacizumab. Consequently, the treatment regimen was discontinued and changed to pembrolizumab and lenvatinib. However, after ten days of this regimen, the patient presented with diarrhea. Her vital signs were significant for hypertension. A rise in creatinine level from 2.2 mg/dL to 5.2 mg/dL. Renal ultrasonography showed increased renal cortical echogenicity. Based on these findings, the patient underwent a kidney biopsy to confirm the diagnosis of an intrinsic renal cause. The finding of the left renal biopsy showed acute and chronic thrombotic microangiopathy with global glomerulosclerosis, moderate interstitial fibrosis, tubular atrophy with interstitial nephritis, and severe arteriosclerosis with evidence of fibroid necrosis. On electron microscopy, findings reveal microangiopathic changes consistent with the vascular endothelial growth factor inhibitors effect. As the left renal biopsy confirmed TMA as the cause of her AKI, Lenvatinib was discontinued. However, her renal function progressively declined, leading to ESRD requiring hemodialysis.

Discussion: Lenvatinib-associated TMA is a rare adverse effect. There is a case series of biopsy-proven TMA in patients on lenvatinib after prolonged exposure. However, our patient developed TMA shortly after lenvatinib exposure. TMA should be considered in patients on lenvatinib, and renal biopsy is recommended to confirm the diagnosis.



PUB331

A Rare Case of a Primary Renal Ewing Sarcoma

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Introduction: Ewing's sarcoma is a neuro-ectodermal tumor that is classically found in long bones. A primary renal origin of an Ewing's sarcoma is very rare. It is estimated that there are less than 370 reported cases of a primary renal Ewing's sarcoma. This case presents a rare primary renal Ewing's sarcoma.

Case Description: A previously healthy 15 year old male presented with two months of hematuria and one day of left flank pain, as well as occasional migratory bone pain. Initial imaging with US kidneys and bladder revealed an area of calcification in the lower pole of the left kidney. Further imaging with CT abdomen and pelvis showed a left renal mass with associated calcification with extension into the renal pelvis. There were also lesions visualized in the liver, spine, and pelvis that were concerning for metastases. The patient was later found to have additional metastases in the skull and sternum. Initial differential diagnosis included Wilm's tumor, clear cell sarcoma, malignant rhabdoid tumor, and renal cell carcinoma. Diagnosis of Ewing sarcoma was made by biopsy of a lytic bone lesion and was confirmed on pathology of the left kidney following left nephroureterectomy. The patient is currently undergoing chemotherapy and responding well to treatment.

Discussion: This is a rare case of a primary renal Ewing's sarcoma. While more common primary renal tumors such as Wilm's tumor, clear cell sarcoma, and renal cell carcinoma may be higher on the differential in a patient presenting with a renal mass, it is important to keep less common tumors such as Ewing's sarcoma on the differential, especially in a patient presenting with bone pain and bony metastases. Although a primary renal Ewing's sarcoma is very rare, this patient's presentation was consistent with other cases of primary renal Ewing's sarcoma. In a metanalysis of cases of primary renal sarcoma that included 48 patients, Hakky et al found that 36 (73%) presented with flank pain and 15 (31%) presented with hematuria. This is an aggressive tumor so rapid diagnosis and treatment are key to optimizing outcomes.

PUB332

A Case of Thrombotic Microangiopathy (TMA) Secondary to Bevacizumab Followed by Acute Interstitial Nephritis (AIN) Secondary to Nivolumab: A Strong Case for Serial Biopsies

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Introduction: In recent years, onconephrology has gained prominence as a crucial field at the intersection of oncology and nephrology. With the rapid growth of cancer treatments that are often used concurrently, it has become important for oncologists and nephrologists alike to recognize unique patterns of drug-related kidney injury and develop a consistent and efficient approach to establishing etiology of acute kidney injury (AKI). Here we present a patient who experienced biopsy proven thrombotic microangiopathy (TMA) caused by bevacizumab, was switched to nivolumab which resulted in biopsy proven acute interstitial nephritis (AIN).

Case Description: Patient is a 69-year-old female with a medical history of stage IV malignant mesothelioma of the lung. This was treated with platinum-based therapy, pemetrexed and bevacizumab followed by maintenance therapy with bevacizumab. Patient initially had normal kidney function with a baseline creatinine of 0.9mg/dL, however, 2 years after initiation of therapy her kidney function worsened, with a creatinine rising to 2.4mg/dL and a urine protein to creatinine of 2.7g/g. Patient underwent a kidney biopsy revealing focal segmental and global glomerulosclerosis with microangiopathic features as well as moderate arteriosclerosis. A diagnosis of bevacizumab induced TMA was made and this medication was stopped. Patient then began treatment with the immune checkpoint inhibitor (CPI) nivolumab. Five months after her first kidney biopsy and 3 months after beginning treatment with nivolumab, patient's creatinine rose again to then new peak of 7 mg/dL. Repeat kidney biopsy was obtained revealing acute tubulointerstitial nephritis which was suspected to be secondary to nivolumab. This medication was held, patient was started on a short prednisone course with recovery to baseline kidney function followed by a taper and plan to possibly rechallenge with an CPI.

Discussion: As demonstrated by this case, serial kidney biopsies may be required to ascertain etiologies of recurrent AKI in patients exposed to different cancer treatments. These biopsies can effectively guide oncological treatment and help avoid progression to end-stage kidney disease that would otherwise severely limit further treatment options and preclude patients' participation in new drug trials.

PUB333

Kidney Palliative Care: Key Tool to Facilitate Shared Decision Making

Kaitlyn Lersch, Pooja D. Amarapurkar, Jane O. Schell. *UPMC, Pittsburgh, PA.*

Introduction: Patients with cancer and kidney disease have complex symptoms and needs. This is especially true for those with advanced chronic kidney disease (CKD) who are at risk for worsening progression due to cancer-directed therapies or their side effects. Palliative care is team-based care that focuses on managing symptoms and addressing goals of care including kidney treatment decisions. Our institution developed a specialty kidney palliative care (KPC) team to manage these complex patients through collaboration with referring clinicians. The following case describes how KPC can promote patient-centered care in a patient with advanced CKD and cancer.

Case Description: An 80-year-old man with CKD stage 3bA2 established care with our KPC team. His kidney function remained stable until about a year before his cancer diagnosis, with estimated GFR dropping to the mid-20s. These notable changes prompted a goals of care discussion that led to a decision for medical management without dialysis. He was later diagnosed with metastatic lung cancer. After receiving this diagnosis, the KPC team worked with both the patient and his wife to outline goals of palliative chemotherapy, which included a quality of life with the ability to garden, enjoy reading and be at home with family. Shortly after starting treatment, he required hospitalization for dehydration and AKI in the setting of diarrhea related to the chemotherapy. Due to the strong relationship established with the patient and his family, the KPC team collaborated with his oncology team to help determine that starting dialysis and continuing chemotherapy were not consistent with his goals. These relationships and prior discussions helped the patient choose hospice care, passing away peacefully at home.

Discussion: This case exemplifies how patients with advanced kidney disease and cancer benefit from specialty palliative care. It demonstrates how the KPC team has a role in having early conversations regarding goals, revisiting these goals, and then collaborating with oncology. It allows patients and their families to build trust in their medical team, which is especially needed during challenging decisions. It gives patients and families the opportunity to express their values and receive patient-centered care especially at end of life.

PUB334

Proliferative Glomerulonephritis with Monoclonal IgG Deposits: Yet Another Unusual Presentation

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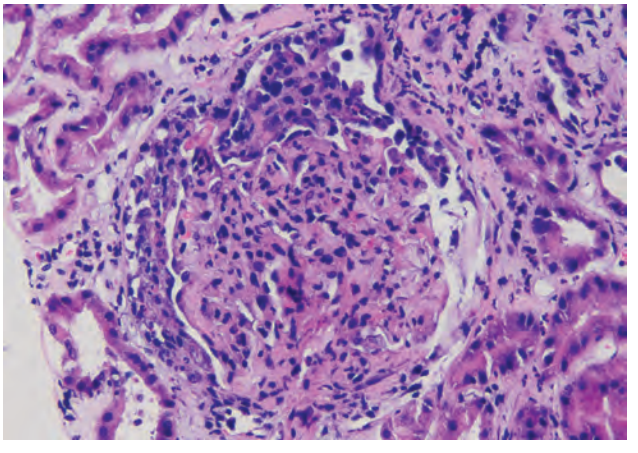
Introduction: Proliferative Glomerulonephritis with Monoclonal IgG Deposits (PGNMID) is a relatively rare diagnosis with variable presentation. When detectable, the disease is typically indolent rather than malignant. Here we report a case of PGMNID which presented clinically as Rapidly Progressive Glomerulonephritis (RPGN).

Case Description: A 62-year-old man presented to his primary care physician's office with complaint of diarrhea for one day and was admitted for acute kidney injury. Urine sediment was active, and the patient had nephrotic range proteinuria. Serologic workup including Antineutrophil cytoplasmic antibody, double strand-DNA antibody, free light chains, electrophoresis and imunofixation, and bone marrow biopsy were negative for any monoclonality. Kidney biopsy showed diffuse proliferative and crescentic glomerulonephritis with IgG3–kappa restricted deposits, consistent with PGNMID. The patient required dialysis initiation and corticosteroids were administered. The patient declined additional immunomodulatory treatment. The patient remains hemodialysis dependent.

Discussion: In summary, we present a case of PGNMID presenting clinically as RPGN without evidence of hematologic malignancy. IgG subclass staining should be performed in such cases without a peripherally detected clone. This case highlights the potential for severe renal damage from monoclonal proteins despite an indolent or even undetectable hematologic clone. The diagnosis needs further studies to better understand the entity and develop a standard treatment regimen for it.



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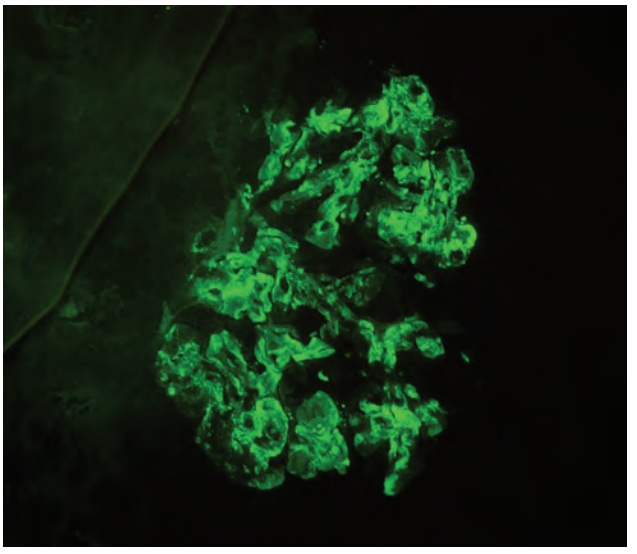

IgG subclass 3

PUB335

A Rare Manifestation of Multiple Myeloma in a Patient with Kidney Injury

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Introduction: Acute kidney injury (AKI) is a common complication of multiple myeloma (MM), most frequently attributed to underlying myeloma cast nephropathy. By contrast, infiltration of kidney tissue by neoplastic plasma cells is a rare occurrence and a rare mechanism of acute kidney injury in these patients.

Case Description: A 75-year-old male with a past medical history of long-standing hypertension and diabetes was admitted for evaluation of AKI. He reported unexplained weight loss but was otherwise asymptomatic. Upon laboratory evaluation, he was found to have increased serum creatinine from his baseline of 1.0 mg/dL to 3.8 mg/dL, a urinalysis remarkable for proteinuria, and a urine protein and creatinine ratio of 8.3 g/g. Further evaluation revealed free kappa and lambda light chains of 1.0/432 mg/dl with a ratio of 0.0025. Serum protein electrophoresis showed a monoclonal free lambda. Serological work up was negative. Renal ultrasound was unremarkable. A kidney biopsy demonstrated a Lambda light chain-restricted plasma cell infiltration and a Light chain proximal tubulopathy, non-crystalline type (lambda light chain-restricted). Subsequently, he underwent a bone marrow biopsy showing a lambda-restricted plasma cell myeloma with 50% plasma cells and started on daratumumab-based therapy.

Discussion: The etiology of kidney disease in patients with multiple myeloma can be multifactorial. On kidney biopsy, a broad spectrum of kidney lesions has been described. This case demonstrated a rare mechanism of acute kidney injury in a patient with MM and highlights the importance of kidney biopsy in the diagnosis and prognosis of these patients.

PUB336

Renal Involvement in Chronic Lymphocytic Leukemia: A Case Report

Vaishnavi Singh, Peter Van. *Willis-Knighton Health System, Shreveport, LA.*

Introduction: Chronic Lymphocytic Leukemia (CLL) is a primary bone marrow malignancy characterized by the clonal expansion of mature B lymphocytes. Although CLL primarily affects the bone marrow and peripheral blood, extra-medullary involvement can occur, including renal manifestations. Kidney disease in CLL patients can have significant implications on prognosis.

Case Description: We present a case of a 51-year-old female with a 12-year history of CLL who presented with weakness, hematuria, proteinuria, and elevated creatinine. Initially, she was suspected to have acute tubular injury secondary to the usage of nonsteroidal anti-inflammatory drugs. Over time, her renal function progressively declined, necessitating the initiation of dialysis. A kidney biopsy revealed renal involvement of CLL, showing leukemic infiltration along with findings suggestive of membranoproliferative glomerulonephritis and the possibility of cryoglobulinemic glomerulonephritis. However, due to limited sample, additional immunofluorescence studies could not be performed. Treatment with Rituximab, an anti-CD20 monoclonal antibody, was initiated. The patient was also started on ibrutinib, a Bruton's tyrosine kinase inhibitor, and is currently being managed with it.

Discussion: Renal involvement in CLL is a complex process that can occur through various mechanisms, including leukemic infiltration, glomerular diseases, extrarenal obstruction, tumor lysis syndrome, electrolyte disorders, and medication side effects. In our case, the kidney biopsy demonstrated interstitial infiltrates of small CD20+/CD5+ B cell lymphocytes, indicating direct leukemic infiltration. Additionally, the presence of membranoproliferative glomerulonephritis raised the possibility of cryoglobulinemic glomerulonephritis. This case report underscores the importance of recognizing and managing kidney involvement in CLL patients. Understanding the multifaceted mechanisms of renal disease in CLL can facilitate early diagnosis and appropriate treatment selection, potentially improving patient outcomes. Further research is warranted to enhance our understanding of CLL-related kidney disease and refine treatment strategies.

PUB337

AKI, Glomerulonephritis, and Tubulointerstitial Nephritis Following Prescription of Anticancer Drugs: VigiBase Analysis

Soo-Young Yoon,[1] Dae Kyu Kim,[1] Hyo Jin Lee,[1] Yang Gyun Kim,[2] Ju young Moon,[2] Hyeon Seok Hwang,[1] Kyunghwan Jeong,[1] Jin sug Kim.[1] *[1]Kyung Hee University Hospital, Dongdaemun-gu, Seoul, Republic of Korea; [2]Kyung Hee University Hospital at Gangdong, Gangdong-gu, Seoul, Republic of Korea.*

Background: Anticancer drugs can have varying effects on the kidneys, depending on their characteristics. Some drugs may be nephrotoxic and can potentially cause renal impairment. This is due to the damage, which can range from mild to severe, inflicted on renal tissues during drug processing and elimination. We aimed to to analyze the risk of renal adverse reactions from several types of anticancer drugs using a global reporting system.

Methods: We conducted an analysis on VigiBase, the World Health Organization pharmacovigilance database, consisting of 120,715,116 reports from Dec 1967 to Jul 2022 via disproportionate Bayesian reporting method. Information component (IC) compares observed and expected values to find the associations of 259 anticancer drugs with acute kidney injury (AKI), 101 anticancer drugs with glomerulonephritis (GN), and 91 anticancer drugs with tubulointerstitial nephritis (TIN). We further categorized the anticancer drugs into five groups: cytotoxic therapy, hormone therapy, immunotherapy, targeted therapy, and miscellaneous group.

Results: We observed 22,426 AKI, 1,312 GN, and 1,084 TIN reports which were reported as anticancer drug-related renal adverse reactions. Analyzing IC_{025} of each anticancer drugs separately, AKI cases following 85 of 259 anticancer drugs significantly increased. GN case reports after administering 16 of 101 anticancer drugs were statistically significant. We observed significantly higher TIN events in 17 of 91 anticancer drugs which we assessed. Notably, immunotherapy and targeted therapy anticancer drugs were frequently associated with renal injuries, while no significant renal adverse reactions were observed in the hormone therapy group across all AKI, GN, and TIN categories.

Conclusions: AKI, GN and TIN were substantially observed following the administration of anticancer drugs. Noticeably, renal adverse reactions following immunotherapy and targeted therapy, which have been experiencing an increase in utilization, were more prominent when compared to hormone therapy. Clinicians should consider the increased risk of renal adverse reactions after specific anticancer drugs.

PUB338

Anti-Complement Factor H Autoantibodies of the IgM Class and Atypical Hemolytic Uremic Syndrome (aHUS)

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Introduction: We have recently reported anti-complement factor H autoantibodies of the IgM class as a rare cause of atypical hemolytic uremic syndrome (aHUS).

Case Description: Herein, we describe the case of a 53 yo woman diagnosed with gastric MALT (mucosal-associated-lymphoid tissue) lymphoma at the age of 39yo treated with Rituximab and Bendamustine achieving minimal residual disease. Following diagnosis of the laboratory work-up for complement abnormalities excluded regulatory gene mutations whereas it revealed a very high level anti-CFH autoantibodies of the IgM class (with undetectable anti-FH IgG and IgA). Auto-antibody title was repeatedly confirmed high ranging from 34 and 66 AU/mL (normal value < 10.3 AU/mL) over an observation period of 6 months. C3 levels were also low, ranging from 58 and 62 mg/dL (normal values 90-180 mg/dL) with normal C4. Soluble C5b9 was very high during the acute phase (1881 ng/mL (normal values 139-463 ng/mL) and progressively decreased on eculizumab treatment reaching the normal level of 331 ng/mL. The patient is presently continuing C5-inhibition and aHUS remains into remission.

Discussion: This case-report underlines that auto-antibodies to CFH are not only of the IgG class but also of of the IgM class thus the latter should be part of the diagnostic workup of any case of aHUS.

PUB339

Vitamin B12 Deficiency: Equivocal or Pernicious?

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Introduction: Screening for vitamin B12 is not recommended in healthy individuals. Deficiency can include a wide range of symptoms. The iconic finding of B12 deficiency is macrocytic, megaloblastic anemia, and increased methylmalonic acid. Several reported cases of B12 deficiency have been mistaken for MAHA, thrombocytopenia, and in this review, TTP. Characteristics of TTP include fever, microangiopathic hemolytic anemia, thrombocytopenia, renal injury, and/or neurological symptoms. We present the case of a 63-year-old male with B12 deficiency originally misdiagnosed with TTP.

Case Description: This is a 63-year-old male with PMH significant for stroke who presented to the ED at an outside facility due to a fall in his garage. He experienced agitation, multiple skin lesions on the arms consistent with bruising, and reports of suicidal ideation. For severe anemia, patient was transfused. Hematology/oncology suggested catheter placement for plasmapheresis. The patient was transferred to our facility where nephrology was consulted to evaluate thrombocytopenia with possible TTP and begin plasmapheresis. Given suicidal ideations, psychiatry involuntarily committed the patient upon arrival. Nephrology believed this to be B12 deficiency with pancytopenia, not TTP due to elevated MCV. B12 was 276. Nephrology was concerned for pernicious anemia and recommended against plasma exchange. The patient regardless refused plasmapheresis. He did agree to 1000 mcg IM of cyanocobalamin, administered every 24 hours over 3 days. MRI confirmed absence of subacute combined degeneration. Labs improved substantially after treatment. Full workup was performed for B12 deficiency. He continued to have agitation but was deemed competent and the involuntary commitment was lifted with the patient discharged.

Discussion: Vitamin B12 is considered deficient with levels measuring less than 200 ng/L, with borderline deficiency of 200-400 ng/L considered equivocal, with recommendations to follow up with MMA levels to determine if this is true deficiency. MMA levels are highly sensitive and specific for identifying vitamin B12 deficiency. Psychiatric symptoms of B12 deficiency may be permanent, especially with prolonged time to treatment. In this case, the high MCV and pancytopenia lead to the suspicion of pernicious anemia, which was confirmed with elevated MMA and homocysteine, positive parietal cell and intrinsic factor antibodies.

PUB340

Renal Amyloid A (AA) Amyloidosis in a 24-Year-Old Drug User

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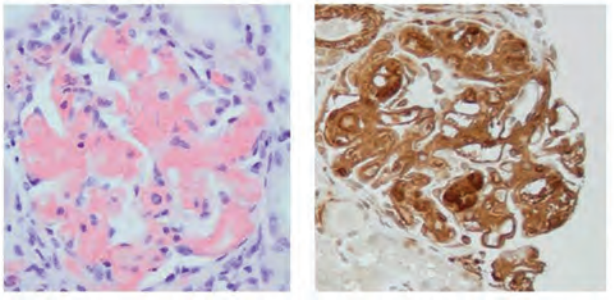
Introduction: Amyloidosis is an infiltrative disease caused by misfolded proteins depositing in tissues. There are currently described 14 types of amyloid that can involve the kidney. Herein we report a case of AA amyloidosis occurring in a 24-year-old male with a history of intravenous drug abuse.

Case Description: The patient is a 24-year-old male with a past medical history of intravenous drug abuse for 3 years and no other significant clinical or family history. He presented with bilateral edema and bilateral pleural effusions. Serum creatinine was 1.67 mg/dL (baseline 1mg/dL). Urinalysis showed 3+ protein and 1+ blood, serum albumin was 0.9 g/dL. In a kideny biopsy, the glomeruli showed diffuse infiltration of the mesangium by Congo red-positive amyloid. Immunofluorescence did not show dominance for either kappa or lambda light chain or other heavy chains. Electron microscopy showed randomly arranged fibrils with an average diameter of 10.4 nm. IHC for amyloid A was positive; a transthyretin/prealbumin was negative. Liquid chromatography-tandem mass spectroscopy (LC-MS) confirmed the presence of AA amyloid.

Discussion: Herein we describe a 24-year old patient, which, to the best of our knowledge, is the youngest described in the literature with AA amyloidosis associated with drug abuse. The patient had no history of inflammatory disorders, and no family history of amyloidosis or renal disease. Therefore, amyloid was attributed to the drug abuse. AA amyloid can be misdiagnosed as AL amyloid, and immunohistochemistry can be unreliable, so confirmatory testing by LC-MS should be performed if there is any discrepancy. For AA amyloidosis treatment focuses on controlling the underlying inflammatory process with the goal of reducing the amount of circulating SSA protein by reducing is production in the liver. Unfortunately, this patient was lost to follow up.



Congo Red positivge material in the glomerulus that stains positively by IHC with an antibody to Amyloid A.

PUB341

Proteasome Components in the Low-Centrifugation Pellet of Urinary Extracellular Vesicles

Dana Bielopolski,[1,3] Luca Musante,[4] Douglas Barrows,[1] Henrik Molina,[1] Jonathan N. Tobin,[5,1] Rhonda Kost,[1] Uta Erdbruegger.[2] *[1]The Rockefeller University, New York, NY; [2]University of Virginia, Charlottesville, VA; [3]Rabin Medical Center, Petah Tikva, Israel; [4]University of Pennsylvania, Philadelphia, PA; [5]Clinical Directors Network Inc, New York, NY.*

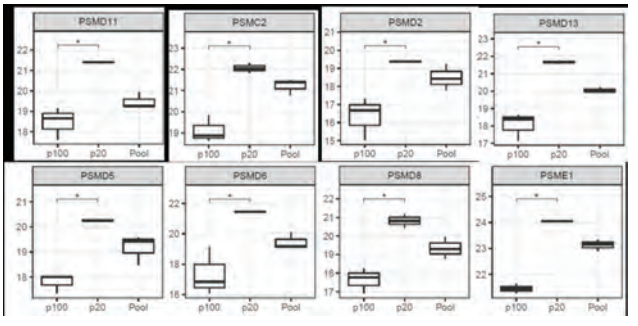
Background: High-speed ultracentrifugation is a commonly employed technique for isolating small extracellular vesicles (EVs). In contrast, the low-speed centrifugation pellet can be an advantageous source for large EVs. In this study we sought to describe and compare the characteristics of EV pellets obtained through different centrifugation velocities, with a specific focus on their protein content and cellular localization.

Methods: A healthy volunteer provided a morning urine sample that was divided into three aliquots. Each urine aliquot underwent centrifugation to eliminate cell debris, and the resulting supernatant was then subjected to a centrifugation at 21,200g to generate a pellet known as P20. The supernatant from P20 was subsequently centrifuged at 164,000g, resulting in a pellet referred to as P100. The P20 pellets were subjected to uromodulin depletion using a low ionic strength buffer, while the P100 pellets were purified using size exclusion chromatography. The individual pellets were analyzed using mass spectrometry separately and combined.

Results: in all three replicates 929 proteins were identified the P20 pellets, 1103 proteins in the P100 pellets, and 1676 proteins in the combined P20 and P100 pellets. 398 proteins were uniquely identified in P100 and 224 were uniquely identified in P20. 473 proteins were uniquely expressed in the combined P20+ P100 that were not identified in either fraction alone. The abundance of S19 proteasome subunit components were increased in P20 compared to P100.

Conclusions: Implementing low centrifugation along with a high ionic strength buffer effectively prevents co-sedimentation and increases detection yield. The uEVs P20 pellet contained proteasome components, specifically the 19S subunit indicating a shared pathway potentially associated with apoptosis.

Funding: Private Foundation Support



Abundance of proteosome related proteins in the different EV fractions. Asterix marks a statistically significant difference (<0.05)

PUB342

Renal Interstitial Fibrosis Association with Hypertension (HTN), Diabetes Mellitus (DM), Ultrasound Measured Sinus Fat, and Parenchymal Thickness

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Background: Interstitial fibrosis is an important component of a kidney biopsy to determine chronic renal disease. In this study we wanted to determine the correlation between biopsy proven interstitial fibrosis, HTN, DM, ultrasound measured sinus fat as well as parenchymal thickness.

Methods: Retrospective cross-sectional study included all kidney biopsies performed by the interventional Nephrology division in the Nephrology department at Ochsner medical center over 2 years from 2021- 2023. Demographic factors, HTN and DM were registered. Renal function was calculated using CKD MB. The extent of interstitial fibrosis was obtained from kidney biopsy results. The sinus fat length was measured from longitudinal sagittal US image. The total renal length was measured on the same image. The renal parenchymal thickness was measured by subtracting the longitudinal sagittal length of the sinus fat from the total kidney length. The percentage of sinus fat length was measured by dividing the length of sinus fat over the total renal length for the ipsilateral side of the biopsy. SPSS 25 was used statistics analysis.

Results: Total biopsies were 60. Mean age: 50 years. (SD 17.5, SE 2.27). Male gender was 45%. Mean BMI 29.3 kg/m2 (SD 7.2, SE 0.9) 23 % had DM, 55 % had HTN and 23% had both. Mean Interstitial fibrosis 20%. which was significantly more among patinets with HTN and DM (33%) as compaired to patients with only HTN (23%) or thouse without HTN or DM (12%). Mean S. Cr. 2.3 mg/dl (SD 2.2, SE 0.28) Mean eGFR: 42ml/min. (SD 19.3, SE 2.5)

Conclusions: Interstitial fibrosis was significantly associated with age, gender, HTN, DM, S. creatinine and eGFR but not sinus fat length or parenchymal thickness. Patients with HTN and DM had more interstitial fibrosis compared patients with HTN alone, and patients without HTN or DM.

Independent Variables	Correlation Coefficient	p Value
Age	0.36	0.005
Gender	-0.39	0.002
BMI	0.2	NS
HTN	0.43	0.001
DM	0.38	0.003
S. Creatinine	0.49	<0.0001
eGFR	-0.45	<0.0001
Sinus fat percentage	-0.16	NS
Parenchymal thickness	0.25	NS

PUB343

Statin Therapy Activates a Programme of Skeletal Muscle Wasting In Vitro

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Background: Skeletal muscle wasting is a serious and common complication of chronic kidney disease (CKD) which starts very early in the disease process. This is an important clinical problem as it is strongly associated with increased risk of mortality and decreased quality of life. Despite its prevalence and impact, mechanisms of skeletal muscle (SM) wasting are unclear. One possible contributor is statin medication that CKD patients are frequently prescribed, which are documented to have negative effects upon muscle health. The aim of this study was to assess the effect of simvastatin therapy on protein degradation in human derived primary skeletal muscle cells (HDMC's).

Methods: Isolated HDMCs were cultured for 4 days in medium supplemented with foetal bovine serum (FBS, 20%), followed by 7 days in either 2% horse serum (HS) to establish mature myotubes. HDMC's (n = 5 CKD patients) were incubated with either 10μM and 30μM simvastatin for 24h and effects upon atrophy were assessed by myotube diameter by immunofluorescence, and activation of protein degradation and inflammation pathways by PCR.

Results: Cells exposed to10μM and 30μM simvastatin displayed significant reductions in myotube diameter (Control = 9.904μm ± 2.56, 10μM = 8.424μm ± 1.68 and 30μM = 7.998μm ± 2.05, p=0.0036. 10μm statin therapy significantly increased the mRNA expression of RRIM63 (a muscle specific E3 ligase; 3.7-fold increase, p=0.005) and resulted in significant intramuscular inflammation (IL6 = 1.6- fold increase, p=0.008 and TNFα = 2.7-fold increase, p<0.001). Similar effects were seen with 30μm statin therapy which resulted in significant inflammation (IL6 = 1.7-fold increase, p=0.001, TNFα = 2.2-fold higher, p=0.025 and CCL2 = 2.2-fold increase, p=0.027).

Conclusions: Short term exposure of HDMS's to 10μM and 30μM simvastatin resulted in myotube atrophy, likely to be regulated by an increase in intramuscular inflammation. Whilst statin therapy has strongly beneficial effects for these patients in terms of reducing cardiovascular risk, an unwanted side effect is muscle wasting. It is unknown if this is an effect that is restricted to simvastatin alone, or also occurs with other statin use. This early pilot data suggests that we might need to think about strategies to preserve muscle mass in patients that are prescribed this class of drugs.

PUB344

Comparison of Two Scores for Renal ANCA-Associated Vasculitis (AAV) in Predicting Renal Outcomes

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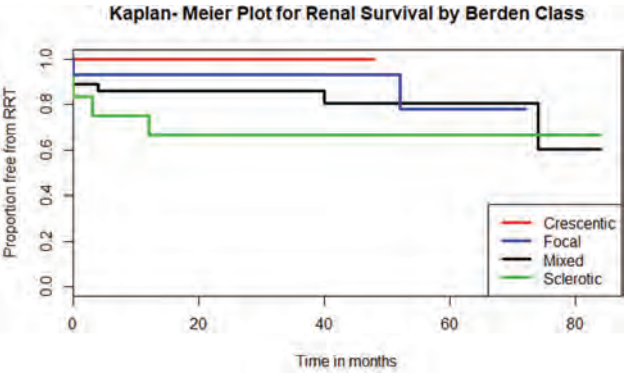
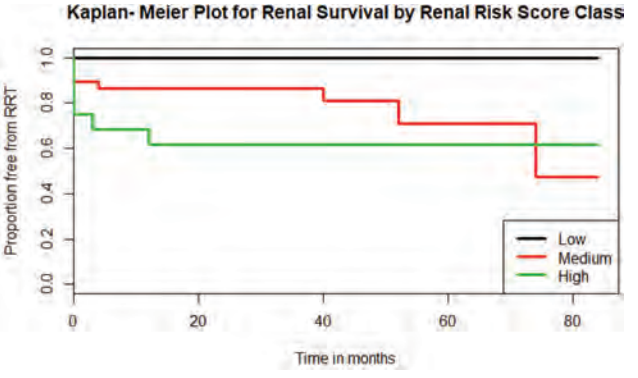
Background: ANCA associated vasculitis (AAV) is a rare but important cause of renal impairment and ESRD. Two classifications used for prognostication of renal AAV at presentation are Berden et al (Histopathologic classification of ANCA-associated glomerulonephritis. J Am Soc Nephrol.2010.21(10)) and the renal risk score -Brix et al (Development and validation of a renal risk score in ANCA-associated glomerulonephritis. Kidney Int.2018.94(6)). We aimed to test the 2 scores in our regional vasculitis centre's renal AAV cohort.

Methods: Review of records and renal biopsy of patients who presented from January 2012 to December 2016.

Results: 83 patients were included. 14 developed ESRD. 8 required early RRT but recovered and are not counted as ESRD. Berden Class We found no statistically significant relation between Berden class and ESRD and it did not predict recovery from early need for RRT. As KM curves cross at 52 months- fig 1-we calculated Cox proportional hazard up to 48 months. There was no statistically significant hazard There was significant association with creatinine at 1 year but not 4 Renal Risk Score Again the KM plot-fig 2-overlap. Cox hazard analysis up to 48 months found a hazard ratio of 4.178 for risk score class (p= 0.0017). The classification of our cohort using the renal risk score statistically significantly associated with ESRD but did not predict recovery from RRT. Also the renal risk class significantly associated with creatinine at 1 and 4 years.

Conclusions: In our cohort renal risk score by Brix et al performed better as predictor of ESRD and future creatinine than Berden class.





PUB345

The Role of Mitochondrial Metabolism in Inflammation Process of Brain-Dead (BD) Patients

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Background: As previously established, the renal prognosis of the recipient depends on the donor type. The decline in renal function has been observed to be greater in deceased donors (DD). We analyzed a cohort of brain-dead patients (DD). This could be related to the pre-implantation inflammation state and the development of fibrotic processes. Succinate, an intermediate in mitochondrial metabolism, plays a key role in the inflammatory processes of different pathologies. On the other hand, we observed previously, the involvement of adenosine pathway (linked to mitochondrial ATP production) in the same process. The aim of this study was to determine whether DD samples, succinate and purinergic pathways are involved in the infiltration of inflammatory cells.

Methods: Serum and whole cell extracts from circulating monocytes of 27 Brain Dead (BD) and 10 healthy volunteers (HV) were incubated in a Custom Quantibody array to determine the levels of 18 monocyte/macrophage markers (CCL2/MCP-1, CCL3/MIP-1a, CD163, B7-1/CD80, B7-2/CD86, ICAM-1, IFN-γ, IL-10, IL-13, IL-1b, IL-4, IL-4 Rα, IL-6, RANTES, TACE, TGF-β1, TNF-α and VEGF). Succinate levels were measured in serum from the same samples with the EnzyChromTM Succinate Assay Kit. All statistical data was analyzed using GraphPad Prism 5.

Results: The results showed that in BD serum compared to HV ones, there was a significant increase in the expression of cytokines involved in monocyte recruitment and adhesion. Serum levels of IL-6, implicated in polarization of macrophages towards the proinflammatory subtype, were higher in BD. Concerning monocyte protein extracts, a significant increase in anti-inflammatory M2 proteins, such as CD163, IL-4Ra and IL-13 was observed. BD succinate levels in sera were increased in the same way.

Conclusions: Taken together, these results would indicate that in BD samples, there would be recruitment and differentiation of monocytes to macrophages towards the M1 or M2 subtype. Most of the molecules found to be upregulated belong to proteins related to the M2 phenotype, leading us to suggest that in BD, the process is mainly reparative/pro-fibrotic.

PUB346

Improving Transition of Care in Pediatric Patients with CKD via a Remote Education Program

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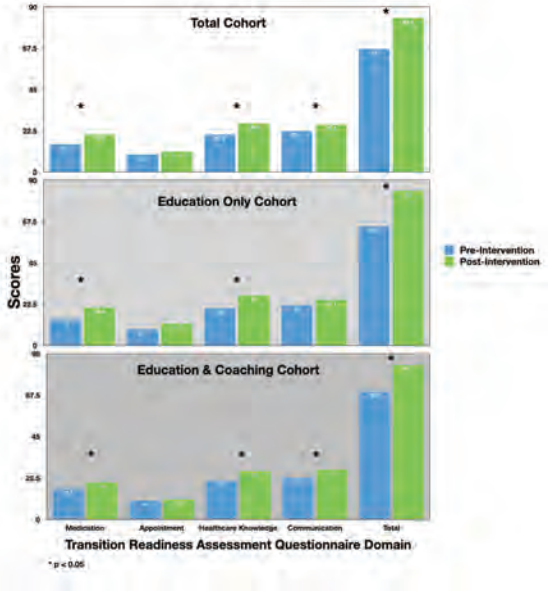
Background: Healthcare transition is the process of preparing a pediatric patient for the adult care model. There are no studies evaluating methods for improving transition readiness in patients with chronic kidney disease (CKD). Our project evaluates the effectiveness of an education program.

Methods: Eligible patients between 14-22 years of age with CKD stage 2 or higher were approached about this quality improvement project at a single pediatric center covering a 7 state referral region. Transition readiness was assessed by electronically administering the Transition Readiness Assessment Questionnaire (TRAQ), a validated tool evaluating 4 key domains of readiness. All patients received written and verbal education to address deficit domains. Coaching sessions were also offered, reinforcing written information and occurring every 3 months via telephone. After 6 months, a follow-up TRAQ was administered. Paired t-test was employed to compare pre- to post-education scores, and repeated measures ANOVA was used to evaluate the effects of coaching sessions.

Results: Thirty-four patients enrolled in the program, with 15 patients being eligible for the 6-month follow-up TRAQ survey. Ten patients (67%) completed the follow-up survey, and 5 of them requested for coaching sessions. Both cohorts showed significant improvements in multiple domains (Figure 1). Coaching and education sessions did not show more significant improvement than education alone in transition readiness.

Conclusions: Our preliminary data suggest that education and coaching sessions may be an effective, feasible method for improving transition readiness from pediatric to adult CKD care. Additional research is needed to assess this intervention in a larger cohort and to see if this intervention will translate to improved clinical outcomes.

Figure 1: Changes in Transition Readiness after Education and/or Coaching Interventions



PUB347

Efficacy and Safety of Eculizumab in Enteroaggregative E. coli-Associated Partial Hemolytic Uremic Syndrome

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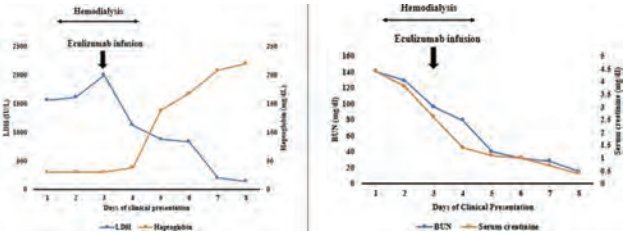
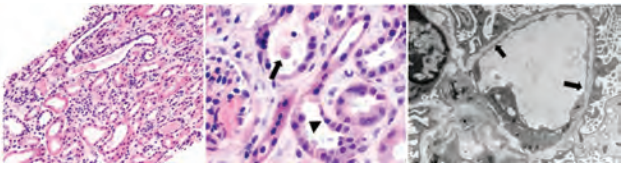
Introduction: Partial hemolytic uremic syndrome (HUS) presents atypically without the full triad of classical HUS. We report the utility of eculizumab in enteroaggregative *E.coli* (EAEC) associated partial HUS.

Case Description: A 2-year-old previously healthy female presented with vomiting. Evaluation showed an afebrile normotensive child with non-immune hemolytic anemia, oliguric acute kidney injury (AKI) but without thrombocytopenia and peripheral schistocytes. Bloody stools appeared later; stool examination for Shiga toxin (ST) was negative but positive for EAEC. Bone marrow examination showed no malignancy. Serum complements were normal but soluble complement 5b-9 was elevated. She required several sessions of hemodialysis (HD) and received one dosage of eculizumab with rapid reversal of AKI and hemolytic markers (Fig 1). Kidney biopsy revealed acute tubular injury (ATI) and segmental glomerular basement membrane splitting, with no glomerular or vascular thrombosis (Fig 2). No further dosages of eculizumab were required. Genetic testing was negative for complement mutations or deficiencies. A follow-up 4 weeks later showed persistent normalization of renal function and hematological markers, without any adverse effects.

Discussion: Efficacy of eculizumab in atypical HUS and in severe ST associated HUS has been described. We report its efficacy in EAEC associated partial HUS as well. Typical histologic manifestations of HUS may not be present in partial HUS as shown here. In one study of HUS patients, ATI was present in 70% and GBM duplication was present in 76% of those without peripheral schistocytes. This is an interesting novel finding which will need to be studied further.



Rapid normalization of hematological and renal parameters with eculizumab



Acute tubular injury with tubular dilatation and epithelial attenuation. Epithelial cell sloughing (arrow) and mitotic figure (arrowhead)

Glomerular capillary peripheral loop with GBM splitting (arrow)

PUB348

Assessment of Tryptophan Metabolism in Pediatric ESKD

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Background: End-stage kidney disease (ESKD) is associated with dysregulated tryptophan metabolism leads to systemic accumulation of toxic tryptophan metabolites derived from the indole and kynurenine pathways, which have been linked to systemic inflammation and an increased risk of thrombotic events and cardiovascular disease. Our study aimed to identify clinical variables that impact the plasma concentration of toxic tryptophan metabolites in children with ESKD on chronic hemodialysis (HD) and peritoneal dialysis (PD).

Methods: We designed a single-center cross-sectional study of children on chronic dialysis. Patients who received a kidney transplant between enrollment and sample collection were excluded. A total of 18 subjects had samples collected (HD n = 10; PD n = 8). Clinical characteristics are shown in Table 1. Serum specimens were collected at the time of routine monthly labs and were analyzed by liquid chromatography tandem mass spectrometry to measure tryptophan metabolites of the serotonin, indole, and kynurenine pathways. The association of target metabolites with demographic and clinical variables was determined t-test and Pearson correlation coefficients.

Results: Patients with residual renal function had a lower kynurenine: tryptophan (kyn:tryp) ratio (0.213 +/- 0.0553 vs 0.291 +/- 0.0564: t = - 2.885: p = 0.011). Serum serotonin level was positively correlated with the normalized protein catabolic rate (nPCR) ($r = 0.568$, $p = 0.0175$). However, there were no differences based on demographic variables, dialysis modality, or dialysis vintage.

Conclusions: Dialysis modality does not appear to influence tryptophan metabolism in children with ESKD. However, residual renal function is associated with a lower kyn:tryp ratio, which could reflect a reduction in systemic inflammation and immune dysregulation. The correlation between serum serotonin levels and nPCR suggests that nutrition status could influence serotonin-mediated pathways involved in neurocognitive outcomes. Larger prospective studies are needed to further evaluate the association of dysregulated tryptophan metabolism and clinical outcomes associated with pediatric kidney disease.

Patient Characteristics

	HD	PD
Total	10 (4M, 6F)	8 (6M, 2F)
Age (mo)	114 +/- 57	92 +/- 75
Vintage (mo)	18 +/- 9	21 +/- 16

PUB349

Audio/Podcasts and Art: A Collaboration Between the Renal Patient Support Group (RPSG) and the Kidney Disease and Renal Support Group (KDARs) for Kids and ZtormLabostix Productions

Shahid N. Muhammad. The Renal Patient Support Group (RPSG); The Kidney Disease and Renal Support Group (KDARs) for Kids; ZtormLabostix Productions. *Coventry University, Coventry, United Kingdom.*

Background: Chronic Kidney Disease (CKD) is 'recognized' as a silent, irreversible long-term condition (LTC), and tends to establish itself as a health complication and/ or co-morbidity. Service user access to educational support surrounding kidney care can be challenging between health sectors owing to clinical environments. **Aims:** To understand how Audio/ Podcasts and Art offer a collaborative basis for Service Users and Service Providers to align healthcare practices. **Objectives:** The Audio/ Podcasts and Art have

been focused between two leading educational social media platforms to help highlight pertinent aspects surrounding healthcare and disease.

Methods: The Audio/ Podcasts and art here focus on how healthcare professionals and service users could be working together through social media to improve experiences.

Results: Collaboratively, between the RPSG, KDARs and ZtormLabostix Productions, there is the useage of several social media platforms, including four (4) YouTube Channels and two (2) Sound Cloud Channels with over 600 audio/ podcasts, and educational webinars highlighting context supporting service users and service providers surrounding nephrology/ paediatric nephrology, clinical medicine, and biomedical science. Audio/ Podcasts and Art can prompt service user and service providers to join up healthcare.

Conclusions: The RPSG is supports over 10,000 service users amongst adult population and KDARs is supporting near 2,000 service users amongst a paediatric/ young people population. Audio/ Podcasts and Art can help incorporate practice excellence.

Audio/Podcasts through Art - ZtormLabostix Production

PUB350

The Impact of Pathological Findings of Mitochondrial Disorders in Low-Birth-Weight Infants

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Introduction: Preterm infants with a low birth weight (LBW) show reduced numbers of nephrons at birth and a higher risk of developing kidney dysfunction during their lifetime. They demonstrate oligonephronia and focal segmental glomerulosclerosis (FSGS) lesions in their glomeruli. We examined the association between mitochondrial disorders and the pathological characteristics of LBW-related nephropathy.

Case Description: Methods: We retrospectively evaluated the renal pathology in 6 infants including pairs of twins and 2 LBW infants demonstrating renal dysfunction. In addition to routine staining, the kidney biopsy specimens were analyzed using cytochrome c oxidase subunit IV (COX IV) and transcription factor A (TFAM) staining. Results: FSGS was diagnosed in 2 and oligonephronia in 4 infants. The mean density of glomeruli was 3.8/mm^2 (0.3–7.2) Granular swollen epithelial cells (GSECs), which have previously been reported exclusively in patients with mitochondrial cytopathy, were observed in the distal tubules and/or collecting ducts in all 6 infants. Electron microscopic examination revealed that these GSECs included an increased number of enlarged mitochondria. Furthermore, we observed unbalanced expression patterns of COX IV and low expression of TFAM in the glomeruli and a part of the tubular cells.

Discussion: FSGS, a characteristic feature of glomerular involvement in patients with mitochondrial cytopathy is very commonly observed in LBW infants. In our study, all infants did not show FSGS lesions because a renal biopsy was performed in the early stages of the disease in contrast to previous reports. However, most patients revealed similar pathological changes of mitochondrial cytopathy such as unbalanced expression of TFAM, which plays a role in maintaining the mitochondrial DNA. This finding suggests that these lesions could appear during early childhood, resulting in the development of FSGS in the future. Conclusions: These findings could suggest the application of a new approach targeting mitochondrial DNA to prevent the development of LBW-related nephropathy.

PUB351

Correlation of Serum Creatinine in Pregnant Mothers and Preterm Neonates

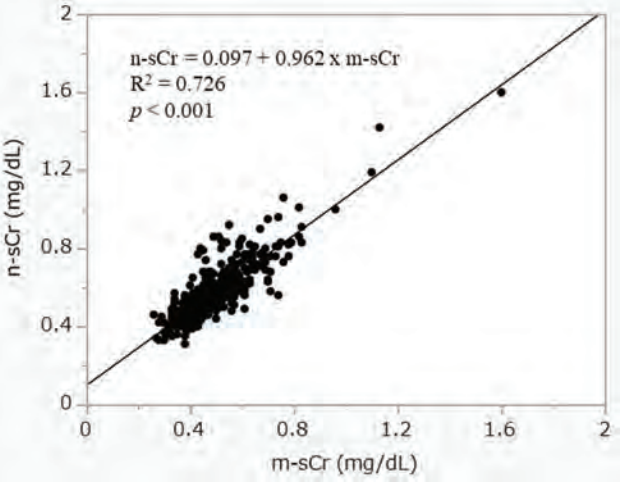
Wataru Shimabukuro,[1] Shogo Nakada,[2] Kohei Shimada,[2] Kazuya Hamada,[1,2] Hideki Goya,[1,3] Noriko Kinjo,[1,2] Tomohide Yoshida,[1,3] Keiko Mekaru,[3] Koichi Nakanishi.[1,2] *[1]Department of Child Health and Welfare (Pediatrics), Graduate School of Medicine, University of the Ryukyus, Nishihara, Japan; [2]Department of Pediatrics, University of the Ryukyus Hospital, Nishihara, Japan; [3]Maternity and Perinatal Care Center, University of the Ryukyus Hospital, Nishihara, Japan.*

Background: Neonatal serum creatinine (n-sCr) in the first few days of life have been reported to correlate with maternal serum Cr (m-sCr). To our knowledge, no regression equation was reported on the correlation between n-sCr after birth and m-sCr before delivery. The purpose of this study is to perform a simple linear regression analysis and to obtain a regression equation indicating the association between n-sCr within 24 hours after birth in preterm neonates and m-sCr within 7 days prior to delivery.

Methods: From March 2017 to October 2022, among 659 preterm neonates treated in the University of the Ryukyus Hospital, cases who died before discharge, cases with multiple births, chromosomal/genetic abnormalities, congenital anomalies of the kidney and urinary tract, severe heart disease, congenital diaphragmatic hernia, intrathoracic lymphangioma, cases whose mother were on dialysis, and cases in which n-sCr and m-sCr were not measured in pairs were excluded. A simple linear regression analysis of all 366 cases and three subgroups (gestational age [GA] ≦27 weeks [n=27], 28-31 weeks [n=60], ≧32 weeks [n=279]) was performed.

Results: In all cases, median (IQR) weeks of GA, birth weight, n-sCr, and m-sCr were 33.9 weeks (32.0-35.1 weeks), 1,901 g (1,575-2,260 g), 0.55 mg/dL (0.47-0.63 mg/dL) and 0.47 mg/dL (0.41-0.56 mg/dL), respectively. The regression equation for all cases and subgroups (GA ≦27, 28-31, ≧32 weeks) was n-sCr=0.097+0.962×m-sCr (R^2=0.726, p<0.0001), n-sCr=0.104+0.949×m-sCr (R^2=0.934, p<0.0001), n-sCr=0.098+0.930×m-sCr (R^2=0.835, p<0.0001), and n-sCr=0.094+0.975×m-sCr (R^2=0.647, p<0.0001), respectively.

Conclusions: This study showed that n-sCr=0.1+m-sCr approximately, regardless of the gestational age. n-sCr at birth in preterm infants reflect m-sCr and should not be used to determine the presence of kidney dysfunction in preterm neonates.



PUB352

Food Insecurity and Trends in Risk Factors for CKD in Adolescents

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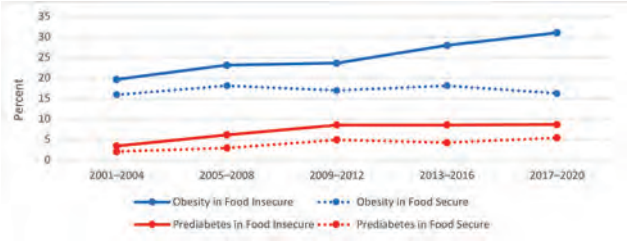
Background: The high prevalence of obesity and prediabetes in adolescents in the United States is a public health concern. We hypothesize that food insecurity may promote the burden of these conditions, which can increase chronic kidney disease (CKD) risk. We explored trends in obesity and prediabetes and how they may differ by food insecurity.

Methods: We included 10,013 adolescents (12–17 years) from the National Health and Nutrition Examination Survey (2001–March 2020). HbA1c of 5.7%–6.4% and/or a random glucose of 140–199 mg/dL defined prediabetes. Body mass index (BMI, kg/m^2) percentiles were calculated from BMI Z-scores corresponding to the participants' sex and age (in months) from the 2000 Centers for Disease Control and Prevention growth charts. A BMI percentile >95% defined obesity. Household food security classified as marginal, low, or very low were deemed food insecure. Analyses applied sample weights.

Results: The mean age was 14.5 (SEM=0.02) years, 51% were male, and 90% had health insurance. The sample included 58% Whites, 14% Blacks, 14% Mexican Americans, 8% non-Hispanic Others, and 7% Other Hispanics. Nearly 20% had obesity and 5% had prediabetes. During 2001–March 2020, the prevalence significantly rose for obesity (17%–22%) and prediabetes (2%–7%). Obesity and prediabetes prevalence were higher in food insecure adolescents (Figure). Among those, over 30% were obese and 9% were prediabetic in 2017–March 2020 (Figure).

Conclusions: Food insecurity may exacerbate rising trends of CKD risk factors like obesity and prediabetes in adolescents. Identifying food insecure adolescents may improve healthy food access and lower risk for CKD in adulthood.

Funding: Other U.S. Government Support



PUB353

Mexican Wolf Hunting! Epidemiological Report on Mexican Lupus Nephropathy in Pediatric Age

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Background: Childhood-onset systemic lupus erythematosus (cSLE) exhibits worse survival rates than its adult counterpart, primarily due to renal involvement. The epidemiology of renal involvement in cSLE is poorly understood in Latin America. Existing research primarily relies on studies involving both adults and children. In contrast, our study provides the unique epidemiological panorama of an exclusively pediatric center.

Methods: Retrospective, analytical, cross-sectional study. Patients diagnosed with cSLE in our center in the period 2000-2020 for men and 2010-2020 for women were included. No patient was excluded. The data on renal involvement correspond to the time of diagnosis.

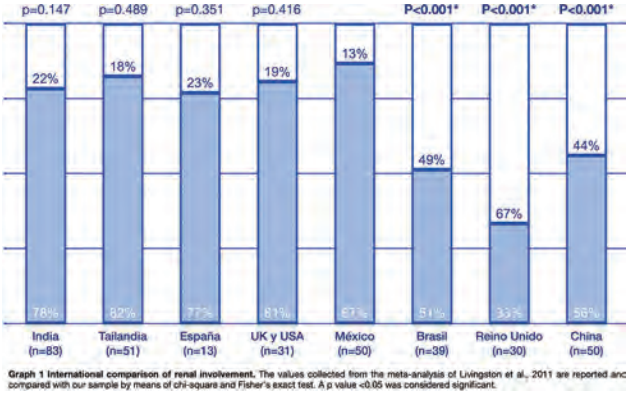
Results: Renal involvement occurred in 100% of men against 82.1% of the women (p=0.032). Only 60.9% of the men and 28.4% of the women underwent biopsy (p=0.005). Urinalysis reported a higher frequency of granular casts (p=0.019) and proteinuria (p=0.006) in men than women. Furthermore, estimated glomerular filtration rate was significantly lower in men (p=0.002). Finally, when comparing the frequency of renal involvement, no difference was found between our sample and countries with the highest renal involvement reported in pediatric literature.

Conclusions: cLSE in the Mexican population is, at the renal level, among the most aggressive reported in literature; with males being the most affected group. Despite the high frequency of renal involvement, biopsy was underutilized.

Funding: Government Support - Non-U.S.

	Male	Female	P*
Age			
Age (mean ± SD, years)	12.26 ± 2.1	12.63 ± 2.9	0.143
Renal involvement			
	100% (23/23)	82.1% (55/67)	**0.032***
Renal function			
EGFR✦ (mean ± SD)	64.1 ± 44.5	102.7 ± 51.4	**0.002***
Renal biopsy			
Biopsy	60.9% (14/23)	28.4% (19/67)	**0.005***
LN1	0	2.9% (2/67)	1
NL2	0	8.9% (6/67)	0.332
NL3	21.7% (5/23)	0	**0.001***
NL4	34.8% (8/23)	11.9% (8/67)	**0.024***
NL5	4.3% (1/23)	0	0.256
Crescentic	0	1.5% (1/67)	1
Others	0	2.9% (2/67)	1
Urinalysis			
Granular casts	65.2% (15/23)	34.4% (22/64)	**0.019***
Proteinuria	95.7% (22/23)	64.2% (43/64)	**0.006***

Table 1. Renal compromise. Quantitative variables were evaluated by means of the T-student test, while the qualitative ones with Chi-square test and Fisher's exact test; considering a 95% confidence interval. ✦ Estimated Glomerular Filtration Rate was calculated by Schwartz's formula.



Graph 1 International comparison of renal involvement. The values collected from the meta-analysis of Livingston et al., 2011 are reported and compared with our sample by means of chi-square and Fisher's exact test. A p value <0.05 was considered significant.

PUB354

Poor Sleep Efficiency and Shorter Sleep Duration Associated with Increased Blood Pressure in Pediatric Hemodialysis Patients

Jonathan S. Chawla,[1] Molly R. Vega,[2] Shweta S. Shah,[1] Kevin Kaplan,[1] Jessica Geer,[2] Cortney T. Zimmerman,[2] Ayse Akcan Arikan,[1] Sarah J. Swartz,[1] Leyat Tal,[1] Poyyapakkam Srivaths.[1] *[1]Baylor College of Medicine Department of Pediatrics, Houston, TX; [2]Texas Children's Hospital, Houston, TX.*

Background: Cardiovascular disease (CVD) is the leading cause of death in pediatric (ped) patients (pts) with end-stage kidney disease (ESKD). Hypertension (HTN) is an important modifiable risk factor for CVD in this population. Poor sleep is associated with HTN in adults and ped pts without other comorbidities. We previously used actigraphy (ATG) to demonstrate high prevalence of poor sleep efficiency (SE) and inadequate total sleep time (TST) in a cohort of ped hemodialysis (HD) pts. We hypothesize poor sleep per ATG will be associated with elevated BP in ped pts on HD.

Methods: In this prospective cohort study, pts 8-18 years on HD for > 3 months were asked to wear an ActiGraph™ accelerometer on non-dominant wrist for one week, logging sleep/wake times daily. Oscillometric BP obtained pre-, mid-, & post-HD and indexed to 95%ile. Pts considered hypertensive if pre-HD BP was >95% for age, sex, and height per published AAP standards. Central BP taken with SphygmoCor® EM3 and compared to published standards and cutoffs for age, sex, and height.

Results: 21 pts completed ATG. 62% male, mean age 15±2.9yr, mean HD vintage 1±1.1yr, mean BMI Z-score -0.63±1.4. All pts had three 240min HD sessions per week. 43% (n=9) met AAP definition of HTN per pre-HD oscillometric BP. Central BP was elevated in 48% (n=10). Pre-HD BP persistently correlated with shorter TST and lower SE by Pearson's R (see Table). Paired T-tests comparing pts with and without HTN by office BP showed that pts with HTN slept 1.65hr less than pts without HTN on nights following HD (p=0.035).

Conclusions: This is the first study assessing sleep quality and its association with HTN in ped HD pts, using actigraphy to provide objective measures of sleep quality and duration. The significant association of shorter TST and lower SE with higher BP represents actionable changes that can reduce CV mortality by improving sleep hygiene and identifying patients that warrant polysomnography to assess for obstructive sleep apnea.

		Index of office SBP by 95%ile		Index of DBP by office 95%ile	
Total sleep time (TST)	HD day	R = -0.31	p = 0.18	R = -0.25	p = 0.29
	Non HD day	R = -0.52	**p = 0.02***	R = -0.51	**p =0.02***
	Average	R = -0.50	**p = 0.02***	R = -0.40	p = 0.07
Sleep efficiency (SE)	HD day	R = -0.40	p = 0.08	R = -0.51	**p = 0.02***
	Non HD day	R = -0.38	p = 0.10	R = -0.32	p = 0.18
	Average	R = -0.44	**p = 0.04***	R = -0.48	**p = 0.03***

Table: Results of Pearson's R analyses, showing persistent correlation between higher BP and shorter sleep time and lower sleep efficiency.

PUB355

Etiologic Associations, Clinical Characteristics, and Histologic Findings of Children with Acute Interstitial Nephritis

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Background: To explore the etiologic factors of acute interstitial nephritis (AIN) in Chinese children confirmed by kidney biopsy, and its correlation with clinical and pathological manifestations.

Methods: The clinical and pathological manifestations of 21 children diagnosed with AIN in Peking University First Hospital from January 2012 to December 2022 were retrospectively analyzed. According to final diagnosis, the patients were divided into Tubulointerstitial nephritis and uveitis (TINU) group and non-TINU group. T-test, Mann-Whitney U test and Fisher's exact probability test were used for comparison between the groups.

Results: Twenty-one patients were included in this study, accounting for 1.6% of kidney biopsy patients during the same period. Ten cases (48%) were characterized as TINU, 2 cases (10%) were associated with Sjögren syndrome, 1 case (5%) was likely drug induced, and 1 case (5%) was sarcoidosis. The etiology for 7 cases (33%) remained unclear. Compared with the non-TINU group, the TINU group had a higher proportion of uveitis (P=0.024) at the same time with AIN,higher proportion of late-onset uveitis (P<0.05) diagnosed after the onset of the AIN, and a lower proportion of metabolic acidosis (P=0.024). There was no significant difference between the TINU group and the non-TINU group in other clinical manifestations, laboratory tests, and pathological findings. In the TINU group, three cases had preceding infection within 20 days before onset; four patients had received at least one antibiotic due to fever or respiratory tract infection symptoms before renal biopsy: one case received NSAIDs and one case received traditional Chinese medicines in concert with antibiotics.

Conclusions: The proportion of TINU in children with AIN in China is likely to be severely underestimated, given that the clinical manifestations, laboratory tests, and pathological findings of TINU in children are similar to those caused by other causes of AIN. Therefore, it is recommended that all pediatric AIN patients suspected to be related to medication, infections, or unclear etiology undergo a systematic eye examination and receive regular follow-up visits from ophthalmologists for at least one year.

Funding: Private Foundation Support

PUB356

Clinical Characteristics of Pediatric ANCA Vasculitis

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Background: Pediatric ANCA-associated glomerulonephritis (AAGN) is a rare diagnosis with limited data detailing the natural history or clinical characteristics that can be used for clinical prediction at the time of diagnosis.

Methods: Single-center retrospective cohort of pediatric patients diagnosed with ANCA vasculitis by kidney biopsy between 2002 – 2022. Patient characteristics were compared by Wilcoxon-rank sum and chi-squared for continuous and categorical variables, respectively. Survival analysis was done with Kaplan-Meier and Cox proportional hazards for a composite outcome of end-stage kidney disease or death.

Results: Seventeen patients (<20yr) were diagnosed with AAGN, accounting for 1.4% of all pediatric kidney biopsies performed during the study period. Median (IQR) age at diagnosis was 15 (12-17) years old with most patients diagnosed with pANCA disease, and a slight female preponderance. There was no statistically significant difference in the extra-renal symptoms at presentation between the cANCA and pANCA groups, however a trend towards more patients with pANCA presenting with fever. Seven of 17 patients (41%) reached the composite end-point at a median time of 7 yrs. Increased proteinuria and C4 complement level were associated with increased hazard of ESKD/death HR 2.29 (1.00 – 5.28) and HR 1.28 (1.06 – 1.53), respectively.

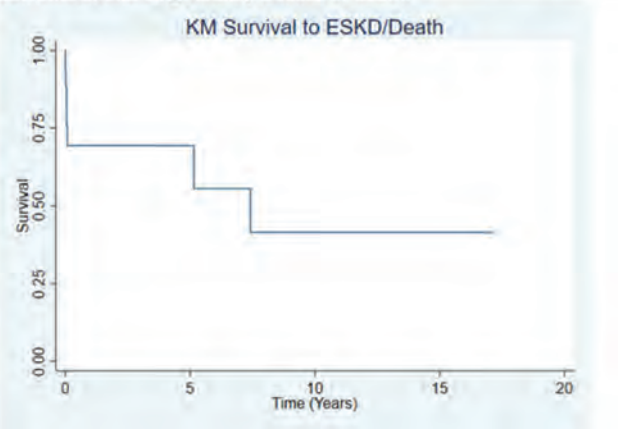
Conclusions: Pediatric AAGN is a rare diagnosis in pediatric patients presenting during adolescence and associated with significant morbidity. Proteinuria and higher C4 at diagnosis were associated with increased hazard of ESKD/Death. Role of C4 in this disease is unclear and warrants further exploration in a larger cohort.

Table 1: Clinical characteristics

Clinical Factor		Total	cANCA	pANCA	p-value
		N=17	n=6	n=11	
Age (Years)		15 (12,17)	16 (14, 20)	13 (7, 17)	0.17
Sex	Male	7 (41%)	3 (50%)	4 (36%)	0.64
	Female	10 (59%)	3 (50%)	7 (64%)	
C3 (mg/dL)		125 (118, 142)	125 (121, 134)	123.5 (118, 143)	0.71
C4 (mg/dL), mean (SD)		26 (21, 30)	22.8 (3.8)	28.3 (6.8)	0.12
PR3 (Arbitrary Units)		5.2 (0, 123.6)	151.65 (64.2, 605)	3.1 (0, 5.2)	0.002
MPO (Arbitrary Units)		23.5 (2.1, 100)	2.75 (0, 8.8)	69.5 (23.5, 100)	0.019
Serum Creatinine (mg/dL)		1.50 (0.8, 3.5)	1.10 (0.80, 2.20)	2.00 (0.70, 3.70)	0.55
UPC (mg/mg Cr)		1.87 (0.8, 4.08)	1.60 (0.49, 3.34)	1.87 (0.90, 5.05)	0.44

Values reported as median (IQ) unless otherwise specific.
Dgx – diagnosis, UPC – protein to creatinine ratio

Figure 1: Kaplan-Meier survival analysis for time to composite primary outcome of end-stage kidney disease or death.



PUB357

Obinutuzumab in Recurrent Focal Segmental Glomerulosclerosis After Pediatric Kidney Transplantation: A Case Report

Marina Vivarelli, Luca Antonucci, Francesca Semeraro, Manuela Colucci, Martina Riganati, Raffaella Labbadia, Andrea Cappoli, Francesco Emma, Isabella Guzzo. *Ospedale Pediatrico Bambino Gesu, Roma, Italy.*

Introduction: Recurrence of immuno-mediated forms of FSGS after kidney transplant occurs in about 30% of cases and is often associated with poor outcome. Currently, standardized therapeutic protocols are not available. Possible options are plasmapheresis, rituximab, cyclosporine, and immunoadsorption. We describe a pediatric FSGS recurrence treated with the 2nd generation humanized anti-CD20 antibody obinutuzumab.

Case Description: A 3 years-old child with multidrug-resistant FSGS underwent a related-donor kidney transplant. Twelve hours after anastomosis, he developed a severe anuric FSGS recurrence (Fig.1a), treated with high doses of steroids, cyclosporine, rituximab, and plasmapheresis, with poor response. About 3 weeks later, obinutuzumab was given as rescue therapy. One week after drug infusion, proteinuria became sub-nephrotic (48 mg/dL), and kidney function normalized (Fig.1a). After about 7 months on plasmapheresis and standard immunosuppression, proteinuria was absent with a subsequent reduction in plasmapheresis' frequency. A complete and lasting depletion of total CD19+ and memory CD19+CD27+ B cells was maintained for more than 12 months after obinutuzumab infusion (Fig.1b). About one year after transplant, plasmapheresis was discontinued. One month later, in parallel with B-cell reappearance, low-grade proteinuria reappeared (Fig.1a). Therefore, a second rituximab infusion associated with plasmapheresis was planned.

Discussion: To our knowledge, this is the first case of pediatric post-transplant FSGS recurrence treated with obinutuzumab, which determined remission and long-lasting B-cell depletion. Further clinical trials are needed to establish the real efficacy of this approach.

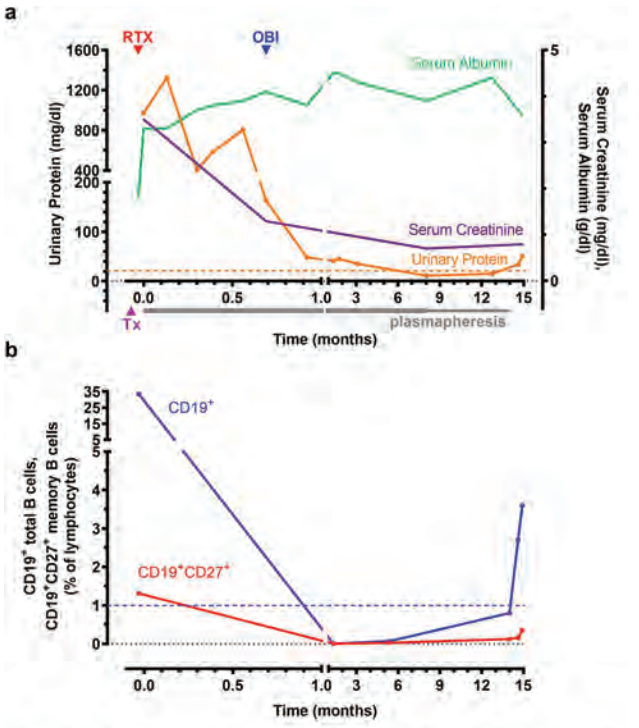


Figure 1. a) Clinical course of patient after kidney transplantation; dashed line represents the normal range of proteinuria. **b)** Multicolor flow cytometry analysis of circulating total CD19+ B cells and memory CD19+CD27+ B cells; dashed line represents the cut-off of CD19+ B cell recovery. RTX, rituximab; OBI, oobinumumab; Tx, transplantation.

PUB358

Ravulizumab De Novo in Pediatric Patients with Atypical Hemolytic Uremic Syndrome (aHUS): First Worldwide Cases

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Introduction: Ravulizumab is a long-acting C5 inhibitor that has recently demonstrated its effectiveness for the control of hemolytic uremic syndrome compared to eculizumab, allowing average annual infusion times (up to 70 percent less). There is still no evidence in the literature of naive treatment with this drug in pediatrics. Our objective is to present the first two pediatric cases worldwide using de novo Ravulizumab (in the onset of the disease and post-kidney transplant).

Case Description: 13-year-old girl with history of bloody stools, vomiting and compromise of consciousness with TMA, AKI III evolves to anuria and convulsive episode requiring corticosteroid boluses, 6 plasmapheresis sessions and 4 intermittent hemodialysis. Normal ADAMTS- 13, negative direct Coombs and decreased complement. Due to persistent TMA and requirement of renal replacement therapy (RRT), ravulizumab was started with a loading dose (2400mg) and a second one after 2 weeks. The need for RRT ceased with improvement of hemolysis and renal function. Genetic:CFHR3-CFHR1 deletion. Case 2:7-year-old girl in chronic hemodialysis secondary to aHUS (CD46 mutation) was admitted for kidney transplant from a living donor. Low-intermediate immunological risk and high CMV infectious risk. Induction treatment: Basiliximab, tacrolimus, mycophenolate and steroids. First dose of Ravulizumab was infused the day before transplantation (900mg), well tolerated. The patient has had a favorable evolution of renal function with normal creatinine value at discharge. Protein/Creatinine urine ratio increased to a maximum of 8mg/mg (negative DSA levels). The option of renal biopsy was discarted due to a decrease in proteinuria. She received second dose after 2 weeks, remain stable with no data on recurrence of her underlying disease today.

Discussion: Ravulizumab was satisfactory both in the acute phase of the disease and in the immediate post-transplantation. In the first case we observed a functional recovery from the first dose with no notable adverse effects up today, as in post-transplant patient, maintaining a good control of TMA despite more spaced dosing (8 weeks). The inclusion of this drug in the therapeutic arsenal opens a new safe treatment route in pediatric patients with aHUS.

PUB359

Tolerance and Pathologic Tonsillar Findings Change in Intractable Immunoglobulin A Vasculitis (IgAV) with Nephritis in Two Child Cases

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Introduction: Background Several studies have reported that regulatory T (Treg) cells are critical for maintaining tolerance in immunoglobulin A nephropathy (IgAN). We herein report the tolerance changes and the pathologic tonsillar features in 2 cases (a 12-year-old girl; ISKDC grade IVa and a 14-year-old girl; grade IIIb) with intractable IgAV nephritis who underwent tonsillectomy for disease control. Serum CD4-positive and CD25-positive cells, and Foxp3 levels were detected. In addition, immunohistochemical staining for tonsillar CD4, CD8, HLA-DR, and cytokeratin was performed.

Case Description: Outcomes Additional tonsillectomy decreased proteinuria and they achieved partial clinical remission after this treatment. Serum CD4-positive and CD25-positive cells were elevated in one case, but Foxp3 levels showed no apparent change in the two cases. T-cell nodules were enlarged by infiltration of HLA-DR-positive cells. Histopathological findings of tonsils showed infiltration with both CD4-positive and CD8-positive cells was prominent in interfollicular areas. Cytokeratin staining showed that the layer of crypt epithelium was replaced by squamous epithelium.

Discussion: Take-away lesson The efficacy of tonsillectomy for IgAN is thought to be due to the regulation of tolerance abnormalities. Replacement from the layer of crypt epithelium implies the involution of lymphoepithelial symbiosis. The distribution of CD4 and CD8 is characteristic in the tonsils of those with IgAN. These pathologic findings in IgAV nephritis patients suggest the existence of a similar tolerance abnormality in the tonsils of those with IgAV nephritis. Our results may help to clarify intolerance in IgAV nephritis, although further studies are necessary to clarify the clinical efficacy of tonsillectomy for IgAV nephritis patients.

PUB360

A Boy with Henoch-Schönlein Purpura Nephritis and Mutations in CD151

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Introduction: Glucocorticoid (GC) and immunosuppressants (IS) have been found to be effective on treating Henoch-Schönlein purpura nephritis (HSPN). The children with HSPN may be with genetic defect when they don't respond to GC and IS. Here we report a boy with HSPN, who didn't respond to GC and IS, carried mutations in the *CD151* gene.

Case Description: A 15-year-old boy with no family history of kidney disease was admitted for evaluation of recurrent proteinuria in 2022. He initially presented with abdominal pain and purpuric rash on his bilateral lower legs in 2014, and developed recurrent proteinuria. His first renal biopsy tissues in 2018 revealed HSPN with mesangial deposits of IgA together with IgM by immunofluorescence technique. However, his proteinuria was negative to 3+ for many years although he used mycophenolate mofetil and prednisone. The second renal biopsy was performed in 2022, and the renal tissues revealed focal segmental glomerulosclerosis (FSGS) with no evidence of immunocomplex deposition. A homozygous mutation in the *CD151* gene, c.606C>A, p.Y202*, 52, was identified using whole-exome sequencing in the boy, and the same heterozygous mutation was in his parents. Then, the boy was treated with a combination of benazepril and losartan, and his proteinuria reduced to 1+ - 2+.

Discussion: The boy with HSPN, based on his abdominal pain, purpuric rash on his bilateral lower legs, proteinuria and first renal pathology, didn't respond to mycophenolate mofetil and prednisone, so we performed the second renal biopsy. The second renal pathology revealed FSGS with no evidence of immunocomplex deposition, which is inconsistent with HSPN, therefore we suspected the boy may be with genetic defect. A homozygous missense mutation in the *CD151* gene identified in the boy confirmed our hypothesis. CD151 encoded by the *CD151* gene is implicated in the integrity of basement membranes in kidney, skin and inner ear. Mutations in the *CD151* gene can cause isolated proteinuria and FSGS as well. The patients with mutations in *CD151* and nephrotic syndrome have no reponse to GC and IS, which could explain that the boy had persistent proteinuria for many years with treatment with both mycophenolate mofetil and prednisone. In conclusion, the children with HSPN is necessary to detect genetic defect when they don't respond to GC and IS.

PUB361

Implementing a Structured Transition from Pediatric to Adult Care Can Impact Clinical Outcomes in Young Adult Kidney Transplant Recipients

Brian Coburn, Clarkson Crane, Elizabeth G. Ingulli. *Rady Children's Hospital San Diego, San Diego, CA.*

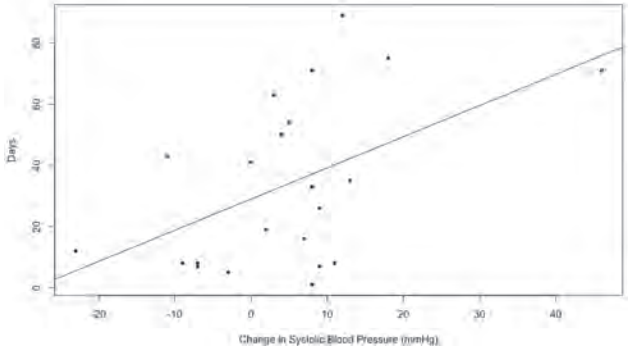
Background: The transition period between pediatric and adult care is a challenging time marked with high risk and vulnerability, and is described as the period with the highest rate of graft loss in young adult kidney transplant recipients. Data are limited regarding HCT outcomes, but some studies suggest improvements in patient outcomes with a structured transition protocol.

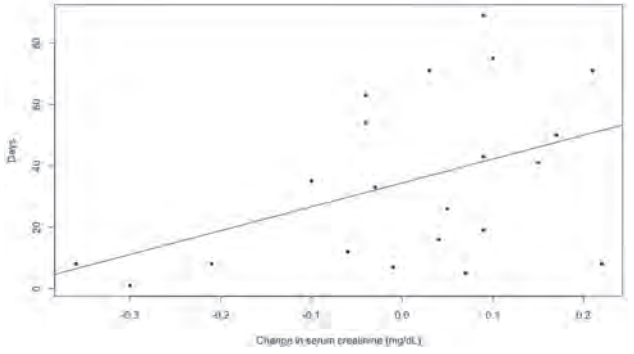
Methods: A retrospective chart review of patients who transitioned from Rady Children's Hospital San Diego (RCHSD) to UC San Diego (UCSD) transplant clinic from the years 2020-2023 is being performed to examine metrics such as change in creatinine

and blood pressure during this period of transition. We will look at outcomes following the implementation of our transitions program which includes strutted transition-specific visits to assess and address individual areas of need before they transition.

Results: Our initial study population consists of 24 patients, 50% female. The data show a weak positive correlation between days from last RCHSD clinic visit and first UCSD clinic visit and blood pressure elevation that is not statistically significant (rho=0.393, p=0.071). The data show a weak positive correlation with an increase in the number of days between last RCHSD clinic visit and first UCSD visit and increasing creatinine which is not statistically significant (rho=0.399, p=0.073).

Conclusions: Further research will be conducted to determine if an established kidney transplant transitions program can decrease gaps in care and improve outcomes in young adult patients with a kidney transplant.





PUB362

Horseshoe Kidney with Childhood Recurrent Urinary Tract Infection: A Harbinger of CKD Progression and Opportunity for Interventions

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Introduction: Congenital anomalies of the kidney and urinary tract (CAKUT) constitute the most common malformations diagnosed prenatally and account for most chronic kidney disease (CKD) in children. We report a case of a woman with childhood recurrent urinary tract infections (UTIs) who was incidentally diagnosed with a horseshoe kidney in adulthood complicated by advanced CKD.

Case Description: A 62-year-old woman with non-nephrotic range proteinuric stage 4 CKD secondary to CAKUT was referred for kidney transplant evaluation. From age 6 months to 12 years old, she experienced recurrent UTIs and persistent borderline elevated blood pressure yet was never seen by a pediatric nephrologist. At age 52, she was found to have abnormal kidney function during a pre-operative laboratory procedure, and an abdominal and pelvic MRI showed an atrophic right kidney, bilateral nephrolithiasis, bilateral renal cysts, and a horseshoe kidney (Figure 1). While the frequency of UTIs decreased, with the most recent episode of UTI 5 years prior, her eGFR had progressively declined from 24 to 16 ml/min/1.73 m^2 over a 5-year period.

Discussion: Although one-third of patients with horseshoe kidneys are asymptomatic and are incidentally diagnosed in adulthood, our patient presented with kidney complications early in life that necessitated further investigation by her pediatrician and transfer to adult care. Pediatricians play a vital role in the early diagnosis and management of CAKUT and need to recognize the prodromal signs, including low birth weight, recurrent UTIs, and hypertension. Recurrent UTIs during childhood should prompt a search for CAKUT and early therapy to prevent CKD and improve patient health outcomes. Moreover, patients with CAKUT can benefit from a continuum of care by a multidisciplinary team.

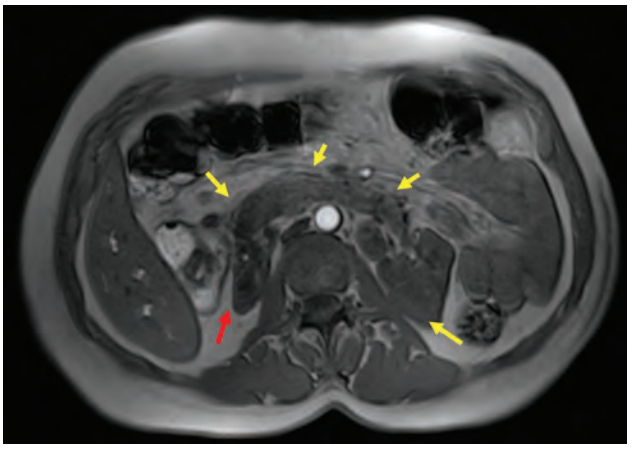


Figure 1. Axial MRI without contrast showing a horseshoe kidney (yellow arrows) with atrophy of the right kidney (red arrow).

PUB363

AKI with COVID-19 Infection due to Drug Interaction of Tacrolimus and Nirmatrelvir/Ritonavir

Eun jeong Ko, Chul Woo Yang. *The Catholic University of Korea, Seoul, Republic of Korea.*

Background: The mortality of SARS-CoV-2 infection of kidney transplant recipients(KTR) is higher than that of general population. Nirmatrelvir(NR) is a good option for outpatient-based antiviral treatment by reducing mortality.

Methods: However, NR is metabolized mainly by cytochrome 3A4(CYP3A4), which also metabolize calcineurin inhibitor(CNI). Hence, t co-administration of these two drug could results in drug interaction increasing serum tacrolimus(TAC) level almost 50 times. We report serial three cases of KTR prescribed NR with/without AKI.

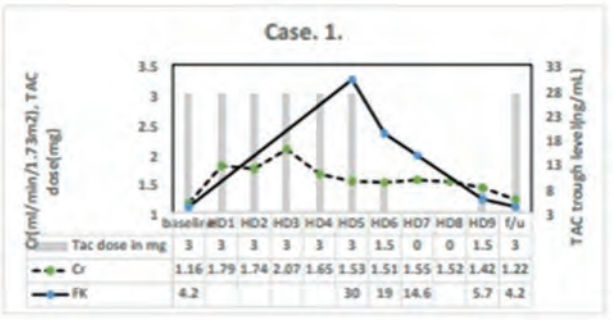
Results: In case 1, the patient took these two drug together, inducing acute kidney injury(AKI) due to CNI toxicity. After discontinuation of TAC, renal function was recovered. Contrastively, in case 2, three days of simultaneous administration of NR and TAC led to AK, progressed even though discontinuation of TAC. Intravenous hydration with cessation of TAC improved renal function. In case 3, patient was informed to stop TAC for 5 days with NR initiation, resulting harmless to renal function with stables serum TAC concentration after NR taking.

Conclusions: Instruction for patient for drug interaction of TAC with NR is important for KTR.

Baseline Characteristics

Case No.	1	2	3
Age	54	55	75
Gender	Male	Male	Female
Post-transplant years	7	0.75	1.66
Primary renal disease	Diabetes mellitus	Diabetes mellitus	Unknown
Tacrolimus dose (mg/day)	1.5mg bid	1.5mg bid	1.5mg bid
Steroid dose	None	Prandin 12mg qd	Prandin 6mg qd
Baseline serum creatinine (mg/dl)	1.16	1.24	0.69
Baseline tacrolimus trough level	4.2	8.8	5.7

(A)



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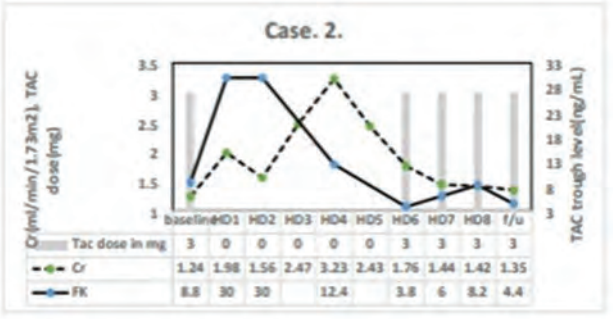

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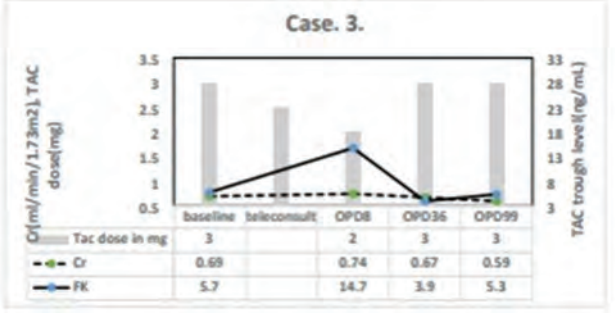


PUB364

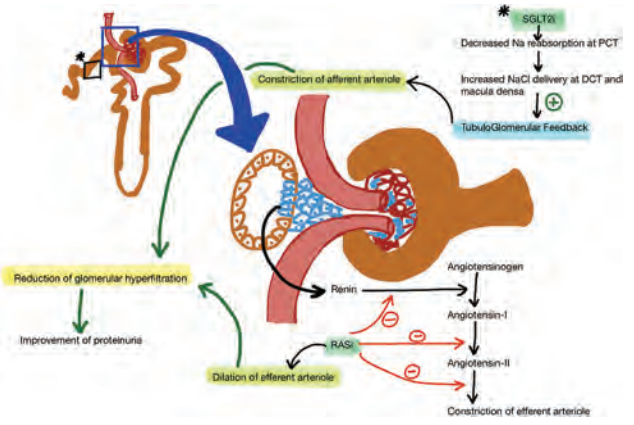
SGLT2 Inhibitors in Membranous Nephropathy: Worthy of Consideration?

Sehajpreet Kaur, Sulekho Egal, Iktej S. Jabbal, Fernando M. Abanilla.
AdventHealth Sebring, Sebring, FL.

Introduction: SGLT2i have encouraging evidence supporting their benefits beyond diabetic kidney disease, as seen in DAPA-CKD and EMPA-KIDNEY trials as well as case reports on IgA nephropathy and Alport syndrome. We describe the early results of SGLT2i therapy in 2 patients with membranous nephropathy (MN), which, we believe, has not yet been reported in the literature.

Case Description: A 67-year-old type 2 diabetic female with CKD stage 3b, PLA2R negative MN, sepsis, and AKI, developed increasing proteinuria (baseline 1.6 to 3.2 g/g UACR) despite irbesartan therapy. The addition of 10 mg empagliflozin daily improved UACR to 3.1 from 3.2 g/g over 5 days of hospitalization. A 68-year-old non-diabetic male who presented with scrotal edema, chronic bilateral leg swelling, and massive proteinuria of 8.8 g/g UPCR was diagnosed with nephrotic syndrome with PLA2R negative MN on renal biopsy. Increasing UPCR to 12.5 g/g prompted the addition of 10 mg empagliflozin daily after optimisation of lisinopril to 40 mg daily. However, 2 months of follow-up resulted in worsening of proteinuria to 15.8 g/g. For both patients, proteinuria serological workup was negative with workup for malignancy pending.

Discussion: As illustrated in Image 1, SGLT2i can synergize with RASi to improve proteinuria, which warrants their exploration in MN. While patient 1 had significant improvement in renal function over 5 days of treatment but empagliflozin could not be continued due to clinical inertia, patient 2 improved clinically but had an early negative response to proteinuria despite 2 months of dual therapy with empagliflozin and lisinopril. An underlying unidentified malignancy or other causes of secondary MN could be attributable. Our case series was limited by small sample size, medication non-adherence, and absence of long-term follow-up. Nonetheless, this calls for the medical community's attention to explore the use of SGLT2i in MN and other proteinuric non-DKD using prospective, randomized controlled trials.



PUB365

Baclofen Toxicity in Patients with ESRD on Hemodialysis (HD)

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University of Florida College of Medicine - Jacksonville, Jacksonville, FL.

Introduction: Baclofen, a commonly prescribed muscle relaxant is a GABA agonist with potential toxicity in patients with CKD.

Case Description: We report three cases of potential Baclofen toxicity in patients with ESRD on HD. The 1st case was a 68-year-old female with PMH of DM, HTN & ESRD on HD, presented with a fall associated with altered mental status (AMS) & inability to move both right extremities, a GCS of 6 & intubated. Home medications included Carvedilol, Doxazosin, Gabapentin (300 mg BID), Hydralazine, Baclofen (5 mg TDS) & Nifedipine. Brain CT without acute abnormality but MRI revealed a small 3 mm left parieto-occipital lobe subdural hematoma with no mass effect or intercurrent hemorrhage with no plan for intervention. The 2nd case was a 50-year-old male with PMH of HTN, CVA, Paroxysmal A Fib & ESRD on HD, presented with AMS, GCS of 15 & no intracranial abnormality. Home medications included Amlodipine, Baclofen (10 mg BID), Carvedilol, Losartan & Sevelamer. Another case of a 66-year-old male with PMH of HIV, HTN, ESRD on HD, transverse myelitis with lower extremity weakness, presented with AMS. Initial workup was negative. Clinical status later improved. However, a week later he became disoriented & unable to follow commands after he was started on baclofen 10 mg bid for muscle spasms. Workup was inconclusive. All of the above cases had no other potential causes for AMS including infection or any signs of uremic encephalopathy other than use of Gabapentin by one of the patients. In the first two cases, patients had missed a couple of dialysis (HD) sessions. Baclofen toxicity was suspected in all cases, exacerbated by missed HD treatments in two cases. There was marked improvement of mentation soon after resumption of HD.

Discussion: Baclofen is a lipophilic compound which is primarily absorbed in the GI & largely excreted by the kidneys. Baclofen toxicity is rare in the general population. It manifest rapidly in patients with impaired renal function who receive this medication. AMS is one of the major manifestations of toxicity, developing with as little as a single dose. However, due to small molecular weight, low volume of distribution & relatively low protein binding, Baclofen is easily dialyzable. Although no medical inhibitor of Baclofen toxicity is available, hemodialysis was effective in treating this condition here, and is the preferred therapeutic modality.

PUB366

Suspecting and Treating Toxic Alcohol Ingestion: A Case of Incorrect Management of Ethylene Glycol Poisoning in the Community Healthcare Setting

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Introduction: Poisonings by the toxic alcohols (methanol, ethylene glycol) can present with nonspecific symptoms but delays in treatment increase the risk of irreversible organ damage and death. Measurement of serum concentrations of the toxic alcohols would be ideal for establishing a diagnosis and monitoring treatment, but obtaining these serum concentrations in a timely fashion is not feasible in the community hospital where this patient presented. Consequently, treatment with the antidote must be given expediently if only suspicion is high.

Case Description: A 37 year old female with an vague psychiatric history presented to the ED with acute respiratory failure and altered mental status. The patient was somnolent and her mental status deteriorating. Presenting labs were significant for leukocytosis with left shift, high anion gap metabolic acidosis w AG of 64, hypocalcemia, hyperkalemia, high serum osmolal gap of 12, high serum osmolality of 305, benign urinalysis, and UDS positive for cocaine. Toxic alcohol levels were ordered but would not return for several

days due to the lab's lack of liquid/gas chromatography. Nephrology was consulted and recommended early emergent intermittent hemodialysis in the setting of severe acidemia, hyperkalemia, and AKI. Fomepizole was never given.

Discussion: A high anion gap metabolic acidosis of unknown cause, acute kidney injury, and an increased serum osmolal gap established a high suspicion for toxic alcohol ingestion early in this patient. Nephrology appropriately initiated intermittent hemodialysis urgently, however the administration of fomepizole was deferred pending a definitive diagnosis via serum concentration of toxic alcohols using high pressure liquid chromatography. This result was not available to providers for several days as is often the case in small community hospitals. Delays in treating toxic alcohol poisonings lead to worse outcomes, therefore therapy with the antidote should be initiated rapidly when unexplained high anion gap metabolic acidosis with high osmolal gap is present, as was the case with this patient. To improve treatment outcomes there should be a standard treatment algorithm agreed upon by each hospital as to when fomepizole should be administered without a definitive diagnosis.

PUB367

Prevalence, Clinical Profile and Risk Factors of Cefepime Induced Neurotoxicity among Chronic Kidney Disease Patients in a Tertiary Hospital in Southern Philippines

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Background: Cefepime induced neurotoxicity is a clinically diagnosed adverse event that presents in vast array of neurologic symptoms, from mild cognitive and behavioural changes to seizure and coma. Although a highly recognized clinical adverse event the diagnosis and standard clinical criteria is still lacking. We aimed to characterize the clinical profile and possible associated risk factors of cefepime induced neurotoxicity among Filipino chronic kidney disease patients.

Methods: This is a retrospective, case control study of adult chronic kidney disease patients treated with Cefepime in a tertiary hospital in Southern Philippines from January 2020 to June 2022. Patients who were treated with cefepime with new onset neurologic deteriotion were included while those with baseline neurologic abnormality or alternative cause for neurologic symptoms as ruled out by additional diagnostic tests were excluded. The Naranjo scale was utilized to establish the likelihood of causality.

Results: A total of 263 medical charts were reviewed but only 132 cases were included. Majority of patients were on hemodialysis (126), six of whom developed neurotoxicity. The overall prevalence of cefepime induced neurotoxicity is 4.5%, with higher prevalence rate at 10% among patients given non renally adjusted dose. The median age of patients with CIN was 54 ± 14, predominantly females (5 vs 1). Half of the cohort presented with agitation while the other 50% had decreased level of consciousness. The appearance of symptoms has a latency period of 5 days following initiation of therapy. Five (5) patients responded to hemodialysis and discontinuation of cefepime, while one (1) patient responded to appropriate dose adjustment. Resolution of symptoms was observed 2 days after providing therapy. All patients (6) recovered without neurologic deficit. Binary regression analysis identified female gender (OR 9.65) and congestive heart failure (OR 12.1) increased the likelihood of cefepime neurotoxicity.

Conclusions: Overall prevalence of cefepime induced neurotoxicity is comparable to preceding studies, with higher prevalence rate among patients who were given non-renally adjusted dose. Possible additional risk factors for CIN were female gender and heart failure.

PUB368

Higher Intragraft Granzyme-B+ and PhosphoSMAD-3+ Cell Staining Are Associated with Inflammatory Interstitial Fibrosis and Tubular Atrophy in Renal Allograft Recipients

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Background: Inflammatory **I**nterstitial fibrosis and tubular atrophy (i-IF/TA), a histological lesion reported in late biopsy, is associated with graft survival. Cytotoxic T cell secrets Granzyme-B, cleaves cytoskeleton protein, and activates pro-IL-1β, and TGF-β into their active form, leading to inflammation, fibrosis, and apoptosis of cells. Association of Granzyme-B+ cytotoxic T cell and phospho-SMAD-3 expression has been not studied in i-IF/TA in depth. We studied the circulating and intragraft Granzyme-B+ cytotoxic T cell and fibrosis pathway mediator p-SMAD-3+ cell in renal transplant patients with biopsy proven i-IFTA.

Methods: The circulating frequency of CD3+CD8+Granzyme-B+ cytotoxic T (CTLc) was measured by the flowcytometry; serum and PBMCs culture supernatants Granzyme-B and cytokines TGF-β, IL-1β level by the ELISA, Intragraft Granzyme-B mRNA transcript expression by the RT-PCR and Granzyme-B$^+$, pSMAD-3$^+$ cell were analyzed by immunohistochemistry. Independent T-test for continuous variables and Pearson correlation were applied for different variables.

Results: The circulating frequency of cytotoxic-T cell ($CD3^+CD8^+$Granzyme-B^+) in SGF vs i-IF/TA was (27.96±4.86 vs 23.19±3.85%, p=0.011), $CD3^+$T cell was (66.08±6.8 vs 65.18±9.35%; p=0.68), $CD3^+CD8^+$T cell was (37.29±4.11 vs 34.68±5.43%; p=0.28). Serum Granzyme-B level was in SGF vs IF/TA was (100.82±22.41 vs 130.32±46.60, p=0.038 pg/ml), serum TGF-β level was (367.50±31.50 vs 318.81±48.39, p=0.005), IL-1β level was (49.14±17.03 vs 63.69±23.13, p=0.076). Intragraft Granzyme-B mRNA expression in SGF vs i-IF/TA was (1.01±0.048 vs 2.10±1.02-fold, p<0.001). Granzyme-B^+ cell/mm^2 count was (0.40±0.69 vs 2.20±1.27; p=0.001). Intragraft phosphorylated SMAD-3$^+$ cell was (3.70±1.82 vs 6.73±3.21; p=0.008). The intragraft Granzyme-B+ cell was positively correlated with pSMAD-3+ cell (r=0.315, p=0.047). The frequency of circulating CTLc was negatively correlated with urine proteinuria (r= -0.51, p<0.001), serum creatinine (r= -0.28, P=0.007) and eGFR (r= -0.28, p=0.037). While urine proteinuria was positively correlated with serum Granzyme-B level (r= 0.343, p=0.001), intragraft Granzyme-B mRNA transcript expression (r= 0.38, p<0.001).

Conclusions: Higher intragraft Granzyme-B^+ Cytotoxic T-cell and phosphoSMAD-3 positive cells are associated with i-IF/TA in RTRs.

PUB369

Identification of APOL1 with Probe-Independent Polymerase Chain Reaction (PCR) Method

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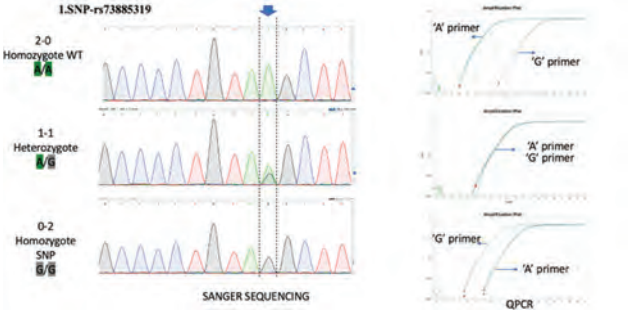
Background: Circulating APOL1 in plasma can kill the Trypanosoma brucei which causes sleeping sickness found in sub-Saharan Africa. 2 coding sequence variants G1/G2 in APOL1 actually provide more resistance against a subtype. These variants are specifically presented in African-American population group and found to be associated with increased risk of chronic kidney disease. In this study, we determine a method to identify risk variants using prob-independent qPCR approach in transplant patients with high African-American population group. Additionally we want to explore available haplotypes for all variants with respect to transplant outcome.

Methods: We used PBMNC samples from patients and perfusate samples from donor to isolate DNA. Perfusate samples during transportation of organ from donor to recipient patient and blood samples of recipients were collected. DNA is isolated using SDS lysis buffer and proteinase K. After DNA isolation, constructed primers were used to amplify APOL1 gene segment including SRA domain (which is including the possible regions of G1/G2). Sanger sequencing were used as control to detect any SNPs and deletions of APOL1 risk variants. Special constructed primers were used to quantify either SNP mutations or wild type and deletion or wild type.

Results: 97 % of our donors do not have APOL1 risk alleles, however we have very high percentage (27% 2 Risk Allele, 33% 1 Risk Allele) of APOL1 variants in patients. We have limited numbers to compare all risk allele haplotypes. With new kidney transplant patients, we may estimate haplotypes effect on long term outcomes. In short term period, there is not much significant differences compared the groups.

Conclusions: Our technique allows clinicians and researchers in the field to be able to identify ApoL1 genotyping with QPCR in 3-4 hours. Retrospective studies might allow to compare these findings with long term allograft rejection and can create an estimation for patients for early-late stage transplant outcomes with haplotype evaluation.



PUB370

Unveiling a Protective Role of Endomucin in Endothelial Cells During Kidney Allograft Rejection

Ahmad Halawi,[1,2] Connor J. O'Brien,[1] Tamara Merhej,[1] Nour K. Younis,[1] Rania El Fekih,[1] Sacha A. De Serres,[3] Jamil R. Azzi.[1] *[1]Brigham and Women's Hospital, Boston, MA; [2]Mount Auburn Hospital, Cambridge, MA; [3]Universite Laval, Quebec, QC, Canada.*

Background: Understanding the role of endothelial cells in autoimmune and alloimmune mediated kidney diseases promises to develop more targeted therapies. Our single nuclei RNA sequencing (snRNA seq) identified an unexpected role for endothelial cells in cellular rejection. Notably, we reported a novel role of endomucin (EMCN), a molecule known for its anti-adhesive and anti-inflammatory properties, in kidney allograft rejection.

Methods: We performed snRNA seq of human kidney allografts with non-rejection, borderline rejection, and T-cell mediated rejection (TCMR) based on Banff criteria. We performed pathway analysis focusing on immune and endothelial cells. As validation for our endothelial cells findings, we isolated and cultured blood outgrowth endothelial cells (BOECs) from different patients using our optimized protocol (S Beland et al., JASN 2023). We stimulated BOECs with INFg, TNFa, and allogeneic PBMCs. We studied the expression of EMCN and ICAM1 over time under different stimulation using Flow cytometry.

Results: Our snRNA seq showed that TCMR samples had enrichment for allograft rejection pathway, suggesting that our borderline sample reflects an early rejection. Hence, this allows for studying the early stages of rejection. Pathway analysis of endothelial cells (ECs) of borderline and non-rejecting samples showed that focal adhesion and IFN-gamma pathways were significantly enriched compared to TCMR. Major genes related

to focal adhesion were upregulated in borderline, suggesting a role of focal adhesion as a physical obstacle to immune migration. ECs upregulated EMCN in early rejection, suggesting a critical role in protecting against T cell adhesion and infiltration in the allograft. EMCN was then downregulated when rejection advanced. Similarly, in our in vitro model, activated human ECs downregulated the constitutive expression of EMCN when stimulated with allogeneic PBMCs, contrary to ICAM1, which was significantly upregulated. This observation was not seen when ECs were stimulated by IFNg and TNFa, suggesting that the effect of immune cells on ECs is not mediated by these cytokines.

Conclusions: Our data showed that late during rejection, focal adhesion and EMCN are downregulated in endothelial cells suggesting a possible role in protecting the graft from immune invasion and rejection.

PUB371

Variability in Commensal Gut Microbiota Associated with Tacrolimus Metabolism in a Longitudinal Kidney Transplant Cohort Study

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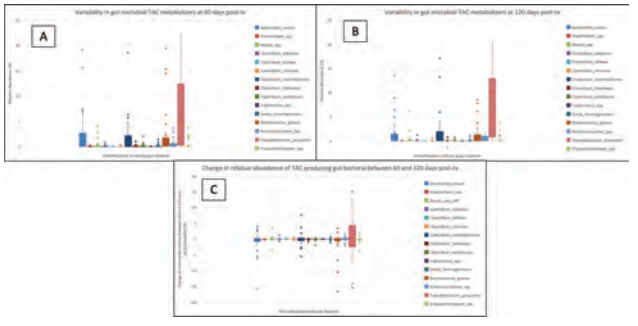
Background: Tacrolimus (TAC), an immunosuppressant used with mycophenolate mofetil (MMF), has a narrow therapeutic range which is associated with outcomes in kidney transplant recipients (KTRs). Evidence of an association with the gut microbiome and TAC metabolism is emerging. Multiple commensal gut bacteria, including *Faecalibacterium prausnitzii*, have been shown to metabolize TAC to a less potent metabolite through keto-reductase activity. We hypothesized that the gut microbiome of KTRs would exhibit high variability in TAC metabolizers.

Methods: We evaluated the relative abundance of 22 known gut microbial TAC metabolizers in a cohort of 40 KTRs who had stool samples collected at 60 and 120 days post-transplant (tx). All KTRs received oral MMF and TAC twice daily. Microbiota were characterized by sequencing the V4 variable region of the 16S rRNA gene.

Results: We detected 15 out of 22 previously reported tacrolimus metabolizers among the gut microbiota, with the most abundant being *Faecalibacterium prausnitzii* at 7.54% average relative abundance at 60 days post-tx (range 0.06% - 22.15%) (FIG 1A) and 7.95% (range 0.02 – 20.45%) at 120 days post-tx (FIG 1B). We did not find a statistically significant change in relative abundance of these organisms between 60 and 120 days post-transplant (Fig 1C, P> 0.05 for all microbiota). Overall, these 15 TAC metabolizing microbiota accounted for 15.6% (range 0.1 – 41.1%) of the total gut microbiome composition at 60 days, and 14.1% (range 0.2 – 37.6%) at 120 days.

Conclusions: The gut microbial composition of TAC metabolizers exhibits high variability post-tx, with *Faecalibacterium prausnitzii* as a predominant member. The association between the abundance of these organisms and TAC interpatient variability should be studied to understand the unexplained variation in TAC concentrations among KTRs.

Funding: NIDDK Support



PUB372

Donor LIMS1/GCC2 Region Is an Important Determinant of Allograft Kidney Response to Ischemia and Reperfusion

Yasar Caliskan, Kento Kurashima, Meghan M. Unes, Edward L. Portz, Kana N. Miyata, David S. Brink, Bahar Bastani, John C. Edwards, Krista L. Lentine, Ajay Jain, Mustafa Nazzal. *Saint Louis University, Saint Louis, MO.*

Background: *LIMS1* rs893403-G influences LIMS1 and GCC2 expression and associated with kidney allograft rejection. Using non-utilized human kidneys, we investigated the effects of ischemia reperfusion injury (IRI) on LIMS1, GCC2 and associated gene expressions by normothermic machine perfusion (NMP) model and compared with cold storage (CS).

Methods: Non-utilized deceased donor kidney pairs underwent 6-hr NMP (n=6) and CS (n=6). Perfusion, biochemical, and histologic parameters were recorded. NMP was compared with CS in paired donor kidneys using simulated transplantation with allogeneic red blood cells, followed by assessment of the gene expression. Genotyping for rs893403 variant performed by Sanger sequencing.

Results: Kidneys were successfully perfused with evidence of urine output (Table 1). Transcriptomic analyses showed induction of GCC2, HIF-1α and KIM-1 expression in kidneys with rs893403-GG genotype compared to kidneys with rs893403 AG/AA (rejection risk donor genotype) under NMP (p=0.017, p<0.001 and p=0.17, respectively) (Fig.1a-b). Change in GCC2 expression after 6 hrs of NMP was significantly correlated with change in LIMS1 (r=0.94, p=0.005), KIM1 (r=0.83, p=0.04), TGF-β (r=0.89, p=0.019) and HIF-1α (r=0.943, p=0.005) expressions. Change in GCC2 expression during NMP was not correlated with donor characteristics including age, KDPI, Remuzzi score, cold ischemia time and urine output.

Conclusions: NMP significantly increased the GCC2 expression in kidneys with *LIMS1* rs893403-GG variant. Donor rs893403 genotype is important in the transcriptomic response to IRI and understanding the interaction between LIMS1, GCC2 and HIF-1α will help to develop genotype and pathway specific therapies for rejection.

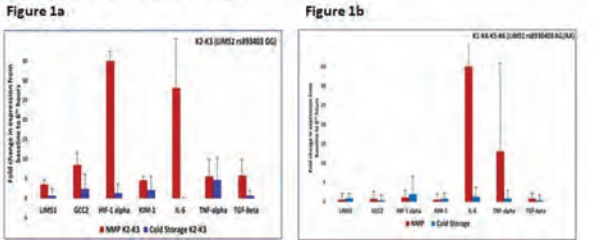
Funding: Private Foundation Support

Table 1. Characteristics of ischemic nonutilized donor kidneys

	K1 CS	K1 NMP	K2 CS	K2 NMP	K3 CS	K3 NMP	K4 CS	K4 NMP	K5 CS	K5 NMP	K6 CS	K6 NMP
LIMS1 rs893403	AG	AG	GG	GG	GG	GG	AG	AG	AA	AA	AG	AG
Donor type	DCD	DCD	DCD	DCD	SCD	SCD	DCD	DCD	SCD	SCD	DCD	DCD
Age	58	58	59	59	70	70	14	14	57	57	56	56
Sex	F	F	F	F	F	F	F	F	F	F	F	F
KDPI (%)	88	88	88	88	100	100	CRRT	CRRT	69	69	74	74
Previous HMP	+	+	+	+	-	-	+	+	-	-	+	+
CIT (hours)	42	42	32	32	17	17	39	39	51	51	31	31
Urine output (mL/hour)	0	58	0	108	0	75	0	3	0	4	0	17

Abbreviations: CIT: cold ischemia time, CS: Cold storage, CRRT: continuous renal replacement treatment, DCD: donation after circulatory death, HMP: Hypothermic machine perfusion, KDPI: kidney donor profile index, NMP, Normothermic machine perfusion, RRVs: renal risk variants, SCD: standard criteria donor

Figure 1a and 1b. Histogram of RT-PCR results based on *LIMS* rs893403 genotype showing the differences in relative gene expression profile on baseline and at 6 hours of normothermic machine perfusion (NMP) vs cold storage.



PUB373

Cognitive Improvement in ESRD Patients After Renal Transplantation: A Prospective Observational Study

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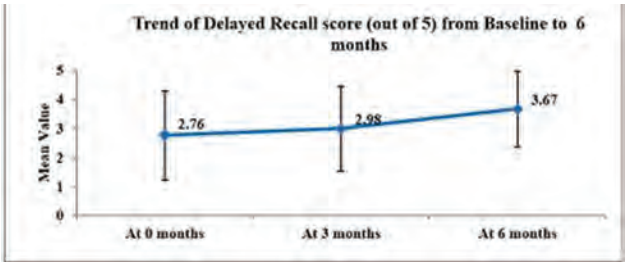
Background: Although there is a well-established survival benefit of renal transplant, the evidence of its effect on cognitive function is limited and not entirely consistent. Up to 30 - 70 % of end stage renal disease patients are reported to have cognitive deficits. The etiology of cognitive impairment in chronic kidney disease patients is multifactorial. Kidney transplantation can correct the metabolic derangements and eliminate the fluid and osmotic shifts that patients can experience on dialysis; however, cognitive impairments still persist post-transplant. Further research is warranted to better understand the impact of kidney transplant on a wide array of cognitive domains.

Methods: 100 patients, age between 18 to 60 years who underwent renal transplantation in Medanta Hospital, India were prospectively studied from September, 2021 to December 2022. The aim was to determine the proportion of patients showing cognitive improvement 3 months and 6 months post renal transplant using Montreal Cognitive Assessment (MoCA) and to find the cognitive domains which show significant improvement 3 months and 6 months post transplant.

Results: Proportion of patients showing cognitive improvement 3 months and 6 months post transplant was 26% and 56%, respectively. The mean MoCA score (out of total of 30) at pre transplant, at 3 months and 6 months post-transplant was 24.08 ± 3.08, 24.32 ± 2.90 and 25.28 ± 3.05, respectively. Mean MoCA score after 6 months of transplant, when compared to the mean score at pre transplant level was found to be statistically significant (p value <0.001). Delayed recall showed significant improvement 3 months and 6 months post-transplant (p value- 0.016 and < 0.001 respectively).

Conclusions: Significant cognitive improvement was seen 6 months post renal transplant. Delayed recall showed significant improvement 3 months and 6 months post transplant.

Montreal Cognitive assessment (MoCA) score		Mean Difference	Std. Error	p value	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
At 0 months	At 3 months	-0.24	0.105	0.071	-0.495	0.015
	At 6 months	-1.200	0.303	**<.001**	-1.938	-0.462
At 3 months	At 6 months	-.960	0.272	**0.002**	-1.622	-0.298



PUB374

LECT2 Amyloidosis in Allografts

Jonnathan O. Cázares Lara, Orlando E. Falcón-Antonio, Maria J. Ballesteros Alfaro, Enrique A. Alamo Capula, Eduardo Carrillo Maravilla. *Instituto Nacional de Ciencias Medicas y Nutricion Salvador Zubiran, Ciudad de Mexico, Mexico.*

Introduction: LECT2 deposits are subclinical. The risk of transplanting an allograft with this condition is not zero.

Case Description: In 2011, a 26-year-old male was found with a serum (Cr) of 1.6 and a protein in the urine of 2.37 g/day. The histopatology reported glomerulonephritis IgA. Years later, patients brother was ruled out as a donator due to proteinuria, and the cross-match test was performed with the patients father. In 2022, he underwent kidney transplant but two months later due to proteinuria, a renal graft biopsy was performed that showed mild LECT2 FIAT amyloidosis.

Discussion: LECT-2 is a chemotactic factor for neutrophils. It is involved in cell proliferation, inflammation, immunomodulation, and carcinogenesis. Its gene is located in a chromosome that harbors a cluster of genes involved in immune regulation. LECT-2 is produced in the liver and increases in response to proinflammatory stimuli such as hepatic steatosis. ALECT2 can be found in association with other types of amyloidosis, plasma cell dyscrasia, membranous nephropathy, carcinomas, or autoimmune disease. Amyloidosis restricted to the kidney is uncommon. The 88%%–92% of cases reported are in Hispanics. The median age is 69 years old, and men and women are equally affected. The proteinuria could be not present in 21%, nephrotic range proteinuria was noted in only 33%, and when it is present, you need to consider concomitant nephropathy (as IgA nephropathy), and end-stage renal disease ranges from approximately 30% to 40%. In our patient, the time for a novo or recurrent amyloidosis is too short. The Hispanic background in the father and the proteinuria in his brother, lean us towards a case of familiar donor-derived ALECT2. It has been reported that ALECT2 does not interfere with the allograft function.

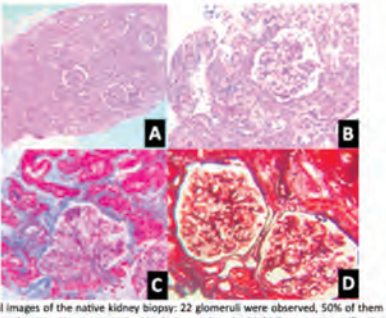


Figure 1- Histopathological images of the native kidney biopsy: 22 glomeruli were observed, 50% of them with global sclerosis and 8.7% with segmentary sclerosis, since panoramic view in image A and with high power magnification (B) as well as slight mesangial expansion and proliferation (D). In the interstice it was characterized a moderate fibrosis state (calculated as 30%) but it was not observed any deposition of material out of collagen with Masson's trichrome stain (C).

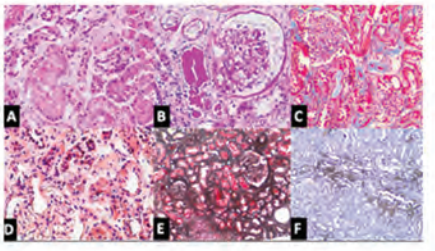


Figure 2.- Histopathological images of transplanted kidney: a rarefactive, well-defined globular deposition was observed since the initial H&E stain (A) evaluation with low power magnification lens (x 100); the rest of routine histochemical stains, remarked the presence of this material, but mostly with PAS (B) and Masson trichromic stain (C), present within the glomerular basement membrane, mesangium, intertitium and arteriolar walls. With the amyloid specific stain, Congo red (D), it highlights the presence giving a brick red aspect, nonetheless the polarized light microscope showed negative birefringence. The characterization of the deposition material with immunohistochemistry analysis for LECT2 amyloid (Abcam, OTI2A11) resulted positive (E).

PUB375

Risks and Harms of Minimizing Total Immunosuppression in Stable Kidney Transplant Recipients

Bruno Watschinger, Bernhard Gromann, Peter Hlavac, Robin Ristl, Bettina Kroyer, Katharina Hohenstein-Scheibenecker. *Medizinische Universitat Wien, Wien, Austria.*

Background: While minimizing steroids or calcineurin inhibitors was advocated to be advantageous for kidney transplant outcomes, the effect of total cumulative immunosuppression on patient /allograft survival has not yet been evaluated. In our retrospective single center study, we investigated the long-term impact of cumulative immunosuppression exposure in a large cohort of patients with stable graft function.

Methods: 887 stable patients (s-creatinine <2 mg/dl @ 1 yr and stable GFR slope in the preceding 3 months, transplanted from 1/2000 to 12/2012 and followed exclusively at our institution; median follow-up 6, 3 (1-15,3) yrs were studied. Graft function and immunosuppressive (IS) therapy were recorded at 84.140 patient visits. Individual drug exposure was calculated by grading each drug (no=0, low=1, medium=2, high dose=3) and then adding single drug grades (in mono, dual, triple therapies) to a cumulative score that represents a low (0-3), intermediate (4-6) or high (7-9) total IS exposure load. This load, calculated over time, was used in adjusted Cox-regression models with time-dependent covariates, together with Kaplan-Meier survival analysis. Patient/allograft survival was compared between the 3 exposure groups.

Results: 84 of these stable patients (9.5%) lost their graft during the observation period, 89 patients (10%) died with a functioning graft. In single drug analysis, variant exposure levels of steroids or calcineurin inhibitors did not show differences in graft and patient survival. Conversely, cumulative exposure was associated with differentiated outcomes. An intermediate total IS load yielded the best graft survival, while patients with low (HR = 4.68; CI 1.6-13.9, p=0.005) or high (HR = 2.08; CI 1.2-3.6, p=0.008) cumulative IS exposure had a significantly elevated risk for graft failure. Patient survival did not differ between the groups.

Conclusions: Analyzing the effects of single drugs does not capture the risk for graft loss in patients with stable allograft function @ 1 yr. High and low cumulative total immunosuppression exposures are independent risk factors for graft failure but do not impact patient survival. Thus, the degree of total, cumulative immunosuppression should be carefully considered, whenever individual immunosuppressants are minimized.

PUB376

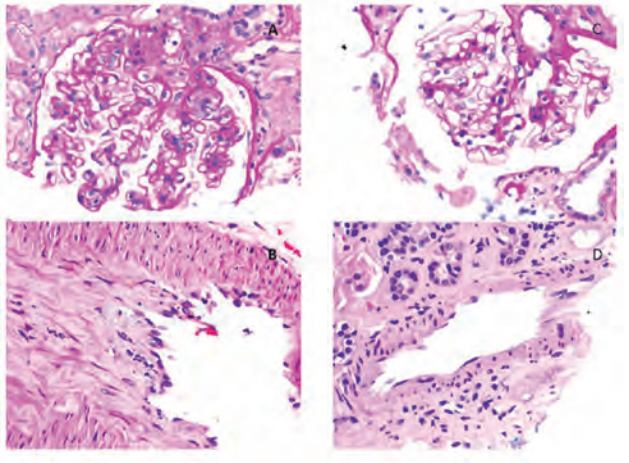
Successful Treatment of Kidney Transplant Rejection in the Setting of COVID-19 Infection

Mohammad Atari,[1] Michael B. Kuperman,[2] Prathap Simhadri,[3] Bushra Syed,[1] Sanjana Kapoor,[1] Pradeep Vaitla.[1] *[1]The University of Mississippi Medical Center, Jackson, MS; [2]Arkana Laboratories, Little Rock, AR; [3]AdventHealth Daytona Beach, Daytona Beach, FL.*

Introduction: Kidney transplant recipients are at increased risk for complications from COVID-19 infection. There are no guidelines for rejection treatment in the setting of COVID-19 infection.

Case Description: A 44-year-old male with a history of living donor kidney transplant underwent a kidney biopsy due to rising creatinine that showed features suspicious for chronic active antibody-mediated rejection and acute vascular rejection 2A, with De novo class II DSAs emergence. The patient tested positive for COVID-19 and was asymptomatic with normal CXR. Cycle threshold was 21 indicating high viral replication, nucleocapsid antibodies were negative, but he had a suitable spike antibodies titer. Rejection was treated with pulse steroids, IVIg, and immunosuppression optimization. COVID-19 was treated with three doses of remdesivir. Two weeks later, the patient was treated with thymoglobulin, PLEX, and rituximab. Follow-up biopsy showed no rejection, and creatinine improved.

Discussion: Kidney transplant rejection with active COVID-19 infection is challenging and requires an individualized approach. Rejection treatment may lead to clinical deterioration, but untreated rejection may lead to graft failure. COVID-19 infection severity can be assessed by symptoms, chest images, cycle threshold to assess viral replication, anti-nucleocapsid antibodies as a marker for natural immunity against COVID-19, and spike antibodies as a response to vaccination. Dexamethasone is used in severe COVID-19 infection, rejection treatment with a reduced dose pulse steroids, IVIg, and PLEX, with remdesivir to prevent the progression of COVID-19 infection, seems to be relatively safe. If the patient remains stable, more intense rejection therapies can be commenced two weeks after COVID-19 diagnosis.



A. PAS x400: 1st biopsy image showing glomerulitis in the peripheral capillary loops

B. H&E x600: 1st biopsy showing lymphocytes undermining an activated endothelial cell layer (v1)

C. PAS x400: 2nd biopsy showing a normal glomerulus with no glomerulitis

D. H&E x400: 2nd biopsy showing a normal artery with no endothelialitis

PUB377

Recurrent Atypical Hemolytic Syndrome (AHUS) Manifested by Atypical Postinfectious Glomerulonephritis

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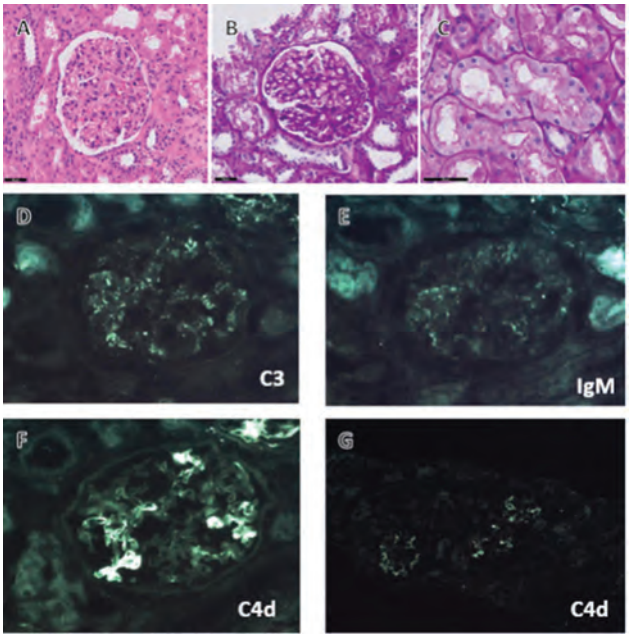
Introduction: Atypical hemolytic uremic syndrome(aHUS) is a rare disorder of the complement pathway, Results of kidney transplantation(KT) in patients with genetic predisposition to aHUS bring about recurrent disease.

Case Description: A 45-aged male kidney transplant recipient was admitted for rapid deterioration of graft function after 1 month from KT. Serum creatinine raised from 1.43 mg/dl to 2.72mg/dl within 2 weeks. Furthermore, anemia(serum Hb 6.8g/dl), thrombocytopenia(platelet 72 x 109 /L), elevation of LDH(458mg/dl), decrease of haptoglobin(<10mg/dl), and microangiopathic hemolytic anemia(MAHA) were also found, suggesting TMA. He has kept on deflazacort, tacrolimus, and mycophenolate mofetil, so firstly tacrolimus was switched to rapamune, still no improvement. Shiga toxin was negative and ADAMTS13 activity was negative. Even though plasmapheresis for 7 times, no clinical response were seen. Graft biopsy pathology reported as postinfectious glomerulitisnephritis, inconsistent with clinical feature. on revewing his chart retrospectively, he had malignant hypertension with severely decreased renal function (serum Cr 23.35mg/dl), anemia (Hb 5.7g/dl), elevated LDL (304mg/dl), and decreased complement 3(56mg/dl), 9 years ago, his first visit to clinic. Also, native kidney biopsy revealed TMA, still we missed futher evaluation. Afterall, we performed genetic study for aHUS, next generation sequence(NGS) revealed heterozygous mutation for complement factor I(CFI)(c.119A>C), pathogenic for aHUS, confiremd recurrent aHUS after KT.

Discussion: Clarifying primary renal disease of transplant candidate is crucial, especially screening for genetic study for aHUS.



Microscopy and immunofluorescence of kidney biopsy in case patient

PUB378

Should We Treat Asymptomatic Bacteriuria (ASB) in Post-Transplant Patients: A Systematic Review and Meta-Analysis

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Background: Urinary tract infections (UTIs) are the most common infectious complication in kidney transplant recipients (KTRs). Therefore, routine screening for and treatment of asymptomatic bacteriuria (ASB) is a common practice in post-kidney-transplant surveillance. However, little is known about the impact of antimicrobial therapy on ASB in KTRs. Some data reports overtreatment of ASB increases the risk of Clostridioides difficile infection in this population. This study aimed to investigate whether antibiotics reduce the risk of UTI in KTR with ASB.

Methods: We searched MEDLINE, EMBASE and Cochrane Library from inception to March 2023. Included studies were RCTs or cohort studies that compared the incidence of UTI among treated ASB group versus untreated ASB group, using the random-effects to calculate risk ratios (RR) and 95% confidence intervals (CIs). Secondary outcomes included rate of graft rejection, hospitalization and mortality.

Results: Five RCTs and 6 cohort studies were included in the analysis with a total of 1750 subjects (699 treated ASB group and 1051 untreated ASB group). Our study showed that there was no statistically significant difference in incidence of UTI between the ASB group with treatment and ASB group without treatment (pooled RR 1.07, 95% CI 0.77-1.48, p=0.682, I2=16.9%). Secondary outcome analysis revealed none of the outcomes were significantly different between these two groups including acute graft rejection rate (pooled RR 0.79, 95% CI 0.43-1.48, p=0.464, I2=0.0%), hospitalization rate (pooled RR 1.34, 95% CI 0.99-1.81, p=0.061, I2=23.8%), and all-cause mortality (pooled RR 1.20, 95% CI 0.96-1.51, p=0.110, I2=0.0%).

Conclusions: There is no difference of incidence of UTI, acute graft rejection rate, hospitalization rate, and all-cause mortality rate among treated ASB group versus untreated ASB group in kidney transplant recipient patients.

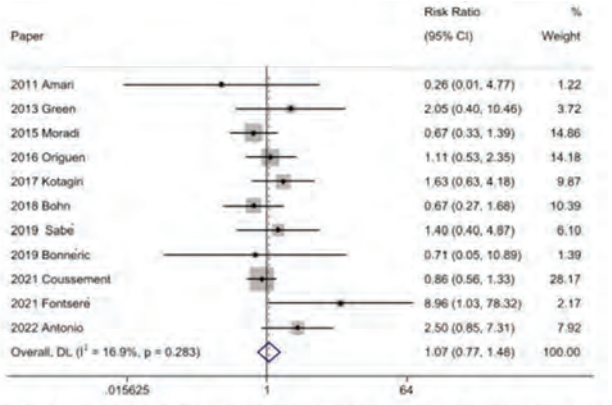

Figure 1: Forest plot of the included studies comparing the incidence of UTI among treated ASB group versus untreated ASB group (p = 0.682)

PUB379

Successful Treatment of Ganciclovir-Resistant Cytomegalovirus (CMV) in Kidney Transplant Patients by Reduction of Immunosuppression and Withdrawal of Valganciclovir

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Introduction: Cytomegalovirus (CMV) is a common opportunistic infection after kidney transplant, causing increased morbidity, mortality and graft loss. Resolution of infection requires both antiviral drugs and the host immune response. Ganciclovir (GCV) and Valganciclovir (VGCV) are currently 1st-line treatment, though GCV-resistant (GCV-R) CMV is increasingly reported. Treatment of GCV-R CMV infection involves use of the 2nd-line agents Cidofovir, Foscarnet or Maribavir. We propose a therapeutic strategy combining withdrawal of GCV with reduction in immunosuppression in refractory CMV replication.

Case Description: We describe 3 patients who underwent kidney transplantation from CMV-positive deceased donors. One seronegative recipient received VGCV prophylaxis. All developed CMV syndrome at a mean 40 days post-transplant. One patient developed chronic inflammatory demyelinating polyneuropathy, requiring intravenous immunoglobulin. In all cases mycophenolate mofetil was withdrawn and eGFR-adjusted doses of GCV or VGCV commenced. A persistent/increasing viral load following > 4 weeks treatment led to resistance testing. A *UL97* mutation was identified in all cases, one patient also demonstrating a *UL54* mutation. GCV-R was diagnosed at a mean 160 days post-transplant. Given persistent viremia despite prolonged, adequate dose treatment, we decided to withdraw VGCV and monitor CMV viral load. By a mean of 60 days following VGCV withdrawal we could show a 50% reduction in viral load with no detectable GCV-R virus and ultimately a complete and sustained virological clearance in all patients.

Discussion: We demonstrate that in patients treated for CMV but with persistent GCV-R viremia without evidence of invasive CMV disease, VGCV withdrawal may be a therapeutic strategy, rather than commencement of problematic second-line drugs. GCV resistance is an adaptive process, we propose that discontinuing GCV significantly reduces selection pressure for *UL97* mutants. As resistance mutations are often not maintained in the population after drug cessation, we believe this allows immune clearance of the CMV, perhaps aided by the improved white cell count on withdrawal of VGCV, as seen with our 3 cases. This approach potentially promotes re-population with 'wild type' GCV-sensitive strain which may respond to subsequent challenge with GCV.

PUB380

Tacrolimus-Induced Post-Transplant (pT) Thrombotic Microangiopathy (TMA)

Emad A. Odeh. *Al-Bashir Hospital, Amman, Jordan.*

Introduction: TMA is a well-recognized complication that may occur at any time pT. It has a significant impact on graft and patient survival. TMA may result from the recurrence of the original disease. Or denovo. Patient presentation with pT-TMA varies from localized form affect the graft and diagnosed only by biopsy, to systemic form, consist of hemolysis, thrombocytopenia and kidney injury. Here we present a case of TAC induce pT-TMA which was treated by changing tacrolimus(TAC) to cyclosporin(CsA) with plasma exchange(PLEX).

Case Description: A 33 year-old male known to have HTN, ESKD on regular hemodialysis for 9-months, before receiving living-related kidney transplant from his mother. Pre-transplant preparation yielded HLA matching of 50%. Negative lymphocytotoxicity by CDC. Induction with basiliximab (2 doses), pulse steroid, extended-release TAC(0.2mg/kg/day) and mycophenolate mofetile (MMF)720mg*2. The early pT period went smoothly without delay in graft function. On the 4th pT day platelate count(PLT) dropped to 135000 with stable hemoglobin(hb), creatinine(Cr), and blood film(BF) showed NO schistocytes. The MMF dose decreased to 360mg*2, after which the PLT normalized and the patient was discharged with a Cr of 1.2mg/dl on:TAC-trough level of 17ng/ml. MMF360mg*2 and prednisone. After 2 weeks:the patient suffered from hand tremor, TAC-level:15. Stable Cr, hb and PLT. The TAC dose was decreased, 1 week later the tremor increased despite the TAC level being 10. Further investigation: Cr-2, a drop in hb, PLT(122000), and 30% schistocytes on-BF. The patient was afebrile, urinalysis was normal, negative CMV and BKV. The diagnosis of TMA was made, plan for kidney biopsy and to change TAC to CsA. Later PLT dropped to80000 and Cr became 2.2. Given this situation we considered not to wait biopsy, and plasma exchange was started. After 5 PLEX sessions, the PLT became230000, Cr-1.3, and BF showed less than 4%schistocytes. The biopsy showed borderline cellular rejection. Negative c4d. No glomerulitis, PTC, and no thrombi. 9 months later the patient doing well with Cr of 1.3.

Discussion: The take-home messages are: TMA can occur any time pT.CNI may induce TMA while drug level within therapeutic range. The absence of thrombi in a kidney biopsy sample doesn't exclude renal TMA, so if you've enough data to diagnose TMA, dont't waste time and start treatment immediately. Removal of TAC may not be enough in some cases of TAC-induce TMA, and the addition of PLEX may required.

PUB381

Evaluation of Indications for Genetic Assessment in Living Kidney Transplant Donors and Relevant Canadian Practices in Light of the Current International Guidelines

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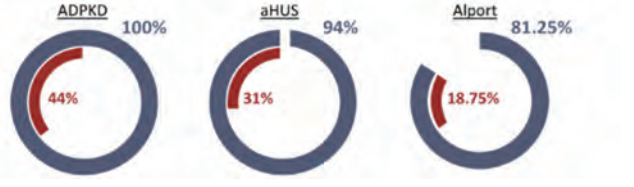
Background: End stage renal disease (ESRD) is a prevalent condition with tendency for familial clustering. Living kidney donor transplantation is a superior treatment option, however, up to 40% of living kidney transplant donors (LKTDs) are biologically related to their recipients which subjects recipients to worse graft survival and donors to higher future risk of ESRD. Genetic testing of potential LKTDs could improve risk assessment and inform safety of donation, however, the strategies to evaluate these donors are still evolving. In this context, the standard use of genetic testing for LKTDs in Canada is unknown.

Methods: International guidelines were reviewed to compare the indications for genetic assessment of LKTDs. Surveys were sent to 25 Canadian adult transplant centers to examine their protocols and relevant practices for LKTDs genetic assessment.

Results: Response rate was 70%. Generally, donor's family history of chronic kidney disease does not preclude donation after informed discussion regarding risks and benefits. Autosomal Dominant Polycystic Kidney Disease, Alport syndrome and atypical Hemolytic Uremic Syndrome are the most frequently encountered conditions. Based on our case scenario questions, most centers assess LKTDs on a case-by-case basis and a minoroity have specific policies for donor genetic evaluation. The current Canadian transplant centers practices generally align with available international guidelines' recommendations. The most cited guidelines are KDIGO, CSN/CST, and Kidney Paired Donation Protocol.

Conclusions: Canadian transplant centers have diverse strategies for genetic evaluation of LKTDs, mostly based on case-by-case assessment. Current recommendations are largely based on expert opinion due to lack of a reliable body of evidence and inefficiency of the current testing modalities. More studies are needed to provide stronger, evidence-based recommendations to ensure safety of donation. Prognostic risk assessment scores could be helpful for better quantification of long term effects of abnormal genetic testing.

Fig 1: Percentage of the most commonly encountered genetic conditions in the Canadian transplant centers [Blue] versus percentage of center having donor evaluation protocols for the same conditions [Red].



PUB382

Impact of Deceased-Donor Characteristics: Outcomes of Donor Kidney Pairs Accepted for Transplantation

Christoph F. Mahler, Christian Nusshag, Claudius Speer, Louise Benning, Matthias Schaier, Markus Mieth, Arianeb Mehrabi, Martin G. Zeier, Christian Morath, Florian Kälble. *Universitat Heidelberg, Heidelberg, Germany.*

Background: To support acceptance decisions in kidney transplantation, deceased-donor based scores are increasingly used. Yet, the performance of these algorithms remains moderate and the impact of donor characteristics is controversial.

Methods: We analysed 52 kidney donor pairs (104 grafts) transplanted in different individuals. Recipients were followed for up to 3 years. Poor function (three-month estimated glomerular filtration rate (eGFR) <30 ml/min) and early graft loss (EGF) were the primary discriminatory factor. We reasoned that a relevant impact of donor variables would result in a high concordance rate of graft failure.

Results: Graft loss was significantly more frequent in recipients with reduced function or failure of the partner graft (Log-rank: p=0.006, Figure 1). This difference remained significant when we adjusted for recipient age, PRA and wait time

(Cox HR: 3,2; 95% CI: 1.06-9.83, p=0.03). Yet, there was no difference between rates of death with functioning graft (p=0.3). Relevant risk factors were donor- and recipient age, donor eGFR and HLA-mismatches.

Conclusions: Our results suggest that in kidney transplantation donor factors have a relevant impact on early transplantation outcomes. The use of donor-based clinical scores could potentially improve acceptance decisions and post-transplant outcomes.

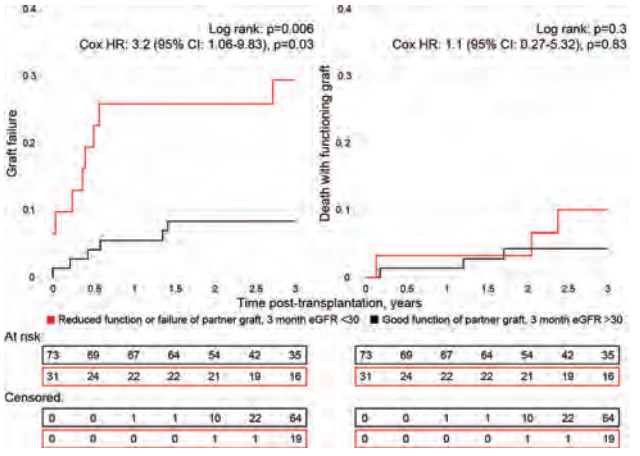


Figure 1: Cumulative incidence of graft failure by partner graft function. For grafts with early reduced graft function (eGFR<30), the incidence of graft failure in the respective partner graft is substantially higher (left panel). In contrast there was no significant difference in death with functioning graft between groups.

PUB383

Clinical Usefulness of Bortezomib-Based Desensitization Therapy in Highly Sensitized Living and Deceased Donor Kidney Transplantation

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Background: The aim of this study is to investigate the usefulness of bortezomib based desensitization (BZB-DSZ) therapy in highly sensitized living and deceased donor kidney transplantation.

Methods: We reviewed retrospectively 20 patients underwent BZB-DSZ protocol, of which 14 were living donor kidney transplantation (LDKT) candidates and 6 were on wait-list for deceased donor kidney transplantation (DDKT) between July 2012 and Nov 2022 in our center. We applied this protocol to LDKT candidates with positive T-CDC (complement dependent cytotoxicity) crossmatch at baseline or refractory to DSZ using rituximab and plasmapheresis (RTX/PP). Among DDKT candidates, we applied this protocol when (i) waiting time ≥ 10 years (ii) panel reactive antibody values ≥ 50% and (iii) previous history of a positive T cell crossmatch with potential deceased donor.

Results: Out of the 20 patients who received the BZB-DSZ protocol in both LDKT and DDKT candidates, 16 (80%) proceeded with transplantation, 1 refused the transplant, and 3 are awaiting for DDKT. Among LDKT candidates, 8 out of 10 (80%) candidates with a positive T-CDC turned negative. Mostly the mean fluorescence intensity (MFI) level of donor specific anti-HLA antibody (HLA-DSA) markedly decreased to target level (MFI<5,000). In four cases that were refractory to RTX/PP based DSZ, the MFI value of HLA-DSA showed a marginal decrease and was identified as HLA-DQ. Among DDKT candidates, the count of strong HLA-DSA (MFI>10,000) mostly decreased after DSZ. Out of them, 3 showed negative T cell crossmatch test to deceased donor, so we could proceed with DDKT. All 16 cases did not show hyper-acute rejection after transplantation and 8 cases (50%) showed biopsy-proven allograft rejection, with an antibody-mediated rejection rate of 87.5% within the first year of transplantation. Currently, overall renal function has been maintained stable through appropriate treatment. Death censored allograft survival during median follow-up duration of 35 months was 93.75%. Out of the 16 transplanted patients, 3 received antiviral treatment for CMV viremia, and 1 of them expired due to pneumonia sepsis.

Conclusions: Bortezomib based desensitization is effective to reduce HLA-DSA and enables highly sensitized patients to take kidney transplantation, and showed acceptable allograft outcomes.

PUB384

Correlation of Tc99m-Diethylene-Triamine-Pentaacetate (DTPA) Clearance to Long-Term Outcomes of Kidney Donors

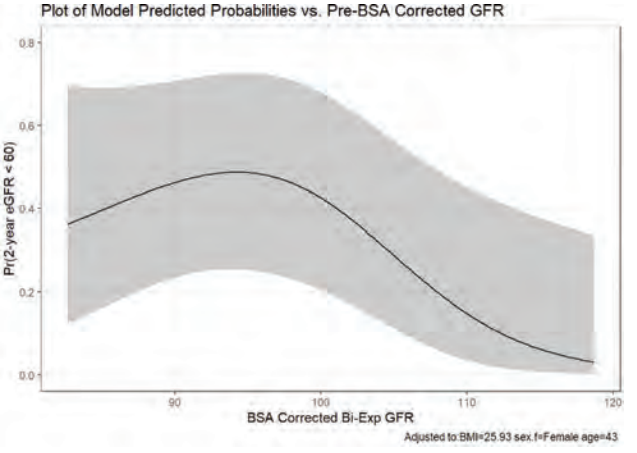
Niketna Vivek, Jared V. Grice, Trey W. Mcgonigle, Shi Huang, Austin M. Hilvert, Hamideh Ale Ali, Beatrice P. Concepcion, Anthony J. Langone, Heidi M. Schaefer, Rachel C. Forbes. *Vanderbilt University Medical Center, Nashville, TN.*

Background: Live kidney donors allow for gold-standard transplantation. Evaluating candidates entails assessment of kidney function. An eGFR <60 ml/min is a contraindication to donation. A method for assessing donors is measured GFR (mGFR) based on radioisotope (Tc99m-DTPA) clearance from the plasma. However, there is little existing literature quantifying the relationship between pre-donation mGFR values to long term donor function.

Methods: This study included all donors (N=107) at one institution (1/17-12/20) with preoperative DTPA-Tc99m and 2 year follow up eGFR. Serum-creatinine eGFR calculations were performed. Pre-donation mGFR for donors with 2 year eGFR above and below 60 ml/min were compared using Wilcoxon rank sum test. A logistic regression model was fitted for the binary indicator of 2-year eGFR < 60 including a nonlinear effect for preoperative mGFR. To visualize the effect of preoperative mGFR on 2-year eGFR, the model-estimated probability (2-year eGFR < 60) was plotted against pre-donation mGFR. A linear regression model on 2-year eGFR was fitted.

Results: Wilcoxon test showed significant differences in pre-donation mGFR values between 2-year eGFR >60 ml/min group compared to the <60 ml/min group (98 vs 83, p<0.001). In the logistic regression model, the effect of mGFR was marginally significant (p=0.065) with evidence for nonlinearity. As pre-donation mGFR increases beyond 95 ml/min, the probability of the patient having a 2 year eGFR <60 decreases (Figure 1). In the linear regression model, pre-mGFR was significantly positively related to the 2-year eGFR (p=0.015).

Conclusions: Current model implies there is a significant decrease in the probability of having eGFR < 60 when pre-donation mGFR begins around 110. Though there is a clear, positive relationship between pre-donation mGFR and 2-year eGFR, more work is required to better understand how mGFR can aid in inclusion criteria for donors.



PUB385

Unexpected Medical Conditions Discovered During Live Donor Kidney Evaluation

Alexandra Lee,[1,2] Christina A. Raker,[1,2] George P. Bayliss,[1,2] Reginald Y. Gohh,[1,2] Basma O. Merhi.[1,2] *[1]Lifespan Health System, Providence, RI; [2]Brown University, Providence, RI.*

Background: Living donor kidney transplantation is the preferred method of treatment for patients with end-stage kidney disease, with greater survival outcomes and graft success rates than deceased donor transplants. Potential living kidney donors (PLKD) are screened medically and psychosocially to ensure donation will not impact their long-term health. Our transplant center has noticed an increasing number of otherwise healthy PLKDs excluded from donation due to a previously unknown condition during the medical evaluation process. Our objective was to characterize newly diagnosed conditions to better understand how to improve living donor kidney transplantations.

Methods: Data was collected by electronic medical record review of PLKDs screened between December 2012 and April 2023, and included age, race, gender, relationship to recipient, and reason for exclusion as well as method of diagnosis.

Results: Of the 223 excluded PLKDs, over half were due to newly diagnosed conditions (Figure 1). The most common conditions were diabetes mellitus, hypertension, and renal issues (Figure 2). Some infrequent yet notable conditions detected were sickle cell trait and horseshoe kidney. The majority of newly diagnosed PLKDs were female (Figure 1).

Conclusions: Over half of excluded PLKDs were diagnosed with new conditions, all of which have severe health consequences if not properly treated. While these results may reflect changing donation criteria, they also raise concerns regarding gaps in primary care in our area.

Funding: Private Foundation Support

Figure 1 shows the outcomes of our center's PLKDs between December 2012 and April 2023.

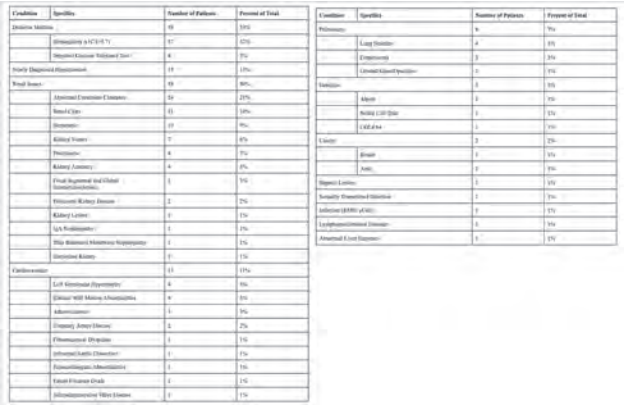


Figure 2 categorizes the newly diagnosed conditions of 115 prospective donors.

PUB386

Relationship Between Prognosis and kt/V After Kidney Transplantation in Peritoneal Dialysis Patients

Young Eun Park, A Young Kim, Kyu-hyang Cho, Jong-Won Park, Jun-Young Do, Seok hui Kang. Dept of Internal Medicine-Nephrology, Yeungnam University Medical Center. *Yeungnam University Medical Center, Daegu, Republic of Korea*.

Background: In dialysis patients, control of kt/v and metabolic acidosis may affect patient outcome. Studies have shown that metabolic acidosis control helps early recovery of renal function after kidney transplantation (KT). However, studies on the correlation with kt/v are rare. We hypothesized that pretransplant kt/v control would affect renal function after KT.

Methods: The subjects were 61 patients who underwent a KT at our hospital during peritoneal dialysis. We calculated the average value of kt/v measured three times before KT. Group A was classified as kt/v 1.7 or higher, and group B was classified as less than 1.7. Primary endpoint was a comparison of serum creatinine levels between the two groups on days 1, 2, 3, 5 and 7 after surgery. Secondary endpoint was to compare urine output and serum blood urea nitrogen levels between the two groups.

Results: The mean age was 54.6±10.1 in group A and 45.8±12.0 in group B. Among the factors that may affect the prognosis after KT, the donor's serum creatinine level and patients' base serum creatinine level and ischemic time showed significant differences between the two groups. There was no difference in serum albumin and blood urea nitrogen levels between the two groups. Serum creatinine improvement after KT was significantly slower in group A than in group B. There was no difference in blood urea nitrogen and urine volume between the two groups.

Conclusions: It was found that the improvement of serum creatinine level after kidney transplantation was rather slow in the group with high kt/v. In the group with high kt/v, donor serum creatinine level was high and the ischemic time was long. These factors seem to have more influence on the prognosis than kt/v itself. Due to the small number of subjects, additional studies on kt/v and the prognosis after KT are needed.

PUB387

Vitamin C Deficiency After Kidney Transplantation: Results of the TransplantLines Biobank and Cohort Study

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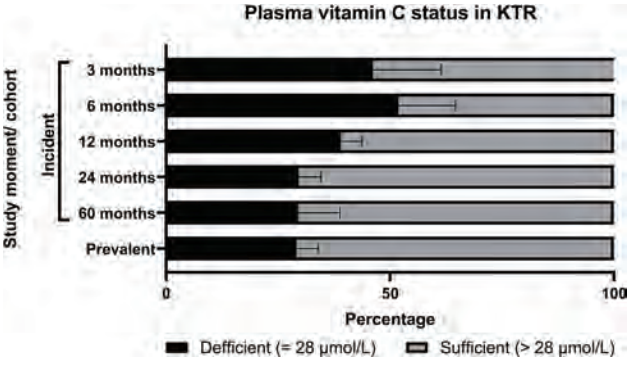
Background: Vitamin C is an essential antioxidant nutrient whose deficiency has been associated with higher mortality and graft failure risk in kidney transplant recipients (KTR). We investigated the trajectory, prevalence, and determinants of vitamin C deficiency post-kidney transplantation.

Methods: Plasma vitamin C was measured in 579 KTR at 3, 6, 12, 24 and 60 months post-transplantation. An additional cohort of 374 KTR (median 8 years post-transplantation) was added to study the long-term determinants of vitamin C deficiency. Deficiency was defined as plasma vitamin C ≤28 µmol/L. Diet was assessed by a 177-item food frequency questionnaire, including data on supplementation.

Results: At inclusion, the 953 KTR were 62% male, mean age 55 years and mean eGFR 55 ml/min/1.73m^2. The intraindividual coefficient of variation of plasma vitamin C during follow-up was 17%. Prevalence of vitamin C deficiency ranged from 52% (6 months post-transplantation) to 29% (prevalent KTR, Fig 1). At ≥12 months post-transplantation, diabetes mellitus was the main clinical characteristic associated with higher risk of vitamin C deficiency (OR 2.30, 95% CI 1.46-3.61). Higher dietary vitamin C was associated with a lower risk of deficiency (OR 0.38, 95% CI 0.24-0.61 per 100 mg/day) and, on average, supplemented KTR had 19 µmol/L higher plasma vitamin C than non-supplemented KTR (p<0.001).

Conclusions: Plasma vitamin C is stable after kidney transplantation with a high prevalence of deficiency among KTR, particularly among KTR with diabetes mellitus. Higher intake of vitamin C, both dietary and supplemented, decreased the risk of deficiency among KTR. Further research is warranted to assess if correcting vitamin C deficiency improves patient and graft survival in KTR.



Prevalence of vitamin C deficient KTR was 46%, 52%, 39%, 30%, 30% and 29% at 3, 6, 12, 24, 60 months post-transplantation and prevalent transplantation, respectively.

PUB388

A Single-Center Case Series of Successful Abdominal Organ Transplantation from SARS-CoV-2-Infected Donors to Uninfected Recipients: Do We Need Rigorous Monitoring?

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Background: There is limited documentation of **h**ematogenous transmission of SARS-CoV-2 in nonlung transplants from infected donors to uninfected recipients.

Methods: We analyzed sixteen recipients (7 Liver, 9 Kidney) transplanted from SARS-CoV-2- NAT+ deceased donors from 12/25/2021 to 2/28/2022 who were followed for at least 90 days. Primary outcomes included COVID positivity, allograft loss, and all-cause mortality. Secondary outcomes included biopsy-proven rejection [BPAR], DSAs, DGF, and opportunistic infections. Unlike previous studies, we followed the recipients clinically with the intent to treat if they developed SARS-CoV-2 symptoms.

Results: All donors were SARS-CoV-2 PCR positive 72 hours before donation. No recipients developed SARS-CoV-2 infection. The nadir serum creatinine and eGFR were 1.33 mg/dL and 64 mL/min/1.732 m2 for KTx, respectively. The median ALT was 14.5 IU/L, AST 13 IU/L, and ALP 74 IU/L. Two KTx lost allograft, and one LTx died with a failed allograft. However, this was unrelated to their SARS-CoV-2 positive donor status. One BPAR in the LTx was treated with steroids. No DSAs or BPAR were reported in the KTx. Six KTx experienced DGF, and four are off dialysis. Two KTx developed CMV infection due to an error in reporting the CMV serostatus by the donor center. We did not do serial testing for SARS-CoV-2 by PCR, imaging, or cycle threshold score pre- or post-transplant for donor/recipient and had comparable outcomes to previous studies.

Conclusions: Due to the low risk of transmission, serial testing might not be necessary and thus, could be reciprocated at small-volume transplant centers.

PUB389

Epstein-Bar Virus (EBV)-Associated Plasmacytoma/Congophilic Lambda Light Chain (LC) Casts Four Months After Kidney Transplant Causing Death of the Patient

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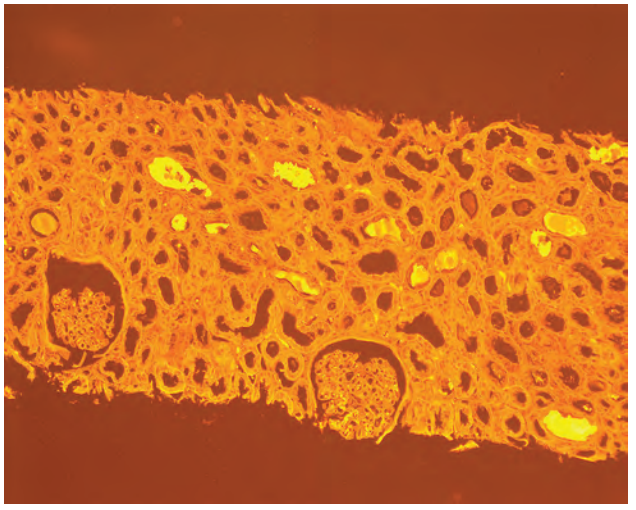
Introduction: 66-yr-old lady with out any prior hematological history admitted with allograft failure 4 months after having donation after brain death (DBD) kidney transplant. Work up showed EBV associated plasma cell neoplasm(PCN) with monoclonal LC in kidney. Her disease course was rapidly deteriorated despite hemodialysis and chemotherapy to multiogran failure, shock and death.

Case Description: 66-yr-old lady with h/o diabetic kidney disease status post DBD kidney transplant admitted with renal failure and nephrotic range proteinuria. Admission vitals temp 98.4 f, BP 131/67 mmHg, HR 96 bpm, RR 20. Physical examination on admission was unremarkable. Laboratory results on admission H and H 11.0 mg/dl and 34 % Cr 5.8 mg/dl, urine protein/creatinine 26.41 g/g and urine microalbumin/creatinine 11.53 g/g, free Lambda light chain 983.2 mg/dl, kappa chains 1.54.SPEP M-component 0.35 gm/dL, free lambda light identified in the gamma region. IgG low at 480. Renal biopsy showed acute tubular injury with congophilic lambda light chain intratubular casts. EBV PCR 160 K IU/mL, 5.2 log 10 IU/mL. Bone marrow biopsy showed 1% plasma cells, lambda light chain restricted with positive EBV. Flow cytometry showed monoclonal plasma cells with positive for CD138, CD38, CD19, cytoplasmic lambda LC. Immunosuppression with triple regimen was adjusted accordingly until PCN was diagnosed. Hemodialysis initiated because of fluid overload and anuric renal failure. After first chemotherapy (Cyclophosphamide, Bortezomib, Dexamethasone), she did have multiorgan failure and expired.

Discussion: Plasmacytoma like PTLD is a rare presentation and have poor prognosis. Prevalence was less than 0.1%. It is reasonable to have systematic screening of light chains in KDIGO recommendations before and after kidney transplantation to prevent the death of patient and graft.



Congophilic casts

PUB390

Daratumumab Is Effective for the Treatment of Antibody-Mediated Kidney Rejection

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Introduction: ABMR of kidney allografts has been difficult to treat with TPE, IVIG, rituximab and tocilizumab. We present a patient with ABMR that was reversed with the use of SC daratumumab (Dara).

Case Description: A 69-year old man had his first kidney transplant on 2008. He developed chronic ABMR that was unresponsive to rituximab and tocilizumab. He had a second transplant on October 2021. He had no DSA, CDC and flow crossmatches were negative. His discharge serum creatinine was 0.95 mg/dL and biopsy was normal. 16 days post-transplant, he had proteinuria of 4.4 gms/24 hrs, creatinine rose to 1.56 mg/dL, dd-cfDNA (Prospera) was raised at 3.78%. A repeat biopsy showed MVI, g+ptc=4 with +ve C4d staining. MMDx confirmed severe early ABMR. His DSA, anti-AT1-R, MICA antibodies, endothelial cell crossmatch were negative. As he had previously failed rituximab and tocilizumab, he gave informed consent to be treated with SC daratumumab 1800 mg weekly for 4 doses then 3 monthly for 3 doses for a total of 10 months, ending on September 2022. After 4 doses of Dara, his proteinuria decreased to 1.5 gms/24 hrs, creatinine; 1.42 mg/dL, dd-cfDNA decreased to 1.41%. In March 2022, his proteinuria; 1.0 gm/24 hrs, creatinine; 1.36 mg/dL, dd-cfDNA had normalized to 0.14%. His biopsy showed MVI, g+ptc=3, mild C4d staining, MMDx improved to mild early-stage ABMR. In June 2022, his proteinuria; 0.20 gm/24 hrs, creatinine; 1.41 mg/dL, dd-cfDNA was 0.57%. In September 2022, he had no proteinuria, creatinine; 1.45 mg/dL and dd-cfDNA was 0.28%. In January 2023, he had no proteinura, creatinine; 1.32 mg/dL, dd-cfDNA was 0.55%. His biopsy had no ABMR, g+ptc=0, negative C4d staining and MMDx had no ABMR.

Discussion: We report a man with rapid onset ABMR that was successfully reversed with SC Dara over a 10-month period with complete remission in proteinuria, slight decrease in creatinine, progressive improvements in serial dd-cfDNA and resolution of rejection findings on serial biopsies and MMDx. SC Dara was tolerated with minimal side effects. It was conveniently administered as an out-patient over 15 minutes. Dara had been reported to reverse ABMR in a patient who had an ABO-I kidney transplant. Dara had been used to desensitise patients prior to kidney transplant. However, this is the first patient who had an ABMR successfully reversed with SC Dara. We are continuing to enrol more patients with proven ABMR to be treated with SC Dara.

PUB391

Correlation of Urine Analysis Findings with Biopsy-Proven Acute Kidney Transplant Rejection

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Background: Although the incidence of acute kidney transplant rejection within the first year has decreased, it remains a major cause of allograft dysfunction. Kidney biopsy remains the gold standard to diagnose rejection. Urine analysis is used in evaluating kidney dysfunction, but no previous studies correlated urine analysis findings with acute rejection.

Methods: We performed a descriptive study evaluating urine analysis findings (proteinuria, hematuria, and pyuria) at the time of biopsy-proven acute rejection in adult kidney transplant recipients. We examined the most recent urine samples before kidney biopsies. We excluded patients with acute rejection who have other histopathological findings that may impact urine analysis findings (advanced diabetic glomerulosclerosis, collapsing glomerulopathy, FSGS, active glomerulonephritis, BK nephropathy, anatomical abnormalities, or concomitant chronic rejection).

Results: Between 2020 and 2023, 44 biopsy-proven acute rejection episodes were diagnosed in 38 patients. Eighteen biopsies showed acute TCMR, ten showed AMR, sixteen showed mixed rejection, and of all the biopsies ten had evidence of vascular rejection. Thirty-six episodes (81.1%) were preceded by abnormal urine analysis. Thirty urine samples (66.6%) tested positive for protein (≥10 mg/dL), thirteen samples (29.5%) tested positive for hematuria (≥3 RBCs/HPF), and eighteen samples (40.9%) tested positive for pyuria (≥3 WBCs/HPF). Of the eight normal samples, 3 were in the setting of AMR, 4 in the setting of TCMR, and 1 in the setting of mixed rejection. Interestingly, mixed rejection was associated with the highest likelihood of having abnormal urine analysis (93.75%).

Conclusions: There is no single urine analysis abnormality that correlates well acute rejection. Although various degree of proteinuria is not uncommon, it is non-specific. Even in the setting of glomerular injury as seen in glomerulitis, hematuria and/or pyuria are inconsistently seen at low rates.

Urine analysis abnormalities in various types of rejection

Rejection subtypes (n)	Urine analysis with abnormalities; n (%)	Protein (≥10 mg/dL); n (%)	RBCs (≥3/HPF); n (%)	WBCS (≥3/HPF); n (%)
Biopsy-proven acute rejection (44)	36 (81.1%)	29 (66%)	13 (29.5%)	18 (40.9%)
Antibody-Mediated Rejection (AMR) (10)	7 (70%)	6 (60%)	2 (20%)	2 (20%)
Acute T-Cell-Mediated Rejection (TCMR) (18)	14 (77.7%)	9 (50%)	5 (27.7%)	9 (50%)
Mixed Rejection (16)	15 (93.75%)	14 (87.50%)	6 (37.50%)	7 (43.70%)
Biopsies with Vascular Rejection (10)	8 (80%)	6 (60%)	3 (30%)	4 (40%)

PUB392

Skin Lesion Unmasking Disseminated Nocardia in Renal Transplant Recipient

Sarah Abu Kar, Amber Anwar, Laura Binari, Saed Shawar. *Vanderbilt University Medical Center, Nashville, TN.*

Introduction: Nocardiosis is a rare opportunistic infection that can cause localized or systemic diseases. Therefore, a high index of suspicion is required for the diagnosis as it carries high mortality if not treated early. We present a disseminated Nocardia infection presenting with an isolated skin lesion.

Case Description: A 47-year-old male suffering from end-stage renal disease due to hypertension underwent a deceased donor kidney transplant in 2/ 2022. He was induced with Alemtuzumab and maintained on tacrolimus, mycophenolate mofetil, and prednisone. He also received prophylactic Dapsone for 6 months (due to a reported sulfonamide allergy) and Valcyte for 4 months post-transplantation. His course was complicated by AMR in 12/ 2022, treated with PLEX, IVIG, and Rituximab. Three months later, he presented with an ulcerated skin nodule on the medial aspect of his right knee. It started after a few days of soil-related teaching activities involving planting and terrarium work. No other symptoms were reported, treated with antibiotics for one week without improvement, so a biopsy and wound culture from the lesion revealed Nocardia pseudobrasiliensis. Subsequent diagnostic workup, including a chest CT scan and an MRI of the brain, uncovered a spiculated lung lesion, a consolidation in the left lower lobe, and two cerebral abscesses. Bronchoscopy with BAL and LP results were negative for malignancy and infection. Additionally, all non-invasive fungal markers were negative. In collaboration with the infectious diseases and pulmonology teams, a diagnosis of disseminated nocardiosis was concluded, aligning with the patient's symptomology. Treatment commenced with linezolid, Bactrim (after consulting with Allergy and tolerating the medication well), and imipenem-cilastatin, which was later adjusted to Bactrim and Linezolid based on sensitivity. Follow-up imaging showed a reduction in the sizes of both the lung nodule and brain abscess, indicating successful treatment progress.

Discussion: Skin lesions can pose diagnostic challenges in transplant patients, necessitating vigilance for atypical presentations of opportunistic infections and proactive biopsy for unresponsive lesions. However, Nocardia, when identified early and treated with targeted antibiotics, can result in successful outcomes for renal transplant recipients.

PUB393

Ultra-Long Survivors of Kidney Transplantation: 40 Years and More of Graft Function

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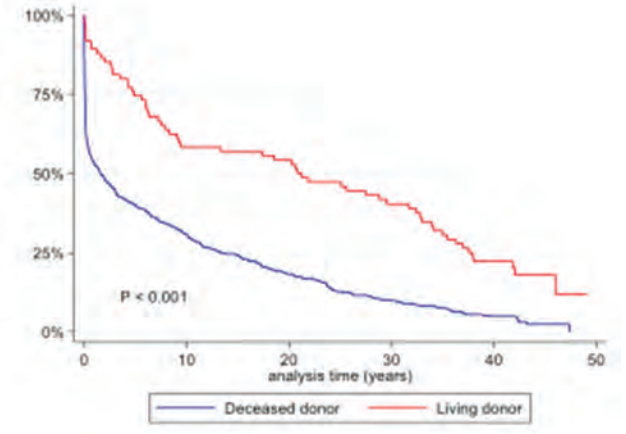
Background: It is nearly sixty years since the first kidney transplant in Ireland in 1964. We examined our cohort of patients with allografts functioning for over forty years. We sought to identify factors associated with this ultra-long-term allograft survival and to describe clinical features of these patients.

Methods: A retrospective analysis of the Irish National Kidney Transplant Registry included all kidney transplants performed in Ireland between 1st January 1970 and 31st March 1983. Follow-up was until 31st March 2023.

Results: 428 transplants occurred in 394 patients. There were 33 (8.4%) patients with graft function for ≥40 years, of whom 25 are functioning at date of analysis. 4 patients were lost to follow-up. Kaplan-Meier estimated survival at 20, 30 & 40 years was 25%, 15% & 8% respectively for all grafts; figure 1 illustrates survival differences between

living and deceased donor grafts. Multivariate analysis identified age at transplant (HR 1.02, CI 1.00–1.04), male recipient (HR 1.39, CI 1.04–1.45) and living vs. deceased donor (HR 0.42, CI 0.27–0.67) as significantly associated with long-term graft loss. The median age at death was 49 years (IQR 40 – 59). The most common causes of death were cardiovascular disease and malignancy. The major causes of graft loss were death with a functioning graft and interstitial fibrosis/tubular atrophy. The median creatinine of 25 surviving grafts was 1.21 mg/dL (range 0.75-3.64 mg/dL). Most (61%) patients were prescribed a combination of azathioprine/glucocorticoid. Comorbidities included non-melanoma skin cancer (67%), coronary artery disease (24%) and invasive malignancy (30%). Skin cancer was by far the commonest malignancy, with 93 incidences in 22 patients.

Conclusions: Of those who survive to forty years, graft function is excellent maintained on low-level immunosuppression. Recipient female sex and living donor kidney transplantation are associated with improved graft survival.



PUB394

Impact of Donation After Circulatory Death on Outcomes of Expanded Criteria Donor Kidney Transplants

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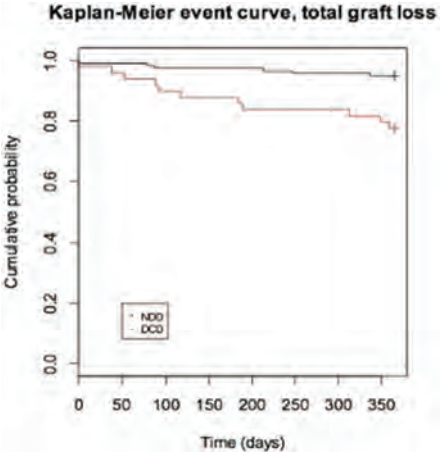
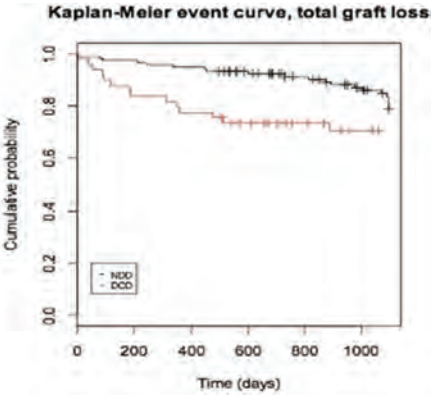
Background: Expanded criteria donor (ECD) kidneys experience suboptimal outcomes compared to standard criteria donor (SCD) kidneys.

Methods: To examine the additional impact of deceased organ category, donation after circulatory death (DCD) and neurological determination of death (NDD), on ECD outcomes, we examined 1- & 3-year patient and graft survival in all ECD kidney recipients in our institution between January 2008 and December 2017.

Results: Of 166 ECD recipients, 49 (29.5%) were DCD and 117 (70.5%) were NDD. Delayed graft function was higher in the DCD/ECD group 61.2 % vs 32.0 % among NDD/ECD recipients. Graft loss was significantly increased among DCD/ECD (HR for graft loss 4.81 (95% CI, 1.78, 13.01), *p* value 0.002 at 1 year and 2.03 (95% CI, 1.03, 4.0), *p* value 0.042 at 3 year). Death-censored graft loss was higher among DCD/ECD (HR was 10.12 (95% CI, 2.14, 47.92), *p* value 0.004 at 1 year and 2.83 (95% CI, 1.24, 6.46) *p* value 0.014 at 3 years). There was no statistically significant difference in all-cause mortality.

Conclusions: Our study demonstrated that DCD/ECD kidneys have lower graft survival compared to NDD/ECD kidneys. Time on dialysis, waiting time and panel reactive antibody should be taken into account when offering these organs to patients.





PUB395

Safety and Efficacy of Mycophenolate Reduction After Kidney Transplantation

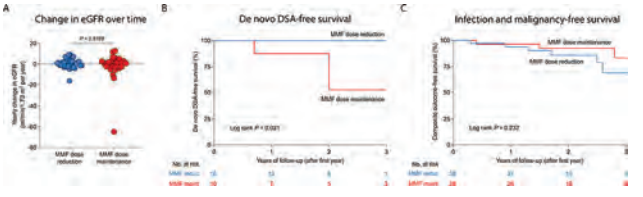
Karim Yatim, Ayman Al Jurdi, Guilherme Taborda Ribas, Leela Morena, Leonardo V. Riella. *Massachusetts General Hospital, Boston, MA.*

Background: Adjusting the dose of maintenance immunosuppression (IS) after kidney transplantation is essential to balance the risk of allograft rejection with that of infections and malignancy. Contrary to tacrolimus, there are no high-quality data to guide mycophenolate (MMF) dose changes in kidney transplant recipients (KTRs). The aim of this study is to determine the allograft and patient outcomes in KTRs who underwent MMF dose reductions compared to those who did not at our institution.

Methods: We conducted a retrospective cohort study of all kidney transplants from 1/1/2015 to 12/31/2020 who received MMF-based IS. The "intervention" group included KTRs who underwent MMF dose reduction after the first year, while the control group was KTRs whose MMF dose was maintained. The primary safety outcomes were graft failure or death, de novo DSA development, allograft rejection, and eGFR change during follow-up. The primary efficacy outcome was a composite of new viral infections (CMV, EBV and BKV), infections requiring hospitalization and malignancy. We excluded patients who developed infections or malignancy prior to MMF reduction from our analysis. Follow-up was censored at occurrence of the outcome, last follow-up or five years.

Results: 69 KTRs met the inclusion criteria. Mean age was 49.5±15.3 years, 61% were male (n=42), 59% received a deceased donor allograft (n=41), and 86% (n=59) received Thymoglobulin. 42 KTRs (61%) had a reduction in the MMF dose after 1 year of transplantation to ≤500 mg BID. No deaths occurred during follow-up. 3 (4%) KTRs developed rejection during follow-up: 1 mixed acute rejection in the MMF dose maintenance group, and 2 cellular rejections in MMF dose reduction group. There was no change in eGFR between groups (Figure 1A). DSA occurred in 3 KTRs (4%), all in the MMF dose maintenance group (Figure 1B). There was no difference in the incidence of composite outcome of infections and malignancy (Figure 1C).

Conclusions: MMF dose reduction after the first year may be a safe strategy in low-risk KTRs. Larger prospective studies are needed to confirm these findings and establish the long-term benefits of this intervention regarding infection and malignancy.



PUB396

Tacrolimus Intrapatient Variability as a Tool to Gauge Nonadherence in Adolescent Kidney Transplant Recipients

Tara B. Gavcovich,[1,2] Vaka Sigurjonsdottir,[1,2] Marissa J. Defreitas,[1,2] Claudia Serrano,[1,2] Wacharee Seeherunvong,[1,2] Chryso P. Katsoufis,[1,2] Wendy R. Glaberson,[1,2] Melisa Oliva,[1,2] Adela D. Mattiazzi,[1,2] Carolyn L. Abitbol,[1,2] Jayanthi Chandar.[1,2] *[1]Jackson Memorial Hospital, Miami, FL; [2]University of Miami School of Medicine, Miami, FL.*

Background: Long-term survival of kidney allografts is limited by rejection, a common cause of graft loss in adolescent transplant recipients. High tacrolimus intrapatient variability (IPV) has been associated with DSA formation and increased risk of rejection. Non-adherence is considered a cause of high tacrolimus IPV, but has not been demonstrated conclusively.

Methods: This cross-sectional retrospective study included kidney-only transplant recipients ≥11 to ≤23 years old, ≥10 months post-transplant at the Miami Transplant Institute, and maintained on tacrolimus. A composite adherence score ranging from 0-4 points was developed using four tools, each awarded 1 point if positive: (1) patient reported non-adherence on Basel Assessment of Adherence to Immunosuppressive Medical Scale (BAASIS©); (2) provider report; (3) inability to recall medications; and (4) intentional missed visits. A composite score ≥1 was considered non-adherent. Tacrolimus levels were monitored at least monthly. IPV is the coefficient of variation: SD/mean tacrolimus concentration x 100%, using tacrolimus samples in the 6 months prior to adherence assessment. Levels drawn while hospitalized/sickness or mis-timed levels were excluded.

Results: 33 patients were enrolled, 60.6% male, median age 16 years (IQR 13-19). Non-adherence was noted in 18 (54.5%) patients. The median tacrolimus IPV was significantly higher in non-adherent (32%, IQR 14-37.5) compared to adherent patients (18%, IQR 13-22), p=0.02 (Figure 1a). There was a significant positive correlation between tacrolimus IPV and BAASIS© score (r= 0.45, 95% CI 0.13 - 0.69), p<0.01 and composite adherence score (r= 0.56, 95% CI 0.26 - 0.76), p<0.001 (Figure 1b).

Conclusions: Tacrolimus IPV was significantly higher in non-adherent patients. Recognizing high IPV may be a useful tool to detect non-adherence in adolescent kidney transplant recipients at high risk of rejection, allowing for early interventions to prevent adverse graft outcomes.

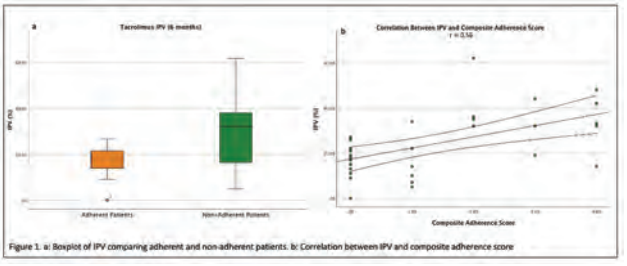


Figure 1. a) Boxplot of IPV comparing adherent and non-adherent patients. b) Correlation between IPV and composite adherence score

PUB397

Disseminated Intravascular Coagulation in the Immediate Postoperative Period After a Simultaneous Kidney Pancreas Transplant (SPK)

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Introduction: Disseminated intravascular coagulation(DIC) is a clinico- pathological syndrome associated with consumptive coagulopathy and defibrination with a potential of causing micro/macrovascular thromboses and hemorrhage. DIC is commonly caused by inflammation, drugs, sepsis, severe trauma or major surgery, cancer, obstetric complications, immune reactions. While there are multiple cases of DIC in deceased donors, there is no data or case reports on recipients developing DIC immediately post-op after SPK.

Case Description: 59-year-old female underwent a SPK for a history of ESRD secondary to IDDM2. Measured PRA was 61%/43%. DBD Donor -18 year old female who died from Anoxia. KDPI - 9% and P-PASS <17. No DSA noted and was a 2/6 HLA ABDR Match. CIT- was less than 15 hours for both organs. Intraoperative course was unremarkable. Within 4 hrs she became obtunded and hypotensive progressing to multipressor shock. Labs showed a drop in hemoglobin-9.7g/dl to 6.5g/dl(N 12-16), platelets-239 to 84 10*9/L (N 150-450 10*9/L). She was emergently taken back for rexploration. There was no anastomotic leak, only nonspecific diffuse oozing into the abdomen. Both grafts were healthy and no signs of hyperacute rejection. Her coagulation parameters deteriorated-PT-12.3 to 30.1(N 9-12 seconds), aPTT- 33.1 to 65.9 (N 25-36 seconds), INR- 1.1 to 2.5(N 0.9-1.1), D-dimer-14.90 and fibrinogen 135. International Society on Thrombosis and Hemostasis criteria met for overt DIC. She was treated with blood products per protocol, CT scan showed extensive Hepatic and splenic infarcts in addition she developed purpura fulminans and multi-organ failure. Final diagnosis-Hemorrhagic shock due to DIC.

Discussion: SPK has evolved as the gold standard treatment for patients with ESRD with IDDM2 in surgically acceptable candidates. it is a more complex procedure with a higher complication rate. Rexploration is seen in >20% with the most common etiology being anastamotic leaks, intraabdominal fluid collections, Intrabdominal infections, graft pancreatitis and graft thrombosis. Cases of DIC have been reported after surgical interventionsm but to our knowledge there is no documented case of rapid onset DIC in a patient post SPK. This case highlights the need to consider DIC in a postoperative setting after DIC in patients with hemorrhagic shock which has previously not been reported.

PUB398

To Bleed or to Thrombose: The Potential Risks and Complications of Blood Thinners in Kidney Transplant Recipients

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Background: Many patients on the kidney transplant waitlist are on anticoagulation (AC) or antiplatelet therapy for various indications and co-morbidities. These medications are associated with increased risk of bleeding, especially when patients undergo invasive procedures, such as a kidney transplant. On the other hand, withholding AC or antiplatelet therapy in the perioperative period, can lead to complications such as vascular thrombosis and subsequent allograft loss. The aim of our study was to review co-morbidities and allograft function of kidney transplant recipients (KTRs) on these medications at the time of transplant.

Methods: Single center, retrospective cohort study of adult KTRs transplanted between Jan 2017 and December 2019 in our center.

Results: We had 333 KTRs who met the study criteria. Of them, 38.9% of were on Aspirin pre-txp, 5.4% were on Plavix and 8.4% were on Coumadin as anticoagulation. Of the 333 KTRs, 22 patients (6.6%) developed a hematoma and 8 patients (2.4%) developed thrombosis. Usage of pre-operative AC or antiplatelet therapy did not differ between KTRs who developed these complications and those who did not. Compared to KTRs who did not develop a hematoma post-KT, patients with hematomas had longer length of stay (LOS)(p<0.001), higher intervention rate in the OR (54.5% vs 5.5%, p<0.001) or by CVIR (45.5% vs 13.9%, p=0.001) within 30 days post-KT. KTRs with hematoma also had higher serum creatinine (Cr) at 30 days (p=0.003), 90 days (p=0.001), 1 year (p= 0.001) and at the latest follow up (p<0.001). Overall patient survival was also significantly lower in this group (p<0.05). KTRs with thrombosis had longer LOS (p<0.001) and higher Cr after 30 days (p<0.05) when compared to those without. KTRs with thrombosis had lower graft survival (p=0.05).

Conclusions: Bleeding or thrombosis complications post-transplant are associated with significant morbidity but they did not occur more frequently in patients that were on AC or antiplatelet therapy pre-transplant. While this is a single-center study, it contributes to existing data, and highlights the fact that the risks and benefits of AC therapy should be assessed for each patient to individualize the management approach.

PUB399

Risk Factors for Fractures in Renal Transplantation: A Population-Based Cohort Study

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Background: Kidney transplant recipients are at an increased risk of fractures, and targeted preventive strategies are needed. Therefore, we investigated a large population-based cohort to identify the transplant recipient-specific risk factors for fractures in Taiwanese kidney transplant recipients.

Methods: We conducted a retrospective cohort study using the National Health Insurance Research Database. Patients who underwent renal transplantation between 2003 and 2015 were identified and followed until December 31, 2015 to observe the development of fractures. Variables associated with the development of post-transplant fractures were identified by calculating hazard ratios in a Cox regression model.

Results: 5309 renal transplant recipients were identified, of whom 553 (10.4%) were diagnosed with post-transplant fractures. Independent predictors of post-transplant fractures included an age at transplant ≥65 years (p<0.001), female sex (p<0.001), fractures within 3 years prior to transplantation (p<0.001), and diabetes (p<0.001). In addition, daily prednisolone dose >2.9-5.3 mg/day (p<0.001), >5.3-8.7 mg/day (p<0.001) and >8.7 mg/day (p<0.001) were also independent predictors of post-transplant fractures. Conversely, the use of peritoneal dialysis before renal transplantation (p=0.021), hypertension (p=0.005), and the use of tacrolimus (p<0.001), azathioprine (p=0.006), mycophenolate mofetil (p=0.002), mTOR inhibitors (p=0.004) and calcium supplements (p=0.009) were inversely correlated with post-transplant fractures.

Conclusions: We recommend minimizing daily glucocorticoids in conjunction with immunosuppressive regimens such as tacrolimus, azathioprine, mycophenolate mofetil, mTOR inhibitors and calcium supplements, especially in older female recipients, and in recipients with diabetes and a history of prior fractures.

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Table 1 Characteristics of the renal transplant recipients with and without fracture

	Total N=5309	Fracture N=553	Without fracture N=4756	P value
Female	2436 (45.9%)	286 (51.7%)	2150 (45.2%)	*0.004
Age at transplant	46.8±11.6	50.0±11.9	46.4±11.5	*<0.001
Age at transplant ≥ 65 years	249 (4.7%)	50 (9.0%)	199 (4.2%)	*<0.001
Fracture in the 3 years prior to transplant	214 (4.0%)	54 (9.8%)	160 (3.4%)	*<0.001
Pre-transplant factors				
Renal osteodystrophy	133 (2.5%)	16 (2.9%)	117 (2.5%)	0.537
Parathyroidectomy	412 (7.8%)	33 (6.6%)	379 (8.0%)	0.096
Pre-transplant dialysis modality				*0.001
Hemodialysis	3386 (63.8%)	382 (69.1%)	3004 (63.2%)	
Peritoneal dialysis	1198 (22.6%)	90 (16.3%)	1108 (23.3%)	
Pre-emptive	725 (13.7%)	81 (14.6%)	644 (13.5%)	
Comorbidity				
Osteoporosis	103 (1.9%)	19 (3.4%)	84 (1.8%)	*0.007
Hyperthyroidism	59 (1.1%)	8 (1.4%)	51 (1.1%)	0.427
Hypertension	4023 (75.8%)	408 (73.8%)	3615 (76.0%)	0.247
Diabetes mellitus	1546 (29.1%)	214 (38.7%)	1332 (28.0%)	*<0.001
Systemic lupus erythematous	204 (3.8%)	18 (3.3%)	186 (3.9%)	0.448
Hyperlipidemia	1042 (19.6%)	128 (23.1%)	914 (19.2%)	*0.028
Coronary artery disease	630 (11.9%)	70 (12.7%)	560 (11.8%)	0.543
Cerebrovascular disease	318 (6.0%)	30 (5.4%)	288 (6.1%)	0.554
Chronic obstructive pulmonary disease	221 (4.2%)	34 (6.1%)	187 (3.9%)	*0.014
Obesity	18 (0.3%)	0 (0%)	18 (0.4%)	0.247
Malnutrition	26 (0.5%)	3 (0.5%)	23 (0.5%)	0.748
Inflammatory bowel disease	35 (0.7%)	6 (1.1%)	29 (0.6%)	0.172
Rheumatoid arthritis	41 (0.8%)	5 (0.9%)	36 (0.8%)	0.611
Hypogonadism and postmenopausal disorders	164 (3.1%)	26 (4.7%)	138 (2.9%)	*0.021
Alcoholism	13 (0.2%)	0 (0.0%)	13 (0.3%)	0.385
Post-transplant factors				
Daily steroid dosage (mg/day)	8.8±23.7	9.6±15.6	8.7±24.5	0.425
Mean dosage of glucocorticoids (mg/day)				*<0.001
0-2.9	1327 (25.0%)	100 (18.1%)	1227 (25.8%)	
>2.9-5.3	1328 (25.0%)	127 (23.0%)	1201 (25.3%)	
>5.3-8.7	1327 (25.0%)	144 (26.0%)	1183 (24.9%)	
>8.7	1327 (25.0%)	182 (32.9%)	1145 (24.1%)	
Bone-protective medication				
Bisphosphonate therapy	160 (3.0%)	23 (4.2%)	137 (2.9%)	0.096
Calcium	1151 (21.7%)	114 (20.6%)	1037 (21.8%)	0.521
Vitamin D	695 (13.1%)	59 (10.7%)	636 (13.4%)	0.074
Calcium with vitamin D	69 (1.3%)	6 (1.1%)	63 (1.3%)	0.638
Immunosuppressive medications				
Tacrolimus	4356 (82.0%)	392 (70.9%)	3964 (83.3%)	*<0.001
Cyclosporine	1957 (36.9%)	258 (46.7%)	1699 (35.7%)	*<0.001
Azathioprine	137 (2.6%)	10 (1.8%)	127 (2.7%)	0.226
Mycophenolate mofetil/Mycophenolic acid	5046 (95.0%)	508 (91.9%)	4538 (95.4%)	*<0.001
mTOR inhibitors	2074 (39.1%)	208 (37.6%)	1866 (39.2%)	0.459

*p<0.05

Table 1

Table 2 Cox regression analysis for post-transplant fracture risk in renal transplant recipients

	Univariate		Multivariate	
	HR (95% CI)	P value	HR (95% CI)	P value
Age at transplant ≥ 65 years	2.756 (2.060-3.688)	*<0.001	3.165(2.341-4.279)	*<0.001
Female recipient	1.203 (1.018-1.421)	*0.030	1.492 (1.257-1.771)	*<0.001
Fracture in the 3 years prior to transplant	3.259 (2.461-4.315)	*<0.001	2.994 (2.254-3.987)	*<0.001
Pre-transplant factors				
Renal osteodystrophy	1.393 (0.847-2.291)	0.191		
Parathyroidectomy	1.000 (0.703-1.423)	0.999		
Pre-transplant dialysis modality				
Hemodialysis	1		1	
Peritoneal dialysis	0.694 (0.552-1.172)	0.002	0.761 (0.603-0.959)	*0.021
Pre-emptive	0.922 (0.725-1.172)	0.505	0.901 (0.700-1.160)	0.419
Comorbidity				
Osteoporosis	1.177 (0.744-1.862)	0.486		
Hyperthyroidism	1.085 (0.540-2.181)	0.819		
Hypertension	0.794 (0.657-0.960)	*0.017	0.753 (0.617-0.918)	*0.005
Diabetes mellitus	1.473 (1.241-1.748)	*<0.001	1.594 (1.330-1.911)	*<0.001
Systemic lupus erythematous	0.785 (0.491-1.255)	0.311		
Hyperlipidemia	0.878 (0.720-1.071)	0.200		
Coronary artery disease	0.890 (0.693-1.144)	0.365		
Cerebrovascular disease	0.769 (0.532-1.112)	0.162		
Chronic obstructive pulmonary disease	1.121 (0.792-1.587)	0.518		
Obesity	0.049 (0.000-14.833)	0.301		
Malnutrition	0.984 (0.316-3.059)	0.977		
Inflammatory bowel disease	1.271 (0.568-2.843)	0.559		
Rheumatoid arthritis	0.983 (0.407-2.371)	0.970		
Hypogonadism and postmenopausal disorders	0.957 (0.645-1.421)	0.828		
Alcoholism	0.050 (0.000-37.530)	0.374		
Post-transplant factors				
Mean dosage of glucocorticoids (mg/day)				
0-2.9	1		1	
>2.9-5.3	1.433 (1.102-1.862)	*0.007	1.794 (1.373-2.343)	*<0.001
>5.3-8.7	2.155 (1.667-2.786)	*<0.001	2.902 (2.227-3.782)	*<0.001
>8.7	6.692 (5.202-8.609)	*<0.001	9.617 (7.393-12.510)	*<0.001
Bone-protective medication				
Bisphosphonate therapy	1.218 (0.802-1.849)	0.354		
Calcium	0.742 (0.603-0.912)	*0.005	0.746 (0.600-0.928)	*0.009
Vitamin D	0.686 (0.524-0.899)	*0.006	0.811 (0.612-1.076)	0.146
Calcium with vitamin D	0.583 (0.261-1.304)	0.189		
Immunosuppressive medications				
Tacrolimus	0.564 (0.469-0.678)	*<0.001	0.520 (0.413-0.654)	*<0.001
Cyclosporine	1.207 (1.020-1.427)	*0.028	0.827 (0.673-1.017)	0.072
Azathioprine	0.510 (0.273-0.954)	*0.035	0.415 (0.221-0.779)	*0.006
Mycophenolate mofetil/Mycophenolic acid	0.626 (0.462-0.850)	*0.003	0.586 (0.421-0.816)	*0.002
mTOR inhibitors	0.752 (0.633-0.893)	*0.001	0.768 (0.643-0.917)	*0.004

*p<0.05

Table2

PUB400

Paragonimiasis Mimicking Ureter Stone in Living Kidney Donor

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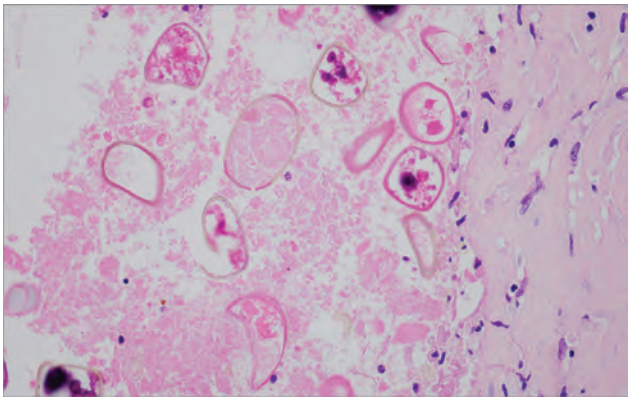
Introduction: Extrapulmonary paragonimiasis mainly involve pleural, subcutaneous, cerebral, and spinal infection. Other extrapulmonary paragonimiasis has been reported in hepatic, splenic, abdominal, urinary, and gynecologic organs. We report a case of paragonimiasis mimicking ureter stone in living kidney donor.

Case Description: We decided kidney transplantation between the married couple. The living donor was 61 year old male, and his CT angio abdomen scan showed about 0.6 cm stone at left proximal ureter, and small size periureteral low density lesion at the left proximal ureter. In operation, we found of a lump of soft tissue in periureter, measuring 4.5x4x2.5cm, yellowish adipose tissue-like appearance. Frozen specimen cut surface showed cystic appearance filled with yellowish necrosis like material, and was diagnosed as parasite infection, morphologically paragonimiasis. Kidney transplantation was done steadily, and post-operative course progressed smoothly.

Discussion: Donor showed positive in P.westermani Ab and Cysticercus Ab, but recipent showed negative. After further interview, he had history of paragonimiasis and taking praziquantel 15 years ago. We prescribed to her praziquantel 1,800 mg for 3 days. In post transplant three month, her serum creatinine incresed from 0.95 mg/dL to 1.57 mg/dL, and sonogram showed hydronephrosis. We decided double J stent insertion through percutaneous nephrostomy, and follwed up for eight months cautiously. Even though waiting, proximal ureter stricture was incurred, and she has been regular double J stent exchange under general anesthesia. Even if extraplumonary paragonimiasis involving ureter is very uncommon, the meticulous history taking and examination would be needed in transplantation work up.



Parasite infection, Morphologically paragonimiasis

PUB401

Clinical Course of a Kidney Transplant Recipient with Epstein-Barr Virus Viremia Treated with Maribavir

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Introduction: Impaired T-cell immunity following kidney transplantation increases the risk of both primary infection and reactivation of latent Epstein-Barr Virus (EBV). EBV viremia is managed primarily with reduction in maintenance immunosuppression, but with varied results. We present the first clinical case of a kidney transplant (KT) recipient with EBV viremia treated with Maribavir, a novel therapeutic that inhibits EBV transcription and viral replication.

Case Description: A 70-year-old Taiwanese female with a history of end stage kidney disease secondary to diabetic nephropathy underwent a deceased donor KT with thymoglobulin induction. She received maintenance immunosuppression with tacrolimus, mycophenolate, and prednisone. At the time of transplantation, she was at moderate risk for EBV infection with both donor and recipient EBV IgG antibodies positive (recipient IgG 526 Unit/mL; IgM <10 Unit/mL). Six months later she had worsening leukopenia and was diagnosed with EBV viremia that initially resolved with reduction of mycophenolate. Sixteen months following KT she again developed EBV viremia. She had persistent and worsening viremia despite cessation of mycophenolate, dose reduction of tacrolimus, and Prednisone to 2.5 mg daily. She was initiated on IV immunoglobulin 500 mg/kg, but treatment was discontinued after her first dose due to the development of severe myalgia, transaminitis, and hemolytic anemia. She was then initiated on off-label Maribavir 200mg twice daily with significant improvement in viremia. Figure 1 summarizes her treatment course.

Discussion: Maribavir is a novel benzimidazole riboside compound that inhibits EBV DNA polymerase processivity factor (BMRF-1), reduces some EBV glycoproteins, and inhibits EBV viral transcription. Maribavir treatment was well tolerated at 200mg twice daily. Maribavir is the only intervention that was associated with a significant reduction in EBV viremia in this patient.

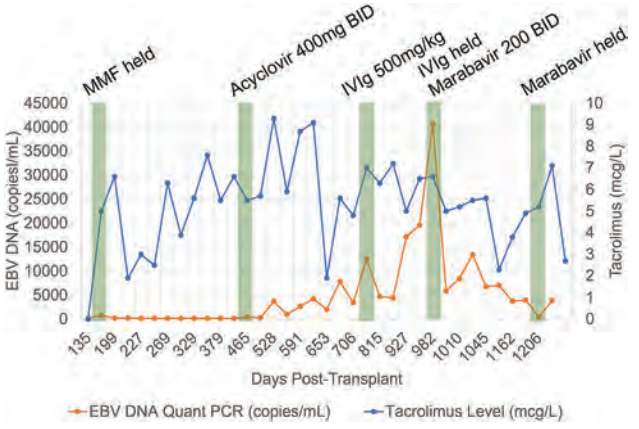

Figure 1: Clinical Course with EBV PCR Trend

PUB402

The Molecular Microscope Diagnostics System (MMDx) May Have the Potential to Differentiate Molecular T Cell-Mediated Rejection (TCMR) Among Kidney Transplant Recipients with Chronic-Active TCMR

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Background: Treatment of chronic-active T-cell mediated rejection (caTCMR) lacks consensus, causing many different therapeutic approaches. If changes in transcript patterns analyzed by the Molecular Microscope Diagnostic System (MMDx) may differentiate among these cases with caTCMR and offer additional diagnostic value needs to be evaluated.

Methods: In this single-center cohort of 326 indication kidney transplant biopsies assessed by histology and MMDx at the University Hospital Zurich, we analyzed 15 cases with caTCMR after the exclusion of overlapping pathologies such as BK nephropathy, pyelonephritis, and acute interstitial nephritis. 7 cases with combined acute TCMR and caTCMR were compared to 8 cases with caTCMR only.

Results: 3 of 7 cases (43%) with combined acute TCMR and caTCMR, and 1 of 8 cases (13%) with caTCMR only showed pure molecular TCMR. In addition, 3 of 7 cases (43%) with combined acute TCMR and caTCMR, and 4 of 8 cases (50%) with caTCMR only showed mixed molecular ABMR/TCMR with histologic ABMR in 5 of 7 cases (71%). Among 3 of 8 cases (38%) with caTCMR only but no molecular rejection, 2 cases showed an all ABMR rejection phenotype score (sum of R4, R5, and R6) ≥0.20, and 1 case showed a TCMR phenotype score (R2) ≥0.10.

Conclusions: The MMDx may have the potential to differentiate histologic caTCMR into molecular TCMR, molecular ABMR/TCMR, or no molecular rejection. Whether the observed minor molecular findings are attributable to undetected overlapping pathologies, cortex/medulla sampling variations, or a suspected continuum of caTCMR needs to be studied.

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PUB403

Five Scenarios Across the Antibody-Mediated Rejection (ABMR) Continuum: The Added Value of the Molecular Microscope Diagnostic System (MMDx) Confirmed by Follow-Up Biopsies

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Background: The Molecular Microscope Diagnostic System (MMDx) has evolved to be an essential tool in suspected antibody-mediated rejection (ABMR). However, cost and availability limit a generalized use making it even more important to outline specific scenarios in which MMDx may add significant diagnostic value.

Methods: In this single-center cohort we analyzed 22 kidney allograft biopsies, including 9 follow-up biopsies assessed by histology and MMDx.

Results: "Isolated glomerulitis": Two cases w/o DSA showed isolated glomerulitis (g1, ptc0, v0). On a follow-up biopsy one year later, histology no longer demonstrated glomerulitis, and MMDx confirmed no rejection in each biopsy. "MVI in the absence of DSA": Two cases showed MVI (g+ptc≥2) in the absence of DSA. On follow-up biopsy, histology showed ongoing MVI in one case, confirmed by MMDx in each biopsy. On follow-up biopsy in the second case, histology showed no MVI (g0, ptc0), and MMDx confirmed no ABMR in each biopsy. "MVI in ABOi transplantation": Two cases after ABOi transplantation were diagnosed with TCMR plus MVI in the absence of DSA, confirmed by MMDx with molecular TCMR. After successful treatment of TCMR, MVI persisted on follow-up biopsy without any clinical suspicion for ABMR. MMDx showed no ABMR in each biopsy. "Mixed rejection": In two cases with malcompliance, ABMR could not be diagnosed according to Banff with concomitant TCMR, but MMDx suggested ABMR/TCMR in both cases. After treatment for ABMR/TCMR, one case showed ongoing ABMR by histology and MMDx, while the other case showed resolved ABMR by histology and MMDx. "Early active ABMR": One case showed no rejection on histology one week post-transplant but minor ABMR by MMDx. On follow-up biopsy two weeks later, ABMR was confirmed by histology and MMDx. Four other cases with early active ABMR within the first two post-transplant weeks showed ABMR by histology and MMDx.

Conclusions: The MMDx appears to have added value across the ABMR continuum, both to confirm and reject the diagnosis of ABMR. In addition to the Banff 2019 recommendation, scenarios such as MVI in ABOi transplantation and mixed rejection should be considered as indications for the MMDx. Earlier diagnosis of early active ABMR, while possible with MMDx, is likely the exception.

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PUB404

First Year After Transplant Infections in a Young Kidney Transplant Cohort: Is Preemptive Transplant Protective?

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Background: Infection after a kidney transplant is a serious cause of morbidity and mortality. Weighing the risks and benefits of immunosuppression is of paramount importance to patient wellbeing and transplant survival.

Methods: This is a prospective observational study looking at the variety of infections in a young cohort with living related kidney transplant. Fifty-one records of patients who had a kidney transplant between Jan 2020 and Jan 2022 were followed up and clinically significant infections were investigated and documented.

Results: This was a young transplant cohort with a mean age of 28.4 ± 10.4 yrs. Females were 45.1%. The commonest infection was lower urinary tract infection *(UTI)* (27.3%) followed by SARS-COV2 and Herpes Zoster (15.2%). Median Tacrolimus level was (7.8) ng/ml and was slightly higher in the group without infection (8.95) ng/ml P=0.21. Haemoglobin was higher in the group without infection median (10.8) gm/dl (7.3-15.3) compared to (10.2) gm/dl in the group without infection (7.8-14) odds ratio *(OR)* = 0.78 confidence interval *(CI)* (0.5-1.1). More infections were recorded in Kidney transplant recipients *(KTR)* from donors over the age of 60 (0R =2.6 ;95% CI :0.5-12; P=0.2). Post transplant diabetes *(PTDM)* was more prevalent in the group with infection (25%) (OR 1.9 p =0.365). In the group without infection, 59.3% had a preemptive transplant compared to 20.8% in the group with infection (OR= 0.18; 95% CI: 0.052-0.631; P=0.007).

Conclusions: This study shows that the distribution of infection in this cohort with living related kidney transplantation. Lower urinary tract infection was the commonest infection followed by SARS-COV2 and Herpes Zoster. We observed a lower incidence of infection with preemptive transplantation.

Table (1) Baseline characteristics for Kidney transplant recipients with and without infection.

Baseline characteristics	Total (n = 51)	Kidney transplant Recipient With infection (n = 24)	Kidney transplant Recipient Without infection (n = 27)	OR (95%C.I)	p
Age (years)					
Mean ± SD.	28.4 ± 10.4	26 ± 9.6	30.6 ± 10.8	0.955 (0.901 – 1.012)	0.122
Median (Min. – Max.)	27(12 – 54)	25.5(12 – 51)	30 (12 – 54)		
Gender					
Male	28 (54.9%)	13 (54.2%)	15 (55.6%)	0.945 (0.313 – 2.854)	0.921
Female	23 (45.1%)	11 (45.8%)	12 (44.4%)		
Aetiology of ESKD					
Unknown	19 (37.3%)	6 (25.0%)	13 (48.1%)	0.359 (0.109 – 1.184)	0.092
HTN	8 (15.7%)	2 (8.3%)	6 (22.2%)	0.318 (0.058 – 1.756)	0.189
GN	7 (13.7%)	3 (12.5%)	4 (14.8%)		0.760
SLE	3(5.9%)	3(12.5%)	0 (0.0%)	–	–
ADPKD	2(3.9%)	0(0%)	2 (7.4%)	–	–
VUR	2(3.9%)	2(8.3%)	0 (0.0%)	–	–
Alport	1(2%)	0(0%)	1 (3.7%)	–	–
DM type 1	1(2%)	1(4.2%)	0 (0.0%)	–	–
Preeclampsia	1(2%)	1(4.2%)	0 (0.0%)	–	–
Amyloidosis	1(4.2%)	0 (0.0%)	0 (0.0%)	–	–
CIN	2(3.9%)	2(8.3%)	0 (0.0%)	–	–
ATG	43(84.3%)	20(83.3%)	23 (85.2%)	0.870 (0.192 – 3.936)	0.856
Tacrolimus Level					
Mean ± SD.	8.8 ± 3.1	8.2 ± 3.9	9.30 ± 2.0	0.882 (0.722 – 1.077)	0.217
Median (Min. – Max.)	8.8(1.4 – 19.9)	7.8(1.4 – 19.9)	8.95 (6.50 – 13.8)		
MMF	48(94.1%)	22(91.7%)	26(96.3%)	0.423 (0.036 – 4.985)	0.494
Donor>60 years	9(17.6%)	6(25%)	3 (11.1%)	2.667 (0.586 – 12.128)	0.204
Slow graft function	1(2%)	0(0%)	1 (3.7%)	–	–
PTDM	10(19.6%)	6(25%)	4 (14.8%)	1.917 (0.469 – 7.831)	0.365
Haemoglobin					
Mean ± SD.	10.4 ± 1.7	10.1 ± 1.7	10.7 ± 1.7	0.779 (0.550 – 1.104)	0.160
Median (Min. – Max.)	10.3(7.3 – 15.3)	10.2(7.8 – 14)	10.8(7.3 – 15.3)		
Preemptive Tx	21(41.2%)	5(20.8%)	16(59.3%)	0.181 (0.052 – 0.631)	0.007

SD: Standard deviation C.I: Confidence interval
OR: Odds ratio LL: Lower limit UL: Upper Limit

PUB405

Quality Improvement Initiative to Enhance Post-Renal Allograft Biopsy Follow-Up

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Background: Kidney transplant recipients who undergo allograft biopsies are often discharged on the same day with instructions to schedule a subsequent visit with Transplant Clinic for results and further management plans. Such patient-initiated follow-ups can lead to care delays and patient dissatisfaction. Furthermore, inadequate documentation of communication with patients regarding biopsy results can contribute to confusion among physicians. We thus implemented patient-centered interventions to improve 30-day follow-up and identify potential late-onset complications of kidney allograft biopsy. These interventions include concurrent scheduling of biopsy and post-biopsy follow-up visits, reminding patients of their appointment on the day of the biopsy, post-procedure phone check-ins, and improved documentation of biopsy result communications.

Methods: We analyzed a pre-intervention sample of 23 renal allograft biopsies from January to April 2021. Post-intervention, we reviewed all 24 renal allograft biopsies performed from January to April 2022. We compared the rates of 30-day follow-ups, either through telehealth or in-person visits with documented biopsy result discussions, over a four-month period before and after the intervention.

Results: No significant differences were observed in baseline clinical characteristics between pre-and post-intervention groups: Age: 53 ± 2.7 vs 48 ±2.9 years, p=0.11; Male: 65.2% vs 45.8%, p=0.18. The 30-day follow-up rate was 87.0% (20/23) pre-implementation and 100% (24/24) post-implementation, (p=0.07). The average interval between biopsy and follow-up date shortened from 18 ± 3.6 days pre-intervention to 12 ± 1.5 days post-intervention (p=0.07). The rate of major treatment modification during follow-up visits was 52.2% before the intervention and 66.7% after it (p=0.31).

Conclusions: The implementation of these patient-centered interventions led to an improvement in post-renal allograft biopsy follow-up rates, although not statistically significant with a borderline p-value. The limited study power due to small sample size may have contributed to this outcome. We observed that over 50% of transplant recipients require treatment modifications post-biopsy, emphasizing the need for prompt follow-up. Hence, further studies exploring ways to improve follow-up efficacy are warranted.

PUB406

Missed Diagnosis as Risk Factor for Graft Loss: Analysis of the Tuscany Kidney Transplant Waitlist

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Background: A significant percentage of patients on the kidney transplant waitlist have no primary diagnosis. Nonetheless, recurrence of glomerulonephritis (GN) is the second leading cause of graft loss and the majority of patients with unknown etiology of ESKD (uESKD) are frequently labelled as "presumed GN". Furthermore, the burden of inherited kidney diseases in uESKD population is actually uncertain. By far, it is not known whether the lack of primary diagnosis represents a risk factor for graft loss.

Methods: A total number of 537 patients placed on the transplant waitlist in Tuscany were examined retrospectively up to April 2023. We evaluated, by univariate and multivariate analysis, if the lack of diagnosis was a risk factor for graft failure in patients waiting for their first or further transplant.

Results: Out of 537 patients listed in the Tuscany area, 43.5% had missed diagnosis. The distribution by gender, age and comorbidities were comparable between patients waiting for their first or further transplant. In our cohort, 32.6% of patients were waiting for re-transplant, among them 45.4% with uESKD, mostly represented by presumed GN (66.6%). In multivariate analysis, both primary GN (p<0.013, CI: 0.176-0.815) and presumed GN prior to transplant (p<0.043, CI: 0.222-0.978) proved to be a risk factor for graft loss.

Conclusions: A significant percentage of patients placed on the kidney transplant waitlist presents an uESKD, which embraces presumed GN and inherited kidney diseases. Besides primary GN, presumed GN prior to transplant appears to be a risk factor for graft loss but, unlike in primary GN, a targeted therapeutic approach is not feasible. Our study has some limitations, such as possible confounding factors/selection bias in listing ESKD patients. Additional analysis are needed to confirm these findings. Meanwhile we have been implementing a regional program to reduce the percentage of uESKD of both immune-mediated and inherited kidney diseases. A multidisciplinary team has developed a specific algorithm based on AI-related tools, to help guiding the diagnostic process by genetic evaluations, more extensive use of biopsy and proteomic-related analytical techniques.

PUB407

Therapeutic Plasma Exchange with TPE 2000 Membrane for Antibody-Mediated Cardiac Transplant Rejection

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Introduction: The removal of pathogenic substances by therapeutic plasma exchange (TPE), as a treatment for antibody-mediated rejection (AMR) in cardiac transplant, has gain a way as a modern medical therapy. Membrane filtration with TPE 2000 (Fig. 1), targets large-molecular-weight substances present in plasma as immunoglobulin. TPE could be offered as initial therapeutic intervention as it rapidly removes antibodies and cytokines from patients' plasma with a technology already in ICU: CRRT machines.

Case Description: A 24-year-old woman, post cardiac transplantation 4 months prior, arrived to ER with dyspnea, orthopnea and oliguria. BP 91/64 mmHg, HR 120bpm, 24 RR, O2 sat 85%. Echocardiography: LVEF 20%, severe cardiac graft dysfunction. A myocardial biopsy was performed. She presented pulseless electrical activity and ALS were performed for 2 minutes with success. Inotropic and vasopressors were started, orotracheal intubation was required. Biopsy shows changes compatible with AMR. Steroids and TPE were offered. 5 sessions with TPE 2000 membrane, prescription with 1.5L plasma exchange with albumin at 25% (Table 1). Vasopressor reduction, inotropic withdrawal, and LVEF increase to 40% were achieve after treatment.

Discussion: Allograft dysfunction due to AMR is one of the worst complications post heart transplantations. In this case we were able to evaluate allograft improvement. LVEF pre-TPE 20% to post-TPE 40%. This can guide us to continue the research about TPE in AMR as there is no evidence-based guidelines that establish this therapy for patients as complex as this are.

Figure 1

Table 1

Weight (kg)	Htco (%)	Plasma Volume (ml)	Plasma Exchange (1.5)	Blood flow	Substitution Flow (ml/h)	Plasma UF (ml/h)	Total Volume (ml)
54	49	1823	2,735	120	1000	0	3000
54	38.5	2159	3,300	120	1000	0	3500
54	40	2106	3,200	120	1000	100	3500
54	32	2387	3,580	120	1000	100	3500
54	26	2596	3,893	120	1000	100	3510

PUB408

Evolution of Kidney Function Following Living Donor Nephrectomy

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Background: The Glomerular filtration rate (GFR) pre and post renal donation can vary according to the population and lifestyle, so there is a long -term risk of developing renal disease, so the long -term follow -up is of the utmost importance.

Methods: Retrospective, descriptive and analytical study of donors registered at the National Medical Center "20 de Noviembre" from May 2016 to August 2021 with 1 year follow -up. The objective is to determine the evolution of renal function per year in renal organ donors.

Results: We find 23 women (51%) and 22 men (49%) whose basal characteristics were: age 41 years, serum creatinine (Crs) of 0.76 mg/dl, eGFR CKD-EPI 108 ml/min/1.73m2; Creatinine clearance (CrCl) 106 ml/min; and GFR with DTPA 126 ml/min. A significant difference was found at one year of evolution between the pre and post-donation values of: Crs (Dif. = 0.35 mg/dl; p <0.0001); eGFR CKD-EPI (Dif. = 32.3 ml/min/1.73m2; p <0.0001); and CrCl (Dif. = 36.4 ml/min; p <0.0001). Also there is a difference between Crs values between women and men (0.94 vs 1.3 mg/dl; p <0.0001, 95% IC 0.46 - 0.24) and CrCl (56.5 vs. 71.3 ml/min; p = 0.005, 95% IC 24.8 24.8 - 4.6). There was no significant difference between pre- and post-donation albuminuria (p = 0.06) with an average of 24.3 mg/day (± 86.9 mg/day), no difference between genres (p = 0.51).

Conclusions: The decrease in the glomerular filtration rate and creatinine clearance in our population was on average of 32 to 36 ml/min, without finding an association between the body mass index and the development of hypertension to this, however, with a trend associated with the age of donation.

Comparison of the renal function basal vs post nephrectomy

Variable	Basal	One year post nephrectomy	Results
Creatinine mg/dl	0.76 (± 0.16)	1.1 (± 0.25)	Dif= 0.35 p<0.0001 CI 95% 0.32-0.39
eGFR CKD EPI ml/min/1.73m2	108 (± 16.4)	76 (± 17.4)	Dif= 32.3 p<0.0001 CI 95% 35.4-29.2
eGFR MDRD ml/min/1.73m2	102.3 (± 19.9)	65.4 (± 14.9)	Dif= 36.9 p<0.0001 CI 95% 33.6-40.1
CrCl ml/min	106 (± 24)	63.9 (± 15.2)	Dif= 36.4 p<0.0001 CI 95% 47-25.9

PUB409

Heart Failure with Reduced Ejection Fraction (HFrEF): Contraindication to Kidney Transplant?

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Background: Heart failure is frequent complication of advanced CKD and many transplant candidates will have reduced ejection fraction (EF). Data remains limited on whether heart failure with reduced EF (HFrEF) at the time of transplant is associated with an increased risk of graft failure and mortality. In this study, we sought to compare the patient and graft survival between the cohorts of patients with or without HFrEF undergoing renal transplantation.

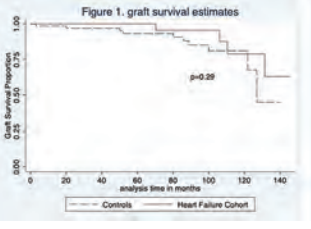
Methods: We performed a retrospective matched cohort analysis of 32 patients with pre-transplant EF </=45% (HF cohort) and 67 patients with EF >45% (control cohort) based on transthoracic echocardiogram, transplanted between January 25, 2011 and July 21, 2015. Patients without pre-transplant EF were excluded from the analysis.

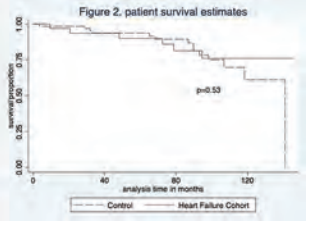
Results: Baseline characteristics were similar except ATG induction was less frequent in the HF cohort (Table1). At a median of 86 months post-transplant, no statistically significant difference was observed between the control and HF cohorts on the overall graft survival (Figure 1, p=0.29) and the overall patient survival (Figure 2, p=0.53). There was no statistically significant difference in the mean creatinine levels at 1 year post-transplant between the control (1.41 mg/dL) and HF (1.48 mg/dL) cohorts, as well as in the hospitalization rates within 1 year of transplant.

Conclusions: In this pilot study, we examined the graft and patient survival outcomes of renal transplant patients with heart failure and found no significant differences compared to matched controls. Our data suggests that ESKD patients with low EF prior to transplant may have significant improvement in their heart function post-transplantation. Low EF alone should not be a contraindication to kidney transplant.

Table 1. Study Cohort

Patient Baseline Characteristics	HF cohort (n=32)	Control cohort (n=67)	p value
Average Age (yr.)	54 ± 12.9	53 ± 13.7	0.99
Male sex	24 (75.0%)	54(80.6%)	
Ethnicity			0.42
White/Black/Hispanic/Asian	41%/31%/16%/13%	55%/16%/13%/12%	
ESRD etiology			0.09
Diabetes mellitus	9 (28.1%)	13 (19.4%)	
Hypertension	12 (37.5%)	18 (26.9%)	
IgA nephropathy	1 (3.1%)	9 (13.4%)	
Focal segmental glomerulosclerosis (FSGS)	3 (9.4%)	4 (6.0%)	
Polycystic kidney disease	3 (9.4%)	9 (13.4%)	
Pre-emptive transplant	2 (6.3%)	23 (34.3%)	0.96
Living donor kidney	16 (50.0%)	36 (53.7%)	0.73
Thymoglobulin / Simulect induction	22 (68.8%) / 10(31.3%)	63 (94.0%) / 4(6.0%)	0.001
Left ventricular ejection fraction (LVEF), pre-transplant	39.10%	60.60%	
Post-transplantation Clinical Outcomes			
Outcomes (total patient count)			
Delayed graft function (DGF)	9 (28.1%)	13 (19.4%)	0.33
Hospitalization within 1 year	14 (43.8%)	36 (53.7%)	0.36
Acute rejection within 1 year	1 (3%)	6 (9%)	0.29
Total deaths	6 (18.8%)	14 (20.9%)	
Other Outcomes			
Mean creatinine at 1 year (mg/dL)	1.48 ± 0.49	1.41 ± 0.51	0.52
Mean eGFR at 1 year (mL/min/1.73m2)	50	53	
Mean urine microalbumin/creatinine at 1 year (g/g)	0.04	0.12	0.41





PUB410

Effectiveness of Evusheld (Tixagevimab/Cilgavimab) in Reducing Breakthrough COVID-19 Infections Among Vaccinated Kidney Transplant Recipients

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Background: Transplant patients are at high risk of COVID-19 infection and its complications. Up to 33% of transplant patients have inappropriate response to COVID-19 vaccination with 2% mortality risk. Studies showed significant reduction with breakthrough COVID-19 infection post Evusheld administration. An Evusheld Clinic was launched at our center, in late July 2022, to facilitate the Evusheld administration to our kidney transplant patients. The aim of this study was to evaluate the efficacy of Evusheld pre-exposure prophylaxis preventing breakthrough COVID-19 infection among vaccinated kidney transplant patients in a single center study.

Methods: We conducted a retrospective analysis of all kidney transplant patients at our center with breakthrough COVID-19 infection post-Evusheld administration between August 1, 2022 and January 6, 2023. Chi square and Fisher Exact test were performed using SPSS Statistics 23 with a 0.05 significance value.

Results: 217 patients were included (Male: 66.8%; Age: 56.9±14.2years). 127 (58.5%) patients received Evusheld 300 mg through our clinic between August 1 - November 30, 2022. By January 6, 2023, 27 (12.4%) patients developed breakthrough infection since August 1, 2022, compared with a total of 76 (35.9%) COVID-19 infections since the pandemic in March 2020. 19 (15%) breakthrough infections were reported post-Evusheld administration compared with 8 (9%) cases in patients who did not receive Evusheld (*P*=0.18). All Evusheld patients with breakthrough infections were fully vaccinated (3 vaccine doses) compared with 75% of those with no Evusheld and breakthrough infections (*P*=0.08). Time from the last COVID-19 vaccination to infection was not significantly different among patients with and without Evusheld [4.6 (0.5-8.8) vs. 6.5 (92-8-10.6); *P*=0.46].

Conclusions: Evusheld 300 mg did not decrease the risk of breakthrough COVID-19 infection among fully vaccinated kidney transplant patients. Studies with higher doses of Evusheld and further COVID-19 vaccination are still required to determine efficacy of prevention of breakthrough COVID-19 infection among transplant patients.

PUB411

Analyzing the Influence of Demographic Factors on Kidney Transplantation Willingness Among Central Virginia Kidney Disease Patients

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Background: Kidney transplantation (KT) offers increased quality of life and improved clinical outcomes (including patient survival) as compared to dialysis treatment. Barriers in access to earlier steps of transplantation (i.e. referral and evaluation)

are inadequately reported in the current research field. The study aimed to identify educational barriers, racial barriers, socioeconomic-based barriers, and culture-based barriers. Resources seeking to develop educational interventions for both patients and providers may aid in reducing existing barriers.

Methods: A survey consisting of fourteen total questions was administered to patients of varying stages of kidney disease at the Prince George, Southside, and Midlothian Clinic locations in Central Virginia. The study sought to evaluate the role of race and education level on familiarity of kidney transplantation/donation, comfortability with KT, and trust in health care systems.

Results: 103 patients across the three Central Virginia clinics were surveyed between late-March to mid-April of 2023. 47 (43.93%) of respondents identified as African American and 54 (50.47%) as White. Familiarity with the concept of kidney transplantation and comfortability with kidney transplantation in relation to education level of survey respondents was found to be statistically significant with p-values of p=0.008 and p=0.02, respectively (with p-value of <0.05). Strictly within the White Race, statistical significance (write actual p-value) was found in comparing education level of respondents to familiarity with kidney transplantation, trust in the healthcare system to provide safe transplantation, likeliness to consider kidney donation, and comfortability with kidney transplantation.

Conclusions: Based on the analysis of the survey responses, we were able to determine the comfortability with kidney transplantation and familiarity with kidney transplantation have some relation to education level in kidney-disease patients located within Central Virginia. Based on such results, it is likely that organ donation apprehension continues to be rooted in culture. Future education initiatives should take these exhibited racial differences into account for success in striving for transplant equity.

PUB412

Identifying Barriers to Kidney Transplantation in a Veteran Population

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Background: Kidney transplantation is the treatment of choice for end-stage kidney disease patients and improves survival. The Edward Hines, Jr. VA Hospital recently became a regional referral center for kidney transplantation for Veteran patients. The kidney transplant referral process involves being timely seen by the pre-transplant evaluation team, completing all the necessary initial testing for transplant, and submitting a whole package through the transplant referral and cost evaluation/reimbursement (TRACER) process. Once TRACER is submitted, the transplant center has 5 days to review and accept or decline the evaluation. Not all patients get the workup completed or get evaluated for listing due to multiple factors. Our aim was to investigate the barriers to listing for kidney transplantation at our hospital.

Methods: We analyzed data from 45 patients from our hospital who were referred to the Hines VA transplant center from March 2019 through December 2022. All analyses were performed in R version 4.2.3, Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

Results: Baseline characteristics of the patients are shown in the Table. The barriers identified are depicted in the Figure. Non-compliance of patients in completing the pre-transplant workup was the most frequent barrier, with other common barriers being delay in colonoscopy and presence of malignancy. A Kaplan-Meier estimate of median wait time from referral to evaluation revealed a marginal difference by age group, with longer wait times associated with increasing age.

Conclusions: There are multiple barriers to kidney transplant listing, with the most important being non-compliance of patients. This points toward improving patient education as a major focus to improving the pre-transplant evaluation process.

Funding: Private Foundation Support

Baseline characteristics (N=45)

Age	25-49 - 7 (15.6%) 50-65 - 21 (46.7%) >65 - 17 (37.8%)
Race	Missing - 2 White - 17 (39.5%) African American - 25 (58.1%) Other - 1 (2.3%)
Sex	Male - 44 (97.8%) Female - 1 (2.2%)
Comorbidities	DM - 37 (82.2%) HTN - 42 (93.3%) COPD - 8 (17.8%) Malignancy - 7 (15.6%) Obesity - 13 (28.9%) Cardiac Issues - 19 (42.2%) Psychiatric issues - 10 (22.2%) History of stroke - 6 (13.3%)

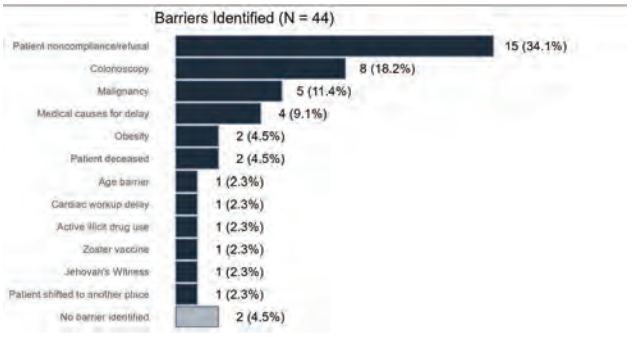


Figure - Kidney Transplant barriers

PUB413

Providing Medication Education to Renal Transplant Recipients: Are We Getting It Right?

Sadia Jahan, Tiah Doody, Jasmine Goh, Hanh Tran. *Central and Northern Renal and Transplantation Service, Adelaide, SA, Australia.*

Background: Successful medication-taking behaviour by kidney transplant recipients is associated with long-term survival and is dependent on knowledge of medication regimens with medication counselling playing a major role in this. The optimal way of medication education delivery is not known, and our project is to evaluate current forms and to obtain feedback on alternative strategies. At our centre in Adelaide Australia, renal transplant recipients receive medication-related education from a clinical pharmacist in the post-transplantation phase in the form of verbal education and provision of a locally developed information booklet (seventeen A5 pages) and individualised medication list approximately 2-3 days post transplantation.

Methods: We utilised the validated Kidney Transplant Understanding Tool (K-TUT) to determine our patients' level of knowledge regarding their transplant medications. We also developed a patient survey assisting in classifying level of health literacy related to transplant medication knowledge.

Results: As part of feasibility, we present results from eight patients with 2/8 from Indigenous background and 2/8 patients' primary language being non-English. K-TUT scores were distributed between 41 and 66 (1 point for correct answer and 0 point for incorrect answer with total score of 69). In terms of the questions asked about preparedness for medicines post-transplant, direct quotes include "I was a bit nervous because I didn't realise there were so many tablets to start off with so that was a bit of a shock" and "No, I wasn't confident at first, I was a bit scared of how much tablet I had to take". One emerging theme is that the information booklet is not being read (7/8) with comments such as "I just didn't have time" and "I had so much going on". Another theme pertains to different delivery of education in the form of "mobile app would be good, (explaining) the tablets" and "A mobile app would probably be handy because the doctor and pharmacist can update it quickly".

Conclusions: Data from our patients have clear emerging themes, and it will be prudent to continue recruitment into the study, to clearly identify areas for improvement with knowledge about possible implementation of alternative education strategies.

PUB414

Bone Mineral Metabolism Alterations in Kidney Transplant Recipients in a Colombian Caribbean Fourth-Level Hospital

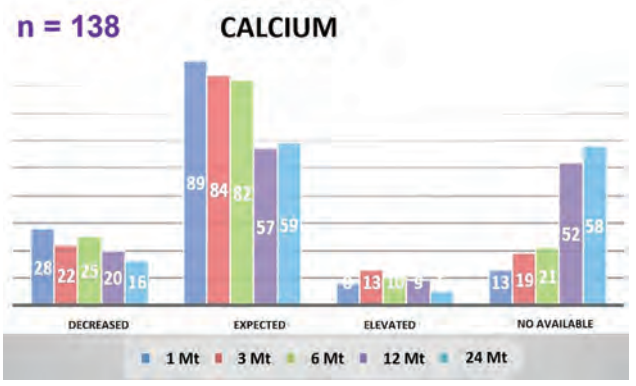
Karen G. Lasso,[1] Omar Cabarcas Barbosa,[1] William B. Riascos,[1] Alex Dominguez-Vargas,[2] Maria I. Pulgar,[3] Henry J. Gonzalez Torres,[1] Gustavo Aroca Martinez.[1] *[1]Universidad Simon Bolivar Facultad de Ciencias de la Salud, Barranquilla, Colombia; [2]Universidad del Norte Division Ciencias de la Salud, Barranquilla, Colombia; [3]Clinica de la Costa Ltda, Barranquilla, Colombia.*

Background: Bone mineral disorders are frequent in patients with chronic kidney disease (CKD). Renal transplantation inherits the morbid burden of the previous subject, increasing the risk of calcification disorders and cardiovascular disease. Surveillance should be strict in this population. The aim of this study is to describe the bone mineral metabolism alterations in renal transplant recipients in a fourth level hospital from the Colombian Caribbean.

Methods: A longitudinal study. Patients ≥18 years from the Local CKD Registry Cohort and functional renal allograft with at least 6 months of follow-up in the transplant program were enrolled. Clinical and laboratory variables from pathology follow-up examinations were retrospectively evaluated.

Results: A total of 138 patients, mostly men (59%), with a mean age of 43.7±12.3 years were included. A high prevalence of alterations in bone mineral metabolism was found: 78.36% at one-month post-transplant, 66.66% at 3 months, 69.56% at 6 months and 45.65% at 12 months. The most common alterations were: hyperparathyroidism (63%), hypocalcemia, hyperphosphatemia and hypovitaminosis D.

Conclusions: In this study, patients who underwent renal transplantation exhibited a significant prevalence of persistent hyperparathyroidism, irrespective of hypercalcemia. These findings highlight the critical need for diligent monitoring and effective management of bone mineral disorders in post-transplantation patients.



PUB415

Metabolic Profiles in Renal Transplantation: Assessing Hyperglycemia and Dyslipidemia Prevalence in Kidney Transplant Recipients from the Colombian Caribbean

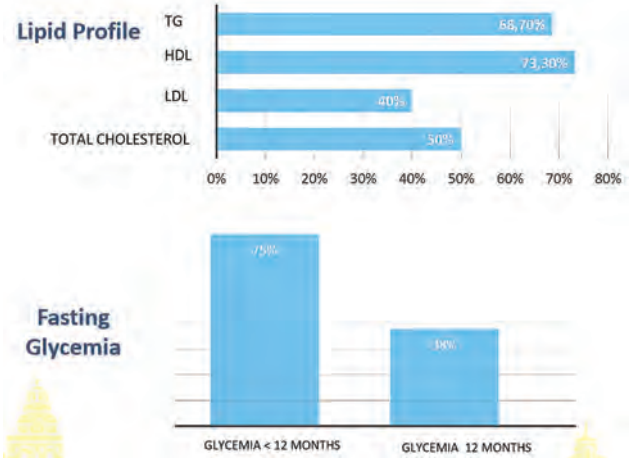
Karen G. Lasso,[1] William B. Riascos,[1] Omar Cabarcas Barbosa,[1] Alex Dominguez-Vargas,[2] Maria I. Pulgar,[3] Henry J. Gonzalez Torres,[1] Gustavo Aroca Martinez.[1] *[1]Universidad Simon Bolivar Facultad de Ciencias de la Salud, Barranquilla, Colombia; [2]Universidad del Norte Division Ciencias de la Salud, Barranquilla, Colombia; [3]Clinica de la Costa Ltda, Barranquilla, Colombia.*

Background: The renal transplant patient is at high risk of metabolic complications such as hyperglycemia, dyslipidemia, overweight, obesity and hyperuricemia. These conditions may affect the graft, cause early dysfunction and increase morbidity and mortality. The aim of this study was to determine the prevalence of metabolic disorders in renal transplant recipients in a fourth level hospital from the Colombian Caribbean.

Methods: This was a descriptive cross-sectional study that included patients aged 18 years and older from the Local CKD Registry Cohort with a functional renal allograft. Clinical and laboratory variables from pathology follow-up examinations were retrospectively evaluated.

Results: A total of 138 patients were included, mainly men (59%). The average age was 43.7±12.3 years. Mean paraclinical values were: glycemia 106.3±25.4 mg/dL, total cholesterol 206.5±37.6, LDL 117.9±62, HDL 37.1±8.2, VLDL55.6±26, and triglycerides 274.1±133 were recorded. Prevalence of altered lipid profile parameters and altered fasting glycemia were observed at different times during the period evaluated, including at 12 months post-transplantation.

Conclusions: In this study, the most common metabolic disorders in renal transplant recipients are hyperglycemia and dyslipidemia. Early detection and targeted interventions should focus on controlling hyperglycemia and dyslipidemia to mitigate the long-term consequences associated with these disorders in renal transplant recipients.



PUB416

De Novo Membranous Nephropathy and Humoral Rejection: A Different Presentation with a Shared Alloimmune Trigger

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Introduction: Membranous nephropathy (MN) is a glomerulopathy that can occur in a primary or secondary form. It is known that the primary form is related to the presence of autoantibodies against podocyte surface antigens, such as phospolipase A2 receptor (PLA2R) in up to 80% of cases. *De novo* MN has been described and related to humoral rejection, with the presence of circulating donor-specific antibodies (DSA) and biopsy findings of microvascular inflammation and C4d deposition in peritubular capillaries.

Case Description: A 26-year-old patient with CKD of unknown etiology underwent kidney transplantation from a deceased donor. The immunosuppression was tacrolimus and sodium mycophenolate. He had variable serum concentrations of tacrolimus despite maintenance of the dose, due to possible poor adherence. After 7 years of transplantation, he showed a significant increase in creatinine within a 3-month interval, as well as 24-hour proteinuria of 6 grams. He underwent a renal biopsy that demonstrated glomerular capillary loops with frequent spikes and holes, glomerulitis, 30-40% interstitial fibrosis and the presence of pericapillaritis. Immunofluorescence showed strong C4d deposition. Complementation of immunofluorescence with research for podocyte autoantibodies was requested, with positive research for IgG1, and negative for IgG4, PLA2R, THSD7A, NELL1, EXT1 and EXT2. DSA research showed the presence of antibody against HLA A1 (MFI: 13029). Intravenous immunoglobulin was administered, with partial improvement in creatinine. The patient evolved with graft loss 1 year after treatment.

Discussion: De novo membranous nephropathy after kidney transplantation may be associated with humoral rejection and be induced by alloimmune responses. The case above strengthens this hypothesis, as it fulfills the classic BANFF criteria for humoral rejection: presence of circulating DSA, glomerulitis and pericapillaritis on light microscopy and positive c4d on immunofluorescence. Furthermore, the search for the main autoantibodies involved in the pathogenesis of the primary nephropathy (IgG4, PLA2R, THSD7A, NELL1, EXT1 and EXT2) was negative, but positive for the IgG1 subclass that is related to de novo MN. The distinction between both is important for defining the treatment and prognosis.

PUB417

Zoom Before Clinic: How Telehealth Transforms Access for Kidney Transplantation Evaluation in the Post-COVID Era

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Background: In 2020, In response to the SARS-CoV-2 pandemic, our center implemented a telehealth (TH) appointment option for kidney transplantation (KT) evaluation. TH has been shown to decrease travel time to clinic appointments and improve healthcare access for patients living in rural locations. It is unknown whether TH impacts KT patients' access to initial evaluation and waitlisting. We investigated the patient demographics of those who utilized TH for KT evaluation and the impact TH had on the early stages of KT evaluation.

Methods: We performed a retrospective cohort study of adults referred for KT evaluation from 01/31/2020 -12/31/2021. We compared baseline clinical and sociodemographic characteristics between patients who were 1) seen in person (IP) vs. seen via TH for their first KT clinic appointment and 2) whether TH impacted KT waitlisting.

Results: 620 patients were evaluated for KT during the study period, 343 (55.3%) attended their first appointment IP, 277 (44.7%) attended via TH. TH decreased the time from referral to evaluation by 22 days (117 vs 95; p<0.001). Patients who utilized TH lived further from the transplant center (34 vs 28 miles, p=0.01), were younger (55 vs 60 years; p=0.003), were more likely to be English speaking (93% vs 81%; p<0.001) and employed (37% vs 27%; p=0.009) and were less likely to be on dialysis (36% vs 52%; p<0.001). There was no significant difference in the rates of waitlisting between IP vs TH (31% vs 33%; p=0.3).

Conclusions: The use of TH services during early stages of the KT process decreases the time from referral to evaluation, but does not affect rates of waitlisting for KT. Inequities in TH use for KT evaluation are of concern meriting further attention to ensure equitable access.

Funding: NIDDK Support

Characteristic	Overall N = 620[1]	In person N=343[1]	Telehealth N = 277[1]	p-value[2]
Days to be Seen	105 (66, 166)	117 (76, 195)	95 (63, 143)	**<0.001**
Waitlisted	203 (33%)	106 (31%)	97 (35%)	0.300
Distance from center	30 (16, 57)	28 (15, 49)	34 (18, 78)	**0.010**
Age	58 (46, 66)	60 (50, 67)	55 (43, 65)	**0.003**
Gender: Female	229 (37%)	133 (39%)	96 (35%)	0.300
Marital Status				
Divorced/Widowed/Separated	79 (13%)	46 (13%)	33 (12%)	0.600
Married/Partnered	337 (54%)	189 (55%)	148 (53%)	0.700
Single	174 (28%)	91 (27%)	83 (30%)	0.300
Unknown	30 (4.8%)	17 (5.0%)	13 (4.7%)	0.900
Preferred Language				
English	534 (86%)	277 (81%)	257 (93%)	**<0.001**
Other	42 (6.8%)	35 (10%)	7 (2.5%)	**<0.001**
Spanish	21 (5.0%)	25 (7.3%)	6 (2.2%)	**0.004**
Unknown	13 (2.1%)	6 (1.7%)	7 (2.5%)	0.500
Insurance				
Medicaid	85 (14%)	48 (14%)	37 (13%)	0.800
Medicare	312 (50%)	181 (53%)	131 (47%)	0.200
Other	36 (5.8%)	18 (5.2%)	18 (6.5%)	0.500
Private	186 (30%)	95 (28%)	91 (33%)	0.200
Unknown	1 (0.2%)	1 (0.3%)	0 (0%)	>0.900
Race/ Ethnicity				
Asian	85 (14%)	54 (16%)	31 (11%)	0.100
Hispanic Latino	77 (12%)	45 (13%)	32 (12%)	0.600
Multiracial Other	5 (0.8%)	3 (0.9%)	2 (0.7%)	>0.900
Native American	53 (8.5%)	30 (8.7%)	23 (8.3%)	0.800
Non-Hispanic Black	74 (12%)	46 (13%)	28 (10%)	0.200
Non-Hispanic White	273 (44%)	139 (41%)	134 (48%)	0.050
Unknown	53 (8.5%)	26 (7.6%)	27 (9.7%)	0.300
Employment				
Unemployed	389 (63%)	226 (66%)	163 (59%)	0.071
Unknown	34 (5.5%)	23 (6.7%)	11 (4.0%)	0.140
Employed	197 (32%)	94 (27%)	103 (37%)	**0.009**
Renal Disease				
Congenital/Hereditary	13 (2.1%)	8 (2.3%)	5 (1.8%)	0.600
Diabetes Mellitus	282 (45%)	157 (46%)	125 (45%)	0.900
Glomerulonephritis	113 (18%)	52 (15%)	61 (22%)	**0.028**
Hypertensive	86 (14%)	56 (16%)	30 (11%)	**0.049**
Other	95 (15%)	58 (17%)	37 (13%)	0.200
PKD	30 (4.8%)	11 (3.2%)	19 (6.9%)	**0.035**
Unknown	1 (0.2%)	1 (0.3%)	0 (0%)	>0.900
Dialysis				
Hemodialysis	278 (45%)	178 (52%)	100 (36%)	**<0.001**
No Dialysis	210 (34%)	106 (31%)	104 (38%)	0.062
Peritoneal Dialysis	69 (11%)	31 (9.0%)	38 (14%)	0.065
Unknown	63 (10%)	28 (8.2%)	35 (13%)	0.067

[1] Median (IQR); n (%)

[2] Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test

PUB418

Desensitization Protocol in Pakistan: Is It Worth Doing? A Case Series

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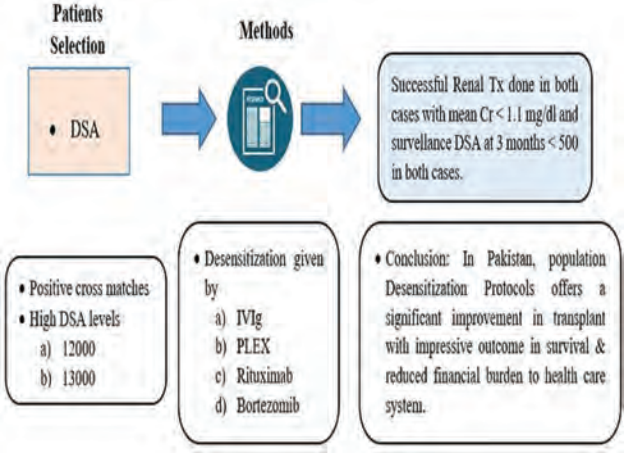
Introduction: Comparing with dialysis treatment for ESRD patients, renal transplant proffers significant survival and quality of life benefits. However, all-inclusive rates of transplantation still remain less for highly sensitized patients. For such cases, advanced approaches include (I) combinations of IVIg, rituximab, PE, bortezomib (II) pair donor exchange (PDE) (III) deceased donor allocation system (DDAS). At present, there are no guidelines for desensitization protocols and most of the published data is based upon * best practices * for desensitization that require individualization among patients. In countries like Pakistan with non-availability of PDE or DDAS, desensitization protocols should be utilized for highly sensitized patients.

Case Description: Methodology: We report two cases of highly sensitized live related renal transplant patients who underwent successful renal transplantation, after application of desensitization protocol using combination of IVIg, rituximab and PLEX in the first case and with addition of bortezomib to previously mentioned combination in second case. **Results:** Our first patient had positive DSA with MFI of 12000. After desensitization with combination of 2 Rituximab doses, 8 PLEX & IVIg, achieved MFI of 1700, and was therefore proceeded for renal transplant. In our second case, same protocol with addition of 3 doses of Bortezomib IV). DSA decreased significant to 2700 from 13000. Followup DSA at intervals of 1 and 3 months showed values in range of 400-600, Cr of 1.0 to 1.1mg/dl.

Discussion: Desensitization offers a significant improvement in renal transplant rates with impressive outcomes. In third world countries like Pakistan, where mostly adequate dialysis is not available and mortality rate is high, also overall financial burden is also a significant issue, performing renal transplant in highly sensitized population showed a preferable treatment option.



PUB419

Neurocognitive Concerns in Infants and Toddlers Awaiting a Kidney Transplant

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Background: The KDIGO (Kidney Disease Improving Global Outcomes) guidelines suggest neurocognitive assessment in pediatric kidney transplant candidates with end-stage kidney disease (ESKD) before 5 years of age. However, there are limited data delineating the neuropsychological characteristics of infants and toddlers awaiting a kidney transplant.

Methods: Twenty-five infants and toddlers between ages 0 and 2 years completed the Bayley Scales of Infant and Toddler Development (3rd Edition and 4th Edition) at our center as part of their pre-transplant evaluations. Descriptive analyses were performed to summarize the distribution of characteristics within this population. We used one-sample t-tests to compare the standard scores of study participants with the population mean. Pearson correlations were used to examine the correlations between the Bayley scores and age at the evaluation as well as the dialysis duration.

Results: The mean age of this cohort was 1 year (SD 0.76). Within this cohort, 68% of patients were white, 72% were male, and 72% had congenital anomalies of the kidney and the urinary tract (CAKUT). Of all patients, 28% received no dialysis, while 44% received dialysis for more than 1 year. The mean dialysis duration was 432 days (SD 474 days). The mean scores of cognitive assessment (mean 86.7, SD 2.99), language assessment (mean 79.2, SD 2.81), and motor assessment (mean 78, SD 17.3) were significantly lower than the population means (t=-4.43, t=-7.40, t=-5.84, respectively, p<.001). We found a significantly positive correlation between age and motor scores (r=.45, p=0.04) and a significantly negative correlation between dialysis duration and Bayley subscales, including cognitive (r=-.50, p=0.02), language (r=-.62, p=.004), and motor scales (r=-.63, p=0.003).

Conclusions: We found a significant correlation between dialysis duration and cognitive, language, and motor scores on the Bayley Scales of Infant and Toddler Development among children awaiting a kidney transplant. Moreover, the cognitive, language, and motor scores of infants and children awaiting a kidney transplant are significantly lower than the population means. Infants and children in this group may benefit from early physical therapy, occupational therapy, and speech therapy.

PUB420

Sex Differences in Non-Nephrologist Care Providers' Knowledge and Perceptions of Female Reproductive Health in CKD: A Survey Protocol

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Background: Chronic kidney disease (CKD) affects 12% of females globally and has important implications for reproductive health. Despite recommendations for multidisciplinary reproductive care, many females with CKD are managed independently by non-nephrologist care providers. This study aims to assess sex differences in non-nephrologist care providers' knowledge and perceptions of reproductive health in females with CKD.

Methods: A web-based survey will be developed following a literature review and consultations with experts in the field, as well as patient partners. Non-nephrologist care providers' knowledge and perceptions of reproductive health in females with CKD will be assessed, specifically as it relates to sexual health, menstruation, fertility, pregnancy, and menopause. Survey validity, clarity, and usability will be evaluated through pre-testing. The survey will be available in the world's 10 most commonly spoken languages. Snowball sampling will be employed via targeted emails to international and national reproductive healthcare provider organizations, as well as through social media platforms.

Results: Numeric and Likert-scale survey responses will be descriptively analyzed and free-text survey responses will undergo conventional content analysis. All results will be stratified by sex.

Conclusions: An improved understanding of sex differences in non-nephrologist care providers' knowledge and perceptions of female reproductive health in CKD can help identify gaps in care delivery and optimize reproductive health for this underserved population.

PUB421

Clinicopathological Study of Nine Cases of Proteinuria in Pregnancy, Including Hypertensive Disorders of Pregnancy

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Introduction: Advanced maternal age is a risk factor for prenatal complications including hypertensive disorder of pregnancy (HDP). Furthermore, severe proteinuria during pregnancy suggests the possibility of HDP and/or pregnancy-related renal complications, increasing the risk of worsening maternal renal prognosis.

Case Description: Over the past seven years, we experienced nine pregnant cases with severe proteinuria that required intervention from the internal medicine department. The average maternal age of all cases was 37.6 years old, and seven of the patients were advanced age pregnancy (>35 years old). Among the cases, seven presented nephrotic

syndrome (NS) and eight patients underwent renal biopsy, revealing in IgA nephropathy (n=1), minor change NS (MCNS) (n=2), focal segmental glomerulosclerosis (FSGS) (n=3), and thrombotic microangiopathy (n=2). Five patients were diagnosed with HDP and their mean gestational age at diagnosis was 36 weeks, with blood pressure (BP) of 155/86 mmHg, and urinary protein (U-P) level of 9.5 g/g Cr at any time. All HDP cases received antihypertensive therapy. Three of them improved proteinuria through medication alone, one required continuous hemodiafiltration for pulmonary edema after birth, and another case received plasmapheresis for obstetrical DIC and acute kidney injury. The four non-HDP patients were diagnosed at a mean gestational age of 27 weeks, with a BP of 122/74 mmHg, and U-P level of 7.34 g/g Cr at any time. These cases included IgA nephropathy, FSGS (cellular variant and tip variant), and MCNS, respectively, and underwent steroid therapy resulting in remission.

Discussion: We encountered nine cases of proteinuria in pregnancy, including HDP cases. A majority of the patients were of advanced maternal age, which is considered a risk factor for HDP. Our findings suggest that antihypertensive therapy can be expected to improve severe urinary protein levels in HDP cases although their histopathological findings were varied. On the other hand, it was crucial to identify the cause of proteinuria and to treat the underlying disease appropriately. Therefore, it is also important to perform renal biopsies whenever possible.

PUB422

Perceptions of Gynecologic Health and Health Care in Females Living with CKD: A Survey Protocol

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Background: Chronic kidney disease (CKD) affects more than 12% of females globally and its prevalence is increasing rapidly. CKD is often accompanied by gynecological health complications, with implications for menstruation, menopause, sexual health, fertility, and pregnancy. However, patient perceptions of gynecologic health and healthcare in females living with CKD are poorly understood. This study aims to assess the perceptions of gynecologic health and healthcare of females living with CKD.

Methods: An exploratory web-based survey will be developed following a thorough literature review and after consulting with experts in the fields of nephrology and gynecology, and with the engagement of patient partners. The questions will address patient perceptions of gynecologic health and healthcare-related to menstruation, menopause, sexual health, fertility, pregnancy, and urinary incontinence. Survey pre-testing with patient partners will assess face validity, clarity, length, usability, and technical functionality. The web-based survey will utilize adaptive questioning to help reduce survey complexity. Self-identified adult females with CKD will be invited to participate through national and international CKD patient organizations, as well as through social media platforms.

Results: Numeric responses will be analyzed using descriptive statistics and open-ended responses will be analyzed using conventional content analysis.

Conclusions: This study will be the first to our knowledge to assess comprehensive gynecologic health and healthcare-related perceptions of females living with CKD, and will aid in the integration of patient perspectives into future research and clinical initiatives.

PUB423

Biomarker Associations with Kidney Failure and Death

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Background: The NURTuRE CKD cohort comprises a wide range of biomarker measurements and outcome data for 2996 CKD patients based in the UK. A comparative study that outlines the relative importance of various biomarkers with respect to predicting mortality and kidney failure (KF) is of interest in biomarker selection for future studies.

Methods: Using biomarker data from the NURTuRE CKD cohort, we compared the means of patients who suffered KF (defined as dialysis start or transplant) or death within 2 years versus those who did not. A log-transform was applied to biomarkers with skew > 4, and a square root transform to biomarkers with skew between 1 and 4. After these transformations, all skews were within -1 and 1. Mean biomarker differences in the positive and negative groups were then assessed by computing deviations from the negative group means, scaled by the standard deviations of the negative group.

Results: Figure 1 shows mean biomarker differences scaled by standard deviation. For example, the first blue bar indicates that eGFR (after normalization) was about 1.25 standard deviations lower on average in patients who suffered kidney failure within 2 years compared with those who did not. Similarly, the first orange bar indicates 0.5 standard deviations lower eGFR in patients who died within 2 years compared with those who did not. The markers associated with the 4 largest differences for kidney failure were eGFR, serum-Creatinine, serum-Cystatin C, and Urine-ACR. The markers associated with the 4 largest differences for death were serum-Troponin, Age, serum-brain natriuretic peptide (BNP), and serum-growth differentiation factor-15 (GDF15).

Conclusions: The top four biomarkers associated with mortality (Troponin, Age, BNP, GDF15) are distinct from the top four biomarkers of kidney failure (eGFR, Creatinine, Cystatin-C, ACR). Perhaps unsurprisingly, the kidney failure markers are all related to kidney function, whereas the mortality markers are related to cardiac disease.

Funding: Commercial Support - AstraZeneca

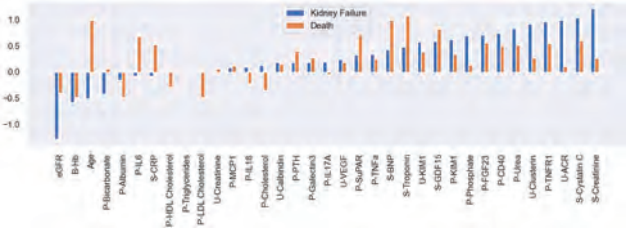

Figure 1: Mean biomarker differences in patients who suffered kidney failure or death within 2 years vs those who did not, scaled by standard deviation.

PUB424

The Variation of Estimated Glomerular Filtration Rate (eGFR) with Changes of Body Weight and Body Composition in a Health Check-Up Cohort Without CKD

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Background: Obesity is well known risk factor to chronic kidney disease, cardiovascular disease, and mortality. However, the effect of weight change within normal weight range on renal function has not been studied, well.

Methods: We enrolled non-CKD participants who had repeated routine health check-up at baseline, one-year, and three-year follow-up period. We measured fat-free weight (FFW) and fat-free percent (FFP) in body weight by InBody test. We analyzed the relationship between changes of body weight, BMI, FFW, and FFP during one-year follow-up period and variation of eGFR during three-year follow-up period. We define rapid decline of renal function as a decrease in eGFR ≥ 5 ml/min/1.73 m^2/year.

Results: Enrolled 1837 participants had eGFR of 101.1 (60.2~187.5) ml/min/1.73 m^2 and urine proteinuria by dipstick test less than one positive. Indicators of body composition were body weight of 66.8 (39.5~117.4) kg, BMI of 23.7 (15.2~36.2) kg/m2, FFW of 53.1 (30.9~78.1) kg, and FFP 78.4 (59.4-95.5) % at baseline examination. During one year period, the change of eGFR was related to percent change of FFP (factor B=0.197, p=0.012) and FFW (factor B=0.347, p<0.001), positively. There were 366 (19.9 %) participants with rapid decline of eGFR during 3 years. With multiple logistic regression analysis, the factors related to rapid decline of eGFR during 3 years were the percent change of FFW [RR 1.054 (95% CI: 1.011-1.099), p=0.013, Table]. With the quintile group of percent change of FFW, multiple logistic regression to estimate rapid decline of eGFR showed increased relative risk to 1.400 (95% CI: 1.009-1.943, p=0.008) in highest quintile group compared to third and fourth quintile group.

Conclusions: During short-term period, the change of fat-free weight was related to increase of eGFR, however, it was related to decline of renal function in long-term period. That suggested initial glomerular hyperfiltration by increase of fat-free weight would have resulted in decline of eGFR in the end.

Table. Multivariate logistic regression to detect risk factors for rapid decrease in renal function during 3 years

	Factor B	Wald	RR	95% CI of RR		p-value
Quintile group of percent change of FFW (Compared to 3rd and 4th quintile group)		**11.89**				**0.008**
1st quintile	-0.265	2.037	0.767	0.533	1.104	0.153
2nd quintile	0.304	3.304	1.355	0.976	1.881	0.069
5th quintile	**0.336**	**4.05**	**1.4**	**1.009**	**1.943**	**0.044**
Percent change of fat-free weight in body weight (FFW)	**0.053**	**6.216**	**1.054**	**1.011**	**1.099**	**0.013**
Percent change of Fat weight in body weight	uc	0.674	uc	uc	uc	0.412
Percent change of fat-free percent in body weight (FFP)	uc	1.519	uc	uc	uc	0.218
Percent change of body weight	uc	0.846	uc	uc	uc	0.358
Percent change of body mass index (BMI)	uc	1.048	uc	uc	uc	0.306

* Adjusted by age, gender, cholesterol, calcium, phosphorus, eGFR, urine protein by dipstick test and presence of diabetes mellitus

* uc: unable to calculate

PUB425

Prevalence of Asymptomatic Urinary Leptospira Carriage Among Young Adults at Risk of Mesoamerican Nephropathy

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Background: Leptospirosis is a bacterial zoonosis with a range of clinical manifestations including acute kidney injury. Chronic carriage of leptospira is well-described in several species, but it remains unclear whether this occurs in humans. Furthermore, chronic experimental infection with leptospira is associated with progressive

kidney injury in small animal models and asymptomatic carriage of leptospira has been proposed as a cause of CKD of unknown aetiology, one form of which is Mesoamerican Nephropathy (MeN). Determining the burden of asymptomatic leptospiral infection is challenging as serological assays may not be sensitive to antibodies against all serovars and immunity may wane over time. We therefore explored the evidence for asymptomatic carriage of urinary leptospira in a young adult population at risk of MeN.

Methods: Samples were analysed at multiple timepoints per individual from a community-based, longitudinal study of apparently healthy young adults (mean age = 24.2, mean baseline eGFR = 110.5 ml/min/1.73m^2, % male = 83.2) from rural north-west Nicaragua followed-up annually for 7 years. Serum anti-leptospira IgG antibodies were measured in 346 participants using a commercial ELISA kit and an established nested 16S PCR method was used to screen for leptospiral DNA in urine in 94 participants. Sanger sequencing was used to confirm leptospiral species in a subset of 16S PCR positive samples.

Results: None of the participants had recent symptoms of acute leptospiral illness. 55 (59%) participants were 16S PCR positive at ≥1 timepoint and 18% were positive at 2 timepoints. Sequencing of a subset demonstrated 29% of 16S PCR positive samples were consistent with leptospiral DNA, suggesting an overall prevalence of asymptomatic carriage of 17%. Overall, 8.7% (30/346) of participants tested IgG positive for leptospira in at least one timepoint of whom 12 seroreverted at follow-up testing. Rates of seropositivity were similar between 16S PCR positive and negative groups.

Conclusions: Asymptomatic urinary shedding of leptospires is common in a young population at risk of MeN which appears to be persistent or recurrent in some cases. Serological assays do not reliably identify individuals shedding urinary leptospiral DNA.

PUB426

Albuminuria and Incident Atrial Fibrillation in Community-Dwelling Adults: The REGARDS Study

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Background: Higher urinary albumin-to-creatinine ratio (ACR) is associated with increased risk of atrial fibrillation (AF). ACR is more strongly associated with incident stroke and coronary heart disease in Black compared to White adults. We aimed to determine whether similar racial differences exist for AF.

Methods: Prospective cohort study of community-dwelling adults ≥45 years old enrolled in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Modified Poisson regression with robust variance estimates was used to examine the association of ACR measured at the baseline visit with the validated outcome of incident AF based on electrocardiogram or self-report of physician-diagnosis at the second in-home visit approximately 10 years later. Models were adjusted for demographic variables and AF risk factors including eGFR.

Results: Among 11,929 participants (mean age 63 years, 45% male, 36% Black), there were 1,042 (8.7%) with incident AF. In the fully adjusted model (see Figure), compared to ACR <10 mg/g, the association between ACR and incident AF did not differ between Black (RR_{adj}=1.06; 95% CI: 0.76-1.47) and White (RR_{adj}=1.06; 95% CI: 0.89-1.25) participants in the ACR ≥10 and <30 mg/g category. In contrast, compared to ACR <10 mg/g, ACR ≥30 mg/g was associated with greater risk of incident AF in White (RR_{adj}=1.33; 95% CI: 1.08-1.64) but not in Black (RR_{adj}=1.14; 95% CI: 0.77-1.69) participants, although the multiplicative interaction term was not significant (p=0.84).

Conclusions: The association between urinary ACR and incident AF did not appreciably differ by race.

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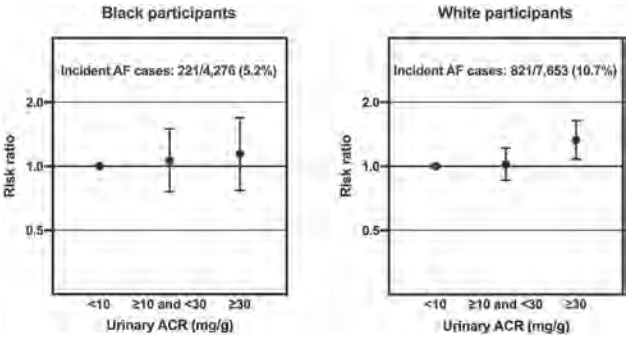

RRs and 95% CIs for incident AF among Black and White participants by ACR categories. The model was adjusted for age, sex, and geographic region of residence, education, income, smoking, alcohol consumption, waist circumference, exercise, systolic blood pressure, cholesterol, coronary heart disease, stroke, diabetes, statins, antihypertensives, RAAS inhibitors, and eGFR.

PUB427

Associations of Causes of CKD with Disease Progression and Mortality: Insights from the Fukuoka Kidney disease Registry (FKR) Study

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Background: The Kidney Disease: Improving Global Outcomes guidelines recognize the significance of causes of chronic kidney disease (CKD), glomerular filtration rate, and albuminuria as predictors of kidney outcome and prognosis. However, limited research has explored the relationship between clinically-diagnosed causes of CKD and prognosis, in comparison to biopsy-proven causes.

Methods: We examined 3,119 patients with non-dialysis-dependent CKD who participated in the Fukuoka Kidney disease Registry Study, a multicenter prospective cohort study. Patients were divided into six groups: IgA nephropathy, chronic glomerulonephritis (non-biopsy-proven), diabetic nephropathy, hypertensive nephrosclerosis, chronic interstitial nephritis, and polycystic kidney disease. The primary outcomes included a composite kidney outcome, defined by a 1.5-fold increase in serum creatinine and/or development of end-stage kidney disease, and all-cause mortality. The risks for these outcomes were estimated using a Fine–Gray proportional subdistribution hazards model. IgA nephropathy, the most prevalent primary glomerulonephritis, served as the reference group.

Results: During the median follow-up period of five years, 1,221 patients developed the composite kidney outcome, and 346 patients died. Compared to IgA nephropathy, the multivariable-adjusted subdistribution hazard ratios (sHRs) for the composite kidney outcome were significantly higher in diabetic nephropathy (sHR 1.45) and polycystic kidney disease (sHR 2.07), while chronic interstitial nephritis showed a significantly lower risk (sHR 0.71). The risk of all-cause mortality was significantly higher in hypertensive nephrosclerosis (sHR 1.90).

Conclusions: The causes of CKD were associated with the risks of the composite kidney outcome and all-cause mortality, underscoring their clinical relevance in predicting prognosis. These findings suggest that different causes of CKD have distinct impacts on patient outcomes, emphasizing the importance of tailored management strategies based on the underlying causes.

PUB428

Influence of Consecutive AKI Episodes on CKD Progression

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Background: Is a well-known fact that AKI leads to progression of preexisting CKD. Despite this evidence, we find that some patients after successive AKI episodes progress and some that do not. We aimed to study potential risk factors for worsening CKD stage when suffering from AKI on CKD (AoCKD) besides AKI severity.

Methods: Retrospective, study of hospitalized patients that suffered at least 3 AoCKD episodes during a 4-y period. We defined progression as the change to a higher CKD stage compared to the stage of the first AoCKD event, or HD dependence at discharge. In-hospital mortality was not considered an indicator of progression. We defined high Charlson's (ChI) as Score ≥3, classified AKI with the KDIGO-2012 criteria, compared clinical variables and searched for risk factors for progression.

Results: We included 458 AoCKD episodes of 129 individuals. 58 (45%) progressed, 13 were HD dependent at discharge (22% of progressors); they had a higher ChI, were classified in KDIGO-AKI stage 3 and needed acute HD more frequently. We found no statistically significant differences in age, admission in ICU, time to nephrology consultation, KDIGO-AKI stage 2, and in-hospital mortality (Table 1A-B). When analyzing variables, we found risk factors for progression OR: Need for

HD 2.98 (1.22–7.27), KDIGO-3 stage 3.00 (1.46–6.16), High ChI 8.6 (1.10–69.70), and being hospitalized in a Medical Ward 2.22 (1.22–4.10) (Table 2).

Conclusions: We found that relatively less patients are progressors, could this finding be explained because CKD confers a physiological adaptation to AKI? We observed that factors that promoted CKD progression were: AKI severity in a dose dependent manner; High ChI ≥3, need for HD and being hospitalized in medical ward, due to a skew of no-progressors being hospitalized in surgical wards? All these factors are not modifiable, so we should be more creative and search for non-traditional factors to try to find modifiable ones, to tackle CKD progression due to AoCKD.

	Non-Progr (71)	Progressors (58)	P Value
Table 1 A			
Characteristics			
Masc. Sex	49 (70)	36 (61)	0.19
Age	77 ± 9	74 ± 13	0.09
HTN	67 (96)	55 (93)	0.41
DM	**31 (44)**	**36 (61)**	**0.04**
Charlson's I.	**5.8 ± 2.3**	**7.5 ± 2.5**	**<0.001**
ICU	20 (29)	10 (17)	0.09
Qx	**29 (41)**	**11 (19)**	**0.004**
Table 1 B			
Results			
KDIGO-AKI-2012			
Stage 1	**38 (54)**	**16 (27)**	**0.002**
Stage 2	8 (11)	7 (12)	0.58
Stage 3	**24 (34)**	**36 (61)**	**0.002**
Time to Consult.	3,9 ± 3.8	4.3 ± 4.8	0. 74
Hospital Stay	18 ± 16	14 ± 11	0.08
Acute HD	**9 (13)**	**18 (31)**	**0.01**
Mortality	35 (50)	23 (39)	0.14
Table 2			
Risk Factors	**OR**	**CI 95%**	**P Value**
Acute HD	**2.98**	(1.22 – 7.27)	**0.010**
KDIGO-AKI 3	**3.00**	(1.46 – 6.16)	**0.002**
High Chl	**8.60**	(1.10 – 69.7)	**0.018**
MD Ward	**2.22**	(1.22 – 4.10)	**0.004**

PUB429

Nonalcoholic Fatty Liver Disease (NAFLD) and Sarcopenia in CKD Stages 1-5 Non-Dialysis Patients

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Background: NAFLD is a chronic liver disease characterized by excess fat accumulation in the liver. It is associated with metabolic syndrome and often has comorbidities such as obesity, diabetes, and dyslipidemia. NAFLD has been associated with various non-liver comorbidities, including cardiovascular disease, CKD, and sleep apnea, closely related to Sarcopenia. Sarcopenia, defined as low muscle mass and impaired muscle function, is associated with NAFLD and worse outcomes. This crossover study aims to assess the prevalence of Sarcopenia in CKD patients with NAFLD evaluated by bioelectrical impedance (BIA).

Methods: 854 CKD pts, age 72,02(14,07),40.2% female, 41.2%, DM2, 48.4% obese men (%fat mass>25%) and 29% obese female (% fat mass >35%), GFR-EPI 51.6 (26.8) ml/min/1.73m2, UACR 258.36 (630), were enrolled. NAFLD was evaluated by BIA (Bioscan I8, Maltron, London) using the manufacturer software based on the fat/muscle ratio, staging NAFLD in 5 stages (0-4). Sarcopenia defined as EWGSOP2 (2018); cut-off points for dynapenia <27kg for men and <16kg for women of dominant arm muscle strength and muscle mass <20kg male and <15kg female. AGEs by autofluorescence were read by (DiagnOtics, Groningen, Netherlands)), and vascular Age was obtained from the Koetsier equation(AGEs0.83)/0.24. Data were processed with SPSS 27. A p-value <0.05 was considered statistically significant.

Results: NAFLD incidence was 89.8%. 36.9% female and 63.1% men. Obese 86.4% and Diabetic 94%. Sarcopenia was identified in 6 men (1.23%) and 12 women (4.24%) p<0.001. Comparing NAFLD all stages vs Non-NAFLD: %Fat mass 35 (8.39) vs 27,58 (8.03)% (p<0.001); GFR-EPI 50.09(25.5) vs 66.14(32.09) (p<0.001). Vascular age-age : 16.7(25) vs 14.74(p<0.001). Stages incidence: Healthy 10.2%; Stage1 10.7%; Stage2 15.1%, Stage3 17.4% Stage 4(severe)46.6%. UACR 257.6 (629) vs 265 (638) (NS).

Conclusions: NAFLD is highly frequent in CKD patients-associated obesity, DM2 and lower GFREPI. Unexpectedly, according to EWGSOP2 (2018) criteria, Sarcopenia is scant, more frequent in women. NAFLD related parameters were %fat Mass, DM2, obesity, GFR-EPI and average of vascular age, showing an inflammatory and premature aging status. BIA is a valuable tool, non observer dependent, non-invasive and easy to use.

Funding: Other NIH Support - SERGAS. National Health Service Spain

PUB430

Results from a Chinese Multispecialty Delphi Consensus to Optimize Renin-Angiotensin-Aldosterone System Inhibitor (RAASi) Usage and Hyperkalaemia (HK) Management in Patients with CKD and Heart Failure (HF)

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Background: This consensus aims to establish a multi-speciality approach to the optimal use of RAASi and management of hyperkalemia (HK) in patients with CKD and HF.

Methods: A steering group of cardiology and nephrology experts from across China convened to discuss challenges to HK management and the optimal use of RAASi. 41 statements for a consensus questionnaire were created and distributed further among cardiologists and nephrologists across 21 provinces in China. Consensus was assessed using a modified Delphi technique, with agreement defined as 'strong' (≥75% and <90%) and 'very strong' (≥90%). The result was also compared with those from a similar consensus in Europe and North America (E&NA).

Results: A total of 150 responses from China were received evenly distributed between cardiologists and nephrologists. All statements achieved the 75% consensus agreement threshold, which includes identification of risk factors for HK in cardiorenal patients, preventive measurements and correction of hyperkalaemia for patients at risk of HK, cross-specialty alignment between Cardiology and Nephrology, and education of clinicians and patients. Some variation was identified between E&NA and China responses regarding to the maintenance of RAASi therapy at a maximal dose in the face of HK, but generally there was broad agreement across common statements.

Conclusions: Based on the agreement levels from respondents, the steering group were able to create a compelling set of recommendations to improve patient outcomes with RAASi therapy and HK management in China.

Funding: Commercial Support - AstraZeneca

PUB431

Can Serum Sodium Minus Chloride Level at the Initiation of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers in CKD Patients Predict New Onset of Hyperkalemia?

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Background: ACE inhibitor (ACE-I) and angiotensin receptor blocker (ARB) have renoprotective effect on chronic kidney disease (CKD) patients. However, one of their side effects is hyperkalemia, and it is associated with poor prognosis in CKD patients. Although hyperchloremic acidosis is known as a risk factor for hyperkalemia in CKD patients, it is unclear whether hyperchloremic acidosis at the initiation of ACE-I or ARB is a risk factor for hyperkalemia after initiation of these drugs.

Methods: We conducted a retrospective observational study in a single hospital. Non-dialysis CKD patients who were initiated on ACE-I or ARB between January 2011 and December 2021 were enrolled. Because serum bicarbonate level is not routinely measured, we defined hyperchloremic acidosis as serum sodium minus chloride level ([Na] - [Cl]) < 36 mEq/L from the physiological approach. The eligible patients were divided into groups with and without hyperchloremic acidosis at the initiation of ACE-I or ARB. The primary outcome was hyperkalemia, defined as serum potassium level ([K]) > 5.0 mEq/L at the first blood test after the initiation. Multivariate logistic regression analysis was performed adjusted by baseline data; age, sex, diabetes, eGFR, [K], hypoalbuminemia, and use of drugs that influence [K].

Results: In this study, 1143 patients were enrolled, and 766 patients (67%) had [Na] - [Cl] < 36 mEq/L at baseline. In multivariate analysis, only eGFR and [K] at initiation were significantly associated with hyperkalemia (odds ratio (OR);95% confidence interval (CI) were 0.96;0.93–0.98 and 5.99; 2.50–15.6, respectively). From the subgroup analysis which included the patients who were measured [Na] - [Cl] after the initiation as well, of the 353 patients with [Na] - [Cl] ≥ 36 mEq/L at baseline, 150 patients (42.4%) developed hyperchloremic acidosis after the initiation. Additionally, [Na] - [Cl] < 36 mEq/L after the initiation was significantly associated with hyperkalemia in multivariate analysis (OR 2.45; 95% CI 1.15–6.06).

Conclusions: ACE-I or ARB may affect the acid-base status of CKD patients. Therefore, [Na] - [Cl] < 36 mEq/L at the initiation of these drugs could not predict newly onset hyperkalemia.

PUB432

Clinical Characteristics, Treatment Patterns, and Renal-Related Events in Patients with Diagnosed CKD: Results from Regional Health Information System in China

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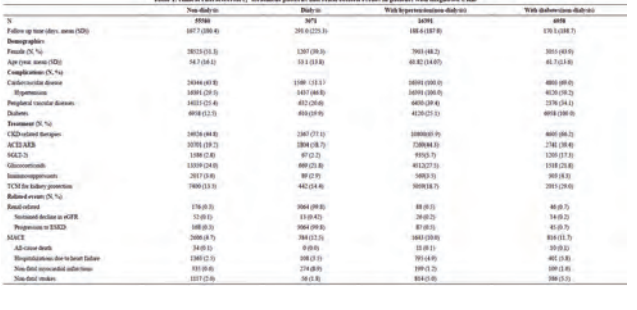
Background: The clinical characteristics, treatment patterns and renal-related events of diagnosed chronic kidney disease (CKD) provide evidence that can improve CKD management. However, the situation in China remains under-investigated.

Methods: We included adults with electronic health records (2020.01-2021.12) in Xuzhou, China. Clinical diagnosis of CKD was defined as having diagnostic keywords and International Classification of Disease (ICD)-10 codes related to primary cause or stages of CKD. All patients with diagnosed CKD were required to have at least one follow up visit after being enrolled, and were further categorized into dialysis and non-dialysis groups. Among the non-dialysis, individuals diagnosed with hypertension and diabetes were categorized as two independent subgroups.

Results: A total of 58,651 patients with diagnosed CKD were identified, including 55580 non-dialysis and 3071 dialysis individuals. Cardiovascular diseases accounts for 43.8% of all non-dialysis individuals, followed by peripheral vascular disease (25.4%) and diabetes (12.5%). 44.8% of all non-dialysis patients had received CKD-related therapies, including ACEI/ARB (19.2%), SGLT-2i (2.8%), glucocorticoids (24.0%), immunosuppressants (3.6%), traditional Chinese medicine for kidney protection (13.3%), et al. A total of 176 renal-related events (0.3%) occurred during follow-up period, including 52 cases of sustained decline in eGFR and 168 cases of progression to ESKD. Besides, 2606 individuals experienced MACE events (4.7%). Compared to the general population of non-dialysis patients, individuals with hypertension or diabetes had higher incidence of renal related events (hypertension:0.5%, diabetes:0.7%) and MACE events (hypertension:10.0%, diabetes:11.7%).

Conclusions: Patients with diagnosed CKD in this cohort frequently complicate cardiovascular diseases. Despite being diagnosed with kidney disease, the proportion of individuals receiving CKD-related therapies remains low, and the incidence of renal-related and MACE events should be noticed.



PUB433

Hospitalizations Among Adults with CKD: Results from KNOW-CKD Study

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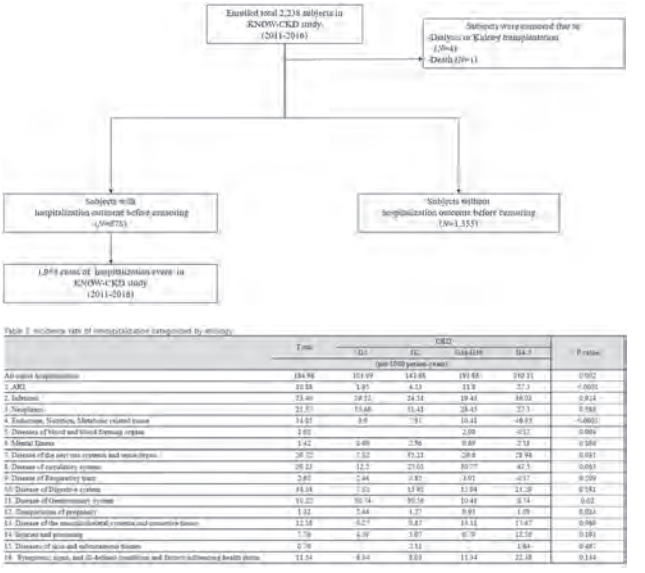
Background: Chronic kidney disease (CKD) patients are hospitalized for various causes. Hospitalization increases the readmission rate and mortality rate, seriously deteriorating patients' quality of life. For this reason, it is crucial to analyze the causes of hospitalization in CKD patients in a broader perspectives according to CKD grades.

Methods: This study was conducted as a prospective cohort of CKD patients, entitled KoreaN Cohort Study for Outcomes in Patients With Chronic Kidney Disease (KNOW-CKD). A total of 2,238 patients were examined in this study, and the causes of hospitalization were classified into 16 disease categories. The incidence rate ratio (IRR) according to CKD grade was compared using Poisson regression analysis. Hospitalization ratio of KNOW-CKD patients was also compared with hospitalization data of general population procured from Korea National Sample Cohort Database.

Results: The all-cause hospitalization incidence was 184.96 per 1000 person-years. The most common cause of hospitalization was circulatory system disease, followed by infection and digestive system disease. When analyzing the incidence rate of all-cause hospitalization according to the CKD grades, patients had an incidence of 101.99, 143.68, 193.86, and 310.11 per 1000 person-years. In the hospitalizations for acute kidney injury, endocrine, nutrition, metabolic related cause, nervous system disease, and genitourinary system, the IRR increased as the grade advanced. IRR of KNOW-CKD patients was 5.92(95% CI; 5.66-6.19; P-value<0.001) compared to general population.

Conclusions: CKD patients were hospitalized for various causes, with incidence increased by grades. Thus, early detection and intervention is tremendously important to reduce hospitalization burden and improve patients' quality of life.

Funding: Government Support - Non-U.S.



PUB434

Results from a Cross-Specialty Consensus on Optimal Management of the CKD Patient: From Screening to Complications

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Background: Chronic kidney disease (CKD) affects around 10% of the global population and has been estimated to affect around 50% of individuals with type 2 diabetes and 50% of those with heart failure. The guideline recommended approach is to manage with disease-modifying therapies, but real-world data suggests that prescribing rates do not reflect this in practice. We wished to establish consensus on optimal management of the CKD patient.

Methods: An international steering group of experts specialising in internal medicine, endocrinology/diabetology, nephrology and primary care medicine developed 42 statements on aspects of CKD management including identification and screening, risk factors, holistic management approach, guidelines, cross-specialty alignment, and education. Consensus was determined using an online survey. The survey was distributed to cardiologists, nephrologists, endocrinologists, and primary care physicians across 11 countries. The threshold for consensus agreement was established *a priori* by the steering group at 75%.

Results: 274 responses were received, 25 responses from Argentina, Australia, Brazil, Guatemala, Mexico, Singapore, South Korea, Taiwan, Thailand, Turkey, and 24 responses from Egypt: 53 responses from cardiologists, 52 from nephrologists, 55 from endocrinologists, and 114 from primary care physicians. 37 statements attained very high agreement (≥90%) and 5 attained high agreement (≥75% and <90%). Strong alignment between roles was seen across the statements, and across different levels of experience (2-5 years or 5+ years), some variation was observed between countries.

Conclusions: There is a high degree of consensus regarding aspects of CKD management among healthcare professionals. Based on these strong levels of agreement, the steering group derived twelve key recommendations focused on diagnosis and management of CKD. Two key recommendations are provided below: - Early screening for CKD in high-risk groups using eGFR and uACR as the screening method of choice is cost-effective for the health system - Intervene early in CKD patients with proven therapies (i.e., SGLT2i, RAASi, DMTs) to delay/prevent progression to kidney failure

Funding: Commercial Support - AstraZeneca

PUB435

Predictors of Disease Progression in Patients with CKD: Results from a Real-World Study

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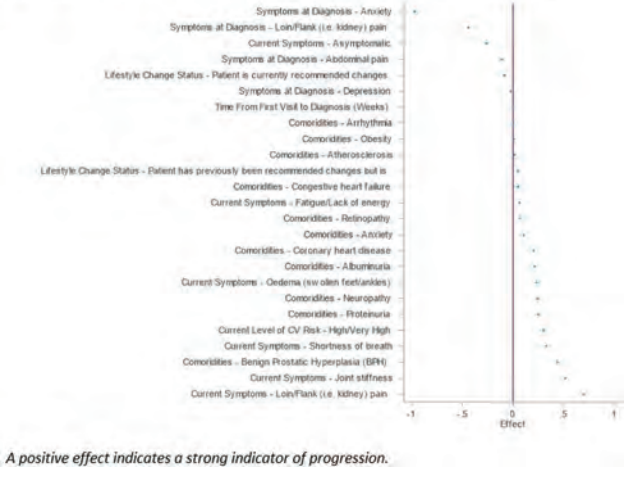
Background: Clinical decision making is difficult due to the complex heterogeneous nature of chronic kidney disease (CKD) and its variable rate of progression. We aimed to understand the key predictors of CKD progression and subsequent impact on patients.

Methods: Data were drawn from the Adelphi CKD Disease Specific Programme™, a cross-sectional survey of physicians and patients conducted in the USA from Jan-June 2022. Physicians recorded patient demographics, disease characteristics, concomitant conditions treatment history and consultation history. Non dialysis (ND) patients reported their current and most troublesome symptoms. Elastic net regression analysis was conducted.

Results: Physicians provided data for 1525 ND patients, of these 379 also provided data. Mean [SD] age was 61.9 [13.87], 57% were male, and 55% were white. Almost half of patients had progressed (CKD stage) since diagnosis (47%). Regression analysis identified the strongest predictors of CKD progression to include: kidney pain, joint stiffness and shortness of breath, high/very high cardiovascular risk and proteinuria [Figure 1]. The strongest predictor, kidney pain, was reported as a current symptom by 10% of patients and of those, 59% reported this to be their most troublesome symptom. Of the patients experiencing joint stiffness (11%) and shortness of breath (13%), approximately a third of these patients reported them to be their most troublesome symptom(s) (31% and 35% respectively).

Conclusions: Presence of kidney pain is a strong predictor of CKD progression and in our study was shown to be most troublesome for over half of the patients experiencing it. In addition to treating the most prevalent symptoms, physicians should aim to control/ treat less prevalent symptoms to help slow progression and improve patient outcomes.

Figure 1: Elastic net regression coefficient plot to show predictors of CKD progression



A positive effect indicates a strong indicator of progression.

PUB436

Changes in GFRe in a Cohort of Qom Indigenous over a 15-Year Interval

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Background: The Qom ethnic group lives in the province of Chaco, one of the lower incomes in Argentina. In the last 15 years, they access to better living conditions. Illiteracy is 8%. The nutritional transition of poor populations goes from the double burden of malnutrition to obesity. The objective of this work is to describe the changes of eGFR by CKDEpi, and the frequency of proteinuria, obesity, HT, and DM in a cohort of the Qom ethnic group, inhabitants of suburban neighborhoods of the city of Resistencia, Chaco, Argentina, in two cross-sections (2003-2018).

Methods: A descriptive, observational study of two cross-sections was carried out in 2003 and in 2018, visiting each participant's home, and were included after signing the informed consent. Glycemia was measured by the Hexokinase Enzymatic Method, and Creatininemia, and Creatininuria by the Jaffé kinetic method. Proteinuria was classified according to the PrU/CrU index following KDigo (2012). Diabetes Mellitus (DM) by the medical report. Nutritional status according to WHO. HT according to JNC 7. GFR by CKDEpi formula. Risk Progression RR) by KDIGO risk categories.

Results: 65 people were studied. The mean age in 2003 was 33.57 ± 12.53 and 49.09 ± 12.40 years old in 2018; 38 (62.3%) were female. The eGFR in 2003 was 101.10 ± 15.39 ml/min and in 2018, 102.10 ± 15.85 ml/min; 19.7% and 23% (p= 0.02) respectively presented proteinuria. HT increased from 26.22 to 62.69%; 14.2% developed DM. Obesity increased from 26.2% to 60.6%. Low RR raised from 68.3% to 76, 66%, 10% to 21.66% moderate and high RR only 1.66% in 2018. The correlation between GFRe in 2003 and 2018 is shown in Figures 1 and 2.

Conclusions: This epidemiological study shows that eGFR tends to increase due to obesity and DM and to decrease in patients with HT in a 15 years interval.

Funding: Private Foundation Support

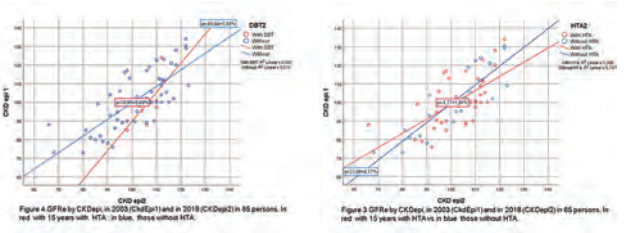

Figure 1. Correlation between CKDEPI1 (2003) and CKDEPI2 (2018).

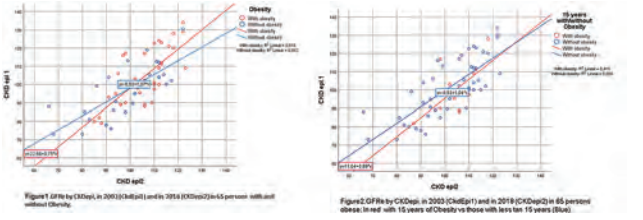

Figure 2. A Correlation CKDEpi1 (2003) and CKDEpi2 (2018).

PUB437

Association of Bicarbonate Use and Incident ESKD Among US Veterans with Incident CKD

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Background: Treatment of metabolic acidosis delayed the decline of kidney function in patients with chronic kidney disease (CKD) in small clinical trials, but the effects of bicarbonate therapy on end-stage kidney disease (ESKD) in unselect populations with all stages of CKD remains unclear. We examined the association of sodium bicarbonate use with incident ESKD in a large national cohort of US Veterans.

Methods: In a cohort of 50,540 patients with incident CKD (eGFR <60 mL/min/1.73m^2), we examined the association of de novo prescription of bicarbonate containing medications with incident ESKD (defined as initiation of kidney replacement therapy). We examined associations in Cox proportional hazard models adjusted for demographics, major comorbidities, baseline eGFR, urine albumin-creatinine ratio (UACR), and use of renin angiotensin-system inhibitors.

Results: We identified 11,896 incident new bicarbonate users. Overall mean (SD) age was 65 (10) years, with 3.0% female, 15.3% Black, and 5.5% Hispanic, and baseline eGFR of 35 (11). Bicarbonate users were more likely to be male, Black, current smokers, had higher frequencies of diabetes and liver disease and lower eGFR compared to non-users. ESKD developed in 4860 patients (event rate 37.4/1000 patient years, 95% CI: 36.3-38.4). Bicarbonate use (vs. non-use) was associated with higher risk of incident ESKD in the unadjusted (HR: 8.68, 95% CI: 8.17-9.23) and in the fully adjusted model (1.48, 1.38-1.60), Table.

Conclusions: In this large national cohort of US Veterans with long follow-up time, bicarbonate use was associated with higher risk of incident ESKD. Further studies are needed to test the effects of bicarbonate replacement in patients with CKD.

Funding: NIDDK Support, Veterans Affairs Support

Table. Hazard Ratio and 95% Confidence Interval of Incident ESKD Among Bicarbonate Users vs. Non-Users

Models	HR (95% CI)	P
Model 1: Unadjusted	8.68 (8.17-9.23)	<0.0001
Model 2: Adjusted for demographics	6.48 (6.08-6.91)	<0.0001
Model 3: Adjusted for demographics and comorbidity	5.84 (5.47-6.23)	<0.0001
Model 4: Adjusted for demographics, comorbidity, and eGFR	1.93 (1.79-2.08)	<0.0001
Model 5: Adjusted for demographics, comorbidity, eGFR, UACR	1.50 (1.39-1.61)	<0.0001
Model 6: Adjusted for demographics, comorbidity, eGFR, UACR, ACE inhibitor/ARB	1.48 (1.38-1.60)	<0.0001

PUB438

Invasive Fungal Infection Associated with SGLT2 Inhibitor Use

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Introduction: Sodium-glucose co-transporter-2 inhibitors (SGLT2i) are a relatively newer class of medications approved by the U.S. Food and Drug Administration (FDA) in 2013 to treat Type 2 Diabetes Mellitus. Over the last few years, the indications for SGLT2i have been expanded to decrease the risk of kidney disease and cardiovascular disease. SGLT2 inhibitors are associated with an increased risk of euglycemic diabetic ketoacidosis, urinary tract infections, and genital mycotic infections. We present a case of candida fungemia and renal abscess in a patient on an SGLT2 inhibitor.

Case Description: A 75-year-old white male with a history of hypertension, obesity, CKD stage IIIB with baseline creatinine(Cr) of 1.6 mg/dl, and BPH presented to the hospital with fever and lethargy. He had been on valsartan and empagliflozin over 2 years. He underwent a biopsy of the prostatic lesion a week before the presentation. He did not have exposure to antibiotics prior to presentation. Urinalysis showed the presence of glucose and WBC with fungal elements on microscopy. Computed tomography of the abdomen showed fluid in the superior pole of the left kidney with surrounding inflammatory changes concerning renal abscess. There were inflammatory changes in the left renal collecting system with thickening of the urothelium and bladder wall. He underwent percutaneous abscess drainage; blood cultures, abscess fluid cultures, and urine cultures grew Candida tropicalis. He was initially given intravenous fluconazole, later transitioned to oral fluconazole therapy for a total of 6 wks. The patient was discharged home in stable condition.

Discussion: SGLT2 inhibitors are being widely prescribed due to their beneficial effects on kidney and cardiovascular outcomes among the diabetic and non-diabetic populations. SGLT2 inhibitors, through the induction of renal glycosuria, create a conducive environment for the proliferation and colonization of candida in the genital tract. SGLT-2 inhibitors related to fungal infections are common, but most are limited and present as vulvovaginitis in women and balanitis in men. However, invasive fungal infections should be considered in patients with complex urinary anatomy and undergoing urological surgeries. It is reasonable to stop SGLT-2 inhibitors prior to elective urological surgery to minimize the risk of invasive fungal infections.

PUB439

Effect of Dapagliflozin on eGFR Slope in Nondiabetic CKD Patients

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Background: Treatment with sodium-glucose co-transporter-2 inhibitors (SGLT2i) has a great impact of renal protection showing a significant improvement in eGFR decline in patients with CKD. However, the timing of eGFR crossing between patients receiving placebo and SGLT2i is inconsistent. In this study, we aimed to determine factors associated with eGFR slope one year after the initiation of SGLT2i in non-diabetic CKD patients.

Methods: We conducted a cohort study on 260 non-diabetic CKD patients in whom dapagliflozin was initiated at 5 or 10 mg daily from August 2021 and July 2022. Among them, one-year follow up was completed in 138 patients. The total slope (TS) was estimated by using two measurements of eGFR levels at the baseline and one-year follow-up, while the long-term (LS) slope was calculated using two eGFR levels at one month after the first dose of dapagliflozin and one-year follow-up. Multivariate linear regression was used to identify characteristics with an independent association with TS and LS. The baseline slope (BS) before dapagliflozin initiation and TS and LS was compared using-paired-t-test in CKD patients according to characteristics, respectively.

Results: The mean age was 62±13 years and 105 (40%) were male. The baseline eGFR were 43±15 mL/min/1.73m^2 and the proteinuria was 0.61±0.94 g/gCre. The underlying kidney diseases included glomerulonephritis in 109 (42%) patients and hypertensive nephrosclerosis in 106 (41%). The administration of renin-angiotensin blocker and 5mg of dapagliflozin was observed in 170 (65%) patients and 109 (42%). BS was -1.67 mL/min/1.73m^2/yr, while TS and LS was -1.45 mL/min/1.73m^2/yr (p=0.56 vs. BS), and -0.4 mL/min/1.73m^2/yr (p=0.02 vs. BS, p=0.003 vs.TS), respectively. In multivariate analysis, TS was significantly associated with BS, while an independent association of LS with overweight was found. TS was significantly improved compared with BS in patients with G4-5 and BS < -3 mL/min/1.73m^2/yr. We found significant improvements in LS compared with BS were observed in patients with nephrosclerosis, less proteinuria, taking renin-angiotensin blockers and 10mg of dapagliflozin as well as G4-5 and fast eGFR decline.

Conclusions: In non-diabetic CKD patients dapagliflozin may have the potential to significantly improve eGFR slope in high CKD risk category, possibly within a relatively short period.

PUB440

Extrarenal Pelvis: Benign Anatomical Variation Mimicking Hydronephrosis

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Introduction: Extrarenal pelvis is a normal anatomical variant in which the renal pelvis is outside of the renal hilum without affecting kidney function. It can be challenging to differentiate from hydronephrosis. We report a case of a woman with stable kidney function who was referred for an incidental kidney imaging. A kidney ultrasound confirmed the diagnosis of extrarenal pelvis.

Case Description: A 67-year-old woman with non-proteinuric stage 2 chronic kidney disease presumably secondary to hypertension presented with chronic low back pain after a motor vehicle accident 1 year ago. She denied lower urinary tract symptoms, bladder or bowel incontinence, or focal neurological deficits. A pelvic CT scan incidentally showed right extrarenal pelvises without calculi or hydronephrosis (Figures 1A and 1B). A kidney ultrasound revealed the right kidney with normal echogenicity and contour and an extrarenal pelvis measuring up to 1.5 cm without hydronephrosis, focal kidney mass or shadowing stones (Figure 1C). The patient remains having no symptoms and signs of urinary tract obstruction and follow-up serum creatinine has been stable at 0.7 – 0.9 mg/dL.

Discussion: While imaging may show similar findings between the extrarenal pelvis and hydronephrosis, which appears as interconnected areas with branching of decreased echogenicity consistent with fluid, normal or stable kidney function without evidence of obstructive uropathy clinically suggests extrarenal pelvis. Reassuring patients with extrarenal pelvis that their condition is benign and does not require therapy is imperative.

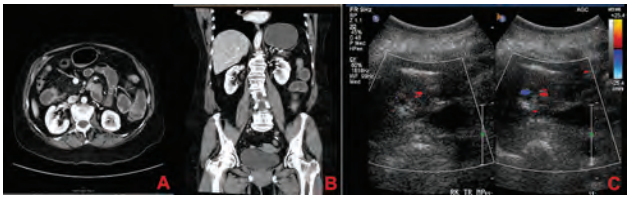

Figure 1. Right extrarenal pelvis by abdominal CT scan [cross-sectional (A) and coronal (B) planes] and kidney ultrasound [transverse view (C)]

PUB441

Predictability of GFR with Cystatin C: A Case Report

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Introduction: Chronic Kidney Disease (CKD) is a common single entity or frequent comorbid in the United States, affecting 1 in every 7 persons, leading to multiple cardiovascular and metabolic complications.[1]CKD is defined by structural or functional abnormalities of the kidney, with or without decreased GFR of <60 mL/min/1.73m2 for ≥3 months, with or without kidney damage.[2] Measurement of GFR in clinical practice can be complex, time consuming, and cumbersome to perform. Traditionally, GFR is measured using creatinine based equations, CKD-EPI, MDRD, Cockroft-Gaulet equations. However, confirmation of creatinine-based estimated GFRs (eGFR) must take into account subjects who have high muscle mass, taking creatine supplements, low muscle mass, vegan diet, liver disease, extreme weakness.[3]

Case Description: We report a 31 year old Caucasian muscular male, with no established primary care, who was referred in an ambulatory setting for elevated creatinine thought to be CKD. Upon evaluation, he has good muscle mass, reporting muscle pains from workout, uses muscle building supplements. His family history is significant for breast cancer in mother, no kidney diseases or nephrolithiasis. His surgical history is significant for tonsillectomy at the age of 22 years. His initial labs show creatinine (Cr) of 1.45, BUN 26, eGFR 66ml/min/1.73m2, electrolytes within range. In view of elevated Cr, patient was advised to stop taking Creatine supplements. Repeat labs in 2 weeks continued to demonstrate elevated Cr to 1.54, with preserved GFR. Renal US and UA insignificant, HbA1c 5.4%, neg HIV, Hep: B/C neg. Patient was advised to discontinue all nutritional supplements. Repeat labs in 6 months, showed Cr of 1.48, BUN 21, GFR of 64min/ml/1.73m2, urine protein/creatinine ratio 0.07, Hgb 13.2. In view of this, Cystatin C was obtained with intent to follow up with renal biopsy. Results for Cystatin C 0.7, eGFR by Cystatin C 126ml/min/1.73m2, sCr 1.34.

Discussion: Cystatin C is a useful clinical biomarker to estimate GFR. It has been found to provide a more accurate estimate of GFR in certain patient populations, unlike Creatinine which has limitations of age, gender, body muscle mass, and ethnicity. In our case, Cr was elevated and eGFR was decreased, that led to misdiagnosis of CKD. Using Cystatin C established more accurate GFR and ruled out CKD. We suggest the use of cystatin C into diagnostic criteria and treatment guidelines for CKD.

PUB442

Ultrasound Measured Renal Sinus Fat, Parenchymal Thickness, Interstitial Fibrosis, and Their Association with Renal Function

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Background: Renal ultrasound is valuable for nephrologists in clinical practice to determine the proper management. Measuring renal sinus fat and renal parenchymal thickness was proven to have some clinical implications. In this study we wanted to determine the correlation between ultrasound measured renal sinus fat length, parenchymal thickness and interstitial fibrosis with renal function.

Methods: This is a retrospective cross-sectional study for patients biopsied by the Interventional Nephrology division in Ochsner Medical Center over 2 years 2021-2023. Patients without ultrasound reports were excluded. The demographic factors were recorded from the electronic files. The eGFR was calculated by CKDMB equation within the time closest to the biopsy. The sinus fat length was measured on longitudinal sagittal US image. The total renal length was measured on the same image. The renal parenchymal thickness was measured by subtracting the longitudinal sagittal length of the sinus fat from the total kidney length. The percentage of sinus fat length was measured by dividing the length of sinus fat over the total renal length using the ipsilateral site of the biopsy. SPSS 25 was utilized for the descriptive statistics. Two tails Spearman correlation was used to calculate the significant correlation. P< 0.01 was needed to reject the null hypothesis.

Results: Total patients included were 52. Mean age: 50 years. (SD 17.5, SE 2.27). Male gender 45%. Mean BMI 29.3 kg/m2 (SD 7.2, SE 0.9) DM was present in 23% of the patients. HTN was present in 55% of the patients. Mean Interstitial fibrosis was 20% Mean S. Cr. 2.3mg/dl (SD 2.2, SE 0.28) Mean eGFR: 42ml/min. (SD 19.3, SE 2.5)

Conclusions: There was a significant correlation between ultrasound measured sinus fat length percentage and parenchymal thickness with renal function. Sinus fat and parenchymal thickness were not associated with age, gender, BMI, DM or HTN. Interstitial fibrosis was significantly associated with S.Creatinine and eGFR.

Association of renal Sinus fat ratio, parenchymal thickness and interstitial fibrosis with renal function

Independent variables	S. Creatinine correlation coefficient (p value)	eGFR correlation coefficient (p value)
Sinus fat ratio	-0.39 (0.004)	0.34 (0.01)
Parenchymal thickness	0.38 (0.005)	-0.31(0.025)
Interstitial fibrosis	0.5 (<0.0001)	-0.48 (<0.0001)

PUB443

Is the Predicted Skin-to-Kidney Distance by Analytical Method Useful? A Correlation and Association with Ultrasound-Guided Percutaneous Kidney Biopsy

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Background: Approach techniques and the use of a distance prediction formula (DPF) have been created, using weight and height to estimate the depth of the skin-kidney distance (SKD) in percutaneous renal biopsy (PRB)* ultrasound guided. Its validation and usefulness are still an opportunity area.

Methods: Our objective is to correlate SKD derived by DPF in native PRB compared to real-time ultrasound stratified by body mass index (BMI) categories and evaluate its usefulness and sample quality. This is a cross sectional study spawning data from 2018-2022 in Interventional Nephrology Service of the National Institute of Cardiology Dr. Ignacio Chávez. Sampling was performed in real time guided ultrasound. DPF= (Body weight [hectograms]/height [centimeters])–0.5 in all cases. Pearson analysis was made and further stratified between BMI categories and by type of biopsy approach. Dispersion analysis was made by Bland-Altman plots at 1.96SD. Binary logistic regression models were fitted to evaluate the association between SKD and the quality of sample.

Results: 300 of 501 PRB were analyzed. The mean BMI was 25.7 kg/m². 71% were performed with transverse approach. 45.7% were classified as normal-weight, 34% overweight and 20.3% obese. The mean SKD measured by ultrasound was 4.3 (+/- 0.6) cm and by DPF of 3.61 cm (+/-0.42), deriving a correlation of 0.42 (95% CI:0.28-0.55, p<0.001). After stratification, subjects with overweight and obesity had a lower correlation and higher variability compared to subjects with normal weight (Fig. 1). Finally, SKD was not associated with the sample quality (OR:1.13, 95% IC: 0.87-1.47, p=0.36).

Conclusions: The formula has a moderate correlation in subjects with normal weight, but not with overweight and obesity. There is no association between the depth, sample quality and complications, hence, its further usefulness must be evaluated for other outcome.

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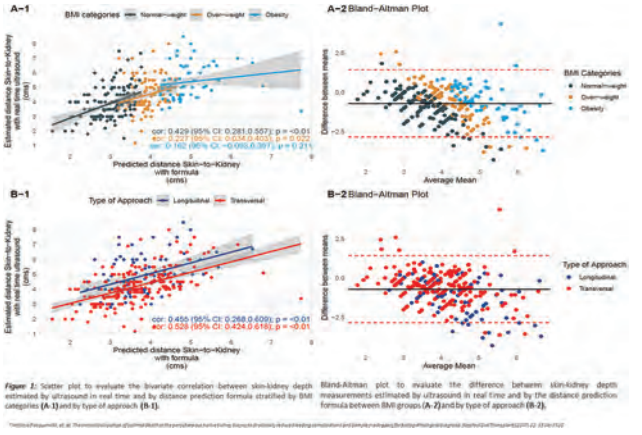

Figure 1: Scatter plot to evaluate the bivariate correlation between skin-kidney depth estimated by ultrasound in real time and by distance prediction formula stratified by BMI categories **(A-1)** and by type of approach **(B-1)**. Bland-Altman plot to evaluate the difference between skin-kidney depth measurements estimated by ultrasound in real time and by the distance prediction formula between BMI groups **(A-2)** and by type of approach **(B-2)**.

PUB444

Reducing Hospital Admissions for Cardiorenal Syndrome Using Lung Ultrasound-Guided Volume Assessment in the Clinic

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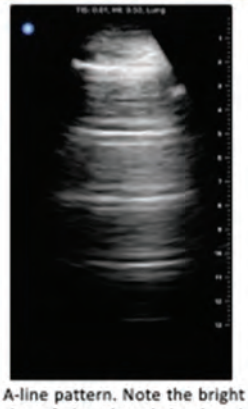
Background: Point-of-care ultrasound is used at the bedside to integrate the clinical assessment of patients' volume status. Volume assessment is an important clinical tool, as volume overload is a leading cause of admission and readmission. There is increased risk of mortality following each admission. Lung Ultrasound has been used across many specialties, including Cardiology, Emergency Medicine, Critical Care, and Nephrology. Volume status is a quintessential part of the physical exam, especially for those with Cardiorenal Syndrome. It is important that specialties such as Nephrology use all the available tools for volume assessment, including point-of-care ultrasound.

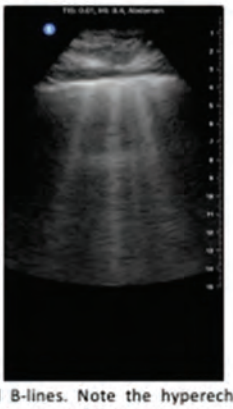
Methods: The use of point-of-care lung ultrasound can help the clinician assess the patient's volume status and adjust diuretic therapy in the clinic. We evaluated a total of ten patients with Cardiorenal Syndrome. Their volume status was assessed using lung ultrasound. Oral diuretic dose and frequency were adjusted according to the findings on physical exam and on the lung ultrasound.

Results: The ten patients had an A-line pattern on lung ultrasound. Three patients had mild edema of the lower extremities and no changes of diuretic dose. The 10 patients continue to be euvolemic without admission to the hospital.

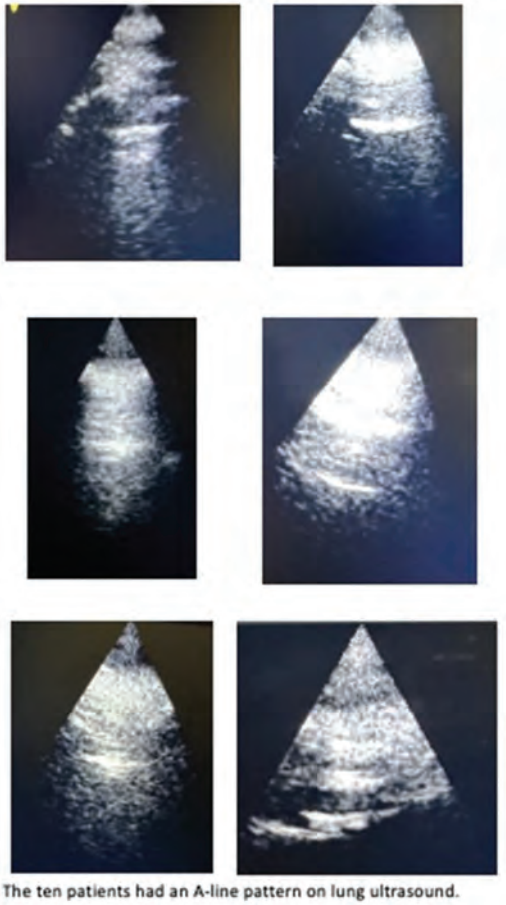
Conclusions: Use of Lung ultrasound in the Nephrology clinic allowed quantification of pulmonary congestion. This may identify the patients with Cardiorenal Syndrome who respond well to diuretic intensification, help them maintain euvolemia, and avoid admission.



Lung ultrasound A-line pattern. Note the bright horizontal lines at integer multiples of the pleural depth, which diminish in intensity with increasing depth.



Lung ultrasound B-lines. Note the hyperechoic vertical lines extending from the pleural line, radiating to the edge of the ultrasound field.



The ten patients had an A-line pattern on lung ultrasound.

PUB445

Assessing Hospice Referral Quality and Length of Stay in Renal Patients at the Iowa City VA

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Background: Quality assessment of hospice referrals is crucial, but assessment within the Veterans' Health Administration (VHA) and its concurrent care (CC) coverage is understudied. This study evaluates the quality of hospice care at the Iowa City VA (ICVA) in nephrology patients, including LOS, referral patterns, and the effectiveness of a flagging system for hospice enrollment.

Methods: Our objectives were to implement a standardized system for tracking hospice LOS through Electronic Health Records (EHR) flagging, assess hospice LOS, identify gaps in LOS and referral patterns, and evaluate the accuracy of flag placement for hospice enrollment. We identified ICVA patients who died following hospice referral between October 2018 and July 2021 using an internal database. Focused chart reviews provided LOS, hospice diagnosis, referral source, and time lag between hospice enrollment and flag placement. Additional chart review focused on patients with LOS <7 days to identify potential gaps in care. Median LOS was compared using Kruskal-Wallis, and Chi2 analysis assessed enrollment rates across groups.

Results: Analysis included 661 patients. Common hospice diagnoses were cancer (47.4%), cardiac disease (13.3%), and respiratory illness (13.0%). Among CC patients, cancer was the predominant diagnosis (80.4%). The median hospice LOS was 27.5 days (range: 0-912), while CC LOS was 62 days (range: 4-721). The mean gap between hospice enrollment and flag placement was 3.8 days, with a median discrepancy of 1 day and mode of 0 days (range: 0-514 days). Hospice LOS did not significantly vary by diagnosis, year, or referral source, and CC LOS did not vary by diagnosis. Renal disease patients were underrepresented in both groups and had comparatively shorter median LOS (14 days). Approximately 20% of patients had a short LOS (7 days or less).

Conclusions: Manual flagging of patient charts provides a reliable method to track hospice enrollment date and LOS, with potential implications for the VHA. Our study identified areas for improvement, particularly in the care of nephrology patients with renal disease and those with short LOS. Implementing interventions to address these findings can enhance end-of-life care in nephrology within the ICVA.

PUB446

Molecular and Metabolic Alterations of Lipoproteins and Fatty Acids in CKD

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Background: Chronic kidney disease (CKD) has a significant impact on lipid and lipoprotein metabolism and homeostasis. These modifications play a crucial role in promoting, modulating, and accelerating CKD and secondary cardiovascular disease (CVD). The changes in lipid and lipoprotein profile encompass variations in protein composition, incorporation of small molecules, and post-translational modifications. Metabolic changes can induce mitochondrial dysfunction and cellular damage, contributing not only to cardiovascular complications but also to the progression of kidney damage.

Methods: An extensive analysis of available literature regarding the alterations in lipid and lipoprotein metabolism in patients with chronic kidney disease was carried out. Relevant studies, research articles, and clinical data were identified through comprehensive searches of databases. The selected information focuses on the modifications in lipid and lipoprotein profiles, including changes in concentration and molecular structure, and their implications for the pathophysiology of CKD and the development of cardiovascular disease.

Results: Lipoprotein abnormalities, such as elevated triglyceride-rich lipoproteins, LDL, and altered HDL, are not only associated with changes in concentration but also exhibit structural changes that impact their biological activity. These modifications can initiate pro-inflammatory and pro-atherogenic processes and induce oxidative stress. Additionally, patients with CKD commonly experience disturbances in serum fatty acid levels, leading to disruptions in fatty acid metabolism, mitochondrial dysfunction, and cellular damage. These lipid and lipoprotein abnormalities interact with the inflammatory and oxidative environment in CKD, further exacerbating cardiovascular risk.

Conclusions: The competing risk of non-atherosclerotic cardiovascular death in individuals with declining kidney function poses additional challenges for therapeutic interventions. Understanding the relationships between lipid and lipoprotein modifications, kidney dysfunction, and the genesis and/or progression of cardiovascular disease in patients with CKD will provide valuable insights for the development of effective therapeutic strategies.

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PUB447

Alteration of the Gut Microbiota in CKD

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Background: The gut microbiota, consisting of trillions of microorganisms, plays crucial roles in various physiological processes. However, it also contributes to the progression of chronic kidney disease (CKD).

Methods: The information presented in this article is based on existing literature related to gut microbiota in patients with CKD. Relevant studies, research articles, and clinical data were collected from various databases and sources. The selected information focuses on the pathophysiology, clinical consequences, and underlying mechanisms of gut microbiota in CKD.

Results: The human gut microbiome comprises bacterial species from major phyla, including Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, and Verrucomicrobia. Changes in the composition of these phyla result in an imbalance between beneficial and pathogenic bacteria, exacerbating CKD. Additionally, CKD-associated modifications of the gut microbiome lead to metabolic changes and the accumulation of uremic metabolites, such as amines, indoles, and phenols. These metabolites negatively affect renal function and contribute to comorbidities like atherosclerosis and cardiovascular diseases. Uremic toxins were categorized based on known toxicity and experimental evidence, playing a significant role in CKD. Small water-soluble compounds, protein-bound compounds, and middle molecules are representative uremic toxins, with their production influenced by the gut microbiota. Gut-derived uremic metabolites damage the intestinal epithelial barrier, increase gut permeability, and facilitate the translocation of bacteria and endotoxins into the bloodstream. This leads to endotoxemia, inflammation, and further acceleration of CKD progression.

Conclusions: While the importance of the gut microbiome in CKD pathophysiology is recognized, the underlying mechanisms remain incompletely understood. An overview of the current research on CKD, the gut microbiota, alterations in the microbiome, production of uremic toxins, and degradation of the gut epithelial barrier would lead to identification of novel theapeutic targets.

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PUB448

Cortical Iron Deposition Is Associated with Kidney Fibrosis and Can Be Assessed by Magnetic Resonance Imaging

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Background: Fibrosis is responsible for the loss of kidney function as a result of several insults, such as ischemia-reperfusion injury or hyperfiltration. This process can continue even after cessation of the primary insult, as documented in acute kidney injury to chronic kidney disease. Recently, we discovered that iron accumulation is a hallmark of fibrotic diseases, and its deposition accompanies the progression of the disease.

Methods: In a cohort of patients with diabetic kidney disease (DKD), we studied iron deposits through Pearls staining, and its correlation with histological parameters. In a second time, we evaluated prospectively iron deposits through Magnetic Resonance Image (MRI) in a cohort of kidney transplant (KT) recipients who underwent a kidney biopsy and its association with IFTA (interstitial fibrosis and tubular atrophy).

Results: We classified DKD biopsies according to iron deposition (Table 1). The group with positive staining significantly exhibited more IFTA. In the prospective study, we collected data from 15 KT recipients. Mean age, time from KT to biopsy and eGFR were respectively 58.3 years old, 4.3 years and 44.4 ml/min/1.73m2. We found that patients with high IFTA score presented with significantly higher deposits (p=0.005), than patients with low IFTA score. We also found positive and significant correlation between iron deposits and IFTA (r=0.7537, p=0.0012).

Conclusions: Iron deposits are associated with fibrosis, and its detection through MRI could be considered a non-invasive marker.

Table 1. Analysis considering absence (Negative) or presence (Positive) iron staining in diabetic nephropathy biopsies

Variables	Negative N=10	Positive N=16	P value
Gender (Male/Female)	9/1	11/5	0.44
Age (years, SD)	66.9 (5.5)	61.4 (11.1)	0.16
eGFR (ml/min/1.73 m2)	31.2 (14.7)	21.9 (15.2)	0.14
Proteinuria (g/d, SD)	2.46 (3.1)	4.0 (3.4)	0.26
Glomerulosclerosis (%, SD)	31.2 (25.1)	38.4 (23.6)	0.26
Interstitial Fibrosis (0/1/2/3)	(4/2/4/0)	(0/2/6/8)	0.01

eGFR, estimated glomerular filtration rate; SD, standard deviation

PUB449

Not All Controls Are Made Equal: Comparison of Single-Cell Gene Expression in Human Kidney Reference Samples

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Background: Defining molecular mechanism of kidney disease relies on comparison to healthy reference tissue. With the rapid development of molecular analysis tools understanding advantages and limitations of the different reference tissue sources is critical. Here, we compared single-cell gene expression data from four different reference tissue sources including percutaneous kidney biopsies in healthy volunteers (HV), unaffected parts of tumor-nephrectomies (TN) and two sources of living kidney donor biopsies (LD). Diabetic kidney disease data (DKD) (KPMP) was included as a disease comparator.

Methods: Kidney tissue was procured as published (PMC8330551) with institutional approval and after informed consent of study participants. Single cell data from 10 HV, 16 TN, 18 LD, 27 DKD samples were generated. Integration of single cell data (10x Chromium) from all sample groups was done using reciprocal principal component analysis in Seurat R package. For comparative analyses, each group was down sampled to 15000 cells.

Results: The integrated dataset was annotated to 19 cell types which encompassed major kidney cell types. An adaptive/maladaptive proximal cell state based on markers from the published KPMP kidney atlas study had low representation in HV compared to other groups. Similarly, low expression of injury markers including NGAL and KIM1 and low representation of immune cell types were observed in HV. Principal component analysis clustered HV away from the other reference groups. 155 genes that were common among the over-expressed genes in HV compared to other groups with ion import across plasma membrane as top enriched term. TN had the greatest number of uniquely differentially expressed genes compared to HV with WNT signaling as a top enriched term. mRNA processing and hypoxia are enriched for the few uniquely differentially expressed genes in LD vs HV.

Conclusions: Immune and maladaptive epithelial cell proportion in HV group was lower than the other groups. However, each reference sample group had unique features. These differences could be explained when the transcript data is integrated with clinical, demographic and pathologic parameters; these integrated analyses are ongoing.

Funding: NIDDK Support, Private Foundation Support

PUB450

Apolipoprotein C3-Rich Low-Density Lipoprotein (LDL) Induces Human Aortic Endothelial Cells Senescence via FBXO31/p53/p21

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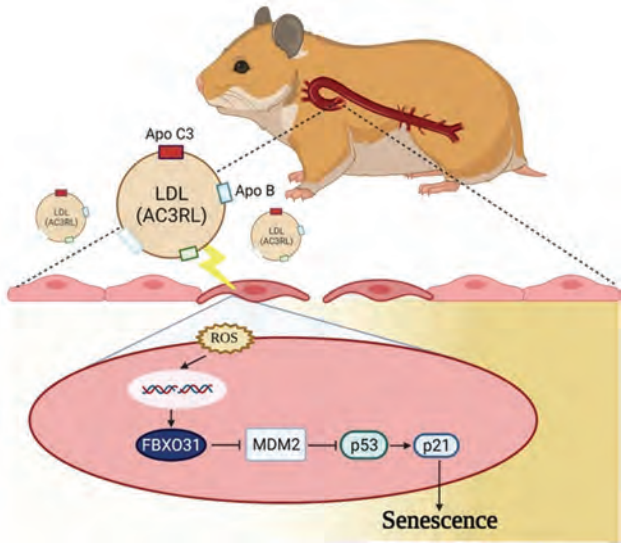
Background: Apolipoprotein C3 (ApoC3) delays the catabolism of triglyceride-rich particles. However, the effects of ApoC3 on uremic dyslipidemia progression is unknown.

Methods: Plasma samples were obtained from diabetic kidney disease (DKD) patients recruited at our outpatient clinic. Low-density lipoprotein (LDL) was separated from other lipids by sequential potassium bromide density centrifugation. ApoC3-rich low-density lipoprotein (AC3RL) was isolated from plasma LDL with the affinity-purified method.

Results: AC3RL induced human aortic endothelial cells (HAEC) senescence in a dose-dependent manner. Reactive oxygen species (ROS) was involved in AC3RL-Induced HAEC senescence. The level of FBXO31, p53 and p21 were markedly increased in AC3RL-induced HAECs. Moreover, silencing FBXO31 attenuated AC3RL-induced DNA damage and reduced cellular senescence.

Conclusions: Inhibiting FBXO31 may protect endothelial damage and arrest the progression of DKD by linking AC3RL elevation to aging and uremic dyslipidemia.

Funding: Private Foundation Support



Apolipoprotein C3-Rich LDL Induces Cells Senescence via FBXO31/p53/p21

PUB451

Role of Cell-Extracellular Matrix (ECM) Interactions for Renal Tubular Epithelial Cell Phenotypes in the Context of Progressive CKD

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Background: Chronic kidney disease (CKD) is mainly defined by interstitial fibrosis of the renal parenchyma and progressive atrophy of proximal tubules (PT). The latter is characterized by pronounced thickening and multilamellation of the tubular basement membrane, whereas fibrosis is promoted by accumulation of extracellular matrix (ECM) translating into increased matrix rigidity. The role of mechanotransduction via integrin adhesion complexes (IAC) as well as the corresponding signaling programs activated in this context remain elusive. Here, we aimed to elucidate the functional role of the ILK-Pinch-Parvin (IPP) complex as an essential part of the IAC in PT damage response and CKD.

Methods: Morphometric assessment of ischaemia-reperfusion injury (IRI) mouse models was performed. Transcriptome studies of human proximal tubular epithelial cells (hRPTECs) under pro-fibrotic conditions were analyzed. CRISPR/Cas9 genome editing was employed to generate knockout cell lines of the IPP complex (ILK, PARVA and PARVA/PARVB double KO), complemented by functional assays.

Results: TGFb treatment (resembling pro-fibrotic conditions) resulted in a partial epithelial-to-mesenchymal transition (pEMT) state of hRPTECs. Transcriptome analysis demonstrated an altered regulation of several matrisome and adhesome genes, including members of the IPP complex. Similar alterations were observed in PTs of IRI mice. Further characterization using IPP-KO cell lines revealed an altered cytoskeleton, cell morphology and total number of IACs, as well as an altered distribution of the latter. Interestingly, PARVA/B double KOs lacked the ability to form a proper cytoskeleton, resulting in a significant reduction in cell area and IACs. Further genetic perturbation studies demonstrated the strong interdependence of individual IPP-complex members for stabilization and regulation of IACs. IPP-KO cell lines failed to form a multilayered and interconnected extracellular matrix, demonstrating a key role of IPP proteins in mechanosignaling.

Conclusions: We have established a simplified model to investigate processes of pEMT in hRPTECs resembling hallmark features of tubular remodeling in CKD. In vivo, transcriptome and functional data indicate a central role of the IPP-complex in orchestrating cell-matrix interactions as an underlying theme of tubular atrophy.

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

PUB452

New Targets for Cardiovascular Disease (CVD) in CKD: Proteomic Analysis of Indoxyl Sulfate-Treated Endothelial Cells and Extracellular Vesicles (EVs)

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Background: CKD is characterized by an accumulation of uremic toxins that promote endothelial damage, generating CVD. The proteome of damaged endothelial cells and the release of extracellular vesicles (EVs), that can function as mediators and/or biomarkers, have been studied to clarify the mechanisms underlying the pathogenesis of cardiovascular complications in kidney disease and identify potential diagnostic and therapeutic targets. Thus, the study aimed to describe changes in the levels of proteins in both endothelial cells and their EVs treated with indoxyl sulfate (IS).

Methods: HUVEC were cultured in two different conditions: control (n=5) and IS-treated (250 μM, 24 h; n=5), and EVs released by the cells were isolated. Proteins from cells and EVs were isolated and analyzed using mass spectrometry to identify and quantify their protein patterns.

Results: In the proteomic analysis of cells, a total of 5871 proteins (5836 groups) were identified, while 3614 proteins (3546 groups) were identified in EVs (FDR<1%). Among these proteins, 145 showed significant differential expression (75 downregulated, 70 upregulated) and 141 differentially expressed in EVs (77 downregulated, 64 upregulated in IS-treated cells vs. control). In addition, reduced levels of proteins involved in replication and mitotic error prevention (MCM2, TACC3), and translation initiation factors (EIF3H, EIF3F, EIF4E) were detected in cells. These changes were accompanied by increased expression of transcriptional inhibitors (ING5, CTCF), caspase 3 and the downregulation of serpin-B3 (apoptosis inhibitor). Additionally, a reduction in extracellular matrix proteins (collagens, ECM1, fibronectin, perlecan) was observed in EVs and an MMP1 increase. Furthermore, elevated levels of complement components (C5, CFI), bactericidal protein LYZ, chemotactic protein S100A7, adhesion molecule ICAM-1, and immune activation marker CALML5 were detected.

Conclusions: The study suggests that IS induces cellular endothelial damage and inhibits proliferation. The results show that IS-treated EVs have a proinflammatory effect that may trigger the activation of immune cells. These newly identified molecules are promising as potential diagnostic markers and therapeutic targets for CKD.

PUB453

IL-33-Mediated Mast Cell Activation Promotes Renal Fibrosis by Regulating the Phenotype of Neutrophil

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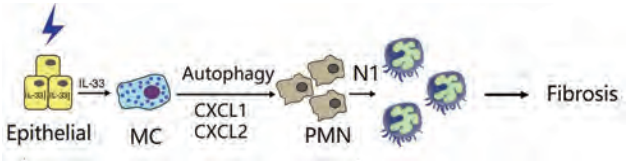
Background: To investigate the mechanism that IL-33 activates mast cell and promotes its degranulation, which then recruits and regulates the phenotype of neutrophil in the development of renal fibrosis.

Methods: Analyzed the correlation between the density of infiltrating MC in kidney and renal fibrosis. mIL-33, anti-ST2 antibody and Rapamycin were used to clarify the impact of autophagy on mast cell activation and degranulation. Then, the maturation and phenotypic changes of neutrophils were detected. Finally, using MC knockout mice were transfused with mast cells inhibited of autophagy and mIL-33 to detect the maturation and phenotypic changes of neutrophil after kidney injury.

Results: (1)The degree of mast cell infiltration in renal biopsy specimen of IgA nephropathy patients was positively correlated with the degree of renal interstitial fibrosis. Knockout mast cell eliminated UUO-induced renal fibrosis and neutrophil infiltration, while reconstituted with mast cells aggravated UUO-induced renal fibrosis and neutrophil infiltration. (2)Neutrophil infiltration was correlated with the progression of renal fibrosis, and gradually differentiates into pro-inflammatory phenotype. Knocking down neutrophil can significantly inhibit the progression of renal fibrosis. (3)In the early stage of renal injury, renal tubular epithelial cells secreted IL-33, which activates mast cells through its receptor ST2, inhibited autophagy and promoted degranulation, then secreted CXCL1. (4)Both mast cells and CXCL1 can promote neutrophil maturation and differentiate into pro-inflammatory phenotype in vitro. In vivo, reconstituted with mast cells inhibited of autophagy can reduce neutrophil infiltration and alleviate the differentiation. Recombinant IL-33 can enhance neutrophil infiltration in kidney and promote the differentiation of neutrophil into pro-inflammatory phenotype.

Conclusions: In the early stage of renal injury, the injured renal tubular epithelial cells could secrete IL-33, activated mast cells by inhibiting autophagy and then promoted degranulation, which recruited neutrophil infiltration in the kidney and gradually differentiated into pro-inflammatory phenotype. Together, these effects accelerated the process of renal fibrosis.

Funding: Government Support - Non-U.S.



Model summarizing

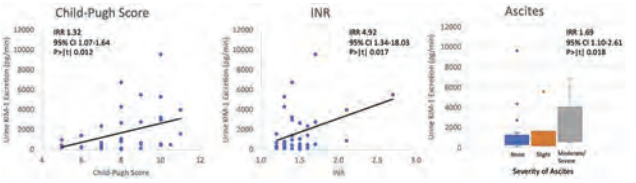


Figure: Associations of measures of liver disease with urine KIM-1 excretion in patients with cirrhosis: (a) Child-Pugh Score, (b) INR (c) Ascites, categorized as none (0), slight (1), and moderate/severe (2); IRR = incidence rate ratio.

PUB454

Protective Role of Tulsi (Holy Basil) Extract in Renal Epithelial Wound Repair

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Background: Wound/injury from a resultant reactive oxygen species (ROS) can ultimately leads to chronic kidney disease (CKD). ROS productions are much higher in proximal tubular (PT) cells, which makes them vulnerable to oxidative damage, thus predispose to CKD. We tested the effect of Tulsi Chai (TC) and its ability to protect renal epithelial cells from the ROS in a wound-healing model. We induced CKD-like condition in our model by introducing calcium phosphate (CaP) crystals into PT cells in a scratch wound.

Methods: Hydrothermally extracted Tulsi extracts used as TC to investigate its wound healing property towards mechanical injury, cell survival and reversal of oxidative stress on human proximal tubular kidney-2 (HK-2) cells. H_2O_2 (crude) and CaP crystals (pathogenic) were used as ROS-inducers on the cells to impose different treatment (dose and concentrations) regiments. Cell survival was determined by Trypan blue exclusion assay, cytoplasmic reactive oxygen species (ROS) level was determined by H_2O_2 release assay. Apoptosis was examined using AnnexinV and DAPI staining whereas necrosis was identified by propidium iodide staining and Lactate Dehydrogenase (LDH) release. Wound healing assay and the molecular mechanism for wound healing were evaluated by gene expression and phosphorylation.

Results: Pretreatment of TC in HK2 cells caused a significant cell-survival and reduction of ROS generation in a concentration dependent manner. Reversal of H_2O_2-induced HK2 cell death and cytotoxicity by cell viability and extracellular LDH release indicate the protective role of TC. Wound closure and the rate of repair of wound by TC were found to be directly proportional to the amount of TC pretreatment. CaP-induced apoptosis and necrosis as investigated with the HK-2 cells showed reduction in apoptotic, necrotic and cell wall fragmentation for cells preconditioned with TC in a dose dependent manner. TC mitigated the ROS-induced phosphorylation of phospho-P38 (pP38) in our CaP-induced wound closer model.

Conclusions: Our study shows that TC has the ability to remediate both mechanical and ROS induced wounds on renal tubular cells, hence, may have the potential for natural regenerative substance for CKD patients.

Funding: NIDDK Support

PUB455

Subclinical Proximal Tubular Injury in Nonhospitalized Patients with Cirrhosis

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Background: Cirrhosis leads to a reduction in kidney blood flow via splanchnic vasodilation and reflexive neurohormonal activation. These hemodynamic changes may adversely impact tubular health in the absence of clinically apparent kidney injury. We tested the association of cirrhosis with the urine excretion of kidney injury molecule-1 (KIM-1), a marker of tubular injury, in stable outpatients with end-stage liver disease (ESLD).

Methods: We recruited 39 adult patients with ESLD undergoing outpatient evaluation for liver transplantation. We selected a comparison group of 58 control individuals without liver disease from two previously completed studies, matched to the cirrhosis group by estimated glomerular filtration rate (eGFR). We measured urine KIM-1 concentrations in 24-hour urine samples by electrochemiluminescence (Mesa Scale Discovery). We used linear regression to quantify associations of urine KIM-1 excretion with the presence of cirrhosis and measures of liver disease severity.

Results: The cirrhosis group was characterized by a mean age of 57 ±9 years; 28% female; mean eGFR of 66 ±20 ml/min/1.73m2; and mean Model for End-stage Liver Disease (MELD) and Child-Pugh Scores of 17±4 and 8 ±2, respectively. The median urine KIM-1 excretion was 1688 pg/min (IQR 306, 2683 pg/min) in the cirrhosis group versus 180 pg/min (IQR 118, 356 pg/min) in the control group. After adjustment for eGFR, age, and sex, the presence of cirrhosis was associated with an estimated 4.0-fold greater urine excretion of KIM-1 (95% confidence interval 2.7, 6.2-fold greater; p-value <0.001). Among the cirrhosis group, higher Child-Pugh Scores, international normalized ratios (INR), and the severity of ascites were associated with higher urine excretion of KIM-1 (Figure).

Conclusions: Cirrhosis is associated with subclinical proximal tubular injury, demonstrated by increased urine excretion of KIM-1, in stable outpatients with ESLD.

PUB456

PM2.5 Induces Epithelial-to-Mesenchymal Transition by Oxidative Stress in Renal Tubular Kidney Cells

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Background: The incidence and prevalence of chronic kidney disease (CKD) are increasing worldwide. Recently, the exposure to air pollution, especially particulate matter$_{2.5}$ ($PM_{2.5}$) was newly identified to be a potential risk factor for CKD, however there are no studies on whether exposure to $PM_{2.5}$ is a direct cause of CKD occurrence and exacerbation. Epithelial-to-mesenchymal transition (EMT) of tubular cells is one of the early mechanisms of progression of renal disease. Therefore, the identification of association between fine dust and EMT may allow to reveal the casualty toward CKD.

Methods: Fine dust collected by $PM_{2.5}$ filter (Ulaanbaatar, Mongolia) was dissolved in DMSO by sonication. Renal tubular kidney cells (NRK) were treated with dissolved $PM_{2.5}$ (2 & 5 μL/mL). EMT was evaluated by morphological changes of NRK cells and the expressions of E-cadherin, α-SMA, and vimentin after the stimulation with $PM_{2.5}$ and TGF-β (5 ng/mL) by WB and immunostaining. ROS generation was assessed by DCF-DA and MitoSox staining. RNA-seq analysis (Ebiogen, Korea) was performed to investigate which upregulated/downregulated-genes are associated with $PM_{2.5}$-induced phenotype transition in NRK cells.

Results: $PM_{2.5}$ at the concentrations of 2 and 5 μL/mL did not alter LDH release and cell proliferation up to 48 hours of exposure. $PM_{2.5}$ induced EMT of NRK cells assessed by morphologic changes associated with a decreased E-cadherin expression and de-novo expression of α-SMA and vimentin. $PM_{2.5}$ also increased DCF-DA and Mito-Sox staining. RNA-seq analysis demonstrated the differences in gene expression related to EMT (16.7%), adipokine (15.9%), apoptotic process (13.7%), and oxidative stress (12.8%). Among them, lipocalin 2 (LCN2), Interleukin-11 (IL-11), and hyaluronan synthase 2 (HAS2) expression showed the highest fold difference (2.7-folds, 2.5-folds, and 2.0-folds, respectively) between control and $PM_{2.5}$-treated NRK cells.

Conclusions: This data suggest that exposure to $PM_{2.5}$ induces EMT and oxidative stress in NRK cells, which may be one of the possible mechanisms for the association between fine dust exposure and the development of renal disease.

Funding: Government Support - Non-U.S.

PUB457

Transcriptomic Assessment of GRP78 as a Mediator of CKD

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Background: Protein misfolding causes endoplasmic reticulum (ER) stress and activation of the unfolded protein response (UPR). The 78-kDa glucose-regulated protein (*GRP78*) is an ER stress-induced chaperone protein and regulator of UPR. *GRP78* overexpression protects rat ventricular cardiomyocytes from ischemia-reperfusion injury and regulates the profibrotic response to high glucose in glomerular mesangial cells. Homozygous knockout of *GRP78* is lethal in mice. We hypothesized that genetically altered *GRP78* expression or rare variants in *GRP78* would be associated with chronic kidney disease (CKD).

Methods: We assessed genetic variants' impact on *GRP78* gene expression in the expression quantitative trait loci genetics consortium (n=31,684). We used a two-sample Mendelian Randomization analysis to assess the effect of genetically predicted *GRP78* expression on CKD (n=480,698), cross-sectional eGFR (n=1,508,659), eGFR decline (n=343,339), and urinary albumin-to-creatinine ratio (uACR; n=348,964) using European ancestry summary-level genome-wide association studies (GWAS). The prevalence of *GRP78* missense and loss-of-function variants was assessed in gnomAD, BRAVO, and in 157,528 UK Biobank participants. We performed linear regression to test for association between GRP78 rare variant carrier status and kidney phenotypes adjusted for age, sex, and ancestry.

Results: The latest GWAS reports association of variants near *GRP78* and eGFR (lowest P=8.9e-09). A 13-variant Mendelian randomization instrument explained 2.8% of variability in *GRP78* expression, but was not associated with cross-sectional eGFR, eGFR decline, CKD, or uACR (P>0.05). *GRP78* is relatively intolerant of genetic variability, with a loss-of-function upper bound fraction of 0.41 and missense observed/expected ratio of 0.41. Presence of rare-variants was marginally associated with a 6.4% increase in

uACR (P=0.01), a 1.5% decline in eGFRCys (P=0.02), but not significantly associated with cross-sectional eGFR (β=-0.004,P=0.5) or CKD (OR=1.31,95% CI:1-1.73,P=0.05).

Conclusions: *GRP78* is relatively intolerant of genetic variation consistent with selection against heterozygous variation. Nevertheless, GWAS and rare variant analysis show a nominal association of variants around *GRP78* with kidney phenotypes. In contrast, genetically-predicted variation in *GRP78* expression was not associated with kidney phenotypes.

PUB458

Growth Restriction, but Not Prematurity, Is Associated with Renal Microinflammation in Early Adulthood

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Background: Low birth weight (LBW), i.e. birth weight <2.5kg, is associated with an increased risk of adult-onset chronic kidney disease and kidney failure, but the mechanistic basis of this association is unknown. We hypothesize that reduced nephron endowment in these patients results in chronic glomerular hyperfiltration, which eventually leads to renal immune cell infiltration and inflammation, creating a pro-fibrogenic milieu. We aimed to characterize the urine immune cell and cytokine composition in young adults born LBW, and compare them with normal birth weight controls.

Methods: We recruited a cohort of 40 LBW participants, comprising 25 participants born prematurely and 15 born growth-restricted (IUGR) at term, as well as 16 age- and sex- matched normal birth weight controls. Urine immune cells were quantified by flow cytometry (markers: CD45, CD3, CD56, CD19, CD14) and urine cytokine composition by multiplex ELISA. The 3 participant groups were first compared using ANOVA, and if significant with p≤0.05, post-hoc tests were then performed with Tukey's HSD test.

Results: The 3 participant groups were comparable in terms of serum creatinine (p=0.206), Cystatin C (p=0.709), as well as urine albumin:creatinine ratio (p=0.485). Of the cell markers studied, urine CD3+ T-cell (p=0.048) and CD14+ macrophages (p=0.007) differed between groups. This was due to Term IUGR participants having a higher level of urinary CD3+ T-cells (9.5±2.2% vs 3.6±0.7%, p=0.041) and CD14+ macrophages (0.17±0.04% vs 0.05±0.01%, p=0.005) compared to controls. Participants also differed in urine IL-6 concentrations (p=0.009), with Term IUGR participants having higher urinary IL-6 compared to controls (1.1±0.3 vs 0.43±0.1 pg/mg creatinine, p=0.047).

Conclusions: Young adults who were born growth-restricted at term displayed incipient nephropathy characterized by renal microinflammation. If validated, indices of renal microinflammation can be used to identify high-risk patients for long-term follow-up, and provide a basis for early intervention using targeted immunological therapies.

Funding: Government Support - Non-U.S.

AUTHOR INDEX

The number refers to the location of the body of the abstract in the publication section

KEYWORD INDEX

The number refers to the location of the body of the abstract in the publication section

FR-OR108

Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Focal Segmental Glomerulosclerosis (FSGS): Results from the Phase 3 DUPLEX Trial

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Background: SPAR is a dual endothelin angiotensin receptor antagonist (DEARA) that reduced proteinuria in patients with FSGS in the phase 2 DUET trial. DUPLEX evaluated the antiproteinuric and nephroprotective potential of SPAR vs active control IRB in patients with FSGS. DUPLEX met its interim efficacy endpoint (FSGS partial remission endpoint [FPRE]), with 42% of patients achieving FPRE with SPAR vs 26% with IRB at 36 wk. Here, we present results from the primary analysis.

Methods: In this phase 3 randomized trial, patients (ages 8-75 y) with FSGS, excluding secondary causes, with a urine protein/creatinine ratio (UP/C) ≥1.5 g/g and an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 at screening were randomized 1:1 to SPAR or IRB (target dose, 800 and 300 mg/d, respectively) for 108 wk. The primary endpoint was eGFR slope. Other efficacy endpoints are listed in the **Table**. Safety was assessed and evaluated by a data monitoring committee.

Results: 371 patients were randomized to SPAR (n=184) or IRB (n=187). After 108 wk, SPAR showed a 50% reduction in UP/C vs 32% with IRB, with more than twice as many patients achieving complete remission of proteinuria (**Table**). The differences in eGFR total and chronic slope for SPAR vs IRB were 0.3 and 0.9 mL/min/1.73 m^2 per year (P>.05). Additional efficacy results are listed in the **Table**. SPAR was well tolerated, with a safety profile comparable to IRB.

Conclusions: In the largest randomized trial in FSGS to date, SPAR achieved a clinically meaningful reduction in proteinuria, although the eGFR slope–based primary endpoints were not met. Overall, results support the potential clinical benefit of SPAR for FSGS. Dr Rheault and Dr Trachtman contributed equally.

Funding: Commercial Support - Travere Therapeutics

Table. Efficacy Results

Endpoint	Definition and timing	SPAR (n=184)	IRB (n=187)	Difference for SPAR vs IRB (95% CI)[a]
eGFR total slope, LS mean (95% CI), mL/min/1.73 m^2 per year[b]	From d 1 to wk 108	−5.4 (−6.9 to −3.9)	−5.7 (−7.2 to −4.3)	0.3 (−1.7 to 2.4), ns
eGFR chronic slope, LS mean (95% CI), mL/min/1.73 m^2 per year[c]	From wk 6 to 108	−4.8 (−6.3 to −3.3)	−5.7 (−7.2 to −4.2)	0.9 (−1.3 to 3.0), ns
Change in eGFR, LS mean (95% CI), mL/min/1.73 m^2	From baseline to 4 wk post treatment	−10.4 (−12.6 to −8.1)[d]	−12.1 (−14.4 to −9.9)[d]	1.8 (−1.4 to 4.9), ns
Change in UP/C, %	From baseline to wk 108	−50.0	−32.3	GMR, 0.74 (0.58 to 0.93)
FPRE, %	Defined as UP/C ≤1.5 g/g and ≥40% reduction from baseline, at wk 108	37.5	22.6	RR, 1.60 (1.13 to 2.25)
Complete remission of proteinuria, %	Defined as UP/C <0.3 g/g; at any time during the 108-wk double-blind treatment period	18.5	7.5	RR, 2.47 (1.37 to 4.45)
End-stage kidney disease, n (%)	Defined as confirmed eGFR <15 mL/min/1.73 m^2 or RRT; at any time during the study	12 (7)	21 (11)	RR, 0.58 (0.31 to 1.07)
Confirmed 50% reduction in eGFR, end-stage kidney disease, or renal death, n (%)[e]	At any time during the study	21 (11.4)	31 (16.6)	RR, 0.68 (0.43 to 1.10)

eGFR, estimated glomerular filtration rate; FSGS, focal segmental glomerulosclerosis; FPRE, FSGS partial remission endpoint; GMR, geometric mean ratio; IRB, irbesartan; LS, least squares; ns, not significant; RR, relative risk; RRT, renal replacement therapy; SPAR, sparsentan; UP/C, urine protein/creatinine ratio.
[a] Unless otherwise specified.
[b] Primary endpoint in the US.
[c] Primary endpoint in other countries.
[d] Patients who completed treatment in the double-blind period (sparsentan, n=129; irbesartan, n=136).
[e] Renal death was defined as death in a patient who reached end-stage kidney disease prior to initiating renal replacement therapy where another cause of death has not been reported.

FR-OR109

Pivotal Results of the Phase 3 PROTECT Trial of Sparsentan (SPAR) vs. Irbesartan (IRB) in Patients with Immunoglobulin A Nephropathy (IgAN)

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Background: SPAR, a dual endothelin angiotensin receptor antagonist (DEARA), showed a significantly greater reduction in urine protein excretion vs IRB in patients (pts) with biopsy-proven IgAN in an interim 36-wk analysis of the PROTECT trial (−49.8% vs −15.1%, respectively; P<.0001) (Heerspink et al. *Lancet*. 2023). Based on these data, SPAR was granted accelerated approval in the US for adults with primary IgAN at risk of rapid disease progression. We will present the pivotal double-blind PROTECT trial results on the efficacy and safety of SPAR vs IRB. These results will be available after database lock in Sep 2023.

Methods: PROTECT is a phase 3, international, randomized, double-blind, parallel-group, active-controlled trial evaluating the efficacy and safety of SPAR vs IRB in adults with IgAN at high risk of progression to kidney failure despite maximized treatment with an angiotensin-converting enzyme inhibitor and/or angiotensin receptor blocker. Pts with biopsy-proven IgAN, urine protein excretion ≥1.0 g/d, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2 were randomized 1:1 to SPAR 400 mg/d or IRB 300 mg/d for up to 110 wk. The final analysis will report the 2-year rate of eGFR change (chronic and total slope), kidney composite endpoint (rate of >40% eGFR decline, kidney failure, or death), change in proteinuria by visit, rates of complete (<0.3 g/d) and partial (<1.0 g/d) proteinuria remission, and long-term safety and tolerability. Analyses used will be a mixed model random coefficients analysis (eGFR slope), mixed model for repeated measures (change in proteinuria), and logistic regression model (remission and composite endpoints).

Results: A total of 404 pts were randomized to SPAR (n=202) or IRB (n=202). We will present eGFR chronic and total slopes over 2 years, incidence of the kidney composite endpoint, percent change from baseline in urine protein-creatinine ratio through wk 110, and proportion of pts who achieved complete or partial proteinuria remission at any time within 110 wk. Safety and tolerability data will be presented.

Conclusions: The phase 3 trial results on kidney function and outcomes, proteinuria, and safety with SPAR vs IRB over 2 years may significantly impact the treatment landscape of pts with IgAN.

Funding: Commercial Support - Travere Therapeutics

FR-OR110

AYAME Study: Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Bardoxolone Methyl in Diabetic Kidney Disease (DKD) Patients

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Background: Bardoxolone methyl (BARD) is an activator of the Keap1-Nrf2 pathway. Previous study demonstrated that BARD improves the estimated glomerular filtration rate (eGFR). However, the phase 3 study was terminated prematurely because of an imbalance in heart failure (HF) between BARD and placebo groups. The subsequent phase 2 TSUBAKI study demonstrated no incidence of HF and an improved GFR as determined by inulin clearance in diabetic kidney disease (DKD) patients without the risk factors of HF. We conducted an event-driven study to evaluate the efficacy and safety of BARD in more than 1,000 patients.

Methods: A phase3 (AYAME) study was conducted in DKD patients and comprises a screening period, a treatment period of 3-4 years, and a post-treatment observation period of 16 weeks. Eligible patients had eGFR ≥15.0 - <60 ml/min/1.73m^2 and urinary albumin creatinine ratio (UACR) ≤3500 mg/g without the risk factors of HF. The primary and the key secondary endpoints were the time to onset of a ≥30% decrease in the eGFR or end-stage kidney disease (ESKD: dialysis, kidney transplantation or eGFR ≤6) and a ≥40% decrease in the eGFR or ESKD, respectively. Other secondary endpoints included the time to onset of ESKD. The safety endpoints were adverse events and time to onset of cardiac events, including HF.

Results: 1013 patients were råandomized (1:1) to receive BARD or placebo. The mean eGFR (standard deviation, [SD]) and UACR (SD) at baseline were 37.84 (12.64) ml/min/1.73 m^2 and 712.39 (834.22) mg/g, and were generally comparable among the groups. The primary outcome occurred in 153 of 507 patients in the BARD group and 229 of 506 patients in the placebo group (hazard ratio (HR), 0.56; 95% CI, 0.45 to 0.69; P<0.001). A key secondary outcome occurred in 122 patients in the BARD group and 172 patients in the placebo group (HR, 0.69; 95% CI, 0.55 to 0.87; P=0.0018). ESKD occurred 69 patients in the BARD group and 62 patients in the placebo group without significant differences (HR, 1.21; 95% CI, 0.86 to 1.71; P=0.2706). Cardiac events occurred 24 events in the BARD group and 26 events in the placebo group, and there were no other safety concerns.

Conclusions: AYAME study achieved its primary and key secondary endpoint without major safety concern, while BARD did not decrease the occurrence of ESKD.

Funding: Commercial Support - Kyowa Kirin Co., Ltd.

FR-OR111

Aldosterone Synthase Inhibition with or Without Background Sodium Glucose Cotransporter 2 Inhibition in CKD: A Phase II Clinical Trial

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Background: High aldosterone levels accelerate chronic kidney disease (CKD) progression. We tested the efficacy and safety of BI 690517, a novel aldosterone synthase inhibitor (ASI), in participants (pts) with CKD.

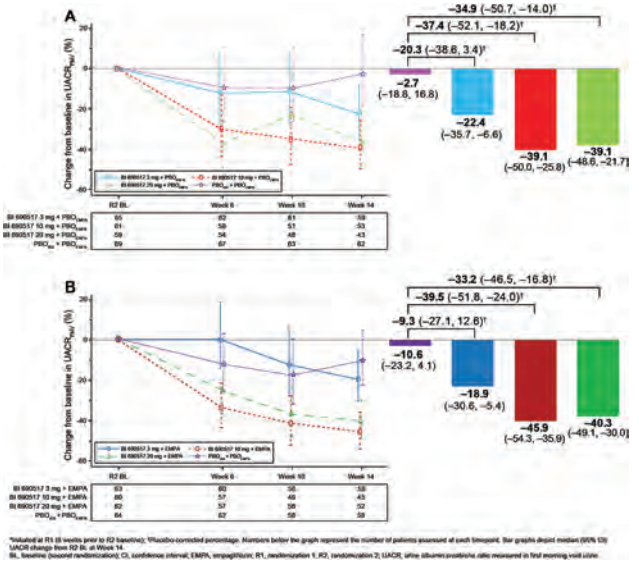
Methods: In this double-blind trial (NCT05182840), adults with CKD on a renin angiotensin system inhibitor (RASi) were first randomized (R1) 1:1 to an 8-week run-in to background (BG) empagliflozin 10 mg (EMPA) or placebo (PBO_{EMPA}) and then randomized a second time (R2) 1:1:1:1 to BI 690517 (3, 10, or 20 mg) or PBO_{ASI}.

The primary endpoint was change from R2 baseline (BL) in urine albumin:creatinine ratio (UACR) from the first morning void at Week 14. A secondary endpoint was UACR ≥30% reduction from R2 BL at Week 14.

Results: Of 714 pts randomized in R1, 586 were randomized in R2. At R2 BL, mean (SD) age was 63.8 (11.3) years, 58.4% of pts were White, 66.6% were male, and 70.6% had type 2 diabetes. BL median (IQR) UACR was 426.3 (205–889) mg/g and mean (SD) eGFR was 51.9 (17.7) mL/min/1.73m^2. BI 690517 dose dependently reduced UACR (Figure). Largest median (95% CI) PBO_{ASI}-corrected change was −39.5% (−51.8, −24.0) for BI 690517 10 mg on EMPA BG. Among BI 690517 3–20mg pts, changes in UACR ≥30% were achieved by 53.5% on EMPA BG and 43.2% on PBO_{EMPA} BG. BI 690517 (3–20mg)-related adverse events were reported in 19.2% of pts on EMPA BG and 18.5% of those on PBO_{EMPA} BG.

Conclusions: BI 690517 was well tolerated and dose dependently reduced UACR on top of BG RASi and EMPA/PBO_{EMPA} in pts with CKD. BI 690517 and EMPA showed additive anti-albuminuric efficacy that may translate into greater kidney protection.

Funding: Commercial Support - Boehringer Ingelheim



Percentage change from R2 BL in UACR up to Week 14 following BI 690517 treatment administered with A) EMPA-matched placebo or B) EMPA 10 mg.

FR-OR112

ZENITH-CKD: A Phase 2B Study of Zibotentan in Combination with Dapagliflozin and Dapagliflozin Alone in Patients with CKD

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Background: Despite treatment of CKD with RAS and SGLT2is, many patients have residual albuminuria which may be associated with rapid CKD progression. The albuminuria-lowering efficacy and safety of zibotentan, a selective ET-A receptor antagonist, were examined when administered concomitantly with an SGLT2i in a phase 2b dose-ranging trial.

Methods: ZENITH-CKD, a randomized, double-blind, active-controlled trial, was conducted in 170 clinical sites in 18 countries. Adults with a urinary albumin-creatinine ratio (UACR) of 150 to 5000 mg/g and eGFR ≥20 mL/min/1.73m^2 not on SGLT2i were randomized to 1 of 6 treatment arms. Enrollment to 5 mg zibotentan monotherapy, 5 mg zibotentan/10 mg dapagliflozin, and placebo was discontinued at 62 participants. Enrollment continued across 3 other treatment arms: 0.25 mg/10 mg zibotentan/dapagliflozin, 1.5 mg/10 mg zibotentan/dapagliflozin, dapagliflozin/placebo 10 mg. The primary efficacy endpoint was change from baseline to week 12 in log-transformed UACR, assessed using mixed model repeated measures (in patients who received at least 1 dose of study treatment). Adverse events were recorded as safety endpoints. (NCT04724837)

Results: From April 28, 2021, to January 17, 2023, 447 patients were enrolled and received 0.25 mg/10 mg zibotentan/dapagliflozin (n=91), 1.5 mg/10 mg zibotentan/dapagliflozin (n=179), or 10 mg dapagliflozin/placebo (n=177). Overall, 58.4% of patients had type 2 diabetes, mean baseline eGFR was 46.7 mL/min/1.73m^2, and geometric mean UACR was 538.3 mg/g. At week 12, vs dapagliflozin alone, adjusted percentage mean change in UACR was greater in the 0.25 mg/10 mg and 1.5 mg/10 mg zibotentan/dapagliflozin groups (-27.0% [90% CI -38.4%, -13.6%] and -33.7% [90% CI -42.5%, -23.5%]). No increase in BNP, body weight, or total body water was seen for the 0.25 mg/10 mg zibotentan/dapagliflozin group; modest increases were observed in the 1.5 mg/10 mg zibotentan/dapagliflozin group. One SAE of heart failure occurred in the 0.25 mg/10 mg zibotentan/dapagliflozin group and two occurred in the 1.5 mg/10 mg zibotentan/dapagliflozin group.

Conclusions: ZENITH-CKD confirmed 0.25 mg/10 mg zibotentan/dapagliflozin is highly effective in reducing albuminuria, is well tolerated, and could be an attractive option to further delay CKD progression.

Funding: Commercial Support - AstraZeneca (NCT04724837)

FR-OR113

ALdosterone Antagonist Chronic HEModialysis Interventional Survival Trial (ALCHEMIST): Primary Results

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Background: There is currently no strong evidence-based pharmacological therapy to improve the excessively poor cardiovascular (CV) prognosis in chronic hemodialysis patients (HD). We aimed to investigate the effects of the steroidal mineralocorticoid receptor antagonist, spironolactone on CV outcomes in a high-risk HD population.

Methods: We conducted an international, multicenter, double-blind, randomized, placebo-controlled event-driven trial in HD patients with at least one CV comorbidity, abnormality or risk factor. Spironolactone 25 mg every other day was first administered open-label during a 4-week run-in period. Patients were excluded prior to randomization if serum potassium was greater than or equal to 5.5 mmol/l on two occasions during this run-in period or on the day of randomization. Randomized patients received spironolactone or placebo, both titrated up to 25 mg/day according to a pre-specified algorithm based on serum potassium monitoring. The primary outcome was the time to first MACE-expanded adjudicated event (cardiovascular death or non-fatal myocardial infarction (MI), acute coronary syndrome (ACS), stroke or hospitalization for heart failure (HHF)). The win ratio including 1. all-cause death 2. Time to a CV event (HHF, non-fatal MI, ACS or stroke) was tested in a hierarchical statistical strategy as secondary endpoint. We assumed that a total of 750 randomized patients followed for 2 years would provide 80% power to detect a risk reduction of the primary endpoint by 30% with a alpha risk of 5%. Assuming a 10% run-in withdrawal rate, 825 patients would have to be included in the run-in phase. Safety endpoints included incidence of severe hyperkalemia >6 mmol/L, as monitored at pre-specified visits, and as reported by investigators as serious adverse event. Clinicaltrials.gov NCT01848639

Results: First visit in first patient occurred on June 2013 and last visit in last patient occurred on November 2022. 823 patients were recruited. ALCHEMIST primary results will be presented at the ASN 2023 annual meeting.

Conclusions: ALCHEMIST was the first international double-blind randomized CV outcome trial of spironolactone vs placebo in high-risk HD.

Funding: Government Support - Non-U.S.

FR-OR114

Effect of a Multi-Component Intervention to Improve Patient Access to Kidney Transplantation and Living Kidney Donation

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Background: Patients with advanced chronic kidney disease (CKD) have the best chance for a longer and healthier life if they receive a kidney transplant. However, many barriers prevent patients from receiving a transplant.

Methods: We conducted a pragmatic, two-arm, parallel-group, cluster-randomized trial of a multi-component intervention designed to target several barriers which prevent kidney transplantation and living donation. The trial included all 26 CKD programs in Ontario, Canada, from Nov 2017 to Dec 2021. These programs care for patients with advanced CKD (patients approaching the need for dialysis or receiving maintenance dialysis). Using covariate-constrained randomization, we allocated the CKD programs (1:1) to provide the intervention or usual care for 4.2 years. The intervention had 4 main components: (1) administrative support to establish local quality improvement teams; (2) transplant educational resources; (3) an initiative for transplant recipients and living donors to share stories and experiences; and (4) program-level performance reports and oversight by administrative leaders. The primary outcome was a composite of all completed steps toward receiving a kidney transplant. Each patient could complete up to 4 steps: step 1, referred to a transplant center for evaluation; step 2, had a potential living donor contact a transplant center for evaluation; step 3, added to the deceased donor waitlist; and step 4, received a transplant from a living or deceased donor.

Results: The 26 CKD programs (13 intervention, 13 usual care) during the trial period cared for 20 375 potentially transplant-eligible patients with advanced CKD (intervention [n=9780 patients], usual care [n=10 595 patients]). Despite evidence of intervention uptake, the step completion rate did not significantly differ between the intervention versus usual-care groups: 5334 vs. 5638 steps; 24.8 vs. 24.1 steps per 100 patient-years; adjusted hazard ratio 1.00 (95% CI, 0.87–1.15). Results were consistent in multiple analyses.

Conclusions: This province-wide strategy did not increase the rate of completed steps toward receiving a kidney transplant. Improving access to transplantation remains a global priority. Future efforts can build on lessons learned. Protocol: PMID 33948191 Protocol, Process evaluation: PMID 35340770 Statistical analytic plan: PMID 36438439 ClinicalTrials.gov record: NCT03329521

Funding: Commercial Support - Partnership grant funding received from Astellas Canada, Government Support - Non-U.S.

FR-OR115

MDR-101-MLK Update: Operational Immune Tolerance Achieved in Living Related HLA-Matched Kidney Transplant Recipients

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Background: We describe the updated results from a Phase 3 RCT in recipients of HLA-matched living donor (LD) kidney transplants (KTxp) who received investigational cellular product, MDR-101, for induction of immune tolerance and elimination of immunosuppressive (IS) drugs vs standard of care (SOC) (NCT03363945).

Methods: Eligible adult, recipients (R) of a 1st kidney from an HLA-matched related LD were randomized 2:1 to Investigational Arm (IA; n=20) or Control Arm (CA; n=10). Peripheral blood CD34+ and CD3+ cells for MDR-101 were collected via apheresis from the same kidney donor. IA-Rs were transplanted day (D) 0 and received rATG (D0-4), total lymphoid irradiation (10 fractions), initiation of CNI, followed by an MDR-101 infusion (D11). Steroids were withdrawn by D10 and MMF was given D11-D39. CNI monotherapy continued till D180 and tapered to complete withdrawal 1-year post-transplant (tx) if donor hematopoietic mixed chimerism was ≥5%, and no rejection (BPAR), GvHD, or kidney loss. CA-Rs received IS per institutional SOC.

Results: 20 IA-Rs received tolerance induction conditioning including MDR-101 infusion. 1 IA-R not an HLA-matched (a protocol deviation) and <6 mos of chimerism did not qualify for IS withdrawal. 19 IA-Rs successfully discontinued IS 1-year post-tx. To date, the number of IA-Rs and time remaining off IS: for 12 mos (n=17/19), 12-24 mos (n=17/19), 24 mos (n=12/14). 4 IA-Rs remain off IS and are yet to reach 24 mos off IS. 3 IA-Rs resumed IS: recurrent IgAN (18.7 mos off IS), recurrent IgAN and rejection (4.8 mos off IS), and rejection (11.2 mos off IS). No GvHD, PTLD or other malignancies occurred. No death occurred in either group. 1 IAR developed recurrent IgAN and after study completion had graft loss (4.3 years post-tx). D365 mean eGFR was 64.37 mL/min (IA-R) and 58.78 mL/min (CA-R). D730 mean eGFR was 62.37 mL/min (IA-R) and 62.22 mL/min (CA-R).

Conclusions: MDR-101 can safely achieve donor mixed chimerism and operational immune tolerance with complete elimination of all IS with no death, graft loss, or GvHD in HLA-matched LD recipients. The protocol anticipated treatment success of at least 48% IA-R IS-Free for at least 24 mos was met.

TH-PO1113

Graft Function and Other Outcomes in Kidney Transplant Recipients Converting from Immediate-Release to Prolonged-Release Tacrolimus

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Background: CHORUS (NCT02555787) was a long-term, prospective, global, non-interventional study investigating clinical outcomes in kidney transplant recipients (KTRs) converted from twice-daily, immediate-release tacrolimus to once-daily, prolonged-release tacrolimus (PRT; Advagraf®, Astellas Pharma Europe, Ltd.) under standard practice conditions.

Methods: This study enrolled KTRs (≥18 years, N=4389) who converted to PRT based on the judgment of their treating physician. Based on the post-transplant time of conversion, KTRs were grouped into early converters (ECs; ≤6 months) or late converters (LCs; >6 months). The primary endpoint was the change in renal function (measured by estimated glomerular filtration rate, eGFR) from conversion up to 5 years; secondary endpoints included graft survival (GS). GS was also assessed using subgroup variables: converters after <3 vs ≥3 years of transplant; no changes vs changes in immunosuppressive (IS) regimen (other than PRT); coefficient of variation (CV) for tacrolimus levels <35% vs ≥35%

Results: The full analysis set included 4028 KTRs (ECs, 1060; LCs, 2968). Mean eGFR at conversion was 56.1 mL/min/1.73m²; it remained stable post-conversion in the overall and LCs, with improvements in the ECs over 5 years. Kaplan-Meier estimate of 5-year GS was 95.0% (ECs, 88.1%; LCs, 97.3%). GS was higher in KTRs with no changes vs KTRs with changes in IS regimen. GS was similar in KTRs in <35% and ≥35% tacrolimus CV subgroups. GS was higher in converters after ≥3 years vs <3 years of transplant. GS was higher in LCs vs ECs across all subgroups (**Table**).

Conclusions: Results from this large cohort of KTRs showed overall stable renal function. Graft survival was high 5 years post-transplant, supporting the long-term use of PRT. In addition, some KTR subgroups (IS regimen changes, ECs with ≥35% CV, converters after <3 years) may benefit from closer monitoring.

Table. Kaplan-Meier estimate of the 5-year graft survival rate in different subgroups, % [95% CI]

	No changes in immunosuppressive regimens (other than once-daily, prolonged-release tacrolimus)	Changes in immunosuppressive regimen (other than once-daily, prolonged-release tacrolimus)	<35% tacrolimus coefficient of variation	≥35% tacrolimus coefficient of variation	Missing tacrolimus coefficient of variation	Converters with <3 years between transplantation and conversion	Converters with ≥3 years between transplantation and conversion
Overall (N=4028)	n=3519 95.0 [95.3; 96.7]	n=509 87.9 [84.7; 90.5]	n=3121 96.9 [96.3; 97.5]	n=802 91.6 [89.3; 93.6]	n=245 78.3 [72.3; 83.2]	n=2362 91.5 [90.2; 92.5]	n=1666 99.8 [99.4; 99.9]
Early converters (n=1060)	n=903 90.6 [88.4; 92.4]	n=157 74.1 [66.3; 80.4]	n=796 92.6 [90.4; 94.3]	n=190 76.8 [72.0; 84.8]	n=68 54.8 [40.4; 67.1]	n=1060 88.1 [85.9; 90.0]	n=0
Late converters (n=2968)	n=2616 97.9 [97.2; 98.3]	n=352 93.0 [90.6; 96.0]	n=2325 98.3 [97.7; 98.8]	n=466 96.5 [94.4; 97.9]	n=177 85.0 [79.6; 90.3]	n=1302 94.1 [92.6; 95.3]	n=1666 99.8 [99.4; 99.9]

TH-PO1114

Clinical Impact of the Predigraft/iBox System as a Clinical Decision Support for Kidney Transplant Patients' Management: Mid-Term Results of a Prospective Randomized Controlled Trial (RCT)

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Background: Computer based decision support systems are emerging tools for decision-making optimization but their clinical benefit for patient care has not been demonstrated.

Methods: We designed a European multicenter RCT with 16 centers from Europe (France, UK, Spain, Germany, Austria, Israel). Kidney recipients were randomly (1:1) assigned from 3 mos up to 10 yrs after transplant to receive either SOC or management guided by a companion software Predigraft that provides automatic iBox patient risk assessment and prognostic trajectories. The primary endpoint was the number of allograft biopsies amenable to therapeutic changes. This study presents the interim period results at 9 mos after randomization.

Results: 507 total subjects were recruited, among which 252 Predigraft and 254 SOC. The mean time from transplant to inclusion was 4.4±5,7 yrs. Mean recipient and donor

age were 52±14 and 52±15 yrs respectively. Other baseline characteristics were similar between groups. The mean follow-up time after randomization was 9.6±3.6 months. In Predigraft, 398 iBox alerts were recorded among which 232 (58%) were deemed clinically relevant by physicians and 133 (33%) were followed by a change in clinical management and/or therapeutics. 61 total biopsies were performed overall, 32 Predigraft and 29 SOC respectively (incidence of 12.6 vs 11.4%, p=NS). Biopsies revealed rejection (TCMR or ABMR) in 28% Predigraft vs 10% SOC respectively (p=0.08), CNI toxicity (28% vs 17%, p=0.2), and others including BKVN, AKI, IFTA, recurrent GN and Borderline lesions (50% vs 27%, p=0.07). Finally, the rate of biopsies leading to therapeutic changes (primary endpoint) was 25/32 (78.1%) in Predigraft compared with 3/29 (10.3%) in SOC (p<0.0001). Treatment modifications mostly included change in IS regimen type, dose, target in 20/32 (62.5%) in Predigraft vs 3/29 (10.3%) in SOC respectively, p<0.001).

Conclusions: These results show the ability of an automatized computer-based decision support system to screen for allograft instability and help to improve the rate of clinically relevant biopsies enabling therapeutic changes including detection of allograft rejection.

Funding: Commercial Support - Predict4Health

TH-PO1115

Multi-Center International Study to Validate a Pre-Transplant Blood-Based Next-Generation Sequencing (NGS) Signature Predicting Risk of Acute Rejection After Kidney Transplant

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Background: Demographic and clinical features of both a kidney donor and recipient are utilized to estimate risk and likelihood of graft failure. Unfortunately, many of these features have performed poorly at predicting likelihood of early acute rejection (EAR). Clinically and analytically validated biomarkers are needed to assist in guiding medical management in the early months following transplant. We report on the development and validation of a novel, next-generation sequencing (NGS) biomarker assay which interrogates the immunologic profile of pre- transplant patients receiving a cadaveric donor kidney. By applying algorithm-enabled clinical decision trees, an RNA targeted NGS feature set predicting the likelihood of EAR was developed. The assay is performed in a CLIA environment to provide clinical grade results.

Methods: 14 participating sites in US, Italy, Spain, France and Australia contributed to the validation cohort of 122 participants. All participants had blood collected prior to surgery. Patients were followed at 1 and 3 month visits and had a protocol biopsy at 3 months as well as anytime for-cause; all biopsies were read centrally. Clinical endpoint of EAR was histopathology according to BANFF criteria which included TCMR 1A or higher, ABMR or mixed EAR.

Results: The assay performance results in risk classification of low risk or high-risk correlated to defined outcome of EAR on histopathology in the first 60 days following transplant producing an AUC of 0.719, p = 0.013. The sensitivity was 0.78, and the specificity was 0.64; the odds ratio was 6.133.

Conclusions: The correlation of a blood-based NGS signature with kidney biopsy histopathology provides a diverse and robust platform of enriched clinical evidence not traditionally reported in kidney transplant. A pre-transplant immunologic risk assessment tool has the potential to yield a novel, more precise level of evidence for clinicians and their patients at a critical time in their pre-surgical preparedness.

Funding: Commercial Support - Verici Dx

TH-PO1116

Exploring the Pharmacokinetics, Pharmacodynamics, and Safety of Apixaban in Hemodiafiltration: Insights from the HEMOCIONA Study

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Background: Atrial fibrillation (AF) is common among hemodialysis (HD) patients, and increases the risk of stroke. Since vitamin K antagonists increase the risk of bleeding and vascular calcifications, direct oral anticoagulants (DOACs) has attracted considerable attention. However, there is limited experience with DOACs in HD patients and concerns have been raised about their potential accumulation. Consequently, DOACs are currently not recommended in HD patients. Our study aims to assess the safety of low-dose of apixaban, based on long-term their pharmacokinetic profile, for patients with nonvalvular AF undergoing hemodiafiltration.

Methods: We conducted a single-center phase 2 clinical trial to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), and safety of apixaban at a dose of 2.5 mg twice daily (BID) over a period of 4 weeks. Plasma levels were obtained during the middle dialysis session of the week, as well as the day before and after for PK/PD assessments. Concentration of apixaban was directly measured in plasma, urine and dialysis wasted liquid using a validated liquid chromatography-mass spectrometry/mass spectrometry LC-MS/MS). Blood samples for the determination of Anti-FXa activity A (AXA) were collected at the same time points as the PK samples.

Results: A total of 11 patients (8 male, 3 female) with a mean age of 67±3 years old were enrolled. The main result was the demonstration of the absence of accumulation of apixaban since daily exposure (mean (%CV) AUC_{0-12}) appeared similar the day of dialysis of the first week (1030 (0.51) mcg*h/mL), and after 4 weeks (921 (0.42) mcg*h/mL). Hemodiafiltration had no impact on apixaban plasma concentration and patients without residual diuresis did not show higher apixaban levels. A close temporal relationship between apixaban plasma concentrations and AXA was observed across the dosing intervals. No bleeding events were observed.

Conclusions: Our results have significant clinical implications, as they provide PK/PD data that justify the use of 2.5 mg BID in patients with atrial fibrillation on hemodiafiltration. Our findings emphasize the importance of considering intersubject variability in drug response and adopting individualized treatment approaches.

Funding: Government Support - Non-U.S.

TH-PO1117

SGLT2 Inhibition in Alport Syndrome: First Large-Scale Trial to Plan a Randomized Controlled Trial in Children

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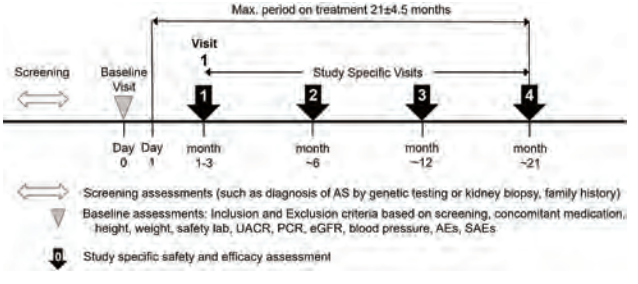
Background: Trials with >10,000 patients showed positive outcomes of SGLT2is in elderly patients with CKD. These trials included no children and no young adults with Alport syndrome (AS).

Methods: This multicenter, international study (NCT02378805) assessed 99 patients with AS from 12 countries after start of SGLT2i at early CKD-stages.

Results: Mean age of children (n=10) was 16 years (range 9 to 17), eGFR >90ml/min/1.73qm, and UAPR was >1.0g/gCrea. Only adults with in-label use of SGLT2i (n=89) were analyzed. At baseline, mean age was 37±14 years, eGFR 63±35 ml/min/1.73qm, and albuminuria (UACR) 1822±1484 mg/g creatinine. Because of country- and center-specific different routines and visit intervals, all data are compared to baseline (fig. 1). At V1 month 1 to 3, UACR decreased by 34% (p<0.001), and eGFR dropped by 6% (p=0.05). At V2 (mean 5.7 months), UACR dropped by 29% (p=0.003), as did eGFR by 6% (p<0.001). At V3 (11.7 months), UACR dropped by 24%, and eGFR did by 15% (n=26; p=0.001). BMI decreased from 27.8±6.3 to 27.2±6 kg/qm and serum albumin increased (3.8±0.7 vs 3.9±0.4 g/dL). Blood pressure decreased slightly from 127/82 to 126/80 mmHg. At V4 (21 months), UACR dropped by 27%, and eGFR did by 10% (n=12; p=0.02). Compared to baseline, eGFR slope changed from -13.6 (V1), -8.4 (V2), -7.7 (V3), to -4.1 ml/min/year at V4. At a total of 50 patient-years at risk, adverse drug reactions occurred in 7/66 patients (11%).

Conclusions: For the first time, the effect of SGLT2i in a large number of young patients with AS was investigated: patients were much younger than non-diabetic CKD patients in EMPA-Kidney (37 vs. 64 years), had a similar BMI and blood pressure, a much better eGFR (63 vs. 39 ml/min/qm), and a four times higher UACR (1822 vs. 461 mg/gCrea). Patients with AS showed an intermediate response in UACR reduction. In month 12 and 21, the positive effect on long-term eGFR slope is still inconclusive. For that reason, efficacy and safety of SGLT2i in children will be addressed in the upcoming first Pediatric RCT, DOUBLE PRO-TECT Alport (NCT05944016).

Funding: Government Support - Non-U.S.



TH-PO1118

NAVKIDS[2] Trial: A Multi-Centre, Waitlisted, Mixed Methods, Randomized Controlled Trial of a Patient Navigator Intervention in Children with CKD

Germaine Wong. NAVKIDS[2] Trial Steering Committee. *Sydney School of Public Health, The University of Sydney, Sydney, NSW, Australia.*

Background: Inequitable access to care is a major impediment to optimal health in children with chronic kidney disease (CKD). Patient navigators help patients and caregivers to navigate complex health systems, with the goal of improving accessibility to healthcare and community supports. However, the efficacy of patient navigation in improving the overall health of children with CKD is unknown.

Methods: In this multi-center, waitlisted, randomized control trial, we randomly assigned children with CKD (aged 0-16 years, of low socioeconomic backgrounds) (1:1) to receive immediate patient navigation (immediate) or wait for six months before receiving the intervention (waitlist). The primary outcome, assessed by intention to treat, was self-rated health (SRH) of the child at six months post-randomization.

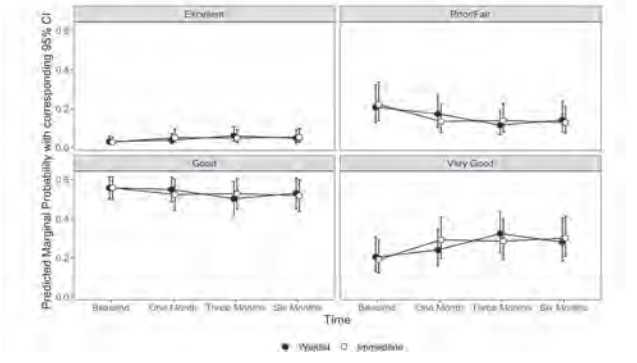
We analysed repeated measures of the primary outcome from baseline to six months post-randomisation using cumulative logit mixed effects models. Semi-structured interviews were analysed thematically to understand caregivers' perspectives on the intervention.

Results: Of 398 children who were screened, 162 were enrolled (mean age (standard deviation): 8.8 (4.8) years, boys (64.8%)), with 80 and 82 assigned to the immediate and waitlist groups, respectively. There were no differences in the child's SRH between the immediate and waitlist groups at baseline (p=0.92). There were also no cumulative differences in the child's SRH between the immediate and waitlist groups over the 6 months period (p=0.70). Caregivers reported five themes: easing mental strain, facilitating care coordination, strengthening capacity to provide care, reinforcing care collaborations, alleviating family tensions.

Conclusions: In children with CKD, the child's SRH did not differ significantly between the immediate and waitlist groups over time. However, caregivers may have gained skills and capacity related to care from the program.

Funding: Government Support - Non-U.S.

Figure 1. Marginal estimated probability plots from an ordinal mixed-effects model of each category of child self-rated health over time for the waitlist and immediate groups



TH-PO1119

The TRANSNephro Study Examining a New Transition Model for Post-Kidney Transplant Adolescents: A Multicenter, Randomized Controlled Trial

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Background: Allograft loss is highest in adolescents due to non-adherence and transfer of health care. This multicenter, randomized controlled trial aimed to evaluate whether support by a central case manager and a corresponding app during transition may improve the outcome.

Methods: Adolescent patients in 18 German and Austrian centers one year before planned transfer were randomized 1:1 to a control group that received transition as by center standard or to an intervention group. The intervention consisted of a central case manager, a communication app, and joined transition rounds for one year before and one after transfer. Primary endpoint was the coefficient of variation (CoV) of the trough level of the Calcineurininhibitor as a surrogate marker for medication adherence. Important secondary endpoints were acute rejections, graft loss, eGFR, and quality of life. For the assessment, least square (LS) mean differences and corresponding 95% confidence intervals (CIs) were estimated within an analysis of covariance (ANCOVA) model.

Results: A total of 220 patients was assessed for eligibility. Of these, 102 patients were randomized, 49 to the intervention and 53 to the control group. We analyzed 84 patients in the modified intention-to-treat (mITT) analysis (38 intervention vs 46 control patients) and 60 patients in the per protocol (PP) analysis (25 intervention vs 35 control patients). No difference in CoV was observed between the two groups, neither in the mITT (LS mean difference [95% CI]:0.01 [-0.17, 0.18], p=0.9574) nor in the PP analysis (LS mean difference [95% CI]:-0.01 [-0.19, 0.16], p=0.8748). We observed a trend for a lower mean eGFR at adult clinic outpatient phase in the intervention group. We saw only low numbers of graft-related events and observed no differences between the groups with respect to quality of life.

Conclusions: The addition of our case-manager-based intervention to standard of care transition, did not improve adherence and other outcome parameters in adolescent kidney graft recipients. We assume that non-adherent patients may have decided not to take part in the trial, as adherence was already good at study start. It thus is a future challenge to design multicenter trials on transition that include multiple interventions for a better transition in order to stop the long-term decrease in graft function.

TH-PO1120

Limited Antiproteinuric Efficacy of Dapagliflozin (DPG) in Adolescents with Proteinuric CKD

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Background: While reducing proteinuria is renoprotective in CKD, it might persist despite renin-angiotensin-aldosterone (RAAS) blockade. SGLT2 inhibitors, known to be antiproteinuric in adult-onset CKD, have not been tested in children.

Methods: This single-center trial examined the antiproteinuric efficacy & safety of DPG in adolescents with CKD (CTRI/2022/04/042032). After written consent & baseline evaluation, consecutive eligible patients, 11-19 yr old with eGFR >45 ml/min/1.73 m^2 & proteinuria >0.5 g/m^2/d despite optimal RAAS blockade, received Dapavel® at 5 mg/d x 2-wk, followed by 10 mg/d x 10-wk. Biochemistry & 24-hr urine protein/albumin were repeated at 4, 8 & 12-wk, and ambulatory blood pressure at 12-wk.

Results: Of 49 screened, 25 patients (76% boys, chiefly glomerular CKD), were enrolled at median eGFR 93 ml/min/1.73 m^2 & proteinuria 1.4 g/m^2/d (**Table 1**). **Fig. 1** shows outcomes at 4 & 12-wk. At 12-wk, proteinuria declined by median 1.3% and eGFR by 13.4%; 4 (16%) patients achieved the FSGS proteinuria reduction endpoint. 3 patients noted giddiness; none had serious adverse events.

Conclusions: Therapy with DPG for 12-wk has limited antiproteinuric efficacy in adolescents with CKD. Controlled studies should examine the antiproteinuric effect and optimal dose & duration of SGLT2 inhibitors in children.

Table 1: Baseline characteristics n=25

Boys, %	19 (76)
Age at onset, yrs	8 (5-11)
Age at enrolment, yrs	16 (13-18)
Diagnosis	
CNI-resistant FSGS	11 (44)
Alport syndrome	7 (28)
GN; others	4 (16); 3 (12)
Concomitant therapies	
ACE-inhibitor; ARB	24 (96); 1 (4)
Prednisolone; others	2 (8); 1 (4)
Blood pressure	
Normal; ambulatory hypertension	19 (76); 5 (20)
Masked; whitecoat hypertension	0 (0); 1 (4)
Baseline investigations	
Serum albumin, g/dL	3.85 (3.15-4.20)
eGFR, l/1.73 m2	93 (68-127)
24-hr urine protein, g/m2/d	1.35 (1.03-2.60)
24-hr urine PCR, mg/mg	2.38 (1.56-5.91)
24-hr urine ACR, mg/g	1720 (830-3940)

Categorical data are shown as n (%) and continuous ones as median (interquartile range)
ACE-I angiotensin converting enzyme inhibitors; ARB aldosterone receptor blocker; CNI calcineurin inhibitor; eGFR estimated glomerular filtration rate; FSGS focal segmental glomerulosclerosis

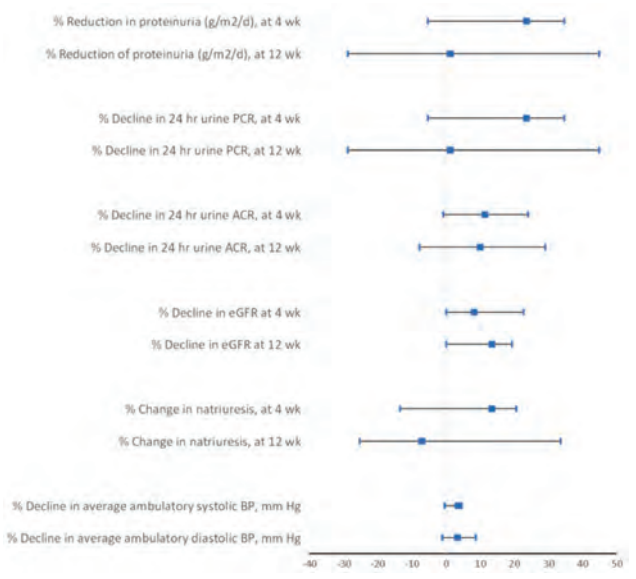
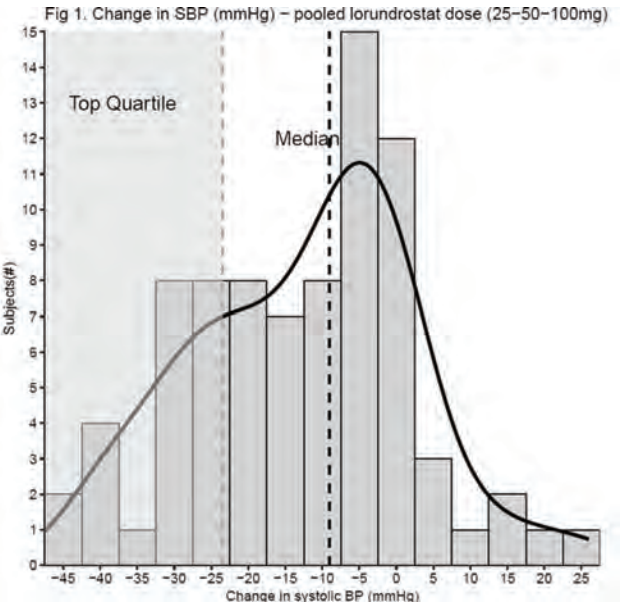


Fig. 1. Outcomes at 4- and 12-wk, as median (interquartile range).



TH-PO1121

Identification of a Hypertensive Endotype with a Median Treatment Effect of -32mmHg in Response to the Novel Aldosterone Synthase Inhibitor Lorundrostat

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Background: Uncontrolled and treatment-resistant hypertension are common challenges faced by clinicians. We previously reported the novel aldosterone synthase inhibitor, lorundrostat, 25mg BID, 50mg QD or 100mg QD, demonstrated median serum aldosterone reduction of 65-70% and observed mean systolic BP(SBP) reduction of -10.1, -13.2 and -14.1mmHg, respectively (n=25-28), vs placebo (-4.1 mmHg, n=29). The top quartile of the pooled group (n=81) had a median [IQR] SBP reduction of -32mmHg (n=21, [-37.5 to -27]); the bottom quartile had no change (Fig 1).

Methods: To identify predictive factors differentiating these groups, BP response to lorundrostat 100mg QD was compared in subjects with low plasma renin activity (PRA) ≤1.0ng/ml/hr vs PRA >1.0ng/ml/hr.

Results: Low PRA was not a useful predictor of response (low [n=25] -12.1 [2.68] mmHg, normal to high [n=30] -11.4 [2.48] mmHg). A correlation was observed between BMI and SBP reduction (r= -0.27, p=0.017). In the planned development doses of 50mg and 100mg QD, reduction in placebo-adjusted median (CI) SBP of -16.7 (-25.5, -7.9) mmHg and -12.3 (-21.6, -3.1) mmHg in subjects with BMI ≥30kg/m^2 (n=15,12), respectively, was observed (p=0.002 and 0.030). No significant effect of lorundrostat on SBP in subjects with BMI 25-30kg/m^2 (n=11,9) was seen (2.2 and -4.5 mmHg, respectively). Elevated baseline BP was similarly predictive of a favorable median SBP reduction in the 50mg and 100mg QD cohorts (lowest tertile of baseline SBP -3.5, -2.5 mmHg, highest tertile -34.3, -17.5mmHg, respectively), possibly due to the relative importance of aldosterone-mediated hypertension in obese individuals. A positive association was also observed between obesity and serum leptin at baseline (r=0.47, p<0.001).

Conclusions: While this association does not establish cause and effect, serum leptin is a direct stimulus for adrenal aldosterone production, and its investigation as a predictor of lorundrostat response warrants further investigation.

Funding: Commercial Support - Mineralys Therapeutics

TH-PO1122

Wearable Device for Noninvasive Blood Pressure Monitoring of ICU Patients

Forrest Miller. *Alio, Broomfield, CO.*

Background: Blood pressure (BP) is a cardinal vital sign used in cardiovascular clinical decision-making. The traditional approach for BP measurement in intensive care units (ICU) involves the use of an invasive arterial line (A-line). A-line measurements require technique and practice and introduce the risk of clinical complications that could result in thrombosis or sepsis. This study evaluated the performance of cuffless BP monitoring with a novel wearable device ("SmartPatch") compared to the gold standard A-line.

Methods: A retrospective IRB-approved study was conducted to evaluate the performance of an algorithm to track BP metrics-systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP)–noninvasively and compare them against invasive arterial line (on left radial) values in 26 subjects. Simultaneous arterial line BP and photoplethysmography (PPG) data from SmartPatch were collected from post-surgery patients admitted to a neuro-ICU unit over an average of 2 hours. The PPG data was pre-processed, assessed for signal quality, and fed into an Artificial Neural Network (ANN) model to train with the A-line BP data as reference.

Results: A total of 6.07 hours of data was segmented into 6 sec PPG recordings resulting in ~1900 data points to be analyzed. An ANN model was trained and validated with leave one out-cross validation (LOO-CV) to tune the model parameters and assess the performance. Mean of errors and Pearson correlation coefficient r were used to assess the performance of the ANN model. The mean of errors and the experimental standard deviation for SBP was: -1.207 (SD: 9.17) mmHg, MAP: -0.144 (SD: 5.09) mmHg and DBP: -0.161 (SD: 5.10) mmHg. These values fall within the limits set by the ISO 81060-2 (2018) standard. The ANN-generated BP values were correlated to the A-line with Pearson r = 0.81 (SBP), 0.68 (DBP) and 0.79 (MAP).

Conclusions: The ANN model was trained using LOO-CV to predict SBP, DBP & MAP. The results demonstrated quantitative accuracy within the limits set by the ISO 81060-2 (2018) standard when validated against the A-line BP. This noninvasive cuffless BP measurement from a wearable device could enable more consistent, accurate, and cost-effective patient care in remote monitoring settings.

TH-PO1123

Long-Term Renal Benefit with Nefecon in Chinese Patients with Primary Immunoglobulin A Nephropathy: Two-Year NefIgArd Trial Results

Hong Zhang,[1] Jens Kristensen,[2] Andrew M. Stone,[3] Bei Wang,[4] Lisa H. Ying,[4] Zhengying Zhu.[4] *[1]Peking University First Hospital, Beijing, China; [2]Calliditas Therapeutics AB, Stockholm, Sweden; [3]Stone Biostatistics Ltd., Crewe, United Kingdom; [4]Everest Medicines Ltd., Shanghai, China.*

Background: Immunoglobulin A (IgA) nephropathy (IgAN) is most prevalent in people of East Asian ancestry. Nefecon is a novel targeted-release oral budesonide product designed to act in the distal ileum to reduce excess galactose-deficient IgA1 production. The 2-year NefIgArd trial demonstrated that Nefecon 16 mg/day for 9 months led to a statistically significant treatment benefit on estimated glomerular filtration rate (eGFR) with Nefecon vs placebo. Here, we present results for all patients enrolled in NefIgArd from mainland China, including previously unreported patients.

Methods: NefIgArd was a global, double-blind Phase 3 study. Patients with primary IgAN on optimized supportive care were randomized 1:1 to 9 months of Nefecon 16 mg/day or placebo, followed by a 15-month observational period off study drug.

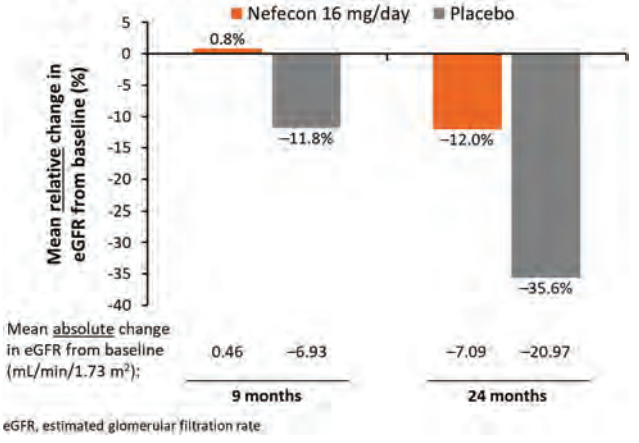
The 9-month primary endpoint was change in urine protein-creatinine ratio (UPCR). The 2-year primary endpoint was time-weighted average of eGFR over 2 years.

Results: Baseline characteristics of all 62 Chinese patients were similar to the global study population and were balanced across treatment arms. There was a 9.58 mL/min/1.73 m^2 (95% CI 1.95, 19.78) treatment benefit in the 2-year primary endpoint with Nefecon vs placebo (3.74 vs 13.32 mL/min/1.73 m^2 average eGFR decline, respectively). At 24 months, the mean absolute changes in eGFR from baseline (Fig. 1) suggested that 66% of the eGFR decline observed with placebo could be prevented with 9 months of Nefecon treatment. Mean UPCR reduction was 31% greater at 9 months and 52% greater over 12–24 months with Nefecon vs placebo. No new safety signals were identified.

Conclusions: Compared with placebo, 9 months of Nefecon treatment provided clinically relevant preservation of eGFR and durable proteinuria reduction over 2 years, supporting a disease-modifying effect in Chinese patients with primary IgAN.

Funding: Commercial Support - Calliditas Therapeutics AB; Everest Medicines Ltd.

Figure 1: Mean change in eGFR at 9 and 24 months



eGFR, estimated glomerular filtration rate

TH-PO1124

Sibeprenlimab in Patients with IgA Nephropathy: A Phase 2 Trial

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Background: A Proliferation-Inducing Ligand (APRIL) is implicated in the pathogenesis of immunoglobulin A nephropathy (IgAN). Sibeprenlimab is a humanized IgG2 monoclonal antibody that blocks APRIL signaling.

Methods: VIS649-201 (NCT04287985) is a global, multicenter, randomized, double-blind, placebo-controlled study evaluating monthly intravenous (IV) sibeprenlimab 2, 4 or 8 mg/kg added to background optimized renin–angiotensin–aldosterone system blockade for 12 months in adults with IgAN. Patients with estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2, and proteinuria ≥1.0 g/d or urine protein creatinine ratio (uPCR) ≥0.75 g/g, were included.

Results: 155 participants were randomized: 56.8% male; 74.2% Asian; median age 39 years. At Month 12, compared with placebo, sibeprenlimab groups demonstrated significant reductions in 24-hour uPCR (Figure, Table) and clinically relevant smaller changes in eGFR (sibeprenlimab, −2.7 to +0.2 mL/min/1.73 m^2; placebo, −7.4 mL/min/1.73 m^2; Table). The incidence of treatment-emergent adverse events (TEAEs) was 78.6% (sibeprenlimab pooled) and 71.1% (placebo), with comparable distribution of serious, severe, and drug-related TEAEs.

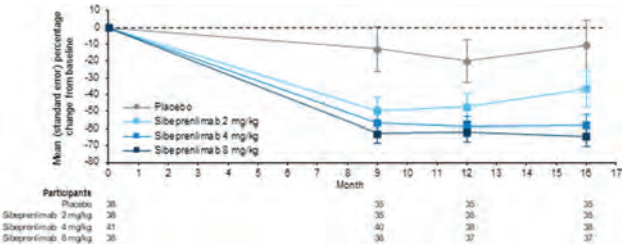
Conclusions: These results suggest that IV sibeprenlimab may provide an effective and well-tolerated treatment option to slow disease progression of IgAN, and support the ongoing Phase 3 VISIONARY trial of subcutaneous sibeprenlimab in patients with IgAN (NCT05248646).

Funding: Commercial Support - Visterra, Inc. (Waltham, MA), a member of the Otsuka family of companies.

Efficacy and Safety Data

Parameter	Sibeprenlimab 2 mg/kg (n = 38)	Sibeprenlimab 4 mg/kg (n = 41)	Sibeprenlimab 8 mg/kg (n = 38)	Placebo (n = 38)
Median baseline urine protein excretion, g/day (range)	1.47 (0.67–6.92)	1.93 (0.33–8.60)	1.90 (0.76–12.44)	2.13 (0.76–8.48)
Geometric mean ratio reduction in 24-h uPCR from baseline at Month 12, % (standard error)	47.2 (8.2)	58.8 (6.1)	62.0 (5.7)	20.0 (12.6)
Geometric mean uPCR reduction at Month 12 relative to placebo, % (standard error)	53.96 (13.7) $P = 0.048$	48.45 (10.4) $P = 0.0013$	52.52 (9.7) $P = 0.0004$	–
Median baseline eGFR, mL/min/1.73 m^2 (range)	58.0 (35.0–154.0)	64.0 (35.0–133.0)	56.0 (34.0–109.0)	68.5 (33.0–116.0)
Least squares mean eGFR change from baseline at Month 12, mL/min/1.73 m^2 (standard error)	−2.7 (1.8)	+0.2 (1.7)	−1.5 (1.8)	−7.4 (1.8)
Least squares mean difference in eGFR at Month 12 relative to placebo, mL/min/1.73 m^2 (standard error)	+4.6 (2.5) $P = 0.063$	+7.6 (2.4) $P = 0.002$	+5.8 (2.5) $P = 0.020$	–
Any TEAE, n (%)*	28 (73.7)	33 (80.5)	31 (81.6)	27 (71.1)
Serious TEAE, n (%)	2 (5.3)	2 (4.9)	1 (2.6)	2 (5.3)

*Lower incidence of infections in pooled sibeprenlimab group vs placebo.



Percentage Change in 24-Hour uPCR From Baseline Over Time

TH-PO1125

Povetacicept, an Enhanced Dual BAFF/APRIL Antagonist, in Autoantibody-Associated Glomerulonephritis (GN)

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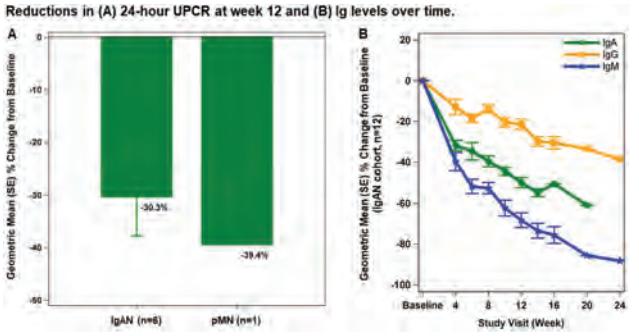
Background: Inhibition of BAFF and/or APRIL has shown promise in IgA nephropathy (IgAN), primary membranous nephropathy (pMN), and lupus nephritis (LN), with the potential to exert a disease-modifying effect. Povetacicept (ALPN-303) is an Fc fusion of a variant TACI domain engineered for more potent dual BAFF/APRIL inhibition vs WT TACI or anti-BAFF or -APRIL Abs. In healthy volunteers, povetacicept was well tolerated and reduced Ig (including Gd-IgA1) levels and Ab-secreting cells. This is a report of an open-label, multiple ascending dose experience with povetacicept in GN.

Methods: RUBY-3 (NCT05732402) is a ph 1b/2a study of povetacicept 80 or 240 mg SC Q4W for 24 wk, with an optional 24-wk extension. Eligible participants (pts) are aged ≥18 y with biopsy-confirmed IgAN, pMN, or LN, and on maximally tolerated ACEi/ARB therapy, with well-controlled BP, and disease-specific immunosuppressive therapy where applicable. Primary objective is safety; secondary objectives include PK, PD, immunogenicity, biomarkers, and efficacy.

Results: As of 1Sep23, 12 pts with IgAN and 1 with pMN have enrolled at the lower povetacicept dose level of 80 mg; 6 and 1 pts, respectively, have completed ≥12 wk. The 240-mg IgAN cohort has also begun enrolling. Povetacicept has been well tolerated, with no serious or severe TEAEs, IgG <3 g/L, or administration-related reactions. In IgAN, UPCR was reduced by 30% at 12 wk (n=6) and expected decreases in Ig levels were seen (**Fig**). The first enrolled pt achieved a urinary protein excretion level below the threshold of detection (<0.56 g/g) by 24 wk, preceded by a 43% reduction in Gd-IgA1 at 4 wk. In pMN (n=1), a 39% UPCR reduction (**Fig**) and 77% reduction in anti-PLA2R were seen at 12 wk. Updated data will be presented.

Conclusions: Initial experience indicates povetacicept is well tolerated during multiple-dose administration in GN, with highly encouraging early reductions in UPCR and disease-specific biomarkers in pts with IgAN and pMN.

Funding: Commercial Support - Alpine Immune Sciences, Inc.



TH-PO1126

Clinical Value of Adding Dapagliflozin in Patients with Nephrotic Syndrome

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Background: The potential utilization of SGLT2 inhibitors in glomerular disease patients undergoing immunosuppression therapy has remained underexplored. This study evaluates the clinical impact of dapagliflozin in non-diabetic primary nephrotic syndrome patients.

Methods: We conducted a randomized controlled clinical trial with 60 non-diabetic primary nephrotic syndrome patients, equally assigned to dapagliflozin and control groups. The dapagliflozin group received dapagliflozin 10 mg/day in addition to standard care, while the control group received standard care alone. Baseline characteristics, including age, gender, nephrotic syndrome etiology, proteinuria levels, estimated glomerular filtration rate (eGFR), and immunosuppression doses, were well-matched. Both groups were followed for 6 months. 1ry outcomes included changes in proteinuria (measured by urine PCR, UPCR) and eGFR. 2ry outcomes encompassed alterations in body weight and lipid profile changes. Pregnant or breastfeeding females and patients with secondary nephrotic syndrome were excluded.

Results: Both groups exhibited significant reductions in proteinuria after 6 months, with the dapagliflozin group achieving a mean UPCR reduction of -94.7%, and the control group -86.7% ($p < 0.001$). However, the comparative percentage change in proteinuria between both groups did not reach statistical significance ($p = 0.158$). Dapagliflozin initially led to a transient eGFR decline followed by recovery, while the control group maintained stable eGFR. Dapagliflozin also resulted in a significant mean body weight reduction of 3.91 kg ($p < 0.001$) and notable improvements in triglyceride levels compared to the control group ($p = 0.045$). Although no major safety concerns arose, the dapagliflozin group exhibited a slightly higher incidence of urinary tract infections.

Conclusions: In primary nephrotic syndrome patients, adjunct dapagliflozin may enhance the standard of care. While notable, the reduction in proteinuria was comparable to that of the control group by the study's end. Furthermore, after 6 months, eGFR remained stable in both groups. However, significant weight loss and serum triglyceride reduction were particularly pronounced in the dapagliflozin group. Further long-term investigations are necessary to address potential immunosuppression-related confounding effects in patients with primary glomerular disease.

TH-PO1127

Efficacy and Safety of Ravulizumab in a Phase 2 Randomized Controlled Trial in IgA Nephropathy

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Background: IgA nephropathy (IgAN) is the most prevalent primary glomerular disease, often progressing to ESKD. Complement activation leads to glomerular damage by immune complex deposition and release of proinflammatory cytokines. Terminal complement inhibition specifically targets the pathophysiology of IgAN and may provide improved renal outcomes.

Methods: This primary analysis of a phase 2 RCT (NCT04564339) evaluated ravulizumab (RAV) (IV; weight-based dosing Q8W) vs placebo (PBO) in adults with primary IgAN. Eligible patients (pts) (18–75 years) with biopsy-confirmed IgAN, proteinuria ≥1g/d, on stable maximally tolerated RASi with stable blood pressure ≥3 months were enrolled. The primary endpoint was % change in proteinuria from baseline to week (wk) 26 based on 24-hour urine. Secondary endpoints included spot UPCR and change in baseline eGFR at wk 26, safety, and PK/PD.

Results: 66 pts were randomized 2:1 to RAV (n=43) or PBO (n=23). Mean age was 40.1 years, 46% were female, and 21% were Asian. At 26 wks, proteinuria reduction was greater with RAV vs PBO, 40.3% vs 10.9% (treatment effect 33.1%, 90% CI, 14.7%, 47.5%; p=0.0012). In RAV-treated pts, proteinuria reduction was rapid and sustained through wk 26 (**Figure 1**) and eGFR remained stable. RAV was well-tolerated with a safety profile similar to that of PBO and no new safety concerns **(Table 1)**.

Conclusions: This analysis supports clinically meaningful efficacy of RAV based on rapid and sustained proteinuria reduction, providing proof-of-concept for a phase 3 trial of RAV as a potential treatment for IgAN.

Funding: Commercial Support - Alexion, AstraZeneca Rare Disease

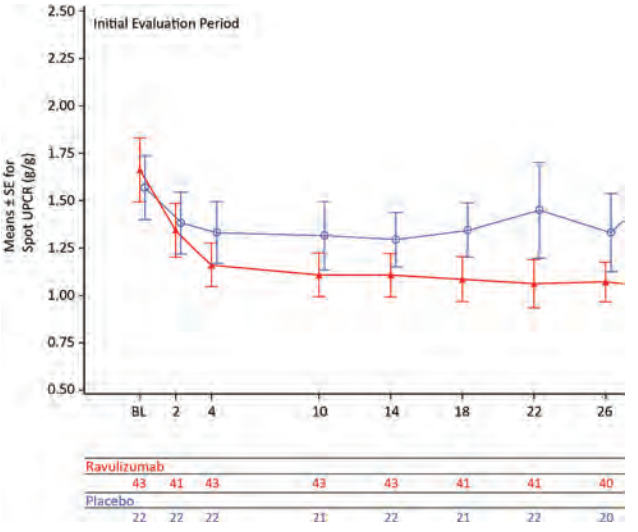

Table 1: Treatment-emergent adverse events up to 26wks

	Ravulizumab N=43	Placebo N=23
Any adverse event, n (%)	32 (74.4)	19 (82.6)
Investigator-assessed as related to study drug	9 (20.9)	6 (26.1)
Serious adverse event, n (%)	1 (2.3)*	0 (0.0)

*COVID occurred in one patient as an SAE that led to hospitalization and was investigator-assessed as unrelated to study drug and resolved during the study. AEs of special interest included meningococcal infections; there were no AEs of special interest. No AEs or SAEs leading to withdrawal from the study occurred and no deaths were reported.

TH-PO1128

Long-Term Nedosiran Safety and Efficacy in Primary Hyperoxaluria Type 1 (PH1): Interim Analysis of PHYOX3

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Background: Primary hyperoxaluria (PH) is a family of rare genetic disorders of hepatic glyoxylate metabolism leading to oxalate overproduction, causing calcium oxalate stones, and may result in kidney damage/failure. Nedosiran is an RNAi therapy in development for treatment of PH. Nedosiran silences hepatic LDH expression encoded by the *LDHA* gene to reduce oxalate production.

Methods: This 30-month interim analysis of the ongoing PHYOX3 study (NCT04042402) reports long-term safety/efficacy of monthly s.c. nedosiran in participants with PH1 who continued from a single-dose nedosiran trial PHYOX1 (NCT03392896). Participants (≥6 yrs) who had no prior kidney/liver transplant, dialysis, or evidence of systemic oxalosis were eligible.

Results: Thirteen participants with PH1 rolled into PHYOX3. At baseline, mean (SD) age was 24 (6.6) years (53.8% female; 61.5% White) and mean (SD) estimated glomerular filtration rate (eGFR) was 77.6 (21.82) mL/min/1.73m^2. Mean eGFR remained stable (62–84.2 mL/min/1.73m^2) to month 30. Mean urinary oxalate (Uox) excretion showed a sustained reduction from baseline (≥60%) to month 30 (**Figure**). At every visit, at least 10 (76.9%) participants achieved normal (<0.46 mmol/24h; upper limit of assay-normal [ULN]) or near-normal (≥0.46 to <0.60 mmol/24h; ≥ULN to <1.3 × ULN) 24h Uox excretion. All participants experienced ≥1 adverse event (AE), mostly mild or moderate severity (76.9% treatment-related). Three serious AEs were reported (not treatment-related). Of 398 total injections in the study, 2.5% had an injection-site reaction. There were no deaths or study discontinuations due to AEs.

Conclusions: Nedosiran was well-tolerated in patients with PH1 and resulted in a sustained reduction in Uox excretion for up to 30 months. No safety signals were identified to date. Analysis of long-term effects on kidney function are ongoing.

Funding: Commercial Support - Dicerna Pharmaceuticals, Inc., a Novo Nordisk Company (Lexington, MA)

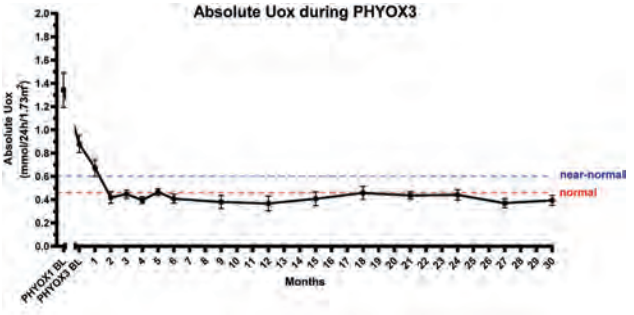

Figure. Sustained Uox reduction from baseline with once-monthly nedosiran. Mean (±SEM) absolute Uox from baseline (BL); n=13 for all visits except month 4 (n=12). Dashed lines represent normal/near-normal 24h Uox excretion.

TH-PO1129

The Kidney Transplant Fast Track (KTFT) Intervention Reduced Time to Kidney Transplant Waitlisting

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Background: Kidney transplantation (KT) is the optimal treatment for end-stage kidney disease (ESKD), but the KT evaluation process is lengthy, time consuming, and burdensome to patients. In December 2012, our transplant center implemented a one-day streamlined and coordinated-care evaluation process, Kidney Transplant Fast Track (KTFT), but it has not been evaluated for efficacy (i.e., reduced time to waitlisting and KT receipt).

Methods: In 2015, we initiated a quasi-experiment to determine the efficacy of the KTFT (n=1118) compared to usual care historical controls (n=1152) from our previous cohort study. We conducted a pre-transplant workup interview with all participants and followed their transplant status via medical record review through 08/2022. Also, we examined whether cultural factors (e.g., medical mistrust, health literacy, religious objection) predicted time to waitlisting and KT. We used Fine-Gray proportional hazards modeling to examine predictors of time from evaluation to waitlisting and KT receipt, controlling for demographic and medical factors.

Results: Over a 7-year follow-up period, compared to historical controls, KTFT patients had a 44% greater chance of being wait-listed (SHR=1.44, CI=1.26-1.63, p<.0001). There was a non-statistically significant trend toward higher KT rates. Greater medical mistrust or religious objections to transplantation uniquely predicted time to waitlisting. Medical mistrust, religious objection, and lower health literacy also uniquely predicted longer time to KT.

Conclusions: We developed an effective streamlined coordinated care evaluation process for ESKD patients that reduced the time to complete evaluation and increased the rates of transplant waitlisting. We also identified unique cultural predictors of barriers to waitlisting and KT.

Funding: NIDDK Support, Private Foundation Support

TH-PO1130

Twice Weekly vs. Thrice Weekly Hemodialysis in Patients with Residual Kidney Function

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Background: The most recent 2015 update of the Kidney Disease Outcomes Quality Initiative (KDOQI) dialysis adequacy guidelines increased the contribution assigned to residual kidney function in calculating standard Kt/V_{urea} (stdKt/V). However, no study has yet assessed the effect of prescribing twice weekly hemodialysis (HD) according to this guideline on patients' symptoms or uremic solute levels.

Methods: 24 HD patients with residual kidney urea clearance (Kru) 4.7±1.8 ml/min completed a cross-over trial comparing 4 weeks of twice weekly (2X) HD and 4 weeks of thrice weekly (3X) HD (NCT03874117). Patients were enrolled if they had Kru >2.5 ml/min and had been on HD for at least 2 months. During the 2X period, HD was prescribed to achieve stdKt/V 2.2 incorporating Kru using the 2015 KDOQI guidelines. During the 3X period, HD was prescribed to achieve a per treatment spKt/V 1.3 regardless of Kru. Symptom scores and pre-treatment plasma levels of urea, secreted solutes p-cresol sulfate (PCS) and hippurate (HIPP), and beta-2 microglobulin (β2m) were compared at the end of each 4-week period.

Results: Symptoms were significantly better with 2X HD, as assessed by the KDQOL36 Symptom component (2X: 86±14 vs. 3X: 82±18, p 0.001), Dialysis Symptom Index (2X: 26±26 vs. 3X: 33±31, p 0.008), and post-dialysis recovery time (2X: 1.6±0.8 vs. 3X: 1.9±1.0, p 0.01). 2X HD provided adequate stdKt/V of 2.7±0.5 without a significant increase in treatment time (2X: 195±21 min vs. 3X: 191±17 min, p 0.07). Kru, ultrafiltration rate, and pre-treatment plasma potassium were similar, and no patients were withdrawn for fluid overload or hyperkalemia. Plasma analysis showed an expected higher pre-treatment level of urea with 2X HD (76±22 vs. 54±13 mg/dl, p <0.001) while the levels of PCS (4.0±1.6 vs. 3.7±1.3 mg/dl, p 0.39), HIPP (2.7±3.0 vs. 2.2±1.9 mg/dl, p 0.84), and β2m (22±7 vs. 21±6 mg/L, p 0.80) were not significantly higher with 2X than 3X HD.

Conclusions: We show that 2X HD can be safely prescribed with the increased contribution assigned to Kru by the 2015 KDOQI guidelines. With 2X HD, symptoms were improved and the continuous function of the residual kidneys controlled fluid gain, potassium, and plasma levels of uremic solutes without a need to increase treatment time.

Funding: NIDDK Support

TH-PO1131

Hemodialysis Vascular Access Complications: Insights from the ASCEND-D Trial

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Background: Daprodustat (Dapro) is a hypoxia-inducible factor–prolyl hydroxylase inhibitor (HIF-PHI) approved in the United States for treating anemia of chronic kidney disease (CKD) in adult patients (pts) receiving dialysis for at least 4 months. Dapro provides an oral alternative to erythropoiesis-stimulating agent (ESA) therapy. There are concerns that increasing hemoglobin in the dialysis population, such as with ESAs and HIF-PHIs, may cause thromboembolic events (TEEs). In the phase 3 ASCEND-D study, which randomized (1:1) 2964 pts with CKD undergoing dialysis and receiving ESAs to receive Dapro or ESA (NCT02879305; *N Engl J Med.* 2021;385:2325–2335), a trend toward a lower incidence of first occurrence of TEEs was observed with Dapro (185/1487 [12.4%]) compared with ESA (215/1477 [14.6%]). Here, we examine the occurrence of vascular access thrombosis (VAT), the most frequent type of TEE in the ASCEND-D study.

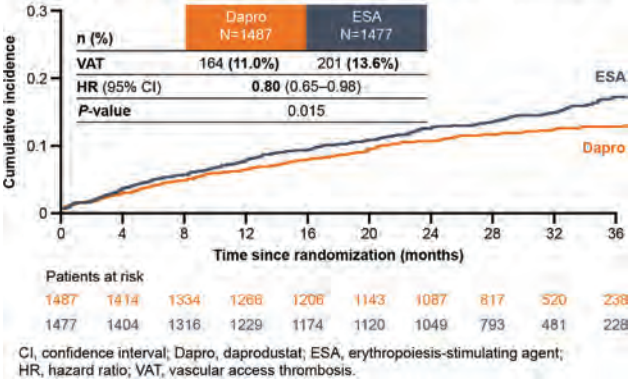
Methods: Adjudicated TEEs (including VAT) were a component of a prespecified principal secondary outcome. VAT was predefined as the absence of bruit or thrill and/or an inability to successfully initiate dialysis via the arteriovenous access after initial successful use. All suspected TEEs were adjudicated by the blinded Clinical Events Committee (CEC) according to predefined criteria. *Post hoc* analyses of time to first occurrence of VAT and recurrent events of VAT were performed.

Results: The CEC adjudicated 1088 potential TEEs, including VAT. First occurrence of adjudicated VAT occurred in 164/1487 (11.0%) and 201/1477 (13.6%) pts in the Dapro and ESA groups, respectively; hazard ratio 0.80 (95% CI: 0.65–0.98; *P*=0.015; **Figure**). Based on a recurrent events analysis of VAT using the negative binomial model, the rate ratio was 0.80 (95% CI: 0.63–1.01).

Conclusions: In the ASCEND-D study, there was a reduced incidence of VAT events with Dapro compared with ESAs.

Funding: Commercial Support - The study and this analysis were funded by GSK.

Kaplan–Meier Plot of Time to First Occurrence of VAT (*post hoc* analysis)



CI, confidence interval; Dapro, daprodustat; ESA, erythropoiesis-stimulating agent; HR, hazard ratio; VAT, vascular access thrombosis.

TH-PO1132

SARS-CoV-2 Testing During Routine Hemodialysis Care: A Nationwide Pragmatic Clinical Trial

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Background: Patients receiving dialysis face relatively high risks from viral infections including SARS-CoV-2. Early detection could facilitate treatment, reduce transmission, and strengthen public health surveillance. We evaluated the acceptability of routine SARS-CoV-2 screening among asymptomatic patients in dialysis facilities.

Methods: We conducted a pragmatic, cluster randomized trial in 57 US hemodialysis facilities from Feb-July 2023 in partnership with US Renal Care and Ascend Clinical Laboratory (NCT05225298). We tested patient level acceptability of two strategies for offering SARS-CoV-2 rtPCR tests: static frequency every two weeks (arm 1) versus dynamic frequency based on county COVID-19 levels (arm 2). We used wastewater surveillance if available or else CDC case and hospitalization rates to determine frequency of testing in the dynamic arm: weekly, biweekly or every four weeks for high, medium or low community levels, respectively). We randomized facilities by county and offered testing for three months.

Results: 2389 patients participated and 12,553 tests were offered (Table). A median of 6 versus 4 tests were offered per patient at static versus dynamic facilities. Test acceptability and positivity rates were 8.0% vs 7.7% (p=0.45), and 2.0% vs. 1.9% (p=0.56), at static versus dynamic facilities.

Conclusions: In this national trial integrating routine SARS-CoV-2 test offer in dialysis care in which a diverse group of patients participated, we found test acceptability was poor and did not vary by testing strategy. A dynamic testing strategy anchored to community transmission resulted in fewer tests offers per patient. Positivity rates among those tested indicate continued risk for transmission even during low COVID-19 incidence.

Funding: Other NIH Support - NIH RADxUP Grant, Commercial Support - Abbott Clinical Laboratories provided test kits; Ascend Clinical Labs processed test

	Static	Dynamic	P-value^
Facility level			
Facilities, n	28	29	
Participating patients per facility$	37 (25-45)	43 (34-59)	0.07
Region			
Northeast	4 (4.3%)	4 (13.8%)	0.99
Midwest	5 (17.9%)	5 (17.2%)	
South	13 (46.4%)	14 (48.3%)	
West	6 (21.4%)	6 (20.7%)	
Patient level			
Patients, n	1069	1320	
Age$	63 (54-73)	65 (54-74)	0.04
Race/Ethnicity			
White	382 (35.7%)	494 (37.4%)	0.12
Black	394 (36.9%)	492 (37.3%)	
Asian	26 (2.4%)	34 (2.6%)	
Hispanic	165 (15.4%)	174 (13.2%)	
Native Hawaiian or Pacific Islander	26 (2.4%)	49 (3.7%)	
American Indian	72 (6.7%)	66 (5.0%)	
Missing	4 (0.4%)	11 (0.8%)	
Accepted at least 1 test	276 (25.8%)	227 (17.2%)	<0.01
Test level			
Total tests offered, n	6347	6206	
Tests offered per patient$	6 (6-6)	4 (3-6)	<0.01
Total tests accepted	509 (8.0%)	475 (7.7%)	0.45
Positive (among accepted tests)	10 (2.0%)	9 (1.9%)	0.56

$ median (p25-p75); ^Exact/Pearson chi-square test or Wilcoxon rank-sum (Mann–Whitney) test for the difference, as appropriate.

TH-PO1133

Real-World Effectiveness of Hemodialysis Modalities

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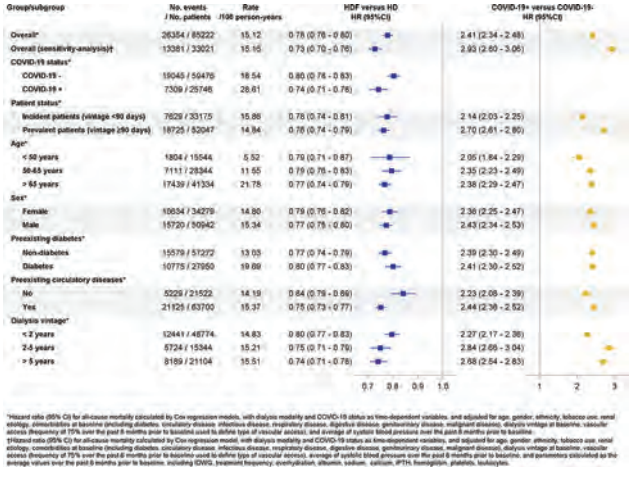
Background: Results from the CONVINCE clinical trial suggest a 23% mortality risk reduction among patients receiving hemodiafiltration (HDF). We assessed the real-world effectiveness of HD modality (HDF versus hemodialysis (HD)) in a large, unselected patient population treated prior to and during pandemic years.

Methods: We included EuCliD data from 85,222 adult HD patients who were treated in EMEA NephroCare Clinics between 2019 and 2022 in the analyses. Cox proportional hazard models with HD modality and COVID-19 status as time-varying covariates and adjusted for multiple confounders were used to estimate all-cause mortality. Subgroup analyses were performed for age, patient status (incident/prevalent), COVID-19 status, diabetes, circulatory disease, and dialysis vintage.

Results: The mean age of the population was 63.2 years and 60% were male. During the median follow-up of 22.6 months, a documented COVID-19 infection was associated with an overall 2.4-fold increased all-cause mortality risk. Compared with HD patients, those treated with HDF had an adjusted hazard ratio for all-cause mortality of 0.78 (95% CI, 0.76-0.80). The pattern of a beneficial effect of HDF was consistently observed among all subgroups. Patients with a documented COVID-19 infection and those with a history of circulatory disease had a slightly more reduced effect estimate in subgroup analyses (Figure 1).

Conclusions: Our results suggest that hemodiafiltration has a beneficial effect on all-cause mortality in a large, unselected patient population and across patient subgroups that were treated in real-world settings. Our observational study complements evidence generated by the CONVINCE trial and adds to the growing body of real-world evidence on hemodiafiltration.



TH-PO1134

Patient-Reported Health Status of Adults with Kidney Failure Receiving Hemodiafiltration vs. Hemodialysis: Results from the CONVINCE Randomized Controlled Clinical Trial

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Background: The CONVINCE trial showed a significant survival benefit for patients receiving high-dose hemodiafiltration as compared with conventional high-flux hemodialysis (N Engl J Med 2023; 389:700-709). A further objective was to compare the patient-reported health status between both interventions.

Methods: The CONVINCE Trial is multi-center, prospective randomized, open label, controlled trial, comparing benefits and safety of high-dose hemodiafiltration (HDF) versus high-flux hemodialysis (HD). The perceived health status was assessed in eight domains (physical function, cognitive function, fatigue, sleep disturbance, depression, anxiety, pain interference, social participation) using instruments from the Patient-Reported Outcome Measurement Information System PROMIS® before randomization and every three-month after over three years. The main analyses compared the mean change from baseline using an omnibus test for all eight domains, and a Linear Mixed Model to identify group x time interaction effects for specific domains.

Results: 1,360 patients have been enrolled, 677 receiving hemodialysis and 683 hemodiafiltration, with a median observation time of 30 month. For 84% of all treated patients PRO assessments could be analyzed (10,681 questionnaires). On average patients described statistically significant health deteriorations in all domains, with most pronounced declines in physical function scores. *Potential group differences between HDF vs HD will be disclosed at the ASN Congress.*

Conclusions: As of today, the CONVINCE trial has applied the most comprehensive assessment of PROs within a large RCT comparing HDF with HD, deepening the

understanding of the determining factors of perceived health of patients receiving renal replacement therapies. *The relevance of potential group differences will be discussed at the conference.*

Funding: Government Support - Non-U.S.

TH-PO1135

Short- and Long-Term Effectiveness of Existing Insomnia Therapies for Patients Undergoing Hemodialysis (SLEEP-HD)

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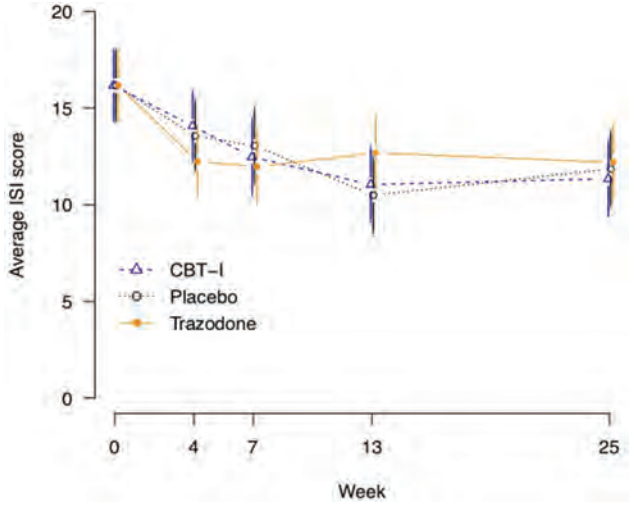
Background: Nearly 50% of patients undergoing in-center hemodialysis report chronic insomnia, yet efficacy and safety of treatments is not known. This trial tested the comparative effectiveness of cognitive behavioral therapy for insomnia (CBT-I), trazodone, and placebo for insomnia in this population.

Methods: We undertook a randomized, multicenter, double-blinded, placebo-controlled trial in 26 dialysis units. Patients undergoing in-center hemodialysis with insomnia severity index (ISI) score ≥ 10 and sleep disturbances on ≥ 3 nights/week for ≥ 3 months were randomized 1:1:1 to 6-week treatment with telehealth CBT-I or trazodone or placebo. The primary outcome was the ISI score at 7- and 25-weeks.

Results: 923 patients were pre-screened, 411 had insomnia, and 126 were randomized to CBT-I (n=43), trazodone (n=42), or placebo (n=41). The ISI scores decreased in each group: CBT-I (baseline mean ± SD, 16.1 ± 4.8; 7-weeks, 12.3 ± 6.0), trazodone (baseline mean ± SD, 17.2 ± 5.4; 7-weeks, 12.5 ± 6.2), and placebo (baseline mean ± SD, 15.2 ± 4.4; 7-weeks 12.5 ± 5.3) and there was no significant difference in the average 7-week scores across groups. There was no meaningful difference in ISI scores at 25-weeks. There was no significant difference in other patient-reported outcomes at any time point, or use of sleeping aids, or with actigraphy. Serious adverse events, particularly cardiovascular hospitalizations, were more frequent with trazodone (Relative risk: trazodone vs. CBT-I, 12.2 (1.83, 519.2); trazodone vs. placebo, 3.1 (0.97-13.22)).

Conclusions: In patients undergoing in-center hemodialysis with chronic insomnia, there was no meaningful difference in the short- or long-term effectiveness of CBT-I or trazodone compared with placebo. Participants receiving trazodone had higher incidence of serious adverse events.

Funding: NIDDK Support



TH-PO1136

Abstract Withdrawn

TH-PO1137

Peer Mentorship to Reduce Hospitalizations Among Patients Receiving Maintenance Hemodialysis: Results of the PEER-HD Trial

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Background: Hospitalizations contribute to up to 40% of the cost of care among patients receiving maintenance dialysis. PEER-HD is a pragmatic trial to test the impact on ED visit and hospitalization rates of a peer mentor led intervention in patients receiving hemodialysis.

Methods: This is a multi-center randomized controlled trial of 194 patient-participants (134 in Bronx NY and 60 in Nashville TN). Fourteen mentor-participants were recruited and trained. Patient-participants, identified as having high risk of hospitalization, were then recruited from affiliated dialysis facilities and those assigned to intervention (n=99) were matched to mentors. Mentors placed weekly telephone calls to assigned mentees over 3 months, after which patient-participants were observed for up to 15 months. The number of per patient-participant composite events during follow-up was recorded (median 12 months, range 2-18 months). The comparison of primary outcome between the intervention and usual care groups was made using Poisson regression with log of follow-up time as offset. Because there was significant interaction by study site we stratified the analyses.

Results: The mean age was 51.7 years, 51.5% were female, 56.2 % self-identified as Black and 39.2% self-identified as Hispanic. Baseline characteristics did not differ between randomized groups. The rates of ED visits and hospitalizations were 0.17 per patient-month in intervention group and 0.20 per patient-month in usual care group (incident rate ratio (IRR)=0.86; CI 0.70-1.06, p=0.15). Among the 134 patient participants in Bronx, NY there was a significantly lower rate of outcome in those assigned to intervention as compared to usual care (IRR= 0.70; CI 0.54-0.90; p=0.007). Among the 60 patients from Nashville, TN the difference in primary outcome was not significantly different (IRR= 1.25; CI 0.89-1.76, p=0.20). Post-hoc analysis showed that removal of 1 medically complex outlier made significant the overall effect of the intervention on outcome (IRR=0.85; CI 0.86-0.96, p=0.02).

Conclusions: Peer mentorship was not effective overall in reducing rate of hospitalization and ED visits, but was effective in Bronx NY. The protective effect of peer mentorship may be population specific, affected by area practice patterns or related to differences in mentoring activities.

Funding: NIDDK Support

TH-PO1138

Association of CKD-Associated Pruritus (CKDaP) with More Sleep Disorders, Increased Pain, and Worse Fatigue in US Hemodialysis Patients

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Background: Patients & their advocates emphasize symptom-based management for those afflicted with ESKD. There is an active call-to-action for Nephrology healthcare providers (NHCPs) to provide a holistic treatment plan: one that equally prioritizes symptom-based & biochemically-focused care. Three symptoms ESKD patients experience are sleep disorders, pain, & fatigue. These components are part of a cluster of symptoms known as SPADE in the Nephrology literature. This study investigates the association of CKDaP, an under– recognized & reported symptom, with these components.

Methods: A retrospective analysis of 81310 difelikefalin-naïve, >30-day hemodialysis vintaged in-center patients were stratified into the 5 validated groups of CKDaP burden descriptors in question 20 of the KDQOL-36 instrument. The burden of sleep disorder, pain, & fatigue were independently measured using questions 6, 8, & 25 of the KDQOL-36, respectively. Scores were re-coded from 0 (highest burden) to 100 based on the Rand Corporation's survey scoring instructions. ANOVA & logistic regression were used across pruritic levels. Mean (SD) are reported.

Results: Nearly 58% of patients experienced moderate or greater pruritic burden. Those patients with a greater CKDaP burden were statistically likely to have worse sleep, fatigue, & pain, both independently and in aggregate (table).

Conclusions: This data shows a strong association of CKDaP with 1) sleep disorders, 2) pain, & 3) fatigue. Patients afflicted with CKDaP endure a greater individual & aggregate symptom burden than those without. NHCPs who detect CKDaP & quantify its burden can potentially identify patients experiencing a) numerically higher-than-expected & b) more severe co-morbidities.

Funding: Commercial Support - CSL Vifor

Symptom	Extent bothered by itching in last 4 weeks					
	Not at all (n=16,974)	Somewhat (n=16,859)	Moderately (n=23,856)	Very Much (n=14,972)	Extremely (n=8,649)	Overall p value
Sleep	54.2 (27.7)	48.6 (26.4)	43.2 (26.0)	37.9 (26.4)	33.5 (28.0)	< 0.0001
Pain	77.2 (27.8)	70.7 (28.9)	62.4 (30.6)	56.4 (32.5)	48.7 (35.2)	< 0.0001
Fatigue	80.6 (24.3)	74.7 (24.4)	64.7 (27.9)	57.8 (30.7)	48.4 (35.5)	< 0.0001
Total	212.1 (60.7)	194.0 (60.5)	170.4 (63.6)	152.2 (67.3)	130.6 (74.7)	< 0.0001

TH-PO1139

The Association Between Pruritus Severity and Mental Health-Related Quality of Life in over 80,000 Hemodialysis Patients

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Background: Chronic kidney disease associated pruritus is common in hemodialysis (HD) patients and can impact quality of life (QoL). The Kidney Disease Quality of Life 36-Item Short Form Health Survey (KDQOL-36) captures patient reported health-related QoL and symptoms including pruritus (q 20) and mental health-related factors, such as depression (q 11) and anxiety (q 9). Another tool, Patient Health Questionnaire-2 (PHQ2), measures depressive symptoms. The goal of this cross-sectional, retrospective database analysis was to evaluate the association of depression and anxiety scores with varying levels of pruritus.

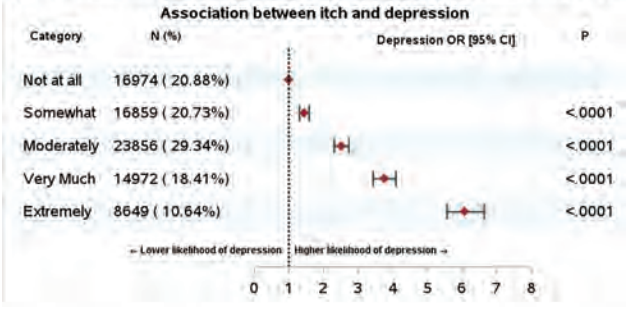
Methods: Fresenius Kidney Care, adult, in-center HD patients with SF-36 measured between 1/1/21 and 2/28/23 are eligible. Patients answering that they are burdened by at least "moderate" pruritus were included in the analysis. A random sample of patients from the "not at all" and "somewhat" bothered respondents was selected. This stratified sampling technique was used to guarantee patients from each itch severity group will be adequately represented in the study population. ANOVA and logistic regression were used to test the mean scores (0=highest burden to 100=lowest burden) or odds ratios across itch levels. PHQ2 scores > 3 have been a screening tool for depression and were used to dichotomize scores into depression present or absent.

Results: 81,310 patients had completed SF-36, of which 77,978 (96%) also had PHQ2 completed within 30 days. Burden of anxiety ($p<0.0001$) and depression ($p<0.0001$) symptoms was more likely as itch intensity increased. Mean scores for anxiety and depression differed by pruritis severity. Next, using PHQ2 scores of > 3 to define depression, we found a stepwise increased risk of depression with each increase in pruritus intensity score (Figure 1). Patients who were extremely bothered by pruritus had 6 times the odds of having depression when compared to those patients "not at all bothered" by pruritus ($p<0.001$).

Conclusions: These data have shown a strong association of pruritus with depression and anxiety.

Funding: Commercial Support - CSL Vifor

Figure 1. Association of itch burden and the presence of depression (PHQ2 > 3)



TH-PO1140

Strategies for the Management of Atrial Fibrillation in PatiEnts Receiving Dialysis (SAFE-D)

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Background: Atrial fibrillation (AF) is common in patients receiving maintenance dialysis. The role of oral anticoagulation (OAC) in this population is uncertain as dialysis recipients were excluded from landmark randomized control trials (RCTs).

Methods: Objective: To investigate the feasibility of conducting a full-scale RCT to assess the efficacy and safety of OAC in dialysis recipients with AF. **Design, setting, and participants:** We conducted a parallel-group, open-label allocation- concealed pilot RCT from December 2019 to December 2022 at 28 centres in Canada and Australia (ClinicalTrials.gov Identifier: NCT03987711). We included adults (≥18 y) undergoing maintenance dialysis with a history of non-valvular AF who met CHADS-65 criteria (i.e. age ≥ 65 y or the presence of at least one stroke risk factor). Exclusion criteria included contraindications to warfarin or apixaban, the need for anticoagulation for conditions other than AF and lack of clinician equipoise. **Interventions:** Dialysis recipients were randomized 1:1:1, stratified by centre, to receive dose-adjusted warfarin (targeting an INR of 2-3), apixaban, or no OAC. Follow-up was 26 weeks. **Outcomes:** We identified two thresholds for feasibility: recruitment of the target population within 24 months and retention of ≥ 80% of participants in their allocated arm at the end of follow-up. Principal secondary outcomes were ischemic stroke or systemic embolism, and bleeding (defined by International Society of Thrombosis and Hemostasis criteria).

Results: We screened 892 patients and enrolled 151(mean age 71.6 ± 10 y; 25% women; $CHADS_2$-VASc score 4 (IQR 3-5); prior stroke, 13%, prior major bleeding, 9%) who were allocated to apixaban (n =51), warfarin (n=52) or no OAC (n=48). We completed recruitment in 30 months (allowing for pauses related to the pandemic) and 83% of participants completed follow-up in their allocated treatment arm. Stroke occurred in 2 participants (1 apixaban, 1 no OAC), and 27 participants had at least one bleeding event (12 warfarin, 8 apixaban, 7 no OAC) of which 8 were major (4 warfarin, 2 apixaban, 2 no OAC). Death occurred in 15 participants (9 warfarin, 2 apixaban, 4 no OAC). Time in the therapeutic range for warfarin users was 58% (IQR 47%-70%).

Conclusions: This pilot RCT supports the feasibility of conducting a definitive RCT to inform the effect of OAC on clinical outcomes in dialysis recipients with AF.

Funding: Government Support - Non-U.S.

TH-PO1141

The FAGOTTO Trial: Randomized Controlled Trial for Impact on Renal Hemodynamics of the SGLT2 Inhibitor Canagliflozin in Diabetic Kidney Disease

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Background: Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have a potential to maintain renal function in the long-term despite of a dip on glomerular filtration rate (GFR) slope shortly after administration. We evaluated change of renal hemodynamics during GFR dip in patients (pts) with type 2 diabetic kidney disease (DKD) with moderate renal dysfunction [30 ≤ estimated GFR (eGFR) ≤ 60 mL/min/1.73 m^2].

Methods: The FAGOTTO (jRCTs041200069) was a 12-week multicenter, open-label, randomized (1:1=canagliflozin : control), parallel-group trial. We directly measured GFR (mGFR) and effective renal plasma flow (eRPF) by the clearance of inulin and para-aminohippuric acid at baseline and 4 weeks after start of the trial. We also assessed glomerular filtration fraction (FF), renal blood flow (RBF) and renal vascular resistance (RVR). The primary endpoint was change in FF.

Results: A total 111 pts were allocated. Mean age was 71 yrs; 73% were male; mean GFR, albuminuria and HbA1c were 46.0 ml/min, 371 mg/gCr and 6.9 %, respectively. Canagliflozin significantly reduced mGFR by -4.9 ml/min (95% CI: -7.2 to -2.6, P =0.0008), eRPF by -18.5 ml/min (-33.7 to -3.3, P = 0.0093), and RBF by -25.6 ml/min (-52.3 to 1.06, P = 0.021) vs control, respectively. No changes were observed in FF and RVR between these two groups. **Figure** shows the direct values. eGFRs were estimated 54.3, 50.8 and 48.6 ml/min in pts treated with canagliflozin and 54.7, 54.7 and 52.0 in controls at baseline, 4 and 12 weeks in a linear mixed model, respectively. Canagliflozin reduced eGFR after 4-week treatment (P = 0.009) and also 12-week (P = 0.032) vs control using Tukey-Kramer to correct for multiplicity.

Conclusions: SGLT2 inhibition reduced GFR and RPF while remained the levels of FF and RVR in DKD pts with moderate renal dysfunction.

Funding: Commercial Support - Mitsubishi Tanabe Pharma Corporation Co., Ltd.

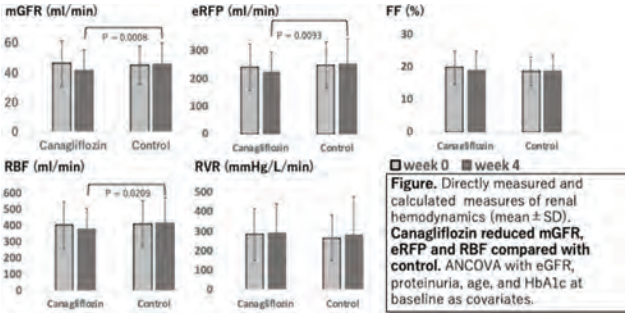

Figure. Directly measured and calculated measures of renal hemodynamics (mean ± SD). **Canagliflozin reduced mGFR, eRFP and RBF compared with control.** ANCOVA with eGFR, proteinuria, age, and HbA1c at baseline as covariates.

TH-PO1142

Impact of Finerenone-Induced Albuminuria Reduction on CKD Outcomes in Type 2 Diabetes: A Causal Mediation Analysis

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Background: In patients with chronic kidney disease (CKD) and type 2 diabetes (T2D), early reduction in urine albumin-to-creatinine ratio (UACR) is associated with improved kidney and cardiovascular outcomes. This post hoc mediation analysis quantified finerenone-induced kidney and cardiovascular (CV) risk reductions over a 4-year period mediated by a change in log UACR between baseline and month 4.

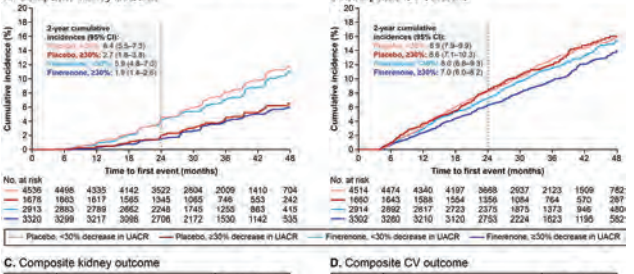
Methods: The analysis used pooled data from two phase 3 trials (NCT02540993 and NCT02545049) investigating the effect of finerenone vs placebo in patients with CKD and T2D. Separate causal mediation analyses were conducted for the composite kidney (kidney failure, sustained ≥57% decrease in estimated glomerular filtration rate from baseline, or kidney death) and CV (CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure) outcomes. The mediated effect of UACR reduction on the risk of cardiorenal outcomes was analyzed as a continuous variable (main finding) and as a dichotomous variable using the guideline-recommended 30% reduction threshold.

Results: Baseline median UACR was 514 mg/g (N=12,512). UACR reduction, analyzed as a continuous variable, mediated 83% and 36% of the treatment effect of finerenone on the kidney and CV outcomes, respectively (**Figure 1 C and D**). When UACR change was analyzed as a dichotomous variable, the proportions mediated were 62% and 25%, respectively (**Figure 1 A and B**).

Conclusions: In patients with CKD and T2D, early albuminuria reduction with finerenone mediated a large proportion of the treatment effect against CKD progression and a modest proportion of the effect against CV outcomes.

Funding: Commercial Support - Bayer AG

Figure 1. Cumulative incidences by treatment and relative reduction in UACR at 4 months and causal mediation analysis



C. Composite kidney outcome

Composite kidney outcome (n=12,400)	Effect	RMS[a] (95% CI)
	Independent of reduction in log UACR	1.02 (0.96–1.09)
	Mediated by reduction in log UACR	1.12 (1.10–1.15)
	Total effect	1.15 (1.07–1.22)
	Proportion mediated	0.83 (0.47–1.00)[b]

D. Composite CV outcome

Composite CV outcome (n=12,344)	Effect	RMS[a] (95% CI)
	Independent of reduction in log UACR	1.05 (1.00–1.16)
	Mediated by reduction in log UACR	1.04 (1.02–1.06)
	Total effect	1.12 (1.03–1.21)
	Proportion mediated	0.36 (0.09–0.63)[b]

Cumulative incidence calculated using an Aalen–Johansen estimator with all-cause death as a competing risk. Causal mediation analyses using change in log UACR (continuous variable) as the mediator. **Panel A** shows that an early change in UACR appeared to be a strong driver for the early separation of the incidence rate functions for the composite kidney outcome; in comparison, treatment group assignment produced a much smaller separation. **Panel B** shows that a separation of incidence rate functions for the composite CV outcome was not evident for the placebo group regardless of UACR change. However, CV event rates were separated as a function of UACR change in the finerenone group. **Panels C** and **D** show that the total effects of finerenone on the composite kidney and CV outcomes, respectively, were decomposed into effects independent of UACR reduction and effects mediated by reduction in log UACR. By comparing the relative magnitudes of the direct and indirect effects, the roles that UACR reduction played in achieving clinical benefits were determined.
[a]Estimates for RMS above 1 indicate greater mean event-free survival time; [b]proportion mediated values were calculated based on the estimates for the effect mediated by reduction in log UACR and the total effect or the corresponding logarithmically transformed RMS times.
CI, confidence interval; CV, cardiovascular; RMS, relative mean survival; UACR, urine albumin-to-creatinine ratio.

TH-PO1143

Results of an Exploratory and Randomized Control Study on DAPagliflozin for the Attenuation of Albuminuria in Patients with HEaRt Failure and Type 2 Diabetes Mellitus: DAPPER Study

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Background: Sodium-glucose cotransporter 2 (SGLT2) inhibitors reduce the urinary albumin-to-creatinine ratio (UACR) in patients with elevated albuminuria in the presence or absence of heart failure (HF) or type 2 diabetes mellitus (T2D). However, these effects have not yet been reported in the presence of both HF and T2D.

Methods: DAPPER is a multicenter, randomized, open-labeled, standard treatment-controlled trial that enrolled patients at 18 sites in Japan. Eligible participants with both HF and T2D were randomly assigned to a dapagliflozin or control (anti-diabetic drugs other than SGLT 2 inhibitors) with a 1:1 allocation. The primary outcome was the changes in UACR from baseline after a two-year observation, and the secondary endpoints were cardiovascular (CV) events and parameters related to HF.

Results: Between May 2017 and March 2020, 294 patients were randomly assigned to the dapagliflozin-group (n=146) or control-group (n=148). The mean age was 72.1 years and 29% were female. The mean HbA1c was 6.9%, mean NT-proBNP was 429.1 pg/mL, mean estimated GFR was 65.7 ml/min/1.73 m^2, and median UACR was 25.0 mg/g Cr in the dapagliflozin-group and 25.6 mg/g Cr in the control-group. In the dapagliflozin-group, when 122 patients completed the study, 107 (87.7%) had been taking 5 mg daily. The primary outcome did not differ between the dapagliflozin and control groups. Among the secondary endpoints, the mean decrease in left ventricular end-diastolic dimensions was greater in the dapagliflozin-group than in the control-group. The composite endpoint, defined as CV death or hospitalization for CV events, hospitalization for HF events, hospitalization for all causes, and an additional change in prescriptions for HF were also suppressed in the dapagliflozin-group.

Conclusions: Although dapagliflozin 5 mg daily, the major dose of the present study, did not reduce urinary albumin excretion in HF patients with T2D compared to the control, dapagliflozin decreased CV events and suppressed left ventricular remodeling.

Funding: Commercial Support - AstraZeneca K. K., Ono Pharmaceutical Co., LTD.

TH-PO1144

Efficacy and Safety of Sotagliflozin in Patients with Type 1 Diabetes and CKD

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Background: People with T1D, chronic kidney disease (CKD) and poor glycemic control are at high risk of kidney failure and cardiovascular events. Sodium-glucose cotransporter (SGLT) inhibitors improve glycemic control in adults with T1D but with an increased risk of diabetic ketoacidosis (DKA). This *post hoc* analysis evaluated the efficacy and safety of sotagliflozin (SOTA), a dual SGLT1 & 2 inhibitor, in patients with T1D and CKD.

Methods: Using patient-level data from inTandem 1 & 2, the effects of SOTA (200 or 400 mg daily) added to optimized insulin therapy on A1C, body weight (BW), systolic

blood pressure (SBP), eGFR, total insulin dose, adjudicated severe hypoglycemia (SH) and DKA were compared to placebo in a patient subgroup with T1D and CKD (eGFR <60 mL/min/1.73 m^2 and/or UACR ≥30 mg/g).

Results: In the 1575 patients, 237 (15%) had CKD. At baseline, patients with CKD were older, had longer T1D duration, lower eGFR, lower insulin pump use, higher total daily insulin dose, SBP, and UACR compared to the overall cohort. Relative to placebo, treatment with SOTA provided similar significant reductions in A1C, SBP and BW in the CKD and overall cohorts, but numerically smaller % reduction in total insulin dose at week 24 in the CKD cohort (Table 1). SOTA *vs.*placebo was associated with lower SH and higher DKA risk. However, the relative risk of SH and DKA appeared to be lower in the CKD *vs.* overall cohort over 52 weeks (Table 1). The expected acute eGFR decline followed by stabilization with SOTA was preserved in the CKD cohort.

Conclusions: In patients with T1D and CKD, treatment with SOTA had similar A1C and SBP lowering effects, and a lower relative risk of SH and DKA vs. the overall cohort.

Funding: Commercial Support - Lexicon Pharmaceuticals

	CKD Cohort			Overall Cohort		
	Placebo N = 76	Sotagliflozin 200 mg N = 85	Sotagliflozin 400 mg N = 76	Placebo N = 526	Sotagliflozin 200 mg N = 524	Sotagliflozin 400 mg N = 525
A1C, %	-0.13 (-0.29, 0.03)	-0.48 (-0.63, -0.33)*	-0.45 (-0.61, -0.29)*	-0.13 (-0.29, 0.03)	-0.48 (-0.63, -0.33)*	-0.45 (-0.61, -0.29)*
Body weight, kg	-0.15 (-0.83, 0.53)	-1.55 (-2.20, -0.91)*	-2.58 (-3.25, -1.91)*	0.47 (0.20, 0.74)	-1.70 (-1.97, -1.44)*	-2.55 (-2.82, -2.28)*
SBP, mmHg	-2.1 (-5.0, 0.7)	-4.8 (-7.5, -2.0)	-6.9 (-9.7, -4.1)*	-0.6 (-1.5, 0.3)	-2.6 (-3.5, -1.7)*	-4.1 (-5.0, -3.2)*
Total insulin dose, %	0.4 (-3.5, 4.2)	-4.2 (-8.0, -0.5)	-5.2 (-9.0, -1.4)**	1.1 (-0.5, 2.8)	-6.1 (-7.7, -4.4)*	-8.4 (-10.1, -6.8)*
Severe hypoglycemia, n (%)	13 (17.1)	6 (7.1)	3 (3.9)	39 (7.4)	30 (5.7)	23 (4.4)
HR (95% CI)	-	0.34 (0.13, 0.91)	0.20 (0.06, 0.70)	-	0.76 (0.47, 1.22)	0.58 (0.35, 0.97)
DKA, n (%)	1 (1.3)	4 (4.7)	2 (2.6)	1 (0.2)	15 (2.9)	20 (3.8)
HR (95% CI)	-	3.2 (0.4, 29.0)	1.9 (0.2, 20.8)	-	15.0 (2.0, 113.3)	20.3 (2.7, 151.2)

HR = Hazard Ratio, CI = confidence interval.
*p<0.01, **p<0.05 for the difference in LS mean change between sotagliflozin and placebo.
Efficacy endpoints were presented as LS mean change from baseline at Week 24 (95% CI) to be consistent with the primary endpoint time point in the individual trials.
Safety endpoints were presented from the entire 52 week follow up plus 30 days after last study dose.

Table 1. Selected key efficacy and safety endpoints by study treatment and cohort.

TH-PO1145

The ALL STAR CKD Trial: Pleiotropic Effect of Atorvastatin Focused on Renoprotection in Patients with CKD

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Background: Statins have been recognized for their pleiotropic effects which include anti-inflammation, antioxidant, improved endothelial function, stabilization of atherosclerotic plaques, and also reducing proteinuria. In this trial, we evaluated renoprotective effect of atorvastatin beyond lipid lowering in patients with chronic kidney disease (CKD) and hyperlipidemia.

Methods: The ALL STAR CKD (UMIN000006662) study was a 6-month multicenter, open-label, randomized (1:1= atorvastatin : ezetimibe), parallel-group trial of CKD patients with serum low-density lipoprotein cholesterol (LDL) ≧ 140 mg/dL (if patients with diabetes mellitus, LDL ≧ 120). The patients were allocated to receive once-daily atorvastatin 10 mg or ezetimibe 10mg: intestinal absorption of cholesterol inhibitor. We directly measured Glomerular Filtration Rate (mGFR) by the clearance of inulin at baseline and 6 months after start of the trial. We also assessed estimated GFR based by creatinine (eGFRcr) and cystatin C (eGFRcyst), and protein/albuminuria. The primary endpoint was the change in mGFR after 6 months of treatment in the atorvastatin group (Group A) and ezetimibe groups (Group E).

Results: A total 117 patients (men 53%, 56.7 years) were randomized. Mean eGFRcr, albuminuria and LDL were 54.3 ml/min, 178 mg/gCr and 150 mg/dL at the baseline, respectively. Serum LDL levels in Group A were significantly lower than those in Group E at six months after start of the trial (Group A vs Group E; 83.7 ± 25.1 vs 114.5 ± 19.0 mg/dL). When we compared the mean change from baseline to six months between the two groups by Wilcoxon rank-sum test, there were no significant differences in any parameters including mGFR (Group A vs Group E; 1.4 ± 11.2 vs -1.1 ± 18.9 ml/min: P = 0.09), eGFRcr (-6.7 ± 9.5 vs -6.1 ± 9.5 ml/min: P = 0.87), eGFRcyst (3.7 ± 8.1 vs 2.1 ± 6.4 ml/min: P = 0.37), proteinuria (-0.02 ± 0.36 vs 0.14 ± 0.65 g/gCr: P = 0.23) and albuminuria (124 ± 617 vs 244 ± 698 mg/gCr: P = 0.40).

Conclusions: The present trial did not demonstrate renoprotective effects of atorvastatin after 6-month treatment, as either reservation of GFR or anti- proteinuria. A longer-term observation might be needed to detect a renoprotective power of statins as a pleiotropic effect of atorvastatin in CKD patients.

TH-PO1146

A Clinical Decision Support Intervention Results in a Clinically Significant Decrease in Mean Systolic Blood Pressure in a Pragmatic Clinical Trial in a Primary Care Setting

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Background: Patients with chronic kidney disease (CKD) and hypertension (HTN) are at high risk for kidney failure and cardiovascular morbidity and mortality. Although both CKD and uncontrolled HTN are not difficult to diagnose, both often go unrecognized by primary care physicians (PCPs).

Methods: We conducted a pragmatic, randomized controlled trial involving PCPs and their patients in an academic medical center. Individual PCPs were randomized to intervention or usual care. All adult patients with a visit to a PCP were eligible and those with evidence in the electronic health record of CKD and uncontrolled HTN were automatically enrolled. The intervention consisted of a clinical decision support (CDS) intervention that delivered anti-hypertensive treatment recommendations (renin-angiotensin-aldosterone system (RAAS) inhibitors or hydrochlorothiazide for those on maximal RAAS inhibition). The primary outcome was the change in mean systolic blood pressure (SBP) between baseline and 180 days compared between arms. A secondary outcome was orders placed for recommended anti-hypertensive medications.

Results: The study included 184 PCPs and 2026 patients. Patient mean age was 75.3 years; 60% were female, and 71% were White. 80% of patients had an SBP measurement at 180 days +/- 60 days. We observed a 2.9 mmHg greater reduction in SBP in patients in the CDS intervention arm compared to usual care (95% CI 1.27,4.53; p=0.005). PCPs also placed more orders for recommended anti-hypertensive medications in the intervention arm (Table 1; p<0.0001).

Conclusions: A CDS intervention resulted in a clinically significant decrease in mean systolic blood pressure in a pragmatic clinical trial in a primary care setting.

Funding: NIDDK Support

Table 1: Primary and Secondary Outcomes

Measurement Variable	Intervention	Usual Care	p-value
Primary Outcome: Difference in SBP from baseline to 180 days			
Change in SBP, mmHg (95% CI)	-14.6 (-13.1, -16.0)	-11.7 (-10.2, -13.1)	0.005
Secondary Outcome			
Any ACE, ARB, or HCTZ ordered, % (95% CI)	24.3 (20.5, 27.7)	10.2 (0.07, 13.8)	<0.0001

SBP=Systolic Blood Pressure, CI=Confidence Interval, ACE=Angiotensin Converting Enzyme Inhibitor, ARB=Angiotensin Receptor Blocker, HCTZ=Hydrochlorothiazide

TH-PO1147

A Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled Study of Enarodustat for the Treatment of Renal Anemia in Chinese Non-Dialysis CKD Patients

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Background: Enarodustat (ENA) is a novel Hypoxia-inducible factor-prolyl hydroxylase inhibitor indicated for treating anemia in chronic kidney disease (CKD) patients. This phase 3 trial was conducted to establish the efficacy and safety of ENA in Chinese non-dialysis CKD (ND-CKD) patients.

Methods: This was a randomized, phase 3, double-blind, placebo-controlled, extended open-label, multicenter clinical study (NCT06016036). It consisted of a 4-week screening period, 8-week double-blind period (DBP), 16-week open-label period (OLP), and a 2-week safety follow-up period. Patients in the investigational drug group received once-daily ENA tablets at an initial dose of 4 mg/d for week1-5, then were adjusted in the range of 1/2/4/6/8 mg/d for every 4 weeks based on Hb levels and its changes.

The primary endpoint was the change in Hb levels from baseline (week1) averaged over week7–9. Secondary endpoints included Hb levels, its changes and proportion of the iron therapy, etc. Exploratory endpoints included iron parameters, etc.

Results: In total, 156 patients which had not received erythropoiesis-stimulating agents (ESA) treatment for ≥8 weeks were randomized in a 2:1 ratio to receive ENA (n=103) or placebo (PLA, n=53). In DBP, the change of Hb from baseline (mean±SD) averaged over week7–9 was 15.99±9.46g/L vs 0.14±8.08 g/L in ENA and PLA group (P<0.001). The mean Hb increase in the first 4 weeks was 11.82±9.56g/L vs 1.58±7.56g/L, the difference(LSM±SE) was 10.23 ±1.55 g/L (P<0.001). 85.3% vs 30% (P<0.001) of patients achieved a Hb level of ≥100g/L averaged over week7–9. In ENA group, the cumulative proportion of iron therapy decreased from 45.6% at baseline to 13.4% during the OLP, and the mean hepcidin levels decreased 57.7% (P<0.0001) from baseline at week9. Regarding the safety results, the incidences of adverse events (77.7% vs 79.2%) and adverse drug reactions (18.4% vs 15.1%) in ENA and PLA group were similar. There were no significant clinical changes in lipid parameters in ENA group.

Conclusions: Enarodustat was more effective in treating anemia in ESA-Naïve Chinese ND-CKD patients than placebo. Meanwhile, it had a similar safety profile with the placebo.

TH-PO1148

Abstract Withdrawn

TH-PO1149

Real-World Effectiveness of SGLT2 Inhibitors on the Progression of Kidney Disease in Non-Diabetic CKD Patients with and Without Albuminuria

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Background: In renal outcome trials, SGLT2 inhibition slows the progression of kidney injury in patients with & without type 2 diabetes (T2D). It is imperative to examine the renal effects of SGLT2 inhibition specifically among patients with chronic kidney disease (CKD) without T2D in a real-world setting.

Methods: We collected de-identified data on adult patients without diabetes who had an estimated glomerular filtration rate (eGFR) of 25-60 ml/min/1.73m^2 & initiated SGLT2 inhibitor (SGLT2i) dapagliflozin or empagliflozin between 9/2020-11/2022 in Maccabi Healthcare Services, a large Israeli health maintenance organization. We assessed the effect of SGLT2i on renal function, measured as the change in eGFR slope over time. The index date was defined as the date of the first dispensing of SGLT2i. Annual baseline slope was calculated by using all eGFR measurements within 2 years prior to index date (median of 7 measurements), while annual follow-up slope was calculated by using all evaluations during 90-900 days after index date (median of 5 measurements). For both periods, at least 180 days between first & last eGFR measurements were required. Paired t-test was used to compare differences between baseline & follow-up annual slopes.

Results: This analysis included 354 patients with CKD without T2D who received SGLT2i & were followed for a median of 527 days. The mean age was 72.8±11.8, 26% were women & 91% used renin-angiotensin system blockade. The mean eGFR was 45.4±9.5 ml/min/1.73m^2. 146 (41%) of participants had urinary albumin-to-creatinine ratio (UACR)<30mg/g, 81 (23%) had UACR of 30-300mg/g, 74 (21%) had UACR>300mg/g & 53 (15%) had no UACR evaluation within 1 year before index date. The slope of eGFR over time was -5.6±7.7 ml/min/1.73m^2 per year at baseline & it was improved to -1.7±6.8 ml/min/1.73m^2 per year after SGLT2i administration, (p<0.001). This effect was independent of UACR (Table 1).

Conclusions: In real-world study of patients with CKD without T2D, SGLT2 inhibition was associated with a slower rate of kidney function decline, regardless of baseline UACR levels.

Funding: Commercial Support - AstraZeneca

Table 1

UACR (mg/g)	No. of patients	Baseline Slope	Therapy Slope	P value
≤30	146	-5.9±9.2	-0.8±6.6	<0.001
30-300	81	-5.5±7.4	-1.7±8.0	<0.005
>300	74	-5.0±5.2	-3.5±4.9	0.09

TH-PO1150

Effect of Curcumin on Vascular and Cognitive Function in CKD: A Randomized Controlled Trial

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Background: Chronic kidney disease (CKD) increases the risk of developing cardiovascular disease (CVD) and cognitive impairment. Curcumin is a polyphenol that has been reported to improve vascular and cognitive function in middle-aged and older adults, however its effects on vascular and cognitive function in patients with CKD are unknown. We hypothesized that 12-month curcumin supplementation would improve vascular and cognitive function in patients with CKD.

Methods: 88 adults with CKD (stage 3B or 4) participated in a 12-month, randomized, double-blind, placebo-controlled, parallel-arms intervention to examine the effects of curcumin (Longvida, 2000 mg/day) on vascular and cognitive function. Our primary outcomes were endothelial function and aortic stiffness determined from brachial artery flow-mediated dilation (FMD) and carotid-femoral pulse wave velocity (cfPWV), respectively. Our secondary outcomes were endothelium- independent dilation via nitroglycerin mediated dilation and cognitive function assessed via the NIH Toolbox Cognition Battery.

Results: 75% of the participants were male, 56% had diabetes, and 15% had a history of CVD. The mean±SD age and eGFR were 66±8 years and 34.7±10.8 ml/min/1.73m2, respectively. The median (IQR) UACR was 81.9 mg/g (9.7-417.3). Following 12-months of curcumin supplementation, we observed no change in brachial artery FMD, nitroglycerin mediated dilation, or cfPWV (P>0.05; Table 1). Additionally, we observed no change in processing speed, executive function, memory, or language (P>0.05; Table 1). eGFR, UACR, hemoglobin A1c, and blood pressure were unchanged (P>0.05).

Conclusions: 12-month curcumin supplementation did not change vascular or cognitive function in patients with CKD.

Funding: Other NIH Support - NHLBI

Change in primary and secondary outcomes according to study group

Variable	Curcumin	Placebo	P value
FMD, %	-0.7 (-2.1,1.1)	-0.1 (-1.5,1.5)	0.69
cfPWV, m/s	0.3±2.4	0.4±4.2	0.94
Nitroglycerin dilation, %	-1.3±7.7	-1.3±6.5	0.97
Processing speed*	-0.9±8.9	1.8±7.0	0.15
Executive function*	2.6±9.0	2.3±9.5	0.86
Memory*	2.2±9.2	2.6±8.5	0.83
Language*^	-0.5±5.8	-1.3±4.5	0.51

*Age-adjusted T-score

TH-PO1151

Electronic Health Record-Based Population Health Management to Optimize Care in CKD: Kidney CHAMP Randomized Clinical Trial

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Background: Large gaps in clinical care in patients with chronic kidney disease (CKD) lead to poor outcomes. We tested the effectiveness of an electronic health record (EHR)-based population health management (PHM) intervention at reducing CKD progression and improving evidence-based care in high-risk CKD.

Methods: In a pragmatic cluster randomized clinical trial, we randomized 101 primary care practices to either intervention or usual care, and enrolled patients aged 18-85 years with estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2, with high risk of CKD progression and not seeing a nephrologist. Multifaceted intervention included nephrology e-consult, pharmacist-led medication management, and CKD education. Primary outcome was time to ≥40% reduction in eGFR or End Stage Kidney Disease.

Results: Among 1,596 patients with mean age 74±9 years, 58% were females, 8% were Black, and mean eGFR 36.8±7.9 ml/min/1.73m^2. Over a median follow-up of 17.4 months, there was no significant difference in rate of primary outcome between the two arms (adjusted hazards ratio 0.99, 95% CI 0.69, 1.42; P=0.94). Angiotensin converting enzyme inhibitor/Angiotensin receptor blocker (ACEi/ARB) exposure was more frequent in intervention arm compared to control (rate ratio 1.22, 95%CI 1.04 to 1.44, P=0.018). There was no difference in secondary outcomes of hypertension control and exposure to unsafe medications, or adverse events between the arms.

Conclusions: Among patients with moderate to high-risk CKD, a multi-faceted EHR-based PHM intervention resulted in more exposure days to ACEi/ARB but did not reduce risk of CKD progression or hypertension control versus usual care. Several COVID pandemic related factors likely contributed to null findings in our study.

Funding: NIDDK Support

TH-PO1152

Control of Secondary Hyperparathyroidism with Extended-Release Calcifediol Is Associated with Slower CKD Progression

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Background: Insufficient levels of serum total 25-hydroxyvitamin D (25D) increase the risk of secondary hyperparathyroidism (SHPT) in patients with stage 3 or 4 chronic kidney disease (CKD). SHPT develops and advances in most CKD patients because 25D is not reliably raised with cholecalciferol or ergocalciferol. SHPT is associated with accelerated CKD progression and dialysis onset, but mitigation of disease progression by effective control of SHPT has not been previously examined.

Methods: Progressive changes in estimated glomerular filtration rate (eGFR) were examined post-hoc in 166 patients with vitamin D insufficiency, SHPT and stage 3-4 CKD during 1-year of treatment with extended-release calcifediol (ERC) in pivotal trials (Sprague 2016). ERC was administered daily at 30 mcg increasing, as needed, after 12 weeks to 60 mcg to achieve a targeted ≥30% reduction in iPTH. Measurements of eGFR were obtained at baseline (BL) and quarterly intervals, and 25D (DiaSorin), calcium (Ca), phosphorus (P) and plasma intact parathyroid hormone (iPTH; Roche Elecsys) at BL and monthly. Mean BL or quarterly iPTH levels of ≤100 pg/mL were considered "controlled" and, if maintained at 4 of these 5 assessments, "consistently controlled".

Results: ERC treatment increased mean (±SE) serum 25D from 20.1±0.4 ng/mL at BL to 77.8±2.0 at end of treatment (EOT; $p<0.001$) and decreased mean iPTH from 146.6±4.7 pg/mL at BL to 104.4±6.5 at EOT ($p<0.01$) without clinically meaningful changes in mean serum Ca or P. Decreases in mean iPTH were unaffected by BL eGFR. Average eGFR decline was 2.3±0.5 mL/min/1.73m^2 over the 1-year treatment period but differed significantly and proportionally with duration of iPTH control, being maximal (4.1±0.7) in subjects who never achieved control (n=44) and minimal (0.61±1.2) in subjects achieving consistent control (n=51; $p<0.05$). The number of subjects achieving an increase in eGFR by EOT rose in proportion to the duration of iPTH control achieved from 6 (no control) to 18 (consistent control).

Conclusions: A post-hoc analysis of pivotal clinical trial data with ERC indicates that early, sustained, effective treatment of SHPT is associated with mitigation of eGFR decline in patients with insufficient 25D and stage 3-4 CKD. Prospective studies with ERC are warranted to confirm these findings.

Funding: Commercial Support - OPKO Health

TH-PO1153

Heart Failure and Edema Events Associated with Sodium Zirconium Cyclosilicate vs. Patiromer Treatment

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Background: Sodium zirconium cyclosilicate (SZC) and patiromer (PAT) are potassium binders that differ by exchange ion, sodium, and calcium, respectively. There is limited data on whether using sodium exchange could impact the risks of hospitalizations for heart failure (HHF) or severe edema in patients with hyperkalemia. We assessed the occurrence rates of pre-specified major encounters potentially related to electrolyte-/fluid-related imbalances when stratified by new users of PAT or SZC.

Methods: Using Cerner Real World Data, we conducted a retrospective cohort study among patients who were newly initiated on SZC or PAT between June 1, 2018, and December 31, 2021. Adults (≥ 18 years) were followed from their first SZC or PAT prescription (index date) until the end of the 6-month follow up period. We analyzed the occurrence of pre-specified outcomes, discontinuation of or switch from index medication or death. Based on baseline demographic and clinical characteristics, 1 PAT initiator was propensity score matched with 2 SZC initiators. Primary outcomes were any HHF, primary HHF, major edema encounter (MEE), or death. Cox Proportional Hazard regression models were used to estimate the association between SZC or PAT use and each outcome in the overall population and subgroups with/without prior heart failure (HF).

Results: The final cohort included 9,929 PAT initiators matched to 19, 849 SZC initiators. Mean age was 66 years old; about 50% had a history of chronic kidney disease stages 3-5, and 34% a history of HF. Incidence rates (IR) and risks of all outcomes: HHF (any/primary), MEE, and death were significantly higher in the SZC cohort compared to the PAT cohort. These findings were consistent among subgroups with/without prior HF (Fig. 1).

Conclusions: In this real-world data, SZC use (vs. PAT) is associated with increased risk of pre-specified encounters potentially sodium-/fluid-related, including among patients with/without pre-existing HF.

Funding: Commercial Support - Vifor

Total matched cohort	SZC (N=19,840) *N (IR)*	PAT (N=9,923) *N (IR)*	Risk Difference (95% CI)	Crude HR (95% CI)	Adjusted HR (95% CI)
Any HHF	2,877 (0.092)	1,490 (0.071)	0.022 (0.017 ; 0.026)	1.396 (1.303 ; 1.439)	1.373 (1.337 ; 1.410)
Primary HHF	2,433 (0.074)	1,474 (0.069)	0.009 (0.004 ; 0.013)	1.398 (1.285 ; 1.431)	1.373 (1.337 ; 1.409)
Death	1,854 (0.054)	927 (0.026)	0.008 (0.005 ; 0.032)	1.314 (1.285 ; 1.344)	1.287 (1.255 ; 1.320)
MEE	532 (0.015)	221 (0.009)	0.004 (0.004 ; 0.007)	1.352 (1.232 ; 1.382)	1.330 (1.298 ; 1.363)
Those with NO prior history of HF	**SZC (N=13,229) *N (IR)***	**PAT (N=6,564) *N (IR)***			
Any HHF	718 (0.031)	362 (0.022)	0.009 (0.006 ; 0.012)	1.420 (1.281 ; 1.460)	1.390 (1.348 ; 1.433)
Primary HHF	594 (0.025)	332 (0.020)	0.005 (0.002 ; 0.008)	1.424 (1.284 ; 1.464)	1.392 (1.350 ; 1.436)
Death	1,167 (0.048)	317 (0.018)	0.029 (0.026 ; 0.033)	1.364 (1.327 ; 1.403)	1.331 (1.290 ; 1.372)
MEE	294 (0.012)	105 (0.006)	0.006 (0.004 ; 0.008)	1.410 (1.372 ; 1.449)	1.379 (1.338 ; 1.422)
Those with prior history of HF	**SZC (N=6,611) *N (IR)***	**PAT (N=3,359) *N (IR)***			
Any HHF	2,259 (0.262)	1,228 (0.217)	0.045 (0.028 ; 0.061)	1.339 (1.277 ; 1.403)	1.326 (1.266 ; 1.390)
Primary HHF	1,839 (0.198)	1,142 (0.167)	0.031 (-0.014 ; 0.012)	1.337 (1.278 ; 1.400)	1.322 (1.267 ; 1.382)
Death	787 (0.067)	310 (0.042)	0.024 (0.018 ; 0.031)	1.212 (1.165 ; 1.260)	1.195 (1.143 ; 1.248)
MEE	228 (0.020)	116 (0.016)	0.004 (-0.000 ; 0.008)	1.234 (1.188 ; 1.281)	1.228 (1.177 ; 1.282)

Fig. 1: Incidence rates (per person-months), risk difference, crude and adjusted hazard ratios for SZC use (vs. PAT)

TH-PO1154

Real-World Effectiveness of Finerenone in Chinese CKD Patients Without Type 2 Diabetes

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Background: No evidence has been reported for using finerenone in non-diabetic chronic kidney disease (CKD), although it is proven effective and safe for patients with CKD and type 2 diabetes(T2D).

Methods: This real-world retrospective study included Chinese CKD patients without T2D between November 2022 and August 2023. Patients received standard CKD treatment plus finerenone at dose of 10 or 20 mg once daily. Urinary albumin to creatinine ratio (UACR), estimated glomerular filtration rate (eGFR), and serum potassium (sK^+) were examined at baseline, 1 month, and 3 months after treatment.

Results: Totally 16 patients were analyzed (mean age: 55.38±14.37 years; 12 [75.0%] males) (Table 1). UACR was remarkably reduced compared to baseline at 1 month post-treatment and further reduced at 3 months post-treatment, with a median reduction of 200.41 mg/g (IQR, 84.04-1057.10, P=0.028; percent change, 44.52% [IQR, 31.79%-65.42%]) (Figure 1a). No significant eGFR decline was observed through 3 months follow up(Figure 1b). sK^+ levels remained within the range of 3.5-5.5 mmol/L with only minor fluctuations compared to baseline (Figure 1c). No treatment discontinuation or hospitalization due to hyperkalemia occurred.

Conclusions: Finerenone showed good effectiveness and safety in CKD without T2D patients in 3 month follow up. It should be verified by Future large prospective studies.

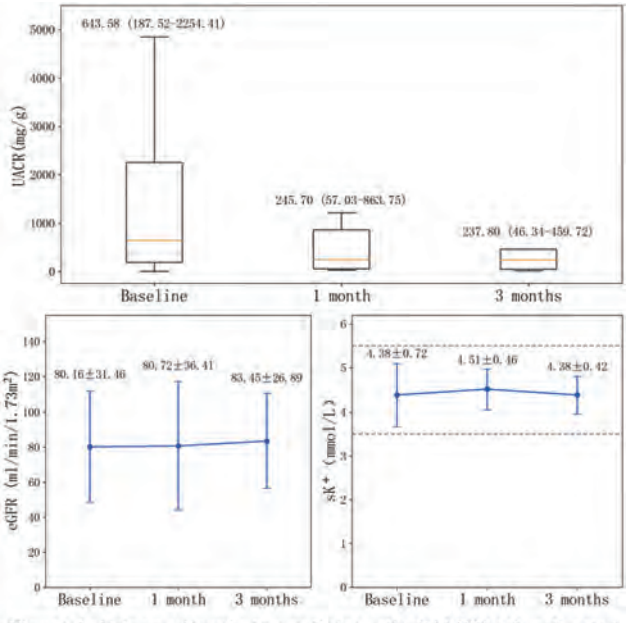

Figure 1. Urinary albumin to creatinine ratio (UACR) (a), estimated glomerular filtration rate (eGFR) (b), and serum potassium (sK^+) (c) levels at baseline, 1 month, and 3 months after finerenone treatment. Data are presented as mean ± standard deviation or median (interquartile range) according to normality. Dashed lines in Figure 1c present the range of 3.5-5.5 mmol/L.

Table 1. Baseline patient characteristics

Characteristics	Mean ± SD / n (%)
Age (years)	55.38±14.37
Male sex	12 (75.0%)
Clinical diagnosis	
Chronic nephritis	8 (50.0%)
Nephrotic syndrome	2 (12.5%)
Etiological diagnosis	
IgA nephropathy	2 (12.5%)
Membranous nephropathy	2 (12.5%)
Henoch-Schonlein purpura nephritis	1 (6.3%)
Polycystic kidney disease	1 (6.3%)

SD, standard deviation.

TH-PO1155

Hexasodium Fytate (SNF472) for Treatment of Calciphylaxis

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Background: Calciphylaxis (or calcific uremic arteriolopathy, CUA) is a rare serious condition with no approved therapies characterized by severely painful ischemic skin lesions due to calcification in arterioles. CALCIPHYX was a phase 3, randomized, double-blind, placebo-controlled trial of hexasodium fytate, or SNF472, a selective inhibitor of vascular calcification, in patients on maintenance hemodialysis with calciphylaxis.

Methods: Adults with ≥1 ulcerated calciphylaxis lesion and Pain VAS score of ≥50/100 received SNF472 7 mg/kg or placebo IV during hemodialysis 3 times weekly for 12 weeks. Alternate primary efficacy outcomes were BWAT-CUA (an 8-item modification of the Bates-Jensen Wound Assessment Tool to assess relevant features of calciphylaxis) and Pain Visual Analog Scale (VAS). Safety outcomes included CUA wound-related complications.

Results: A total of 148 patients were screened, 71 were enrolled, and treatment was completed by 34 (91.9%) and 26 (76.5%) subjects in the SNF472 and placebo groups, respectively. At baseline, mean (SD) BWAT-CUA score was 19.8 (5.21), Pain VAS was 69.1 (27.9), and 69.0% of patients were treated with sodium thiosulfate. At Week 12, mean (SD) absolute change from baseline in BWAT-CUA was -5.3 (5.2) in the SNF472 group and -6.0 (6.2) in the placebo group, corresponding to a LS mean (SE) difference of 0.27 (1.33) (95% CI: -2.46, 3.00; p=0.88). Mean (SD) change from baseline in Pain VAS was -19.5 (26.9) in the SNF472 group and -32.2 (38.5) in the placebo group, corresponding to a LS mean (SE) difference of 11.49 (7.93) (95% CI: -4.80, 27.78; p=0.15). SNF472 was safe and well tolerated. Adverse events (AEs) leading to death were less frequent in patients randomized to SNF472: 1 (2.6%) vs. 6 (18.2%) in patients randomized to placebo. CUA wound-related AEs (11 [29.9%] vs. 16 [48.5%]) and wound-related infections (1 [2.6%] vs. 7 [21.2%]) were also less frequent in patients randomized to SNF472.

Conclusions: CALCIPHYX did not meet either alternate primary efficacy outcome. BWAT-CUA and Pain VAS improved similarly in both groups. There were numerically fewer AEs leading to death and CUA-wound related events and infections in patients treated with SNF472 compared to placebo. Detailed primary and post-hoc analyses will be presented.

Funding: Commercial Support - CSL Vifor

TH-PO1156

Targeting Vascular Calcification in Calciphylaxis

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Background: Despite recent advances in the understanding of calcification inhibitors, there is no approved therapy for calciphylaxis-- a serious vascular calcification disorder that predominantly affects patients with end stage kidney disease. We sought to examine the link between pharmacotherapeutic strategies targeting vascular calcification (vitamin K, intravenous sodium thiosulfate, intralesional sodium thiosulfate, bisphosphonate, and calcimimetiic) and clinical outcomes in calciphylaxis.

Methods: We analysed data from phase 2, double-blind, placebo-controlled trial of phytonadione (vitamin K1) that enrolled adult hemodialysis patients with calciphylaxis (ClinicalTrials.gov #, NCT02278692). Eligible patients (n=26) underwent randomization to receive either oral phytonadione 10 mg (n=13) or placebo (n=13) thrice weekly for 12 weeks. Selection of other vascular calcification treatments was up to the clinician's discretion. We examined the associations between calcification treatments and clinical outcomes (pain intensity and skin lesion total surface area analysed as comparison between the end of trial and baseline). We explored whether the effect of phytonadione is influenced by the administration of co-treatments.

Results: Improvements in pain intensity and total lesion surface area were seen among 58% and 46% of patients, respectively. Phytonadione therapy led to improvements in pain intensity (92% phytonadione vs. 8% placebo, p<0.001) and total lesion surface area (69% phytonadione vs. 31% placebo, p=0.018) in higher number of patients compared with placebo. Intralesional sodium thiosulfate was administered to 39% of trial participants, 50% of trial participants were treated with cinacalcet, all received intravenous thiosulfate, and none received etelcalcetide or bisphosphonate. Intralesional sodium thiosulfate or cinacalcet by themselves were not associated with improvements in clinical outcomes. The effect of phytonadione was seen even among patients not treated with Intralesional sodium thiosulfate or cinacalcet.

Conclusions: Early data demonstrate that the effect of phytonadione is seen even in the absence of application of cinacalcet and intralesional sodium thiosulfate. Whether the effect differs according to the applicaiton of intravenous sodium thisulfate needs further investigation.

Funding: Private Foundation Support

TH-PO1157

A Randomized, Controlled, Open-Label, Multicenter Study Evaluating the Efficacy and Safety of Lower Starting Dose Roxadustat for Anemia Treatment in Patients with CKD Not on Dialysis

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Background: Roxadustat is approved in China for chronic kidney disease (CKD)-associated anemia (CKD-anemia) treatment with and without dialysis. We assessed the non-inferiority of lower starting dose (LSD) roxadustat versus standard starting dose (SSD) for stage 3–5 CKD-anemia treatment without dialysis.

Methods: In this non-inferiority trial, patients were randomized (1:1) to a weight-based SSD (<60 kg: 70 mg three times per week [TIW]; ≥60 kg: 100 mg TIW) or LSD (<60 kg: 50 mg TIW; ≥60 kg: 70 mg TIW). Treatment was for 16 weeks (assessments every 2 weeks for 8 weeks, then every 4 weeks). The primary efficacy endpoint was the mean hemoglobin (Hb) change from baseline over weeks 12–16. Adverse events (AEs) were assessed during the treatment period and 4 weeks after completion.

Results: In total, 254 patients were randomized. The SSD (n=128) and LSD (n=126) groups had comparable baseline characteristics. The baseline Hb was 89.4 g/L (7.0) for LSD & 90.6g/L (6.7) for SSD. In the per protocol set (PPS) (n=226), the mean Hb change from baseline over 12–16 weeks was 21.6 g/L for LSD and 26.4 g/L for SSD (–4.78 g/L, 95% confidence interval [CI] –7.77 to –1.79 g/L [<–5 g/L non-inferiority margin]). In the PPS, 47.8% of the LSD patients achieved Hb 100–120 g/L over weeks 12–16 versus 47.7% for the SSD (odds ratio 1.158, 95% CI 0.671 to 1.996; P=0.60). The full analysis set (n=249) had similar results. The LSD group had significantly lower rates of change in Hb from baseline to weeks 4 (P=0.03), 8 (P=0.03), and 16 (P<0.01). There were 3 (2.4%) of the LSD & 2 (1.6%) of the SSD patients received rescue therapy. In the safety set (n=250), 68.0% of patients had treatment-emergent AEs (LSD 72.2%; SSD 63.7%). The proportions of treatment-emergent serious AEs (24.6% vs 10.5%) and drug-related AEs (4.0% vs 2.4%) were numerically higher with the LSD than the SSD.

Conclusions: Non-inferiority was not established for the LSD compared with the SSD in stage 3–5 CKD non-dialysis patients. The proportion of patients who achieved Hb 100–120 g/L over weeks 12–16 for both groups was similar; patients receiving the LSD had less Hb fluctuation. Both dosages were well tolerated, however, LSD did not show a better safety profile.

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TH-PO1158

CER-001, an Engineered High-Density Lipoprotein, Shows Beneficial Pleiotropic Effects in Patients with Sepsis in RACERS: A Phase 2A Randomized Control Trial

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Background: The cytokine storm, an excessive immune response in sepsis, leads to acute kidney injury (AKI) and multi-organ failure. Our recent research highlighted the diverse properties of HDL, including LPS scavenging, anti-inflammatory effects, and preservation of endothelial integrity in an LPS-induced AKI swine model. Subsequently, we investigated the effects of CER-001, an apoA-I-containing engineered HDL, in a Phase 2a clinical trial.

Methods: We conducted an open-label, randomized, dose-ranging trial (RACERS study, N° EUDRACT 2020-004202-60) in 20 septic patients with intra-abdominal infection or urosepsis. Patients were randomized to receive standard of care (SOC; n=5) or SOC + CER-001 (5 mg/kg BID, 10 mg/kg BID, or 20 mg/kg BID; n=5 per group) on days 1, 2, 3, and 6. The primary outcomes were safety and efficacy in preventing AKI onset and/or progression, while secondary outcomes included changes in inflammatory and endothelial dysfunction markers.

Results: Patients were enrolled from the ICU and Nephrology Unit during the early phase of sepsis (median time from hospital admission: 2 days). CER-001 treatment was well tolerated, and no serious adverse events were attributed to its use. Rapid normalization of apoA-I levels with CER-001 was associated with significant and sustained LPS removal ($p<0.05$ on days 3, 6 and 9) and subsequent immunomodulation. CER-001 treatment led to rapid and significant decreases in pro-inflammatory cytokines (e.g., IL-6, IL-8, TNF-α, MCP-1), endothelial dysfunction markers (sVCAM, sICAM) and mortality biomarker (sTREM-1), resulting in improved clinical outcomes regardless of sepsis type or severity. CER-001-treated patients had a reduced risk of developing or progressing to severe AKI and, in a subset of critically ill patients, a shorter ICU stay and decreased need for organ support.

Conclusions: CER-001 replicates the beneficial pleiotropic effects of natural HDL by scavenging LPS, reducing inflammation, and protecting the endothelium. Therefore, CER-001 represents a promising therapeutic strategy for sepsis management, improving outcomes and mitigating the cytokine storm and associated organ damage often observed in our patients.

Funding: Commercial Support - Abionyx Pharma SA

TH-PO1159

Abstract Withdrawn

TH-PO1160

Results of a Randomized Placebo-Controlled Double-Blind Adaptive Phase 2 Study (AKITA) Evaluating RMC-035 for the Prevention of AKI in Patients Undergoing Cardiac Surgery

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Background: Acute Kidney Injury (AKI) is a common and serious complication following cardiac surgery and is associated with multiple acute and long-term kidney-related adverse outcomes, such as renal replacement therapy, irreversible loss of kidney function, progression of preoperative chronic kidney disease (CKD) and transition to End Stage Kidney Disease (ESKD). RMC-035 is a recombinant, modified therapeutic protein, mimicking endogenous Alpha-1-Microglobulin, that harbors potent anti-oxidative and heme-binding capacity.

Methods: Global multi-center Phase 2 randomized double-blind adaptive design parallel group study in patients at high AKI risk undergoing open-chest coronary bypass and/or valve surgery with use of cardio-pulmonary bypass. Enrichment for high AKI risk was accomplished by incorporating mandatory AKI risk factors to the eligibility criteria. Patients with eGFR <30 mL/min were excluded from the study. 177 subjects were randomized 1:1 and treated with either RMC-035 or placebo. Study drug was administered up to 2 days after surgery, in total 5 IV infusions. The primary efficacy endpoint was AKI (KDIGO definition) within 72h after surgery. Important secondary endpoints included eGFR change from baseline up to Day 30/90 and MAKE (Major Adverse Kidney Events), a composite defined by death, any post-surgery dialysis or ≥25% eGFR decline from baseline on Day 30/90.

Results: Efficacy results on AKI, eGFR & MAKE and safety will be shared after availability of top-line results which are expected around September 20.

Conclusions: Conclusions will be shared after availability of top-line results, expected around September 20.

Funding: Commercial Support - Guard Therapeutics